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NON-EXENTERATIVE SURGICAL MANAGEMENT OF RECURRENT ENDOMETRIAL CARCINOMA

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Abstract

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Objective: To examine the role of non-exenterative secondary cytoreductive surgery (SCS) compared with non-surgical treatments and identify predictors of improved survival for patients with recurrent endometrial cancer (EC).

Methods: All patients undergoing primary surgical management for EC 1/1/2009–12/31/2017 who subsequently developed recurrence were retrospectively identified. Survival was determined from date of diagnosis of first recurrence to last follow-up and estimated using Kaplan-Meier method. Differences in survival were analyzed using Log-rank and Wald tests, based on Cox Proportional Hazards model.

Results: Among 376 patients with recurrent EC, median time to recurrence was 14.3 months (range, 0.2–102.2), post-recurrence median survival 29 months, median follow-up 29.2 months (range, 0–116). Sixty-one patients (16.2%) received SCS, 257 (68.4%) medical management (MM) (chemotherapy and/or radiation therapy), 32 (8.5 %) hormonal therapy, 26 (6.9%) no further therapy. Patients selected for SCS were younger, had more endometrioid histology, more stage I disease at initial diagnosis, no residual disease after primary surgery, longer interval to first recurrence or progression, and the longest OS (57.6 months) (95% CI, 33.3–not reached). On multivariate analysis SCS was an independent predictor of improved survival. Among the 61 SCS patients, age <70 at time of initial diagnosis, and endometrioid histology, were associated with improved post-relapse survival univariately (p=0.008, 0.03, respectively).

Conclusions: While MM was the most common treatment for first recurrence of EC, patients selected for surgery demonstrated the greatest survival benefit even after controlling for tumor size, site, histology, stage, time to recurrence. Careful patient selection and favorable tumor factors likely play a major role in improved outcomes. Surgical management should be considered whenever feasible in medically eligible patients, with additional consideration given to our suggested criteria.

Keywords

Recurrent endometrial cancer; Endometrial cancer; Surgical cytoreduction; Chemotherapy; Radiation therapy

INTRODUCTION

Endometrial cancer (EC) is the most common gynecologic malignancy in the United States, with an estimated 65,620 new cases and 12,590 deaths in 2020 [1]. The incidence of EC is on the rise and is likely attributable, in part, to increasing life expectancy and higher prevalence of obesity and metabolic syndrome [2, 3]. The rise in incidence parallels an increase in mortality rate. The recurrence rate is stable, ranging between 11–14% [1, 4–6]. Patients with recurrent EC represent a heterogenous group that varies by histological subtype, previous adjuvant therapy, time interval to recurrence, and size and site(s) of disease. To date, the literature focusing on management of recurrent EC is primarily retrospective, with small case numbers [7]. Retrospective data suggest that previous therapy, site of recurrence, interval to recurrence, and patient performance status are significant factors, and these are primarily what clinicians rely upon for decision-making [8–11]. The management of recurrent EC remains a challenge. Therapeutic strategies vary significantly, and may include surgical resection, radiation therapy, cytotoxic chemotherapy, hormonal

therapy, or a combination of these. More recently immunotherapy has been incorporated as a treatment option.

Historically, surgery was limited to curative-intent pelvic exenterations for patients with central pelvic recurrences [12, 13]. Subsequent studies have investigated the role of non-exenterative surgery for advanced or recurrent disease [6, 14–17]. In this study, we evaluated patients with EC who underwent primary surgical treatment at our institution and developed a recurrence. We aimed to identify key clinical and pathologic features which might influence treatment selection for recurrent disease and impact oncologic outcomes. In addition, we investigated key variables associated with survival among patients selected for non-exenterative surgery.

METHODS

Study design and data collection

After obtaining IRB approval, we retrospectively identified 2864 patients undergoing primary surgical management for EC at Memorial Sloan Kettering Cancer Center (MSKCC) between January 1, 2009 and December 31, 2017. Histologically confirmed carcinosarcomas, sarcomas, or dedifferentiated carcinomas were excluded (n=296). The remaining 2568 patients had histologically confirmed endometrioid, serous, clear cell, or mixed histologies. Among these patients 396 were found to have recurred by December 31st, 2020. Demographic, clinical and pathologic data were abstracted from the medical records. Patients were grouped by type of subsequent therapy versus no further therapy at time of recurrence. Ultimately, 376 patients were analyzed in the study after excluding patients lost to follow-up, with no clinicopathologic information after diagnosis of recurrence (n=19), and patients who underwent IR-guided ablation, as there was an insufficient number of cases (n=1) to perform statistically meaningful comparisons. Patients undergoing pelvic exenteration at time of secondary cytoreduction were also excluded (Supplementary Figure 1).

Primary surgical staging, all of which was performed at MSKCC, included, at minimum, a hysterectomy. All additional procedures were performed within the guidelines of the National Comprehensive Cancer Network (NCCN) [18]. Adjuvant therapy after primary surgery was selected using NCCN guidelines and clinical best practice, including chemotherapy and/or radiation therapy, or no further therapy [18]. Clinical follow-up reflected best practice guidelines and included physical exam, symptom review, and imaging based on symptoms or exam findings [19]. Follow-up included clinical assessments every 3–6 months for the first 2 years, and every 6–12 months thereafter [18].

Recurrence data were abstracted from documented physical exam, imaging, and pathology in the medical record. Size and sites of recurrent disease were abstracted from operative and pathology reports. Sites of recurrence were categorized by anatomical location: (1) pelvic only; (2) nodal only; (3) pelvic and nodal; (4) distant (extra-pelvic); (5) peritoneal carcinomatosis only.

Management of recurrence was classified as follows: (1) secondary cytoreductive surgery (SCS); (2) medical management (MM); (3) hormonal therapy (4) no further therapy. Medical management comprised of radiation therapy (n=47), chemotherapy with or without radiation therapy (n=191), and a few cases of targeted or immune therapy on trial (n=19); it did not include hormonal therapy. Selection for SCS was at the discretion of the attending physician, as no validated guidelines exist. Each patient's overall health, recurrence characteristics, feasibility and safety of resection, were considered in the decision-making process. Perioperative data were abstracted, and included total operative time, estimated blood loss (EBL), residual disease, length of stay (LOS), complications, and adjuvant therapy. Complications were graded based on published institutional parameters, in which grade 1 requires bedside care or oral medications, grade 2 requires intravenous medications or transfusions, grade 3 includes radiologic, endoscopic, or operative interventions, grade 4 results in chronic disability or organ resection; and grade 5 is death [20].

Statistical Analysis

Descriptive statistics were provided for the whole cohort, as well as across the four treatment modalities. The differences among all four treatment groups were tested using the Kruskal-Wallis test for continuous variables and Fisher's exact test for categorical variables. To examine the difference between SCS and MM, the Wilcoxon Rank-Sum test was used for continuous variables and Fisher's exact test for categorical variables.

Progression-free survival (PFS) was calculated from date of surgery to date of first recurrence or progression (PFS1). Progression-free survival was also reported from first recurrence to date of second recurrence, progression, death, or last follow-up (PFS2). Overall survival (OS) was defined as time elapsed in months from date of first recurrence to date of death or last follow-up. Follow-up data were collected until January 1, 2020. The median survival time and 2-year survival rate were estimated using the Kaplan-Meier method. In the univariate setting, the Log-rank test and the Wald test, based on Cox Proportional Hazards model, were applied to obtain p-values for survival outcomes. Due to the time-dependent nature of selecting and administering a treatment modality for first recurrence, a landmark analysis was performed. Landmark time of 26 days from first recurrence was used, based on the data. Multivariate models to predict PFS2 and OS were built, based on the results of univariate analyses. Stepwise selection was also applied. The final multivariate models excluded patients who underwent no further therapy, due to the small sample size of this subgroup (N=26). Estimation of hazard ratios (HRs) was non-robust, as shown by wide confidence intervals (CIs). Statistical analysis was conducted using SAS 9.4.

RESULTS

Patient characteristics grouped by treatment modalities for recurrent disease

A total of 376 patients with recurrent EC, who met the inclusion criteria, were identified. The median time to first recurrence was 14.3 months (range, 0.2–102.2 months). Median age at time of primary surgical resection was 66 years (range, 28–93 years). Median BMI was 29.5 kg/m2 (range, 14.2–60.3 kg/m2). The histologic subtypes were as follows: 183 (48.7%)

endometrioid; 146 (38.8%) serous; 47 (12.5%) clear cell or mixed. Initial surgical stage was equally distributed between early-stage (I/II) disease versus late-stage (III/IV) disease. After primary surgery, 314 (83.5%) patients received adjuvant therapy.

Of the 376 patients with recurrence, 61 (16.2%) were selected for SCS, 257 (68.4%) for MM, 32 (8.5%) for hormonal therapy, and 26 (6.9%) had no further therapy. Compared across treatment modalities, the median age at initial diagnosis for patients who had no further therapy and those who had hormonal therapy was 67.5 (range, 33–92) and 69.5 (range, 47–86) years, respectively, compared with 66 years (range, 28–92) for patients treated with MM; patients undergoing SCS had the youngest median age of 62 years (range, 39–83.3) (p=0.004). There was no significant difference in BMI across treatment modalities (p=0.198). Histology and stage did not differ significantly across treatment modalities; however, these variables did differ significantly between patients undergoing SCS versus MM. Thirty-seven (60.7%) of the 61 SCS patients had endometrioid histology, compared with 117 of the 257 (45.5%) MM patients (p=0.033). Among SCS patients, 31 (50.8%) had endometrioid FIGO grade 3 or high-grade histology, compared with 177 (68.9%) MM patients (p=0.022). Thirty-five (57.4%) SCS patients and 108 (42%) MM patients had stage I disease at initial diagnosis; there were only 6 (9.8%) SCS patients with stage IV disease at initial diagnosis, compared with 67 (26.1%) MM patients (p=0.014). Time to first recurrence or progression differed significantly across treatment modalities. Patients undergoing SCS had the longest median PFS1 after primary surgery: 19.4 months (range, 2.4–88.3; p<0.001). Table 1A.

The presence of a grade 3 or greater complication at time of primary surgery did not differ across treatment modalities, ranging from 1 (1.6%) among SCS patients to 7 (2.7%) among MM patients (p=1). However, LOS after primary surgery differed. Patients receiving SCS or MM had a 1-day median LOS after primary surgery (range, 0–6; 0–49, respectively) compared with 2 (range, 0–15) and 2.5 (range, 0–18) days for patients receiving hormonal therapy or no further therapy, respectively (p=0.002). Absence of residual disease after primary surgery varied significantly in distribution between treatment modalities; all 61 (100%) SCS patients had no visible disease at completion of their primary surgery, regardless of disease stage, compared with 234 (91.1%) MM patients, 30 (93.8%) patients receiving hormonal therapy, and 23 (88.5%) receiving no further therapy (p=0.033). Adjuvant chemotherapy after primary surgery was equally distributed across treatment modalities, ranging from 80–85% (p=0.891). Distribution of adjuvant radiation therapy differed: 68.9% of SCS patients, 52.1% of MM patients, 53.1% of hormonally treated patients, 38.5% of patients who had no further therapy (p=0.039) (Table 1A).

The clinicopathological characteristics of recurrent disease are reported in Table 1B. Of the 376 recurrences, 175 (46.5%) presented with multiple sites of disease. Among those selected for SCS, 15 (24.6%) had multisite disease compared with 132 (51.4%), 16 (50%), and 12 (46.2%) selected for MM, hormonal therapy, and no further therapy, respectively (p=0.002). Anatomical site of recurrence differed across treatment modalities (p=0.004); however, there was no significant difference in site distribution between the MM and SCS cohorts (p=0.109). Patients treated surgically received a median of 1 (range 1–6) additional therapy,

compared with 2 among patients receiving MM or hormonal therapy (range 1–8, 1–7; p <0.001) (Table 1B).

Secondary cytoreductive surgery characteristics

Table 2 shows the operative characteristics of the 61 patients undergoing SCS as initial treatment after first recurrence. Median operative time was 145 minutes (range, 11–405 minutes) and EBL was 75 mL (range, 5–1800 mL). Complete gross resection (CGR) was documented in 46 patients (75.4%), while the remaining 15 (24.6%) had visible tumor at completion of surgery. There were 9 reported complications within 30 days from surgery; two of these (4.9%) were grade 3 complications: 1 patient with an intra-abdominal fluid collection requiring an interventional procedure, and another patient with postoperative bleeding. There were no grade 4 or 5 complications. The remaining 7 complications were grade 1 or 2. The median LOS was 1 day (range, 0–13 days). Fifty-four (88.5%) patients received adjuvant therapy: 45 received postoperative chemotherapy and/or radiation therapy; the remaining 9 received adjuvant hormonal therapy (Table 2).

Survival across treatment modalities

Two hundred and eighty-eight patients progressed or died after their initial recurrence. Median follow-up was 29.2 months (range, 0–116 months). Median PFS after treatment for first recurrence (PFS2) for the entire cohort was 9.5 months (95% CI, 8.5–10.9); median OS after recurrence was 29 months (95% CI, 24.4–32.5). Patients selected for SCS had a median PFS2 of 14.9 months (95% CI, 10.1–41.8) and OS of 57.6 months (95% CI, 33.3-NE), which were statistically significantly longer than patients selected for other therapeutic modalities (p<0.001). Patients receiving MM had a median PFS2 of 8.6 months (95% CI, 7.5–10.6) and OS of 24.5 months (95% CI, 21–30.6), which differs significantly from the SCS group (p=0.002, p<0.001) (Table 3; Figure 1A).

In addition to therapeutic modality, multiple other clinicopathologic variables were investigated, on univariate analysis, with respect to post-recurrence survival (Supplementary Table 1). Multivariate analysis was used to incorporate any variables identified as significant on univariate analysis; these are reported in Supplementary Table 2. The univariate variables significantly impacting PFS2 included: time to recurrence; factors identified at initial diagnosis and surgery—BMI, histology, FIGO grade, stage, presence of > grade 3 complication, LOS, residual disease, adjuvant therapy; and factors related to recurrence—size of largest tumor, multiplicity of sites, anatomical site distribution, treatment modality (Supplementary Table 1A). With the exception of BMI, these univariate variables also significantly impacted OS, as did age at initial diagnosis (Supplementary Table 1B). The final multivariate models, shown in Supplementary Table 2, exclude the no treatment subgroup. The multivariate model demonstrated that advanced stage, adjuvant therapy after initial surgery, size of tumor at recurrence, extrapelvic recurrence, and selection for non-surgical treatment at time of recurrence, were significantly associated with a decrease in PFS2. Specifically, PFS2 was significantly shorter among patients receiving MM (HR 2.0; 95% CI 1.4–3) and hormonal therapy (HR 2.2; 95% CI 1.4–4.2), compared with SCS (p<0.001) (Supplementary Table 2A). The multivariate model on OS demonstrated that age > 70 years at diagnosis, < 12 months' time to initial recurrence, serous histology, advanced

stage, adjuvant therapy after initial surgery, increased size of tumor at recurrence, extrapelvic recurrence, and non-surgical treatment at time of recurrence, were significantly associated with lower OS. SCS was an independent predictor of improved survival, compared with MM (HR of death 2.1; 95% CI 1.3–3.5) and hormonal therapy (HR 2.3; 95% CI 1.1–4.5) (p=0.012) (Supplementary Table 2B).

Further selection of the surgical patient

A univariate analysis was performed using clinicopathologic factors determined at time of primary surgery or at recurrence, to delineate potential prognostic factors among the 61 SCS patients. Table 4 summarizes the analysis of these factors: age, BMI, histology, grade, stage, complications, LOS, adjuvant therapy at time of primary surgery, time to first recurrence, size of largest recurrent tumor, multiplicity and sites of recurrence, and residual disease at SCS. Age (> 70 years vs. ≤ 70 years) at primary surgery was the only factor significantly associated with a lower PFS2 (HR 2.46; 95% CI 1.1–5.5; p=0.023). Age > 70 years at primary surgery portended worse OS (HR 3.52; 95% CI 1.3–9.5; p=0.008). Among SCS patients, histology also appeared to impact OS: endometrioid histology was associated with improved OS compared with serous (HR 3.4; 95% CI 1.3–8.9) and clear cell or mixed (HR 1.35; 95% CI 0.37–4.93) (p=0.030) histologies (Table 4A, 4B).

Residual disease at time of SCS was investigated as a potential prognostic indicator of greater survival benefit from surgical management. Among the 61 SCS patients, CGR was achieved in 46 (75.4%) cases. There was no statistically significant difference in OS based on CGR (HR 0.96; 95% CI 0.35–2.63; p=0.938) versus non-CGR. Median survival was 57.6 months (95% CI 57.6-not estimable) in the CGR versus 33.1 months (95% CI 24.2--not estimable) in the non-CGR groups (Figure 1B).

DISCUSSION

In this study we examined the role of surgery compared with other treatment modalities for patients with recurrent EC. We investigated surgical selection criteria based on an updated patient group representing current surgical care and techniques. We found that surgical cytoreduction for recurrent disease has a significant impact on survival even when it is non-exenterative. In our study, median survival from time of diagnosis of recurrence was 29 months, with a 56.4% 2-year OS rate. SCS patients had the longest median OS of 57.6 months (95% CI, 33.3–not reached) resulting in an 80.9% 2-year OS rate. These patients required a median of 1 additional line of subsequent therapy. On univariate analysis, after accounting for all significant factors that differed across treatment modalities, the impact of surgery on survival remained significant. Compared with surgery, MM was less effective (HR 2.1; 95% CI 1.3–3.5; p<0.012); hormonal therapy was even less effective (HR 2.3; 95% CI 1.1–4.5; p=0.012). Based on our findings, surgery demonstrated improved oncologic outcomes compared with MM and should be considered, if deemed technically feasible, in medically eligible patients. Similar findings have been reported by others, suggesting that surgical cytoreduction for the treatment of recurrence, even when non-exenterative, confers a significant survival benefit [14–16]. Bristow et al. demonstrated a significant prolongation of post-recurrence survival in patients undergoing surgery, compared with patients receiving

non-surgical intervention [16]. The survival benefit conferred by surgical cytoreduction has been more extensively investigated in the setting of ovarian cancer; some have suggested that it results in improved perfusion and subsequent drug delivery to residual disease, improving performance status; and that (by decreasing the amount of viable tumor cells), it decreases the potential for somatic mutations that can lead to drug resistance [7]. These effects may also explain the survival advantage seen in patients receiving SCS for recurrent EC. Although many variables are accounted for through multivariate analysis, there may be other prognostic factors preferentially selected in SCS patients, such as better performance status, fewer comorbidities, and favorable molecular characteristics. Additional prospective trials are necessary to validate the survival benefit observed in patients with recurrent EC receiving SCS.

In the current study, SCS conferred the greatest survival benefit compared with other treatment modalities. Based on this, it is crucial to determine which patients should be selected for SCS. To date, however, there is no established criteria, and selection remains arbitrary. Based on our analysis, we propose a list of criteria for selecting patients who might benefit from SCS (Table 5). We suggest higher consideration for SCS in patients with the following features from time of diagnosis: age ≤ 70, PFS1 ≥ 19 months, grade 1/2 endometrioid or clear cell histology, early stage (I/II) disease; the following features from time of primary surgery: no residual disease, short LOS (0–6 days), no more than two grade 3 complications, received adjuvant radiation therapy; and the following feature from time of recurrence: single site disease. These features were chosen based on variables that differed significantly between patients selected for SCS versus MM. Features that did not differ statistically in distribution between patients selected for SCS versus MM should merit less consideration. These include BMI at initial diagnosis, adjuvant chemotherapy after primary surgery, size of recurrent tumor, and distant site of recurrent disease. These criteria are based solely on descriptive statistics and warrant further investigation with a prospective trial to evaluate their utility in selecting patients for SCS versus MM. (Table 5).

In patients with recurrent EC who are selected for SCS, extensive surgical procedures may be required, including upper and extra-abdominal surgery. Perioperative morbidity and mortality are of concern. In this series we report acceptable adverse outcomes data, including a 15% complication rate among patients undergoing SCS, with few major complications (3.3%) and no perioperative deaths. There were no prolonged hospital stays (median 1 day; longest 6 days). These findings likely reflect appropriate patient selection based on performance status and medical co-morbidities, the increased use of minimally invasive surgery, and improved perioperative care utilizing the Enhanced Recovery after Surgery (ERAS) protocols. Continued improvements in surgical technique and perioperative care permit more flexibility in selecting patients for surgical resection.

We found that, among the 61 patients undergoing SCS, those with distant or nodal disease did not have a statistically different survival compared with patients with disease confined to the pelvis. Except in 1 case, however, all patients with peritoneal carcinomatosis received non-surgical treatment; therefore, our findings are not applicable in the setting of peritoneal carcinomatosis. Women with recurrent disease are often categorized as having a vaginal or pelvic recurrence versus nodal or distant disease. Those with a vaginal or pelvic recurrence

in a previously irradiated field are considered candidates for pelvic exenteration with curative intent [13, 21]. In the current study, however, we found that surgery is a viable strategy in carefully selected patients who do *not* meet criteria for total pelvic exenteration. Our data indicate that surgical resection of nodal or distant disease is worth considering if it is deemed safe and feasible.

In our series, CGR did not demonstrate a statistically significant survival benefit. Given that a majority achieved CGR (75.4%; n=46), this limited statistical analysis to a small comparator group with those who did not have a documented CGR (n=15). With respect to survival outcomes, the not-estimable upper limit of the CI for both the CGR and non-CGR cases suggests that, with further follow-up, the estimates could change as more events occur. Among the patients in our study who had residual disease at SCS, all residual disease was ≤ 3 cm. The lack of any residual disease > 3 cm might also explain why survival among patients who did not achieve CGR was not significantly different from those who did, and why our median OS of 33.1 months in non-CGR patients is greater than that reported by others (14 to 20 months) [14, 16, 22]. Previously published studies have indicated a survival advantage to CGR or optimal cytoreduction in recurrent EC [15, 16, 23]. In a meta-analysis, Barlin et al. demonstrated that for each 10% increase in patients achieving CGR at debulking for advanced or recurrent EC, there was a significant improvement in survival of 9.3 months [7]. They also reported that for each 10% increase in patients with optimal resection (≤ 2 cm) there was a 16-month improvement in survival that approached statistical significance (p=0.05). Awtrey et al. reported a median survival of 43 months among patients with ≤ 2 cm of residual disease after SCS for recurrent EC, which differed significantly from those with residual disease > 2 cm [15]. While optimal debulking appears to confer survival benefit, further research is warranted to determine a minimal resection level associated with improved survival.

This study is limited by its retrospective design, which introduces bias, most notably regarding patient selection. As the study was not powered, comparisons between groups were numerically limited. The variability in follow-up intervals and screening methods is another limitation. No stringent follow-up protocol was implemented across providers; thus, recurrences could have been missed, or there could have been bias in detecting recurrences because of variations in time intervals and screening methods. Some patients were lost to follow-up. Additionally, not all surgeons have the same technical skills, not all institutions have perioperative care protocols in place, and in some institutions access to other surgical specialists may be limited. These factors limit comparison across multiple institutions.

Lastly, our study ended prior to the recent approval of pembrolizumab for MSI-high tumor and combined pembrolizumab and levatinib for MS-stable or MMR-proficient endometrial tumors. The impact of immunotherapeutic strategies compared with surgery remains to be seen, as does the potential for synergistic treatment. One of the strengths of this study is that it reports on one of the largest cohorts of recurrent EC to date. In addition, by limiting the cases to only those patients who underwent prior primary surgical staging at our institution, multiple possible confounders were excluded.

The landscape of treatment options for recurrent EC is changing. Until there is sufficient data to compare these newer modalities, however, our findings suggest that surgery should be strongly considered whenever it is deemed safe and surgically feasible. The additional criteria defined in this study may help guide treatment recommendations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

1. In recurrent endometrial cancer, secondary cytoreductive surgery (SCS) confers better survival than other treatments.
2. Age <70 at initial diagnosis, and endometrioid histology, were associated with improved survival in SCS.
3. In well-selected, medically eligible patients, surgical management should be considered whenever technically feasible.

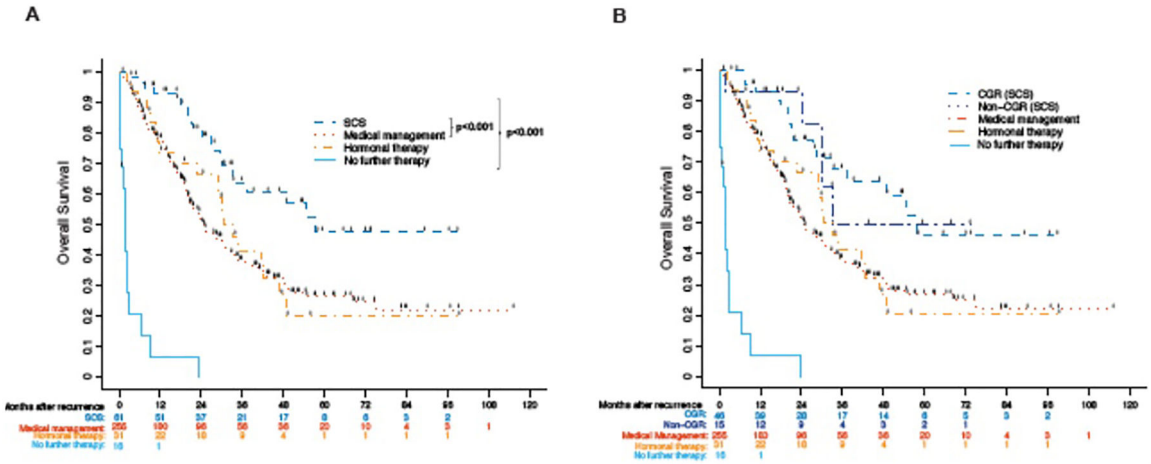

Figure 1:

Overall survival for 376 patients with recurrent endometrial cancer from time of recurrence stratified by treatment modality **(A)** and further stratified by complete gross resection at time of SCS **(B)**.

Table 1

Clinicopathologic characteristics among all recurrences compared across treatment modalities (*N* = 376).

Variable	All recurrences (*N* = 376)	SCS (*N* = 61)	Medical management (*N* = 257)	Hormonal therapy (*N* = 32)	No therapy (*N* = 26)	*p*-Value†	*p*-Value (SCS vs MM)††
1A: Clinicopathologic characteristics at the time of initial diagnosis and primary surgery							
Age at initial diagnosis, years							
Median (range)	66 (28–93)	62 (39–83.3)	66 (28–90)	69.5 (47–86)	67.5 (33–92)	**0.004**	**0.004**
Age ≤70	254 (67.6)	50 (82)	174 (67.7)	16 (50)	14 (53.8)	**0.005**	**0.029**
Age > 70	122 (32.4)	11 (18)	83 (32.3)	16 (50)	12 (46.2)		
BMI at initial diagnosis, kg/m^2							
Median (range)	29.5 (14.2–60.3)	25.3 (19.1–43)	29.7 (14.2–60.3)	28.5 (15.8–51)	25.3 (19.1–43)	0.349	0.739
Normal (BMI < 25)	93 (24.7)	13 (21.3)	62 (24.1)	7 (21.9)	11 (42.3)	0.165*	0.882
Overweight (25 ≤BMI < 30)	104 (27.7)	16 (26.2)	70 (27.2)	14 (43.8)	4 (15.4)		
Obese (BMI ≥30)	179 (47.6)	32 (52.5)	125 (48.6)	11 (34.4)	11 (42.3)		
Progression-free survival (PFS1) (months)							
Median (range)	14.3 (0.2–102.2)	19.4 (2.4–88.3)	13.3 (0.2–102.2)	15.5 (2.5–92.4)	11.6 (1.9–62.2)	**0.002**	**<0.001**
Histology							
Endometrioid	183 (48.7)	37 (60.7)	117 (45.5)	18 (56.3)	11 (42.3)	0.214*	**0.033**
Serous	146 (38.8)	15 (24.6)	109 (42.4)	11 (34.4)	11 (42.3)		
Clear Cell/Mixed	47 (12.5)	9 (14.8)	31 (12.1)	3 (9.4)	4 (15.4)		
FIGO Grade						**0.016***	**0.022**
G1	62 (16.5)	12 (19.7)	37 (14.4)	11 (34.4)	2 (7.7)		
G2	71 (18.9)	18 (29.5)	43 (16.7)	5 (15.6)	5 (19.2)		
G3/high-grade histology	243 (64.6)	31 (50.8)	177 (68.9)	16 (50)	19 (73.1)		
Stage							
I	162 (43.1)	35 (57.4)	108 (42)	11 (34.4)	8 (30.8)	0.065*	**0.014**
II	27 (7.2)	2 (3.3)	19 (7.4)	3 (9.4)	3 (11.5)		
III	96 (25.5)	18 (29.5)	63 (24.5)	9 (28.1)	6 (23.1)		
IV	91 (24.2)	6 (9.8)	67 (26.1)	9 (28.1)	9 (34.6)		
≥Grade 3 Complication							
No	363 (96.5)	60 (98.4)	250 (97.3)	30 (93.8)	23 (88.5)	0.069	1
Yes	13 (3.5)	1 (1.6)	7 (2.7)	2 (6.3)	3 (11.5)		
Length of hospital stay, days							
Median (range)	1 (0–49)	1 (0–6)	1 (0–49)	2 (0–15)	2.5 (0–18)	**0.002**	**0.003**

Variable	All recurrences (*N* = 376)	SCS (*N* = 61)	Medical management (*N* = 257)	Hormonal therapy (*N* = 32)	No therapy (*N* = 26)	*p*-Value[†]	*p*-Value (SCS vs MM)[††]
Residual disease after primary surgery							
Absent	348 (92.6)	61 (100)	234 (91.1)	30 (93.8)	23 (88.5)	**0.033**	**0.011**
Present	28 (7.4)	0 (0)	23 (8.9)	2 (6.3)	3 (11.5)		
Adjuvant Therapy after primary surgery							
No	62 (16.5)	12 (19.7)	41 (16)	5 (15.6)	4 (15.4)	0.891	0.452
Yes	314 (83.5)	49 (80.3)	216 (84)	27 (84.4)	22 (84.6)		
Adjuvant Chemotherapy after primary surgery							
No	133 (35.4)	21 (34.4)	91 (35.4)	11 (34.4)	10 (38.5)	0.988	1
Yes	243 (64.6)	40 (65.6)	166 (64.6)	21 (65.6)	16 (61.5)		
Adjuvant Radiation after primary surgery							
No	173 (46)	19 (31.1)	123 (47.9)	15 (46.9)	16 (61.5)	**0.039**	**0.022**
Yes	203 (54)	42 (68.9)	134 (52.1)	17 (53.1)	10 (38.5)		
Type of radiation therapy							
IVRT	144 (70.9)	26 (61.9)	100 (74.6)	13 (76.5)	5 (50)	0.101	0.097
EBRT	53 (26.1)	16 (38.1)	30 (22.4)	3 (17.6)	4 (40)		
IVRT/EBRT	6 (3.0)	0 (0)	4 (3)	1 (5.9)	1 (10)		
1B: Clinicopathologic characteristics at the time of recurrence							
Size of largest recurrent tumor (cm)[^]							
Median (range)	2.2 (0.2–19.8)	2.6 (0.5–12)	2.2 (0.2–19.8)	2.5 (0.5–12)	2.4 (0.6–19.2)	**0.003**	0.148
Multiplicity of sites of recurrence							
Single	201 (53.5)	46 (75.4)	125 (48.6)	16 (50)	14 (53.8)	**0.002**	**<0.001**
Multiple	175 (46.5)	15 (24.6)	132 (51.4)	16 (50)	12 (46.2)		
Sites of recurrence							
Pelvic alone	72 (19.1)	11 (18)	59 (23)	0 (0)	2 (7.7)	**0.004**[*]	0.109
Nodal alone	60 (16)	10 (16.4)	35 (13.6)	11 (34.4)	4 (15.4)		
Pelvic and nodal	16 (4.3)	3 (4.9)	11 (4.3)	1 (3.1)	1 (3.8)		
Distant +/− pelvic	195 (51.9)	36 (59)	124 (48.2)	18 (56.3)	17 (65.4)		
Peritoneal carcinomatosis alone	33 (8.8)	1 (1.6)	28 (10.9)	2 (6.3)	2 (7.7)		
Subsequent lines of therapy							
Median (range)	1 (1–8)	1 (1–6)	2 (1–8)	2 (1–7)	–	**<0.001**	**<0.001**

Values are presented as numbers (%) unless otherwise specified.

SCS, secondary cytoreductive surgery; BMI, body mass index; IVRT, intravaginal radiation therapy; EBRT, external beam radiation therapy; FIGO, International Federation of Gynecology and Obstetrics.

Bold denotes significant p-values.

^Twenty-four data points not available.

†*p*-values with * are obtained using Monte Carlo estimation for exact test; other *p*-values are obtained using Kruskal Wallis test for continuous and Fisher's exact test for categorical.

††*p*-values are obtained using Fisher's exact test for categorical and Willcoxon rank-sum test for continuous.

Table 2

Intraoperative and postoperative characteristics of secondary cytoreductive surgery for recurrent disease (N = 61)

Variable	
DOD of recurrence to SCS (days)	26 (0–155)
Total Operative Time (min)	145 (11–405)
Estimated Blood Loss (mL) *	75 (5–1800)
Residual Disease	
CGR	46 (75.4)
Non-CGR	15 (24.6)
Complication	
No	51 (85)
Yes	9 (15)
Complication Grade	
1	3 (4.9)
2	4 (6.6)
3	2 (3.3)
Length of stay (days) **	1 (0–13)
Adjuvant therapy	
None	7 (11.5)
Chemo	26 (42.6)
RT	7 (11.5)
Chemo-RT	12 (19.7)
Hormone	9 (14.8)

Values are presented as numbers (%) or median (range)

DOD, Date of diagnosis of recurrence; SCS, secondary cytoreductive surgery; CGR, complete gross resection; Chemo, chemotherapy; RT, radiation therapy

* One data point not available

** Three data points not available

Table 3

Survival analysis based on treatment modality for initial recurrence *(N* = 376)

3A: Progression-free survival after recurrence (PFS2)						
Variable	**N**	**Progression/Death (n)**	**Median PFS2, months (95% CI)**	**2-yr PFS2 rate (95% CI)**	**HR (95% CI)**	***p*-Value**
Whole cohort	376	288	9.5 (8.5–10.9)	25.5% (21.0–30.3)		
All Modalities of Treatment for 1st Recurrence						<0.001
SCS	61	37	14.9 (10.1–41.8)	44.6% (31.2–57.1)	0.13 (0.07–0.24)	
MM	253	199	8.6 (7.5–10.6)	22.6% (17.3–28.2)	0.23 (0.13–0.38)	
Hormonal therapy	31	28	5.9 (3.2–17.2)	21.3% (8.9–37.2)	0.29 (0.16–0.55)	
None	16	15	1.1 (0.4–2.6)	Not Reached	1	
Surgical vs Medical Treatment for 1st Recurrence						
SCS	61	37	14.9 (10.1–41.8)	44.6% (31.2–57.1)	1	0.002
MM	253	199	8.6 (7.5–10.6)	22.6% (17.3–28.2)	1.74 (1.22–2.47)	
3B: Overall survival (OS) after recurrence						
Variable	N	Death (n)	Median OS, months (95% CI)	2-yr OS rate (95% CI)	HR (95% CI)	*p*-Value
Whole cohort	376	212	29 (24.4–32.5)	56.4% (50.8–61.6)		
All Modalities of Treatment for 1st Recurrence						<0.001
SCS	61	21	57.6 (33.3-NE)	80.9% (67.3–89.3)	0.04 (0.02–0.07)	
MM	255	149	24.5 (21–30.6)	51.6% (44.7–58)	0.08 (0.05–0.15)	
Hormone	31	20	33.3 (22.7–46.7)	66.5% (46.6–80.4)	0.08 (0.04–0.16)	
None	16	15	1.8 (0.5–2.6)	Not Reached	1	
Surgical vs Medical Treatment for 1st Recurrence						
SCS	61	21	57.6 (33.3-NE)	80.9% (67.3–89.3)	1	<0.001
MM	255	149	24.5 (21–30.6)	51.6% (44.7–58)	2.32 (1.47–3.66)	

PFS2, progression-free survival after recurrence; SCS, secondary cytoreductive surgery; OS, overall survival; MM, medical management; NE, not estimable.

Table 4

Survival after secondary cytoreductive surgery based on clinicopathologic and surgical characteristics (*N* = 61).*, **

4A: Progression-free survival after secondary cytoreduction surgery

Variable	Total N	Progression/ Death#	Median PFS2, months (95% CI)	2Yr PFS2 rate (95% CI)	HR (95% CI)	*p*-Value
Whole	61	37	15.8 (10.9–42.7)	44.6% (31.2–57.1%)		
Age at initial diagnosis, years						
Age ≤70	50	29	27.7 (12.2–56.8)	50.6% (35.4–63.9%)	1	**0.023**
Age > 70	11	8	11.1 (2.8–17.7)	13.3% (0.7–43.5%)	2.46 (1.1–5.48)	
BMI at initial diagnosis, kg/m^2						
Normal (BMI < 25)	13	10	12.7 (7.4–66.9)	38.5% (14.1–62.8%)	1	0.707
Overweight (25 ≤BMI < 30)	16	11	21 (7.5–56.8)	50% (24.5–71%)	0.81 (0.34–1.92)	
Obese (BMI ≥30)	32	16	17.7 (10.6–NE)	43.2% (23.8–61.2%)	0.71 (0.32–1.59)	
Progression-free survival (PFS1)						
As continuous (6 months increase)					0.89 (0.76–1.05)	0.179
≤12 months	13	9	10.4 (5.7–NE)	30.8% (9.5–55.4%)	1	0.205
>12 months	48	28	18.7 (13.5–42.7)	48.4% (32.7–62.5%)	0.61 (0.29–1.32)	
Histology						
Endometrioid	37	19	29 (10.9–NE)	54.2% (35.6–69.5%)	1	0.310
Serous	15	11	11.1 (5.8–28.5)	32% (10.9–55.7%)	1.76 (0.82–3.77)	
Clear Cell/Mixed	9	7	15.8 (7.4–66.9)	33.3% (7.8–62.3%)	0.99 (0.39–2.51)	
FIGO Grade						
G1	12	4	NR	62.5% (26.8–84.6%)	1	0.236
G2	18	11	27.7 (10.9–66.9)	56.5% (29.7–76.4%)	1.51 (0.48–4.81)	
G3/high-grade histology	31	22	15 (9.9–18.7)	32.2% (16.4–49.2%)	2.26 (0.77–6.58)	
Stage						
I	35	20	27.7 (12.2–66.9)	53.6% (35–69%)		–
II	2	1	5.8, 2.0 (alive)	NR		
III	18	12	14.7 (5.7–42.7)	32.6% (12.1–55.1%)		
IV	6	4	10.3 (3.4–NE)	33.3% (4.6–67.6%)		
≥Grade 3 Complication						
No	60	36	15.8 (10.9–42.7)	45.4% (31.9–58.1%)		–

4A: Progression-free survival after secondary cytoreduction surgery

Variable	Total N	Progression/ Death#	Median PFS2, months (95% CI)	2Yr PFS2 rate (95% CI)	HR (95% CI)	*p*-Value
Yes	1	1	12.7	NR		
Length of hospital stay (as continuous; 1-day increase)					1.11 (0.87–1.41)	0.409
Adjuvant therapy after primary surgery						
No	12	7	27.7 (6.9–56.8)	56.3% (24.4–79.1%)	1	0.777
Yes	49	30	15.7 (10.6–29)	41.6% (27–55.7%)	1.13 (0.49–2.58)	
Adjuvant Chemotherapy after primary surgery						
No	21	11	27.7 (8.9–56.8)	52% (27.6–71.7%)	1	0.616
Yes	40	26	15.7 (10.4–29)	40.6% (24.8–55.9%)	1.2 (0.59–2.44)	
Adjuvant Radiation after primary surgery						
No	19	13	13.5 (9.5–56.8)	39.5% (17.9–60.5%)		0.473
Yes	42	24	17.7 (10.9–66.9)	46.8% (30.2–61.8%)	0.78 (0.39–1.54)	
Size of largest recurrent tumor (as continuous; 1 cm increase)					1.09 (0.99–1.21)	0.08
Multiplicity of Sites of Recurrence						
Single	46	26	27.7 (14.7–56.8)	52.5% (36.3–66.4%)	1	0.065
Multiple	15	11	11 (7.5–13.5)	21.4% (5.2–44.8%)	1.96 (0.95–4.04)	
Sites of recurrence						
Pelvic alone	11	5	29 (5.8–NE)	62.3% (27.7–84%)		–
Nodal alone	10	5	NR	50% (18.4–75.3%)		
Pelvic and nodal	3	3	10.9 (7.5–12.7)	NR		
Distant +/− pelvic	36	23	17.7 (11.1–42.7)	43.9% (26.4–60.1%)		
Peritoneal carcinomatosis alone	1	1	10.6	NR		
Sites of recurrence						
Pelvic	11	5	29 (5.8–NE)	62.3% (27.7–84%)	1	0.587
All other sites of disease	50	32	15.7 (10.9–28.5)	41.5% (27.2–55.2%)	1.3 (0.5–3.37)	

4B: Overall surivival after secondary cytoreduction surgery

Variable	Total N	Progression/ Death#	Median OS in months (95% CI)	2Yr OS rate (95% CI)	HR (95% CI)	*p*-Value
Whole	61	21	58.4 (34.1–NE)	80.9% (67.3–89.3%)		
Age at initial diagnosis, years						
Age ≤70	50	15	NR	84.2% (69.6–92.2%)	1	**0.008**
Age > 70	11	6	29 (8.1–38.4)	61.7% (20.7–86.3%)	3.52 (1.31–9.47)	

4A: Progression-free survival after secondary cytoreduction surgery

Variable	Total N	Progression/ Death#	Median PFS2, months (95% CI)	2Yr PFS2 rate (95% CI)	HR (95% CI)	*p*-Value
BMI at initial diagnosis, kg/m^2						
Normal (BMI < 25)	13	5	NR	76.9% (44.2–91.9%)		0.974
Overweight (25 ≤BMI < 30)	16	8	49.7 (31.1–NE)	93.8% (63.2–99.1%)	1.14 (0.37–3.49)	
Obese (BMI ≥30)	32	8	NR	74.4% (50.9–87.8%)	1.08 (0.35–3.34)	
Progression-free survival (PFS1)						
As continuous (6 months increase)					0.91 (0.73–1.13)	0.385
≤12 months	13	6	NR	61.5% (30.8–81.8%)	1	0.222
>12 months	48	15	58.4 (34.1–NE)	86.9% (71.2–94.3%)	0.56 (0.21–1.44)	
Histology						
Endometrioid	37	10	NR	87.8% (70.5–95.2%)	1	**0.030**
Serous	15	8	30.6 (21.1–38.4)	67.9% (35–86.7%)	3.4 (1.3–8.88)	
Clear Cell/Mixed	9	3	NR	71.4% (25.8–92%)	1.35 (0.37–4.93)	
FIGO Grade						
G1	12	2	31.4 (8.5–90.0)	100%		–
G2	18	4	NR	87.5% (58.6–96.7%)		
G3/high-grade histology	31	15	31.1 (22.6–NE)	69.8% (48.2–83.7%)		
Stage						
I	35	8	NR	82.2% (62.3–92.2%)		–
II	2	1	2.0 (alive), 38.4	100%		
III	18	9	49.7 (21.1–NE)	75.8% (47.3–90.2%)		
IV	6	3	31.1 (18.6–NE)	83.3% (27.3–97.5%)		
≥Grade 3 Complication						
No	60	20	NR	80.5% (66.7–89.1%)		–
Yes	1	1	55.6	100%		
Length of hospital stay (as continuous; 1-day increase)					1.19 (0.88–1.61)	0.253
Adjuvant therapy after primary surgery						
No	12	4	58.4 (11.3–NE)	82.5% (46.1–95.3%)	1	0.765
Yes	49	17	55.6 (31.1–NE)	80.1% (63.9–89.6%)	1.18 (0.4–3.52)	
Adjuvant Chemotherapy after primary surgery						

4A: Progression-free survival after secondary cytoreduction surgery

Variable	Total N	Progression/ Death#	Median PFS2, months (95% CI)	2Yr PFS2 rate (95% CI)	HR (95% CI)	*p*-Value
No	21	6	NR	84% (58.1–94.6%)	1	0.600
Yes	40	15	55.6 (31.1–NE)	79% (60.8–89.5%)	1.29 (0.5–3.32)	
Adjuvant Radiation after primary surgery						
No	19	8	58.4 (30.6–NE)	83.6% (57.3–94.4%)	1	0.940
Yes	42	13	NR	78.9% (60.5–89.4%)	0.97 (0.4–2.34)	
Size of largest recurrent tumor (as continuous; 1 cm increase)					1.08 (0.94–1.23)	0.273
Multiplicity of sites of recurrence						
Single	46	15	NR	79% (62.1–88.9%)	1	0.693
Multiple	15	6	55.6 (29–NE)	85.7% (53.9–96.2%)	1.21 (0.47–3.13)	
Sites of recurrence						
Pelvic alone	11	4	38.4 (18.6–NE)	77.8% (36.5–93.9%)		–
Nodal alone	10	2	33.6 (13.9–49.9)	100%		
Pelvic and nodal	3	1	55.6 (28.7–90.0)	100%		
Distant +/− pelvic	36	14	58.4 (29–NE)	77.2% (57.9–88.5%)		
Peritoneal carcinomatosis alone	1	0	17.9	–		
Site of recurrence						
Pelvic	11	4	38.4 (18.6–NE)	77.8% (36.5–93.9%)	1	0.755
All other sites of disease	50	17	58.4 (33.9–NE)	81.6% (66.4–90.4%)	0.84 (0.28–2.52)	

PFS2, progression-free survival after recurrence; NR, not reached; NE, not estimable.

Bold denotes significant p-values.

* *p*-values are obtained using log-rank test for categorical variables and CoxPH model for continuous variables.

** *p*-value and hazard ratio are not provided for a variable if its certain level of event count is <3.

Table 5

Suggested criteria for the consideration of secondary cytoreductive surgery over medical management for recurrent endometrial cancer based on clinicopathologic and initial surgical features

	Higher Consideration	Lower Consideration
Features from time of diagnosis	Age ≤ 70 at initial diagnosis PFS1 ≥ 19 months Endometrioid/Clear cell FIGO Grade 1/2 Early stage I/II disease at diagnosis	BMI
Features from primary surgery	No residual disease Hospital stay ranging from 0–6 days Received adjuvant radiation therapy	Received adjuvant chemotherapy
Features at time of recurrence	Single site of disease	Size of tumor Distant site of recurrence

PFS1, time interval from initial surgery to first progression/recurrence; BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics