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The use of neoadjuvant chemotherapy in advanced endometrial cancer

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ABSTRACT

The objective of this retrospective cohort study was to review the use of neoadjuvant chemotherapy followed by interval cytoreductive surgery in patients presenting with advanced, unresectable endometrial cancer at two large cancer centers. Patients with advanced endometrial cancer treated with neoadjuvant chemotherapy between 2008 and 2015 were identified from an institutional database. Clinical and surgical variables were analyzed and time to recurrence and death was calculated and compared between surgical groups. Thirty-three patients were identified (mean age 64.8 (range 42–86 years)). Overall, 28% of patients had endometrioid histology, 48% serous, 4% clear cell, 4% carcinosarcoma, 12% mixed and 4% other. Ineligibility for primary surgery was due to unresectable disease (85%), comorbidities (6%) and unknown reasons (9%). All patients received neoadjuvant chemotherapy with 91% of patients receiving carboplatin and paclitaxel. On reimaging, 12% of patients had progressed, 76% had a partial response and 3% had a complete response to chemotherapy. 76% of patients underwent interval surgery, with cytoreduction to no visible residual disease achieved in 52%. Overall, 91% of patients recurred and 85% died during follow-up. Patients undergoing surgery after chemotherapy had significantly longer progression-free survival (11.53 vs. 4.99 months, $p = 0.0096$) and overall survival (24.13 vs. 7.04 months, $p = 0.0042$) when compared to patients who did not have surgery. Neoadjuvant chemotherapy is a feasible treatment option to allow for interval cytoreductive surgery in patients with advanced endometrial cancer not amenable to primary debulking. Patients who undergo surgery after chemotherapy have significantly improved progression free and overall survival.

1. Introduction

Endometrial cancer is the most common gynecologic malignancy in the United States and both the incidence and mortality are increasing with an estimated 65,620 new cases and 12,590 deaths in 2020 (Siegel et al., 2020). Approximately 13% of women diagnosed with endometrial cancer will present with stage III or IV disease (Galaal et al., 2014) at diagnosis. Furthermore, the number of patients presenting with metastatic disease is increasing, a clinical situation which carries a poor prognosis (Morice et al., 2016). Treatment for these patients is multimodal and combines cytotoxic chemotherapy, radiation therapy, newer biologics, immunotherapy and surgery (Morice et al., 2016). Complete surgical cytoreduction has been shown to improve survival in patients with stage IV disease (Barlin et al., 2010; Shih et al., 2011), however depending on the location of metastatic spread or underlying comorbidities, patients may be considered to have unresectable disease at presentation. In these patients, the use of an ovarian cancer treatment paradigm of neoadjuvant chemotherapy followed by interval cytoreductive surgery (Vergote et al., 2010) has been shown to result in high-rates of complete or optimal cytoreduction with low morbidity (Rabinovich, 2016). This approach has largely been studied in uterine papillary serous carcinomas (Wilkinson-Ryan et al., 2015; Vandenput et al., 2009; Despierre et al., 2006; Resnik and Taxy, 1996) due to the histologic similarity to ovarian cancer and propensity for lymphatic and intra-abdominal spread at diagnosis (Black et al., 2016; Santin et al., 2004). However, less has been published about the use of this approach in other histologic subtypes such as endometrioid adenocarcinoma (de Lange et al., 2019; Khouri et al., 2019). The purpose of this study was to review the experience at two large tertiary cancer centers of treating patients diagnosed with unresectable, advanced stage endometrial cancer of any histologic subtype with neoadjuvant chemotherapy.

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2. Materials and methods

Institutional research ethics board approval and consent for use of patient health information was obtained prior to starting the study. In this retrospective cohort study, all patients with advanced endometrial cancer treated with neoadjuvant chemotherapy at Massachusetts General Hospital and Brigham and Women's Hospital were identified from an existing institutional endometrial cancer database. This database contained patients treated at either institution between 2008 and 2015. Patients were excluded if they had primary surgery, if they received primary treatment with an agent other than cytotoxic chemotherapy or if they had uterine sarcoma. Clinical variables were then collected on all identified patients which included age, body mass index and significant comorbidities. The Charlson comorbidity index, which has been used to measure comorbidity in patients with malignancies, was used to calculate an overall score for each patient (Sarfati, 2012). The date of diagnosis and method of diagnosis were recorded along with disease variables at presentation such as location of disease on imaging, the presumed pre-operative stage and Ca-125 level. Clinical and radiographic reports (CT, MRI or PET) were used to identify factors that excluded a primary surgical approach and if due to unresectable disease, the location of unresectable disease was recorded. Details of the neoadjuvant treatment plan including type and cycles of chemotherapy and use of primary radiation were noted and similar information was also gathered on adjuvant treatment for patients who underwent surgery. The response to neoadjuvant treatment was determined using a combination of clinical and radiographic reports and was classified as progressive disease, stable disease and partial or complete response using response evaluation criteria in solid tumours (RECIST 1.1). Surgical variables were recorded from operative notes including the operative mode, degree of cytoreduction (to no visible residual disease, optimal <1 cm residual, suboptimal >1 cm residual or unresectable), procedures performed during cytoreduction, estimated blood loss and surgical complications. Pathology reports were reviewed to determine the final surgical stage, histology and grade. The last date of follow-up was determined from clinical notes. If patients recurred during this time, the date of recurrence, location of recurrence, method of diagnosis, and subsequent treatment were recorded. If patients died during this time, the date of death and cause of death (due to endometrial cancer or not) were noted. Descriptive statistics were used for baseline patient characteristics, with continuous variables described as means ± standard deviations and ranges and categorical variables described as percentages. Kaplan Meier survival curves were used to describe progression free survival and overall survival (defined as time from diagnosis to progression or death) and curves were compared using the log-rank test. All p-values were 2-sided with a $p < 0.05$ considered statistically significant. In accordance with the journal's guidelines, we will provide our data for the reproducibility of this study in other centers if such is requested.

3. Results

Thirty-three patients treated with neoadjuvant chemotherapy for advanced stage endometrial cancer between 2008 and 2015 were identified. Baseline characteristics of the cohort are shown in Table 1. The majority of patients did not have a performance status recorded at diagnosis (45%), while 42% of patients had a performance status of 0 or 1, and 12% of patients 2 or 3. Seven patients had no significant comorbidities, while the remaining patients had one or more cardiac, respiratory, neurologic or other comorbidities including nine patients with morbid obesity. One patient was considered ineligible for primary surgery due to their comorbidities (acute venous thromboembolism) whereas comorbidities did not affect the initial surgical plan in the remaining thirty-two patients.

For diagnosis, 60% of patients received an endometrial biopsy, 60% of patients received a directed biopsy of another site and 12% received a paracentesis for cytology. All patients also had comprehensive imaging at diagnosis except for one patient whose disease was diagnosed incidentally during a laparoscopic cholecystectomy. Based on these diagnostic procedures, patients were assigned a histology pre-operatively as shown in Table 1. Five patients were presumed to have metastatic ovarian cancer at initial diagnosis and were subsequently found to have endometrial cancer based on surgical pathology. The remaining twenty-eight patients were all confirmed to have endometrial cancer initially, with twenty-seven (96%) patients having international federation of gynecology and obstetrics (FIGO) stage IVB disease at presentation. Location of disease on imaging at presentation is seen in Table 1. Of the thirty patients who had a Ca-125 level drawn at diagnosis, 90% had levels above the upper limit of normal (≤35 U/ml). All patients were considered to be ineligible for primary surgical cytoreduction – 88% due to unresectable disease and 3% due to comorbidities, while 9% of patients did not have a clearly recorded reason.

All patients received neoadjuvant chemotherapy with 91% of patients receiving intravenous carboplatin and paclitaxel and 9% of patients receiving different regimens including carboplatin and docetaxel, cisplatin, paclitaxel and adriamycin, and weekly single-agent carboplatin. The average number of cycles of chemotherapy was four (range 1–7), and the majority of patients received three cycles prior to surgery.

Table 1
Cohort characteristics at diagnosis (n = 33).

Patient characteristic	N (%), mean ± SD (range)
Age (years)	64.8 ± 9.03 (range 42–86)
Race	
• White	• 2 (6%)
• Black	• 4 (12%)
• Asian/South Asian	• 24 (73%)
• Other	• 2 (6%)
• Unknown	• 1 (3%)
BMI (kg/m^2)	29.8 ± 7.4 (range 18.6–52.7)
Charlson comorbidity index	8.7 ± 1.4 (range 6–12)
Ca-125 (U/mL) at diagnosis (n = 30)	626.1 ± 938.1 (range 18–4000)
Histology at diagnosis on biopsy	
• Endometrioid	• 5 (15%)
• Serous	• 11 (33%)
• Clear cell	• 1 (3%)
• Carcinosarcoma	• 1 (3%)
• Mixed	• 3 (9%)
• Mullerian adenocarcinoma	• 11 (33%)
• Other	• 1 (3%)
Presumed FIGO stage at diagnosis	
• 3C*	• 5 (15%)
• 4A*	• 1 (3%)
• 4B	• 27 (82%)
Location of disease at diagnosis	
• Upper abdomen/omentum	• 11 (33%)
• Carcinomatosis	• 15 (45%
• Distant lymph nodes	• 9 (27%)
• Lung/pleural	• 14 (42%)
• Bone	• 5 (15%)
• Brain	• 2 (6%)
Response to neoadjuvant chemotherapy (n = 33)	
• Complete response	• 1 (3%)
• Partial response	• 25 (76%)
• Stable disease	• 0 (0%)
• Progressive disease	• 4 (12%)
• Missing information	• 3 (9%)
Interval cytoreductive surgery (n = 33)	
• Yes	• 25 (76%)
• No	• 8 (24%)

Table 1 Legend: SD = standard deviation, BMI = body mass index, FIGO = international federation of gynecology and obstetrics.
* Four 3C patients and one 4A patient presumed to have ovarian cancer at diagnosis.

Ten patients received 6 or more cycles of initial chemotherapy (Fig. 1). Six patients also received neoadjuvant radiation with two patients receiving pelvic external beam radiation therapy, three patients receiving stereotactic or whole brain radiation and three patients receiving radiation to sites of bony metastases. After restaging imaging, 12% of patients had progressive disease, 76% had a partial response and 3% had a complete response to treatment (Table 1). Three patients with missing chemotherapy response information went on to receive interval cytoreductive surgery suggesting at least a partial response to chemotherapy. Overall, eight patients (24%) did not receive interval cytoreductive surgery – four due to disease progression on chemotherapy and four due to disease that remained unresectable despite a response to chemotherapy. The operative characteristics of the twenty-five patients who received interval cytoreductive surgery are shown in Table 2.

On final pathology, one patient had low-grade endometrioid adenocarcinoma, six had high-grade endometrioid adenocarcinoma (grade 2 or 3) and the remainder were diagnosed with other high-risk histologies (Table 2). The surgical histology was different than that found on pre-operative biopsies in three patients. Twenty-four patients (96%) had surgically staged FIGO stage IVB disease while one patient (4%) had FIGO stage IIIC2 disease. Based on operative pathology, two patients had actionable mutations – one had high-level HER2/neu tumour staining and one had a microsatellite unstable tumour.

Of the patients who underwent surgery, twenty patients received adjuvant chemotherapy while five patients did not (Fig. 1). One patient who received only 3 cycles of neoadjuvant chemotherapy declined further adjuvant treatment and the remaining four patients had received six or more cycles of chemotherapy pre-operatively. Eighty-five percent of patients received additional carboplatin and paclitaxel while 15% of patients received alternative regimens such as carboplatin and docetaxel or weekly paclitaxel. Of those receiving chemotherapy after surgery, the majority of patients received three additional cycles of chemotherapy (range 1–5) (Fig. 1). Of the eight patients that did not undergo surgery, two patients received hormonal treatment with letrozole, however none received additional cytotoxic chemotherapy. Only one patient received adjuvant radiation therapy in the form of vaginal brachytherapy. Sixteen patients who underwent surgery had Ca-125 levels measured at the end of adjuvant treatment, with 82% of patients having normalization of their levels from diagnosis.

Overall, thirty patients recurred or progressed after their initial treatment (90%), while one patient did not recur, and two patients were lost to follow up. The patient that did not recur had presented with stage IVB disease due to brain metastases and on final pathology had grade 3 endometrioid disease after her cytoreductive surgery to no residual disease. Fifty percent of patients had their recurrences diagnosed on imaging whereas 30% of patients had their recurrences diagnosed using a combination of Ca-125 and imaging. Of those that had imaging, 50% had imaging to investigate concerning symptoms or clinical exam findings whereas 50% had imaging as part of routine follow up which demonstrated an asymptomatic recurrence. The remaining patients had varying methods of diagnosis including distant biopsies. Fourteen patients who had both pre- and post-treatment Ca-125 levels also had Ca-125 levels at recurrence and in all cases the levels had increased from their post-treatment nadir. The Ca-125 trend in these fourteen patients is shown in Fig. 2. Of these 14 patients, 9 had serous histology, 2 each had endometrioid and mixed histology, and 1 had carcinosarcoma.

Twenty-eight of the thirty patients that recurred had complete recurrence information. Two patients recurred only in the pelvis, three recurred only in lymph nodes, four had a single site of distant recurrence and eighteen had multiple sites of recurrence including a combination of vaginal, pelvic, upper-abdominal and distant sites. At recurrence, 72% percent of patients went on to receive chemotherapy, 18% were

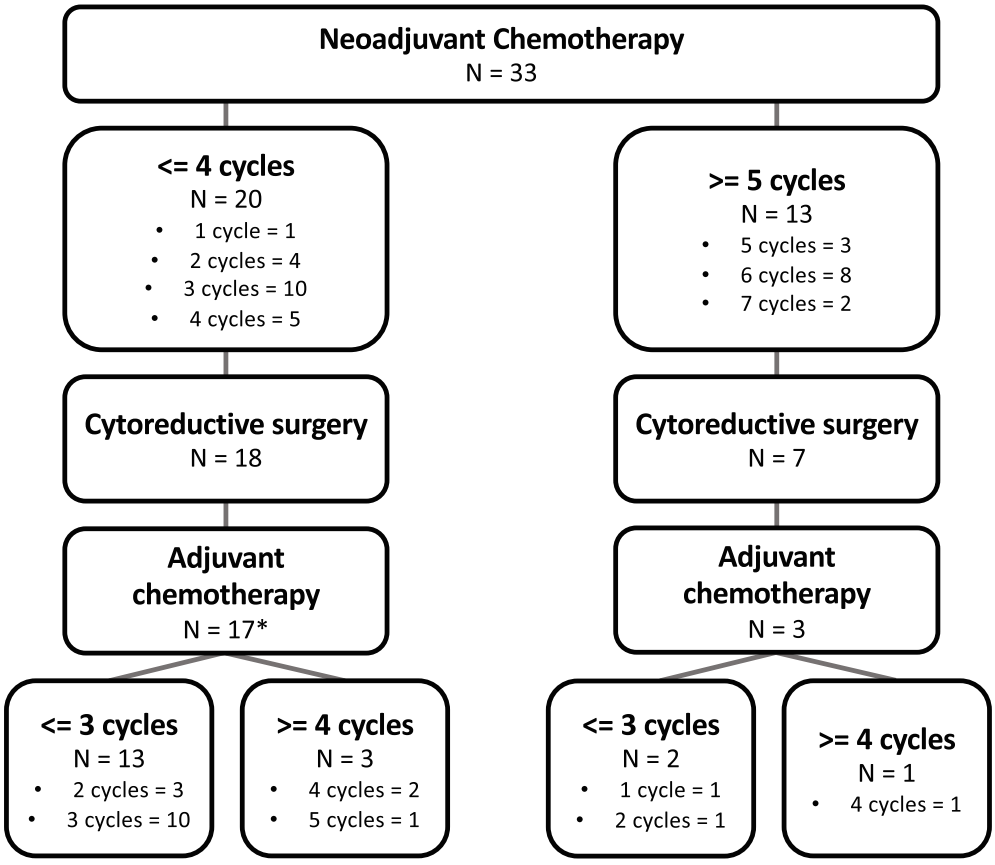

Fig. 1. Cycles of neoadjuvant and adjuvant chemotherapy. *1 patient received an unknown number of adjuvant chemotherapy cycles after cytoreductive surgery.

Table 2
Operative characteristics of patients having interval cytoreductive surgery (n = 25).

Operative characteristic	N (%), mean ± SD (range)
Degree of cytoreduction	
• No visible residual	
• Optimal	• 13 (52%)
• Suboptimal	• 7 (28%)
• Unresectable/aborted	• 3 (12%)
	• 2 (8%)
Mode of operation:	
• Laparotomy	
• Laparoscopy	• 20 (80%)
	• 5 (20%)
Hysterectomy + bilateral salpingo-ophorectomy	
• Yes	
• No*	• 23 (92%)
	• 2 (8%)
Omentectomy	
• Yes	
• No	• 16 (64%)
	• 9 (36%)
Lymphadenectomy (pelvic or para-aortic)	
• Yes	
• No	• 2 (8%)
	• 23 (92%)
Upper abdominal debulking	
• Yes	
• No	• 1 (4%)
	• 24 (96%)
Additional cytoreductive procedures	
• Yes	
• No	• 6 (24%)
	• 19 (76%)
Bowel resection (small or large bowel)	
• Yes	
• No	• 5 (20%)
	• 20 (80%)
Number of bowel resections	
• Small bowel	
• Large bowel	• 4
	• 3
Intra-operative complication	
• Yes	
• No	• 1 (4%)
	• 24 (96%)
Operative time (minutes)	184 ± 76 (90–354)
Estimated blood loss (mL)	284 ± 181 (15–600)
Post-operative histology on final pathology	
• Endometrioid	
• Serous	• 7 (28%)
• Clear cell	• 12 (48%)
• Carcinosarcoma	• 1 (4%)
• Mixed	• 1 (4%)
• Other	• 3 (12%)
	• 1 (4%)
Treatment response seen on final pathology	
• Yes	
• No	• 4 (16%)
• Not specified	• 2 (8%)
	• 19 (76%)
Post-operative FIGO stage	
• IIIC2	
• IVB	• 1 (4%)
	• 24 (96%)

SD = standard deviation, FIGO = international federation of gynecology and obstetrics.

* Both operations aborted prior to hysterectomy due to unresectable disease.

transitioned to hospice care, 8% went on a clinical trial, 4% received immunotherapy and 8% received radiation with or without chemotherapy. Overall, twenty-eight patients died from their endometrial cancer and three patients did not have complete follow-up information. Of the two patients alive at last follow up, one had not recurred, and one had recurrent grade 1 endometrioid disease. Both had undergone cytoreductive surgery to no visible residual disease. The median follow-up time in the entire cohort was 15.6 months (range 3.1–142.2 months). Patients who underwent interval cytoreductive surgery had significantly longer median progression-free survival (11.53 vs. 4.99 months, $p = 0.0096$) and overall survival (24.13 vs. 7.04 months, $p = 0.0042$) when compared to patients who did not have surgery (Fig. 3). In patients that underwent interval cytoreductive surgery, having cytoreduction to no visible residual disease did not result in a progression-free survival ($p = 0.207$) or overall survival advantage ($p = 0.281$) when compared to patients undergoing optimal or suboptimal cytoreduction (Fig. 3).

4. Discussion

Neoadjuvant chemotherapy followed by interval cytoreductive surgery has been shown to be an effective treatment for women with advanced ovarian cancer who are not considered candidates for primary cytoreductive surgery due to comorbidities, poor performance status or extent of disease spread (Vergote et al., 2010; Kehoe et al., 2015). By administering chemotherapy first, patients are spared the morbidity of a large primary surgery and have high rates of interval cytoreduction to no visible residual disease (Vergote et al., 2010; Kehoe et al., 2015). This approach has been extrapolated to patients with advanced endometrial cancer given that aggressive primary surgical cytoreduction to no visible residual disease has been shown to improve survival in this population (Barlin et al., 2010; Shih et al., 2011; Chi et al., 1997; Goff et al., 1994). However, while the majority of published reports endorse the use of neoadjuvant chemotherapy in patients with uterine papillary serous carcinoma, less information is available regarding this approach in patients with other uterine cancer histologies. Herein we report on a cohort of patients presenting with advanced endometrial cancer of varying histologies treated with neoadjuvant chemotherapy and interval cytoreductive surgery. On final pathology, 28% of the cohort had endometrioid adenocarcinoma, 48% had papillary serous carcinoma, 8% had either clear cell carcinoma or carcinosarcoma and 12% of patients had mixed and undifferentiated carcinomas. We found that 76% of patients were able to undergo interval cytoreductive surgery, with cytoreduction to no visible residual disease achieved in 52%. Interval cytoreductive surgery was associated with a 6.5-month improvement in progression-free survival and a 17.1-month improvement in overall survival. However, the degree of cytoreduction was not found to be a significant contributor to progression-free or overall survival in our cohort. Importantly, these surgical results were achieved without requiring a large number of complex procedures such as bowel resections or upper abdominal debulking, and only one of twenty-five patients experienced an intra-operative complication. As well, we found Ca-125 to be a useful marker of recurrence and response to adjuvant treatment in patients whom this had been a marker of disease at diagnosis, which is similar to patients with advanced ovarian cancer (Lheureux et al., 2019).

Our results are consistent with other published studies of neoadjuvant chemotherapy in diverse endometrial cancer cohorts. de Lange et al reported on a similar cohort in their study of 102 patients with advanced endometrial cancer of varying histologies (de Lange et al., 2019). In this study, 57% of patients had a non-serous histology and interval cytoreduction was completed in 78% of patients, while cytoreduction to no visible residual disease was achieved in 60%. Overall survival was longer in patients who underwent interval cytoreductive surgery, while the longest survival benefit was seen in patients with microscopic or optimal (<1 cm residual) cytoreduction. Interestingly, the median overall survival in this microscopic or optimal group was 41 months which is longer than what was found in our study (24.4 months),

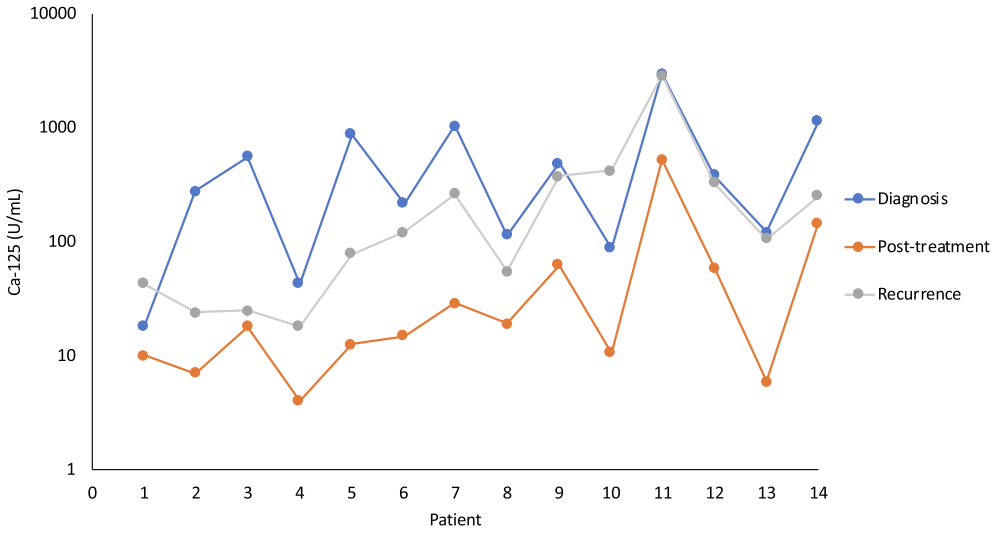

Fig. 2. Ca-125 levels at diagnosis, post-treatment and recurrence (N = 14).

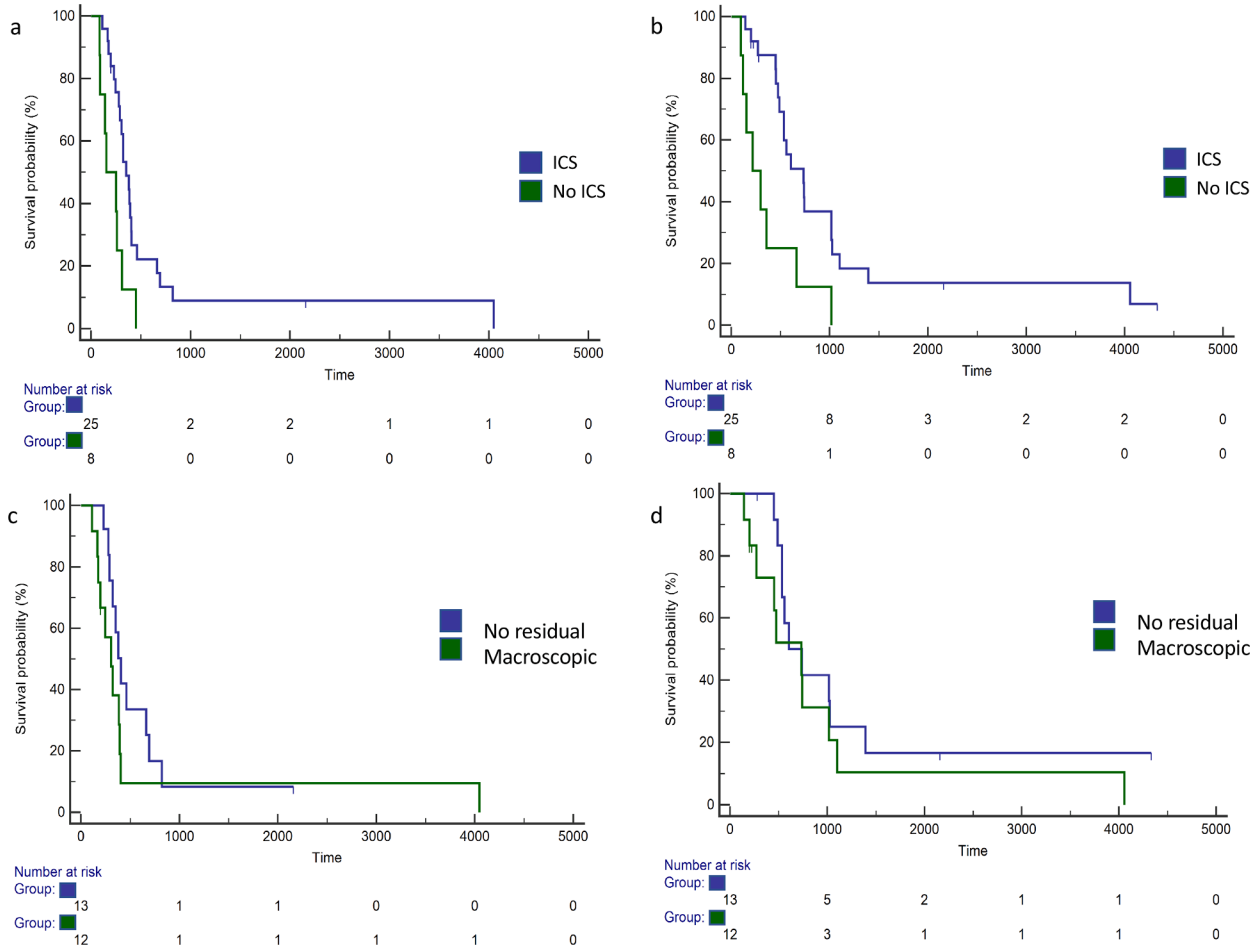

Fig. 3. Progression-free survival and overall survival by interval cytoreductive surgery status and degree of cytoreduction. A: Progression-free survival by interval cytoreductive surgery status, p = 0.0096. B: Overall survival by interval cytoreductive surgery status, p = 0.0042. C: Progression-free survival by degree of cytoreduction, p = 0.207. D: Overall survival by degree of cytoreduction. P = 0.2814. Legend: ICS = interval cytoreductive surger.

and lower rates of recurrence after surgery were noted (90% vs. 60.6%). This may be explained differences in baseline patient characteristics including the lower rate of serous cancers and higher rate of stage 3 disease in their study. Khouri et al also reported on a cohort of thirty-nine patients with advanced endometrial cancer treated with neo-adjuvant chemotherapy (Khouri et al., 2019). Despite low rates of interval cytoreductive surgery (41%), most (81%) patients were at least optimally cytoreduced and a similar survival advantage of ten months

was noted in their surgical cohort. Despite a similar patient population and neoadjuvant treatment strategy, 41% percent of patients in this study did not have interval cytoreduction due to progression of disease on chemotherapy, a rate which is notably higher than the 12% found in our cohort. This is likely explained by the small sample size and retrospective nature of both studies but may also reflect the significant heterogeneity in disease biology seen in patients with advanced endometrial cancer (Gibson et al., 2016; Murali et al., 2014). Eto at al reported on a cohort of 426 patients with stage IVb endometrial cancer of which 29% (125 patients) were treated with neoadjuvant chemotherapy and 59 patients went on to subsequent interval cytoreductive surgery (Eto et al., 2013). Overall, primary surgery resulted in the longest overall survival at twenty-one months as compared to primary chemotherapy or palliative care, however when the primary chemotherapy group was divided into those that received subsequent surgery and those that did not, the survival in the primary surgery and the neoadjuvant chemotherapy followed by interval cytoreductive surgery groups was the same.

Due to its retrospective nature and small sample size, our study has a number of limitations. An inherent selection bias is introduced when examining retrospective cohorts as younger fitter patients may have been offered aggressive primary surgery and older, frailer patients may have been offered only best supportive care. Furthermore, as we are limited to the available records, complete data on all patients was not available and we cannot comment on how clinical or surgical decision making may have affected outcomes. While prospective studies are required in this patient population to truly understand the role of neoadjuvant chemotherapy, these would be difficult given the small number of patients presenting with advanced, disease at diagnosis. Furthermore, while a trend towards improved progression-free survival was noted in patients undergoing microscopic cytoreduction, likely due to the small numbers this trend did not reach significance which is notably different than a number of other published studies. Given the small numbers, we did not perform an analysis of survival based on histology although given larger numbers, this may be an interesting clinical finding. A final limitation of study is the lack of detailed biomarker information which may be helpful in triaging patients to appropriate therapy and may impact the risk of recurrence and death (Raffone et al., 2019; McAlpine et al., 2016).

Despite these limitations, our study in combination with the published literature suggests a role for neoadjuvant chemotherapy and interval cytoreductive surgery in patients with advanced endometrial cancer not amenable to primary resection and highlights the important association between cytoreductive surgery and survival in this patient population.

Author contributions

The contribution of the individual authors is as follows: Dr. Philp was involved in study design, data collection, data analysis and manuscript preparation. Drs. Kanbergs, St. Laurent and Growdon were involved in data collection, statistical analysis and manuscript editing. Dr. Feltmate was involved in study design and manuscript editing and Dr Goodman was the Senior Responsible Author, who developed the idea for the study, supervised data collection and analysis and performed manuscript editing.

Informed consent statement:

Institutional research ethics board approval and consent for use of patient health information was obtained prior to starting the study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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