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Effective Health Care

Bulletin on the effectiveness of health service interventions for decision makers

Management of Gynaecological Cancers

This bulletin reviews evidence concerning the management of ovarian, endometrial and cervical cancers.

- The ovary, endometrium (uterus) and cervix are the fourth, fifth and sixth most common cancer sites after breast, lung and bowel in women in England and Wales. However, the average GP sees only one new patient with ovarian cancer about every five years, and patients with other gynaecological cancers even less frequently.
- Many women do not receive optimal diagnosis, assessment or treatment. Under-treatment leads to reduced survival, whilst over-treatment is wasteful and causes avoidable adverse effects.
- Women with ovarian cancer live longer if they are treated by expert multidisciplinary teams, and if surgery is carried out by specialist gynaecological oncologists.
- Chemotherapy can extend the lives of women with advanced ovarian cancer. Current evidence suggests that the optimal form is paclitaxel/carboplatin.
- Endometrial cancer usually causes vaginal bleeding in post-menopausal women. Transvaginal ultrasound followed by outpatient biopsy offers rapid and accurate diagnosis. If diagnosed and treated early, survival rates are high.
- In cervical cancer, adequate pre-treatment assessment is vital. Surgery alone is sufficient for early cancers; radiotherapy is appropriate for later-stage cancers, but is more likely to cause lasting adverse effects.
- Simultaneous treatment with cisplatin and radiotherapy may increase survival rates in women with high-risk cervical cancer.

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A. Background

This bulletin deals with the management of the three most common gynaecological cancers: ovarian, endometrial, and cervical. It is based on systematic reviews of research evidence carried out to inform *Improving Outcomes in Gynaecological Cancers: Guidance for Commissioners of Cancer Services: The Manual*,[1] and published in *Improving Outcomes in Gynaecological Cancers: The Research Evidence*.[2] A summary of the Manual, written for general practitioners and primary care teams, is also available. These publications are part of a series on improving services for the management of the major cancers. All may be obtained, free of charge, by calling the NHS Response Line on 0541 555 455.

Gynaecological cancers are a diverse group. Ovarian cancer is the most common, with an incidence rate of 20 per 100,000 women, while incidence rates for cervical and endometrial cancer are below 15 per 100,000 (Table 1).

While gynaecological cancers as a whole are more common among older women, the relationship between incidence and age varies according to the cancer site (Figure 1). Symptoms, management and prognosis differ between sites, but the most important form of primary treatment for the majority of women is surgery.

B. Organisation of care

Outcomes seem to be associated with the way services are delivered. The evidence suggests that surgical specialisation, level of patient throughput, multidisciplinary teamwork, and adherence to treatment protocols may affect survival rates. These variables are linked and their effects often cannot be evaluated independently; however, the available evidence consistently suggests that organisation of care is important.

B.1 Specialisation Observational studies provide convincing evidence that management of ovarian cancer by specialist surgeons is associated with better survival. The results of an ongoing prospective study covering the whole of Scotland (adjusted for prognostic factors) show that women with stage III ovarian cancer survived longest after surgery by gynaecological oncologists (surgeons who specialise in gynaecological cancer).[4,5] 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.[5]

Other studies of poorer design 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% CI, 1.05 to 1.71; p=0.02).[6] Similar results have been reported from the USA[7,8] and Australia.[9] Process measures such as adequacy of staging and tumour removal (debulking) also suggest that less specialised surgeons provide inferior treatment.[4,6,7,9,10]

B.2 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.[11] A US study of 30-day mortality after pelvic exenteration, a difficult surgical procedure most often carried out for recurrent cervical cancer, found that higher hospital volumes were associated with significantly lower mortality.[12] This effect was independent of case-mix.

A case-note review of 860 women treated for ovarian cancer in north-west England found no such effect,[13] 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 per year.[14]

B.3 Multidisciplinary teamwork The study of ovarian cancer in Scotland found that follow-up at a multidisciplinary clinic was an independent predictor of survival, reducing the risk of death at five years by 40%.[4] This effect was independent of primary chemotherapy. Audits in England show that management in teaching centres, where specialist treatment, higher patient throughput and multi-disciplinary teamwork are all more probable, is associated with better survival in ovarian cancer,[14,15] cervical cancer,[11] and endometrial cancer.[16]

B.4 Adherence to protocols Women with gynaecological cancer who are treated in accordance with locally agreed protocols are likely to survive for longer.[11,14,16–18]

C. Support for patients

C.1 Reactions to gynaecological cancer Diagnosis and treatment of gynaecological cancer can cause a variety of problems. It is likely to leave women unable to conceive or bear children and some may be unable to experience sexual enjoyment.

Table 1 Gynaecological cancers: Incidence, survival and death rates.[3, 110, 178]

Cancer site	Estimated incidence rate per 100,000 women, 1997	5-year survival (NYCRIS, 1998)	Death rate per 100,000 women, England & Wales 1997	Total deaths, England & Wales 1997
Ovary	20.3	32%	15.0	3,985
Endometrium	13.8	70%	2.9	774
Cervix	10.4	67%	4.6	1,225

High levels of depression, anxiety about cancer recurrence, and persistent tiredness were reported in two studies, even two years after primary treatment.[19,20] 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.[21] 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.[19,22,23]

C.2 Communication and provision of information Many women who have been treated for gynaecological cancer want more information on their disease and potential after-effects of treatment.[19,24,25] The level of knowledge among women with gynaecological cancer has been found to be very poor.[26,27]

Information for cancer patients has a range of beneficial effects including anxiety reduction, enhanced satisfaction and adherence to treatment, and improved self-care.[28–30] 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.[31–34]

C.3 Counselling, psychosocial and educational interventions Many women who have undergone treatment for gynaecological cancer would welcome more emotional support and counselling.[19,25] Most would like a relative or friend present when bad news is broken.[25]

Two controlled studies found that counselling can reduce emotional distress.[33,35] 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.[35] A randomised controlled trial (RCT) 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'.[33]

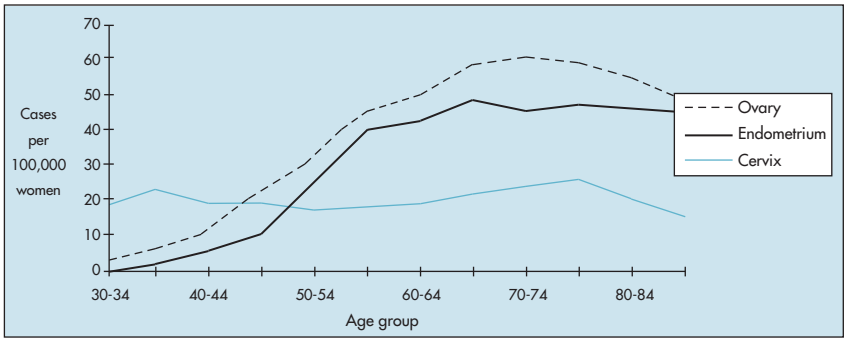

Fig 1 Rates of newly diagnosed cases of gynaecological cancers per 100,000 women, England and Wales, 1992.[3]

D. Ovarian cancer

D.1 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.[36] Results from a recent pilot RCT with seven years follow-up and 22,000 women, suggest that screening could reduce mortality from ovarian cancer.[37] There was, however, 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.[36] Women with one affected first-degree relative face two to three times the population risk.[36,38] 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.[39]

D.2 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.[40]

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 the blood serum. Taking the woman's age into account increases the power of the discrimination. Three studies which used these parameters to determine a risk of malignancy index found that this could offer around 80–90% sensitivity and specificity.[41–43]

The sensitivity and specificity of CA125 alone for the detection of ovarian cancer in women with pelvic masses (using a serum level cut-off 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%.[41-60]

Studies of ultrasound alone report 89–100% sensitivity and 42–75% specificity.[45–47]

D.3 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 between hospitals.[14] Whilst 66% of women who underwent surgery in teaching hospitals in south-east England were managed according to locally agreed guidelines, only 28% of those who had surgery in hospitals without oncology support were treated appropriately. 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.[61] Two meta-analyses of chemotherapy trials reported that residual tumour size was a major determinant of survival.[62,63]

Two RCTs assessed the effectiveness of interval debulking surgery, where remaining tumour is removed in a second operation after chemotherapy. One, which included 319 women, demonstrated a 33% reduction in risk of death (95% CI: 10% to 50%) and six months longer survival after interval debulking.[64] The other was too small to show statistically significant differences.[65]

D.4 Chemotherapy
Chemotherapeutic agents commonly used to treat ovarian cancer are shown in the box below.

Platinum-based chemotherapy improves survival among women with ovarian cancer more advanced than stage I. Meta-analyses of individual data for 5,667 patients in 37 RCTs of chemotherapy regimens (not including taxanes) suggest that, while differences between them are not great, the inclusion of platinum is consistently beneficial.[66] 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 carboplatin had similar effects on survival: HR 1.02 (95% CI: 0.93 to 1.12).

ICON2, a large trial (n=1,526), 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), but carboplatin was considerably less toxic than CAP.[67]

Three US RCTs have assessed the effectiveness of paclitaxel, given in combination with cisplatin or carboplatin (see Table 2). Two trials (total n=1,090), compared paclitaxel/cisplatin with cyclophosphamide/cisplatin.[68–70] 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 RCT compared paclitaxel/cisplatin with single-agent cisplatin and found no significant survival difference between the treatment groups.[71] However, many women randomised to cisplatin received paclitaxel, which makes the results difficult to interpret.

A fourth large trial, ICON3 (n=2,074), compares 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.

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.

Three RCTs compared paclitaxel/cisplatin with paclitaxel/carboplatin.[72–74] None found any difference in efficacy, but quality of life was better with carboplatin.

Current evidence suggests that chemotherapy for advanced ovarian cancer should be paclitaxel/carboplatin. In patients who may not be able to tolerate this combination, carboplatin alone can be effective.

D.5 Recurrent disease Women in trials of second-line chemotherapy for recurrent disease survive for an average of 9.5 months.[75] The response rate is better (25–56%) in women who have over 12 months without disease progression after first-line chemotherapy.[76,77] 21–48% of patients whose disease progresses despite platinum-based chemotherapy may respond to paclitaxel.[78–81] Among women who respond, second-line chemotherapy can prolong survival and has a palliative effect.

E. Endometrial cancer

E.1 Diagnosis Endometrial cancer rarely develops before the menopause, and since 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. While hysteroscopy can detect abnormalities in 95-100% of cases, it does not appear to be a reliable way of identifying cancer.[82,83]

A meta-analysis of 35 studies found that transvaginal ultrasound is an accurate way of excluding endometrial cancer.[84] The probability of endometrial cancer among women with post-menopausal bleeding who do not use HRT 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,

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

Trial	Comparison (doses in mg m2)	Patients	Results (paclitaxel/cisplatin versus other treatment)
GOG 111[68]	Paclitaxel (135, 24 hr infusion) and cisplatin (75) vs cyclophosphamide (750) and cisplatin (75).	n=410 FIGO stage III or IV; suboptimal residual disease.	Overall response: 73% vs 60%. Median progression-free survival: 18 months (95% CI: 16 to 21) versus 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 32-44) versus 24 months (95% CI 21-30)
GOG 132[71]	Paclitaxel (135, 24 hr infusion) and cisplatin (75) vs cisplatin (100).	n=424 FIGO stage III or IV with sub optimal residual disease.	Overall response: 72% vs 74%. Median progression-free survival: 14.1 months versus 16.4 months Median survival: 26.6 months versus 30.2 months. [Comment: Many women randomised to platinum received paclitaxel so the study does not discriminate clearly between groups.]
OV10 (Intergroup: EORTC, NCIC, NOCOVA)[69,70]	Paclitaxel (175, 3 hr infusion) and cisplatin (75) vs cyclophosphamide (750) and cisplatin (75).	n=680 FIGO stage IIb-c, III or IV with optimal or sub-optimal residual disease.	Overall response: 77% vs 66%. Median progression-free survival: 16.6 months versus 12 months, p=0.0001; Median overall survival: 35 months versus 25 months, p=0.0001.

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 RCTs. In one study, the Pipelle detected 60 of 71 endometrial cancers.[85] RCTs have found that the Pipelle offers equivalent diagnostic accuracy to the Vabra aspirator[86,87] and the Novak,[88,89] with less discomfort. The Vabra can sample a greater area but this does not appear to offer any clinical benefit.[90]

Several studies have compared outpatient methods with dilatation and curettage (D&C), which is normally carried out under general anaesthetic. The Novak and Vabra aspirators and the Karman curette are as accurate for diagnosis as D&C.[91,92] The Karman curette was used successfully in 80% of women with post-menopausal 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%.[93]

E.2 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.[97]

An audit examining the relationship 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.[16] Women whose surgery was not in accordance with these guidelines had significantly shorter survival times.

In women with cancer confirmed by biopsy, transvaginal ultrasound can be used to evaluate myometrial invasion. Magnetic resonance (MR) imaging may, however, be more accurate; reported accuracy figures are around 70–80% and 70–95% for ultrasound and MR, respectively.[95–107] MR also allows examination of pelvic lymph nodes. Imaging using computed tomography (CT) appears to be less accurate than ultrasound or MR.[105,108]

E.3 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%.[109,110] It is not clear whether lymph node sampling improves survival;[111] this issue is being addressed in an MRC trial (ASTEC) but results will not be available for some years.[112]

E.4 Radiotherapy Radiotherapy can prolong survival in women with advanced or recurrent disease, or when surgery is not appropriate.[113] 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 RCTs found that it reduced the rate of pelvic recurrence.[114,115] The combination of radiotherapy and surgery can have lasting adverse effects, including lymphoedema.

E.5 Chemotherapy There is no reliable evidence that either chemotherapy or hormone treatment is effective for endometrial cancer. A meta-analysis of six RCTs (n=3,339) 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).[116] A more recent RCT (n=1,012) confirmed this result.[117]

F. Cervical cancer

F.1 Diagnosis and staging The cervical smear programme has reduced the incidence of the most common form of cervical cancer, squamous cell carcinoma, but it cannot identify all cases. It is not designed to detect adenocarcinoma, which develops below the surface of the cervix.

Diagnosis is confirmed by biopsy; this may be sufficient to treat tumours which penetrate less than 3 mm into the cervix.

The effectiveness of different types of imaging for revealing the stage and extent of cervical cancer has been examined in a meta-analysis.[118] 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 this meta-analysis showed no significant difference between CT and MR in accuracy of lymph node evaluation,[118] many studies suggest that MR is more accurate for assessing early disease, whereas CT is better for late disease. Transrectal ultrasound can evaluate tumour extent accurately but is not widely used.[119] Transabdominal pelvic ultrasound is effective for assessing bladder invasion.[120]

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.[121] However, it appears that it is often not used; 94% of women referred for post-operative radiotherapy in Manchester had received no pre-operative imaging.[122]

Audits reveal that inadequate staging of cervical cancer is common.[11,123] 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 ($p<0.0001$).[11]

F.2 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.[124–135] 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). 16% 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.[136]

An audit from south-east England also linked inadequate surgery for cervical cancer with poorer survival.[11] 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 region of England found that 30 of 69 women who had non-radical surgery for cervical cancer had disease more advanced than stage Ia.[123] Surgery for these women was judged inadequate and they underwent repeat surgery or radiotherapy. When radical surgery was carried out, only 30% of procedures included adequate lymph node sampling (10 or more nodes sampled).

F.3 Surgery versus radiotherapy Women with early disease can be treated with either surgery or radiotherapy. These treatment modalities were compared in an RCT which included 343 women with stage Ib or IIa cervical cancer.[121] 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.[137,138]

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 damage to bowel and/or bladder which can develop months or years after treatment. Radiotherapy can also damage the vagina and ovaries, reducing sexual enjoyment and precipitating the menopause.

F.4 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.[113]

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.[139,140] An RCT comparing two relatively low dose-rates reported significantly higher morbidity with the higher rate.[141,142]

F.5 Adjuvant radiotherapy Adjuvant radiotherapy is widely prescribed after radical surgery. Indirect evidence from non-randomised studies suggests it can improve pelvic control, but there is no firm evidence of increased long-term survival.[143,144]

F.6 Concurrent chemo-radiotherapy Five recent RCTs (ranging from 241 to 575 women) have compared radiotherapy alone with platinum-based chemotherapy given during radiotherapy for women with high-risk cervical cancer.[145–149] The results of these studies are remarkably consistent: all show that concurrent chemo-radiotherapy 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 improvement in absolute

survival rates ranged from 10% to 15%. See Table 3 for details.

F.7 Neo-adjuvant chemotherapy Studies of neo-adjuvant chemotherapy (before surgery or radiotherapy) have produced inconclusive results.[150–159] Meta-analysis of these studies shows no benefit.[160]

F.8 Recurrent disease Women with recurrent cervical cancer confined to the pelvis can sometimes be successfully treated by exenterative surgery, which 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.[161–163] There are no long-term survivors when disease is found in the lymph nodes.

G. Follow-up

Care after primary treatment has two distinct aspects:

(i) Management of physical and psychological morbidity.

(ii) 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.[164] 15% 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.[165]

There is no research evidence 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.[4]

H. Palliative treatment and care

Only research evidence dealing specifically with gynaecological cancer is included here. Evidence on provision of palliative care for cancer patients generally is reviewed elsewhere.[28–30]

H.1 Pain A longitudinal study of 151 women with advanced ovarian cancer found that 50% experienced physical distress that persisted over two years;[166] another study found that more than 40% suffered pain which could substantially undermine function.[167] Extent of tumour and difficulty with everyday activities are associated most strongly with pain. Severe pain is also a major symptom of recurrent cervical cancer. While there is evidence that most cancer pain can be controlled effectively,[168,169] no specific studies of pain control in gynaecological cancer were identified.

H.2 Bowel obstruction About a quarter of women with advanced ovarian cancer develop bowel obstruction, and medical or surgical palliative treatment can be used. Case-series suggest that median survival after successful surgery ranges from two to seven months, with a significant risk of re-obstruction.[170–175] There is no information on quality of life.

I. Costs

I.1 Chemotherapy for ovarian cancer The introduction of paclitaxel/cisplatin for first-line treatment of ovarian cancer (see D.4) has been estimated to cost the average district (250,000 women) £258,368 per year.[176] This figure was based on data from Trent and the GOG trial.[68] It was assumed that paclitaxel would offer an average of 1.17 years longer survival than might be expected with carboplatin alone, at an additional cost of £7,200 (95% CI: £4,366 to £50,209) per life year gained.[176] Total expected costs per patient per year, including chemotherapy drugs, supporting treatments and anticipated adverse effects, were £10,427 for paclitaxel/cisplatin and £2,059 for carboplatin. These figures are broadly consistent with figures from studies in Wessex and the US.[176]

The revised cost estimates from more recent trials are £7,000–£11,000 per life year gained and £20,000–£22,000 per progression-free year.[177]

I.2 Centralisation of services Reconfiguring services in accordance with recommendations made in the Guidance Manual[1] is expected to increase surgery and pathology costs by increasing referrals to specialist gynaecological oncology teams. Annual costs for gynaecological surgical referrals at a typical Cancer Centre could almost double, with an estimated average rise of £195,000.

There is considerable variety in the likely impact. Where the majority of women are already treated in the Cancer Centre, little change is expected. However, large increases in referrals to some Centres could increase costs, estimated at up to £480,000 for one Centre examined. 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.

Releasing costs from Cancer Units may be difficult. Cancers represent around 4–7% of gynaecology specialty costs at Units and it is unlikely that medical staff or ward provision will be reduced.

Table 3 RCTs evaluating concurrent chemo-radiotherapy for women with high-risk cervical cancer (all carried out in the US; studies in alphabetical order)

Author	Aim of study	Patient group	Interventions	Results	Comment
Keys[146]	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 4cm diameter but no evidence of disease in lymph nodes. No history of cancer other than non-melanoma skin cancer.	Radiotherapy administered to pelvic region to total dose of 45 Gy, in 1.8 – 2 Gy fractions, followed by low-dose-rate intra-cavitary 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 chemo-radiotherapy, compared with those given radiotherapy alone ($p<0.001$). 3-year survival rates 83% for combined therapy group, vs 74% for women given radiotherapy only ($p<0.008$). Relative risk of death with combined therapy vs 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, vs 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[147]	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 5cm diameter or metastasis to pelvic lymph nodes; disease confined to the pelvis and no history of cancer other than cutaneous.	Radiotherapy administered to pelvic region to total dose of 45 Gy, in 1.8 Gy fractions, followed by low-dose-rate intra-cavitary 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 chemo-radiotherapy. Overall survival rates: 73% for combined therapy group, vs 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[148]	To determine if the 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 vs chemo-radiotherapy: 2.02. Projected 4 year progression-free survival 63% with radiotherapy, 81% with chemo-radiotherapy. No treatment-related deaths. More grade 3 to 4 haematologic adverse effects in combined treatment group.	Addition of chemotherapy to radiotherapy improves outcomes.
Rose[145]	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 administered 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 intra-cavitary 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 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[149]	To compare cisplatin/fluorouracil with hydroxyurea as an adjunct to radiotherapy.	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 National Cancer Institute reports that results of this trial are consistent with others in this table.

J. Implications

The recommendations given below are taken directly from the Guidance Manual.[1] They were identified by the Editorial Committee of the National Cancer Guidance Steering Group as Key Recommendations which, if implemented, would make a major contribution to improving outcomes in gynaecological cancer.

- Dedicated diagnostic and assessment services should be established in Cancer Units, to which all women with possible or suspected gynaecological cancers should be referred. This includes women with symptoms and those who present through the cervical screening programme.
- There should be specialist multiprofessional gynaecological oncology teams based in Cancer Centres. These teams should be responsible for the management of all women with ovarian cancer and the majority of women with other gynaecological cancers.
- The specialist gynaecological oncology and palliative care teams in each Cancer Centre and associated Cancer Units should agree clear local policies

for the management of women with advanced or progressive disease. These policies should be designed to ensure the co-ordination of high quality care between Cancer Centres, Cancer Units, palliative care, primary care and community services.

- There should be rapid and efficient communication systems for liaison and cross-referral between all levels of service. Audit should take place across the entire service delivery network, including the Cancer Centre and all related Units.

Research Methods

A number of computerised databases were searched and 20 relevant journals were hand-searched. Reference lists of papers retrieved were used to identify other potentially relevant studies and additional material was provided by referees and experts in the various fields. Studies were graded and included in the reviews according to predefined criteria. Further details are available in *Improving Outcomes in Gynaecological Cancers: The Research Evidence*.[2]

References

1. National Cancer Guidance Steering Group. *Improving Outcomes in Gynaecological Cancers: The Manual* London: NHS Executive, Department of Health, 1999.
2. National Cancer Guidance Steering Group. *Improving Outcomes in Gynaecological Cancers: The Research Evidence* London: NHS Executive, Department of Health, 1999.
3. Office for National Statistics. Data provided on request, 1998.
4. Junor EJ, Hole DJ, Gillis CR. Management of ovarian cancer: referral to a multidisciplinary team matters. *Br J Cancer* 1994;70:363–70.
5. Junor EJ, Hole DJ. Specialist gynaecologists and survival outcome in ovarian cancer: a Scottish National Study of 1866 patients. *Br J Obstet Gynaecol* (in press).
6. Kehoe S, Powell J, Wilson S, et al. The influence of the operating surgeon's specialisation on patient survival in ovarian carcinoma. *Br J Cancer* 1994;70:1014–7.
7. Nguyen HN, Averette HE, Hoskins W, et al. National Survey of ovarian carcinoma part V. *Cancer* 1993;72:3663–70.
8. Mayer AR, Chambers SK, Graves E, et al. Ovarian cancer staging: does it require a gynecologic oncologist? *Gynecol Oncol* 1992;47:223–7.
9. Grant PT, Beischer NA, Planner RS. The treatment of gynaecological malignancy in a general public hospital. *Med J Aust* 1992;157:378–80.
10. McGowan L. Patterns of care in carcinoma of the ovary. *Cancer* 1993;71:628–33.
11. Wolfe CD, Tilling K, Bourne HM, et al. Variations in the screening history and appropriateness of management of cervical cancer in South East England. *Eur J Cancer* 1996;32A:1198–204.
12. Begg CB, Cramer LD, Hoskins WJ, et al. Impact of hospital volume on operative mortality for major cancer surgery. *JAMA* 1998;280:1747–51.
13. Woodman C, Baghdady A, Collins S, et al. What changes in the organisation of cancer services will improve the outcome for women with ovarian cancer? *Br J Obstet Gynaecol* 1997;104:135–9.
14. Wolfe CD, Tilling K, Raju KS. Management and survival of ovarian cancer patients in south east England. *Eur J Cancer* 1997;33:1835–40.
15. Gillis CR, Hole DJ, Still RM, et al. Medical audit, cancer registration, and survival in ovarian cancer. *Lancet* 1991;337:611–2.
16. Tilling K, Wolfe CD, Raju KS. Variations in the management and survival of women with endometrial cancer in south east England. *Eur J Gynaecol Oncol* 1998;19:64–8.
17. Hogberg T, Carstensen J, Simonsen E. Treatment results and prognostic factors in a population-based study of epithelial ovarian cancer. *Gynecol Oncol* 1993;48:38–49.
18. Munoz KA, Harlan LC, Trimble EL. Patterns of care for women with ovarian cancer in the United States. *J Clin Oncol* 1997;15:3408–15.
19. Cull A, Cowie VJ, Farquharson DI, et al. Early stage cervical cancer: psychosocial and sexual outcomes of treatment. *Br J Cancer* 1993;68:1216–20.
20. Cain EN, Kohorn EI, Quinlan DM, et al. Psychological reactions to the diagnosis of gynecologic cancer. *Obstet Gynecol* 1983;62:635–41.
21. Corney RH, Crowther ME, Everett H, et al. Psychosexual dysfunction in women with gynaecological cancer following radical pelvic surgery. *Br J Obstet Gynaecol* 1993;100:73–8.
22. Abitol MM, Davenport JH. Sexual dysfunction after therapy for cervical carcinoma. *Am J Obstet Gynecol* 1974;119:181–9.
23. Siebel MM, Freeman M, Graves W. Sexual function after surgical and radiation therapy for cervical carcinoma. *South Med J* 1982;75:1195–7.
24. Carlsson ME, Strang PM. Educational group support for patients with gynaecological cancer and their families. *Support Care Cancer* 1996;4:102–9.
25. Corney R, Everett H, Howells A, et al. The care of patients undergoing surgery for gynaecological cancer: the need for information, emotional support and counselling. *J Adv Nurs* 1992;17:667–71.
26. Karani D, Wiltshaw E. How well informed?... new patients with ovarian cancer. *Cancer Nurs* 1986;9:238–42.
27. Berner ES, Partridge EE, Baum SK. The effects of the PDQ patient information file (PIF) on patients' knowledge, enrollment in clinical trials, and satisfaction. *J Cancer Educ* 1997;12:121–5.
28. Cancer Guidance Sub-group of the Clinical Outcomes Group. *Improving Outcomes in Breast Cancer: The Research Evidence* London: NHS Executive, Department of Health, 1996.
29. Cancer Guidance Sub-Group of the Clinical Outcomes Group. *Improving Outcomes in Colorectal Cancer: The Research Evidence* London: NHS Executive, Department of Health, 1997.
30. National Cancer Guidance Group. *Improving Outcomes in Lung Cancer: The Research Evidence* London: NHS Executive, Department of Health, 1998.
31. Elit LM, Levine MN, Gafni A, et al. Patients' preferences for therapy in advanced epithelial ovarian cancer: development, testing, and application of a bedside decision instrument. *Gynecol Oncol* 1996;62:329–35.
32. Mohide EA, Whelan TJ, Rath D, et al. A randomised trial of two information packages distributed to new cancer patients before their initial appointment at a regional cancer centre. *Br J Cancer* 1996;73:1588–93.
33. Cain EN, Kohorn EI, Quinlan DM, et al. Psychosocial benefits of a cancer support group. *Cancer* 1986;57:183–9.
34. Robinson JW, Scott CB, Faris PD. Sexual rehabilitation for women with gynecological cancer: Information is not sufficient. *Canadian Journal of Human Sexuality* 1994;3:131–42.
35. Capone MA, Good RS, Westie KS, et al. Psychosocial rehabilitation of gynecologic oncology patients. *Arch Phys Med Rehabil* 1980;61:128–32.
36. Bell R, Petticrew M, Sheldon T. The performance of screening tests for ovarian cancer: results of a systematic review. *Br J Obstet Gynaecol* 1998;105:1136–47.
37. Jacobs IJ, Skates SJ, MacDonald N, et al. Screening for ovarian cancer: a pilot randomised controlled trial. *Lancet* 1999;353:1207–10.
38. Stratton JF, Pharoah P, Smith SK, et al. A systematic review and meta-analysis of family history and risk of ovarian cancer. *Br J Obstet Gynaecol* 1998;105:493–9.
39. Stratton JF, Gayther SA, Russell P, et al. Contribution of BRCA1 mutations to ovarian cancer. *N Engl J Med* 1997;336:1125–30.
40. Flam F, Einhorn N, Sjovall K. Symptomatology of ovarian cancer. *Eur J Obstet Gynecol Reprod Biol* 1988;27:53–7.
41. Davies AP, Jacobs I, Woolas R, et al. The adnexal mass: benign or malignant? Evaluation of a risk of malignancy index. *Br J Obstet Gynaecol* 1993;100:927–31.
42. Tingulstad S, Hagen B, Skjeldestad FE, et al. Evaluation of a risk of malignancy index based on serum CA125, ultrasound findings and menopausal status in the pre-operative diagnosis of pelvic masses. *Br J Obstet Gynaecol* 1996;103:826–31.
43. Jacobs I, Oram D, Fairbanks J, et al. A risk of malignancy index incorporating CA125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. *Br J Obstet Gynaecol* 1990;97:922–9.
44. Maggino T, Gadducci A, D'Addario V, et al. Prospective multicentre study on CA125 in postmenopausal pelvic masses. *Gynecol Oncol* 1994;54:117–23.
45. Botta G, Zarcone R. Trans-vaginal ultrasound examination of ovarian masses in premenopausal women. *Eur J Obstet Gynecol* 1995;62:37–41.
46. Caruso A, Caforio L, Testa AC, et al. Transvaginal color Doppler ultrasonography in the presurgical characterization of adnexal masses. *Gynecol Oncol* 1996;63:184–91.
47. Luxman D, Bergman A, Sagi J, et al. The postmenopausal adnexal mass: correlation between ultrasonic and pathologic findings. *Obstet Gynecol* 1991;77:726–8.
48. Finkler NJ, Benacerraf B, Lavin PT, et al. Comparison of serum CA125, clinical impression, and ultrasound in the preoperative evaluation of ovarian masses. *Obstet Gynecol* 1988;72:659–63.
49. Franchi M, Beretta P, Ghezzi F, et al. Diagnosis of pelvic masses with transabdominal color Doppler, CA125 and ultrasonography. *Acta Obstet Gynecol Scand* 1995;74:734–9.
50. Schutter EMJ, Kenemans P, Sohn C, et al. Diagnostic value of pelvic examination ultrasound, and serum CA125 in postmenopausal women with a pelvic mass. *Cancer* 1994;74:1398–406.
51. Sengoku K, Satoh T, Saitoh S, et al. Evaluation of transvaginal color Doppler sonography transvaginal sonography and CA125 for prediction of ovarian malignancy. *Int J Gynecol Obstet* 1994;46:39–43.
52. Buy J-N, Ghossain MA, Hugol D, et al. Characterization of adnexal masses: combination of color Doppler and conventional sonography compared with spectral Doppler analysis alone and conventional sonography alone. *Am J Roentgenol* 1996;166:385–93.
53. Carter J, Saltzman A, Hartenbach E, et al. Flow characteristics in benign and malignant gynecologic tumors using transvaginal color flow doppler. *Obstet Gynecol* 1994;83:125–30.
54. Leeners B, Schild RL, Funk A, et al. Colour Doppler sonography improves the pre-operative diagnosis of ovarian tumours made using conventional transvaginal sonography. *Eur J Obstet Gynecol* 1996;64:79–85.
55. Prömpeler HJ, Madjar H, Sauerbrei W. Classification of adnexal tumors by transvaginal color doppler. *Gynecol Oncol* 1996;61:354–63.
56. Rehn M, Lohmann K, Rempen A. Transvaginal ultrasonography of pelvic masses: evaluation of B-mode technique and doppler ultrasonography. *Am J Obstet Gynecol* 1996;175:97–104.
57. Reles A, Wein U, Lichtenegger W. Transvaginal color Doppler sonography and conventional sonography in the preoperative assessment of adnexal masses. *J Clin Ultrasound* 1997;25:217–25.

58. Schneider VL, Schneider A, Reed KL, et al. Comparison of doppler with two-dimensional sonography and CA125 for prediction of malignancy of pelvic masses. *Obstet Gynecol* 1993;81:983–8.

59. Stringini FAL, Gadducci A, Del Bravo B, et al. Differential diagnosis of adnexal masses with transvaginal sonography, color flow imaging, and serum CA125 assay in pre- and postmenopausal women. *Gynecol Oncol* 1996;61:68–72.

60. Timor-Tritsch IE, Lerner JP, Monteagudon A, et al. Transvaginal ultrasonographic characterization of ovarian masses by means of color flow-directed Doppler measurements and a morphologic scoring system. *Am J Obstet Gynecol* 1993;168:909–13.

61. Hunter RW, Alexander ND, Soutter WP. Meta-analysis of surgery in advanced ovarian carcinoma: is maximum cytoreductive surgery an independent determinant of prognosis? *Am J Obstet Gynecol* 1992;166:504–11.

62. Marsoni S, Torri V, Valsecchi MG, et al. Prognostic factors in advanced epithelial ovarian cancer. *Br J Cancer* 1990;62:444–50.

63. Voest EE, Van Houwelingen JC, Neijt JP. A meta-analysis of prognostic factors in advanced ovarian cancer with median survival and overall survival (measured with the log (relative risk)) as main objectives. *Eur J Cancer Clin Care* 1989;25:711–20.

64. van der Burg ME, van Lent M, Buyse M, et al. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. *N Engl J Med* 1995;332:629–34.

65. Redman CW, Warwick J, Luesley DM, et al. Intervention debulking surgery in advanced epithelial ovarian cancer. *Br J Obstet Gynaecol* 1994;101:142–6.

66. Advanced Ovarian Cancer Trialists' Group. Chemotherapy in advanced ovarian cancer: four systematic meta-analyses of individual patient data from 37 randomized trials. *Br J Cancer* 1998;78:1479–87.

67. The ICON Collaborators. ICON2: randomised trial of single-agent carboplatin against three-drug combination of CAP (cyclophosphamide, doxorubicin, and cisplatin) in women with ovarian cancer. *Lancet* 1998;352:1571–6.

68. McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med* 1996;334:1–6.

69. Piccart M, Bertelsen K, Stuart G, et al. Is cisplatin-paclitaxel the standard first-line treatment of advanced ovarian cancer? The EORTC-GCOG, NOCOVA, NCIC CTG and Scottish Intergroup experience. *Proc Annu Meet Am Soc Clin Oncol* 1997;16:abstract 1258.

70. Stuart G, Bertelsen K, Mangioni C, et al. Updated analysis shows a highly significant overall improved survival for cisplatin-paclitaxel as first line treatment of advanced ovarian cancer: mature results of the EORTC-GCOG, NOCOVA, NCIC CTG and Scottish Intergroup trial. *Proc Annu Meet Am Soc Clin Oncol* 1998;17:abstract 1394.

71. Muggia FM, Brady PS, Brady MF, et al. Phase III of cisplatin or paclitaxel versus the combination in suboptimal stage III and IV epithelial ovarian cancer: Gynecological Oncology Group (GOG) study. *Proc Annu Meet Am Soc Clin Oncol* 1997;16:abstract 1257.

72. Du Bois A, Richter B, Warm M, et al. Cisplatin/paclitaxel as first line treatment in ovarian cancer. *Proc Annu Meet Am Soc Clin Oncol* 1998;17:abstract 1395.

73. Neijt JP, Hansen M, Hansen SW, et al. Randomized phase III study in previously untreated epithelial ovarian cancer FIGO stage IIB, IIC, IV, comparing paclitaxel-cisplatin and paclitaxel-carboplatin. *Proc Annu Meet Am Soc Clin Oncol* 1997;16:abstract 1259.

74. Ozols RF, Bundy BN, Fowler J, et al. Randomized phase III study of cisplatin (CIS)/paclitaxel (PAC) versus carboplatin (CARBO)/PAC in optimal stage III epithelial ovarian cancer (OC): A Gynaecologic Oncology Group Trial (GOG 158). *Proc Annu Meet Am Soc Clin Oncol* 1999;18:abstract 1373.

75. Knopf K, Brown M, Kohn E. Lack of improvement in survival in patients with relapsed or refractory epithelial ovarian cancer 1980-97. *Proc Annu Meet Am Soc Clin Oncol* 1998;17:abstract 1386.

76. Markman M, Rothman R, Hakes T, et al. Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. *J Clin Oncol* 1991;9:389–93.

77. Lorusso V, Catino A, Leone B, et al. Carboplatin plus ifosfamide as salvage treatment of epithelial ovarian cancer: a pilot study. *J Clin Oncol* 1993;11:1952–6.

78. Kohn EC, Sarosy G, Bicher A, et al. Dose-intense taxol: high response rate in patients with platinum-resistant recurrent ovarian cancer. *J Natl Cancer Inst* 1994;86:18–24.

79. Einzig AI, Wiernik PH, Sasloff J, et al. Phase II study and long-term follow-up of patients treated with taxol for advanced ovarian adenocarcinoma. *J Clin Oncol* 1992;10:1748–53.

80. Thigpen JT, Blessing JA, Ball H, et al. Phase II trial of paclitaxel in patients with progressive ovarian carcinoma after platinum-based chemotherapy: a Gynecologic Oncology Group study. *J Clin Oncol* 1994;12:1748–53.

81. Trimble EL, Adams JD, Vena D, et al. Paclitaxel for platinum-refractory ovarian cancer: results from the first 1,000 patients registered to National Cancer Institute Treatment Referral Center 9103. *J Clin Oncol* 1993;11:2405–10.

82. Haller H, Matejcic N, Rukavina B, et al. Transvaginal sonography and hysteroscopy in women with postmenopausal bleeding. *Int J Gynaecol Obstet* 1996;54:155–9.

83. Ben-Yehuda OM, Kim YB, Leuchter RS. Does hysteroscopy improve upon the sensitivity of dilation and curettage in the diagnosis of endometrial hyperplasia or carcinoma? *Gynecol Oncol* 1998;68:4–7.

84. Smith-Bindman R, Kerlikowske K, Feldstein VA, et al. Endovaginal ultrasound to exclude endometrial cancer and other endometrial abnormalities. *JAMA* 1998;280:1510–7.

85. Guido RS, Kanbour-Shakir A, Rulin MC, et al. Pipelle endometrial sampling. *J Reprod Med* 1995;40:553–5.

86. Eddowes HA, Read MD, Codling BW. Pipelle: a more acceptable technique for outpatient endometrial biopsy. *Br J Obstet Gynaecol* 1990;97:961–2.

87. Kaunitz AM, Masciello A, Ostrowski M, et al. Comparison of endometrial biopsy with the endometrial Pipelle and Vabra aspirator. *J Reprod Med* 1988;33:427–31.

88. Silver MM, Miles P, Rosa C. Comparison of Novak and Pipelle endometrial biopsy instruments. *Obstet Gynecol* 1991;78:828–30.

89. Stovall TG, Ling FW, Morgan PL. A prospective, randomized comparison of the Pipelle endometrial sampling device with the Novak curette. *Am J Obstet Gynecol* 1991;165:1287–9.

90. Rodriguez GC, Yaqub N, King ME. A comparison of the Pipelle device and the Vabra aspirator as measured by endometrial denudation in hysterectomy specimens: the Pipelle device samples significantly less of the endometrial surface than the Vabra aspirator. *Am J Obstet Gynecol* 1993;168:55–9.

91. Stovall TG, Solomon SK, Ling FW. Endometrial sampling prior to hysterectomy. *Obstet Gynecol* 1989;73:405–9.

92. Suarez RA, Grimes DA, Majmudar B, et al. Diagnostic endometrial aspiration with the Karman Cannula. *J Reprod Med* 1983;28:41–4.

93. Shaker AG, Anderson M, Kitchener HC. An out-patient approach to the management of post-menopausal bleeding. *Br J Obstet Gynaecol* 1991;98:488–90.

94. Creasman WT, Morrow CP, Bundy BN, et al. Surgical pathological spread patterns of endometrial cancer. *Cancer* 1987;60:2035–41.

95. Belloni C, Vigano R, del Maschio A, et al. Magnetic resonance imaging in endometrial carcinoma staging. *Gynecol Oncol* 1990;37:172–7.

96. Chen SS, Rumancik WM, Spiegel G. Magnetic resonance imaging in stage I endometrial carcinoma. *Obstet Gynecol* 1990;75:274–7.

97. Hricak H, Rubinstein LV, Gherman GM, et al. MR imaging evaluation of endometrial carcinoma: results of an NCI cooperative study. *Radiology* 1991;179:829–32.

98. Hricak H, Stern JL, Fisher MR, et al. Endometrial carcinoma staging by MR imaging. *Radiology* 1987;162:297–305.

99. Powell MC, Womack C, Buckley J, et al. Pre-operative magnetic resonance imaging of stage 1 endometrial adenocarcinoma. *Br J Obstet Gynaecol* 1986;93:353–60.

100. Sironi S, Colombo E, Villa G, et al. Myometrial invasion by endometrial carcinoma: assessment with plain and gadolinium-enhanced MR imaging. *Radiology* 1992;185:207–12.

101. Sironi S, Taccagni G, Garancini P, et al. Myometrial invasion by endometrial carcinoma: assessment by MR imaging. *Am J Roentgenol* 1992;158:565–9.

102. Yamashita Y, Harada M, Sawada T, et al. Normal uterus and FIGO stage I endometrial carcinoma: dynamic gadolinium-enhanced MR imaging. *Radiology* 1993;186:495–501.

103. DelMaschio A, Vanzulli A, Sironi S, et al. Estimating the depth of myometrial involvement by endometrial carcinoma: efficacy of transvaginal sonography vs MR imaging. *Am J Roentgenol* 1993;160:533–8.

104. Gordon AN, Fleischer AC, Dudley BS, et al. Preoperative assessment of myometrial invasion of endometrial adenocarcinoma by sonography (US) and magnetic resonance imaging (MRI). *Gynecol Oncol* 1989;34:175–9.

105. Kim SH, Kim HD, Song YS, et al. Detection of deep myometrial invasion in endometrial carcinoma: comparison of transvaginal ultrasound, CT, and MRI. *J Comput Assist Tomogr* 1995;19:766–72.

106. Thorvinger B, Gudmundsson T, Horvath G, et al. Staging in local endometrial carcinoma. Assessment of magnetic resonance and ultrasound examinations. *Acta Radiologica* 1989;30:525–9.

107. Yamashita Y, Mizutani H, Torashima M, et al. Assessment of myometrial invasion by endometrial carcinoma: transvaginal sonography vs contrast-enhanced MR imaging. *Am J Roentgenol* 1993;161:595–9.

108. Varpula MJ, Klemi PJ. Staging of uterine endometrial carcinoma with ultra-low field (0.02 T) MRI: a comparative study with CT. *J Comput Assist Tomogr* 1993;17:641–7.

109. Berrino F, Sant M, Verdecchia A, et al., editors. *Survival of cancer patients in Europe: the EUROCARE study.* Lyon: International Agency for Research on Cancer, 1995.

110. Northern and Yorkshire Cancer Registry and Information Service. Unpublished data, 1998.

111. Kilgore LC, Partridge EE, Alvarez RD, et al. Adenocarcinoma of the endometrium: survival comparisons of patients with and without pelvic node sampling. *Gynecol Oncol* 1995;56:29–33.

112. MRC Protocol. ASTEC: A Study in the Treatment of Endometrial Cancer: A randomised trial of lymphadenectomy and of adjuvant external beam radiotherapy in the treatment of endometrial cancer. 1998.

113. The Swedish Council on Technology Assessment in Health Care. Radiotherapy for cancer. Volume 2: A critical review of the literature. *Acta Oncol* 1996;Supplementum 7.

114. Aalders J, Abeler V, Kolstad P, et al. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. *Obstet Gynecol* 1980;56:419–27.

115. Creutzberg CL, van Putten W, Koper P, et al. Postoperative radiotherapy in stage I endometrial carcinoma: results from a prospective randomized trial of 715 patients. *ESTRO abstract 307* 1998.

116. Martin-Hirsch PL, Lilford RJ, Jarvis GJ. Adjuvant progestagen therapy for the treatment of endometrial cancer: review and meta-analyses of published randomised controlled trials. *Eur J Obstet Gynecol Reprod Biol* 1996;65:201–7.

117. COSA-NZ-UK Endometrial Cancer Study Groups. Adjuvant medroxyprogesterone acetate in high-risk endometrial cancer. *International Journal of Gynecological Cancer* 1998;8:387–91.

118. Scheidler J, Hricak H, Yu KK, et al. Radiological evaluation of lymph node metastases in patients with cervical cancer. A meta-analysis. *JAMA* 1997;278:1096–101.
119. Innocenti P, Pulli F, Savino L, et al. Staging of cervical cancer: reliability of transrectal US. *Radiology* 1992;185:201–5.
120. Deo SV, Shukla NK, Sandhu M, et al. Role of transabdominal pelvic ultrasound and computed tomography in the detection of bladder involvement in advanced cancer of the cervix. *Australas Radiol* 1996;40:218–20.
121. Landoni F, Maneo A, Colombo A, et al. Randomised study of radical surgery versus radiotherapy for stage Ib- IIa cervical cancer. *Lancet* 1997;350:535–40.
122. Coyle CA, Davidson SE, Swindel R, et al. A review of patients referred for post-operative radiotherapy following surgery for carcinoma of the cervix in the North West Region. (personal communication).
123. Jackson S, Murdoch J, Howe K, et al. The management of cervical carcinoma within the South West Region of England. *Br J Obstet Gynaecol* 1997;104:140–4.
124. Averrette HE, Ford JH, Dudan RC. Staging of cervical cancer. *Clin Obstet Gynecol* 1975;18:215.
125. Boyce, Fruchter R, Nicastri AD, et al. Prognostic factors in stage I carcinoma of the cervix. *Gynecol Oncol* 1981;12:154–65.
126. Gauthier P, Gore I, Shingleton HM. Identification of histopathologic risk groups in stage Ib squamous cell carcinoma of the cervix. *Obstet Gynecol* 1985;66:569.
127. Green T. Ureteral suspension for prevention of ureteral complications following radical Wertheim hysterectomy. *Obstet Gynecol* 1966;28:1–11.
128. Inoue T. Prognostic significance of the depth of invasion relating to nodal metastases, parametrial extension, and cell types. *Cancer* 1984;54:3035–42.
129. Lagasse LD, Ballon SC, Berman ML, et al. Pretreatment lymphangiography and operative evaluation in carcinoma of the cervix. *Am J Obstet Gynecol* 1979;134:219.
130. Larson G, Alm P, Gullberg B, et al. Prognostic factors in early invasive carcinoma of the uterine cervix. *Am J Obstet Gynecol* 1983;146:145.
131. Lohe KJ. Early squamous cell carcinoma of the uterine cervix. *Gynecol Oncol* 1978;6:10–30.
132. Morrow P. Panel report: Is pelvic radiation beneficial in the postoperative management of stage Ib squamous cell carcinoma of the cervix with pelvic node metastases treated by radical hysterectomy and pelvic lymphadenectomy? *Gynecol Oncol* 1980;10:105.
133. Nahhas W, Sharkey F, Whitney C. The prognostic significance of vascular channel involvement in deep stromal penetration in early cervical carcinoma. *Am J Clin Oncol* 1983;6:259.
134. Tinga DJ, Timmer PR, Bouma J, et al. Prognostic significance of single versus multiple lymph node metastases in cervical carcinoma Ib. *Gynecol Oncol* 1990;39:175.
135. Van Nagell J, Donaldson E, Parker J. The prognostic significance of cell type and lesion size in patients with cervical cancer treated by radical surgery. *Gynecol Oncol* 1977;5:142.
136. Bissett D, Lamont DW, Nwabineli NJ, et al. The treatment of stage I carcinoma of the cervix in the west of Scotland 1980-1987. *Br J Obstet Gynaecol* 1994;101:615–20.
137. Morley GW, Seski JC. Radical pelvic surgery versus radiation therapy for stage I carcinoma of the cervix (exclusive of microinvasion). *Am J Obstet Gynecol* 1976;126:785–98.
138. Newton M. Radical hysterectomy or radiotherapy for stage I cervical cancer. A prospective comparison with 5 and 10 years follow-up. *Am J Obstet Gynecol* 1975;123:535–42.
139. Patel FD, Sharma SC, Negi PS, et al. Low dose rate vs. high dose rate brachytherapy in the treatment of carcinoma of the uterine cervix: a clinical trial. *Int J Radiat Biol Phys* 1994;28:335–41.
140. Teshima T, Inoue T, Ikeda H, et al. High-dose rate and low-dose rate intracavitary therapy for carcinoma of the uterine cervix. Final results of Osaka University Hospital. *Cancer* 1993;72:2409–14.
141. Haie-Meder C, Kramar A, Lambin P, et al. Analysis of complications in a prospective randomized trial comparing two brachytherapy low dose rates in cervical carcinoma. *Int J Radiat Oncol Biol Phys* 1994;29:953–60.
142. Lambin P, Gerbaulet A, Kramar A, et al. Phase III trial comparing two low dose rates in brachytherapy of cervix carcinoma: report at two years. *Int J Radiat Oncol Biol Phys* 1993;25:405–12.
143. Soisson AP, Soper JT, Clarke-Pearson P, et al. Adjuvant radiotherapy following radical hysterectomy for patients with stage IB and IIA cervical cancer. *Gynecol Oncol* 1990;37:390–5.
144. Kinney WK, Alvarez RD, Reid GC, et al. Value of adjuvant whole-pelvis irradiation after Wertheim hysterectomy for early-stage squamous carcinoma of the cervix with pelvic nodal metastasis: a matched-control study. *Gynecol Oncol* 1989;34:258–62.
145. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med* 1999;340:1144–53.
146. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med* 1999;340:1154–61.
147. Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med* 1999;340:1137-43.
148. Peters WA, III, Liu PY, Barrett RJ, et al. Cisplatin and 5-Fluorouracil plus radiation therapy are superior to radiation therapy as adjunctive in high-risk early-stage carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: report of a phase III intergroup study. (manuscript in submission).
149. Whitney CW, Sause W, Bundy BN, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stages IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes. A Gynecologic Oncology Group and Southwest Oncology Group Study. *J Clin Oncol* 1999;17:1339–48.
150. Chauvergne J, Lhomme C, Rohart J, et al. [Neoadjuvant chemotherapy of stage IIb or III cancers of the uterine cervix. Long-term results of a multicenter randomized trial of 151 patients]. *Bull Cancer* 1993;80:1069–79.
151. Chiara S, Bruzzone M, Merlini L, et al. Randomized study comparing chemotherapy plus radiotherapy versus radiotherapy alone in FIGO stage IIB-III cervical carcinoma. GONO (North-West Oncologic Cooperative Group). *Am J Clin Oncol* 1994;17:294–7.
152. Kumar L, Pokharel YH, Grover GK, et al. Neoadjuvant chemotherapy (CT) followed by radiotherapy (RT) in locally advanced squamous cell cervical cancer (SCC): two randomised studies. *Proc Annu Meet Am Soc Clin Oncol* 1997;16:abstract 1295.
153. Sardi J, Sananes C, Giaroli A, et al. Neoadjuvant chemotherapy in squamous cervical carcinoma stage IIIb. *Gynecol Oncol* 1994;52:104 (abstract 10).
154. Sardi JE, Giaroli A, Sananes C, et al. Long-term follow-up of the first randomized trial using neoadjuvant chemotherapy in stage Ib squamous carcinoma of the cervix: the final results. *Gynecol Oncol* 1997;67:61–9.
155. Souhami L, Gil RA, Allan SE, et al. A randomized trial of chemotherapy followed by pelvic radiation therapy in stage IIIB carcinoma of the cervix. *J Clin Oncol* 1991;9:970–7.
156. Sundfor K, Trope CG, Hogberg T, et al. Radiotherapy and neoadjuvant chemotherapy for cervical carcinoma. A randomized multicenter study of sequential cisplatin and 5-fluorouracil and radiotherapy in advanced cervical carcinoma stage 3B and 4A. *Cancer* 1996;77:2371–8.
157. Symonds RP, Cowie V, E. DS, et al. The Scottish and Manchester randomised trial of neoadjuvant chemotherapy for advanced cervical cancer. I*nternational Journal of Gynecological Cancer* 1997;7 (Suppl 2):Abstract 050.
158. Tattersall MHN, Ramirez C, Coppleson M. A randomized trial comparing platinum-based chemotherapy followed by radiotherapy alone in patients with locally advanced cervical cancer. *International Journal of Gynecological Cancer* 1992;2:244–51.
159. Tattersall MH, Lorvidhaya V, Vootiprux V, et al. Randomized trial of epirubicin and cisplatin chemotherapy followed by pelvic radiation in locally advanced cervical cancer. Cervical Cancer Study Group of the Asian Oceanian Clinical Oncology Association. *J Clin Oncol* 1995;13:444–51.
160. Tierney JF, Stewart LA, Parmar MKB. Can the published data tell us about the effectiveness of neoadjuvant chemotherapy for locally advanced cancer of the uterine cervix? *Eur J Cancer* 1999;35:406–9.
161. Robertson G, Lopes A, Beynon G, et al. Pelvic exenteration: a review of the Gateshead experience 1974–1992. *Br J Obstet Gynaecol* 1994;101:529–31.
162. Shepherd JH, Ngan HYS, Neven P, et al. Multivariate analysis of factors affecting survival in pelvic exenteration. *International Journal of Gynecological Cancer* 1994;4:361–70.
163. Morley GW, Hopkins MP, Lindenauer SM, et al. Pelvic exenteration, University of Michigan: 100 patients at 5 years. *Obstet Gynecol* 1989;74:934–43.
164. Kerr-Wilson RH, McCrum A. Follow-up of patients with gynaecological cancer. *Aust N Z J Obstet Gynaecol* 1995;35:298–9.
165. Steginga SK, Dunn J. Women's experiences following treatment for gynecologic cancer. *Oncology Nursing Forum* 1997;24:1403–8.
166. Kornblith AB, Thaler HT, Wong G, et al. Quality of life of women with ovarian cancer. *Gynecol Oncol* 1995;59:231–42.
167. Portenoy RK, Kornblith AB, Wong G, et al. Pain in ovarian cancer patients. Prevalence, characteristics, and associated symptoms. *Cancer* 1994;74:907–15.
168. Zech DFJ, Grond S, Lynch J, et al. Validation of the World Health Organization Guidelines for cancer pain relief: a 10-year prospective study. *Pain* 1995;63:65–76.
169. Agency for Health Care Policy and Research. *Management of cancer pain* Rockville, MD: Agency for Health Care Policy and Research, 1994.
170. Tunca JC, Buchler DA, Mack EA, et al. The management of ovarian-cancer-caused bowel obstruction. *Gynecol Oncol* 1981;12:186–92.
171. Rubin SC, Hoskins WJ, Benjamin I, et al. Palliative surgery for intestinal obstruction in advanced ovarian cancer. *Gynecol Oncol* 1989;34:16–9.
172. Redman CW, Shafi MI, Ambrose S, et al. Survival following intestinal obstruction in ovarian cancer. *Eur J Surg Oncol* 1988;14:383–6.
173. Zoetmulder FA, Helmerhorst TJ, van Coevorden F, et al. Management of bowel obstruction in patients with advanced ovarian cancer. *Eur J Cancer* 1994;30A:1625–8.
174. Clarke-Pearson DL, Chin NO, DeLong ER, et al. Surgical management of intestinal obstruction in ovarian cancer. I. Clinical features, postoperative complications, and survival. *Gynecol Oncol* 1987;26:11–8.
175. Krebs HB, Goplerud DR. Surgical management of bowel obstruction in advanced ovarian carcinoma. *Obstet Gynecol* 1983;61:327–30.
176. Beard SM, Coleman R, Radford J, et al. *The use of cisplatin and paclitaxel as a first line treatment in ovarian cancer* Guidance note for purchasers: 97/05. Sheffield: Trent Institute for Health Services Research, 1997.
177. Beard SM, Coleman RE, Radford J, et al. *Supplementary document: The use of paclitaxel in the first line treatment of ovarian cancer* Guidance note for Purchasers: 98/10 (Supplement to 97/05). Sheffield: Trent Institute for Health Services Research, in press.
178. Office for National Statistics. *Population and Health Monitor* MB1 98/2. London: Government Statistical Service, 1998.

Effective Health Care

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