

Metastatic or Recurrent Endometrial Tumours: the Role of Systemic Anticancer TreatmentLoaie M El-Helw^{1,2}, Hanaa Elkhenini^{3,4} and Mojca Persic²¹Medical Oncology Unit, Mansoura University, Egypt²the Royal Derby Hospital, UK³Public Health Department, Mansoura University, Egypt⁴North West E-Health Department, the University of Manchester, UKloaiehelw@hotmail.com, loaiehelw@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 cancer 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 disease. On further follow up, 13 of the 229 patients (5.7%) developed recurrence mostly with distant metastases (76.9%). The median time to recurrence was 9.5 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.

[Loaie M El-Helw, Hanaa Elkhenini and Mojca Persic. **Metastatic or Recurrent Endometrial Tumours: the Role of Systemic Anticancer Treatment.** *Cancer Biology* 2016;6(1):35-40]. ISSN: 2150-1041 (print); ISSN: 2150-105X (online). <http://www.cancerbio.net>. 7. doi:[10.7537/marscbj06011607](https://doi.org/10.7537/marscbj06011607).

Key Words: endometrial cancer – recurrence – metastases

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 stage disease (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 cancer in our centre. Eight patients (3.4%) had metastatic disease at initial presentation. Two hundred and twenty nine patients presented with non-metastatic (stage I-III) endometrial cancer 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 cancer. Eleven of them (84.6%) had endometrioid adenocarcinoma, 1 EST (7.7%) and 1 carcinosarcoma (7.7%). At initial presentation and prior to developing recurrent disease stage III and grade 3 were most common (46.1% each). Deep myometrial invasion ($\geq 50\%$ 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 and brachytherapy; 2 patients (15.3%) had brachytherapy only and another 2 (15.3%) had adjuvant

chemotherapy followed by external pelvic radiotherapy and brachytherapy. 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	
Adenocarcinoma	
Endometrioid carcinoma	11 (84.6)
Clear cell carcinoma	0 (0)
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 \geq 50%	4 (30.8)
Lymphovascular invasion	
Present	2 (15.4)
Absent	11 (84.6)
Adjuvant treatment	
Ext RT†, BT‡	5 (38.6)
BT ‡only	2 (15.3)
CT*, Ext RT†, BT‡	2 (15.3)
None (Surgery only)	4 (30.8)
Pattern of recurrence	
Distant Metastases	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 9.5 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 endometrioid adenocarcinoma (9 out of 15 patients; 60%). Three patients (20%) had hormonal treatment with medroxyprogesterone 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)
Medroxyprogesterone 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
Medroxyprogesterone 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
Medroxyprogesterone acetate		1 (33.3)		2 (66.7)	3
Clear cell adenocarcinoma					
Carboplatin and Paclitaxel regimen			1 (100)		1
Endometrial stromal tumours					
Aromatase Inhibitor (Anastrozole)			1 (100)		1
Medroxyprogesterone 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)

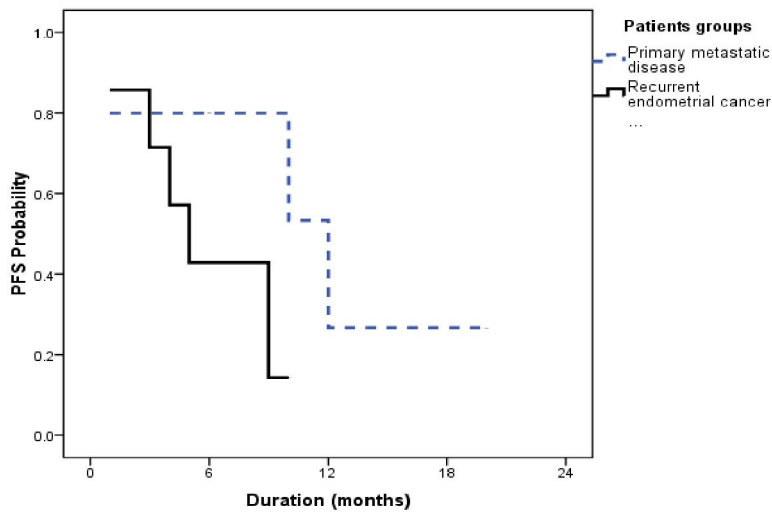
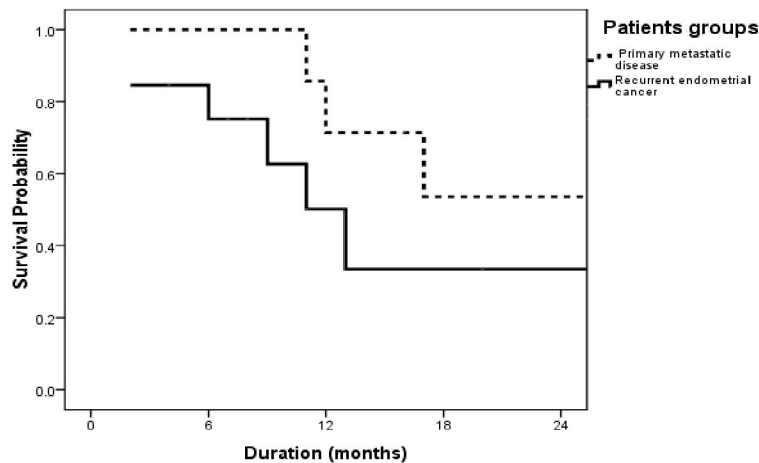


Figure (2) Overall Survival



4. Discussion

In our centre, there was an increasing incidence of endometrial cancer 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 -

therefore- 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 endometrioid 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 myelosuppression 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 stage 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

Loaiehelw@hotmail.com, loaiehelw@gmail.com

References

1. Office for National Statistics: Cancer statistics registrations, London: Cancer incidence and mortality in the United Kingdom 2005-2007. Released 2010; available from <http://www.statistics.gov.uk> 2010.
2. Information Services Division, NHS Scotland: Cancer iIncidence, mortality and survival data. Released 2010; available from <http://www.isdscotland.org>. 2010.
3. Freedman LS, Edwards BK, Ries LAG and Young JL (eds): Cancer Incidence in Four Member Countries (Cyprus, Egypt, Israel, and Jordan) of the Middle East Cancer Consortium (MECC) Compared with US SEER. National Cancer Institute. NIH Pub. No. 06-5873. Bethesda, MD. <http://seer.cancer.gov>, & <http://mecc.cancer.gov>.
4. Elsayed I Salim, Malcolm A Moore, Jawad A Al-Lawati, Jamal Al-Sayyad, Amin Bawazir, Shouki Bazarbashi, Abdulbari Bener, Marilys Corbex, Nagi El-Saghir, Omran S Habib, Wasim Maziak, Ibrahim Abdel-Barr Seif-Eldin, and Tomotaka Sobue: Cancer Epidemiology and Control in the Arab World - Past, Present and Future. *Asian Pacific J Cancer Prev.*, 10, 3-16, 2009.
5. Hacker NF: Uterine cancer. In: Berek JS and Hacker NF (eds). *Practical gynecologic oncology*. 4th ed. Philadelphia, PA; Lippincott Williams & Wilkins, 397-442, 2005.

6. Barakat RR, Goldman NA, Patel DA, Venkatraman ES and Curtin JP: Pelvic exenteration for recurrent endometrial cancer. *Gynecol Oncol.*, 75:99-102, 1999.
7. Awtrey CS, Cadungog MG, Leitao MM, Alektiar KM, Aghajanian C and Hummer AJ: Surgical resection of recurrent endometrial carcinoma. *Gynecol Oncol.*, 102:480-488, 2006.
8. Obel JC, Friberg G and Fleming GF: Chemotherapy in endometrial cancer. *Clin Adv Hematol Oncol.*, 4:459-468, 2006.
9. Temkin SM, and Fleming G: Current Treatment of Metastatic Endometrial Cancer. *Cancer Control.*, 16:38-45, 2009.
10. Evans T, Sany O, Pearmain P, Ganesan R, Blann A, Sundar S: Differential trends in the rising incidence of endometrial cancer by type: data from a UK population-based registry from 1994 to 2006. *Br J Cancer.*, 104:1505-10, 2011.
11. Hoskins PJ, Swenerton KD, Pike JA, Wong F, Lim P and Acquino-Parsons C: Paclitaxel and carboplatin, alone or with irradiation, in advanced or recurrent endometrial cancer: a phase II study. *J Clin Oncol.*, 19:4048-53, 2001.
12. Sorbe B, Andersson H, Boman K, Rosenberg P and Kalling M: Treatment of primary advanced and recurrent endometrial carcinoma with a combination of carboplatin and paclitaxel-long-term follow-up. *Int J Gynecol Cancer*, 18:803-8, 2008.
13. Sovak MA, Dupont J, Hensley ML, Hensley ML, Ishill N and Gerst S: Paclitaxel and carboplatin in the treatment of advanced or recurrent endometrial cancer: a large retrospective study. *Int J Gynecol Cancer*, 17:197-203, 2007.
14. Humber CE, Tierney JF, Symonds RP, Collingwood M, Kirwan J and Williams C: Chemotherapy for advanced, recurrent or metastatic endometrial cancer: a systematic review of Cochrane collaboration. *Ann Oncol.*, 18:409-20, 2007.
15. Decruze SB and Green JA: Hormone therapy in advanced and recurrent endometrial cancer: a systemic review. *Int J Gynecol Cancer*, 17:964-978, 2007.
16. R, Brunetto VL, VanLe L, Bell J, Walker JL and Lee RB: A phase II trial of anastrozole in advanced recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.*, 78:212-6, 2000.
17. M, Oza A, Eisenhauer E, Stanimir G, Carey M and Chapman W: The activity of letrozole in patients with advanced or recurrent endometrial cancer and correlation with biological markers--a study of the National Cancer Institute of Canada Clinical Trials Group. *Int J Gynecol Cancer.*, 14:650-8, 2004.
18. Lincoln S, Blessing JA, Lee RB and Rocereto TF: Activity of paclitaxel as second-line chemotherapy in endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.*, 88:277-81, 2003.
19. Miller DS, Blessing JA, Lentz SS and Waggoner SE: A phase II trial of topotecan in patients with advanced, persistent, or recurrent endometrial carcinoma: a gynecologic oncology group study. *Gynecol Oncol.*, 87:247-51, 2002.
20. Sutton GP, Blessing JA, DeMars LR, Moore D, Burke TW and Grendys EC: A phase II Gynecologic Oncology Group trial of ifosfamide and mesna in advanced or recurrent adenocarcinoma of the endometrium. *Gynecol Oncol.*, 63: 25-7, 1996.
21. Muggia FM, Blessing JA, Sorosky J and Reid GC: Phase II trial of the pegylated liposomal doxorubicin in previously treated metastatic endometrial cancer: a Gynecologic Oncology Group study. *J Clin Oncol.*, 20:2360-4, 2002.
22. Fracasso PM, Blessing JA, Molpus KL, Adler LM, Sorosky JI and Rose PG: Phase II study of oxaliplatin as second-line chemotherapy in endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.*, 103:523-6, 2006.
23. Dizon DS, Blessing JA, McMeekin DS, Sharma SK, Disilvestro P and Alvarez RD: Phase II trial of ixabepilone as second-line treatment in advanced endometrial cancer: gynecologic oncology group trial 129-P. *J Clin Oncol.*, 27:3104-8, 2009.
24. Oza AM, Elit L, Tsao MS, Kamel-Reid S, Biagi J and Provencher DM: Phase II study of temsirolimus in women with recurrent or metastatic endometrial cancer: a trial of the NCIC Clinical Trials Group. *J Clin Oncol.*, 29:3278-3285, 2011.
25. An international Intergroup trial: Randomized Phase III Trial Comparing Concurrent Chemoradiation and Adjuvant Chemotherapy with Pelvic Radiation Alone in High Risk and Advanced Stage Endometrial Carcinoma: PORTEC-3. <https://www.clinicalresearch.nl/portec3>. 2012.