

Cancer Surgery

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Abstract: Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. This is a literature collection on cancer surgery.

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1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

Agra, I. M., A. L. Carvalho, et al. (2008). "Biological markers and prognosis in recurrent oral cancer after salvage surgery." *Arch Otolaryngol Head Neck Surg* **134**(7): 743-9.

OBJECTIVE: To analyze the prognostic effect of epidermal growth factor receptor (EGFR), matrix metalloproteinases 2 and 9, and vascular endothelial growth factor expression in patients with locally recurrent oral carcinoma after salvage surgery. **DESIGN:** Retrospective cohort study. Settings Tertiary center cancer hospital. **PATIENTS:** The charts of 111 patients with local recurrence of oral carcinomas were retrospectively analyzed. The previous treatment consisted of surgery in 33 patients (30.0%), radiotherapy with or without chemotherapy in 46 patients (41.0%), and surgery with adjuvant radiotherapy in 32 patients (29.0%). The expression of EGFR, matrix metalloproteinases 2 and 9, and vascular endothelial growth factor was analyzed with a tissue microarray immunohistochemical technique. **MAIN OUTCOME MEASURES:** Overall survival and cancer-specific survival (CSS). **RESULTS:** The recurrences were diagnosed in less than 1 year in 69 patients (62.2%) and in more than 1 year in 42 patients (37.8%). The prognosis was worse in the group with the disease-free interval of less than 1 year

($P = .01$). Patients with more advanced disease (clinical stage of recurrence, III/IV) had worse rates of CSS ($P = .04$). Cases that were positive for EGFR had a 3-year CSS of 27.2%, while EGFR-negative cases had a 3-year CSS of 64.3% ($P = .001$). The expression of matrix metalloproteinases 2 ($P = .83$) and 9 ($P = .15$) and vascular endothelial growth factor ($P = .86$) was not significant in this group. In multivariate analysis, only the disease-free interval and the overexpression of EGFR were associated with a higher risk of cancer death. **CONCLUSIONS:** Local recurrence in oral carcinomas carries a poor prognosis. A disease-free interval of more than 1 year and a EGFR-negative expression are the main prognostic factors related to better CSS in patients treated with salvage surgery.

Agra, I. M., A. L. Carvalho, et al. (2003). "Postoperative complications after en bloc salvage surgery for head and neck cancer." *Arch Otolaryngol Head Neck Surg* **129**(12): 1317-21.

OBJECTIVE: To analyze the frequency of and risk factors for postoperative complications after en bloc salvage surgery for head and neck cancer. **DESIGN:** Retrospective cohort study. **SETTING:** Patients were evaluated from February 7, 1990, to November 17, 1999, in a tertiary cancer center hospital. **PATIENTS:** Consecutive sample of 124 patients from the hospital database. Only patients with recurrent head and neck squamous cell carcinoma undergoing en bloc salvage resection were eligible for the study. **MAIN OUTCOME MEASURES:** We analyzed the frequency of and risk factors for complications after salvage surgery. **RESULTS:** The tumor location was the lip in 6 patients, oral cavity in 55, oropharynx in 31, larynx in 24, and hypopharynx in 8. Previous treatment was surgery alone in 20 patients, radiotherapy alone in 68, surgery and radiotherapy in 21, and radiotherapy and

chemotherapy in 14. An additional patient received chemotherapy alone before salvage surgery. The clinical stage of the recurrent tumor was I or II in 23 patients and III or IV in 101 patients. Postoperative complications occurred in 66 patients (53.2%). Fifty-three patients (42.7%) had minor complications, and 23 patients (18.5%) had major ones. There were 4 postoperative deaths (3.2%). The major factor associated with the overall occurrence of postoperative complications was the clinical stage of the recurrent tumor ($P = .02$). The occurrence of minor complications correlated with the previously treated site, with complications occurring more often in patients undergoing locoregional vs local treatment ($P = .04$). Major complications were associated with the time between initial treatment and salvage surgery ($P = .05$). **CONCLUSIONS:** Salvage surgery can be performed with acceptable rates of postoperative complications. The clinical stage of the recurrent tumor and the previous site treated were the 2 major factors associated with the occurrence of postoperative complications.

Akman, F. C., N. Dag, et al. (2008). "The impact of treatment center on the outcome of patients with laryngeal cancer treated with surgery and radiotherapy." *Eur Arch Otorhinolaryngol* **265**(10): 1245-55.

For laryngeal cancer, surgical excision of the primary tumor should be undertaken with the aim of achieving tumor-free margins. Adequate pathological assessment of the specimen and the competency of the treatment center play a crucial role in achieving cure. The present study aimed to analyze the significance of place of surgery on the outcome of patients with laryngeal cancer who underwent surgical operation in other centers and were subsequently referred to Dokuz Eylul University Head and Neck Tumour Group (DEHNTG) for postoperative irradiation. Patients were divided into three groups according to their place of surgery. The first group (Group I) consisted of patients who had their surgical operation at DEUH. Patients in the second group (Group II) were referred from centers with oncological surgical experience. The third group (Group III) consisted of patients referred from hospitals with no surgical teams experienced in head and neck cancer treatment. The clinical and pathological features of patients in these three groups were analyzed to assess the impact of place of surgery on clinical outcome as well as the prognostic factors for survival. The study population consisted of 253 patients who were treated between 1991 and 2006 with locally advanced laryngeal cancer according to the protocol of DEHNTG. The median follow-up was 48 (3-181) months. The 5 years overall, loco-regional disease-free and distant disease-free

survivals were 66, 88 and 91%, respectively. When patients' clinical and histopathological features were analyzed for the impact of place of surgery, surgical margin positivity rates were found to be higher in Group III ($P = 0.032$), although the other two groups had more advanced clinical and pathological N stage disease ($P = 0.012$, $P = 0.001$). In multivariate analysis, older age ($P < 0.0001$), presence of perinodal invasion ($P = 0.012$), time interval between surgery and radiotherapy longer than 6 weeks ($P = 0.003$) and tumor grade ($P = 0.049$) were the most significant factors. For loco-regional failure-free survival, advanced clinical stage ($P = 0.002$), place of surgery ($P = 0.031$) and presence of clinical subglottic invasion ($P = 0.029$) were shown to be important prognostic factors. For distant metastasis-free survival, only pathological (+) lymph node status ($P = 0.046$) was a significant factor in multivariate analysis. The significance of place of surgery as well as other well-known prognostic factors underlines the importance of an experienced multidisciplinary treatment team if best results are to be obtained for the patient.

Alfieri, S., A. G. Morganti, et al. (2001). "Improved survival and local control after intraoperative radiation therapy and postoperative radiotherapy: a multivariate analysis of 46 patients undergoing surgery for pancreatic head cancer." *Arch Surg* **136**(3): 343-7.

HYPOTHESIS: Despite aggressive approaches, locoregional tumor control and survival rates for patients with cancer of the pancreatic head remain disappointing. In the present study, we address whether intraoperative and adjuvant radiotherapy may improve the prognosis for these patients. **DESIGN:** A retrospective study. **SETTING:** University hospital. **PATIENTS:** From February 1985 to December 1995, 46 patients with an adenocarcinoma of the pancreatic head underwent pancreatic resection. The last 26 patients also received intraoperative radiotherapy (except 5 patients) and adjuvant external beam radiation therapy. **MAIN OUTCOME MEASURES:** Demographic data, tumor characteristics, surgical procedures, 5-year survival, and local control of disease were analyzed retrospectively. **RESULTS:** The morbidity rate was not increased by adjuvant radiation therapy; it was 43% in patients treated with surgery alone and 57% in patients treated with surgery and radiotherapy ($P = .1$); operative mortality was 8% ($n = 2$) and 9% ($n = 2$), respectively ($P = .8$). Overall 5-year survival and local control were 13% and 48.6%, respectively. The mean \pm SD 5-year survival was 5.5% \pm 5.3% (median, 10.8 months) in the surgery-alone group and 15.7% \pm 8.6% (median, 14.3 months) in the surgery plus radiotherapy group ($P = .06$); local control at 5 years was 29.8% \pm 16.9%

and 58.4% +/- 19.9%, respectively (P<.01). Median metastasis-free survival was 8 and 9 months, respectively (P =.52). Multivariate analysis showed that adjuvant radiotherapy was an independent prognostic factor for survival (P<.01) and local control of the disease (P =.03). CONCLUSION: The present study supports the role of radiotherapy combined with pancreatoduodenectomy for treatment of cancer of the pancreatic head because even if the improvement in overall survival is moderate, it is effective in improving the local control of the tumor.

Allam, M., C. Feely, et al. (2004). "Depth of cervical stromal invasion as a prognostic factor after radical surgery for early stage cervical cancer." *Gynecol Oncol* **93**(3): 637-41.

INTRODUCTION: In the United Kingdom, the Royal College of Pathologists have issued guidelines detailing how the depth of stromal invasion (DOI) in cervical cancer should be measured as a percentage of the overall cervical radius in millimeters. Several studies have found the assessment of the depth of stromal invasion by cancer of the cervix to be of prognostic value. These studies did not take into account patients whose diagnostic procedures required removal of much tumor (large loop excision of the transformation zone [LLETZ] and knife cone biopsies). Furthermore, the Royal College of Pathologists guidelines do not address this issue. MATERIALS AND METHODS: Over the period of 6 years, 228 women had radical hysterectomy (RH) for stage Ib/Ia cervical cancer. The percentage of the depth of stromal invasion was measured according to the Royal College of Pathologist's guidelines in the UK. Patients who had large loop excision of the transformation zone and knife cone biopsies were excluded (91 patients). RESULTS: A Cox regression analysis showed that when nodal involvement, depth of stromal invasion, endothelial lined space invasion (ELSI), and tumor type were fitted simultaneously, only nodal involvement remained as a marker of adverse outcome. CONCLUSIONS: We recommend that when the DOI is measured, account should be taken of the LLETZ/knife cone biopsy size. A randomized controlled trial, which concludes that DOI is an independent prognostic factor, is needed. Until this is properly evaluated, we feel that including DOI as an essential part of the standard pathological report is not warranted.

Ambrogi, V., E. Pompeo, et al. (2003). "The impact of cardiovascular comorbidity on the outcome of surgery for stage I and II non-small-cell lung cancer." *Eur J Cardiothorac Surg* **23**(5): 811-7.

OBJECTIVE: The association between lung malignancy and cardiovascular disease has been

frequently reported though its therapeutic and prognostic implications not thoroughly analyzed. This study aims at assessing the possible impact of coexisting cardiovascular disease on the outcome of surgical treatment of non small cell lung cancer (NSCLC). METHODS: Among 247 consecutive patients undergone surgery for stage I and II NSCLC between 1990 and 1997, 34 (13.7%) had a cardiovascular comorbidity going to be treated by surgery, namely coronary artery disease (n=14), carotid stenosis (n=21), abdominal aortic aneurysm (n=9) and lower limbs arteriopathy (n=7). Among 22 patients (64.7%) who underwent cardiac/vascular surgery first, operation was performed after a median interval of 4.5 weeks. In five of this subset lung cancer was incidentally detected. In the other patients the cardiovascular disease was diagnosed and treated after the lung cancer had been detected and operated with a median interval of 3.5 months from thoracic procedure. Surgical procedures for lung cancer were three pneumonectomies, 12 lobectomies, 19 wedge resections. Uni and multivariate analysis for risk factors was carried out. RESULTS: In the group with cardiovascular comorbidity overall postoperative mortality was 9%, while morbidity rate was 58.8%, both of them primarily caused by cardiovascular disease and significantly higher for major resections. The 3- and 5-year survival rates were 54.8% and 35.5% compared to 69.2% and 56.4% among patients without cardiovascular comorbidity (P=0.01) while the timing of vascular surgery (before or after thoracic procedure) did not significantly affect survival. Multifocal vascular disease resulted the only positive factor at multivariate analysis (P=0.005, Odd Ratio=3.51, 95% Confidence Interval=1.4-8.4). CONCLUSIONS: Cardiovascular disease seems to have significant impact on survival and morbidity in patients undergone surgery for lung cancer, especially in presence of multifocal vascular disease and following major resections. The timing of vascular surgery and the extension of resection should rely on the severity of vascular disease, anaesthesiologist's and surgeon's final evaluation.

Amikura, T., Y. Aoki, et al. (2002). "Survival of patients with advanced ovarian cancer treated with intermittent chemotherapy following cytoreductive surgery and adjuvant chemotherapy." *Int J Clin Oncol* **7**(1): 45-50.

BACKGROUND: The purpose of this study was to report the duration of the progression-free interval (PFI) in advanced ovarian cancer patients who were treated with intermittent maintenance chemotherapy. METHODS: Between 1991 and 1998, 25 patients with stage III or IV ovarian cancer were enrolled in a trial of intermittent maintenance

chemotherapy. All patients underwent cytoreduction surgery, and received adjuvant chemotherapy, after which they were treated with intermittent maintenance chemotherapy every 3 to 4 months for 2 years. RESULTS: The median PFI in the 25 women in the intermittent chemotherapy group was 25 months, while in the 32 patients in the control group it was 18 months ($P = 0.0124$). The median survival of women treated with the intermittent chemotherapy was 34 months, and for the control group patients, it was 35 months ($P = 0.0672$). Multivariate analysis in the intermittent chemotherapy group revealed that the only factor that correlated significantly with PFI was the status after adjuvant chemotherapy ($P = 0.0137$). In patients with no evidence of disease after the adjuvant chemotherapy, the median survival was 39 months in the intermittent chemotherapy group, and 35 months in the control group ($P = 0.0156$). The median PFI was 28 months in the intermittent chemotherapy group, and 18 months in the control group ($P = 0.0012$). CONCLUSION: It would be warranted to perform intermittent maintenance chemotherapy for patients with advanced ovarian cancer, if a clinically disease-free status could be achieved after completion of the standard treatment procedure.

Anagnostopoulos, F. and S. Myrghianni (2009). "Body image of Greek breast cancer patients treated with mastectomy or breast conserving surgery." *J Clin Psychol Med Settings* **16**(4): 311-21.

The aim of this study was to assess and compare the body image of breast cancer patients ($n = 70$) whom underwent breast conserving surgery or mastectomy, as well as to compare patients' scores with that of a sample of healthy control women ($n = 70$). A secondary objective of this study was to examine the reliability and validity of the 10-item Greek version of the Body Image Scale, a multidimensional measure of body image changes and concerns. Exploratory and confirmatory factor analyses on the items of this scale resulted in a two factor solution, indicating perceived attractiveness, and body and appearance satisfaction. Comparison of the two surgical groups revealed that women treated with mastectomy felt less attractive and more self-conscious, did not like their overall appearance, were dissatisfied with their scar, and avoided contact with people. Hierarchical regression analysis showed that more general body image concerns were associated with belonging to the mastectomy group, compared to the cancer-free group of women. Implications for clinical practice and recommendations for future investigations are discussed.

Antoniou, S. A. and I. Mititiuc (2003). "Quality of life following lung cancer surgery: what about before?" *Expert Rev Pharmacoecon Outcomes Res* **3**(4): 375-7.

Lung cancer is the major malignancy worldwide with cigarette smoking being the main risk-factor. In lung cancer patients, quality of life is considered the strongest prognostic factor for survival irrespective of initial performance status, weight loss, stage of disease, number of metastatic sites, and type of treatment. The study evaluates the health-related quality of life of patients after surgical intervention using a generic questionnaire, the Medical Outcome Study Questionnaire Short Form, and compares this outcome with a normal healthy population, lung cancer patients, and coronary artery bypass grafting patients. Compared with healthy controls and coronary bypass patients, lung cancer patients had significantly higher impaired physical functioning scores, comparable with mean scores for anxiety and depression. However, health-related quality of life in lung cancer remains an issue which needs further assessment.

Asoglu, O., M. Muslumanoglu, et al. (2005). "Breast conserving surgery after primary chemotherapy in locally advanced breast cancer." *Acta Chir Belg* **105**(1): 62-8.

PURPOSE: Primary chemotherapy is being given in the treatment of locally advanced breast cancers (LABC), but a major concern is local recurrence after therapy. The aim of this study was to assess the role of breast conserving surgery (BCS) in patients with locally advanced breast cancer. MATERIAL AND METHODS: Twenty-eight patients, presenting LABC (T any, N 012, M0) were treated with primary chemotherapy comprising of cyclophosphamide, doxorubicin and fluorouracil and then BCS followed by radiotherapy were examined between the years 1992-2002 retrospectively. Before neoadjuvant chemotherapy, seven patients (25%) were Stage IIB, 19 patients (68%) Stage IIIA and two patients (7%) Stage IIIB. Survival times and curves were established according to the Kaplan-Meier method and compared by means of the log-rank test. The chi-square test and log rank test were performed for univariate statistical analysis of each prognostic factor. P values in multivariate analysis were carried out by the Cox's proportional hazards regression model. All p values were two-sided in tests and p values <0.05 were considered significant. RESULTS: Clinical down staging was obtained in 25 (89%) of patients. Three (11%) patients had complete clinical response, 22 (78%) patients with partial response and 3 (11%) had stable disease. The primary tumour could not be palpated after chemotherapy in 6 (21%) of 28 patients presenting with palpable mass, therefore

needle localization was performed for BCS. Median follow-up was 51.9 months (ranging 10 to 118 months). Local recurrence was detected in 4 (14%) patients. Distant metastasis developed in 5 (18%) patients. Three of the patients died of distant metastases and two of them are alive at 49 months. Five-year survival rate was 66%. Statistically, there were no significant factors in terms of local recurrence. Histological grade and menopause status were significantly associated with overall survival ($p = 0.018$) and nuclear grade was the one significant factor on distant disease-free survival in univariate analysis ($p = 0.006$). In multivariate analysis, there were no significant factors in terms of overall and distant disease-free survival. **CONCLUSIONS:** Negative margin is more important than the clinical and histological parameters, such as pretreatment stage, clinical response rate, ER and PR in terms of local recurrence. BCS can be performed safely by achieving free surgical margin in patients who have small sized tumour and with either N2 axillary involvement or skin invasion.

Atkin, G. K., F. M. Daley, et al. (2006). "The impact of surgically induced ischaemia on protein levels in patients undergoing rectal cancer surgery." *Br J Cancer* **95**(7): 928-33.

The goal of targeted therapy has driven a search for markers of prognosis and response to adjuvant therapy. The surgical resection of a solid tumour induces tissue ischaemia and acidosis, both potent mediators of gene expression. This study investigated the impact of colorectal cancer (CRC) surgery on prognostic and predictive marker levels. Tumour expression of thymidylate synthase, thymidine phosphorylase, cyclin A, vascular endothelial growth factor (VEGF), carbonic anhydrase-9, hypoxia inducible factor-1 α , and glucose transporter-1 (GLUT-1) proteins was determined before and after rectal cancer surgery. Spectral imaging of tissue sections stained by immunohistochemistry provided quantitative data. Surgery altered thymidylate synthase protein expression ($P=0.02$), and this correlated with the change in the proliferation marker cyclin A. The expression of hypoxia inducible factor-1 α , VEGF, and GLUT-1 proteins was also different following surgery. Colorectal cancer surgery significantly impacts on intratumoral gene expression, suggesting archival specimens may not accurately reflect in situ marker levels. Although rectal cancer was the studied model, the results may be applicable to any solid tumour undergoing extirpation in which molecular markers have been proposed to guide patient therapy.

Bae, J., M. C. Lim, et al. (2009). "Prognostic factors of secondary cytoreductive surgery for patients with recurrent epithelial ovarian cancer." *J Gynecol Oncol* **20**(2): 101-6.

OBJECTIVE: The objective of this study was to identify the prognostic factors of secondary cytoreductive surgery on survival in patients with recurrent epithelial ovarian cancer. **METHODS:** The medical records of all patients who underwent secondary cytoreductive surgery between May 2001 and October 2007 at the National Cancer Center, Korea were reviewed. Univariate and multivariate analyses were executed to evaluate the potential variables for overall survival. **RESULTS:** In total, 54 patients met the inclusion criteria. Optimal cytoreduction to <0.5 cm residual disease was achieved in 87% of patients who had received secondary cytoreductive surgery. Univariate analysis revealed that site of recurrence (median survival, 53 months for the largest tumors in the pelvis vs. 24 months for the largest tumors except for the pelvis; $p=0.007$), progression free survival (PFS) (median survival, 43 months for $PFS \geq 12$ months vs. 24 months for $PFS < 12$ months; $p=0.036$), and number of recurrence sites (median survival, 49 months for single recurred tumor vs 29 months for multiple recurred tumors; $p=0.036$) were significantly associated with overall survival. On multivariate analysis, prognostic factors that correlated with improved survival were site of recurrence ($p=0.013$), and PFS ($p=0.043$). **CONCLUSION:** In the author's analysis, a significant survival benefit was identified for the recurred largest tumors within the pelvis and $PFS \geq 12$ months. Secondary cytoreductive surgery should be offered in selected patients and large prospective studies are needed to define the selection criteria for secondary cytoreductive surgery.

Baiocchi, G., A. Lopes, et al. (2009). "ErbB family immunohistochemical expression in colorectal cancer patients with higher risk of recurrence after radical surgery." *Int J Colorectal Dis* **24**(9): 1059-68.

PURPOSE: Investigate ErbB family expression in colorectal cancer patients with higher risk of recurrence after surgical treatment. **METHODS:** We studied 109 individuals with high risk stage II and stage III patients submitted to radical surgery. ErbB expression was assessed by tissue microarray technique. **RESULTS:** The immunohistochemical expression was considered positive for EGFR, ErbB2, ErbB3, ErbB4 membrane, and ErbB4 cytoplasmic in respectively 57.8%, 8.3%, 69.7%, 11%, and 19.3% of patients. ErbB3 negative expression was associated with lymphovascular invasion. EGFR, ErbB2, and cytoplasmic ErbB4 expression was not associated with prognosis.

Membranous positive ErbB4 expression was an independent prognostic factor for recurrence. ErbB3 negative expression was an independent prognostic factor for recurrence and survival in the multivariate analysis.

CONCLUSIONS: The immunohistochemical expression of ErbB3 and ErbB4 may identify a subgroup with stage II and III colorectal cancer at higher risk of recurrence.

Basili, G., L. Lorenzetti, et al. (2008). "Colorectal cancer in the elderly. Is there a role for safe and curative surgery?" *ANZ J Surg* **78**(6): 466-70.

BACKGROUND: Recent reports place colorectal cancer (CRC) as the third most common cancer for both sexes. Elderly patients are often viewed as high-risk surgical candidates with high rates of emergency presentations and perioperative mortality. The aim of our study was to examine the characteristics and perioperative morbidity and mortality rates of elderly patients presented to CRC surgery. **METHODS:** We retrospectively studied 248 patients who underwent surgery for CRC at our institution between July 2003 and December 2005. Risk factors included sex, age, cancer localization, Dukes' and TNM classification, blood transfusion, preoperative Physiologic and Operative Severity Score for the enUmeration of Mortality and Morbidity score and mode of presentation. Primary outcome was perioperative death. **RESULTS:** The study consisted of 143 men and 105 women. One hundred and thirty-four (54%) patients were more than 75 years of age. In the two older groups, cancer was more common in the proximal colon than in the youngest age group ($P = 0.001$). Of the 25 resections carried out as emergency, 20 were in those who were more than 75 years of age ($P < 0.001$). In elective procedure, perioperative mortality scores were 3.1% in those who were more than 75 years of age versus 0% in those less than 75 years, meanwhile in emergency, rates of 24 versus 0% ($P =$ not significant) were registered. In Cox multivariate regression analysis, age and mode of presentation reached statistical significance. **CONCLUSION:** Old age itself is not an independent negative prognostic factor for CRC surgery. Although emergency operations were associated with poor outcome, most patients survived and left the hospital. This study suggests that, whenever possible, curative intent should be applied in patients with CRC, irrespective of the age.

Behtash, N., Z. Nazari, et al. (2006). "Neoadjuvant chemotherapy and radical surgery compared to radical surgery alone in bulky stage IB-IIA cervical cancer." *Eur J Surg Oncol* **32**(10): 1226-30.

AIM: The aim of this study was evaluation of the efficacy of neoadjuvant chemotherapy (NACT)

and radical hysterectomy on long-term survival in stage IB-IIA locally advanced cervical cancer as compared with radical surgery alone. **METHODS:** We reviewed all patients with cervical cancer stage IB-IIA who were treated with two treatment modalities, i.e. NACT followed by radical hysterectomy and lymphadenectomy, and radical hysterectomy alone between March 1996 and March 2004. There were 22 patients in the NACT group (group 1) and 160 patients in the immediate radical surgery group (group 2). All patients in group 1 were followed for more than 108 months, and long-term survival and factors affecting recurrence were evaluated. **RESULTS:** Nineteen patients in the NACT arm underwent radical surgery. Pelvic lymph node metastasis was found in 8 patients in this group and in 36 in the radical surgery group. Eighteen patients in the NACT group and 96 patients in the radical surgery group were scheduled for adjuvant postoperative chemoradiation. During the 9-year follow-up, recurrence rate was 47.1% and 30.2% in NACT and control groups, respectively. In the NACT group lymph node metastasis was a significant independent risk factor for recurrence. Overall survival in the NACT arm was not statistically significantly lower than the control arm ($p=0.06$). **CONCLUSION:** NACT did not improve long-term overall survival of bulky early-stage cervical cancer patients compared to primary radical surgery.

Benedetti Panici, P., A. De Vivo, et al. (2007). "Secondary cytoreductive surgery in patients with platinum-sensitive recurrent ovarian cancer." *Ann Surg Oncol* **14**(3): 1136-42.

BACKGROUND: Secondary surgical cytoreduction (SCR) represents a promising therapeutic strategy for patients affected by ovarian cancer disease recurrence. The aim of this prospective observational trial was to analyze the role of SCR in patients with platinum-sensitive ovarian cancer. **METHODS:** Patients with platinum-sensitive ovarian cancer underwent SCR by a single surgical team. Clinical and oncologic data were prospectively recorded. A total of 47 patients underwent SCR from 1999 to 2003. **RESULTS:** The mean operating time was 210 minutes, and mean blood loss was 500 mL. The most frequent surgical procedures carried out were splenectomy, lymphadenectomy, bowel resection, and extensive peritonectomy. Optimal cytoreduction was achieved in 41 patients. Thirty-seven patients had no visible tumor at the end of SCR. Overall median survival was 49 months. Patients who achieved optimal residual disease had a median survival of 61 months, whereas patients who had residual disease >1 cm had a median survival of 19 months. **CONCLUSIONS:** Positive CA-125 (cancer antigen 125) was identified as a negative prognostic

factor at multivariate analysis. After careful selection, optimal cytoreduction can be achieved in most patients who are subjected to SCR with acceptable morbidity. Residual tumor and CA-125 represent the most important prognostic factors.

Benzoni, E., G. Terrosu, et al. (2006). "Analysis of clinical outcomes and prognostic factors of neoadjuvant chemoradiotherapy combined with surgery: intraperitoneal versus extraperitoneal rectal cancer." *Eur J Cancer Care (Engl)* **15**(3): 286-92.

Neoadjuvant chemoradiotherapy (CRT) is a widely purposed and performed treatment for rectal cancer. Downstaging effects possibly enhance the rate of curative surgery and may enable sphincter preservation in low-lying tumours. The current study examines the clinical outcomes in patients enrolled in a neoadjuvant CRT-surgery protocol for rectal cancer, distinguishing between intraperitoneal and extraperitoneal cancer. From 1994 to 2003, 58 patients with a primary diagnosis of rectal cancer were enrolled in a single-centre, not randomized study based on 5-week sessions of radiotherapy associated with a 30-day protracted venous 5-FU infusion followed by surgical resection. The study population was divided into two groups according to the localization of the tumour: 18 intraperitoneal and 40 extraperitoneal (EPT). Fifty-eight patients were treated with neoadjuvant CRT and surgery. Overall mortality rate was 25.9%, no deaths were recorded during hospitalization; 10 patients (all EPT) died because of recurrence. Significant differences in disease-free survival and overall survival rates were found between intraperitoneal vs. extraperitoneal tumours ($P = 0.006$), both intraperitoneal vs. extraperitoneal tumours N(0) ($P = 0.04$ and $P < 0.05$) and intraperitoneal vs. extraperitoneal tumours N(+) ($P < 0.05$). We diagnosed all local recurrence and liver metastasis in extraperitoneal tumours ($t = 0.02$ and $t = 0.04$), and only one case of lung metastasis arose from intraperitoneal cancer. Extraperitoneal tumours could be more aggressive than intraperitoneal ones, spreading more precociously, and/or less responsive to the neoadjuvant CRT because of their localization rather than biological differences. Aside from lymph node status, the location of the tumour with respect to the peritoneum border, is also a prognostic factor of survival in rectal cancer treated by neoadjuvant CRT and surgery.

Berman, R. S., L. E. Harrison, et al. (1999). "Growth hormone, alone and in combination with insulin, increases whole body and skeletal muscle protein kinetics in cancer patients after surgery." *Ann Surg* **229**(1): 1-10.

OBJECTIVE: To investigate the impact of growth hormone, alone and in combination with insulin, on the protein kinetics of patients with upper gastrointestinal (GI) tract cancer who have undergone surgery and are receiving total parenteral nutrition (TPN). **SUMMARY BACKGROUND DATA:** Patients with malignancies of the upper GI tract are at increased risk for malnutrition and perioperative death and complications. Standard nutritional support has not significantly altered outcome. Growth hormone (GH) and insulin have been shown to have some benefit in patients with cancer; however, their action in patients undergoing resection has not previously been studied. **METHODS:** Thirty patients undergoing surgery for upper GI tract malignancies were prospectively randomized into one of three nutritional support groups after surgery: 10 patients received standard TPN, 10 received TPN plus daily injections of GH, and 10 received daily GH, systemic insulin, and TPN. The patients underwent a protein kinetic radiotracer study on the fifth day after surgery to determine whole body and skeletal muscle protein kinetics. **RESULTS:** Patients who received standard TPN only were in a state of negative skeletal muscle protein net balance. Those who received GH and insulin had improved skeletal muscle protein net balance compared with the TPN only group. Whole body protein net balance was improved in the GH and the GH and insulin groups compared with the TPN only group. GH and insulin combined did not improve whole body net balance more than GH alone. GH administration significantly increased serum IGF-1 and GH levels. Insulin infusion significantly increased serum insulin levels and the insulin/glucagon ratio. **CONCLUSION:** Growth hormone and GH plus insulin regimens improve protein kinetic parameters in patients with upper GI tract cancer who are receiving TPN after undergoing surgery.

Biggers, B., S. Knox, et al. (2009). "Circulating tumor cells in patients undergoing surgery for primary breast cancer: preliminary results of a pilot study." *Ann Surg Oncol* **16**(4): 969-71.

INTRODUCTION: Circulating tumor cells (CTCs) have recently been shown to be an independent predictor of progression-free and overall survival in patients undergoing treatment for metastatic breast cancer. This study evaluates the presence and significance of CTCs in patient undergoing surgical resection of clinically localized primary breast cancer. **METHODS:** Patients undergoing surgery for clinically localized primary breast cancer were enrolled into a prospective study. Thirty milliliters of blood was drawn and studied using the CellSearch assay. **RESULTS:** Forty-one patients were enrolled at a single tertiary referral

center. Ten patients (24.4%) had detectable CTCs preoperatively (PreOp). Nine (30%) patients were found to have CTCs postoperatively (PostOp). Overall, 16 (39%) were found to have CTCs either PreOp or PostOp. Hormone-negative patients were significantly more likely to have CTCs than hormone-positive patients. No other pathologic factor was predictive of the presence of CTCs. **CONCLUSION:** CTCs are detectable and quantifiable in breast surgery patients. CTCs were more likely to be found in hormone receptor negative patients. Further study will allow correlation with other pathological variables and clinical outcome.

Blanchard, D. K., P. B. Shetty, et al. (2008). "Association of surgery with improved survival in stage IV breast cancer patients." *Ann Surg* **247**(5): 732-8.

OBJECTIVE: This study aims to examine the role of surgery in patients with stage IV breast cancer. **BACKGROUND:** Historically, women who present with metastatic breast cancer are not offered surgical treatment. However, recent reports indicate that surgery may improve outcome. Using a large database of women whom presented with stage IV breast cancer, we compared outcome of patients who had resection of their primary cancer to those who did not. **METHODS:** Of 16,401 patients, 807 had stage IV disease at presentation, and 395 survived >90 days and were included in this analysis. Clinical and tumor characteristics, surgical treatment, and survival were compared for the surgically versus nonsurgically treated patients. **RESULTS:** Two hundred and forty-two patients (61.3%) had definitive surgery for their primary tumor and 153 (38.7%) did not. Patients who underwent surgery were significantly older, were more likely to be white, more often had hormone receptor positive disease, had small primary tumors, and had fewer metastatic sites and less visceral involvement. The median survival of surgically treated patients was 27.1 months versus 16.8 months for patients without surgical resection ($P < 0.0001$). In multivariate analysis, which included surgical treatment, age, race, estrogen and progesterone receptor status, number of metastatic sites, and presence of visceral metastases, surgery remained an independent factor associated with improved survival ($P = 0.006$). **CONCLUSION:** Patients with stage IV breast cancer who had definitive surgical treatment of their primary tumors had more favorable disease characteristics. However, after adjustment for these characteristics, surgical treatment remained an independent factor associated with improved survival.

Blomberg, B. B., J. P. Alvarez, et al. (2009). "Psychosocial adaptation and cellular immunity in

breast cancer patients in the weeks after surgery: An exploratory study." *J Psychosom Res* **67**(5): 369-76.

BACKGROUND: The period just after surgery for breast cancer requires psychosocial adaptation and is associated with elevated distress. Distress states have been associated with decreased cellular immune functioning in this population, which could have negative effects on physical recovery. However, little is known about relations between psychological status [negative and positive mood states and overall quality of life (QOL)] and cellular signaling cytokines that could account for these associations in women undergoing treatment for breast cancer. **METHODS:** The present study examined associations between psychological adaptation indicators (mood, QOL) and T-helper cell type 1 (Th1) cytokine production from stimulated peripheral mononuclear cells in women who had recently undergone surgery for early-stage breast cancer but had not yet begun adjuvant therapy. These associations were evaluated while controlling for relevant disease/treatment, sociodemographic, and health behavior covariates. **RESULTS:** Lower anxiety related to greater production of the Th1 cytokine interleukin-2 (IL-2), while greater positive mood (affection) related to greater production of the Th1 cytokines IL-12 and interferon-gamma (IFN-gamma). Better QOL related to greater production of the Th1 cytokine, tumor necrosis factor-alpha (TNF-alpha). **CONCLUSION:** Individual differences in psychosocial adaptation in women with breast cancer during the period after surgery relate to biological parameters that may be relevant for health and well-being as they move through treatment.

Bollet, M. A., B. Sigal-Zafrani, et al. (2007). "Age remains the first prognostic factor for loco-regional breast cancer recurrence in young (<40 years) women treated with breast conserving surgery first." *Radiother Oncol* **82**(3): 272-80.

PURPOSE: To ascertain the loco-regional recurrence (LRR) rate and its major prognostic factors in patients younger than 40 and to determine the influence of age on the features of breast cancer and its treatment in two age groups: 35 years and [36-39] years. **METHODS AND MATERIALS:** Between 1985 and 1995, 209 premenopausal women, younger than 40, were treated for early breast cancers with primary breast conserving surgery followed by radiotherapy+/-chemotherapy. Median age was 37 years with 66 patients (32%) 35 years and 143 older (68%). Median follow-up was 12 years. Tumours' characteristics were: cT1 in 75%, pN0 in 60%. **RESULTS:** LRR rate was 38% at 10 years, contralateral breast cancer rate 12%. Age was the only prognostic factor for LRR. The relative risk of LRR

increased by 7% for every decreasing year of age. The annual risk of local recurrence peaked between 2 and 3 years after the initial diagnosis and returned to the level of contra-lateral breast cancer at 10 years. The younger population had infiltrating carcinomas that were significantly more commonly ductal, less commonly lobular, and of higher grade - they received chemotherapy more often. **CONCLUSION:** Using conventional methods we could find no explanation as to why age remained the most important prognostic factor for breast cancer LRR. Known prognostic factors such as involved surgical margins seemed erased by adequate radiotherapy doses.

Borreman, P., P. De Leyn, et al. (2009). "Morbidity and mortality after induction chemotherapy followed by surgery in IIIa-N2 non small cell lung cancer." *Acta Chir Belg* **109**(3): 333-9.

OBJECTIVE: To evaluate the frequency and risk of postoperative complications and mortality in patients with IIIa-N2 non small cell lung cancer after induction chemotherapy and surgery. **METHODS:** In a surgical database records from ninety two patients, operated between January 1, 2000 and December 31, 2006 were reviewed. Univariate analysis was used to identify predictors of postoperative complications and in-hospital mortality. **RESULTS:** All cases were histologically confirmed stage IIIa-N2. All patients received preoperative platinum based chemotherapy without radiotherapy. Pneumonectomy was performed in 20 cases (23.5%), from which 9 right sided. (Bi)lobectomy was performed in 53 cases (62.4%) and sleeve lobectomy in 11 cases (17.2%). One wedge resection was performed (1.2%). In 7 cases (7.6%) only an exploration was done. Complications developed in 35 patients (38%). Major complications in 15 patients (16%). No bronchopleural fistulae were observed. Analysis identified increased age and high physiological and operative severity score for the enumeration of mortality and morbidity (POSSUM) as a risk factor to develop complications, and a high simplified comorbidity score as a risk factor to develop a major complication. Higher age, Charlson comorbidity index, simplified comorbidity score and POSSUM were a risk factor for developing pneumonia. **CONCLUSION:** Although surgery after induction therapy for IIIa-N2 NSCLC can be done with a morbidity and mortality comparable to surgery alone, it remains a high risk operation. It should therefore be performed in a center with experience. Bronchial stump protection should be used whenever there is an increased risk for developing a bronchopleural fistula. In deciding whether to do surgery or radiotherapy one should keep in mind the feasibility of performing a complete resection together with a preoperative assessment to predict

complications and mortality. For the preoperative assessment several scoring systems can be used from which we find the simplified comorbidity score most useful.

Bouchardy, C., G. Fioretta, et al. (1999). "Determinants of long term survival after surgery for cancer of the lung: A population-based study." *Cancer* **86**(11): 2229-37.

BACKGROUND: Even if some determinants of lung cancer (LC) prognosis have been established, their independent effect on long term survival remains to be seen. The objective of the current study was to identify the prognostic indicators of long term survival among LC patients treated by surgery. **METHODS:** All patients with LC recorded at the Geneva Cancer Registry between 1977 and 1987 were analyzed by logistic regression, considering as cases (n = 98) those patients alive 10 years after their initial diagnosis and as controls (n = 330) all other patients, excluding those who did not undergo putative curative surgery. The effect of each prognostic factor was evaluated after accounting for age and gender ("crude" effect) and also for other a priori confounding factors (adjusted effect). Additional models considered two staging variables simultaneously to identify the strongest staging determinant. Results were presented as relative risk estimates of long term (>=10 years) survival. **RESULTS:** Age, histology, and stage of disease significantly influenced prognosis regardless of the confounding factors considered. Gender also emerged as a discriminated factor in LC outcome, with a 2.1-fold increased chance (95% confidence interval, 1.6-3.5) of long term survival for women compared with men. Method of discovery, presence of symptoms, period of diagnosis, socioeconomic status, and tumor differentiation did not appear to be associated with long term survival. Extent and size of the tumor were found to be the most reliable prognostic staging factors, whereas adenopathy had no effect after accounting for extension. **CONCLUSIONS:** The current population-based study quantifies the independent effect of the factors modifying the chances of curability in patients with LC. In particular, it provides additional evidence that gender strongly influences long term survival.

Bouche, O., M. Ychou, et al. (2005). "Adjuvant chemotherapy with 5-fluorouracil and cisplatin compared with surgery alone for gastric cancer: 7-year results of the FFCD randomized phase III trial (8801)." *Ann Oncol* **16**(9): 1488-97.

BACKGROUND: The aim of this study was to evaluate the efficacy of adjuvant chemotherapy after resection for gastric cancer in a randomized controlled trial. **PATIENTS AND METHODS:** After

curative resection, stage II-III-IVM0 gastric cancer patients were randomly assigned to postoperative chemotherapy or surgery alone. 5-Fluorouracil (5-FU) 800 mg/m² daily (5-day continuous infusion) was initiated before day 14 after resection. One month later, four 5-day cycles of 5-FU (1 g/m² per day) plus cisplatin (100 mg/m² on day 2) were administered every 4 weeks. RESULTS: The study was closed prematurely after enrollment of 260 patients (79.7% N+), owing to poor accrual. At 97.8 months median follow-up, 5- and 7-year overall survival were 41.9% and 34.9% in the control group versus 46.6% and 44.6% in the chemotherapy group (P=0.22). Cox model hazard ratios were 0.74 [95% confidence interval (CI) 0.54-1.02; P=0.063] for death and 0.70 (95% CI 0.51-0.97; P=0.032) for recurrence. An invaded/removed lymph nodes ratio >0.3 was the main independent poor prognostic factor identified by multivariate analysis (P=0.0001). Because of toxicity, only 48.8% of patients received more than 80% of the planned dose. CONCLUSION: There was no statistically significant survival benefit with this toxic cisplatin-based adjuvant chemotherapy, but a risk reduction in recurrence was observed.

Brennan, M. F. (2005). "Current status of surgery for gastric cancer: a review." *Gastric Cancer* **8**(2): 64-70.

In the last three decades, considerable progress has been made in the diagnosis and management of gastric cancer. This was initiated by the Japanese and taken up by other focus groups in Asia, the United States, and Europe. Exciting prospects have been identified with the molecular characterization of the mutated gene causative for familial gastric cancer, and new developments in endoscopy and laparoscopy for diagnosis, management, and treatment continue. It is now clear that the extent of the gastric resection requires only that an R0 resection be performed and that total gastrectomy is not necessary for all patients with gastric adenocarcinoma. The extent of nodal dissection is defined as a major factor in staging and can influence outcome by stage. The recent development of defining adequate staging based on at least 15 nodes being sampled is a clear example of a simple system that can make major differences in overall management. The role of extended node dissection has been studied in prospective randomized trials showing no overall survival benefit but perhaps benefit to selected subgroups. The importance of the hospital and surgical experience in improving mortality and long-term survival is established. The role of adjuvant therapy, both pre- and postoperative, continues to be evaluated with some frustration that a single trial, as yet unconfirmed by subsequent trials, is considered the "standard of care" in the United States.

The international gastric cancer community can help define the important issues that need to be answered in the coming decades.

Bromage, S. J. and W. J. Cunliffe (2007). "Validation of the CR-POSSUM risk-adjusted scoring system for major colorectal cancer surgery in a single center." *Dis Colon Rectum* **50**(2): 192-6.

PURPOSE: Scoring systems to predict mortality from surgery are important tools used to give information to the operator and patient and in the auditing of clinical practice. This study was designed to validate the recently developed the Colorectal Physiologic and Operative Severity Score for the Enumeration of Mortality and Morbidity (CR-POSSUM) scoring system in a single center for colorectal cancer surgery. We also analyzed whether albumin may have a role in the CR-POSSUM model. METHODS: We compared this model with two other scoring systems: POSSUM and Portsmouth-POSSUM (P-POSSUM) models. In-hospital mortality was used as the outcome, and Hosmer-Lemeshow statistic was used to determine goodness of fit. RESULTS: Complete data were collected prospectively from 304 patients from 1990 to the present. The overall operative mortality was 6.5 percent. Observed to expected ratios were used to compare the scoring systems at a given predicted mortality. The overall observed to expected ratio was 1.25 for CR-POSSUM, 1.59 for P-POSSUM, and 3.37 for POSSUM. The CR-POSSUM model showed a good fit with the data (Hosmer-Lemeshow statistic, 3.86; P = 0.795) and the area under the receiver operator curve was 0.74. After correcting for factors used in the CR-POSSUM, logistic regression showed a significant correlation between albumin and mortality (P = 0.016). CONCLUSIONS: We have shown that the CR-POSSUM model is an accurate predictor of outcome for major colorectal surgery. The POSSUM and P-POSSUM models over-predicted mortality. Albumin, which is not a factor included in these three systems, may be an important addition in improving the accuracy of the CR-POSSUM model.

Bufalari, A., G. Giustozzi, et al. (2006). "Rectal cancer surgery in the elderly: a multivariate analysis of outcome risk factors." *J Surg Oncol* **93**(3): 173-80.

BACKGROUND AND OBJECTIVES: Geriatric population life expectancy is rapidly increasing and the impact of major surgical procedures is not well defined. The purpose of this study was to compare short term surgical results assessing mortality and morbidity and long-term survival and disease-free interval in elective rectal surgery patients older than 65 years of age. The main independent risk factors of mortality, morbidity, and

overall and disease-free survival were also identified. METHODS: Out of 177 rectal cancer accepted consecutively from 1991 to 2002, we studied the main clinical and pathological parameters comparing patients older and younger than 65 years. Data have been collected in a database and variables considered were studied by univariate analysis; independent predictive factors of 30-day mortality and morbidity were identified by multiple logistic regression analysis. Overall, cancer specific and disease-free survival curves were obtained with the Kaplan-Meier method and results compared with the log-rank test. Independent risk factors of overall and disease-free survival have been identified by multivariate logistic regression analysis. RESULTS: In patients younger and older than 65 years postoperative mortality (3.2% vs. 9.6%) and morbidity (30% vs. 29%) were not significantly different. Variables independently associated with 30-day mortality were the duration of surgical procedures and postoperative complications. The Kaplan-Meier survival curves showed a significantly worst overall survival ($P = 0.003$), cancer specific survival ($P = 0.02$), and disease-free survival ($P = 0.03$) in patients aged 65 years or more. Multivariate analysis showed that pT, grading, preoperative CEA level, gender, and site of the tumor along the rectum, the number of blood transfusion and the age group of more than 65 years are independent risk factors for both overall survival and disease-free interval. The presence of residual disease was an adjunctive factor of overall survival, whereas the Astler and Collier staging was a risk factor for the disease-free survival. CONCLUSION: The short-term prognosis for elective rectal cancer procedure in patients over 65 years of age was comparable to that of younger patients, whereas long term cancer-related survival was statistically worst in older patients.

Caine, G. J., P. S. Stonelake, et al. (2007). "Changes in plasma vascular endothelial growth factor, angiopoietins, and their receptors following surgery for breast cancer." *Cancer Lett* 248(1): 131-6.

BACKGROUND: Vascular endothelial growth factor (VEGF), a major angiogenic growth factor, is involved in the pathogenesis of cancer. Plasma VEGF is raised in breast cancer and falls after successful surgery. Less is known about angiopoietins 1 and 2 (Ang-1, Ang-2). All three growth factors act on cells via receptors; Flt-1 for VEGF and Tie-2 for the angiopoietins. Cancer is also marked by abnormalities in platelet activation (marked by soluble P selectin) and inflammation (interleukin-6 [IL6]). We hypothesised altered plasma Ang-1, Ang-2, Flt-1 and Tie-2 in breast cancer that would normalize after 3 and 12 months treatment (i.e., surgery plus chemo/radiotherapy). METHODS: Baseline venous

blood was obtained from 40 women with breast cancer and 30 age-matched women with benign breast disease (BBD) also requiring surgery. Samples were taken again 3 months and 1 year later. Soluble P selectin, IL6, VEGF, Ang-1, Ang-2, Flt-1 and Tie-2 were measured in citrated plasma by ELISA. RESULTS: Women with breast cancer had raised VEGF (7-fold), Ang-1 (50% higher) and Tie-2 (2-fold), but lower Flt-1 (to 26%), compared to the BBD women that broadly correlated with markers of platelet activation and inflammation. A level of Tie-2 or VEGF >95th percentile of the BBD group correctly identified 68% and 52% of the women with breast cancer. After 3 months of treatment, VEGF and Ang-1 normalized (as did IL6 and soluble P selectin) but Tie-2 was significantly lower only after 1 year. There were no significant changes in the women with BBD. CONCLUSIONS: Treatment for breast cancer (surgery followed by chemotherapy and/or radiotherapy) is effective in reducing plasma VEGF, Tie-2 and Ang-1. These may be linked pathogenically with coagulation and inflammation.

Canavese, G., M. Gipponi, et al. (2000). "Sentinel lymph node mapping in early-stage breast cancer: technical issues and results with vital blue dye mapping and radioguided surgery." *J Surg Oncol* 74(1): 61-8.

BACKGROUND AND OBJECTIVES: Axillary lymph node status is the most important prognostic factor in patients with operable breast cancer. Recent studies have demonstrated the possibility of identifying the sentinel lymph node (sN) as a reliable predictor of axillary lymph node status in both cutaneous melanoma and breast cancer. Sentinel lymph node identification proved feasible by either peritumoral dye injection (Patent Blue-V) or radiodetection, with identification rates of 65-97% and 92-98%, respectively. However, some important issues need further definition, namely (a) optimization of the technique for intraoperative detection of the sN, (b) predictive value of the sN with regard to axillary lymph node status, and (c) reliability of intraoperative histology of the sN. We reviewed our experience in sN detection in patients with stage I-II breast cancer to assess the feasibility and accuracy of lymphatic mapping, by vital blue dye or radioguided surgery, and sN histology as a predictor of axillary lymph node status. METHODS: Two groups of patients (55 and 48) were recruited between May 1996 and May 1997 and between October 1997 and February 1998; the patients of the first series underwent vital blue dye lymphatic mapping only, whereas those of the second series had a combined approach with both vital blue dye mapping and radioguided detection of the sN. RESULTS: In the first set of patients, the sN was

identified in 36/55 patients (65.4%); sN histology predicted axillary lymph node status with a 77% sensitivity (10/13), a 100% specificity (23/23), an 88.5% negative predictive value (23/26), and an overall 91.5% accuracy (33/36). The sN was the quasi-elective site of lymph node metastases because in clinically N0 patients nodal involvement was 20-fold more likely at histology in sN than in non-sN (30% and 1.5%, respectively). In the second set of patients, 49 lymphadenectomies were performed because 1 patient had bilateral breast cancer; the sN was identified in 45/49 lymphadenectomies (92%). The sN was intraoperatively negative at frozen-section examination in 33 cases, and final histology confirmed the absence of metastases in 31/33 cases (94%), whereas in 2 cases (6%) micrometastases only were detected. Final histology of the sN predicted axillary lymph node status with an 87.5% sensitivity (14/16), a 100% specificity (29/29), a 93.5% negative predictive value (29/31), and an overall 95.5% accuracy (43/45). **CONCLUSIONS:** Sentinel lymphadenectomy can be better accomplished when both mapping techniques (vital blue dye and radioguided surgery) are used. In this group of patients, agreement of intraoperative histology of the sN with the final diagnosis was 94%, and sN histology accurately predicted axillary lymph node status in 43/45 lymphadenectomy specimens (95.5%) in which an sN was identified.

Carbognani, P., G. Tincani, et al. (2002). "Biological markers in non-small cell lung cancer. Retrospective study of 10 year follow-up after surgery." *J Cardiovasc Surg (Torino)* **43**(4): 545-8.

BACKGROUND: The biological markers in non-small cell lung cancer (NSCLC) have been widely studied and encouraging results have shown that products of some oncogenes and other molecular markers can predict the aggressiveness of the disease and the outcome of the patients. **METHODS:** To verify the reliability of these prognostic markers we have studied retrospectively the expression of c-erbB-2 and 67Ki (growth regulation), p53 (cell cycle regulation and apoptosis), bcl-2 (apoptosis) and CD31 and CD34 (angiogenesis) in 78 patients operated on for NSCLC with curative intent between January 1987 and December 1988 and followed up for 10 years. For the determination of the biological markers we have used the ABC (Avidin-Biotin-Peroxidase complex) immunohistochemical method. The Cox regression model was used for the univariate and multivariate analysis. **RESULTS:** Nineteen patients (24%) were alive after 10 years and 59 (76%) died. The univariate analysis of the relationship between the 10-year survival and the expression of the markers was significant only for p53 ($p=0.0097$). Stratifying the

patients according to the 3 histological subtypes (squamous cell carcinoma, adenocarcinoma and large cell undifferentiated carcinoma) the correlation between markers and survival pointed out that the only significant one was p53 ($p=0.0459$) in adenocarcinoma. In the same way considering the stages p53 was significant in stage IIIa ($p=0.0357$). The multivariate analysis emphasized that p53 was the only significant marker with respect to the 10-year survival ($p=0.0091$). Examining the histological groups significant was only p53 in adenocarcinoma ($p=0.0192$) and in large cell undifferentiated carcinomas ($p=0.0290$). This marker is also significant in pathological stage II ($p=0.0271$) and IIIa ($p=0.0402$). Apart from histology and staging the 10-year survival was 33% for p53 negative versus 10% for p53 positive. In patients with adenocarcinoma the 10-year survival was 40% for p53 negative and 6% for p53 positive. **CONCLUSIONS:** In conclusion our results emphasize the importance of p53 as a prognostic factor in 10-year survival in patients with adenocarcinoma and in stage II and IIIa.

Cardinale, D., A. Colombo, et al. (2007). "Increased perioperative N-terminal pro-B-type natriuretic peptide levels predict atrial fibrillation after thoracic surgery for lung cancer." *Circulation* **115**(11): 1339-44.

BACKGROUND: Postoperative atrial fibrillation (AF) is a complication of thoracic surgery for lung cancer, with a reported incidence that can run as high as 42%. Recently, it has been observed retrospectively that B-type natriuretic peptide predicts AF after cardiac surgery. We performed a prospective study to evaluate the role of N-terminal pro-B-type natriuretic peptide (NT-proBNP) as a marker for risk stratification of postoperative AF in patients undergoing thoracic surgery for lung cancer. **METHODS AND RESULTS:** We measured NT-proBNP levels in 400 patients (mean age, 62 \pm 10 years; 271 men) 24 hours before and 1 hour after surgery. The primary end point of the study was the incidence of postoperative AF. Overall, postoperative AF occurred in 72 patients (18%). Eighty-eight patients (22%) showed an elevated perioperative NT-proBNP value. When patients with either preoperatively or postoperatively elevated NT-proBNP were pooled, a greater incidence of AF was observed compared with patients with normal values (64% versus 5%; $P<0.001$). At multivariable analysis, adjusted for age, gender, major comorbidities, echocardiography parameters, pneumonectomy, and medications, both preoperative and postoperative NT-proBNP values were independent predictors of AF (relative risk, 27.9; 95% CI, 13.2 to 58.9; $P<0.001$ for preoperative NT-proBNP elevation; relative risk,

20.1; 95% CI, 5.8 to 69.4; $P < 0.001$ for postoperative NT-proBNP elevation). **CONCLUSIONS:** Elevation of perioperative NT-proBNP is a strong independent predictor of postoperative AF in patients undergoing thoracic surgery for lung cancer. This finding should facilitate studies of therapies to reduce AF in selected high-risk patients.

Caricato, M., D. Borzomati, et al. (2006). "Prognostic factors after surgery for locally recurrent rectal cancer: an overview." *Eur J Surg Oncol* **32**(2): 126-32.

PURPOSE: Local recurrence of rectal cancer occurs in a considerable group of patients who have undergone radical treatment for primary tumour. The treatment of choice is surgical resection but the prognosis remains poor, as a negative margin excision is possible in only a small subset of patients. A review of prognostic factors for locally recurrent rectal cancer (LRRC) after surgery is presented. **METHODS:** We systematically reviewed the literature for reports on prognostic factors after surgical excision of LRRC. These reports were identified through a review of the Medline database from 1982 to 2004. **RESULTS:** This review highlights the most important prognostic factors for LRRC patients treated with surgery. Data are grouped on the basis of the prognostic factors investigated. **CONCLUSIONS:** R0 resection seems to be the only reliable prognostic factor; however, symptoms, pre-operative CEA doubling time, performance status and pre-operative radiotherapy can help patient selection before surgery. The results of this review provide the basis for improved outcome, aiming to assess patients who would benefit from reoperation.

Celik, N., F. C. Wei, et al. (2002). "Osteoradionecrosis of the mandible after oromandibular cancer surgery." *Plast Reconstr Surg* **109**(6): 1875-81.

Although postoperative radiotherapy has proved effective in improving local control and survival in patients with head and neck cancers, its complications, especially mandibular osteoradionecrosis, reduce the quality of life. Mandibular surgery before the radiotherapy adds an additional risk factor for osteoradionecrosis. This study reviews patients in Chang Gung Memorial Hospital, Taipei, Taiwan, over a 10-year period, who underwent intraoral cancer resection followed by postoperative radiotherapy and thereafter developed osteoradionecrosis of the mandible. A total of 24 men and three women with a mean age of 49.9 years were identified and included in the study. In 10 cases, tumor resection was performed with a marginal mandibulectomy; in eight cases, tumor resection was

performed after mandibular osteotomy; and in three cases, a segmental mandibulectomy was performed, and the defect was reconstructed with a fibula osteoseptocutaneous flap. In six cases, tumor excisions were performed without interfering with the mandibular continuity. Patients received postoperative external beam radiotherapy into the primary site and the neck, with a mean dose (+/-SD) of 5900 +/- 1300 cGy in an average of 35 fractions during an average of 6.5 weeks. The average elapsed time between the end of radiation therapy and clinical diagnosis of osteoradionecrosis of the mandible was 11.2 months (range, 2 to 36 months). The time elapse between the end of the radiation therapy and the diagnosis of osteoradionecrosis was influenced by initial treatment (Kruskal-Wallis test: $n = 27$, chi-square = 12.884, $p < 0.005$), and this period was shorter if the mandibular osteotomy or marginal mandibulectomy was performed (the two lowest mean ranks in the test). However, if the initial surgery resulted in a segmental mandibulectomy reconstructed with a fibula osteoseptocutaneous flap, onset of the osteoradionecrosis was relatively late (Kruskal-Wallis test: $n = 21$, chi-square = 7.731, $p = 0.052$). After resection of osteoradionecrotic bone and surrounding soft tissue, 22 patients underwent reconstructive procedures with a fibula osteoseptocutaneous flap, and five patients underwent reconstructive procedures with an inferior genicular artery osteoperiosteal cutaneous flap. One fibula osteoseptocutaneous flap showed total failure and another showed a 25 percent skin loss; both were revised with pedicled flaps. The skin paddle of an inferior genicular artery flap was replaced with an anterolateral thigh flap because of anatomic variation of the skin vessel. Once the diagnosis of osteoradionecrosis is established, replacement of the dead bone and surrounding tissue with a vascularized free bone flap is inevitable, and a composite osteocutaneous free flap is a good option.

Cil, T., E. Fishell, et al. (2009). "Mammographic density and the risk of breast cancer recurrence after breast-conserving surgery." *Cancer* **115**(24): 5780-7.

BACKGROUND: Women with invasive breast cancer who are treated with breast-conserving surgery and radiotherapy face a cumulative risk of local disease recurrence of approximately 10% at 10 years. To the authors' knowledge, the role of mammographic density as a risk factor for the development of local recurrence has not been thoroughly evaluated to date. **METHODS:** Medical records were reviewed for 335 patients who underwent breast-conserving surgery for invasive breast cancer and for whom a pretreatment mammogram was available. Information was recorded concerning mammographic density as well as tumor

features, patient characteristics, and adjuvant treatments received. Patients were categorized for mammographic density based on the Wolfe classification as either low (<25% density), intermediate (25-50% density), or high (>50% density). A multivariate survival analysis was conducted using the Cox proportional hazards model with local disease recurrence as the primary endpoint. RESULTS: Patients in the high mammographic density group experienced a much greater risk of local disease recurrence compared with women with the least dense breasts (10-year actuarial risks: 21% vs 5%; hazards ratio [HR], 5.7 [95% confidence interval, 1.6-20; P=.006]). The difference in the rates of disease recurrence at 10 years was pronounced for women who did not receive radiotherapy (40% vs 0% for patients with >50% density and <25% density, respectively; P<.0001). CONCLUSIONS: Mammographic breast density is an important risk factor for local breast cancer recurrence among women not receiving breast irradiation. Mammographic density should be taken into consideration when stratifying patients for clinical trials of partial breast radiotherapy. If confirmed, mammographic density might be used to help determine which patients might benefit from radiotherapy.

Colberg, J. W., R. H. Decker, et al. (2007). "Surgery versus implant for early prostate cancer: results from a single institution, 1992-2005." *Cancer J* 13(4): 229-32.

PURPOSE: The aim of this study was to compare the biochemical disease-free survival rates for radical prostatectomy versus transperineal ultrasound-guided prostate implant for patients with early prostate cancer treated at a single institution from 1992 through 2005. MATERIALS AND METHODS: The charts of 741 patients with early prostate cancer (350 implant and 391 surgery) treated from 1992 through 2005 were retrospectively reviewed. Surgery patients were treated by members of the academic Urology Section at Yale University School of Medicine. Implant patients were treated by a combined team from the Urology Section and the Department of Therapeutic Radiology at Yale Medical School. For the 350 implant patients, 35% were treated with iodine-125 and 65% with palladium-103. Of the implant patients 92% were treated with an implant alone and 8% with combined external beam radiation therapy plus an implant and 25% received short-term hormone therapy to downsize the prostate before the implant. Both surgery and implant patients were analyzed based on a group with favorable cancers (clinical stage T1c or T2, prostate-specific antigen <10, and Gleason score <7), an intermediate

group (any 1 factor increased compared with the favorable group), and a poor group (any 2 factors increased compared with the favorable group). The follow-up time varied from 12 to 120 months with a mean/median follow-up time of 44 months/42 months for implant patients and 42 months/40 months for surgery patients. Prostate-specific antigen recurrence for surgery was defined as any detectable prostate-specific antigen after surgery. Prostate-specific antigen recurrence for implant was defined as the prostate-specific antigen nadir plus 2 ng/mL after implant. The biochemical disease-free survival rates were calculated using the life-table method. RESULTS: The 5-year biochemical disease-free survival rates for radical prostatectomy versus implant were identical for the favorable group (93% versus 92%), intermediate group (70% versus 70%), and poor group (50% versus 52%) patients. CONCLUSIONS: From 1992 through 2005, implant therapy produced equivalent 5-year biochemical disease-free survival rates compared with surgery in patients with early prostate cancer treated at a single institution.

Congedo, E., P. Aceto, et al. (2005). "Preoperative anesthetic evaluation and preparation in patients requiring esophageal surgery for cancer." *Rays* 30(4): 341-5.

Esophagectomy for carcinoma of the esophagus is associated with significant mortality and morbidity. Patients with esophageal cancer have frequently obstruction with dysphagia and they often develop malnutrition. In addition, patients can suffer from chronic aspiration leading to a poor preoperative respiratory status. Thorough preoperative evaluation is essential for assessing the operative risk in the individual patient. Respiratory and cardiac problems are the most common complications and assessment of surgical risk, preoperative performance status, particularly with regard to pulmonary and cardiac risk, is likely to be the most important factor. Clinical findings are more predictive of pulmonary complications than results of testing. Cardiac risk is evaluated according to the American College of Cardiology (ACC)/American Heart Association guidelines. With the identification of risk factors, patients undergoing esophageal surgery could be stratified. Appropriate preoperative risk-reduction strategies can be used to decrease morbidity and mortality rates associated with esophagectomy for cancer.

Crispino, P., G. De Toma, et al. (2008). "Role of desmoplasia in recurrence of stage II colorectal cancer within five years after surgery and therapeutic implication." *Cancer Invest* 26(4): 419-25.

BACKGROUND: Colorectal cancer (CRC) metastasis is enhanced in patients with venous embolization increasing the risk of recurrence and therefore mortality rate. Several evidences indicate that stage II patients have an abrupt recurrence within five years from surgery. This fact, led us to investigate the role played by different histological variables on CRC invasiveness. **AIM:** To demonstrate if quantitative and qualitative desmoplastic response and lymphocytic infiltration are prognostic factor involved in the recurrence of CRC within five years from surgery, considering possible clinical and therapeutical implications. **METHODS:** Thirty-four patients with CRC underwent colectomy and the UICC-TNM classification was applied for disease staging. Histological variables were semi-quantitatively evaluated. Qualitative evaluation of desmoplasia was obtained with the hematoxylin-eosin method. **RESULTS:** Survival rate arose 88% at stage II, at five years of follow-up, and the 12% not treated with adjuvant chemotherapy developed metastasis. Desmoplasia is strongly associated with venous neoplastic invasiveness (OR: 21.93; 95%CI: 1.012-475.26, $p = 0.02$), and therefore, with mortality rate (OR: 14.33; 95%CI: 0.67-304, $p = 0.04$). Moreover, mortality rate was significantly higher in patients with immature desmoplasia compare to mature stromal tissue (OR: 15.61, 95%CI: 0.69-343.38, $p = 0.04$). **CONCLUSIONS:** These observations should prompt a future evaluation of desmoplasia to extent more suitably the use of adjuvant chemotherapy in II stage patients. Further clinical trials are needed to determine if these findings will be able to reduce mortality rate, in stage II CRC patients.

Curigliano, G., J. Y. Petit, et al. (2005). "Systemic effects of surgery: quantitative analysis of circulating basic fibroblast growth factor (bFGF), Vascular endothelial growth factor (VEGF) and transforming growth factor beta (TGF-beta) in patients with breast cancer who underwent limited or extended surgery." *Breast Cancer Res Treat* **93**(1): 35-40.

BACKGROUND: To assess if feature, extent and duration of surgery could influence levels of systemic proangiogenic cytokines vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and transforming growth factor beta (TGF-beta). **PATIENTS AND METHODS:** We collected blood samples from 82 consecutive breast cancer patients who underwent various types of surgery, classified according to the magnitude of tissue injury in: minimal (quadrantectomy), moderate (mastectomy without reconstruction), and heavy [mastectomy followed by reconstruction with transversus recto-abdominal muscle cutaneous flap (TRAM)]. Samples were collected one day before surgery (D(-1)), at the

end of surgical tumor removal (D0), and on 1st (D(+1)), 2nd (D(+2)) and 5th (D(+5)) day after surgery. Serum VEGF, bFGF and TGF-beta levels were measured by the enzyme immunoassay method. **RESULTS:** On average a continuous decrease was observed for all growth factors from the day before operation to the 5th day after operation. On day (D(+5)) an increase was observed for patients who underwent extended respect to moderate surgery. These differences were found statistically significant for bFGF and VEGF ($p = 0.05$ and $p = 0.025$ respectively). A statistically different trend for type of operation was observed also for TGF-beta at 24-48 h: a minor reduction, compared to time of operation, was observed for minimal surgery, an intermediate reduction for moderate surgery and a higher decrease for extended surgery. **CONCLUSIONS:** Angiogenic cytokines perioperative levels could be increased on 5th day (D(+5)) by extent of surgery and should induce perioperative stimulation of residual cancer cells. A better understanding of the time interval during which the sequelae of events in wound healing occur may be the basis for defining new therapeutic strategies that can interfere with tumor outgrowth sparing wound healing processes.

D'Amico, A. (2007). "Global update on defining and treating high-risk localized prostate cancer with leuprorelin: a USA perspective--identifying men at diagnosis who are at high risk of prostate cancer death after surgery or radiation therapy." *BJU Int* **99 Suppl 1**: 13-6; discussion 17-8.

Prostate-specific antigen doubling time (PSA-DT) after surgery or radiotherapy (RT) is known to be a predictive factor for death from prostate cancer (prostate cancer-specific mortality, PCSM). An analysis of two multi-institutional databases, including 8669 men with prostate cancer treated with surgery or RT, found that a PSA-DT of <3 months, and the specific value of the PSA-DT when > or = 3 months, appeared to be surrogate endpoints for PCSM after surgery or RT. While many PSA failures occur after local therapy for localized prostate cancer, few of these patients go on to die from their disease, so it is important to identify other factors associated with PCSM, so that the subgroup of high-risk patients can be identified. An analysis was undertaken to determine whether patients at risk of PCSM could be identified using information available at diagnosis. The results showed that risk factors for PCSM were a PSA velocity of >2.0 ng/mL/year, a Gleason score of 8-10 and an increasing PSA level. However, the most important risk factor that had an impact on both PCSM and all-cause mortality was a PSA velocity of >2.0 ng/mL/year. PSA kinetics are being increasingly used in the setting of rising PSA

levels after radical prostatectomy or RT, and several studies showed that the rate of increase in PSA level at the time of recurrence is closely associated with time to cancer death. A PSA-DT of <3 months is associated with a poor prognosis, and represents 15-20% of PSA failures in the general population and 6-7% of PSA failures in a screened population, such as those included in clinical trials. Better risk-assessment models are needed to help to identify at an early stage men who are at high risk of prostate cancer death and those who are at low risk, so that each subgroup can receive the most appropriate therapy for their disease.

Daniels, I. R., S. E. Fisher, et al. (2007). "Accurate staging, selective preoperative therapy and optimal surgery improves outcome in rectal cancer: a review of the recent evidence." *Colorectal Dis* 9(4): 290-301.

OBJECTIVE: The current optimal management of locally advanced rectal cancer has evolved from surgical excision followed by postoperative therapy in patients with involved margins, to an increasing use of a preoperative strategy to 'down-stage and/or down-size' the tumour. This treatment strategy is based on the relationship of the tumour to the mesorectal fascia, the optimal surgical circumferential resection margin that can be achieved by total mesorectal excision. We have reviewed the recent evidence for this strategy. **METHOD:** An electronic literature search using PubMed identified articles on the subject of rectal cancer between January 2000 and December 2005. The search was limited to English language publications with secondary references obtained from key articles. Articles published in high impact factor journals formed the basis of the review, together with articles related to national programmes on the management of rectal cancer. This does lead to a selection bias, particularly as the articles identified had a European bias. **CONCLUSION:** The UK NHS Cancer Plan has outlined the basis for the multidisciplinary team (MDT) management of rectal cancer. Advances in preoperative assessment through accurate staging and the recognition of the importance of the relationship of the tumour to the mesorectal fascia has allowed the selection of patients for a preoperative strategy to down-size/down-stage the tumour if this fascial layer is involved or threatened. Improvements in the quality of surgical resection through the acceptance of the principle of total mesorectal excision have ensured that optimal surgery remains the cornerstone to successful treatment. Further refinements of the MDT process strive to improve outcome. Accurate radiological staging, optimal surgery and detailed histopathological assessment together with consideration of a preoperative neoadjuvant strategy should now form

the basis for current treatment and future research in rectal cancer.

Dardanov, D., T. Betova, et al. (2007). "Investigation of circumferential resection margin in rectal cancer surgery." *J Buon* 12(3): 369-76.

PURPOSE: Literature data suggest that investigation of the circumferential resection margin (CRM) in rectal cancer surgery gives significant information for prognosis of the disease and the quality of the performed operation. The aim of this study was to analyze the clinical and morphological aspects of CRM in pT3 tumors in relation to their significance for rectal cancer treatment and staging. **PATIENTS AND METHODS:** Thirty patients with radically operated pT3 stage rectal cancer were investigated. The resected specimens were studied both macroscopically and microscopically to assess CRM and the quality of the performed operation. **RESULTS:** Six (20%) patients had positive CRM (CRM +; tumor cells in the margin or < 1 mm from it). These cases were characterized with deep infiltration (> 4 mm) in the rectal adventitia (perirectal tissue). Statistically significant correlation was found between CRM status and quality of the resected specimen (including the presence of rectal fascia in CRM). There was no correlation between pathological characteristics of the tumor and the status of CRM. **CONCLUSION:** The status of CRM is a factor independent from TNM classification. The presence of rectal fascia in CRM confirms the good quality of the operation. CRM+ could be a result of inadequate surgery or advanced disease. The status of CRM could be used in the decision-making for postoperative adjuvant treatment.

Dexter, S. P., H. Sue-Ling, et al. (2001). "Circumferential resection margin involvement: an independent predictor of survival following surgery for oesophageal cancer." *Gut* 48(5): 667-70.

BACKGROUND: For rectal carcinoma, the presence of tumour within 1 mm of the circumferential margin is an important independent prognostic factor for both local recurrence and survival. Similar prospective data have not been reported for oesophageal carcinoma and we wished to ascertain the prognostic importance of this variable following potentially curative resection for oesophageal carcinoma. **AIM:** To prospectively assess the impact of circumferential margin involvement (tumour within 1 mm) following potentially curative resection for oesophageal carcinoma. **PATIENTS AND METHODS:** In a prospective study, resection specimens of 135 patients treated with potentially curative oesophageal resection alone were studied for the presence of tumour within 1 mm of the

circumferential margin (margin positive), using inked margins and cross sectional slicing of the specimen. All tumours were also staged using the 1987 UICC TNM classification. Patients were followed for a mean of 19 months, and overall and cancer specific survival analysed. RESULTS: The finding of tumour cells within 1 mm of the circumferential margin (CRM+) was a significant and independent predictor of survival following potentially curative oesophageal resection. Overall, 64 (47%) patients were CRM+. Median survival in this group was 21 months compared with 39 months in the CRM- group ($p=0.015$). The impact of CRM status on survival was only seen in patients with a low nodal metastatic burden (<25% nodes positive). The odds ratio for the risk of dying from oesophageal cancer was 2.08 when the CRM was involved ($p=0.013$). CONCLUSIONS: The presence of tumour within 1 mm of the circumferential margin following potentially curative resection for oesophageal carcinoma is an important independent prognostic variable and should be reported routinely.

Di Giorgio, A., E. Naticchioni, et al. (2008). "Cytoreductive surgery (peritonectomy procedures) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of diffuse peritoneal carcinomatosis from ovarian cancer." *Cancer* **113**(2): 315-25.

BACKGROUND: Because of scarce data from larger series and nonhomogeneous selection criteria, further information is needed on peritonectomy with hyperthermic intraperitoneal chemotherapy (HIPEC) in managing patients with ovarian peritoneal carcinomatosis. METHODS: In an open, prospective, single-center nonrandomized phase 2 study conducted from November 2000 to April 2007, 47 patients with primary advanced or recurrent ovarian cancer and diffuse peritoneal carcinomatosis were enrolled; 22 underwent primary and 25 secondary cytoreduction plus immediate HIPEC followed by systemic chemotherapy. RESULTS: The overall mean Sugarbaker peritoneal cancer index was 14.9 (range, 6-28). A mean of 6 surgical procedures were required per patient (range, 4-10). In 87.3% of the patients debulking achieved optimal cytoreduction (Sugarbaker completeness of cytoreduction [CC] score 0-1), whereas in 12.7% it left macroscopic residual disease (CC-2 or CC-3). Major complications developed in 21.3% of the patients and the in-hospital mortality rate was 4.2%. The mean overall survival was 30.4 months, median survival was 24 months, and mean disease-free survival was 27.4 months. Five-year survival was 16.7%. Univariate (log-rank test and analysis of variance) and multivariate analyses (Cox proportional-hazard model) identified the CC score as

the main factor capable of independently influencing survival. CONCLUSIONS: Peritonectomy procedures combined with HIPEC offer promising long-term survival in patients with diffuse peritoneal ovarian carcinomatosis. They achieve high adequate primary and secondary surgical cytoreduction rates with acceptable morbidity and mortality.

Diaz, R., G. Reynes, et al. (2009). "Long-term results of neoadjuvant chemotherapy and combined chemoradiotherapy before surgery in the management of locally advanced oesophageal cancer: a single-centre experience." *Clin Transl Oncol* **11**(12): 835-41.

INTRODUCTION: Neoadjuvant chemoradiotherapy before surgery is an option in the treatment of locally advanced resectable oesophageal cancer (EC). However toxicity is substantial and the improvement in overall survival (OS) with this approach is controversial. METHODS: This was a prospective, single-centre study of neoadjuvant chemotherapy and concomitant chemoradiotherapy with CDDP and 5-FU and 50.4 Gy of external radiotherapy before possible radical surgery in patients with locally advanced resectable EC. If surgery was not possible, a second-phase radiotherapy boost of 10 Gy and one cycle of modified dose chemotherapy were used. RESULTS: Seventy-three patients included between 1998 and 2007: 96% males, median age 61, 83% squamous cell carcinomas, 23% lower third tumours, 36% stage II and 54% stage III and 47% local lymph node involvement. Eighty-six percent completed the combined protocol. Main grade 3-4 toxicities: mucositis (19%) and infections (8%); 4 toxic deaths. Clinical response rates: complete response 54%, partial response 27%, stable disease 8%. Twenty-five patients proceeded to surgery, with radical resection in 24. Pathological response rate: complete response 32%, partial response 52%, progression 16%. There were 7 postoperative deaths and 16 of 34 patients that did not have surgery received the second-phase RT boost. Survival analysis: Median follow-up of 64 months (range 6-134 months). Median OS of 10.33 months. 2-year and 5-year OS of 22 and 16%. The only significant prognostic factor in OS is the clinical complete response rate: 13.9 vs. 7.7 months ($p=0.0049$). CONCLUSIONS: Our protocol offers a high rate of clinical activity although it is relatively toxic and seems to increase the postoperative mortality, which would blunt any small improvement in survival. The achievement of a complete response is a powerful prognostic factor.

Dixon, A. J., M. P. Dixon, et al. (2007). "Bleeding complications in skin cancer surgery are associated

with warfarin but not aspirin therapy." *Br J Surg* **94**(11): 1356-60.

BACKGROUND: The aim was to identify risk factors for postoperative bleeding following skin cancer surgery. **METHODS:** This was a prospective study of 5950 skin lesions excised in 2394 patients. No patient stopped taking aspirin or warfarin unless the international normalized ratio (INR) exceeded 3.0. **RESULTS:** The rate of postoperative bleeding was 0.7 per cent overall and 2.5 per cent in the 320 patients taking warfarin. The rate of bleeding was 1.0 per cent for skin flap repairs, 0.4 per cent for simple excision and closure, and 5.0 per cent for skin grafts. Diabetic patients and smokers were not at increased risk of bleeding. There were four independent factors for bleeding: age 67 years or older (odds ratio (OR) 4.7 (95 per cent confidence interval 1.8 to 12.2); $P = 0.002$), warfarin therapy (OR 2.9 (1.4 to 6.3); $P = 0.006$), surgery on or around the ear (OR 2.6 (1.2 to 5.7); $P = 0.012$) and closure with a skin flap or graft (OR 2.7 (1.4 to 5.3); $P = 0.004$). Aspirin therapy was not an independent risk factor for bleeding. **CONCLUSION:** Most postoperative bleeds were inconvenient but not life threatening, unlike the potential risk of thromboembolism after stopping warfarin or aspirin. There was no case for discontinuing aspirin before skin surgery, but the INR should be monitored in patients taking warfarin.

Doglietto, G. B., F. Pacelli, et al. (2000). "Surgery: independent prognostic factor in curable and far advanced gastric cancer." *World J Surg* **24**(4): 459-63; discussion 464.

The hospital records of 639 patients affected by primary gastric cancer who were consecutively admitted to our unit during the period 1981-1995 were reviewed. Overall 220 underwent total gastrectomy (38 palliative), 12 had resection of the gastric stump, 195 had distal subtotal gastrectomy (55 palliative), 78 had bypass procedures, 72 had explorative laparotomy, and 62 had no operation. Univariate and multivariate analyses were used to evaluate 5-year survival with respect to the main clinical, pathologic, and treatment variables after both curative and palliative treatments. Overall the 5-year survival after curative treatment (320 patients-operative mortality excluded) was 55.5%: 91.1% for stage IA, 71.5% IB, 62.4% II, 37.5% IIIA, 31.5% IIIB. Among patients who underwent palliative treatment 5-year survival was 13.1% after gastric resection (total or distal subtotal), 4.9% after the bypass procedures, 0 after explorative laparotomy, and 0 after no operation. Univariate and multivariate survival analyses showed that variables independently associated with poor survival were advanced stage, upper location and D1 lymphadenectomy after curative treatment, tumor

spread to distant sites, and nonresectional surgery after palliative treatment. Multivariate analysis showed that even though survival with gastric cancer depends on predetermined factors, the type of surgery can have a significant effect on prognosis after both curative and palliative treatment.

Du, X., J. L. Freeman, et al. (1999). "Temporal and regional variation in the use of breast-conserving surgery and radiotherapy for older women with early-stage breast cancer from 1983 to 1995." *J Gerontol A Biol Sci Med Sci* **54**(9): M474-8.

BACKGROUND: Authorities recommend radiation therapy after breast-conserving surgery for breast cancer. Numerous studies have reported that older women diagnosed with breast cancer are less likely to receive radiation after breast-conserving surgery. It is unclear how care of older women with breast cancer has changed over time. **METHODS:** Women with local or regional stage breast cancer diagnosed between 1983-1995 were identified from the Surveillance, Epidemiology, and End Results (SEER) Cancer Registries. The treatment information in SEER includes type of surgical procedures and receipt of radiation therapy. **RESULTS:** There were small increases in the percentage of women receiving breast-conserving surgery during the 1980s followed by substantial increases in the 1990s. Age was a major factor in determining receipt of radiation therapy after breast-conserving surgery. A large increase in use of radiotherapy after surgery was observed in women aged ≥ 75 , from below 30% in 1983 to over 50% in 1995. Women aged ≥ 75 diagnosed in 1992-1995 were 1.76 and 2.34 times more likely to receive radiation for local and regional stage respectively, as compared to those in 1983-1987. There was no increase in use of radiation for women aged < 65 . **CONCLUSIONS:** There has been a substantial increase in use of breast-conserving surgery and in receipt of radiation therapy after breast-conserving surgery in older women. However, there was a net increase in the percentage of all women with breast cancer who received this surgery without radiotherapy, due to the large increase in the overall percentage of women receiving this surgery.

Dunst, J., C. Rodel, et al. (2001). "Bladder preservation in muscle-invasive bladder cancer by conservative surgery and radiochemotherapy." *Semin Surg Oncol* **20**(1): 24-32.

Organ preservation has been investigated in muscle-invasive bladder cancer over the past decades as an alternative to standard radical cystectomy. The results of large prospective protocols and population-based studies suggest that an organ-preserving approach is possible without deferring the survival

probability. Organ preservation requires a trimodal schedule, including transurethral surgery (transurethral resection of bladder tumor (TURBT)), radiation, and chemotherapy. A complete TURBT is the most important single prognostic factor, and should be attempted. Radiotherapy, in conjunction with concurrent platinum-based chemotherapy, can control the vast majority of urothelial bladder tumors. The histologically-proven complete remission rates of macroscopic tumors (unresectable by TURBT) lie in the range of about 70%. After radiochemotherapy, a histological response evaluation with repeated TURBT is recommended. Patients with residual tumor require salvage cystectomy. In cases of complete remission, patients can maintain their bladders but they should be closely followed over years. The risk of severe late-radiation sequelae is low, in the range of less than 5%. About 75% of long-term survivors maintain a normally functioning bladder.

Felip, E., M. Taron, et al. (2005). "Clinical significance of hypoxia-inducible factor-1a messenger RNA expression in locally advanced non-small-cell lung cancer after platinum agent and gemcitabine chemotherapy followed by surgery." Clin Lung Cancer 6(5): 299-303.

Hypoxia-inducible factor-1a (HIF-1a) is a key regulator of the angiogenic cascade. This study analyzed HIF-1a messenger RNA expression levels using real-time quantitative polymerase chain reaction (PCR) in paraffin-embedded surgical specimens from 54 stage IIB-III patients with non-small-cell lung cancer (NSCLC) treated with induction platinum/gemcitabine followed by surgery between September 1998 and December 2002. Radiographic response was observed in 61% of patients. Median survival was 37.8 months. Forty-five patients with complete resection attained a 52-month median survival, whereas 8 patients with incomplete resection had a 12-month median survival, and 1 unresectable patient had a survival of 14 months. No significant differences were observed in overall survival (OS) or event-free survival (EFS) according to HIF-1a expression levels. Patients were divided into quartiles according to HIF-1a gene expression levels. Median EFS for the 13 patients in the lowest quartile has not been reached yet, whereas median EFS for the 13 patients in the top quartile was 9 months ($P = 0.192$). Similarly, median OS for the 13 patients in the lowest quartile has not been reached yet, whereas median OS for the 13 patients in the top quartile was 52 months ($P = 0.297$). The cisplatin/gemcitabine combination is highly active in neoadjuvant treatment. Hypoxia-inducible factor-1a expression levels analyzed by real-time quantitative PCR in surgery specimens after

platinum/gemcitabine therapy do not correlate with the outcome of patients with stage II/III NSCLC.

Finke, N. M., M. C. Aubry, et al. (2004). "Autopsy results after surgery for non-small cell lung cancer." Mayo Clin Proc 79(11): 1409-14.

OBJECTIVE: To determine the percentage of metastatic and unexpected residual lung cancer at autopsy in patients considered for curative resection of non-small cell lung cancer during a time when computed tomography was available as a preoperative staging tool. **MATERIAL AND METHODS:** Clinical data and surgical and autopsy slides of all patients who underwent curative resection of nonsmall cell lung cancer at the Mayo Clinic in Rochester, Minn, between 1985 and 1999 and who underwent autopsy within 30 days of surgery were reviewed retrospectively for the presence of residual or metastatic disease. **RESULTS:** The study group consisted of 25 men and 7 women, with a mean age of 70 years. A pulmonary metastasis was identified at surgery in 1 patient (3%). Metastases were found in an additional 5 patients (16%) at autopsy, 1 of whom had 2 sites involved. These sites included the liver in 2 and lung, epicardium, adrenal gland, and kidney in 1 each. The average diameter of metastases was 1.6 cm. No factor studied was found to be significantly associated with the presence of unrecognized metastatic disease at autopsy. **CONCLUSION:** The advent of computed tomography as a staging tool has decreased the percentage of patients with undiagnosed metastatic disease at surgery; however, preoperative understaging in lung cancer remains a problem.

Flynn, P. M., J. Paul, et al. (2002). "Does the interval from primary surgery to chemotherapy influence progression-free survival in ovarian cancer?" Gynecol Oncol 86(3): 354-7.

OBJECTIVES: The objective of this study was to determine whether the length of the interval from primary surgery to commencement of chemotherapy has any direct effect on progression-free survival in ovarian cancer. **METHODS:** The progression-free survival of 472 patients enrolled in four trials who had all received platinum-containing chemotherapy (either in combination with a taxane or cyclophosphamide) was subjected to univariate analysis. Dividing subjects into those above and below the median interval from surgery to chemotherapy formed two groups for analysis. The analysis was stratified by study and arm/cohort within study to remove any possible influence of the different studies and study doses. Multivariate analysis was then performed including stage, bulk of residual disease, and performance status as well as interval to starting chemotherapy. **RESULTS:** The median

interval from surgery to chemotherapy was 22 days (range 7-100). Univariate analysis of the above median and below median groups showed worse progression-free survival for those with earlier treatment (hazard ratio 0.84, $P = 0.14$, 95% CI 0.67-1.06); however, those treated earlier tended to have bulkier residual disease (>2 cm; $P = 0.006$). When multivariate analysis was performed incorporating residual disease status, FIGO stage, and performance status, the hazard rate ratio for interval to surgery was 0.99 ($P = 0.91$, 95% CI 0.79-1.24). **CONCLUSIONS:** This study suggests that the interval from surgery to commencement of chemotherapy is not an independent prognostic factor for progression-free survival.

Fowble, B., A. Hanlon, et al. (2001). "Second cancers after conservative surgery and radiation for stages I-II breast cancer: identifying a subset of women at increased risk." *Int J Radiat Oncol Biol Phys* **51**(3): 679-90.

PURPOSE: To assess the risk and patterns of second malignancy in a group of women treated with conservative surgery and radiation in a relatively contemporary manner for early-stage invasive breast cancer, and to identify a subgroup of these women at increased risk for a second cancer. **METHODS AND MATERIALS:** From 1978 to 1994, 1,253 women with unilateral Stage I-II breast cancer underwent wide excision, axillary dissection, and radiation. The median follow-up was 8.9 years, with 446 patients followed for ≥ 10 years. The median age was 55 years. Sixty-eight percent had T1 tumors and 74% were axillary-node negative. Radiation was directed to the breast only in 78%. Adjuvant therapy consisted of chemotherapy in 19%, tamoxifen in 19%, and both in 8%. Factors analyzed for their association with the cumulative incidence of all second malignancies, contralateral breast cancer, and non-breast cancer malignancy were: age, menopausal status, race, family history, obesity, smoking, tumor size, location, histology, pathologic nodal status, region(s) treated with radiation, and the use and type of adjuvant therapy. **RESULTS:** One hundred seventy-six women developed a second malignancy (87 contralateral breast cancers at a median interval of 5.8 years, and 98 non-breast cancer malignancies at a median interval of 7.2 years). Nine women had both a contralateral breast cancer and non-breast cancer second malignancy. The 5- and 10-year cumulative incidences of a second malignancy were 5% and 16% for all cancers, 3% and 7% for contralateral breast cancer, 3% and 8%, for all second non-breast cancer malignancies, and 1% and 5%, respectively, for second non-breast cancer malignancies, excluding skin cancers. Patient age was a significant factor for

contralateral breast cancer and non-breast cancer second malignancy. Young age was associated with an increased risk of contralateral breast cancer, while older age was associated with an increased the risk of a second non-breast cancer second malignancy. A positive family history increased the risk of contralateral breast cancer, but not non-breast cancer malignancies. The risk of a contralateral breast cancer increased as the number of affected relatives increased. Tamoxifen resulted in a nonsignificant decrease in contralateral breast cancer and an increase in non-breast cancer second malignancies. The 5- and 10-year cumulative incidences for leukemia and lung cancer were 0.08% and 0.2%, and 0.8% and 1%, respectively. There was no significant effect of chemotherapy or the regions treated with radiation on contralateral breast cancer or non-breast cancer second malignancy. The most common types of second non-breast cancer malignancies were skin cancers, followed by gynecologic malignancies (endometrial), and gastrointestinal malignancies (colorectal and pancreas). **CONCLUSION:** The 10-years cumulative incidence of a second cancer in this study was 16%. Young age and family history predicted for an increased risk of contralateral breast cancer, and older age predicted for an increased risk of non-breast cancer malignancy. The majority of patients treated with conservative surgery and radiation with or without adjuvant systemic therapy will not develop a second cancer. Long-term follow-up is important to document the risk and patterns of second cancer, and knowledge of this risk and the patterns will influence surveillance and prevention strategies.

Friis, E., J. Horby, et al. (2004). "Thromboembolic prophylaxis as a risk factor for postoperative complications after breast cancer surgery." *World J Surg* **28**(6): 540-3.

Hematoma and bruising (sugillation) are frequent problems after operations for primary breast cancer. In the present study we evaluated the influence of various methods of perioperative thromboembolic prophylaxis on the postoperative incidence of hematoma and sugillation. From June 1994 through August 1996, a series of 425 patients consecutively operated on for primary breast cancer were included. Thromboembolic prophylaxis was low-molecular-weight heparin (LMWH) in 310 patients and thigh-long graded compression (TED) stockings in 102 patients. Postoperative complications including deep vein thrombosis, pulmonary embolism, wound hematoma, and sugillation were recorded, and 17 variables with a potential influence on complications were analyzed by logistic regression analysis. Heparin prophylaxis compared to

prophylaxis with TED stockings was significantly and independently associated with postoperative hematoma [odds ratio (OR) 3, 13; 95% confidence interval (CI) 1.38-7.13] or sugillation (OR 3.34; 95% CI 1.93-5.78). No clinically overt thromboembolic complications were diagnosed. After operations for breast cancer we found that LMWH was significantly associated with postoperative hematoma and sugillation compared to TED stockings for perioperative thromboembolic prophylaxis.

Fujita, T., A. Hara, et al. (1999). "The value of acute-phase protein measurements after curative gastric cancer surgery." *Arch Surg* **134**(1): 73-5.

OBJECTIVE: To determine whether acute-phase protein measurement provides clinically useful information about tumor recurrence. **PATIENTS AND METHODS:** Acute-phase serum protein levels were measured at regular intervals in 43 patients who underwent curative gastrectomy for gastric cancer. At 12 months after surgery, patients were grouped according to the presence or absence of a C-reactive protein response, and were followed up for a minimum of 12 months or until death. **RESULTS:** There was a significant difference ($P = .02$) in a recurrence rate between patients with a C-reactive protein response (3 of 4 patients) and those without such a response (4 of 39 patients). Moreover, serum levels of C4 and alpha1-antitrypsin 12 months after surgery in patients who eventually recurred were significantly ($P < .05$) higher than those in a group without recurrence. **CONCLUSION:** An acute-phase protein response may be a predictive factor in the early stages of tumor recurrence. Acute-phase protein measurement provided clinically useful information about tumor recurrence after curative gastric cancer surgery.

Fukagawa, T., H. Katai, et al. (2009). "Gallstone formation after gastric cancer surgery." *J Gastrointest Surg* **13**(5): 886-9.

BACKGROUND: Gallstone formation is one of the most common complications after gastric cancer surgery, but the mechanism and etiology for such formation are unclear because of a lack of collective clinical investigation. **METHOD:** We evaluated the influence of various surgical factors on the incidence of gallstone formation after gastrectomy. Gallstone formation was confirmed by ultrasound examinations that were routinely carried out after surgery on a periodic basis. **RESULTS:** Gallstone formation occurred in 173 of 672 (25.7%) patients who had undergone gastrectomy with lymph-node dissection for gastric cancer. The types of gastrectomy and reconstruction had no significant effect on the incidence, but the extent of lymph-node

dissection was a significant factor ($p < 0.001$: D1 + alpha vs. D2 + alpha; $p < 0.01$: D2 vs. D2 + alpha). Gallstones were usually formed within 2 years after gastrectomy, but in most cases, gallstone formation was asymptomatic. **CONCLUSION:** The extent of lymph-node dissection was a significant factor in gallstone formation after gastrectomy; therefore, prophylactic cholecystectomy should be considered in cases of extensive lymph-node dissection.

Galizia, G., F. Ferraraccio, et al. (2004). "Prognostic value of p27, p53, and vascular endothelial growth factor in Dukes A and B colon cancer patients undergoing potentially curative surgery." *Dis Colon Rectum* **47**(11): 1904-14.

PURPOSE: Early-stage colon cancer patients (Dukes A or B; pT1-T3 pNO pMO) are excluded from adjuvant chemotherapy following potentially curative surgery because they are expected to have good long-term survival. However, 20 percent to 30 percent of these patients ultimately succumb from recurrent disease. This indicates that the conventional staging procedures may be unable to precisely predict cancer prognosis. **METHODS:** In 65 early-stage colon cancers, we investigated by immunohistochemistry the role of molecular markers such as p27, p53, and vascular endothelial growth factor in identifying high-risk patients who may benefit from adjuvant treatments. **RESULTS:** No clinicopathologic factor, namely Dukes stage, t parameter, number of resected nodes, and vascular or lymphatic invasion, was found to be an independent significant predictor of disease-specific and disease-free survival. In contrast, each molecular marker predicted survival and recurrence rates much better than the conventional Dukes staging system. The best combination of variables for prediction of long-term outcome and recurrence rate included p27, p53, and vascular endothelial growth factor. Interestingly, the greater the number of molecular alterations, the lower the five-year estimated survival function. Nearly all cancer-related deaths were observed among patients whose colon cancers expressed all three molecular alterations. Regardless of Dukes stage, the recurrence rate was found to increase with the increase in the number of molecular alterations. Early-stage colon cancers expressing p27 down-regulation and high p53 and vascular endothelial growth factor immunoreactivity showed a 100 percent actuarial four-year recurrence rate. **CONCLUSIONS:** Assessment of molecular alterations may be useful to identify a higher-risk group of early-stage colon cancer patients who may benefit from adjuvant chemotherapy.

Galizia, G., E. Lieto, et al. (2006). "Prognostic significance of epidermal growth factor receptor

expression in colon cancer patients undergoing curative surgery." *Ann Surg Oncol* **13**(6): 823-35.

BACKGROUND: To investigate the role of epidermal growth factor receptor (EGFR) expression as a prognostic marker for prediction of cancer behavior and clinical outcomes in colon cancer patients undergoing potentially curative surgery. **METHODS:** EGFR determination using a commercially available immunohistochemistry kit was performed in tissues from 149 colon cancer patients receiving primary surgical treatment and in 25 normal colon mucosa specimens from noncancer patients. EGFR positivity was correlated in univariate and multivariate analyses with disease recurrence and survival. In addition, p27, p53, and vascular endothelial growth factor expression were assessed by immunohistochemistry in 104 patients and correlated with EGFR tumor expression and clinical outcome. **RESULTS:** EGFR expression was detected in approximately one third of colon cancer patients (53 of 149; 35.6%). In 126 curatively treated patients, EGFR expression was correlated with disease recurrence and worse survival in both univariate and multivariate analyses. In a multivariate model for predicting recurrence and survival, Dukes' staging, p27, and EGFR expression were the only independent covariates. In particular, in Dukes' A and B patients the 5-year survival probability was 96% for EGFR-negative and high p27 expression cases and was 30.7% for EGFR-positive and low p27 expression cases. **CONCLUSIONS:** EGFR expression was an independent prognostic indicator of disease recurrence and poor survival in colon cancer patients undergoing curative surgery. In the context of novel therapeutic options such as molecularly targeted therapies, these findings suggest that anti-EGFR drugs could be evaluated in the adjuvant treatment of EGFR-positive colon cancer patients.

Galizia, G., E. Lieto, et al. (2007). "Epidermal growth factor receptor (EGFR) expression is associated with a worse prognosis in gastric cancer patients undergoing curative surgery." *World J Surg* **31**(7): 1458-68.

BACKGROUND: In gastric cancer, the recurrence rate is high even after curative surgery. A relevant issue is the identification of independent prognostic factors to select high-risk patients; such features can be used as predictive factors for tailored therapies. In this study we have investigated the role of epidermal growth factor receptor (EGFR) expression as a prognostic marker for predicting cancer behavior and clinical outcome in gastric cancer patients undergoing potentially curative surgery. **METHODS:** Epidermal growth factor receptor determination using a commercially available immunohistochemistry (IHC) kit was performed in

tissues from 82 gastric cancer patients receiving primary surgical treatment and in 25 normal gastric mucosa specimens from noncancer patients. The EGFR positivity was correlated with disease recurrence and survival in univariate and multivariate analyses. **RESULTS:** Forty-four percent (36 cases) of gastric cancers were EGFR positive. In 66 curatively treated patients, EGFR expression correlated with disease recurrence and poorer survival in both univariate and multivariate analyses. In a multivariate model for predicting recurrence and survival, advanced tumor extension (T(3) or T(4)), nodal metastases, and EGFR expression were the only independent covariates. In particular, EGFR expression was shown to be a significant predictor of poor prognosis among gastric cancer patients having the same stage according to the current TNM staging system. **CONCLUSIONS:** These findings suggest that EGFR expression may be useful in identifying high-risk gastric cancer patients undergoing potentially curative surgery. Multimodal treatments should be considered in the adjuvant treatment of these patients.

Gebauer, G., T. Fehm, et al. (2002). "Tumor size, axillary lymph node status and steroid receptor expression in breast cancer: prognostic relevance 5 years after surgery." *Breast Cancer Res Treat* **75**(2): 167-73.

Tumor size, axillary lymph node status and expression of steroid receptors are well-established prognostic factors in breast cancer. However, it is not clear if these prognostic factors are time-dependent variables and lose their significance after several years of disease-free survival. To analyse how long these factors keep their prognostic relevance survival of 1162 breast cancer patients was analysed retrospectively. The post-operative follow-up period was split into consecutive 2-year intervals and each interval was analysed for rate of recurrence and rate of tumor depending deaths. Furthermore, a multivariate analysis was performed for the total follow-up time and for the follow-up period starting 5 years after surgery. Multivariate analysis revealed tumor size, axillary lymph node status and estrogen receptor status as independent prognostic parameters. Analysing separately the rate of recurrences and tumor-related deaths during consecutive 2-year intervals, only the tumor size was a constant prognostic parameter, whereas prognostic relevance of lymph node status decreased. Estrogen receptor status associated with favourable prognosis during the first years after surgery changed to an unfavourable prognostic factor 4 years after surgery. To summarize, prognostic factors obtained at the time of surgery can lose their significance with increasing disease-free survival.

Geller, B. M., P. M. Vacek, et al. (2003). "Factors associated with arm swelling after breast cancer surgery." *J Womens Health (Larchmt)* **12**(9): 921-30.

PURPOSE: As life expectancy improves for women with breast cancer, more women will be living with symptoms of lymphedema. This study reports the incidence of arm or hand swelling and associated risk factors in women with invasive breast cancer following surgery. **METHODS:** Data were obtained from baseline and follow-up interviews of women with invasive breast cancer (n = 145), and mammography and pathology records. The Kaplan-Meier method was used to estimate the probability of developing arm or hand swelling over time. Univariate and multivariate logistic regression analyses were conducted to identify risk factors for arm or hand swelling. **RESULTS:** Of women in this study, 38% self-reported arm or hand swelling. There was a significantly increased risk of arm swelling if women were under 50 years of age, had axillary node dissection, received chemotherapy, worked outside the home, and had a high household income. There was no association of body weight with swelling. A significantly decreased risk of arm swelling was found in women who were on treatment for high blood pressure. After adjustment for nodal dissection, only age had a significant independent effect. **CONCLUSIONS:** Our study highlights two important areas of future research that could reduce the incidence of lymphedema. There is a need to better understand the role that treatment for high blood pressure may play in protecting women from arm edema. Second, the potential effect of weight as a modifiable lymphedema risk factor needs to be studied in more detail in light of the conflicting results of different studies.

Gerestein, C. G., R. A. Damhuis, et al. (2009). "Causes of postoperative mortality after surgery for ovarian cancer." *Eur J Cancer* **45**(16): 2799-803.

Residual disease after cytoreductive surgery is an important prognostic factor in patients with advanced stage epithelial ovarian cancer (EOC). Aggressive surgical procedures necessary to achieve maximal cytoreduction are inevitably associated with postoperative morbidity and mortality. To determine causes of postoperative mortality (POM) after surgery for EOC all postoperative deaths in the southwestern part of the Netherlands over a 17-year period were identified and analysed by reviewing medical notes. Between 1989 and 2005, 2434 patients underwent cytoreductive surgery for EOC. Sixty-seven patients (3.1%) died within 30 days after surgery. Postoperative mortality increased with age from 1.5% (26/1765) for the age group 20-69 to 6.6% (32/486)

for the age group 70-79 and 9.8% (18/183) for patients aged 80 years or older. Pulmonary failure (18%) and surgical site infection (15%) were the most common causes of death. Only a quarter of deaths resulted from surgical site complications. Our results suggest that causes of postoperative mortality after surgery for EOC are very heterogeneous. Given the impact of general complications, progress in preoperative risk assessment, preoperative preparation and postoperative care seem essential to reduce the occurrence of fatal complications.

Gerestein, C. G., D. W. van der Spek, et al. (2009). "Prediction of residual disease after primary cytoreductive surgery for advanced-stage ovarian cancer: accuracy of clinical judgment." *Int J Gynecol Cancer* **19**(9): 1511-5.

OBJECTIVES: Treatment of patients with an advanced-stage epithelial ovarian cancer (EOC) is based on cytoreductive surgery and platinum-based chemotherapy. Amount of residual disease after primary cytoreductive surgery is an important prognostic factor. The objectives of the present study were to evaluate the accuracy and reproducibility of preoperative clinical judgment of residual disease after primary cytoreductive surgery and to compare the predictive performance of the offhand assessment to the predictive performance of prediction models. **MATERIALS AND METHODS:** Fifteen observers (5 gynecologic oncologists, 5 gynecologists, and 5 senior residents) were offered preoperative data of 20 patients with advanced-stage EOC who underwent primary cytoreductive surgery. The observers were asked to predict residual disease after cytoreductive surgery (≤ 1 or > 1 cm). Their estimation was compared with the performance of 2 prediction models. **RESULTS:** Overall, suboptimal cytoreduction was predicted with a sensitivity of 50% and a specificity of 56%. The intraclass correlation coefficient was 0.27. χ^2 Test showed no significant difference in prediction of suboptimal cytoreduction between the different subgroups and prediction models. **CONCLUSIONS:** Clinical judgment of residual disease after primary cytoreductive surgery in patients with advanced-stage EOC shows limited accuracy. Given the poor interobserver reproducibility, prediction models could attribute to uniform treatment decisions and improve counseling.

Giacomelli, L., W. Gianni, et al. (2003). "Persistence of epidermal growth factor receptor and interleukin 10 in blood of colorectal cancer patients after surgery identifies patients with high risk to relapse." *Clin Cancer Res* **9**(7): 2678-82.

PURPOSE: Despite the great number of studies performed to detect circulating markers of disease progression in colorectal cancer, few have shown a clinical use; among those, epidermal growth factor receptor (EGFR) and, more recently, interleukin (IL)-10. In this article, we sought to investigate how primary surgery could affect expression levels of EGFR, IL-6, and IL-10 in blood from colorectal cancer patients. **EXPERIMENTAL DESIGN:** We investigated by reverse transcriptase-PCR assay the expression at mRNA level of EGFR, IL-6, and IL-10 in blood samples taken from 56 colorectal cancer patients. Each gene expression was evaluated 1 day before and 20 days after primary surgery. Persistence of each gene in blood after surgery was then correlated to the relapse free time in a follow-up of 3 years. **RESULTS:** In blood samples taken before surgery, EGFR, IL-6, and IL-10 were found expressed in 62, 100, and 100% of patients, respectively. EGFR expression, but not IL-6 and IL-10, correlates with stage of disease. In the group of 41 patients who underwent follow-up studies, EGFR was found persistently high in 67%; 94% of them had relapse. Persistence of IL-10 after surgery also identifies relapses in 89% of cases. IL-6 persistence was not found to significantly correlate to progression of disease. **CONCLUSIONS:** Persistence of both EGFR and IL-10 in blood of colorectal cancer patients after surgery identifies patients with high propensity to relapse. These findings may suggest a clinical use of preoperative EGFR/IL-10 reverse transcriptase-PCR assay in the prediction of tumor recurrence.

Gil-Bazo, I., V. Catalan Goni, et al. (2005). "Impact of surgery and chemotherapy on von Willebrand factor and vascular endothelial growth factor levels in colorectal cancer." *Clin Transl Oncol* 7(4): 150-5.

INTRODUCTION: von Willebrand factor (vWf) is thought to mediate binding of tumour cells to platelets and to favour their systemic spreading capacity. Platelets involved in tumour angiogenesis are capable of releasing vascular endothelial growth factor (VEGF). Hence, levels of vWf and VEGF may correlate with cancer stage. The objectives are determine the impact of surgery and chemotherapy on vWf and VEGF in colorectal cancer (CRC) patients. **MATERIAL AND METHODS:** Twenty healthy volunteers (group 1), 14 patients with locally advanced CRC (group 2) and 12 patients with metastatic CRC (group 3) were enrolled. Blood samples were taken at recruitment in group 1, and before and after surgery and chemotherapy in groups 2 and 3, respectively. Blood levels of vWf, VEGF, platelet count, C-reactive protein (CRP), ceruloplasmin and carcinoembryonic antigen (CEA) were measured. **RESULTS:** At baseline, group 3

showed higher concentrations of vWf than the other groups ($p < 0.05$). In group 2, vWf became elevated 40% post-surgery ($p = 0.016$), independently of changes in CRP or ceruloplasmin. In group 3, chemotherapy caused a 42% reduction in VEGF ($p = 0.015$). **CONCLUSIONS:** There was a strong correlation between higher vWf levels and more advanced CRC stage at diagnosis. These levels were elevated post-surgery in patients with locally advanced CRC. Chemotherapy significantly decreased VEGF in metastatic CRC patients before CEA showed any significant change.

Goldfarb, Y. and S. Ben-Eliyahu (2006). "Surgery as a risk factor for breast cancer recurrence and metastasis: mediating mechanisms and clinical prophylactic approaches." *Breast Dis* 26: 99-114.

Surgical resection of the primary tumor is a necessary and effective treatment for breast cancer patients. For various reasons discussed, we believe that the short postoperative period is critical for eliminating minimal residual disease (MRD), thus markedly impacting long term survival. Unfortunately, both animal and human studies have shown that surgery induces suppression of anti-metastatic cell-mediated immunity (CMI) at this critical period, which is suggested to worsen patients' prognosis. In this review we examine different aspects of the surgical procedure that cause immunosuppression (e.g., anesthesia and tissue damage), discuss their mediating humoral and cellular mechanisms, and suggest prophylactic interventions feasible in cancer patients to avoid postoperative suppression of CMI. The use of the suggested interventions has been shown to significantly reduce postoperative metastasis in animal models, including mammary adenocarcinoma, and initial data suggest similar efficacy in breast cancer patients. We believe that our recommended prophylactic interventions can easily be applied by health-care practitioners and hold promise in reducing long-term recurrence and metastasis in cancer patients.

Gonzalez-Aragonese, F., N. Moreno-Mata, et al. (2009). "Lung cancer surgery in the elderly." *Crit Rev Oncol Hematol* 71(3): 266-71.

Non-small cell lung cancer (NSCLC) is a typical disease of the elderly, and is becoming increasingly more common as a result of the gradual aging of the population. Although patient age is known to be an independent prognostic factor of postoperative survival, lung resection should not be denied on the basis of age alone. In patients of this kind, careful evaluation and selection is very important. In early-stage NSCLC, surgery is the treatment of choice. In the advanced stages of the

disease treatment usually comprises primary radiotherapy or combined radio-chemotherapy. Preoperative preparation and postoperative care are very important in chest surgery, and particularly in elderly patients. The 5-year survival rate in octogenarians exceeds 40%, but is much lower in pneumonectomized patients (close to 10%). In conclusion, elderly patients should be offered the best treatment possible, bearing in mind that surgery offers the best results when the disease is resectable.

Graham, P. H., S. K. Vinod, et al. (2006). "Stage I non-small cell lung cancer: results for surgery in a patterns-of-care study in Sydney and for high-dose concurrent end-phase boost accelerated radiotherapy." *J Thorac Oncol* **1**(8): 796-801.

PURPOSE: To review results of resection or radical radiotherapy in Sydney to inform patients contemplating treatment options for early-stage non-small cell lung cancer (NSCLC). **METHODS AND MATERIALS:** Sixty-eight resected pathologic stage I patients were identified from a patterns-of-care (POC) study of all 1993 and 1996 NSCLC patients treated at the South Western Sydney Area Health Service and the Northern Sydney Area Health Service. These were compared with 39 clinical stage I patients treated by modern radiotherapy using an accelerated high-dose technique at St George Hospital (SGH). **RESULTS:** Resected POC patients achieved a median survival rate of 67 months and a 5-year survival rate of 54% (95% CI, 40-66%). SGH radiotherapy patients achieved a median survival rate of 43 months and a 5-year survival rate of 30% (95% CI, 13-48%). On multivariate analysis, the only significant factor is performance status, which may reflect comorbidity burden. Cancer-specific 5-year survival rates for surgery (59% [44-71%]) and for radiotherapy (53% [28-72%]) are not significantly different. **CONCLUSIONS:** Modern radiotherapy is a reasonable option for patients to consider for stage I NSCLC and is recommended for medically inoperable patients rather than supportive care or observation.

Greenberg, R., Y. Barnea, et al. (2003). "Detection of hepatocyte growth factor/scatter factor receptor (c-Met) and MUC1 from the axillary fluid drainage in patients after breast cancer surgery." *Isr Med Assoc J* **5**(9): 649-52.

BACKGROUND: Drains are inserted in the dissected axilla of most patients during surgery for breast cancer. **OBJECTIVE:** To evaluate the presence and prognostic value of MUC1 and Met-hepatocyte growth factor/scatter factor in the axillary drainage of these patients. **METHODS:** The study group included 40 consecutive patients with invasive ductal carcinoma of the breast who were suitable for breast-

conserving treatment; 20 malignant melanoma patients found to have negative axillary sentinel lymph node served as the control group. The output of the drains, which had been placed in the axilla during operation, was collected, and the presence of MUC1, Met-HGF/SF and beta-actin were assessed in the lymphatic fluid by reverse transcription-polymerase chain reaction assays. The data were compared to the pathologic features of the tumor and the axillary lymph nodes, and to the estrogen and progesterone receptors status. **RESULTS:** RT-PCR assays of the axillary lymphatic drainage were positive for MUC1 and Met-HGF/SF in 15 (37.5%) and 26 (65%) of the patients, respectively. Patients in whom MUC1 and Met-HGF/SF were not found in the axillary fluid had smaller tumors and less capillary and lymphatic invasion, compared to patients with positive assays ($P < 0.0$ for all these comparisons). The lymph nodes were negative for metastases in all patients with negative assays ($P < 0.001$). The presence of MUC1 and Met-HGF/SF showed negative correlations with the estrogen and progesterone receptors ($P < 0.05$). **CONCLUSION:** MUC1 and Met-HGF/SF can be detected in the axillary fluids of patients with breast cancer. The expression of both tumor markers in the axillary drainage is strongly associated with unfavorable tumor features and can be used as a prognostic factor.

Guller, U., P. Zajac, et al. (2002). "Disseminated single tumor cells as detected by real-time quantitative polymerase chain reaction represent a prognostic factor in patients undergoing surgery for colorectal cancer." *Ann Surg* **236**(6): 768-75; discussion 775-6.

OBJECTIVE: To evaluate the clinical relevance of real-time quantitative polymerase chain reaction (qPCR) detection of CEA and CK20 transcripts, as potentially related to tumor cell dissemination, in blood and peritoneal lavage from patients undergoing surgery for colorectal cancer. **SUMMARY BACKGROUND DATA:** Dissemination of single colorectal cancer cells in the peritoneal cavity, as well as in tumor drainage and peripheral blood vessels, might play a role in the metastasis process, thus affecting the clinical course. However, this phenomenon needs further elucidation. **METHODS:** In a prospective study the authors evaluated the potential of qPCR in the detection of CEA and/or CK20 transcripts in the peritoneal lavage fluid and in the peripheral and mesenteric venous blood of 39 patients undergoing curative resection for colorectal cancer. Peritoneal lavage and peripheral blood was sampled before and after tumor resection; mesenteric venous blood was sampled from the major tumor-draining vein immediately before clamping. After RNA extraction and reverse transcription, qPCR

was performed using specific cDNA primers and probes for CEA and CK20. The dichotomous results from the qPCR were used as a predictor along with other covariates in Cox proportional hazard regression models of long-term outcome (disease-free survival and overall survival). RESULTS: Of 39 patients, 11 were positive. The median follow-up at analysis was 31 months for all patients. The dichotomous qPCR covariate was significant, with $P = .001$ and $.0035$ for disease-free survival and overall survival, respectively, in the proportional hazard regression models with only qPCR. In seven patients, disseminated colorectal cancer cells were found in the peritoneal lavage fluid but not in blood specimens; five of these patients (71%) had recurrence. CONCLUSIONS: These data suggest that detection of mRNA coding for CEA and/or CK20 using qPCR has potential clinical utility as a prognostic marker and should be evaluated in larger clinical studies. Identification of patients at high risk for metastatic disease after curative resection of colorectal cancer might be improved by analyzing peritoneal lavage specimens in addition to blood samples. This is based on the observation that in more than half of qPCR-positive patients, disseminated colorectal cancer cells were detected in peritoneal lavage specimens but not in blood samples, and that 71% of them had recurrence.

Gunther, K., O. Dworak, et al. (2002). "Prediction of distant metastases after curative surgery for rectal cancer." *J Surg Res* **103**(1): 68-78.

BACKGROUND: This study was performed to define selection criteria for adjuvant therapy in rectal cancer. MATERIALS AND METHODS: An immunohistochemical analysis using nine monoclonal antibodies against CEA, CD15s, CD44v6, DCC, E-cadherin, EGF-R, NM23, PAI-1, and P53 was performed on paraffin sections of two matched (age, gender, UICC stage [I-III], year of operation [1982-1991]) groups of patients ($n = 2 \times 64$) with rectal carcinoma curatively treated by surgery alone. The two groups differed only with regard to metachronous distant metastatic spread. In order to exclude the influence of surgery, all patients had to meet the selection criterion "free of locoregional disease." Follow-up was prospective (median 80 months). Conventional staining procedures and immunohistochemical evaluation were used. Tumor grading and lymphatic and extramural venous invasion were also investigated. Analysis was performed with Fisher's exact test and Kaplan-Meier estimates of disease-free survival (log rank). The Cox model was used for multivariate analysis. RESULTS: In univariate analysis only grading ($P < 0.001$) and extramural venous invasion ($P < 0.001$) correlated

significantly with metachronous metastases. In multivariate analysis, beside grading ($P = 0.010$) and extramural venous invasion ($P = 0.011$), CD15s ($P = 0.042$) was also of significance. All other immunohistochemical markers failed. CONCLUSIONS: The histopathological parameters grading and extramural venous invasion appear to be acceptable predictors of metachronous distant spread in curatively resected rectal cancer. In contrast to the immunohistochemical markers, grading seems to better reflect the individual tumor phenotype and its behavior.

Haraguchi, S., K. Koizumi, et al. (2004). "Postoperative respiratory complications of video-assisted thoracic surgery for lung cancer." *J Nippon Med Sch* **71**(1): 30-4.

PURPOSE: We analyzed the risk factors predisposing patients to develop postoperative respiratory complications (PRCs) in VATS lobectomy and segmentectomy for lung cancer, retrospectively. METHODS: Both univariate and multivariate analyses of PRCs were performed in seventy-five patients who had undergone VATS lobectomy and segmentectomy for lung cancer from November 1994 to December 2000. RESULTS: Univariate analysis of the development of PRCs revealed that the significant risk factors were age, ppo%VC, ppo%FEV, ppoFEV, poor pulmonary function, and duration of surgery. Multivariate logistic regression test in regard to the development of PRCs revealed that duration of surgery was the most significant risk factor. On the basis of the receiver operator characteristic analysis, duration of surgery more than 297 min had a sensitivity of 70% and a specificity of 66% for the development of PRCs. CONCLUSIONS: The duration of surgery should be less than five hours not to lose advantages of VATS lobectomy and segmentectomy. Therefore, if the duration of surgery is more than five hours for any reasons, conversion to limited thoracotomy or muscle-sparing methods is recommended.

Harter, P., M. Hahmann, et al. (2009). "Surgery for recurrent ovarian cancer: role of peritoneal carcinomatosis: exploratory analysis of the DESKTOP I Trial about risk factors, surgical implications, and prognostic value of peritoneal carcinomatosis." *Ann Surg Oncol* **16**(5): 1324-30.

BACKGROUND: Almost all retrospective trials pointed out that a benefit of surgery for recurrent ovarian cancer may be limited to patients in whom a macroscopic complete resection could be achieved. Peritoneal carcinomatosis has been reported to be either a negative predictor for resectability or a negative prognostic factor, or both. The role of

peritoneal carcinomatosis in a multicenter trial was investigated. **METHODS:** Exploratory analysis of the DESKTOP I trial (multicenter trial of patients undergoing surgery for recurrent ovarian cancer, 2000 to 2003). **RESULTS:** A total of 125 patients (50%) who underwent surgery for recurrent ovarian cancer had peritoneal carcinomatosis. Univariate analyses showed worse overall survival for patients with peritoneal carcinomatosis compared with patients without carcinomatosis ($P < .0001$). Patients with and without peritoneal carcinomatosis had a complete resection rate of 26% and 74%, respectively ($P < .0001$). This corresponded with the observation that patients with complete resection had a better prognosis than those with minimal residual disease of 1 to 5 mm, which commonly reflects peritoneal carcinomatosis ($P = .0002$). However, patients who underwent complete resection, despite peritoneal carcinomatosis, had a 2-year survival rate of 77%, which was similar to the 2-year survival rate of patients with completely debulked disease who did not have peritoneal carcinomatosis (81%) ($P = .96$). Analysis of prognostic factors did not show any independent effect of peritoneal carcinomatosis on survival in patients who underwent complete resection. **CONCLUSIONS:** Peritoneal carcinomatosis was a negative predictor for complete resection but had no effect on prognosis if complete resection could be achieved. Improving surgical skills might be one step to increase the proportion of patients who might benefit from surgery for recurrent disease.

Hartgrink, H. H., H. J. Bonenkamp, et al. (2000). "Influence of surgery on outcomes in gastric cancer." Surg Oncol Clin N Am **9**(1): 97-117, vii-viii.

Surgery is the only possible curative treatment for gastric cancer. Although outcomes over the years have improved, there are still many controversies in the treatment of gastric cancer. One highly controversial topic is the extent of the operation. Results of recently performed large randomized studies may cause some policies to change. This article addresses the influence of surgery on outcomes of D1-D2 dissections, total versus subtotal gastrectomy, and pancreas and spleen resection and staging. Furthermore, several aspects of patient selection, the surgeon as a prognostic factor, noncurative treatment, and chemotherapy are discussed.

Hashemi, E., A. Kaviani, et al. (2004). "Seroma formation after surgery for breast cancer." World J Surg Oncol **2**: 44.

BACKGROUND: Seroma formation is the most frequent postoperative complication after breast

cancer surgery. We carried out a study to investigate the effect of various demographic, clinical and therapeutic variables on seroma formation. **PATIENTS AND METHODS:** A retrospective cross sectional study of patients who underwent surgical therapy for breast cancer with either modified radical mastectomy (MRM) or breast preservation (BP) was carried out. The demographic data and clinical information were extracted from case records. Seroma formation was studied in relation to age, type of surgery, tumor size, nodal involvement, preoperative chemotherapy, surgical instrument (electrocautery or scalpel), use of pressure garment, and duration of drainage. The multiple logistic regression analysis was performed to estimate odds ratios. **RESULTS:** A total of 158 patients with breast cancer were studied. The mean age of the patients was 46.3 years (SD +/- 11.9). Seventy-three percent underwent modified radical mastectomy and the remaining 27% received breast preservation surgery. Seroma occurred in 35% of patients. In multivariate logistic regression analysis an association of postoperative seroma formation was noted with modified radical mastectomy (OR = 2.83, 95% CI 1.01-7.90, $P = 0.04$). No other factor studied was found to significantly effect the seroma formation after breast cancer surgery. **CONCLUSION:** The findings suggest that the type of surgery is a predicting factor for seroma formation in breast cancer patients.

Hashiguchi, Y., T. Sekine, et al. (1999). "Intraoperative irradiation after surgery for locally recurrent rectal cancer." Dis Colon Rectum **42**(7): 886-93; discussion 893-5.

PURPOSE: This study retrospectively evaluated the effects of intraoperative electron beam irradiation on patients with locally recurrent (pelvic) rectal cancer. **METHODS:** From November 1, 1975, to December 31, 1997, 51 patients underwent surgery for locally recurrent rectal or rectosigmoid cancer, and 27 patients received intraoperative electron beam irradiation. The intraoperative electron beam irradiation dose was 15 to 30 Gy. Kaplan-Meier survival estimates at three and five years were analyzed for the 47 patients who recovered postoperatively. **RESULTS:** Statistically significant factors related to survival included intraoperative electron beam irradiation vs. no intraoperative electron beam irradiation ($P=0.0007$), amount of residual tumor (slight vs. gross; $P=0.0022$), and symptom status ($P=0.0024$). Factors not associated with survival included distant metastases at reoperation, type of surgery for the recurrent tumor, external beam irradiation, pathologic grade, age, and gender. Surgical resection without intraoperative electron beam irradiation resulted in three-year and

five-year survival rates of 5 and 0 percent, respectively. For patients who received intraoperative electron beam irradiation, the three-year survival rate was 43 percent and five-year survival rate was 21 percent. Intraoperative electron beam irradiation was a statistically significant factor related to survival in patients with and without distant metastasis ($P=0.04$ and $P=0.0035$, respectively), with slight residual tumor ($P=0.0003$), or with palliative surgery ($P=0.0276$). **CONCLUSION:** The trends seen in resection with intraoperative electron beam irradiation are encouraging with regard to improvements in survival as compared with studies not using intraoperative electron beam irradiation treatment.

Higashiyama, M., K. Kodama, et al. (2003). "Surgery for pulmonary metastases from colorectal cancer: the importance of prethoracotomy serum carcinoembryonic antigen as an indicator of prognosis." *Jpn J Thorac Cardiovasc Surg* **51**(7): 289-96.

OBJECTIVE: Several investigators have analyzed prognostic factors of surgical treatment for pulmonary metastases from colorectal cancer, but the results remain inconclusive. This study was performed to determine the prognostic implications of the prethoracotomy serum level of carcinoembryonic antigen (CEA) in relation to the postthoracotomy recurrent pattern among patients with this disease. **METHODS:** A retrospective analysis of prognostic factors was undertaken in 100 patients who had consecutively undergone initial surgical resection for pulmonary metastases of colorectal origin. **RESULTS:** The overall 3- and 5-year survival rates were 62.2% and 49.4%, respectively. Univariate analysis revealed that the prethoracotomy serum CEA level and operative curability were strongly associated with prognosis, while in multivariate analysis, only the prethoracotomy serum CEA level was a significant prognostic indicator. Patients with a high level of prethoracotomy serum CEA more frequently exhibited recurrence in extrathoracic sites, especially in the brain. **CONCLUSION:** Before thoracotomy for pulmonary metastases from colorectal cancer, the serum CEA level was the most useful prognostic factor. Patients with elevated serum CEA level should undergo a careful prethoracotomy systemic survey and postthoracotomy follow-up for extrathoracic metastases, in particular brain metastases, and an appropriate combined therapeutic modality should be considered.

Hornbrey, E., C. Han, et al. (2003). "The relationship of human wound vascular endothelial growth factor (VEGF) after breast cancer surgery to circulating

VEGF and angiogenesis." *Clin Cancer Res* **9**(12): 4332-9.

PURPOSE: The assessment of locally produced proangiogenic cytokines may be an indicator of the stromal response of an individual to wounding or cancer. This study describes the profile of VEGF production in human surgical wounds in both breast cancer patients and reduction mammoplasty controls, and assesses the changes in systemic VEGF levels and platelet profiles perioperatively. **EXPERIMENTAL DESIGN:** Perioperative surgical wound fluid samples and blood were collected daily up to 13 days from 52 patients undergoing breast cancer surgery (local tumor burden), delayed breast reconstruction (previous tumor burden but none present at the time of surgery), or breast reduction surgery (noncancer control). Samples were analyzed for VEGF by ELISA. **RESULTS:** VEGF levels in surgical wound fluid were lowest on day 1 followed by an early peak on day 2 of >900% the corresponding serum value. There was a trend in the VEGF response at the day-2 time point: reduction > reconstruction > cancer subgroups, with a significant difference between the reduction and cancer subgroups ($P < 0.05$). There was a 20-30-fold variation in the response between days 1 and 2, and within subgroups. **CONCLUSIONS:** Much higher local concentrations of angiogenic factors may need to be antagonized for effective antiangiogenic therapy, and there is great heterogeneity between patients. The small peripheral blood changes compared with large tumor fluid changes show that there is a tissue barrier. This has relevance for design of antiangiogenic therapy trials, highlighting the need for individually tailored treatment with biologically targeted interventions.

Hotokezaka, M., S. Jimi, et al. (2008). "Factors influencing outcome after surgery for stage IV colorectal cancer." *Surg Today* **38**(9): 784-9.

PURPOSE: According to the classification system of the Japanese Society for Cancer of the Colon and Rectum, Stage IV colorectal cancer is characterized by distant metastasis, which is defined by four factors: liver metastasis (H factor), metastasis to organs other than the liver (M factor), peritoneal dissemination (P factor), and distant lymph node metastasis (N factor). We conducted this study to investigate the postsurgical prognosis of patients with Stage IV colorectal cancer (CRC), in reference to each of these four factors. **METHODS:** We analyzed the medical records of 73 patients who underwent surgery for Stage IV CRC at our hospital between 1991 and 2001. **RESULTS:** Univariate analysis revealed that P0 or P1 CRC ($P < 0.001$), absence of the M factor ($P = 0.024$), well or moderately differentiated

adenocarcinoma ($P < 0.001$), resection of the primary tumor ($P < 0.001$), and curability B surgery ($P < 0.0001$) were associated with a better prognosis than other types of Stage IV CRC. Multivariate analysis revealed that tumor differentiation and surgical curability affected cancer-specific survival significantly. **CONCLUSION:** Surgery with curative intent should be considered for patients with Stage IV CRC defined by the P1 factor or H factor.

Hsu, W. C., N. N. Chung, et al. (2009). "Comparison of surgery or radiotherapy on complications and quality of life in patients with the stage IB and IIA uterine cervical cancer." *Gynecol Oncol* **115**(1): 41-5.

OBJECTIVES: To compare the long-term complications and quality of life of patients with stage IB and stage IIA uterine cervical carcinoma treated by surgery or radiotherapy. **METHODS:** From August 2003 to May 2004, 202 patients with uterine cervical carcinoma were treated with surgery or radiotherapy at two institutions and were enrolled in this study upon follow-up at least 2 years post treatment. All patients completed the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire and complications Questionnaire. **RESULTS:** Constipation ($p < 0.001$), flushing ($p < 0.001$), dysuria ($p < 0.001$), urinary incontinence ($p < 0.01$), dysparia ($p < 0.05$) and vaginal dryness ($p < 0.05$) were statistically higher in the surgery treated group, while diarrhea ($p < 0.001$), bloody stools ($p < 0.001$) and abdominal pain ($p < 0.01$) were higher in the radiotherapy group. Using factor analysis and introducing personal conditioned variables, pelvic neural dysfunction was significantly higher in surgery group and intestinal dysfunction was higher in radiotherapy group. There was no difference in sexual dysfunction between these two modalities. Comparison of EORTC QLQ-C30 showed that the majority of issues had minimal differences between these two treatment modalities, except social functioning ($p < 0.05$; higher in radiotherapy group), constipation ($p < 0.001$; higher in surgery group) and diarrhea ($p < 0.01$; higher in radiotherapy group). **CONCLUSIONS:** In early stage uterine cervical cancer patients, surgery or radiotherapy resulted in different complications, whereas long-term quality of life showed few differences between these two different modalities. These data were helpful for physicians in regards to the changes of patients, and moreover, for rehabilitation and supportive care of the patients after treatment.

Ikeda, M., H. Furukawa, et al. (2002). "Surgery for gastric cancer increases plasma levels of vascular endothelial growth factor and von Willebrand factor." *Gastric Cancer* **5**(3): 137-41.

BACKGROUND: Angiogenesis and hemostatic activation are important factors in tumor progression and metastasis. Because surgical intervention induces tissue hypoxia and hemostatic activation, we analyzed the effect of gastric surgery on the plasma concentrations of vascular endothelial growth factor (VEGF), soluble P-selectin (sP-selectin), and von Willebrand factor (vWf). **METHODS:** Plasma VEGF, sP-selectin, and vWf concentrations were measured in 14 patients with gastric cancer before operation and on postoperative day 1 (POD 1). Correlations between disease stage and the effect of surgical intervention were analyzed. **RESULTS:** The plasma concentrations of these three factors did not correlate with the disease stage. Plasma levels of sP-selectin did not change after operation (before surgery, 87.6 +/- 34.1 ng/ml; on POD 1, 101.1 +/- 48.1 ng/ml; $P = 0.123$). Plasma VEGF and vWf concentrations were significantly elevated on POD 1 (VEGF, 33.3 +/- 20.5 pg/ml before surgery and 61.9 +/- 35.6 pg/ml on POD 1; $P = 0.0013$; vWf, 164 +/- 31.1% before surgery and 211.1 +/- 66.1% on POD 1; $P = 0.027$). **CONCLUSION:** Because VEGF and vWf are involved in angiogenesis, tumor-platelet adhesion, and tumor-endothelial cell adhesion, surgical intervention could influence tumor growth and metastasis.

Inoue, K., Y. Nakane, et al. (2002). "Histopathological grading does not affect survival after R0 surgery for gastric cancer." *Eur J Surg Oncol* **28**(6): 633-6.

AIM: It is unclear whether Histopathological Grading (UICC, TNM Classification) affects survival after resection for gastric cancer. **METHODS:** To investigate the prognostic significance of Histopathological Grading after gastrectomy, 1455 patients who underwent gastric resection for gastric adenocarcinoma were reviewed. **RESULTS:** The R0 (UICC, R Classification) resection rate was inversely correlated with the grade (86.5% for Grade 1, 79.7% for Grade 2 and 69.2% for Grade 3) and the R1 and R2 resection rates increased with the grade. The Histopathological Grading did not influence survival in the 1119 patients who underwent R0 resection (71.0% for Grade 1, 65.7% for Grade 2 and 66.7% for Grade 3). When multivariate analysis was performed for the 1119 cases undergoing R0 resection, the Histopathological Grading was not a determinant prognostic factor. **CONCLUSION:** We conclude that the UICC Histopathological Grading affects R0 resection rates, but does not affect survival independently.

Ishikawa, H., Y. Suzuki, et al. (2000). "Intraoperative radiotherapy and bypass surgery for unresectable

pancreatic cancer." *Hepatogastroenterology* **47**(34): 1151-5.

BACKGROUND/AIMS: Conflicting results have been reported concerning the usefulness of radiotherapy for unresectable pancreatic cancer. We evaluated the clinical efficacy of intraoperative radiotherapy and/or external beam radiotherapy in combination with bypass surgery. **METHODOLOGY:** Twenty-six patients with unresectable pancreatic cancer (16 in Stage II-III and 10 in Stage IV) were treated with intraoperative radiotherapy plus external beam radiotherapy (16 patients) or intraoperative radiotherapy alone (10 patients). The dose of intraoperative radiotherapy was either 25 or 30 Gy and the external beam radiotherapy dose was 31-60 Gy. The feasibility and clinical outcome were analyzed. **RESULTS:** The median survival time for Stage II-III and Stage IV were 11.5 and 6.5 months, respectively. The difference between Stage II-III and Stage IV in survival patterns was statistically significant ($P < 0.05$). For Stage II-III patients, the survival curves between the groups of intraoperative radiotherapy plus external beam radiotherapy and intraoperative radiotherapy alone were not significantly different, and only performance status was a significant factor in the prognosis ($P < 0.05$). Gastrointestinal bleeding was noted in 8%, but did not occur in the patients treated with an external beam radiotherapy dose less than 50 Gy. Palliative radiation was successfully performed to relieve pain, jaundice and appetite-loss and to shorten the hospital stay. **CONCLUSIONS:** The combination therapy with intraoperative radiotherapy and bypass surgery is considered to be tolerable and effective for unresectable pancreatic cancer, and also may improve the quality of life of the patients.

Ishikawa, K., Y. Hashiguchi, et al. (2003). "Extranodal cancer deposit at the primary tumor site and the number of pulmonary lesions are useful prognostic factors after surgery for colorectal lung metastases." *Dis Colon Rectum* **46**(5): 629-36.

PURPOSE: This study was undertaken to identify prognostic factors that can be used to predict prognosis after surgery for lung metastases from colorectal carcinoma. **METHODS:** We reviewed retrospectively the clinical course of 37 patients who underwent surgical resection of primary colorectal cancer and metastatic lung disease at the National Defense Medical College Hospital between September 1986 and July 1999. We analyzed the prognostic factors with special reference to the clinicopathologic factors of primary tumors. **RESULTS:** Multivariate analysis indicated that the existence of an extranodal cancer deposit in the primary lesion (hazard ratio = 4.55, $P = 0.009$) and

three or more lung metastases (hazard ratio = 2.9, $P = 0.04$) were significant indicators for poor prognosis. We divided the patients into two groups: Group A ($n = 12$) had neither of these two parameters, and Group B ($n = 25$) comprised all other patients. This two-ranked classification was significantly related to both survival rates (3-year and 5-year survival rate, 90.9 and 90.9 percent in Group A and 16.1 and 8.1 percent in Group B, respectively; $P = 0.0003$) and disease-free survival after thoracotomy (3-year and 5-year disease-free survival rate, 52.9 and 39.7 percent in Group A and 5.3 and 5.3 percent in Group B, respectively; $P = 0.002$). **CONCLUSION:** An extranodal cancer deposit at the primary tumor site is a new significant prognostic factor after resection of lung metastases from colorectal cancer. A two-ranked classification by extranodal cancer deposit and the number of pulmonary lesions can provide useful prognostic information for the treatment of lung metastasis. Surgical resection of pulmonary metastasis is expected to be very useful for patients in Group A.

Isohata, N., Y. Naritaka, et al. (2008). "Occult lung cancer incidentally found during surgery for esophageal and gastric cancer: a case report." *Anticancer Res* **28**(3B): 1841-7.

A 70-year-old male was admitted to our hospital because of advanced esophageal squamous cell carcinoma and early gastric adenocarcinoma. A esophagectomy and partial gastrectomy with three-field lymph node dissection (neck, mediastinum and abdomen) was performed. Both tumors had lymph node metastases. In addition, three mediastinal lymph nodes (two subcarinal lymph nodes and a middle thoracic paraesophageal lymph node) were involved with adenocarcinoma. To elucidate whether they were metastases from the gastric cancer, an immunohistochemical analysis was performed. The cancer cells in these lymph nodes were positive for cytokeratin (CK) 7 and negative for CK 20, thus suggesting metastasis from a nondigestive organ. Interestingly, they were positive for thyroid transcription factor 1 (TTF-1), indicating metastasis from a lung cancer. Since the preoperative computed tomographic scan showed no evidence of lung cancer, a diagnosis of metastases from an occult lung cancer was finally recorded. Ten months after surgery, the patient was alive without a recurrence or the appearance of a lung cancer.

Iversen, L. H., S. Bulow, et al. (2008). "Postoperative medical complications are the main cause of early death after emergency surgery for colonic cancer." *Br J Surg* **95**(8): 1012-9.

BACKGROUND: Only a few small studies have evaluated risk factors related to early death

following emergency surgery for colonic cancer. The aim of this study was to identify risk factors for death within 30 days after such surgery. **METHODS:** Some 2157 patients who underwent emergency treatment for colonic cancer from May 2001 to December 2005 were identified from the national colorectal cancer registry. Thirty-day mortality rates were calculated and risk factors for early death were identified using logistic regression analysis. **RESULTS:** The overall 30-day mortality rate was 22.1 per cent. The strongest risk factor for early death was postoperative medical complications (cardiopulmonary, renal, thromboembolic and infectious), with an odds ratio of 11.7 (95 per cent confidence interval 8.8 to 15.5). Such complications occurred in 24.4 per cent of patients, of whom 57.8 per cent died. Other independent risk factors were age at least 71 years, male sex, American Society of Anesthesiologists grade III or more, palliative outcome, tumour perforation, splenectomy and adverse intraoperative surgical events. Postoperative surgical complications were noted in 20.4 per cent of the patients but had no statistically significant influence on mortality. **CONCLUSION:** Emergency surgery for colonic cancer is still associated with an increased risk of death. There is a need for a system providing increased safety in the perioperative period.

Iwasaki, A., T. Shirakusa, et al. (2004). "Results of video-assisted thoracic surgery for stage I/II non-small cell lung cancer." *Eur J Cardiothorac Surg* **26**(1): 158-64.

OBJECTIVE: The best indicators for VATS are not well known. Therefore, we review here a series of patients who underwent VATS lobectomy and segmentectomy at our hospital, and we attempt to identify the factors that influence the survival of VATS patients and the backgrounds of such patients. **METHODS:** A thoracoscopic curative approach was attempted in 140 patients (100 lobectomy, 40 segmentectomy) from January 1994 to December 2002. We retrospectively reviewed the VATS patients with non-small cell lung cancer (NSCLC). All patients were subject to lobectomy or segmentectomy, including dissection of hilar and mediastinal lymph nodes that were in pathological stage (p-Stage) I or II. Our VATS approach was a hybrid technique, employing three ports and a small (7 cm diameter) utility thoracotomy to allow access for the instrument and a view. **RESULTS:** The Kaplan-Meier probabilities of survival at 5 years were VATS, 77.3%. According to a univariate analysis of survival curves, the significant prognostic factors ($P < 0.05$) in the patients with VATS in p-Stage I and II were gender, type of histology, and T factor. In addition, the grades of differentiation, surgical procedure

(lobectomy vs. segmentectomy), and extent of metastasis to the hilar lymph node (N0 vs. N1) in VATS were not found to be significant prognostic factors. A multivariate prognostic factor in VATS showed that the histologic cell type, gender, and T factor were predominant. All of the VATS cases that included these three favorable factors (adenocarcinoma, T1, female) were alive. **CONCLUSION:** Stringent selection of candidates for VATS in NSCLC at pathological stages I and II could be an acceptable and valuable approach.

Iwata, T., K. Inoue, et al. (2007). "Factors predicting early postoperative liver cirrhosis-related complications after lung cancer surgery in patients with liver cirrhosis." *Interact Cardiovasc Thorac Surg* **6**(6): 720-30.

We aimed to determine the factors predicting liver cirrhosis-related complications in the early postoperative period after lung cancer surgery in patients with liver cirrhosis. We retrospectively reviewed the medical records of patients who underwent curative surgery for primary lung cancer in our institute from January 1990 to March 2007, finding 37 cases with comorbid liver cirrhosis. These patients were divided into two groups, according to whether liver failure, bleeding, and critical infection had occurred postoperatively. Various clinical parameters were analyzed statistically between the bigeminal groups. Liver cirrhosis-related complications occurred in seven of the 37 patients (18.9%). Transient liver failure occurred in two patients (5.4%) after pulmonary resection. Acute intrathoracic bleeding occurred in four cases (10.8%). Two patients died (5.4%) in both cases due to sepsis. Preoperative total bilirubin ($P < 0.05$), and indocyanine green retention rate at 15 min ($P < 0.05$) were significantly higher in patients with liver failure. Only serum value of total bilirubin was an independent risk factor ($P < 0.05$) by multivariate analysis. In predicting death from infection, only preoperative nutritional status was a significant risk factor ($P < 0.05$). To avoid postoperative cirrhosis-related complications, preoperative preparation to improve their liver function and nutrition status is essential.

Jaklitsch, M. T., A. Pappas-Estocin, et al. (2004). "Thoracoscopic surgery in elderly lung cancer patients." *Crit Rev Oncol Hematol* **49**(2): 165-71.

Age is a recognized risk factor for death after thoracotomy in elderly patients with lung cancer. Among other factors, the genesis of this risk is the physiologic debilitation that occurs after division of the intrathoracic respiratory muscles during thoracotomy, as well as the loss of lung tissue after lung resection. Recent advances in video-assisted

thoracic surgery (VATS) techniques provide an alternative to standard thoracotomy in elderly lung cancer patients, resulting in decreased recovery times and fewer perioperative complications. Likewise, smaller lung resections (VATS-guided limited wedge resection versus lobectomy with thoracotomy) can be adequate oncologic procedures in patients with a limited life expectancy but resectable disease. We studied these alternative procedures in a cohort of thoracic surgical patients at the Brigham and Women's Hospital in Boston, MA. Proposed investigations of the psychosocial implications of thoracic surgery in the elderly, irrespective of the safety of these maneuvers, are addressed.

Jakobsen, E., T. Palshof, et al. (2009). "Data from a national lung cancer registry contributes to improve outcome and quality of surgery: Danish results." *Eur J Cardiothorac Surg* **35**(2): 348-52; discussion 352.

OBJECTIVE: In 1998 The Danish Lung Cancer Group published the first edition of guidelines for diagnosis and treatment of lung cancer. A national registry was implemented in the year 2000 with the primary objective to monitor the implementation of these guidelines and nationwide to secure and improve the quality of the clinical management of lung cancer. The results of this effort are reported with special focus on surgery. **METHODS:** Through systematic nationwide registration a total of 24,153 patients have been included in the period 2000-2007. Indicators describing staging, surgical procedures, complications and survival have been registered in those 5007 patients who underwent surgery. Using an Internet based closed circle with a safe program (firewall and encryption) more than 95% of this subgroup of patients have been notified. Each year the results have been audited locally, regionally and nationally and improvements have been proposed, implemented, monitored and consecutively evaluated by the audit-plenary. **RESULTS:** This strategy has been a contributory factor to significantly improve the results in mortality, survival and surgical procedures. Thus, the 30-days mortality following surgery has decreased from 5.2% to 3.6% and survival has increased from an overall 1- and 2-year survival of 69% and 50% in 2000 to 77% and 60% in 2007, respectively. A number of other key indicators were also improved: the lobectomy rate has increased from 54% to 73% and the pneumonectomy rate has decreased from 23% to 11%. The proportion of patients having surgery within 14 days from referral has increased from 69% to 87%. **CONCLUSIONS:** Establishment of a national lung cancer group with the primary tasks to implement updated national guidelines and to secure valid registration of clinical baseline data and quality parameters has been a

contributory factor to significantly improve the quality of lung cancer surgery.

Jereczek-Fossa, B., A. Badzio, et al. (2000). "Recurrent endometrial cancer after surgery alone: results of salvage radiotherapy." *Int J Radiat Oncol Biol Phys* **48**(2): 405-13.

PURPOSE: Postoperative irradiation of endometrial cancer patients decreases the risk of local recurrence but is associated with a number of long-term sequelae. In a proportion of patients, no immediate postoperative radiotherapy is applied and this treatment is introduced only at relapse. The aim of our study was to assess the long-term results of salvage radiotherapy in previously nonirradiated endometrial cancer patients who developed local recurrence, and to evaluate the impact of patient- and treatment-related factors on treatment efficacy. **METHODS AND MATERIALS:** We performed a detailed retrospective analysis of 73 endometrial cancer patients given radiotherapy for local recurrence after the initial surgery only. The mean age at diagnosis of the recurrence was 63 years (range, 39-78 years). Median time to recurrence was 11 months (range, 1-19 months). All recurrences were staged with the use of Perez modification of the International Federation of Gynecology and Obstetrics (FIGO) staging system for primary vaginal carcinoma. There were five (7%) Stage I patients, 43 (59%) Stage II patients, and 25 (34%) Stage III patients. Forty-four patients (60%) received both external beam irradiation (EBRT) and endovaginal brachytherapy (BRT), 17 (23%) received only BRT, and 12 (17%) received only EBRT. The mean total physical radiation dose was 75.9 Gy (range, 8-130 Gy), and the mean normalized total dose (NTD) calculated on the base of the linear-quadratic model was 86.6 Gy (range, 8.5-171.9 Gy). Median follow-up for alive patients was 8.8 years (range, 3-21 years). The impact of patient-, tumor-, and therapy-related factors on the treatment outcome was evaluated with the use of uni- and multivariate analyses. **RESULTS:** Three- and 5-year overall survival rates were 33% and 25%, respectively. In the univariate analysis, lower stage of recurrent disease ($p < 0.0005$), combined EBRT and BRT ($p = 0.027$), higher total radiation dose ($p = 0.031$), and higher NTD ($p = 0.006$) were significantly correlated with better survival. In the multivariate analysis, only stage of recurrent disease ($p < 0.005$) and high total dose ($p = 0.047$) were independently correlated with better survival. Lower FIGO stage of recurrence ($p = 0.023$) and higher total dose ($p = 0.005$) were also independently correlated with longer time to progression, whereas higher radiotherapy dose was the only factor correlated with better local control ($p = 0.029$). **CONCLUSIONS:** The efficacy of salvage

radiotherapy in endometrial cancer patients with local failure after previous surgery is limited. Factors determining treatment outcome include advancement of the tumor at relapse and radiotherapy dose.

Jestin, P., L. Pahlman, et al. (2008). "Risk factors for anastomotic leakage after rectal cancer surgery: a case-control study." *Colorectal Dis* 10(7): 715-21.

BACKGROUND: With introduction of the total mesorectal excision technique and preoperative radiotherapy in rectal cancer surgery, the local recurrence rate has decreased and the overall survival has improved. One drawback, however, is the high anastomotic leakage rate of approximately 10-18%. Male gender and low anastomoses are known risk factors for such leakage. The aim of this study was to identify potentially modifiable risk factors. **METHOD:** In a case-control study, data from the Swedish Rectal Cancer Registry (1995-2000) were analysed. Cases were all patients with anastomotic leakage after an anterior resection (n = 134). Two controls were randomly selected for each case. The medical records (n = 402) were checked against a study protocol. Due to incorrect recording two cases and 28 controls were excluded from further analyses. **RESULTS:** In the multivariate analysis significant risk factors were American Society of Anesthesiologists score > 2 [OR = 1.40 (95% CI 1.05-1.83)], preoperative radiotherapy [OR = 1.34 (95% CI 1.06-1.69)], intraoperative adverse events [OR = 1.85 (95% CI 1.32-2.58)], level of anastomosis <or= 6 cm [OR = 1.39 (95% CI 1.01-1.90)] and severe bleeding [OR = 1.45 (95% CI 1.14-1.84)]. Diverting stoma protected from leakage [OR = 0.68 (95% CI 0.52-0.88)]. Male gender was a risk factor in the univariate but not in the multivariate analysis [OR = 1.30 (95% CI 1.04-1.63) and OR = 1.26 (95% CI 1.00-1.58), respectively]. Except for a protective stoma, none of the variables considered as possible targets for improvement, such as postoperative epidural anaesthesia, observation at intensive care unit for more than 24 h, and intraabdominal drainage, proved to be protective factors either in the univariate or in the multivariate analyses. **CONCLUSION:** The most important risk factors for leakage were adverse intraoperative events, low anastomoses and preoperative radiotherapy. A diverting stoma is protective and can reduce the consequences when leakage occurs. Further analyses with focus on the surgical technique and individual surgeon may be valuable in identifying targets for improvement.

Jiao, X., J. Sonett, et al. (2002). "Trimodality treatment versus surgery alone for esophageal cancer. A stratified analysis with minimally invasive

pretreatment staging." *J Cardiovasc Surg (Torino)* 43(4): 531-7.

BACKGROUND: Accurate pretreatment staging of esophageal cancer (EC) is important in the evaluation and comparison of results of different treatment modalities. Few studies using minimally invasive staging techniques for this purpose have been reported. We previously demonstrated the usefulness of the thoracoscopic/laparoscopic (Ts/Ls) technique in pretreatment staging of EC. This study was conducted to evaluate the impact of trimodality based on pretreatment Ts/Ls staging diagnosis on EC. **METHODS:** A retrospective study was performed on 2 groups of EC patients. Group A (44 patients) underwent pretreatment Ts/Ls staging and had trimodality treatment. Preoperative therapy consisted of concurrent chemotherapy (5-FU + cisplatinum) and radiotherapy. Group B (33 patients) underwent surgery alone. The study focused on stratified comparison of patterns of recurrence and survival in different pretreatment surgical T, N, and TNM stage categories. **RESULTS:** The 3-year disease free survival of Group A was 40.8% with a median survival of 32.0 months, it was 43.6% with a median survival of 23.6 months in Group B. The difference was not significant (p=0.87). There was no difference in recurrence pattern between the 2 groups. Patients with squamous cell carcinoma in Group A had no local recurrence during the follow-up period while those in Group B had a high local recurrence rate of 40% (p<0.005). When stratified by T factor, patients with locally advanced T stage (T3-4) in Group A had a lower distant recurrence rate than their counterpart patients in Group B (9.1 vs 38.5%, p=0.03), they had a better survival but the difference was not significant (3-year disease free survival: 41.7 vs 17.9%, p=0.14). There were no significant differences in recurrence pattern and survival in different N categories and TNM stages between 2 groups. Multivariate analysis showed that only pretreatment surgical N status was an independent prognostic factor for the whole group (p=0.02). **CONCLUSIONS:** Pretreatment Ts/Ls staging can provide accurate staging information for EC patients. Trimodality treatment was successful in local control for patients with squamous cell carcinoma. It was effective in reducing distant recurrence and might prolong survival in patients with advanced T stages. Pretreatment lymph node status was the most important prognosticator regardless of treatment modality. Pretreatment pathological staging should be included in the future clinical trials on multimodality treatments in EC patients.

Jichen, Q. V., G. Chen, et al. (2009). "Risk factor comparison and clinical analysis of early and late

bronchopleural fistula after non-small cell lung cancer surgery." *Ann Thorac Surg* **88**(5): 1589-93.

BACKGROUND: We retrospectively analyzed risk factors for late bronchopleural fistula after non-small cell lung cancer (NSCLC) surgery and compared with those for early bronchopleural fistula. **METHODS:** In all, 6,239 patients with NSCLC who underwent surgery were studied, and clinical risk factors were examined by univariate and multivariate analysis. This study included 23 patients (0.38%) with late bronchopleural fistula and 43 patients (0.65%) with early bronchopleural fistula among all 6,239 patients. Follow-up data were recorded until December 2005 or until death. Statistical significance was calculated using the log rank test. **RESULTS:** By univariate analysis, patients with radiotherapy after operation, pneumonia after operation, pneumonectomy, and advanced age were related to higher risk of bronchopleural fistula. In the multiple logistic regression models, both pneumonia and operative procedure were among the independent risk factors of early and late bronchopleural fistula. Early bronchopleural fistula was observed primarily in the aged. Late bronchopleural fistula was associated with postoperative radiotherapy. The average intervals of bronchopleural fistula between pneumonectomy and lobectomy were significantly different. Compared with the mortality rate of late bronchopleural fistula (0%), the mortality rate of early bronchopleural fistula (11.6%) was significantly higher. **CONCLUSIONS:** There are both similarities and differences between the risk factors for early and late bronchopleural fistula. We should analyze the different reasons for the occurrence of bronchopleural fistula, and adopt different preventive measures. Different follow-up should be provided for the different operations.

Jin, J., Z. Liao, et al. (2004). "Induction chemotherapy improved outcomes of patients with resectable esophageal cancer who received chemoradiotherapy followed by surgery." *Int J Radiat Oncol Biol Phys* **60**(2): 427-36.

PURPOSE: To investigate the effect of induction chemotherapy (CHT) before trimodality therapy on the outcome of patients with resectable cancer of the esophagus. **METHODS AND MATERIALS:** This retrospective study included 81 consecutive patients with resectable cancer of the esophagus who received neoadjuvant chemoradiotherapy followed by esophagectomy between January 1990 and December 1998 (inclusive). Thirty-nine patients underwent chemoradiotherapy followed by esophagectomy (CHT/RT+S), 42 received additional induction CHT followed by CHT/RT+S (CHT+CHT/RT+S). Of the 81 patients, 47 were entered in institutional or national

prospective trials (6 in the CHT/RT+S and 41 in the CHT+CHT/RT+S group). Induction CHT consisted of three courses of 5-fluorouracil (5-FU), cisplatin, and paclitaxel given in 28-day cycles in 37 patients (88.1%). Concurrent CHT was 5-FU and platinum based. The median radiation dose for patients treated with CHT/RT+S was 30 Gy (range, 30-50.4 Gy) delivered in a median of 10 fractions (range, 10-28 fractions) and 45 Gy (range, 30-45 Gy) in a median of 25 fractions (range, 10-25 fractions) for patients treated with CHT+CHT/RT+S. Esophagectomy was performed 6-8 weeks after completion of concurrent chemoradiotherapy. Most patients underwent transthoracic esophagectomy (n = 66, 82.5%). **RESULTS:** The pretreatment characteristics were well balanced between the two groups except for age. The median follow-up time was 29 months (22 months for the CHT/RT+S group and 38.5 months for the CHT+CHT/RT+S group) for all patients and 49 months for living patients. The actuarial overall survival (OS), disease-free survival (DFS), locoregional control (LRC), and distant metastasis-free survival (DMFS) rate at 5 years for the entire group was 46%, 36.6%, 70.7%, and 53.2%, respectively. Statistically significant differences in the OS, DFS, and LRC rates between the two groups were detected. Specifically, the 5-year OS rate was 22.8% and 71.1% in the CHT/RT+S and CHT+CHT/RT+S group (p = 0.0001), respectively. The 5-year DFS rate was 27.6% and 56.6% in the CHT/RT+S and CHT+CHT/RT+S group (p = 0.003), respectively. The 5-year LRC rate was 64.2% and 85.6% in the CHT/RT+S and CHT+CHT/RT+S group (p = 0.007), respectively. The difference in the DMFS rate between the two groups was statistically significant, with a 2- and 5-year actuarial rate of 63.9% and 51.9%, respectively, in the CHT/RT+S group and 76.9% and 74.1%, respectively, in the CHT+CHT/RT+S group (p = 0.04). The statistically significant differences persisted when patients who received ≥ 45 Gy in each group were compared. Among those patients, the 5-year OS, DFS, LRC, and DMFS rates were 23.1%, 15.4%, 58.6%, and 39.2%, respectively, for those receiving CHT/RT+S, and 71.4% (p = 0.001), 55.8% (p = 0.0008), 84.6% (p = 0.005), and 77.3% (p = 0.009), respectively, for those receiving CHT+CHT/RT+S. The pathologic complete response (pCR) rate was greater in the CHT+CHT/RT+S group compared with in the CHT/RT+S group (p = 0.008). In univariate analysis, young age, good Karnofsky performance status, Stage II disease, total radiation dose, multiple drug regimen for concurrent CHT, pCR, R0 resection, distant disease progression, and CHT+CHT/RT+S treatment proved to be prognostic factors for OS. Lower esophageal/gastroesophageal junction tumor location,

pCR, R0 resection, and CHT+CHT/RT+S treatment were favorable prognostic factors for LRC. Neither the total radiation dose nor multiple drugs for concurrent CHT were negative prognostic factors for LRC. In multivariate analysis, pCR, R0 resection, and treatment with CHT+CHT/RT+S were independent positive predictive factors for OS, and distant recurrences were negative predictive factors for OS. R0 resection, CHT+CHT/RT+S treatment, and lower esophageal/gastroesophageal junction tumor location were positive predictive factors for LRC. The radiation dose was not identified as an independent prognostic factor for either OS or LRC in the multivariate analysis. Meaningful multivariate analysis could not be performed when the multiple drug variable was included in the model because of the small number of patients. CONCLUSION: Significantly greater LRC, DFS, OS, and DMFS were found in patients treated with CHT+CHT/RT+S compared with those treated with CHT/RT+S. The pCR rate was significantly higher in the CHT+CHT/RT+S group. Induction CHT was an independent favorable prognostic factor for both LRC and OS for the population included in this study. Our data suggest that a randomized trial comparing CHT+CHT/RT+S and CHT/RT+S is warranted to assess further the merits of this treatment in patients with this currently very lethal cancer.

Jobsen, J. J., J. van der Palen, et al. (2001). "The impact of age on local control in women with pT1 breast cancer treated with conservative surgery and radiation therapy." *Eur J Cancer* **37**(15): 1820-7.

The aim of the study was to evaluate the importance of young age with regard to local control in a prospective cohort of 1085 women with pathological T1 tumours treated with breast conservative treatment (BCT). Patients were divided into two age groups: 40 years or younger, 7.8%, and older than 40 years, 92.2%. With a median follow-up of 71 months, the local recurrence rate was 10.6% in women < or =40 years, and 3.7% in older women. The local recurrence-free survival (LRFS) was significantly different for the two age groups, respectively 89%, < or =40 years, and 97.6%, >40 years (P=0.0046). A separate analysis showed a significantly decreased LRFS for young women with a positive family history, 75.4% versus 98.4% 5-year LRFS for older women. A worse LRFS for young women with a negative lymph node status was also observed, respectively 84% versus 98% 5-year LRFS (both P<0.001). In a multivariate analysis, taking into account the pre-treatment and treatment factors, age < or =40 years, was the only significant predictor of a decreased LRFS. Thus, young age is an important factor in relation to local control. In a subset analysis,

this significant adverse effect of young age on outcome appears to be limited to the node-negative patients and those with a positive family history. To date, there is no evidence that young women with pT1 breast cancer, treated by mastectomy have an improved outcome when compared with those treated with conservative surgery and radiotherapy. Taking into account results from a subset analysis suggests that giving systemic therapy to a subgroup of women who are < or =40 years, node-negative and/or have a positive family history might give a better local control.

Kai, K., N. Arima, et al. (2009). "Pathological lymph node involvement at surgery is a significant predictive factor of recurrence in locally advanced breast cancer treated with concomitant epirubicin-docetaxel neoadjuvant chemotherapy: a cohort study." *Breast Cancer* **16**(1): 42-8.

BACKGROUND: Neoadjuvant chemotherapy (NAC) is the standard therapy for locally advanced breast cancer. Recently, several studies have revealed that clearance of axillary lymph node involvement is an independent factor for survival irrespective of the response of the primary lesion. However, in daily practice, it is difficult to fully examine every lymph node that has been surgically sampled, in view of pathology laboratory workload and cost. Therefore, in the present study, we adopted the more clinically relevant categorization of evaluating postoperative axillary lymph node status and retrospectively studied its significance in predicting patients' survival. **METHODS:** The study cohort consisted of 35 locally advanced breast cancer patients who are treated with concomitant epirubicin-docetaxel. The clinicopathological factors used for analysis were as follows: ERalpha, PgR, p53, HER2, pathological response (in the primary tumor), and axillary lymph node status at surgery. With regard to axillary lymph node status, we categorized patients into two groups: those with pathological lymph node involvement at surgery (pLNI) and those without. Using multivariate analysis, we evaluated the significance of these factors in predicting disease-free survival after surgery. **RESULTS:** The median follow-up period was 23.4 months (range 4.3-45.4). Multivariate analysis showed significantly reduced disease-free survival associated with pLNI (P = 0.005). **CONCLUSIONS:** pLNI is an excellent prognostic factor for locally advanced breast cancer patients treated with concomitant epirubicin-docetaxel. Use of our criteria may enable large numbers of oncologists to participate in new studies of high-risk cohorts who are refractory to NAC.

Kang, M. K., Y. C. Ahn, et al. (2006). "Preoperative concurrent radiochemotherapy and surgery for stage IIIA non-small cell lung cancer." *J Korean Med Sci* **21**(2): 229-35.

This is to examine whether aggressive multimodality therapy improves the treatment outcomes in stage IIIA non-small cell lung cancer (NSCLC). Fifty-three consecutive NSCLC patients with N2 disease, confirmed by mediastinoscopic biopsy, received preoperative thoracic radiation therapy (45 Gy/5 weeks) concurrent with two cycles of oral etoposide and intravenous cisplatin and surgery. Postoperative radiation therapy (PORT, 18 Gy/2 weeks) was optionally recommended for those with the risk factors of loco-regional recurrence based on the surgical and pathological findings. Surgical resection was performed in 38 patients (71.7%), and down-staging was achieved in 19 patients (50%). The median survival period was 27 months in 38 patients who underwent resection, and the rates at 3-yr of overall survival, loco-regional control, distant metastasis-free survival, and disease-free survival were 44.3%, 87.9%, 32.9%, and 29.3%. Significantly favorable factor regarding overall survival was achieving p0/I stage by the multivariate analysis. PORT was successful in reducing locoregional recurrences in patients with the risk factors. Current preoperative concurrent radiochemotherapy and surgery by the authors resulted in comparable survival with other reports, however, further refinement of multimodality approach may be warranted for more effective reduction of distant metastasis.

Kapp, K. S., D. S. Kapp, et al. (1999). "The prognostic significance of peritoneal seeding and size of postsurgical residual in patients with stage III epithelial ovarian cancer treated with surgery, chemotherapy, and high-dose radiotherapy." *Gynecol Oncol* **74**(3): 400-7.

OBJECTIVE: The aim of this study was to retrospectively analyze the prognostic importance of age, histologic type and grade, ascites, lymph node status, size and type of postoperative residual disease, and radiation dose on disease-specific (DSS) and progression-free survival (PFS) in stage III epithelial ovarian cancer patients who had been treated with radical surgery, postoperative chemotherapy, and high-dose radiotherapy. **METHODS:** Consolidation radiotherapy including whole abdominal radiation, pelvic, and upper abdominal boosts was employed in 46 patients who showed no evidence of residual or progressive disease after completion of multiagent chemotherapy. The median follow-up for all patients was 36 months and 103 months for patients at risk. The prognostic impact of pretreatment and treatment parameters on DSS and PFS was tested in univariate

and multivariate analyses. **RESULTS:** The 5-year DSS and PFS rates for all patients were 38 and 33%, and for patients with 0- or ≤ 2 cm residual tumor 65 and 61%, respectively. In univariate analysis, initial peritoneal seeding (both: $P = 0.02$), ascites ($P = 0.03$; 0.01), size of residual ($0- < \text{or} = 2$ cm vs > 2 cm), and residual miliary subdiaphragmatic (MDS) and localized peritoneal seeding (LPS) in the upper abdomen ($P = 0.0002$; 0.0003) were significantly correlated with DSS and PFS. Dose of radiation ($< \text{or} = 30$ vs > 30 Gy) correlated with DSS only ($P = 0.02$). In multivariate analysis size of residual disease ($0- < \text{or} = 2$ cm vs > 2 cm and/or MDS or LPS) remained the only independent prognostic factor for DSS and PFS (both; $P = 0.001$). **CONCLUSION:** Patients with localized peritoneal seeding who were rendered free of disease elsewhere had an outcome equally poor as that of patients with gross residuals (> 2 cm) in the upper abdomen. If our findings can be confirmed, attempted resection of all localized seeding in patients who are otherwise cytoreducible to no or minimal residual disease may be considered in combination with Taxol-containing regimens as are now being utilized for patients with gross disease.

Karayiannakis, A. J., K. N. Syrigos, et al. (2002). "Circulating VEGF levels in the serum of gastric cancer patients: correlation with pathological variables, patient survival, and tumor surgery." *Ann Surg* **236**(1): 37-42.

OBJECTIVE: To evaluate the clinical usefulness of serum vascular endothelial growth factor (VEGF) levels in gastric cancer patients. **SUMMARY BACKGROUND DATA:** Vascular endothelial growth factor plays an important role in the formation of new blood vessels involved in the growth and metastatic spread of solid tumors, but there is limited information regarding the clinical significance of serum VEGF levels in cancer patients. **METHODS:** Serum VEGF concentrations were measured by an enzyme linked immunosorbent assay in 61 healthy controls and in 58 gastric cancer patients before surgery, and then again at 7 and 30 days after surgery. The association between preoperative serum VEGF levels, clinicopathological features and patient survival, and their changes following surgery were evaluated. **RESULTS:** Serum VEGF levels in gastric cancer patients were significantly higher than those in controls. There was a significant association between serum VEGF levels and disease stage, as well as invasion depth of the tumor and the presence of distant metastases. Serum VEGF levels decreased significantly after radical resection of the primary tumor and increased in patients with unresectable tumors. Multivariate regression analysis showed that serum VEGF level is an independent prognostic factor

for survival. CONCLUSIONS: Serum VEGF levels in gastric patients are significantly higher compared with normal controls and correlate with local tumor extent, disease stage, and the presence of distant metastases. Preoperative serum VEGF concentration decreases significantly after radical resection of the primary tumor and is an independent prognostic factor for patient survival suggesting that determination of serum VEGF levels may be clinically useful.

Karayiannakis, A. J., K. N. Syrigos, et al. (2002). "Clinical significance of preoperative serum vascular endothelial growth factor levels in patients with colorectal cancer and the effect of tumor surgery." *Surgery* **131**(5): 548-55.

BACKGROUND: Vascular endothelial growth factor (VEGF) is an angiogenic cytokine involved in the progression of solid tumors. In this study we evaluated the clinical usefulness of preoperative serum VEGF concentrations in patients with colorectal cancer. The changes in serum VEGF levels after tumor surgery were also evaluated. **METHODS:** Serum VEGF levels were determined by an enzyme-linked immunosorbent assay in the sera of 61 healthy control subjects and 67 patients with colorectal cancer preoperatively and 7 and 30 days after surgery. **RESULTS:** Serum VEGF levels in patients with colorectal cancer (median, 492 pg/mL; interquartile range, 281 to 737 pg/mL) were higher ($P < .0001$) than in control subjects (median, 186 pg/mL; interquartile range, 100 to 273 pg/mL). There was a significant association between serum VEGF levels and disease stage, invasion depth of the tumor, the presence of lymph node and distant metastases, and the degree of differentiation. Curative but not palliative resection of the primary tumor resulted in a significant decrease of preoperative serum VEGF levels but normalized in only 72% of patients. Failure of a return of VEGF to normal after resection for cure was associated with an increased although not statistically significant risk of metastasis during follow-up. Univariate analysis showed a lower survival rate for patients with increased preoperative serum VEGF levels ($P < .002$). Multivariate regression analysis showed that the prognostic value of serum VEGF level was not independent of tumor stage. **CONCLUSIONS:** These findings suggest that VEGF plays an important role in tumor progression and the formation of distant metastases in colorectal cancer. It is at present unclear whether serial estimation of serum VEGF is clinically useful in the prediction of tumor relapse.

Kathirvel, S., A. Saxena, et al. (1999). "Comparison of perioperative morbidity in patients with ovarian malignancy undergoing radical cancer surgery with or

without prior chemotherapy." *Indian J Med Res* **109**: 175-81.

Evaluation was undertaken of the effect of chemotherapeutic drugs on the perioperative morbidity of patients with ovarian malignancy undergoing radical surgery. Twenty patients who had received cytotoxic drugs pre-operatively (group I) were compared with 11 patients in whom radical surgery was the first line of treatment (group II). Pre and post-operative cardiac, pulmonary, renal, hepatic and coagulation functions were compared in both groups, as well as the critical intra- and post-operative events like cardiac pump failure, respiratory dysfunction, rhythm disturbances, blood loss, etc. Demographic data, ASA status, biochemical and haematological parameters and cardiac ejection fractions were comparable in the two groups but patients in group I had significantly higher left ventricular end diastolic dimensions ($P < 0.01$). A higher number of patients in group I had pre-operative respiratory and coagulation factor abnormalities but critical intra- and post-operative events in both groups were comparable. The surgical time was significantly ($P < 0.01$) longer in group I (5.5 +/- 2.5 h) as compared to group II (4.5 +/- 1.5 h). One patient with extensive tumour spread and pre-operatively deranged coagulation profile (group I) died of disseminated intravascular coagulation in the post-operative period. It is concluded that patients with advanced ovarian malignancy, treated with cytotoxic drugs are more likely to have pre-operative cardiac, respiratory and coagulation abnormalities, which should be managed by thorough pre-operative evaluation and intensive intra- and post-operative monitoring.

Katoh, H., K. Yamashita, et al. (2009). "Prognostic significance of peritoneal tumour cells identified at surgery for colorectal cancer." *Br J Surg* **96**(7): 769-77.

BACKGROUND: The prognostic significance of intraperitoneal tumour cells (IPCs) in colorectal cancer is not clear. This study aimed to determine whether detection of IPCs could be used a prognostic marker for selecting patients at high risk of recurrence. **METHODS:** The study included 226 patients with colorectal cancer who underwent elective resection. Clinical variables, including the presence of IPCs, were analysed for their prognostic significance. **RESULTS:** Thirty-three patients (14.6 per cent) were positive for IPCs. Univariable analysis indicated that the presence of IPCs was a significant prognostic factor in patients with stage III colorectal cancer; the 5-year disease-specific survival rate was 14 per cent in IPC-positive patients versus 79 per cent in those without IPCs ($P < 0.001$). Multivariable analysis showed that IPC positivity was the most

robust prognostic factor in stage III disease (hazard ratio 2.2; $P = 0.003$), whereas nodal category (N1 or N2) showed no significant association with prognosis. In addition, IPCs were associated with haematogenous recurrence ($P = 0.004$) rather than peritoneal or local recurrence ($P = 0.077$) in patients with stage III disease. **CONCLUSION:** The presence of IPCs is a significant prognostic factor in patients with stage III colorectal cancer.

Kawai, H., A. Tada, et al. (2005). "Smoking history before surgery and prognosis in patients with stage IA non-small-cell lung cancer--a multicenter study." *Lung Cancer* **49**(1): 63-70.

The prognosis of lung cancer patients with surgically resected non-small-cell lung cancer (NSCLC) can be predicted generally from age, sex, histologic type, stage at diagnosis, and additional treatment. Nine studies have reported that a history of smoking before diagnosis influences the prognosis of the disease in lung cancer patients. In this study, a total of 3082 patients who underwent surgery and were diagnosed with primary pathological stage IA NSCLC at 36 national hospitals from 1982 to 1997 were analyzed for the effect of smoking on survival. Smoking history and other factors influencing either the overall survival or the disease-specific survival rates of patients were estimated with the Cox proportional hazards model. Multivariate analysis demonstrated significant associations between overall survival and age ($P < 0.0001$), sex ($P = 0.0002$), and performance status (PS) ($P < 0.0001$). Disease-specific survival was associated with age ($P = 0.0063$), sex (0.00161), and PS ($P = 0.0029$). In males, disease-specific survival was associated with age ($P = 0.0120$), PS ($P = 0.0022$), and pack-years (number of cigarette packs per day, and years of smoking) ($P = 0.0463$). These results indicate that smoking history (pack-years) is important clinical prognostic factor in estimating disease-specific survival, in male patients with stage IA primary NSCLC that has been surgically resected.

Keith, B., M. Vincent, et al. (2002). "Subsets more likely to benefit from surgery or prophylactic cranial irradiation after chemoradiation for localized non-small-cell lung cancer." *Am J Clin Oncol* **25**(6): 583-7.

After chemoradiation for localized non-small-cell lung cancer, surgery and prophylactic cranial irradiation (PCI) have been used as additional therapies. Less than a third of patients develop brain recurrences, or have local recurrence as their sole initial site of recurrence; these are groups that would benefit from PCI or surgery, respectively. Pretreatment identification of patients more likely to

benefit from surgery or PCI would be useful. A retrospective analysis of 80 patients was performed to determine prognostic factors for such patterns of failure. Twenty-nine patients were subsequently selected for surgery in a nonrandomized manner. Seventeen patients had isolated local initial recurrence and 15 had brain recurrences. In multivariable analysis, female gender and elevated LDH were found to be risk factors for brain recurrence. In the subset with stage III disease ($n = 76$), squamous cell histology was a risk factor for isolated initial local recurrence in both univariable and multivariable analysis. It is possible to identify subsets that may show increased benefit from PCI or surgery.

Kelsen, D. P., K. A. Winter, et al. (2007). "Long-term results of RTOG trial 8911 (USA Intergroup 113): a random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer." *J Clin Oncol* **25**(24): 3719-25.

PURPOSE: We update Radiation Therapy Oncology Group trial 8911 (USA Intergroup 113), a comparison of chemotherapy plus surgery versus surgery alone for patients with localized esophageal cancer. The relationship between resection type and between tumor response and outcome were also analyzed. **PATIENTS AND METHODS:** The chemotherapy group received preoperative cisplatin plus fluorouracil. Outcome based on the type of resection (R0, R1, R2, or no resection) was evaluated. The main end point was overall survival. Disease-free survival, relapse pattern, the influence of postoperative treatment, and the relationship between response to preoperative chemotherapy and outcome were also evaluated. **RESULTS:** Two hundred sixteen patients received preoperative chemotherapy, 227 underwent immediate surgery. Fifty-nine percent of surgery only and 63% of chemotherapy plus surgery patients underwent R0 resections ($P = .5137$). Patients undergoing less than an R0 resection had an ominous prognosis; 32% of patients with R0 resections were alive and free of disease at 5 years, only 5% of patients undergoing an R1 resection survived for longer than 5 years. The median survival rates for patients with R1, R2, or no resections were not significantly different. While, as initially reported, there was no difference in overall survival for patients receiving perioperative chemotherapy compared with the surgery only group, patients with objective tumor regression after preoperative chemotherapy had improved survival. **CONCLUSION:** For patients with localized esophageal cancer, whether or not preoperative chemotherapy is administered, only an R0 resection results in substantial long-term survival. Even microscopically positive margins are an ominous prognostic factor. After a R1 resection,

postoperative chemoradiotherapy therapy offers the possibility of long-term disease-free survival to a small percentage of patients.

Kim, J. G., Y. J. Heo, et al. (2009). "Impact of laparoscopic surgery on the long-term outcomes for patients with rectal cancer." *ANZ J Surg* **79**(11): 817-23.

BACKGROUND: This 20-year retrospective study compared the results of laparoscopic surgery with open surgery for patients with rectal cancer to evaluate the impact of laparoscopic surgery on long-term oncological outcomes for rectal cancer. **METHODS:** We analysed survival data collected over 20 years for patients with rectal cancer (n= 407) according to surgical methods and tumour stage between those treated with laparoscopic surgery (n= 272) and those with open surgery (n= 135). Clinical factors were analysed to ascertain possible risk factors that might have been associated with survival from and recurrence of rectal cancer. A multivariate analysis was applied by using Cox's regression model to determine the impact of laparoscopic surgery on long-term oncological outcomes. **RESULTS:** Overall survival, disease-specific survival and disease-free survival rates were statistically higher in the laparoscopic group than in the open-surgery group. The incidence of local recurrence in the laparoscopic group (7.9%; 95% confidence intervals (CI), 4.2-11.5) was significantly lower than that for the open-surgery group (30.2%; 95% CI, 21.0-39.3; $P < 0.001$). By using a multivariate analysis, laparoscopic surgery for rectal cancer appeared not to be an independent factor for disease-specific survival or disease-free survival. However, the laparoscopic surgery was an independent factor associated with reduced local recurrence (Hazard ratio (HR), 3.408; 95% CI, 1.890-6.149; $P < 0.001$). **CONCLUSION:** Laparoscopic surgery did not adversely affect the long-term oncological outcome for patients with rectal cancer.

Kim, J. H., J. H. Cheon, et al. (2008). "Effectiveness of radical surgery after incomplete endoscopic mucosal resection for early colorectal cancers: a clinical study investigating risk factors of residual cancer." *Dig Dis Sci* **53**(11): 2941-6.

The aim of this study was to determine the need for additional treatment following endoscopic mucosal resection for early colorectal cancer. Risk factors for residual carcinoma were investigated using specimens of curative surgical resection performed after endoscopic mucosal resection. A total of 44 patients who had received imperfect endoscopic mucosal resection initially for early colorectal cancers and, therefore, had undergone subsequent surgical resection were enrolled in this study. Of these, 39

(88.6%) were resected completely by endoscopic mucosal resection based on gross inspection, while the other five cases (11.4%) were incompletely resected. Histopathological examination of specimens of endoscopic mucosal resection revealed that microscopic lateral resection margin was positive in 11 cases (25.0%) and vertical resection margin was positive in 16 cases (36.4%). However, after curative surgery, residual cancer within colorectal tissue was found in only five cases (11.4%), while lymph node metastases were found in three cases (6.8%). Gross incomplete resection ($P < 0.001$) and microscopic vertical margin positivity ($P = 0.031$) were found to be risk factors of residual cancer within the colorectal tissue, whereas lymphovascular invasion was a risk factor for lymph node metastasis ($P = 0.040$). However, no residual cancer cells were found after supplementary surgery in the microscopic lateral resection margin-positive cases. In conclusion, grossly incomplete resection, microscopic vertical resection margin positivity, or the presence of lymphovascular invasion after endoscopic mucosal resection for early colorectal cancer indicate the need for further treatment with surgical resection and lymph node dissection. However, microscopic lateral margin positivity without gross remnant tumor and deep submucosal invasion might not indicate residual cancer. This needs to be further validated by a large scale, prospective study with long-term follow-up.

Kim, J. S., M. A. Kim, et al. (2009). "Biomarker analysis in stage III-IV (M0) gastric cancer patients who received curative surgery followed by adjuvant 5-fluorouracil and cisplatin chemotherapy: epidermal growth factor receptor (EGFR) associated with favourable survival." *Br J Cancer* **100**(5): 732-8.

The aim of this study was to analyse the impact of epidermal growth factor receptor (EGFR), thymidylate synthase (TS), dihydropyrimidine dehydrogenase (DPD), thymidine phosphorylase (TP), aurora kinase (ARK) A/B, and excision repair cross-complementing gene 1 (ERCC1) on the efficacy of adjuvant chemotherapy with 5-fluorouracil and cisplatin (FP) after curative gastric resection. Normal and cancer tissue were separately obtained from gastrectomy samples of 153 patients with AJCC stage III-IV (M0) who subsequently treated with adjuvant FP chemotherapy. TS, DPD, TP, ERCC1, and ARK proteins were measured by immunohistochemistry (IHC). EGFR expression was investigated using a standardized IHC with the EGFR PharmDx assay. Amplification of EGFR gene was analysed using fluorescent in situ hybridisation (FISH). In multivariate analysis, stage, ratio of positive to removed lymph nodes, and EGFR expression were significant prognostic factors for overall survival.

Patients with higher EGFR expression had better overall survival than those with lower expression (relative risk: 0.475 (95% confidence interval, 0.282-0.791, P=0.005). Low EGFR expression might be a predictive marker for relapse in curative resected stage III-IV (M0) gastric cancer patients who received adjuvant FP chemotherapy.

Kimura, Y., Y. Yaegashi, et al. (1999). "Tumor necrosis factor-alpha production after esophageal cancer surgery: differences in the response to lipopolysaccharide stimulation among whole blood, pleural effusion cells, and bronchoalveolar lavage fluid cells." *Surg Today* **29**(1): 10-5.

The body's defense mechanism in response to stress may appear to be the sum of activation and suppression. We investigated chronological changes in tumor necrosis factor-alpha (TNF-alpha) production by local effusion cells and whole blood of esophageal cancer patients who had undergone radical resection. Whole blood, pleural effusion cells, and bronchoalveolar lavage fluid (BALF) cells were obtained from the 20 patients. Whole blood was stimulated with *Escherichia coli* (1 microg/ml), *Staphylococcus aureus* (10 microg/ml), and lipopolysaccharide (LPS) (1 microg/ml), and pleural effusion cells and BALF cells were stimulated with LPS; 24-H incubation and TNF-alpha concentration in supernate was measured by enzyme-linked immunosorbent assay (ELISA). Within 3 h after starting the operation, TNF-alpha production in whole blood was significantly ($P < 0.05$) decreased compared with preoperative value by each stimulation, and this suppression persisted up to day 3. These reductions in postoperative TNF-alpha production correlated with intraoperative hemorrhage. On the other hand, the LPS-induced release of TNF-alpha into pleural effusion cells and BALF cells were markedly increased during the study period. These results indicate that large quantities of cytokines are produced by a second attack, such as infection, in areas where immunocytes accumulate. We believe that the body reacts to surgical stress in a variety of ways. Circulating blood and immunocytes that accumulate in damaged organs are thought to react very differently to stress.

Kirman, I., A. Belizon, et al. (2007). "Perioperative sargramostim (recombinant human GM-CSF) induces an increase in the level of soluble VEGFR1 in colon cancer patients undergoing minimally invasive surgery." *Eur J Surg Oncol* **33**(10): 1169-76.

INTRODUCTION: Experimentally, laparotomy is associated with increased tumor growth. In humans, abdominal surgery is associated with immunosuppression and elevated plasma VEGF levels

that might stimulate tumor growth early after surgery. Avoidance of these surgery-related changes and their consequences may be advantageous. Granulocyte-macrophage colony stimulating factor (GM-CSF) is a non-specific immune system up-regulator that has also been associated, experimentally, with increased release of soluble VEGF Receptor 1 (sVEGFR1) which is an endogenous inhibitor of VEGF. This study's purpose was to determine the impact of perioperatively administered recombinant human GM-CSF (rhu-GM-CSF) on both immune function and plasma sVEGFR1 levels in colorectal cancer patients. **METHODS:** This randomized placebo-controlled study included 36 colorectal cancer patients who underwent minimally invasive resection (17 GM-CSF, 19 Placebo). Patients received 7 subcutaneous injections of either rhu-GM-CSF, 125 microg/m², or saline on preoperative days 3, 2 and 1 and on postoperative days (POD) 1, 2, 3 and 4. A number of immune parameters were followed and plasma levels of soluble VEGF Receptor 1 (sVEGFR1) and VEGF were determined. **RESULTS:** The total WBC, neutrophil, eosinophil, and monocyte counts were significantly higher after surgery in the GM-CSF group; no differences were noted for the other immune parameters. In the GM-CSF group, median plasma sVEGFR1 levels were significantly elevated on POD 1 (188.1 pg/ml), and on POD 5 (142.8 pg/ml) when compared to pre-GM-CSF levels (0 pg/ml) (p -value<0.05 for all comparisons). In the placebo group, the POD5 median sVEGFR1 level (116.3 pg/ml) was elevated and of borderline significance ($p=0.05$) vs the pre-treatment result (0 pg/ml). Of note, both groups had significantly elevated median plasma VEGF levels on POD 5 (Control 435.7 pg/ml; GM-CSF 385.3 pg/ml) when compared to their preoperative results (Control 183.3 pg/ml, $p=0.0013$; GM-CSF 171.5 pg/ml, $p=0.0055$). **CONCLUSIONS:** Perioperative GM-CSF was not associated with an immune function benefit in this study, however, such treatment leads to increased plasma sVEGFR1 levels. Colorectal resection, with or without GM-CSF, was also associated with increased VEGF levels postoperatively. Increased plasma levels of sVEGFR1 after surgery might limit the pro-angiogenic tumor stimulatory effects of VEGF. Further study of GM-CSF's impact on angiogenesis appears warranted.

Kirman, I., V. Cekic, et al. (2005). "Open surgery induces a dramatic decrease in circulating intact IGFBP-3 in patients with colorectal cancer not seen with laparoscopic surgery." *Surg Endosc* **19**(1): 55-9.

BACKGROUND: As shown earlier by the authors via Western blot analysis, open (OS) but not laparoscopic surgery (LS) induces a qualitative decrease in plasma insulin-like growth factor-binding

protein 3 (IGFBP-3) levels on postoperative day 1 (POD 1). Intact IGFBP-3 has tumor suppressive effects, but its degradation products do not. Enzyme linked immunoassay (ELISA) inevitably measures both. In this study, using a novel combined Western blot and ELISA analysis method, precise plasma levels of intact IGFBP-3 on POD2 after open and closed colorectal cancer resection (stage I-III) were determined. METHODS: This study included 15 OS patients with a mean incision length of 26.7 +/- 15.5 cm and 16 LS patients with a mean incision length of 5.3 +/- 3.1 cm. Intact IGFBP-3 levels were determined via ELISA and Western blot analysis in plasma collected preoperatively and postoperatively. RESULTS: In the OS patients, the mean preoperative concentration of intact 43-45 kDa IGFBP-3 protein was 1920 +/- 1430 ng/ml. It decreased dramatically on POD2 to 355 +/- 545 ng/ml ($p < 0.005$). In the LS group, no significant difference was noted between the preoperative level (1305 +/- 807 ng/ml) and the POD2 level (922 + 714 ng/ml). CONCLUSIONS: Open cancer resection, unlike its minimally invasive alternative, induces a dramatic decrease in concentration of intact IGFBP-3, which may have important implications with regard to colon cancer recurrence.

Kirova, Y. M., D. Stoppa-Lyonnet, et al. (2005). "Risk of breast cancer recurrence and contralateral breast cancer in relation to BRCA1 and BRCA2 mutation status following breast-conserving surgery and radiotherapy." *Eur J Cancer* **41**(15): 2304-11.

BRCA1 and BRCA2 germline mutations are associated with a strong risk of breast cancer, which may preclude breast-conserving treatment in carriers. This study examined whether mutation status influenced the rate of breast cancer recurrence following breast-conserving treatment. BRCA1 and BRCA2 genes were screened for germline mutations in 131 patients with a family history of breast and/or ovarian cancer, who had been treated with breast-conserving surgery and radiotherapy. The 131 patients with familial history were matched to 261 patients without, according to age at diagnosis and year of treatment. The follow-up of controls was at least equal to the time-interval between diagnosis and genetic testing in familial cases. Matched cohorts were compared according to rates of breast cancer recurrence as first event and contralateral breast cancer using log-rank tests. BRCA1/2 mutations were found in 20.6% patients with a family history. Nineteen patients had a BRCA1 mutation and 8 had a BRCA2 mutation. Breast cancers in mutation carriers were more often grade III ($p < 10^{-4}$) and oestrogen receptor negative ($p = 0.005$) than tumours in both non-carriers and controls. Median follow-up for all 392

patients was 8.75 years. No significant differences in breast cancer recurrence as first event were seen between BRCA1/2 tumours and controls ($p = 0.47$), carriers and non-carriers with a family history ($p = 0.96$), or non-carriers and controls ($p = 0.10$). On multivariate analysis, age was the most important factor significantly predicting for breast cancer recurrence. The rate of contralateral breast cancer was significantly increased in all patients with a family history: BRCA1/2 carriers versus controls ($p = 0.0003$), non-carriers versus controls ($p = 0.0034$) and carriers versus non-carriers ($p = 0.02$). At a 9-year median follow-up, the rate of ipsilateral breast cancer recurrence was not higher in BRCA1 and BRCA2 mutation carriers than in non-carriers with a family history or sporadic cases. These results support the hypothesis that breast tumours in BRCA carriers are more sensitive to radiation. Therefore, breast-conserving treatment can be offered to these patients. However, longer follow-up is needed to ensure that the rate of new primary cancer in the treated breast does not increase in the long-term.

Kjaerbye-Thygesen, A., K. Frederiksen, et al. (2006). "Do risk factors for epithelial ovarian cancer have an impact on prognosis? Focus on previous pelvic surgery and reproductive variables." *Eur J Gynaecol Oncol* **27**(5): 467-72.

OBJECTIVES: The prognostic impact of risk factors for ovarian cancer development is sparsely explored, but previous sterilisation has been shown to have a negative impact on survival. METHODS: Ovarian cancer cases were from the Danish MALOVA study. Information on previous pelvic surgery as well as reproductive variables was obtained from a personal interview conducted closely after primary surgery. Cox regression models were used to estimate adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for ovarian cancer specific death in relation to previous pelvic surgery and reproductive variables including lifetime number of ovulation years. RESULTS: A total of 295 women with Stage III ovarian carcinomas were identified and followed to death or for a median of 7.3 years (range 5.4-9.5 years). Previously sterilised or hysterectomised women seemed to have a slightly decreased risk of ovarian cancer death (HR = 0.62; 95% CI: 0.36-1.08 and HR = 0.82; 95% CI: 0.55-1.21), although none of these associations reached statistical significance. The prognostic impacts of the individual reproductive variables followed the same pattern as the impact of the variables on ovarian cancer development, although significance was only reached for age at menarche (HR = 0.91 per year; 95% CI: 0.84-0.99). By accumulation of the possible minor effects of the reproductive variables in

calculation of the total lifetime number of ovulation years, we found that survival decreased significantly with increasing number of ovulations (HR = 1.53 per 10 years; 95% CI: 1.09-2.14). **CONCLUSION:** Increasing lifetime number of ovulations was a negative prognostic factor for ovarian cancer specific survival. Previous sterilisation or hysterectomy seemed to be associated with improved survival.

Kondalsamy-Chennakesavan, S., C. Bouman, et al. (2009). "Clinical audit in gynecological cancer surgery: development of a risk scoring system to predict adverse events." *Gynecol Oncol* **115**(3): 329-33.

BACKGROUND: Advanced gynecological surgery undertaken in a specialized gynecologic oncology unit may be associated with significant perioperative morbidity. Validated risk prediction models are available for general surgical specialties but currently not for gynecological cancer surgery. **OBJECTIVE:** The objective of this study was to evaluate risk factors for adverse events (AEs) of patients treated for suspected or proven gynecological cancer and to develop a clinical risk score (RS) to predict such AEs. **METHODS:** AEs were prospectively recorded and matched with demographical, clinical and histopathological data on 369 patients who had an abdominal or laparoscopic procedure for proven or suspected gynecological cancer at a tertiary gynecological cancer center. Stepwise multiple logistic regression was used to determine the best predictors of AEs. For the risk score (RS), the coefficients from the model were scaled using a factor of 2 and rounded to the nearest integer to derive the risk points. Sum of all the risk points form the RS. **RESULTS:** Ninety-five patients (25.8%) had at least one AE. Twenty-nine (7.9%) and 77 (20.9%) patients experienced intra- and postoperative AEs respectively with 11 patients (3.0%) experiencing both. The independent predictors for any AE were complexity of the surgical procedure, elevated SGOT (serum glutamic oxaloacetic transaminase, > or =35 U/L), higher ASA scores and overweight. The risk score can vary from 0 to 14. The risk for developing any AE is described by the formula $100 / (1 + e^{-(3.697 - (RS / 2))})$. **CONCLUSION:** RS allows for quantification of the risk for AEs. Risk factors are generally not modifiable with the possible exception of obesity.

Kondo, E., K. Koda, et al. (2003). "Preoperative natural killer cell activity as a prognostic factor for distant metastasis following surgery for colon cancer." *Dig Surg* **20**(5): 445-51.

BACKGROUND/AIMS: To determine whether preoperative natural killer (NK) cell activity

has any prognostic significance in colon cancer patients. **METHODS:** The study population consisted of 140 patients with colon cancer. NK cell activity was determined within 2 weeks before surgery in 128 patients and at the time of diagnosis in the remaining 12 patients who either did not undergo surgery or who underwent palliative surgery only. Disease progression and postoperative prognosis were examined in relation to NK cell activity. **RESULTS:** Decreases in NK cell activity did not necessarily correspond to tumor stage. In curatively operated stage I-III diseases, preoperative NK cell activity of 20% or less correlated with poor survival. Lower activity was also associated with metachronous distant metastases but not with local recurrences. In particular, more than half the stage III patients with attenuated NK cell activity developed metastases. Multivariate analysis indicated that attenuated NK cell activity was a significant parameter for predicting distant metastasis following curative surgery for colon cancer. **CONCLUSION:** Preoperative NK cell activity has a significant prognostic value in curatively operated colon cancer, particularly for the development of metachronous distant metastasis in stage III patients.

Kondo, M., T. Yokoyama, et al. (2005). "Mutations of epidermal growth factor receptor of non-small cell lung cancer were associated with sensitivity to gefitinib in recurrence after surgery." *Lung Cancer* **50**(3): 385-91.

The epidermal growth factor receptor (EGFR) gene has recently been reported to be mutated in a subset of non-small cell lung cancers (NSCLC), with the mutations being correlated with the patients' drug sensitivity to gefitinib, an EGFR kinase inhibitor. In this study, we searched for EGFR mutations in patients with lung cancer using primary tumor specimens obtained at initial surgery and examined whether their recurrent tumors showed a response to gefitinib depending on the presence of the activating mutation. Among 12 lung cancers that were treated with gefitinib after recurrence, we found that all four tumors which showed a response to gefitinib had an activating mutation in EGFR, whereas none of the remaining eight tumors had a mutation. Southern blot analysis showed that two of the four responsive tumors had the EGFR gene amplification. We also examined another 73 NSCLC specimens (47 males and 26 females; 53 adenocarcinomas and 20 non-adenocarcinomas) which were not treated with gefitinib to determine whether NSCLCs with an EGFR mutation have different clinicopathological properties and/or unique genetic alterations of the other cancer-associated genes. We found that 13 (18%) of 73 tumors had a mutation of the EGFR gene,

with the most being detected in female adenocarcinomas. Comparing the alterations in KRAS and P53 with the EGFR mutation, we found that 10 tumors with the KRAS mutation did not have an EGFR mutation, suggesting that each mutation occurs exclusively during the development of lung cancer. These results suggest that the mutation analysis of the EGFR gene using the specimens obtained at surgery might be useful in selecting the appropriate treatment(s) for recurrent lung cancer patients.

Kopeika, U., I. Taivans, et al. (2007). "Effects of the prolonged thoracic epidural analgesia on ventilation function and complication rate after the lung cancer surgery." *Medicina (Kaunas)* **43**(3): 199-207.

Thoracic epidural analgesia has been considered to have a good anesthetic efficacy and to decrease the postoperative complication rate, while its effect upon the ventilation function is still the topic of many clinical studies. The aim of this study was to evaluate the course of early postoperative period using thoracic epidural analgesia. MATERIAL AND METHODS: A total of 453 patients undergoing the operation due to the non-small cell carcinoma were selected and examined. Their postoperative complications and mortality rate were evaluated. In 79 patients, arterial oxygen saturation (SaO₂), forced vital capacity, forced expiratory volume in the first second, and the efficacy of analgesia were analyzed within the first 7 days after the operation. These patients were divided into subgroups according to the type of the operation--lobectomy or pneumonectomy--and the type of analgesia--thoracic epidural analgesia or opiates administered intramuscularly (control group). RESULTS: A better statistically significant efficacy of analgesia was observed in thoracic epidural analgesia group than in the control group (visual analog pain scale score 2.5 versus 5.3, P<0.01). There was also a statistically significant lower incidence of postoperative complications (20.5% versus 38.8%, respectively). Thoracic epidural analgesia is a factor decreasing the relative risk of complications (RR=0.53, 95% CI 0.28-0.99, P=0.0233). In the lobectomy group, 24 hours after the surgery, forced vital capacity was 61+/-12% in the group receiving thoracic epidural analgesia and 45+/-13% in the control group (P=0.0152); forced expiratory volume in the first second was 56+/-17% and 41+/-11%, respectively (P=0.0308). In the pneumonectomy group, 24 hours after the surgery, forced vital capacity was 47+/-16% in the group receiving thoracic epidural analgesia, 35+/-8% in the control group (P=0.080). Forced expiratory volume in the first second was 47+/-15% and 36+/-7%, respectively (P=0.0449). CONCLUSION: We conclude that analgesia with intramuscularly

administered opioids provides unsatisfactory analgesia, especially in the first days after the operation. Thoracic epidural analgesia is a safe method, which provides a better quality of life for the patient, decreases the postoperative complication rate, and improves the ventilation function after the lung operations.

Kshivets, O. (2001). "Non-small cell lung cancer. The role of chemoimmunoradiotherapy after surgery." *J Exp Clin Cancer Res* **20**(4): 491-503.

The aim of this study was to determine expediency of adjuvant chemoimmunoradiotherapy for radically operated non-small cell lung cancer patients (LCP) with pathologic stage II-III (T1-4N0-2M0G1-3). In retrospective trial (1985-1998) a 5-year survival of 54 consecutive radically operated LCP after adjuvant chemoimmunoradiotherapy (group A) was compared with 5-year survival of 264 LCP, after radical procedures (group C) and with 5-year survival of 86 radically operated LCP after postoperative radiotherapy (group B) (45-50 Gy). I cycle of chemoimmunotherapy was given on day 10-14 after complete resections. Radiotherapy (45-50 Gy) was administered since day 7 after 1 cycle. After irradiation 3-4 courses of CAVT were repeated every 21-28 day. Variables selected for 5-year survival and life span study were sex, age, TNMG, cell type, tumor size. Survival curves were estimated by the Kaplan-Meier method. Differences in curves between groups of LCP were evaluated using a log-rank test. Multivariate proportional hazard Cox regression, multi-factor clustering, structural equation modeling and Monte Carlo simulation were used to determine any significant overall regularity. 5-year survival was superior in group A (64.8%: 35 out of 54 LCP with N0-2; life span=1998.2+/-156.9 days) compared with group B (45.3%: 39 out of 86 LCP with N0-2; life span=1296.4+/-109.5 days) (P<0.001). 5-year survival of group C was 63.6% (168 out of 264 LCP with N0-2; life span=1738.3+/-63.4 days) (P>0.05 for group A and P<0.001 for group B). For LCP with N1-2 5-year survival was significantly superior for group A (63.6%: 21 from 33; life span=1934.0+/-180.9 days) compared with group C (28.1%: 25 out of 89; life span=1056.9+/-91.1 days) (P<0.001) and with group B (35.6%: 21 out of 59; life span=1051.7+/-119.6 days) (P<0.001). Structural equation modeling and Monte Carlo simulation confirmed significant overall differences between 5-year survival (P<0.05) and life span (P<0.001) of LCP with N1-2 in group A with respect to group C or B; however, 5-year survival of LCP for N0 in groups A, B and C were not significantly different.

Kume, H., S. Teramoto, et al. (2006). "Bladder recurrence of upper urinary tract cancer after laparoscopic surgery." *J Surg Oncol* **93**(4): 318-22.

PURPOSE: We reviewed our cases to determine whether laparoscopic nephroureterectomy is a risk factor for the bladder recurrence. **MATERIALS AND METHODS:** From 1996 to 2003, 65 nephroureterectomies were performed: 47 by open and 18 by laparoscopic surgery. In 43 (28 by open, 15 by laparoscopic surgery), bladder cancer was not observed at the time of the operation. Two laparoscopic operations were converted to open surgery because of technical problems. The other 13 with laparoscopic and 28 with open surgery were enrolled into this study. **RESULTS:** Significantly higher recurrence rate was observed in laparoscopic cases (69.2%) than that in open cases (35.7%, $P = 0.0484$) by log rank test. However, the operation time required in laparoscopic surgery (371.5 +/- 90.8 min) was significantly longer than that in the open surgery (229.9 +/- 46.6 min, $P < 0.0001$). In multivariate analysis (Cox proportional hazards model), only the longer operation time (>250 min) was a significant variable ($P = 0.0305$), and laparoscopic surgery in itself was not a significant risk factor ($P = 0.5011$). **CONCLUSIONS:** Although frequent bladder recurrence was observed in laparoscopic cases, the most important risk factor was the longer operation time. Technical improvements including shortening of operation time and earlier ureteral ligation may decrease the bladder recurrence.

Kurzer, E., R. Leveillee, et al. (2006). "Obesity as a risk factor for complications during laparoscopic surgery for renal cancer: multivariate analysis." *J Endourol* **20**(10): 794-9.

BACKGROUND AND PURPOSE: A number of clinical variables are believed to be risk factors for complications of laparoscopic renal surgery. We reviewed our experience with laparoscopic surgery specifically for renal cancers to better clarify which clinical variables were significant risk factors. **METHODS:** Our laparoscopic experience with 210 cases of renal cancer from April 1999 through August 2004 was reviewed. Preoperative clinical characteristics were recorded. Complete information was available for 134 patients: 54 radical nephrectomies, 41 nephroureterectomies, 19 radiofrequency ablations, and 20 partial nephrectomies. Outcomes monitored included blood loss, length of hospital stay, conversion, blood transfusion, and intraoperative, minor postoperative, and major postoperative complications. Multivariate analysis was performed to determine whether any variable was a significant risk factor for adverse outcomes during or after laparoscopic surgery.

RESULTS: The numbers of patients requiring operative conversion or blood transfusions were 6 (4.5%) and 20 (14.9%), respectively. Intraoperative, minor postoperative, and major postoperative complication occurred in 9 (6.7%), 22 (16.4%), and 11 (8.2%) patients, respectively. The year surgery was performed was inversely proportional to the incidence of minor postoperative complications, implying a protective association with the experience of the surgeon. On multivariate analysis, only body mass index (BMI) was found to be a significant risk factor for major postoperative complications with an odds ratio of 1.14 ($P = 0.03$). **CONCLUSIONS:** Laparoscopic surgery is safe, but with every unit increase in the BMI, the risk of a major complication increases by 14%.

Lai, C. H., S. Hsueh, et al. (1999). "Are adenocarcinomas and adenosquamous carcinomas different from squamous carcinomas in stage IB and II cervical cancer patients undergoing primary radical surgery?" *Int J Gynecol Cancer* **9**(1): 28-36.

The aim of this study was to define clinicopathologic features and to investigate prognostic factors in early-stage cervical adenocarcinomas and adenosquamous carcinomas in patients undergoing primary radical surgery. One hundred thirty-four patients with stage IB or II cervical adenocarcinoma or adenosquamous carcinomas treated at a single institution were reviewed and compared to squamous carcinomas ($N = 757$) treated in the same period. Among adeno-adenosquamous carcinomas, stage II disease, parametrial extension, and deep cervical stromal invasion ($>2/3$) were associated with increased risk of pelvic lymph node metastases, while only clinical stage II, DNA index >1.3 (by flow cytometry), and pelvic node metastases were significantly associated with decreased survival by multivariate analyses. The five-year recurrence-free and overall survival rates of patients with adeno-adenosquamous vs squamous carcinoma were 72.2% vs 81.2% ($P = 0.0109$), and 74.1% vs 82.8% ($P = 0.0136$), respectively by Mantel-Cox test. After controlling confounding factors, histologic type (adeno-adenosquamous vs squamous) was confirmed as an independent prognostic factor for recurrence-free survival [relative risk (RR): 1.2792; 95% confidence interval (CI): 1.0628-1.5399, $P = 0.0092$] and overall survival (RR: 1.2594, 95% CI: 1.0467-1.5155, $P = 0.0146$) in the whole series ($N = 891$). Although pattern of relapse by histologic type was not significantly different, patients with recurrent adeno-adenosquamous carcinoma did significantly worse than those with recurrent squamous carcinoma. In conclusion, the prognosis of adeno-adenosquamous carcinoma of the cervix is slightly worse than

squamous tumors. Since salvage of recurrent adeno-adenosquamous carcinoma after primary radical surgery is generally ineffective using conventional treatment, innovative strategies are necessary for the high-risk group after primary surgery and all recurrent adeno-adenosquamous carcinomas regardless of size or site.

Lantz, P. M., N. K. Janz, et al. (2005). "Satisfaction with surgery outcomes and the decision process in a population-based sample of women with breast cancer." *Health Serv Res* **40**(3): 745-67.

OBJECTIVE: To better understand medical decision making in the context of "preference sensitive care," we investigated factors associated with breast cancer patients' satisfaction with the type of surgery received and with the decision process. **DATA SOURCES/DATA COLLECTION:** For a population-based sample of recently diagnosed breast cancer patients in the Detroit and Los Angeles metropolitan areas (N=1,633), demographic and clinical data were obtained from the Surveillance, Epidemiology, and End Results tumor registry, and self-reported psychosocial and satisfaction data were obtained through a mailed survey (78.4 percent response rate). **STUDY DESIGN:** Cross-sectional design in which multivariable logistic regression was used to identify sociodemographic and clinical factors associated with three satisfaction measures: low satisfaction with surgery type, low satisfaction with the decision process, and decision regret. **PRINCIPAL FINDINGS:** Overall, there were high levels of satisfaction with both surgery and the decision process, and low rates of decision regret. Ethnic minority women and those with low incomes were more likely to have low satisfaction or decision regret. In addition, the match between patient preferences regarding decision involvement and their actual level of involvement was a strong indicator of satisfaction and decision regret/ambivalence. While having less involvement than preferred was a significant indicator of low satisfaction and regret, having more involvement than preferred was also a risk factor. Women who received mastectomy without reconstruction were more likely to report low satisfaction with surgery (odds ratio [OR]=1.54, $p<.05$), low satisfaction with the process (OR=1.37, $p<.05$), and decision regret (OR=1.55, $p<.05$) compared with those receiving breast conserving surgery (BCS). An additional finding was that as patients' level of involvement in the decision process increased, the rate of mastectomy also increased ($p<.001$). **CONCLUSIONS:** A significant proportion of breast cancer patients experience a decision process that matches their preferences for participation, and report satisfaction with both the process and the

outcome. However, women who report more involvement in the decision process are significantly less likely to receive a lumpectomy. Thus, increasing patient involvement in the decision process will not necessarily increase use of BCS or lead to greater satisfaction. The most salient aspect for satisfaction with the decision making process is the match between patients' preferences and experiences regarding participation.

Lavelle, K., A. Moran, et al. (2007). "Older women with operable breast cancer are less likely to have surgery." *Br J Surg* **94**(10): 1209-15.

BACKGROUND: Older women are less likely to receive standard management for breast cancer than younger postmenopausal women. Whether differences in general health explain variations in the rates of surgery is not known. **METHODS:** In this prospective cohort study, 76 women aged 65 years or more attending breast units in Greater Manchester completed a survey measuring functional status (Elderly Population Health Status Survey's Activity of Daily Living), generic health status (Short Form 12) and health-related quality of life (European Organization for Research on Treatment of Cancer Quality of Life Questionnaire C30). Case-note review assessed co-morbidity (Charlson Index) and management. Primary surgery for operable breast cancer was investigated using logistic regression. **RESULTS:** A Charlson Index of 1 or more did not predict the use of surgery ($P = 0.363$). However, for each point increase on the 1-4 scale indicating worsening functional status, the odds of having surgery decreased by 16 times (odds ratio 0.063). The odds of a woman of 80 years or more having surgery decreased by a factor of 44 (odds ratio 0.023) compared with women aged 65-79 years, accounting for co-morbidity, functional status, pretreatment stage, social deprivation and type of hospital. **CONCLUSION:** Older women were less likely to have surgery for operable breast cancer than younger women, even after accounting for differences in general health and co-morbidity.

Lee, J. C., S. T. Wang, et al. (2002). "Investigation of the prognostic value of coexpressed erbB family members for the survival of colorectal cancer patients after curative surgery." *Eur J Cancer* **38**(8): 1065-71.

Epidermal growth factor receptor (EGFR), erbB2, erbB3 and erbB4 are four transmembrane glycoproteins belonging to the subtype I tyrosine kinases. They share structure homologies and are believed to direct cellular growth through the ligand-stimulated tyrosine phosphorylation of intracellular substrate. The overexpression of these tyrosine kinases has been linked to various cancers. To

examine the role of the erbB family in the neoplastic transformation of the human colon, we analysed the protein expression of these four members by immunohistochemistry in paraffin-embedded specimens from 125 resected colorectal cancers. Our data showed that for EGFR expression, 62 (50%) were scored as '+', and 2 (2%) as '++'. For erbB2 expression, 39 (31%) were classified as '+', and 5 (4%) as '++'. For erbB3 expression, 43 (34%) were scored as '+', and 3 (2%) as '++'. A significantly higher percentage of overexpressed erbB3 was observed in early stage carcinomas (Dukes' stage A or B) (50%) than in advanced stage cancers (Dukes' stage C or D) (15%) ($P < 0.0001$). For erbB4 expression, 22 (18%) were scored as '+', and 5 (4%) as '++'. Early stage patients had a lower percentage of erbB4 overexpression than the late stage ones (18% versus 28%). Concomitant overexpression of erbB2 and erbB3 occurred in 21% (16/78) of the early stage carcinomas, whereas it occurred in only 2% (1/47) of the late stage ones ($P = 0.003$). Conversely, simultaneous overexpression of erbB2 and erbB4 occurred in 17% (8/47) of the late stage carcinomas but in only 4% (3/78) of the early stage ones ($P = 0.02$). Overexpression of EGFR, erbB2, erbB3 or erbB4 alone was not significantly associated with a shortened survival. However, patients with a simultaneous overexpression of erbB2 and erbB4 had a shorter overall survival time than others in the univariate analysis ($P = 0.01$). This significance disappeared after adjustment for Dukes' staging in the Cox model. In conclusion, overexpressed erbB3 was common in early stage colorectal cancers, but its prevalence was significantly reduced in late stage ones. The percentage of its coexpression with erbB2 was significantly higher in early stage than in late-stage cancers. Heterodimerisation between erbB2 and erbB4 may play a role in the late stages of carcinogenesis.

Lee, J. H., K. W. Ryu, et al. (2007). "Decisions for extent of gastric surgery in gastric cancer patients: younger patients require more attention than the elderly." *J Surg Oncol* **95**(6): 485-90.

BACKGROUND AND OBJECTIVES:

There is a prevailing belief that young patients with gastric adenocarcinomas have a more aggressive disease. **METHODS:** We reviewed the prospectively collected database of 753 gastric adenocarcinomas patients who had undergone curative gastrectomy. Clinicopathological factors and the survival rates for each pathological TNM stage were compared between patients younger than 40 years of age and the others. **RESULTS:** Fifty-four (9.8%) patients were younger than 40 years of age. The overall accuracy of the intra-operative stage was 62.5%; 54.0% in the young

patients and 63.5% in older patients ($P = 0.006$). Intraoperative under-staging was more commonly seen in the younger patients when compared to the older patients. These trends were more prominent in patients with surgical stage I disease. Age proved to be an independent risk factor influencing the accuracy of intraoperative staging using a logistic regression analysis. There was no difference in overall 3-year survival rate between the two age groups for each pathological TNM stage. **CONCLUSIONS:** The present study showed that intra-operative under-staging was more common in young patients with gastric cancer, especially with stage I disease. This finding raises the concern for inaccurate diagnosis and surgical under treatment in younger patients with stage I gastric cancer.

Leigh, Y., V. Seagroatt, et al. (2006). "Impact of socio-economic deprivation on death rates after surgery for upper gastrointestinal tract cancer." *Br J Cancer* **95**(7): 940-3.

We hypothesised that socio-economic deprivation in England may be a prognostic factor for death after oesophagectomy or gastrectomy for cancer of the upper gastrointestinal tract. We analysed statistical data from hospital records linked to death records for patients who underwent operations for oesophageal and gastric cancer in England from April 1998 to March 2002. The patients were stratified into quintiles according to the index of multiple deprivation (IMD) (2000) for their place (ward) of residence. Age and sex standardised death rates at 30 and 90 days for each deprivation quintile were calculated. Following oesophagectomy, death rates showed a significant association with IMD. They increased with increasing levels of deprivation: the odds ratio for death, comparing highest with lowest quintile for deprivation, was 1.37 (95% confidence interval 1.03-1.85) at 30 days and 1.30 (1.04-1.64) at 90 days. Following gastrectomy, the death rates showed smaller and nonsignificant associations with IMD with odds ratios of 1.16 (0.84-1.62) and 1.10 (0.86-1.41), respectively. There is a significant association between social deprivation and death after oesophagectomy, but less of an association, if any, after gastrectomy in current UK practice.

Leo, E., F. Belli, et al. (2009). "Distal clearance margin of 1 cm or less: a safe distance in lower rectum cancer surgery." *Int J Colorectal Dis* **24**(3): 317-22.

PURPOSE: The purpose of this study was to investigate the prognostic role of distal clearance margin (DCM) in lower rectum cancer surgery. **MATERIALS AND METHODS:** Two-hundred-three cancer patients underwent total rectal resection,

possibly followed by adjuvant chemoradiotherapy. DCM was classified as positive or negative (<1, > or =1 cm) and investigated with multivariable proportional hazard models. RESULTS: A total of 52 deaths, 19 local relapses, 40 distant metastases, and three second primaries were observed as first events. Five-year survival with positive, negative <1, or negative > or =1 cm DCM was 51%, 81%, and 69%, respectively ($p = 0.018$). The difference was significant between positive and negative DCM ($p = 0.031$), not between negative <1 and > or =1 cm ($p = 0.106$). Local and distant 5-year incidences according to DCM were 30%, 8%, and 8% ($p = 0.006$) and 38%, 26%, and 19% ($p = 0.857$), respectively. CONCLUSIONS: DCM, but not tumor size, is a prognostic factor after sphincter-saving surgery, which is safe whenever a negative margin is achieved.

Limentani, S. A., A. M. Brufsky, et al. (2006). "Phase II study of neoadjuvant docetaxel/ vinorelbine followed by surgery and adjuvant doxorubicin/cyclophosphamide in women with stage II/III breast cancer." *Clin Breast Cancer* 6(6): 511-7.

BACKGROUND: The purpose of this study was to evaluate the combination of docetaxel plus vinorelbine as neoadjuvant chemotherapy for stage II/III locally advanced breast cancer. PATIENTS AND METHODS: Eligible women with stage IIA-IIIB or locoregional stage IV breast cancer were treated before surgery with 6 cycles of docetaxel 60 mg/m² and vinorelbine 45 mg/m², repeated every 2 weeks with granulocyte colony-stimulating factor and quinolone prophylaxis. Pathologic complete response (pCR), viewed as an early surrogate for disease-free and overall survival, was the primary efficacy endpoint. Sixty patients were enrolled; 60% had T3 or T4 lesions, 67% had clinically palpable lymph nodes, and 52% were hormone receptor positive. RESULTS: Fifty-nine patients were evaluable for pathologic response; 16 (27%) exhibited pCR in the breast alone (T0 Tis NX), 20% exhibited a pCR in the breast and lymph nodes (T0 Tis N0), 24 (41%) had < 5 mm of residual tumor, and 28 (47%) had node-negative disease at surgery. Relative dose intensity was 96% for docetaxel and 95% for vinorelbine. The clinical response rate was 98% (59 of 60 patients), including 38 complete responses (63%). Grade 3/4 neutropenia (95%), neutropenic fever (22%), mucositis (5%), and pulmonary toxicity (5%) occurred in >or= 5% of patients. Constipation was seen early but became insignificant after incorporating a prophylactic laxative regimen. Other toxicities have been minimal. CONCLUSION: With a clinical response rate of 98% and an in-breast pCR rate of 27%, docetaxel/vinorelbine is among the most active neoadjuvant regimens reported for locally advanced

breast cancer. Docetaxel/vinorelbine can be administered in a dose-dense fashion while maintaining relative dose intensity. However, there was a significant incidence of fever and neutropenia despite the use of prophylactic growth factors and quinolones, indicating that lower doses of docetaxel/vinorelbine should be evaluated in future studies.

Limentani, S. A., A. M. Brufsky, et al. (2007). "Phase II study of neoadjuvant docetaxel, vinorelbine, and trastuzumab followed by surgery and adjuvant doxorubicin plus cyclophosphamide in women with human epidermal growth factor receptor 2-overexpressing locally advanced breast cancer." *J Clin Oncol* 25(10): 1232-8.

PURPOSE: To evaluate the combination of docetaxel, vinorelbine, and trastuzumab as neoadjuvant therapy for human epidermal growth factor receptor 2 (HER2)-overexpressing breast cancer. PATIENTS AND METHODS: Patients with stage IIB or III breast cancer, including inflammatory disease, and HER2 overexpression (determined by fluorescent in situ hybridization) were treated with six cycles of docetaxel 60 mg/m² and vinorelbine 45 mg/m² administered every 14 days with granulocyte colony-stimulating factor and quinolone prophylaxis. Trastuzumab was administered as a 4 mg/kg loading dose followed by 2 mg/kg weekly for 12 weeks. The primary efficacy end point was pathologic complete response (pCR) in the breast. RESULTS: Of 31 enrolled patients, 68% had T3 or T4 tumors and 90% were clinically node positive. Twelve patients (39%; 95% CI, 21.6% to 55.9%) achieved pCR in the breast and lymph nodes and 14 patients (45%; 95% CI, 27.6% to 62.7%) achieved pCR in the breast alone, and 19 patients (61%; 95% CI, 44.1% to 78.4%) were node negative after neoadjuvant therapy. Clinical response was documented in 29 patients (94%; 95% CI, 78.6% to 99.2%) with 26 complete responses (84%; 95% CI, 70.9% to 96.8%). The most commonly reported grade 3/4 toxicities were neutropenia (97%), febrile neutropenia (22%), anemia (6%), mucositis/stomatitis (6%), constipation (6%), and skin rash (6%). CONCLUSION: With clinical response and pCR rates of 94% and 39%, respectively, docetaxel, vinorelbine, and trastuzumab is a highly active neoadjuvant therapy for HER2-overexpressing locally advanced breast cancer. Although well tolerated overall, significant febrile neutropenia was observed despite prophylactic measures; therefore, evaluating a similar regimen using lower docetaxel and/or vinorelbine doses is warranted.

Lissoni, P., F. Brivio, et al. (2009). "Effects of the conventional antitumor therapies surgery,

chemotherapy, radiotherapy and immunotherapy on regulatory T lymphocytes in cancer patients." *Anticancer Res* 29(5): 1847-52.

BACKGROUND: Several clinical studies have clearly demonstrated that the immune status is one a major prognostic factor for the survival time in cancer patients. However the main clinical problem is to identify the most prognostically important index within the great number of immune parameters. Recently the evaluation of regulatory T (T-reg) (CD4CD25) lymphocyte count and function with respect to the T helper (TH) (CD4) number has been shown to represent the main immune parameters capable of representing the functional status of the anticancer immunity in cancer patients. This study evaluated the influence of the four main conventional anticancer therapies (surgery, chemotherapy, radiotherapy, immunotherapy) on the CD4/CD4CD25 ratio. **PATIENTS AND METHODS:** The study included 70 patients. The oncological treatments consisted of surgery in 14, chemotherapy in 36, radiotherapy in 12 and immunotherapy (subcutaneous low-dose, S.C.-low, interleukin, IL-2) in 8 patients. The normal value of the CD4/CD4CD25 ratio was greater than 4.0. **RESULTS:** Surgery induced a significant decline in the CD4/CD4CD25 mean ratio. Radiotherapy also induced also a dramatic significant decrease in the CD4/CD4CD25 ratio, whereas the effect of both chemotherapy and immunotherapy reflected the clinical response to the treatments. The CD4/CD4CD25 mean ratio was significantly enhanced in the patients who obtained control of the neoplastic growth, whereas it diminished in progressing patients. **CONCLUSION:** The commonly used anticancer therapies profoundly modify the levels of amounts of T-reg lymphocytes. Because of the fundamental role of T-reg cells in suppressing the anticancer immunity, thus diminishing survival, the monitoring of the CD4/CD4CD25 ratio could constitute an important clinical index during conventional anticancer therapies to predict the prognosis of cancer patients.

Lohsiriwat, V., D. Lohsiriwat, et al. (2008). "Pre-operative hypoalbuminemia is a major risk factor for postoperative complications following rectal cancer surgery." *World J Gastroenterol* 14(8): 1248-51.

AIM: To determine the relationship between pre-operative hypoalbuminemia and the development of complications following rectal cancer surgery, as well as postoperative bowel function and hospital stay. **METHODS:** The medical records of 244 patients undergoing elective oncological resection for rectal adenocarcinoma at Siriraj Hospital during 2003 and 2006 were reviewed. The patients had pre-operative serum albumin assessment. Albumin less than 35 g/L

was recognized as hypoalbuminemia. Postoperative outcomes, including mortality, complications, time to first bowel movement, time to first defecation, time to resumption of normal diet and length of hospital stay, were analyzed. **RESULTS:** The patients were 139 males (57%) and 105 females (43%) with mean age of 62 years. Fifty-six patients (23%) had hypoalbuminemia. Hypoalbuminemic patients had a significantly larger tumor size and lower body mass index compared with non-hypoalbuminemic patients (5.5 vs 4.3 cm; $P < 0.001$ and 21.9 vs 23.2 kg/m²; $P = 0.02$, respectively). Thirty day postoperative mortality was 1.2%. Overall complication rate was 25%. Hypoalbuminemic patients had a significantly higher rate of postoperative complications (37.5% vs 21.3%; $P = 0.014$). In univariate analysis, hypoalbuminemia and ASA status were two risk factors for postoperative complications. In multivariate analysis, hypoalbuminemia was the only significant risk factor (odds ratio 2.22, 95% CI 1.17-4.23; $P < 0.015$). Hospitalization in hypoalbuminemic patients was significantly longer than that in non-hypoalbuminemic patients (13 vs 10 d, $P = 0.034$), but the parameters of postoperative bowel function were not significantly different between the two groups. **CONCLUSION:** Pre-operative hypoalbuminemia is an independent risk factor for postoperative complications following rectal cancer surgery.

Lowery, A. J., K. J. Sweeney, et al. (2008). "The effect of menopause and hysterectomy on systemic vascular endothelial growth factor in women undergoing surgery for breast cancer." *BMC Cancer* 8: 279.

BACKGROUND: Vascular endothelial growth factor (VEGF) is a potent angiogenic cytokine produced physiologically by the uterus. Pathological secretion by tumours promotes growth and metastasis. High circulating VEGF levels potentially have a deleterious effect on breast cancer by promoting disease progression. The aims of this study were to investigate circulating VEGF levels in breast cancer patients and assess the effect of menopause or hysterectomy on systemic VEGF. **METHODS:** Patients undergoing primary surgery for breast cancer and controls matched for age, menopausal and hysterectomy status were prospectively recruited. Serum VEGF, FSH, LH, estrogen, progesterone and platelet levels were measured. Serum VEGF was corrected for platelet load (sVEGFp) to provide a biologically relevant measurement of circulating VEGF. SVEGFp levels were analyzed with respect to tumor characteristics, menopausal status and hysterectomy status. **RESULTS:** Two hundred women were included in the study; 89 breast cancer patients and 111 controls. SVEGFp levels were significantly

higher in breast cancer patients compared to controls ($p = 0.0001$), but were not associated with clinicopathological tumor characteristics. Systemic VEGF levels reduced significantly in the breast cancer patients following tumor excision ($p = 0.018$). The highest systemic VEGF levels were observed in postmenopausal breast cancer patients. Postmenopausal women who had had a previous hysterectomy had significantly higher VEGF levels than those with an intact postmenopausal uterus ($p = 0.001$). **CONCLUSION:** This study identifies an intact postmenopausal uterus as a potential means of reducing circulating levels of VEGF which could confer a protective effect against breast cancer metastatic potential.

Lu, C. H., P. C. Chao, et al. (2004). "Preincisional intravenous pentoxifylline attenuating perioperative cytokine response, reducing morphine consumption, and improving recovery of bowel function in patients undergoing colorectal cancer surgery." *Anesth Analg* **99**(5): 1465-71; table of contents.

Cytokine release during surgery can produce a long-lasting hyperalgesia. Thus, preoperatively-administered cytokine inhibitors might reduce the production of cytokines, decreasing central nervous system sensitization and improving the quality of postoperative pain relief. We investigated the hypothesis that preincisional IV pentoxifylline (PTX) treatment could attenuate the release of proinflammatory (tumor necrosis factor, interleukin (IL)-1beta, IL-6, and IL-8) and antiinflammatory (IL-1 receptor antagonist) cytokines in patients who underwent elective colorectal cancer surgery. Forty patients were randomly assigned to 1 of 2 groups of 20 each: the PTX group received a PTX 5 mg/kg IV infusion before the induction of anesthesia, whereas the control group received an equal volume of normal saline. Venous blood samples were obtained at frequent intervals. After surgery, all patients received patient-controlled analgesia (PCA) morphine for postoperative pain relief. Patients in the PTX group exhibited longer PCA trigger times, less morphine consumption, and a faster return of bowel function compared with patients in the control group. Moreover, the plasma levels of IL-6, IL-8, and IL-1 receptor antagonist were less in the treatment group, and there was no significant difference in wound infections, tumor recurrence, or metastatic rates between groups during a 2-yr follow-up.

Lynch, M. L. and M. I. Brand (2005). "Preoperative evaluation and oncologic principles of colon cancer surgery." *Clin Colon Rectal Surg* **18**(3): 163-73.

Colorectal cancer is the third most common malignancy in men and women and accounts for 10%

of all cancer deaths. The primary risk factor for colorectal cancer is advancing age, but other factors also play a role in its development, including genetic predisposition, smoking, alcohol consumption, obesity, and high-fat, low-fiber diet. Colon cancer survival is primarily related to the stage of disease at diagnosis. The main screening tests for colon cancer are fecal occult blood testing, flexible sigmoidoscopy, double-contrast barium enema, and colonoscopy. The pre-operative evaluation should include a complete blood count, carcinoembryonic antigen (CEA), colonoscopy, and chest radiograph. Other preoperative evaluations are patient specific or of unproven benefit. The operative procedure should include a bowel preparation, parenteral antibiotics, and deep venous thrombosis prophylaxis. The procedure performed must be tailored to the location of the colon cancer but should include complete, en bloc resection of the cancer and its lymphatic drainage, including locally invaded structures. The bowel margins of resection should be at least 5 cm from the tumor to minimize anastomotic recurrences. Laparoscopic colectomy has been shown to be as safe and effective as open colectomy for the treatment of colon cancer. The use of sentinel lymph node biopsy is feasible but has not yet been proved clinically useful. Surveillance after surgery for colon cancer is necessary to monitor for metastatic disease or local recurrence. Several groups have made surveillance recommendations including office visits, colonoscopy, and CEA monitoring.

MacManus, M. R., R. Hicks, et al. (2003). "FDG-PET-detected extracranial metastasis in patients with non-small cell lung cancer undergoing staging for surgery or radical radiotherapy--survival correlates with metastatic disease burden." *Acta Oncol* **42**(1): 48-54.

The prognostic significance of extracranial distant metastasis detected by positron emission tomography (PET) was investigated in patients with non-small cell lung cancer (NSCLC). Forty-two patients staged with ^{18}F -fluorodeoxyglucose-PET-detected distant metastasis before planned surgery ($n = 7$) or radical radiotherapy (RT)/chemoradiotherapy ($n = 35$) for NSCLC were identified from a prospective database. The influence of metastasis number and other prognostic factors was investigated using Cox's regression analysis. Treatment after PET included surgery ($n = 2$), radical RT ($n = 5$), palliative RT ($n = 25$), chemotherapy ($n = 8$) or supportive care ($n = 2$). All but 4 patients had died by the last follow-up. Median survival was 9 months overall, 12 months for 27 patients with single PET-detected metastasis and 5 months for 15 patients with > 1 metastasis ($p = 0.009$). It was found that the Eastern Cooperative

Oncology Group performance status ($p = 0.027$) but not pre-PET stage, weight loss or metastasis site correlated with survival. PET-detected metastatic tumor burden appeared to influence survival and should be evaluated as a prognostic factor in NSCLC.

Mahteme, H. and L. Pahlman (2005). "Good colorectal cancer surgery." *Tech Coloproctol* 9(1): 1-7.

Adenocarcinoma of the colon and rectum is currently diagnosed in about 783,000 new cases annually and 437,000 patients will die of the disease each year worldwide. Colorectal cancer presents as an emergency situation (obstruction, bleeding or perforation) in approximately 25% of cases and with more or less obvious chronic symptoms in the rest of cases. Rectal cancer patients, with a T1 tumour can be offered local excision whereas patients with more advanced cancer must be offered a more radical abdominal procedure. In large bulky tumours (T3 or definitely T4), MRI should guide the choice of preoperative radiotherapy. Three major indications for radiotherapy are reduction of local recurrences in mobile rectal cancer in order to improve survival, down-staging of the tumour in primary irresectable tumours, and downsizing of low-lying tumours in an attempt to perform a sphincter-saving procedure. The surgical strategy is to remove the tumour-bearing bowel segment with, if possible, a locoregional curative procedure, to restore bowel continuity, and to ensure an optimal quality of life. In most situations, it is possible to achieve local radical resection. In rectal cancer surgery, the main problem is to stick to the embryological planes during the whole procedure. The whole mesorectum is taken out as a packet down to the level of division. This TME procedure dramatically reduced the local recurrence rate to 3%-7%. Surgeon case volume may be an important factor in cancer surgery success. Laparoscopic surgery for colorectal cancer has stimulated a great deal of interest in recent years, but there are concerns regarding this type of surgery. In conclusion, modern surgery for colorectal cancer is a well-defined technique where the anatomical planes have to be identified. Care must be taken to learn all the essential steps. Data from the literature strongly support that the surgeon is the most important factor for an excellent outcome.

Makabe, R. and T. Nomizu (2006). "Social support and psychological and physical states among Japanese patients with breast cancer and their spouses prior to surgery." *Oncol Nurs Forum* 33(3): 651-5.

PURPOSE/OBJECTIVES: To assess social support and psychological and physical states among Japanese patients with breast cancer and their spouses

prior to surgery. **DESIGN:** Descriptive, comparative, and correlational. **SETTING:** A general hospital in northern Japan. **SAMPLE:** 38 Japanese patients with breast cancer and their spouses ($N = 76$). **METHODS:** The Japanese versions of three questionnaires were used to collect data before surgery: the Interpersonal Relationship Inventory, the General Health Questionnaire, and the Physical States Interview Form. **MAIN RESEARCH VARIABLES:** Social support (support, conflict, and reciprocity), social network, and psychological and physical states. **FINDINGS:** Significant differences were found in support and reciprocity between patients and their spouses. However, no significant differences were found in social network, conflict, or psychological states between patients and their spouses. Moreover, some significant correlations were found in the variables of conflict, social network, and psychological and physical states. **CONCLUSIONS:** Japanese patients with breast cancer perceived more support and reciprocity than their spouses before their breast surgery. Conflict was significantly correlated with psychological states among Japanese women with breast cancer and their spouses. **IMPLICATIONS FOR NURSING:** Healthcare professionals need to consider social support as an important factor to help Japanese patients with breast cancer and their spouses cope with the disease.

Makabe, R. and T. Nomizu (2007). "Social support and psychological and physical states among Japanese women with breast cancer before and after breast surgery." *Oncol Nurs Forum* 34(4): 883-9.

PURPOSE/OBJECTIVES: To investigate the relationship of social support and psychological and physical states among Japanese women with breast cancer and to compare the variables before and one year after breast surgery. **DESIGN:** A prospective longitudinal study. **SETTING:** A general hospital in northern Japan. **SAMPLE:** 61 Japanese women with breast cancer. **METHODS:** Measures were the Japanese versions of the Interpersonal Relationship Inventory, the General Health Questionnaire, and the Physical States Interview Form. Data were collected at four time points: before (time 1), three months after (time 2), six months after (time 3), and one year after (time 4) breast surgery. **MAIN RESEARCH VARIABLES:** Social support (support, reciprocity, and conflict), social support network, and psychological and physical states. **FINDINGS:** Psychological and physical states correlated significantly at all four time points. Significant correlations also were found between psychological states and support at times 2 and 4 and between psychological states and reciprocity at time 4. Repeated measures analysis of variance showed

significant differences in support, reciprocity, conflict, and physical states but no significant differences in social support network or psychological states. **CONCLUSIONS:** The results of the study suggest that healthcare professionals need to consider social support as an important factor when helping Japanese women adjust to the diagnosis and treatment of breast cancer. **IMPLICATIONS FOR NURSING:** Healthcare professionals need to provide appropriate social support for Japanese women with breast cancer not only at the time of diagnosis of breast cancer but also after breast surgery.

Makela, J. T., H. Kiviniemi, et al. (2000). "Survival after surgery for gastric cancer in patients over 70 years of age." *Ann Chir Gynaecol* **89**(4): 268-72.

BACKGROUND AND AIMS: The increase of the elderly population in western societies will result in a considerable increase of gastric cancer patients older than 70 years requiring surgery. However, higher postoperative morbidity and mortality rates after major surgery in the elderly are well recognized. The aim of this study was to evaluate the risk factors of mortality and predictors of survival in elderly patients with gastric cancer. **METHODOLOGY:** We reviewed the data of the 165 patients evaluated for gastric cancer surgery in the Oulu University Hospital from January 1985 till December 1994 and made a computer analysis. **RESULTS:** Postoperative mortality was 12% both after all laparotomies and after all resections, and 6% after radical resections. Mortality after radical resection did not associate significantly with any clinical variable but morbidity was associated with the number of coexistent diseases. The median and cumulative 5-year survivals after radical resections were 40 months and 38%. Survival was closely related to diagnostic delay, preoperative loss of weight, two or more coexistent disease, location of tumor, and recurrence in univariate analysis, but multivariate analysis showed only preoperative weight loss and recurrent disease to be independent predictors of survival. **CONCLUSIONS:** Age alone is not a risk factor for postoperative mortality or a predictor of survival among elderly patients with gastric cancer. Early detection of malignancy and careful preoperative evaluation of the patients referred for resection are needed to improve survival.

Maniwa, Y., M. Okada, et al. (1998). "Vascular endothelial growth factor increased by pulmonary surgery accelerates the growth of micrometastases in metastatic lung cancer." *Chest* **114**(6): 1668-75.

BACKGROUND: The use of surgery for metastatic lung cancer has been established recently and the indications have been extended to multiple

and bilateral lung metastases. However, in some patients, secondary lung metastasis appears soon after the first pulmonary surgery, making curative treatment very difficult. Postoperative weakness of tumor angiogenesis suppression mechanisms seems to play an important role in the recurrence of lung metastases. To verify this hypothesis, we performed a clinical and an experimental study. **RESULTS AND CONCLUSION:** The clinical study revealed that serum vascular endothelial growth factor (VEGF), also known as vascular permeability factor, increased after pulmonary surgery. The experimental study showed that VEGF played an important role in the rapid growth of dormant micrometastases of the lung. These results suggested that the postoperative increase of VEGF disrupted angiogenesis suppression and induced the growth of dormant micrometastases early in the postoperative period. It was also demonstrated that this effect of VEGF on micrometastases was abolished by AGM-1470, an angiogenesis inhibitor. In conclusion, postoperative treatment with AGM-1470 might inhibit the early recurrence of malignant tumors.

Mannaerts, G. H., H. Martijn, et al. (2000). "Feasibility and first results of multimodality treatment, combining EBRT, extensive surgery, and IOERT in locally advanced primary rectal cancer." *Int J Radiat Oncol Biol Phys* **47**(2): 425-33.

PURPOSE: To assess the outcome of aggressive multimodality treatment with preoperative external beam radiation therapy (EBRT), extended circumferential margin excision (ECME) and intraoperative electron beam radiation therapy (IOERT) in patients with locally advanced primary rectal cancer. **METHODS AND MATERIALS:** Thirty-eight patients with primary locally advanced rectal cancer, but without distant metastases, received multimodality treatment. CT-scan showed extension to other structures in 15 patients (39%) and definite infiltration into the surrounding structures in 23 patients (61%). All patients received preoperative EBRT (dose range 25-61 Gy) and 82% received 50.4 Gy. The resection types were: 12 low anterior resections (31%), 14 abdomino-perineal resections (37%), 6 abdomino-transsacral resections (16%), and 6 pelvic exenterations (16%). The IOERT dose ranged from 10 to 17.5 Gy depending on the completeness of the resection. **RESULTS:** There was no perioperative mortality. The resection margins were microscopically negative in 31 patients (82%), microscopically positive in 4 (10%), and positive with gross residual disease in 3 patients (8%). Pelvic recurrences were observed in 5 patients (13%) including 3 IOERT infield failures. The overall 3-year local control, disease-free survival (DFS), and survival rates were

82%, 65%, and 72%, respectively. Negative resection margins were the most significant prognostic factor with regard to DFS ($p = 0.0003$) and distant control ($p = 0.002$) compared with cancer involved surgical margins. **CONCLUSION:** A high percentage of curative resections can be achieved in this group of patients with locally advanced rectal cancers. Adding IOERT to preoperative EBRT and ECME achieves high local control rates and possibly improves survival.

Mannino, M. and J. R. Yarnold (2009). "Local relapse rates are falling after breast conserving surgery and systemic therapy for early breast cancer: can radiotherapy ever be safely withheld?" Radiother Oncol **90**(1): 14-22.

Rates of local tumour relapse after breast conservation treatment in women with early breast cancer are falling. Explanations for this decline are considered in this review including advances in breast cancer management and aging of the breast cancer population. Breast surgery has become more standardised following publication of practice guidelines and is mostly carried out by specialist surgeons. Systemic therapies (hormonal therapy and chemotherapy) are now more effective and are recommended to a higher proportion of patients than ever before. Radiotherapy techniques have also improved. The contributions of each factor are difficult to quantify precisely, but all are likely to be relevant. In order to identify a subgroup of women that might safely be spared radiotherapy, several factors are analysed, including the prognostic significance for local relapse of tumour characteristics (pathologic data, gene-expression profiles), patient characteristics and life expectancy (age and comorbidities).

Martin, M. A., R. Meyricke, et al. (2007). "Breast-conserving surgery versus mastectomy for survival from breast cancer: the Western Australian experience." Ann Surg Oncol **14**(1): 157-64.

BACKGROUND: The focus of this study was the relative survival rates of breast cancer patients whose treatment was breast-conserving surgery compared with that of mastectomy, adjusting for tumor size and nodal status because these factors may be intrinsically associated with mastectomy being the treatment of choice. Patient age was also accounted for in the model. By adjusting for these factors, we mitigate them as confounders of treatment choice in assessing effects on survival rates. **METHODS:** Data were sourced from linked administrative data from the Western Australian Department of Health Record Linkage Unit. The data consisted of linked records containing the diagnosis, subsequent hospital

admission, and death records of about 3000 women diagnosed with cancer in Western Australia between 1 January 1995 and 31 December 1999. Cox proportional hazards regression was used to investigate survival outcomes of breast-conserving surgery compared with that of mastectomy, adjusting for tumor size, nodal status, and subject age. **RESULTS:** The hazard of death is reduced by a factor of about one half for subjects whose treatment was breast-conserving surgery over treatment by mastectomy. Furthermore, the hazard of death increases substantially for subjects with nodal involvement over subjects for whom there has been no identified spread to regional lymph nodes. Hazard of death increases as both age and tumor size increase. **CONCLUSIONS:** Western Australian breast cancer patients treated with breast-conserving surgery have improved survival outcomes over those treated with mastectomy, after allowing for tumor size, patient age, and lymph node involvement.

Martin-Loeches, M., R. M. Orti, et al. (2002). "Multivariate analysis of the morphometric characteristics of tumours as prognostic factors in the survival of patients with uterine cervix cancer treated with radical surgery." Eur J Obstet Gynecol Reprod Biol **105**(2): 170-6.

OBJECTIVES: To analyse the influence of tumour size and anatomopathological characteristics in the prognosis of patients with early-stage cancer of the uterine cervix treated with radical surgery. **STUDY DESIGN:** A historical study of 114 patients treated at the Maternity Hospital "La Fe" in Valencia was undertaken during the period 1971-1989. The influence of the principal risk factors on prognosis were studied and their effect adjusted using a multivariate analysis based on the Cox proportional hazards model. **RESULTS:** A greater dimension of the tumour, tumour area, tumour volume, tumour-cervix quotient and stromal invasion depth all have a highly significant and negative correlation with survival and disease-free survival intervals. In the multivariate analysis, tumour volume and stromal invasion depth maintained their significance as indicators of an adverse prognosis regarding the disease-free survival interval, as did the stromal invasion depth in the case of survival. **CONCLUSIONS:** The most important prognostic factor in the evolution of patients with a cervical carcinoma is the stromal invasion depth followed by tumour size.

Mastaglia, B. and L. J. Kristjanson (2001). "Factors influencing women's decisions for choice of surgery for Stage I and Stage II breast cancer in Western Australia." J Adv Nurs **35**(6): 836-47.

BACKGROUND: Internal and external factors have been reported to influence decision-making by women for breast cancer surgery. **AIM OF THE STUDY:** The aim of the study was to describe the factors those women with Stage I or Stage II breast cancer, perceived to be important when selecting either modified radical mastectomy or breast conserving treatment. **DESIGN/METHOD:** A descriptive correlational study was conducted. A consecutive sample of women with a diagnosis of breast cancer during a 6-month period was selected from the Health Department of Western Australia Cancer Registry. **RESULTS:** Women who had breast conserving treatment rated the surgeon's preference as a more important factor in decision-making than women who had modified radical mastectomy. The lack of difference in long-term survival between the types of surgery was also a more important influence on decision-making for the breast conserving treatment group compared with women who had received modified radical mastectomy. Women in rural areas tended to choose modified radical mastectomy rather than breast conserving treatment. The surgeon, family and general practitioner were important sources of information. A significant association was found between women's involvement in decision-making and their use of a general practitioner as an information source. Many women wanted the decision about surgery to be entirely their own; the breast conserving treatment group preferred a more active role in decision-making compared with those who chose modified radical mastectomy. Most women had participated in the decision-making process as much as they wished, had enough time in which to make their decisions and had received sufficient information. A correlation between adequacy of information and sufficient time for decision-making was found. **CONCLUSION:** Findings may be useful to nurses and other health professionals who endeavour to provide adequate information and support to women during their initial treatment decision-making experience.

Matsuda, A., T. Matsutani, et al. (2009). "Preoperative plasma adiponectin level is a risk factor for postoperative infection following colorectal cancer surgery." *J Surg Res* **157**(2): 227-34.

BACKGROUND: Adiponectin is produced exclusively by adipose tissues. It is associated with visceral adiposity and various metabolic disorders, and acts as an anti-inflammatory protein that inhibits nuclear factor-kappaB activation. The purpose of this study is to clarify the association between the preoperative plasma adiponectin levels and the development of postoperative infection following colorectal cancer surgery. **METHODS:** Peripheral

blood samples were collected from 41 colorectal cancer patients before surgery and on postoperative days (PODs) 1, 3, 5, and 7. Plasma adiponectin, leptin, and serum C-reactive protein (CRP) levels were measured and the white blood cells (WBCs) were counted. Subcutaneous and visceral fat volumes were quantified by preoperative CT scans. The patients were divided into a group with postoperative infections and an uninfected group. **RESULTS:** In both groups, the postoperative plasma adiponectin levels decreased transiently and then gradually recovered. However, the infected group had significantly lower adiponectin levels throughout the perioperative period than the uninfected group. Logistic regression analysis revealed that preoperative adiponectin level was an independent risk factor for postoperative infection. **CONCLUSIONS:** Preoperative adiponectin levels may be useful for anticipating the development of postoperative infection following colorectal cancer surgery.

Matsuda, K., T. Hotta, et al. (2007). "Repeat reduction surgery after an initial hepatectomy for patients with colorectal cancer." *Oncol Rep* **18**(1): 189-94.

A hepatectomy is the only treatment offering long-term survival in patients with colorectal liver metastases. However, 70-80% of the patients with a complete resection develop recurrent disease after an initial hepatectomy. Sixty-one patients who underwent metastases from colorectal carcinoma with a curative hepatectomy were entered into this study. Recurrence after hepatectomy was observed in 41 patients (67.2%). We reviewed the outcome of these 41 patients. Repeat reduction surgery was performed on 16 out of 41 patients (39.0%). According to a multivariate analysis, repeat reduction surgery and tumor size were found to be independent prognostic factors for the survival rate ($p=0.007$, $p=0.018$). Furthermore, in the group that underwent repeat reduction surgery, the rate of positive lymph nodes was significantly lower in the primary lesions, and the disease-free interval (DFI) was also significantly longer than in the group that did not undergo repeat reduction surgery ($p=0.023$, $p=0.045$), respectively. Repeat reduction surgery was found to be the most important prognostic factor. Patients with a longer DFI and with negative lymph node findings at the primary site may therefore be considered to be good candidates for repeat reduction surgery.

Meguid, R. A., C. M. Hooker, et al. (2009). "Recurrence after neoadjuvant chemoradiation and surgery for esophageal cancer: does the pattern of recurrence differ for patients with complete response and those with partial or no response?" *J Thorac Cardiovasc Surg* **138**(6): 1309-17.

OBJECTIVE: We hypothesized that most relapses in patients with esophageal cancer having neoadjuvant chemoradiation therapy would occur outside of the surgical and radiation fields. **METHODS:** Recurrence patterns, time to recurrence, and median survival were examined in 267 patients who had esophagectomy after neoadjuvant chemoradiation therapy at Johns Hopkins over 19 years. **RESULTS:** Of 267 patients, 82 (30.7%) showed complete response to neoadjuvant therapy, with 108 (40.4%) and 77 (28.8%) showing partial response or no response, respectively. Recurrence developed in 84 patients (patients with complete response 18/82, 21.4%; patients with partial response 39/108, 36.1%; patients with no response 27/77, 35.1%; $P = .055$, respectively). Most patients had recurrences at distant sites (65/84;77.4%) regardless of pathologic response, and subsequent survival was brief (median 8.37 months). Median disease-free survival was short (10 months) and did not differ based on recurrence site for patients with partial response or no response, but was longer for patients with complete response with distant recurrence, whose median disease-free survival was 27.3 months ($P = .008$). By multivariate analysis, no other factor except for pathologic response to neoadjuvant therapy was associated with disease recurrence or death. Patients with partial response or no response were 1.97 and 2.23 times more likely to have recurrence than patients with complete response ($P = .024$ and $P = .012$, respectively). **CONCLUSIONS:** Most esophageal cancer recurrences after neoadjuvant therapy and surgery are distant, and survival time after recurrence is short regardless of pathologic response. Fewer patients achieving complete response had recurrences, and distant recurrences in these patients manifest later than in patients showing partial response and those showing no response. Only pathologic response is significantly associated with disease recurrence, suggesting that tumor biology and chemosensitivity are critical in long-term patient outcome.

Menconi, G. F., M. C. Ambrogi, et al. (1998). "Endothoracic sonography with color Doppler availability during video assisted thoracic surgery (videothoracoscopic operative staging with ultrasound color Doppler) for lung cancer staging." *Surg Endosc* 12(6): 816-9.

BACKGROUND: The preoperative staging of lung cancer can be problematical when we attempt to evaluate T factor (T2-T3 versus T4) and N factor (N0 versus N1-N2). In some cases, radiology tests (CT scan, magnetic resonance imaging) cannot entirely dispel the possibility that the mediastinal structures have been infiltrated. N factor is evaluated

mainly by dimensional criteria. However, mediastinoscopy and mediastinotomy do not allow the full exploration of all mediastinal node stations. **METHOD:** Starting in 1995, we submitted 10 consecutive patients to videothoracoscopic operative staging with ultrasound color Doppler (VOS-USCD). In five cases, preoperative staging showed possible infiltration of the pulmonary artery (T4). In nine cases, we found involvement of the mediastinal nodes, seven patients were N2, and two were N3. Videothoracoscopy was performed under general anesthesia using a double-lumen endotracheal tube. The videothoracoscope and sonographic probe were inserted via three thoracoports placed in the axillary triangle. **RESULTS:** Following the results of VOS-USCD, the staging and subsequently the therapeutic program were modified in seven of 10 cases (70%). **CONCLUSIONS:** Our preliminary experience indicates that VOS-USCD should be applied to the diagnosis of patients in stage IIIA (N2) and that it is particularly valuable for patients in stage IIIB.

Meyer, A., T. Dork, et al. (2007). "Breast cancer in patients carrying a germ-line CHEK2 mutation: Outcome after breast conserving surgery and adjuvant radiotherapy." *Radiother Oncol* 82(3): 349-53.

BACKGROUND AND PURPOSE: Women carrying mutations in the CHEK2 gene are at an increased breast cancer risk. Data about outcome and prognosis for these patients after standard multimodality treatment are scarce at present. **MATERIALS AND METHODS:** One-hundred and fifty (150) patients with non-metastasized early-stage breast cancer (T1-2) receiving postoperative radiotherapy following breast-conservative surgery at our department were included in this analysis. Carriers were identified using mutation-specific restriction enzyme-based screening assays in previous investigations. Twenty-five breast cancer patients were heterozygous for one of three CHEK2 gene mutations (I157T, n=13; 1100delC, n=10; IVS2+1G>A, n=2). The comparison group consisted of 125 early-stage breast cancer patients without a CHEK2 gene mutation (non-carriers). Median follow-up was 87 months for the total cohort of patients. **RESULTS:** Local recurrences occurred in 13 patients (carriers, 3 (12%); non-carriers, 10 (8%)) and distant metastases occurred in 27 patients (carriers, 8 (32%); non-carriers, 19 (15%)). Twenty-five patients had deceased (carriers, 8 (32%); non-carriers, 17 (14%)) with all but 3 deaths related to breast cancer. Actuarial 7-year local relapse-free survival was 86% in carriers versus 90% in non-carriers ($p=0.48$). Actuarial metastasis-free, disease-free and overall survival at 7 years were 64% vs. 84% ($p=0.045$), 59% vs. 78% ($p=0.07$) and 69% vs. 87% ($p=0.10$), respectively. In a

multivariate step-wise Cox regression analysis presence of a CHEK2 mutation remained a borderline significant discriminator for metastasis-free survival ($p=0.048$; OR=0.4; 95% CI 0.2-1.0) next to T-stage ($p=0.001$; OR 0.3; 95% CI 0.1-0.6). CONCLUSIONS: Heterozygosity for a germline CHEK2 mutation appears to represent an adverse prognostic factor in patients with early-stage breast cancer. If confirmed in larger studies these data may serve as a basis for future surveillance and treatment strategies taking into account individual germline mutational status.

Mineo, T. C., V. Ambrogi, et al. (2004). "Prognostic impact of VEGF, CD31, CD34, and CD105 expression and tumour vessel invasion after radical surgery for IB-IIA non-small cell lung cancer." *J Clin Pathol* **57**(6): 591-7.

AIMS: To evaluate the prognostic impact of tumour angiogenesis assessed by vascular endothelial growth factor (VEGF), microvessel density (MVD), and tumour vessel invasion in patients who had undergone radical resection for stage IB-IIA non-small cell lung cancer (NSCLC). METHODS: Fifty one patients (42 men, nine women; mean age, 62.3 years; SD, 6.9) undergoing complete surgical resection (35 lobectomy, 16 pneumonectomy) of pathological stage IB ($n = 43$) and IIA ($n = 8$) NSCLC were evaluated retrospectively. No patient underwent postoperative chemotherapy or neoadjuvant treatment. Tumour specimens were stained for VEGF and specific MVD markers: CD31, CD34, and CD105. RESULTS: VEGF expression significantly correlated with high CD105 expression ($p < 0.0001$) and tumour vessel invasion ($p = 0.04$). Univariate analysis showed that those patients with VEGF overexpression ($p = 0.0029$), high MVD by CD34 ($p = 0.0081$), high MVD by CD105 ($p = 0.0261$), and tumour vessel invasion ($p = 0.0245$) have a shorter overall survival. Furthermore, multivariate Cox regression analysis showed that MVD by CD34 ($p = 0.007$), tumour vessel invasion ($p = 0.024$), and VEGF expression ($p = 0.042$) were significant predictive factors for overall survival. Finally, the presence of both risk factors, tumour vessel invasion and MVD by CD34, was highly predictive of poor outcome (odds ratio, 3.4; 95% confidence interval, 1.7 to 6.5; $p = 0.0002$). CONCLUSIONS: High MVD by CD34 and tumour vessel invasion are more closely related to poor survival than the other neoangiogenetic factors in stage IB-IIA NSCLC. This may be because these factors are more closely related to the metastatic process.

Miner, T. J. (2005). "Palliative surgery for advanced cancer: lessons learned in patient selection and outcome assessment." *Am J Clin Oncol* **28**(4): 411-4.

INTRODUCTION: When considering the appropriate and effective use of palliative procedures, a surgeon is often confronted with a full range of multidisciplinary treatment options and technical considerations that could potentially relieve some of the symptoms of an advanced malignancy. Practitioners must often deliberate over complex choices that can greatly impact a patient's final days. METHODS: Advances in the understanding of surgical palliation are reviewed with emphasis on elements required for sound clinical decision making. RESULTS: Palliation of complications from advanced cancer demands the highest level of surgical judgment. Although consideration of risk in terms of treatment-related toxicity, morbidity and mortality is an important part of the surgical decision making process. Attention to this element should not be the sole factor in making decisions about palliative therapy. Decisions are best made on endpoints such as the probability of symptom resolution, the impact on overall quality of life, pain control, and cost effectiveness. CONCLUSIONS: Regardless of the anatomic site and cause leading to the need for palliative intervention, deliberations over surgical palliation must consider the medical condition and performance status of the patient, the extent and prognosis of the cancer, the availability and success of nonsurgical management, and the individual patient's quality and expectancy of life. Therapy for symptoms must remain flexible and individualized to continually meet the patient's unique and ever changing needs.

Mishra, P. K., R. Pandey, et al. (2009). "Cardiac comorbidity is not a risk factor for mortality and morbidity following surgery for primary non-small cell lung cancer." *Eur J Cardiothorac Surg* **35**(3): 439-43.

OBJECTIVE: We examined the effect of cardiac comorbidity on mortality and postoperative complications following surgery for primary non-small cell lung cancer. METHODS: Between October 2001 to December 2005, 1067 consecutive patients underwent lung resection for primary cancer within a single centre; patient data was collected prospectively. Two hundred and seventy-one patients had a history of cardiac comorbidity, which included 196 angina, 118 myocardial infarction, 36 revascularisation, 10 congestive cardiac failure and 19 rhythm disorders (numbers not mutually exclusive). To account for differences in case-mix we used logistic regression to develop a propensity score for cardiac comorbidity group membership and then performed a propensity-matched analysis. Kaplan-Meier curves were used to assess follow-up mortality. RESULTS: Patients with cardiac comorbidity were more likely to be hypertensive, have severe dyspnoea, diabetes, current

or ex-smokers and were older. After performing propensity matching to account for these differences we successfully matched 199 patients with cardiac comorbidity to 398 patients with no cardiac history. There was no difference in in-hospital mortality (2.5% vs 3%, $p=0.73$), myocardial infarction (0.5% vs 0.3%, $p>0.99$), arrhythmia (15.6% vs 14.1%, $p=0.62$), renal failure (2% vs 1.5%, $p=0.65$), stroke (0.5% vs 0.3%, $p>0.99$), respiratory insufficiency (4% vs 3.3%, $p=0.64$), reintubation (1% vs 2.5%, $p=0.35$), tracheostomy (4% vs 7.8%, $p=0.08$), intensive care readmission (8.5% vs 6.5%, $p=0.37$) and length of stay (8 days vs 8 days, $p=0.98$). Three-year survival was similar (61.4% vs 56.2%, $p=0.39$). No differences in outcomes existed with different cardiac conditions. **CONCLUSION:** With careful assessment and patient selection, patients with cardiac comorbidity were not found to be at increased risk of mortality and morbidity following lung resection for primary non-small cell lung cancer in a propensity-matched population.

Miyoshi, M., H. Ueno, et al. (2006). "Extent of mesorectal tumor invasion as a prognostic factor after curative surgery for T3 rectal cancer patients." Ann Surg **243**(4): 492-8.

OBJECTIVE: To determine the significance of the extent of mesorectal tumor invasion as a prognostic factor for T3 rectal cancer patients. **SUMMARY BACKGROUND DATA:** There is controversy as to which primary lesion characteristics, other than regional lymph node involvement, in T3 rectal cancer are reliable prognostic factors. **PATIENTS AND METHODS:** The extent of mesorectal tumor invasion was evaluated using 2 data sets comprising 196 and 247 patients undergoing curative surgery at separate institutes. When the outer aspect of the muscular layer was not identifiable, an estimate was obtained by drawing a straight line between the 2 break points of the muscular layer. **RESULTS:** We selected 6 mm as the optimal value for subclassification of T3 rectal patients into 2 groups, based on the extent of mesorectal invasion, using the first data set. The overall 5-year survival rate was significantly higher in patients with <6 mm than in those with $>$ or $=6$ mm of mesorectal invasion (72% versus 50%; $P < 0.01$). Similarly, in the second data set, the overall 5-year survival rates of patients with mesorectal invasion <6 mm and $>$ or $=6$ mm were 59% and 37%, respectively ($P < 0.01$). In both data sets, multivariate analyses verified the extent of mesorectal invasion to be an independent prognostic factor, together with nodal involvement. Regarding positive nodal involvement and mesorectal invasion $>$ or $=6$ mm as risk factors, the overall 5-year survival rates with none, one, and both of these factors were

84%, 61%, and 38%, respectively, in the first data set ($P < 0.01$). Prognostic results were similar for the second data set. **CONCLUSION:** Extent of mesorectal invasion, based on a 6-mm cutoff value, is useful for subclassification of T3 rectal cancer patients.

Mizuno, M., M. Kakuta, et al. (2009). "The effects of sense of coherence, demands of illness, and social support on quality of life after surgery in patients with gastrointestinal tract cancer." Oncol Nurs Forum **36**(3): E144-52.

PURPOSE/OBJECTIVES: To examine the relationship between quality of life (QOL) as an index of adaptation status and concepts related to self-care skills of patients who have been diagnosed with and undergone surgery for digestive system cancer: sense of coherence (SOC), social support, demands of illness, and the thought "Why me?" **DESIGN:** Cross-sectional survey. **SETTING:** General hospitals in Japan. **SAMPLE:** 60 patients who had been newly diagnosed with digestive system cancer and had undergone surgery. **METHODS:** Questionnaires were distributed to participants whose discharge date had been determined. The questionnaires were returned through the mail within two weeks of the discharge date. **MAIN RESEARCH VARIABLES:** QOL, SOC, social support, demands of illness, and the thought "Why me?" **FINDINGS:** QOL was strongly correlated with SOC and the demands of illness and was moderately correlated with social support. The only variable that was negatively correlated with SOC was the question, "Why me?" SOC and demands of illness accounted for 54% of the variance in QOL; social support was not a significant factor. **CONCLUSIONS:** This study suggests that SOC is positively correlated with QOL and the demands of illness are negatively correlated with QOL among study participants. **IMPLICATIONS FOR NURSING:** Nursing interventions focusing on SOC and illness demands may have a significant effect on QOL of patients following cancer surgery.

Morgagni, P., D. Garcea, et al. (2008). "Resection line involvement after gastric cancer surgery: clinical outcome in nonsurgically retreated patients." World J Surg **32**(12): 2661-7.

PURPOSE: Resection line infiltration (RLI) after surgical treatment represents an unfavorable prognostic factor in advanced gastric cancer. We performed a retrospective analysis of 89 patients with resection line involvement who did not undergo reoperation. **METHODS:** On behalf of the Italian Research Group for Gastric Cancer, we present the characteristics and outcome of 89 patients who were submitted to surgical resection for gastric cancer from 1988 to 2001 and did not undergo reoperation because

of disease extension or associated pathologies. RESULTS: RLI was significantly higher in patients with T4 tumors and diffuse histological type. Anastomotic leakages were observed in 4.8% of infiltrated esophageal resection margins, whereas 1.9% of infiltrated duodenal resection lines showed duodenal fistulas. Five-year overall survival of patients with RLI was 29%. Prognosis was not affected by RLI in early forms (100% 5-year survival); however, 5-year survival in T2 and T3 stages was significantly lower with respect to the same stages without residual tumor. The influence of RLI on prognosis was confirmed in N0 as well as in N1 and N2 patients. RLI also was an independent prognostic at multivariate analysis (odds ratio = 1.5; 95% confidence interval, 1.08-2.08; P = 0.0144). CONCLUSIONS: RLI significantly affects long-term survival of advanced gastric cancer. The impact on prognosis is independent of lymph node involvement. Patients in good general condition for whom radical surgery is possible should be considered for reoperation.

Morimoto, K., M. Koh, et al. (2002). "Levofloxacin for prophylaxis in breast cancer surgery compared with ofloxacin." *Jpn J Antibiot* **55**(6): 866-74.

BACKGROUND: We found that once-daily use of ofloxacin is beneficial from the standpoints of economy and patient compliance. Levofloxacin, has twice the antimicrobial activity and same toxicity of ofloxacin. We investigated the clinical usefulness of levofloxacin compared with ofloxacin in breast surgery. METHOD: Between July, 1996 and April, 1999, 199 consecutive patients hospitalized in our department for treatment of breast cancer were enrolled in this study with their informed consent and 181 patients were evaluated. RESULTS: Four (4%) of the 99 patients in the levofloxacin group had wound infections, as did 5 (6%) of the 82 patients in the ofloxacin group. The median times needed for wound care, with 25th and 75th percentiles, were 13 [9, 16] days in the levofloxacin group and 11 [9, 16] days in the ofloxacin group. From infected wound three strains of *Staphylococcus aureus* were detected from the levofloxacin group and two strains were from ofloxacin group, but no methicillin-resistant strains were isolated. Multiple regression analysis showed that only wound dehiscence was a significant factor in the occurrence of wound infection and the period of wound care. No signs or symptoms suggesting levofloxacin or ofloxacin toxicity were observed. Laboratory test changes before and after treatment were similar in the two groups. CONCLUSION: It appears that levofloxacin is not superior to ofloxacin in prophylactic efficacy for postoperative wound infection after breast surgery.

Motoyama, S., M. Miura, et al. (2009). "Interferon-gamma 874A>T genetic polymorphism is associated with infectious complications following surgery in patients with thoracic esophageal cancer." *Surgery* **146**(5): 931-8.

BACKGROUND: Cytokines play a major role in the organization of orchestrated responses to infections, and there is an emerging consensus that cytokine gene polymorphisms mediate individual variations in cytokine expression. Our aim in this study was to assess whether cytokine polymorphisms were associated with infectious complications following esophagectomy in a Japanese population. METHODS: The study participants were Japanese patients treated with transthoracic esophagectomy without neoadjuvant treatment. DNA was extracted from blood samples, and genetic polymorphisms for interferon (INF)-gamma, tumor necrosis factor-alpha and -beta, transforming growth factor-beta1, interleukin (IL)-1beta, IL-1 receptor antagonist, IL-2, IL-6, IL-6 receptor, IL-10, and IL-12beta were investigated using the polymerase chain reaction-restriction fragment length polymorphism method. We then assessed the association between gene polymorphisms and postoperative infection. RESULTS: Of the 110 patients studied, 18 (16%) developed a postoperative infection (pneumonia, 14 patients; pyothorax, 5; intraabdominal abscess, 1; neck abscess, 1; sepsis, 2). Although the characteristics of patients who developed postoperative infections did not differ, analysis of the genotypes using the Fisher exact test revealed a significantly (P = .0215) greater incidence of postoperative infections among those carrying the INF-gamma 874 (rs2430561) A/A and A/T genotypes. Moreover, univariate and multivariate logistic regression models showed patients carrying the INF-gamma 874A/T genotype were significantly more likely to develop postoperative infectious complications (odds ratio>3.4). CONCLUSION: Our findings suggest that the IFN-gamma 874A>T polymorphism is potentially predictive of the likelihood that patients undergoing esophagectomy for thoracic esophageal cancer will develop postoperative infections. This polymorphism may therefore have important clinical relevance and should be considered when treatment regimens are designed.

Motoyama, S., R. Saito, et al. (2002). "Survival advantage of using autologous blood transfusion during surgery for esophageal cancer." *Surg Today* **32**(11): 951-8.

PURPOSE: There is evidence that blood transfusion is associated with an increased rate of tumor recurrence. This study was conducted to assess

the survival advantage of giving autologous blood instead of allogeneic blood during surgery for esophageal cancer. **METHODS:** We retrospectively analyzed 62 patients who underwent esophagectomy for thoracic esophageal cancer between January 1991 and February 1995 and received allogeneic blood transfusion, and 61 patients operated on between March 1995 and February 1998, who received autologous blood transfusion. The clinicopathological factors and survival rates were compared between the two groups. **RESULTS:** The clinicopathological factors that influenced prognosis were similar in the two groups; however, a definite survival advantage was evident in the autologous blood transfusion group. According to multivariate analyses, the transfusion of allogeneic blood was an independent prognostic factor ($P = 0.0222$), as was the presence of metastatic lymph nodes. Patients who received allogeneic blood transfusions perioperatively had more than a twofold greater risk (Hazard ratio 2.406) of death over patients who received autologous blood transfusions. **CONCLUSION:** Autologous blood transfusion appears to be an independent prognostic factor for the survival of patients with esophageal cancer.

Mullen, J. T., D. L. Davenport, et al. (2008). "Impact of body mass index on perioperative outcomes in patients undergoing major intra-abdominal cancer surgery." *Ann Surg Oncol* **15**(8): 2164-72.

BACKGROUND: Obesity is an increasingly common serious chronic health condition. We sought to determine the impact of body mass index (BMI) on perioperative outcomes in patients undergoing major intra-abdominal cancer surgery. **METHODS:** A prospective, multi-institutional, risk-adjusted cohort study of patients undergoing major intra-abdominal cancer surgery was performed from the 14 university hospitals participating in the Patient Safety in Surgery Study of the National Surgical Quality Improvement Program (NSQIP). Demographic, clinical, and intraoperative variables and 30-day morbidity and mortality were prospectively collected in standardized fashion. Analysis of variance, Bonferroni multiple comparisons of means tests, and multivariable logistic regression analysis were performed. **RESULTS:** We identified 2258 patients who underwent esophagectomy ($n = 29$), gastrectomy ($n = 223$), hepatectomy ($n = 554$), pancreatectomy ($n = 699$), or low anterior resection/proctectomy ($n = 753$). Patients were stratified by National Institutes of Health (NIH)-defined BMI obesity class, with 573 (25.4%) patients classified as obese (BMI > 30 kg/m²). There were no differences in mean work relative value units, total time of operation, or length of stay amongst the BMI classes. After adjusting for other risk factors, obesity

was not a risk factor for death or major complications but was a risk factor for wound complications. The risk of postoperative death was greatest in underweight patients (odds ratio [OR] 5.24; 95% confidence interval [CI] 1.7-16.2). **CONCLUSION:** In patients undergoing major intra-abdominal cancer surgery, obesity is not a risk factor for postoperative mortality or major complications. Importantly, underweight patients have a fivefold increased risk of postoperative mortality, perhaps a consequence of their underlying nutritional status.

Mynster, T., I. J. Christensen, et al. (2000). "Effects of the combination of blood transfusion and postoperative infectious complications on prognosis after surgery for colorectal cancer. Danish RANX05 Colorectal Cancer Study Group." *Br J Surg* **87**(11): 1553-62.

BACKGROUND: The frequency of postoperative infectious complications is significantly increased in patients with colorectal cancer receiving perioperative blood transfusion. It is still debated, however, whether perioperative blood transfusion alters the incidence of disease recurrence or otherwise affects the prognosis. **METHODS:** Patient risk variables, variables related to operation technique, blood transfusion and the development of infectious complications were recorded prospectively in 740 patients undergoing elective resection for primary colorectal cancer. Endpoints were overall survival ($n = 740$) and time to diagnosis of recurrent disease in the subgroup of patients operated on with curative intention ($n = 532$). The patients were analysed in four groups divided with respect to administration or not of perioperative blood transfusion and development or non-development of postoperative infectious complications. **RESULTS:** Overall, 19 per cent of 288 non-transfused and 31 per cent of 452 transfused patients developed postoperative infectious complications ($P < 0.001$). The median observation period was 6.8 (range 5.4-7.9) years. In a multivariate analysis, risk of death was significantly increased among patients developing infection after transfusion ($n = 142$) compared with patients receiving neither blood transfusion nor developing infection ($n = 234$): hazard ratio 1.38 (95 per cent confidence interval (c.i.) 1.05-1.81). Overall survival of patients receiving blood transfusion without subsequent infection ($n = 310$) and patients developing infection without preceding transfusion ($n = 54$) was not significantly decreased. In an analysis of disease recurrence the combination of blood transfusion and subsequent development of infection (hazard ratio 1.79 (95 per cent c.i. 1.13-2.82)), localization of cancer in the rectum and Dukes classification were independent risk factors. **CONCLUSION:** Blood transfusion per se

may not be a risk factor for poor prognosis after colorectal cancer surgery. However, the combination of perioperative blood transfusion and subsequent development of postoperative infectious complications may be associated with a poor prognosis.

Mynster, T. and H. J. Nielsen (2001). "Storage time of transfused blood and disease recurrence after colorectal cancer surgery." *Dis Colon Rectum* **44**(7): 955-64.

BACKGROUND: Perioperative blood transfusion and subsequent development of postoperative infectious complications may lead to poor prognosis of patients with colorectal cancer. It has been suggested that the development of postoperative infectious complications may be related to the storage time of the transfused blood. Therefore, we studied the relationship between blood storage time and the development of disease recurrence and long-term survival after colorectal cancer surgery. **METHODS:** Preoperative and postoperative data were prospectively recorded in 740 patients undergoing elective resection for primary colorectal cancer. None of the patients received preoperative or postoperative chemotherapy or radiation therapy. Endpoints were overall survival and disease recurrence in the subgroup of patients operated on with curative intention who also survived the first 30 days after operation. Storage of buffy-coat-depleted red cells suspended in saline, adenine, glucose, and mannitol blood for 21 days was used as cut-off point. **RESULTS:** Median follow-up was 6.8 years (range, 5.4 years to 7.9 years), and median overall survival was 4.6 years for 288 nontransfused patients and 3.0 years for 452 transfused patients ($P = 0.004$). The survival of patients receiving blood exclusively stored < 21 days was 2.5 years. For patients receiving any blood stored \geq 21 days, survival was 3.7 years ($P = 0.12$). Among patients with curative resection ($n = 532$), the hazard ratio of disease recurrence was 1.5 (95 percent CI; 1.1 to 2.2) and 1.0 (95 percent CI; 0.7 to 1.4) in the two transfused groups, respectively, compared with the nontransfused group after multivariable correction for patient age, gender, colonic/rectal tumor localization, Dukes classification, blood loss, and postoperative infectious complications. **CONCLUSION:** Transfusion of buffy-coat-depleted red cells suspended in saline, adenine, glucose, and mannitol blood stored for < 21 days may be an independent risk factor for development of recurrence after elective colorectal cancer surgery.

Nagashima, T., M. Sakakibara, et al. (2008). "Preoperative cytologic morphometry may assist in predicting patient outcome after surgery in papillary

thyroid cancer." *Anal Quant Cytol Histol* **30**(4): 231-6.

OBJECTIVE: To evaluate the quantitative estimations of various cytologic nuclear features on smears obtained by preoperative fine-needle aspiration and to examine their correlation with patient outcome after surgery for papillary thyroid cancer. **STUDY DESIGN:** The subjects consisted of 142 patients with common type papillary thyroid cancer. The aspirated smears were examined quantitatively with a standard microscope connected to a computerized video system, and the mean nuclear area, nuclear perimeter, form factor (FF) and the coefficient of variation of the nuclear area (NACV) were measured and calculated. All of the surgically treated patients were followed through serial clinical evaluations, and correlations between the cytologic parameters and patient outcomes were analyzed. **RESULTS:** Local relapses or distant metastases were identified in 13 (9.2%) of the 142 patients in the median follow-up period of 160 (range, 108-234) months. Recurred cases had higher FF values than disease-free cases ($p = 0.0017$), especially in local relapse ($p = 0.0015$). Distant metastases were frequently observed in the cases with a high NACV value ($p = 0.0020$). **CONCLUSION:** Preoperative quantitative estimations of cytologic nuclear features provide preoperative clinical information that may predict patient outcome and be useful for designing individual protocols.

Nakagoe, T., K. Fukushima, et al. (2002). "Evaluation of sialyl Lewis(a), sialyl Lewis(x), and sialyl Tn antigens expression levels as predictors of recurrence after curative surgery in node-negative colorectal cancer patients." *J Exp Clin Cancer Res* **21**(1): 107-13.

This study aimed to determine whether sialyl Lewis(a) (Le(a)), sialyl Lewis(x) (Le(x)), or sialyl Tn antigen expression could identify a subset of node-negative colorectal cancer patients that are at high risk for recurrence after curative surgery. Tumor tissue samples from 90 patients with node-negative colorectal cancer, who had undergone surgical resection, were analyzed immunohistochemically for the expression of each antigen. Patients were classified as having low or high antigen expression depending on whether more or less than 40% of the field showed positive staining. The main outcome measure for each variable was disease-free interval. Sialyl Le(a), sialyl Le(x), and sialyl Tn antigens were expressed in 53 (58.9%), 41 (45.6%), and 34 (37.8%) carcinomas, respectively. The median follow-up was 83.5 months. Patients with high sialyl Le(x) expression had shorter disease-free intervals than those with low sialyl Le(x) expression ($P = 0.0041$);

the expression of sialyl Le(a) or sialyl Tn antigens did not show a significant relationship with disease-free survival. Cox's regression analysis revealed that sialyl Le(x) expression was an independent predictor for disease-free survival, separate from T factor or tumor location. High sialyl Le(x) expression may be useful in identifying a subset of node-negative colorectal cancer patients who are at high risk for recurrence.

Nakamura, H., T. Haruki, et al. (2008). "Smoking affects prognosis after lung cancer surgery." *Surg Today* **38**(3): 227-31.

PURPOSE: To study the effects of smoking on the postoperative outcome of lung cancer surgery. **METHODS:** The subjects were 571 patients who underwent surgery for primary lung cancer. The patients were divided into the following groups according to their smoking history: a nonsmoker group (n = 218), a former smoker group (n = 140), and a current smoker group (n = 213). **RESULTS:** The 5-year survival rates were 56.2%, 40.9%, and 34.0% in the nonsmoker, former smoker, and current smoker groups, respectively. These differences were significant. According to a multivariable analysis, smoking was a significant factor affecting the postoperative prognosis of patients undergoing surgery for lung cancer. In analyzing the causes of death, there were more deaths caused by other diseases such as multiple organ cancer, respiratory disorder, cardiovascular disease, and surgery-related events in the former smoker and current smoker groups than in the nonsmoker group. **CONCLUSIONS:** Smoking was significantly predictive of a poor prognosis after lung cancer surgery.

Nakamura, T., H. Mitomi, et al. (2008). "Risk factors for wound infection after surgery for colorectal cancer." *World J Surg* **32**(6): 1138-41.

BACKGROUND: Among complications after surgery for colorectal cancer, wound infections may prolong hospitalization and increase healthcare costs. This study was designed to clarify the incidence, risk factors, and pathogens responsible for wound infections after surgery for colorectal cancer. **METHODS:** The study group comprised 144 patients (94 men and 50 women) with colorectal cancer in whom the same surgeon at Kitasato University Hospital performed resection from January 2004 through December 2005. Their mean age was 67.1 years (range = 38-90). To identify risk factors for surgical wound infections, we examined the following 11 variables: gender, age (>65 vs. <or=65 years), body-mass index (>25 vs. <or=25 kg/m²), the presence or absence of diabetes mellitus, physical status according to the American Society of

Anesthesiologists classification (ASA score), stage of cancer according to the TNM staging system, surgical procedure (laparoscopic colectomy vs. open colectomy), procedure type (right colectomy vs. left colectomy vs. anterior resection), operation time (>180 vs. <or=180 min), intraoperative bleeding volume (>120 vs. <or=120 ml), and the presence or absence of intraoperative transfusion. Tissue specimens of infected wounds were cultured to identify pathogens. **RESULTS:** Postoperative wound infections occurred in 12% (17/144) of the patients. In univariate analyses, the incidence of wound infection was 26% (11/43) in patients who underwent open colectomy compared with 6% (6/101) in those who underwent laparoscopic colectomy. This difference was significant (P = 0.001). In multivariate analyses, only surgical procedure was identified as an independent risk factor for wound infection. The odds ratio for open colectomy compared with laparoscopic colectomy was 3.322 (P = 0.021). Pus from infected wounds was cultured in 7 of the 17 patients and cultures were positive for pathogens in 5 patients: 1 laparoscopic colectomy and 4 open colectomy. Bacteroides species were the most common pathogen. **CONCLUSION:** To prevent wound infections after surgery for colorectal cancer, laparoscopic surgery should be performed when indicated.

Nam, R. K., L. Sugar, et al. (2007). "Expression of the TMPRSS2:ERG fusion gene predicts cancer recurrence after surgery for localised prostate cancer." *Br J Cancer* **97**(12): 1690-5.

The prostate-specific gene, TMPRSS2 is fused with the gene for the transcription factor ERG in a large proportion of human prostate cancers. The prognostic significance of the presence of the TMPRSS2:ERG gene fusion product remains controversial. We examined prostate cancer specimens from 165 patients who underwent surgery for clinically localised prostate cancer between 1998 and 2006. We tested for the presence of TMPRSS2:ERG gene fusion product, using RT-PCR and direct sequencing. We conducted a survival analysis to determine the prognostic significance of the presence of the TMPRSS2:ERG fusion gene on the risk of prostate cancer recurrence, adjusting for the established prognostic factors. We discovered that the fusion gene was expressed within the prostate cancer cells in 81 of 165 (49.1%) patients. Of the 165 patients, 43 (26.1%) developed prostate-specific antigen (PSA) relapse after a mean follow-up of 28 months. The subgroup of patients with the fusion protein had a significantly higher risk of recurrence (58.4% at 5 years) than did patients who lacked the fusion protein (8.1%, P<0.0001). In a multivariable analysis, the presence of gene fusion was the single

most important prognostic factor; the adjusted hazard ratio for disease recurrence for patients with the fusion protein was 8.6 (95% CI=3.6-20.6, $P < 0.0001$) compared to patients without the fusion protein. Among prostate cancer patients treated with surgery, the expression of TMPRSS2:ERG fusion gene is a strong prognostic factor and is independent of grade, stage and PSA level.

Ng, C. S., S. Wan, et al. (2007). "Video-assisted thoracic surgery lobectomy for lung cancer is associated with less immunochemokine disturbances than thoracotomy." *Eur J Cardiothorac Surg* **31**(1): 83-7.

OBJECTIVE: Major surgery is immunosuppressive and could have an impact on postoperative tumor immunosurveillance and recurrence in cancer patients. Low circulating levels of insulin growth factor binding protein (IGFBP)-3 have been linked to advance prostate and the development of colonic cancers. This prospective study examined the early postoperative circulating levels of IGFBP-3, matrix metalloproteinase (MMP)-9, and tissue inhibitor of metalloproteinase (TIMP)-1 in early stage non-small cell lung cancer (NSCLC) patients undergoing major lung resection by VATS versus thoracotomy. **METHODS:** Forty-two consecutive patients with resectable primary NSCLC were assigned to VATS or thoracotomy approach over a 7-month-period. Blood samples were collected preoperatively and postoperatively on days (POD) 1 and 3 for enzyme linked immunosorbent assay determination of IGFBP-3, MMP-9 and TIMP-1 levels in the serum. **RESULTS:** There were no demographic differences between the two groups. VATS lung resection was associated with lower levels of MMP-9 and TIMP-1 on POD1 (median 628 vs 1311ng/ml, $p=0.009$; and 131 vs 211ng/ml, $p=0.004$, respectively) but higher levels of IGFBP-3 on POD3 (1366 vs 1144ng/ml, $p=0.02$), when compared with the thoracotomy approach. There was no perioperative mortality. **CONCLUSIONS:** VATS major lung resection for NSCLC is associated with higher circulating levels of IGFBP-3, and lower levels of MMP-9 and TIMP-1, compared to the thoracotomy approach. The clinical relevance of these postoperative changes on tumor biology following lung resection for cancer warrants further investigation.

Nichols, Ward, et al. (1999). "Influence of perioperative immunotherapy on serum cytokines and soluble cytokine receptors in patients undergoing surgery for colorectal cancer." *Colorectal Dis* **1**(5): 286-91.

OBJECTIVE: The cellular immune response is suppressed following surgery for colorectal cancer. As cytokines influence the patient's immunological responsiveness, we have measured serum cytokines and their soluble receptors in patients receiving perioperative immunotherapy for colorectal cancer. **PATIENTS AND METHODS:** Fifty-two patients were randomized to receive low dose recombinant IL-2 (rIL-2) alone; rIL-2 with interferon-alpha (IFN-alpha) or no immunotherapy. Serum cytokines and cytokine receptor levels were measured preoperatively and on post-operative days 1, 4, 7 and 10 using ELISA kits. **RESULTS:** Circulating levels of IFN-gamma were undetectable in the majority of patients, although IFN-gammaR levels were increased in all three groups on the first post-operative day ($P < 0.05$). Similarly, IL-2 was undetectable in most subjects and not enhanced by treatment. However, IL-2R was significantly induced in all patients ($P < 0.001$), and these levels were higher in both treatment groups when compared with control ($P < 0.005$). Tumour necrosis factor-alpha (TNF-alpha) was universally undetectable, but the TNF-R p55 and p75 subunits were induced in all patients ($P < 0.005$); and as with IL-2R, this was greater in the treatment groups ($P < 0.01$). Finally, IL-6 production was induced in all groups ($P < 0.005$), but this was only noted on day 1. **CONCLUSION:** Soluble cytokine receptors are induced by surgery, and levels of IL-2R and TNF-R are enhanced by exogenous rIL-2 and rIL-2 with IFN-alpha. This augmentation suggests increased immunocompetence associated with low dose perioperative immunotherapy.

Nitori, N., H. Hasegawa, et al. (2009). "Impact of visceral obesity on short-term outcome after laparoscopic surgery for colorectal cancer: a single Japanese center study." *Surg Laparosc Endosc Percutan Tech* **19**(4): 324-7.

PURPOSE: This prospective study was conducted to clarify the association between the short-term outcome of laparoscopic colorectal surgery and visceral obesity (VO) based on waist circumference (WC). **METHODS:** WC and body mass index (BMI) were preoperatively measured in 98 consecutive patients with colorectal cancer undergoing laparoscopic surgery between June 2004 and February 2006. VO was defined as both BMI ≥ 25 kg/m² and WC ≥ 85 cm in male patients, or WC ≥ 90 cm in female patients. **RESULTS:** The patients were divided into VO (n=21) and non-VO (n=77). Systemic complications were significantly more frequent in VO than in non-VO (19.0% vs. 3.9%, $P=0.036$), and VO was the only significant independent risk factor (odds ratio 8.1, $P=0.018$). BMI itself had no impact on outcome. **CONCLUSIONS:** WC is a potentially

useful index for the assessment of surgical risk in laparoscopic colorectal surgery.

Nitori, N., H. Hasegawa, et al. (2008). "Sexual function in men with rectal and rectosigmoid cancer after laparoscopic and open surgery." *Hepatogastroenterology* **55**(85): 1304-7.

BACKGROUND/AIMS: Postoperative sexual dysfunction is a serious problem in rectal cancer patients. Although laparoscopic surgery for rectal cancer is reportedly feasible, there are few studies comparing male sexual function after laparoscopic and after open surgery. The aim of this study was to investigate and compare the incidences and degrees of this complication between laparoscopic and open surgery for rectal cancer. **METHODOLOGY:** Male patients undergoing anterior resection for rectal cancer between 1994 and 2001 without recurrence were identified in a database. A retrospective analysis of sexual function before and after surgery was conducted using a postal questionnaire consisting of 5 questions regarding libido, erection, rigidity, ejaculation, and satisfaction. **RESULTS:** Of 68 sexually active male patients who returned the questionnaires, 29 (42.6%) underwent laparoscopic surgery (LS) and 39 (57.4%), open surgery (OS). Each parameter was reduced following LS as well as OS. No significant difference was found between the changes in each score and the total score between LS and OS. According to univariate analysis, the lower tumor location was significantly associated with sexual dysfunction ($p = 0.0111$). **CONCLUSIONS:** Male sexual dysfunction following laparoscopic surgery for rectal cancer is commensurate with that after open surgery. Lower tumor location is the only factor associated with male sexual dysfunction.

Obermair, A. and P. Sevelde (2001). "Impact of second look laparotomy and secondary cytoreductive surgery at second-look laparotomy in ovarian cancer patients." *Acta Obstet Gynecol Scand* **80**(5): 432-6.

OBJECTIVE: Currently, no prospective study supports or refutes the value of secondary cytoreductive surgery in patients with ovarian cancer. We therefore reviewed the surgical data of patients who underwent second-look laparotomy (SLL) with or without secondary cytoreductive surgery at our department. **METHODS:** Analysis is based on the data of 179 patients who had FIGO stage II (suboptimally staged), stage III or IV ovarian cancer, who received a platinum-based first-line chemotherapy, who were clinically considered to be tumor-free or had at least a clinically partial response to first-line chemotherapy, and who underwent SLL. In patients with macroscopic tumor the diagnostic

SLL was followed by a secondary cytoreductive surgery in order to remove as much tumor as possible. Patients with a positive SLL were given second-line chemotherapy. Survival from SLL until death was considered the primary statistical endpoint. **RESULTS:** In 78 out of 179 (43.5%) a negative SLL could be confirmed pathologically. Patients with negative findings, with microscopic, and macroscopic disease at SLL had a median survival of 66.6, 57.2, and 19.0 months, respectively ($p=0.0001$). In patients who underwent a secondary cytoreductive operation and in whom residual tumor was none, less than 2 cm, or more than 2 cm, the median survival was 22.9, 17.8, and 15.5 months, respectively ($p=0.325$). **CONCLUSIONS:** The presence of macroscopic tumor at SLL is an adverse prognostic factor whereas the role of secondary cytoreductive surgery at SLL appears to be limited in the routine management of ovarian cancer patients.

Oh, D., H. Lim do, et al. (2007). "The role of adjuvant radiotherapy in microscopic tumor control after extrahepatic bile duct cancer surgery." *Am J Clin Oncol* **30**(1): 21-5.

OBJECTIVES: To evaluate effects of radiotherapy (RT) after surgery for extrahepatic bile duct (EHBD) cancer. **METHODS:** There were 60 patients with EHBD cancer treated with postoperative RT. Surgical extents were R0 in 24 patients, R1 in 23, and R2 in 13. The indications for adjuvant RT were positive resection margin, lymph node metastasis, or more than pT2. Radiation was delivered to tumor bed and regional lymphatics, and for R1 or R2 patients, boost RT was planned. Overall survival (OS) and progression-free survival (PFS) was calculated and survival in the R0 and R1 patients with negative lymph nodes was compared. The pattern of treatment failures and prognostic factors were analyzed. **RESULTS:** The 2- and 5-year survival rates were 36.6% and 12.3% for OS, and 31.2% and 16.2% for PFS. In comparison of R0 with R1 patients who had negative lymph node, 2-year OS and PFS were 53.0% and 55.0% in R0, and 40.7% and 36.7% in R1 ($P = ns$). The first site of failure was loco-regional in 29 patients. The lymph node metastasis was a significant prognostic factor in OS ($P = 0.04$) and PFS ($P = 0.02$). **CONCLUSIONS:** Lymph node metastasis was a poor prognostic factor and adjuvant RT may be useful in patients with microscopic residual tumor. However, because there were high loco-regional recurrences, additional study is needed to determine more effective RT such as increased RT dose or use of radiosensitizers.

Ohsumi, S., K. Shimozuma, et al. (2009). "Factors associated with health-related quality-of-life in breast

cancer survivors: influence of the type of surgery." *Jpn J Clin Oncol* **39**(8): 491-6.

OBJECTIVE: To determine if health-related quality-of-life (QOL) differences existed between breast cancer (BC) survivors receiving mastectomy and those receiving breast-conserving treatment (BCT). Factors associated with QOL in long-term BC survivors were also identified. **METHODS:** One hundred patients who had previously undergone BC surgery and were alive without recurrence for >5 years were asked to answer the patient-administered questionnaires to assess their QOL (Functional Assessment of Cancer Therapy scale-Breast: FACT-B) and psychological distress (Hospital Anxiety and Depression Scale: HADS). Of them, 93 responded to the questionnaires affirmatively. **RESULTS:** Although none of the QOL scores were related to the surgical procedures, statistically significant relationships were found between age and the scores of FACT-General and social/family well-being (SWB), and between the educational status and scores of SWB in univariate analyses. There was no statistically significant relationship between psychological distress and each factor examined. In multivariate analyses, significant correlations were established between scores of the FACT-BC subscale (FACT-BCS) and the type of surgery and between those on the FACT SWB subscale and age at study or educational status. Namely, patients who had undergone BCT, younger patients and patients with higher educational background scored higher QOL. **CONCLUSIONS:** Among the BC survivors, those who underwent BCT experienced significantly but slightly better QOL than those who received mastectomy in FACT-BCS assessments. Younger patients and patients with higher educational backgrounds experienced significantly better SWB.

Ohta, Y., Y. Tanaka, et al. (2007). "Predicting recurrence following curative surgery in stage I non-small cell lung cancer patients using an angiogenesis-associated factor." *J Exp Clin Cancer Res* **26**(3): 301-5.

There are still difficulties in determining the risk of recurrence to decide whether to perform selective adjuvant treatment for stage I non-small cell lung cancer. This study reviewed 122 stage I patients who underwent curative surgery to assess the usefulness of an angiogenesis-associated factor as a predictor of recurrence. By immunohistochemical examination, we collected information about tumor-induced vascular endothelial growth factor (VEGF)-A and -C expression at the primary site. During the median follow-up period of 120 months, the overall 10-year survival rate was 53.5%. The 10-year survival rates according to VEGF-A/C expression were as

follows: VEGF-A high/VEGF-C high group, 26.0%; VEGF-A high/VEGF-C low group, 42.7%; VEGF-A low/VEGF-C high group, 73.1%; VEGF-A low/VEGF-C low group, 65.1%. The VEGF-A high/VEGF-C high group showed the worst outcome. The diagnostic values of the marker combination for predicting recurrence were as follows: sensitivity, 71.4%; specificity, 63.8%; and accuracy, 65.6%. When stratified by T factor, preferable high values for both negative predictive value and specificity were obtained in patients with stage IA disease. In order to select the patients eligible for selective adjuvant therapy at early stages, especially in stage IA disease, simultaneous assessment of tumor-induced VEGF-A/C warrants further study.

Ohtsuka, T., Y. Kitajima, et al. (2009). "Infectious complications after gastric cancer surgery accelerate a rapid hepatic recurrence." *Hepatogastroenterology* **56**(94-95): 1277-80.

BACKGROUND/AIMS: Rapid hepatic recurrence is sometimes experienced after gastric or pancreatobiliary cancer surgery. The aim of this study was to investigate the risk factors for the timing of hepatic recurrence. **METHODOLOGY:** The medical records of 20 patients who had hepatic recurrence after either a gastrectomy for gastric cancer (11 patients) or a pancreatoduodenectomy for pancreatobiliary cancer (9 patients) between 2002 and 2007 were retrospectively reviewed. The cumulative recurrence rate of liver metastasis was calculated using the Kaplan-Meier method, and 14 possible factors affecting the rapid hepatic recurrence were analyzed by univariate and multivariate analyses. **RESULTS:** The median time for the hepatic recurrence after the operation was 4.9 months (range 1 to 20.4 months). Among 14 factors, only postoperative infectious complications significantly accelerated the hepatic recurrence based on a univariate analysis ($p = 0.049$). Two more factors, gastric cancer and preoperative tumor marker elevation, had a tendency to affect the rapid recurrence, but did not show statistical significance (both $p = 0.06$). A multivariate analysis revealed that postoperative infectious complications ($p = 0.005$) and gastric cancer ($p = 0.04$) were significant and independent factors. Five of 11 patients with gastric cancer suffered from postoperative infectious complications, 4 of which were associated with pancreatic leakage after a pancreatectomy, and all 5 patients had hepatic recurrence within 3 months after the operation. **CONCLUSIONS:** Postoperative infectious complications are thus considered to accelerate a rapid hepatic recurrence after a gastrectomy for gastric cancer.

Ojima, H., S. Sasaki, et al. (2003). "Utility of serosal stamp cytology as an indicator for high-risk peritoneal metastasis in colorectal cancer surgery." *Hepatogastroenterology* **50**(49): 87-90.

BACKGROUND/AIMS: Although peritoneal lavage cytology is widely performed during surgery for gastric cancer and the results have been reported to provide an accurate prognostic factor, its value has not been well established in colorectal cancer. In this study, we demonstrated the utility of serosal stamp cytology from the viewpoint of cell adhesion molecules. **METHODOLOGY:** Between 1997 and 1999, peritoneal lavage cytology and serosal stamp cytology were performed in 34 patients with resectable colorectal cancer. Epithelial cadherin (E-cadherin) was examined as an index of the progress degree of peritoneal metastasis. **RESULTS:** Although peritoneal lavage cytology was positive in one case, serosal stamp cytology was positive in 10 cases. E-cadherin expression was lost in all peritoneal lavage cytology and/or serosal stamp cytology positive patients. **CONCLUSIONS:** Our data indicate that serosal stamp cytology is more sensitive and simple than peritoneal lavage cytology. Serosal stamp cytology may be useful in identifying patients at high risk for peritoneal recurrence.

Okada, M., J. Kigawa, et al. (1998). "Indication and efficacy of radiation therapy following radical surgery in patients with stage IB to IIB cervical cancer." *Gynecol Oncol* **70**(1): 61-4.

OBJECTIVE: To determine the role of radiation therapy following radical surgery in patients with cervical cancer. **METHOD:** A total of 104 patients with International Federation of Gynecology and Obstetrics stage IB to IIB cervical cancer who underwent radical hysterectomy and pelvic lymph node dissection at Tottori University Hospital between 1988 and 1994 were entered in this study. The criteria for postoperative radiotherapy included positive lymph node involvement, compromised surgical margin, parametrial extension, or deep stromal invasion of cervix with less than 3 mm of distance from serosa. Postoperative radiotherapy consisted of 10-20 Gy whole pelvis and an additional parametrial dose with a midline block to deliver a total of 44-50 Gy to the pelvic side wall. **RESULTS:** Sixty-two patients (59.6%) who met the criteria received postoperative radiotherapy. Lymph node metastasis was most frequent in stage IIB followed by stage IIA and then stage IB (36.7, 22.2, and 10.7%, respectively). Parametrial extension was observed 8.7% of patients with stage IB and 27.7% of those with stage IIA. The estimated 5-year survival rate for patients undergoing surgery alone was 97.6% and that for patients receiving postoperative radiotherapy was

82.7% ($P = 0.038$). Multivariate analysis showed that lymph node metastasis and parametrial extension were major prognostic factor, but the survival rate did not relate to depth of stromal invasion. **CONCLUSION:** Postoperative radiotherapy may improve the survival of patients with cervical cancer exhibiting lymph node metastasis or parametrial extension.

Omloo, J. M., G. W. Sloof, et al. (2008). "Importance of fluorodeoxyglucose-positron emission tomography (FDG-PET) and endoscopic ultrasonography parameters in predicting survival following surgery for esophageal cancer." *Endoscopy* **40**(6): 464-71.

BACKGROUND AND STUDY AIMS: To assess the prognostic importance of standardized uptake value (SUV) for 18F-fluorodeoxyglucose (FDG) at positron emission tomography (PET) and of EUS parameters, in esophageal cancer patients primarily treated by surgery. **PATIENTS AND METHODS:** Between October 2002 and August 2004 a prospective cohort study involved 125 patients, with histologically proven cancer of the esophagus, without evidence of distant metastases or locally irresectable disease based on extensive preoperative work-up, and fit to undergo major surgery. Follow-up was complete until October 2006, ensuring a minimal potential follow-up of 25 months. **RESULTS:** The median SUV was 0.27 (interquartile range 0.13 - 0.45), and was used as cutoff value between high ($n = 62$) and low ($n = 63$) SUV. Patients with a high SUV had a significantly worse disease-specific survival compared with patients with a low SUV ($P = 0.04$). Tumor location ($P = 0.005$), EUS T stage ($P < 0.001$), EUS N stage ($P = 0.006$) and clinical stage ($P < 0.006$) were also associated with disease-specific survival. However, in multivariate analysis only EUS T stage appeared to be of independent prognostic significance ($P = 0.007$). **CONCLUSION:** In esophageal cancer patients, EUS T stage, EUS N stage, location and SUV of the primary tumor are pretreatment factors that are associated with disease-specific survival. However, only EUS T stage is an independent prognostic factor.

Opatt, D., M. Morrow, et al. (2007). "Conflicts in decision-making for breast cancer surgery." *Ann Surg Oncol* **14**(9): 2463-9.

BACKGROUND: Little is known about the interaction among surgeons, patients, and other physicians in selecting breast cancer surgery. **METHODS:** We contacted attending surgeons ($n = 456$) of a population-based sample of 2645 breast cancer patients diagnosed in Detroit and Los Angeles from December 2001 to January 2003. Eighty percent completed a written survey with clinical scenarios. **RESULTS:** The mean surgeon age was 50 years, 50%

practiced in a community hospital, and breast cancer averaged 31% of practice volume. The mean number of years in practice was 17.2. Female surgeons made up 14.4% of the sample and 35% of the high-volume surgeons. Conflict with patients and other providers was reported by 58% and 32% of surgeons, respectively. When the patient preferred mastectomy and the surgeon favored BCS, conflict was reported by 49.9% of surgeons. Compared with low-volume surgeons, high-volume surgeons were significantly more likely to report conflict in this scenario (44% vs 62%; $P = .047$). When another provider preferred mastectomy and the respondent surgeon favored BCS, conflict was reported by 34% of surgeons and was more common for high-volume surgeons ($P < .001$). In a logistic regression model, surgeon volume and practice setting were strongly associated with conflict in this scenario. CONCLUSION: High-volume surgeons and those in cancer centers more frequently endorse current clinical guidelines that favor BCS over mastectomy, resulting in greater conflict with patients. These findings support patient reports that patient choice is a key factor in continued mastectomy use.

O'Riain, S. C., D. J. Buggy, et al. (2005). "Inhibition of the stress response to breast cancer surgery by regional anesthesia and analgesia does not affect vascular endothelial growth factor and prostaglandin E2." *Anesth Analg* **100**(1): 244-9.

Angiogenesis is essential for breast cancer metastases formation and is mediated by vascular endothelial growth factor (VEGF) and prostaglandin E2 (PGE2). We hypothesized that serum levels of VEGF and PGE2 are increased by the stress response to breast cancer surgery and attenuated by paravertebral anesthesia and analgesia (PVAA). Thirty women undergoing mastectomy were enrolled in this prospective, randomized study, to receive general anesthesia (GA) and postoperative opioid analgesia (morphine 0.1 mg/kg bolus and patient-controlled infusion) or GA and PVAA (72-h infusion). All patients received rectal diclofenac. Venous blood samples were taken preoperatively and at 4 and 24 h postoperatively for serum glucose, cortisol, C-reactive protein, VEGF, and PGE2. PVAA inhibited the surgical stress response, as indicated by significantly less plasma glucose, cortisol, and C-reactive protein. VEGF and PGE2 values did not differ significantly between the groups. Mean (SD) percentage change in VEGF at 4 and 24 h respectively were 3% +/- 44% versus 9% +/- 80%, $P=0.29$ and 5% +/- 43% versus -10% +/- 63%, $P=0.41$ for patients with combined general and PVAA and GA alone, respectively. Mean percentage change in postoperative PGE2 at 4 and 24 h respectively was 10% +/- 17% versus 11% +/- 69%,

$P=0.29$ and 34% +/- 19% versus 47% +/- 18%, $P=0.15$. We conclude that despite inhibiting the surgical stress response, PVAA had no effect on serum levels of putative breast cancer angiogenic factors, VEGF and PGE2.

Ottosson, S., K. Magnusson, et al. (1999). "Acute hematologic feasibility of G-CSF supported dose-escalated FEC therapy as adjuvant treatment after breast cancer surgery." *Anticancer Res* **19**(5C): 4429-34.

A study of the feasibility of gradually increased epirubicin and cyclophosphamide dosage in an FEC regimen with G-CSF (granulocyte colony stimulating factor) support in 18 high-risk breast cancer patients as adjuvant treatment was carried out. The FEC regimen was initiated with 5-fluorouracil 600 mg/m², epirubicin 75 mg/m² and cyclophosphamide 900 mg/m² together with G-CSF 5 micrograms/kg subcutaneously on days 2-15 q 3 weeks for nine cycles, increasing individually through four dose levels to a maximum of 5-FU 600 mg/m² (not escalated), epirubicin 120 mg/m² and cyclophosphamide 1800 mg/m². Transient cytopenias were regularly observed without major clinical complications. Rapid recovery and a biphasic overshoot of granulocytes required individualization of G-CSF support. During the 6-month treatment period, a general decline in granulocytes, platelets and haemoglobin was observed, resulting in maximal dose intensity in the middle of the treatment period. Compared to a conventional FEC regimen (5-Fluorouracil 600 mg/m², Epirubicin 60 mg/m², Cyclophosphamide 600 mg/m² q 3 w) without dose reductions, it was feasible to increase the dose of epirubicin by more than 50 per cent with an increased dose intensity between 25 and 70 per cent. The dose of cyclophosphamide was increased by more than 100 per cent. All patients suffered from complete alopecia and moderate nausea, but there was no acute cardiac or severe mucosal toxicity. It was concluded that intensified, G-CSF supported FEC therapy can be safely administered in an outpatient setting, provided the patients are thoroughly informed and adequately monitored. High-risk patients are enrolled in a study comparing the described regimen and a myeloablative regimen including peripheral stem-cell support. Breast cancer seems to respond to chemotherapy in a dose dependent manner, suggesting the use of dose intensified regimens (1,8,9,11). This approach is currently under investigation in studies comparing standard regimens with myelo-ablative regimens in high-risk primary breast cancer (3,10). In a Scandinavian multicenter study (2), two high dose regimens, G-CSF supported dose-escalated FEC and myeloablative cyclophosphamide-thiotepacarbolatin

with peripheral stem cell support, are compared as adjuvant therapy in operable high-risk breast cancer. This phase I study was performed to assess the feasibility and achievable dose intensity of an individually dose-escalated FEC regimen not in previous use.

Pacelli, F., M. Bossola, et al. (2008). "Is malnutrition still a risk factor of postoperative complications in gastric cancer surgery?" *Clin Nutr* 27(3): 398-407.

OBJECTIVE & AIMS: The present study aimed at retrospectively evaluating the incidence of mortality and major and minor postoperative complications in patients who underwent surgery for gastric cancer between 2000 and 2006 stratified according to the preoperative percentage weight loss, serum albumin levels and body mass index (BMI). **METHODS:** One hundred and ninety-six patients affected by gastric cancer admitted to the Division of Digestive Surgery of the Catholic University of Rome between January 2000 and December 2006 were considered eligible and were included in the study. According to the weight loss, patients were divided into three groups: (1) 0-5%; (2) 5.1-10%; (3) >10%. On the basis of serum albumin levels, were divided into three groups: (1) <3.0 g/dl; (2) 3.0-3.4 g/dl; (3) >3.5 g/dl. According to BMI, were divided into four groups: (1) <18.5 kg/m²; (2) 18.5-24.9 kg/m²; (3) 25.0-29.9 kg/m²; (4) >30.0 kg/m². Postoperative complications and mortality were reported. Complications were classified by objective criteria as major or minor, and as infectious or non-infectious. **RESULTS:** The postoperative mortality was 0%. Major infectious complications occurred in 20 patients (10.2%), major non-infectious in 18 (9.2%), minor infectious in 21 (10.7%), whereas minor non-infectious complications were absent. The rate of major infectious, major non-infectious and minor infectious postoperative complications was similar in patients with absent or light weight loss (8.8%, 8.8%, 10.6%, respectively), mild weight loss (15.3%, 11.5%, 9.6%, respectively), or severe weight loss (6.4%, 6.4%, 12.9%, respectively). Similarly, the rate of postoperative complications did not differ between patients with serum albumin <3.0 g/dl (10.8%, 8.1%, 8.1%, respectively); between 3.0 and 3.4 (8.8%, 13.3%, 17.7%, respectively) or > or =3.5 g/dl (10.5%, 7.9%, 8.7%, respectively). According to BMI, the rate of postoperative complications was: 11.7%, 5.8%, and 5.8% for BMI <18.5 kg/m²; 9.4%, 8.2%, and 11.7% for BMI between 18.5 and 24.9 kg/m²; 10.7%, 10.7%, and 9.2% for BMI between 25 and 29.9 kg/m²; 10.3%, 10.3% and 13.7% for BMI >30 kg/m². Then, we evaluated the postoperative morbidity only in patients who underwent total gastrectomy or distal subtotal gastrectomy associated

with extended lymphadenectomy. In this group of patients, the rate of postoperative complications was comparable in patients with 0-5% (8.8%, 7.7%, 10%, respectively), 5.1-10% (14.6%, 9.7%, 9.7%, respectively), and >10% (7.1%, 7.1%, 14.3%, respectively) weight loss. Also stratifying the patients according to the serum albumin levels, the rate of postoperative complications did not differ significantly (serum albumin <3.0 g/dl: 14.8%, 11.1%, 14.8%, respectively; serum albumin between 3.0 and 3.4 g/dl: 6.2%, 12.5%, 15.6%, respectively; serum albumin > or =3.5 g/dl: 10.4%, 5.8%, 7.0%, respectively). According to BMI, the rate of postoperative complications was: 7.6%, 0%, and 7.6% for BMI <18.5 kg/m²; 9.5%, 9.5%, and 11.1% for BMI between 18.5 and 24.9 kg/m²; 12.5%, 8.3%, and 10.4% for BMI between 25 and 29.9 kg/m²; 9.5%, 9.5% and 9.5% for BMI >30 kg/m². **CONCLUSION:** The present study suggests that weight loss and hypoalbuminemia are not associated with an increased risk of mortality and morbidity in patients who underwent surgery for gastric cancer. This study may represent a stimulus for further studies aiming at evaluating the actual role of malnutrition in the development of postoperative complications in major abdominal surgery.

Pan, H. C., J. Sheehan, et al. (2005). "Gamma knife surgery for brain metastases from lung cancer." *J Neurosurg* 102 Suppl: 128-33.

OBJECT: The authors conducted a study to evaluate the safety and efficacy of gamma knife surgery (GKS) for the treatment of brain metastases from lung cancer. **METHODS:** Between February 1993 and May 2003 191 patients underwent treatment for 424 brain metastases from non-small (171 cases) and small cell lung carcinoma (20 cases). Imaging and clinical status were monitored every 3 months following the treatment. Kaplan-Meier survival curves, Cox proportional hazards regression for risk factor analysis, and nonparametric methods for evaluating tumor response were used. There was no difference in median survival following combined whole-brain radiation therapy (WBRT) and gamma knife surgery (14 months) and GKS alone (15 months). There was also no difference between the median survival rates for either tumor type. In the multivariate analysis, age less than 65 years, Karnofsky Performance Scale score greater than 70, normal neurological status, multiple GKS treatments, and pre-GKS craniotomy were related to longer survival. Tumor control rates varied according to the volume of the metastases and were as follows: 84.4% (< 0.5 cm³), 94% (0.5-2 cm³), 89.1% (2-4 cm³), 93.4% (4-8 cm³), 85.7% (8-14 cm³), and 87.5% (> 14 cm³). Four lesions required post-GKS craniotomy due

to swelling or rapid tumor progression. The rate of tumor shrinkage was higher when a volume was 2 cm³, lower in cystic lesions, lower in tumors with previous WBRT, and lower for margin doses less than 14 Gy. CONCLUSIONS: The risk-benefit ratio of GKS in this series was satisfactory. There was no difference in response rates of the two tumor types, and WBRT did not improve the duration of survival.

Park, J. S., S. B. Kang, et al. (2007). "Economics and the laparoscopic surgery learning curve: comparison with open surgery for rectosigmoid cancer." *World J Surg* 31(9): 1827-34.

BACKGROUND: Wide-ranging costs of laparoscopic surgery (LAP) are associated with variations in the experience levels of surgeons. There is no available report on the changes of economic outcomes relative to the LAP learning curve in the treatment of colorectal cancer. In the present study, we have compared changes in economic outcomes according to the LAP learning curve with the economic outcomes of open surgery (OS) for rectosigmoid cancer. METHODS: A total of 197 patients with rectosigmoid cancer were included in this analysis; 116 received LAP and 81 received OS. Scatter of operative times demonstrated an early learning period of 37 cases in LAP. The following outcomes were compared between LAP and OS during the early learning period and experienced periods; operating room (OR) costs, OR-related hospital profit, total hospital charge, and patient payment. During the median interval of two periods according to the laparoscopic surgery learning curve, there was an inflation rate of about 10% on the medical charges such as operation, radiology, laboratory, and admission fee. RESULTS: Operating room costs were significantly higher after LAP during the two periods, but the median difference between LAP and OS decreased during the experienced period (\$3,055 to \$1,850). With increasing operative experience in LAP, the OR-related hospital deficit improved (-\$1,072 to-\$840). Total hospital charges were significantly higher for LAP than for OS in the early learning period ($p < 0.05$), but they were similar in the experienced period (\$7,983/patient versus \$7,045/patient, $p > 0.05$). During the experienced period, patients paid a lower surcharge for LAP (\$1,885-\$1,118). CONCLUSIONS: Total hospital charges for laparoscopic surgery were substantially higher than those of open surgery during the early learning period, but become similar during the experienced period. The shortening of the learning period is a critical factor for achieving cost-effective laparoscopic surgery.

Park, J. W., S. B. Lim, et al. (2009). "Carcinoembryonic antigen as a predictor of pathologic response and a prognostic factor in locally advanced rectal cancer patients treated with preoperative chemoradiotherapy and surgery." *Int J Radiat Oncol Biol Phys* 74(3): 810-7.

PURPOSE: To evaluate the role of serum carcinoembryonic antigen (CEA) as a predictor of response to preoperative chemoradiotherapy (CRT) and prognostic factor for rectal cancer. MATERIALS AND METHODS: The study retrospectively evaluated 352 locally advanced rectal cancer patients who underwent preoperative CRT followed by surgery. Serum CEA levels were determined before CRT administration (pre-CRT CEA) and before surgery (post-CRT CEA). Correlations between pre-CRT CEA levels and rates of good response (Tumor regression grade 3/4) were explored. Patients were categorized into three CEA groups according to their pre-/post-CRT CEA levels (ng/mL) (Group A: pre-CRT CEA ≤ 3 ; B: pre-CRT CEA >3 , post-CRT CEA ≤ 3 ; C: pre- and post-CRT CEA >3 ng/mL), and their oncologic outcomes were compared. RESULTS: Of 352 patients, good responses were achieved in 94 patients (26.7%). The rates of good response decreased significantly as the pre-CRT CEA levels became more elevated (CEA [ng/mL]: ≤ 3 , 36.4%; 3-6, 23.6%; 6-9, 15.6%; >9 , 7.8%; $p < 0.001$). The rates of good response were significantly higher in Group A than in Groups B and C (36.4% vs. 17.3% and 14.3%, respectively; $p < 0.001$). The 3-year disease-free survival rate was significantly better in Groups A and B than in Group C (82% and 79% vs. 57%, respectively; $p = 0.005$); the CEA grouping was identified as an independent prognostic factor ($p = 0.025$). CONCLUSIONS: In locally advanced rectal cancer patients, CEA levels could be of clinical value as a predictor of response to preoperative CRT and as an independent prognostic factor after preoperative CRT and curative surgery.

Park, S. S., C. S. Kim, et al. (2005). "Gastric cancer confined to the muscularis propria: a possible candidate for laparoscopic surgery or adjuvant therapy." *Scand J Gastroenterol* 40(4): 450-4.

OBJECTIVE: Gastric cancer confined to the muscularis propria (mp) has a favorable prognosis, but still belongs to the advanced category. Many oncologists have difficulties in selecting treatment modalities owing to the confused situation of mp cancer. To clarify the therapeutic strategy, the clinicopathological characteristics were investigated, and the risk factors, of this intermediate-stage gastric cancer, evaluated. MATERIAL AND METHODS: A total of 155 patients who underwent curative resection for primary gastric cancer between 1993 and 2001

were diagnosed with mp cancer. The patients were divided into recurrent and non-recurrent groups and analyzed clinicopathologically. RESULTS: The rate of recurrence was 20%. A multivariate analysis disclosed only lymphatic metastasis as an independent risk factor for recurrence of mp cancer. Hematogenous metastasis accounted for 37% of the recurrent patterns, and the liver (83.3%) was the most common organ. The 5-year survival rate of all mp cancer patients was 80.9%, but that of patients with recurrent disease was 19.2%. The median survival time of the recurred patients was 24 months, and 74% of those patients died within 3 years. CONCLUSIONS: Lymph node metastasis is the only significant risk factor of mp cancer. Patients with lymphatic metastasis should undergo postoperative adjuvant therapy. On the other hand, patients with mp cancer without lymph node involvement have an excellent prognosis and could be candidates for laparoscopic gastric surgery.

Pavlidis, T. E., G. Marakis, et al. (2008). "Does emergency surgery affect resectability of colorectal cancer?" *Acta Chir Belg* **108**(2): 219-25.

OBJECTIVE: Emergency surgery for colorectal cancer is common in daily practice, and is mainly implied by bowel obstruction. It is related to increased morbidity and mortality. Its relation with the stage and resectability of the disease is uncertain. This study aims to further clarify these parameters. PATIENTS AND METHODS: Over the past 24-year period 121 patients had an emergency operation (12%) from a total of 1009 patients with colorectal carcinoma. There were 59 men (48.8%) and 62 women (51.2%) with a mean age of 68 years (range 21-93); 61 patients (50.4%) were \geq 70-years-old. The data of all these patients were studied retrospectively in comparison with those who underwent elective surgery. Emergency cases were further divided into two age groups (\geq 70 and $<$ 70 years) and compared. The tumour location was mainly in the left colon, whereas obstruction was the predominant reason for acute presentation. RESULTS: On operation, absence of macroscopic spread was noted in 57.8% of emergency cases and 72% of elective cases ($p < 0.05$). The resectability rates were 75% and 90% respectively ($p < 0.05$), and were not significantly affected by the age factor. There were no differences in the grade of malignant cell differentiation or in the depth of microscopic invasion ($p > 0.05$) in either group. For emergency operations, the morbidity was 20% (24 patients) and the 30-day mortality rate was 5.8% (7 patients). Both parameters were higher in patients \geq 70-years-old. CONCLUSION: Emergency surgery for colorectal carcinoma is related to lower resectability

and to higher--but acceptable--postoperative morbidity and mortality rates, when compared with elective surgical management.

Pecorelli, S., F. Odicino, et al. (2002). "Interval debulking surgery in advanced epithelial ovarian cancer." *Best Pract Res Clin Obstet Gynaecol* **16**(4): 573-83.

Cytoreductive surgery and chemotherapy are the mainstay for the treatment of advanced epithelial ovarian cancer. In order to minimize the tumour burden before chemotherapy, cytoreductive surgery is usually performed first. The importance of the amount of residual disease as the main prognostic factor for patients suffering from advanced disease has been almost universally accepted even in the absence of prospective randomized trials addressing the benefit of cytoreductive surgery. In the last decade, the value of debulking surgery after induction chemotherapy - interval debulking surgery, IDS - has been widely debated, especially after the completion of a prospective randomized study from the EORTC addressing the introduction of a surgical procedure with debulking intent preceded and followed by cytoreductive chemotherapy. The rationale of such a strategy in the context of the primary treatment of advanced ovarian cancer lies in a higher cytoreducibility to the 'optimal' status forwarded, and possibly facilitated, by chemotherapy. The results demonstrated a prolongation of both progression-free survival and median survival in favour of patients randomized to IDS (5 and 6 months, respectively). Multivariate analysis revealed IDS to be an independent prognostic factor which reduced the risk of death by 33% at 3 years and by 48% in subsequent re-evaluation after more than 6 years of observation. Despite the above, results have been questioned by many, leading the GOG to perform a similar study which has been concluded very recently. Nevertheless, the main concern regarding the application of IDS in all instances relates to the morbidity of two major surgical procedures integrated within a short period during which cytotoxic chemotherapy is also administered. Neoadjuvant chemotherapy has been recently proposed to avoid a non-useful surgical procedure in patients considered 'optimally unresectable' after diagnosis of advanced ovarian cancer. Whether or not this newer approach will translate into a longer survival with a better quality of life is going to be addressed by a novel EORTC study. Finally, the concept of a 'chemical' cytoreduction preceding and facilitating a subsequent 'surgical' effort has been recently introduced also in the treatment of recurrent disease. The EORTC has recently initiated a prospective randomized study (LOROCSON - Late Onset Recurrent Ovarian

Cancer: Surgery or Not) to validate the importance of such an approach to be balanced with medical treatment alone not only in terms of survival but also as far as quality of life is concerned.

Peled, N., D. Flex, et al. (2009). "The role of routine bronchoscopy for early detection of bronchial stump recurrence of lung cancer: 1 year post-surgery." *Lung Cancer* **65**(3): 319-23.

BACKGROUND: Local recurrence after complete resection (R(0)) occur in approximately 20% of patients with stage I disease and in up to 50% with stage III. This study focuses on early detection of stump recurrence by a routine bronchoscopy. **METHODS:** Prospective analysis 1 year after surgery between April 2006 and April 2008. **RESULTS:** 104 NSCLC patients (age 69.1±9.6 years) participated in the study; 97 underwent lobectomy and 7 pneumonectomy. 61% were stage I, 25% stage II, 10% IIIA, 5% IIIB and 1% stage IV. 66% had N0, 21% had N1 disease, 9% N2 disease and 4% had N3. Bronchoscopy was performed 12.9±3.8 months after surgery. Nine percents had stump polyp, 5 (5%) had a suspicious mucosa. Four of the nine polyps were malignant. Nine other patients had squamous metaplasia and two had squamous dysplasia. Malignant stump recurrence was observed in four cases, all had a stump polyp. All had R(0), but two had short (<1.0 cm) tumor-free bronchial margin, two had N1 disease and two N2 disease. Fisher exact analysis showed short bronchus (p=0.003), N2 vs. N0-1 (p=0.012), and N1 vs. N0 (p=0.011) as significant risk factor for stump recurrence. For stump recurrence, one patient underwent completion pneumonectomy and has no evidence for disease (32.2 months), two patients were treated by chemotherapy and one patient died from pneumonia before therapy. **CONCLUSION:** Routine bronchoscopy 1 year after thoracic resection for NSCLC is justified in patients who are at high risk for local recurrence, i.e. short free bronchial margins and N2/N1 disease.

Penel, N., E. Y. Amela, et al. (2007). "A simple predictive model for postoperative mortality after head and neck cancer surgery with opening of mucosa." *Oral Oncol* **43**(2): 174-80.

The aim of this study was to determine the risk factors for the mortality during the first 30 days after a major head and neck cancer surgery. Two hundred and sixty one consecutive surgical procedure were prospectively studied at Oscar Lambret Cancer Centre within a 36-months period. Twenty variables were recorded for each patient. The significant risk factors for postoperative mortality were assessed by univariate and multivariate analysis. Overall 30-days mortality rate was 3.83% [95% CI 3.13-4.53]. In

univariate analysis identified four risk factors: female gender (odd ratio 4.25 [95% CI 1.03-17.56]), age equal or superior than 70 (odd ratio 5.06 [95% CI 1.35-18.36]), current alcohol addiction (odd ratio 3.65 [1.02-13.06]) and laryngeal location (odd ratio 4.23 [CI 95% 1.18-3.38]). In multivariate analysis only female gender and laryngeal location remained significant. The incidence of postoperative mortality was 1.63% for patients without risk factor and was 6.41% for those with one or two risk factors. This model identifies easily high-risk patients for major head and neck cancer surgery. A multicenter validation is necessary.

Peters, W. P., G. L. Rosner, et al. (2005). "Prospective, randomized comparison of high-dose chemotherapy with stem-cell support versus intermediate-dose chemotherapy after surgery and adjuvant chemotherapy in women with high-risk primary breast cancer: a report of CALGB 9082, SWOG 9114, and NCIC MA-13." *J Clin Oncol* **23**(10): 2191-200.

PURPOSE: The prognosis for women with primary breast cancer involving multiple axillary nodes remains poor. High-dose chemotherapy with stem-cell support produced promising results in initial clinical trials conducted at single institutions. **PATIENTS AND METHODS:** Seven hundred eighty-five women aged 22 to 66 years with stage IIA, IIB, or IIIA breast cancer involving 10 or more axillary lymph nodes were randomized after surgery and standard adjuvant chemotherapy to either high-dose cyclophosphamide, cisplatin, and carmustine (HD-CPB) with stem-cell support or intermediate-dose cyclophosphamide, cisplatin, and carmustine (ID-CPB) with G-CSF support but without stem cells. Planned treatment for all patients included locoregional radiation therapy. Hormone-receptor-positive patients were to receive 5 years of tamoxifen. Event-free survival (EFS) was the primary end point. **RESULTS:** Median follow-up was 7.3 years. Event-free survival was not significantly different between the two treatment groups (P = .24). The probability of being free of an event at 5 years with HD-CPB was 61% (95% CI, 56% to 65%), and was 58% (95% CI, 53% to 63%) for ID-CPB. Thirty-three patients died of causes attributed to HD-CPB, compared with no therapy-related deaths among women treated with ID-CPB. Overall survival for the two arms was identical at 71% at 5 years (P = .75). **CONCLUSION:** HD-CPB with stem-cell support was not superior to ID-CPB for event-free or overall survival among all randomized women with high-risk primary breast cancer.

Petersen, S., M. Freitag, et al. (1998). "Anastomotic leakage: impact on local recurrence and survival in

surgery of colorectal cancer." *Int J Colorectal Dis* **13**(4): 160-3.

Anastomotic leakage is a serious complication in colorectal surgery, especially in the treatment of adenocarcinoma located in the left-sided colon and rectum. It is controversial whether anastomotic leakage is a prognostic factor for local recurrence and/or survival in this disease. To evaluate the impact of anastomotic dehiscence on the outcome of surgery we reviewed data on 467 consecutive patients with adenocarcinoma of the left colon and rectum treated between 1985 and 1995 in our Department. Of these, 41 (8.8%) developed anastomotic leakage. The overall-survival differed nonsignificantly ($P = 0.57$) between leakage and nonleakage groups. Of 331 patients with curative resection 29 showed an anastomotic leakage. There were 46 R0-resected patients who died under disease-related conditions: 7 patients in the leakage group (24.1%) and 39 in the nonleakage group (12.9%; $P = 0.045$). In the curatively resected group 5 of 29 patients developed local recurrence in the leakage group (17.2%) but only 26 of 302 patients in the nonleakage group (8.6%; $P = 0.0357$). Multivariate analysis showed only the factors of age, stage of resection, staging of lymph nodes, and tumor staging as independent prognostic factors for overall survival. For local recurrence the multivariate analysis revealed tumor staging and anastomotic leakage as independently significant. Anastomotic leakage thus appears to be a prognostic factor for local tumor recurrence of colorectal cancer. In addition, disease-related survival is considerably decreased under leakage conditions. Anastomotic leakage was not shown in this study to be an independent prognostic factor for overall survival due to the lack of statistical significance.

Pettersson, A., L. Richiardi, et al. (2007). "Age at surgery for undescended testis and risk of testicular cancer." *N Engl J Med* **356**(18): 1835-41.

BACKGROUND: Undescended testis, which is a risk factor for testicular cancer, is usually treated surgically, but whether the age at treatment has any effect on the risk is unclear. We studied the relation between the age at treatment for undescended testis and the risk of testicular cancer. **METHODS:** We identified men who underwent orchiopexy for undescended testis in Sweden between 1964 and 1999. Cohort subjects were identified in the Swedish Hospital Discharge Register and followed for the occurrence of testicular cancer through the Swedish Cancer Registry. Vital statistics and data on migration status were taken from the Register of Population and Population Changes for the years 1965 through 2000. We estimated the relative risk of testicular cancer

using Poisson regression of standardized incidence ratios, comparing the risk in the cohort with that in the general population. We also analyzed the data by means of Cox regression, using internal comparison groups. **RESULTS:** The cohort consisted of 16,983 men who were surgically treated for undescended testis and followed for a total of 209,984 person-years. We identified 56 cases of testicular cancer during follow-up. The relative risk of testicular cancer among those who underwent orchiopexy before reaching 13 years of age was 2.23 (95% confidence interval [CI], 1.58 to 3.06), as compared with the Swedish general population; for those treated at 13 years of age or older, the relative risk was 5.40 (95% CI, 3.20 to 8.53). The effect of age at orchiopexy on the risk of testicular cancer was similar in comparisons within the cohort. **CONCLUSIONS:** Treatment for undescended testis before puberty decreases the risk of testicular cancer.

Phernambucq, E. C., B. Biesma, et al. (2006). "Multicenter phase II trial of accelerated cisplatin and high-dose epirubicin followed by surgery or radiotherapy in patients with stage IIIa non-small-cell lung cancer with mediastinal lymph node involvement (N2-disease)." *Br J Cancer* **95**(4): 470-4.

To assess the therapeutic activity of accelerated cisplatin and high-dose epirubicin with erythropoietin and G-CSF support as induction therapy for patients with stage IIIa-N2 non-small-cell lung cancer (NSCLC). Patients with stage IIIa-N2 NSCLC were enrolled in a phase II trial. They received cisplatin 60 mg m⁻² and epirubicin 135 mg m⁻² every 2 weeks for three courses combined with erythropoietin and G-CSF. Depending on results of clinical response to induction therapy and restaging, patients were treated with surgery or radiotherapy. In total, 61 patients entered from March 2001 to April 2004. During 169 courses of induction chemotherapy, National Cancer Institute of Canada (NCI-C) grade III/IV leucocytopenia was reported in 35 courses (20.7%), NCI-C grade III/IV thrombocytopenia in 26 courses (15.4%) and NCI-C grade III/IV anaemia in six courses (3.6%). Main cause of cisplatin dose reduction was nephrotoxicity (12 courses). Most patients received three courses. There were no chemotherapy-related deaths. Three patients were not evaluable for clinical response. Twenty-eight patients had a partial response (48.3%, 95% CI: 36-61.1%), 24 stable disease and six progressive disease. After induction therapy, 30 patients underwent surgery; complete resection was achieved in 19 procedures (31.1%). Radical radiotherapy was delivered to 25 patients (41%). Six patients were considered unfit for further treatment. Median survival for all patients was 18 months. Response rate of accelerated cisplatin and

high-dose epirubicin as induction chemotherapy for stage IIIa-N2 NSCLC patients is not different from more commonly used cisplatin-based regimen.

Pisanu, A., A. Montisci, et al. (2007). "Curative surgery for gastric cancer in the elderly: treatment decisions, surgical morbidity, mortality, prognosis and quality of life." *Tumori* **93**(5): 478-84.

AIMS AND BACKGROUND: Surgical risk is deemed to be higher in the aged population because there are often comorbidities that may affect the postoperative result. This consideration is important for the treatment decision-making for gastric cancer in the elderly. The aim of this study was to identify factors influencing mortality, morbidity, survival and quality of life after curative surgery for gastric cancer in patients aged 75 years and older, and to plan their appropriate management. **METHODS AND STUDY DESIGN:** From January 1993 to December 2004, 135 patients underwent surgery at our department because of gastric cancer. Ninety-four of these patients (69.6%) underwent potentially curative gastrectomy. A cross-sectional study of 23 patients aged 75 years and older and 71 younger patients who underwent curative gastrectomy was carried out: patient characteristics, tumor characteristics, management, morbidity, mortality, survival, and quality of life were evaluated. **RESULTS:** Elderly patients had significantly more comorbidities and a poorer nutritional status than younger patients. The surgical procedures were similar in both groups and the overall morbidity rate was 27.9% and the overall mortality rate 8.5%. Medical mortality was significantly higher in elderly patients, and the presence of comorbidities was the only independent factor affecting mortality. The 5-year survival rate was 56.2% in the older group versus 62.1% in the younger group and tumor stage was the only prognostic factor influencing survival. Quality of life after surgery was similar in both groups. The significantly better postoperative functional outcome after subtotal gastrectomy suggested a better compliance of elderly patients with subtotal than total gastrectomy. **CONCLUSIONS:** In the elderly, surgical strategies must be modulated on the basis of comorbidities, tumor stage and future quality of life. Since elderly patients have no worse prognosis than younger patients, age is not a contraindication to curative resection for gastric cancer. Subtotal gastrectomy should be the procedure of choice mainly in elderly patients as it offers better quality of life.

Pourel, N., N. Santelmo, et al. (2008). "Concurrent cisplatin/etoposide plus 3D-conformal radiotherapy followed by surgery for stage IIB (superior sulcus T3N0)/III non-small cell lung cancer yields a high rate

of pathological complete response." *Eur J Cardiothorac Surg* **33**(5): 829-36.

INTRODUCTION: Optimal preoperative treatment of stage IIB (Pancoast)/III non-small cell lung cancer (NSCLC) remains undetermined and a subject of controversy. The goal of our study is to confirm feasibility and pathological response rates after induction chemoradiation (CRT) in our community-based treatment center. **PATIENTS AND METHODS:** Patients were selected according to functional and resectability criteria. Induction treatment comprised 3D conformal 4500 cGy radiotherapy delivered to the primary tumor and pathologic hilar and/or mediastinal lymph nodes on CT scan with an extra-margin of 1-1.5 cm. Concurrent chemotherapy regimen was cisplatinum 20mg/m² d1-d5 and etoposide 50mg/m² d1-d5, d1-5 d29-33. Within 3-4 weeks after CRT completion, operability was re-assessed accordingly. Surgery was performed 4-6 weeks after CRT completion in patients (pts) deemed resectable. Inoperable pts were referred for a 20-25 Gy boost +/-1 extra-cycle of cisplatinum+etoposide. **RESULTS:** From 1996 to 2005, 107 pts were initially selected for treatment and received induction chemoradiation (stage IIB-Pancoast 18, IIIA 58 and IIIB 31, squamous cell carcinoma 48%, adenocarcinoma 44%, large-cell undifferentiated carcinoma 14%). After preoperative evaluation, 72 pts (67%) had a thoracotomy (pneumonectomy 21, lobectomy 45, bilobectomy 5) and all but one (unresectable tumor) had a macroscopic complete resection. During the 3-month postoperative time, five patients (6.9%) died, four after pneumonectomy (right 3, left 1). The analysis of tumoral samples showed a pathological complete response rate or microscopic residual foci of 39.5%. Median follow-up time was 22.3 months (survivors: 36.8 months), 2-year and 3-year overall survival rates were 55% and 40%, respectively (median=26.7 months) for all the intention-to-treat population (n=107), 62% and 51% (median=36.5 months) for 71 resected pts, 41% and 16% for 36 non-resected pts (median=19.1 months). On multivariate analysis, surgical resection and tumoral necrosis >50% (or pathological complete response) were the most pertinent predictive factors of the risk of death (hazard ratio=0.50 and 0.48, p=0.006 and 0.038, respectively). **CONCLUSION:** Surgery was feasible after induction chemoradiation, particularly lobectomy in PS 0-1, stage IIB (Pancoast)/III NSCLC pts but pneumonectomy carries a high risk of postoperative death (particularly, right pneumonectomy). Pathological response to induction chemoradiation was complete in 39.5% of patients and was a significant predictive factor of overall survival.

Pujol, P., J. P. Daures, et al. (1999). "Time at surgery during menstrual cycle and menopause affects pS2 but not cathepsin D levels in breast cancer." *Br J Cancer* **79**(5-6): 909-14.

Many studies have addressed the clinical value of pS2 as a marker of hormone responsiveness and of cathepsin D (Cath D) as a prognostic factor in breast cancer. Because pS2 and Cath D are both oestrogen induced in human breast cancer cell lines, we studied the influence of the menstrual cycle phase and menopausal status at the time of surgery on the levels of these proteins in breast cancer. A population of 1750 patients with breast cancer, including 339 women in menstrual cycle, was analysed. Tumoral Cath D and pS2 were measured by radioimmunoassay. Serum oestradiol (E2), progesterone (Pg), follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels at the day of surgery were used to define the hormonal phase in premenopausal women. There was a trend towards a higher mean pS2 level in the follicular phase compared with the luteal phase (17 ng mg⁻¹ and 11 ng mg⁻¹ respectively, P = 0.09). Mean pS2 was lower in menopausal patients than in women with cycle (8 ng mg⁻¹ and 14 ng mg⁻¹ respectively, P = 0.0001). No differences in mean Cath D level were observed between the different phases of the menstrual cycle, or between pre- and post-menopausal women. In the overall population, pS2 was slightly positively associated with E2 and Pg levels and negatively associated with FSH and LH, probably reflecting the link between pS2 and menopausal status. In premenopausal women, no association was found between pS2 and E2, Pg, FSH or LH levels. There were no correlations between Cath D level and circulating hormone levels in the overall population. However, in the subgroup of premenopausal women with ER-positive (ER+) tumours, E2 was slightly associated with both pS2 and Cath D, consistent with oestrogen induction of these proteins in ER+ breast cancer cell lines. There are changes in pS2 level in breast cancer throughout the menstrual cycle and menopause. This suggests that the choice of the pS2 cut-off level should take the hormonal status at the time of surgery into account. In contrast, the level of Cath D is unrelated to the menstrual cycle and menopausal status.

Qiu, H., P. Sirivongs, et al. (2000). "Molecular prognostic factors in rectal cancer treated by radiation and surgery." *Dis Colon Rectum* **43**(4): 451-9.

PURPOSE: The aim of this study was to determine the biologic significance of tumor response and the prognostic value of molecular markers in a group of patients with rectal cancer treated with preoperative radiation therapy and radical surgery.

METHODS: Microsatellite instability, microvessel count, and immunohistochemistry for proliferating cell nuclear antigen, p53, p21, bcl-2, and vascular endothelial growth factor were performed in the preradiation biopsy specimen of 72 patients with rectal cancer treated by preoperative radiation therapy and radical curative surgery. Preoperative tumor stage by endorectal ultrasound was compared with pathology stage of the resected specimen. Mean follow-up was 50 months. **RESULTS:** Twenty-eight patients (39 percent) responded to radiation therapy. The response was complete in 8 (12 percent) and partial in 20 patients (27 percent). Tumors with positive nodes in the surgical specimen were less likely to have responded to preoperative radiation (P = 0.03). Only p21 expression was individually associated with response to radiation (56 vs. 30 percent; P = 0.03). Tumors that were p53-negative/p21-positive or p21-positive/bcl-2-positive were also more likely to respond to radiation (83 vs. 35 percent; P = 0.03 and 71 vs. 31 percent; P = 0.01, respectively). The tumor relapsed in 21 patients (29 percent): locally in 7 (10 percent) and distally in 14 (19 percent). Recurrence was associated with lack of response to radiation, female gender, distal tumor location, high proliferating cell nuclear antigen labeling index, and low microvessel count. Probability of survival was greater for patients with well or moderately differentiated tumors and tumors that responded completely to radiation. **CONCLUSIONS:** Tumor response to radiation is associated with improved tumor control and overall survival rate, and p21 expression is a marker of tumor radiosensitivity in patients with rectal cancer. Furthermore, a high proliferating cell nuclear antigen labeling index and a low microvessel count in the preradiation biopsy specimen may be prognostic indicators for tumor recurrence.

Quirke, P., R. Steele, et al. (2009). "Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial." *Lancet* **373**(9666): 821-8.

BACKGROUND: Local recurrence rates in operable rectal cancer are improved by radiotherapy (with or without chemotherapy) and surgical techniques such as total mesorectal excision. However, the contributions of surgery and radiotherapy to outcomes are unclear. We assessed the effect of the involvement of the circumferential resection margin and the plane of surgery achieved. **METHODS:** In this prospective study, the plane of surgery achieved and the involvement of the circumferential resection margin were assessed by local pathologists, using a standard pathological

protocol in 1156 patients with operable rectal cancer from the CR07 and NCIC-CTG CO16 trial, which compared short-course (5 days) preoperative radiotherapy and selective postoperative chemoradiotherapy, between March, 1998, and August, 2005. All analyses were by intention to treat. This trial is registered, number ISRCTN 28785842. FINDINGS: 128 patients (11%) had involvement of the circumferential resection margin, and the plane of surgery achieved was classified as good (mesorectal) in 604 (52%), intermediate (intramesorectal) in 398 (34%), and poor (muscularis propria plane) in 154 (13%). We found that both a negative circumferential resection margin and a superior plane of surgery achieved were associated with low local recurrence rates. Hazard ratio (HR) was 0.32 (95% CI 0.16-0.63, $p=0.0011$) with 3-year local recurrence rates of 6% (5-8%) and 17% (10-26%) for patients who were negative and positive for circumferential resection margin, respectively. For plane of surgery achieved, HRs for mesorectal and intramesorectal groups compared with the muscularis propria group were 0.32 (0.16-0.64) and 0.48 (0.25-0.93), respectively. At 3 years, the estimated local recurrence rates were 4% (3-6%) for mesorectal, 7% (5-11%) for intramesorectal, and 13% (8-21%) for muscularis propria groups. The benefit of short-course preoperative radiotherapy did not differ in the three plane of surgery groups ($p=0.30$ for trend). Patients in the short-course preoperative radiotherapy group who had a resection in the mesorectal plane had a 3-year local recurrence rate of only 1%. INTERPRETATION: In rectal cancer, the plane of surgery achieved is an important prognostic factor for local recurrence. Short-course preoperative radiotherapy reduced the rate of local recurrence for all three plane of surgery groups, almost abolishing local recurrence in short-course preoperative radiotherapy patients who had a resection in the mesorectal plane. The plane of surgery achieved should therefore be assessed and reported routinely.

Robertson, J. F., W. Odling-Smee, et al. (2003). "Pharmacokinetics of a single dose of fulvestrant prolonged-release intramuscular injection in postmenopausal women awaiting surgery for primary breast cancer." *Clin Ther* 25(5): 1440-52.

OBJECTIVE: The aim of this study was to describe the pharmacokinetics of 3 different single doses of fulvestrant-a new estrogen receptor (ER) antagonist that downregulates the ER with no known agonist effects-administered as a prolonged-release IM formulation. METHODS: Pharmacokinetic data were obtained in a randomized, partially blinded, placebo-controlled, parallel-group, Phase I/II multicenter trial involving postmenopausal women

with primary breast cancer (clinical stages T1-T3, with tumors that were ER positive or of unknown ER status) awaiting curative-intent surgery. Patients received either IM fulvestrant (50, 125, or 250 mg), oral tamoxifen (20 mg, once daily), or oral placebo (once daily). Treatment started 2 to 3 weeks before surgery and blood was taken at various times up to 12 weeks after fulvestrant administration to assess pharmacokinetic variables. RESULTS: A total of 200 patients entered the trial, of whom 58 took part in the pharmacokinetic analysis (50 mg, $n = 20$; 125 mg, $n = 16$; 250 mg, $n = 22$). Following single IM injections of fulvestrant, the median time to maximum concentration was 6.98, 6.98, and 6.96 days in the 50-, 125,- and 250-mg dose groups, respectively, with an overall range of 2 to 19 days). The plasma concentration-time profiles were primarily controlled by the rate of absorption from the injection site; post-peak plasma concentrations declined over time and were measurable up to 84 days after administration of fulvestrant 125 and 250 mg. Plasma concentrations at 28 days were 2- to 5-fold lower than the maximum value. Plasma concentration data for the 250-mg dose were best described by a 2-compartment pharmacokinetic model, with an apparent terminal phase half-life of approximately 49 days, beginning approximately 3 weeks after administration. Mean area under the plasma concentration-time curve for days 0 through 28 (AUC 0-28) was proportional for fulvestrant 50, 125, and 250 mg. For a doubling of the dose, an analysis of covariance model of the pharmacokinetic data projected an estimated increase in AUC 0-28 of a factor of 1.84 (95% CI, 1.67 to 2.04). CONCLUSIONS: The IM formulation of fulvestrant used in this study had predictable, dose-linear pharmacokinetics. The prolonged-release properties of this formulation suggested that it may be well suited for the once-monthly dosing schedule intended for clinical use.

Rocino, A., A. Carola, et al. (1999). "Major surgery for a gastric cancer in a haemophilic with high inhibitor titre successfully performed by the use of recombinant FVIIa." *Haemophilia* 5(6): 441-4.

A total gastrectomy with omentectomy and resection of the distal oesophagus in a 69-year-old haemophilia A patient with high inhibitor of 128 Bethesda units is described. Surgery was successfully performed after infusion of 112 microg kg-1 bw of recombinant FVIIa. Ninety-two microg kg-1 were given thereafter at time intervals of 2 h until 12 h, then every 3 h until 24 h, and every 4 h until 48 h after surgery. Doses were gradually reduced in the following days and finally discontinued on day 28 after surgery. The complete treatment schedule required the administration of a total of 708 mg of

recombinant FVIIa. Using this approach, we observed normal haemostasis, and there were no signs of excessive postoperative bleeding or wound haematoma. No clinical side-effects or evidence of systemic activation of coagulation occurred during the treatment. As judged from the clinical course of this major surgery, recombinant FVIIa appears to be highly efficacious and safe and should be used as first line treatment in high titre inhibitor patients with cross-reactivity to porcine factor VIII, undergoing surgery.

Roukos, D. H., M. Lorenz, et al. (2001). "Pathological serosa and node-based classification accurately predicts gastric cancer recurrence risk and outcome, and determines potential and limitation of a Japanese-style extensive surgery for Western patients: a prospective with quality control 10-year follow-up study." *Br J Cancer* **84**(12): 1602-9.

UICC classification accurately predicts overall survival but not recurrence-risk. We report here data of overall and first site-specific recurrence following curative surgery useful for the development of recurrence-oriented preventive target therapies. Patients who underwent resection for gastric cancer were stratified according to curability of surgery [curative (R0) vs non-curative resection], extent of surgery [limited (D1) vs extended (D2) node dissection] and pathological nodal/serosal status. The intent-to-treat principle, log-rank test and Cox regression analysis were used for statistical analysis of time-to-event (recurrence, death) endpoints. Curative resection only produced a chance of cure whereas survival was very poor following non-curative resection ($P < 0.0001$). For D2 R0 subgroup of patients, a pathological serosa and a node state-based classification into three groups, proved to be of clinical implication. Risk of recurrence after a median follow-up of 92 months was low among patients with both serosa and node-negative cancer (first group; 11%), moderate among those with either serosa or node-positive cancer (second group; 53%) and very high among those with both serosa and node-positive cancer (third group; 83%). In multivariate analysis, the relative risks of recurrence and death from gastric cancer among patients in the second and third groups, as compared to those in the first, were 7.07 (95% CI, 2.36-21.17; $P = 0.0002$) and 16.19 (95% CI, 5.76-45.54; $P < 0.0001$) respectively. First site-specific recurrence analysis revealed: low rate of loco-regional recurrence alone (12%), serosa state determinant factor of the site-recurrence (peritoneal for serosa-positive and haematogenous for serosa-negative cancers) and dramatic increase of all types of recurrence by the presence of nodal metastases. Our findings demonstrate that a pathological serosa- and

node-based classification is very simple and predicts accurately site-specific recurrence-risks. Furthermore they reveal that risk of recurrence following curative D2 surgery alone is low for serosa- and node-negative cancers, but very high in serosa- and node-positive cancers suggesting the need for new therapeutic strategies in this subgroup of patients.

Rouzier, R., P. Morice, et al. (2005). "Survival in cervix cancer patients treated with radiotherapy followed by radical surgery." *Eur J Surg Oncol* **31**(4): 424-33.

AIM: To determine the incidence and predictive value of residual disease in the hysterectomy specimens of cervical cancer patients treated with primary radiotherapy, with or without chemotherapy, followed by surgery and to determine whether pathologically confirmed residual disease is a surrogate marker of outcome. METHODS: The medical records of patients treated for stage IB/II carcinoma of the cervix in a single institution between 1985 and 2000 were retrospectively analysed into two different groups, depending on whether they had received radiotherapy or concurrent chemo-radiotherapy. Six to 8 weeks after irradiation, all patients underwent radical or extrafascial hysterectomy and pelvic and para-aortic lymphadenectomy. RESULTS: A total of 403 patients were included in the study (360 in the radiotherapy only group and 43 in the chemo-radiotherapy group). One hundred and seventy-eight patients had residual disease on hysterectomy specimens in the radiotherapy group. Considering only the stages IB2 and II, 126 (52%) and 16 (37%) patients had residual disease on hysterectomy specimens in the radiotherapy group and in the chemo-radiotherapy group, respectively ($P=0.08$). Residual disease was associated with pelvic and para-aortic nodal metastases. The 5-year local control and overall survival rates were 88 and 86%, respectively, in the patients with complete pathologic response and 73 and 62%, respectively, in the patients with residual disease ($P<0.001$). In multivariate analysis, FIGO stage, residual disease, and pathologic nodal involvement were independent predictive factors of both local recurrence and overall survival. CONCLUSION: Pathologically confirmed residual disease on hysterectomy specimen is an independent and strong predictive factor of both local recurrence and overall survival.

Saarilahti, K., M. Kajanti, et al. (2003). "Cyclin A and Ki-67 expression as predictors for locoregional recurrence and outcome in laryngeal cancer patients treated with surgery and postoperative radiotherapy." *Int J Radiat Oncol Biol Phys* **57**(4): 986-95.

PURPOSE: To investigate the association between the cancer cell proliferation fraction and the risk of recurrence in laryngeal cancer patients treated without systemic therapy. **METHODS AND MATERIALS:** Paraffin-embedded tumor samples from 90 laryngeal cancer patients were stained for cyclin A and the Ki-67 antigen by immunohistochemistry. The patients were treated with partial or total laryngectomy followed by postoperative radiotherapy to a total dose of 50 Gy or greater. The median follow-up time was 91 months (minimum 48 months). **RESULTS:** High cyclin A expression (>19% positive cancer cell nuclei, the highest tertile) was associated with a high rate of locoregional tumor recurrence and unfavorable disease-free and overall survival as compared with cases with a lower expression ($p = 0.025$, 0.032 , and 0.042 , respectively). In a multivariate analysis, high cyclin A expression was an independent predictor of poor disease-free survival (RR 2.4, 95% CI 1.2-4.9, $p = 0.013$) and overall survival (RR 2.1, 1.2-3.6, $p = 0.012$), together with a poor Karnofsky's performance status and the presence of positive margins at surgery. Ki-67 expression was not an independent predictor of survival, but cancers with high Ki-67 expression (>34% nuclei positive, the highest tertile) recurred more frequently locoregionally when treated with split-course radiotherapy than when treated with a continuous course of therapy ($p = 0.035$), whereas the presence of a planned split did not influence the frequency of locoregional recurrences when Ki-67 expression was lower ($p = 0.93$). **CONCLUSION:** Cancer cell cyclin A expression is a novel predictive factor for outcome in laryngeal cancer treated with surgery and postoperative radiotherapy. Planned gaps in the radiotherapy course are deleterious in patients with a high proliferative fraction, and immunostaining for the Ki-67 antigen may be useful in identification of such patients.

Sadahi, S., T. Suzuki, et al. (2005). "Detection of carcinoembryonic antigen messenger RNA-expressing cells in portal and peripheral blood during surgery does not influence relapse in colorectal cancer." *Ann Surg Oncol* **12**(12): 988-94.

BACKGROUND: No consensus has been reached on whether cancer cells detected in blood during colorectal cancer (CRC) surgery may serve as a prognostic indicator. **METHODS:** One hundred patients with CRC who underwent curative surgery were the subjects. Portal and peripheral blood were collected immediately after celiotomy and examined for carcinoembryonic antigen (CEA) messenger RNA (mRNA) by using competitive semi-nested reverse transcriptase-polymerase chain reaction. The median follow-up period was 59 months (range, 49-74

months). **RESULTS:** Until now, recurrence has been confirmed in 13 patients (13%). The 4-year recurrence rate was 6.7% (3 of 45) in patients with CEA mRNA-positive portal blood and 20.8% (10 of 48) in patients with CEA mRNA-negative portal blood ($P = .09$); it was 5.6% (2 of 36) and 19.3% (11 of 57) in patients with CEA mRNA-positive peripheral blood and CEA mRNA-negative blood, respectively ($P = .12$). There was no difference in disease-free survival between the CEA mRNA-positive and -negative groups. The multivariate analysis showed that the presence of tumor cells in portal or peripheral blood was a factor that reduced recurrence. The relative risks were .17 ($P = .01$) for the portal vein and .24 ($P = .07$) for the peripheral vein. **CONCLUSIONS:** The detection of cancer cells in blood taken during surgery is not considered to be a poor-prognostic factor in CRC.

Sadahi, S., T. Suzuki, et al. (2007). "Detection of carcinoembryonic antigen messenger RNA-expressing cells in peripheral blood 7 days after curative surgery is a novel prognostic factor in colorectal cancer." *Ann Surg Oncol* **14**(3): 1092-8.

BACKGROUND: The significance of detection of circulating cancer cells in blood during surgery in patients with colorectal cancer (CRC) remains controversial. Experimental study revealed that the cancer cells injected from the vein disappeared completely until 7 days. The aim of this study was to clarify that the detection of circulating cancer cells in blood taken later than 7 days after curative surgery may be a prognostic factor. **METHODS:** Two hundred consecutive patients with CRC who underwent potentially curative surgery were the subjects. Peripheral blood was collected between 7 and 10 days after resection. Cancer cells were detected using reverse transcriptase-polymerase chain reaction targeting carcinoembryonic antigen (CEA) messenger RNA (mRNA). The median follow-up period was 52 months (range: 34-69 months). **RESULTS:** The overall positive incidence of CEA mRNA was 22%. Detection of CEA mRNA was not significantly related to conventional clinicopathological findings. Recurrence has been confirmed in 55 patients (28%). The recurrence rate was significantly higher in patients with rectal cancer, deep penetration, lymph node metastasis, preoperative chemoradiotherapy and positive CEA mRNA. The CEA mRNA positive patients showed significantly poorer disease free survival (DFS) and overall survival (OS) than the negative patients (DFS, $P = 0.007$; OS, $P = 0.04$). Multivariate analysis revealed that the positive expression of CEA mRNA ($P < 0.01$) as well as the tumor location and TNM stage classification was identified as the significant risk factors for recurrence. **CONCLUSIONS:** Detection of

CEA mRNA expressing cells in peripheral blood 7 days after curative surgery is a novel independent factor predicting recurrence in patients with CRC.

Sagen, A., R. Karesen, et al. (2009). "Physical activity for the affected limb and arm lymphedema after breast cancer surgery. A prospective, randomized controlled trial with two years follow-up." *Acta Oncol* **48**(8): 1102-10.

BACKGROUND. The influence of physical activity on the development of arm lymphedema (ALE) after breast cancer surgery with axillary node dissection has been debated. We evaluated the development of ALE in two different rehabilitation programs: a no activity restrictions (NAR) in daily living combined with a moderate resistance exercise program and an activity restrictions (AR) program combined with a usual care program. The risk factors associated with the development of ALE 2 years after surgery were also evaluated. **MATERIAL AND METHODS.** Women (n = 204) with a mean age of 55+/-10 years who had axillary node dissection were randomized into two different rehabilitation programs that lasted for 6 months: NAR (n = 104) or AR (n = 100). The primary outcomes were the difference in arm volume between the affected and control arms (Voldiff, in ml) and the development of ALE. Baseline (before surgery) and follow-up tests were performed 3 months, 6 months, and 2 years after surgery. Data were analyzed using ANCOVA and regression analysis. **RESULTS.** Voldiff did not differ significantly between the two treatment groups. Arm volume increased significantly over time in both the affected and the control arms. The development of ALE from baseline to 2 years increased significantly in both groups (p < 0.001). The only risk factor for ALE was BMI > 25 kg/m(2). **CONCLUSION.** Patients that undergo breast cancer surgery with axillary lymph node dissection should be encouraged to maintain physical activity in their daily lives without restrictions and without fear of developing ALE.

Sakorafas, G. H. and M. G. Sarr (2003). "Pancreatic cancer after surgery for chronic pancreatitis." *Dig Liver Dis* **35**(7): 482-5.

BACKGROUND: Chronic pancreatitis is known to be a risk factor for pancreatic cancer. **AIMS:** To identify patients who were diagnosed with pancreatic cancer after undergoing surgery for histologically documented chronic pancreatitis. **PATIENTS/METHODS:** Records of 484 consecutive patients who underwent surgery for chronic pancreatitis from 1976 to 1997 were reviewed. **RESULTS:** Pancreatic cancer was diagnosed after a mean of 3.4 years (range: 2 months-1 years) in 14

patients (2.9%). In four patients, pancreatic cancer became evident within 12 months of surgery for chronic pancreatitis, suggesting cancer was present at the original surgery. Cancer presented with recurrent or persistent pain, jaundice, and/or weight loss. Pancreatic resection was possible in eight patients, but in the others, the cancer was inoperable. There was one long-term survivor (alive 14 years postoperatively), but for the others mean survival was 10 months (16 months after resection vs. 4 months for inoperable cancer). **CONCLUSION:** Pancreatic malignancy should be suspected in patients who have had surgery for chronic pancreatitis when symptoms (such as recurrent pain, jaundice, weight loss, or anorexia) recur. Attempts at curative pancreatic resection are indicated and can offer palliation and the potential for a cure.

Salmon, P., J. Hill, et al. (2006). "The role of child abuse and age in vulnerability to emotional problems after surgery for breast cancer." *Eur J Cancer* **42**(15): 2517-23.

Emotional problems are common after breast cancer, but patients differ in their vulnerability. Childhood abuse is a risk factor for emotional problems in adult women, and we tested whether it explains some of the variability in emotional problems after breast cancer. Women with primary breast cancer (N=355) 2-4 d after surgery (mastectomy or wide local excision) self-reported current emotional distress, post-traumatic stress, self-blame, bodily shame and recollections of childhood sexual, physical and emotional abuse. Multiple logistic regression analyses tested the relationship of each emotional problem to abuse, distinguishing three age-groups, divided at 50 and 65 years. Emotional distress, post-traumatic stress, self-blame and shame were present in 49%, 8%, 22% and 13% of women, respectively. Each problem was more common in women who recalled one or other form of abuse. Apart from emotional distress, emotional problems were less common in older women. Older women were also less likely to recall abuse, and recall of abuse contributed statistically to explaining the relationship of youth to emotional problems. Childhood abuse is a risk factor for emotional problems after surgical treatment for breast cancer, and the challenge of identifying and helping those patients in whom emotional problems reflect pre-morbid vulnerabilities needs careful consideration. Because both emotional problems and abuse are strongly age-linked, future research should avoid generalisations across the age spectrum.

Sartori, F., L. Bortolotti, et al. (1999). "The role of surgery in integrated therapies for non-small-cell lung cancer." *Ann Oncol* **10 Suppl 5**: S73-6.

Surgery represents the best treatment for early-stage non-small-cell lung cancer (NSCLC). In selected cases, even locally-advanced cancers may be suitable for surgical treatment. The combination of chemotherapy (with or without radiotherapy) and surgery has proved potentially useful in improving survival, but pre-operative treatment may represent a risk factor for the onset of post-operative complications. Studies performed to date indicate the need for further multidisciplinary research with a view to identifying more advantageous treatment modalities, particularly for locally-advanced NSCLC.

Sato, N., K. Koeda, et al. (2001). "Cytokine profile of serum and bronchoalveolar lavage fluids following thoracic esophageal cancer surgery." *Eur Surg Res* **33**(4): 279-84.

OBJECTIVES: The body's response to stress is comprised of two opposing reactions, namely inflammation and immunosuppression. The balance between these two reactions not only changes over time, but also varies among different cells or organs. Limited information is available regarding the cytokine balance of circulating blood and inflammatory sites after thoracic surgical stress. **DESIGN:** The subjects of the present study were 10 patients undergoing esophageal cancer surgery which requires thoracolaparotomic manipulation. The postoperative levels of interleukin (IL)-8, IL-10, IL-1 receptor antagonist (IL-1ra) and soluble tumor necrosis factor receptor I (sTNF-RI) in bronchoalveolar lavage fluids (BALFs) and peripheral blood were measured by enzyme-linked immunosorbent assay. The absolute concentration of cytokines in lower respiratory tract ([cytokine](LRT)) was estimated by using the ratio of urea concentration in BALF and serum. **RESULTS:** The levels of these cytokines in peripheral blood peaked within 24 h of start of the surgery (IL-8 85.6 +/- 29.8 pg/ml; IL-10 65.1 +/- 10.6 pg/ml; IL-1ra 2,807.8 +/- 652.8 pg/ml, and sTNF-RI 3,996.3 +/- 380.1 pg/ml). The level of [IL-8](LRT) immediately after surgery was approximately 20 times higher than that in peripheral blood, and the level of [IL-1ra](LRT) was approximately 4 times higher. In contrast, the level of [IL-10](LRT) immediately after surgery was comparable to that in peripheral blood, but the level of [sTNF RI](LRT) immediately after surgery was approximately one fifth of that in peripheral blood. **CONCLUSIONS:** The balance between pro- and anti-inflammatory reactions varies from one part of the body to the next, and changes over time after surgery. The profile of stress-induced pro-inflammatory cytokines and anti-inflammatory cytokines should be analyzed further to establish appropriate and effective cytokine modulatory therapeutic approaches.

Schillaci, G., F. Rondelli, et al. (2009). "Endothelial progenitor cells are mobilized after major laparotomic surgery in patients with cancer." *Int J Immunopathol Pharmacol* **22**(4): 1035-41.

The progression of cancer is largely dependent on neoangiogenesis. Circulating endothelial progenitor cells (EPC) have the ability to form complete vascular structures in vitro and play a crucial role in tumor vasculogenesis. Emerging evidence suggests that surgical injury may induce the mobilization of EPC in animal models, and this might have a negative effect on the prognosis of cancer patients. We studied 20 patients (10 men, 65+/-13 years) undergoing laparotomy for surgical treatment of various forms of abdominal cancer, and 20 age- and sex-matched healthy control subjects. The number of circulating EPC, defined as CD34+/KDR+ cells identified among mononuclear cells isolated from peripheral venous blood, was determined preoperatively and at days 1 and 2 after surgery. Surgery induced a significant increase in circulating EPC levels at day 1 (from 278/mL, interquartile range 171-334, to 558/mL, interquartile range 423-841, $p < 0.001$) and day 2 (709/mL, interquartile range 355-834, $p < 0.001$) compared with baseline values. EPC levels did not change in control subjects. Seven subjects who underwent laparotomic surgery for non-neoplastic disease also showed an increase in EPC levels after surgery ($p = 0.009$ and $p = 0.028$ at day 1 and day 2, respectively). We conclude that patients undergoing elective laparotomic surgery for cancer demonstrate an increase in EPC post-operatively. The potential adverse effects of surgical stress-induced EPC mobilization on tumor and metastasis growth in cancer patients need to be addressed in future studies.

Schoppmeyer, K., N. Fruhauf, et al. (2006). "Tumor cell dissemination in colon cancer does not predict extrahepatic recurrence in patients undergoing surgery for hepatic metastases." *Oncol Rep* **15**(2): 449-54.

Patients undergoing resection of hepatic metastases of colorectal cancer have a high risk of extrahepatic recurrence, most likely caused by early tumor cell dissemination or the manipulation of liver tumors during surgical resection. Using immunocytochemistry, we studied 47 patients for cytokeratin (CK)-positive (+) cells in: a) bone marrow (BM) samples to determine whether tumor cell dissemination had already occurred before surgery; and b) blood samples directly taken from the hepatic vein before and during surgery of liver metastases. In addition, normal and malignant liver tissues were evaluated for markers known to be involved in tumor progression and metastasis [urokinase plasminogen activator (uPA), Her-2/neu, epidermal growth factor

receptor (EGF-R)] using sandwich enzyme immunoassays. CK+ cells were detected in the BM of 26/47 patients (55%), in blood samples of 14/47 patients (30%) before surgery and 11/47 patients (23%) during surgery with a median detection rate of 1 (range, 1-14) CK+ cell per 4×10^6 MNC. No CK+ cells were found in 15/47 patients (32%) in any sample studied. Tumor tissue was obtained from 32/47 patients and normal liver tissue from 24/32 patients. While no differences were found for EGF-R and Her-2/neu, a 9-fold higher expression of uPA could be demonstrated in tumor tissue of 20/32 patients (63%) compared to normal liver tissue. When all obtained results were correlated with clinical outcome, neither the detection of CK+ cells nor the expression pattern in the tumor tissue, or the combination of both, was predictive for extrahepatic recurrence or overall survival after a mean observation time of 43 months (range, 26-54 months). Although uPa is overexpressed in liver metastases of colorectal cancer, and dissemination of CK+ cells during surgery of these metastases is a frequent event in colon cancer, these findings do not predict extrahepatic recurrence. Further characterization of single cells, especially those spread during surgery, will help to identify those patients with an increased risk of later relapse.

Sereno Moyano, M., E. Casado Saenz, et al. (2009). "WITHDRAWN: The combination of FOLFOX4 and bevacizumab may enable salvage surgery of unresectable liver metastases in colon cancer." *Anticancer Drugs* **20 Special Issue 1**: S4-S6.

withdrawn by publisher: Colorectal cancer treatment has experienced important advances in the last 5 years. New targeted therapies have been included in the classical regimens based on 5-fluorouracil, oxaliplatin, or irinotecan. This new approach has brought great revolution in the treatment of this type of cancer. Bevacizumab (Avastin), a new anti-vascular endothelial growth factor drug, has been shown to improve overall survival in combination with chemotherapy in first-line and second-line settings as compared with standard chemotherapy regimens alone. This case report demonstrates our experience with bevacizumab in a colon cancer patient with liver, lung, and regional lymph node metastases who had a relapse in the liver after adjuvant treatment with capecitabine (Xeloda). The addition of bevacizumab to the FOLFOX4 regimen resulted in a partial response that provided an opportunity for salvage hepatic surgery.

Sesterhenn, A. M., A. A. Dunne, et al. (2006). "Complications after CO(2) laser surgery of laryngeal

cancer in the elderly." *Acta Otolaryngol* **126**(5): 530-5.

CONCLUSION: Cancer of the larynx in elderly patients should be treated with curative intention, if the extension of the primary tumour allows safe resection. Transoral CO(2) laser microsurgery is associated with a low rate of major complications and can be regarded as suitable even for elderly patients. Age itself should never be the sole factor in deciding which therapy should be undertaken. OBJECTIVES: In the industrialized nations the age group beyond 75 years will grow steadily, requiring special attention by medical professionals in the future. Nowadays laryngeal cancer is often treated by transoral CO(2) laser microsurgery. Because of a variety of comorbidities, the incidence of perioperative complications in the group of elderly patients is of increasing interest. To date, no references in the literature have discussed complications after transoral CO(2) laser microsurgery in this age group. Patients and methods. Twenty-four patients over the age of 75 suffering from squamous cell carcinoma of the larynx and treated by transoral CO(2) laser microsurgery since 1998 were analysed for intraoperative and postoperative complications. RESULTS: There was no evidence of surgery-related complications at all. Postoperatively, 6 of 24 patients complained about dysphagia. Due to intraoperative placement of nasogastric feeding tubes in these six cases further complications such as pneumonia resulting from aspiration could have been avoided.

Shikama, N., S. Sasaki, et al. (2003). "Risk factors for local-regional recurrence following preoperative radiation therapy and surgery for head and neck cancer (stage II-IVB)." *Radiology* **228**(3): 789-94.

PURPOSE: To discover possible risk factors for local-regional recurrence (LRR) following preoperative radiation therapy and curative surgery for head and neck squamous cell carcinoma (SCC) (stage II-IVB). MATERIALS AND METHODS: Clinical records from 1987 to 1999 of 161 patients with head and neck SCC (oral cavity, 80 patients; larynx, 50; hypopharynx, 19; oropharynx, 12) who underwent preoperative radiation therapy and surgery were retrospectively reviewed. One hundred thirty-two (82%) of the patients had stage III or IV cancer. The median radiation dose was 38 Gy. RESULTS: The 5-year overall survival rate and LRR rate were 58% and 35%, respectively. At multivariate analysis, oral cavity cancer ($P = .020$), clinical T stage ($P = .016$), clinical N stage ($P = .017$), and status of surgical margins ($P = .008$) emerged as variables that were significantly associated with LRR. The analysis of only those patients with lymph node involvement

showed that oral cavity cancer ($P = .008$), advanced N-stage cancer ($P = .045$), and long interval between the start of preoperative radiation therapy and surgery ($>$ or $=7$ weeks) ($P = .019$) emerged as variables that were significantly associated with LRR. **CONCLUSION:** Oral cavity cancer, advanced T or N stage of disease, and unsatisfactory margins were risk factors for LRR. A long interval ($>$ or $=7$ weeks) was a risk factor for LRR in patients with lymph node involvement.

Shiono, S., J. Yoshida, et al. (2007). "Risk factors of postoperative respiratory infections in lung cancer surgery." *J Thorac Oncol* **2**(1): 34-8.

BACKGROUND: Postoperative infections have been a major issue in lung cancer surgery. We changed our perioperative prophylactic antibiotic policy to a single dose of cefazolin before and after surgery in July 2002. **OBJECTIVE:** To identify the risk factors of postoperative pneumonia and empyema in lung cancer patients undergoing surgical resection. **METHODS:** From July 1992 through September 2003, 2105 patients underwent primary lung cancer resection at our division. We reviewed 1855 eligible patients for possible risk factors of pneumonia and empyema. **RESULTS:** Postoperative respiratory infections developed in 69 (3.7%) patients. There were 58 (3.1%) pneumonia cases and 18 (1.0%) cases of empyema. The mortality rate was 0.8% (15 patients). Nine (0.5%) patients died from postoperative respiratory infections. Multivariate analysis showed age 75 years or older, forced expiratory volume in 1 second as a percentage of forced vital capacity (FEV1%) less than 70%, advanced pathologic stage, and induction therapy to be independent risk factors of pneumonia. For postoperative empyema, advanced age was the significant factor. Twelve of 18 patients (67%) with empyema were complicated with bronchopleural fistula. The infection incidence rate did not change significantly after we modified our prophylactic antibiotic policy to a single dose of cefazolin before and after surgery. **CONCLUSIONS:** Lung cancer patients with advanced age, low FEV1%, advanced pathologic stage, or induction therapy had a risk for pneumonia after lung cancer surgery. Postoperative empyema was associated with advanced age.

Shukla, P. J., G. Barreto, et al. (2008). "Revision surgery for incidental gallbladder cancer: factors influencing operability and further evidence for T1b tumours." *HPB (Oxford)* **10**(1): 43-7.

BACKGROUND AND AIM: There is a need to increase the available data on revision radical surgery for incidental gallbladder cancer and to determine factors influencing operability. We aimed to assess the impact of stage of disease (pT) and the

type of primary surgery (laparoscopy versus open) on resectability rates. **MATERIAL AND METHODS:** The data of 90 consecutive patients referred to the Tata Memorial Hospital between 1 January 2003 and 30 April 2007 for revision radical surgery for incidental gallbladder cancer were reviewed retrospectively. **RESULTS:** Of the 90 patients who underwent revision surgery, accurate data on T-stage was available in 76, and of these 76 patients, 44 (57.8%) had prior laparoscopic simple cholecystectomy, while 32 (42.2%) had undergone open surgery. The median time interval between the two surgeries was 2 months (range 4 weeks to 11 months). By T-stage, 23 patients had T1b disease, while 33 and 20 patients had T2 and T3 disease, respectively. Successful revision surgery could be undertaken in 71% of patients (54/76) and 29.6% of these had residual disease confirmed by histopathological examination. **CONCLUSIONS:** T-stage is an important factor in determining operability as confirmed by our study. As the T-stage of the disease increased, the chances of finding residual disease increased, while operability decreased. Furthermore, the case for revision surgery is strengthened because the incidence of lymph nodal disease is high even for pT1b cancers. The type of primary surgery does not affect operability in patients undergoing revision radical surgery for incidental gallbladder cancer.

Siersema, P. D. and R. van Hillegersberg (2008). "Treatment of locally advanced esophageal cancer with surgery and chemoradiation." *Curr Opin Gastroenterol* **24**(4): 535-40.

PURPOSE OF REVIEW: This article reviews developments in the treatment of locally advanced esophageal cancer with surgery and chemoradiation published in 2007. **RECENT FINDINGS:** Overall long-term survival is the same for patients after transhiatal or transthoracic esophagectomy. The pathology report of the resected specimen should contain information on lymph node status, such as size, location and lymph node ratio. If surgery is performed in patients with advanced esophageal cancer, there is small survival advantage if combined with neoadjuvant therapy, that is chemoradiation. Prognostic factors are a good performance status, a major response to chemoradiation and an early metabolic response with fluorine-18 fluorodeoxyglucose PET. Definitive chemoradiation may have similar results as combination treatment including surgery in selected patients with esophageal squamous cell cancer. Salvage surgery should be considered if definitive chemoradiation fails, provided that an R0 resection can be performed. Nutritional status is a prognostic

factor in patients undergoing treatment of esophageal cancer. **SUMMARY:** In 2007, refinements of the nodal status in the tumor, node, metastasis system were proposed. Chemoradiation followed by surgery is increasingly being used in patients with advanced esophageal cancer. Evidence suggests that definitive chemoradiation could be a reliable treatment option in selected patients with esophageal squamous cell cancer.

Sillah, K., E. A. Griffiths, et al. (2009). "Clinical impact of tumour involvement of the anastomotic doughnut in oesophagogastric cancer surgery." Ann R Coll Surg Engl **91**(3): 195-200.

INTRODUCTION: Published colorectal cancer surgery data suggest no role for the analysis of the anastomotic doughnuts following anterior resection. The usefulness of routine histological analysis of the upper gastrointestinal doughnut is not clear. Our study assessed the impact of cancer involvement of the doughnut on clinical practice. Factors associated with doughnut involvement and the effect on patients' survival were also analysed. **PATIENTS AND METHODS:** The clinicopathological details of 462 patients who underwent potentially curative oesophagogastric resection for cancer with a stapled anastomosis between 1994 and 2006 in two specialist centres were retrospectively analysed. Univariate, multivariate and survival analyses were carried out. **RESULTS:** Approximately 5% of doughnuts (22 of 462) were histologically involved with cancer. Microscopic involvement of the proximal resection margin, local lymph node metastasis and lymphatic invasion within the main resected specimen were independently associated with doughnut involvement (all $P < 0.05$). However, these three factors taken together failed to predict doughnut involvement. Doughnut involvement was an independent adverse prognostic factor for overall survival ($P = 0.0013$). **CONCLUSIONS:** In contrast to findings in colorectal surgery, doughnut involvement with cancer appears to have useful prognostic information following oesophagogastric resection. Routine histological analysis of upper gastrointestinal doughnuts is justified. Doughnut involvement could potentially strengthen the indications for adjuvant therapy in the future.

Sjostrom, L., A. Gummesson, et al. (2009). "Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial." Lancet Oncol **10**(7): 653-62.

BACKGROUND: Obesity is a risk factor for cancer. Intentional weight loss in the obese might protect against malignancy, but evidence is limited.

To our knowledge, the Swedish Obese Subjects (SOS) study is the first intervention trial in the obese population to provide prospective, controlled cancer-incidence data. **METHODS:** The SOS study started in 1987 and involved 2010 obese patients (body-mass index [BMI] ≥ 34 kg/m² in men, and ≥ 38 kg/m² in women) who underwent bariatric surgery and 2037 contemporaneously matched obese controls, who received conventional treatment. While the main endpoint of SOS was overall mortality, the main outcome of this exploratory report was cancer incidence until Dec 31, 2005. Cancer follow-up rate was 99.9% and the median follow-up time was 10.9 years (range 0-18.1 years). **FINDINGS:** Bariatric surgery resulted in a sustained mean weight reduction of 19.9 kg (SD 15.6 kg) over 10 years, whereas the mean weight change in controls was a gain of 1.3 kg (SD 13.7 kg). The number of first-time cancers after inclusion was lower in the surgery group ($n=117$) than in the control group ($n=169$; HR 0.67, 95% CI 0.53-0.85, $p=0.0009$). The sex-treatment interaction p value was 0.054. In women, the number of first-time cancers after inclusion was lower in the surgery group ($n=79$) than in the control group ($n=130$; HR 0.58, 0.44-0.77; $p=0.0001$), whereas there was no effect of surgery in men (38 in the surgery group vs 39 in the control group; HR 0.97, 0.62-1.52; $p=0.90$). Similar results were obtained after exclusion of all cancer cases during the first 3 years of the intervention. **INTERPRETATION:** Bariatric surgery was associated with reduced cancer incidence in obese women but not in obese men. **FUNDING:** Swedish Research Council, Swedish Foundation for Strategic Research, Swedish Federal Government under the LUA/ALF agreement, Hoffmann La Roche, Cederroths, AstraZeneca, Sanofi-Aventis, Ethicon Endosurgery.

Sonneveld, D. J., H. S. Koops, et al. (1999). "Surgery versus surveillance in stage I non-seminoma testicular cancer." Semin Surg Oncol **17**(4): 230-9.

Today, the standard treatment for patients with clinical Stage I non-seminomatous testicular germ cell tumors (NSTGCT) following orchidectomy is either primary retroperitoneal lymph node dissection (RPLND) or close surveillance with cisplatin-based polychemotherapy in case of a relapse. Both treatment modalities provide excellent overall survival rates up to 100%. Consequently, selection of the most appropriate management option is not primarily guided by survival considerations. The choice between the available options, each having its merits and its drawbacks, should be made based on a number of factors including treatment-related morbidity, views and expertise of the physician, patient preferences, the expected degree of patient

compliance, and prognostic factor analysis. To date, the role of adjuvant chemotherapy as an alternative management option for patients with clinical Stage I NSTGCT at high risk of occult metastases is limited. This systemic treatment modality would be a realistic alternative if the reliability of prognostic factors to identify high-risk Stage I patients could be improved. This review addresses relevant issues in the management of patients with clinical Stage I NSTGCT to provide information that will allow a rational selection of the most appropriate management option.

Sorensen, L. T., J. Horby, et al. (2002). "Smoking as a risk factor for wound healing and infection in breast cancer surgery." *Eur J Surg Oncol* **28**(8): 815-20.

AIM: Clinical studies suggest that smoking is associated with wound necrosis after breast cancer surgery. However, the significance of smoking as a risk factor for wound infection, skin flap necrosis, and epidermolysis when adjusting for other potential risk factors remains to be studied. METHODS: From June 1994 through August 1996, 425 patients underwent breast cancer surgery as simple mastectomy, modified radical mastectomy, or breast conserving surgery. The patients were evaluated postoperatively for wound infection, skin flap necrosis, and epidermolysis. Association between these complications and 17 patient, operative, and postoperative variables were analysed by three separate multiple logistic regression analyses. RESULTS: When compared to non-smoking, smoking was significantly associated with wound infection after all types of surgery (light smoking (1-14 grams per day): [odds ratio (OR)=2.95, 95% confidence interval (95% CI)=1.07-8.16], and heavy smoking (≥ 15 grams per day): OR=3.46 (1.52-7.85). A similar significant association was found as regards skin flap necrosis and epidermolysis after simple mastectomy and modified radical mastectomy: both light and heavy smoking were predictive for skin flap necrosis: light smoking: OR=6.85 (1.96-23.90), heavy smoking: OR=9.22 (2.91-29.25) and for epidermolysis: light smoking: OR=3.98 (1.52-10.43) and heavy smoking: OR=4.28 (1.81-10.13). No significant dose-response relation was disclosed. Other risk factors and confounders associated with complicated wound healing were adjusted for in the analysis: diabetes, obesity, alcohol, NSAIDs, duration of surgery, and surgical experience. CONCLUSION: Independent of other risk factors, smoking is predictive for post-mastectomy wound infection, skin flap necrosis, and epidermolysis.

Stamatis, G., W. Eberhard, et al. (2004). "Surgery after multimodality treatment for non-small-cell lung cancer." *Lung Cancer* **45 Suppl 2**: S107-12.

Neoadjuvant treatment for Locally advanced non-small-cell lung cancer (NSCLC) stage IIIA and IIIB promises higher resection rates because of a reduction of the primary tumour and sterilisation of mediastinal nodes ("downstaging"). In this study we analyse the perioperative course and the long-term survival of patients with trimodality treatment. Between 03/1991 and 12/2002, 392 patients with NSCLC underwent resection after induction treatment. Included were 266 males and 126 females, age 55.8 +/- 9 (28-74), of whom 218 were stage-IIIA patients, 174 were stage-IIIB patients. Induction treatment included 3 courses of chemotherapy with cisplatin/etoposide or cisplatin/paclitaxel, followed by one course of chemotherapy with cisplatin/etoposide as well as hyperfractionated accelerated radiotherapy of the primary tumour and the mediastinal nodes with 45 Gy, followed by surgery. Before induction treatment all patients underwent mediastinoscopy. In patients with N3 disease mediastinoscopy was repeated before surgery. Resections included 133 pneumonectomies (34%), 15 bilobectomies (4%), 55 sleeve lobectomies (14%), 168 lobectomies (42.5%), 6 segmentectomies (1.5%), and 15 explorative thoracotomies (4%). In-hospital mortality rates amounted to 4.6% (18 patients) while postoperative morbidity ran up to 46% (180 patients). Morbidity and mortality rates were significantly higher in patients with Karnofsky status lower than 80% and patients older than 65 years. Bronchopleural fistulas occurred in 16 patients (3.2%). The protection of the bronchial stump or anastomosis with viable tissue, like pericardial fat, proves to be a significant factor for the reduction of septic complications. For NSCLC, the 5- and 7-year survival rates were 36% and 31%, respectively, for stage IIIA, and 26% for stage IIIB. This intensive trimodality treatment proves to be feasible. Treatment-related toxicities are overall moderate and acceptable. Accurate cardiopulmonary evaluation before surgery and reinforcement of bronchial stump or anastomosis can contribute to reducing complications. Induction treatment demonstrated a "downstaging effect", so that a clear trend for organ-sparing resection was observed. Long-term survival rates for selected groups look very promising when compared to historical controls.

Stehr, S. N. and A. R. Heller (2006). "Omega-3 fatty acid effects on biochemical indices following cancer surgery." *Clin Chim Acta* **373**(1-2): 1-8.

Epidemiological studies have indicated that a high intake of saturated fat and/or animal fat increases the risk of colon and breast cancer. Laboratory and clinical investigations have shown a reduced risk of colon carcinogenesis after alimentation with omega-3 fatty acids, as found in fish oil. Mechanisms

accounting for these anti-tumor effects are reduced levels of PGE(2) and inducible NO synthase as well as an increased lipid peroxidation, or translation inhibition with subsequent cell cycle arrest. Further, omega-3 eicosapentaenoic acid is capable of down-regulating the production and effect of a number of mediators of cachexia, such as IL-1, IL-6, TNF-alpha and proteolysis-inducing factor. In patients with advanced cancer, it is possible to increase energy and protein intake via an enteral or parenteral route, but this seems to have little impact on progressive weight loss. Fish oil administration improved patients' conditions in cancer cachexia and during radio- and chemotherapy. In patients undergoing tumor resection surgery we observed improvement of liver and pancreas biochemical indices when omega-3 fatty acids were administered. This paper is a review of recent developments in the field of nutrition in cancer patients with emphasis on the acute phase response following cancer surgery and the beneficial aspects of fish oil administration.

Steinert, R., M. Hantschick, et al. (2008). "Influence of subclinical tumor spreading on survival after curative surgery for colorectal cancer." *Arch Surg* **143**(2): 122-8.

OBJECTIVE: To determine epithelial cell dissemination in patients with localized colorectal cancer. **DESIGN:** Prospective observational study. **SETTING:** Academic hospital. **PARTICIPANTS:** Two hundred twenty-two patients operated on for colorectal cancer. **MAIN OUTCOME MEASURES:** Epithelial cell dissemination was determined using immunohistochemistry or cytology in histologically negative lymph nodes, the peritoneal cavity, and bone marrow. Prognostic significance was determined in relation to 140 clinicopathological variables. Median follow-up was 61 months. **RESULTS:** Of 140 patients who underwent curative surgery; 25 (17.9%) died of cancer-related causes; 10 (7.1%), of other causes; and 11 (7.8%) developed local recurrence. Tumor cells were present in the peritoneal cavity of 22% of patients, but this finding had only borderline influence on disease-free survival ($P = .07$). Lymph node micrometastases correlated with T category but not with survival. The presence of epithelial cells in the bone marrow was detected in 64% of patients but was not associated with tumor stage or survival. Multivariate analysis failed to identify occult tumor cell dissemination into any body compartment as an independent prognostic factor of disease-free survival. **CONCLUSIONS:** Tumor cells disseminate into various body compartments in early stages of disease. In about two-thirds of patients, tumor cells are left in the body after so-called curative surgery. However, the presence of minimal residual disease has no

independent prognostic significance in relation to established risk factors for tumor progression. Thus, other factors, such as the presence of a cellular metastatic phenotype and/or ineffective immunological response, must play an important role.

Stoeckle, E., P. Paravis, et al. (2004). "Number of residual nodules, better than size, defines optimal surgery in advanced epithelial ovarian cancer." *Int J Gynecol Cancer* **14**(5): 779-87.

The objective of the present study was to improve the definitions of optimal and suboptimal surgery in ovarian cancer. A retrospective prognostic factor analysis was done in a series of 433 patients with advanced ovarian cancer (stages III and IV) treated during the cisplatin era from 1980 to 1997 with assessment of postoperative residual disease by number and ranges of size of peritoneal nodules. Mean age of patients was 56.7 years. Median follow-up of patients alive was 138 months (range: 6-266 months). Median overall survival was 23 months. Significant prognostic factors for overall survival in univariate analysis were age, the presence of ascites, FIGO stage, treatment period, histological subtype, grade, results of surgery as defined by size and number of residual nodules. In multivariate analysis, quality of surgery defined by no versus few versus numerous residual nodules showed to remain an independent prognostic factor for outcome ($P = 0.003$), whereas size of residual nodules did not achieve significance. In conclusion, only complete surgery (no residual nodules) confers a real survival advantage. Cytoreduction to few and small nodules is associated with favorable outcome and could be qualified as optimal. Otherwise, cytoreduction leaving numerous nodules, whatever their size, remains suboptimal. Such patients should be considered for neo-adjuvant chemotherapy.

Supiot, S., J. Bennouna, et al. (2006). "Negative influence of delayed surgery on survival after preoperative radiotherapy in rectal cancer." *Colorectal Dis* **8**(5): 430-5.

OBJECTIVE: In Europe, until recently the standard treatment for locally advanced rectal cancer was preoperative radiotherapy (RT). The objective of this study was to evaluate the influence on survival of intervals between diagnosis and treatment. **PATIENTS AND METHODS:** The influence on survival of intervals between diagnosis and surgery (Dg-Surg), diagnosis and initiation of RT (Dg-Rad), and completion of RT and surgery (Rad-Surg) was evaluated in a retrospective series of patients treated with preoperative RT. Between 1991 and 1998, 102 patients received treatment with preoperative RT without concomitant chemotherapy at the Rene

Gauducheau Cancer Center. Patients generally received 45 Gy (80%) in 25 fractions over 35 days for T2-T3-T4 N0-N1 M0 rectal adenocarcinoma located mainly (62.7%) in the lower third of the rectum (< or = 5 cm from anal margin). Thirty-five pN1 patients were treated with postoperative chemotherapy. Differences between survival were assessed by the log-rank test, and prognostic factors by the Cox test. RESULTS: Median time was 14.7 weeks for Dg-Surg, 4.6 weeks for Dg-Rad and 5.1 weeks for Rad-Surg. Median follow-up from diagnosis was 57.4 months. Five-year local relapse-free survival was 83.9%, metastasis-free survival 64% and overall survival 60.8%. No factor was predictive of tumour response to RT. Log-rank and multivariate analysis showed that overall survival was significantly influenced by lower-third tumours, pT, pN and Dg-Surg (poorer survival when > or = 16 weeks: OR = 2.59, P = 0.005). Metastasis-free survival correlated significantly with Dg-Surg (> or = 16 weeks: OR = 2.05, P = 0.05). CONCLUSION: An interval of more than 16 weeks between diagnosis and surgery may reduce overall survival of patients treated with preoperative RT for locally advanced rectal cancer. Surgery should be performed shortly after completion of RT for patients with no possibility of sphincter preservation, or a minimal risk of morbidity from an abdominoperineal excision.

Swenson, K. K., M. J. Nissen, et al. (2009). "Case-control study to evaluate predictors of lymphedema after breast cancer surgery." *Oncol Nurs Forum* **36**(2): 185-93.

PURPOSE/OBJECTIVES: To identify risk factors for lymphedema after breast cancer surgery. DESIGN: Multisite case-control study. SETTING: Lymphedema clinics in the upper midwestern region of the United States. SAMPLE: 94 patients with lymphedema and 94 controls without lymphedema, matched on type of axillary surgery and surgery date. METHODS: The Measure of Arm Symptom Survey, a patient-completed tool, assessed potential risk factors for lymphedema. Severity of lymphedema was measured by arm circumference, and disease and treatment factors were collected via chart review. MAIN RESEARCH VARIABLES: Risk factors for lymphedema after breast cancer surgery. FINDINGS: On univariate analysis, patients with lymphedema were more likely than controls to be overweight (body mass index ≥ 25) ($p = 0.009$). They also were more likely to have had axillary radiation ($p = 0.011$), mastectomy ($p = 0.008$), chemotherapy ($p = 0.033$), more positive nodes ($p = 0.009$), fluid aspirations after surgery ($p = 0.005$), and active cancer status ($p = 0.008$). Strength training ($p = 0.014$) and air travel ($p = 0.0005$) were associated with less lymphedema

occurrence. On multivariate analysis, the only factor significantly associated with lymphedema was being overweight ($p = 0.022$). CONCLUSIONS: Being overweight is an important modifiable risk factor for lymphedema. Axillary radiation, more extensive surgery, chemotherapy, and active cancer status also were predictive of lymphedema. IMPLICATIONS FOR NURSING: This study provides evidence that excess weight contributes to lymphedema; strength training and airline travel did not contribute to lymphedema.

Sztefko, K., D. Hodorowicz-Zaniewska, et al. (2009). "IGF-I, IGF-II, IGFBP2, IGFBP3 and acid-labile subunit (ALS) in colorectal cancer patients before surgery and during one year follow up in relation to age." *Adv Med Sci* **54**(1): 51-8.

PURPOSE: To investigate the changes of IGF system in colon cancer patients in relation to age, the serum IGF-I, IGF-II, IGFBP2, IGFBP3 and ALS were measured by immunochemistry before surgery, as well as one and six months after surgery. MATERIAL AND METHODS: One hundred and twenty six patients were included into the study: group I (<50 yrs, N=21); group II (50 to <55 yrs, N=16); group III (55 to <65 yrs, N=34); group IV (65 to <75 yrs, N=42) and group V (> or =75 yrs, N=13). RESULTS: Before surgery: only the mean value of IGF-I concentration in group I was significantly higher as compared to group V ($p < 0.01$). One month after surgery: 1) a decrease in the mean values of IGF-I, IGF-II, IGFBP3 and ALS levels was observed, but only for IGF-II (groups II-V), IGFBP3 (groups II-V) and ALS (groups III-V) the changes were significant; 2) the mean value of ALS level in group I was higher as compared to group III-V ($p < 0.05$ to 0.02); 3) higher mean values of IGF-I/albumin, IGFBP3/albumin and ALS/albumin were noted for group I as compared to group V ($p < 0.01$ to 0.001); 4) the mean levels of IGFBP2 were significantly lower in group I as compared to groups II, III, IV and V ($p < 0.001$ in all cases). CONCLUSIONS: In colon cancer patients IGF-I, IGFBP3 and ALS decrease with age, but the relation between them exists regardless the patient's age and time of observation. Lower IGFBP2 level together with higher IGF-I might contribute to more aggressive course of disease in colon cancer patients below 50 years of age.

Takeda, Y., Y. Nonaka, et al. (2001). "Correlation between timing of surgery in relation to the menstrual cycle and prognosis of premenopausal breast cancer patients." *Biomed Pharmacother* **55 Suppl 1**: 133s-137s.

The timing of surgery in relation to menstrual phase might affect the progress of disease

in premenopausal women with operable breast cancer. In the present study, the records were examined of 28 such cases treated between 1990 and 1999, and compared for recurrence-free survival with reference to the phases of the menstrual cycle defined by Hrushesky and Senie. During the follow-up period, breast cancer relapse occurred in five patients, and one patient died of another disease unconnected with recurrent breast cancer. The recurrence rate was not significantly different between two phases classified by either Hrushesky or Senie. However, patients with early-stage breast cancer operated during the perimenstrual phase and those with advanced breast cancer which was resected during the peri-ovulatory phase appeared to have a better prognosis than patients operated on during the other phases. Since the prognosis for breast cancer patients is dependent not only on the menstrual cycle but also on many other factors, it is concluded that the menstrual cycle cannot constitute an absolute prognostic factor.

Takei, H., J. Horiguchi, et al. (2002). "Predictive value of estrogen receptor status as assessed by ligand-binding assay in patients with early-stage breast cancer treated with breast conserving surgery and radiation therapy." *Oncol Rep* 9(2): 375-8.

It is important to determine which factors are predictive for the prognosis of patients treated with breast conserving surgery (BCS) and radiation therapy (RT) in order to make a decision as to the adjuvant treatment. Although estrogen receptor (ER) is known to be a predictive marker for antiestrogens in breast cancer, the prognostic effect of hormone receptors has not been fully analyzed in Japanese breast cancer patients treated with BCS and RT. A total of 153 breast cancer patients having up to three positive nodes in the axilla as identified histologically and treated with both BCS and RT with or without systemic therapy were enrolled in this study. All tumors were measured for ER and progesterone receptor (PR) using ligand-binding assay (LBA). ER was inversely related to patients' age, however, PR was not related to any clinical features. When ER was classified into negative, weakly positive and strongly positive categories, with cut-off levels of zero and 50 fmol/mg protein, the relapse-free survival (RFS) was significantly better in patients with tumors having strongly positive ER than in patients with tumors having negative ER. Multivariate analysis revealed that ER as well as nodal status, was an independent predictive factor for RFS, however, PR was not. As a result, we believe that ER measured by LBA is valuable for predicting prognosis of early-stage breast cancer patients treated with BCS and RT.

Tan, J. E., S. G. Orel, et al. (1999). "Role of magnetic resonance imaging and magnetic resonance imaging-guided surgery in the evaluation of patients with early-stage breast cancer for breast conservation treatment." *Am J Clin Oncol* 22(4): 414-8.

Magnetic resonance imaging (MRI) may be more sensitive than mammography for detecting breast cancer and may have an adjunctive role in assessing patients with early-stage disease for breast conservation treatment. This study was performed to analyze the impact of breast MRI on the clinical management of 83 patients being considered for breast conservation treatment. Eighty-three consecutive cases of patients undergoing breast MRI during standard workup and evaluation for breast conservation treatment from 1993 to 1996 were retrospectively reviewed. Records were reviewed for patient and tumor characteristics, mammographic findings, MRI findings, timing of MRI study, findings from MRI-guided surgery (when done), and whether the patient underwent breast conservation treatment. MRI definitely altered management in 15 patients (18%), may have affected management in 4 patients (5%), and did not change management in 64 patients (77%). Thirteen patients underwent additional surgery because of MRI findings; the positive predictive value for MRI-guided surgery was 38% (5 of 13). Ultimately, 82% of the patients received breast conservation treatment. No predictive factor was identified to characterize the patients most likely to have management affected by MRI findings. These findings suggest that breast MRI may be useful in the evaluation of patients with early-stage breast cancer for breast conservation treatment. A larger study population and outcome data will be required to confirm these findings and to define those patients most likely to benefit from breast MRI.

Tanaka, M., Y. Hashiguchi, et al. (2003). "Tumor budding at the invasive margin can predict patients at high risk of recurrence after curative surgery for stage II, T3 colon cancer." *Dis Colon Rectum* 46(8): 1054-9.

PURPOSE: The aim of this study was to identify indicators that can predict patients at high risk of tumor recurrence in Stage II, T3 colon cancer. **METHODS:** A total of 138 patients classified as Stage II, T3 underwent curative resection of colon cancer between 1981 and 1993. Clinical variables included age, gender, bowel obstruction, tumor location, and emergency presentation. For each colon tumor specimen, the following histopathological variables were assessed: maximum tumor diameter (<5 vs. ≥5 cm), depth, tumor grade (well and moderate vs. other), lymphatic and venous invasion (absent vs. present), perineural invasion, tumor necrosis, and

tumor margin (expanding vs. infiltrating). We also categorized tumor budding, defined as a single cancer cell or small clusters of undifferentiated cancer cells in the invasive frontal lesion, into two categories: none or minimal (BD-1), and moderate or severe (BD-2). Univariate analysis for factors regarding recurrence and disease-specific survival were performed with the logistic regression model and the log-rank test. RESULTS: Among the factors analyzed, tumor budding was the only factor that was significantly associated with recurrence and survival. The numbers of patients with BD-1 and BD-2 tumors were 111 and 27, respectively. Forty-eight percent of BD-2 tumor patients developed recurrence, compared with 4.5 percent of BD-1 tumor patients ($P < 0.0001$). The cumulative disease-specific survival rates at five years for patients with BD-1 and BD-2 tumors were 98 and 74 percent, respectively ($P < 0.0001$). CONCLUSION: The presence of moderate or severe budding at the invasive margin in Stage II, T3 colon cancer indicated a high risk of tumor recurrence after curative surgery, providing useful information for the decision regarding postoperative adjuvant chemotherapy.

Tanisada, K., T. Teshima, et al. (2000). "A preliminary outcome analysis of the Patterns of Care Study in Japan for esophageal cancer patients with special reference to age: non surgery group." *Int J Radiat Oncol Biol Phys* 46(5): 1223-33.

BACKGROUND: The Patterns of Care Study (PCS) was imported to Japan from the United States in July 1996. A preliminary outcome analysis of the PCS for esophageal cancer patients in Japan was made with special reference to age, because the elderly population is rapidly increasing in Japan. PATIENTS AND METHODS: From July 1996 to February 1998, external PCS audits were performed for 37 institutions nationwide and detailed information of 561 esophageal cancer patients treated during the period 1992-1994 was collected by using the fifth PCS data format developed in the United States. This format was provided courtesy of the American College of Radiology. For this study, patients who had not undergone surgery ($n = 336$) were selected. The patients were classified into three age groups: < 65 years old ($n = 119$), between 65 and 74 years ($n = 93$), and 75 years or older ($n = 123$). Cox's proportional hazards model was used for the statistical analysis, with survival, acute/subacute complication and late complication of grade 3 or more based on RTOG criteria, as the endpoints. RESULTS: Significant prognostic factors for the entire non-surgery group were Karnofsky Performance Status (KPS) ($p = 0.0007$), stage ($p = 0.0001$), and external irradiation dose ($p = 0.0001$). For the younger group, KPS ($p =$

0.0004), stage ($p = 0.0197$), and utilization of brachytherapy ($p = 0.0010$) were significant, while for the intermediate age group it was KPS ($p = 0.0027$), history of pulmonary disease ($p = 0.0339$), stage ($p = 0.0001$), and external dose ($p = 0.0001$), and for the elderly group, stage ($p = 0.0001$) and external irradiation dose ($p = 0.0224$) were significant. Significant risk factors for complications for the entire group were stage ($p = 0.0411$), external dose ($p = 0.0163$), and stratification of institution (academic vs. nonacademic) ($p = 0.0114$). Significant risk factors for the younger group were history of pulmonary disease ($p = 0.0495$) and external dose ($p = 0.0037$), and the other age groups showed no significant risk factors. CONCLUSION: Age was not a significant prognostic or risk factor for esophageal cancer patients in the non-surgery group treated with radiation therapy. Therefore, radiation therapy represented an important treatment modality for the elderly as well as for the younger esophageal cancer patients. External dose was a treatment-related prognostic factor for the elderly as well as for the intermediate age group.

Temple, L. K., J. Bacik, et al. (2005). "The development of a validated instrument to evaluate bowel function after sphincter-preserving surgery for rectal cancer." *Dis Colon Rectum* 48(7): 1353-65.

PURPOSE: Sphincter-preserving surgery is technically feasible for many rectal cancers, but functional results are not well understood. Therefore, the purpose of this study was to develop an instrument to evaluate bowel function after sphincter-preserving surgery. METHODS: A 41-item bowel function survey was developed from a literature review, expert opinions, and 59 patient interviews. An additional 184 patients who underwent sphincter-preserving surgery between 1997 and 2001 were asked to complete the survey and quality-of-life instruments (Fecal Incontinence Quality of Life, European Organization for Research and Treatment of Cancer QLQ 30/Colorectal Cancer 38). A factor analysis of variance was performed. Test-retest reliability was evaluated, with 20 patients completing two surveys within a mean of 11 days. Validity testing was done with clinical variables (gender, age, radiation, length of time from surgery), surgical variables (procedure: local excision, low anterior resection, coloanal anastomosis), reconstruction (J-pouch, straight), anastomosis (handsewn, stapled), and quality-of-life instruments. RESULTS: The survey response rate was 70.1 percent (129/184). Among the 127 patients with usable data, 67 percent were male, the median age was 64 (range, 38-87) years, and the mean time for restoration of bowel continuity after sphincter-preserving surgery was 22.9 months. Patients had a

median of 3.5 stools/day (range, 0-30), and 37 percent were dissatisfied with their bowel function. Patients experienced a median of 22 symptoms (range, 7-32), with 27 percent reported as severe, 37 percent as moderate, and 36 percent as mild. The five most common symptoms were incomplete evacuation (96.8 percent), clustering (94.4 percent), food affecting frequency (93.2 percent), unformed stool (92.8 percent), and gas incontinence (91.8 percent). The factor analysis identified 14 items that collapsed into three subscales: FREQUENCY (alpha = 0.75), DIETARY (alpha = 0.78), and SOILAGE (alpha = 0.79), with acceptable test-retest reliability for the three subscales and total score (0.62-0.87). The instrument detected differences between patients with preoperative radiation (n = 67) vs. postoperative radiation (n = 15) vs. no radiation (n = 45) (P = 0.02); local excision (n = 10) vs. low anterior resection (n = 55) vs. coloanal anastomosis (n = 62) (P = 0.002); and handsewn (n = 18) vs. stapled anastomosis (n = 99) (P = 0.006). The total score correlated with 4 of 4 Fecal Incontinence Quality of Life (P < 0.01) and 9 of 17 European Organization for Research and Treatment of Cancer subscales (all P < 0.01). CONCLUSIONS: Patients undergoing sphincter-preserving surgery for rectal cancer have impaired bowel function, and those treated with radiation, coloanal anastomoses, or handsewn anastomoses have significantly worse function. This reliable and valid instrument should be used to prospectively evaluate bowel function after sphincter-preserving surgery in patients undergoing rectal cancer therapy.

Terauchi, F., H. Nishi, et al. (2009). "Prognostic factor on optimal debulking surgery by maximum effort for stage IIIC epithelial ovarian cancer." *J Obstet Gynaecol Res* **35**(2): 315-9.

OBJECTIVES: The aim of this study was to assess the prognostic factor of radical surgery in patients with stage IIIC ovarian cancer. STUDY DESIGN: Fifty-two patients were subjected to the study. The complete resection or optimal primary cytoreductive surgery (OPCS) was set as the maximum effort, and the accomplishment rate and prognosis were assessed. In addition, the poor prognosis cases among the OPCS-accomplished were evaluated with several factors based on univariate and multivariate analyses. RESULTS: The OPCS accomplishment rate was 84.6%. A worse prognosis was obtained in the more-than-4-weeks-delayed postoperative chemotherapy group, assessing poor-outcome cases in the OPCS group. A case that required more than three colon resections was the significant factor for the delay of postoperative chemotherapy. CONCLUSIONS: OPCS should be performed with maximum effort to improve the

prognosis of stage IIIC ovarian cancer. We should avoid any delay in starting postoperative chemotherapy. In cases that require more than three colon resections, it seems that 'perioperative management' should be reconsidered and that priority should be given to postoperative management so that chemotherapy can be started soon after the operation.

Thorne, A. L., S. J. Mercer, et al. (2006). "Reduction in late diagnosis of colorectal cancer following introduction of a specialist colorectal surgery service." *Ann R Coll Surg Engl* **88**(6): 562-5.

INTRODUCTION: An audit of patients presenting with colorectal cancer to our district general hospital during a 2-year period from November 1994 found that 12.1% of cases were diagnosed later than 6 months after initial presentation to a physician. This audit was repeated for a 2-year period from December 2001, to determine whether the introduction of a specialist coloproctology surgery service had led to a reduction in late diagnosis of colorectal cancer. PATIENTS AND METHODS: Case notes were reviewed of all patients presenting with colorectal cancer between December 2001 and November 2003. Late diagnosis was defined as diagnosis of colorectal cancer more than 6 months after their first attendance to either their general practitioner or district general hospital. The results were compared with those of the previous study. RESULTS: Of a total of 218 patients presenting with colorectal cancer during the study period, 14 (6.4%; 10 men and 4 women) satisfied the criteria for late diagnosis, with the longest delay being 12.5 months. Reasons for late diagnosis were false-negative reporting of barium studies (n = 3), inaccurate tumour biopsy (n = 2), concurrent pathology causing anaemia (n = 4), inappropriate delay in definitive investigation (n = 3), and refusal of investigation by patients (n = 2). CONCLUSIONS: There has been a reduction of nearly 50% (12.1% to 6.4%) in the proportion of patients with a late diagnosis of colorectal cancer compared with our previous audit. It is suggested that an important factor in this improvement in diagnosis has been the introduction of a specialist coloproctology surgery service.

Thorpe, H., D. G. Jayne, et al. (2008). "Patient factors influencing conversion from laparoscopically assisted to open surgery for colorectal cancer." *Br J Surg* **95**(2): 199-205.

BACKGROUND: Intraoperative conversion from laparoscopically assisted to open surgery for colorectal cancer is thought to be influenced by several patient factors. Analysis of the Conventional versus Laparoscopic-Assisted Surgery In Colorectal Cancer (CLASICC) Trial data aimed to identify these

risk factors. **METHODS:** Of 488 laparoscopically assisted procedures attempted, 143 (29.3 per cent) were converted to open operation. Patient factors considered in multivariable analyses were age, sex, previous abdominal incisions, body mass index (BMI), tumour site, tumour diameter, pathological tumour (pT) and pathological node (pN) stage, extent of tumour spread from the muscularis propria, liver and peritoneal metastases, and American Society of Anesthesiologists (ASA) grade. As BMI was missing for 30.7 per cent of patients, two approaches were employed: one considered BMI as a possible risk factor and one did not. **RESULTS:** When BMI was taken into consideration, male sex (odds ratio (OR) 2.07; $P = 0.020$), BMI (OR 1.10; $P = 0.006$) and extent of tumour spread from the muscularis propria (OR 1.08; $P < 0.001$) were independent predictors of conversion. When BMI was not considered, extent of tumour spread (OR 1.07; $P < 0.001$) and male sex (OR 2.05; $P = 0.004$) were again identified, as were tumour site (OR 2.11; $P = 0.005$) and ASA grade (II versus I, OR 0.92; III versus I, OR 2.74; $P = 0.012$). **CONCLUSION:** Intraoperative conversion is more likely with larger BMI, in men, patients with rectal cancer, those graded ASA III or when there is greater local tumour spread.

Tiezzi, D. G., J. M. Andrade, et al. (2008). "Breast conserving surgery after neoadjuvant therapy for large primary breast cancer." *Eur J Surg Oncol* **34**(8): 863-7.

AIM: The aim of this study was to evaluate the safety of breast conserving surgery in patients with breast tumours satisfactorily downstaged after neoadjuvant therapy. **METHODS:** A retrospective cohort study was undertaken to analyze the loco-regional recurrence (LRR) after breast conserving surgery. We enrolled 88 patients with breast cancer subjected to neoadjuvant therapy (NAT group) who achieved an objective response due to neoadjuvant treatment and compared them with 191 patients with early breast cancer (EBC group) who were submitted to primary conserving surgery. Lumpectomy or quadrantectomy with axillary lymph node dissection was performed in all patients who received adjuvant radiotherapy. Systemic adjuvant therapy was offered to all patients. The mean periods of observation were 61.3 months in the NAT group and 67.5 months in the EBC group. **RESULTS:** The mean age was 53 years in the NAT group and 56 years in the EBC group ($p=0.04$). There was no histological type and histological grade difference between groups. In the NAT group, the mean diameter of residual tumour was lower and the mean volume of breast tissue resection was higher than in the EBC group ($p=0.01$ and $p=0.002$, respectively). The ipsilateral recurrence

rate was 7.9% in the NAT group and 7.8% in the EBC group ($p=0.9$). The most important predictive factor of recurrence in the NAT group was the age of patient. **CONCLUSION:** Breast conserving therapy is a safe procedure in satisfactorily downstaged breast cancer after neoadjuvant therapy.

Togashi, K., F. Konishi, et al. (2000). "Predictive factors for detecting colorectal carcinomas in surveillance colonoscopy after colorectal cancer surgery." *Dis Colon Rectum* **43**(10 Suppl): S47-53.

PURPOSE: The aim of this study was to identify the high-risk groups for metachronous colorectal carcinoma among patients who undergo colorectal cancer surgery. **METHODS:** Three hundred forty-one patients undergoing colorectal cancer surgery who had undergone surveillance colonoscopy at least twice during a period of more than three years were analyzed. A metachronous colorectal carcinoma was defined as a new colorectal carcinoma detected by surveillance colonoscopy after surgery. **RESULTS:** Surveillance colonoscopy was performed 4.6 times per patient during an average of 6.2 years. Twenty-two metachronous colorectal carcinomas in 19 patients were detected, and 14 (64 percent) of 22 were detected within five years of surgery. The cumulative incidence of developing colorectal carcinomas during a five-year period was 5.3 percent. Seventeen (77 percent) of 22 carcinomas were 10 mm or less in size. Ten (71 percent) of the 14 carcinomas in early stages showed a flat appearance. Univariate analysis showed that extracolonic malignancy, coexistence of adenoma, and synchronous multiple colorectal carcinoma were significant predictive factors for detecting colorectal carcinomas in surveillance colonoscopy and that family history of colorectal carcinoma was a possible predictive factor. Multivariate analysis performed with Cox proportional hazards regression model showed that extracolonic malignancy and the coexistence of adenoma were significant predictive factors. **CONCLUSION:** We recommend that patients with the above predictive factors receive surveillance colonoscopy meticulously and regularly.

Tokunaga, Y., H. Hosogi, et al. (2002). "Prognostic value of thymidine phosphorylase/platelet-derived endothelial cell growth factor in advanced colorectal cancer after surgery: evaluation with a new monoclonal antibody." *Surgery* **131**(5): 541-7.

BACKGROUND: Thymidine phosphorylase (TP) is an essential enzyme for activation of 5-fluorouracil and its derivatives and identical to platelet-derived endothelial cell growth factor. In colorectal cancer (CRC), previous studies evaluating the relationship between TP expression and

clinicopathologic features have yielded inconsistent results. These studies used monoclonal antibody 654-1, which stained CRC cells weakly. Now, a new monoclonal antibody, 1C6-203, more sensitive than 654-1, is available. **METHODS:** This study included 80 patients whose CRCs were classified into stages II to IV and completely resected surgically in our institute. TP expression in CRC was evaluated by using immunohistochemical staining with 1C6-203. Relationships between TP expression and clinicopathologic variables that might have affected the patients' prognosis were evaluated. Survival curves were calculated with the Kaplan-Meier method, and differences were evaluated with log-rank test. Cox proportional hazards model was used in the univariate and multivariate survival analyses. **RESULTS:** TP expression showed a positive correlation with advances in histologic differentiation ($P = .025$), lymph node metastasis ($P = .083$), lymphatic invasion ($P = .049$), venous invasion ($P = .042$), and cancer stage ($P = .002$). The patients' survival rates after surgery were higher ($P = .0041$) in those with negative TP than in those with positive TP. The overall estimated hazard ratio for death in patients with TP expression was 6.24 according to univariate analysis ($P = .013$). Multivariate analysis showed that TP was a significant prognostic factor adjusted for other clinicopathologic variables. **CONCLUSIONS:** With a new highly sensitive monoclonal antibody to TP, the present results indicated that TP expression is associated with CRC progression and invasion and closely correlated with poor prognosis in postoperative CRC patients. Moreover, TP expression is an independent prognostic factor in CRC patients.

Tokunaga, Y., M. Nakagami, et al. (2003). "Prognostic effects of dihydropyrimidine dehydrogenase in advanced colorectal cancer after surgery: immunohistochemistry using a new monoclonal antibody." *Anticancer Res* **23**(2C): 1763-8.

BACKGROUND: The response rate of 5-FU and its clearance are due to the activity of dihydropyrimidine dehydrogenase (DPD), which is the first and rate-limiting enzyme for the catabolism of 5-FU. Although several studies have evaluated the relationship between DPD expression and chemosensitivity to 5-FU in patients with colorectal cancer (CRC), only a few studies on DPD expression and clinicopathological features have been conducted using immunohistochemical staining since a monoclonal antibody for DPD has not been established. Now, a new monoclonal antibody (2H9-1b) for human DPD is available. **PATIENTS AND METHODS:** This study included 100 patients whose CRCs were classified into stage II to IV and

completely resected surgically in our institute. DPD expression in CRC was evaluated by using immunohistochemical staining with 2H9-1b. The relationship between DPD expression and clinicopathological variables that might have affected the patients' prognosis were evaluated. Survival curves were calculated with the Kaplan-Meier method and differences were evaluated with the log-rank test. The Cox proportional hazards model was used in the univariate and multivariate survival analyses. **RESULTS:** DPD expression showed a positive correlation with advances in lymphatic invasion ($p = 0.066$), venous invasion ($p = 0.033$) and cancer stage ($p = 0.033$). The patients' survival rates after surgery were significantly ($p = 0.018$) higher in those DPD-negative than in those DPD-positive. The overall estimated hazard ratio for death in patients with DPD expression was 4.79 according to univariate analysis ($p = 0.033$). Multivariate analysis showed that DPD expression tended to be a prognostic factor less potent than other variables such as lymph node metastasis and venous invasion. **CONCLUSION:** With a new sensitive monoclonal antibody to human DPD, the present results indicated that DPD expression is associated with CRC progression and invasion, and closely correlated with poor prognosis in postoperative CRC patients. Moreover, DPD expression is a prognostic factor in CRC patients.

Tomimaru, Y., M. Yano, et al. (2006). "Factors affecting the prognosis of patients with esophageal cancer undergoing salvage surgery after definitive chemoradiotherapy." *J Surg Oncol* **93**(5): 422-8.

BACKGROUND AND OBJECTIVES: Although salvage surgery after definitive chemoradiotherapy (CRT) is common, the safety and indication has not yet been established. **METHODS:** We retrospectively compared the mortality and morbidity of 24 patients who underwent salvage surgery with those of historical controls treated with neoadjuvant CRT followed by planned esophagectomy during the same period, and analyzed the prognostic factor of salvage surgery. **RESULTS:** Preoperative serum albumin (3.7 vs. 4.1 g/dl, $P = 0.0157$) and lymphocyte count (763 vs. 964/mm³), $P = 0.0111$) in the salvage group were significantly lower than those in the neoadjuvant group. A significant difference was also observed in operation time (567 vs. 474 min, $P = 0.0381$), C-reactive protein (CRP) on postoperative day 1 (11.2 vs. 8.7 mg/dl, $P = 0.0021$), and postoperative systemic inflammatory response syndrome (SIRS) duration (3.5 vs. 2.9 days, $P = 0.0486$). There were three hospital deaths in the salvage group, whereas no patient died in the neoadjuvant group. Multivariate analysis showed curability (R0 vs. R1 + R2) to be the strongest

prognostic factor of salvage surgery ($P = 0.0064$). R1 + R2 operation was more frequently performed in the salvage group (33% vs. 13%), and the reason for all cases was unresectable T4, which had been underestimated preoperatively. **CONCLUSIONS:** Salvage surgery is a highly invasive and morbid operation, which is performed on immunocompromised hosts. The indication must be carefully considered, with care taken to avoid non-curative surgery.

Tsuji, T., T. Sawai, et al. (2004). "Platelet-derived endothelial cell growth factor expression is an independent prognostic factor in colorectal cancer patients after curative surgery." *Eur J Surg Oncol* **30**(3): 296-302.

AIMS: Platelet-derived endothelial cell growth factor (PD-ECGF) is an angiogenic factor that undergoes increased expression in colorectal carcinomas, but its prognostic value is a topic of debate. The aim of this study is to clarify the prognostic value of PD-ECGF expression in colorectal carcinomas. **METHODS:** PD-ECGF expression was measured by enzyme-linked immunosorbent assay in frozen materials from 134 colorectal cancer patients who had received curative resections. Patients were divided into high expression and low expression groups based upon selected cut-off value. Correlations among PD-ECGF expression, clinicopathologic features, and disease-free interval were studied by univariate and multivariate analysis. To evaluate the origin of PD-ECGF, serial sections of the 134 tumours were stained for PD-ECGF and CD68. **RESULTS:** PD-ECGF expression in the normal mucosa was 34.4 ± 15.5 (Units/mg protein) and the cut-off value was 65.4 (mean+2SD). There were no significant correlations between clinicopathological features and PD-ECGF expression. The disease-free interval for the high PD-ECGF expression group was significantly longer than that of the low expression group ($P=0.05$). A multivariate Cox's regression analysis revealed that high PD-ECGF expression is an independent factor for better outcome. In immunohistochemical study, almost all tumour cells were negative for PD-ECGF, but stromal macrophages were predominantly positive for PD-ECGF. **CONCLUSIONS:** The PD-ECGF expression originated from stromal macrophages was a predictor for favorable outcome after curative resections for colorectal cancer.

Turanli, S. (2009). "The role of surgery in breast cancer patients with isolated bone metastases at the time of diagnosis." *J Surg Oncol* **100**(2): 95-9.

BACKGROUND: Surgery for the primary tumor in breast cancer patients with synchronous isolated bone metastasis is applied for palliation. The

aim was to determine whether surgical removal of the primary tumor provides a better survival and disease progression. **METHODS:** Forty-four patients were diagnosed between the dates June 2004 and January 2007 and these patients are classified according to the removal of the primary tumor or not. Patients and tumor characteristics, removal of the primary tumor, and response to systemic therapy are examined as the factors that were affecting overall survival and time to progression of the disease. **RESULTS:** The median follow-up time was 37.5 months. Mean time to progression and overall survival was longer for the patients who received surgery than the patients who did not (20.4 vs. 18.4 months and 57.6 vs. 44.5 months, respectively), but these were not significant ($P = 0.58$, $P = 0.39$). In multivariate analysis, response to systemic treatment [$(P = 0.03)$, hazard ratio = 0.44, 95% confidence interval = 0.20-0.93] was independent factor associated with overall survival. **CONCLUSION:** The response to systemic therapy is the major factor on survival in the breast cancer patients with isolated bone metastasis. Excision of the primary tumor has no effect on time to progression and overall survival.

Uchiyama, A., T. Morisaki, et al. (1999). "Hepatocyte growth factor and invasion-stimulatory activity are induced in pleural fluid by surgery in lung cancer patients." *Br J Cancer* **81**(4): 721-6.

Hepatocyte growth factor (HGF) is a stromal cell-derived cytokine that can stimulate matrix invasion by carcinoma cells. We analysed the concentrations of HGF and invasion-stimulatory activity in pleural fluid after lung surgery. The concentration of HGF in pleural fluids was measured by enzyme-linked immunosorbent assay in seven patients who underwent pulmonary resection for primary or metastatic lung cancer. The effect of the pleural fluid on cancer cell invasion across reconstituted basement membrane (Matrigel) was assessed with a Boyden chamber assay using a lung adenocarcinoma cell line, A549. HGF levels in the pleural fluid after lung surgery ranged from 6.0 to 23.0 ng ml⁻¹ (average: 10.2 ± 4.3 ng ml⁻¹). The matrix invasion of lung carcinoma cells in the presence of the pleural fluid was significantly higher than that in the presence of culture medium alone or sera from normal subjects ($P < 0.01$). The invasion-stimulatory activity of the pleural fluid was strongly inhibited by HGF-neutralizing antibody. Positive correlation was found between the HGF level and invasion-stimulatory activity in the pleural fluids and normal sera ($P = 0.0073$). This is the first report demonstrating that the lung surgery induces a considerable amount of HGF, which is closely

correlated with the invasion-stimulatory activity of the pleural fluid.

Ueno, H., H. Mochizuki, et al. (2004). "Preoperative parameters expanding the indication of sphincter preserving surgery in patients with advanced low rectal cancer." *Ann Surg* **239**(1): 34-42.

OBJECTIVE: To clarify the preoperative parameters of the required distal margin that can be applied to the criteria of sphincter-preserving surgery in rectal cancer. **SUMMARY BACKGROUND DATA:** Although aggressive sphincter-preserving surgery, including intersphincteric resection, is beginning to be applied to low rectal tumors, unexpected distal cancer spread might undermine local control in patients undergoing such a procedure. The 'two-centimeter rule' of distal clearance is predominant at present, whereas preoperative criteria to determine the individual required distal margin have not yet been established. **METHODS:** First, by reviewing 556 rectal cancers, promising risk parameters of intramural distal spread (IM) were selected and, subsequently, such parameters were examined in regard to whether they could be evaluated preoperatively. Furthermore, 80 patients with lower rectal cancers located above the anal canal who were undergoing abdominoperineal resection were reviewed as to whether IM risk factors could be used as criteria to identify the low rectal cancer with or without anal canal involvement. **RESULTS:** IM was observed in 10.6% (IM \geq 10 mm: 2.3%) of the patients examined, and the incidence was higher in tumors with certain unfavorable histologic characteristics, including tumor "budding," in their submucosal region at the distal edge (24.4%) than in those with no such histology (5.3%). Regarding such unfavorable histology as IM risk factor, together with 3/4 or more annularity and type 3 gross appearance, IM rates were 3.3% (IM \geq 10 mm: 0.5%) in the no-risk group, 9.1% (IM \geq 10 mm: 1.7%) in the one-risk group, and 29.1% (IM \geq 10mm: 7.8%) in the multiple-risks group. These results were reproduced well even if such risk factors were evaluated endoscopically or histologically on preoperative biopsy specimens. Furthermore, no anal canal involvement was observed in 32 tumors without IM risk; however, microscopic cancer spread down to the anal canal, including that into outside of the internal sphincter muscle, was observed in 9.1% of tumors with one IM risk and in 26.7% of multiple-risk tumors. **CONCLUSIONS:** The preoperative evaluation of particular parameters related to IM enabled the accurate selection of rectal cancer to which the one-centimeter rule of distal clearance can be applied. This could allow us to expand the

indication of sphincter preservation for very low rectal cancer patients.

Ulutin, H. C., D. Ash, et al. (2003). "Brachytherapy boost to the tumour bed in high risk patients after limited surgery for breast cancer." *Clin Oncol (R Coll Radiol)* **15**(3): 156-9.

The results of treatment for 174 patients at high risk of local recurrence, referred for radiotherapy after conservative surgery for early breast cancer, are evaluated. Microscopic margin involvement, extensive carcinoma in situ, and vascular/lymphatic invasion were the main risk factors for local recurrence. Whole-breast irradiation (40 Gy in 15 fractions over 3 weeks) followed with a brachytherapy boost (Ir192 wire implant or PDR Ir192) of 25 Gy was applied. Median follow-up was 80 months. The actuarial 6-year overall survival rate was 91% and the within breast recurrence-free survival was 88%. The most common risk factor among those recurring within the breast was involved surgical margins (13 out of 17). Cosmesis was reported to be good or excellent in 79% of cases. In patients at high risk for local recurrence, tumour-bed boost with brachytherapy can provide satisfactory local control after limited surgery and external radiotherapy.

van de Pol, S. M., P. A. Doornaert, et al. (2006). "The significance of anemia in squamous cell head and neck cancer treated with surgery and postoperative radiotherapy." *Oral Oncol* **42**(2): 131-8.

The objective of this study was to investigate the prognostic significance of the hemoglobin (Hb) levels at different timepoints in locally advanced squamous cell carcinoma of the head and neck (SCCHN). Included were 111 patients. The hemoglobin levels were assessed before surgery (PreS-Hb), between surgery and radiotherapy (HbAAC), before postoperative radiotherapy (PreRT-Hb) and at the end of radiotherapy (EndRT-Hb). HbAAC takes into account the duration of anemia during the interval between surgery and radiotherapy. Higher HbAAC corresponds with lower Hb levels. Five year locoregional control (LRC) among patients with HbAAC \geq median was 72% and significantly worse as compared to the 88% in case of HbAAC $<$ median ($p = 0.0097$). Multivariate analysis for LRC showed that the HbAAC was a prognostic factor. Overall survival (OS) after 3 years was 77% in case of HbAAC $<$ median and 34% in case of HbAAC \geq median ($p < 0.0002$). Multivariate analysis for OS showed that the PreS-Hb and HbAAC were prognostic factors. Hb level between surgery and radiotherapy is an important prognostic factor for both LRC and OS among patients with SCCHN treated with surgery and postoperative radiotherapy.

van der Burg, M. E. and I. Vergote (2003). "The role of interval debulking surgery in ovarian cancer." *Curr Oncol Rep* 5(6): 473-81.

The mainstay of treatment for advanced ovarian cancer is the multimodality approach of debulking surgery and paclitaxel-platinum chemotherapy. The size of residual lesions after primary surgery remains the most important prognostic factor for survival. Optimal primary debulking surgery can be performed in approximately 40% of patients and up to 80% if it is done by gynecologic oncologists, but sometimes at the cost of considerable morbidity and even mortality. Based on a trial conducted by the European Organization for Research and Treatment of Cancer, optimal as well as suboptimal interval debulking surgery increases overall (P=0.0032) and progression-free survival (P=0.0055). However, not all patients who have undergone suboptimal primary debulking surgery seem to benefit from interval debulking surgery. Preliminary data from the Gynecologic Oncology Group interval debulking study (GOG-152) indicate that, if the gynecologic oncologist makes a maximal effort to resect the tumor, patients who have undergone suboptimal debulking surgery probably gain little benefit from interval debulking surgery.

Varella-Garcia, M., T. Mitsudomi, et al. (2009). "EGFR and HER2 genomic gain in recurrent non-small cell lung cancer after surgery: impact on outcome to treatment with gefitinib and association with EGFR and KRAS mutations in a Japanese cohort." *J Thorac Oncol* 4(3): 318-25.

BACKGROUND: Sensitivity to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and frequency of activation mutations in EGFR is lower in Caucasian than Asian non small-cell lung cancer (NSCLC) patients. Increased EGFR gene copy numbers evaluated by fluorescence in situ hybridization (FISH) has been reported as predictor of clinical benefit from EGFR-TKIs in Caucasian NSCLC patients. This study was carried out to verify whether EGFR FISH had similar performance in Japanese patients. **METHODS:** A cohort of 44 Japanese patients with recurrent NSCLC after surgery was treated with gefitinib 250 mg daily. The cohort included 48% females and 52% never-smokers; 73% had prior chemotherapy and 57% had stage III-IV at the time of surgery. Adenocarcinoma was the most common histology (86%). FISH was performed using the EGFR/Chromosome Enumeration Probe 7 and PathVysion DNA probes (Abbott Molecular). Specimens were classified as FISH positive when showing gene amplification or high polysomy (> or = 4 copies of the gene in > or =

40% of tumor cells). Tumor response to gefitinib was assessed by RECIST for 33 patients with measurable diseases. **RESULTS:** Twenty-nine tumors (66%) were EGFR FISH+ and 23 (53%) were HER2 FISH+. Overall response rate was 52%, representing 65% of EGFR FISH+ patients and 29% of EGFR FISH- patients (p = 0.0777). Survival was not impacted by the EGFR FISH (p = 0.9395) or the HER2 FISH (p = 0.0671) status. EGFR FISH+ was significantly associated with HER2 FISH+ (p = 0.015) and presence of EGFR mutation (p = 0.0060). EGFR mutation significantly correlated with response (p < 0.0001) and survival after gefitinib (p = 0.0204). EGFR and HER2 FISH status were not associated with KRAS mutation. **CONCLUSION:** Frequency of EGFR FISH+ status was higher and its predictive power for TKI sensitivity was lower in this Japanese cohort than in Western NSCLC cohorts. These findings support differences in the mechanisms of EGFR pathway activation in NSCLC between Asian and Caucasian populations. Confirmation of these results in larger cohorts is warranted.

Vergote, I. (2004). "Role of surgery in ovarian cancer: an update." *Acta Chir Belg* 104(3): 246-56.

Rupture of an ovarian malignant tumor should be avoided at the time of surgery for an early ovarian cancer. Laparoscopic removal of ovarian cysts should be restricted to patients with preoperative evidence that the cyst is benign. Degree of differentiation is the most important independent prognostic factor in stage I disease and should be used in decisions on therapy in clinical practice and the future FIGO-classification of Stage I. In early ovarian cancer staging adequacy and tumor grade were the only 2 statistical significant prognostic factors for survival in the multivariate analysis of the EORTC ACTION-trial. According to the present data there is no scientific basis to rely only on adjuvant chemotherapy or on optimal staging procedure in medium and high risk stage I ovarian cancer. Primary debulking surgery by a gynecologic oncologist remains the standard of care in advanced ovarian cancer. Optimal debulking surgery should be defined as no residual tumor load. Interval debulking is defined as an operation performed after a short course of induction chemotherapy, usually 2 or 3 cycles. Based on the randomized EORTC-GCG trial, interval debulking by an experienced surgeon improves survival in some patients who did not undergo optimal primary debulking surgery. Based on the GOG 152 data, interval debulking surgery does not seem to be indicated in patients who underwent primarily a maximal surgical effort by a gynecological oncologist. Open laparoscopy is probably the most valuable tool for evaluating the operability primarily or at the time

of interval debulking surgery. In retrospective analyses neoadjuvant chemotherapy followed by interval debulking surgery does not seem to worsen prognosis compared to primary debulking surgery followed by chemotherapy. However, we will have to wait for the results of the EORTC-GCG/NCI Canada randomized trial to know whether neoadjuvant chemotherapy followed by interval debulking surgery is as good as primary debulking surgery in some or all stage IIIc and IV patients. The most suitable candidates for secondary debulking surgery are those who had an initial complete response to chemotherapy, a long treatment-free interval (e.g. more than 12 months), and resectable disease (without diffuse carcinomatosis).

Vironen, J. H., M. Kairaluoma, et al. (2006). "Impact of functional results on quality of life after rectal cancer surgery." *Dis Colon Rectum* **49**(5): 568-78.

PURPOSE: Quality of life is an important outcome measure that has to be considered when deciding treatment strategy for rectal cancer. The aim of this study was to find out the impact of surgery-related adverse effects on quality of life. **METHODS:** The RAND-36 questionnaire and questionnaires assessing urinary, sexual, and bowel dysfunction were administered to 94 patients with no sign of recurrence a minimum of one year after curative surgery. Results were compared with age-matched and gender-matched general population. **RESULTS:** Eighty-two (87 percent) patients answered the questionnaires. Major bowel dysfunction was as common after high anterior resection as after low anterior resection. Urinary complaints occurred as often after anterior resection as after abdominoperineal resection, but sexual dysfunction was more common after abdominoperineal resection. Overall, the patients reported better general health perception but poorer social functioning than population controls. In particular, elderly patients reported a significantly better quality of life in many dimensions than their population controls. There was no significant difference in quality of life between treatment groups. Major bowel dysfunction after anterior resection impaired social functioning compared with that of patients without such symptoms. Urinary dysfunction impaired social functioning and impotence impaired physical and social functioning. **CONCLUSIONS:** Quality of life after rectal cancer surgery is not worse than that of the general population. The major adverse impact of bowel and urogenital dysfunction is on social functioning. These adverse effects need to be discussed with the patient and preoperative function needs to be taken into account when choosing between treatment options. Permanent colostomy is

not always the factor that disrupts a person's quality of life most.

Wagner, W., R. Hermann, et al. (2000). "Prognostic value of hemoglobin concentrations in patients with advanced head and neck cancer treated with combined radio-chemotherapy and surgery." *Strahlenther Onkol* **176**(2): 73-80.

PURPOSE: Hemoglobin levels are currently the focus of interest as prognostic factors in patients with head and neck cancer. Most published clinical trials have confirmed hemoglobin to possess a significant influence on survival in patients treated with radiotherapy. In our study we have investigated the prognostic value of hemoglobin in a combined modality schedule. **PATIENTS AND METHODS:** Forty-three patients with advanced head and neck tumors were treated with combined radio-chemotherapy. The therapy comprised 2 courses of induction chemotherapy with ifosfamide (1,500 mg/m², day 1 to 5) and cisplatin (60 mg/m², day 5) followed by hyperfractionated accelerated radiotherapy with a total dose of only 30 Gy. Surgery involved tumor resection and neck dissection. **RESULTS:** The 1-year overall survival rate and the 2-year survival rate were 79% and 56%, respectively. The 1- and 2-year recurrence-free survival rates were 68% and 49%, respectively. Prognostic factors with an impact on survival were seen in tumor size (T3 vs T4, p = 0.0088), response to radio-chemotherapy at the primary site (no vital tumor rest vs vital tumor rest, p = 0.045), response to lymph node radio-chemotherapy (no vital tumor cells vs vital tumor cells, p = 0.013) and level of hemoglobin after radio-chemotherapy (Hb > or = 11.5 g/dl vs < 11.5 g/dl, p = 0.0084). **CONCLUSION:** In our study hemoglobin level after radio-chemotherapy was identified for the first time to be also a significant prognostic factor (univariate analysis) in head and neck cancer patients who underwent combined radio-chemotherapy. Besides chemotherapy plus low-dose irradiation achieved similar results in comparison with radical resection and high-dose radiotherapy at least for the first 2 years after therapy. Relapsing disease could be treated with 1 additional course of radiotherapy which is supposed to be well tolerated.

Wakabayashi, H., K. Ishimura, et al. (2004). "Analysis of prognostic factors after surgery for stage III and IV gallbladder cancer." *Eur J Surg Oncol* **30**(8): 842-6.

AIM: Survival and prognostic factors were analysed in patients who had undergone surgical resection with curative intention with the aim of identifying groups of patient with stage III and IV gallbladder cancer on the TNM classification who

might benefit from surgery. **METHODS:** Thirty-seven patients with advanced gallbladder cancer were studied, the cumulative survival rate for each group was calculated for each pTNM factor. **RESULTS:** The 5-year survival rates in the stage III patients were 83.3%, while those for the stage IVA patients were 46.2%, and those for the stage IVB patients 16.7%. **CONCLUSIONS:** In patients with invasion of adjacent organs, including the liver and gastrointestinal tract, and rated as pT3 or pT4, extended surgery excising the invaded tissue may be justified. In patients with pN2 lymph-node metastasis, even without adjacent organ invasion, radical surgery may not achieve a good outcome.

Wallner, C., M. M. Lange, et al. (2008). "Causes of fecal and urinary incontinence after total mesorectal excision for rectal cancer based on cadaveric surgery: a study from the Cooperative Clinical Investigators of the Dutch total mesorectal excision trial." *J Clin Oncol* **26**(27): 4466-72.

PURPOSE: Total mesorectal excision (TME) for rectal cancer may result in anorectal and urogenital dysfunction. We aimed to study possible nerve disruption during TME and its consequences for functional outcome. Because the levator ani muscle plays an important role in both urinary and fecal continence, an explanation could be preoperative damage of the nerve supply to the levator ani muscle. **METHODS:** TME was performed on cadaver pelvis. Subsequently, the anatomy of the pelvic floor innervation and its relation to the pelvic autonomic innervation and the mesorectum were studied. Additionally, data from the Dutch TME trial were analyzed to relate anorectal and urinary dysfunction to possible nerve damage during TME procedure. **RESULTS:** Cadaver TME surgery demonstrated that, especially in low tumors, the pelvic floor innervation can be damaged. Furthermore, the origin of the levator ani nerve was located in close proximity of the origin of the pelvic splanchnic nerves. Analysis of the TME trial data showed that newly developed urinary and fecal incontinence was present in 33.7% and 38.8% of patients, respectively. Both types of incontinence were significantly associated with each other ($P = .027$). Low anastomosis was significantly associated with urinary incontinence ($P = .049$). One third of the patients with newly developed urinary and fecal incontinence also reported difficulty in bladder emptying, for which excessive perioperative blood loss was a significant risk factor. **CONCLUSION:** Perioperative damage to the pelvic floor innervation could contribute to fecal and urinary incontinence after TME, especially in case of a low anastomosis or damage to the pelvic splanchnic nerves.

Wang, S. L., Z. Liao, et al. (2006). "Investigation of clinical and dosimetric factors associated with postoperative pulmonary complications in esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery." *Int J Radiat Oncol Biol Phys* **64**(3): 692-9.

PURPOSE: To assess the association of clinical and especially dosimetric factors with the incidence of postoperative pulmonary complications among esophageal cancer patients treated with concurrent chemoradiation therapy followed by surgery. **METHOD AND MATERIALS:** Data from 110 esophageal cancer patients treated between January 1998 and December 2003 were analyzed retrospectively. All patients received concurrent chemoradiotherapy followed by surgery; 72 patients also received irinotecan-based induction chemotherapy. Concurrent chemotherapy was 5-fluorouracil-based and in 97 cases included taxanes. Radiotherapy was delivered to a total dose of 41.4-50.4 Gy at 1.8-2.0 Gy per fraction with a three-dimensional conformal technique. Surgery (three-field, Ivor-Lewis, or transhiatal esophagectomy) was performed 27-123 days (median, 45 days) after completion of radiotherapy. The following dosimetric parameters were generated from the dose-volume histogram (DVH) for total lung: lung volume, mean dose to lung, relative and absolute volumes of lung receiving more than a threshold dose (relative V(dose) and absolute V(dose)), and absolute volume of lung receiving less than a threshold dose (volume spared, or VS(dose)). Occurrence of postoperative pulmonary complications, defined as pneumonia or acute respiratory distress syndrome (ARDS) within 30 days after surgery, was the endpoint for all analyses. Fisher's exact test was used to investigate the relationship between categorical factors and incidence of postoperative pulmonary complications. Logistic analysis was used to analyze the relationship between continuous factors (e.g., V(dose) or VS(dose)) and complication rate. Logistic regression with forward stepwise inclusion of factors was used to perform multivariate analysis of those factors having univariate significance ($p < 0.05$). The Mann-Whitney test was used to compare length of hospital stay in patients with and without lung complications and to compare lung volumes, VS5 values, and absolute and relative V5 values in male vs. female patients. Pearson correlation analysis was used to determine correlations between dosimetric factors. **RESULTS:** Eighteen (16.4%) of the 110 patients developed postoperative pulmonary complications. Two of these died of progressive pneumonia. Hospitalizations were significantly longer for patients with postoperative pulmonary complications than for those without (median, 15 days vs. 11 days, $p = 0.003$). On

univariate analysis, female gender ($p = 0.017$), higher mean lung dose ($p = 0.036$), higher relative volume of lung receiving ≥ 5 Gy (V5) ($p = 0.023$), and smaller volumes of lung spared from doses ≥ 5 -35 Gy (VS5-VS35) ($p < 0.05$) were all significantly associated with an increased incidence of postoperative pulmonary complications. No other clinical factors were significantly associated with the incidence of postoperative pulmonary complications in this cohort. On multivariate analysis, the volume of lung spared from doses ≥ 5 Gy (VS5) was the only significant independent factor associated with postoperative pulmonary complications ($p = 0.005$). CONCLUSIONS: Dosimetric factors but not clinical factors were found to be strongly associated with the incidence of postoperative pulmonary complications in this cohort of esophageal cancer patients treated with concurrent chemoradiation plus surgery. The volume of the lung spared from doses of ≥ 5 Gy was the only independent dosimetric factor in multivariate analysis. This suggests that ensuring an adequate volume of lung unexposed to radiation might reduce the incidence of postoperative pulmonary complications.

Werther, K., S. Sorensen, et al. (2003). "Circulating vascular endothelial growth factor six months after primary surgery as a prognostic marker in patients with colorectal cancer." *Acta Oncol* **42**(8): 837-45.

High preoperative circulating vascular endothelial growth factor (VEGF) is predictive of poor prognosis in patients with colorectal cancer (CRC). However, postoperative circulating VEGF has not yet been evaluated as a prognostic marker in CRC patients. In 318 consecutive patients who had undergone curative resection of primary CRC, the prognostic value of VEGF concentrations in plasma and serum obtained 6 months postoperatively was analysed and the results compared with the prognostic value of postoperative carcinoembryonic antigen (CEA) concentrations in matched serum samples. In univariate analyses, high serum and plasma VEGF (> 533 pg/ml and > 112 pg/ml, respectively) had no significant ($p = 0.17$ and $p = 0.13$, respectively) impact on overall survival. On the contrary, high serum CEA (> 5 ng/ml) was significantly ($p < 0.0001$) correlated to a poor prognosis. Finally, in multivariate analyses, the combination of high serum CEA and high serum VEGF was significantly (hazard ratio 3.0, $p = 0.02$) associated with poor survival compared to high serum CEA and low serum VEGF. It is concluded that 6 months postoperatively serum CEA is a better prognostic marker than corresponding serum and plasma VEGF. However, high serum VEGF within high serum CEA was an even better

predictor of overall survival than high serum CEA alone.

Wiig, J. N., S. G. Larsen, et al. (2008). "Preoperative irradiation and surgery for local recurrence of rectal and rectosigmoid cancer. Prognostic factors with regard to survival and further local recurrence." *Colorectal Dis* **10**(1): 48-57.

OBJECTIVE: Local recurrence after rectal cancer surgery is an important clinical problem. METHOD: 150 patients with local recurrence after rectal/rectosigmoid cancer, stage M0, underwent surgery after preoperative irradiation (46-50 Gy). RESULTS: The overall 5-year survival was 27% (44% R0, 38% R1 and 17% R2-stage). Corresponding survival/local recurrence rates were 52%/27% for R0- and 14%/63% for R1-stage. No R2-resected survived 4 years. A normal pretreatment CEA level was significantly associated with increased survival but normalization following preoperative therapy was not associated with an improvement in prognosis. Survival and local recurrence were also significantly influenced by the type of primary operation. Several factors were significant for the prediction of an R0-resection in univariate analysis, but only CEA and symptoms at the time of recurrence predicted an R0-resection in multivariate analysis. A long latency time to recurrence did not significantly influence prognosis. CONCLUSION: Preoperative irradiation and surgery can result in an R0-resection and a long survival in patients with recurrence after initial treatment for rectal or rectosigmoid cancer. Also patients with an R1-resection can benefit from surgery since a substantial number will die without further local recurrence. An R0-resection is the main prognostic factor followed by CEA level, sex and type of primary operation. Normalization of CEA after preoperative treatment is not of prognostic significance. The value of the Norwegian follow-up regimen is questioned.

Win, T., L. Sharples, et al. (2005). "Effect of lung cancer surgery on quality of life." *Thorax* **60**(3): 234-8.

BACKGROUND: Health related quality of life (HRQOL) after surgery is important, although very limited data are available on the QOL after lung cancer surgery. METHODS: The effect of surgery on HRQOL was assessed in a prospective study of 110 patients undergoing potentially curative lung cancer surgery at Papworth Hospital, 30% of whom had borderline lung function as judged by forced expiratory volume in 1 second. All patients completed the EORTC QLQ-C30 and LC13 lung cancer module before surgery and again at 1, 3 and 6 months postoperatively. RESULTS: On average, patients had

high levels of functioning and low levels of symptoms. Global QOL had deteriorated significantly 1 month after surgery ($p = 0.001$) but had returned to preoperative levels by 3 months ($p = 0.93$). Symptoms had worsened significantly at 1 month after surgery but had returned to baseline levels by 6 months. Low values on the preoperative HRQOL scales were not significantly associated with poor surgical outcome. However, patients with low preoperative HRQOL functioning scales and high preoperative symptom scores were more likely to have poor postoperative (6 months) QOL. The only lung function measurement to show a marginally statistically significant association with quality of life at 6 months after surgery was percentage predicted carbon monoxide transfer factor (Tlco). **CONCLUSION:** Although surgery had short term negative effects on quality of life, by 6 months HRQOL had returned to preoperative values. Patients with low HRQOL functioning scales, high preoperative symptom scores, and preoperative percentage predicted Tlco may be associated with worse postoperative HRQOL.

Wu, Y., L. Saldana, et al. (2002). "Plasma vascular endothelial growth factor is useful in assessing progression of breast cancer post surgery and during adjuvant treatment." *Int J Oncol* **20**(3): 509-16.

Vascular endothelial growth factor (VEGF) has been shown to induce angiogenesis in vivo and in vitro. However, the association of plasma VEGF with tumor histopathology in high risk groups such as African American and non-white Hispanic women with breast cancer is not well understood. There is limited information on the prognostic relevance of plasma VEGF in patients who have had surgery and adjuvant treatment for breast cancer. In this study, we measured plasma VEGF from 125 minority women with primary breast tumor removal and were completing adjuvant treatment. The control group consisted of 20 subjects without cancer. We examined the association between plasma VEGF and other tumor characteristics such as steroid hormone receptors, tumor size, regional nodes, stage, recurrence, and overall survival. Our results confirmed that plasma VEGF levels were significantly higher in breast cancer patients than normal subjects. Plasma VEGF level increased in patients with increase in tumor size, and at late stage III/IV disease. Univariate analysis showed plasma VEGF to be a significant predictor of overall survival ($RR=2.5$, $p=0.02$). Multivariate analysis showed plasma VEGF not only to be an independent predictor of overall survival ($RR=4.6$, $p=0.02$) but also of local recurrence ($RR=6.0$, $p=0.04$). Tamoxifen in combination with CMF or CAF can reduce plasma VEGF level in patients with estrogen receptor positive tumor but not

in estrogen receptor negative tumor. Our findings suggest that plasma VEGF should be considered as a tumor marker for breast cancer progression, and inhibitors of angiogenesis should be factored into the treatment protocol for patients who demonstrate increase in plasma VEGF levels at any stage of the disease.

Wyatt, G. K. and L. L. Friedman (1998). "Physical and psychosocial outcomes of midlife and older women following surgery and adjuvant therapy for breast cancer." *Oncol Nurs Forum* **25**(4): 761-8.

PURPOSE/OBJECTIVES: To investigate the patterns of functioning and psychosocial adjustment of midlife and older women following surgery for breast cancer. Differences between those who received follow-up adjuvant therapy and those who did not also were compared. **DESIGN:** 2 x 3 mixed design with one between-groups factor (type of treatment) and one within-subjects factor (time). **SETTING:** Four midwestern hospitals. **SAMPLE:** 46 patients with breast cancer who are age 55 or older. **METHODS:** Baseline data about presurgical functional status and other variables were obtained during the first week after surgery. Follow-up data were obtained at six weeks, three months, and six months postsurgery. Data were collected via telephone interviews and mailed questionnaires. **MAIN RESEARCH VARIABLES:** Functional status, patient symptomatology, quality of life (QOL), demands of illness, and type of treatment (surgery only versus surgery plus adjuvant therapy). **FINDINGS:** No differences existed between the two treatment groups at baseline, with the exception of lower functional status reported by the surgery-only group. In the surgery-only group, functional status improved significantly from six weeks to three months postsurgery. The most frequently reported symptoms of both groups included fatigue and pain. **CONCLUSIONS:** These results suggest that both groups did equally well, regardless of whether they received adjuvant therapy (radiation or chemotherapy). Neither QOL nor demands of illness differed between the two groups, nor did these scores change significantly over time following surgery. **IMPLICATIONS FOR NURSING PRACTICE:** These findings suggest that women undergoing surgery for breast cancer, whether they receive adjuvant therapy or not, may have functional and psychosocial needs that could be effectively addressed by nursing interventions pre- and postsurgery.

Yadav, B. S., S. C. Sharma, et al. (2007). "Patterns of relapse in locally advanced breast cancer treated with neoadjuvant chemotherapy followed by surgery and radiotherapy." *J Cancer Res Ther* **3**(2): 75-80.

AIMS: To define the clinical and pathological predictors of locoregional recurrence (LRR) in locally advanced breast cancer (LABC) patients treated with neoadjuvant chemotherapy (NACT). **MATERIALS AND METHODS:** We retrospectively reviewed the outcome of 141 patients with stage II to stage III carcinoma breast treated at Department of Radiotherapy, PGIMER, Chandigarh from 1998-2002. Mean age of the patients was 46 years, 49% of patients were premenopausal and 51% were postmenopausal. The tumor stage was T2 in 18%; T3 in 61% and T4 in 26% of the patients. NACT regimen given was FAC (5-fluorouracil, adriamycin and cyclophosphamide) in 85% and CMF (cyclophosphamide, methotrexate and 5-Fu) in 15% patients. **RESULTS:** After NACT, surgery was possible in 95% patients. Conservative surgery was possible in 23% patients and mastectomy was done in 72% of patients. Pathological complete response (pCR) was seen in 18% patients and pathological partial response (pPR) in 69% of patients. Stable and progressive disease was seen in 6% and 7% of patients respectively. Adjuvant radiation therapy was given to 86% patients. Six percent patients developed progressive disease and 4% of patients did not turn up for radiation. Five year LRR was 6% and relapse free survival (RFS) was 94%. Thirty-two (23%) patients developed distant metastasis resulting in distant metastasis free survival of 77%. The factors that correlated positively with LRR on univariate analysis included tumor stage, stage and pathological nodal stage. However, on multivariate analysis, tumor stage and pathological nodal stage were significant. Factors that correlated for distant relapse were tumor stage, response to chemotherapy, type of surgery, extracapsular extension (ECE) and tamoxifen therapy. On multivariate analysis only ECE was the significant factor that correlated with distant relapse free survival. **CONCLUSION:** Thus, tumor stage and pathological nodal stage remains the most important predictor of LRR in LABC. Factors that correlated for distant relapse were tumor stage, response to chemotherapy, type of surgery and ECE and tamoxifen therapy.

Yaghan, R., P. D. Stanton, et al. (1998). "Oestrogen receptor status predicts local recurrence following breast conservation surgery for early breast cancer." *Eur J Surg Oncol* **24**(5): 424-6.

AIMS: To evaluate factors predicting locoregional recurrence in patients treated for early breast carcinoma by breast conservation surgery with or without radiotherapy. **METHODS:** A retrospective study of 256 patients was carried out, with special emphasis on the role of oestrogen receptor status. Other parameters studied included age, menopausal status, size of primary tumour, tumour type, axillary

nodal status and adjuvant therapy. **RESULTS:** Multivariate analysis showed the following parameters to be independent predictors of locoregional recurrence. Radiotherapy (57% reduction in hazard, $P = 0.004$); expression of oestrogen receptors (52% reduction in hazard, $P = 0.008$); tamoxifen therapy (46% reduction in hazard, $P = 0.023$); tumour size (40% increase in hazard per cm, $P < 0.001$). **CONCLUSIONS:** Within this study, lack of oestrogen receptor expression was a strong independent factor associated with a higher rate of locoregional recurrence. This may be of value in selecting a group of patients less suitable for breast conservation surgery.

Yano, M., H. Shiozaki, et al. (2002). "Neoadjuvant chemotherapy followed by salvage surgery: effect on survival of patients with primary noncurative gastric cancer." *World J Surg* **26**(9): 1155-9.

The prognosis for gastric cancer patients who undergo noncurative resection is extremely poor. This study evaluated the effects of neoadjuvant chemotherapy for primary noncurative gastric cancer. Thirty-four patients with biopsy-proven noncurative gastric cancer were treated with either of two neoadjuvant chemotherapies: FEMTXP (5-fluorouracil, epirubicin, methotrexate, cisplatin) or THP-FLPM (pirarubicin, 5-fluorouracil, leucovorin, cisplatin, mitomycin C). Noncurability was determined by conventional staging procedures, staging laparoscopy, and exploratory laparotomy. After chemotherapy the resectability of the tumors was reassessed. Patients who were judged to be candidates for curative resection underwent salvage surgery. Of the final 33 patients, 8 (24.2%) showed a major response [0 complete response (CR), 8 partial response (PR)]. In three patients the second laparoscopy revealed disappearance of the peritoneal metastasis. Of the 33 patients, 14 (42.4%) underwent salvage surgery, including 8 curative resections (2 curability A, 6 curability B). Pathologic examinations revealed a grade 2 response in eight patients but no grade 3 response. Univariate analysis showed the following to be significant prognostic factors: histology type (differentiated type vs. undifferentiated type; $p = 0.035$), T4 as a noncurative factor (T4 vs. T3 or less; $p = 0.025$), clinical response (PR + no change vs. progressive disease; $p = 0.002$), and salvage surgery (resected vs. unresected; $p = 0.001$). Among these factors, salvage surgery was found to be the only independent prognostic factor by multivariate analysis, with a relative risk of 0.253 and a 95% confidence interval of 0.066 to 0.974. The treatment was well tolerated. Major toxicities of WHO grade 3 or more were leukopenia in 20 (60.6%), gastrointestinal toxicities in 5 (15.2%), renal toxicities

in 2 (6.1%), and alopecia in 1 (3.0%). In conclusion, neoadjuvant chemotherapy is effective for primary noncurative gastric cancer when salvage surgery can be performed. A chemotherapy regimen with a higher complete response rate would improve the prognosis of this dismal disease even more.

Yokota, T., Y. Kunii, et al. (2002). "Prognostic factors of gastric cancer tumours of less than 2 cm in diameter: rationale for limited surgery." *Eur J Surg Oncol* **28**(3): 209-13.

BACKGROUND: A recent trend in the surgical treatment of patients with early gastric cancer in Japan has been to limit surgery to an extent that ensures complete cure and improvement in the patient's quality of life. If a gastric cancer tumour can be completely eradicated by laparoscopic surgery, the patient can be cured of cancer without major operative stress. A small gastric cancer tumour of less than 2 cm in diameter is an indication for laparoscopic surgery, but little is known about what protocol of surgical treatment is appropriate for this type of tumour. **PATIENTS AND METHODS:** The clinicopathological features of 150 patients with gastric cancer tumour of less than 2 cm in diameter were reviewed retrospectively from hospital records between 1985 and 1995. The results of retrospective analysis of clinicopathological data of 24 patients with advanced cancer were compared with those of 126 patients with early cancer. Univariate and multivariate analyses of patients with small gastric cancer tumours were performed to evaluate the prognostic significance of clinicopathological features. **RESULTS:** A significant difference was seen between the gross tumour appearances in the two groups; Borrmann type-4 tumours were more common in the advanced group. Lymph-node metastasis, lymphatic vessel invasion and vascular invasion were found more frequently in the advanced cancer group than in the early cancer group. Scirrhoust type was more common in the advanced cancer group. In univariate analysis, unfavourable prognostic factors included deep cancer invasion, presence of lymph-node metastasis, lymphatic invasion and vascular invasion. Using Cox's proportional hazard regression model, only nodal involvement emerged as an independent statistically significant prognostic parameter associated with long-term survival. **CONCLUSION:** Laparoscopic surgery should not be performed on tumours that are Borrmann type in macroscopic appearance and scirrhoust-type histologically. Lymph-node metastasis is an independent prognostic factor. We recommend laparoscopic surgery involving local resection of the stomach without lymphadenectomy for small, early gastric cancer tumours that satisfy the criteria mentioned above. However, the validity of

this recommendation should be tested by a prospective randomized control trial in the future.

Yokoyama, Y., T. Sakamoto, et al. (1999). "Evaluation of cytoreductive surgery with pelvic and paraaortic lymphadenectomy and intermittent cisplatin-based combination chemotherapy for improvement of long-term survival in ovarian cancer." *Eur J Gynaecol Oncol* **20**(5-6): 361-6.

The present study was designed in order to assess the therapeutic values of pelvic and paraaortic lymphadenectomy in cytoreductive surgery and intermittent systematic chemotherapy combining cisplatin, doxorubicin, and cyclophosphamide, namely, intermittent PAC for improvement of the long-term prognosis of patients with epithelial ovarian cancer. Intermittent PAC was administered every 3 months over a period of approximately 2 years. One hundred and fifty-five patients with epithelial ovarian cancer were enrolled in the study. The estimated 10-year survival rate of 42 patients with stage I or II ovarian cancer who received pelvic and paraaortic lymphadenectomy and the intermittent PAC was significantly higher than that of 31 patients with the same stages who did not (83.9% vs. 61.1%, $p<0.05$). Similarly, the estimated 10-year survival rate of 38 patients with stage III or IV ovarian cancer who underwent the above-mentioned treatments was significantly high compared with that of 44 patients in the same advanced stages who did not (60.4% vs. 25.0%, $p<0.01$). As for pelvic and paraaortic lymphadenectomy, there was no significant difference in the estimated 10-year survival rates between patients with and without retroperitoneal lymph node metastasis. Multivariate analysis revealed that the performance of pelvic and paraaortic lymphadenectomy was the most important factor leading successful clinical remission of the advanced ovarian cancers. Cytoreductive surgery including pelvic and paraaortic lymphadenectomy and to intermittent PAC were thus suggested to be capable of dramatically improving the long-term survival even in advanced epithelial ovarian cancers.

Yoshida, K., T. Inoue, et al. (2004). "Treatment results of radiotherapy with or without surgery for posterior pharyngeal wall cancer of oropharynx and hypopharynx: prognostic value of tumor extension." *Radiat Med* **22**(1): 30-6.

PURPOSE: We have been treating posterior pharyngeal wall cancer of the oropharynx and hypopharynx with external radiotherapy according to our policy reported in the 1970s. **MATERIALS AND METHODS:** Between 1968 and 1995, 51 patients were treated. Treatment policy was decided on the basis of the treatment response after 40 Gy of

radiotherapy. Thirty-six good responders were treated with radical radiotherapy, eight poor responders received radical surgery, and the other seven patients could not receive radical treatment because of tumor or patient factors. RESULTS: The 5-year local control and cause-specific survival rates were 56% and 48% for all 51 patients. The 5-year local control rate was 52% for radical radiotherapy. Tumors limited to the posterior wall showed better treatment results (76% for both local control and cause-specific survival) than tumors involving the posterocoid area (0% and 10%). CONCLUSION: Radiotherapy for carefully selected patients dependent on response after 40 Gy of radiotherapy is a useful policy. Tumor extension is an important prognostic factor.

Yovino, S., Y. Kwok, et al. (2005). "An association between preoperative anemia and decreased survival in early-stage non-small-cell lung cancer patients treated with surgery alone." *Int J Radiat Oncol Biol Phys* 62(5): 1438-43.

PURPOSE: Surgical resection is the mainstay of therapy for patients presenting with Stage I and II non-small-cell lung cancer (NSCLC). Despite optimal staging and surgery, these patients are still at significant risk for failure. The purpose of this study is to report a retrospective analysis of the outcome of patients treated with surgery alone, as well as to analyze prognostic factors associated with survival. MATERIALS AND METHODS: From May 2000 to November 2002, there was a total of 125 patients who were treated with surgery for NSCLC at University of Maryland Medical Center. Of these, 82 Stage I and II patients who received surgery alone as the definitive therapy were identified. The median age of the entire cohort was 68 years (range, 43-88 years). There were 48 males and 34 females. Sixty-three patients (76.8%) underwent lobectomies whereas 19 patients (23.2%) underwent nonlobectomy (wedge resection or segmentectomy) procedures. Patients who received neoadjuvant or adjuvant radiation therapy or chemotherapy were excluded from the study. Factors included in univariate and multivariate analyses were age, sex, tumor histology, pathologic stage, p53 status, preoperative hemoglobin (Hgb), and type of surgery performed. Endpoints of the study were relapse-free survival (RFS) and overall survival (OS). RESULTS: Median follow-up was 20.8 months (range, 0.4-43.2 months). For the entire cohort, the 2-year RFS was 66.0% and 2-year OS was 76.3%. Median survival for the entire cohort has not been achieved. In univariate analysis, the only factor that achieved statistical significance was preoperative Hgb level. Patients who had preoperative Hgb <12 mg/dL experienced significantly worse RFS (mean RFS: 26.6 months vs. 34.9 months, $p = 0.043$) and OS (median OS: 27

months vs. 42.5 months, $p = 0.011$). For Stage I patients ($n = 72$), the 2-year RFS and OS were 66.4% and 77.1%, respectively. In the subgroup of stage IA patients ($n = 37$), there was a trend toward decreased overall survival in the anemic patients (2-year OS of 65.6% vs. 90.9%, $p = 0.07$). For Stage II patients ($n = 10$), the 2-year RFS and OS were 60.0% and 66.7%. In the Cox multivariate regression analysis, the only factor that achieved statistical significance was preoperative Hgb, with patients with Hgb <12 mg/dL having decreased RFS (RR 4.1, $p = 0.020$) and OS (RR 2.9, $p = 0.026$). There was a trend toward worse RFS ($p = 0.056$) and OS ($p = 0.068$) in p53-negative patients ($n = 39$). Stage, histologic type, type of surgery performed, age, and sex did not affect outcome. CONCLUSIONS: In our cohort of mostly Stage I NSCLC patients treated with surgery only, preoperative Hgb <12 mg/dL predicted for worse outcome. This effect was observed even in the traditionally low-risk subgroup of completely resected stage IA patients. Much has been written in the literature about anemia causing possible worsening of tumor hypoxia within solid tumors, thereby increasing radio-resistance. This has been a popular argument to explain poorer outcomes of anemic patients with solid tumors who undergo radiotherapy. However, our data suggest that anemia may be a sign of a more aggressive tumor that is at an increased risk of failure independent of the treatment modality.

Zang, R. Y., Z. Y. Zhang, et al. (1999). "Cytoreductive surgery for stage IV epithelial ovarian cancer." *J Exp Clin Cancer Res* 18(4): 449-54.

We tried to determine the role of cytoreductive surgery for stage IV epithelial ovarian cancer and in what conditions this surgical procedure could carry the best benefits. From January 1986 to December 1997, seventy-one of 73 patients with stage IV epithelial ovarian cancer who were treated in Cancer Hospital of Shanghai Medical University were retrospectively reviewed. Clinical information including age, grade, histology, presence of ascites, size of residual disease, site of extra-abdominal metastasis, whether initially presenting as metastatic disease or not, neo-adjuvant chemotherapy, platinum-based chemotherapy and second-line chemotherapy was obtained. Survival was calculated by life-table and survival curves were computed using the Kaplan-Meier method with differences in survival estimated by log-rank test. Independent prognostic factors were identified by Cox's proportional hazards regression model. The median age of the patients' population was 54 years (range 22-82), median follow-up time was 12 months (range 3 to 130) and estimated 5-year survival rate 6.1%. Thirty out of 71 (42.3%) patients were successfully debulked (< or = 1 cm) at the time of

initial surgery. There was a significant difference in five-year survival rate between patients optimally (14.1%) vs suboptimally (0%) cytoreduced, with an estimated median survival in the optimal group of 23 months vs 9 months in the suboptimal group ($P=0.0001$, long-rank test). When the variables were factorized, only in patients with malignant pleural effusion or positive supraclavicular lymph nodes, optimal cytoreduction could get the greatest benefits. Multivariate analysis revealed that the size of residual disease and ascites were independent factors of survival. However, only ascites was the prognostic factor of progression-free survival. Optimal cytoreductive surgery is an important determinant of survival in women with stage IV epithelial ovarian cancer, mainly in those with malignant pleural effusion or positive supraclavicular lymph node pathology.

Zhang, C. H., W. H. Zhan, et al. (2007). "Spleen preservation in radical surgery for gastric cardia cancer." *Ann Surg Oncol* **14**(4): 1312-9.

BACKGROUND: In gastric cardia cancer (GCC), the spleen is usually removed when the tumor is resected. This allows thorough lymph node dissection in the splenic hilus. However, the long-term effect of splenectomy on patient survival is controversial. The purpose of this study was to investigate the effect of spleen preservation on survival following radical resection for gastric cardia cancer. **METHODS:** We reviewed the records of 116 GCC patients (Siewert types II and III) who underwent radical resection with D2 or D3 lymphadenectomy between July 1994 and December 2003. Survival status was ascertained in December 2004 and data from 108 patients were analysed. Of these 108 patients, 38 underwent splenectomy and 70 had splenic preservation. Clinicopathological features and prognostic data of the splenectomy(+) and splenectomy(-) groups were compared. **RESULTS:** Seventy-four patients (68.5%) had lymph node involvement; 18 (16.7%) had involvement of nodes in the splenic hilus. Postoperative morbidity in the two groups was similar. Overall 5-year survival was higher in the splenectomy(-) group than the splenectomy(+) group (38.7% versus 16.9%, $P=.008$). Multivariate regression indicated that tumor invasion ($P=.009$) and lymph node metastasis ($P=.001$) were independent prognostic factors--they predicted decreased survival--with or without splenectomy. Although splenectomy was associated with lower survival, it was not an independent prognostic factor ($P=.085$). **CONCLUSIONS:** Splenectomy does not improve survival of patients who undergo curative resection for gastric cardia cancer. Thus, the spleen

should be preserved in patients without direct cancer invasion of the spleen.

Zhou, X., J. Wang, et al. (2008). "Analysis of prognostic factors for surgery after neo-adjuvant therapy for stage III non-small cell lung cancer." *J Huazhong Univ Sci Technol Med Sci* **28**(6): 677-80.

In order to explore the possibility to predict the risk factors for postoperative complications and survival time, the clinical data of 152 patients (including 116 males and 36 females) who had undergone neo-adjuvant therapy and surgery for stage IIIA and B non-small cell lung cancer (NSCLC) were retrospectively analyzed. Demographic data, preoperative functional parameters, staging, induction regimen (chemotherapy alone or associated with radiotherapy), associated disorders, and data about operation were collected. Chi-square test and multivariate analysis fitting the unconditional logistic regression model were performed to identify predictors of postoperative complications, while Kaplan-Meier and multivariate Cox proportional hazard model were employed to identify predictors of survival time, respectively. The univariate analysis demonstrated that forced expiratory volume in 1 second predicted percent (FEV1%, $P=0.040$) and associated disorders ($P=0.020$) were the predictive factors of complications, but multivariate analysis found no independence factors ($P>0.05$) of it. Univariate Kaplan-Meier analysis showed that stage ($P=0.050$) and pneumonectomy ($P=0.018$) affected the survival time. However, multivariate Cox proportional hazard model analysis demonstrated that only pneumonectomy ($P=0.026$) was associated with a decreased survival time, but no differences between right and left pneumonectomy were found. The results suggest that the risk factor for postoperative complications is acceptable, and pneumonectomy is associated with increased mortality, which should be performed only in stage III NSCLC patients.

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