Management of gynaecological cancers

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This paper is based on *Effective Health Care* 5(3), June 1999, which deals with cancers of the ovary, endometrium, and cervix.¹ The bulletin summarises systematic reviews of research evidence used to inform national cancer guidance documents, published as *Improving Outcomes in Gynaecological Cancers*.^{2,3} These publications are part of a series on improving services for the management of the major cancers, all of which may be obtained by calling the UK NHS response line on 0541 555 455.

Introduction

Cancer of the ovary is the most common of this group, with an incidence rate of 20 per 100 000 women; it also has the poorest prognosis. One third of women survive for five years, compared with over two thirds of those diagnosed with endometrial or cervical cancer. Ovarian and endometrial cancer are more common in older women, whereas the incidence of cervical cancer varies little with age among women over 30 (fig 1).

Surgical specialisation, level of patient throughput, multidisciplinary teamwork, and adherence to treatment protocols may all affect survival rates. These variables are linked and their effects often cannot be evaluated independently.

Specialisation

Observational studies show that management of ovarian cancer by specialist surgeons is associated with better survival. The results (adjusted for prognostic factors) of an ongoing study in Scotland reveal that women with stage

III ovarian cancer survived longest after surgery by gynaecological oncologists (surgeons who specialise in gynaecological cancer).^{5,6} They achieved a 25% lower death rate at three years than gynaecologists. Death rates were 33% higher after surgery by general surgeons, compared with gynaecologists.⁶

Other studies of poorer design also link survival with surgical specialisation. In the West Midlands, general surgeons achieved significantly poorer survival rates than gynaecologists; multivariate analysis gave an adjusted hazard ratio (HR) of 1.34 (95% confidence intervals (CI) 1.05 to 1.71; $p=0.02$).⁷ Similar results have been reported from the US^{8,9} and Australia.¹⁰ Process measures such as adequacy of staging and tumour removal (debulking) also suggest that less specialised surgeons provide inferior treatment.^{5,7,8,10,11}

Patient throughput

It is unlikely that surgeons who deal with very low patient numbers would be able to develop or maintain the necessary skills and expertise for this work. There is some evidence of better results for patients with cervical cancer when larger numbers are treated: survival rates are higher in non-teaching hospitals with larger workloads than in those where workloads are low.¹² A US study of 30 day mortality after pelvic exenteration, a difficult surgical procedure most often undertaken for recurrent cervical cancer, found that higher hospital volumes were associated with significantly lower mortality.¹³ This effect was independent of case mix.

A casenote review of 860 women treated for ovarian cancer in north west England found no such effect,¹⁴ but the criterion for high volume (more than six cases in two years) may have been too low to detect differences. Audit data show that some hospitals manage just one case of ovarian cancer each year.¹⁵

Multidisciplinary teamwork

The Scottish study found that follow up of women with ovarian cancer at a multidisciplinary clinic improved five year survival by 27% (after adjustment for use of chemotherapy).⁵ Audits in England show that management in teaching centres, where specialist treatment, higher patient throughput, and multidisciplinary teamwork are all more probable, is associated with better survival in ovarian cancer,^{15,16} cervical cancer,¹² and endometrial cancer.¹⁷

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Figure 1 Rates of newly diagnosed cases of gynaecological cancers per 100 000 women, England and Wales, 1992.⁴

Adherence to protocols

Women with gynaecological cancer who are treated in accordance with locally agreed protocols are likely to survive for longer.^{12 15 17–19}

Support for patients

REACTIONS TO GYNAECOLOGICAL CANCER

Diagnosis and treatment of gynaecological cancer is likely to leave women unable to conceive or bear children and some may be unable to experience sexual enjoyment. Two years after primary treatment, many women continue to suffer from depression, anxiety about cancer recurrence, and persistent tiredness.^{20 21}

The prevalence of sexual problems appears to vary with the treatment received. A UK study of women who had undergone radical pelvic surgery for vulval or cervical cancer found that about half reported a deterioration in their sexual relationships and two thirds had sexual difficulties.²² Other studies of women treated for cervical cancer suggest that the majority find sex less enjoyable after radiotherapy, but that non-radical surgery causes few problems.^{20–24}

COMMUNICATION AND PROVISION OF INFORMATION

Many women who have been treated for gynaecological cancer want more information on their disease and the potential after effects of treatment.^{20 25 26} The level of knowledge among women with gynaecological cancer has been found to be very poor.^{27 28}

Information for patients with cancer has a range of beneficial effects including anxiety reduction, enhanced satisfaction and adherence to treatment, and improved self care.^{29–31} Studies involving women with gynaecological cancer show that providing information can improve mood and allow women to participate in treatment decisions, and that they find the information useful.^{32–35}

COUNSELLING, PSYCHOSOCIAL, AND EDUCATIONAL INTERVENTIONS

Many women who have undergone treatment for gynaecological cancer would welcome more emotional support and counselling.^{20 26} Most would like a relative or friend present when bad news is broken.²⁶

Two controlled studies found that counselling can reduce emotional distress.^{34 36} A study of 97 women with newly diagnosed gynaecological cancer, which compared individual counselling with assessment only, found that counselled patients reported less anxiety and depression, were more likely to resume sexual activity and participate in leisure activities, and had better relationships with carers.³⁶ A randomised controlled trial involving 80 women found that themed counselling based on information about cancer and positive health strategies, given individually or in groups, was superior to “standard group counselling”.³⁴

Ovarian cancer

SCREENING AND HIGH RISK WOMEN

A systematic review of screening found that ovarian cancer can be detected in asymptomatic women, but there is as yet no evidence that this enhances survival.³⁷

Results from a recent pilot randomised controlled trial with seven years follow up and 22 000 women, suggest that screening could reduce mortality from ovarian cancer.³⁸ There was no significant difference in ovarian cancer death rates between the entire control and screened groups (relative risk 2.0, 95% CI 0.78 to 5.13), but the power of the study was not sufficient to detect such a difference.

Screening may be more appropriate for women at higher risk but there is no clear evidence to support it.³⁷ Women with one affected first degree relative face two to three times the population risk.^{37 39} When more than one relative is affected, the risk is much higher (relative risk of 11); about 14% of such women are likely to develop ovarian cancer. The main genetic marker is BRCA1 mutation, found in 5% (95% CI 3% to 8%) of women with ovarian cancers diagnosed before the age of 70.⁴⁰

ASSESSMENT OF WOMEN WITH SYMPTOMS

Ovarian cancer often causes vague symptoms such as bloating, persistent abdominal discomfort, irregular bowel habit, or backache with weight loss. The non-specific nature of these symptoms can delay diagnosis by up to a year.⁴¹

When women present with pelvic masses, it is possible to distinguish most benign cysts from malignant tumours by combining ultrasound findings with the level of the cancer marker, CA125, in blood serum. Taking the woman's age into account increases the power of the discrimination. Three studies which used these variables to determine a risk of malignancy index found that this could offer around 80–90% sensitivity and specificity.^{42–44}

The sensitivity and specificity of CA125 for the detection of ovarian cancer in women with pelvic masses (using a serum level cutoff of 35 u/ml) have been reported to be 72–100% and 81–98%, respectively; raising the cut off level to 65 u/ml reduces sensitivity slightly to 72–83%, but improves specificity to 93–99%.^{42–61} Studies of ultrasound alone report 89–100% sensitivity and 42–75% specificity.^{46–48}

SURGERY

Surgery is currently the first intervention used to treat ovarian cancer, but in most women the disease is too far advanced by the time of diagnosis for complete removal of the tumour to be possible.

Audit results show marked variations among hospitals.¹⁵ While 66% of women who underwent surgery in teaching hospitals in south east England were managed according to locally agreed guidelines, this was true of only 28% of those who had surgery in hospitals without oncology support. Women not managed according to guidelines died significantly sooner (HR 1.48, 95% CI 1.34 to 4.78).

A meta-analysis of 58 studies suggests that maximal surgical reduction of tumour bulk may increase median survival time slightly, but this analysis was confounded by surgeon and chemotherapy variables.⁶² Two meta-analyses of chemotherapy trials reported that residual

Table 1 Chemotherapeutic agents commonly used to treat ovarian cancer

Type of drug	Chemotherapeutic agents	Comment
Non-platinum	Cyclophosphamide, doxorubicin (adriamycin)	Older cytotoxic drugs, usually given in combination
Platinum	Cisplatin, carboplatin	May be given as single agents or in combination with others
Taxane	Paclitaxel (taxol)	New generation agent

tumour size was a major determinant of survival.^{63 64}

Two randomised controlled trials assessed the effectiveness of interval debulking surgery, where remaining tumour is removed in a second operation after chemotherapy. One trial, which included 319 women, showed a 33% reduction in risk of death (95% CI 10% to 50%) and six months longer survival after interval debulking.⁶⁵ The other trial was too small show statistically significant differences.⁶⁶

CHEMOTHERAPY

Table 1 shows chemotherapeutic agents commonly used to treat ovarian cancer.

Platinum based chemotherapy improves survival among women with ovarian cancer more advanced than stage I. Meta-analyses of individual data for 5667 patients in 37 randomised controlled trials of chemotherapy regimens (not including taxanes) suggest that, although differences between them are not great, the inclusion of platinum is consistently beneficial.⁶⁷ The addition of platinum to single agents or combinations improved survival rates at five years by 5%, from 25% to 30%: HR 0.88 (95% CI 0.79 to 0.98). Cisplatin and carbopla-

tin had similar effects on survival: HR 1.02 (95% CI 0.93 to 1.12).

ICON2, a large trial (n=1526), found no difference in effects on survival between CAP (cyclophosphamide, doxorubicin, cisplatin) and carboplatin. Mean survival time with either treatment was 33 months (HR 1.0, 95% CI 0.86 to 1.16; p=0.98), but carboplatin was considerably less toxic than CAP.⁶⁸

Three US randomised controlled trials have assessed the effectiveness of paclitaxel, given in combination with cisplatin (table 2). Two trials (total n=1090) compared paclitaxel/cisplatin with cyclophosphamide/cisplatin.⁶⁹⁻⁷¹ These reported median survival times of 38 and 35 months in the groups given paclitaxel, compared with 24 and 25 months in control groups, but paclitaxel/cisplatin caused more severe adverse effects.

The third randomised controlled trial compared paclitaxel/cisplatin with single agent cisplatin and found no significant survival difference between the treatment groups. However, many women randomised to cisplatin received paclitaxel, which makes the results difficult to interpret.⁷²

A fourth large trial, ICON3 (n=2074), compared paclitaxel/carboplatin with carboplatin alone or with CAP. Preliminary data were presented in May 1999 at the American Society of Clinical Oncology conference, but these are not sufficiently reliable to guide policy or practice.

Three randomised controlled trials compared paclitaxel/cisplatin with paclitaxel/carboplatin.⁷³⁻⁷⁵ None found any difference in efficacy, but quality of life was better with carboplatin.

Table 2 Randomised controlled trials evaluating paclitaxel for primary treatment of ovarian cancer (studies in alphabetical order)

Trial	Comparison (doses in mg m ²)	Patients	Results (paclitaxel/cisplatin versus other treatment)	Comments
GOG 111 ⁶⁹	Paclitaxel (135, 24 hour infusion) and cisplatin (75) v cyclophosphamide (750) and cisplatin (75)	n=410; FIGO stage III or IV; suboptimal residual disease	Overall response: 73% v 60%. Median progression free survival: 18 months (95% CI 16 to 21) v 13 months (95% CI 11 to 15); relative risk: 0.7 (95% CI 0.5 to 0.8, p<0.001). Median survival: 38 months (95% CI 32 to 44) v 24 months (95% CI 21 to 30)	
GOG 114 (unpublished)	Paclitaxel (135, 24 hour infusion) and cisplatin (75) v cyclophosphamide (750) and cisplatin (75)	n=589; optimal debulking of residual disease	Results not yet available	
GOG 132 ⁷²	Paclitaxel (135, 24 hour infusion) and cisplatin (75) v cisplatin (100)	n=424; FIGO stage III or IV with suboptimal residual disease	Overall response: 72% v 74%. Median progression free survival: 14.1 months v 16.4 months. Median survival: 26.6 months v 30.2 months	Many women randomised to platinum received paclitaxel so study does not discriminate clearly between groups
ICON3 (International Collaborative Ovarian Neoplasm Study) Unpublished; preliminary data presented at ASCO, May 1999	Paclitaxel (175, 3 hour infusion) and carboplatin (6AUC) v cyclophosphamide (500), doxorubicin (50), cisplatin (50), or carboplatin 6AUC	n=2074; 20% FIGO stage I/II, 64% III, 16% IV; 46% had residual disease bulk >2 cm (suboptimal)	Median follow up 18 months. No differences among groups in progression free or overall survival. Possible trend towards better outcome with paclitaxel in patients with residual disease. Fewest adverse effects with carboplatin alone	Data not sufficiently mature to assess differences between subgroups, or to draw definite conclusions about medium term or long term effectiveness
OV10 (Intergroup: EORTC, NCIC, NOCOVA) ^{70 71}	Paclitaxel (175, 3 hour infusion) and cisplatin (75) v cyclophosphamide (750) and cisplatin (75)	n=680; FIGO stage IIb-c, III or IV with optimal or suboptimal residual disease	Overall response: 77% v 66%. Median progression free survival: 16.6 months v 12 months, p=0.0001. Median overall survival: 35 months v 25 months, p=0.0001	

Current evidence therefore suggests that chemotherapy for advanced ovarian cancer should be paclitaxel/carboplatin. In patients who may be unable to tolerate this combination, carboplatin alone can be effective.

Recurrent disease

Women in trials of second line chemotherapy for recurrent disease survive for an average of 9.5 months.⁷⁶ The response rate is better (25–56%) in women who have over six months free from disease progression after first line chemotherapy.^{77–78} In total, 21–48% of patients whose disease progresses despite platinum based chemotherapy may respond to paclitaxel.^{79–82} Among women who respond, second line chemotherapy can prolong survival and has a palliative effect.

Endometrial cancer

DIAGNOSIS

Endometrial cancer rarely develops before the menopause, and because it causes abnormal vaginal bleeding, it can usually be diagnosed at an early stage. Hysteroscopy, which allows visual inspection of the uterine lining, is often used for diagnosis. Although hysteroscopy can detect abnormalities in 95–100% of cases, it does not appear to be a reliable way of identifying cancer.^{83–84}

A meta-analysis of 35 studies found that transvaginal ultrasound is an accurate way of excluding endometrial cancer.⁸⁵ The probability of endometrial cancer among women with post-menopausal bleeding who do not use hormone replacement therapy is 10%; but with a normal transvaginal ultrasound scan, the probability of cancer in these women falls to 1%. Using ultrasound allows the majority of women to be quickly reassured, with biopsy reserved for those whose ultrasound result is abnormal.

A range of methods and devices are used for outpatient endometrial biopsy, but most have not been directly compared in randomised controlled trials. In one study, the Pipelle detected 60 of 71 endometrial cancers.⁸⁶ The Pipelle offers equivalent diagnostic accuracy to the Vabra aspirator^{87–88} and the Novak,^{89–90} with less discomfort. The Vabra can sample a greater area but this does not appear to offer any clinical benefit.⁹¹

Several studies have compared outpatient methods with dilatation and curettage (D&C), which is normally done under general anaesthetic. The Novak and Vabra aspirators and the Karman curette are as accurate for diagnosis as D&C.^{92–93} The Karman curette was used successfully in 80% of women with postmenopausal bleeding in a dedicated outpatient clinic; no cases of endometrial cancer were missed. Reported pain was mild for 72% of women, moderate for 24%, and severe for 4%.⁹⁴

PRE-TREATMENT STAGING

The optimum treatment for endometrial cancer depends on the stage and grade of the disease, and the risk of tumour in lymph nodes. When the cancer is confined to the endometrium or affects less than a third of the

thickness of the wall of the uterus (myometrium), the lymph nodes are likely to be clear, and surgical removal of the tumour by hysterectomy is relatively straightforward. Deeper penetration is associated with greater risk of nodal disease.⁹⁵

An audit examining the relation between clinical management and outcome in south east England found that 30% of women had all staging investigations and 32% were treated according to locally agreed guidelines.¹⁷ Women whose surgery was not in accordance with these guidelines had significantly shorter survival times ($p=0.0086$).

In women with cancer confirmed by biopsy, transvaginal ultrasound can be used to evaluate myometrial invasion. Magnetic resonance imaging (MRI) may, however, be more accurate; reported accuracy figures are around 70–80% and 70–95% for ultrasound and MRI, respectively.^{96–108} MRI also allows examination of pelvic lymph nodes. Imaging using computed tomography appears to be less accurate than ultrasound or MRI.^{106–109}

SURGERY

Around 90% of women with endometrial cancer are treated by primary surgery (total abdominal hysterectomy or more extensive operations), and five year survival rates are over 70%.^{110–111} It is not clear whether lymph node sampling improves survival¹¹²; this issue is being addressed in a Medical Research Council trial (ASTEC), but results will not be available for some years.¹¹³

RADIOTHERAPY

Radiotherapy can prolong survival in women with advanced or recurrent disease, or when surgery is not appropriate.¹¹⁴ Surgery is regarded as preferable when the disease is not too far advanced, but there has been no direct comparison between modalities.

Adjuvant radiotherapy (given after surgery) is widely used. There is no reliable evidence that it influences survival, but two randomised controlled trials found that it reduced the rate of pelvic recurrence.^{115–116} The combination of radiotherapy and surgery can have lasting adverse effects, including lymphoedema.

CHEMOTHERAPY

No reliable evidence exists that either chemotherapy or hormone treatment is effective for endometrial cancer. A meta-analysis of six randomised controlled trials ($n=3339$) which compared progestogens with no hormone treatment showed no significant reduction in death rates (odds ratios 1.17, 95% CI 0.94 to 1.45, for all deaths and 1.05, 95% CI 0.79 to 1.41 for endometrial cancer deaths).¹¹⁷ A more recent randomised controlled trial ($n=1012$) confirmed this result.¹¹⁸

Cervical cancer

STAGING

The effectiveness of different types of imaging for revealing the stage and extent of cervical cancer has been examined in a systematic review.¹¹⁹ Most of the studies included are of

early cancers, where careful pre-treatment evaluation is important to inform the choice between surgery and radiotherapy. Although meta-analysis showed no significant difference between computed tomography and MRI in accuracy of lymph node evaluation,¹¹⁹ many studies suggest that MRI is more accurate for assessing early disease, whereas computed tomography is better for late disease. Transrectal ultrasound can evaluate tumour extent accurately but is not widely used.¹²⁰ Transabdominal pelvic ultrasound is effective for assessing bladder invasion.¹²¹

Pre-operative imaging can provide information about stage which is important for optimum management, and to avoid the combination of surgery and radiotherapy, which causes more morbidity than either treatment individually.¹²² However, it appears that it is often not used; 94% of women referred for post-operative radiotherapy in Manchester had had no pre-operative imaging.¹²³

Audits reveal that inadequate staging of cervical cancer is common.^{12 124} In south east England, the likelihood of staging according to locally agreed guidelines was 21% in teaching hospitals, 11.5% in non-teaching hospitals with oncology support, and 7% in other hospitals ($p < 0.0001$).¹²

SURGERY

Cone biopsy may be sufficient to treat very early cervical cancer. If the disease is more extensive, radical hysterectomy, which includes lymph node excision (lymphadenectomy), may be necessary. The probability of lymph node invasion is related to the depth of cancer in the cervix.^{125–136} When the tumour is less than 3 mm deep (stage Ia1), the risk of positive nodes is below 1%, rising to 4% with a depth of 3–5 mm (stage Ia2). Sixteen per cent of women with stage Ib tumours have positive pelvic nodes.

A retrospective survey of 191 women treated for stage Ib cervical cancer in Scotland reported 86.3% five year survival after radical hysterectomy and 68.1% after non-radical hysterectomy, which does not normally include lymph node dissection ($p = 0.008$). This difference persisted after adjustment for age, node status, and tumour pathology.¹³⁷ An audit from south east England also linked inadequate surgery for cervical cancer with poorer survival.¹² Women with stage Ib tumours were particularly likely to receive treatment which was not in accordance with locally agreed guidelines (46% appropriately treated, compared with 66–74% of women with other stage cervical cancers; $p < 0.0001$). Women treated less aggressively than guidelines recommended were less likely to survive (HR 3.98, 95% CI 2.30 to 6.89), as were those whose lymph nodes were not examined (HR 6.47, 95% CI 1.45 to 28.77). Radical hysterectomy was more frequent in teaching hospitals.

An audit from the South West Health Authority region of England found that 30 of 69 women who had non-radical surgery for cervical cancer had disease more advanced than stage Ia.¹²⁴ Surgery for these women was judged inadequate and they underwent repeat

surgery or radiotherapy. When radical surgery was undertaken, only 30% of procedures included adequate lymph node sampling (10 or more nodes sampled).

SURGERY VERSUS RADIOTHERAPY

Women with early disease can be treated with either surgery or radiotherapy. These treatment modalities were compared in a randomised controlled trial which included 343 women with stage Ib or IIa cervical cancer.¹²² The five year survival rate was 83% in both groups. Surgery and adjuvant radiotherapy led to more complications than either treatment alone. Two earlier studies also found equivalent survival in stage Ib-IIb cancer with surgery and radiotherapy.^{138 139}

Although survival rates with surgery or radiotherapy are similar, the pattern of adverse effects differs. Whereas injury from surgery is likely to resolve, radiotherapy can cause diarrhoea, cystitis, and tiredness during or soon after treatment, and some women suffer damage to bowel or bladder, or both, which can develop months or years after treatment. Radiotherapy can also damage the vagina and ovaries, reducing sexual enjoyment and precipitating the menopause.

Primary radiotherapy

Cervical cancer of stage IIb to IV, where the tumour is too extensive for complete surgical excision, is normally treated with a combination of external beam radiotherapy and brachytherapy delivered inside the uterus.¹¹⁴

The effectiveness of brachytherapy does not appear to be related to the rate at which it is given, although dose rate may affect the incidence of adverse effects. Two poorly designed trials which compared low and high dose rates give conflicting evidence on morbidity.^{140 141} A randomised controlled trial comparing two relatively low dose rates reported significantly higher morbidity with the higher rate.^{142 143}

Adjuvant radiotherapy

Adjuvant radiotherapy is widely prescribed after radical surgery to reduce the risk of recurrence in women with positive nodes. Indirect evidence from non-randomised studies suggests it can improve pelvic control, but there is no firm evidence of increased long term survival.^{144 145}

Concurrent chemoradiotherapy

Five randomised controlled trials (sizes ranging from 241 to 575 women) have compared radiotherapy alone with platinum based chemotherapy given during radiotherapy for women with high risk cervical cancer (table 3).^{146–150} The results of these studies are remarkably consistent: all show that concurrent chemoradiotherapy using cisplatin can significantly improve survival despite more severe adverse effects. Relative survival rates at three years for women with stage Ib to IVa cervical cancer and adverse prognostic factors (bulky or locally advanced disease, involved lymph nodes or parametrial invasion) increased by around

50% with the addition of cisplatin to radiotherapy. The improvements in absolute survival rates ranged from 10% to 15%.

Neo-adjuvant chemotherapy

Studies of neoadjuvant chemotherapy (given before surgery or radiotherapy) have produced

inconclusive results.¹⁵¹⁻¹⁶⁰ Meta-analysis of these studies shows no benefit.¹⁶¹

RECURRENT DISEASE

Women with recurrent cervical cancer confined to the pelvis can sometimes be successfully treated by exenterative surgery, which

Table 3 Concurrent chemoradiotherapy for women with high risk cervical cancer (studies in alphabetical order). All randomised controlled trials undertaken in the US

Author	Aim of study	Patient group	Interventions	Results	Comment
Keys ¹⁴⁷	To compare the effectiveness of radiotherapy alone with radiotherapy given concurrently with cisplatin chemotherapy	374 women randomised, 369 in analysis. Patients had bulky stage Ib cervical cancer of at least 4 cm diameter but no evidence of disease in lymph nodes. No history of cancer other than non-melanoma skin cancer	Radiotherapy given to pelvic region to total dose of 45 Gy, in 1.8 - 2 Gy fractions, followed by low dose rate intracavitary brachytherapy. All patients had extrafascial hysterectomy 3-6 weeks after radiotherapy. Women randomised to cisplatin given concurrently with radiotherapy, or no chemotherapy. Median duration of follow up 36 months	Relative likelihood of disease free survival was significantly higher in women who received cisplatin chemoradiotherapy, compared with those given radiotherapy alone ($p < 0.001$). 3 year survival rates 83% for combined treatment group <i>v</i> 74% for women given radiotherapy only ($p < 0.008$). Relative risk of death with combined treatment <i>v</i> radiotherapy only: 0.54 (95% CI 0.34 to 0.86). No treatment related deaths. 35% of women in combined treatment group had moderate or severe adverse effects <i>v</i> 13% in radiotherapy group. No significant differences between groups in rate of serious late effects	Results show that cisplatin, given concurrently with radiotherapy, leads to better survival than radiotherapy alone. Extrafascial hysterectomy after radiotherapy now rarely used. Power calculation required 346 patients
Morris ¹⁴⁸	To compare the effectiveness of radiotherapy alone with radiotherapy given concurrently with cisplatin/fluorouracil chemotherapy	403 women randomised, 388 in analysis. Main reason for withdrawal: violation of protocol. Patients had stage IIb, III, or IVa cervical cancer, or stage Ib or IIa tumours of at least 5 cm diameter or metastasis to pelvic lymph nodes; disease confined to the pelvis and no history of cancer other than cutaneous	Radiotherapy given to pelvic region to total dose of 45 Gy, in 1.8 Gy fractions, followed by low dose rate intracavitary brachytherapy. Women randomised to cisplatin/fluorouracil given concurrently with radiotherapy, or no chemotherapy. Median duration of follow up 43 months	Relative likelihood of disease free survival was 0.48 (95% CI 0.35 to 0.66) for women who received radiotherapy alone, compared with those given cisplatin/fluorouracil chemoradiotherapy. Overall survival rates 73% for combined treatment group <i>v</i> 58% for women given radiotherapy only ($p < 0.001$). Disease free survival at 5 years: 67% with combined therapy, 40% with radiotherapy only. Higher rates of short term adverse effects with combined treatment, but no significant differences between groups in the seriousness of late effects	Results show that cisplatin/fluorouracil, given concurrently with radiotherapy, leads to markedly better survival than radiotherapy alone. Power calculation required 400 patients
Peters ¹⁴⁹	To determine if addition of chemotherapy to radiotherapy improves the survival of women with early stage, high risk cervical cancer	268 women (241 in analysis) with stage Ia2, Ib, or IIa cervical cancer, initially treated with radical hysterectomy and pelvic lymphadenectomy, who had positive pelvic lymph nodes and/or positive margins and/or microscopic involvement of the parametrium	Patients randomised to radiotherapy or chemotherapy using cisplatin and 5-FU concurrently with radiotherapy. Radiotherapy: 49 Gy in 29 fractions to pelvis	Progression free and overall survival significantly higher in women who received chemotherapy ($p = 0.01$). Hazard ratio for overall survival in radiotherapy <i>v</i> chemoradiotherapy: 2.02. Projected 4 year progression free survival 63% with radiotherapy, 81% with chemoradiotherapy. No treatment related deaths. More grade 3 to 4 haematological adverse effects in combined treatment group	Addition of chemotherapy to radiotherapy improves outcomes
Rose ¹⁴⁶	To compare the effectiveness of 3 types of chemotherapy when given concurrently with radiotherapy	575 women randomised, 526 in analysis. Main reason for withdrawal: violation of protocol. Patients had stage IIb, III, or IVb cervical cancer confined to the pelvis and no history of other cancers	Radiotherapy given to whole pelvic region in 24 fractions to 40.8 Gy or 30 fractions to 51 Gy, followed by one or two applications of low dose intracavitary brachytherapy or additional external beam treatment. Women randomised to chemotherapy with cisplatin, cisplatin/fluorouracil/hydroxyurea (combination chemotherapy), or hydroxyurea, given concurrently with radiotherapy. Median duration of follow up 35 months	Relative risk (RR) of progression or death 0.57 (95% CI 0.42 to 0.78) and 0.55 (95% CI 0.40 to 0.75), respectively for groups given cisplatin and combination chemotherapy compared with hydroxyurea, after adjustment for stage of disease. Progression free survival at 2 years was 67% in group given cisplatin, 64% in combined chemotherapy group, 47% in hydroxyurea group. 205 patients dead after median follow up of 35 months; 59 in group given cisplatin, 57 in group given combination chemotherapy, 89 in group given hydroxyurea. No treatment related deaths. Combination chemotherapy caused more than double the rate of moderate or severe haematological adverse effects than single agent treatment	Results suggest that cisplatin alone, given concurrently with radiotherapy, produces the best results (maximum survival with minimum toxicity). Authors discuss dose dependent adverse effects of brachytherapy. Power calculation required 495 patients
Whitney ¹⁵⁰	To compare cisplatin/fluorouracil with hydroxyurea as an adjunct to radiotherapy for women with stage IIb-IVa cervical cancer	Women with stage IIb-IVa cervical cancer and negative para-aortic lymph nodes	(No details available)	Improved survival in group given cisplatin. (No details available)	No details available, but NCI reports that results of this trial are consistent with others in this table

involves removal of most pelvic organs. When cases are carefully selected and managed by surgical teams experienced in this procedure, a five year survival rate of 50% is possible.¹⁶²⁻¹⁶⁴ There are no long term survivors when disease is found in the lymph nodes.

Follow up

Care after primary treatment has two distinct aspects:

- Management of physical and psychological morbidity
- Prompt detection of recurrent disease.

There is no consensus on what follow up is appropriate. A UK study found that 584 of 684 consultant gynaecologists surveyed used 106 different follow up protocols.¹⁶⁵ Fifteen per cent reported no routine follow up.

Many women who have completed treatment for gynaecological cancer continue to require support and some will need treatment for adverse effects. A study of 82 women free from disease found that half reported worrying physical effects, 49% were depressed, and 39% reported persistent psychosocial difficulties. Fatigue, pain, bladder dysfunction, and sexual problems were common.¹⁶⁶

No research evidence exists that shows routine follow up to be effective for reducing deaths from recurrent cancer among women who had treatment with curative intent. The only evidence linking follow up with improved survival is in ovarian cancer, for which treatment is rarely curative. For women with ovarian cancer, follow up in multidisciplinary clinics is beneficial.⁵

Palliative treatment and care

A study of 151 women with advanced ovarian cancer found that 50% experienced physical distress that persisted over two years¹⁶⁷; another found that more than 40% suffered pain which could substantially undermine function.¹⁶⁸ Although evidence exists that most cancer pain can be controlled,¹⁶⁹⁻¹⁷⁰ no specific studies of pain control in gynaecological cancer were identified.

About a quarter of women with advanced ovarian cancer develop bowel obstruction and medical or surgical palliative treatment can be used. Case series reports suggest that median survival after successful surgery ranges from two to seven months, with a significant risk of re-obstruction.¹⁷¹⁻¹⁷⁶ There is no information on quality of life.

Costs

CHEMOTHERAPY FOR OVARIAN CANCER

The introduction of paclitaxel/cisplatin for firstline treatment of ovarian cancer has been estimated to cost the average district (250 000 women) £258 368 each year.¹⁷⁷ Total expected costs for each patient each year, including chemotherapy drugs, supporting treatments, and anticipated adverse effects, are £10 427 for paclitaxel/cisplatin and £2059 for carboplatin. Revised cost estimates for paclitaxel/cisplatin, using information from more recent trials, are

£7000-£11 000 for each life year gained and £20 000 £22 000 for each progression free year.¹⁷⁸

CENTRALISATION OF SERVICES

Reconfiguring services so that the majority of women are treated by specialist gynaecological oncology teams could almost double the cost of gynaecological surgical referrals to a typical NHS cancer centre, with an estimated average rise of £195 000.² There is considerable variety in the likely impact, depending on the magnitude of the change in referral patterns. The anticipated additional costs for an average centre are £85 000 for ovarian cancer, £50 000 for endometrial cancer, and £34 000 for cervical cancer. Costs would increase further with greater provision of post-operative, palliative, and terminal care at cancer centres.

Conclusions

There is consistent evidence of widespread inadequacies in the management of gynaecological cancer in Britain. Many women do not receive optimal diagnosis, assessment, or treatment. Increased surgical specialisation, management by expert multidisciplinary teams, and greater adherence to evidence based treatment guidelines are likely to lead to improved outcomes.

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