

## Literature for Lymphoma Studies

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**Abstract:** Cancer is the cells that grow out of control. Cancer cells can also invade other tissues. Growing out of control and invading other tissues are what makes a cell a cancer cell. Involved in more than 100 diseases, the cancer can cause serious illness and death. Normally, the cells become cancer cells because of DNA damage. This material is a literature collection of the researches on the cancer and the lymphoma.

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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.

### Literatures

Abali, H., O. O. Eren, et al. (2003). "Coincidental detection of T-cell rich B cell lymphoma in the para-aortic lymph nodes of a woman undergoing lymph node dissection for cervical cancer: a case report." *Int J Gynecol Cancer* **13**(5): 687-9.

The diagnosis of cervical squamous cell carcinoma with concurrent T-cell rich B cell lymphoma in dissected lymph nodes has not been reported to our knowledge. In our case, the biopsy of an exophytic lesion at the uterine cervix showed squamous cell carcinoma in a 50-year-old woman presenting with postcoital bleeding. Type III hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic, para-aortic lymph node dissections were performed. Pathologic examination revealed a T-cell rich B cell lymphoma in some lymph nodes beside squamous cell carcinoma in several of others. ELISA for human immuno-deficiency virus (HIV) was negative. The cervical carcinoma was staged as FIGO clinical stage IB1 and the lymphoma as Ann Arbor IIA. Six cycles of CHOP (cyclophosphamide, adriamycin, vincristine, and prednisolon) chemotherapy for the lymphoma and concomitant pelvic chemoradiotherapy with cisplatin for cervical cancer were given. In this rare coincidence, the best available therapy for each of the diseases should be

considered individually. We also suggest that HIV screening test be carried out, because both diseases may be related to human immuno-deficiency virus, although our patient is HIV-negative.

Abali, H., O. O. Eren, et al. (2003). "Coincidental detection of T-cell rich B-cell lymphoma in the paraaortic lymph nodes of a woman undergoing lymph node dissection for cervical cancer." *Int J Gynecol Cancer* **13**(4): 548-50.

The diagnosis of cervical squamous cell carcinoma with concurrent T-cell rich B-cell lymphoma in dissected lymph nodes has not been reported to our knowledge. We report such a case. The biopsy of an exophytic lesion at the uterine cervix showed squamous cell carcinoma in a 50-year-old woman presenting with postcoital bleeding. Type III hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic, paraaortic lymph node dissections were performed. Pathologic examination revealed a T-cell rich B-cell lymphoma in some lymph nodes beside squamous cell carcinoma in several of others. ELISA for human immuno-deficiency virus (HIV) was negative. The cervical carcinoma was staged as FIGO clinical stage IB1 and the lymphoma as Ann Arbor IIA. Six cycles of CHOP (cyclophosphamide, adriamycin, vincristine, and prednisone) chemotherapy for the lymphoma and concomitant pelvic chemo-radiotherapy with cisplatin for cervical cancer were given. In this rare coincidence; the best available therapy for each of the diseases should be considered individually. We also suggest that HIV screening test be carried out, because both diseases may be related to human immuno-deficiency virus, although our patient was HIV-negative.

Abrey, L. E., L. Ben-Porat, et al. (2006). "Primary central nervous system lymphoma: the Memorial Sloan-Kettering Cancer Center prognostic model." *J Clin Oncol* **24**(36): 5711-5.

**PURPOSE:** The purpose of this study was to analyze prognostic factors for patients with newly diagnosed primary CNS lymphoma (PCNSL) in order to establish a predictive model that could be applied to the care of patients and the design of prospective clinical trials. **PATIENTS AND METHODS:** Three hundred thirty-eight consecutive patients with newly diagnosed PCNSL seen at Memorial Sloan-Kettering Cancer Center (MSKCC; New York, NY) between 1983 and 2003 were analyzed. Standard univariate and multivariate analyses were performed. In addition, a formal cut point analysis was used to determine the most statistically significant cut point for age. Recursive partitioning analysis (RPA) was used to create independent prognostic classes. An external validation set obtained from three prospective Radiation Therapy Oncology Group (RTOG) PCNSL clinical trials was used to test the RPA classification. **RESULTS:** Age and performance status were the only variables identified on standard multivariate analysis. Cut point analysis of age determined that patients age  $\leq 50$  years had significantly improved outcome compared with older patients. RPA of 282 patients identified three distinct prognostic classes: class 1 (patients  $< 50$  years), class 2 (patients  $\geq 50$ ; Karnofsky performance score [KPS]  $\geq 70$ ) and class 3 (patients  $\geq 50$ ; KPS  $< 70$ ). These three classes significantly distinguished outcome with regard to both overall and failure-free survival. Analysis of the RTOG data set confirmed the validity of this classification. **CONCLUSION** The MSKCC prognostic score is a simple, statistically powerful model with universal applicability to patients with newly diagnosed PCNSL. We recommend that it be adopted for the management of newly diagnosed patients and incorporated into the design of prospective clinical trials.

Ahles, T. A., A. J. Saykin, et al. (2005). "Quality of life of long-term survivors of breast cancer and lymphoma treated with standard-dose chemotherapy or local therapy." *J Clin Oncol* **23**(19): 4399-405.

**PURPOSE:** This study compared the quality of life (QOL) of long-term survivors of breast cancer and lymphoma who had been treated with standard-dose systemic chemotherapy or local therapy only. **PATIENTS AND METHODS:** Long-term survivors (mean, 10.0  $\pm$  5.3 years after treatment) of breast cancer or lymphoma who had been treated with systemic chemotherapy (breast, n = 141, age = 57.0  $\pm$  10.1 years; lymphoma, n = 66, age = 55.8  $\pm$  13.5 years) or local therapy only (breast, n = 294, age = 65.8  $\pm$  9.1 years; lymphoma, n = 37, age = 50.4  $\pm$  12.8 years) were interviewed by phone using the Quality of Life-Cancer Survivors Tool. **RESULTS:** Multivariate analysis of covariance, controlling for

sex, age, education, stage of disease, and time since last treatment, revealed that survivors who had been treated with systemic chemotherapy scored significantly lower on overall QOL compared with survivors treated with local therapy only (P = .04). Analysis of covariance on the subscale scores revealed that, compared with survivors who received local therapy, survivors treated with chemotherapy scored significantly lower on the Social subscale (P < .0001), but no differences emerged on the Psychological or Spiritual subscales. There was a statistically significant interaction between treatment and diagnosis (P = .01), as measured by the Physical subscale, indicating that lymphoma survivors treated with chemotherapy scored worse than all other groups. **CONCLUSION:** Important QOL differences emerged between the chemotherapy and local therapy groups, suggesting that long-term QOL may vary depending on the type of treatment and diagnosis.

Ahmad, I., U. Saeed, et al. (2009). "Primary bone lymphoma: a series from a cancer institute in Pakistan." *J Pak Med Assoc* **59**(3): 179-81.

Primary bone lymphoma (PBL) is an uncommon tumour. Numerous studies have been reported from Western countries, but none from Southeast Asia. We reviewed a series of seven consecutive patients diagnosed and treated with PBL at our hospital between March 2002 and January 2007. All patients underwent chemotherapy with half receiving radiotherapy as their initial treatment. Six (84%) patients were male and 1 (16%) female with a median age of 33 (range: 23-85). All had diffuse large B-cell lymphoma (DLBCL) of bone except one (85 - M) who had chest wall cutaneous T-cell lymphoma with iliac blade involvement. The femur was the most frequently involved site (43%). Except for three patients that involved the lymph nodes, all patients had disease limited to bone. The 5-year overall survival rate was 43%. Although the number of patients was small, the data presented here revealed several characteristics of PBL.

Ait-Tahar, K., A. P. Liggins, et al. (2009). "Cytolytic T-cell response to the PASD1 cancer testis antigen in patients with diffuse large B-cell lymphoma." *Br J Haematol* **146**(4): 396-407.

The identification of immunogenic cancer testis antigens (CTAs) as immunotherapeutic targets represents one approach to improve treatment options for diffuse large B-cell lymphoma (DLBCL). We previously identified PASD1 [PAS (Per ARNT Sim) domain containing 1 (PASD1)], a DLBCL-associated CTA that was expressed in a range of hematopoietic malignancies. The aim of the present study was to investigate the presence of a cytotoxic T-cell (CTL)

response to PASD1 in DLBCL patients. A significant gamma-interferon (IFN) release was detected in 21/29 HLA-A\*0201-positive DLBCL patients (18 de novo DLBCL, two transformed DLBCL and one T-cell rich B-cell lymphoma) following short-term culture of their peripheral blood mononuclear cells stimulated with five HLA-A\*0201-restricted PASD1 peptides. No significant responses were detected in 21 HLA-A\*0201-negative DLBCL patients (12 de novo DLBCL, seven transformed DLBCL, two T-cell rich B-cell lymphoma) or six normal subjects. CTL cell lines were able to lyse PASD1-positive tumour cells in a major histocompatibility complex-Class I dependent manner. The presence of a gamma-IFN response correlated with PASD1 protein expression in the tumour cells in 12/15 cases studied. This is the first report of a CTL response to a CTA in DLBCL. Our results provide additional valuable evidence supporting PASD1 as a potential immunotherapeutic target for the treatment of DLBCL and other malignancies.

Alm El-Din, M. A., S. A. El-Badawy, et al. (2008). "Breast cancer after treatment of Hodgkin's lymphoma: general review." Int J Radiat Oncol Biol Phys 72(5): 1291-7.

The improved survival rates among patients with Hodgkin's lymphoma over the past few decades have come with increased incidence of second malignancies. One of the major concerns among female survivors is the significantly elevated risk of breast cancer that appears with extended follow-up. In this review, we include the published literature regarding the risk of breast cancer after irradiation for Hodgkin's lymphoma. We also present the possible long-term surveillance strategies and the optimal time to start screening these women. This could potentially help in early detection of secondary breast cancers and consequently improve outcomes. Furthermore, because of prior radiotherapy, the management of the breast cancer among this unique population has been controversial. We discuss the characteristics of breast cancer that occurs after Hodgkin's lymphoma and also treatment options that could be implemented.

Alm El-Din, M. A., J. K. Feng, et al. (2008). "Lumpectomy and partial breast irradiation for early-stage breast cancer following mantle irradiation for Hodgkin's lymphoma." Nat Clin Pract Oncol 5(7): 426-9.

**BACKGROUND:** A 57-year-old woman who received treatment with mantle irradiation and systemic chemotherapy for Hodgkin's lymphoma diagnosed at the age of 42 underwent screening mammography, which revealed abnormal density at the upper outer quadrant of the left breast.

**INVESTIGATIONS:** Left breast ultrasound and MRI, ultrasound-guided biopsy, immunohistochemistry, chest X-ray. **DIAGNOSIS:** Stage T1bN0M0 left breast cancer. **MANAGEMENT:** Lumpectomy, sentinel lymph-node biopsy and fractionated partial breast irradiation using 3-dimensional conformal technique.

Alm El-Din, M. A., K. S. Hughes, et al. (2009). "Breast cancer after treatment of Hodgkin's lymphoma: risk factors that really matter." Int J Radiat Oncol Biol Phys 73(1): 69-74.

**PURPOSE:** To evaluate the risk of breast cancer (BC) and the contributing risk factors in women after supradiaphragmatic irradiation (SDI) for Hodgkin's lymphoma (HL). **SUBJECTS AND METHODS:** Medical records of 248 women 60 years of age or less who received SDI for stage I/II HL between 1964 and 2001 at Massachusetts General Hospital were retrospectively reviewed. **RESULTS:** The median age at SDI was 26 years (range, 5.7-59.3). The median follow-up was 15.2 years (range, 0.1-41.3). In 36 patients, BC developed (bilaterally in 11 patients) at a median interval of 18.4 years (range, 4.3-33.8) after SDI. Based on data from the National Cancer Institute Surveillance, Epidemiology, and End Results program, the standardized morbidity ratio (SMR) for the first BC after SDI was 9.78 (95% confidence interval [CI], 4.64-18.11,  $p < 0.0001$ ). The SMR of patients who received radiation before age of 30 years was 19.05 (95% CI, 12.33-28.13) compared with 4.64 (95% CI, 2.31-8.30) for patients aged 30 years or more at the time of treatment ( $p < 0.00003$ ). Risk for BC was significantly higher 15 years or more after SDI compared with the risk during the first 15 years ( $p = 0.0026$ ). None of HL characteristics or treatment details was associated with higher risk of BC after adjusting for age and calendar time. **CONCLUSIONS:** Age at irradiation and time since therapy appear to be the only significant risk factors for development of BC after treatment of HL. The risk is significantly higher 15 years or more after radiation and for women treated before age 30 years. Long-term surveillance strategies are indicated for women at risk.

Alm El-Din, M. A., K. S. Hughes, et al. (2009). "Clinical outcome of breast cancer occurring after treatment for Hodgkin's lymphoma: case-control analysis." Radiat Oncol 4: 19.

**BACKGROUND:** To evaluate diagnosis, management and outcome of breast cancer (BC) occurring after irradiation for Hodgkin's lymphoma (HL). **METHODS:** 39 cases of BC in 28 HL survivors were retrospectively reviewed. 21 patients were included in a case-control analysis. **RESULTS:** The median age at diagnosis of HL and BC was 25.3 and

45.3 years, respectively. The median interval to develop BC was 16.1 years. Eleven women (39.2%) had bilateral disease. Mode of detection of the index breast cancers was by mammographic screening in 17 patients (60.7%), palpable lump in 8 patients (28.6%), clinical examination in two patients (7.1%), and unknown in one patient (3.6%). Case-control analysis showed that histological features and prognosis of BC after HL were similar to those of primary BC, however, for BC after HL, mastectomy was the predominant surgery ( $P = .001$ ) and adjuvant radiotherapy and anthracycline-based chemotherapy were less frequently used as compared to primary BC ( $P < .001$  and  $.003$ , respectively). **CONCLUSION:** The previous history of HL does not appear to be a poor prognostic factor for BC occurring thereafter.

Altundag, K., O. Altundag, et al. (2004). "Possible interaction between activator protein-1 and proto-oncogene B-cell lymphoma gene 6 in breast cancer patients resistant to tamoxifen." *Med Hypotheses* **63**(5): 823-6.

About 75% of breast tumors are positive for the estrogen receptor (ER) or progesterone receptor (PgR) or both, and estrogen is the main stimulant in the development and growth of these tumors. Tamoxifen, an estrogen receptor antagonist has been endocrine treatment for hormone-sensitive breast cancer for more than 20 years. However, the underlying cause of treatment failure in many breast cancer patients receiving tamoxifen is resistance to tamoxifen. The mechanisms of tamoxifen and the molecular events responsible for resistance to tamoxifen are not fully understood. Two ER subtypes, ERalpha and ERbeta, activate the Activator Protein-1 (AP-1) response elements, and through interactions between ERs and the AP-1 transcription factors c-fos and c-jun, these transcription factors regulate the genes involved in many cellular processes, including proliferation, differentiation, cell motility, and apoptosis. Thus, the interaction between ERs and AP-1 could be important clinically and could have bearing on the response to tamoxifen. Tamoxifen acts as an agonist on genes under the control of an AP-1 response elements when ERalpha or ERbeta is expressed. AP-1 blockade suppresses mitogenic signals from multiple different peptide growth factors as well as estrogen, and inhibits the growth of MCF-7 breast cancer cells both in vitro and in vivo. Tamoxifen actually activate the AP-1 transcription factor. Increased AP-1 activity in breast cancer cells can lead to tamoxifen resistance. The proto-oncogene B-cell lymphoma gene 6 (BCL-6) has been characterized as a regulator of B-lymphocyte growth and development. BCL-6 is also expressed in the mammary epithelium in nonpregnant animals and

during early pregnancy and is expressed in 68% of histologically high-grade ductal breast carcinomas, which are clinically the most aggressive. BCL-6 is a potent repressor of transcriptional activity mediated by AP-1 factors. We hypothesize that increased BCL-6 in breast cancer cells might block tamoxifen resistance by repressing AP-1, eventually resulting in apoptosis. We also suggest that BCL-6 expression must be analyzed in ER-positive breast cancer patients and the results must be correlated with predictive and prognostic factors and survival.

Amos Burke, G. A., J. Imeson, et al. (2003). "Localized non-Hodgkin's lymphoma with B-cell histology: cure without cyclophosphamide? A report of the United Kingdom Children's Cancer Study Group on studies NHL 8501 and NHL 9001 (1985-1996)." *Br J Haematol* **121**(4): 586-91.

We have examined the outcome for children treated on two consecutive United Kingdom Children's Cancer Study Group studies of localized B-cell non-Hodgkin's lymphoma (NHL). The first study (NHL 8501; 1985-1989) included cyclophosphamide in the treatment regimen at a total cumulative dose of 4 g/m<sup>2</sup> whereas the regimen in the succeeding study (NHL 9001; 1990-1996) did not include cyclophosphamide. Ninety children with confirmed B-cell NHL were treated in the two studies (NHL 8501, n = 33 and NHL9001, n = 57). With a median follow-up of 7.5 years, overall survival for localized B-cell NHL did not differ between the two regimens with observed 3-year survivals of 94% [95% confidence interval (CI) 80-98%] and 89% (95% CI 79-95%) respectively ( $P = 0.47$ ). There was also no difference in the event-free survival between children treated on regimen NHL 8501 and NHL 9001 [91% (95% CI 76-97%) vs 84% (95% CI 73-92%) after 3 years;  $P = 0.34$ ]. Although the difference in the number of failed remissions between NHL 8501 and 9001 (0/33 vs 6/57) approached statistical significance ( $P = 0.08$ , Fisher's exact test), there was no overall statistical difference between the treatment failures on either regimen ( $P = 0.34$ ). Substantial long-term survival can be achieved for many children with localized B-cell NHL without the use of cyclophosphamide. Further studies are needed to identify whether all clinical or histopathological subgroups will benefit equally from the omission of cyclophosphamide.

Anderlini, P., R. Saliba, et al. (2008). "Fludarabine-melphalan as a preparative regimen for reduced-intensity conditioning allogeneic stem cell transplantation in relapsed and refractory Hodgkin's lymphoma: the updated M.D. Anderson Cancer Center experience." *Haematologica* **93**(2): 257-64.

**BACKGROUND:** The role of reduced-intensity conditioning allogeneic stem cell transplantation in relapsed/refractory Hodgkin's lymphoma remains poorly defined. We here present an update of our single-center experience with fludarabine-melphalan as a preparative regimen. **DESIGN AND METHODS:** Fifty-eight patients with relapsed/refractory Hodgkin's lymphoma underwent RIC and allogeneic stem cell transplantation from a matched related donor (MRD; n=25) or a matched unrelated donor (MUD; n=33). Forty-eight (83%) had undergone prior autologous stem cell transplantation. Disease status at transplant was refractory relapse (n=28) or sensitive relapse (n=30). **RESULTS:** Cumulative day 100 and 2-year transplant-related mortality rates were 7% and 15%, respectively (day 100 transplant-related mortality MRD vs. MUD 8% vs. 6%, p=ns; 2-year MRD vs. MUD 13% vs. 16%, p=ns). The cumulative incidence of acute (grade II-IV) graft-versus-host disease in the first 100 days was 28% (MRD vs. MUD 12% vs. 39%, p=0.04). The cumulative incidence of chronic graft-versus-host disease at any time was 73% (MRD vs. MUD 57% vs. 85%, p=0.006). Projected 2-year overall and progression-free survival rates are 64% (49-76%) and 32% (20-45%), with 2-year disease progression/relapse at 55% (43-70%). There was no statistically significant differences in overall survival progression-free survival, and disease progression/relapse between MRD and MUD transplants. There was a trend for the response status pretransplant to have a favorable impact on progression-free survival (p=0.07) and disease progression/relapse (p=0.049), but not on overall survival (p=0.4). **CONCLUSIONS:** Fludarabine-melphalan as a preparative regimen for reduced-intensity conditioning allogeneic stem cell transplantation in progression-free survival Hodgkin's lymphoma is associated with a significant reduction in transplant-related mortality, with comparable results in MRD and MUD allografts. Optimizing pretransplant response status may improve patients' outcome.

Aneja, R., S. N. Vangapandu, et al. (2006). "Development of a novel nitro-derivative of noscapine for the potential treatment of drug-resistant ovarian cancer and T-cell lymphoma." *Mol Pharmacol* **69**(6): 1801-9.

We have shown previously that an antitussive plant alkaloid, noscapine, binds tubulin, displays anticancer activity, and has a safe pharmacological profile in humans. Structure-function analyses pointed to a proton at position-9 of the isoquinoline ring that can be modified without compromising tubulin binding activity. Thus, many noscapine analogs with

different functional moieties at position-9 were synthesized. Those analogs that kill human cancer cells resistant to other antimicrotubule agents, vincas and taxanes, were screened. Here, we present one such analog, 9-nitro-noscapine (9-nitro-nos), which binds tubulin and induces apoptosis selectively in tumor cells (ovarian and T-cell lymphoma) resistant to paclitaxel, vinblastine, and teniposide. 9-Nitro-nos treatment at doses as high as 100 microM did not affect the cell cycle profile of normal human fibroblasts. This selectivity of 9-nitro-nos for cancer cells represents a unique edge over the other available antimicrotubule agents. 9-Nitro-nos perturbs the progression of cell cycle by mitotic arrest, followed by apoptotic cell death associated with increased caspase-3 activation and appearance of terminal deoxynucleotidyl transferase dUTP nick-end labeling-positive cells. Thus, we conclude that 9-nitro-nos has great potential to be a novel therapeutic agent for ovarian and T-cell lymphoma cancers, even those that have become drug-resistant to currently available chemotherapeutic drugs.

Ansell, S. M., D. J. Inwards, et al. (2008). "Low-dose, single-agent temsirolimus for relapsed mantle cell lymphoma: a phase 2 trial in the North Central Cancer Treatment Group." *Cancer* **113**(3): 508-14.

**BACKGROUND:** The objective of this study was to test a low dose of (25 mg weekly) of the mammalian target of rapamycin kinase inhibitor temsirolimus for patients with relapsed mantle cell lymphoma (MCL). **METHODS:** Patients with relapsed or refractory MCL were eligible to receive temsirolimus 25 mg intravenously every week as a single agent. Patients who had a tumor response after 6 cycles were eligible to continue drug for a total of 12 cycles or 2 cycles after complete remission and then were observed without maintenance. **RESULTS:** Of 29 enrolled patients, 28 were evaluable for toxicity, and 27 were evaluable for efficacy. The median age was 69 years (range, 51-85 years), 86% of patients had stage IV disease, and 71% had > or = 2 extranodal sites. Patients had received a median of 4 prior therapies (range, 1-9 prior therapies), and 50% were refractory to the last treatment. The overall confirmed response rate was 41% (11 of 27 patients; 90% confidence interval [CI], 22%-61%) with 1 complete response (3.7%) and 10 partial responses (37%). The median time to progression in all eligible patients was 6 months (95% CI, 3-11 months), and the median duration of response for the 11 responders was 6 months (range, 1-26 months). Hematologic toxicities were the most common, with 50% (14 of 28 patients) grade 3 and 4% (1 of 28 patients) grade 4 toxicities observed. Thrombocytopenia was the most frequent cause of dose reduction. **CONCLUSIONS:** Single-

agent temsirolimus at a dose of 25 mg weekly is an effective new agent for the treatment of MCL. The 25-mg dose level retained the antitumor activity of the 250-mg dose with less myelosuppression. Further studies of temsirolimus in combination with other active drugs for MCL and other lymphoid malignancies are warranted.

Arora, N. K., A. S. Hamilton, et al. (2007). "Population-based survivorship research using cancer registries: a study of non-Hodgkin's lymphoma survivors." *J Cancer Surviv* **1**(1): 49-63.

**INTRODUCTION:** Several recent reports have recommended use of population-based cancer registries for evaluating the long-term health outcomes of cancer survivors. Drawing upon experiences from a study of survivors of non-Hodgkin's Lymphoma (NHL), we discuss conceptual and methodological challenges to and opportunities for conducting population-based survivorship research using cancer registries. **MATERIALS AND METHODS:** Survivors of aggressive NHL diagnosed between June 1998 and August 2001, 2-5 years prior to the study, were sampled from the Los Angeles Surveillance Epidemiology and End Results (SEER) registry. A conceptual framework was developed to systematically evaluate the association of sociodemographic, clinical, social, psychological, and behavioral factors with survivors' health-related quality of life. Data were collected primarily by a mailed questionnaire; medical records were also abstracted. **RESULTS:** Of 744 eligible survivors identified from the registry, 181 (24.3%) were lost to follow-up; 408 responded to the questionnaire (54.8%); 155 (20.8%) refused. Those lost to follow-up included a significantly higher proportion of younger, male, and Hispanic survivors compared to the other two groups ( $P \leq 0.01$ ). There were no sociodemographic or clinical differences among the questionnaire respondents and survivors who refused study participation. Medical records were abstracted for 59.8% of the respondents. A high percentage of agreement was seen between survivors' self-report and medical record documentation of key treatments and disease status ( $\geq 95\%$  for survivors with complete records). **CONCLUSIONS:** The cancer registry served as a valuable resource for recruiting one of the largest population-based samples of NHL survivors. The methodology and example of a conceptual framework utilized in this study provide a model for future population-based cancer survivorship research.

Assaf, C., S. Gellrich, et al. (2007). "CD56-positive haematological neoplasms of the skin: a multicentre study of the Cutaneous Lymphoma Project Group of

the European Organisation for Research and Treatment of Cancer." *J Clin Pathol* **60**(9): 981-9.

**BACKGROUND:** Cutaneous lymphomas expressing CD56, a neural cell adhesion molecule, are characterised in most cases by a highly aggressive clinical course and a poor prognosis. However, prognostic subsets within the CD56+ group have been difficult to identify due to the lack of uniform clinicopathological and immunophenotypical criteria. **METHODS:** A multicentre study was conducted by the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer to define prognostic parameters and establish diagnostic and therapeutic guidelines for CD56+ haematological neoplasms presenting primarily in the skin. **RESULTS:** Four different subtypes of lymphoproliferations with CD56 expression were identified: (1) haematodermic neoplasm; (2) skin infiltration as the first manifestation of CD56+ acute myeloid leukaemia; (3) nasal-type extranodal natural killer/T-cell lymphoma; and (4) "classical" cases of cutaneous T-cell lymphoma (CTCL) with co-expression of the CD56 molecule. Patients in the first three groups had a poor outcome (93% died) with a median survival rate of 11 months (95% CI 2-72 months), whereas all patients with CD56+ CTCL were alive at the last follow-up. **CONCLUSION:** Results show that CD56+ cutaneous lymphoproliferative disorders, with the exception of CD56+ CTCL have a very poor prognosis. It is therefore clinically important to separate CD56+ CTCL from the remaining CD56+ haematological disorders.

Atra, A., C. R. Pinkerton, et al. (2004). "Acute neurotoxicity in children with advanced stage B-non-Hodgkin's lymphoma and B-acute lymphoblastic leukaemia treated with the United Kingdom children cancer study group 9002/9003 protocols." *Eur J Cancer* **40**(9): 1346-50.

We reviewed the pattern of acute neurotoxicity in children with B-non-Hodgkin's lymphoma (B-NHL) and B-acute lymphoblastic leukaemia (ALL) treated with the UKCCSG 9002/9003 protocols. Among 175 patients, 21 (12%) developed acute neurotoxicity: 9002 protocol (n=11/112) and 9003 (n=10/63). There were 20 boys and the median age was 10 years. Patients with neurological symptoms due to other causes were excluded. Acute neurological symptoms developed following induction chemotherapy in 7 patients, or after a more intensive course of chemotherapy containing high-dose methotrexate (n=14). Nine patients required their chemotherapy to be altered because of the acute neurotoxicity. One patient died of cerebral haemorrhage but none of the remaining six deaths was attributed to acute neurotoxicity. We

conclude that acute neurotoxicity is common in children treated with the 9002/9003 protocols and tends to be transient. Intrathecal and systemic chemotherapy including high-dose methotrexate is probably the most common predisposing factor. Modification of subsequent chemotherapy is not invariably necessary.

Balhorn, R., S. Hok, et al. (2007). "Selective high-affinity ligand antibody mimics for cancer diagnosis and therapy: initial application to lymphoma/leukemia." *Clin Cancer Res* **13**(18 Pt 2): 5621s-5628s.

**PURPOSE:** More than two decades of research and clinical trials have shown radioimmunotherapy to be a promising approach for treating various forms of cancer. Lym-1 antibody, which binds selectively to HLA-DR10 on malignant B-cell lymphocytes, has proved to be effective in delivering radionuclides to non-Hodgkin's lymphoma and leukemia. Using a new approach to create small synthetic molecules that mimic the targeting properties of the Lym-1 antibody, a prototype, selective high-affinity ligand (SHAL), has been developed to bind to a unique region located within the Lym-1 epitope on HLA-DR10. **EXPERIMENTAL DESIGN:** Computer docking methods were used to predict two sets of small molecules that bind to neighboring cavities on the beta subunit of HLA-DR10 surrounding a critical amino acid in the epitope, and the ligands were confirmed to bind to the protein by nuclear magnetic resonance spectroscopy. Pairs of these molecules were then chemically linked together to produce a series of bidentate and bisbidentate SHALs. **RESULTS:** These SHALs bind with nanomolar to picomolar K<sub>d</sub>'s only to cell lines expressing HLA-DR10. Analyses of biopsy sections obtained from patients also confirmed that SHAL bound to both small and large cell non-Hodgkin's lymphomas mimicking the selectivity of Lym-1. **CONCLUSIONS:** These results show that synthetic molecules less than 1/50th the mass of an antibody can be designed to exhibit strong binding to subtle structural features on cell surface proteins similar to those recognized by antibodies. This approach offers great potential for developing small molecule therapeutics that target other types of cancer and disease.

Barath, Z., R. Radics, et al. (2006). "Multidrug resistance reversal by 3-formylchromones in human colon cancer and human mdr1 gene-transfected mouse lymphoma cells." *In Vivo* **20**(5): 645-9.

Several new 3-formylchromone derivatives proved to be modifiers of multidrug resistance in mouse lymphoma cells and in human Colo320 colon

cancer cells. There is apparently a structure-activity relationship between the antiproliferative multidrug resistance-reversing effect and the chemical structure of the 3-formylchromones. The total polar surface areas and the ground state dipole moments of the molecules are presumed to play a key role in the multidrug resistance-reversing effect. The log P values can provide an adequate explanation for the selective cytotoxicity against cancer cells.

Belch, A., C. T. Kouroukis, et al. (2007). "A phase II study of bortezomib in mantle cell lymphoma: the National Cancer Institute of Canada Clinical Trials Group trial IND.150." *Ann Oncol* **18**(1): 116-21.

**BACKGROUND:** We evaluated the activity and toxic effects of bortezomib in patients with mantle cell lymphoma. **PATIENTS AND METHODS:** Thirty patients, including 29 eligible patients, were enrolled; 13 had received no prior chemotherapy. The dose of bortezomib was 1.3 mg/m<sup>2</sup> given on days 1, 4, 8 and 11 every 21 days. Response was assessed according to the International Workshop Criteria for non-Hodgkin's lymphoma and toxicity graded using the National Cancer Institute Common Toxicity Criteria version 2.0. **RESULTS:** There were 13 responding patients (46.4%; 95% confidence interval=27.5% to 66.1%), including one unconfirmed complete remission. The median response duration was 10 months. Response rates were similar in previously untreated (46.2%) and treated (46.7%) patients. Neurological toxicity and myalgia led to treatment discontinuation in 10 patients after two to seven treatment cycles. Five serious adverse events (including two deaths) associated with fluid retention were observed in the first 12 patients. We subsequently excluded patients with baseline effusions, dyspnea or edema; no further events were seen. **CONCLUSIONS:** Bortezomib is active in treating patients with mantle cell lymphoma. While cumulative neuromuscular toxic effects limited therapy duration and specific issues related to fluid retention require further evaluation, continued study of this drug in combination regimens is warranted.

Birgegard, G., P. Gascon, et al. (2006). "Evaluation of anaemia in patients with multiple myeloma and lymphoma: findings of the European CANCER ANAEMIA SURVEY." *Eur J Haematol* **77**(5): 378-86.

**OBJECTIVES:** Until recently, no prospective epidemiologic survey of lymphoma and multiple myeloma (L/MM) in European cancer patients had been conducted; furthermore, data on prevalence, incidence, and treatment patterns of L/MM were limited or unavailable. Here we define anemia prevalence, incidence, and treatment patterns, and identify anemia risk factors in European L/MM

patients. **METHODS:** Data for a subgroup of 2360 L/MM patients in the European Cancer Anaemia Survey (ECAS) were analyzed; variables included age, gender, tumor type/stage, cancer and anemia treatment, WHO performance status, and hemoglobin (Hb) levels. **RESULTS:** 2316 patients were evaluable (1612 L and 704 MM). Anemia rate at enrollment was 52.5%. At enrollment, Hb levels correlated significantly with WHO scores ( $r = -0.306$ ,  $P < 0.001$ ). Anemia prevalence during ECAS was 72.9% (MM, 85.3%; non-Hodgkin's lymphoma, 77.9%; Hodgkin's disease, 57.4%); incidence in chemotherapy patients was 55.4%. Only 47.3% of patients anemic any time during ECAS received anemia treatment; overall Hb nadir for initiating treatment was 8.9 g/dL (epoetin, 9.5 g/dL; transfusion, 8.2 g/dL). Factors found to significantly ( $P < 0.03$ ) increase anemia risk were low initial Hb, female gender, persistent/resistant disease, and platinum chemotherapy. **CONCLUSIONS:** L/MM patients have a high prevalence and incidence of anemia; however, anemia is not optimally treated. Anemia is common in L/MM patients and, given its known adverse impact on physical functioning and quality-of-life variables including fatigue and cognitive function, anemia management should be an integral part of their care. Predictive factors identified by ECAS may help clinicians develop optimal anemia treatment strategies for L/MM patients.

Bishara, M. R., C. Ross, et al. (2009). "Primary anaplastic large cell lymphoma of the breast arising in reconstruction mammoplasty capsule of saline filled breast implant after radical mastectomy for breast cancer: an unusual case presentation." *Diagn Pathol* 4: 11.

**BACKGROUND:** Primary non-Hodgkin lymphoma (NHL) of the breast represents 0.04-0.5% of malignant lesions of the breast and accounts for 1.7-2.2% of extra-nodal NHL. Most primary cases are of B-cell phenotype and only rare cases are of T-cell phenotype. Anaplastic large cell lymphoma (ALCL) is a rare T-cell lymphoma typically seen in children and young adults with the breast being one of the least common locations. There are a total of eleven cases of primary ALCL of the breast described in the literature. Eight of these cases occurred in proximity to breast implants, four in relation to silicone breast implant and three in relation to saline filled breast implant with three out of the eight implant related cases having previous history of breast cancer treated surgically. Adjuvant postoperative chemotherapy is given in only one case. Secondary hematological malignancies after breast cancer chemotherapy have been reported in literature. However in contrast to acute myeloid leukemia (AML), the association between lymphoma and administration of

chemotherapy has never been clearly demonstrated. **CASE PRESENTATION:** In this report we present a case of primary ALCL of the breast arising in reconstruction mammoplasty capsule of saline filled breast implant after radical mastectomy for infiltrating ductal carcinoma followed by postoperative chemotherapy twelve years ago. **CONCLUSION:** Primary ALK negative ALCL arising at the site of saline filled breast implant is rare. It is still unclear whether chemotherapy and breast implantation increases risk of secondary hematological malignancies significantly. However, it is important to be aware of these complications and need for careful pathologic examination of tissue removed for implant related complications to make the correct diagnosis for further patient management and treatment. It is important to be aware of this entity at this site as it can be easily misdiagnosed on histologic grounds and to exclude sarcomatoid carcinoma, malignant melanoma and pleomorphic sarcoma by an appropriate panel of immunostains to arrive at the correct diagnosis of ALCL.

Blayney, D. W., B. W. McGuire, et al. (2005). "Increasing chemotherapy dose density and intensity: phase I trials in non-small cell lung cancer and non-Hodgkin's lymphoma." *Oncologist* 10(2): 138-49.

Dose densification and dose escalation of cytotoxic chemotherapy may be important in improving the cure rates of chemotherapy-responsive cancers. We conducted two phase I studies, in non-small cell lung cancer (NSCLC) and in lymphoma, to explore the possibility of intensifying chemotherapy by compressing the delivery of and escalating the dose of standard combination chemotherapy. One study used etoposide and cisplatin chemotherapy in patients with unresectable stage III or IV NSCLC, intensifying chemotherapy by reducing the cycle length. The second study used cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP chemotherapy, in the treatment of stage II-IV intermediate or immunoblastic high-grade lymphoma, intensifying chemotherapy first by reducing the cycle length and then by escalating the dosages of cyclophosphamide and doxorubicin. Filgrastim support was used during dose intensification. Fifty-five patients with NSCLC and 49 with non-Hodgkin's lymphoma (NHL) were enrolled and treated in successive cohorts. At standard dosages and intervals of chemotherapy, filgrastim support resulted in incidences of grade 3 and 4 neutropenia that were between 62% and 77% lower than those in the no-filgrastim control; the mean duration of neutropenia was, likewise, more than 80% lower. Absolute neutrophil counts were  $\geq 2 \times 10^9/l$  at day 14 in virtually 100% of patients receiving filgrastim. In the NSCLC trial, etoposide and cisplatin

were intensified by >50%, and in the lymphoma trial, cyclophosphamide was intensified by 270% and doxorubicin was intensified by 87%. Chemotherapy reductions or delays for neutropenia were rare in the groups receiving filgrastim; but at higher chemotherapy intensities, dose-limiting thrombocytopenia was encountered. We conclude that the delivery of myelosuppressive chemotherapy in both a dose-intense and a dose-dense manner is feasible with filgrastim support.

Bluhm, E. C., C. Ronckers, et al. (2008). "Cause-specific mortality and second cancer incidence after non-Hodgkin lymphoma: a report from the Childhood Cancer Survivor Study." *Blood* **111**(8): 4014-21.

Second primary malignancies and premature death are a concern for patients surviving treatment for childhood lymphomas. We assessed mortality and second malignant neoplasms (SMNs) among 1082 5-year survivors of non-Hodgkin lymphoma (NHL) in the Childhood Cancer Survivor Study, a multi-institutional North American retrospective cohort study of cancer survivors diagnosed from 1970 to 1986. Standardized mortality ratios (SMRs) and standardized incidence ratios (SIRs) were calculated using US population rates. Relative risks for death and solid tumor SMNs were calculated based on demographic, clinical, and treatment characteristics using Poisson regression models. There were 87 observed deaths (SMR = 4.2; 95% CI, 1.8-4.1) with elevated rates of death from solid tumors, leukemia, cardiac disease, and pneumonia. Risk for death remained elevated beyond 20 years after NHL. Risk factors for death from causes other than NHL included female sex (rate ratio [RR] = 3.4) and cardiac radiation therapy exposure (RR = 1.9). There were 27 solid tumor SMNs (SIR = 3.9; 95% CI, 2.6-5.7) with 3% cumulative incidence between 5 and 20 years after NHL diagnosis. Risk factors were female sex (RR = 3.1), mediastinal NHL disease (RR = 5.2), and breast irradiation (RR = 4.3). Survivors of childhood NHL, particularly those treated with chest RT, are at continued increased risk of early mortality and solid tumor SMNs.

Blum, K. A., J. L. Johnson, et al. (2007). "Single agent bortezomib in the treatment of relapsed and refractory Hodgkin lymphoma: cancer and leukemia Group B protocol 50206." *Leuk Lymphoma* **48**(7): 1313-9.

Constitutive activation of nuclear factor-kappaB (NF-kappaB) has been described in patient-derived Reed - Sternberg cells and Hodgkin lymphoma (HL) cell lines and contributes to the proliferation and survival of HL. Therapeutic inhibition of the proteasome with bortezomib may inhibit over-expression of nuclear NF-kappaB by

preventing degradation of I-kappaB, which sequesters NF-kappaB in the cytoplasm. To evaluate this hypothesis, the Cancer and Leukemia Group B (CALGB) conducted a multi-institutional phase II trial of single agent bortezomib in patients with relapsed or refractory classical HL. Thirty patients received bortezomib 1.3 mg/m<sup>2</sup> on days 1, 4, 8, 11 and every 21 days for a median of 2 cycles (range, 1 - 8). Patients were heavily pre-treated with a median of four prior therapies, and 83% were previously transplanted. No responses were observed, 9 patients had stable disease, and 21 progressed. The median progression-free and overall survivals were 1.4 months [95% CI, (1.28, 1.91)] and 14.8 months [95% CI (11.2, 22.3)], respectively. Grade 3 - 4 adverse events, primarily thrombocytopenia, occurred in 15 patients. Therefore, although well tolerated, 1.3 mg/m<sup>2</sup> bortezomib administered biweekly has no single agent activity in relapsed/refractory classical HL.

Blum, K. A., J. L. Johnson, et al. (2006). "Prolonged follow-up after initial therapy with 2-chlorodeoxyadenosine in patients with indolent non-Hodgkin lymphoma: results of Cancer and Leukemia Group B Study 9153." *Cancer* **107**(12): 2817-25.

**BACKGROUND:** The objective of this study was to determine the efficacy and toxicity of 2-chlorodeoxyadenosine (2-CdA) in patients with untreated, indolent non-Hodgkin lymphoma (NHL). **METHODS:** For this multicenter, single-arm, Phase II study, 44 patients with treatment-naive, stage III or IV, indolent NHL (International Working Formulation subtypes A, B, and C) were enrolled. Patients received 0.14 mg/kg per day of 2-CdA as a 2-hour bolus infusion for 5 consecutive days every 28 days until maximal response or a total of 6 cycles. **RESULTS:** Thirty-eight patients were eligible for response evaluation. The overall response rate was 100% (95% confidence interval [95% CI], 90.8-100%), and the complete response rate was 31.6% (95% CI, 17.5-48.7%). In the intent-to-treat population, the median failure-free survival was 2.0 years (95% CI, 1.3-3.4 years), and the overall survival rate was 7.0 years (95% CI, 4.3-9.4 years). Six patients had sustained remissions that lasted a median of 8.7 years (range, from 5.9 years to > or =11 years). Although 68% of patients experienced at least 1 grade 3 or 4 event, consisting primarily of myelosuppression, severe infections were rare, with only 8 grade 3 infections. Four late malignancies (prostate adenocarcinoma, ductal carcinoma in situ, and myelodysplasia) and 4 patients with large cell transformation were reported. **CONCLUSIONS:** 2-CdA is an active, well-tolerated therapy for patients with untreated, indolent NHL.

Brown, J. E., S. P. Ellis, et al. (2006). "Effect of chemotherapy on skeletal health in male survivors from testicular cancer and lymphoma." Clin Cancer Res **12**(21): 6480-6.

**PURPOSE:** There are concerns over the late effects of cancer therapy, including accelerated bone loss leading to increased risk of osteoporosis. Treatment-related bone loss is well recognized in breast and prostate cancer, due to overt hypogonadism, but there has been little evaluation of the skeletal effects of chemotherapy alone in adults. This study assesses the extent of bone loss due to previous chemotherapy in men. **EXPERIMENTAL DESIGN:** The bone mineral density (BMD) of men who had received previously chemotherapy with curative intent for lymphoma or testicular cancers was compared with that of an age-matched population of men from a cancer control population that had not received chemotherapy. BMD was measured by dual-energy X-ray scanning. Additionally, measurement of sex hormones and the bone turnover markers N-telopeptide fragment of type I collagen and bone-specific alkaline phosphatase were done. All statistical tests were two sided. **RESULTS:** One hundred fifteen chemotherapy-treated patients and 102 cancer controls were recruited. There was no statistical difference in BMD between the chemotherapy and control groups at either spine or hip and the mean BMD values in both groups were no lower than that of a reference population. There were no significant differences in estradiol, luteinizing hormone, and testosterone, but follicle-stimulating hormone values were significantly higher in the chemotherapy group ( $P=0.011$ ). The mean values of NH<sub>2</sub>-terminal telopeptide fragment of type I collagen and bone-specific alkaline phosphatase were within the reference ranges. **CONCLUSIONS:** The absence of accelerated bone loss following chemotherapy is reassuring and suggests that standard dose cytotoxic chemotherapy has no lasting clinically important direct effects on bone metabolism.

Burns, L. J., D. J. Weisdorf, et al. (2003). "IL-2-based immunotherapy after autologous transplantation for lymphoma and breast cancer induces immune activation and cytokine release: a phase I/II trial." Bone Marrow Transplant **32**(2): 177-86.

We determined the safety, immune activating effects, and potential efficacy of i.v. infusion of ex vivo interleukin-2 (IL-2) activated natural killer (NK) cells (part I) or IL-2 boluses (part II) during daily s.c. IL-2 administration following hematopoietic recovery from autologous transplantation. In all, 57 patients with relapsed lymphoma ( $n=29$ ) or metastatic breast cancer ( $n=28$ ) were enrolled. In part I of the study, 34 patients were enrolled at three dose levels of ex vivo IL-2-activated NK cells. Lymphaphereses were

performed on days 28 and 42 of s.c. IL-2 administration. Following overnight ex vivo IL-2 activation of the pheresis product, the cells were reinfused the following day. In part II, 23 patients were enrolled at three dose levels of supplemental i.v. IL-2 bolus infusions, given on days 28 and 35 during s.c. IL-2 administration. Toxicities were generally mild, and no patient required hospitalization. Lytic function was markedly enhanced for fresh peripheral blood mononuclear cells (PBMNCs) obtained 1 day postinfusion of either IL-2-activated cells or IL-2 boluses. IL-2 boluses transiently increased the levels of IL-6, IFN-gamma, TNF-alpha and IL1-beta, with increases in IL-6 and IFN-gamma being dose dependent. A total of 37 patients (19 patients with lymphoma, 18 with breast cancer) treated with an optimum dose of post-transplant immunotherapy (defined as having received  $1.75 \times 10^6$  IU/m<sup>2</sup>/day of s.c. IL-2 plus at least one of the planned ex vivo IL-2-activated cell infusions/IL-2 boluses) could be matched with controls from the Autologous Blood and Marrow Transplant Registry database. The matched-pairs analysis demonstrated no improvement in disease outcomes of survival and relapse. We conclude that IL-2-activated cells/IL-2 boluses can be safely administered, generate PBMNCs with enhanced cytotoxicity against NK-resistant targets, and increase cytokine levels. With this dose and schedule of administration of IL-2, no improvement in patient disease outcomes was noted. Alternative strategies will be needed to exploit the immunotherapeutic potential of IL-2-activated NK cells.

Cairo, M. S., R. Spoto, et al. (2003). "Childhood and adolescent large-cell lymphoma (LCL): a review of the Children's Cancer Group experience." Am J Hematol **72**(1): 53-63.

We reviewed the clinical characteristics, treatment, and outcome of 67 children with localized and 212 with disseminated large-cell lymphoma (LCL) treated during a 20-year period in 5 consecutive Children's Cancer Group (CCG) non-Hodgkin's lymphoma (NHL) trials. Clinical outcomes for patients treated on the four earlier studies with moderate-dose chemotherapy administered over 12-18 months were compared with patients treated most recently with short, intensive therapy. Median age at diagnosis was 12 years (range: 0-19 years). Male to female ratio was 1.8:1.0. Five-year event-free survival (EFS) was 92%  $\pm$  3.3% and 50  $\pm$  3.5% for patients with localized LCL and disseminated LCL, respectively. After adjustment for lactate dehydrogenase (LDH), age at diagnosis, and BM involvement, short and intensive therapy as delivered on the most recent study, CCG-5911, was associated with an improved outcome ( $P < 0.05$ ) compared to the

four previous studies. Elevated LDH ( $>$  or  $=$  500 IU/L) at diagnosis and young age ( $<$ 5 years) were both significant independent predictors of poorer long-term EFS ( $P < 0.05$ ). Long-term survival after relapse or other treatment failure was only 31%  $\pm$  4.7%. In summary, more recent shorter and intense therapy appears to be associated with superior event-free survival for children and adolescents with disseminated LCL. Large numbers of patients treated with shorter and intense therapy are required to confirm these preliminary observations.

Cairo, M. S., R. Spoto, et al. (2003). "Burkitt's and Burkitt-like lymphoma in children and adolescents: a review of the Children's Cancer Group experience." *Br J Haematol* **120**(4): 660-70.

Historically, the survival of children and adolescents with Burkitt's and Burkitt-like lymphoma had been poor. Recently, short and intensive chemotherapy appears to have improved disease outcome. We therefore reviewed the results of four successive Children's Cancer Group trials conducted on 470 children with disseminated Burkitt's and Burkitt-like lymphoma. Of the patients studied, the median age was 8 years (0-21 years), the male:female ratio was 4:1, 58% had lactate dehydrogenase (LDH)  $>$  or  $=$  500 IU/l, 23% had M2 or M3 bone marrow (BM), and 12% demonstrated central nervous system involvement. In a multivariate analysis, the 4-year event-free survival (EFS) in patients  $>$  or  $=$  15-years-old compared with  $<$  15-year-old was 34  $\pm$  7 versus 59  $\pm$  2% ( $P < 0.05$ ), the 4-year EFS of M2/M3 compared with M1 BM was 38  $\pm$  5 versus 63  $\pm$  3% ( $P < 0.001$ ), and the 4-year EFS with LDH  $>$  or  $=$  500 IU/l compared with LDH  $<$  500 IU/l was 49  $\pm$  3 versus 71  $\pm$  4% ( $P < 0.001$ ). Furthermore, patients treated on the most recent protocol, which was short and more intensive, had a significantly improved survival compared with those on previous trials (4-year EFS 80  $\pm$  6 versus 54  $\pm$  2%,  $P < 0.001$ ). In summary, the outcome for childhood Burkitt's and Burkitt-like lymphoma has recently improved with the use of short and intensive B-cell non-Hodgkin's lymphoma-directed therapy.

Calabro, L., E. Fonsatti, et al. (2005). "Methylation-regulated expression of cancer testis antigens in primary effusion lymphoma: immunotherapeutic implications." *J Cell Physiol* **202**(2): 474-7.

Primary effusion lymphoma (PEL) is a large B-cell neoplasm with an unfavorable prognosis and limited therapeutic options. In this study, cancer testis antigens (CTA) were investigated as potential immunotherapeutic targets in patients with PEL. Baseline expression of a panel of 11 CTA was highly heterogeneous among five PEL cell lines. In

particular, the investigated CTA were not expressed in BC-2 and BC-3 cells, while BC-1, HBL-6, and BCBL-1 cells tested positive for 6, 8, and 9 CTA, respectively. The DNA hypomethylating agent 5-aza-2'-deoxycytidine (5-AZA-CdR) invariably induced or up-regulated the expression of all investigated CTA in all cell lines analyzed. The de novo expression of CTA was still detectable at mRNA and protein level at least 2 months after the end of 5-AZA-CdR treatment. These findings, and the concomitant up-regulation of HLA-class I antigens and ICAM-1 by 5-AZA-CdR, support its clinical use to set-up innovative chemo-immunotherapeutic approaches in PEL.

Capra, M., M. Hewitt, et al. (2007). "Long-term outcome in children with Hodgkin's lymphoma: the United Kingdom Children's Cancer Study Group HD82 trial." *Eur J Cancer* **43**(7): 1171-9.

**BACKGROUND:** The aim of United Kingdom Children's Cancer Study Group (UKCCSG) HD82 was to establish the efficacy of chlorambucil/vinblastine/procarbazine/prednisolone (ChIVPP) in the treatment of childhood Hodgkin's lymphoma stages II-IV and radiotherapy (RT) alone in stage I patients. We report on the status of these patients to a follow-up of 20 years. **METHODS:** Treatment consisted of 35Gy involved-field RT for stage I and ChIVPP alone for stages II-IV. Adjuvant RT (35Gy) was administered to those with bulky mediastinal disease. **RESULTS:** Of the 358 patients, the 10-year EFS/OS per stage is I (65.4%/92.6%), II (80.0%/93.3%), III (68.8%/85.0%), IV (45.5%/72.7%). The corresponding 20-year OS rates are similar with a combined (all stage) rate dropping from 89.3% to 89.0% over the decade. The cumulative 20-year malignancy rate is 7.29%. **CONCLUSION:** Single modality treatment provided relatively low EFS at 10-years but comparable long-term OS, relative to contemporary published combined modality regimens, for stages I-III but not for stage IV patients.

Cheung, M. C., A. E. Haynes, et al. (2007). "Rituximab in lymphoma: a systematic review and consensus practice guideline from Cancer Care Ontario." *Cancer Treat Rev* **33**(2): 161-76.

Rituximab is the first antibody-based therapy approved in cancer. The role of this treatment for non-Hodgkin's lymphoma has evolved significantly since its introduction. We aimed to systematically review the literature on rituximab in non-Hodgkin's lymphoma and provide consensus guidelines as to the rational use of this agent. Validated methodology from the Cancer Care Ontario Program in Evidence-Based Care was applied. A comprehensive literature search was completed by reviewers from the Hematology Disease Site Group of Cancer Care Ontario. Data were

abstracted from randomized controlled trials of rituximab-containing regimens for patients with non-Hodgkin's lymphoma. Twenty-three randomized controlled trials (RCTs) of rituximab-based therapy were analyzed. Consistent and clinically important benefits in progression-free and overall survival and were seen in the following settings: (1) addition of rituximab to combination chemotherapy for initial treatment of diffuse large B-cell lymphoma and other aggressive B-cell lymphomas; (2) addition of rituximab to combination chemotherapy for initial and subsequent treatment of follicular lymphoma and other indolent B-cell lymphomas; and (3) use of rituximab alone as extended maintenance therapy in patients with indolent B-cell lymphomas who have responded to initial treatment. The consensus opinion of the Hematology Disease Site Group is that rituximab is recommended for these indications.

Cheung, T. W. (2004). "AIDS-related cancer in the era of highly active antiretroviral therapy (HAART): a model of the interplay of the immune system, virus, and cancer. "On the offensive--the Trojan Horse is being destroyed"--Part B: Malignant lymphoma." *Cancer Invest* **22**(5): 787-98.

The impact of highly active antiretroviral therapy (HAART) on the incidence of non-Hodgkin's lymphoma was less obvious initially, although primary central nervous system lymphoma (PCNSL) has dropped precipitously since the introduction of HAART. The pathogenesis of acquired immunodeficiency syndrome-related lymphoma is multifactorial. Epstein-Barr virus plays a significant role in these diseases, especially Burkitt lymphoma and PCNSL. Data regarding the effect of HAART on the natural history and treatment outcomes of these malignancies are emerging. The possibility of direct and indirect roles of human immunodeficiency virus in the carcinogenesis suggests that antiretroviral therapy may be an important component of the treatment for these malignancies. The simultaneous administration of HAART and chemotherapy does not appear to significantly alter the toxicity profile, although the information with respect to the interaction of HAART and chemotherapy is limited. The use of biological agents, for example, monoclonal antibody against CD-20, is being explored to improve the clinical outcome of this disease.

Contreras-Galindo, R., M. H. Kaplan, et al. (2008). "Human endogenous retrovirus K (HML-2) elements in the plasma of people with lymphoma and breast cancer." *J Virol* **82**(19): 9329-36.

Actively replicating endogenous retroviruses entered the human genome millions of years ago and became a stable part of the inherited genetic material.

They subsequently acquired multiple mutations, leading to the assumption that these viruses no longer replicate. However, certain human tumor cell lines have been shown to release endogenous retroviral particles. Here we show that RNA from human endogenous retrovirus K (HERV-K) (HML-2), a relatively recent entrant into the human genome, can be found in very high titers in the plasma of patients with lymphomas and breast cancer as measured by either reverse transcriptase PCR or nucleic acid sequence-based amplification. Further, these titers drop dramatically with cancer treatment. We also demonstrate the presence of reverse transcriptase and viral RNA in plasma fractions that contain both immature and correctly processed HERV-K (HML-2) Gag and envelope proteins. Finally, using immunoelectron microscopy, we show the presence of HERV-K (HML-2) virus-like particles in the plasma of lymphoma patients. Taken together, these findings demonstrate that elements of the endogenous retrovirus HERV-K (HML-2) can be found in the blood of modern-day humans with certain cancers.

Copie-Bergman, C., C. Locher, et al. (2005). "Metachronous gastric MALT lymphoma and early gastric cancer: is residual lymphoma a risk factor for the development of gastric carcinoma?" *Ann Oncol* **16**(8): 1232-6.

**BACKGROUND:** Helicobacter pylori plays a major role in the pathogenesis of primary gastric MALT lymphoma (GML) and gastric carcinoma. The occurrence of these two diseases metachronously in a same patient is a rare event. **PATIENTS AND METHODS:** Gastric biopsies and gastrectomy resection specimens of four patients who developed GML and early gastric cancer (EGC) were analysed by morphology, immunohistochemistry and molecular biology. **RESULTS:** Four patients (three males and one female; mean age 48 years) were diagnosed with GML. Helicobacter pylori infection was observed in three cases. Two patients had localized disease (stages IE and IIE, respectively) and were treated with H. pylori eradication therapy followed by an alkylating agent for one patient. Two patients had disseminated disease (stage IV), and were treated with an alkylating agent. Three cases were t(11;18) positive. All patients achieved initially complete lymphoma remission. Long-term endoscopic surveillance detected an EGC at the same location as the lymphoma in all patients at a mean time of 9.5 years (range 2.5-17 years) after lymphoma diagnosis. Gastrectomy specimens showed residual GML in all cases. **CONCLUSION:** Prolonged residual GML could constitute an additional risk factor for the development of gastric carcinoma. Long-term endoscopic surveillance is mandatory in

patients treated conservatively for gastric MALT lymphoma.

Crump, M., T. Baetz, et al. (2004). "Gemcitabine, dexamethasone, and cisplatin in patients with recurrent or refractory aggressive histology B-cell non-Hodgkin lymphoma: a Phase II study by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG)." *Cancer* **101**(8): 1835-42.

**BACKGROUND:** Gemcitabine has been shown to have activity as a single agent in lymphoma and, when combined with cisplatin, is effective therapy for a number of solid tumors. The authors wished to determine the response rate and toxicity of gemcitabine, dexamethasone, and cisplatin for recurrent or refractory non-Hodgkin lymphoma (NHL). Fifty-one eligible patients were evaluable for toxicity and response. The median age of the patients was 57 years (range, 18-84 years) and most had diffuse large-cell lymphoma. After 2 cycles, there were 8 complete responses (CR; 16%) and 17 partial responses (PR; 33%). There was an overall response rate (RR) of 49% (95% confidence interval = 37-63%). The RR after completion of all protocol chemotherapy (including those who received > 2 cycles of GDP) was 53% (11 CR, 16 PR). Grade 3 and 4 neutropenia occurred in 33% and 39% of patients, respectively. Grade 3 and 4 thrombocytopenia occurred in 24% and 4% of patients, respectively. Seven patients (14%) experienced febrile neutropenia. Of the 35 patients < 66 years, 22 (63%) proceeded to SCT. **CONCLUSIONS:** GDP is an active regimen in B-cell NHL and can be administered with acceptable toxicity to outpatients. A Phase III trial comparing GDP with standard cisplatin-based chemotherapy is now ongoing through the National Cancer Institute of Canada Clinical Trials Group.

Danzon, A., A. Belot, et al. (2009). "Incidence and survival of gastric non-Hodgkin's lymphoma: a population-based study from the Association of the French Cancer Registries (FRANCIM)." *Acta Oncol* **48**(7): 977-83.

**BACKGROUND:** Most epidemiological studies on gastric lymphomas (GL) were carried out before changes in therapy were introduced. The aim of the study was to measure the incidence of GL and to estimate survival. **MATERIAL AND METHODS:** Data were provided by the Association of the French Cancer Registries database. Age-standardized incidence rates were calculated for 786 incident cases diagnosed between 1978 and 2002. Crude and relative survival were calculated for 361 cases diagnosed between 1989 and 1997. Effects specific to sex, age at diagnosis, year of diagnosis, and grade of malignancy were estimated in multivariate analysis. **RESULTS:**

Incidence was stable during the study period. However, high-grade GL frequency increased whereas low-grade and not otherwise specified (NOS) GL frequencies were respectively stable and decreased. At 5 years, relative survival was 63% in men and 60% in women. Patients aged 75 or older had a five-year relative survival of 33%. Age at diagnosis was the only significant prognostic factor in multivariate analysis. Time trend improvement in prognosis was observed. **DISCUSSION:** Results in elderly patients show that therapeutic regimens should be specifically designed and assessed for them. The prognosis improvement trend is probably related to the implementation of changes in management of patients and has to be confirmed by more recent data.

De Bruin, M. L., J. Sparidans, et al. (2009). "Breast cancer risk in female survivors of Hodgkin's lymphoma: lower risk after smaller radiation volumes." *J Clin Oncol* **27**(26): 4239-46.

**PURPOSE:** We assessed the long-term risk of breast cancer (BC) after treatment for Hodgkin's lymphoma (HL). We focused on the volume of breast tissue exposed to radiation and the influence of gonadotoxic chemotherapy (CT). The relative risk remained high after prolonged follow-up (> 30 years after treatment: SIR, 9.5; 95% CI, 4.9 to 16.6). Mantle field irradiation (involving the axillary, mediastinal, and neck nodes) was associated with a 2.7-fold increased risk (95% CI, 1.1 to 6.9) compared with similarly dosed (36 to 44 Gy) mediastinal irradiation alone. Women with  $\geq 20$  years of intact ovarian function after radiotherapy at young ages (< 31 years) experienced significantly higher risks for BC than those with fewer than 10 years of intact ovarian function. **CONCLUSION:** Reduction of radiation volume appears to decrease the risk for BC after HL. In addition, shorter duration of intact ovarian function after irradiation is associated with a significant reduction of the risk for BC.

De Giacomo, T., M. Martelli, et al. (2006). "Lung cancer after treatment for non-Hodgkin lymphoma." *Minerva Chir* **61**(6): 467-71.

**AIM:** Because of the improvement in treatment and survival of patients with lymphoma, late sequelae, including secondary cancers have been extensively studied. Lung cancer is one of the two most common solid tumors after Hodgkin's disease but fewer studies have been published about lung cancer after non-Hodgkin lymphoma (NHL). **METHODS:** Over the last five years at our Institution we have observed 16 patients, 13 male and 3 female, with a mean age of 61 years, previously treated for NHL and lung cancer. Median latency between NHL and lung cancer was 7 years. In 6 patients (37.5%) the

latency period was shorter than 5 years and 3 of them developed lung cancer within 2 years after the end of NHL therapy. RESULTS: Ten patients underwent lung complete resection. Two, 3 and 5 year survival rate was respectively 52.7%, 26.3% and 13%. In contrast, the median survival of non surgical patients was 9 months. Comparison of survival between surgical and non-surgical group demonstrated a statistically significant better survival for surgically treated patients ( $P < 0.04$ ). CONCLUSIONS: Surgery can improve survival in patients with history of NHL and lung cancer. Early diagnosis and treatment is crucial. NHL survivors should undergo careful follow-up and surveillance for secondary malignancy.

de Roover, A., O. Detry, et al. (2006). "Report of two cases of gastric cancer after bariatric surgery: lymphoma of the bypassed stomach after Roux-en-Y gastric bypass and gastrointestinal stromal tumor (GIST) after vertical banded gastroplasty." *Obes Surg* **16**(7): 928-31.

We report two new cases of gastric cancer diagnosed after a bariatric operation. The first case is a 66-year-old male who 3 years after gastric bypass suffered from a perforation of the fundus that was found to be secondary to a diffuse large B-cell lymphoma of the distal stomach. The second case is a 47-year-old woman who presented 12 years after a vertical banded gastroplasty with a gastric pouch outlet obstruction caused by a gastrointestinal stromal tumor (GIST). Based on the few reports of cancer in the literature, analysis of these cases suggests that the main risk of gastric cancer after bariatric surgery comes from the delayed diagnosis of malignancy.

DeAngelo, D. J., D. Yu, et al. (2007). "Nelarabine induces complete remissions in adults with relapsed or refractory T-lineage acute lymphoblastic leukemia or lymphoblastic lymphoma: Cancer and Leukemia Group B study 19801." *Blood* **109**(12): 5136-42.

Nelarabine (506U78) is a soluble pro-drug of 9-beta-D-arabinofuranosylguanine (ara-G), a deoxyguanosine derivative. We treated 26 patients with T-cell acute lymphoblastic leukemia (T-ALL) and 13 with T-cell lymphoblastic lymphoma (T-LBL) with nelarabine. All patients were refractory to at least one multiagent regimen or had relapsed after achieving a complete remission. Nelarabine was administered on an alternate day schedule (days 1, 3, and 5) at 1.5 g/m<sup>2</sup>/day. Cycles were repeated every 22 days. The median age was 34 years (range, 16-66 years); 32 (82%) patients were male. The rate of complete remission was 31% (95% confidence interval [CI], 17%, 48%) and the overall response rate was 41% (95% CI, 26%, 58%). The principal toxicity was grade 3 or 4 neutropenia and thrombocytopenia,

occurring in 37% and 26% of patients, respectively. There was only one grade 4 adverse event of the nervous system, which was a reversible depressed level of consciousness. The median disease-free survival (DFS) was 20 weeks (95% CI, 11, 56), and the median overall survival was 20 weeks (95% CI, 13, 36). The 1-year overall survival was 28% (95% CI, 15%, 43%). Nelarabine is well tolerated and has significant antitumor activity in relapsed or refractory T-ALL and T-LBL.

Engert, A., A. del Giglio, et al. (2009). "Incidence of febrile neutropenia and myelotoxicity of chemotherapy: a meta-analysis of biosimilar G-CSF studies in breast cancer, lung cancer, and non-Hodgkin's lymphoma." *Onkologie* **32**(10): 599-604.

The aim of this meta-analysis of 3 clinical studies, conducted with breast cancer, lung cancer, and non-Hodgkin's lymphoma patients, was to compare a new granulocyte colony-stimulating factor (G-CSF) biosimilar, XM02, with filgrastim in terms of its prophylactic effect on the development of febrile neutropenia (FN) during the first chemotherapy cycle in relation to the myelotoxic potency of the applied chemotherapy regimen. The incidence of FN in the first cycle of chemotherapy under primary G-CSF prophylaxis is low (in the range of 12-16%) and not directly correlated with the myelotoxic potency of the applied chemotherapy regimen. XM02 demonstrated to be non-inferior to filgrastim regarding the incidence of FN, irrespective of the myelotoxicity of the chemotherapy regimen.

Escalon, M. P., N. S. Liu, et al. (2005). "Prognostic factors and treatment of patients with T-cell non-Hodgkin lymphoma: the M. D. Anderson Cancer Center experience." *Cancer* **103**(10): 2091-8.

BACKGROUND: T-cell non-Hodgkin lymphomas (T-NHL) are more aggressive and patients have a poorer prognosis compared with patients with the corresponding B-cell lymphomas. Although intensive treatments have been developed, it is unknown whether they are more effective than CHOP chemotherapy (cyclophosphamide, doxorubicin, oncovorin, and prednisone). METHODS: The authors' retrospective study evaluated the clinical outcome of 135 previously untreated patients with T-NHL who were treated at The University of Texas M. D. Anderson Cancer Center (Houston, TX) between 1996 and 2002. Lymphomas with T-cell histologies with the exception of mycosis fungoides were included. RESULTS: The estimated median overall survival was 46 months. Thirty-seven percent of the patients received CHOP therapy, 48% received intensive therapy, and 15% received other therapy. The estimated 3-year overall survival rates were 62% for

the patients treated with CHOP therapy and 56% for the patients who received intensive therapy. After the exclusion of patients with anaplastic large cell lymphoma (ALCL), who are known to have a better prognosis than patients with other T-NHLs, the estimated 3-year overall survival rates were 43% for the patients treated with CHOP therapy and 49% for the patients who received intensive therapy. Parameters that may be independent prognostic factors for survival in T-NHL, excluding ALCL, included ECOG performance status  $\geq$  2, beta-2-microglobulin level  $>$  2 mg/L, lactate dehydrogenase level higher than normal, bulky disease  $\geq$  7 cm, and a higher international prognostic index and tumor score. CONCLUSIONS: The current study data suggested that patients treated with intensive therapies did not fare better than those treated with CHOP therapy. New treatment regimens need to be developed for patients with T-NHL.

Ferreira, M. J., N. Duarte, et al. (2006). "Interaction between doxorubicin and the resistance modifier stilbene on multidrug resistant mouse lymphoma and human breast cancer cells." *Anticancer Res* **26**(5A): 3541-6.

The hydroxystilbene trans-3,5,3',4'-tetrahydroxystilbene (piceatannol) (1), isolated from the methanol extract of *Euphorbia lagascae* defatted seeds, was methylated to yield the derivatives trans-3,5,3',4'-tetramethoxystilbene (2), (trans-3,5-dihydroxy-3',4'-dimethoxystilbene) (3) and trans-3,5,3'-trihydroxy-4'-methoxystilbene (4). The structures of the compounds were assigned by spectroscopic methods (IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR and MS). The ability of piceatannol (1) and the three methylated derivatives to modulate the transport activity of P-glycoprotein (P-gp) and apoptosis induction on the L5178 mouse lymphoma cell line containing the human MDRI gene was studied by flow cytometry. The results of checkerboard experiments indicated that the type of interaction was additive between doxorubicin and compound 2 on the human MDRI gene-transfected mouse lymphoma cells. However, in the MCF7/dox human breast cancer cells, the interaction was non-additive. The degree of additive and non-additive interactions were close to the borderline of the FIX values corresponding to the two types of interactions.

Friedman, M., K. R. Lee, et al. (2005). "Anticarcinogenic effects of glycoalkaloids from potatoes against human cervical, liver, lymphoma, and stomach cancer cells." *J Agric Food Chem* **53**(15): 6162-9.

Methods were devised for the isolation of large amounts of pure alpha-chaconine and alpha-

solanine from Dejima potatoes and for the extraction and analysis of total glycoalkaloids from five fresh potato varieties (Dejima, Jowon, Sumi, Toya, and Vora Valley). These compounds were then evaluated in experiments using a tetrazolium microculture (MTT) assay to assess the anticarcinogenic effects of (a) the isolated pure glycoalkaloids separately, (b) artificial mixtures of the two glycoalkaloids, and (c) the total glycoalkaloids isolated from each of the five potato varieties. All samples tested reduced the numbers of the following human cell lines: cervical (HeLa), liver (HepG2), lymphoma (U937), stomach (AGS and KATO III) cancer cells and normal liver (Chang) cells. The results show that (a) the effects of the glycoalkaloids were concentration dependent in the range of 0.1-10  $\mu$ g/mL (0.117-11.7 nmol/mL); (b) alpha-chaconine was more active than was alpha-solanine; (c) some mixtures exhibited synergistic effects, whereas other produced additive ones; (d) the different cancer cells varied in their susceptibilities to destruction; and (e) the destruction of normal liver cells was generally lower than that of cancer liver cells. The decreases in cell populations were also observed visually by reversed-phase microscopy. The results complement related observations on the anticarcinogenic potential of food ingredients.

Fritzsche, F. R., S. Pahl, et al. (2006). "Anaplastic large-cell non-Hodgkin's lymphoma of the breast in periprosthetic localisation 32 years after treatment for primary breast cancer--a case report." *Virchows Arch* **449**(5): 561-4.

Primary, as well as secondary, lymphomas of the breast are rare diseases and might, in some cases, be misdiagnosed as breast cancer on routine hematoxylin/eosin stainings. We report a case of an anaplastic large cell lymphoma in a 72-year-old woman with a history of breast cancer treated with breast-ablative surgery and a subsequent silicon implant 32 years ago. Clinically, she presented with an ulceration of the skin, which had developed within a few months. On conventional histology, the tumor cells were mimicking poorly differentiated invasive ductal carcinoma with a prominent leukocytic infiltrate. The immunoprofile of the tumor showed negativity for cytokeratins and led to the diagnosis of a CD30-positive anaplastic large cell lymphoma.

Ganor, Y., I. Grinberg, et al. (2009). "Human T-leukemia and T-lymphoma express glutamate receptor AMPA GluR3, and the neurotransmitter glutamate elevates the cancer-related matrix-metalloproteinases inducer CD147/EMMPRN, MMP-9 secretion and engraftment of T-leukemia in vivo." *Leuk Lymphoma* **50**(6): 985-97.

Glutamate is the major excitatory neurotransmitter of the nervous system. We previously found that glutamate activates normal human T-cells, inducing their adhesion and chemotaxis, via its glutamate receptors of the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) subtype 3 (GluR3) expressed in these cells. Here, we discovered that human T-leukemia (Jurkat) and cutaneous sezary T-lymphoma (HuT-78) cells also express high levels of GluR3. Furthermore, glutamate (10 nM) elevates CD147/EMMPRIN, a cancer-associated matrix metalloproteinases (MMPs) inducer, promoting spread of many tumors. Glutamate-induced CD147 elevation in both cancerous and normal human T-cells was mimicked by AMPA (glutamate/AMPA-receptor agonist) and blocked by CNQX (glutamate/AMPA-receptor antagonist). Importantly, glutamate also increased gelatinase MMP-9 secretion by T-lymphoma. Finally, ex vivo pre-treatment of T-leukemia with glutamate enhanced their subsequent in vivo engraftment into chick embryo liver and chorioallantoic membrane. Together, these findings reveal that glutamate elevates cancer associated proteins and activity in T-cell cancers and by doing so may facilitate their growth and spread, especially to and within the nervous system. If so, glutamate receptors in T-cell malignancies should be blocked.

Ghielmini, M., K. Rufibach, et al. (2005). "Single agent rituximab in patients with follicular or mantle cell lymphoma: clinical and biological factors that are predictive of response and event-free survival as well as the effect of rituximab on the immune system: a study of the Swiss Group for Clinical Cancer Research (SAKK)." *Ann Oncol* **16**(10): 1675-82.

**BACKGROUND:** Predictive factors of rituximab efficacy and its effect on the immune system are still not defined. **PATIENTS AND METHODS:** Three hundred and six patients with follicular or mantle cell lymphoma received four weekly doses of rituximab (induction) and no further treatment (arm A) or four more doses at 2-month intervals (arm B). **RESULTS:** Response rate to induction was 44%. Independent predictive factors for response were disease bulk <5 cm, follicular histology, normal hemoglobin and low lymphocyte count. Factors associated with event-free survival (EFS) were having responded to induction, having received not more than one line of therapy, Ann Arbor stage I-III, high lymphocyte count, disease bulk <5 cm, Fc-gamma receptor genotype VV and receiving prolonged treatment. B cells were suppressed by treatment but recovered after a median of 12 months in arm A and 18 months in arm B. The median IgM level after 1 year was normal in arm A but was

decreased to 73% of baseline in arm B. We observed 24 serious adverse events, equally distributed between arms. Ten patients receiving induction only and six patients receiving prolonged treatment developed a second tumor. **CONCLUSIONS:** We defined the characteristics predicting response and EFS to rituximab. Prolonged treatment results in longer EFS at the cost of a longer reduction in B cell and IgM levels, but without additional clinical toxicity.

Ghielmini, M., S. F. Schmitz, et al. (2005). "Effect of single-agent rituximab given at the standard schedule or as prolonged treatment in patients with mantle cell lymphoma: a study of the Swiss Group for Clinical Cancer Research (SAKK)." *J Clin Oncol* **23**(4): 705-11.

**PURPOSE:** To evaluate the effect of single-agent rituximab given at the standard or a prolonged schedule in patients with newly diagnosed, or refractory or relapsed mantle cell lymphoma (MCL). **PATIENTS AND METHODS:** After induction treatment with the standard schedule (375 mg/m<sup>2</sup> weekly x 4), patients who were responding or who had stable disease at week 12 from the start of treatment were randomly assigned to no further treatment (arm A) or prolonged rituximab administration (375 mg/m<sup>2</sup>) every 8 weeks for four times (arm B). **RESULTS:** The trial enrolled 104 patients. After induction, clinical response was 27% with 2% complete responses. Among patients with detectable t(11;14)-positive cells in blood and bone marrow at baseline, four of 20, and one of 14, respectively, became polymerase chain-reaction-negative after induction. Anemia was the only adverse predictor of response in the multivariate analysis. After a median follow-up of 29 months, response rate and duration of response were not significantly different between the two schedules in 61 randomly assigned patients. Median event-free survival (EFS) was 6 months in arm A versus 12 months in arm B; the difference was not significant (P = .1). Prolonged treatment seemed to improve EFS in the subgroup of pretreated patients (5 months in arm A v 11 months in arm B; P = .04). Thirteen percent of patients in arm A and 9% in arm B presented with grade 3 to 4 hematologic toxicity. **CONCLUSION:** Single-agent rituximab is active in MCL, but the addition of four single doses at 8-week intervals does not seem to significantly improve response rate, duration of response, or EFS after treatment with the standard schedule.

Goldspiel, B. R. (2004). "Chemotherapy dose density in early-stage breast cancer and non-Hodgkin's lymphoma." *Pharmacotherapy* **24**(10): 1347-57.

Delivering standard-dose chemotherapy on schedule is important for survival in early-stage breast

cancer and non-Hodgkin's lymphoma. Trials of dose-escalated regimens, in which higher-than-standard doses of chemotherapy are used, have produced equivocal results. In contrast, dose-dense regimens, in which standard doses are given with shorter (usually 14-day) intervals between cycles, have been more efficacious than standard 21-day regimens in trials in both early-stage breast cancer and non-Hodgkin's lymphoma. Furthermore, a shorter course of chemotherapy is likely to cause less disruption in patients' lives. Despite the evidence of the importance of maintaining chemotherapy dose intensity (the amount of drug administered/unit of time), undertreatment of patients with early-stage breast cancer and non-Hodgkin's lymphoma is common. Neutropenia is the primary dose-limiting toxicity of many chemotherapy regimens, and it is frequently managed by dose reductions and delays that decrease dose intensity. Colony-stimulating factors reduce the prevalence and severity of neutropenia and its complications, and their proactive use can improve adherence to the planned schedule of both standard-dose and dose-dense chemotherapy. The promising results with dose-dense chemotherapy in early-stage breast cancer and non-Hodgkin's lymphoma indicate that it should be tested in patients with other chemosensitive tumors.

Green, L. D., L. Mack, et al. (2006). "Anaplastic thyroid cancer and primary thyroid lymphoma: a review of these rare thyroid malignancies." *J Surg Oncol* **94**(8): 725-36.

**BACKGROUND:** To review the current literature on the treatment of anaplastic thyroid cancer (ATC) and thyroid lymphoma (TL). **RESULTS:** Both anaplastic carcinoma (ATC) and TL represent rare forms of thyroid cancer. ATC behaves in a highly aggressive manner, resulting in significant morbidity and mortality. Multimodality therapy consisting of both radiotherapy (RT) and chemotherapy is essential in obtaining local/regional control. Although ATC has been relatively chemo resistant, newer agents such like taxotere show promise. The role of surgery in the treatment of ATC continues to evolve, presently it should be reserved for patients who have shown an initial response to multimodality therapy and in patients in whom a complete macroscopic resection can be achieved with minimal morbidity. The successful treatment of TL currently lies in accurately diagnosing the histological subtype. Both large B-cell and mixed lymphomas are best treated with multimodality therapy consisting of CHOP combined with hyper-fractionated RT. MALT lymphomas with their more indolent course may be amenable to single modality RT or total thyroidectomy if diagnosed at an early stage. **DISCUSSION:** Although both ATC

and TL are rare, it is important for surgeons to be aware of the need for multimodality therapy when treating these patients and to understand the limited role surgery plays in diagnosis and treatment.

Hainsworth, J. D., S. Litchy, et al. (2003). "Single-agent rituximab as first-line and maintenance treatment for patients with chronic lymphocytic leukemia or small lymphocytic lymphoma: a phase II trial of the Minnie Pearl Cancer Research Network." *J Clin Oncol* **21**(9): 1746-51.

**PURPOSE:** To assess the efficacy and toxicity of first-line single-agent rituximab, followed by re-treatment with rituximab at 6-month intervals, in previously untreated patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). **PATIENTS AND METHODS:** Forty-four previously untreated patients with CLL/SLL received rituximab 375 mg/m<sup>2</sup> weekly for 4 consecutive weeks. All patients were required to have one or more indications for treatment. Patients with objective response or stable disease continued to receive identical 4-week rituximab courses at 6-month intervals, for a total of four courses. **RESULTS:** The objective response rate after the first course of rituximab was 51% (4% complete responses). Twenty-eight patients received one or more additional courses of rituximab. At present, the overall response rate is 58%, with 9% complete responses. After a median follow-up of 20 months, the median progression-free survival (PFS) time was 18.6 months, and the 1- and 2-year PFS rates were 62% and 49%, respectively. Treatment was well tolerated, with only two episodes of grade 3 to 4 infusion-related toxicity. No cumulative toxicity or opportunistic infections occurred. **CONCLUSION:** Single-agent rituximab, used at a standard dose and schedule, is active in the first-line treatment of patients with CLL/SLL, producing substantially higher response rates than previously reported in relapsed or refractory patients (51% v 13%, respectively). Re-treatment with rituximab at 6-month intervals is well tolerated. The PFS time of 18.6 months in patients with CLL/SLL seems shorter than the 36- to 40-month median PFSs previously reported with first-line plus maintenance rituximab in patients with follicular lymphoma. Additional follow-up is required to fully assess the impact of this treatment strategy.

Hainsworth, J. D., S. Litchy, et al. (2005). "Rituximab plus short-duration chemotherapy as first-line treatment for follicular non-Hodgkin's lymphoma: a phase II trial of the minnie pearl cancer research network." *J Clin Oncol* **23**(7): 1500-6.

**PURPOSE:** To evaluate the feasibility and efficacy of rituximab with short-duration

chemotherapy in the first-line treatment of patients with follicular non-Hodgkin's lymphoma (NHL). **PATIENTS AND METHODS:** Patients with previously untreated stage II-IV follicular NHL, grade 1 or 2, were eligible for this multicenter phase II trial. All patients received four weekly doses of rituximab (375 mg/m<sup>2</sup> intravenous), followed by three courses of combination chemotherapy (either cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP], or cyclophosphamide, vincristine, and prednisone [CVP]) plus rituximab. Patients were evaluated for response after completing treatment, and were then followed up at 3-month intervals. **RESULTS:** Between January 2000 and July 2001, 86 patients were treated. Eight-two patients (95%) completed treatment; no patient was withdrawn due to toxicity. The overall response rate was 93%, with 55% complete responses. After a median follow-up of 42 months, the 3- and 4-year actuarial progression-free survivals were 71% and 62%, respectively. Five patients (6%) died from lymphoma; the overall actuarial survival at 3 years was 95%. Grade 3/4 leukopenia occurred in 53% of patients, but only six patients (7%) had neutropenia or fever. Grade 3/4 nonhematologic toxicities were uncommon. **CONCLUSION:** Rituximab plus short-course chemotherapy is well tolerated as first-line treatment for patients with follicular NHL. The overall and complete response rates are similar to those reported with chemotherapy/rituximab combinations of longer duration. The actuarial progression-free survival of 62% at 4 years is encouraging, but further follow-up is necessary. Rituximab plus short-course chemotherapy may prove to be as effective as longer-duration chemotherapy and currently provides an attractive option for first-line treatment of elderly patients and others who tolerate chemotherapy poorly.

Hainsworth, J. D., S. Litchy, et al. (2005). "Maximizing therapeutic benefit of rituximab: maintenance therapy versus re-treatment at progression in patients with indolent non-Hodgkin's lymphoma--a randomized phase II trial of the Minnie Pearl Cancer Research Network." *J Clin Oncol* **23**(6): 1088-95.

**PURPOSE:** To compare the benefit of maintenance rituximab therapy versus rituximab re-treatment at progression in patients with previously treated indolent non-Hodgkin's lymphoma. **PATIENTS AND METHODS:** Between June 1998 and August 2002, 114 patients who had received previous chemotherapy for indolent non-Hodgkin's lymphoma were treated with a standard 4-week course of rituximab. Patients with objective response or stable disease were randomly assigned to receive either maintenance rituximab therapy (standard 4-

week courses administered at 6-month intervals) or rituximab re-treatment at the time of lymphoma progression. The duration of rituximab benefit was measured from the date of first rituximab treatment until the date other treatment was required. **RESULTS:** Ninety (79%) of 114 patients had objective response or stable disease after initial rituximab treatment, and were randomly assigned to treatment. Progression-free survival was prolonged in the maintenance group (31.3 v 7.4 months; P = .007). Final overall and complete response rates were higher in the maintenance group. Duration of rituximab benefit was similar in the maintenance and re-treatment groups (31.3 v 27.4 months, respectively). More maintenance patients remain in continuous remission, and more are currently in complete remission. Both treatment approaches were well tolerated. **CONCLUSION:** In patients who have objective response or stable disease with single-agent rituximab therapy, duration of rituximab benefit is substantially prolonged with either scheduled maintenance treatment or rituximab re-treatment at the time of progression. At present, the magnitude of benefit with either approach appears similar. However, additional follow-up of this trial is required, and completion of phase III randomized trials is necessary to definitively answer this question.

Hainsworth, J. D., E. R. Vazquez, et al. (2008). "Combination therapy with fludarabine and rituximab followed by alemtuzumab in the first-line treatment of patients with chronic lymphocytic leukemia or small lymphocytic lymphoma: a phase 2 trial of the Minnie Pearl Cancer Research Network." *Cancer* **112**(6): 1288-95.

**BACKGROUND:** The purpose of the current study was to evaluate the efficacy and toxicity of the combination of fludarabine and rituximab, followed by alemtuzumab, as first-line treatment for patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). **METHODS:** In a nonrandomized phase 2 trial, 41 patients who had previously untreated CLL or SLL and required treatment received 4 cycles of the fludarabine and rituximab combination followed 5 weeks later by 4 weeks (12 doses) of intravenous alemtuzumab therapy. The response to treatment was evaluated after completion of treatment with fludarabine and rituximab, and again after the completion of alemtuzumab consolidation. **RESULTS:** Initial treatment with the combination of fludarabine and rituximab was well tolerated, and produced a 71% overall response rate (13% complete response). Thirty-four patients began treatment with intravenous alemtuzumab, but this drug was relatively poorly tolerated when given at a short interval after

fludarabine and rituximab, and only 20 patients (49% of total) were able to complete the prescribed course. Five patients had an improvement in their response with alemtuzumab; the final complete response rate was 21%. The median progression-free survival for the entire group was 42 months. Toxicity with alemtuzumab included infusion-related toxicity, myelosuppression, and opportunistic infections. CONCLUSIONS: The intravenous schedule of alemtuzumab employed in the trial was relatively poorly tolerated in this community-based trial. The relatively low complete response rates after treatment with the combination of fludarabine and rituximab and after the completion of treatment suggest that these abbreviated courses may compromise efficacy. The generalized use of alemtuzumab as consolidation therapy cannot yet be recommended for community practice. However, optimization of the route of administration, duration of treatment, and interval after completion of induction therapy may improve efficacy, and further investigation is ongoing.

Hall, G. W., N. Katzilakis, et al. (2007). "Outcome of children with nodular lymphocyte predominant Hodgkin lymphoma - a Children's Cancer and Leukaemia Group report." *Br J Haematol* **138**(6): 761-8.

This report describes the clinical outcomes and follow-up records of 42 children with nodular lymphocyte predominant Hodgkin lymphoma (LPHL) treated on United Kingdom Children's Cancer Study Group (UKCCSG) HD1 (1982-1992) and HD2 protocols (1992-2000). The clinical records of 42 children with LPHL treated between 1982 and 2000 were reviewed retrospectively. All 42 had histology reviewed centrally and confirmed as LPHL by an expert panel. In both trials, only patients with stage IA disease had the option of being treated with either involved field radiation alone or combination chemotherapy consisting of chlorambucil, vinblastine, procarbazine and prednisolone (ChlVPP). Patients with all other stages were treated with ChlVPP chemotherapy. Thirty-five patients (83%) presented with early stage disease (Stages I & II). All 42 patients achieved a complete remission (CR). Six children relapsed after primary therapy. The 5- and 10-year relapse-free survival rates were 87% and 82% respectively. Forty-one are currently alive in CR. In conclusion, children with low-stage LPHL treated between 1982 and 2000 according to the UK strategy for classical Hodgkin lymphoma (HL) had an excellent prognosis. There have been no second malignancies or transformations to B-cell non-Hodgkin lymphoma.

Hardell, L. (2008). "Pesticides, soft-tissue sarcoma and non-Hodgkin lymphoma--historical aspects on the precautionary principle in cancer prevention." *Acta Oncol* **47**(3): 347-54.

BACKGROUND: After the 2(nd) World War a long range of chemical agents have been introduced on the market, both in Sweden and most other countries. From the 1950's several pesticides gained increasing use in agriculture and forestry. In the 1970's public concern increased in Sweden especially regarding use of phenoxy herbicides to combat deciduous wood, although statements from different authorities were reassuring of the safety. MATERIALS AND METHODS: At the end of the 1970's the author and his colleagues published the first scientific evidence of an association between exposure to phenoxyacetic acids, chlorophenols and certain malignant tumours, i.e., soft-tissue sarcoma and malignant lymphoma. The study subjects were also exposed to contaminating dioxins such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Later studies showed also an association between certain persistent organic pollutants such as polychlorinated biphenyls and non-Hodgkin lymphoma (NHL) with an interaction with titers of antibodies to Epstein-Barr virus early antigen. These results have been corroborated in other studies. DISCUSSION: Over the years industry and its allied experts have attacked our studies, but in 1997 IARC classified TCDD as a human carcinogen, Group I. The increasing incidence of NHL in Sweden levelled off about 1990. The author postulated that the regulation or ban of the use of chlorophenols, certain phenoxy herbicides and some persistent organic pollutants in Sweden back in the 1970s has contributed to the now decreasing incidence of NHL. Unfounded criticism from industry experts may prohibit the precautionary principle and early warnings of cancer risk can be ignored. Cancer risks by certain chlorinated phenols may serve as a model of how the precautionary principle should be used by taking early warnings seriously.

Hardell, L. and M. Eriksson (2003). "Is the decline of the increasing incidence of non-Hodgkin lymphoma in Sweden and other countries a result of cancer preventive measures?" *Environ Health Perspect* **111**(14): 1704-6.

Is the decline of the increasing incidence of non-Hodgkin lymphoma (NHL) in Sweden and other countries a result of cancer preventive measures? The yearly age-standardized incidence of NHL increased significantly in Sweden during 1971-1990, for men an average of 3.2% and for women 3.1%. The corresponding figures for 1991-2000 were -0.8% and -0.2%, respectively. A decline of the increasing incidence has also been seen in other countries, such

as the United States, Finland, and Denmark. Immunosuppression is one established risk factor for NHL, possibly with interaction with Epstein-Barr virus. Phenoxyacetic acids and chlorophenols, both pesticides, have been associated with NHL. Use of these chemicals was banned in Sweden in 1977 and 1978, respectively. Also, persistent organic pollutants such as polychlorinated biphenyls, hexachlorobenzene, chlordanes, and dioxins have been shown to increase the risk. Exposure of the whole population occurs predominantly through the food chain. Exposure to such chemicals was highest in the 1960s and 1970s. Because of regulation in the 1970s, exposure has declined substantially in the population. The change in incidence of NHL in Sweden and other countries may serve as a good example of how prohibition and limitation of exposure may be reflected in cancer statistics some decades later.

Hemminki, K., Y. Jiang, et al. (2003). "Skin cancer and non-Hodgkin's lymphoma as second malignancies. markers of impaired immune function?" *Eur J Cancer* **39**(2): 223-9.

Successes in cancer therapy have led to increasing numbers of cancer survivors, who are at risk of developing second primary cancers. Therapy- or disease-induced suppression of the immune function may predispose cancer patients to a second malignancy. An excess of squamous cell skin cancers (SCC) and non-Hodgkin's lymphomas has been found in immunosuppressed patients. We used the nationwide Swedish Family-Cancer Database on 10.2 million individuals to calculate the risk of second primary skin cancers and non-Hodgkin's lymphomas following a previous malignancy. A total of 4301 second skin cancers and 1672 non-Hodgkin's lymphomas were identified. Standardised incidence ratios (SIRs) and 95% Confidence Intervals (CIs) were calculated and compared. Among 14 different sites for male or female first primary malignancies, 11 of these sites were followed by an increased risk of skin cancer (SIRs for males for risk of skin cancer as a second primary cancer: 14.1 for SCC; 9.7 for melanoma; 6.1 for leukaemia as the first site; SIRs for females for risk of skin cancer: 14.6 for SCC; 6.8 for larynx; 6.2 for upper aerodigestive tract (UADT) as the first site). The risk of non-Hodgkin's lymphoma was increased after 10 of 14 different male neoplasms and 12 of 17 different female neoplasms. (SIRs for males for risk of non-Hodgkin's lymphoma as a second primary cancer: 6.4 for non-Hodgkin's lymphoma; 3.2 for leukaemias; 3.1 for multiple myeloma as the first site; SIRs for females for risk of non-Hodgkin's lymphoma as a second primary cancer: 12.5 for leukaemias; 7.0 for Hodgkin's disease; 3.6 for

UADT as the first site). The high, and after certain sites, very high risks of second skin cancer and non-Hodgkin's lymphoma suggest that immune suppression may be a contributory mechanism.

Hill, D. A., E. Gilbert, et al. (2005). "Breast cancer risk following radiotherapy for Hodgkin lymphoma: modification by other risk factors." *Blood* **106**(10): 3358-65.

The importance of genetic and other risk factors in the development of breast cancer after radiotherapy (RT) for Hodgkin lymphoma (HL) has not been determined. We analyzed data from a breast cancer case-control study (105 patients, 266 control subjects) conducted among 3 817 survivors of HL diagnosed at age 30 years or younger in 6 population-based cancer registries. Odds ratios (ORs) and excess relative risks (ERRs) were calculated using conditional regression. Women who received RT exposure ( $> \text{ or } = 5$  Gy radiation dose to the breast) had a 2.7-fold increased breast cancer risk (95% confidence interval (CI) 1.4-5.2), compared with those given less than 5 Gy. RT exposure ( $> \text{ or } = 5$  Gy) was associated with an OR of 0.8 (95% CI, 0.2-3.4) among women with a first- or second-degree family history of breast or ovarian cancer, and 5.8 (95% CI, 2.1-16.3) among all other women (interaction  $P = .03$ ). History of a live birth appeared to increase the breast cancer risk associated with RT among women not treated with ovarian-damaging therapies. Breast cancer risk following RT varied little according to other factors. The additional increased relative risk of breast cancer after RT for HL is unlikely to be larger among women with a family history of breast or ovarian cancer than among other women.

Hoang-Xuan, K., L. Taillandier, et al. (2003). "Chemotherapy alone as initial treatment for primary CNS lymphoma in patients older than 60 years: a multicenter phase II study (26952) of the European Organization for Research and Treatment of Cancer Brain Tumor Group." *J Clin Oncol* **21**(14): 2726-31.

**PURPOSE:** To assess the efficacy and toxicity of chemotherapy alone in patients older than 60 years with primary CNS lymphoma. **PATIENTS AND METHODS:** Fifty patients with a median age of 72 years and a median Karnofsky performance score (KPS) of 50 were eligible for this multicenter phase II study. The protocol consisted of high-dose methotrexate (MTX), lomustine, procarbazine, methylprednisolone, and intrathecal chemotherapy with MTX and cytarabine. The patients received one induction cycle; if objective response was achieved, five additional maintenance cycles were administered every 6 weeks. The median follow-up of patients was 3 years. **RESULTS:** Twenty four patients (48%)

achieved an objective response (complete response [CR], 42%; partial response, 6%), with a median duration of CR of 27 months (range, 3 to 47+ months). Overall median survival time was 14.3 months, and 1-year progression-free survival was 40% (95% confidence interval [CI], 26% to 53%). Myelosuppression was the most frequent side effect, with grade 3 to 4 neutropenia in 19% of patients. One patient died during chemotherapy, as a result of pulmonary embolism. Most patients improved or preserved their cognitive functions (47% and 45% of the patients, respectively) and KPS (36% and 52% of the patients, respectively) until relapse, whereas cognitive and KPS decline attributed to delayed treatment neurotoxicity occurred in 8% and 12% patients, respectively. **CONCLUSION:** In the elderly, this chemotherapy regimen compares favorably with radiotherapy (RT) alone and reduces considerably the risk of delayed neurotoxicity associated with combined chemoradiotherapy. Chemotherapy alone is an appropriate strategy in older patients to delay or avoid RT.

Hodgson, D. C., E. S. Gilbert, et al. (2007). "Long-term solid cancer risk among 5-year survivors of Hodgkin's lymphoma." *J Clin Oncol* **25**(12): 1489-97.

**PURPOSE:** Hodgkin's lymphoma (HL) survivors are known to be at substantially increased risk of solid cancers (SC). However, no investigation has used multivariate modeling to estimate the relative risk (RR), excess absolute risk (EAR), and cumulative incidence for specific attained ages and ages at HL diagnosis. **PATIENTS AND METHODS:** We identified 18,862 5-year HL survivors from 13 population-based cancer registries in North America and Europe. Poisson regression was used to evaluate the effects of age at diagnosis, attained age, latency, sex, treatment, and year of diagnosis on the RR and EAR of SC. **RESULTS:** Among 1,490 identified SC, 850 were estimated to be in excess. For most cancer sites, both RR and EAR decreased with age at HL diagnosis and showed strong dependencies on attained age. For a patient diagnosed at age 30 years and survived to  $>$  or  $=$  40 years, modeled risks were significantly elevated for cancers of the breast (RR = 6.1), other supradiaphragmatic sites (RR = 6.0), and infradiaphragmatic sites (RR = 3.7); the largest RR (20-fold) was observed for malignant mesothelioma. Thirty-year cumulative risks of SC for men and women diagnosed at 30 years were 18% and 26%, respectively, compared with 7% and 9%, respectively, in the general population. For young HL patients, risks of breast and colorectal cancers were elevated 10 to 25 years before the age when routine screening would be recommended in the general population. **CONCLUSION:** Multivariable modeling

demonstrates for the first time temporal changes in SC risk not evident in unadjusted analyses, and can facilitate the development of individualized risk assessment and the creation of screening strategies for early detection.

Hodgson, D. C., E. S. Koh, et al. (2007). "Individualized estimates of second cancer risks after contemporary radiation therapy for Hodgkin lymphoma." *Cancer* **110**(11): 2576-86.

**BACKGROUND:** Estimates of radiation-related second cancer risk among Hodgkin lymphoma survivors are largely based on radiation therapy (RT) fields and doses no longer in use, and these estimates do not account for differences in normal tissue dose among individual patients. This study gives individualized estimates for the risks of lung and female breast cancer expected with contemporary involved-field RT and low-dose (20 Gy) RT for mediastinal Hodgkin lymphoma. **METHODS:** Three RT plans were constructed for 37 consecutive patients with mediastinal Hodgkin lymphoma: 35 Gy mantle RT, 35 Gy involved-field RT (IFRT), and 20 Gy IFRT. For each of the 111 RT plans, individual-level dosimetry data were incorporated into a cell initiation/inactivation/proliferation model to estimate the excess relative risk (ERR) and cumulative incidence of radiation-induced second cancer. **RESULTS:** ERR estimates were compatible with results of epidemiological studies. Compared with 35 Gy mantle radiation therapy, 35 Gy IFRT was predicted to reduce the 20-year ERRs of breast and lung cancer by 63% and 21%, respectively, primarily because of lower normal tissue doses with the omission of axillary RT. Low-dose (20 Gy) IFRT was associated with a 77% and 57% decrease in these ERRs. Patient-specific differences in normal tissue dose with IFRT led to 11-fold and 3.6-fold variations among individual's estimates of breast and lung cancer ERR, respectively. **CONCLUSIONS:** Contemporary IFRT is predicted to substantially reduce risk of secondary breast and lung cancer compared with mantle RT, with considerable variation in risk among individuals. Individualized prospective risk estimates could facilitate patient-specific counseling and the development of more effective RT techniques.

Hoskin, P. J., L. Lowry, et al. (2009). "Randomized comparison of the stanford V regimen and ABVD in the treatment of advanced Hodgkin's Lymphoma: United Kingdom National Cancer Research Institute Lymphoma Group Study ISRCTN 64141244." *J Clin Oncol* **27**(32): 5390-6.

**PURPOSE:** This multicenter, prospective, randomized controlled trial compared the efficacy and toxicity of two chemotherapy regimens in advanced

Hodgkin's lymphoma (HL): the weekly alternating Stanford V and the standard, twice-weekly regimen of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). PATIENTS AND METHODS: Patients had stage IIB, III, or IV disease or had stages I to IIA disease with bulky disease or other adverse features. Radiotherapy was administered in both arms to sites of previous bulk (> 5 cm) and to splenic deposits, although this was omitted in the latter part of the trial for patients achieving complete remission (CR) in the ABVD arm. A total of 520 patients were randomly assigned and were assessed for the primary outcome measure of progression-free survival (PFS). Five hundred patients received protocol treatment, and radiotherapy was administered to 73% in the Stanford V arm and to 53% in the ABVD arm. RESULTS: The overall response rates after completion of all treatment were 91% for Stanford V and 92% for ABVD. During a median follow-up of 4.3 years, there was no evidence of a difference in projected 5-year PFS and overall survival (OS) rates (76% and 90%, respectively, for ABVD; 74% and 92%, respectively, for Stanford V). More pulmonary toxicity was reported for ABVD, whereas other toxicities were more frequent with Stanford V. CONCLUSION: In a large, randomized trial, the efficacies of Stanford V and ABVD were comparable when given in combination with appropriate radiotherapy.

Howell, S. J., C. Searle, et al. (2009). "The UK national breast cancer screening programme for survivors of Hodgkin lymphoma detects breast cancer at an early stage." *Br J Cancer* **101**(4): 582-8.

**BACKGROUND:** Supradiaphragmatic radiotherapy (SRT) to treat Hodgkin's lymphoma (HL) at a young age increases the risk of breast cancer (BC). A national notification risk assessment and screening programme (NRASP) for women who were treated with SRT before the age of 36 years was instituted in the United Kingdom in 2003. In this study, we report the implementation and screening results from the largest English Cancer Network. **METHODS:** A total of 417 eligible women were identified through cancer registry/hospital databases and from follow-up (FU) clinics. Screening results were collated retrospectively, and registry searches were used to capture BC cases. **RESULTS:** Of the 417 women invited for clinical review, 243 (58%) attended. Of these 417 women, 23 (5.5%) have been diagnosed with BC, a standardised incidence ratio of 2.9 compared with the age-matched general population. Of five invasive BCs diagnosed within the NRASP, none involved axillary lymph nodes compared with 7 of 13 (54%) diagnosed outside the programme ( $P < 0.10$ ). The mean latency for BC cases was 19.5+/-8.35 years and the mean FU duration for

those unaffected by BC was 14.6+/-9.11 years ( $P < 0.01$ ), suggesting that those unaffected by BC remain at high risk. Recall and negative biopsy rates were acceptable (10.5 and 0.8%, respectively). **CONCLUSIONS:** The NRASP appears to detect BC at an early stage with acceptable biopsy rates, although numbers are small. Determination of NRASP results on a national basis is required for the accurate evaluation of screening efficacy in women previously treated with SRT.

Hsi, E. D., S. H. Jung, et al. (2008). "Ki67 and PIM1 expression predict outcome in mantle cell lymphoma treated with high dose therapy, stem cell transplantation and rituximab: a Cancer and Leukemia Group B 59909 correlative science study." *Leuk Lymphoma* **49**(11): 2081-90.

The proliferation index in mantle cell lymphoma (MCL) has not been validated in the context of aggressive therapy regimens in the rituximab era. We assessed Ki67 and PIM1 (a cell cycle-related gene upregulated in blastoid MCL) expression by immunohistochemistry in a phase II study Cancer and Leukemia Group B 59909 of aggressive chemotherapy and rituximab followed by autologous stem cell transplantation plus rituximab in untreated MCL patients <70 years of age. As a continuous variable or using a cutoff of 35%, higher image analysis (IA Ki67,  $n = 52$ ) was associated with shorter progression free survival (PFS) ( $P < \text{or} = 0.030$ ) and event free survival (EFS) ( $P < \text{or} = 0.017$ ). PIM1 expression ( $n = 50$ ) was associated with PFS ( $P = 0.033$ ) and EFS ( $P = 0.043$ ). Bivariate Cox models showed IA Ki67 and PIM1 were independent of clinical factors. High Ki67 (>35%) is an important independent prognostic marker in aggressively treated MCL in the rituximab era. PIM1 expression predicts poor outcome and, given its potential role as a therapeutic target, deserves further study.

Hsu, F. Y., Y. Zhao, et al. (2007). "Downregulation of NPM-ALK by siRNA causes anaplastic large cell lymphoma cell growth inhibition and augments the anti cancer effects of chemotherapy in vitro." *Cancer Invest* **25**(4): 240-8.

The fusion protein, nucleophosmin-anaplastic lymphoma kinase (NPM-ALK), results from the chromosome translocation t(2;5)(p23;q25) and is present in 50-70 percent of anaplastic large-cell lymphomas (ALCLs). NPM-ALK is a constitutively activated kinase that transforms cells through stimulating several mitogenic signaling pathways. To examine if the NPM-ALK is a potential therapeutic target in ALCL, we used siRNA to specifically downregulate the expression of the NPM-ALK in ALCL cell lines. In this report, we demonstrated

viability loss in t(2;5)-positive ALCL cell lines, SUDHL-1 and Karpas 299 cells, but not in lymphoma cell lines without the chromosome translocation, Jurkat and Granta 519 cells. Further study demonstrated that the downregulation of NPM-ALK resulted in decreased cell proliferation and increased cell apoptosis. When used in combination with chemotherapeutic agents, such as doxorubicin, the inhibition of the NPM-ALK augments the chemosensitivity of the tumor cells. These results revealed the importance of continuous expression of NPM-ALK in maintaining the growth of ALCL cells. Our data also suggested that the repression of the fusion gene might be a potential novel therapeutic strategy for NPM-ALK positive ALCLs.

Hudis, C. A. and N. Schmitz (2004). "Dose-dense chemotherapy in breast cancer and lymphoma." *Semin Oncol* **31**(3 Suppl 8): 19-26.

Adjuvant combination chemotherapy reduces the risk of relapse and death for patients with invasive breast cancer and adds to the benefits obtained with hormonal treatment. Generally, anthracycline-containing regimens are superior to non-anthracycline regimens, treatments longer than 6 months are not advantageous and high-dose chemotherapy regimens, which require autologous hematopoietic stem cell support, have not proved consistently superior. The development and evaluation of the taxanes was highly anticipated as they have shown high levels of efficacy while appearing to be non-cross-resistant with partially non-overlapping toxicities. A role for taxanes in the adjuvant or neoadjuvant setting is now widely acknowledged, although they are not currently approved for treatment of early breast cancer in Europe. In patients with aggressive lymphoma who receive cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy, 40% to 70% of patients attain a complete remission, depending on risk factors such as age and extranodal involvement. Second- and third-generation regimens like m-BACOD (methotrexate, bleomycin, cyclophosphamide, etoposide), Pro-MACE-CytaBOM (prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine, methotrexate), and MACOP-B (methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin) have largely failed to improve treatment outcome. The use of monoclonal anti-CD20 antibodies or dose escalation have shown promising results in improving relapse-free and survival rates. In patients with breast cancer, the key Cancer and Leukemia Group B 9741 trial showed that dose-dense doxorubicin, cyclophosphamide, and paclitaxel chemotherapy with granulocyte colony-stimulating

factor (G-CSF), repeated every 2 weeks, is superior to the same regimen administered at standard 3-weekly intervals. In lymphoma, dose-dense CHOP chemotherapy has shown superiority over standard CHOP regimens, particularly in elderly patients with aggressive non-Hodgkin's lymphoma. G-CSF factor is essential to enable the administration of dose-dense chemotherapy and any reduction in its use leads to significant increases in infectious complications. Current evidence suggests that dose-dense chemotherapy, enabled by G-CSF, is an important breakthrough in the evolution of chemotherapy for breast cancer and lymphoma.

Igdem, S., S. Okkan, et al. (2008). "Cervical cancer coexisting with small lymphocytic lymphoma detected during positron emission tomography/computed tomography simulation: a case report." *Eur J Gynaecol Oncol* **29**(4): 405-7.

**BACKGROUND:** Positron emission tomography (PET)/computed tomography (CT) simulation in cervical cancer may help radiation oncologists to better define the target volumes. It may also detect extrapelvic lesions and incidental second malignancies, leading to significant changes in treatment management. **CASE:** A 63-year-old woman who was deemed inoperable due to carcinoma of the cervical stump extending to the parametria and paraaortic lymph nodes detected on MR images presented for extended field radiotherapy. PET/CT simulation revealed an FDG avid mass in the cervical stump, and an enlarged axillary lymphadenopathy showing moderate FDG uptake. The excisional biopsy was consistent with small lymphocytic lymphoma (SLL). **CONCLUSION:** In our case, PET/CT simulation not only led to changes in treatment management, but also revealed a very rare coexistence of SLL and invasive squamous cell carcinoma of the cervix.

Imataki, O., Y. Tamai, et al. (2009). "The utility of FDG-PET for managing patients with malignant lymphoma: analysis of data from a single cancer center." *Intern Med* **48**(17): 1509-13.

**OBJECTIVE:** (18)F-fluorodeoxyglucose (FDG) positron-emission tomography (PET) has been widely applied to malignant lymphoma both for initial staging and response evaluation. The objective is to compare the efficacy of the less common, but more easily implemented modality, CT, with that of FDG. **METHODS:** We retrospectively reviewed consecutive patients diagnosed with malignant lymphoma in our hospital between October 2002 and March 2006, and compared the efficacy of FDG-PET and CT. The standard reference was defined by the pathology and clinical course of patients followed for more than 3

months. RESULTS: Thirty-three cases for staging and 62 cases for response evaluation after treatment were included. We calculated the sensitivity and specificity of each modality. The accuracy of the diagnostic modality was evaluated using receiver operating characteristic (ROC) analysis. The sensitivity and specificity of the initial staging were 87% and 100% on CT evaluation and 87% and 100% on FDG-PET, respectively. Sensitivity and specificity of the re-staging were 81% and 78% on CT evaluation and 82% and 97% on FDG-PET, respectively. The diagnostic accuracy of FDG-PET was comparable with that of CT both in initial staging and response evaluation. The maximum standardized uptake value was not associated with patient survival. In subgroup analysis, a tendency of lower sensitivity in the initial staging was found in FDG-PET for follicular lymphoma and CT for diffuse large B-cell lymphoma. CONCLUSION: Although different staging procedures appear better suited to certain subtypes of lymphoma, in general CT imaging might be as useful as FDG-PET in initial staging in selected patients.

Inoue, Y., H. Tamaki, et al. (2007). "False-positive FDG-PET findings due to bone metastasis from prostate cancer in staging of non-Hodgkin's lymphoma." *Eur J Haematol* **79**(1): 88-90.

Inwards, D. J., P. A. Fishkin, et al. (2008). "Long-term results of the treatment of patients with mantle cell lymphoma with cladribine (2-CDA) alone (95-80-53) or 2-CDA and rituximab (N0189) in the North Central Cancer Treatment Group." *Cancer* **113**(1): 108-16.

BACKGROUND: The objective of this study was to test cladribine (2-CDA) alone and in combination with rituximab in patients with mantle cell lymphoma (MCL). METHODS: Patients with MCL were treated on 2 sequential trials. In Trial 95-80-53, patients received 2-CDA as initial therapy or at relapse. In Trial N0189, patients received combination 2-CDA and rituximab as initial therapy. In both trials, 2-CDA was administered at a dose of 5 mg/m<sup>2</sup> intravenously on Days 1 through 5 every 4 weeks for 2 to 6 cycles, depending on response. In Trial N0189, rituximab 375 mg/m<sup>2</sup> was administered on Day 1 of each cycle. RESULTS: Results were reported for 80 patients. Twenty-six previously untreated patients and 25 patients who had recurrent disease with a median age of 68 years received single-agent 2-CDA. The overall response rate (ORR) was 81% with 42% complete responses (CRs) in the previously untreated group. The median progression-free survival (PFS) was 13.6 months (95% confidence interval [95% CI], 7.2-22.1 months), and 81% of patients remained alive at 2 years. The ORR was 46% with a 21% CR rate in the recurrent disease group. The median PFS was 5.4

months (95% CI, 4.6-13.1 months), and 36% of patients remained alive at 2 years. Twenty-nine eligible patients with a median age of 70 years received 2-CDA plus rituximab. The ORR was 66% (19 of 29 patient), and the CR rate was 52% (15 of 29 patients). The median duration of response for patients who achieved a CR had not been reached at the time of the current report, and only 3 of the patients who achieved a CR developed recurrent disease at a median follow-up of 21.5 months. CONCLUSIONS: 2-CDA had substantial single-agent activity in both recurrent and untreated MCL, and the results indicated that it may be administered safely to elderly patients. The addition of rituximab to 2-CDA may increase the duration of response.

Jeanneret-Sozzi, W., A. Taghian, et al. (2008). "Primary breast lymphoma: patient profile, outcome and prognostic factors. A multicentre Rare Cancer Network study." *BMC Cancer* **8**: 86.

BACKGROUND: To assess the clinical profile, treatment outcome and prognostic factors in primary breast lymphoma (PBL). METHODS: Between 1970 and 2000, 84 consecutive patients with PBL were treated in 20 institutions of the Rare Cancer Network. Forty-six patients had Ann Arbor stage IE, 33 stage IIE, 1 stage IIIE, 2 stage IVE and 2 an unknown stage. Twenty-one underwent a mastectomy, 39 conservative surgery and 23 biopsy; 51 received radiotherapy (RT) with (n = 37) or without (n = 14) chemotherapy. Median RT dose was 40 Gy (range 12-55 Gy). RESULTS: Ten (12%) patients progressed locally and 43 (55%) had a systemic relapse. Central nervous system (CNS) was the site of relapse in 12 (14%) cases. The 5-yr overall survival, lymphoma-specific survival, disease-free survival and local control rates were 53%, 59%, 41% and 87% respectively. In the univariate analyses, favorable prognostic factors were early stage, conservative surgery, RT administration and combined modality treatment. Multivariate analysis showed that early stage and the use of RT were favorable prognostic factors. CONCLUSION: The outcome of PBL is fair. Local control is excellent with RT or combined modality treatment but systemic relapses, including that in the CNS, occurs frequently.

Jensen, A. O., H. F. Thomsen, et al. (2009). "Use of oral glucocorticoids and risk of skin cancer and non-Hodgkin's lymphoma: a population-based case-control study." *Br J Cancer* **100**(1): 200-5.

In North Jutland County, Denmark, we investigated whether use of oral glucocorticoids was associated with an increased risk of developing basal cell carcinoma (BCC), squamous cell carcinoma (SCC), malignant melanoma (MM), and non-

Hodgkin's lymphoma (NHL). From the Danish Cancer Registry we identified 5422 BCC, 935 SCC, 983 MM, and 481 NHL cases during 1989-2003. Using risk-set sampling we selected four age- and gender-matched population controls for each case from the Civil Registration System. Prescriptions for oral glucocorticoids before diagnosis were obtained from the Prescription Database of North Jutland County on the basis of National Health Service data. We used conditional logistic regression to estimate incidence rate ratios (IRRs), adjusting for chronic medical diseases (information about these were obtained from the National Patient Registry) and use of other immunosuppressants. We found slightly elevated risk estimates for BCC (IRR, 1.15 (95% CI: 1.07-1.25)), SCC (IRR, 1.14 (95% CI: 0.94-1.39)), MM (IRR, 1.15 (95% CI: 0.94-1.41)), and NHL (IRR, 1.11 (95% CI: 0.85-1.46)) among users of oral glucocorticoids. Our study supports an overall association between glucocorticoid use and risk of BCC that cannot be explained by the presence of chronic diseases or concomitant use of other immunosuppressants.

Jimenez, V. H. (2006). "Coexistence between renal cell cancer and Hodgkin's lymphoma: a rare coincidence." *BMC Urol* **6**: 10.

**BACKGROUND:** Renal cell carcinoma is the most common kidney tumor in adults and accounts for approximately 3% of adult malignancies. An increased incidence of second malignancies has been well documented in a number of different disorders, such as head and neck tumors, and hairy cell leukemia. In addition, treatment associated second malignancies (usually leukemias and lymphomas but also solid tumors) have been described in long term survivors of Hodgkin's lymphoma (HL), Non Hodgkin's lymphoma and in various pediatric tumors. **CASE PRESENTATION:** We present the case of a 66 year-old woman with abdominal pain and dyspnea. We performed a thorax CT scan that showed lymph nodes enlargement and subsequently by presence of abdominal pain was performed an abdominal and pelvis CT scan that showed a right kidney tumor of 4 x 5 cms besides of abdominal lymph nodes enlargement. A radical right nephrectomy was designed and Hodgkin's lymphoma was diagnosed in the abdominal lymph nodes while renal cell tumor exhibited a renal cell cancer. Patient received EVA protocol achieving complete response. **CONCLUSION:** We described the first case reported in the medical literature of the coexistence between Hodgkin's lymphoma and renal cell cancer. Previous reports have shown the relationship of lymphoid neoplasms with solid tumors, but they have usually described secondary forms of cancer related to chemotherapy.

Jones, J. A., E. B. Avritscher, et al. (2006). "Epidemiology of treatment-associated mucosal injury after treatment with newer regimens for lymphoma, breast, lung, or colorectal cancer." *Support Care Cancer* **14**(6): 505-15.

**Goals of work:** Oral and gastrointestinal (GI) mucositis are frequent complications of chemotherapy and radiotherapy for cancer, contributing to not only the morbidity of treatment but its cost as well. The risk associated with specific chemotherapeutic agents, alone and in combination, has been characterized previously. In the current study, we sought to estimate the risk associated with newer regimens for the treatment of non-Hodgkin's lymphoma (NHL) and common solid tumors. **Methods:** We reviewed published studies reporting phase II and III clinical trials of dose-dense regimens for breast cancer and NHL, TAC (docetaxel, adriamycin, cyclophosphamide) chemotherapy for breast cancer, and infusional 5-fluorouracil-based regimens for colorectal cancer. Platinum-, gemcitabine-, and taxane-based regimens for lung cancer, either alone or in combination with radiotherapy, were also considered. Using modified meta-analysis methods, we calculated quality-adjusted estimates of the risk for oral and GI mucositis by tumor type and regimen. Case reports are used to emphasize the relevance of the findings for patient care. **Main results:** Our findings demonstrate that mucosal toxicity remains an important complication of cancer treatment. Moreover, innovations in drug combinations, scheduling, or mode of administration significantly modulate the risk for both oral and GI mucositis. **Conclusions:** Ongoing review of the clinical trial experience will remain important as newer, targeted agents enter standard clinical practice.

Jonker-Pool, G., H. J. Hoekstra, et al. (2004). "Male sexuality after cancer treatment--needs for information and support: testicular cancer compared to malignant lymphoma." *Patient Educ Couns* **52**(2): 143-50.

Testicular cancer (TC) as well as malignant lymphoma (ML), both have nowadays an excellent prognosis. However, both types of cancer may be diagnosed at young adulthood and patients may experience sexual concerns. In this article the need for information and support concerning sexuality will be explored, and the traumatic impact of cancer diagnosis with respect to this will be considered. A total of 264 patients with testicular cancer, median age 36 (S.D. 9.7) years, and 50 patients with malignant lymphoma, median age 42 (S.D. 11.7) years returned a questionnaire concerning sexual functioning; four items assessed the need for information or support concerning sexuality, at diagnosis and at follow-up. It

appeared that more than half of the patients with testicular cancer reported a lack of information and support concerning sexuality during treatment; 67% of them still had a need for information at follow-up. These rates were significantly lower for patients with malignant lymphoma. Especially patients with testicular cancer who suffered sexual dysfunction reported extremely high needs for information and support. According to these findings it can be concluded that more attention should be paid to the doctor-patient communication with respect to sexual concerns in general, and especially where it concerns patients with testicular cancer.

Kalender, M. E., A. Sevinc, et al. (2007). "Metachronous non-Hodgkin's lymphoma in a patient with localized prostate cancer." *Med Oncol* **24**(4): 466-8.

**INTRODUCTION:** A higher frequency of second malignancies is observed in patients with prostate cancer. We report a case of indolent non-Hodgkin's lymphoma diagnosed 2 years after prostate carcinoma. **CASE REPORT:** A 65-year-old man with diagnosis of localized prostate adenocarcinoma was presented with fatigue 2 years after prostatectomy operation. Abdominal ultrasonography showed hepatomegaly and paraaortocaval, parailiac, and perivascular multiple lymph nodes. The complete blood count revealed anemia and thrombocytopenia. Bone marrow biopsy demonstrated small lymphocytic lymphoma. **CONCLUSION:** Lymphoma should be suspected in cases with newly appeared adenopathy and/or cytopenias during follow-up. In patients with clinically organ-confined prostate cancer, indolent lymphoma should be in the differential diagnosis of newly appeared lymphadenopathy.

Katz, J. N., G. W. Brick, et al. (2008). "Elective palliative total hip replacement in a patient with lymphoma and advanced lung cancer." *Arthritis Rheum* **59**(8): 1194-6.

Kelemen, L. E., J. R. Cerhan, et al. (2006). "Vegetables, fruit, and antioxidant-related nutrients and risk of non-Hodgkin lymphoma: a National Cancer Institute-Surveillance, Epidemiology, and End Results population-based case-control study." *Am J Clin Nutr* **83**(6): 1401-10.

**BACKGROUND:** Factors related to DNA damage and altered immunologic responses, such as reactive oxygen species production, are associated with the risk of non-Hodgkin lymphoma (NHL). **OBJECTIVE:** The aim was to evaluate NHL risk with intakes of vegetables, fruit, and nutrients involved in antioxidant activities. **DESIGN:** Incident case subjects aged 20-74 y were identified between 1998 and 2000

from a National Cancer Institute-sponsored study by using four Surveillance, Epidemiology, and End Results registries. Control subjects, who were selected by random dialing (< 65 y) and from Medicare files (> or = 65 y), were matched to cases by age, center, race, and sex. Of 1321 case and 1057 control subjects who enrolled, dietary data were collected on a subset (466 cases and 391 controls). Carotenoid intakes were estimated by using updated values from the US Department of Agriculture nutrient databases. Unconditional logistic regression models were used to estimate odds ratios (ORs) and 95% CIs. **RESULTS:** NHL risk was inversely associated with higher number of weekly servings of all vegetables (multivariable OR for highest compared with lowest quartile: 0.58; 95% CI: 0.35, 0.95; P for trend = 0.04), green leafy vegetables (OR: 0.59; 95% CI: 0.36, 0.96; P for trend = 0.01), and cruciferous vegetables (OR: 0.62; 95% CI: 0.39, 1.00; P for trend = 0.05) and with higher daily intakes of lutein and zeaxanthin (OR: 0.54; 95% CI: 0.32, 0.91; P for trend = 0.06) and zinc (OR: 0.58; 95% CI: 0.36, 0.91; P for trend = 0.02). An effect modification by exercise and NHL subtype was observed with some food groups and nutrients. **CONCLUSION:** Higher intakes of vegetables, lutein and zeaxanthin, and zinc are associated with a lower NHL risk.

Kempf, W., S. Ostheeren-Michaelis, et al. (2008). "Granulomatous mycosis fungoides and granulomatous slack skin: a multicenter study of the Cutaneous Lymphoma Histopathology Task Force Group of the European Organization For Research and Treatment of Cancer (EORTC)." *Arch Dermatol* **144**(12): 1609-17.

**BACKGROUND:** Granulomatous cutaneous T-cell lymphomas (CTCLs) are rare and represent a diagnostic challenge. Only limited data on the clinicopathological and prognostic features of granulomatous CTCLs are available. We studied 19 patients with granulomatous CTCLs to further characterize the clinicopathological, therapeutic, and prognostic features. **OBSERVATIONS:** The group included 15 patients with granulomatous mycosis fungoides (GMF) and 4 with granulomatous slack skin (GSS) defined according to the World Health Organization-European Organization for Research and Treatment of Cancer classification for cutaneous lymphomas. Patients with GMF and GSS displayed overlapping histologic features and differed only clinically by the development of bulky skin folds in GSS. Histologically, epidermotropism of lymphocytes was not a prominent feature and was absent in 9 of 19 cases (47%). Stable or progressive disease was observed in most patients despite various treatment modalities. Extracutaneous spread occurred in 5 of 19

patients (26%), second lymphoid neoplasms developed in 4 of 19 patients (21%), and 6 of 19 patients (32%) died of their disease. Disease-specific 5-year survival rate in GMF was 66%. CONCLUSIONS: There are clinical differences between GMF and GSS, but they show overlapping histologic findings and therefore cannot be discriminated by histologic examination alone. Development of hanging skin folds is restricted to the intertriginous body regions. Granulomatous CTCLs show a therapy-resistant, slowly progressive course. The prognosis of GMF appears worse than that of classic nongranulomatous mycosis fungoides.

Kho, M. E., E. M. Lepisto, et al. (2008). "Reliability of staging, prognosis, and comorbidity data collection in the National Comprehensive Cancer Network (NCCN) non-Hodgkin lymphoma (NHL) multicenter outcomes database." *Cancer* **113**(11): 3209-12.

**BACKGROUND:** Clinical trials and outcomes studies often rely on nonphysicians to abstract complex data from medical records, but the reliability of these data are rarely assessed. **METHODS:** We used standardized charts of patients with non-Hodgkin lymphoma to assess the reliability of key clinical data elements abstracted by 6 clinical research associates (CRAs), 3 project staff, and 3 medical oncologists. We assessed reliability on 5 variables: MD-reported and rater-determined disease stage; International Prognostic Index (IPI; low-low intermediate, intermediate-high, high); Charlson comorbidity index score; and presence of any item from the Charlson index. Intraclass correlation coefficients (ICCs) of 0-0.20 were indicative of "slight", 0.21-0.40 indicated "fair", 0.41-0.60 indicated "moderate", 0.61-0.80 "substantial" and >0.80 "almost perfect" reliability. **RESULTS:** By outcome, the ICC (95% confidence interval) values for MD-reported stage, rater-determined stage, and IPI were 0.86 (0.67, 0.94), 0.82 (0.59, 0.93), and 0.80 (0.55, 0.92), respectively. In contrast, the ICC (95% confidence interval) of the Charlson score, or presence of any Charlson comorbidity item was 0.47 (0.03, 0.75) and 0.61 (0.23, 0.83), respectively. Reliability varied by rater group; no rater group was consistently more reliable than others. **CONCLUSIONS:** Trained CRAs abstracted key clinical variables with a very high degree of reliability, and performed at a level similar to study trainers and oncologists. Elements of the Charlson index were less reliable than other data types, possibly because of inherent ambiguity in the index itself.

Kikuchi, A., T. Mori, et al. (2008). "Outcome of childhood B-cell non-Hodgkin lymphoma and B-cell acute lymphoblastic leukemia treated with the Tokyo

Children's Cancer Study Group NHL B9604 protocol." *Leuk Lymphoma* **49**(4): 757-62.

From June 1996 to January 2001, 91 patients with B-cell non-Hodgkin lymphoma or B-cell acute lymphoblastic leukemia up to 18 years of age were enrolled in Tokyo Children's Cancer Study Group (TCCSG) NHL B9604 protocol study. Five-day intensive chemotherapy courses including high-dose methotrexate and high-dose cyclophosphamide were used for localized disease (Groups A and B). High-dose cytarabine was added for advanced disease (Groups C and D). Fifteen patients experienced an adverse event. There were three induction failures, eight relapses (three local, four bone marrow (BM), one BM + local), two toxic deaths and two second malignant neoplasm. Event-free survival at 6 years in Group D and in all patients was 82.4% +/- 9.2% and 81.9% +/- 4.4%, respectively. The TCCSG NHL B9604 protocol achieved an excellent treatment outcome especially in patients with the most advanced disease (Group D: high BM blast cell burden and/or central nervous system involvement).

Kim, Y. H., R. Willemze, et al. (2007). "TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC)." *Blood* **110**(2): 479-84.

Currently available staging systems for non-Hodgkin lymphomas are not useful for clinical staging classification of most primary cutaneous lymphomas. The tumor, node, metastases (TNM) system used for mycosis fungoides (MF) and Sezary syndrome (SS) is not appropriate for other primary cutaneous lymphomas. A usable, unified staging system would improve the communication about the state of disease, selection of appropriate management, standardization of enrollment/response criteria in clinical trials, and collection/analysis of prospective survival data. Toward this goal, during the recent meetings of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC), the representatives have established a consensus proposal of a TNM classification system applicable for all primary cutaneous lymphomas other than MF and SS. Due to the clinical and pathologic heterogeneity of the cutaneous lymphomas, the currently proposed TNM system is meant to be primarily an anatomic documentation of disease extent and not to be used as a prognostic guide.

Koh, E. S., T. H. Tran, et al. (2007). "A comparison of mantle versus involved-field radiotherapy for Hodgkin's lymphoma: reduction in normal tissue dose and second cancer risk." *Radiat Oncol* 2: 13.

**BACKGROUND:** Hodgkin's lymphoma (HL) survivors who undergo radiotherapy experience increased risks of second cancers (SC) and cardiac sequelae. To reduce such risks, extended-field radiotherapy (RT) for HL has largely been replaced by involved field radiotherapy (IFRT). While it has generally been assumed that IFRT will reduce SC risks, there are few data that quantify the reduction in dose to normal tissues associated with modern RT practice for patients with mediastinal HL, and no estimates of the expected reduction in SC risk. **METHODS:** Organ-specific dose-volume histograms (DVH) were generated for 41 patients receiving 35 Gy mantle RT, 35 Gy IFRT, or 20 Gy IFRT, and integrated organ mean doses were compared for the three protocols. Organ-specific SC risk estimates were estimated using a dosimetric risk-modeling approach, analyzing DVH data with quantitative, mechanistic models of radiation-induced cancer. **RESULTS:** Dose reductions resulted in corresponding reductions in predicted excess relative risks (ERR) for SC induction. Moving from 35 Gy mantle RT to 35 Gy IFRT reduces predicted ERR for female breast and lung cancer by approximately 65%, and for male lung cancer by approximately 35%; moving from 35 Gy IFRT to 20 Gy IFRT reduces predicted ERRs approximately 40% more. The median reduction in integral dose to the whole heart with the transition to 35 Gy IFRT was 35%, with a smaller (2%) reduction in dose to proximal coronary arteries. There was no significant reduction in thyroid dose. **CONCLUSION:** The significant decreases estimated for radiation-induced SC risks associated with modern IFRT provide strong support for the use of IFRT to reduce the late effects of treatment. The approach employed here can provide new insight into the risks associated with contemporary IFRT for HL, and may facilitate the counseling of patients regarding the risks associated with this treatment.

Kouroukis, C. T., A. Belch, et al. (2003). "Flavopiridol in untreated or relapsed mantle-cell lymphoma: results of a phase II study of the National Cancer Institute of Canada Clinical Trials Group." *J Clin Oncol* 21(9): 1740-5.

**PURPOSE:** To determine the response rate and toxicity of flavopiridol in patients with previously untreated or relapsed mantle-cell lymphoma. **PATIENTS AND METHODS:** Adult patients with previously untreated or in first or second relapse of previously responsive mantle-cell lymphoma were given flavopiridol 50 mg/m<sup>2</sup>/d by intravenous bolus

for 3 consecutive days every 21 days with anti-diarrheal prophylaxis. Flavopiridol was continued until disease progression, unacceptable toxicity, or stable disease for four cycles. Disease was reassessed every two cycles. **RESULTS:** From 33 registered patients, 30 were eligible after pathology review, 30 were assessable for toxicity, and 28 were assessable for response. A median of four cycles of treatment was administered; 90% of patients received at least 90% of planned dose-intensity. No complete responses were seen; three patients had a partial response (11%), 20 patients had stable disease (71%), and five patients had progressive disease (18%). The median duration of response was 3.3 months (range, 2.8 to 13.2 months). The most common toxicities were diarrhea (97%), fatigue (73%), nausea (47%), and vomiting (27%). At least one non-hematologic grade 3 or 4 toxicity was seen in 14 patients (47%). Hematologic toxicity was modest. **CONCLUSIONS:** Flavopiridol given as a daily bolus for 3 consecutive days every 3 weeks has modest activity as a single agent for mantle-cell lymphoma. The number of stable and partial responses that was seen indicates that it is biologically active and may delay progression. Future studies in mantle-cell lymphoma should test this agent with other active agents and using different schedules.

Krishnan, B. and G. J. Morgan (2007). "Non-Hodgkin lymphoma secondary to cancer chemotherapy." *Cancer Epidemiol Biomarkers Prev* 16(3): 377-80.

Increased long-term survival seen in patients with solid and hematologic cancers achieved as a result of aggressive chemoradiotherapy has come at a price. Therapy-related acute myeloid leukemia has been frequently documented in these patient cohorts, and its biology well studied. Recognition of secondary non-Hodgkin lymphoma as a cause of significant morbidity and mortality in these patients is equally important. The patterns of incidence and latency of secondary lymphomas is distinct from that of myeloid malignancies and other solid cancers. We have systematically analyzed and summarized reports from various groups over the last three decades. Risk of secondary lymphomas increases after the first 5 years of completion of chemotherapy or radiotherapy and persists for more than three decades. This reinforces the need for long-term follow-up of all patients exposed to chemoradiotherapy and confirms that chemotherapeutic agents can cause lymphoma.

Krol, A. D., S. le Cessie, et al. (2003). "Primary extranodal non-Hodgkin's lymphoma (NHL): the impact of alternative definitions tested in the Comprehensive Cancer Centre West population-based NHL registry." *Ann Oncol* 14(1): 131-9.

**BACKGROUND:** The definition of primary extranodal non-Hodgkin's lymphoma (NHL) is a controversial issue, especially in patients where both nodal and extranodal sites are involved. **PATIENTS AND METHODS:** The impact of different definitions of primary extranodal NHL on incidence and prognosis is explored using data from a population-based NHL registry. **RESULTS:** Using liberal criteria, 389 (34%) cases were classified as primary extranodal NHL. Overall survival (OS) rates of nodal and extranodal NHL patients defined this way were comparable; however, extranodal NHL patients had a better disease-free survival (DFS). When strict criteria were applied, 231 cases (20%) were classified as primary extranodal NHL. OS and DFS rates of extranodal NHL patients defined this way were superior to nodal NHL patients; however, the difference in OS was reversed after correction for differences in International Prognostic Index and malignancy grade. **CONCLUSION:** This study illustrates the selection bias that is introduced when a strict definition of primary extranodal NHL, that excludes cases with disseminated disease, is used. Patients with primary extranodal NHL were found to have a superior DFS, irrespective of which definition of primary extranodal NHL was used.

Kurtz, D. M., L. K. Tschetter, et al. (2007). "Subcutaneous interleukin-4 (IL-4) for relapsed and resistant non-Hodgkin lymphoma: a phase II trial in the North Central Cancer Treatment Group, NCCTG 91-78-51." *Leuk Lymphoma* **48**(7): 1290-8.

Interleukin-4 (IL-4), a pleiotropic cytokine, has in vitro activity against non-Hodgkin lymphoma (NHL). This phase II study was conducted to learn the efficacy and toxicity of IL-4 in patients with NHL. Patients with relapsed or refractory indolent or aggressive NHL were eligible to receive 2.5 or 5.0 mcg/kg of subcutaneous IL-4 for 28 days of a 42-day cycle. Patients with response and acceptable toxicity after two cycles were eligible to continue treatment for six cycles. The target overall response rate (ORR) was 20%. Forty-one patients were enrolled and assessable for toxicity; two were ineligible after histology review. The ORR was 13% (5/39) with one complete and four partial responses. All responders were treated with 5.0 mcg/kg; the median time to progression was 84 days, the median duration of response for responders was 8.3 months. The most common toxicities of any grade in all patients were edema (66%), malaise (56%), and elevated liver function tests (56%). Grade 3 and 4 toxicities were more common at 5.0 mcg/kg, leading to a reduction in the starting dose. Although the study observed anti-tumor activity with IL-4, the ORR goal of the study was not achieved. Agents that target the IL-4 receptor can

potentially benefit patients with NHL; however, alternative schedules using IL-4 in shorter duration and in combination with other agents would be required to overcome toxicities observed in this study.

Laack, N. N., K. V. Ballman, et al. (2006). "Whole-brain radiotherapy and high-dose methylprednisolone for elderly patients with primary central nervous system lymphoma: Results of North Central Cancer Treatment Group (NCCTG) 96-73-51." *Int J Radiat Oncol Biol Phys* **65**(5): 1429-39.

**PURPOSE:** The aim of this study was to evaluate the efficacy, toxicity, and survival of whole-brain radiotherapy-treated (WBRT) and high-dose methylprednisolone (HDMP)-treated in elderly patients with primary central nervous system lymphoma (PCNSL). **METHODS AND MATERIALS:** Patients with PCNSL who were 70 years and older received 1 g of methylprednisolone daily for 5 days, 30 days after WBRT. Patients then received 1 g of methylprednisolone every 28 days until progression. The primary endpoint was overall survival (OS) at 6 months. Results were compared with those in patients on the previous North Central Cancer Treatment Group (NCCTG) trial who received pre-WBRT cytoxan, adriamycin, vincristine, prednisone (CHOP) and high-dose cytarabine (CHOP-WBRT). A planned interim analysis was performed. The current regimen would be considered inactive if survival was not improved from patients treated with CHOP-WBRT. **RESULTS:** Nineteen patients were accrued between 1998 and 2003. Median age was 76 years. Interim analysis revealed a 6-month survival of 33%, resulting in closure of the trial. Toxicity, OS, and event-free survival (EFS) were similar to those in patients more than 70 years of age who received CHOP-WBRT. The subgroup of patients who received HDMP had longer OS (12.1 vs. 7.0 months,  $p = 0.76$ ) and EFS (11.7 vs. 4.0 months,  $p = 0.04$ ) compared with the CHOP-WBRT patients alive 60 days after the start of treatment. **CONCLUSIONS:** Patients on-study long enough to receive HDMP had prolongation of OS and EFS compared to patients receiving CHOP-WBRT. Although the numbers of patients are too small for statistical conclusions, the HDMP regimen deserves further study.

LaCasce, A. S., M. E. Kho, et al. (2008). "Comparison of referring and final pathology for patients with non-Hodgkin's lymphoma in the National Comprehensive Cancer Network." *J Clin Oncol* **26**(31): 5107-12.

**PURPOSE:** Before the implementation of the WHO lymphoma classification system, disagreement about pathologic diagnosis was common. We sought to estimate the impact of expert review in the modern era by comparing final pathologic diagnoses at five

comprehensive cancer centers with diagnoses assigned at referring centers. PATIENTS AND METHODS: Patients in the National Comprehensive Cancer Network (NCCN) non-Hodgkin's lymphoma (NHL) database with a documented pathologic diagnosis before presentation and a final pathologic diagnosis of any of five common B-cell NHLs were eligible. After central review of discordant cases, we estimated the rate of pathologic concordance, then investigated the etiology of discordance as well its potential impact on prognosis and treatment. RESULTS: The overall pathologic discordance rate was 6% (43 of 731 patients; 95% CI, 4% to 8%). For the majority of cases in which the referring diagnosis was apparently final, no additional studies were conducted at the NCCN center, and the change in diagnosis reflected a different interpretation of existing data. Concordance was highest for diffuse large B-cell lymphoma (95%) and follicular lymphoma (FL; grades 1, 2, and not otherwise specified, 95%) and lowest for grade 3 FL (88%). Of the 43 pathologically discordant cases, 81% (35 patients) might have experienced a change in treatment as a result of the pathologic reclassification. CONCLUSION: In the era of the WHO lymphoma classification system, the majority of common B-cell NHLs diagnosed in the community were unchanged by second opinion review by an expert hematopathologist. However, for one patient in 20, there was a discordance in diagnosis that could have altered therapy.

Landmann, E., I. Oschlies, et al. (2008). "Secondary non-Hodgkin lymphoma (NHL) in children and adolescents after childhood cancer other than NHL." Br J Haematol **143**(3): 387-94.

The emergence of non-Hodgkin lymphoma (NHL) during childhood and adolescence as a secondary neoplasm (SN) after previous cancer other than NHL is rare. To describe the characteristics and outcome of NHL following previous cancer other than NHL in children and adolescents, this study analysed the data of patients reported to the NHL-Berlin-Frankfurt-Munster study centre from 1986 to 2005. Out of the total of 2968 NHL-patients registered, 11 patients were assessed as having suffered from NHL as a proven SN. Four additional children had most likely suffered from NHL as an SN, but a late relapse of the first neoplasm could not be ruled out unequivocally. In the patients with proven SN, median age at diagnosis of the primary malignancy was 3.9 years (range 2-11.7). The median age at diagnosis of NHL was 7.6 years (range 4.7-18). Only lymphoblastic (n = 7) and diffuse large B-cell (n = 4) lymphomas were diagnosed as SN. The estimated 5-year event-free survival from time of diagnosis of NHL was 91% [95% confidence interval (CI) 74-

100%] in patients with proven SNs and 84% (95% CI 63-100%) when the patients with probable SNs were included in the analysis. We concluded that secondary NHL in children and adolescents confers a favourable prognosis.

Lawrie, C. H., T. Marafioti, et al. (2006). "Cancer-associated carbohydrate identification in Hodgkin's lymphoma by carbohydrate array profiling." Int J Cancer **118**(12): 3161-6.

Tumor-associated carbohydrates have potential not only as diagnostic tools but also as specific therapeutic targets. Their identification, however, has been hampered by the lack of suitable technologies. We used carbohydrate array technology to compare serum antibody (IgG and IgM) levels against 37 different carbohydrates between classical Hodgkin's lymphoma (cHL) patients and age/sex-matched healthy controls. Serum IgM levels measured by ELISA against 2 of the 5 carbohydrates identified using this technique, L-alpha-arabinose (L-Araf) and alpha-N-acetylgalactosamine (GalNAc(alpha)), were higher (F values of 11.30 and 18.27, respectively) in a cohort of cHL patients (n = 16) than either diffuse large B-cell lymphoma patients (n = 18) or control sera (n = 12). Higher anti-L-Araf IgM levels in cHL patients were associated with cytosine arabinoside treatment (p < 0.05). The GalNAc(alpha) glycotope, Tn, was found to be heterogeneously expressed in the Reed-Sternberg cells of 9/20 (45%) cHL cases, but not in malignant cells of 25 cases of lymphocyte-predominant HL or another 21 hematological disorders (291 cases) examined immunohistochemically. Tn was expressed in 41/238 (17%) classical HL cases present on a tissue microarray. Expression was associated with CD79a and LMP1 expression and negatively with p27(KIP1) expression (p < 0.05). Kaplan-Meier survival analysis revealed a trend towards improved relapse-free survival with Tn expression although this was not statistically significant (p = 0.271). We suggest that this technique could provide a powerful tool for identifying novel carbohydrates in other cancers.

Lee, R. C., D. Zou, et al. (2008). "Costs associated with diffuse large B-cell lymphoma patient treatment in a Canadian integrated cancer care center." Value Health **11**(2): 221-30.

OBJECTIVE: The objective of this study was to provide a detailed comparative microcosting analysis for two cancer treatment pathways to contribute evidence for resource allocation and operational decision-making in a Canadian cancer care context. METHODS: We estimated direct medical costs (in 2004 CAN\$) of the entire pathway of care for diffuse large B-cell lymphoma (DLBCL) patients in a

large Canadian cancer treatment center. Patient samples were defined as those who received R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; n = 85) or CHOP (i.e., without rituximab; n = 86) as first-line treatment. All subsequent treatments including palliative care for these patient samples were assessed. Hospitalization costs and unit costs of medical resources were collected from integrated medical organizations. Individual patient resource consumption was assessed via medical chart review. **RESULTS:** For first-line treatment, drug cost was the largest contributor to total cost, followed by hospitalization cost. Rituximab was the largest contributor to mean cost differences between R-CHOP and CHOP treatments. For treatments subsequent to first-line treatment, no significant cost differences were found. Hospitalization and transplantation costs were the two largest constituents of total costs subsequent to first-line treatment, followed by drug cost. Patients with advanced stage disease cost significantly more than patients with limited stage disease. **CONCLUSION:** This is the first detailed microcosting study that has employed consistent local data to estimate total medical costs for DLBCL patients in Canada. This information is useful for resource allocation planning and operational decisions, because it provides more substantive, relevant evidence as compared to aggregated, literature or extrapolated information.

Lee, S. T., Y. F. Jiang, et al. (2007). "BiovaxID: a personalized therapeutic cancer vaccine for non-Hodgkin's lymphoma." *Expert Opin Biol Ther* 7(1): 113-22.

The clonal immunoglobulin molecule, idiotype (ID), expressed on the surface of B-cell malignancies can function as a tumor-specific antigen. BiovaxID is a patient-specific therapeutic cancer vaccine composed of the tumor idiotype conjugated to a carrier protein, keyhole limpet hemocyanin (KLH). In a Phase II clinical trial, administration of ID-KLH vaccine together with granulocyte-macrophage colony-stimulating factor to follicular lymphoma patients in complete remission induced tumor-specific cellular and humoral immunity and molecular remissions, and was associated with prolonged disease-free survival. A randomized, double-blind, Phase III clinical trial is ongoing to definitively determine the clinical benefit of BiovaxID plus granulocyte-macrophage colony-stimulating factor vaccination in patients with follicular lymphoma.

Li, R. and S. W. Morris (2008). "Development of anaplastic lymphoma kinase (ALK) small-molecule inhibitors for cancer therapy." *Med Res Rev* 28(3): 372-412.

Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase (RTK) involved in the genesis of several human cancers; indeed, ALK was initially identified in constitutively activated and oncogenic fusion forms--the most common being nucleophosmin (NPM)-ALK--in a non-Hodgkin's lymphoma (NHL) known as anaplastic large-cell lymphoma (ALCL) and subsequent studies identified ALK fusions in the human sarcomas called inflammatory myofibroblastic tumors (IMTs). In addition, two recent reports have suggested that the ALK fusion, TPM4-ALK, may be involved in the genesis of a subset of esophageal squamous cell carcinomas. While the cause-effect relationship between ALK fusions and malignancies such as ALCL and IMT is very well established, more circumstantial links implicate the involvement of the full-length, normal ALK receptor in the genesis of additional malignancies including glioblastoma, neuroblastoma, breast cancer, and others; in these instances, ALK is believed to foster tumorigenesis following activation by autocrine and/or paracrine growth loops involving the reported ALK ligands, pleiotrophin (PTN) and midkine (MK). There are no currently available ALK small-molecule inhibitors approved for clinical cancer therapy; however, recognition of the variety of malignancies in which ALK may play a causative role has recently begun to prompt developmental efforts in this area. This review provides a succinct summary of normal ALK biology, the confirmed and putative roles of ALK fusions and the full-length ALK receptor in the development of human cancers, and efforts to target ALK using small-molecule kinase inhibitors.

Liu, H. L., Y. Chen, et al. (2005). "Regulating expressions of cyclin D1, pRb, and anti-cancer effects of deguelin on human Burkitt's lymphoma Daudi cells in vitro." *Acta Pharmacol Sin* 26(7): 873-80.

**AIM:** To investigate anticancer effects and molecular mechanism of deguelin on human Burkitt's lymphoma Daudi cells in vitro and compare the cytotoxicities of deguelin on Daudi cells and human peripheral blood mononuclear cells (PBMC). **METHODS:** The effects of deguelin on the growth of Daudi cells were studied by 3-(4, 5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium (MTT) assay. Apoptosis were detected through Hoechst 33258 staining and Annexin V/PI double-labeled cytometry. The effect of deguelin on the cell cycle of Daudi cells were studied by a propidium iodide method. The expressions of cyclin D1 and pRb were checked by Western blot. **RESULTS:** The proliferation of Daudi cells were decreased in deguelin-treated group with a 24-h IC50 value of 51.55 nmol/L. Deguelin induced Daudi cells apoptosis was in a time- and dose-dependent manner. G0/G1 phase increased and S

phase decreased in Daudi cells treated with deguelin. With deguelin 0, 5, 10, 20, and 40 nmol/L treatment for 24 h, G0/G1 phase increased from 37.34% to 56.56%, whereas S phase decreased from 37.72% to 21.36%. PBMC was less sensitive to the cytotoxic effect of deguelin than Daudi cells. The expression of cyclin D1 and pRb protein were decreased sharply in Daudi cells treated with deguelin. **CONCLUSION:** Deguelin is able to inhibit the proliferation of Daudi cells by regulating the cell cycle that arrested cells at G0/G1 phase and inducing the cell apoptosis. Moreover, deguelin selectively induced apoptosis of Daudi cells with low toxicity in PBMC. The antitumor effects of deguelin were related to down-regulating the expression of cyclin D1 and pRb protein.

Liu, Q., L. Fayad, et al. (2006). "Improvement of overall and failure-free survival in stage IV follicular lymphoma: 25 years of treatment experience at The University of Texas M.D. Anderson Cancer Center." J Clin Oncol **24**(10): 1582-9.

**PURPOSE:** Advanced-stage follicular lymphoma is considered incurable. The pace of improvements in treatment has been slow. This article analyzes five sequential cohorts of patients with stage IV follicular lymphoma treated between 1972 and 2002. **METHODS:** Five consecutive studies (two were randomized trials) involving 580 patients were analyzed for overall survival (OS), failure-free survival (FFS), and survival after first relapse. A proportional hazards analysis, and subset analyses using the follicular lymphoma international prognostic index (FLIPI) score were performed. Treatment regimens included: cyclophosphamide, doxorubicin, vincristine, prednisone, bleomycin (CHOP-Bleo); CHOP-Bleo followed by interferon alfa (IFN-alpha); a rotation of three regimens (alternating triple therapy), followed by IFN-alpha; fludarabine, mitoxantrone, dexamethasone (FND) followed by IFN-alpha; and FND plus delayed versus concurrent rituximab followed by IFN-alpha. **RESULTS:** Improvements in 5-year OS (from 64% to 95%) and FFS (from 29% to 60%) indicate steady progress, perhaps partly due to more effective salvage therapies, but the FFS data also indicate improved front-line therapies; these observations held true after controlling for differences in prognostic factors among the cohorts. The FLIPI model adds rigor to and facilitates comparisons among the different cohorts. An unexpected finding in this study was a trend toward an apparent FFS plateau. **CONCLUSION:** Evolving therapy, including the incorporation of biologic agents, has led to stepwise significant outcome improvements for patients with advanced-stage follicular lymphoma. The apparent plateau in the FFS curve, starting approximately 8 to

10 years from the beginning of treatment, raises the issue of the potential curability of these patients.

Lorigan, P., J. Radford, et al. (2005). "Lung cancer after treatment for Hodgkin's lymphoma: a systematic review." Lancet Oncol **6**(10): 773-9.

Developments in modern chemotherapy and radiotherapy mean that most patients with Hodgkin's lymphoma can now be cured. However, the long-term effects of anticancer treatment include an increased risk of a second malignant disease. We have done a systematic review of studies reporting long-term complications of the treatment of Hodgkin's lymphoma published in English since 1985. These studies show that risk of lung cancer is significantly increased in patients treated for Hodgkin's lymphoma, with a reported mean relative risk of 2.6-7.0 and a significantly increased absolute excess risk. The absolute excess risk increases with time from treatment, for as long as 20-25 years, and is highest in patients treated at age 45 years or older. Both chemotherapy and radiotherapy contribute to the risk, and evidence suggests that the effects are additive. Cigarette smoking seems to multiply the risk associated with both chemotherapy and radiotherapy. In the high-risk group of patients, 50-150 patients per 1000 are expected to develop lung cancer by 10-20 years after treatment. The role of screening in this group of patients has not yet been assessed, but an international study combining CT with genomic and proteomic assessment is planned.

Lowe, E. J., R. Sposto, et al. (2009). "Intensive chemotherapy for systemic anaplastic large cell lymphoma in children and adolescents: final results of Children's Cancer Group Study 5941." Pediatr Blood Cancer **52**(3): 335-9.

**BACKGROUND:** Anaplastic large cell lymphoma (ALCL) is characterized by advanced disease at presentation (70-80% of pediatric cases) and accounts for 10-15% of all childhood lymphomas. Treatment strategies for pediatric ALCL vary from short pulse B-NHL chemotherapy to prolonged leukemia like therapy. The optimal treatment strategy is unknown. **METHODS:** CCG-5941 used a compressed aggressive multiagent T-cell lineage chemotherapy regimen consisting of a 3-week induction therapy (vincristine, prednisone, cyclophosphamide, daunomycin, asparaginase) followed by a 3-week consolidation period (vincristine, prednisone, etoposide, 6-thioguanine, cytarabine, asparaginase, methotrexate) followed by six courses of maintenance chemotherapy at 7-week intervals (cyclophosphamide, 6-thioguanine, vincristine, prednisone, doxorubicin, asparaginase, methotrexate etoposide, cytarabine). Total therapy

was 48 weeks. RESULTS: Eighty-six children (male 56%, female 44%) with non-localized ALCL (CD30+) were treated. The majority of tumors were positive for ALK (90%) and of T lineage (83%). Extranodal disease was common (mediastinum 35%, skin 15%, lung 14%, bone 12%, bone marrow 13%, liver 6%, and other viscera 17%). Grade 4 neutropenia occurred in 82% of patients. The 5-year EFS was 68% (95% CI of 57-78%) and the 5-year OS was 80% (95% CI of 69-87%). There were 21 relapses and 4 toxic deaths as first events. Relapse occurred early with 17 (81%) relapses occurring within 2 years of diagnosis and 12 (57%) while receiving therapy. Univariate analysis for risk factors only identified bone marrow involvement predicting lower EFS (P = 0.03). CONCLUSIONS: CCG-5941 demonstrated efficacy similar to previously reported regimens but with significant hematologic toxicity.

Martinet, S., M. Ozsahin, et al. (2003). "Outcome and prognostic factors in orbital lymphoma: a Rare Cancer Network study on 90 consecutive patients treated with radiotherapy." *Int J Radiat Oncol Biol Phys* 55(4): 892-8.

PURPOSE: To assess the outcome and prognostic factors in patients with orbital lymphoma treated by radiotherapy (RT). METHODS AND MATERIALS: Between 1980 and 1999, 90 consecutive patients with primary orbital lymphoma were treated in 13 member institutions of the Rare Cancer Network. A full staging workup was completed in 56 patients. Seventy-eight patients had low-, 6 intermediate-, and 6 high-grade lymphoma, and 75 had a single orbital localization. All patients underwent RT with a median dose of 34.2 Gy (range 4.0-50.4). Eleven patients received chemotherapy in addition to RT. RESULTS: After RT, local control was achieved in 97% of the patients. Local progression occurred in 2% and local relapse 1%. The rate of systemic relapse was 20%, and 9% of the patients developed metachronous contralateral eye involvement. The 5-year disease-free survival, overall survival, and cause-specific survival rate was 65%, 78%, and 87%, respectively. In univariate analyses, the statistically significant favorable prognostic factors were younger age, low grade, normal erythrocyte sedimentation rate, absence of muscular infiltration, complete response to treatment, conjunctival localization, and normal lactate dehydrogenase value for overall survival, disease-free survival, and freedom from treatment failure. In multivariate analysis, the favorable factors were younger age and low grade for overall and disease-free survival; a favorable response, conjunctival localization, and complete staging were highly significant for disease-free survival and freedom from

treatment failure. Neither the RT technique nor the total dose influenced the outcome. Cataract and xerophthalmia were the most prominent late toxicities. CONCLUSION: Moderate- to low-dose RT alone is able to control primary orbital lymphoma with low morbidity. A full staging workup is warranted in these patients. Prognostic factors were identified that could be useful in the overall management of this uncommon site of primary lymphoma.

McCaw, D. L., A. S. Chan, et al. (2007). "Proteomics of canine lymphoma identifies potential cancer-specific protein markers." *Clin Cancer Res* 13(8): 2496-503.

PURPOSE: Early diagnosis of cancer is crucial for the success of treatment of the disease, and there is a need for markers whose differential expression between disease and normal tissue could be used as a diagnostic tool. Spontaneously occurring malignancies in pets provide a logical tool for translational research for human oncology. Lymphoma, one of the most common neoplasms in dogs, is similar to human non-Hodgkin's lymphoma and could serve as an experimental model system. EXPERIMENTAL DESIGN: Thirteen lymph nodes from normal dogs and 11 lymph nodes from dogs with B-cell lymphoma were subjected to proteomic analysis using two-dimensional PAGE separation and matrix-assisted laser desorption/ionization time-of-flight analysis. RESULTS: A total of 93 differentially expressed spots was subjected to matrix-assisted laser desorption/ionization time-of-flight tandem mass spectrometry analysis, and several proteins that showed differential expression were identified. Of these, prolidase (proline dipeptidase), triosephosphate isomerase, and glutathione S-transferase were down-regulated in lymphoma samples, whereas macrophage capping protein was up-regulated in the lymphoma samples. CONCLUSIONS: These proteins represent potential markers for the diagnosis of lymphoma and should be further investigated in human samples for validation of their utility as diagnostic markers.

Meyer, R. M., M. K. Gospodarowicz, et al. (2005). "Randomized comparison of ABVD chemotherapy with a strategy that includes radiation therapy in patients with limited-stage Hodgkin's lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group." *J Clin Oncol* 23(21): 4634-42.

PURPOSE: We report results of a randomized trial comparing ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy alone with treatment that includes radiation therapy in patients with limited-stage Hodgkin's lymphoma. PATIENTS AND METHODS:

Patients with nonbulky clinical stage I to IIA Hodgkin's lymphoma were stratified into favorable and unfavorable risk cohorts. Patients allocated to radiation-containing therapy received subtotal nodal radiation if favorable risk or combined-modality therapy if unfavorable risk. Patients allocated to ABVD received four to six treatment cycles. RESULTS: We evaluated 399 patients. Median follow-up is 4.2 years. In comparison with ABVD alone, 5-year freedom from disease progression is superior in patients allocated to radiation therapy ( $P = .006$ ; 93% v 87%); no differences in event-free survival ( $P = .06$ ; 88% v 86%) or overall survival ( $P = .4$ ; 94% v 96%) were detected. In a subset analyses comparing patients stratified into the unfavorable cohort, freedom from disease progression was superior in patients allocated to combined-modality treatment ( $P = .004$ ; 95% v 88%); no difference in overall survival was detected ( $P = .3$ ; 92% v 95%). Of 15 deaths observed, nine were attributed to causes other than Hodgkin's lymphoma or acute treatment-related toxicity. CONCLUSION: In patients with limited-stage Hodgkin's lymphoma, no difference in overall survival was detected between patients randomly assigned to receive treatment that includes radiation therapy or ABVD alone. Although 5-year freedom from disease progression was superior in patients receiving radiation therapy, this advantage is offset by deaths due to causes other than progressive Hodgkin's lymphoma or acute treatment-related toxicity.

Mohren, M., U. Essbach, et al. (2003). "Acute myelofibrosis in a patient with diffuse large cell non Hodgkin's lymphoma and renal cancer." *Leuk Lymphoma* 44(9): 1603-7.

Relapse after anthracycline based combination chemotherapy is frequently seen in patients with aggressive non Hodgkin's Lymphomas (NHL), whereas complications such as secondary leukemia or solid tumor rarely occur. We report a patient with diffuse large cell (DLC) NHL and concurrent renal cancer, who developed acute myelofibrosis (AMF) later in the course of her disease. This 60-year-old female patient presented with pancytopenia and a right sided renal mass. Diagnostic work up revealed severe bone marrow infiltration by DLC NHL and renal cancer T1N0M0G2. Cytogenetic and molecular evaluation of bone marrow cells showed three distinct clones, (a normal 46XX karyotype, a ringed chromosome 7 and a third clone with an enlarged chromosome 2 as well as several fragments). The patient underwent nephrectomy and eventually received 6 cycles of CHOP 14 chemotherapy. Anemia persisted followed by severe granulocytopenia and thrombocytopenia 6

weeks later. Repeated bone marrow biopsy showed absence of lymphoma and/or cancer metastasis, but massive myelofibrosis with an increased number of atypical megakaryocytes. Considering the short clinical course and the absence of hepatosplenomegaly AMF was diagnosed. The concurrence of three distinct neoplasms within a short period of time as well as the complex cytogenetic aberrations found in her bone marrow cells reflect a strong individual susceptibility to malignant disease in this patient.

Monnard, V., A. Sun, et al. (2006). "Primary spinal epidural lymphoma: patients' profile, outcome, and prognostic factors: a multicenter Rare Cancer Network study." *Int J Radiat Oncol Biol Phys* 65(3): 817-23.

PURPOSE: To assess the clinical profile, treatment outcome, and prognostic factors in primary spinal epidural lymphoma (PSEL). METHODS AND MATERIALS: Between 1982 and 2002, 52 consecutive patients with PSEL were treated in nine institutions of the Rare Cancer Network. Forty-eight patients had an Ann Arbor stage IE and four had a stage IIE. Forty-eight patients underwent decompressive laminectomy, all received radiotherapy (RT) with ( $n = 32$ ) or without chemotherapy ( $n = 20$ ). Median RT dose was 36 Gy (range, 6-50 Gy). RESULTS: Six (11%) patients progressed locally and 22 (42%) had a systemic relapse. At last follow-up, 28 patients were alive and 24 had died. The 5-year overall survival, disease-free survival, and local control were 69%, 57%, and 88%, respectively. In univariate analyses, favorable prognostic factors were younger age and complete neurologic response. Multivariate analysis showed that combined modality treatment, RT volume, total dose more than 36 Gy, tumor resection, and complete neurologic response were favorable prognostic factors. CONCLUSIONS: Primary spinal epidural lymphoma has distinct clinical features and outcome, with a relatively good prognosis. After therapy, local control is excellent and systemic relapse occurs in less than half the cases. Combined modality treatment appears to be superior to RT alone.

Mora, J., D. A. Filippa, et al. (2003). "Lymphoblastic lymphoma of childhood and the LSA2-L2 protocol: the 30-year experience at Memorial-Sloan-Kettering Cancer Center." *Cancer* 98(6): 1283-91.

BACKGROUND: Until the 1970s, diffuse lymphoblastic lymphoma (DLBL) was considered incurable. With intensive multidrug regimens, the majority of patients can now be cured. In the current study, the authors present what to their knowledge is the longest follow-up presented to date (median, 20 years for survivors) of the largest group of DLBL patients treated with a single protocol at a single

institution. **METHODS:** Between 1971-1990, a total of 95 consecutive patients (age < 21 years) with DLBL were treated with the LSA(2)-L(2) protocol at the Memorial Sloan-Kettering Cancer Center (MSKCC). Patients with Stage I-II disease were treated for 2 years. In 1980, the protocol was modified and patients with Stage III and IV disease were treated for 3 years. In addition, before the modification, patients with Stage IV disease received a cumulative dose of 15,600 mg/m<sup>2</sup> of cyclophosphamide for 3 years; after 1980, these patients received the same dosage as the other patients (i.e., 8400 mg/m<sup>2</sup>) for 2 years. Radiation therapy initially was administered to all patients with bulky disease in the primary tumor site. Until 1977, the dose of radiation was 20-55 grays (Gy); from 1977 to 1989, the dose was 20 Gy. After the fifth year of completion of treatment, all patients were evaluated comprehensively every 2 years. **RESULTS:** The overall survival (OS) of the patients was 79% with a median follow-up of 20 years. The overall event-free survival (EFS) was 75% (71 of 95 patients). Seventeen patients developed a disease recurrence and 15 died of disease. The OS and EFS rates for patients with Stages I-II disease (n = 8) were 87% and 87%, respectively, and the OS and EFS rates for patients with Stage III disease (n = 41) were 90% and 85%, respectively. The OS and EFS for patients with Stage IVA disease (with bone marrow [BM] involvement of < 25%) (n = 19) were 79% and 73%, respectively, whereas the OS and EFS for patients with Stage IVB disease (BM involvement of > 25%) (n = 27) were 74% and 70%. Of the 29 patients with Stage IV disease who were treated with the original protocol, 7 died of disease (1 of 8 patients with Stage IVA disease and 6 of 21 patients with Stage IVB disease). Of the 17 patients with Stage IV disease who were treated with the modified protocol, 3 died of disease (2 of 11 patients with Stage IVA disease and 1 of 6 patients with Stage IVB disease). Six patients developed secondary malignancies, four of whom died. **CONCLUSIONS:** Long-term EFS can be achieved in the majority of patients with widely disseminated pediatric DLBL. Chemotherapy alone appears to be sufficient prophylaxis against disease recurrence in the central nervous system. No disease-related or treatment-related deaths were reported to occur > 4.5 years after diagnosis in the current study.

Moser, E. C., E. M. Noordijk, et al. (2005). "Late non-neoplastic events in patients with aggressive non-Hodgkin's lymphoma in four randomized European Organisation for Research and Treatment of Cancer trials." *Clin Lymphoma Myeloma* 6(2): 122-30.

**BACKGROUND:** A significant proportion of patients with aggressive non-Hodgkin's lymphoma (NHL) become long-term survivors. A European

Organisation for Research and Treatment of Cancer database of patients with aggressive NHL, consistently treated with doxorubicin-based chemotherapy since 1980, afforded the possibility to explore late complications in this patient group. **PATIENTS AND METHODS:** Of 951 randomized patients, complete data on late complications could be collected in 757 patients who were alive > or = 2 years after the start of therapy and were seen at yearly follow-ups (median follow-up, 9.4 years; range, 2.1-20.4 years). We computed cumulative incidences of late events in a competing risk model by Gray (death being the competing event) to avoid bias caused by the high percentage of NHL-related deaths. Risk factors were estimated in a Cox proportional-hazards model and also evaluated with the Gray test. **RESULTS:** Late non-neoplastic events were found in 46% of the 757 patients. At 15 years, the cumulative incidences of cardiac disease and infertility were 20% and 29%, respectively. Renal insufficiency (11%), acquired hypertension (8%), and disabling neuropathy (13%) were also frequent. Salvage treatment was a risk factor in most cases. Smoking, age > 50 years during treatment, and preexistent hypertension were the main risk factors for cardiovascular disease. In-field radiation therapy (RT) was related to hypothyroidism, lung fibrosis, hypertension, gastrointestinal toxicity, and renal insufficiency but not to cardiovascular events. Autologous stem cell transplantation and cisplatin- and MOPP (mechlorethamine/vincristine/procarbazine/prednisone)-containing therapies were associated with infertility and renal insufficiency. **CONCLUSION:** Altogether, almost half the patients with aggressive NHL experienced events addressed as late non-neoplastic complications. Salvage therapy, smoking, age > 50 years, and in-field RT are important risk factors.

Moser, E. C., E. M. Noordijk, et al. (2006). "Risk of second cancer after treatment of aggressive non-Hodgkin's lymphoma; an EORTC cohort study." *Haematologica* 91(11): 1481-8.

**BACKGROUND AND OBJECTIVES:** Second cancer has been associated with non-Hodgkin's Lymphoma (NHL) treatment, but few studies have addressed this issue considering specific treatments. **DESIGN AND METHODS:** We estimated risk by standardized incidence ratios (SIR) and absolute excess risk (AER) based on general population rates (European Network of Cancer Registries) in 748 patients (aged 15-82 years) treated for aggressive NHL in four successive EORTC (European Organization for Research on Treatment of Cancer) trials. **RESULTS:** All patients received fully-dosed CHOP-like chemotherapy, 65% received involved-field radiotherapy and 14% high-dose

treatment. Half of the patients needed salvage treatment and 37% were followed for more than 10 years. The cause of death was NHL in 79% of the patients; 4% died of second cancer (median survival 8.9 (0.8- 20.5) years). Cumulative incidences (death from any cause being a competing event) were 5% and 11% for solid cancer and 1% and 3% for acute myeloid leukemia/myelodysplastic syndrome at 10 and 15 years, respectively. Cancer risk appeared age-related: in young patients high risks were observed for leukemia (SIR 16.7,95% CI 1.4-93.1,AER 5.0), Hodgkin's lymphoma (SIR 60.1,95% CI 12.4-175.2, AER 15.7), colorectal cancer (SIR 12.5, 95% CI 2.6-36.5, AER 14.7) and lung cancer (SIR 15.4; 95% CI 4.2-39.4, AER 19.8), while risk in patients older than 45 years matched that in the normal population. The risk of cancer was significantly raised by smoking and salvage treatment. INTERPRETATION AND CONCLUSIONS: Half of the patients die of aggressive NHL before living long enough to experience second cancer. Only young patients have a high risk of second cancer during follow-up beyond 10 years.

Nagata, S., A. Nishimura, et al. (2007). "Primary breast lymphoma in the right breast during treatment for left breast cancer." *World J Surg Oncol* **5**: 134.

**BACKGROUND:** Primary breast lymphoma is a rare condition, and distinguishing it from breast cancer is important because their treatments differ radically. Moreover, a recent report showed that mastectomy offered no benefit in the treatment of primary breast lymphoma. **CASE PRESENTATION:** A 59-year-old woman was treated with adjuvant chemotherapy and local radiation after surgery for left breast cancer. She presented with a rapidly growing mass in the right breast at 20 months after surgery. Mammography and computed tomography revealed a massive tumour. She was diagnosed with primary breast lymphoma by aspiration cytology, and surgery was performed. Histopathological and immunohistochemical findings confirmed a diffuse large B-cell type primary breast lymphoma. **CONCLUSION:** In this case, the lymphoma exhibited rapid growth despite chemotherapy for a malignancy in the contralateral breast. The patient had developed bronchiolitis obliterans organizing pneumonia due to radiation. Therefore, surgical treatment of the lymphoma was selected.

Nakao, M., T. Oguri, et al. (2009). "Small-cell lung cancer arising after chemotherapy for a patient with lymphoma of pulmonary mucosa-associated lymphoid tissue-a case report." *Gan To Kagaku Ryoho* **36**(10): 1711-4.

A 76-year-old woman was admitted to our hospital with infiltrations evident in the right lower lobe on chest computed tomography. Bronchoscopic biopsy showed lymphoma of mucosa-associated lymphoid tissue (MALT). Lymphoma of the pulmonary MALT became enlarged at 8 months after diagnosis and dyspnea developed. Four courses of chemotherapy(rituximab+ cladribine)resulted in a partial response. However, 14 months after the chemotherapy, she developed multiple lung and liver tumors accompanied by disseminated intravascular coagulation syndrome. A histological examination of bone marrow aspiration showed small cell carcinoma. We administered one course of carboplatin and etoposide, but bone marrow suppression was so severe that further chemotherapy was precluded. To our knowledge, this is a rare case of small cell lung cancer arising from the treatment of lymphoma of pulmonary MALT.

Naresh, K. N., S. Advani, et al. (2004). "Report of an International Network of Cancer Treatment and Research workshop on non-Hodgkin's lymphoma in developing countries." *Blood Cells Mol Dis* **33**(3): 330-7.

The International Network of Cancer Treatment and Research (INCTR) recently organized a workshop on non-Hodgkin lymphomas (NHLs) in selected developing countries with the purpose of examining existing information relating to the pathology and management of these neoplasms, and identifying potential areas for research. This report provides a summary of the information presented and is focused primarily on the pathology of NHLs in children and adults. In most countries, the WHO classification of lymphomas was used and most participating centers included immunohistochemistry using a wide array of lymphoid antibodies as part of routine diagnosis. Some of the series had been reviewed by an external panel of experts. B-cell lymphomas accounted for 82-88% of all NHLs. The proportions of chronic lymphatic leukemia (4-6%), mantle cell lymphoma (MCL, 3-5%), and plasmacytoma (2-4%) were similar in the series presented. However, there was a significant variation in the proportion of follicular lymphoma (FL), which accounted for 15% and 11% in India and Kuwait, but less than 5% in Pakistan and Egypt. All of these frequencies are significantly lower than those reported in Western series. Diffuse large B-cell lymphoma accounted for about 35% of cases in India but for more 50% in other countries, but this difference was not accounted for by an increased incidence in a single lymphoma subtype in India, but rather an apparent paucity of several subtypes (such as mantle cell and marginal zone lymphomas (MZL)) in other series.

There were relatively high frequencies of Burkitt lymphoma in Egypt (7%) and precursor T-cell lymphoblastic lymphoma in India (6-7%). Peripheral T-cell lymphomas (PTCLs) (not otherwise specified and angioimmunoblastic subtypes) accounted for 3-5% of NHLs, and extranodal lymphoma of T/NK cell type was rare (<1%). These differences in the relative proportions of NHL subtypes among developing countries and between developing countries and the rest of the world presumably arise from differences in environmental and genetic factors that influence lymphomagenesis and strongly suggest that more research in developing countries would provide valuable insights into the pathogenesis of lymphoid neoplasms.

Noordijk, E. M., P. Carde, et al. (2006). "Combined-modality therapy for clinical stage I or II Hodgkin's lymphoma: long-term results of the European Organisation for Research and Treatment of Cancer H7 randomized controlled trials." *J Clin Oncol* **24**(19): 3128-35.

**PURPOSE:** In early-stage Hodgkin's lymphoma (HL), subtotal nodal irradiation (STNI) and combined chemotherapy/radiotherapy produce high disease control rates but also considerable late toxicity. The aim of this study was to reduce this toxicity using a combination of low-intensity chemotherapy and involved-field radiotherapy (IF-RT) without jeopardizing disease control. **PATIENTS AND METHODS:** Patients with stage I or II HL were stratified into two groups, favorable and unfavorable, based on the following four prognostic factors: age, symptoms, number of involved areas, and mediastinal-thoracic ratio. The experimental therapy consisted of six cycles of epirubicin, bleomycin, vinblastine, and prednisone (EBVP) followed by IF-RT. It was randomly compared, in favorable patients, to STNI and, in unfavorable patients, to six cycles of mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, and vinblastine (MOPP/ABV hybrid) and IF-RT. **RESULTS:** Median follow-up time of the 722 patients included was 9 years. In 333 favorable patients, the 10-year event-free survival rates (EFS) were 88% in the EBVP arm and 78% in the STNI arm ( $P = .0113$ ), with similar 10-year overall survival (OS) rates (92% v 92%, respectively;  $P = .79$ ). In 389 unfavorable patients, the 10-year EFS rate was 88% in the MOPP/ABV arm compared with 68% in the EBVP arm ( $P < .001$ ), leading to 10-year OS rates of 87% and 79%, respectively ( $P = .0175$ ). **CONCLUSION:** A treatment strategy for early-stage HL based on prognostic factors leads to high OS rates in both favorable and unfavorable patients. In favorable patients, the combination of EBVP and IF-RT can replace STNI as

standard treatment. In unfavorable patients, EBVP is significantly less efficient than MOPP/ABV.

Oehadian, A., N. Koide, et al. (2007). "Differential expression of autophagy in Hodgkin lymphoma cells treated with various anti-cancer drugs." *Acta Med Indones* **39**(4): 153-6.

**AIM:** autophagy is a pivotal physiological process for survival during starvation, differentiation and normal growth control. It is defined as the process of sequestering cytoplasmic proteins or even entire organelles into the lytic compartment (lysosome/vacuole). This study investigates the expression of autophagy in Hodgkin lymphoma cells treated with various anti-cancer drugs. **METHODS:** Hodgkin's lymphoma cells (HD-My-Z cells) were cultured with various anti-cancer drugs, such as bleomycin, adriamycin, gemcitabine and paclitaxel. Autophagy was detected by fluorescent pattern of light chain 3(LC3) proteins and the apoptotic cell death was determined by annexin V binding. **RESULTS:** autophagy was detected in HD-My-Z cells treated with gemcitabine, but not with bleomycin, adriamycin and paclitaxel. Adriamycin exhibited the strongest cytotoxic action, and the cytotoxic action of bleomycin and gemcitabine was less marked compared with adriamycin. Paclitaxel did not cause significant cell death in the cells. **CONCLUSION:** autophagy was differentially expressed in Hodgkin lymphoma cells treated with anti-cancer drugs and the expression did not correspond to the apoptotic cell death.

O'Flaherty, C., F. Vaisheva, et al. (2008). "Characterization of sperm chromatin quality in testicular cancer and Hodgkin's lymphoma patients prior to chemotherapy." *Hum Reprod* **23**(5): 1044-52.

**BACKGROUND:** Although the incidences of testicular cancer and Hodgkin's lymphoma have increased in young men over the past decade, combination chemotherapy has improved survival. As fertility is of importance to these patients, characterization of sperm chromatin structure is needed. We assessed sperm chromatin in testicular cancer and Hodgkin's lymphoma patients prior to chemotherapy, in comparison with control community and idiopathic infertile volunteers. **METHODS:** DNA damage was assessed with the sperm chromatin structure assay (SCSA), terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) and comet assays; reactive thiols (SH) and DNA compaction were determined with the monobromobimane (mBBr) and chromomycin A3 (CMA3) assays, respectively. **RESULTS:** Both testicular cancer (37%) and Hodgkin's lymphoma (81%) patients had normospermic samples with

increased DNA damage, compared with controls. Cancer patients also had higher reactive thiols and CMA3 staining, indicating low DNA compaction. CONCLUSIONS: Sperm DNA integrity and compaction were affected in testicular cancer and Hodgkin's lymphoma patients prior to chemotherapy. Although SCSA, TUNEL and comet assays all detected DNA damage, the latter was optimal for use in cancer patients. A combination of the comet assay with tests that evaluate sperm DNA compaction, such as flow cytometry-based CMA3 and mBBr assays, is a reliable strategy to characterize sperm chromatin quality in cancer patients at the time of sperm banking.

Olsen, E., E. Vonderheid, et al. (2007). "Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC)." *Blood* **110**(6): 1713-22.

The ISCL/EORTC recommends revisions to the Mycosis Fungoides Cooperative Group classification and staging system for cutaneous T-cell lymphoma (CTCL). These revisions are made to incorporate advances related to tumor cell biology and diagnostic techniques as pertains to mycosis fungoides (MF) and Sezary syndrome (SS) since the 1979 publication of the original guidelines, to clarify certain variables that currently impede effective interinstitution and interinvestigator communication and/or the development of standardized clinical trials in MF and SS, and to provide a platform for tracking other variables of potential prognostic significance. Moreover, given the difference in prognosis and clinical characteristics of the non-MF/non-SS subtypes of cutaneous lymphoma, this revision pertains specifically to MF and SS. The evidence supporting the revisions is discussed as well as recommendations for evaluation and staging procedures based on these revisions.

Otley, C. C. (2006). "Non-Hodgkin lymphoma and skin cancer: A dangerous combination." *Australas J Dermatol* **47**(4): 231-6.

There is a significant association between non-Hodgkin lymphoma, including chronic lymphocytic leukaemia, and both melanoma and non-melanoma skin cancer. This review highlights the existing data on the phenomenon of accelerated skin cancer in patients with non-Hodgkin lymphoma and specifically chronic lymphocytic leukaemia. The outcomes of patients with non-Hodgkin lymphoma (including chronic lymphocytic leukaemia) and non-melanoma skin cancer are worse than in patients

without concomitant lymphoreticular malignancy, as shown by increased rates of local recurrence, regional metastasis and death. Pathogenic factors may be common between non-Hodgkin lymphoma and chronic lymphocytic leukaemia and skin cancer. The treatment of skin cancer in patients with non-Hodgkin lymphoma must factor in the worse prognosis and adapt standard therapeutic approaches to minimize the risk of metastasis and death. Preventive strategies and early detection are paramount in this high-risk population.

Parveen, Z. and K. Thompson (2009). "Subcutaneous panniculitis-like T-cell lymphoma: redefinition of diagnostic criteria in the recent World Health Organization-European Organization for Research and Treatment of Cancer classification for cutaneous lymphomas." *Arch Pathol Lab Med* **133**(2): 303-8.

Subcutaneous panniculitis-like T-cell lymphoma is a primary T-cell lymphoma that preferentially involves the subcutaneous tissue. Although subcutaneous panniculitis-like T-cell lymphoma has been recognized as a distinctive entity in the category of peripheral T-cell lymphoma in the World Health Organization classification, its diagnostic criteria has been redefined by the recent World Health Organization-European Organization for Research and Treatment of Cancer classification for primary cutaneous lymphomas. Subcutaneous panniculitis-like T-cell lymphoma is now restricted to primary cutaneous T-cell lymphoma expressing alphabeta T-cell receptor phenotype. These lymphomas are usually CD3(+), CD4(-), CD8(+), and CD56(-), and usually have an indolent clinical course. The clinicopathologic features, differential diagnosis, immunophenotypic characteristics, and molecular features of subcutaneous panniculitis-like T-cell lymphoma are presented in light of the recent World Health Organization-European Organization for Research and Treatment of Cancer classification.

Perkins, S. L., M. A. Lones, et al. (2003). "B-Cell non-Hodgkin's lymphoma in children and adolescents: surface antigen expression and clinical implications for future targeted bioimmune therapy: a children's cancer group report." *Clin Adv Hematol Oncol* **1**(5): 314-7.

Paraffin-embedded diagnostic biopsy materials from a large cohort of pediatric and adolescent patients with mature B-cell non-Hodgkin's lymphoma (NHL) treated on the Children's Cancer Group arm of an international cooperative trial were studied to determine their phenotypic features and the feasibility of using targeted bioimmune therapies. There were 345 patients eligible for analysis: 208 with Burkitt's lymphoma (BL), 43 with high-grade B-cell

lymphoma, Burkitt-like (HGBL), and 94 with diffuse large B-cell lymphoma (DLBCL). Samples were immunophenotyped centrally using a standard panel that included CD20, CD79a, CD3, and CD45RO. Additional staining with CD22 was performed on a subset of cases. Immunophenotypic studies showed positive staining with CD20 in 100% of cases of BL and HGBL and in 98% of cases with DLBCL. CD22 expression was present in all cases of BL and DLBCL and in 87% of cases HGBL. This study indicates that immune-based therapies such as rituximab and ibritumomab-tiuxetan (anti-CD20) and epratuzumab (anti-CD22) are feasible in pediatric cases of mature B-cell NHLs.

Peterson, B. A., J. Johnson, et al. (2007). "High dose CHOP: a phase II study of initial treatment in aggressive non-Hodgkin lymphoma. Cancer and Leukemia Group B 9351." *Leuk Lymphoma* **48**(5): 870-80.

Cyclophosphamide and doxorubicin, two important drugs in the treatment of lymphoma, exhibit a relationship between dose and fractional cell kill, and because of their toxicity profiles, they are candidates for significant dose escalation. We performed a phase II trial to determine the response rate, toxicity, and feasibility of escalated doses of both drugs as part of high dose CHOP in diffuse aggressive lymphoma. Patients who had advanced, previously untreated diffuse aggressive lymphomas (IWF E-H) and an International Prognostic Index of intermediate to high risk were eligible. Treatment was cyclophosphamide 2 gm/m<sup>2</sup>/day intravenously on Days 1 and 2 (total cycle dose 4 gm/m<sup>2</sup>), doxorubicin 35 mg/m<sup>2</sup>/day as a continuous infusion on Days 1 and 2 (total 70 mg/m<sup>2</sup>), vincristine 1.4 mg/m<sup>2</sup> (maximum 2 mg) on Day 1 and prednisone 100 mg/day orally on Days 1 - 5 repeated every 3 weeks for a total of four cycles. G-CSF, prophylactic antibiotics, and mesna were provided. A total of 99 patients were enrolled; 98 received therapy. Major toxicities were Grade 4 neutropenia and thrombocytopenia occurring in 97% and 92%, respectively. Serious infections occurred in 53%. Treatment-related mortality was 2%. The overall response rate is 85%, and two-year failure free and overall survival are 39% and 64%, respectively. Persistent or relapsed lymphoma was the overwhelming cause of death. Six patients have developed AML or MDS. In view of the substantial toxicity accompanying high dose CHOP, the observed outcome suggests that its efficacy is not sufficient to make further study feasible.

Pettengell, R., M. Aapro, et al. (2009). "Implications of the European Organisation for Research And

Treatment Of Cancer (EORTC) guidelines on the use of granulocyte colony-stimulating factor (G-CSF) for lymphoma care." *Clin Drug Investig* **29**(8): 491-513.

Febrile neutropenia (FN) is a potentially life-threatening complication of myelosuppressive chemotherapy. The European Organisation for Research and Treatment of Cancer (EORTC) guidelines recommend use of primary granulocyte colony-stimulating factor (G-CSF) prophylaxis if the overall FN risk to a patient is  $\geq 20\%$ , or if a reduction in chemotherapy dose intensity correlates with a poorer outcome. Many of the regimens used for treatment of lymphoma, including R-CHOP (rituximab combined with cyclophosphamide, doxorubicin, vincristine and prednisolone), are associated with an FN risk of approximately 20% or higher. Individual patient factors that may increase the risk of FN such as advanced age or advanced disease should be taken into account when assessing the need for G-CSF support. Predictive models are being developed to facilitate individual risk assessment. Additional anti-infective prophylaxis may be indicated in some settings. There is now much evidence for the benefits of G-CSF in reducing the incidence of FN and facilitating delivery of chemotherapy, including dose-escalated and dose-dense (interval-reduced) regimens. If given according to guidelines, G-CSF has the potential to reduce FN and related morbidity. Furthermore, by facilitating delivery of planned chemotherapy, use of G-CSF may potentially influence survival in the curative setting. Implementation of the EORTC guidelines will lead to a greater proportion of patients receiving G-CSFs, but the costs involved should be at least partly offset by a reduction in FN and its associated costs, including those of hospitalization.

Piekarz, R. L., R. W. Robey, et al. (2004). "T-cell lymphoma as a model for the use of histone deacetylase inhibitors in cancer therapy: impact of depsipeptide on molecular markers, therapeutic targets, and mechanisms of resistance." *Blood* **103**(12): 4636-43.

Depsipeptide (FK228) is a novel histone deacetylase inhibitor currently in clinical trials and the first to demonstrate clinical activity in patients. Responses have been observed in patients with T-cell lymphomas, despite prior treatment with multiple chemotherapeutic agents. To better understand the effects of histone deacetylase inhibitors on T-cell lymphoma, the human T-cell lymphoma cell line HUT78 was tested for sensitivity and molecular response to depsipeptide. Treatment with depsipeptide, as well as other histone deacetylase inhibitors, caused induction of histone acetylation, induction of p21 expression, and substantial apoptosis

without significant cell cycle arrest. Treatment with the caspase inhibitor z-VAD-fmk significantly inhibited depsipeptide-induced apoptosis, enabling detection of cell cycle arrest. Treatment with depsipeptide increased expression of the interleukin-2 (IL-2) receptor, and combination with the IL-2 toxin conjugate denileukin difitox resulted in more than additive toxicity. Cells selected for resistance to depsipeptide overexpressed the multidrug resistance pump, P-glycoprotein (Pgp). However, cells selected for resistance to depsipeptide in the presence of a Pgp inhibitor had a Pgp-independent mechanism of resistance. These studies confirm the activity of depsipeptide in a T-cell lymphoma model and suggest a general sensitivity of T-cell lymphoma to histone deacetylase inhibitors, an emerging new class of anticancer agents.

Poortmans, P. M., H. C. Kluin-Nelemans, et al. (2003). "High-dose methotrexate-based chemotherapy followed by consolidating radiotherapy in non-AIDS-related primary central nervous system lymphoma: European Organization for Research and Treatment of Cancer Lymphoma Group Phase II Trial 20962." *J Clin Oncol* **21**(24): 4483-8.

**PURPOSE:** To confirm the feasibility and estimate the efficacy of methotrexate (MTX), teniposide, carmustine, and methylprednisolone (MBVP) chemotherapy combined with radiotherapy (RT) for patients with non-AIDS-related primary CNS lymphoma (PCNSL) treated in a multicenter setting. **PATIENTS AND METHODS:** Treatment consisted of two cycles of MBVP (MTX 3 g/m<sup>2</sup> days 1 and 15, teniposide 100 mg/m<sup>2</sup> days 2 and 3, carmustine 100 mg/m<sup>2</sup> day 4, methylprednisolone 60 mg/m<sup>2</sup> days 1 to 5, and two intrathecal injections of MTX 15 mg, cytarabine 40 mg, and hydrocortisone 25 mg) followed by 40 Gy of RT. Primary end points were response and safety of this regimen. **RESULTS:** Twelve centers included 52 patients who were all analyzed on an intent-to-treat basis. Median follow-up of all patients was 27 months. One patient progressed and died before treatment, and five patients died during treatment. Four patients received RT after one cycle of chemotherapy, and 42 patients completed the entire treatment. Hematologic grade 3 and 4 toxicity was seen in 78% of patients for leukocytes and 24% of patients for platelets. The overall response rate of all 52 patients was 81%. Two patients who did not fulfill the criteria of objective response survived more than 1 year; one of them is still alive without disease. Eighteen patients died; 11 deaths were a result of tumor, five were probably treatment-related, one was caused by late leukoencephalopathy, and one was a result of intercurrent disease. Median estimated overall survival was 46 months. **CONCLUSION:**

MBVP followed by RT for PCNSL has a high response rate. However, the 10% toxic death rate during treatment in a multicenter setting underlines the need for highly specialized care.

Pulford, K., S. W. Morris, et al. (2004). "Anaplastic lymphoma kinase proteins in growth control and cancer." *J Cell Physiol* **199**(3): 330-58.

The normal functions of full-length anaplastic lymphoma kinase (ALK) remain to be completely elucidated. Although considered to be important in neural development, recent studies in *Drosophila* also highlight a role for ALK in gut muscle differentiation. Indeed, the *Drosophila* model offers a future arena for the study of ALK, its ligands and signalling cascades. The discovery of activated fusion forms of the ALK tyrosine kinase in anaplastic large cell lymphoma (ALCL) has dramatically improved our understanding of the pathogenesis of these lymphomas and enhanced the pathological diagnosis of this subtype of non-Hodgkin's lymphoma (NHL). Likewise, the realisation that a high percentage of inflammatory myofibroblastic tumours express activated-ALK fusion proteins has clarified the causation of these mesenchymal neoplasms and provided for their easier discrimination from other mesenchymal-derived inflammatory myofibroblastic tumour (IMT) mimics. Recent reports of ALK expression in a range of carcinoma-derived cell lines together with its apparent role as a receptor for PTN and MK, both of which have been implicated in tumorigenesis, raise the possibility that ALK-mediated signalling could play a role in the development and/or progression of a number of common solid tumours. The therapeutic targeting of ALK may prove to have efficacy in the treatment of many of these neoplasms.

Querfeld, C., N. Mehta, et al. (2009). "Alemtuzumab for relapsed and refractory erythrodermic cutaneous T-cell lymphoma: a single institution experience from the Robert H. Lurie Comprehensive Cancer Center." *Leuk Lymphoma* **50**(12): 1969-76.

We present the results of an open-label clinical trial and the clinical use of alemtuzumab in 19 heavily pretreated patients with advanced erythrodermic cutaneous T-cell lymphomas (CTCL) (erythrodermic mycosis fungoides and Sezary syndrome). Ten patients received alemtuzumab intravenously using an escalating dose regimen with a final dose of 30 mg three times weekly for 4 weeks followed by subcutaneous administration for 8 weeks. Nine patients were treated with only the SQ or IV dosing. The overall response rate was 84%, with 9 (47%) complete and 7 (37%) partial remissions. The median follow-up was 24 months (range, 6 to 62+

months). Median overall survival was 41 months whereas median progression free survival was 6 months. Minimal residual disease by T-cell gene rearrangement studies was detected in 11 patients who achieved complete response and partial response. Toxicities included myelosuppression and infections; however, the majority of side effects were of Grade 2 in severity and transient. One patient was diagnosed with a concurrent lymphoma (mantle cell lymphoma) 6 months after completing alemtuzumab therapy. Alemtuzumab is particularly effective in patients with erythrodermic CTCL with acceptable toxicities. Combined strategies with alemtuzumab may achieve molecular remissions with longer response durations.

Rabinovsky, R., J. W. Uhr, et al. (2007). "Cancer dormancy: lessons from a B cell lymphoma and adenocarcinoma of the prostate." *Adv Cancer Res* **97**: 189-202.

Cancer dormancy delineates a situation in which residual tumor cells persist in a patient with no apparent clinical symptoms. Although the precise mechanisms underlying cancer dormancy have not been explained, experimental models have provided some insights into the factors that might be involved in the induction and maintenance of a tumor dormant state. The authors of the present chapter studied a murine B cell lymphoma that can be made dormant when interacting with antibodies directed against the idiotype on its immunoglobulin Ig receptor. This experimental model of antibody-induced dormancy enabled the isolation and characterization of dormant lymphoma cells. The results indicated that anti-Ig antibodies activate growth-inhibiting signals that induced cycle arrest and apoptosis. This process appeared to be balanced by the growth of the tumor cells such that the tumor did not expand. In contrast, antibodies against HER-2-expressed on prostate adenocarcinoma (PAC) cells were not growth inhibitory. However, an immunotoxin (IT) prepared by conjugating HER-2 to the A-chain of ricin (RTA) was internalized by PAC cells, followed by induction of cycle arrest and apoptotic death. Infusion of HER-2-specific IT into PAC-bearing immunodeficient mice did not eradicate the tumor but retained it dormant over an extended period of time. Hence, certain aspects of signaling receptors expressed on cancer can be manipulated by antibodies to induce and maintain a tumor dormant state.

Raderer, M., A. Puspok, et al. (2003). "Early cancer of the stomach arising after successful treatment of gastric MALT lymphoma in patients with autoimmune disease." *Scand J Gastroenterol* **38**(3): 294-7.

**BACKGROUND:** Extranodal marginal zone B-cell lymphoma of the mucosa associated lymphoid

tissue (MALT lymphoma) arises in lymphoid tissue acquired through chronic antigenic stimulation as exemplified by *Helicobacter pylori*. Secondary development of gastric cancer, however, is thought to be a rare event. The detection of a signet ring cell carcinoma during follow-up endoscopy after successful therapy of MALT lymphoma in a patient with Sjogren's syndrome prompted us to analyse the frequency of subsequent gastric cancer in patients with underlying autoimmune disease (AD). **METHODS:** Patients with early stage MALT lymphoma and an underlying AD were evaluated for the occurrence of a secondary gastric cancer during the course of follow-up. Data analysed included the type of AD, stage of MALT lymphoma, *H. pylori* status, treatment for MALT lymphoma and response, follow-up, the presence of a secondary cancer, and time to development of cancer. In all patients, histologic samples were reassessed for the extent of gastritis, presence of intestinal metaplasia or focal atrophy at the time of lymphoma diagnosis. **RESULTS:** A total of eight patients with overt AD at the time of diagnosis of MALT lymphoma were identified. All patients were women aged between 56 and 77 years; 5 had Sjogren's syndrome, 2 had autoimmune thyroiditis (1 along with psoriasis) and 1 suffered from polymyalgia rheumatica. All patients had early stage MALT lymphoma restricted to the mucosa and submucosa at the time of diagnosis, and the presence of *H. pylori* was found in all cases. Two of these patients achieved complete remission (CR) of the lymphoma following *H. pylori* eradication, while six were judged unresponsive and underwent chemotherapy, resulting in CR in all cases. One patient died from stroke while being in CR for 2 months following chemotherapy. Two patients (25%) developed early cancer limited to the gastric mucosa while being in CR from lymphoma for 9 and 27 months, respectively, and underwent partial gastrectomy. Final staging of gastric cancer revealed pT1pN0M0 in both cases. Of the remaining 5 cases, 1 patient had a local lymphoma relapse 18 months after CR and was salvaged with radiotherapy. In the remaining 4 patients, no evidence of lymphoma recurrence or a second malignancy has been found so far by regular follow-up every 3 months for a time-span between 52 and 63 months after initial diagnosis. **CONCLUSION:** Patients with concurrent MALT lymphoma and an underlying autoimmune condition show not only an impaired response to *H. pylori* eradication but might also be at increased risk for the development of gastric cancer. In view of this, such patients should be followed closely by regular endoscopies after remission of MALT lymphoma.

Raemaekers, J., H. Kluin-Nelemans, et al. (2002). "The achievements of the EORTC Lymphoma Group. European Organisation for Research and Treatment of Cancer." *Eur J Cancer* **38 Suppl 4**: S107-13.

From 1964 onwards, the EORTC Lymphoma Group has conducted seven consecutive randomised phase 3 trials on early stage Hodgkin's lymphoma aiming at increasing efficacy, while decreasing short- and long-term toxicity. Staging laparotomy is definitely abandoned and replaced by identification of prognostic subgroups based on pretreatment clinical characteristics. Event-free and overall survival significantly improved from about 50 and then 70%, in the early years, to over 80 and then 90% more recently. Radiotherapy fields have become more restricted, whereas chemotherapy has become standard. Longitudinal quality-of-life assessment has become an integral part of our studies. In advanced stages, overall outcome has improved as well with 6-year survival rates of over 80%. In aggressive types of NHL, the second generation chemotherapy schedule CHVmP-BV was superior to CHVmP. We could not show any advantage for intensification of upfront treatment with autologous stem cell transplantation.

Ramadan, K. M., T. Shenkier, et al. (2007). "A clinicopathological retrospective study of 131 patients with primary bone lymphoma: a population-based study of successively treated cohorts from the British Columbia Cancer Agency." *Ann Oncol* **18**(1): 129-35.

**BACKGROUND:** Primary bone lymphoma (PBL) is a distinct clinicopathological entity. Although PBL has been reviewed in several small studies, few reflect recent improvements in primary treatment. **METHODS:** We used the British Columbia Cancer Agency Lymphoid Cancer Database to identify all patients with PBL (1983-2005). All were staged in a uniform manner and treated with era-specific protocols. **RESULTS:** We identified 131 patients with a median age of 63 years (18-87). One third had disease in long bones and another one third had disease in the spine, of which half presented with spinal cord compression. Patients with diffuse large-cell lymphoma (DLCL) (n=103, 79%) had 5- and 10-year overall survivals (OS) of 62% and 41%, respectively. Multivariate analysis identified three prognostic groups: age<60 with International Prognostic Index (IPI) 1-3 (n=43), age>or=60 with IPI 0-3 (n=23) and age>or=60 with IPI 4-5 (n=33), with markedly different 5-year OS of 90%, 61% and 25%, respectively (P<0.0001). Neither primary site nor pathological fracture at presentation had an impact on OS. The 3-year progression-free survival in patients who received rituximab plus combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOPR) chemotherapy

was 88% compared with 52% in those who received CHOP-like chemotherapy without rituximab (P=0.005). The 10-year OS for those with advanced-stage disease who received irradiation plus chemotherapy was 25% versus 56% for those who received chemotherapy alone (P=0.025). Patients received irradiation if spinal cord compression was present or residual disease at the end of chemotherapy was thought to require it. **CONCLUSIONS:** PBL is usually of DLCL type and has an improved outcome with CHOPR. Younger patients with good IPI score have a favorable prognosis.

Rizzieri, D. A., J. L. Johnson, et al. (2004). "Intensive chemotherapy with and without cranial radiation for Burkitt leukemia and lymphoma: final results of Cancer and Leukemia Group B Study 9251." *Cancer* **100**(7): 1438-48.

**BACKGROUND:** The objective of the current study was to evaluate the efficacy of intensive chemotherapy with and without cranial radiation for central nervous system (CNS) prophylaxis in adults with Burkitt leukemia or lymphoma. **METHODS:** Patients received 18 weeks of therapy. Prophylactic cranial radiation (2400 centigrays) and 12 doses of triple intrathecal chemotherapy were administered to the first cohort of patients. A subsequent cohort received the same therapy, with the exceptions that intrathecal therapy was reduced to six doses and radiotherapy was administered only to high-risk individuals. **RESULTS:** The median follow-up durations were 6.8 years in Cohort 1 and 4.1 years in Cohort 2. Three occurrences of transverse myelitis, 2 severe neuropathies, 3 cases of aphasia, and 1 case of blindness were documented in the first cohort of 52 patients (Cohort 1). In the subsequent cohort of 40 patients (Cohort 2), none of these occurrences were observed, and patients experienced less neurologic toxicity overall (61% vs. 26%; P=0.001). Responses were similar, and the 3-year event-free survival rate was 0.52 (95% confidence interval, 0.38-0.65) for Cohort 1 and 0.45 (0.29-0.60) for Cohort 2. **CONCLUSIONS:** Intensive, short-duration chemotherapy with less intensive CNS prophylaxis led to control at this sanctuary site with little neurotoxicity and may be curative for adults with Burkitt leukemia or lymphoma.

Salar, A., J. M. Ramon, et al. (2005). "Double diagnosis in cancer patients and cutaneous reaction related to gemcitabine: CASE 1. Synchronous mucosa-associated lymphoid tissue lymphoma and gastrointestinal stromal tumors of the stomach." *J Clin Oncol* **23**(28): 7221-3.

Sanna, G., K. Lorizzo, et al. (2007). "Breast cancer in Hodgkin's disease and non-Hodgkin's lymphoma survivors." *Ann Oncol* **18**(2): 288-92.

**BACKGROUND:** Better therapeutic approaches for patients with Hodgkin's disease (HD) and non-Hodgkin's lymphomas (NHL) resulted in high cure rates, at cost of serious late side effects. Second primary tumours are a major concern for long-term survivors, and breast cancer (BC) is the most common solid tumour among women treated for HD. **Materials and methods:** Fifty-three women treated for primary BC with previous history of malignant lymphoma were identified in our institution, 35 with HD (66%), 18 (34%) with NHL. A comparison group was randomly selected from our database matching for each patient with previous lymphoma, two patients with primary BC (rate 1 : 2) for age, stage (pathological tumour size [pT] status and nodal status), year of diagnosis, and estrogen and progesterone status (positive versus negative). The primary end points were disease-free survival (DFS) and overall survival (OS). **RESULTS:** The two groups of patients were compared for biological features: histopathological diagnosis, grading, lymphatic invasion, c-erbB2 overexpression, and Ki-67. Considering these variables, no significant differences were observed between the two groups with the exception of Ki-67, which was found higher in those with previous HD or NHL (65% versus 49%, respectively,  $P = 0.0526$ , borderline significant). Comparing the two groups for treatment approach, no differences were found for surgical and medical therapy (endocrine therapy and chemotherapy). However, regarding patients with node-positive disease (14 versus 35 patients), five patients in the lymphoma group (36%), compared with 24 (69%) in the matched group received anthracycline-based therapy ( $P = 0.0345$ ). As expected, radiotherapy was used very differently in the two groups, with 36% of patients in the study group undergoing intraoperative radiotherapy with electrons versus 10% in the control group ( $P = 0.0001$ ). Five-year DFS was 54.5% for the study cohort compared with 91% for controls ( $P < 0.0001$ ). Five-year OS percentages were also statistically different (86.6% and 98.6%, respectively,  $P = 0.031$ ). **CONCLUSIONS:** Previous history of malignant lymphoma is a negative prognostic factor for women diagnosed subsequently with BC. Some undertreatment of women with the latter might be hypothesised as the reason for the worse outcome. Influence of other variables, like previous exposure to cytotoxics, or some unknown biological features related to the previous disease and treatment, should still be investigated in the attempt to improve the dire outcome of these patients.

Savage, S. A., H. A. Wotherspoon, et al. (2008). "Cancer waiting times: what is the value of a lymphoma waiting time?" *Scott Med J* **53**(3): 5-7.

**BACKGROUND AND AIM:** Waiting times for patients with lymphoma have been reported across the United Kingdom since 2005. Lymphoma however, is not a single disease but a wide spectrum of lymphoid tumours that range from the most malignant to the most indolent, from highly curable to incurable. We now question the value of the current system that reports lymphoma waiting time on a quarterly basis and makes no allowance for the different types of lymphoma. **METHOD:** Four hundred and sixty nine cases of lymphoma were registered in the west of Scotland in 2004. Complete datasets were available on 428. Patient demographic data, subtypes of lymphoma, biopsy site and referral urgency data were linked to the waiting times analysis for 2004 for the three subtypes, Lymphoma (HL), Diffuse Large B Cell (DLBC) and follicular Non Hodgkin Lymph (NHL). **RESULTS:** Patients with HL were younger, more likely to receive urgent referral and have a diagnosis made from neck node biopsy than the other two groups. Patients with DLBC NHL however had the shortest interval between presentation and the start of treatment and were subsequently more likely to receive treatment within 62 days than patients with either follicular NHL ( $p < 0.001$ ) or HL ( $p < 0.05$ ). **CONCLUSION:** Lymphoma subtype is a major factor determining the rate of progress from presentation to the start of treatment, hence the waiting time.

Schillaci, O. (2006). "Single-photon emission computed tomography/computed tomography in lung cancer and malignant lymphoma." *Semin Nucl Med* **36**(4): 275-85.

In nuclear oncology, despite the fast-growing diffusion of (18)F-fluorodeoxyglucose positron emission tomography (FDG-PET), single-photon emission computed tomography (SPECT) studies can still play an useful clinical role in several applications. The main limitation of SPECT imaging with tumor-seeking agents is the lack of the structural delineation of the pathologic processes they detect; this drawback sometimes renders SPECT interpretation difficult and can diminish its diagnostic accuracy. Fusion with morphological studies can overcome this limitation by giving an anatomical map to scintigraphic data. In the past, software-based fusion of independently performed SPECT and CT images proved to be time-consuming and impractical for routine use. The recent development of dual-modality integrated imaging systems that provide functional (SPECT) and anatomical (CT) images in the same scanning session, with the acquired images coregistered by means of the hardware, has opened a new era in this field. The first

reports indicate that SPECT/CT is very useful in cancer imaging because it is able to provide further information of clinical value in several cases. In SPECT, studies of lung cancer and malignant lymphomas using different radiopharmaceutical, hybrid images are of value in providing the correct localization of tumor sites, with a precise detection of the involved organs, and the definition of their functional status, and in allowing the exclusion of disease in sites of physiologic tracer uptake. Therefore, in lung cancer and lymphomas, hybrid SPECT/CT can play a role in the diagnosis of the primary tumor, in the staging of the disease, in the follow-up, in the monitoring of therapy, in the detection of recurrence, and in dosimetric estimations for target radionuclide therapy.

Senff, N. J., E. M. Noordijk, et al. (2008). "European Organization for Research and Treatment of Cancer and International Society for Cutaneous Lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas." *Blood* **112**(5): 1600-9.

Primary cutaneous B-cell lymphomas (CBCL) represent approximately 20% to 25% of all primary cutaneous lymphomas. With the advent of the World Health Organization-European Organization for Research and Treatment of Cancer (EORTC) Consensus Classification for Cutaneous Lymphomas in 2005, uniform terminology and classification for this rare group of neoplasms were introduced. However, staging procedures and treatment strategies still vary between different cutaneous lymphoma centers, which may be because consensus recommendations for the management of CBCL have never been published. Based on an extensive literature search and discussions within the EORTC Cutaneous Lymphoma Group and the International Society for Cutaneous Lymphomas, the present report aims to provide uniform recommendations for the management of the 3 main groups of CBCL. Because no systematic reviews or (randomized) controlled trials were available, these recommendations are mainly based on retrospective studies and small cohort studies. Despite these limitations, there was consensus among the members of the multidisciplinary expert panel that these recommendations reflect the state-of-the-art management as currently practiced in major cutaneous lymphoma centers. They may therefore contribute to uniform staging and treatment and form the basis for future clinical trials in patients with a CBCL.

Seo, D. B., K. S. Kwon, et al. (2007). "Metachronous gastric MALT lymphoma and early gastric cancer: a case report." *Korean J Gastroenterol* **49**(4): 245-50.

Metachronous association between gastric lymphoma and early gastric cancer is a rare event. Recent studies have suggested that a relationship exists between gastric mucosa-associated lymphoid tissue (MALT) lymphoma and gastric carcinoma although the mechanism is unknown. Herein, we report a 53-year-old man who visited to our hospital due to melena. Esophagogastroduodenoscopy (EGD) revealed a MALT lymphoma on the greater curvature of lower body. The patient received anti-Helicobacter pylori eradication therapy, followed by 6 cycles of chemotherapy and radiation therapy, and achieved complete remission 12 months after the therapy. Three years later, he revisited our hospital with epigastric pain. EGD revealed an early gastric cancer on the anterior wall of proximal antrum, nearly opposite to the previous lymphoma site, and a partial gastrectomy was performed. To the best of our knowledge, this is the first case report of metachronous MALT lymphoma and subsequent gastric carcinoma in Korea.

Sheen-Chen, S. M. and H. L. Eng (2007). "Development of malignant lymphoma subsequent to breast cancer." *Eur J Cancer Care (Engl)* **16**(4): 331-2.

The development of malignant lymphoma following breast cancer has not been described before. Here we report the development of malignant lymphoma at the ipsilateral chest wall subsequent to the surgical treatment of breast cancer. A 48-year-old woman underwent modified radical mastectomy due to breast carcinoma. Tamoxifen (10 mg twice daily) was given 3 years after the operation and continued for about 3 years. The patient was well until she recently (17 years after the initial operation) noted a small lump at her left anterior chest wall near the axilla. The local tumour mass was initially assumed to be a local recurrent lesion of breast cancer. Excisional biopsy was performed and eventually was histologically diagnosed to be malignant lymphoma. In view of the therapeutic implication, the development of second malignancy should not be mistaken as a progression of the known primary malignancy. Only with the awareness of such entity, can the prompt diagnosis and proper treatment be achieved.

Shenkier, T. N., N. Voss, et al. (2005). "The treatment of primary central nervous system lymphoma in 122 immunocompetent patients: a population-based study of successively treated cohorts from the British Columbia Cancer Agency." *Cancer* **103**(5): 1008-17.

BACKGROUND: The objective of this study was to evaluate the clinical outcome of a population-based cohort of immunocompetent patients with primary central nervous system lymphoma (PCNSL)

treated with 3 different strategies over 13 years. METHODS: One hundred twenty-two consecutive patients (median age, 66 years) with PCNSL were identified. Three treatment strategies were employed: 1) whole-brain irradiation with (from January, 1990, to June, 1991) or without (from April, 1995, to December, 1999) cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-type chemotherapy (n=50 patients); 2) combined-modality therapy, including 1 g/m<sup>2</sup> methotrexate plus whole-brain irradiation (from July, 1991, to March, 1995; n=34 patients); and 3) 8 g/m<sup>2</sup> methotrexate alone (from January, 2000, to March, 2003) with whole-brain irradiation reserved for those with progressive disease (n=38 patients). Treatment failure was defined as progressive disease, disease recurrence, death from toxicity or lymphoma, or toxicity that necessitated a change in primary treatment. RESULTS: The median failure-free survival was 7 months, and the median overall survival (OS) was 17 months. The median OS was similar in all 3 eras. In this population-based analysis, one-third of patients did not receive the treatment strategy of the era. Therefore, the data also were analyzed by treatment received. On multivariate analysis (including era of treatment), 3 factors—age > 60 years, lactate dehydrogenase > normal, and omission of methotrexate—were associated significantly with poorer OS (hazard ratio: 2.3, 2.2, and 2.3, respectively). CONCLUSIONS: Outcomes for a general population with PCNSL remained constant despite different treatment strategies over three eras. For the two-thirds of patients who could receive potentially curative treatment, age, lactate dehydrogenase level, and receipt of > or = 1 g/m<sup>2</sup> methotrexate appeared to be important determinants of OS.

Shenkier, T. N., N. Voss, et al. (2002). "Brief chemotherapy and involved-region irradiation for limited-stage diffuse large-cell lymphoma: an 18-year experience from the British Columbia Cancer Agency." *J Clin Oncol* **20**(1): 197-204.

PURPOSE: To evaluate clinical outcome of patients with limited-stage diffuse large-cell lymphoma (DLCL) treated with three cycles of chemotherapy followed by involved-region irradiation (IRRT). PATIENTS AND METHODS: Adults with limited-stage DLCL were treated with brief doxorubicin-containing chemotherapy regimens between 1980 and 1998. IRRT was administered 3 to 4 weeks after the third chemotherapy treatment in a dose equivalent to 30 Gy in 10 fractions. RESULTS: Three hundred and eight patients (median age, 64 years) were included, and 299 experienced complete remission. After a median follow-up of 86 months, 64 patients developed progressive disease, and 104

patients died (43 from lymphoma, three from toxicity, and 58 from other causes). Actuarial overall and progression-free survival (PFS) rates were, respectively, 80% and 81% at 5 years and 63% and 74% at 10 years. For subgroups identified using the Miller modification of the International Prognostic Index (IPI), the overall survival rates at 5 and 10 years were, respectively, 97% and 89% (no factors), 77% and 56% (one or two factors), and 58% and 48% (three or four factors), and the 5-year and 10-year PFS rates were, respectively, 94% and 89% (no factors), 79% and 73% (one or two factors), and 60% and 50% (three or four factors). Men with testicular presentation, had a definitely inferior outcome. CONCLUSION: Long-term outcome with three cycles of doxorubicin-based chemotherapy and IRRT confirms that this is a successful approach for the majority of patients with limited-stage DLCL. Subgroups with worse prognoses can be identified, and these patients should be offered alternative treatment approaches.

Shibakura, M., K. Niiya, et al. (2002). "Camptothecin induces urokinase-type plasminogen activator gene-expression in human RC-K8 malignant lymphoma and H69 small cell lung cancer cells." *Acta Med Okayama* **56**(5): 223-7.

We previously reported that anthracyclines, which could generate reactive oxygen species (ROS), could induce the urokinase-type plasminogen activator (uPA) gene expression in human RC-K8 malignant lymphoma cells and in H69 small cell lung cancer (SCLC) cells. In screening other uPA-inducible anti-cancer agents, we found that camptothecin (CPT) and its derivative, SN38, could induce uPA in RC-K8 and H69 cells. CPT and SN38, which are also used for the treatment of lymphoma and SCLC, significantly increased the uPA accumulation in the conditioned media of both cells in a dose-dependent manner. The maximum induction of uPA mRNA levels was observed 24 h after stimulation. Pretreatment with pyrrolidine dithiocarbamate (PDTC), an anti-oxidant, inhibited the CPT-induced uPA mRNA expression. Thus, CPT induces uPA through gene expression, and, therefore, CPT may influence the tumor-cell biology by up-regulating the uPA/plasmin system.

Smith, B. D., E. J. Glusac, et al. (2004). "Primary cutaneous B-cell lymphoma treated with radiotherapy: a comparison of the European Organization for Research and Treatment of Cancer and the WHO classification systems." *J Clin Oncol* **22**(4): 634-9.

PURPOSE: To determine the relationship between the WHO and European Organization for Research and Treatment of Cancer (EORTC) pathologic classifications for primary cutaneous B-cell

lymphoma (CBCL) and the implication of this relationship on initial treatment. **PATIENTS AND METHODS:** Patients with primary CBCL treated with radiotherapy were identified retrospectively. Initial biopsy specimens were reviewed by two dermatopathologists and classified according to the EORTC and WHO systems. Primary outcomes were recurrence-free and overall survival. **RESULTS:** Thirty-four patients were identified; initial biopsy specimens were adequate for classification in 32 patients. Four different composite histopathologic subtypes of lymphoma were identified: 53% (17 of 32) follicle center cell by EORTC and diffuse large B-cell by WHO (FCC/DLB), 25% (eight of 32) follicle center cell by EORTC and follicular by WHO (FCC/Fol), 13% (four of 32) marginal zone by EORTC and WHO (MZ/MZ), and 9% (three of 32) large B-cell of the leg by EORTC and diffuse large B-cell by WHO (Leg/DLB). Five-year relapse-free survival ranged from 62% to 73% for FCC/DLB, FCC/Fol, and MZ/MZ but was 33% for Leg/DLB ( $P = .6$ ). Five-year overall survival was 100% for FCC/DLB, FCC/Fol, and MZ/MZ but was 67% for Leg/DLB ( $P = .07$ ). At 5 years, 21% of all patients had developed extracutaneous disease. **CONCLUSION:** Two-thirds of primary cutaneous FCC lymphomas by EORTC criteria satisfy WHO criteria for DLB lymphoma. Unlike DLB lymphoma presenting in nodal or noncutaneous sites, these lesions are associated with an indolent course and may be treated with local radiotherapy alone.

Stahlberg, A., N. Zoric, et al. (2005). "Quantitative real-time PCR for cancer detection: the lymphoma case." *Expert Rev Mol Diagn* 5(2): 221-30.

Advances in the biologic sciences and technology are providing molecular targets for diagnosis and treatment of cancer. Lymphoma is a group of cancers with diverse clinical courses. Gene profiling opens new possibilities to classify the disease into subtypes and guide a differentiated treatment. Real-time PCR is characterized by high sensitivity, excellent precision and large dynamic range, and has become the method of choice for quantitative gene expression measurements. For accurate gene expression profiling by real-time PCR, several parameters must be considered and carefully validated. These include the use of reference genes and compensation for PCR inhibition in data normalization. Quantification by real-time PCR may be performed as either absolute measurements using an external standard, or as relative measurements, comparing the expression of a reporter gene with that of a presumed constantly expressed reference gene. Sometimes it is possible to compare expression of reporter genes only, which improves the accuracy of

prediction. The amount of biologic material required for real-time PCR analysis is much lower than that required for analysis by traditional methods due to the very high sensitivity of PCR. Fine-needle aspirates and even single cells contain enough material for accurate real-time PCR analysis.

Staratschek-Jox, A., Y. Y. Shugart, et al. (2002). "Genetic susceptibility to Hodgkin's lymphoma and to secondary cancer: workshop report." *Ann Oncol* 13 Suppl 1: 30-3.

Although the occurrence of familial Hodgkin's lymphoma (HL) is a rare event, genetic susceptibility as a cause of HL and its influence on treatment outcome may not be rare. However, results obtained from the analysis of HL families will probably have broad implications with regard to understanding common pathogenic factors leading to the development of the disease. The description of anticipation among the affected offspring of HL patients further strengthens the view that heritable factors contribute to development of HL. Moreover, the finding that particular human leukocyte antigen (HLA) alleles are associated with susceptibility to HL may be regarded as a hint to the presence of an as yet undefined infectious agent, leading to the growth of a malignant lymphoma cell clone in those patients that are more susceptible to this agent due to their HLA genotype. In addition, since an intrinsic genomic instability was observed in a proportion of HL patients, it is plausible that these patients are not only susceptible to the causation of HL, but are also at a higher risk of developing therapy-related (TR) secondary cancers following treatment. Estimation of sister chromatid exchange was established as a tool to identify patients at higher risk of TR cancer. In this context the use of therapeutic agents known to increase genomic instability should be carefully considered prior to determining the best treatment. The future identification of heritable factors contributing to HL will be of importance both with regard to diagnosis as well as treatment of HL patients.

Tam, C. S., R. Bassett, et al. (2009). "Mature results of the M. D. Anderson Cancer Center risk-adapted transplantation strategy in mantle cell lymphoma." *Blood* 113(18): 4144-52.

In this study, we analyzed the long-term outcome of a risk-adapted transplantation strategy for mantle cell lymphoma in 121 patients enrolled in sequential transplantation protocols. Notable developments over the 17-year study period were the addition of rituximab to chemotherapy and preparative regimens and the advent of nonmyeloablative allogeneic stem cell transplantation (NST). In the autologous transplantation group ( $n = 86$ ), rituximab

resulted in a marked improvement in progression-free survival for patients who received a transplant in their first remission (where a plateau emerged at 3-8 years) but did not change the outcomes for patients who received a transplant beyond their first remission. In the NST group, composed entirely of patients who received a transplant beyond their first remission, durable remissions also emerged in progression-free survival at 5 to 9 years. The major determinants of disease control after NST were the use of a peripheral blood stem cell graft and donor chimerism of at least 95%, whereas the major determinant of death was immunosuppression for chronic graft-versus-host disease. Our results show that long-term disease-free survival in mantle cell lymphoma is possible after rituximab-containing autologous transplantation for patients in first remission and after NST for patients with relapsed or refractory disease.

Taslipinar, A., E. Bolu, et al. (2009). "Insulin-like growth factor-1 is essential to the increased mortality caused by excess growth hormone: a case of thyroid cancer and non-Hodgkin's lymphoma in a patient with pituitary acromegaly." *Med Oncol* **26**(1): 62-6.

The effects of growth hormone are mediated in part by stimulating the production of insulin-like growth factor-1. Insulin-like growth factor-1 has significant effects on cell proliferation and differentiation, it is a potent mitogen, and it is a powerful inhibitor of programmed cell death (apoptosis). Insulin-like growth factor-1 also has a well-established role in the transformation of normal cells to malignant cells. Case reports on a possible association between elevated growth hormone and cancer risk in a variety of patient groups have been published. Here, we describe clinical and laboratory findings for a patient with acromegaly who first developed thyroid cancer, and then, in the follow up period, probably due to poorly controlled insulin-like growth factor-1 levels, developed a large cell non-Hodgkin's lymphoma. A search revealed that a case with these peculiarities had not previously been reported.

Tempest, H. G., E. Ko, et al. (2008). "Sperm aneuploidy frequencies analysed before and after chemotherapy in testicular cancer and Hodgkin's lymphoma patients." *Hum Reprod* **23**(2): 251-8.

**BACKGROUND** Multicolour fluorescent in situ hybridization was utilized to detect sperm aneuploidy for chromosomes 13, 21, X and Y in testicular cancer and Hodgkin's lymphoma chemotherapy patients. **METHODS** Aneuploidy was assessed before, and 6, 12 and/or 18-24 months after, the initiation of chemotherapy, and compared with age matched controls. 635 396 sperm were scored blindly

with 5000 sperm/patient/chromosome/ time point, where sperm was available. (First two phrases have been reversed). **RESULTS** Comparing testicular cancer and Hodgkin's lymphoma patients to each other and with controls, cancer-specific differences were identified. Hodgkin's lymphoma patients, particularly, exhibited significantly increased aneuploidy frequencies for all chromosomes throughout treatment. At 6 months, all cancer patients showed significantly increased frequencies of XY disomy and nullisomy for chromosomes 13 and 21. In general, aneuploidy frequencies declined to pretreatment levels 18 months after treatment initiation, but increased aneuploidy frequencies persisted in some chromosomes for up to 24 months. **CONCLUSIONS** Because of elevated aneuploidy frequencies prior to and up to 24 months from the start of chemotherapy, patients should receive genetic counselling about the potentially increased risk of an aneuploid conceptus from sperm cryopreserved prior to chemotherapy, and for conceptions up to 2 years after the initiation of treatment.

Thomas, C., C. Cans, et al. (2004). "No long-term increase in sperm aneuploidy rates after anticancer therapy: sperm fluorescence in situ hybridization analysis in 26 patients treated for testicular cancer or lymphoma." *Clin Cancer Res* **10**(19): 6535-43.

**PURPOSE:** Lymphomas and testicular cancers are the most frequent malignancies among young men. With recent improvement of survival rates, for many patients, the question is raised of the consequences of the anticancer treatments on their fertility and more specifically of a potential genetic risk for the offspring. This article presents the study of sperm aneuploidy rates in the largest population of cancer-treated patients studied thus far. **EXPERIMENTAL DESIGN:** In the present study, 38 patients were initially included 7 months to 5 years after a cancer treatment by chemotherapy and/or radiotherapy for testicular cancer (n = 19) or lymphoma (n = 19). Twelve of them were azoospermic. Sperm aneuploidy rates of chromosomes X, Y, 13, 18, and 21 were analyzed by multicolor fluorescent in situ hybridization in the 26 other patients. **RESULTS:** In most cases, the disomy/diploidy rates after cancer therapy did not significantly differ from those observed in the group of control healthy donors. Only five patients (one lymphoma and four testicular cancer) showed significant but still moderate increases in disomic and/or diploid sperm. For the lymphoma patient, the short posttherapeutic delay after the treatment could explain the elevated aneuploidy rates, whereas no risk factor in the clinical, biological, or therapeutic records could be identified in any of the four testicular cancer

patients with elevated sperm aneuploidy rates. CONCLUSIONS: These data suggest an absence of long-term effect of anticancer therapy on sperm aneuploidy rates, and therefore, no long-term increased risk of aneuploidy for the offspring obtained either spontaneously or after assisted reproductive techniques.

Toda, K., H. Shibuya, et al. (2009). "Radiation-induced cancer after radiotherapy for non-Hodgkin's lymphoma of the head and neck: a retrospective study." *Radiat Oncol* 4: 21.

**BACKGROUND:** survivors of non-Hodgkin's lymphoma (NHL) are well known to be at an increased risk of second malignancies. In this study, we evaluated the incidence and clinical features of head and neck cancer (HNC) occurring after radiotherapy (RT) for NHL. **MATERIALS AND METHODS:** We investigated the clinical records of 322 patients who had received RT for early-stage NHL of the head and neck at our institute between 1952 and 2000. **RESULTS:** There were 4 patients with a second HNC developing in the irradiated field, consisting of 2 patients with gum cancer, 1 case with tongue cancer and 1 case with maxillary sinus cancer. The pathological diagnosis in all the 4 patients was squamous cell carcinoma (SCC). Two of the patients (one with gum cancer and one with maxillary sinus cancer) died of the second HNC, while the remaining 2 patients are still living at the time of writing after therapy for the second HNC, with neither recurrence of the second tumor nor relapse of the primary tumor. The ratio of the observed to the expected number (O/E ratio) of a second HNC was calculated to be 12.7 (95%CI, 4.07-35.0), and the absolute excess risk (AER) per 10,000 person-years was 13.3. The median interval between the RT and the diagnosis of the second HNC was 17.0 years (range, 8.7 to 22.7 years). **CONCLUSION:** The risk of HNC significantly increased after RT for early-stage NHL. These results suggest that second HNC can be regarded as one of the late complications of RT for NHL of the head and neck.

Travis, L. B., D. Hill, et al. (2005). "Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma." *J Natl Cancer Inst* 97(19): 1428-37.

**BACKGROUND:** Many women develop breast cancer after treatment for Hodgkin lymphoma (HL) at a young age. We estimated this future risk, taking into account age and calendar year of HL diagnosis, HL treatment information, population breast cancer incidence rates, and competing causes of death. **METHODS:** Relative risks of breast cancer for categories defined by radiation dose to the chest (0,

20- < 40 Gy, or > or = 40 Gy) and use of alkylating agents (yes or no) were estimated from a case-control study conducted within an international population-based cohort of 3817 female 1-year survivors of HL diagnosed at age 30 years or younger from January 1, 1965, through December 31, 1994. To compute cumulative absolute risks of breast cancer, we used modified standardized incidence ratios to relate cohort breast cancer risks to those in the general population, enabling application of population-based breast cancer rates, and we allowed for competing risks by using population-based mortality rates in female HL survivors. **RESULTS:** Cumulative absolute risks of breast cancer increased with age at end of follow-up, time since HL diagnosis, and radiation dose. For an HL survivor who was treated at age 25 years with a chest radiation dose of at least 40 Gy without alkylating agents, estimated cumulative absolute risks of breast cancer by age 35, 45, and 55 years were 1.4% (95% confidence interval [CI] = 0.9% to 2.1%), 11.1% (95% CI = 7.4% to 16.3%), and 29.0% (95% CI = 20.2% to 40.1%), respectively. Cumulative absolute risks were lower in women treated with alkylating agents. **CONCLUSIONS:** Breast cancer projections varied considerably by type of HL therapy, time since HL diagnosis, and age at end of follow-up. These estimates are applicable to HL survivors treated with regimens of the past and can be used to counsel such patients and plan management and preventive strategies. Projections should be used with caution, however, in patients treated with more recent approaches, including limited-field radiotherapy and/or ovary-sparing chemotherapy.

Tsavaris, N., C. Kosmas, et al. (2004). "Breast cancer after curative chemotherapy in non-Hodgkin's lymphoma: examination of the role of drug resistance and retrospective comparison to the outcome of de novo breast cancer." *Oncol Rep* 11(4): 899-903.

We examined the outcome of patients who developed breast cancer after curative chemotherapy (CHOP) for aggressive non-Hodgkin's lymphoma (NHL) in comparison to the outcome of a retrospectively selected matched-pair group of patients with de novo breast cancer, and evaluated the role of drug resistance-related protein (MDR, MRP, LRP) expression in breast cancer tissue. Twenty-two patients presented with breast cancer (BC) in complete remission after CHOP for NHL. The median age was 62 (49-70) years, each had high/intermediate grade B-cell NHL treated with 6 courses of CHOP, and were in complete remission. These patients were compared to a matched-pair group of de novo BC patients selected from our database over the same time period. Breast cancer tissue was stained by immunohistochemistry for drug resistance proteins LRP, MRP, and MDR.

Breast cancer developed after a median of 26 (9-49) months of NHL diagnosis; breast tumor grades 1-2 were seen in 12, and grade 3 in 10 patients; 15 were negative and 7 weakly positive for estrogen and progesterone receptors. Twelve patients were stage IIIA/B, and 10 stage IV and were treated with conventional chemotherapy regimens. All progressed early in liver (n=13), brain (n=9), lung (n=6), bone (n=8), lymph nodes (n=7) and soft tissue (n=5), and received second-line chemotherapy with mitomycin-C + vinblastine or taxanes. The overall survival was 11.8 (6-26) months (p<0.01). Time from NHL to breast cancer development was 19 (14-27) months in patients with positive drug resistance proteins (group A), and 37 (26-56) months in patients with 1 or 2 positive resistance proteins (group B) (p<0.001). In patients with stage IIIA/B disease, there was no difference between the examined and control matched-pair group in median TTP, but there was in overall survival (OS) (23 vs 36 months, p=0.029). In advanced disease, there were more responders in the control vs the examined group (p=0.07). Patients in the control matched-pair group had more prolonged OS when compared to group A patients who developed BC in <24 months from NHL to BC (p=0.017). We conclude that breast cancer developing shortly after a complete response in NHL, is an aggressive disease variant with minimal potential for response to conventional chemotherapy. Analysis of drug resistance mechanisms concerning MDR, MRP and LRP indicates that most of these patients have BC that overexpress these proteins leading to the suggestion that these mechanisms might be a part of the aggressive disease phenotype and partially explain the poor outcome.

Tsimberidou, A. M., S. Wen, et al. (2007). "Assessment of chronic lymphocytic leukemia and small lymphocytic lymphoma by absolute lymphocyte counts in 2,126 patients: 20 years of experience at the University of Texas M.D. Anderson Cancer Center." *J Clin Oncol* **25**(29): 4648-56.

**PURPOSE:** Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are currently considered the same entity, but controversy remains over whether CLL and SLL should be treated similarly. We assessed whether characteristics of patients with CLL and SLL differ in ways other than the absolute lymphocyte count (ALC) and evaluated treatment outcomes and prognostic factors. **METHODS:** We searched the electronic database for patients with CLL or SLL who presented to The University of Texas M.D. Anderson Cancer Center (Houston, TX) between 1985 and 2005. We reviewed patient records to determine presenting characteristics, treatment, and clinical outcomes. Cox models using

training and validation sets of patients and resampling methods were used to develop a model predicting survival. **RESULTS:** Among 2,126 consecutive CLL/SLL patients, 312 (15%) had ALC less than  $5 \times 10^9/L$ . Patients with ALC less than  $5 \times 10^9/L$  had lower rates of cytogenetic abnormalities (P = .0002) and higher rates of CD38-positive results (P = .0002) and had mutated immunoglobulin heavy-chain variable region gene status (P = .034). Rates of response, survival, and failure-free survival (FFS) were not different among ALC groups. Regimens that included rituximab and a nucleoside analog were associated with superior rates of response and FFS compared with other therapies, irrespective of ALC. Deletion 17p or 6q with or without other cytogenetic abnormalities, age at least 60 years, beta2-microglobulin at least 2 mg/L, albumin less than 3.5 g/dL, and creatinine at least 1.6 mg/dL were each found to independently predict shorter survival and formed the basis of a scoring system. **CONCLUSION:** Patients with CLL or SLL can be treated similarly. A new prognostic score is proposed.

Tsurusawa, M., T. Taga, et al. (2008). "Favourable outcomes in children with diffuse large B-cell lymphoma treated by a short-term ALL-like regimen: a report on the NHL960 study from the Japanese Childhood Cancer and Leukemia Study Group." *Leuk Lymphoma* **49**(4): 734-9.

In the NHL960 non-LB study, we treated diffuse large B-cell lymphoma (DLBCL) using a short-term ALL-like protocol. Thirty children up to 16 years of age with DLBCL were stratified into group 1 with stage I/II disease, or group 2 with stage III/IV disease. Their ages ranged from 9 months to 16 years of age, with a median of 9 years of age. The Murphy's stages were stage I in 7, stage II in 10, stage III in 6, and stage IV in 7 subjects. They received an ALL-like treatment without prophylactic cranial irradiation for 6 or 9 months. All children achieved a complete remission. Two patients with stage 3 disease experienced recurrences at 18 and 37 months after the start of chemotherapy. They responded to a short intensive regimen with Rituximab, followed by stem cell transplantation, and are alive without disease. The follow-up time ranged from 41 to 124 months with a median of 80 months. For all patients analyzed in this study, their overall survival and event-free survival (EFS) at 7-years was 100% and 93% +/- 4%, respectively. The 7-year EFS according to the treatment group was 100% for group 1, and 83% +/- 11% for group 2, respectively.

van der Kaaij, M. A., N. Heutte, et al. (2007). "Gonadal function in males after chemotherapy for early-stage Hodgkin's lymphoma treated in four

subsequent trials by the European Organisation for Research and Treatment of Cancer: EORTC Lymphoma Group and the Groupe d'Etude des Lymphomes de l'Adulte." *J Clin Oncol* **25**(19): 2825-32.

**PURPOSE:** To analyze fertility in male patients treated with various combinations of radiotherapy and chemotherapy, with or without alkylating agents, or with radiotherapy alone for Hodgkin's lymphoma. **PATIENTS AND METHODS:** Follicle-stimulating hormone (FSH) levels were measured in patients with early-stage upper-diaphragmatic disease enrolled in four European Organisation for Research and Treatment of Cancer (EORTC) trials (H6-H9). Median follow-up after therapy was 32 months. Patients with FSH measurement at least 12 months after end of treatment (n = 355) were selected to assess post-treatment fertility. Patients with FSH measurement 0 to 9 months after therapy (n = 349) were selected to analyze fertility recovery; of these, patients with elevated FSH (> 10 U/L; n = 101) were followed until recovery. Factors predictive for therapy-related infertility were assessed by logistic regression. **RESULTS:** The proportion of elevated FSH was 3% and 8% in patients treated with radiotherapy only or with nonalkylating chemotherapy (doxorubicin, bleomycin, vinblastine, dacarbazine [ABVD], epirubicin, bleomycin, vinblastine, prednisone [EBVP]); it was 60% (P < .001) after chemotherapy containing alkylating agents (mechlorethamine, vincristine, procarbazine, prednisone [MOPP], MOPP/doxorubicin, bleomycin, vinblastine [ABV], bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone [BEACOPP]). After a median time of 19 months, recovery of fertility occurred in 82% of patients treated without alkylating chemotherapy. This proportion was 30%, statistically (P < .001) lower in those treated with alkylating chemotherapy, and median time to recovery was 27 months. The post-treatment proportion of elevated FSH increased significantly (P < .001) with the dose of alkylating chemotherapy administered, and recovery was less frequent and slower after higher doses. Age more than 50 years and stage II disease also contributed to poor outcome. **CONCLUSION:** Fertility can be secured after nonalkylating chemotherapy for Hodgkin's lymphoma. In contrast, alkylating chemotherapy has a dismal effect, even after a limited number of cycles.

van Spronsen, D. J., M. L. Janssen-Heijnen, et al. (2005). "Independent prognostic effect of co-morbidity in lymphoma patients: results of the population-based Eindhoven Cancer Registry." *Eur J Cancer* **41**(7): 1051-7.

The prevalence of co-morbidity among elderly lymphoma patients is associated with a decrease in the use of chemotherapy. This study assessed the independent prognostic effect of co-morbidity in 1551 unselected lymphoma patients, diagnosed between 1995 and 2001 in the area of the population-based Eindhoven Cancer Registry. The prevalence of serious co-morbidity was 58% for patients with Hodgkin's disease (HD) who were over 60 years of age and 66% for patients with non-Hodgkin's lymphoma (NHL) who were over 60 years of age. The administration of chemotherapy declined in the presence of co-morbidity for elderly patients with early-stage HD and elderly patients with aggressive NHL. Co-morbidity was associated with a 10-20% decline in 5-year survival. Whether less frequent application of chemotherapy in the presence of co-morbidity is justified as far as complications, prognosis and quality of life are concerned requires further investigation.

Vink, S. R., A. H. van der Luit, et al. (2007). "Lipid rafts and metabolic energy differentially determine uptake of anti-cancer alkylphospholipids in lymphoma versus carcinoma cells." *Biochem Pharmacol* **74**(10): 1456-65.

Perifosine is a member of the class of synthetic alkylphospholipids (APLs) and is being evaluated as anti-cancer agent in several clinical trials. These single-chain APLs accumulate in cellular membranes and disturb lipid-dependent signal transduction, ultimately causing apoptosis in a variety of tumor cells. The APL prototype edelfosine was previously found to be endocytosed by S49 mouse lymphoma cells via lipid rafts. An edelfosine-resistant cell variant, S49(AR), was found to be cross-resistant to other APLs, including perifosine. This resistance was due to defective synthesis of the raft constituent sphingomyelin, which abrogated APL cellular uptake. Sensitivity of S49 cells to edelfosine was higher than perifosine, which correlated with a relatively higher uptake. Human KB epidermal carcinoma cells were much more sensitive to APLs than S49 cells. Their much higher APL uptake was highly dependent on intracellular ATP and ambient temperature, and was blocked by chlorpromazine, independent of canonical endocytic pathways. We found no prominent role of lipid rafts for APL uptake in these KB cells; contrary to S49(AR) cells, perifosine-resistant KBr cells display normal sphingomyelin synthesis, whereas APL uptake by the responsive KB cells was insensitive to treatment with methyl-beta-cyclodextrin, a cholesterol-sequestrator and inhibitor of raft-mediated endocytosis. In conclusion, different mechanisms determine APL uptake and consequent apoptotic toxicity in lymphoma versus carcinoma

cells. In the latter cells, APL uptake is mainly determined by a raft- and endocytosis-independent process, but metabolic energy-dependent process, possibly by a lipid transporter.

Wahner-Roedler, D. L., D. F. Nelson, et al. (2003). "Risk of breast cancer and breast cancer characteristics in women treated with supradiaphragmatic radiation for Hodgkin lymphoma: Mayo Clinic experience." *Mayo Clin Proc* **78**(6): 708-15.

**OBJECTIVE:** To evaluate the overall risk of breast cancer and breast cancer characteristics in women given supradiaphragmatic radiation therapy for Hodgkin lymphoma. **PATIENTS AND METHODS:** Medical records of 653 female patients who received supradiaphragmatic radiation therapy for Hodgkin lymphoma at the Mayo Clinic in Rochester, Minn, between 1950 and 1993 were abstracted, and follow-up questionnaires were mailed. In 4 patients, breast cancer was diagnosed before Hodgkin lymphoma was discovered. **RESULTS:** The median age of 649 patients at supradiaphragmatic radiation therapy was 31.8 years (range, 2.6-86.5 years). The median duration of follow-up was 8.7 years (range, < 1-47.9 years). In 30 patients, breast cancer developed (bilaterally in 4 patients) after supradiaphragmatic radiation therapy; the median interval was 19.9 years (range, 0.7-423 years). The median age at breast cancer diagnosis was 44.4 years (range, 27.5-70.8 years). The standardized morbidity ratio for breast cancer after supradiaphragmatic radiation therapy was 2.9 (95 % confidence interval [CI], 2.0-4.2) ( $P < .001$ ). Breast cancer risk significantly increased 15 to 30 years after patients received supradiaphragmatic radiation therapy, and risk was inversely related to age at supradiaphragmatic radiation therapy until age 30 years. The standardized morbidity ratio for patients younger than 30 years at supradiaphragmatic radiation was 8.5 (95% CI, 53-13.1) vs 1.2 (95% CI, 0.5-2.2) for those aged 30 years or older ( $P < .001$ ). Splenectomy increased breast cancer risk ( $P = .01$ ). Breast cancer detection was by self-examination in 15 cancers, by mammography in 13, and by clinical examination in 4; in 2 cancers, the mode of detection was unknown. Modified radical mastectomy was used to treat breast cancer. **CONCLUSION:** The increased risk of breast cancer in survivors of Hodgkin lymphoma given supradiaphragmatic radiation therapy appears to be limited to patients who are younger than 30 years at radiation therapy or to those who have undergone splenectomy.

Wahner-Roedler, D. L. and I. A. Petersen (2004). "Risk of breast cancer and breast cancer

characteristics in women after treatment for Hodgkin lymphoma." *Drugs Today (Barc)* **40**(10): 865-79.

Radiotherapy is important in the treatment of Hodgkin lymphoma. Although the risk of recurrent Hodgkin lymphoma decreases in long-term survivors, the incidence of radiation-induced cancers increases with time. Breast cancer is the main long-term concern for women. Risk factors associated with breast cancer development include age at irradiation, time since treatment and radiation dose received. The risk of developing breast cancer appears to be limited to women treated before age 30 years. The median time to breast cancer after radiotherapy is 15 years. Higher radiation doses are associated with higher risks. While the histology of breast cancers occurring after treatment for Hodgkin lymphoma appears similar to that of spontaneously occurring breast cancers, the age at diagnosis in these women is significantly younger, often at an age before regular breast screening is implemented. In this article, we review findings from retrospective studies on Hodgkin lymphoma and breast cancer including the risk factors, breast cancer characteristics, breast cancer management and options for primary and secondary prevention. The treatment goals for young female patients with Hodgkin lymphoma include: 1) manipulation of radiation dose and fields without compromising the outcome of the primary malignancy; 2) possible reversible manipulation of hormonal status without permanent effects on fertility; and 3) development of nonsurgical options for primary prevention of radiation-induced breast cancers. Carefully designed studies addressing these strategies and their interplay are needed.

Wang, X. S., S. A. Giralt, et al. (2002). "Clinical factors associated with cancer-related fatigue in patients being treated for leukemia and non-Hodgkin's lymphoma." *J Clin Oncol* **20**(5): 1319-28.

**PURPOSE:** To describe fatigue severity, fatigue interference, and associated factors in hematologic malignancies. **PATIENTS AND METHODS:** Patients being treated for leukemia and non-Hodgkin's lymphoma ( $n = 228$ ) completed the Brief Fatigue Inventory to rate fatigue severity and functional interference caused by fatigue. Data on patient demographics, Eastern Cooperative Oncology Group performance status, other physical symptoms, current treatments, and laboratory values were also collected. Descriptive statistics, bivariate correlation, and logistic regression were used for data analysis. **RESULTS:** Fifty percent of the sample reported severe fatigue, which was defined as a "fatigue worst" rating of 7 or greater. More patients with acute leukemia (61%) reported severe fatigue compared with those with chronic leukemia (47%) and non-

Hodgkin's lymphoma (46%). Increased fatigue severity significantly compromised patients' general activity, work, enjoyment of life, mood, walking, and relationships with others. Fatigue severity was strongly associated with performance status, use of opioids, blood transfusions, gastrointestinal symptoms, and sleep disturbance items, as well as with low serum hemoglobin and albumin levels. Regression analysis indicated that nausea was the significant clinical predictor of severe fatigue (odds ratio, 13), and low serum albumin was the significant laboratory value predictor (odds ratio, 3.8). CONCLUSION: Disabling fatigue occurs with high frequency in hematologic malignancy, supporting a need to develop better methods of fatigue management. Better control of gastrointestinal and other symptoms may be of benefit. The mechanism and relationship between low albumin and severe fatigue needs to be investigated further, and longitudinal studies of the effects of treatment, host factors, and other symptoms are needed.

Williams, D. M., R. Hobson, et al. (2002). "Anaplastic large cell lymphoma in childhood: analysis of 72 patients treated on The United Kingdom Children's Cancer Study Group chemotherapy regimens." *Br J Haematol* **117**(4): 812-20.

From June 1990 to June 1998, 72 patients with anaplastic large cell lymphoma (ALCL) were treated with short intensive multi-agent regimens [non-Hodgkin's lymphoma (NHL) 9000 and 9602]. Diagnosis was based on morphological and immunophenotypic criteria. Treatment for stage I disease consisted of eight courses (2 x vincristine, doxorubicin, prednisolone; 2 x methotrexate; 2 x cytarabine, thioguanine; and 2 x methotrexate etoposide). For stage II, III and non-central nervous system (CNS) stage IV, two COPADM (cyclophosphamide, doxorubicin, prednisolone, methotrexate, vincristine), two CYM (cytarabine methotrexate) and a COPADM was given. For CNS-positive disease, treatment was intensified and contained methotrexate 8 g/m<sup>2</sup> and cytarabine 3 g/m<sup>2</sup>. Fifty-nine patients (82%) achieved a remission. Thirteen of these relapsed, with a median time to relapse from the start of treatment of 5 months (range 3-14). Relapse included a new site in 9/13 patients. The probabilities of overall and event free survival at 5 years were 65% (53-76%) and 59% (47-70%), respectively, with a median follow up of 4.3 years. Mediastinal and visceral involvement at presentation were found to be predictive of an increased risk of failure.

Witzig, T. E., S. M. Geyer, et al. (2008). "Salvage chemotherapy with rituximab DHAP for relapsed non-

Hodgkin lymphoma: a phase II trial in the North Central Cancer Treatment Group." *Leuk Lymphoma* **49**(6): 1074-80.

The aim of this study was to learn the toxicity and efficacy of adding 4 doses of rituximab to a standard platinum-based salvage regimen for relapsed CD20+ B-cell non-Hodgkin lymphoma. Patients were treated with rituximab 375 mg/m<sup>2</sup> days 1,8,15, 22 (cycle 1 only); cisplatin 100 mg/m<sup>2</sup> over 24 h on day 3, cytosine arabinoside 2 g/m<sup>2</sup> IV every 12 h x two doses on day 4, dexamethasone 40 mg PO/IV days 3-6, and G-CSF days 5-14. The ORR was 82% (47/57) with 33% (19/57) complete remissions and 49% (28/57) partial remissions. The duration of response (DR) for the 47 responders was 10.5 months (95% CI: 5.3-16.8). The median time to progression (TTP) was 10.3 months (95% CI: 5.3-14.0), the median event-free survival (EFS) was 5.3 months (95% CI: 3.9-11.0), and the median overall survival was 30.5 months (95% CI: 17.8-60.6). We conclude that rituximab can be safely added to standard DHAP.

Witzig, T. E., A. M. Vukov, et al. (2005). "Rituximab therapy for patients with newly diagnosed, advanced-stage, follicular grade I non-Hodgkin's lymphoma: a phase II trial in the North Central Cancer Treatment Group." *J Clin Oncol* **23**(6): 1103-8.

PURPOSE: Patients with newly diagnosed, advanced-stage, follicular grade 1 non-Hodgkin's lymphoma (NHL) are often asymptomatic and can be observed without immediate chemotherapy. The goals of this study were to assess the overall response rate (ORR) to rituximab in this patient population and to determine the time-to-progression (TTP) and time-to-subsequent-chemotherapy (TTSC). PATIENTS AND METHODS: Eligible patients had untreated follicular grade 1 NHL, and measurable stage III/IV disease. Patients received rituximab 375 mg/m<sup>2</sup> intravenous weekly x 4 doses and were then followed for response and progression; no maintenance therapy was provided. RESULTS: Thirty-seven patients were accrued; one patient was ineligible. The median age was 59 years (range, 29 to 83 years). Six patients (18%) had elevated lactate dehydrogenase levels. The ORR was 72%, with 36% complete remissions. Fourteen (39%) of 36 patients remain in unmaintained remission, two died without disease progression, and three died with disease progression. Twenty (56%) of 36 patients have disease progression. The median TTP was 2.2 years (95% CI, 1.3 to not yet reached). Eighteen patients have subsequently been treated with chemotherapy, with a median TTSC of 2.3 years (95% CI, 1.6 to not yet reached). Patients with a high lactate dehydrogenase level had a lower ORR of 33% and a short TTP of only 6 months. CONCLUSION: Rituximab can be safely administered to patients with

advanced-stage follicular grade 1 NHL with efficacy and minimal toxicity. This therapy is highly active and offers an acceptable alternative to observation in this patient population. Patients with high LDH should not be considered for rituximab monotherapy.

Wolf, S., D. Mertens, et al. (2006). "Ala228 variant of trail receptor 1 affecting the ligand binding site is associated with chronic lymphocytic leukemia, mantle cell lymphoma, prostate cancer, head and neck squamous cell carcinoma and bladder cancer." *Int J Cancer* **118**(7): 1831-5.

Allelic loss of chromosome 8p21-22 is a frequent event in various human cancers including mantle cell lymphoma (MCL), prostate cancer, head and neck squamous cell carcinoma (HNSCC) and bladder cancer. The tumor necrosis factor-related apoptosis inducing ligand (TRAIL) receptors, including TNFRSF10A and TNFRSF10B, are located within this chromosomal region. Since recent studies demonstrate that chronic lymphocytic leukemia (CLL) and prostate cells are TRAIL induced apoptosis, TRAIL-receptors are strong tumor suppressor candidate genes in human cancers exhibiting loss of chromosomal material in 8p21.3. However, no mutation of the TRAIL receptor genes has been reported in CLL, MCL, prostate cancer, HNSCC so far. In this study we analyzed the complete coding region of TNFRSF10A and TNFRSF10B in a series of 32 MCL and 101 CLL samples and detected a single nucleotide polymorphism (SNP) in TNFRSF10A (A683C) with tumor specific allele distribution. We examined allele distribution in 395 samples of different tumor entities (prostate cancer, n = 43; HNSCC, n = 40; bladder cancer, n = 179) and compared them to 137 samples from healthy probands. We found the rare allele of TNFRSF10A is more frequent in CLL, MCL, prostate cancer, bladder cancer and HNSCC. The A683C polymorphism did not cosegregate with other TNFRSF10A polymorphisms previously described. Thus screening for 683A-->C nucleotide exchanges may become important in diagnosis and/or treatment of these malignancies.

Worrillow, L. J., A. G. Smith, et al. (2008). "Polymorphic MLH1 and risk of cancer after methylating chemotherapy for Hodgkin lymphoma." *J Med Genet* **45**(3): 142-6.

**BACKGROUND AND OBJECTIVE:** Methylating agents are effective chemotherapy agents for Hodgkin lymphoma, but are associated with the development of second primary cancers. Cytotoxicity of methylating agents is mediated primarily by the DNA mismatch repair (MMR) system. Loss of MLH1, a major component of DNA MMR, results in

tolerance to the cytotoxic effects of methylating agents and persistence of mutagenised cells at high risk of malignant transformation. We hypothesised that a common substitution in the basal promoter of MLH1 (position -93, rs1800734) modifies the risk of cancer after methylating chemotherapy. **METHODS:** 133 patients who developed cancer following chemotherapy and/or radiotherapy (n = 133), 420 patients diagnosed with de novo myeloid leukaemia, 242 patients diagnosed with primary Hodgkin lymphoma, and 1177 healthy controls were genotyped for the MLH1 -93 polymorphism by allelic discrimination polymerase chain reaction (PCR) and restriction fragment length polymorphism assay. Odds ratios and 95% confidence intervals for cancer risk by MLH1 -93 polymorphism status, and stratified by previous exposure to methylating chemotherapy, were calculated using unconditional logistic regression. **RESULTS:** Carrier frequency of the MLH1 -93 variant was higher in patients who developed therapy related acute myeloid leukaemia (t-AML) (75.0%, n = 12) or breast cancer (53.3%, n = 15) after methylating chemotherapy for Hodgkin lymphoma compared to patients without previous methylating exposure (t-AML, 30.4%, n = 69; breast cancer patients, 27.2%, n = 22). The MLH1 -93 variant allele was also over-represented in t-AML cases when compared to de novo AML cases (36.9%, n = 420) and healthy controls (36.3%, n = 952), and was associated with a significantly increased risk of developing t-AML (odds ratio 5.31, 95% confidence interval 1.40 to 20.15), but only in patients previously treated with a methylating agent. **CONCLUSIONS:** These data support the hypothesis that the common polymorphism at position -93 in the core promoter of MLH1 defines a risk allele for the development of cancer after methylating chemotherapy for Hodgkin lymphoma. However, replication of this finding in larger studies is suggested.

Yamada, T., N. Iwao, et al. (2003). "A case of malignant lymphoma of the ovary manifesting like an advanced ovarian cancer." *Gynecol Oncol* **90**(1): 215-9.

**BACKGROUND:** In recent years, true primary ovarian lymphoma has been considered to carry a favorable prognosis, although most studies of supposedly primary ovarian lymphoma have reported a poor outcome. **CASE:** A 47-year-old woman presented with signs and symptoms suggestive of an advanced ovarian cancer. Ultrasonography and magnetic resonance imaging revealed bilateral abdominal tumors, each measuring 10 cm in diameter, thickened omentum, and a large amount of ascitic fluid, but no enlarged lymph nodes. The diagnosis of malignant lymphoma was established from the biopsy

specimen after exploratory laparotomy. Six years following chemotherapy, the patient is alive and disease free without additional surgery. CONCLUSION: The prognosis of ovarian lymphoma was evaluated according to clinical stage, modality of onset, histologic type, and phenotype. It remains controversial whether this case can be considered truly primary ovarian lymphoma and not merely a localized initial manifestation of a generalized disease. But if this case of advanced ovarian lymphoma were not primary, it could still be managed successfully with chemotherapy appropriate for the specific histology.

Yap, L. M., R. Blum, et al. (2003). "Clinical study of primary cutaneous B-cell lymphoma using both the European Organization for Research and Treatment of Cancer and World Health Organization classifications." *Australas J Dermatol* 44(2): 110-5.

Primary cutaneous B-cell lymphoma (PCBCL) is rare, with few series reported in the literature. Its classification and treatment remain controversial. Biopsy specimens of 13 patients with PCBCL were classified according to both the European Organization for Research and Treatment of Cancer (EORTC) and the new World Health Organization (WHO) classifications. Treatment and clinical outcomes were documented. Using the EORTC classification there were seven men and six women aged 32-85 years (mean = 51 years) with follicle centre cell (FCC) lymphoma (nine), immunocytoma (two) and primary cutaneous large B-cell lymphoma of the leg (PCLBCL-leg) (two). When the WHO classification was used, the nine patients with FCC were reclassified as follicle centre (five) and diffuse large B-cell lymphoma (four). Most patients had localized disease (12). Initial treatment consisted of radiotherapy alone (seven), combination chemotherapy alone (one), combined chemoradiotherapy (three) and surgery (two). Twelve patients achieved complete remission (median follow up 28 months, range 10-167 months). One patient with PCLBCL-leg died from progressive cutaneous disease. Most localized PCBCL lesions (except PCLBCL-leg) have a favourable prognosis. We recommend that clinicians be familiar with the important differences in the EORTC and WHO classifications. Further large prospective studies comparing the WHO and EORTC classifications are required to more clearly delineate the outcomes of the increasing number of patients who are classified as DLBCL by the WHO system.

Yoshimura, C., S. Nomura, et al. (2002). "Comparison of interleukin-12 with lung cancer and malignant lymphoma undergoing autologous peripheral blood

stem cell transplantation." *J Cancer Res Clin Oncol* 128(1): 29-36.

PURPOSE: High-dose chemotherapy with peripheral blood stem cell transplantation (PBSCT) has become an important treatment for solid tumors including lung cancer. METHODS: We measured IL-12 levels in patients with lung cancer undergoing autologous PBSCT in order to elucidate the role of IL-12 in immune response recovery following stem cell transplantation. RESULTS: Compared to IL-12 levels at 1 week after PBSCT for lung cancer patients, those at 3 weeks were significantly increased ( $P < 0.01$ ). In contrast, serum IL-12 levels in malignant lymphoma patients did not change significantly. There were no significant differences in levels of other cytokines between 1 week and 3 weeks after transplantation in patients with lung cancer. The frequency of helper/inducer T cells was increased in peripheral blood 1 week after transplantation in both lung cancer and malignant lymphoma patients. There was a significant increase in activated T cell numbers following PBSCT. Furthermore, high levels of other activated T cells persisted in the post-PBSCT period in patients with lung cancer and the number of cytotoxic T cells significantly increased. Natural killer (NK) cell numbers also tended to increase, although that of malignant lymphoma was not significant. A strong correlation was observed between serum IL-12 levels and NK cell numbers and interferon-gamma levels in lung cancer not but in malignant lymphoma patients. The analysis of transfused PBSC showed that the numbers of granulocyte/macrophage colony-forming units were similar in lung cancer and malignant lymphoma patients. However, the number of CD34+ cells was significantly higher in lung cancer than in malignant lymphoma patients. All of the CD34+ subpopulations were lower in percentage in patients with lung cancer than in patients with malignant lymphoma. In particular, the CD34+ CD33-subpopulation was significantly lower in percentage in lung cancer patients. CONCLUSION: Our findings suggest that PBSC in lung cancer are potent mediators of anticancer activity and that they might play an immunotherapeutic role against autologous malignant cells.

Zebrack, B. J., L. K. Zeltzer, et al. (2002). "Psychological outcomes in long-term survivors of childhood leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma: a report from the Childhood Cancer Survivor Study." *Pediatrics* 110(1 Pt 1): 42-52.

OBJECTIVE: To evaluate and compare psychological outcomes in long-term survivors of pediatric leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma and sibling controls. METHODS: Adult survivors of childhood leukemia,

Hodgkin's disease, and non-Hodgkin's lymphoma (N = 5736) and sibling controls (N = 2565) were administered a long-term follow-up questionnaire allowing assessment of symptoms associated with depression and somatic distress. RESULTS: The majority of respondents in this study did not demonstrate symptomatology indicative of depression or somatic distress. Survivors, however, were significantly more likely than sibling controls to report symptoms of depression and somatic distress. Women were significantly more likely to indicate symptoms of depression and somatic distress than were men; however, this difference did not vary by survivor/sibling status. Similarly, socioeconomic (SES) variables predicted symptomatic levels of depression and somatic distress for both survivors and siblings, and these effects did not vary by survivor/sibling status. Among leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma survivors, in addition to gender and SES, the only treatment variable that predicted scores indicating depressive symptomatology was exposure to intensive chemotherapy. Exposure to intensive chemotherapy also predicted scores indicative of somatic distress symptoms. No other medical variables, including diagnostic category, age at diagnosis, time since diagnosis, and duration of treatment, predicted symptomatic scores for depression and somatic distress. CONCLUSIONS: This large, sibling-controlled, multisite study of young adult survivors of childhood leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma found that survivors had significant increased risk for reporting symptoms of depression and somatic distress and that intensive chemotherapy added to this risk. However, being a cancer survivor did not compound the effects of gender and SES variables on the 2 outcomes measured. The ability of SES, gender, and treatment-related variables to predict psychological symptoms in this cohort of childhood survivors and sibling controls calls for future research into varied biological and psychosocial pathways by which cancer influences future psychosocial functioning.

Zouhair, A., D. Weber, et al. (2002). "Outcome and patterns of failure in testicular lymphoma: a multicenter Rare Cancer Network study." *Int J Radiat Oncol Biol Phys* 52(3): 652-6.

PURPOSE: To assess the outcome and patterns of failure in patients with testicular lymphoma treated by chemotherapy (CT) and/or radiation therapy (RT). METHODS AND MATERIALS: Data from a series of 36 adult patients with Ann Arbor Stage I (n = 21), II (n = 9), III (n = 3), or IV (n = 3) primary testicular lymphoma, consecutively treated between 1980 and 1999, were

collected in a retrospective multicenter study by the Rare Cancer Network. Median age was 64 years (range: 21-91 years). Full staging workup (chest X-ray, testicular ultrasound, abdominal ultrasound, and/or thoracoabdominal computer tomography, bone marrow assessment, full blood count, lactate dehydrogenase, and cerebrospinal fluid evaluation) was completed in 18 (50%) patients. All but one patient underwent orchidectomy, and spermatic cord infiltration was found in 9 patients. Most patients (n = 29) had CT, consisting in most cases of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) with (n = 17) or without intrathecal CT. External RT was delivered to scrotum alone (n = 12) or testicular, iliac, and para-aortic regions (n = 8). The median RT dose was 31 Gy (range: 20-44 Gy) in a median of 17 fractions (10-24), using a median of 1.8 Gy (range: 1.5-2.5 Gy) per fraction. The median follow-up period was 42 months (range: 6-138 months). RESULTS: After a median period of 11 months (range: 1-76 months), 14 patients presented lymphoma progression, mostly in the central nervous system (CNS) (n = 8). Among the 17 patients who received intrathecal CT, 4 had a CNS relapse (p = NS). No testicular, iliac, or para-aortic relapse was observed in patients receiving RT to these regions. The 5-year overall, lymphoma-specific, and disease-free survival was 47%, 66%, and 43%, respectively. In univariate analyses, statistically significant factors favorably influencing the outcome were early-stage and combined modality treatment. Neither RT technique nor total dose influenced the outcome. Multivariate analysis revealed that the most favorable independent factors predicting the outcome were younger age, early-stage disease, and combined modality treatment. CONCLUSIONS: In this multicenter retrospective study, CNS was found to be the principal site of relapse, and no extra-CNS lymphoma progression was observed in the irradiated volumes. More effective CNS prophylaxis, including combined modalities, should be prospectively explored in this uncommon site of extranodal lymphoma.

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