

Progress in the management of solid tumours

Gynaecological cancer

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Summary

Gynaecological cancer encompasses a number of tumours with different epidemiology, pathology and treatment strategies. This article reviews the principal clinical advances and areas of development in cancer of the ovary, cervix, endometrium and vulva.

Keywords: ovarian cancer; cervical cancer; endometrial cancer; vulval cancer

Gynaecological cancer encompasses a number of tumours with different epidemiology, pathology, and treatment strategies. In general terms they are regarded as less common tumours, with the exception of vulval and vaginal cancer which are rare and very rare, respectively. The relative frequency of these cancers in relation to other tumour sites is shown in the table. During the past 10 years gynaecological oncology has become recognised as a true sub-specialty in the UK with increasing emphasis on expert multiprofessional teamwork as the best model for delivering high-quality care. This has been given increased impetus with the publication of the Calman/Hine report.¹ A recent joint response to the Calman/Hine report from the Royal College of Obstetricians and Gynaecologists and the British Gynaecological Cancer Society has recommended a 'hub and spoke' model based on a framework of a Gynaecological Cancer Centre with surrounding Associate Units.² This model requires a greater concentration of care, a move away from the current broad-based arrangement which involves a large number of consultants in almost all District General Hospitals.

In addition to this agenda for change, there have been a number of clinical advances and several new trials are underway. The purpose of this paper is to review the principal clinical advances and areas of development in cancer of the ovary, cervix, endometrium and vulva.

Table Annual incidence of most common cancers in the UK*

Type of cancer	Annual incidence
Lung	43 178
Skin	36 553
Breast	32 023
Colon	19 865
Prostate	14 271
Bladder	12 911
Stomach	12 478
Rectum	11 588
Ovary	5 836
Cervix	4 706
Uterus	4 160

Sources: Cancer statistics: registrations. England and Wales 1989 (HMSO 1994); Cancer registration statistics. Scotland 1981-90 (ISD Publications 1993); Northern Ireland Cancer Registration Scheme 1991 (The Ulster Cancer Foundation)

Ovarian cancer

This is not only the most common of the gynaecological cancers but is by far the most lethal, having an overall 5-year survival of only 30% in the UK. Most of the survivors come from stages I and II with only around 10% surviving with advanced disease. The reason for this poor overall survival is that the majority of cases present at an advanced stage due to a lack of typical symptoms in the early stages. The natural history of ovarian tumours is very inconsistent; some ovarian tumours remain localised while enlarging to a considerable size, while in other cases widespread peritoneal metastases are discovered in the presence of a relatively small volume primary ovarian tumour. The reasons for this inconsistency are not clear but factors such as angiogenesis probably play a part. An increased understanding of the biology of ovarian cancer will be essential if major progress is to be made.

The aetiology of sporadic ovarian cancers is assumed to be an accumulation of genetic mutations but as yet all of the key events are ill understood. What is clear is that, in a subset of perhaps 5-10% of cases, a familial predisposition to developing ovarian cancer occurs as a consequence of inherited predisposition, and more than 80% of these are linked with the BRCA1 gene.³ The discovery of the BRCA1 gene, which has now been cloned,⁴ makes it possible to identify those women who have inherited a mutation in the gene and who therefore carry a high risk of developing ovarian cancer. This not only allows appropriate counselling to be provided but also selects women for ovarian screening and where appropriate, prophylactic oophorectomy. By being able to quantify individual risk, women can now make an informed choice about their management if they happen to be in this cancer-prone group.

OVARIAN CANCER SCREENING

Unlike cervical cancer, no precursor lesion of ovarian cancer has yet been identified and therefore screening for pre-invasive disease of the ovary is not possible. What is possible is to attempt to screen for ovarian cancer and two approaches have been adopted. The first is to use ultrasound screening of the ovaries to identify abnormalities⁵ and the second is to use a tumour marker such as CA125 and then concentrate on the use of ultrasound for women with an abnormal tumour marker result.⁶ The advantage of screening with ultrasound is a high sensitivity but there are problems with specificity and cost. The use of tumour markers has the problem of reduced sensitivity but it is possible to determine the cut off point of the test such that you can achieve higher levels of specificity. These issues have been well reviewed recently by Jacobs⁷ and analysed in a

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systematic review by Bell *et al.*⁸ Although non-randomised trials have indicated that both of these methods can detect cancers, neither has been shown to be effective in reducing deaths from ovarian cancer. In order for this to be the case, tumours will need to be detected while still stage I, and at an earlier stage than would have been the case had they presented clinically. Bell's systematic review of ovarian screening has pointed out this lack of proven effectiveness not only in population screening but also in screening high-risk women, and has gone on to recommend that randomised trials be carried out to demonstrate whether or not ovarian screening can be shown to be both effective and cost-effective. There are currently three new trials in progress, two in the UK and one in the USA, but these require the participation of a very large number of women and will therefore be both expensive and take a considerable time to complete satisfactorily. In the meantime, in the UK, it is recommended that women who are shown to be at increased risk are offered ovarian screening; a non-randomised study of such women is currently underway, sponsored by the UK Co-ordinating Committee for Cancer Research. In this study, 3000 women proven to be at high risk will be screened using annual CA125 and ultrasound, but a significant number of women will probably opt for prophylactic oophorectomy.

SURGERY FOR OVARIAN CANCER

It has been accepted for a long time that the primary treatment for ovarian cancer should begin with surgery and since the late 1960s it has been recommended that this should take the form of maximum cytoreduction.⁹ A large number of non-randomised studies has indicated that women who have suboptimal debulking have a worse prognosis than those in whom there is a minimum residue of disease at the end of the surgical operation.¹⁰ There must be some uncertainty as to the true effectiveness of aggressive debulking in ovarian cancer because no randomised controlled trials have been performed, and it may be that an inability to debulk a particular tumour may relate more to its intrinsic biology with associated prognostic factors than to the cytoreduction itself. Non-debulkable tumours may be more invasive with a worse profile of prognostic factors. Nevertheless, worldwide it is still accepted that aggressive initial debulking is the optimal form of surgical management. The other purpose of initial laparotomy is to stage the disease and characterise the histopathology and currently it is accepted that all women in whom the disease has progressed beyond the ovaries, ie, stage II and above, should be managed with chemotherapy.

INTERVAL DEBULKING SURGERY

Most reported series of ovarian cancers demonstrate an optimal debulking rate of only 40–50% of cases. Because bulk residual disease is known to indicate a poor prognosis, it has been proposed for some time that further surgery to attempt to debulk disease further may be an effective intervention. In 1996, the EORTC published a randomised trial of interval debulking surgery.¹¹ In this study women with bulk residual disease who responded to chemotherapy were randomised to a second debulking procedure after three cycles of chemotherapy or simply to continue to six cycles. Following interval debulking, a further three cycles of chemotherapy were given. Women in the interval debulking arm demonstrated an overall survival time of 6 months more than the group which did not have interval debulking surgery. This was an important result, in part because it suggests that surgery itself does have a significant part to play in the disease management. Whether the second surgery simply further retards the disease or whether it reduces tumour burden for subsequent chemotherapy is not certain. What is also not certain is whether this interval debulking would be as effective an intervention if used in conjunction with paclitaxel/platinum because its superior activity may reduce the effect that the surgery can have. The Medical Research Council (MRC) has recently funded a confirmatory trial of interval debulking surgery which is about to get underway in the UK and it will be interesting to see whether the effect is sustained with the use of paclitaxel.

CHEMOTHERAPY OF OVARIAN CANCER

Until recently the 'gold standard' chemotherapy for ovarian cancer was either single agent carboplatin or cisplatin combined with an alkylating agent. Meta-analyses have shown that these two regimens are approximately equivalent. During the last 3 years, however, trials have been published which have indicated a clear superiority when paclitaxel is used in conjunction with platinum as first-line chemotherapy. The first trial to report this was performed in the USA,¹² and compared cisplatin and cyclophosphamide with cisplatin and paclitaxel. In the cisplatin/paclitaxel arm the disease-free survival was 18 months compared with 12 months in the cisplatin/cyclophosphamide group, and the

Ovarian cancer

- screening for ovarian cancer is as yet unproven in either population or high risk groups
- optimal management of ovarian cancer requires expert multidisciplinary teams
- paclitaxel/platinum is now considered optimal chemotherapy
- interval debulking may be useful for chemosensitive tumours where there was bulk residual disease

Box 1

median overall survival was increased from 26 months to 38 months. This improvement in survival must be seen as very significant in the context of ovarian cancer. A confirmatory trial by EORTC and Scottish and Canadian groups recently also reported a significant increase in median overall survival from 25 to 35 months.¹³ These two studies, which included almost 1000 patients, have been followed by an even larger MRC study (ICON 3) which has completed accrual of 2000 women and which will report initial results within one to two years. However, it is now generally accepted by medical oncologists that optimal chemotherapy for ovarian cancer consists of platinum and paclitaxel and a recent German study¹⁴ which compared cisplatin/paclitaxel with carboplatin/paclitaxel found equivalent progression-free survival with improved quality of life in the carboplatin/paclitaxel group. Widespread use of paclitaxel will increase the cost of treating ovarian cancer considerably but it does appear to represent a significant advance in the management of ovarian cancer.

Although we are not seeing significant improvements in long-term cure following ovarian cancer, we are beginning to see improvements in overall survival, and advances in our biological understanding of the disease should lead to further improvements in management during the years to come.

Cervical cancer

SCREENING

The incidence of cervical cancer has fallen steadily in the UK since the introduction of national computerised call and recall in the cervical screening programme. Improved management of the programme together with quality assurance measures and national coverage now in excess of 80% of the target population, its effectiveness is now apparent with a reduction of both the incidence and death rate of cervical cancer. The Health of the Nation target set in the early 1990s envisaged a 20% reduction in death rate by the year 2000. This has now been exceeded, and there are now just over 3000 cases a year with just over 1300 deaths per year in the UK. Screening using exfoliative cytology may be approaching its maximum potential now, and there is recognition that an inherent lack of sensitivity must be overcome if further significant gains are to be made in cervical screening. The principal contender for this is the use of human papillomavirus (HPV) testing, and considerable interest now surrounds this new technology. It has been accepted for a number of years that the human papillomavirus is responsible for early events in cervical carcinogenesis and this close association of HPV with cervical neoplasia makes it potentially a valuable marker. Studies in Holland have indicated that HPV testing may have the potential both to improve sensitivity and also perhaps to increase screening intervals in these women who are HPV negative.¹⁵ Studies are now underway in the UK to examine the potential role of HPV in population screening. It is currently envisaged that this would be done in conjunction with conventional cervical cytology but it will be some time before its true effectiveness as a screening tool is understood. There is, of course, a risk that the use of HPV testing will lead to a reduction in specificity which could lead to unnecessary further investigation, hence the need for rigorous trials to establish not only its true clinical effectiveness but also cost-effectiveness. There is also preliminary evidence that screening adequately screened women beyond the age of 50 may not be cost effective.¹⁶

DIAGNOSIS AND MANAGEMENT

The standard management of cervical cancer has been established for many years. Disease confined to the cervix is divided into Stages Ia and Ib. Stage Ia disease, or micro-invasive disease, is associated with a negligible incidence of lymph node metastasis and can usually be managed by conservative surgery in the form of a cone biopsy or if the patient does not wish to retain fertility a simple total hysterectomy. Stage Ib or frankly invasive cervical cancer, can be managed equally effectively by radical surgery or radical radiotherapy.¹⁷ Radical surgery takes the form of a radical hysterectomy and pelvic lymph node dissection, the purpose of which is both to achieve local control and to establish the lymph node status of the disease. Surgery is very much to be preferred in premenopausal women in whom vaginal function and ovarian function can be well preserved but it is increasingly being used in older women. Radiotherapy for Stage Ib disease may take the form of external beam radiation followed by brachytherapy with insertion of a caesium source into the cervix. In small volume Stage Ib disease it may not be necessary to treat with external beam radiation, in which case two insertions of caesium are undertaken. For advanced cervical cancer, which may range from early parametrial invasion to a pelvis frozen with tumour extending to both pelvic side walls, management is external beam radiation

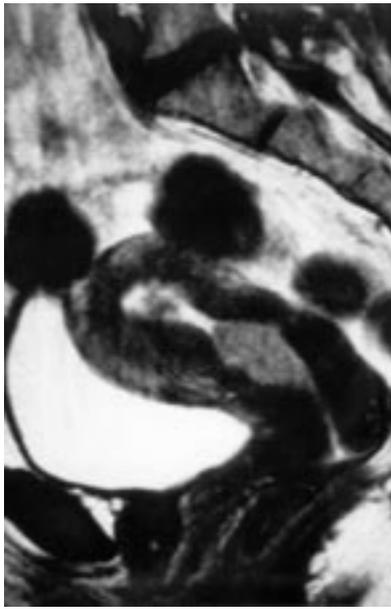


Figure 1 MRI scan in the sagittal plane showing tumour in the upper cervical canal.

Cervical cancer

- screening for cervical cancer is now achieving reductions in death but further improvement may be achievable with HPV testing
- careful planning by radiology is required for bulky Stage Ib tumours to avoid the morbidity associated with radical surgery followed by radical radiotherapy
- laparoscopic surgery is being used for lymphadenectomy but this is as yet of unproven value
- radical trachelectomy is being advocated by some, in order to preserve fertility with small volume Stage I disease

Box 2

combined with brachytherapy. Selection of treatment is particularly important in bulky Stage Ib disease, ie, tumours in excess of 4 cm across, particularly with poor differentiation. It is known that the incidence of positive lymph nodes is higher in this group of patients and in cases with positive pelvic nodes it may be preferable to treat with radiation rather than with surgery in order to avoid both radical surgery and radiation. Magnetic resonance imaging (MRI) is useful in determining the extent of the tumour locally¹⁸ (figure 1), although it is not quite as useful as computed tomography (CT) in detecting involved lymph nodes at the pelvic side wall. Pre-operative imaging is now a valuable means of treatment planning which should involve joint discussions between the gynaecological oncologist and the clinical oncologist.

Because of the success of the screening programme, more cervical cancers are being discovered at an early stage and with small volume disease. One question is whether women who wish to retain their fertility may undergo less radical surgery than has hitherto been performed in the presence of small-volume Stage Ib tumours. The technique of radical trachelectomy and lymphadenectomy has been described and early experience reported.¹⁹ In this approach the cervix is removed in a radical fashion with some parametrial tissue and the lymphadenectomy can then be undertaken laparoscopically. The rationale of this operation is to preserve the corpus of the uterus for fertility purposes. A number of these operations have been performed in several centres and, while the procedure is feasible, the true effectiveness of the operation in terms of long-term cure and successful pregnancies has not yet been established. It will be important to monitor the results of such procedures in order to see whether they can be adopted more widely but for the time being it is best concentrated in the hands of a small number of centres so that the results can be ascertained.

CERVICAL CANCER

Neo-adjuvant chemotherapy

During recent years there has been increasing interest in the use of chemotherapy, particularly the role of neo-adjuvant chemotherapy, where the chemotherapy is given prior to radiotherapy in an attempt to achieve a reduction in tumour volume. To date, nine randomised trials have been performed and the results are not consistent. A recent meta-analysis has concluded that, overall, there is no indication that neo-adjuvant chemotherapy is of value in cervical cancer (J Tierney, personal communication). Another setting for the use of chemotherapy is in surgically established node-positive disease, where it could be given prior to adjuvant radiation in an attempt to reduce the risk of recurrence. The MRC have now started a randomised trial in which women with node-positive disease following surgery will be randomised to either radiation and chemotherapy or radiation alone in an effort to establish whether chemotherapy is effective.

Concomitant chemoradiation

In March 1999, the US National Cancer Institute made public the results of several trials not due to be published (by the *New England Journal of Medicine*) until April 1999. These trials indicate a medium-term survival advantage for platinum-based chemotherapy given concomitantly with radiation over radiation alone. These data provide a solid body of evidence for the use of chemoradiation for cervical cancer, although this has not yet been properly evaluated in the UK.

Endometrial cancer

Endometrial cancer has always tended to be regarded as the least challenging of the gynaecological cancers. The reasons for this are firstly that it has a high cure rate, as a result of generally presenting early with postmenopausal bleeding, and secondly that its treatment is reasonably straightforward. Nevertheless, there is still an overall death rate of almost 30% which means that there is scope for improvement in the management. For years the standard treatment in the UK has been total abdominal hysterectomy and bilateral salpingo-oophorectomy, followed by adjuvant radiotherapy if there is poorly differentiated disease with deep myometrial invasion.

There is currently some interest in the role of lymphadenectomy in endometrial cancer, both as a means of staging the disease and perhaps of achieving higher cure rates. A number of gynaecological oncologists believe that lymphadenectomy can help to select patients who require adjuvant radiation following hysterectomy. If lymphadenectomy were to demonstrate that there was no evidence of extra-uterine disease, then one could argue that even women with high-risk endometrial tumours do not require adjuvant radiotherapy because

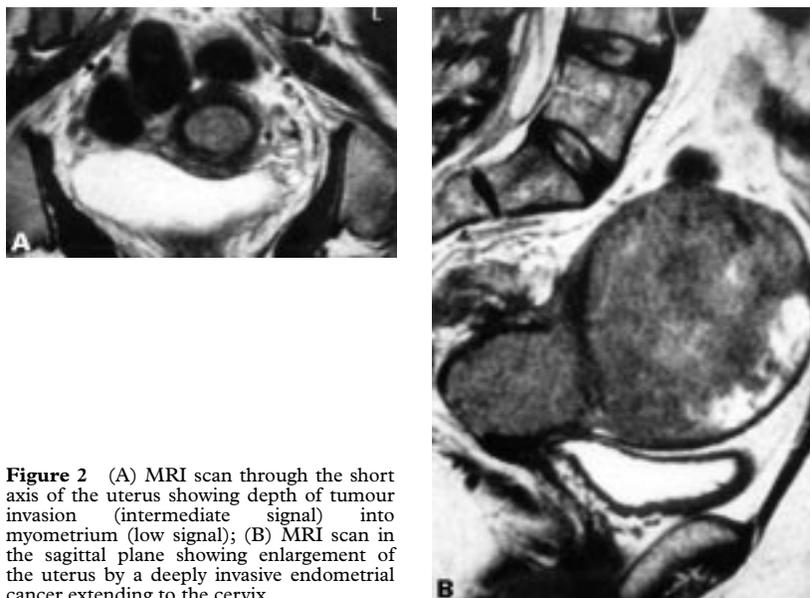


Figure 2 (A) MRI scan through the short axis of the uterus showing depth of tumour invasion (intermediate signal) into myometrium (low signal); (B) MRI scan in the sagittal plane showing enlargement of the uterus by a deeply invasive endometrial cancer extending to the cervix

local control is assured by the hysterectomy and external beam radiation is not required for the control of extra-uterine disease. Lymphadenectomy may also be useful because removal of any involved nodes may improve survival. A recent case-controlled study²⁰ suggested that women who had had a lymphadenectomy showed improved survival but a study of this sort does not allow for case mix or surgical expertise. It may be that the women who had a lymphadenectomy were more likely to be fitter and operated on by specialised surgeons.

The other issue of considerable interest currently concerns the effectiveness of adjuvant radiotherapy. In a randomised trial performed 20 years ago in Norway, women with high-risk endometrial cancer all had brachytherapy, and half also had external beam radiation. There was improved control of pelvic disease in the radiation arm but no improvement in overall survival.²¹ A recent report from The Netherlands has confirmed this result.²² Because of the lack of evidence surrounding the effectiveness of lymphadenectomy and of adjuvant radiation, a randomised trial has been set up by the MRC in which women are randomised initially to have hysterectomy with or without lymphadenectomy; those women in whom the tumour has high-risk features (irrespective of node status) will then be randomised to receive external beam radiation or to have no external beam radiation. This study will hopefully determine the true effectiveness of lymphadenectomy and of adjuvant radiation in the management of endometrial cancer.

Advances have been made in the assessment of endometrial cancer pre-operatively and MRI now offers an excellent means of assessing tumour depth and local extent (figure 2). This could be a means of selecting women for lymphadenectomy.

Vulval cancer

Vulval cancer is quite rare, with fewer than 1000 cases per year in the UK. Conventional management of this disease is a vulvectomy combined with groin node dissection to remove the inguinal and upper femoral nodes. The traditional *en bloc* vulvectomy, in which large amounts of skin were removed and which was associated with severe disfigurement around the vulval region, has been replaced by a local vulvectomy and separate groin incisions. This has resulted in a much improved cosmetic effect, and despite the concern of microscopic residual disease in the skin between the vulva and the groin, there are no indications that this more conservative form of surgery is associated with increased recurrence rates.

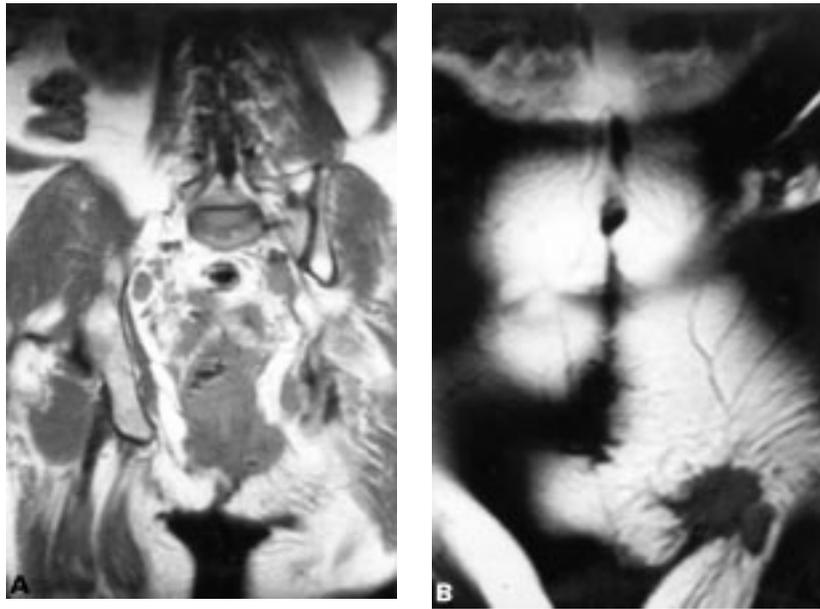
Groin node dissection is associated with the risk of chronic leg oedema and although this does not happen very often, it can be quite a difficult problem. Because of morbidity, there is now a growing interest in trying to detect cases in which groin node dissection may not be required. MRI can be useful in identifying involved nodes but whether this is better than clinical evaluation is not known (figure 3). Experience has taught us that, if the depth of invasion in the vulva is less than 1 mm, then the risk of lymph node dissection is minimal.^{23 24}

Endometrial cancer

- adjuvant radiotherapy, though widely used with high-risk tumours, has not been shown to improve survival
- pelvic lymphadenectomy, widely practised in the US and Australia, has not been shown to improve survival
- tamoxifen is acknowledged to increase the incidence of endometrial cancer

Box 3

Figure 3 (A) MRI scan in the coronal plane showing enlarged pelvic nodes (bilateral) from vulval cancer; (B) MRI scan in the coronal plane showing metastatic inguinal nodes in the left groin from a primary vulval cancer



A pre-operative biopsy, which should always be performed in order to confirm the tumour type, also provides information on the depth of the tumour and enables optimal surgical planning. It would be ideal if women in whom there is no clinical evidence of lymph node involvement could undergo some sort of imaging-guided biopsy of the lymph nodes; in the absence of nodal disease they could thus avoid groin node dissection. Clinical studies of this sort are in progress.

Before general acceptance of this trend away from groin node dissection, a great deal of evaluation will be required. Although a vulvectomy and groin node dissection are associated with significant surgical morbidity, most of it is short-term and the procedure is extremely effective. The consequences of inadequate surgery are very severe in terms of local recurrence or the progression of groin node disease, both of which can make salvaging very difficult indeed. There is no doubt that optimal care requires these cases to be managed by expert gynaecological oncologists, in order that surgery is best tailored to the individual patient.

Laparoscopic surgery

Primary surgery plays a significant role in the management of gynaecological cancer. Hysterectomy, radical hysterectomy, and lymphadenectomy can all be performed laparoscopically and these new techniques are now being used in women with endometrial and cervical cancer. In exploring the key issues which require to be addressed if this surgery is to be more widely adopted, several questions arise:-

- can minimal access surgery replace open surgery for cancer where the operative intent is to cure?
- is laparoscopic surgery associated with an improved quality of life?
- is laparoscopic surgery cost-effective?
- can laparoscopic surgery achieve new therapeutic boundaries?
- does laparoscopic surgery bring new complications and morbidity?

In considering these issues it is clear that far more thorough evaluation of these methods is required, preferably through randomised trials but initially through detailed observational studies. Perhaps the most useful role for laparoscopic surgery currently is pelvic lymphadenectomy, where a surgical staging can be accomplished without recourse to open surgery.

It is by no means clear whether minimal access surgery for gynaecological cancer will be a significant advance. Clearly, if robust studies prove its effectiveness and it is cost-effective then its use should become widespread, but for the time being those who advocate its use must take responsibility for proving its effectiveness.

Conclusions

Much has happened in gynaecological cancer in the past 10 years. Cervical screening has had a major impact and research is now being conducted on the benefits of ovarian screening. The chemotherapy for ovarian cancer has improved significantly. Surgical trials are taking place in both ovarian and endometrial cancer. Major improvement in prognosis will require new advances in treatment but for the time being we must endeavour to ensure that the treatments we already have are used to optimal effect.

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