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Advanced stage (IIIC/IV) endometrial cancer: Role of cytoreduction and determinants of survival

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ABSTRACT

Objective: Primary aim of this study was to assess the impact of optimal cytoreduction in women who had surgical treatment of advanced stage (IIIC/IV) endometrial cancer. Secondary objective was to define demographic and surgico-pathologic variables that exerted a significant influence on survival outcomes.
Study design: Records of 45 patients with stage IIIC/IV Endometrial cancer who underwent surgery with cytoreductive intent between 2010 and 2016 were analysed. Data on disease distribution, surgical procedures, adjuvant therapy and survival times was collated. Survival curves were plotted by Kaplan Meier method and median survival estimates were compared using log rank test. Cox proportional hazards model was used to identify independent variables predictive of survival.
Results: 28 women (62.2%) had undergone primary surgery and 17 (37.8%) received neoadjuvant chemotherapy prior to delayed primary surgery. Optimal cytoreduction to </= 1 cm visible disease was achieved in 29 women (64.4%). Among 29 women who had optimal debulking, 24 had no visible disease. Median overall survival for the entire study cohort was 24 months. Median progression free survival in the optimal cytoreduction group was 16 months as opposed to 11.5 months in women who had > 1 cm residual disease (p = 0.02). Median overall survival was 29 months in patients who had optimal cytoreduction and 17.5 months in women who had bulky residual disease (p=0.002). Only poor performance status (p = 0.035), presence of bowel disease (p = 0.05) and suboptimal cytoreduction (p = 0.006) retained significance as predictors of poor survival on multivariate analyses. Suboptimal cytoreduction surgery, compared to optimal cytoreduction, showed a 3.55-fold increased risk of death independent of performance status and anatomic region with disease (Hazard Ratio 3.55 (95% confidence interval 1.44–8.73) p = 0.006).
Conclusion: Survival analyses demonstrate significantly better progression free survival and overall survival when optimal cytoreduction is achieved. A prospective, multicentre study is recommended to establish conclusive evidence.

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Introduction

Endometrial cancer is unique in that relatively few cases are diagnosed in the advanced stages. Surgical stage III/IV disease accounts for over 50% of uterine cancer related deaths and the treatment strategies for these patients has evolved from hormonal therapy with progestational agents, to radiation and chemotherapy [1–3].The association between residual disease following surgery and survival has been explored in the initial studies of Memarzadeh, Bristow and Chi et al [4–6].Following the meta-analyses presented by Barlin et al in 2010 [7], further survival data was published on the role of cytoreduction in women who have received neoadjuvant chemotherapy (NACT) and those with pure endometrioid carcinomas [8,9]. In the period extending from January 2010 to December 2016, 45 patients with Stage IIIC/IV endometrial cancer were identified to have undergone surgical management with

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cytoreductive intent at a tertiary level gynaecological cancer centre. This group comprised a mixed cohort of patients who had either upfront primary cytoreductive surgery (PCS) or delayed interval surgery following neoadjuvant chemotherapy. The primary aim of the study was to assess the role of cytoreduction on survival outcomes in this group and compare it with the latest evidence in literature. The second objective was to identify demographic, surgico-pathologic and therapeutic variables that could predict a survival advantage and additionally define the characteristics of our long-term (>/ = 36 months) survivors.

Methods

A review of the cancer centre database identified all women diagnosed with macroscopic or radiological Stage IIIC/IV Endometrial carcinoma (FIGO 2009) between January 2010 and December 2016. Patients who received palliative chemotherapy or hormones (due to extensive disseminated disease or poor performance status) and those with sarcomatous histology such as uterine carcinosarcomas were excluded at the outset. Following discussion at the cancer centre multidisciplinary team meeting, women were scheduled to receive either neoadjuvant chemotherapy or undergo upfront primary cytoreductive surgery. The criteria for choosing neoadjuvant treatment at the multidisciplinary meeting was radiological impression of unresectable disease, presence of extra-abdominal metastasis (both liver parenchymal and thoracic metastases) and poor performance status. Three cycles of neoadjuvant treatment was administered before interval imaging to assess chemotherapeutic response. RECIST criteria was used to grade response to chemotherapy and regimen change was advocated if there was disease progression with first line chemotherapy. Women who showed disease progression with 2nd line neoadjuvant chemotherapy did not undergo surgery and continued treatment with palliative intent. Individual patient data was collected from electronic patient records, radiological reports, operative notes, outpatient records and pathology reports. Data collated onto the study worksheets included demographic information such as age at diagnosis, disease stage, ethnicity, performance status, and medical co-morbidities & pathology specifications. The site and distribution of metastatic disease (categorised into 6 areas such as extrauterine pelvic disease, retroperitoneal nodes, upper abdomen, omentum, bowel & extra-abdominal metastases) was recorded to assess patterns of disease spread and facilitate analyses of the effect of both location and presence of multisite disease on overall survival. Details of extent of surgery and residual disease status was obtained. Optimal cytoreduction was defined as residual disease equal to and less than 1 cm and included patients without any gross visible disease. Sub-optimal cytoreduction was defined by presence of bulky residual disease greater than 1 cm. Follow-up data included postoperative adjuvant therapies, time to progression, length of follow-up, date and cause of death. Progression free survival was defined as the interval from initiation of treatment until the date of clinical or radiological recurrence or progression. Overall survival was calculated from date of initiation of treatment until death from any cause. As this was a retrospective study, no ethical approval was sought. This study has been included in the research registry (Researchregistry4005) and the work has been reported in line with the STROCSS criteria [10].

Statistical analysis

Descriptive statistics are presented as mean (standard deviation), frequency (percentage) or median (interquartile range) as appropriate. Patient characteristics and demographics associated with overall survival were evaluated using the log rank test. Significant associations (univariate analysis p value <0.25) were included in a multivariate Cox proportional hazards model which was used to identify independent variables predictive of survival (p value <0.05). Survival curves were calculated using the method of Kaplan and Meier and median survival estimates were compared by the log-rank test. Chi-square tests was used to identify factors associated with surgical outcome. Data was analysed using Stata software, version 14.2 (Stata Corp LP, College Station, Texas).

Results

Patient characteristics and Disease distribution

45 women were identified to have met the study eligibility criteria including 12 patients at stage 3C (with bulky and enlarged pelvic and predominantly para-aortic lymph nodal disease), 32 patients with stage 4B and 1 patient with stage 4A disease. 28 women (62.2%) had undergone primary surgery and 17 (37.8%) received neoadjuvant chemotherapy prior to delayed primary surgery.22 women (48.9%) were less than 65 years of age and 71.1% (32) were of White Caucasian ethnicity.43 women (95.6%) had a performance score of 0–1. Co- morbidities as hypertension, Diabetes, Venous thromboembolism, pre-existing cardiac arrhythmias were present in 29 women (64.4%).The most common histological type was uterine papillary serous carcinoma (UPSC) and mixed UPSC tumours comprising 27 patients (60%) followed by Endometrioid subtype (28.9%) and clear cell carcinoma in 5 women (11.1%).Disease distribution by anatomic region involvement is demonstrated in Table 1. This stratification was done to be included in survival analysis. Metastatic disease was most commonly seen in the extrauterine pelvis (82.2%), retroperitoneal lymph nodes (55.6%) and omentum (42.2%). Bowel metastatic disease was noted in 7 women (15.6%), upper abdominal disease in 11.1% and extra-abdominal metastases in sites such as liver parenchyma, lung, supraclavicular, para-cardiac and inguinal lymph nodes in 8(17.8%). Disease was present in greater than 3 anatomic regions in 16 patients (35.6%).

Surgical results

28(62.2%) women had primary cytoreductive surgery and 17 (37.8%) women had received neoadjuvant chemotherapy prior to interval cytoreduction. All 45 women underwent exploratory laparotomy with the intent to perform complete surgical staging and maximal cytoreduction. The surgical procedures performed are listed in Table 2. Optimal cytoreduction to </ = 1 cm visible disease was achieved in 29 women (64.4%) and 16 (35.6%) women had residual disease equating to suboptimal cytoreductive status. Amongst the women who had optimal debulking, 24 (53.3%) had no visible disease. The reasons for suboptimal cytoreduction were grossly enlarged (>4 cm) and adherent retroperitoneal adenopathy in the para- aortic region and coeliac axis, disseminated large volume peritoneal disease, disease extension to the pelvic side wall and pararectal fossa.

Adjuvant Treatment

17 women had received 3–6 cycles of neoadjuvant chemotherapy prior to undergoing delayed primary surgery. Most patients in this group had standard Carboplatin /Taxol regimes whilst 2 had received Cisplatin/Doxorubicin due to poor response with the former regimen.1 patient had received Capecitabine in the presumption of having locally advanced rectal cancer but final histological analyses revealed grade 3 endometrioid carcinoma. All these women received further cycles of Carboplatin /Taxol chemotherapy to achieve completion of adjuvant treatment. In

Table 1
Patient characteristics, Survival Analysis and predictive factors for overall survival.

Demographics	Proportion	Median survival (months)	Univariate analyses		Multivariate Analyses	
			Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
1.Age						
< 65 years	**22 48.9 %**	**25.5**				
>/= 65 years	**23 51.1 %**	**21**	**1.49 (0.68 -3.26)**	**0.309**		
2.Ethnicity						
Caucasian	**32 71.1 %**	**25.5**	**0.97(0.41- 2.32)**	**0.950**		
Other ethnicity	**13 28.9 %**	**24**				
3. Performance status						
0-1	**43 95.6%**	**26**	**0.08 (0.01-0.45)**	**0.003**	**0.15(0.28-0.88)**	**0.035**
>1	**2 4.4%**	**12.5**				
4. Co- morbidities						
Yes	**29 64.4%**	**24**	**1.06(0.47 -2.39)**	**0.875**		
No	**16 35.6 %**	**24**				
5. Histology						
UPSC / Mixed UPSC	**27 60.0%**	**24**	**2.17(0.79-5.91)**	**0.129**	**1.89(0.67-5.31)**	**0.231**
endometrioid	**13 28.9%**	**38**				
Clear cell	**5 11.1%**	**21**	**2.35(0.62-8.8)**	**0.205**	**2.15(0.56-8.22)**	**0.262**
Therapeutic variables	**Proportion**	**Median survival (months)**				
1.Residual disease						
</= 1 cm -optimal	**29 64.4 %**	**29**				
>1 cm - suboptimal	**16 35.6 %**	**17.5**	**3.26(1.46-7.29)**	**0.004**	**3.55(1.44-8.73)**	**0.006**
2. NACT vs PCS						
NACT	**17 37.8 %**	**29**	**1.26 (0.56 -2.85)**	**0.574**		
Primary CRS	**28 62.2 %**	**22.5**				
Anatomic region with disease	**Proportion**	**Median survival (months)**				
Bowel disease						
yes	**7 15.6%**	**21**	**1.98(0.79-4.97)**	**0.146**	**2.75(0.99-7.61)**	**0.05**
No	**38 84.4%**	**25.5**				
Extra-abdominal metastasis						
yes	**8 17.8%**	**25**	**0.54 (0.16-1.82)**	**0.321**		
No	**37 82.2%**	**24**				
Disease =/> 3 regions						
Yes	**16 35.6%**	**23.5**	**1.07 (0.48-2.37)**	**0.865**		
No	**29 64.4%**	**24**				
Pelvis (extrauterine)						
yes	**37 82.2%**	**26**	**1.07 (0.37-3.11)**	**0.898**		
No	**8 17.8%**	**20.5**				
Omentum						
yes	**19 42.2%**	**28**	**0.75(0.34-1.66)**	**0.483**		
No	**26 57.8%**	**22.5**				
Retroperitoneal LN						
yes	**25 55.6%**	**24**	**0.81(0.37-1.77)**	**0.605**		
No	**20 44.4%**	**23.5**				
Upper abdomen						
yes	**5 11.1%**	**26**	**0.61(0.14-2.60)**	**0.508**		
No	**40 88.9%**	**24**				

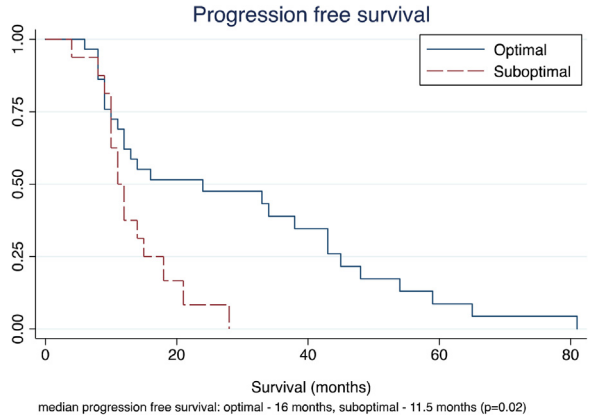
the PCS group, 27 out of the 28 women received postoperative chemotherapy with the standard regimens. 30 patients in the entire cohort also received extended beam pelvic radiotherapy.

Survival Analyses

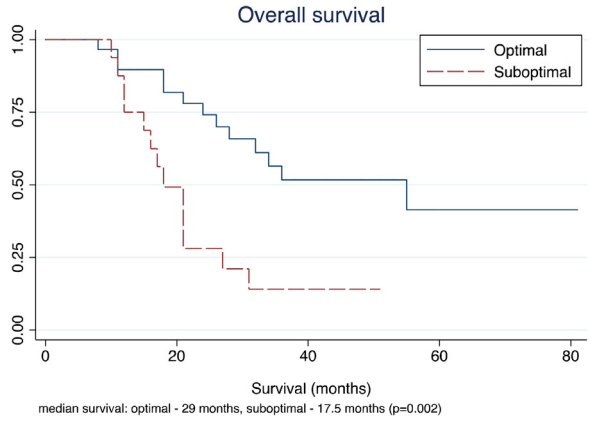
The median follow-up period was 24 months (range 8–81 months). The median overall survival for the entire study group was 24 months and the median progression free survival was 14 months. Median progression free survival in the optimal cytoreduction group was 16 months (Graph 1) as opposed to 11.5 months in women who had residual disease greater than 1 cm ($p = 0.02$). Median overall survival was 29 months in patients who had optimal cytoreduction (Graph 2) and 17.5 months in women who had bulky residual disease ($p = 0.002$). Therefore, survival analyses and Kaplan Meier Curves demonstrate superior progression free survival and Overall survival when optimal cytoreduction is achieved. Subgroup Analyses of survival curves in patients with only UPSC/Mixed UPSC was undertaken (Graphs 3 & 4). The median progression free survival in optimally debulked women with high grade serous tumours was 14 months as opposed to 12 months in those with suboptimal cytoreduction. Whilst this did not reach statistical significance, the median overall survival in this subset of women with optimal cytoreduction was 29 months and significantly better than the 16 months survival achieved in patients with bulky residual disease ($p = 0.04$). Significant predictors of reduced survival on univariate analysis using the log rank test (Table 1) were poor performance status, presence of bowel

Table 2
Operative procedures.

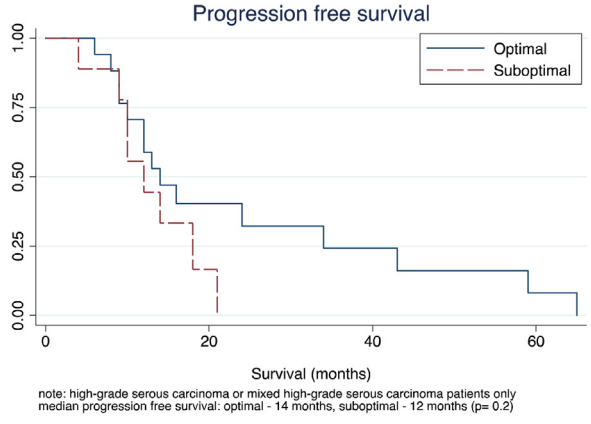
Operative procedure	Number /Proportion
TAH +/- BSO	*44 (97.7%)*
Pelvic lymphadenectomy	*45 (100 %)*
Para-aortic lymphadenectomy	*33 (73.3%)*
Supra-colic omentectomy	*39 (86.6%)*
Large bowel resection	*2 (4.4%)*
Inguinal node resection	*1 (2.2%)*
Partial cystectomy	*1 (2.2%)*
Radical hysterectomy	*1 (2.2%)*



Graph 1. Kaplan Meier Survival plot of Progression Free Survival in women with optimally versus sub-optimally debulked Endometrial cancer.

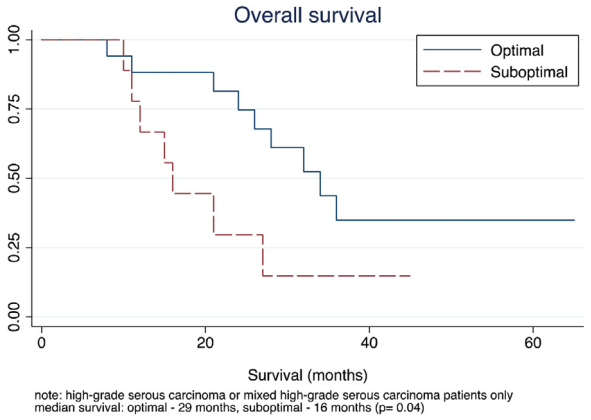


Graph 2. Kaplan Meier Survival plot of Overall Survival in women with optimally versus sub-optimally debulked Endometrial cancer.



Graph 3. Kaplan Meier Survival plot of Progression free survival in women with optimally versus sub-optimally debulked High grade serous Endometrial cancer.

disease, endometrioid histology and suboptimal cytoreduction (p value <0.25). Multivariate analysis was used to simultaneously examine the effect on survival of age < 65 years, ethnicity, performance status, histology, residual disease, treatment approach (NACT vs PCS), site of disease including extra-abdominal metastases and multisite disease. After controlling for these factors, only poor performance status (p value=0.03), presence of disease in bowel (p value=0.05) and suboptimal cytoreduction



Graph 4. Kaplan Meier Survival plot of Overall Survival in women with optimally versus sub-optimally debulked High grade serous Endometrial cancer.

(p value=0.006) retained significance as predictors of poor survival. Suboptimal cytoreduction surgery, compared to optimal cytoreduction, showed a 3.5-fold increased risk of death independent of performance status and anatomic region with disease (Hazard Ratio 3.55 (95% confidence interval 1.44–8.73) p = 0.006).

Long term survivors

Survival assessment concluded in December 2017. 19 women out of 45 (42.32%) were alive at the end of this period. 13 women (28.8%) had survived 36 months or longer and constituted our long- term survivors whose characteristics merited further analysis (Table 3).2 women were dead of disease, 2 were alive with disease and 9 out 13 had no evidence of disease. All had good performance status, 9 out of 13 (69.2%) were less than or equal to 65 years in age and 11 of 13(84.6%) had optimal cytoreductive surgery.11 out of 29 optimally cytoreduced women belonged to this group whilst only 2 out 16 women in the suboptimal group survived beyond 36 months. Although the numbers are small, this analysis suggests that our long- term survivors appear to be of a younger age with good performance status, endometrioid histology and have undergone optimal cytoreduction.

Comment

Griffiths in 1975 noted the direct correlation in ovarian cancer between the size of residual disease remaining after surgical cytoreduction and overall survival [11]. Whilst benefit in extending the same treatment paradigm to patients with advanced Endometrial cancer remained unclear for a long time, the meta-analyses of Barlin et al in 2009 opinioned that achieving optimal cytoreduction significantly prolonged survival for these women [7]. We, therefore sought to update the published evidence on cytoreductive outcomes by presenting the survival analyses of a combined cohort of patients who underwent either upfront surgery or delayed surgery following neoadjuvant chemotherapy for stage IIIC/IV endometrial cancer. Our study included women with all epithelial histological types. Available evidence dwells on patients with mainly uterine papillary serous carcinoma with near similar number of studies encompassing all histological types (Table 4). Shih et al in 2011 reported on survival of 58 patients with Endometrioid subtype alone and demonstrated superior survival again weighted towards microscopic residual disease status group [9]. No other demographic factors in this study had a significant impact on overall survival and whilst poor performance status was significant on multivariate analyses, there were only 2 patients in this group and therefore this finding is subject to further debate.

Table 3
Long term Survivors (>36 months) following cytoreductive surgery for Advanced Endometrial cancer.

Patient	Age	Histology	Metastatic sites	PS	Surgical result	NACT or PCS	Last Followup (months) / disease status
1	57	HGS/EEC	pelvis	1	Optimal	NACT	65 / NED
2	66	Clear cell	Pelvis/om	1	optimal	NACT	73 / AWD
3	37	G3 EEC	Pelvis/bowel	0	optimal	NACT	81 / NED
4	72	G1 EEC	Om, upper abd, extra-abd	0	Suboptimal	NACT	51 / NED
5	52	G2 EEC	Pelvis/om	1	optimal	NACT	45 / NED
6	59	HGS	om	1	optimal	NACT	51 / AWD
7	65	HGS	Om, retrop nodes	0	optimal	PCS	59 / NED
8	50	HGS	Pelvis, retrop nodes	0	Suboptimal	PCS	46 / AWD
9	58	G2 EEC	Pelvis, retrop nodes,om	0	optimal	PCS	49/ NED
10	69	HGS	Pelvis, bowel	1	optimal	PCS	43 / NED
11	43	G3 EEC	pelvis	0	optimal	PCS	38 / NED
12	65	HGS	Pelvis, om, retrop nodes	0	optimal	NACT	36 / DOD
13	68	G2 EEC	Pelvis, retrop nodes	1	optimal	PCS	55 / DOD

Disease status: NED (no evidence of disease), DOD (dead of disease), AWD (alive with disease); PS – Performance status Abd -abdomen, Retrop – Retroperitoneal, Om - Omentum.

Table 4
Comparison of survival data following cytoreductive surgery for advanced stage (stage III/IV) endometrial cancer.

Author	Tumour histology	NACT Vs PCS	FIGO stage	Optimal defn	Total patients	Optimal CR (n)	Suboptimal CR (n)	Optimal CR (%)	Optimal median OS (months)	Suboptimal median OS (months)	p-value	Reference
Chi	**ALL endo**	**PCS**	**IV**	**</=2**	**55**	**24**	**21**	**53**	**31**	**12**	**<0.01**	[6]
Bristow	**ALL endo**	**PCS**	**IVB**	**</=1**	**65**	**36**	**29**	**55**	**34**	**11**	**0.0001**	[5]
Ayhan	**ALL endo**	**PCS**	**IVB**	**</=1**	**37**	**22**	**15**	**59**	**25**	**10**	**0.001**	[13]
Lambrou	**ALL endo**	**PCS**	**IIIC /IV**	**</=2**	**58**	**42**	**16**	**72**	**18**	**7**	**0.001**	[18]
Van Wijk	**ALL endo**	**PCS**	**III/ IV**	**Nil gross vis**	**67**	**50**	**17**	**75**	**66% 5 yr survival**	**41% 5 yr survival**	**<0.01**	[19]
Bristow	**UPSC**	**PCS**	**IV**	**</=1**	**31**	**16**	**15**	**52**	**26**	**10**	**<0.001**	[14]
Memarzadeh	**UPSC**	**PCS**	**IIIC/ IV**	**Nil gross vis**	**35**	**20**	**15**	**57**	**40**	**10**	**<0.001**	[4]
Moller	**UPSC**	**PCS**	**IV**	**</=1**	**49**	**26**	**23**	**53**	**15**	**8**	**>0.05**	[20]
Thomas	**UPSC**	**PCS**	**IIIC/ IV**	**</=1**	**70**	**42**	**28**	**60**	**20**	**12**	**0.02**	[21]
Vandenput	**UPSC**	**NACT**	**IV**	**</=1**	**30**	**24**	**6**	**80**	**23**	**12**		[8]
Shih	**Endometrioid**	**PCS**	**IV**	**Nil gross vis**	**58**	**9**	**32**	**15.5**	**42.2**	**19**	**<0.001**	[9]
Lee	**UPSC**	**PCS**	**IV**	**</=1**	**48**	**36**	**12**	**75**	**26.5**	**12.6**	**<0.001**	[17]
Current study	**ALL endo**	**PCS & NACT**	**IIIC/ IV**	</=1	45	29	16	64.4	29	17.5	0.002	

The distribution of metastatic disease in our study reflects that established in previous reports. Multivariate analysis revealed that presence of bowel disease also reached significance in prediction of poor survival. No survival difference was noted in the presence of extra –abdominal metastases and this is similar to the findings of Goff and Chi et al who implied that the volume of tumour is more important than its site at this stage [6,12]. Most patients received the current standard chemotherapy regimens for treatment of advanced stage disease ie Carboplatin and Taxol. Previous studies have established that sequential usage of adjuvant chemotherapy and radiotherapy led to better survival and reduced risk of disease progression [15,16]. As this was the standard of adjuvant treatment for nearly all women in this study, analysis of the effect of chemotherapy or radiotherapy was not undertaken. Table 5 demonstrates that median OS of 29 months in our analysis also compares favourably to the OS range of 18–42 months reported in the preceeding studies. The optimal cytoreduction rate of 64.4% achieved in this study is comparable to the results (52%–80%) in all previously published work. It is interesting to note that the highest rate was achieved by Vandenput et al reporting 80% optimal cytoreduction amongst the 30 women who had Neoadjuvant treatment. Prospective studies exploring the benefits of Neo-adjuvant treatment are awaited to establish its role in facilitating R0 (zero residual disease) surgical result. Uterine Papillary serous carcinomas (UPSC) represent a more aggressive histological type of endometrial cancer and were subject to separate analyses. The range of optimal median OS in patients with UPSC was 15–40 months and this is similar to the 29 months OS in this subgroup as opposed to a survival of 16 months in women who had residual disease. Barlin et al did not seek to analyse PFS but our study has shown a statistically significant difference in PFS as well (16 months optimal vs 11.5 months suboptimal - p value 0.02) and is consistent with the findings of Memarzadeh and Lee et al [4,17]. There have been only 2 studies which have looked at long term survivors following surgical treatment of advanced stage disease. Lee et al when analysing the long- term survivors with stage 4 UPSC confined to the abdomen found that the 5-year DFS and OS estimates were 12% and 19%, respectively. The characteristics (ie younger age, good performance status, endometrioid histology and optimal cytoreduction) identified in our study to have a favourable bearing on long term survival mirror the results of the Bristow study [5]. On multivariate analyses, the factors which held significance in prediction of overall survival were optimal cytoreduction, presence of disease in bowel and poor performance status. These findings are similar to all previously published studies which emphasise that the most significant and often

solitary predictor of survival in the treatment of women with advanced stage Endometrial cancer is the cytoreductive status [1–5]. The strengths of this study dwell on its addition to the limited body of evidence on the impact of cytoreduction in women with advanced stage endometrial cancer. The limitations are the retrospective nature, the small sample size derived from a single centre and inclusion of women of all histological types. Therefore, this analysis serves as a pilot study in demonstrating the survival benefit associated with optimal cytoreduction. We recommend awaiting the results of a prospective, multicentre trial to establish conclusive evidence.

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None sought.

Conflict of Interest

The authors declare no conflict of interest.

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