Neoadjuvant therapy or upfront surgery in advanced endometrial cancer: A systematic review and meta-analysis of clinical outcomes

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Abstract

Background Neoadjuvant therapy is increasingly used in the first-line setting in people with advanced endometrial cancer despite a paucity of evidence for this approach. Objective To systematically evaluate the literature in this area. Search Strategy Electronic searches of Ovid MEDLINE, Ovid Embase, Clinical trials.gov and the International clinical trials registry platform were performed for studies published between 1990 and 2021 comparing neoadjuvant therapy with upfront debulking surgery in Stage 3 or 4 endometrial cancers. Selection Criteria Studies reporting overall survival, progression free survival, adverse events and/or quality of life in those undergoing neoadjuvant therapy or upfront debulking. Data Collection and Analysis Odds ratios (OR) and log hazard ratios (HR) along with 95% confidence intervals (CI) were calculated and pooled for analysis. Risk of bias was assessed using the ROBINS-I tool. Main Results Eight non-randomised studies with a total of 50,510 patients were identified. These showed that patients undergoing primary chemotherapy had similar survival outcomes to those undergoing primary surgery (HR 1.26 (95% CI 0.95-1.69)). Fewer patients in the neoadjuvant group had surgery but those that did were less likely to be suboptimally cytoreduced (OR 0.24; 95% CI 0.21-0.28). Surgical morbidity was no different between the two approaches (OR 0.51, 95% confidence interval 0.08-3.25). However, the potential for bias in these studies is very high. Conclusion There is significant uncertainty as to whether the outcomes for those undergoing primary cytoreductive surgery or neoadjuvant chemotherapy in the presence of unresectable disease are better. Prospective reporting of outcomes is needed.

Introduction

Endometrial cancer is the most common gynaecological malignancy within developed countries , with a lifetime risk of 3% within the UK . Both the incidence and the mortality are thought to be increasing , with incidence rates in the UK doubling since 2018 .

Most women present with early-stage disease (Stages 1 and 2) that is confined to the uterus . For these women, the mainstay of treatment is surgical resection; alongside adjuvant chemotherapy or radiotherapy where risk factors for recurrence are present . These well-established treatment regimens result in a 5-year overall survival of 85% for Stage 1 and 55% for Stage 2 . Comparatively, women with more extensive disease spread (Stage 3 and 4) or poor performance status have much worse prognosis . Although they account for only 15% of patients with endometrial cancer, they make up more than half of the disease related mortality.

There is a paucity of studies investigating the current treatment options for advanced stage endometrial cancer; particularly those outlining the most effective order of treatments. Despite this, the popularity of neoadjuvant chemotherapy in this context is increasing. This paradigm has emerged from the theory that because high grade serous ovarian carcinoma shows both histological similarity as well as a similar

pattern of disease to many advanced endometrial cancers ,that results of studies in ovarian cancers may be applicable to women with endometrial cancer. Several European studies have shown that the use of neoadjuvant chemotherapy prior to debulking surgery in advanced ovarian cancer is associated with slightly longer overall and progression free survival as well as less post operative morbidity .

The objective of this review was to systematically analyse the current literature and to determine whether the evidence supports the use of neoadjuvant chemotherapy / radiotherapy in advanced stage endometrial cancer. It is hoped that the findings of this review may guide future studies in this area.

Materials and methods

Patient Involvement

Patients were involved in the generation of this research question.

Core outcome sets

No core outcome sets are available currently

Search strategy

We have registered the protocol for this review in PROSPERO (CRD42020219461) and subsequently published it in full. In brief, a systematic search of studies was conducted using the Ovid MEDLINE, Ovid Embase, Clinical trials.gov and the International clinical trials registry platform between 1990 and 2021. The full search strategy including terms is listed within the appendix. Reference lists of included studies were hand-searched for additional references. Thie search was designed by two clinical investigators (YLW & AM) with support from information specialists at the University of Manchester.

Eligibility criteria

Two review authors independently screened the titles and abstracts of all studies from the electronic searches (AM and KB). Any discrepancies were resolved by discussion and non-English studies were translated. The full-texts of the remaining articles were obtained and a further round of eligibility screening was performed.

Studies were considered for inclusion if the population included people with newly diagnosed FIGO Stage 3 or Stage 4 endometrial cancer who were undergoing neoadjuvant chemotherapy or radiotherapy prior to surgery and compared to those undergoing chemotherapy or radiotherapy post primary surgery. Included studies also had to report on overall survival, progression free survival and/or extent of cytoreduction, completion of planned treatment modalities or adverse events. Both randomised and non-randomised studies were considered. Abstracts from unpublished studies were not included in our final analysis.

Data analysis and synthesis

Two investigators independently assessed the risk of bias using the ROBIN-I tool for non-randomised studies . Data was extracted by two investigators independently (YLW & IES). Certainty of our results was assessed using the GRADE approach.

We analyzed and visualised the data using R software. We reported the hazard ratio when comparing overall survival and progression free survival outcomes. Odds ratio (OR) with 95% CI were used to measure differences in the rates of cytoreduction and treatment related toxicity outcomes. Where we were unable to extract the HRs and their variances for survival-type data from some of included studies, we contacted the authors for further data and/or we estimated the log HR (intervention relative to comparison) by Log

rank test p-value with number of events (Numazaki et al, Ryan et al studies), or we depicted the log HR and standard error of log HR from the Kaplan-Meier curve for other studies (Chambers et al, Wright et al) . Regarding cytoreduction and treatment-related toxicity, we used the OR as a measure of association. We meta-analyzed the HRs and ORs by using the generic inverse-variance method and Peto method respectively. Random-effects models were performed to pool effect sizes. The restricted maximum likelihood estimator was used to calculate the heterogeneity variance $\tau 2$. We used Knapp-Hartung adjustments to calculate the confidence interval around the pooled effect.

Results

Results of the search

We identified 2763 unique references over the course of two searches (August 2020 and October 2021)(For electronic search strategy see Figure S1). The titles and abstracts of all 2763 references from both searches were screened and 48 full texts were retrieved for further assessment. The process is summarised in Figure 1.

In total, 8 studies met our inclusion criteria. No studies were found that compared neoadjuvant radiotherapy for advanced disease with primary surgery. Therefore, this intervention will not be discussed further in our results.

No studies reported on any ongoing or completed randomised trials answering our question. All of the studies were retrospective cohort studies. The characteristics of the included studies are summarised in Table S1.

Quality of the evidence

We used the GRADE approach to assess the certainty of the evidence in the included studies and found that overall, the certainty of evidence for the reported outcomes was very low. As all studies included in this review are of an observational nature, they are all at significant risk of bias due to the non-randomised nature of treatment group allocation. We have used the ROBINS-I tool to try to understand the degree and nature of biases present in each study and how closely that each of the studies were to estimating the likely outcome of a randomised trial. This is summarised in Figure S2.

Of the eight non-randomised studies that met our criteria, six were considered at serious risk of bias and two were considered at moderate risk of bias using ROBINS-I criteria. The domains where bias was mostly likely to occur were in the classification of the intervention, indirectness and deviation from intended interventions. In several of the studies, allocation to the neoadjuvant chemotherapy and interval debulking arm was determined by evidence of receipt of both treatments. More detail on the results of our risk of bias assessments are presented in Table S2.

Effect of interventions

The effect of the interventions on clinical outcomes is summarised in Table 1.

Primary Outcomes

Overall survival

Six of the eight studies contributed to our meta-analysis. These studies included the outcomes 50 328 patients with advanced stage endomentrial cancer. Bogani et al and Eto et al were excluded due to insufficient data. Bogani et al reported a median overall survival of 16.7 in the neoadjuvant group compared to 18.0 months in primary surgery control group (p=0.349; log-rank test). Eto et al reported a median overall survival of

21 months (95% CI: 17–26) in the primary surgery group and 12 months (95% CI: 9–15) in the primary chemotherapy group

The remaining studies demonstrate no difference in the five-year survival of those undergoing neoadjuvant chemotherapy versus primary surgery (HR for neoadjuvant chemotherapy 1.26 (95% CI 0.95-1.69)) (Figure 2). However, due to the serious risk of bias in these studies, the true effect size is very uncertain and may fall in either direction. There is a high level of heterogeneity between the studies comparing neoadjuvant chemotherapy and primary surgery (I^2 88%, p<0.01). We examined the effect of stage and cointerventions on this finding in our sensitivity analyses and found that this did not change our conclusions (Figure S3 and S4).

Progression free survival

Two studies reported on progression-free survival . These studies included outcomes from 227 patients. Wilkinson-Ryan et al found that there was no significant difference in progression free survival between patients with Stage 4 endometrial cancer who had neoadjuvant chemotherapy followed by surgery and those that had primary surgery followed by adjuvant chemotherapy (10.4 versus 12.0 months p=0.29). Holman et al also found no significant difference in progression free survival between those who had neoadjuvant chemotherapy followed by surgery and those that had primary surgery followed by adjuvant chemotherapy (8.8 versus 12.2 months, p 0.07)

Secondary outcomes

Extent of resection achieved

Three studies looked at the extent of the resection achieved with each intervention. This included data from 478 patients with Stage 4 endometrial cancer. In total, 312 of these patients had surgery as part of their treatment. Bogani and Wilkinson-Ryan et al reported that complete cytoreduction occurred more frequently in those undergoing neoadjuvant chemotherapy (OR 2.05; 95% CI 0.2-21.36 and OR 4.58; 95% CI 1.11-18.91). However, in both these cohorts, patients who had primary chemotherapy but did not have interval debulking were excluded. Eto et al. considered all patients who had upfront chemotherapy. In this study, 52.8% (66 of 125) of those receiving primary chemotherapy did not undergo debulking surgery.

Based on intention to treat, Eto et al found that patients receiving chemotherapy as their initial treatment were less likely to be completely cytoreduced. All three studies reporting on completeness of debulking suggest that the use of neoadjuvant chemotherapy results in a smaller proportion of patients being optimally (OR 0.49; 95% CI 0.45-0.53) or suboptimally cytoreduced (OR 0.24; 95% CI 0.21-0.28).

Completion of all modalities of treatment planned

Across the included studies, a mean of 34.8% (range 28.6 - 63%) of patients receiving primary chemotherapy went on to have interval debulking surgery. Conversely, 96.9% (range 64.6-100%) of those undergoing primary surgery had adjuvant chemotherapy.

Adverse events

Three studies considered the risk of adverse events The only adverse events considered by the authors were surgical adverse events. The included studies incorporated data from 2257 patients, 1862 of whom had surgery as part of their treatment. Meta-analysis of the three studies considering any adverse event suggest that surgical morbidity is similar in patients undergoing interval surgery (OR 0.51, 95% confidence interval 0.08-3.25) (Figure 3). The certainty of this conclusion is, however, very low. Bogani et al also noted that patients receiving neoadjuvant chemotherapy had shorter hospital stays (4 vs 6 days; p=0.011) and may have had slightly shorter operative times (127 [62] vs 177.6 [84.5] minutes; p=0.072). None of the studies measured chemotherapy related toxicities amongst their outcomes.

Quality of life

None of the studies measured quality of life as one of their outcomes.

Discussion

Main Findings

Our review aimed to compare the outcomes of those people with advanced stage endometrial cancer who were treated with neoadjuvant chemotherapy initially rather than upfront surgery. We identified 8 non-randomised studies with a total of 50,433 subjects that could be analysed further.

Six of the included studies suggested that there was no statistically significant survival benefit of primary surgery over neoadjuvant chemotherapy, whilst two suggested a possible benefit of primary surgery. When combining these studies, we saw no significant difference in overall survival. Notably, the two studies where primary surgery was favoured included patients with Stage 3 disease i.e., spread confined to the pelvis but not extending to adjacent viscera. When considering the effect of neoadjuvant chemotherapy in patient with Stage 4 disease only, overall survival was not significantly different.

Of the two studies reporting on progression free survival, one favoured upfront surgery; whilst the other showed no significant difference in time to progression . As seen with overall survival, the study including Stage 3 patients favoured upfront surgery.

Those patients that had neoadjuvant chemotherapy and went on to surgery, were more likely to be completely cytoreduced and have less residual disease than those undergoing primary surgery. However, this did not translate to any difference in overall survival outcomes. This may, in part, be due to the high proportion of patients in the neoadjuvant chemotherapy groups (68.2% (395 of 579)) that did not undergo surgery. There was no difference in the incidence of surgical complications in those that underwent surgery following neoadjuvant chemotherapy compared to those that underwent primary surgery. As complications relating to chemotherapy and quality of life during and after treatment were not reported in these studies, it is not possible to comment on the tolerability of either approach.

Overall completeness and applicability of evidence

In trying to include as many studies as possible that evaluated the comparative effect of neoadjuvant chemotherapy on outcomes, we have included studies that have incorporated patients from different histological subgroups, stages and who received various adjuvant therapies.

Three of the eight studies included only patients with serous endometrial cancer , whilst the remainder included patients with all histological types. We did not see any significant difference in outcomes when we considered these studies separately. Six of the eight studies considered patients with Stage 4 disease ; whilst two considered patients with both Stage 3 and 4 disease . As we have previously discussed, the studies that included Stage 3 patients appear to favour primary surgery. This would support the paradigm of continuing to offer primary surgery to patients with resectable disease confined to the pelvis and considering neoadjuvant chemotherapy in patients with unresectable Stage 4 disease.

Five of the eight studies were based on North American cohorts . Both Tobias et al. and Chambers et al. derived their data from the National Cancer database. There, therefore, was a potential that patients were double counted in the meta-analysis. This overlap is likely to be small however as Tobias et al limited their study to women of 70 or under with no significant comorbidities; whilst Chambers restricted their study to those over 65.

Strengths and potential biases in the review process

Our review builds on the findings of previous reviews looking at the role of neoadjuvant chemotherapy in advanced endometrial cancer. Rather than summarising the evidence for a reduction in disease burden and improved survival compared to no treatment or chemotherapy alone, we have compared the outcomes of those undergoing neoadjuvant chemotherapy with those undergoing primary surgery. We also include a meta-analysis of our data.

To limit the potential for biases due to the review process, we used multiple databases in our literature searches and hand-searched reference lists, conference abstracts and guidelines. We did not limit our searches on language. However, we were not able to obtain individual patient data from authors to perform individual patient data meta-analyses. Therefore, all results presented are a synthesis of published grouped data. We were unable to fully explore the association of factors not previously considered by the authors of the original studies. Furthermore, as all the included studies were retrospective cohort studies and not registered *a priori* , publication bias is a potential problem.

One of the main issues in using retrospective data to compare the outcomes in patients treated with neoadjuvant chemotherapy and primary surgery is in the potential bias in allocation to groups. Typically, the decision to proceed to interval debulking is based on whether there is evidence of response to chemotherapy and that the patient remains surgically fit. This is a decision made after the start of treatment. Those selected to proceed to interval debulking are those that are deemed most likely to be completely debulked and to derive a survival benefit from surgery. Conversely, those that do not receive interval surgery are those expected to have a poorer prognosis. Thus, those studies that considered patients who had primary chemotherapy followed by interval surgery separately from those that had primary chemotherapy alone, will favour better survival in the primary surgery group. Considering all those who received primary chemotherapy as those where there was an intention to treat, is also not without issues. This is because it is not clear if those receiving chemotherapy as their initial treatment were receiving it with the intention of considering debulking after a predetermined number of cycles or if was given with palliative intent. Cointerventions such as adjuvant radiotherapy also introduced potential for bias caused by a deviation in intended interventions. It is also unclear as to whether there was bias due to deviations from intended interventions. Some surgeons may systematically perform less radical surgeries in one group or the other either due to confounding factors such as frailty, age, comorbidities or disease factors such as extent and location of disease.

Interpretation

Several studies and international guidelines have suggested that neoadjuvant chemotherapy may be a useful adjunct in the treatment of those with advanced endometrial cancer. Like Huang et al. , we conclude that women undergoing neoadjuvant chemotherapy are likely to have similar survival outcomes to those having primary debulking surgery. However, we did not find that surgical morbidity was lower in those undergoing interval surgery compared to those who had primary surgery when we pooled the data from three studies. Huang et al based their conclusion on two single centre retrospective studies, whilst our review includes a more recent much larger registry study.

Our review suggests that the proportion of patients who have chemotherapy initially but then do not proceed to interval surgery is a lot larger than those previously reported in several case studies. De Lange et al demonstrated that 4% of patients had a complete response and 72% had a partial response to neoadjuvant chemotherapy in their retrospective single arm study of people with stage 3 and 4 endometrial cancer. In their study, 80% of patients went on to have interval debulking. Similarly, Philp et al report a 76% partial response rate and 3% complete response rate in patients undergoing neoadjuvant chemotherapy . 76% of the cohort went on to have interval surgery. It is unclear whether this is because the criteria for assessing eligibility for surgery may have differed or that their inclusion criteria differed from those in the studies included in our review. A major issue with retrospective studies in this setting is the inability to separate those receiving chemotherapy with curative or palliative intent. A small prospective study of neoadjuvant chemotherapy in

30 patients with surgically demonstrated transperitoneal disease demonstrated similar response rates to those of Philp and de Lange (i.e. complete or partial response in 74% of patients). However, the external validity of these findings is limited by their single centre nature and the small numbers of patients included. Most of the patients included in our review are derived from registry studies. These studies include patients from a broader range of institutions than those represented in de Lange, Philp and Vandenput et al. Differences in the proportion of patients proceeding to interval surgery may arise from differences in the willingness to embark on ultra-radical surgery. Drawing from the experience in ovarian cancer, it appears that the proportion of clinicians that agree with the principle of ultra-radical surgery varies from country to country . Data from the Ovarian Cancer Audit Feasibility Pilot project in England suggests that even within a country there is significant variation in accessibility of surgery and chemotherapy for women with advanced ovarian disease .

Norell et al. suggests that willingness to undertake ultraradical surgery and by implication the extent of cytoreduction is correlated with overall survival in ovarian cancer. This concept has yet to be explored in much depth in advanced stage endometrial cancer. Two recent meta-analyses, one in primary cytoreduction and the other in advanced and recurrent disease suggest a possible correlation. Albright et al. found that patients who achieved complete or optimal debulking had significantly improved progression-free and overall survival (HR 2.6; range 1.7-4.1) . Barlin et al estimated, through their meta-analysis, that for every 10% increase in patients who were completely cytoreduced, there would be an increase in survival of 9.3 months . Data from our review is too limited to comment on this same principle applies to women who have undergone neoadjuvant chemotherapy.

Conclusion

Whilst overall survival in those receiving primary cytoreductive surgery or neoadjuvant chemotherapy is similar, there is sufficient uncertainty that no definitive recommendations can be made. As the number of endometrial cancer patients in whom there is clinical equipoise as to whether a neoadjuvant approach or primary surgery approach should be used first line is low, randomised control trials are unlikely to be feasible. Moreover, the growing acceptance of the neoadjuvant approach potentially compromises the ability to collect data from a balanced group of patients receiving one or other treatment strategy. Prospective enrolment of such patients to an international registry of rare uterine cancers, the treatment modalities and their outcomes is urgently needed to inform decision making going forward.

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Disclosure of interest

None of the authors have any conflicts of interest to declare

Contribution to authorship

YLW, AM and KB devised the study protocol, screened studies for eligibility, assessed risk of bias and drafted the final manuscript. IES devised the study protocol, performed data extraction and analysis and drafted the final manuscript. RJE devised the study protocol and revised the final manuscript.

Details of ethics approval

No ethics approval was required for this study.

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References

Table/Figure caption list

Table 1: Summary of findings

Figure 1: PRISMA flow chart of identified studies

Figure 2: Meta-analyses of studies reporting on overall survival

Figure 3: Meta-analyses of studies reporting on surgical adverse events

Supplementary data

Table S1- Included study characteristics

Table S2- Summary of risk of bias assessments

Figure S1 – Electronic search strategy

Figure S2 – Summary of risk of bias with overall survival

Figure S3 – Forest plot of overall survival by cointervention

Figure S4 - Forest plot of overall survival by FIGO Stage

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