Surgical Oncology 43 (2022) 101811

Contents lists available at ScienceDirect

Surgical Oncology

journal homepage: www.elsevier.com/locate/suronc

Review

Cytoreductive surgery in recurrent endometrial cancer: A new paradigm for surgical management?

Joëlle Dhanis [a,b], Dominic Blake [c], Stuart Rundle [c], Johanna M.A. Pijnenborg [a], Anke Smits [a,c,*]

[a] Department of Obstetrics and Gynecology, Radboud University Medical Center, Geert Grooteplein Zuid 10, 6525GA, Nijmegen, the Netherlands
[b] Faculty of Medical Sciences, Radboud University, Geert Grooteplein Noord 21, 6525EZ, Nijmegen, the Netherlands
[c] Department of Gynaecological Oncology, Queen Elizabeth Hospital, Queen Elizabeth Avenue, NE9 6SX, Gateshead, United Kingdom

ARTICLE INFO

Keywords:
Recurrent endometrial cancer
Cytoreductive surgery
Salvage therapy
Survival

ABSTRACT

The objective was to review the literature on the effect of surgical cytoreduction in recurrent endometrial cancer on survival, and identify baseline and clinical factors associated with improved survival. In addition, we sought to assess the effect of previous radiotherapy on surgical achievement. This review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. We performed a search of PubMed and Cochrane Library to identify studies comparing cytoreductive surgery to medical management and studies reporting on patients receiving cytoreductive surgery as part of multi-modal treatment. Primary outcomes included overall survival and progression free survival, secondary outcomes included factors associated with improved survival. A total of 11 studies fulfilled the inclusion criteria, comprising 1146 patients. All studies were retrospective studies. Cytoreduction as part of treatment for recurrent endometrial cancer was associated with prolonged overall survival and progression free survival. Complete cytoreduction was an independent factor associated with improved survival. Other factors associated with prolonged survival were tumor grade 1, endometrioid histology, ECOG performance status 0, and isolated pelvic recurrences. Factors associated with obtaining complete cytoreduction included solitary disease, tumor size <6 cm and ECOG performance status 0. Previous radiotherapy was not associated with achieving complete cytoreduction. Cytoreductive surgery may benefit patients meeting specific selection criteria based on a limited number of retrospective studies, with complete cytoreduction showing the largest survival gain. However, further prospective studies are needed to validate the survival benefit and aid in patient selection.

1. Introduction

Endometrial cancer is the sixth most common cancer in women globally, with an estimated worldwide incidence of over 417,000 in 2020, of which over 130,000 were diagnosed in Europe alone [1]. Endometrial cancer is usually detected at an early stage and treated surgically by hysterectomy and bilateral salpingo-oophorectomy with or without further staging procedures to inform the need for adjuvant treatment [2]. Outcomes following treatment for endometrial cancer are relatively good with 5-year overall survival of 76% for all stage disease, and a 5-year overall survival of up to 92% for FIGO stage 1 disease [3]. Survival is impacted by several factors including patient characteristics such as age and comorbidities, and tumor characteristics including stage of disease and tumor grade [4,5]. Despite optimal surgical and adjuvant treatment, the overall risk of recurrence of endometrial cancer is 10%–15% [6].

Optimal management for patients with recurrent endometrial cancer remains challenging and varies according to the type of recurrence, disease site, as well as previous applied treatment. Local pelvic recurrences without prior irradiation are more commonly treated with salvage radiotherapy and subsequent five-year survival rates range from 55% to 85% [7]. However, there is no consensus on treatment on previously irradiated locoregional recurrent disease or distant recurrences. Previous radiotherapy is generally considered a relative contra-indication to additional radiotherapy for recurrent disease and is also associated with increased complexity of surgery due to loss of tissue planes and impaired tissue healing [8].

Historically, radical salvage surgery, namely pelvic exenteration has

* Corresponding author. Department of Obstetrics and Gynecology, Radboud university medical center, Geert Grooteplein Zuid 10, 6525GA, Nijmegen, the Netherlands. Tel.: 0031644404756
E-mail addresses: joelledhanis99@gmail.com (J. Dhanis), anke.smits@radboudumc.nl (A. Smits).

https://doi.org/10.1016/j.suronc.2022.101811
Received 3 April 2022; Received in revised form 14 June 2022; Accepted 3 July 2022
Available online 8 July 2022

been the mainstay of surgery for selected women with an isolated central pelvic recurrence of endometrial cancer following prior radiotherapy treatment [9–12]. The aim of such surgery is complete resection, usually necessitating removal of the rectum and bladder en-bloc with the recurrent tumor. Recently, surgical cytoreduction, akin to that employed in the management of recurrent ovarian cancer, has gained interest as a potential surgical strategy for recurrent endometrial cancer. Cytoreductive surgery is defined as removal of all visible disease without reference to margins including single site disease. In combination with selected post-surgical systemic therapies, cytoreductive surgery may show equivalent or better survival outcomes without the high burden of post-surgical morbidity associated with pelvic exenteration [13]. Furthermore, cytoreductive surgery is not limited to the pelvis and therefore opens up surgical treatment options for patients previously considered inoperable.

We performed a systematic literature search and narrative review to summarize existing evidence for the effect of cytoreduction for recurrent endometrial cancer on survival, and identify factors associated with improved survival. In addition, we aimed to assess the impact of previous radiotherapy on surgical management for recurrent endometrial cancer.

2. Materials and methods

2.1. Criteria for considering studies for this review

This review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines [14]. Studies reporting on the effect of cytoreduction on survival for recurrent endometrial cancer were identified. Studies comparing management including surgical cytoreduction to medical management, as well as studies reporting on patients receiving cytoreduction as part of multi-modal treatment were included. Study designs considered for this review were randomized control trials (RCT's), cohort studies and case series. Primary outcomes were overall survival and progression free survival. Secondary outcomes comprised factors associated with improved survival such as baseline characteristics (i.e. age, performance status) and clinical characteristics (initial stage of disease, histology, site of recurrence, disease free interval, adjuvant treatment. We excluded publications in languages other than English and unpublished studies without full text availability. We further excluded studies in which the majority of patients had non-epithelial cancers and those in which patients underwent pelvic exenterations.

2.2. Search strategy

The search protocol was based on the PRISMA guidelines. A systematic search was performed in PubMed and Cochrane Library using the terms "endometrial neoplasms", "neoplasm recurrence", "surgery" and "survival". The full search strategy for this review has been added in Appendix 1. Furthermore, the reference lists of eligible studies were searched to further identify additional studies eligible for inclusion. Our search was performed in February 2022 and included studies published between 1979 and 2022.

2.3. Study selection and data extraction

Publication title and abstract of all studies identified by the search were screened. Studies that did not meet the inclusion criteria were excluded. Potentially relevant studies were retrieved in full text and were reviewed independently by two reviewers (JD and AS). Disagreements regarding inclusion or exclusion were discussed with a third person (JP) to reach consensus. We excluded studies evaluating pelvic exenterations alone and literature reviews. The following variables were extracted by both reviewers: study design, year of publication, country, inclusion period, study size, baseline and clinical characteristics of patients (including stage and primary histology), primary treatment, site of recurrence, histology of recurrence, type of surgery, type of adjuvant therapy, (median) survival (i.e. overall and progression-free survival), operative complications and operative mortality. Recurrence sites were categorized into pelvic (including pelvic lymph nodes), abdominal (including para-aortic lymph nodes), extra-abdominal or a combination.

2.4. Assessment of risk of bias

We assessed study bias using the Risk of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) and the Cochrane Risk of Bias Tool for Randomized Controlled Trials presented by the Cochrane Collaboration [15]. This assessment tool assesses bias due to confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurements of outcomes and the selection of reported results. Two reviewers (JD and AS) applied the ROBINS-I tool and the Cochrane Risk of Bias Tool for Randomized Controlled Trials and resolved differences by discussion.

3. Results

3.1. Study selection

A total of 884 articles were identified by the search strategy. Following title and abstract review, 24 articles were retrieved in full text of which 8 met the inclusion criteria for this review. A search of reference lists of included studies identified an additional 34 articles of which 12 were retrieved in full text. A further 3 of these studies met the inclusion criteria. This resulted in a total of 11 articles, all unique studies (Fig. 1).

3.2. Included studies

3.2.1. Type of studies

Four of the included studies were retrospective cohort studies while seven were retrospective case series and are summarized in respectively Table 1 and Table 2. Ten studies were single institution analyses while one study was a multicenter analysis [16]. A total of 1146 patients with recurrent endometrial cancer were included in the selected studies, of whom the majority (N = 717) underwent cytoreductive surgery. The number of patients per study ranged from 20 to 376. Four studies compared management including cytoreductive surgery to non-surgical treatment which consisted of chemotherapy (62%), radiotherapy (27%), chemoradiation (4%) or targeted/hormonal treatment (7%) (Table 1) [17–20]. Seven studies reported on a study group of patients receiving cytoreduction as part of treatment (Table 2) [16,21–26]. Inclusion periods varied, with studies including patients over a period of 7–31 years [19,25].

3.2.2. Study population

The pattern of recurrence varied among included studies, with the majority being pelvic (59%–79%) and extra-abdominal (38%–64%) recurrences [16–18,20,21,23,26]. Three studies excluded isolated vaginal recurrences and half of the studies excluded extra-abdominal recurrences [18,20–22,25,26]. Six studies reported multiple sites of recurrent disease in 44%–80% of included patients, while three studies reported mainly single site recurrent disease (54%–74% of included patients) [17–26]. In all studies endometrioid adenocarcinoma was the most frequently included primary histological type (70%, range 55%–91%) [25,26]. All but two studies exclude sarcomas as primary histology [18,23]. In nine studies, the majority of patients were initially diagnosed with FIGO stage 1 disease (54%, range 43%–71%), while in two studies the largest group of patients (31% and 34%) were diagnosed with FIGO stage 3 disease [17,19]. All studies reported on primary treatment, with most patients having received primary surgery without adjuvant treatment. Median time to recurrence varied from 14 to 161 months [16,26].

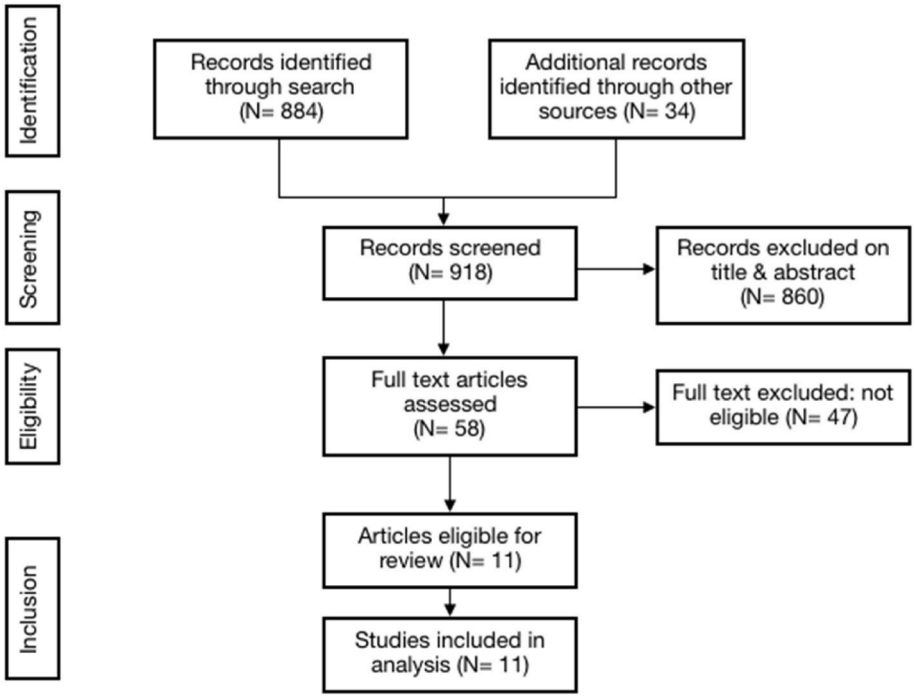

Fig. 1. Literature search. Flow chart of the literature search.

All studies described cytoreductive surgery, with possible pelvic and/or para-aortic lymph node dissection (25%–67%), bowel resection (9%–55%) or omentectomy (11%–36%) [21–23,25,26]. All studies included data on adjuvant therapy. Post-operative chemotherapy was used in 24%–64% of included patients, depending on the study, radiotherapy in 3%–44% of patients, and a combination of chemoradiation in 7%–20% of patients. The number of patients receiving surgical treatment without further adjuvant treatment (N = 9) varied from 4% to 25% among studies.

3.3. Survival

3.3.1. Overall survival

Four studies compared cytoreductive surgery with non-surgical treatments and all showed a significant difference in survival in favor of cytoreductive surgery [17–20] **(**Table 1**)**. Median follow-up varied from 22 to 34 months [17,19]. Bristow et al. reported a significantly longer median overall survival of 28 months of the surgical cohort (N = 35, surgery + radiotherapy N = 15, surgery + chemotherapy N = 10, surgery + chemoradiation N = 6) versus 13 months of the non-surgical cohort (N = 29; chemotherapy N = 15, radiotherapy N = 6, chemoradiation N = 2, hormonal therapy N = 6) [17]. McAlarnen et al. showed significantly improved two-year overall survival rates of 67% in the surgical treatment group (N = 4, surgery + radiotherapy N = 2, surgery + chemotherapy N = 1, surgery alone N = 1) and 68% in the multimodal group (N = 13, surgery + chemotherapy + radiotherapy) versus 53% in the non-surgical treatment group (N = 5, chemotherapy N = 3, radiotherapy N = 1, chemoradiation N = 1). Patients' primary disease comprised mostly FIGO stage 1 diseases and with the majority having pelvic recurrences. Comparability of performance status or comorbidities across groups was not reported [18]. Neither Bristow et al. nor McAlarnen et al. specified the motivation for treatment allocation. A recent study by Moukarzel et al. found a significant prolonged median overall survival of 58 months for surgical treatment (N = 61) versus 15 months for non-surgical treatment (N = 257). The non-surgical group included chemotherapy with or without radiotherapy (N = 191), radiotherapy alone (N = 47), or targeted/immune therapy (N = 19). The surgical group received cytoreductive surgery alone (N = 7), or a combination of cytoreductive surgery combined with chemotherapy (N = 26), radiotherapy (N = 7), both chemotherapy and radiotherapy (N = 12) or hormonal treatment (N = 9). Whether cytoreductive surgery or medical management was the treatment of choice, was determined by the patient's clinical status, recurrence characteristics, feasibility and safety of resection [20]. Lastly, Shikama et al. found median overall survival to be significantly better for patients receiving surgical treatment (N = 29, of which 1 received cytoreductive surgery alone, 24 received surgery with chemotherapy, 1 with radiotherapy, 1 with both chemotherapy and radiotherapy and 2 with other treatments) compared to patients treated with chemotherapy (N = 44) or radiotherapy (N = 27). They showed an median overall survival of 45 months for the surgical cohort versus 16 and 26 months for patients treated with chemotherapy and radiotherapy respectively. Five-year survival rates were 67, 28 and 25% after surgery, chemotherapy and radiotherapy for recurrence, respectively. Treatment allocation was decided by the expected feasibility of achieving complete resection [19].

3.3.2. Progression free survival

Two of the comparative studies assessed median progression free survival. In the study by McAlarnen et al., 2-year progression free survival was greater in the multimodal cohort (62%), consisting of surgery combined with chemo- and radiotherapy, compared to the surgical treatment group (38%) and non-surgery cohort (40%) [18]. Moukarzel et al. found a significant prolonged progression free survival of 25 months for surgical treatment (N = 61) versus 9 months for non-surgical treatment (N = 257) [20].

For the non-comparative case series, reported overall survival varied between 9 and 22 months for suboptimal cytoreduction, 43–59 months for optimal cytoreduction and up to 68 months for complete cytoreduction [21,22,24]. Reported five-year progression free survival rates were 42% for complete cytoreduction [23], with a progression free survival of 9–21 months [21,22,25]. Median follow-up periods varied from 14 to 161 months [16,26].

Table 1
Comparative studies on surgical versus non-surgical treatment.

Study	Year	Country	Study size (n)	Inclusion period	Type of recurrence	Treatment (n)	Outcome	
							OS (months)	PFS (months)
Bristow	2006	USA	61	1997 – 2005	Pelvic: 36% Distant: 64%	Surgical (35):* - Surgery + RT: 15 - Surgery + CT: 20 - Surgery + RT + CT: 6 Non-surgical [26]:* - RT: 6 - CT: 15 - RT + CT: 2 - Hormonal: 6	Surgical: 28 Non-surgical: 13 Complete: 39 Residual disease: 14	–
McAlarnen	2019	USA	22	2007 – 2018	Pelvic: 59% Abdominal: 41%	Multimodal [13]: - Surgery + RT + CT: 13 Surgical [4]: - Surgery + RT: 2 - Surgery + CT: 1 - Surgery: 1 Non-surgical [5]: - RT: 1 - CT: 3 - RT + CT: 2	2-year survival: Multimodal: 68% Surgical: 67% Non-surgical: 53%	2-year survival: Multimodal: 62% Surgical: 38% Non-surgical: 40%
Moukarzel	2021	USA	376	2009 – 2017	Pelvic: 35% Abdominal: 13% Distant: 52%	Surgical (61): - Surgery + RT: 7 - Surgery + CT: 26 - Surgery + RT + CT: 12 - Hormone: 9 - Surgery: 7 Non-surgical (315): - RT: 47 - CT: 191 - Targeted therapy: 19 - Hormonal: 32 - None: 26	Surgical: 58 Non-surgical: 25	Surgical: 15 Non-surgical: 9
Shikama	2019	Japan	112	1985 – 2016	Pelvic: 79% Distant: 21%	Surgical [29]: - Surgery + RT: 1 - Surgery + CT: 24 - Surgery + RT + CT: 1 - Surgery: 1 - Other: 2 Non-surgical (83): - RT: 44 - CT: 15 - RT + CT: 12 - Best supportive care: 12	Surgical: 45 CT: 16 RT: 26 5-year survival Surgical: 67% CT: 28% RT: 25% Complete: 68 Residual disease: 20	–

* Bristow et al. reported numbers of treatment groups are overlapping; RT: radiotherapy; CT: chemotherapy.

3.4. Perioperative factors associated with survival

3.4.1. Cytoreduction

The removal of all visible disease was achieved in the majority of patients in eight studies, with rates varying from 57% to 75% [17,19,20,22–26]. All but two studies assessed the association between the presence of residual disease after surgery and overall survival [18,20]. Six studies compared complete cytoreduction (no visible disease) to visible disease and showed that complete cytoreduction was significantly associated with improved overall survival with five-year overall survival rates increasing from 30%-37% to 60%–66% and overall survival of 39–68 months versus 14–22 months [16,17,23–26]. Factors associated with obtaining complete cytoreduction were solitary disease, tumor size <6 cm and an ECOG performance status of 0 [21,23,24]. Advancing age and presence of carcinomatosis negatively impacted achieving complete cytoreduction and survival [22,24]. Location of recurrence was not associated with rates of complete cytoreduction [17,19,22,24]. In addition, three studies comparing optimal cytoreduction (<1 cm visible disease) to suboptimal cytoreduction (>1 cm visible disease) found a significant survival benefit of optimal cytoreduction compared to suboptimal cytoreduction with a survival difference varying from 22 to 48 months [19,22,24]. Awtrey et al. showed improved two-year overall survival rates from 22% to 89% and a survival difference of 33 months, but only differentiated between <2 cm and >2 cm (suboptimal) residual disease [21]. When assessing progression free survival, three studies showed a significantly prolonged progression free survival for complete cytoreduction (9,1 versus 1,5 months for complete cytoreduction versus any residual disease) and significantly improved five-year overall survival rates (42% versus 19%) [23,25]. Campagnutta et al. showed a prolonged progression free survival of 11 months for optimal debulking compared to suboptimal debulking [22]. Factors associated with improved progression free survival were grade 1 primary tumor and pelvic site of recurrence [16,20]. Five studies reported on the association between post-operative treatment and survival [16,18,19,21,24]. McAlarnen et al. reported that adjuvant radiotherapy and chemotherapy were associated with prolonged overall survival compared to no adjuvant therapy [18]. Four studies found no significant association between adjuvant therapy and improved survival [16,19,21,24].

3.4.2. Radiotherapy

All but one study included a significant proportion of previously irradiated patients, with rates varying between 23% and 59% [16,21]. Four studies assessed the association of primary radiotherapy and obtaining complete cytoreduction, comprising a total of 202 patients of whom 82 received radiotherapy. All studies reported that previous radiotherapy was not associated with decreased rates of complete

Table 2
Non-comparative studies on surgical treatment.

Study	Year	Country	Study size (n)	Inclusion period	Type of recurrence	Post-operative treatment	Outcome	
							OS [months]	PFS [months]
Awtrey	2005	USA	27	1993 – 2003	Pelvic: 78% Mix: 11%	RT: 12 CT: 10 Hormone: 1 None: 4	Optimal: 43 Suboptimal: 10	Optimal: 21 Suboptimal:5
Campagnutta	2003	Italy	75	1988 – 2000	Pelvic: 33% Abdominal: 55% Distant: 12%	RT: 3 CT: 29 RT + CT: 12 Hormone: 2	Optimal: 59 Suboptimal:9	Optimal: 14 Suboptimal: 3
Germanova	2019	Czech republic	230	1997 – 2013	Local: 36% Pelvic: 54% Abdominal: 24% Distant: 8%	RT: 53 CT: 104 RT + CT: 15 Other: 20 None: 44	5-year: Complete: 66% Optimal: 45% Suboptimal: 37%	–
Papadia	2015	Italy	64	2003 – 2014	Pelvic: 60% Abdominal: 35% Distant: 5%	RT: 15 CT: 32 RT + CT: 4	5-year: Complete: 60% Residual disease: 30%	5-year: Complete: 42% Residual disease: 19%
Ren	2014	China	75	1995 – 2012	Local: 6,7% Pelvic: 58,7% Abdominal: 5,3% Distant: 1,3% Mix: 28%	RT: 6 CT: 48 RT + CT: 8 None: 13	Complete: 68 Optimal: 44 Suboptimal: 22	–
Scarabelli	1998	Italy	20	1988 – 1995	Pelvic: 35% Abdominal: 65%	RT: 2 CT: 10 Hormone: 1 None: 5	–	Complete: 9,1 Residual disease: 1,5
Turan	2015	Turkey	34	1993 – 2013	Pelvic: 26,5% Abdominal: 17,7% Distant: 37,5% Mix: 20,5%	RT: 12 CT: 14 RT + CT: 5 Hormone: 1	Complete: 66 Residual disease: 13	–

RT: radiotherapy; CT: chemotherapy.

cytoreduction [21–23,26].

3.4.3. Other factors

Other factors significantly associated factors with improved survival in recurrent endometrial cancer in multivariate analyses included endometrioid histology, ECOG performance status 0 and a grade 1 primary tumor (Table 3) [16,23–25]. Turan et al. found late recurrences (>20 months), adjuvant radiotherapy after initial surgery, normal CA-125 level at time of recurrence and single recurrences to be associated with improved overall survival, but no multivariate analysis was performed [26]. An overview of all prognostic factors associated with survival is summarized in Table 3.

Morbidity and mortality was reported in the majority of included studies, with morbidity rates varying from 14% to 42%, comprising mainly grade 1 and 2 complications (Clavien-Dindo classification) [17,19,21,23–25]. Three perioperative deaths have been reported in our included studies, but were reported in older case series (1998 and 2004) (22, 25).

3.5. Quality of the studies

All included studies were of non-randomized retrospective cohort design or case series. An evaluation of bias using the ROBINS-1 tool is illustrated in Table 4 for the cohort studies. All case series studies are considered to be at serious risk of bias according to the ROBINS-1 tool due to their inherent lack of non-randomization, selective reporting, patient attrition and lack of information on one or more key domains. Seven of the included studies used a multi-variate analysis to reduce the risk of bias, whilst some studies only used univariate analysis due to a small study population (N = 22, 27 and 34) [16–26]. In addition, there may have been inconsistent treatment strategies throughout the years considering the length of inclusion periods and evolving treatment methods, and of a lot of heterogeneity of adjuvant treatments [17–19]. Lastly, studies varied in histology and stage inclusion, leading to heterogeneity of study populations. Quality of evidence was not assessed using GRADE, following the retrospective design of the studies.

Table 3
Prognostic factors associated with survival.

	Positively associated	Negatively associated
Survival	Complete cytoreduction Optimal cytoreduction Grade 1 primary tumor Pelvic site of recurrence Endometrioid histology ECOG performance status 0	Advancing age Carcinomatosis

4. Discussion

This review summarizes the existing literature on the impact of surgical debulking for recurrent endometrial cancer on survival, as well as identifying factors contributing to improved survival to guide current practice. Overall, we observed that all studies reported significantly improved overall survival for patients who underwent cytoreductive surgery as part of treatment compared to patients only receiving non-surgical treatment for recurrent endometrial cancer. Furthermore, complete cytoreduction was shown to be a significant independent factor associated with improved overall survival and progression free survival, with survival benefit demonstrated for optimal cytoreduction compared to suboptimal cytoreduction [20,24,27]. Factors that contributed to improved survival included endometrioid histology, good performance status (ECOG performance status 0), grade 1 primary tumor and pelvic site of recurrence [16,20,23–25]. To aid future treatment allocation for recurrent endometrial cancer, we present an overview of identified baseline and clinical characteristics and suggested treatments based on the results of this review in Fig. 2.

Thus far, this is the first systematic assessment of the role of surgical

Table 4
Quality of the studies (ROBINS-1).

	Confounding	Selection of participants	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of reported results
Bristow	X	-	-	?	?	+	-
McAlarnen	X	-	-	?	?	+	-
Moukarzel	-	+	+	?	?	+	-
Shikama	-	+	+	?	?	+	-

X Serious risk; - Moderate risk; + Low risk; ? No information.

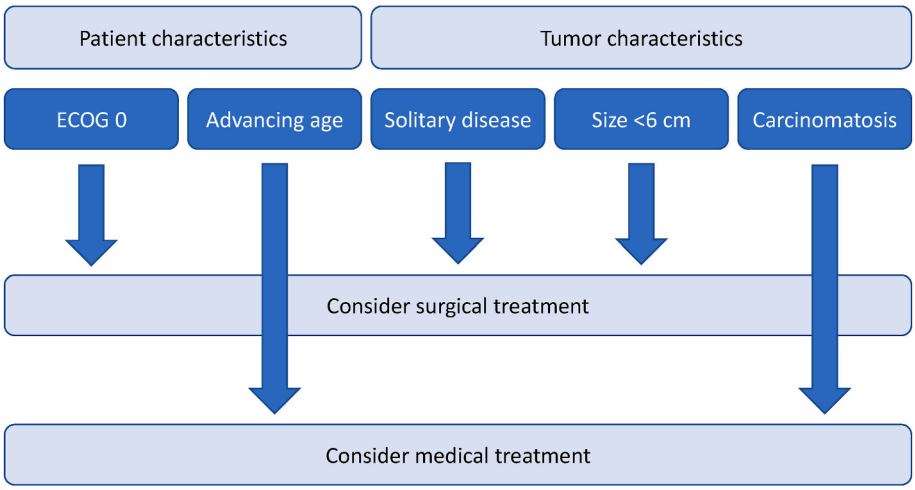

Fig. 2. Baseline and clinical characteristics guiding treatment for recurrent endometrial cancer. Identified baseline and clinical characteristics guiding treatment allocation.

cytoreduction for recurrent endometrial cancer patients alone. A review by Barlin et al. evaluated the role of cytoreductive surgery in advanced (N = 515) and recurrent (N = 157) endometrial cancer patients. In line with our findings, they demonstrated that complete cytoreduction was associated with improved overall survival outcome, with each 10% increase in proportion of patients undergoing complete cytoreduction, showing a 9-month survival benefit. In addition, they showed that in cases with residual disease of 2 cm or more this survival benefit was lost, supporting adequate patient selection and the primary aim of achieving complete cytoreduction [27]. We identified factors associated with complete cytoreduction which included solitary disease, tumor size <6 cm and a good performance status [21,23,24]. A recent study by Legge et al. also found multiple recurrences to be associated with the inability to perform complete cytoreduction [2].

Our review demonstrated that surgical cytoreduction of recurrent endometrial cancer should be considered as part of treatment, with the primary aim of achieving complete surgical resection. Patient selection is key in this process, with patients who have small, isolated recurrent disease and a good performance status being ideal candidates to offer surgical treatment. Reported morbidity and mortality of included studies were favorable, with morbidity comprising mainly grade 1 and 2 complications, with no mortality reported the more recent case series [22,25]. In addition, modifiable patient factors such as performance status provide the opportunity to further reduce morbidity and improve survival outcomes through prehabilitation and post-operative recovery programs [28,29]. This has already been implemented in ovarian cancer surgery, resulting in improved survival outcomes [13]. Despite clinical experience, our review also suggests that obtaining complete cytoreduction is not impeded by previous radiotherapy. Surgical treatment should therefore be considered irrespective of previous radiotherapy treatment.

Evidence-based treatment guidelines for non-vaginal recurrent disease are lacking due to the limitations of non-randomized studies with a retrospective design and small patient cohorts. A review by Rütten et al. recently summarized treatment strategies for recurrent endometrial cancer. They confirm that local and locoregional recurrences can be treated curatively with surgery or (chemo)radiation. Distant recurrences can be palliatively treated with systemic therapies such as chemotherapy or hormonal therapy, with a possible role for immunotherapy [30]. However, immunotherapy following selection through molecular profiling, is currently only considered in the post-chemotherapy setting [30,31].

Consideration of cytoreductive surgery with the aim of complete cytoreduction as part of treatment could provide an opportunity for improving survival for recurrent endometrial cancer and should therefore be explored. The role of surgery is considered within a multimodal approach, as only a small population within our review received surgical treatment alone. Further studies should also focus on delineating patient groups benefitting from surgical treatment alone, identifying predictors for achieving complete cytoreduction and defining standardized multimodal treatment strategies for recurrent endometrial cancer. Prospective trials and data collection are needed to further establish a survival benefit and guide patient selection.

Strengths of this systematic review include the most recent and comprehensive literature search to date, and evaluating solely recurrent endometrial cancer. The review however is limited by the non-

randomized and retrospective designs of the studies, small patient populations, individualized selection of patients over a long time period and heterogeneity of treatments. The reported improved outcomes following cytoreductive surgery may be partly due to patient selection, which was highly individualized and usually involved patients with less aggressive disease and acceptable surgical profiles (i.e. younger age and good performance status), which were not extensively described. However, surgical treatment with the aim of complete cytoreduction could provide a novel opportunity to improve survival for recurrent endometrial cancer and should therefore be explored.

5. Conclusion

The results of this systematic review support the view that cytoreductive surgery has a role in the management of recurrent endometrial cancer. Cytoreductive surgery may benefit patients meeting specific selection criteria based on a limited number of retrospective studies, with complete cytoreduction showing the largest survival gain. Solitary disease, tumor size <6 cm and a good performance status were patient factors associated with achieving complete cytoreduction, whilst advancing age and presence of carcinomatosis showed a negative association. Previous radiotherapy was not found to influence the feasibility of achieving complete surgical debulking, therefore patients with previous radiotherapy should be considered candidates for surgical management of recurrent endometrial cancer. However, further studies with prospective data collection are needed to outline the survival benefit, further guide patient selection and to standardize management.

Declarations

Ethics approval and consent to participate - Ethical approval was not needed as this was a systematic review.

Funding

There were no sources of funding nor grants.

Authors' contributions

JD was responsible for the search, study selection, analysis and write up of the manuscript. DB and SR contributed to the write up and review of the manuscript. HP was responsible for conception, design and write up of the manuscript. AS was responsible for conception, design, study selection, analysis and write up of the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

Acknowledgements

Not applicable.

APPENDIX

Appendix 1 Search strategy

1. ((“Endometrial Neoplasms" [Mesh] AND “Neoplasm Recurrence, Local" [Mesh]) OR recurrent endometrium cancer*[tiab] OR recurrent endometrium carcinoma*[tiab] OR recurrent endometrial cancer*[tiab] OR recurrent endometrial carcinoma*[tiab] OR recurrent Endometrial Neoplasm*[tiab] OR recurrent Endometrium Neoplasm*[tiab] OR recurrent endometrium malign*[tiab] OR recurrent endometrial malign*[tiab])
2. (“surgery” [Subheading] OR “Hysterectomy" [Mesh] OR “Salpingo-oophorectomy” [Mesh] OR Surg*[tiab] OR Resection [tiab] OR hysterectom*[tiab] OR Salpingo-oophorectom*[tiab] OR Bilateral salpingo-oophorectom*[tiab])
3. (“survival” [Mesh] OR “Disease-free survival" [Mesh] OR survival* [tiab] OR overall survival [tiab] OR disease-free survival [tiab])
4. #1 AND #2 AND #3

References

[1] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, et al., Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA A Cancer J. Clin. 71 (3) (2021) 209–249.
[2] F. Legge, S. Restaino, L. Leone, V. Carone, C. Ronsini, G.L.M. Di Fiore, et al., Clinical outcome of recurrent endometrial cancer: analysis of post-relapse survival by pattern of recurrence and secondary treatment, Int. J. Gynecol. Cancer 30 (2) (2020) 193–200.
[3] UK CR, Uterine cancer statistics, n.d. [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer.
[4] H. Donkers, R. Bekkers, L. Massuger, K. Galaal, Socioeconomic deprivation and survival in endometrial cancer: the effect of BMI, Gynecol. Oncol. 156 (1) (2020) 178–184.
[5] K.K. Ward, N.R. Shah, C.C. Saenz, M.T. McHale, E.A. Alvarez, S.C. Plaxe, Cardiovascular disease is the leading cause of death among endometrial cancer patients, Gynecol. Oncol. 126 (2) (2012) 176–179.
[6] Y. Xu, C. Burmeister, R.K. Hanna, A. Munkarah, M.A. Elshaikh, Predictors of survival after recurrence in women with early-stage endometrial carcinoma, Int. J. Gynecol. Cancer 26 (6) (2016) 1137–1142.
[7] M.A. Elshaikh, S. Vance, D.K. Gaffney, M. Biagioli, A. Jhingran, S. Jolly, et al., ACR appropriateness criteria(R) management of recurrent endometrial cancer, Am. J. Clin. Oncol. 39 (5) (2016) 507–515.
[8] F.H. van Wijk, M.E. van der Burg, C.W. Burger, I. Vergote, H.C. van Doorn, Management of recurrent endometrioid endometrial carcinoma: an overview, Int. J. Gynecol. Cancer 19 (3) (2009) 314–320.
[9] V. Chiantera, M. Rossi, P. De Iaco, C. Koehler, S. Marnitz, V. Gallotta, et al., Pelvic exenteration for recurrent endometrial adenocarcinoma: a retrospective multi-institutional study about 21 patients, Int. J. Gynecol. Cancer 24 (5) (2014) 880–884.
[10] F. Khoury-Collado, M.H. Einstein, B.H. Bochner, K.M. Alektiar, Y. Sonoda, N. R. Abu-Rustum, et al., Pelvic exenteration with curative intent for recurrent uterine malignancies, Gynecol. Oncol. 124 (1) (2012) 42–47.
[11] R.R. Barakat, N.A. Goldman, D.A. Patel, E.S. Venkatraman, J.P. Curtin, Pelvic exenteration for recurrent endometrial cancer, Gynecol. Oncol. 75 (1) (1999) 99–102.
[12] A. Brunschwig, The surgical treatment of advanced carcinoma of the cervix, N. Y. State J. Med. 48 (15) (1948) 1733.
[13] P. Harter, A. du Bois, M. Hahmann, A. Hasenburg, A. Burges, S. Loibl, et al., Surgery in recurrent ovarian cancer: the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) DESKTOP OVAR trial, Ann. Surg Oncol. 13 (12) (2006) 1702–1710.
[14] M.J. Page, D. Moher, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, et al., PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews, BMJ 372 (2021) n160.
[15] J.A.C. Sterne, M.A. Hernan, B.C. Reeves, J. Savovic, N.D. Berkman, M. Viswanathan, et al., ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions, BMJ Br. Med. J. (Clin. Res. Ed.) 355 (2016).
[16] A. Germanova, F. Raspagliesi, L. Chiva, L. Dusek, M. Arvas, E. Leblanc, et al., Oncological outcome of surgical management in patients with recurrent uterine cancer-a multicenter retrospective cohort study-CEEGOG EX01 Trial, Int. J. Gynecol. Cancer 29 (4) (2019) 711–720.
[17] R.E. Bristow, A. Santillan, M.L. Zahurak, G.J. Gardner, R.L. Giuntoli 2nd, D. K. Armstrong, Salvage cytoreductive surgery for recurrent endometrial cancer, Gynecol. Oncol. 103 (1) (2006) 281–287.
[18] L.A. McAlarnen, K. Ryan, W. Adams, A. Gliniewicz, A.D. Winder, M.R. Liotta, et al., Salvage treatment in recurrent endometrial cancer of the pelvis and peritoneal cavity, Gynecol Oncol Rep 29 (2019) 1–6.
[19] A. Shikama, T. Minaguchi, W. Takao, Y. Hosokawa, K. Nishida, N. Tasaka, et al., Predictors of favorable survival after secondary cytoreductive surgery for recurrent endometrial cancer, Int. J. Clin. Oncol. 24 (10) (2019) 1256–1263.
[20] L.A. Moukarzel, K.F. Braxton, Q.C. Zhou, S. Pedra Nobre, A. Iasonos, K.M. Alektiar, et al., Non-exenterative surgical management of recurrent endometrial carcinoma, Gynecol. Oncol. 162 (2) (2021) 268–276.
[21] C.S. Awtrey, M.G. Cadungog, M.M. Leitao, K.M. Alektiar, C. Aghajanian, A. J. Hummer, et al., Surgical resection of recurrent endometrial carcinoma, Gynecol. Oncol. 102 (3) (2006) 480–488.
[22] E. Campagnutta, G. Giorda, G. De Piero, F. Sopracordevole, M.C. Visentin, L. Martella, et al., Surgical treatment of recurrent endometrial carcinoma, Cancer 100 (1) (2004) 89–96.
[23] A. Papadia, F. Bellati, A. Ditto, G. Bogani, M.L. Gasparri, V. Di Donato, et al., Surgical treatment of recurrent endometrial cancer: time for a paradigm shift, Ann. Surg Oncol. 22 (13) (2015) 4204–4210.

[24] Y. Ren, B. Shan, D. Shi, H. Wang, Salvage cytoreductive surgery for patients with recurrent endometrial cancer: a retrospective study, BMC Cancer 14 (2014) 135.
[25] C. Scarabelli, E. Campagnutta, G. Giorda, G. DePiero, F. Sopracordevole, M. Quaranta, et al., Maximal cytoreductive surgery as a reasonable therapeutic alternative for recurrent endometrial carcinoma, Gynecol. Oncol. 70 (1) (1998) 90–93.
[26] T. Turan, T. Tasci, A. Karalok, I. Ureyen, O. Kocak, O. Turkmen, et al., Salvage cytoreductive surgery for recurrent endometrial cancer, Int. J. Gynecol. Cancer 25 (9) (2015) 1623–1632.
[27] J.N. Barlin, I. Puri, R.E. Bristow, Cytoreductive surgery for advanced or recurrent endometrial cancer: a meta-analysis, Gynecol. Oncol. 118 (1) (2010) 14–18.
[28] S.P. Bisch, C.A. Jago, E. Kalogera, H. Ganshorn, L.A. Meyer, P.T. Ramirez, et al., Outcomes of enhanced recovery after surgery (ERAS) in gynecologic oncology - a systematic review and meta-analysis, Gynecol. Oncol. 161 (1) (2021) 46–55.
[29] G. Nelson, J. Bakkum-Gamez, E. Kalogera, G. Glaser, A. Altman, L.A. Meyer, et al., Guidelines for perioperative care in gynecologic/oncology: enhanced Recovery after Surgery (ERAS) Society recommendations-2019 update, Int. J. Gynecol. Cancer 29 (4) (2019) 651–668.
[30] H. Rutten, C. Verhoef, W.J. van Weelden, A. Smits, J. Dhanis, N. Ottevanger, et al., Recurrent endometrial cancer: local and systemic treatment options, Cancers 13 (24) (2021).
[31] A. Oaknin, A.V. Tinker, L. Gilbert, V. Samouelian, C. Mathews, J. Brown, et al., Clinical activity and safety of the anti-programmed death 1 monoclonal antibody dostarlimab for patients with recurrent or advanced mismatch repair-deficient endometrial cancer: a nonrandomized phase 1 clinical trial, JAMA Oncol. 6 (11) (2020) 1766–1772.