Review
Centralisation of services for gynaecological cancers — A Cochrane systematic review

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Objective. Gynaecological cancers are the second most common cancers among women. It has been suggested that centralised care improves outcomes but consensus is lacking. This systematic review assesses the effectiveness of centralisation of care for patients with gynaecological cancer, in particular, survival advantage.

Methods. A comprehensive search of the Cochrane Gynaecological Cancer Group Trials Register, CENTRAL (The Cochrane Library, Issue 4, 2010), MEDLINE, and EMBASE up to November 2010 was conducted. Registers of clinical trials, abstracts of scientific meetings, and reference lists of included studies were also searched. Randomised controlled trials (RCTs), quasi-RCTs, controlled before-and-after studies, interrupted time series studies, and observational studies were included and multivariable analysis to adjust for baseline case mix were used.

Results. Five retrospective observational studies met the inclusion criteria. Meta-analysis of three studies assessing over 9000 women suggested that institutions with gynaecologic oncologists on site may prolong survival in women with ovarian cancer, compared to community or general hospitals: hazard ratio (HR) of death was 0.90 (95% confidence interval (CI) 0.82 to 0.99). Similarly, another meta-analysis of three studies assessing over 50,000 women, found that teaching centres or regional cancer centres may prolong survival in women with any gynaecological cancer compared to community or general hospitals (HR 0.91; 95% CI 0.84 to 0.99). The largest of these studies included all gynaecological malignancies and assessed 48,981 women, so the findings extend beyond ovarian cancer. One study compared community hospitals with semi-specialised gynaecologists versus general hospitals and reported non-significantly better disease-specific survival in women with ovarian cancer (HR 0.89; 95% CI 0.78 to 1.01). The findings of included studies were highly consistent.

Conclusions. The meta-analysis provides evidence to suggest that women with gynaecological cancer who received treatment in specialised centres had longer survival than those managed elsewhere.

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Introduction

Gynaecological cancers are among the most common cancers in women. Globally, a woman’s risk of developing cancer of the ovaries, uterus or cervix by the age of 65 is 2.2%; cancers of the vulva and vagina are less common. Gynaecological cancers account for 25% of all new cancers diagnosed among women aged up to 65 years in developing countries, compared to 16% in the developed world [1]. The treatment options often vary according to the stage of disease, the histological subtype and co-morbidity of the woman.

The practice in many developed countries is to recommend centralised care for the majority of cancer patients. For example, in the United Kingdom, cancer networks crossing organisational boundaries, incorporating teaching and non-teaching hospitals were established in response to the Calman–Hine report [2]. This model of care assumes that care of most cancers is improved by centralising care within concentrated highly specialised services that include a multi-disciplinary team comprising expert surgeons, radiologists, pathologists, medical and clinical oncologists, palliative care physicians and specialised nursing staff and other health professionals. Previously, in many countries, cancer care at all levels was administered by general surgeons and physicians within non-specialised hospitals.

There is still uncertainty on whether centralised services for cancer actually improve survival and morbidity [3–9]. The cost of developing such a framework of care is significant and the heavy investment required for such cancer service can only be justified if patients are experiencing better clinical outcomes. Furthermore, a centralised approach often involves patients travelling relatively far away from their local community hospitals, and the social impact on patient wellbeing needs to be justified by evidence of improved care and better outcomes.

The focus of this review was to assess whether clinical outcomes differ between centralised specialised centres and local non-specialised units.

Materials and methods

Inclusion criteria for review

Randomised controlled trials (RCTs), quasi-RCTs, controlled before-and-after studies, interrupted time series studies, and observational studies were included. Case–control studies that did not have concurrent comparison groups, not population-based and case series with fewer than 200 patients were excluded. To minimise selection bias, for non-randomised studies, we only included studies that used statistical adjustment for baseline case mix using multivariate analysis. The participants were female adult patients (at least 18 years of age) with a gynaecological malignancy: endometrial, cervical or vulval. Patients being managed in a gynaecological cancer tertiary/regional referral centre were compared to management of patients elsewhere. We excluded studies if they were only restricted to the effect of the surgeon expertise or volume. The primary outcome was overall survival: survival until death from all causes. Secondary outcomes were progression-free survival and adverse event according to ‘Common terminology criteria for adverse events’ version 3 (CTCAE 2006: www.ctep.cancer.gov/forms/CTCAEv3.).

Search method

A comprehensive electronic search of the Cochrane Gynaecological Cancer Group Trials Register, CENTRAL (The Cochrane Library, Issue 4, 2010), MEDLINE, and EMBASE up to November 2010 was conducted. Registers of clinical trials, abstracts of scientific meetings, and reference lists of included studies were also searched. The MEDLINE, EMBASE and CENTRAL search strategies were based on terms related to the review topic (e.g. Centralised Hospital Services, Teaching hospitals, University Hospitals, Cancer care Facilities, Oncology service, gynaecologic oncologist, ovarian neoplasm, endometrial neoplasms, Cervical neoplasms). We also identified all relevant articles found on PubMed and using the ‘related articles’. A search was also performed on resources such as Metaregister, Physicians Data Query, www.controlled-trials.com/rct, www.clinicaltrials.gov and www.cancer.gov.clinicaltrials but no relevant studies/trials were identified. Conference proceedings were also searched through ZETOC (www.zetoc.mimas.ac.uk) and WorldCat Dissertations. We searched papers in all languages and carried out translations when necessary.

Data extraction

All titles and abstracts retrieved by electronic searching were downloaded to a reference management database, Endnote. All duplicates were removed and the remaining references were independently examined by four review authors (YLW, AB, TE, MK). Titles and abstracts from other sources were added to Endnote. Studies that clearly did not meet the inclusion criteria were excluded and copies of full text articles were obtained for potentially relevant references. Three review authors (YLW, AB, MK) independently assessed the eligibility of the retrieved papers and resolved disagreements by discussion.

Data analysis

For the included studies, the following data were extracted: author, year of publication and journal citation, country, setting, inclusion and exclusion criteria, study design and methodology, study population, intervention details, definition of gynaecological oncology surgeons, definition of specialised centres, comparison of surgeon and setting, risk of bias, duration of follow up and outcomes. For time-to-event (overall and progression-free survival) data, we extracted the log of the hazard ratio [log(HR)] and its standard error (SE) from study reports. This HR compared the risk of death among women treated in specialised centres with the risk of death among women treated in non-specialised centres; hence a HR less than one indicated better survival in specialised centres. The risk of bias assessment was done using the Cochrane Collaboration’s tool [10]. For measurement of treatment effect, HR was used. For clinically similar studies, the adjusted results were pooled in a meta-analysis and 95% confidence interval (CI) was reported for the pooled estimate. Where possible, subgroup analyses and separate analyses were undertaken, grouping the studies by tumour sites and the different types of intervention.

Results

A total of 8689 unique references were identified from the search strategy. Two review authors (YLW and AB, MK and TE) independently assessed the titles and abstracts and excluded 8634 irrelevant publications at this stage. The remaining 56 potentially eligible articles in full text were retrieved and 51 reports were further excluded as they did not fulfil the eligibility criteria, leaving a total of five studies that qualified for the review.
Five retrospective observational studies [3,11–14] adjusted for case mix using a multivariate analysis met the inclusion criteria. The five studies enrolled a total of 62,987 women with gynaecological cancer; data were available for 62,191 of these. The women included in this review were diagnosed from 1990 up to 2003, with most being treated from the late 1990s onwards.

Three studies [11,12,14] reported exclusively on patients with ovarian cancer. One study [3] included women with any of five gynaecological cancers (cervical, ovarian, endometrial, uterine sarcoma, and vulval); it reported data for all cancers combined, and by cancer site. One study [13] reported on various cancer sites including both ovarian cancer and non-gynaecological malignancies; it reported data separately by cancer site. The number of patients included varied from 250 patients [12] to 48,981 [3].

The mean duration of follow-up was 913 days (range 733 to 1101 days) [12] and 3 years (range = 0 to 10 years) [14]. The duration of follow-up was not reported in the other three studies [3,11,13].

**Effects of intervention**

1. Institutions with gynaecologic oncologists on site (specialised centres) vs. community or general hospital
- **Meta-analysis** of three studies [11,13,14], adjusting for 10-year age band and TNM tumour stage at diagnosis, assessing 9041 participants, found that women with ovarian cancer who received treatment from a specialised cancer centre with gynaecologic oncologists on site had significantly better survival than women who received treatment from community or general hospitals (HR 0.88; 95% CI 0.80 to 0.97; I² = 0%). This statistically significant pooled result arose although none of the three studies individually found a significant difference in overall survival between the two different hospital settings. The one study [13], which was adjusted for 10-year age band but not for TNM tumour stage at diagnosis found that women who received treatment at a hospital with a radiotherapy and oncology department had significantly better survival than those who attended a district general hospital. The results of using this alternative model in the meta-analysis were similar to those of the previous meta-analysis (HR 0.88; 95% CI 0.80 to 0.97; I² = 0%). See Fig. 1.

2. Teaching or regional cancer centre versus community or general hospital
- The meta-analysis of three studies [3,11,12], assessing 51,283 participants, found that women treated in a teaching or regional cancer centre had significantly better survival than women who received treatment from community or general hospitals (HR 0.91; 95% CI 0.95 to 0.99). The percentage of the variability in effect estimates that was due to heterogeneity rather than chance was not important (I² = 0%); two of the studies included only women with ovarian cancer, whereas the study by Brookfield et al.[3] study included women with any form of gynaecological cancer. This statistically significant pooled result arose even though two of the three studies [3,12] individually found no significant difference in overall survival between the two different hospital settings, and the third [11] found a difference of borderline significance (P = 0.05, meta-analysis). In one study, which assessed 233 participants, no statistically significant difference in progression-free survival was demonstrated between women who attended a teaching or regional cancer centre and those who received treatment from a community or general hospital (HR 0.91; 95% CI 0.54 to 1.55). See Fig. 2.

Overall, the evidence favours centres with specialised care rather than community or general hospitals, although the quality of the evidence is low because of the high risk of bias of the included retrospective observational studies. Furthermore, although the pooled estimate indicates that centralisation improves overall survival by 10%, this could be as low as 1% or as high as 18%.

**Discussion**

The five included studies assessed a total of 62,191 women, 28,341 of whom had ovarian cancer; one of these studies [3] also assessed 33,850 women with other gynaecological cancers. The four [3,11,13,14] of the five included studies were large and one [3] was very large, including over 40,000 women. The inclusion criteria were strict and we included only studies that adjusted for case-mix. All studies reported an adjusted HR, which is the best statistic to summarise the difference in survival between two treatment groups over the duration of a study [15]. The findings of our two meta-analyses on overall survival were highly consistent, although one analysis assessed institutions with gynaecological oncologists on site and the other assessed teaching or regional cancer centres. Furthermore, although none of the individual studies within the meta-analyses found a statistically significant benefit of centralisation, their results were consistent and their pooled results were statistically significant.
significant, showing better survival in women who received centralised care. The studies that reported disease-specific survival [14] and progression-free survival [12] likewise reported better outcomes in women receiving centralised care and again, although their findings were not statistically significant, they were quantitatively consistent with the findings of the meta-analyses.

One of the main limitations of the review was that all the included studies were performed in developed countries (Canada, Netherlands, UK, and US). As the organisation of care for gynaecological cancer may vary widely between countries, the findings of the review will most likely have limited applicability in developing countries. A further limitation was that only one study [2] included women with gynaecological cancers other than ovarian cancer. Although this was a large study which assessed women with other gynaecological cancers, evidence from further studies, ideally in other countries, is needed in order to confirm the benefits of centralisation for such women. Finally, the review was unable to assess adverse events as these were not reported by any of the included studies.

While the evidence suggested that women treated in specialised centres had better survival than women treated elsewhere, the means whereby this benefit was achieved remain unclear and, indeed, it was beyond the scope of the review to investigate this issue. Although some authors have argued that centralisation of cancer care encourages a multidisciplinary team approach which has benefits for overall survival [16,17], the evidence for this remains equivocal [18]. No attempt to estimate the cost-effectiveness of centralisation of gynaecological cancer which would obviously be important to policy-makers was made. We did not attempt to compare quality of life of patients in centralised and non-centralised care, and none of the included studies reported this outcome. The lack of evidence to inform anything more than the survival outcomes of patients makes it difficult to assess the overall effectiveness of centralisation.

The main methodological limitation of the review is that all the included studies were at high risk of bias due to their retrospective, observational nature: they satisfied, at most, four of the criteria used to assess risk of bias. We cannot be sure that statistical adjustment for important prognostic factors fully controlled for systematic differences between women who received centralised and non-centralised care.

Two recent systematic reviews have considered the effect of hospital and physician characteristics on outcomes for ovarian cancer [19,20]; both reviews differed in scope from our review and neither review adequately assessed the risk of bias in included studies. [20] reviewed the effect of gynaecological oncologists and specialist centres on a variety of outcomes, searching databases from 1991 to 2006 and including nineteen studies. Six of these studies compared survival in specialised and non-specialised hospitals; two of these studies were included in our review [11,13]; the remaining four small studies did not meet our inclusion criteria. The other three studies included in our review [3,12,14] were published simultaneously or subsequent to the searches performed by [20]. Despite the differences in included studies, Vernooij et al. [20] concluded that long-term survival was better for women treated in specialised hospitals, consistent with our findings. Furthermore, the authors also concluded that survival was better if surgery was performed by gynaecological oncologists in women with Stage III or greater disease, though this advantage appeared to be lost when all stages were included [20]. The probable improvements in staging and debulking observed in specialised units, with no increase in major complication rates, are likely to be instrumental in improving the overall survival rate. A review specifically aimed at correlating institution and physician characteristics with ovarian cancer survival, surgical outcomes, completeness of staging, and compliance to chemotherapy regimens [19]. Although the authors found 17 studies of the impact of hospital characteristics on survival from ovarian cancer, it is difficult to compare their conclusions with ours as the hospital characteristics considered were extremely varied and no meta-analyses were performed.

Many studies were excluded from this review because outcomes in specialised and non-specialised centres were not compared. Nevertheless these studies provide an explanation as for the better survival achieved in specialised centres. For example, several studies have found that patients with ovarian cancer operated on by a gynaecological oncologist are more appropriately staged [21,22], receive better cytoreduction [21,23], are more likely to receive chemotherapy [24] and have better survival outcomes [22,25–27]. Furthermore, some large population studies support the notion that university hospitals achieve better outcomes than hospitals without all the necessary support, such as radiotherapy services [28].

There are population studies demonstrating a survival advantage for women with ovarian, endometrial, and cervical cancer managed in high-volume centres [28–30] while some others do not [31,32]. For example, in a study that assessed the costs and effects of centralised care and regular care for women with an ovarian malignancy in the Netherlands, it was concluded that not all women suspected of having ovarian cancer should be operated on by a gynaecological oncologist [33].

A consistent finding in many studies is the observation that patients managed at specialised/university cancer centres have different characteristics from those managed at district or non-teaching hospitals. For example, patients at specialised centres tend to have a different age distribution [28,34], to have more advanced disease [22,28] and to be demographically different [34,22]. While statistical adjustments are generally made to control for these differences, other unrecorded patient characteristics may influence treatment and prognosis.
Survival from the different gynaecological cancers varies considerably. Survival from uterine cancer is among the highest for any cancer in women, while that from ovarian cancer is the lowest of all gynaecological cancers [35,36]. This suggests that in developed countries, it may be most practical to prioritise centralisation of care for advanced ovarian cancer in the first instance.

Many countries do not have the resources to provide centralised specialised multidisciplinary management for all gynaecological cancers. Furthermore, the incidence and burden of gynaecological cancer vary between different countries. Hence the services whose centralisation would benefit most patients are likely to differ between countries. For example, in the developing world, radiotherapy services for advanced cervical cancer are likely of higher priority than ultra-radical surgery for ovarian cancer, followed by chemotherapy.

Conclusion

This review provides evidence to suggest that women with gynaecological cancer who received treatment from specialised centres or hospitals with specialist resources had longer survival than those managed elsewhere. The evidence was stronger for ovarian cancer than for other gynaecological cancers. Additionally, studies of the impact of centralisation of care on quality of life of patients are required, as evidence in this area is lacking. Most of the available evidence addresses ovarian cancer in developed countries; future studies should be extended to other gynaecological cancers within different healthcare systems. Health economics studies are needed in order to prioritise those aspects of management whose centralisation would deliver most benefit to patients in different healthcare systems.

Conflict of interest statement

There is no known conflict of interests.

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References