# Metastatic or Recurrent Endometrial Tumours: the Role of Systemic Anticancer Treatment

Loaie M El-Helw[1, 2], Hanaa Elkhenini[3,4] and Mojca Persic [2]

[1]Medical Oncology Unit, Mansoura University, Egypt
[2] the Royal Derby Hospital, UK
[3] Public Health Department, Mansoura University, Egypt
[4] North West E-Health Department, the University of Manchester, UK
loaieelhelw@hotmail.com, loaieelhelw@gmail.com

**Abstract:** In patients with recurrent or metastatic endometrial tumours, cure is unlikely unless the recurrence is limited to an isolated resectable lesion**.** We aimed to review the incidence and management of metastatic or recurrent endometrial tumours in our centre from August 2010 till August 2013. Patients' notes and electronic records were reviewed. A total of 237 patients with endometrial tumours were managed in our centre in that period. Eight patients (3.4%) had metastasis at initial presentation and 229 patients (96.6%) had stages I-III. On further follow up, 13 of the 229 patients (5.7%) developed recurrence mostly with distant metastasis (76.9%). The median time to recurrence was 10 months. Carboplatin and paclitaxel (CP) was the most commonly used palliative regimen (58.8%) in those patients. Complete response to CP regimen was obtained in 33.3%, partial response in 22.3% and stable disease in 33.3%. Patients with isolated vaginal recurrence were treated with brachytherapy. The median progression free and overall survival durations were 9 months and 17 months respectively. In conclusion, distant metastasis was the most common pattern of recurrence. We believe that adjuvant chemotherapy should be evaluated –further- in high risk endometrial cancer patients through randomized clinical studies.
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## 1. Introduction

Endometrial cancer is the fourth most common cancer in women in the UK [1-2]. In Egypt it represents 2.6-3.5% of all cancer incidences [3-4]. High risk for recurrence includes deep myometrial invasion, grade 3, serous or clear cell histology [5]. A small minority present with solitary metastasis which is amenable to surgical resection and/or radiation [6, 7]. The prognosis is otherwise poor with a median survival of 12 months [8]. The mainstay of treatment of such patients remains hormonal treatment or systemic chemotherapy [9].

In this work we reviewed the incidence and management of patients presented to our centre with metastatic disease at the time of initial diagnosis and those with earlier stages (I-III) who developed recurrence after completing their definitive management.

## 2. Patients and Methods

Notes and electronic records of patients with metastatic or recurrent endometrial cancer presented to our center from August 2010 till August 2013 were reviewed. We studied the presentation, management at initial presentation and at relapse. Data analysis was performed using SPSS statistical package version 16.0. Progression free and overall survival probabilities were calculated using Kaplan Meier method. We compared our findings with the published literature.

## 3. Results

Between August 2010 and August 2013, 237 patients were diagnosed with endometrial tumours in our centre. Eight patients (3.4%) had metastatic diseases at initial presentation. Two hundred and twenty nine patients presented with non-metastatic (stages I-III) endometrial tumours with the highest incidences were in 2012 (81 patients) and 2011 (79) compared to 2013 (38) and 2010 (31). Thirteen patients (5.7%) had recurrence on further follow up. The median time to recurrence was 10 months (range 1-16 months) and recurrence rate was highest in patients diagnosed in 2010 (18.8%).

Table 1 shows the characteristic of 13 patients with recurrent endometrial tumours. Eleven of them (84.6%) had endometriod adenocarcinoma, 1 EST (7.7%) and 1 carcinosarcoma (7.7%). At initial presentation and prior to developing recurrent diseases, stage III and grade 3 were most common (46.1% each). Deep myometrial invasion (≥50% of myometrial thickness) was identified in 4 patients (30.8%) and lymphovascular invasion in 2 patients (15.4%).

Following initial surgical treatment 5 patients (38.6%) had adjuvant external pelvic radiotherapy; 2 patients (15.3%) had brachytherapy and another 2 (15.3%) had adjuvant chemotherapy followed by external pelvic radiotherapy. Four patients (30.8%) had no adjuvant treatment.

**Table (1) Characteristic of patients with recurrent endometrial cancer**

| Variables | Number of Patients (%) |
|---|---|
| **Total patients number** | **13 (100)** |
| **Histological subtypes** | |
| Endometriod carcinoma | 11 (84.6) |
| Endometrial stromal tumours | 1 (7.7) |
| Carcinosarcoma | 1 (7.7) |
| **Stage at initial diagnosis** | |
| I | 4 (30.8) |
| II | 3 (23.1) |
| III | 6 (46.1) |
| **Histological grade** | |
| Grade 1 | 1 (7.8) |
| Grade 2 | 6 (46.1) |
| Grade 3 | 6 (46.1) |
| **Myometrial invasion** | |
| Less than <50% | 9 (69.2) |
| More than ≥50% | 4 (30.8) |
| **Lymphovascular invasion** | |
| Present | 2 (15.4) |
| Absent | 11 (84.6) |
| **Adjuvant treatment** | |
| Ext RT† | 5 (38.6) |
| BT ‡only | 2 (15.3) |
| CT*, Ext RT† | 2 (15.3) |
| None (Surgery only) | 4 (30.8) |
| **Pattern of recurrence** | |
| Distant Metastasis | 10 (77) |
| Local recurrence | 3 (23) |
| **Sites of recurrence** | |
| Vagina | 6 (46.2) |
| Paraaortic lymph nodes | 4 (30.7) |
| Peritoneum | 3 (23.1) |
| Lung | 2 (15.4) |

CT*: Chemotherapy, Ext RT†: External radiotherapy, BT‡: Brachytherapy

Distant metastasis was the most common pattern of recurrence in this group of patients (77%). Fewer patients had isolated local pelvic recurrence (23%). The median time to recurrence was 10 months (range 1-16 months). The median number of sites of metastases was 2 (range 1-3) with the most common sites were vagina vault (46.2%), paraaortic lymph nodes (30.7%), peritoneum (23.1%) and lung (15.4%).

Table 2 describes the use of systemic anticancer treatment (SACT) in our patients with recurrent (13 patients) or primary metastatic disease (8 patients). Carboplatin and paclitaxel (CP) was the most commonly used regimen in patients with endometriod adenocarcinoma (9 out of 15 patients; 60%). Three patients (20%) had hormonal treatment with medroxyprogestrone acetate. The details of SACT are shown in table 2.

**Table (2) Treatment of 21 patients with metastatic/recurrent disease in relation to histological subtypes**

| Treatment in different histological subtypes | Total number of patients (%) |
|---|---|
| **Endometriod adenocarcinoma** | **15** |
| Carboplatin and paclitaxel regimen | 9 (60) |
| Medroxyprogestrone acetate | 3 (20) |
| Best supportive care | 3 (20) |
| **Clear cell adenocarcinoma** | **2** |
| Carboplatin and paclitaxel regimen | 1 (50) |
| Best supportive care | 1 (50) |
| **Endometrial stromal tumours** | **2** |
| Medroxyprogestrone acetate | 1 (50) |
| Aromatase inhibitor | 1 (50) |
| **Carcinosarcoma** | **2** |
| Carboplatin and paclitaxel regimen | 1 (50) |
| Best supportive care | 1 (50) |

Only 16 patients were candidate for SACT (table 3). The overall response was 18.75% complete response (CR), 25% partial response (PR) and 37.5 % stable disease (SD). In relation to histological subtypes, the overall response was 55.6% in patients with endometriod adenocarcinoma when treated with CP regimen. Other response rates are as shown in table (3).

**Table (3) Response to systemic anticancer treatment in 16 patients with metastatic or recurrent endometrial cancer**

| Response | CR* N¶ (%) | PR† N¶ (%) | SD‡ N¶ (%) | PD§ N¶ (%) | TOTAL N¶ |
|---|---|---|---|---|---|
| **Overall response to systemic treatment** | 3 (18.75) | 4 (25) | 6 (37.5) | 3 (18.75) | 16 |
| **Response in relation to histological subtypes and types of systemic treatment** | | | | | |
| **Adenocarcinomas** | | | | | |
| **Endometriod adenocarcinoma** | | | | | |
| Carboplatin and Paclitaxel regimen | 3 (33.3) | 2 (22.3) | 3 (33.3) | 1 (11.1) | 9 |
| Medroxyprogestrone acetate | | 1 (33.3) | | 2 (66.7) | 3 |
| **Clear cell adenocarcinoma** | | | | | |
| Carboplatin and Paclitaxel regimen | | | 1 (100) | | 1 |
| **Endometrial stromal tumours** | | | | | |
| Aromatase Inhibitor (Anastrazole) | | | 1 (100) | | 1 |
| Medroxyprogestrone acetate | | | 1 (100) | | 1 |
| **Carcinosarcoma** | | | | | |
| Carboplatin and Paclitaxel regimen | | 1 (100) | | | 1 |

CR*: Complete Response, PR†: Partial Response, SD‡: stable disease, PD§: Progressive Disease, N¶: Number.

In patients who presented with primary metastatic disease, the median PFS was 12 months (range 3 – 21 months); the median survival duration was not reached. The 2 years survival probability was 53%. In patients with recurrent endometrial cancer, the median PFS was 5 months (2.4 – 7.5 months), the median survival duration was 13 months (range 8-17 months) and 2 years survival probability was 33% (figure 1 and 2).

Figure (1) Progression Free Survival (PFS)

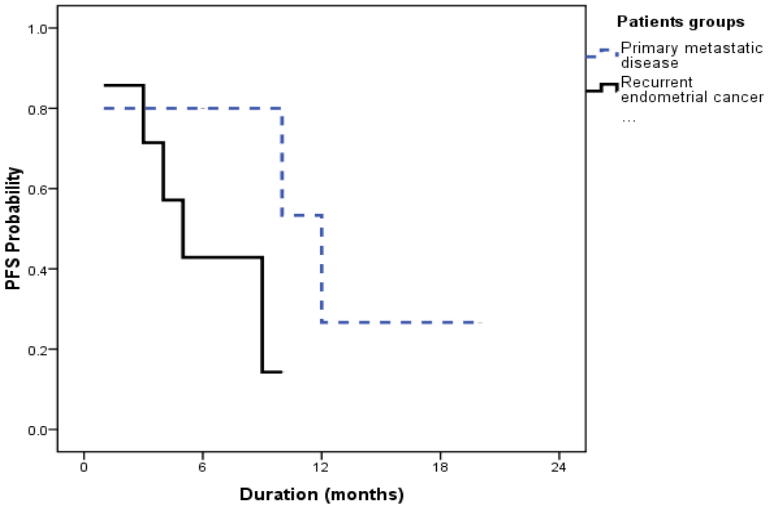
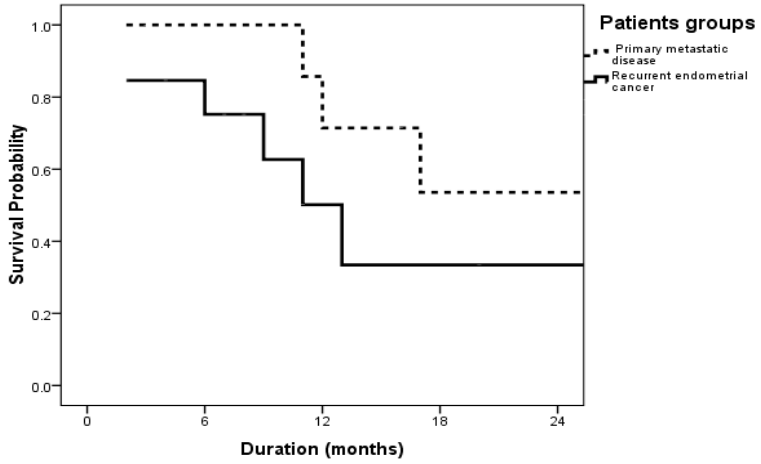



Figure (2) Overall Survival




## 4. Discussion

In our centre, there was an increasing incidence of endometrial tumours between 2011 and 2012. A similar trend was reported in a study by Evans and colleagues who documented increase incidence in type 1 (oestrogen-dependent type) endometrial cancer, mostly in the 60-79 age group. Although type 2 endometrial cancer (non-oestrogen-dependent) showed no significant increase in incidence, the survival in the latter group has decreased significantly [10]. Among our patients who had recurrent disease, we identified high risk factors at initial presentation as documented in the literature; stage 3, grade 3, clear cell subtype, deep myometrial invasion and lymphovascular invasion. Distant metastasis was the most common pattern of recurrence [5]. Six patients were in stage 3 at initial diagnosis, 2 of them received adjuvant chemotherapy prior to proceeding adjuvant radiotherapy. The other 4 patients had significant co-morbidities which precluded adjuvant CT.

We studied the outcome of treatment in our patients with metastatic or recurrent disease. We compared that to other studies. Carboplatin and paclitaxel (CP) was the most commonly used regimen in treating patients with endometriod adenocarcinoma. Overall response of 55.6% was obtained (CR and PR). Further 33.3% SD was achieved. This corresponds to response rates of 46%–78% which were reported in phase II trials [11-13]. A meta-analysis of 6 trials showed improved progression-free survival (PFS)

with more intensive chemotherapy compared with less intensive chemotherapy but a comparable overall survival. Grade 3 and 4 toxicities, particularly in the form of myelosupression and gastrointestinal toxicity, was higher in patients receiving more intense chemotherapy regimens [14]. Among our patients, the lower response rate, PFS and OS in patients with recurrent disease compared to patients who initially presented with metastatic disease indicate the aggressive behaviour of endometrial cancer on the event of recurrence. It is noticed that although the median PFS was 5 months in patients with recurrent endometrial cancer, a small number of patients continued to survive for a longer duration (median survival was 13 months). This is most likely due to different tumour behaviour with some patients having indolent tumour and others more aggressive ones. It is, therefore important to identify these 2 diverse groups so that treatment options would be tailored accordingly.

Hormonal treatment is a logical option in patients with endometrial cancer, since the uterus is a sex steroid-responsive target organ. The oestrogen receptors (ERs) and progesterone receptors (PRs) status in metastatic endometrial cancer has predictive value in determining response to hormonal therapy, which support the use of these assays in the management of patients with metastatic disease. However 10% of women with hormone receptor-negative tumours have been reported to have an objective response to hormonal therapy [15]. One of our 3 patients (33%) treated with medroxyprogesterone acetate, had PR and PFS of 10 months. Response rates between 26 to 89% have been reported in patients with ERs or PRs-positive compared with responses of 8 to 17 percent in women with receptor-negative disease.[15] Aromatase inhibitors have showed responses between 9 and 50 percent with median PFS of 6.7 months in 2 phase II trials [16,17].

Given the increasingly frequent use of platinum agents in combination with doxorubicin and/or paclitaxel in the adjuvant setting, women who have disease recurrence after first-line chemotherapy for advanced disease have limited choices for additional treatment.

As a salvage agent, paclitaxel may be the most active single agent with a reported overall response rate of 27 to 37 percent in women previously unexposed to the drug [18]. Other active agents are topotecan [19], ifosfamide [20], pegylated liposomal doxorubicin [21], oxaliplatin [22] and ixabepilone [23].

A phase II trial of temsirolimus in both chemo-naïve and heavily pre-treated patients with endometrial cancer was recently completed by the National Cancer Institute of Canada (NCIC). Partial response of 14% and SD of 69% with median response durations of 5.1 and 9.7 months respectively were reported. In pre-treated patient, PR and SD rates of 4 and 48 percent and median durations of 4.3 and 3.7 months respectively were seen [24].

In conclusion, adjuvant chemotherapy is currently underutilized in patients with endometrial cancer and hence distant metastasis is the most common pattern of recurrence. This emphasizes the role of adjuvant chemotherapy in patients with risk factors for systemic failure. Ongoing clinical trials are –currently- investigating the rule of adjuvant systemic chemotherapy in early stages high risk endometrial cancer [25]. On recurrence, treatment options should be tailored to tumour behaviour. There is as a need for investigating new second lines regimens in patients who has further progression.

**Corresponding Author:**
Dr Loaie M El-Helw
The Royal Stoke Hospital
Stok-On-Trent, UK, ST4 6QG
Loaieelhelw@hotmail.com, loaieelhelw@gmail.com

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