Indian Journal of Gynecologic Oncology (2024) 22:86
https://doi.org/10.1007/s40944-024-00850-9

ORIGINAL ARTICLE

Advanced endometrial cancers—outcome of patients undergoing cytoreductive surgery: a retrospective study

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Received: 30 May 2023 / Revised: 19 February 2024 / Accepted: 7 April 2024 / Published online: 19 May 2024

Abstract

Objectives The objective of the study was to assess the overall and disease free survival in patients with advanced (Stage III and IV) endometrial cancer who undergo cytoreductive surgery, and to assess the factors affecting recurrence in these patients.

Methodology 80 patients with advanced endometrial cancer who were diagnosed and had undergone surgery in Regional Cancer Center, Thiruvananthapuram between 2008 and 2018 were included. Patients who underwent neoadjuvant chemotherapy or radiotherapy initially and surgery later were also included for analysis.

Results Mean age was 59.9 yrs. Patients with Stage III disease constituted 81.2% ($n=65$) of the population whereas 18.8% ($n=15$) had stage IV endometrial cancer. There were 53 patients (66.3%) with endometrioid histology whereas 12 (15%) had serous carcinoma, 6 (7.5%) had clear cell carcinoma and 9 (11.2%) had carcinosarcoma. Majority of the patients, 69 (86.3%) had primary surgery, while 11 (13.7%) had upfront chemotherapy or radiotherapy before surgery. Complete cytoreduction was achieved in 72 (90%) of the patients who underwent surgery. Adjuvant treatment was chemotherapy and radiation was given in 41 patients (51.2%), while 15 (18.8%) received chemotherapy alone and 18 (21.3%) received radiotherapy alone. Median follow up period was 92 months. Relapse occurred in 50 patients (62.5%) and death in 49 patients (61.2%). 5 year DFS was 39% and OS was 46.9%. Factors significantly correlating to recurrence on univariate analysis included age more than 60 years, non endometrioid histology, high grade, LVSI and pelvic nodal metastases. However on multivariate analysis, only non endometrioid histology was found to have a significant correlation with recurrence. Factors significantly correlating to survival were age more than 60 yrs, Pre op Albumin less than 4 g%, non endometrioid histology, high grade, presence of LVSI and site of recurrence in lung and para aortic lymph nodes. However on multivariate analysis, only non endometrioid histology was found to have a significant correlation with survival.

Conclusion In carefully selected patients with advanced endometrial cancer, a combination of surgical cytoreduction with appropriate adjuvant treatment and neoadjuvant treatment when indicated gives good results with an acceptable morbidity and mortality and reasonable overall survival.

Keywords Advanced endometrial cancer · Cytoreductive surgery · Recurrence · Survival

Introduction

Endometrial cancer (EC) is the most common gynecologic cancer in the western world with an age standardized incidence of 21.1 per 100,000 in North America as compared to 8.8 per 100,000 in Western Asia [1]. The incidence in India is reported to be 4.2 per 100,0000 as in 2022 [2]. With increasing rates of obesity and life expectancy, the incidence will continue to increase [3]. SEER data suggest that there is also a rise in advanced-stage and high-risk histologies, which will further impact the rate of mortality [4]. Endometrial cancers have traditionally been designated as type I or type II tumors, with type II cancers

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being characteristically much more aggressive, with more extrauterine spread at the time of diagnosis, compared to type I cancers [5, 6]. Endometrial cancer is generally associated with a favorable prognosis, largely because of the fact that approximately 70% of patients present with stage I disease. Survival rates are generally high, approximately 75%, in these early stage uterine cancers [7]. The 10–15% of endometrial cancers that extend beyond the uterus at diagnosis have reported survival rates as low as 5–15%, accounting for over half of all deaths related to uterine cancer [8]. When unresectable, advanced endometrial carcinoma has a median survival of 2–8 months [9, 10].

Endometrial cancer is staged surgically. Surgical intervention with total hysterectomy and bilateral salpingo oophorectomy with peritoneal washings, pelvic and paraaortic lymph node dissection if indicated, and surgical debulking is warranted in cases with intra-abdominal disease (i.e. ascites and/or omental, nodal, ovarian, or peritoneal involvement). Cytoreductive surgery in advanced ovarian cancer is well studied and accepted as the standard of care; however, the existing literature for advanced or recurrent endometrial cancer is limited to small, nonrandomized, retrospective studies [11]. These studies have shown that surgical cytoreduction is an independent prognostic factor for progression free survival PFS) and overall. For early-stage disease, surgery alone or in combination with adjuvant treatment gives a good clinical outcome. However in patients with advanced endometrial cancer with spread to the lymph nodes, parametria, adnexa or with metastases to the omentum or other organs, the prognosis remains poor and the optimal treatment practice varies.

Women with advanced FIGO stage III and IV endometrial carcinoma constitute a heterogeneous group of patients who are at risk for both local and systemic disease recurrence. Primary surgical cytoreduction, whenever feasible is the standard management. These patients may further receive chemotherapy, radiotherapy or hormonal treatment each alone or in combination depending on the adverse pathologic factors. In the subset of patients with parametrial or extensive vaginal disease or distant metastases at presentation, neo adjuvant therapy—chemotherapy or radiation may be considered.

More recently, as a result of The Cancer Genome Atlas (TCGA) group [12] performing the genomic analysis of endometrial cancers, four distinct molecular subtypes have been identified—the Polymerase Epsilon ultra-mutated, microsatellite instability hypermutated, copy-number-low, and, copy number high groups which can be identified by a combination of immunohistochemistry (IHC) and mutation analysis. This classification has further allowed risk stratification, prognostication and directing adjuvant treatment.

Methodology

The aim of the study was to assess the outcome of patients with advanced endometrial cancers including Stage III and Stage IV cancers. It was a retrospective study which included all patients with advanced endometrial cancer diagnosed during the period between 1st January 2008 and 31st December 2018, who underwent surgery in Regional Cancer Center (RCC), Thiruvananthapuram. Patients with endometrioid histology, uterine serous cancers, clear cell cancers and uterine carcinosarcomas were included in the study. Patients who underwent neoadjuvant chemotherapy or radiotherapy were also included. The main outcomes studied were the overall and disease free survival in these patients, rates of recurrence, the sites of recurrence and also the factors affecting recurrence.

Details of patient demographics, stage and histopathology of disease, details of the surgery, whether complete cytoreduction was achieved, whether neo adjuvant treatment was given, details of adjuvant treatment given, details of disease recurrence and further course were obtained from hospital records and follow up information was updated for survival analysis. Follow up data until December 2021 was taken.

Statistical analysis

Descriptive statistics such as mean, median and frequency and percentages were estimated. Kaplan Meier method was used for survival estimation. Disease free survival will be calculated from completion of treatment till recurrence. Overall survival will be assessed from date of diagnosis until date of last follow up or death. Statistical significance of survival curves were estimated using Log Rank test. Logistic regression model was used for risk factor analysis.

Results

A total of 80 patients with advanced endometrial cancer were included in the study. Mean age of the population was 59.9 yrs (range 36–82 yrs). Patients were followed up for a median period of 92 months. 92.5% of the patients were postmenopausal and 7.5% were pre menopausal.

Out of a total of 80 patients, there were 14 (17.5%) patients with Stage III A, 4 (5%) patients with Stage III B, 21 (26.25%) patients with Stage III C1, 26 (32.5%) with Stage III C2, 3 (3.75%) with Stage IV A, and 12 (15%) patients with Stage IV B disease. A confirmatory cystoscopy was done in one out of the three patients with IV A. The rest

Table 1 Histopathologic features

Stage	*N*	%
IIIA	14	17.5
IIIB	4	5
IIIC1	21	26.25
IIIC2	26	32.5
IVA	3	3.75
IVB	12	15
Total	80	100
Histology		
Endometrioid	53	66.3
Serous	12	15
Clear cell CA	6	7.5
Carcinosarcoma	9	11.2
Total	80	100
Grade		
Grade 1	4	5
Grade 2	29	36.2
Grade 3	47	58.8
Peritoneal cytology		
Negative	77	96.3
Positive	3	3.8
Pelvic node		
Negative	21	26.3
Positive	41	51.2
Not assessed	18	22.5
Para aortic node		
Negative	29	36.3
Positive	28	35

were diagnosed as IV A from the imaging. Histopathologic features of the patients are discussed in Table 1

Histopathology was endometrioid in 53 (66.3%) patients, serous in 12 (15%) patients, clear cell in 6 (7.5%) patients and carcinosarcoma in 9 (11.3%) patients. There were 47 (58.8%) patients with Grade 3 endometrial cancer. Myometrial invasion was found to be more than 50% in 22 patients (27.4%) and less than 50% in 13 (16.3%) patients. Serosal breach by tumor was present in 13 patients (16.3%).

Cervical involvement was present in 35 (43.7%) patients. A positive peritoneal cytology was found in 3 (3.8%) patients. Adnexal involvement was present in 29 (36.3%) patients and Lymph vascular space involvement in 28 (35%) patients. Pelvic nodes were negative in 21 (26. 3%) patients, positive in 41 (51.2%) patients and not assessed in 18 (22.5%) patients. Para aortic nodes were negative in 29 (36.3%) patients, positive in 28 (35%) patients and not assessed in 23 (28.7%) patients.

All the cases were discussed in multidisciplinary tumour board meetings. In cases diagnosed to be advanced preoperatively, decision on upfront cytoreductive surgery (CRS)/ Neoadjuvant chemotherapy (NACT) was taken based on imaging, and whether a complete cytoreduction would be achievable. The neoadjuvant modality was decided by the treating consultant.

69 (86.3%) patients had primary surgery, while 11 (13.7%) had upfront chemotherapy or radiotherapy before surgery. 6 patients received neoadjuvant chemotherapy alone, 3 patients received neoadjuvant radiotherapy alone and 2 patients received both.

The patients who received neoadjuvant chemotherapy alone included one patient with stage IIIB involving parametrium, two patients with Stage IIIC2 disease who had bulky para aortic nodes infiltrating large vessels, one patient with Stage IV A disease infiltrating the urinary bladder and two patients with Stage IVB disease with omental nodules. All patients with Stage III also received radiotherapy after surgery whereas patients with Stage IV, did not.

3 patients received neoadjuvant radiotherapy alone, one patient with Stage III B disease with parametrial involvement and two patients with Stage IV A disease, one of which had bladder infiltration and one had rectal infiltration. 2 patients received neoadjuvant chemoradiotherapy, of which one had Stage III B with parametrial involvement and one had Stage IV A with bladder infiltration.

Being advanced malignancies, surgical approach was open in 70 (87.5%) patients and laparoscopic in 10 (12.5%) patients. Minimal access procedures were all done in the upfront setting for presumed uterine confined disease, and accompanied by sentinel node biopsy. These patients had metastases in the sentinel node in the final histopathology and were hence Stage III. Complete cytoreduction to no gross residual disease was achieved in 72 (90%) of patients.

Surgical procedure done was Hysterectomy and bilateral salpingo oopherectomy alone in 3 patients, Hysterectomy, bilateral salpingo oopherectomy and sentinel lymph node biopsy in 10 patients, Hysterectomy, bilateral salpingo oopherectomy and bilateral pelvic node dissection in 15 patients, Hysterectomy, bilateral salpingo oopherectomy, pelvic and para aortic node dissection in 28 patients, Hysterectomy, bilateral salpingo oopherectomy, pelvic and para aortic node dissection and omentectomy in 9 patients, Type B Hysterectomy, bilateral salpingo oopherectomy, pelvic and para aortic node dissection in 7 patients, Hysterectomy, bilateral salpingo oopherectomy and omentectomy in 6 patients, Anterior exenteration in 1 patient, Hysterectomy, bilateral salpingo oopherectomy and inguinal node dissection in 1 patient.

Hysterectomy and bilateral salpingo oopherectomy alone was done in three patients. Two patients were elderly, with poor performance status, who were high risk for surgery and were hence planned for only TAH and BSO. Both were Stage III A on final histopathology, one due to ovarian metastasis and the other had tumor breaching the serosa. A third patient was found to have a large para aortic nodal mass infiltrating

Table 2 Adjuvant treatment

Adjuvant treatment	*N*	%
None	5	6.3
External beam RT (EBRT)	1	1.3
Brachytherapy (BT)	2	2.5
EBRT + BT	15	18.8
Chemotherapy	15	18.8
Chemotherapy + EBRT	41	51.2
Hormones	1	1.3

Table 3 Recurrence patterns

Histology	Vault relapse	Nodal relapse	Distant mets	Total
Endometrioid	2 (100%)	7 (58.3%)	18 (50%)	27
Serous	0	3 (25%)	7 (19.4%)	10
Clear cell	0	1 (8.3%)	3 (8.3%)	4
Carcinosarcoma	0	1 (8.3%)	8 (22.2%)	9
Total	2 (100%)	12 (100%)	36 (100%)	50

the large vessels which could not be dissected off, hence only TAH BSO was done (Table 2).

All the patients were planned for adjuvant treatment, but 5 patients did not take the treatment—3 patients defaulted and 2 were elderly and had poor performance status, so the planned adjuvant treatment could not be started.

5 (6.3%) patients did not have any adjuvant treatment. 41 (51.2%) of the patients received both chemotherapy and radiation—both external beam radiotherapy and brachytherapy. 15 (18.8%) of the patients received chemotherapy alone. 15 (18.8%) received only radiotherapy which included both external beam radiotherapy and brachytherapy, 1.3% received only external beam radiotherapy, 2.5% received only brachytherapy and 1.3% received hormonal treatment (Table 3).

After a median follow up period of 92 months, the 5 year disease free survival the entire study population was 39.50 patients (62.5%) had recurrences. Site of relapse was at the vault in 2 patients, at the pelvic or para aortic nodes in 12 patients, peritoneal in 12 patients and distant mets in 36 patients. Among the 26 patients with endometrioid histology, 2 patients (7.6%) had relapse at the vault, 7 patients (25.9%) had a nodal relapse and 18 patients (66.6%) had a distant relapse. Among the 10 patients with serous histology, 7 had distant mets and 3 had nodal metastasis. Among the 9 patients with carcinosarcoma, 8 had distant mets and 1 had nodal mets (Figs. 1 and 2).

On univariate analysis, the factors significantly associated with recurrence were age > 60 yrs, non endometrioid histology, grade 3 histology, lymph vascular space involvement and pelvic nodal metastasis. On multivariate analysis, only non endometrioid histology had a significant correlation with recurrence and survival.

5 year overall survival was 46.9%. Death occurred in 61.2% of patients. On univariate analysis, factors significantly associated with survival were age > 60 yrs, pre operative albumin levels less than 4 g%, non endometrioid histology, grade 3 histology, and the presence of lymph vascular space involvement and recurrence in the lung and para aortic lymph nodes. On multivariate analysis, only non endometrioid histology had a significant correlation with recurrence and survival.

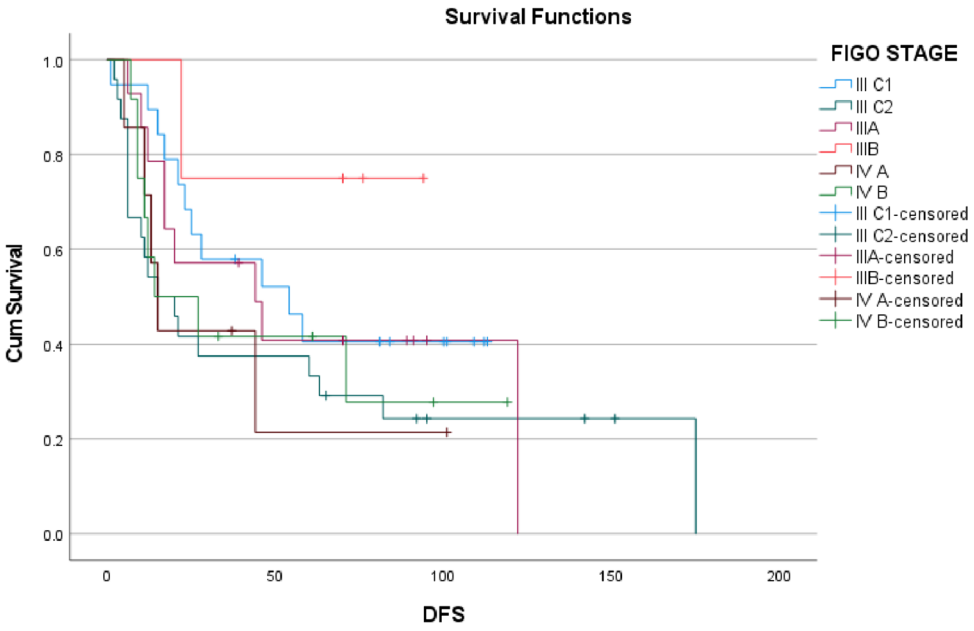

Fig. 1 Disease free survival

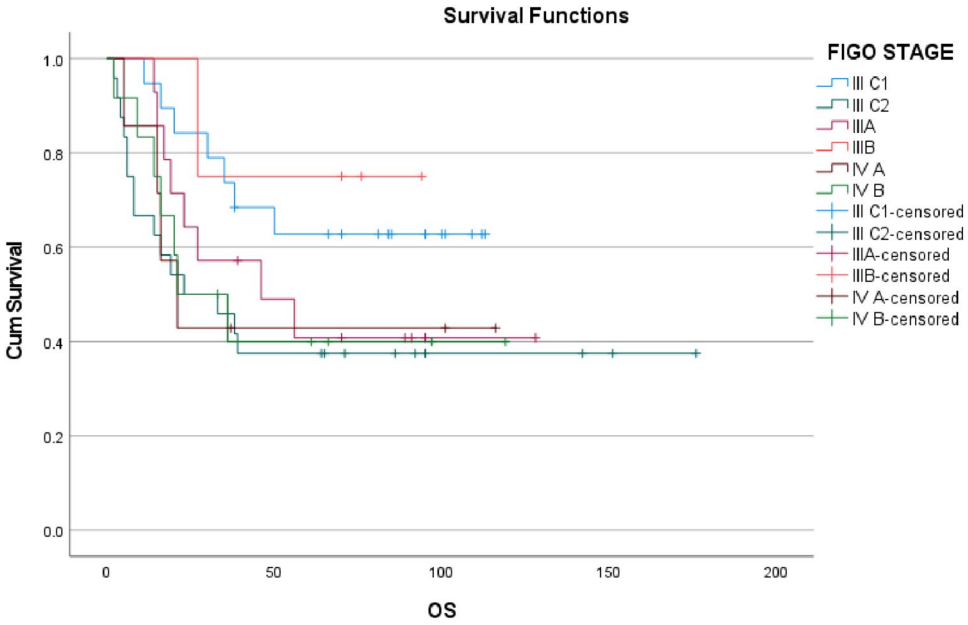

Fig. 2 Overall survival

The overall survival in the group of patients who received neoadjuvant treatment for advanced disease was 45.5% while patients who had upfront surgery had an overall survival of 37.7%. However, the difference was not statistically significant, probably due to the small number of patients in the neoadjuvant group.

Discussion

The present study was a retrospective study that assessed the clinical outcome of various histopathological types of advanced endometrial cancer. Majority of our patients had primary surgery, of which 90% had a complete cytoreduction.

The ESMO ESGO ESTRO consensus on endometrial cancer recommends that surgery should be considered for patients with bulky FIGO stage IIIA–IV if successful cytoreduction with no macroscopic residual disease is anticipated [13]. A meta analysis of retrospective data showed that no residual disease was associated with an improvement in median OS; however, there was no significant difference in survival for patients with 0–2 cm of residual disease [14]. In our study complete cytoreduction to no gross residual disease was achieved in 90% of patients.

In a study of the survival impact of cytoreduction in advanced endometrial cancer, Alagkiozidis et al. reported that cytoreductive surgery to R0 is associated with improved overall survival in advanced uterine cancer and that this effect is uniform among histologies [15].

Platinum based combination chemotherapy with or without external beam radiation was the most commonly used adjuvant treatment across all histotypes in the present study. In a large retrospective study of advanced endometrial cancers by Monk et al., it was reported that combination chemotherapy based on platinum was the most common treatment as both first and second-line systemic therapy in the advanced endometrial cancer [16].

The 5 year disease overall survival in the present study was 54% in Stage III disease and 41.5% in Stage IV disease. As reported in the SEER database, overall survival is 69% in Stage III and 18.4% in Stage IV [17]. The differences may be explained by the fact that ours is a retrospective case series and hence may be prone to bias. Also in case of patients who were assigned to neo adjuvant treatment prior to surgery, the assignment of stage is mainly by imaging and maybe subject to bias.

Preoperative reduction of tumor burden by chemotherapy can facilitate surgery in patients previously considered to have an unresectable disease, identify patients with chemo sensitive tumors that are more likely to benefit from surgery, and enable a less aggressive surgery thus reducing morbidity, shortening operating time and hospitalization, and improving patients' quality of life. Following the progressively increasing use of neo-adjuvant chemotherapy (NAC) in ovarian cancer patients, more physicians tend to employ neo-adjuvant chemotherapy followed by interval debulking and chemotherapy for advanced stage EC [18].

Neoadjuvant chemotherapy followed by interval debulking has also been applied for advanced Stage IV endometrial cancers with good results. Neoadjuvant chemotherapy is well tolerated in patients with unfavorable disease-related characteristics, maximal debulking rates were higher, complications rate lower and hospital stay shorter compared to

patients that had primary surgery [10]. Neoadjuvant chemotherapy resulted in 80% of optimal interval debulking surgery for the treatment of serous endometrial cancer with transperitoneal spread [11].

In patients with parametrial disease neoadjuvant radiation may be considered. Neoadjuvant chemoradiotherapy with or without image-based HDR brachytherapy followed by extrafascial hysterectomy is a viable option for patients with endometrial cancer clinically extending to cervix/parametria who may be suboptimal candidates for upfront surgical staging due to extent of disease necessitating radical hysterectomy and increased risk of complications in a patient population often of advanced age with significant co-morbidities [15].

The strengths of the study include the long follow up period and availability of complete follow up data for the study participants. Limitations of the study include the retrospective nature of the study. As the study spanned a long period of ten years from 2008 to 2018, many of the recent advancements in diagnostic imaging, histopathologic characterization of tumors with immunohistochemical markers and the advances in adjuvant treatment have not been uniformly utilized in the study. The recently introduced molecular characterization is not incorporated in the study. Because the duration of the study was long, there is considerable variability in the nature of adjuvant treatment used.

Conclusion

In carefully selected patients with advanced endometrial cancer, a combination of surgical cytoreduction with appropriate adjuvant treatment and neoadjuvant treatment when indicated, gives good results with an acceptable morbidity and mortality and reasonable overallsurvival.

Declarations

Conflict of interest The authors hereby declare that there is no conflict of interest.

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