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Carcinoma of the Endometrium

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Contents

Abstract

The incidence of endometrial cancer is highest among relatively affluent Caucasians. Although it has a comparatively low mortality rate compared with other gynaecological cancers, it is capable of aggressive behaviour. Endometrial cancer is uncommon in premenopausal women. The incidence rises with age and is significantly increased when there is exposure to unopposed estrogen, including hormone replacement therapy (HRT). Even when HRT is given in the form of estrogen and cyclical progesterone there is probably some increased risk. The long term use of tamoxifen for breast cancer is also associated with an increased incidence of endometrial cancer.

Transvaginal ultrasound and pipelle or hysteroscopy endometrial biopsies are tending to replace the traditional dilation and curettage in establishing a diagnosis.

90% of endometrial tumours are surgically resectable on presentation. This remains the first line management – minimally, a total abdominal hysterectomy and bi-lateral salpingo oophorectomy. Prognostic factors include the histological grade, the depth of invasion of the myometrium, the presence or absence of lymph-vascular space invasion and involved regional nodes, tumour volume, and the presence or absence of involvement of the cervix. The pelvis is a major anatomical site at risk of recurrence, and since cytotoxic chemotherapy and hor-

mone therapies have limited effectiveness, radiotherapy is the adjuvant therapy of choice where adverse prognostic factors are present.

A move towards more radical surgery – the addition of lymphadenectomy with a total abdominal hysterectomy and bi-lateral salpingo oophorectomy, may modify the value of adjuvant therapy and has highlighted the need to demonstrate the exact place of post operative radiotherapy in the management of endometrial cancer. The ASTEC trial in the UK, run by the Medical Research Council, has the dual aims of determining the benefit of lymphadenectomy and of post operative adjuvant radiotherapy in patients with endometrial cancer confined to the corpus.

Patients who are not medically fit for surgery or who have inoperable disease are managed with radical radiotherapy but the results in both these groups are inferior to those obtained with radical surgery. Spread outside the pelvis to para-aortic nodes may still be salvaged with local irradiation, but systemic disease is incurable and treatment is largely palliative including consideration of local irradiation, hormone therapy or chemotherapy for symptomatic relief.

As reliable techniques for diagnosis are refined an even larger proportion of patients will be diagnosed with early disease. This, together with the development of new cytotoxic agents and sophisticated radiotherapy techniques to reduce normal tissue morbidity, will require the establishment of further clinical trials to refine optimal management.

Carcinoma of the endometrium is common among Caucasians with a relatively high socio-economic status. Although the incidence remains relatively low in Asia, there are approximately 4000 new cases per annum recorded in the UK and 36 000 cases in the US where is it is the most common form of gynaecological cancer. In both countries, the incidences of the 3 major gynaecological cancers – uterine, cervical and ovarian – are comparable. The mortality rates however are quite different – 30% for uterine cancer, 55% for cervical cancer, and 80 to 85% for ovarian cancer. That endometrial cancer has a relatively good prognosis should not disguise the fact that some of these tumours can behave very aggressively.[1,2]

1. Aetiology

The average age at presentation is 60 years and the incidence increases with age. As life expectancy increases so too will the incidence of endometrial cancer.[3] There is a well known association with diabetes mellitus of late onset type II, hypertension and obesity. These 3 conditions tend to be mutually associated anyway but some common underlying factors can be isolated, chiefly exposure to unopposed estrogens. There is a higher than average history of menstrual disorder and endometrial cancer is more common in patients who have an early menarche and a late menopause. It also occurs more frequently in women of low parity. Conversely, the risk of these tumours is reduced by multiple pregnancies.[4] Obesity is associated with increased estrogen production secondary to increased peripheral aromatisation.[5] This effect is more significant in postmenopausal women because the ovaries are no longer contributing to hormone output. Consequently, the estrogen sensitive tissues of obese women are exposed to more than their leaner counterparts. The same basic principle underlies the findings by several investigators of a negative association between smoking and endometrial cancer, and this strongly modifies the known increased risk with bodyweight.[6-8] Franks et al.[9] considered that smoking after the natural onset of menopause is associated with a 70% reduction in risk of endometrial cancer among estrogen users and a 50% risk reduction in non-estrogen users.

1.1 Hormone Replacement Therapy and Endometrial Cancer

It is well known that the risk of endometrial cancer increases steeply if unopposed estrogens are used as hormone replacement therapy (HRT) in the presence of the intact uterus. The Postmenopausal Estrogen/Progestin Intervention (PEPI) trial, which was reported in 1996,[10] looked at the effects of hormone replacement therapy on endometrial histology in postmenopausal women who had been randomised in receive placebo, estrogen only or 1 of 3 estrogen plus progesterone regimens. This was a 3-year, multicentre, randomised, double-blind, placebo-controlled trial. Estrogens were seen to enhance the development of endometrial hyperplasia and the addition of progesterone protected the endometrium from the hyperplastic changes. However, 2 other publications have thrown doubt on the tolerability of combined estrogen/progesterone preparations. Gruber et al.[11] investigated patients with endometrial cancer after combined HRT and found 'evidence that supraphysiologic estrodial levels despite combination with cyclical progestin therapy increase the risk of endometrial cancer'.

Weiderpass et al.[12] in a case study of 709 patients with incidental carcinoma of the endometrium compared with 3368 controls, came to the same conclusion – treatment with estrogen alone was associated with a marked dose- and duration-dependant increase in the relative risk of endometrial cancer. However, an increased risk was also seen in women for whom the cyclical use of progesterone lasted for fewer than 16 days of the cycle. The conclusion was that progesterone needed to be continuously applied to reduce the risks of endometrial cancer with HRT to a minimum.

The association between HRT and endometrial cancer has led some clinicians to refuse to prescribe HRT following radical treatment of the condition. This is confusing two different categories of risk. That unopposed estrogen is implicated in the development of uterine cancer is not in doubt. However, after radical surgical treatment where the uterus has been removed there is no longer a target organ present. In this situation therefore 'risk' is related to whether or not any occult cancer cells remaining after treatment might be stimulated into vigorous growth. Thus, the worst that could result from HRT given after a hysterectomy is shortening of the latent period to first recurrence. It will not convert a 'cure' to a treatment failure. For most women with severe post menopausal symptoms, HRT after radical surgical treatment for uterine cancer would be acceptable.

1.2 Endometrial Cancer and Tamoxifen

The association between tamoxifen and endometrial cancer is difficult to quantify. Both breast and endometrial cancer are common malignancies and are known to share several aetiological factors. Ewartz et al.[13] showed that these factors are quite independent of the drugs used in the management of breast cancer and these additional factors probably account, at least in part, for the wide variations in the reported incidences of endometrial cancer during tamoxifen therapy. However, there is general acceptance that exposure to tamoxifen for 12 months or more is associated with increasing hyperplastic and dysplastic changes in the endometrium and an increasing risk as exposure is continued to frank carcinomatous change.[14] Such tumours have generally been regarded as having relatively good prognostic features. However, a recent report by Berman et al.[15] suggests that tamoxifen-induced unterine neoplasia may have a more aggressive character than previously thought. They reported a nationwide case-controlled study of patients taking tamoxifen and found that long term users were more likely than non-users to develop mixed mesodermal tumours and uterine sarcomas together with an increased incidence of other high risk factors [high International Federation of Obstetrics and Gynaecology (FIGO) Stage, p53 positive]. The risks of uterine cancer were related to the duration of use after cessation of the drug. While the benefits of tamoxifen in breast cancer clearly outweighed such risks, the author questioned the use of tamoxifen as a preventative agent in healthy women.

1.3 Other Aetiological Factors

Simopoulos[16] and other investigators have shown an association between fat intake and endometrial cancer but this is probably principally through the medium of obesity (see section 1). Endometrial cancer is unusual in premenopausal women and very rare in pregnancy, although Vaccorello et al.[17] have reviewed the literature on 3 reported cases. Jeyarajah (UK Brachytherapy meeting March 1977) described several alterations involving p*53* mutations, the Ki-ras mutation and over expression of oncogenes such as *c-myc* and *c-neu* but has not found a single frequent genetic event in endometrial cancer. Others have reported the prognostic significance of p*53*, *PCNA* and *C-erb B-2* in endometrial cancer.[18,19] Such studies may aid detection of a high-risk group and may have a place in the future in screening, therapy and prevention. Howver, routine genetic profiling is not as yet a standard part of management. There is a positive family history of endometrial cancer in 15% of patients. Previous pelvic irradiation increases the risk of another pelvic malignancy, including endometrial cancer, but because of the potentially long latent period and changes in radiation techniques over the past 25 years it is difficult to quantify the risk associated with modern treatment regimes.

There appears to be a positive association with thyroid disorders and analysis of 198 patients with endometrial cancers has shown 13% to have a history of thyroid disease (unpublished observations).

2. Histopathology

Over 90% of uterine cancers arise within the epithelium and are endometrial adenocarcinomas. These can be subdivided into 4 distinct groups: (i) adenocarcinomas and adenoacanthomas (squamous metaplasia) account for 80% of epithelial tumours; (ii) papillary adenocarcinomas; (iii) clear cell carcinomas; (iv) mixed adenosquamous carcinomas.

These last 3 variants occur with equal incidence. Uterine sarcomas are uncommon accounting for only 5% of uterine cancers. These are classified as follows: (i) endometrial stromal – low grade or high grade; (ii) leiomyosarcomas; (iii) nonspecific mesenchymal; (iv) mixed mesendermal (epithelial and stromal elements).

Uterine sarcomas are not considered further in this review.

Since endometrial adenocarcinomas arise from the lining of the uterus they will at first expand into the uterine cavity as well as involving progressively more of the lining. At the same time, the myometrium will be steadily invaded until it and the serosal covering is completely breached. Histologically, the tumour is graded from 1 to 3 depending on the nuclear morphology and such grading gives an indication of aggressiveness. The histological grade is an important prognostic factor but histopathological studies also show a reliable relationship between lymph node metastases and myometrial penetration by the tumour and its overall size. Where there is only superficial invasion, the incidence of nodal involvement is reported variously between 5 and 8%, whereas for deep invasion the figure rises to approximately 50%.[20]

Demonstration of nodal involvement is an important aspect of management and if the pelvic nodes are known to be involved then about 60% of these women will also have involved para-aortic nodes.[21]

2.1 Lymphatic Drainage

There are 3 lymph node areas at direct risk. The fundus drains through the lymphatics of the infundibulo pelvic ligament and follows the pathways of ovarian drainage to the para-aortic nodes. The lower part drains directly to the pelvic nodes but there is also lymphatic access via the round ligament to the inguinal nodes.

The FIGO staging for uterine cancer is outlined in table I.

3. Presentation and Natural History

The most common symptom is postmenopausal vaginal bleeding which may be both sudden and of a significant amount. As most patients are post-

Table I. FIGO staging for uterine cancer

Tumour stage		
I- Confined to corpus (G1, G2 or G3)	a	Cancer confined to endometrium
	b	Myometrial invasion <50%
	c	Myometrial invasion >50%
II- Cervix involved (G1, G2 or G3)	a	Endocervical glands only
	b	Cervical stromal invasion but does not extend beyond uterus
III (G1, G2 or G3)	a	Involves serosa of uterus or adnexiae, or positive ascities or peritoneal washings
	b	Vaginal involvement- direct or metastatic
	c	Para aortic or pelvic node involvement
IV (G1, G2 or G3)	a	Involves mucosa of bladder or rectum
	b	Distant metastases and involvement of other abdominal or inguinal lymph nodes

FIGO = International Federation of Gynaecology and Obstetrics; **G1** = well differentiated; **G2** = moderately differentiated; **G3** = poorly differentiated.

menopausal when they present, this bleeding will be an abnormal event so they will seek medical advice earlier rather than later. Bleeding usually occurs at a relatively early stage and as a consequence about 90% of uterine tumours are still operable at the time of presentation. The uterus will act as an anatomical barrier to spread and will gradually enlarge to accommodate the increase in tumour mass but with the passage of time the risk of lymph node involvement increases. If the serosa overlying the uterus is breached then peritoneal spread can occur. Vascular metastases are generally, although not always, a late event with lung, bone, brain and liver the principle sites. In theory, uterine tumours can access the peritoneal cavity and the ovaries via the fallopian tubes, although the ambient flow of fluid through the tubes tends to prevent this. The ovaries are not an uncommon site of metastatic disease and it may be very difficult to say from the clinical picture whether the patient has a primary endometrial tumour, which has spread to the ovaries or vice versa.

3.1 Prognostic Factors

Adenocarcinomas and adenoacanthomas account for the bulk of uterine carcinomas.

There are 4 principle prognostic variables: (i) the depth of invasion of myometrium; (ii) lympho vascular space invasion; (iii) the macroscopic diameter of the tumour or tumour volume; and (iv) the histological grade.

Other significant but less dominant prognostic factors are: (i) the presence or absence of involvement of the cervix; (ii) whether or not peritoneal cytology is positive; (iii) the presence or absence of adnexial metastases; and (iv) a raised CA125 level at presentation.

Kamura et al.,[22] reporting on 175 patients undergoing total or radical hysterectomy, showed the relevance of all of these factors to the incidences of pelvic lymph node metastases. Feltmate et al.,[23] looking at predictions of recurrence, found that the lymphovascular space invasion was the strongest predictor of recurrence regardless of postoperative therapy. However, the numbers in this study were small (65).[23] The tumour markers CA125 and CA199 are both raised in 60% of patients with advanced uterine cancer. Rose et al.[24] reported serial serum CA125 measurement in the evaluation of recurrent endometrial cancer and concluded that if elevated at diagnosis then this was an important marker of recurrent disease. Other prognostic predictors that have been reported are: (i) the levels of cyctosolic cathepsinn D – low levels predict poor prognosis,[25] and (ii) high metallothionein expression, which has been found to be associated with aggressive tumour types.[26]

4. Diagnosis

Although endometrial cancers may be picked up by cervical screening cytology, the examination of cervical smears and posterior fornix pool material is not a reliable screening test. Such investigations are not a sufficient response if a patient presents with postmenopausal bleeding. The traditional specific examination of Dilation and Curettage (D&C) has now been largely replaced by trans-

vaginal ultrasound scanning, and pipelle sampling of the endometrium.

Experience with transvaginal ultrasonography has rapidly increased and the practice of regular assessment of endometrial thickness by this method for those women who are taking HRT or tamoxifen has increased. The rising incidence of endometrial cancer in affluent Western countries may be considered an argument for transvaginal ultrasound screening, if not for the general population, at least for those patients for whom a family history, genetic analysis and immunohistochemistry predict a higher than average risk.[27] Cicinelli et al.[28] considered transvaginal ultrasound a useful screening technique but with the disadvantage of low specificity. However, they point out that microhysteroscopy allows 'an atraumatic and direct investigation of the uterine cavity' and as it does not require an anaesthetic or hospitalisation (as does a D&C) this could be a routine screening procedure for patients at risk.

Youssif and McMillan[29] describe the pipelle endometrial biopsy, which is available as hysteroscopy as 'safe, economical and acceptable to patients, clinicians and pathologists'. They remark that transvaginal sonography can reduce the number of biopsies required and the 2 procedures together can reach 100% in diagnostic accuracy. An additional value of the transvaginal ultrasound scan is its ability to show the degree of myometrial invasion.[30] Hysteroscopic biopsy does carry a risk of embolic vascular seeding but the risk is small.[31] Although transvaginal ultrasound may be a useful screening procedure, it is insufficient on its own to establish a diagnosis – this requires tissue sampling.

5. Treatment

The majority of patients with endometrial cancer are postmenopausal women for whom there are no issues regarding maintenance of fertility. This, together with the fact that 90% of the tumours are operable at presentation, has led to total abdominal hysterectomy (TAH) and bilateral salpingo oophorectomy (BSO) being widely accepted as the treatment of choice; a total hysterectomy because the cervix maybe invaded and a bi-lateral salpingo oophorectomy because of the significant incidence of ovarian metastases. The establishment of transvaginal ultrasonography and hysteroscopy may lead to greater early stage disease detection and this together with the availability of a prognostic 'profile' may strengthen arguments for more conservative surgery for selected patients.

Some patients may not be fit for surgery – a significant number of patients are elderly, overweight or have diabetes mellitus and/or hypertension, and may therefore be poor operative risks. With the steady improvements in peri- and postoperative management that have occurred over the last 20 years the definition of 'poor operative risk' has of course changed.

40 years ago most patients with endometrial cancer would have been offered preoperative irradiation using inserted intracavity sources.[32] The neoadjuvent irradiation was justified on the grounds that it would cause significant tumour reduction prior to surgery and secondly that the chances of surgical seeding were reduced. The use of brachytherapy at this early stage also reflected the limitations of external beam radiotherapy of the time and of post hysterectomy morbidity, which could delay postoperative irradiation (if histopathological findings suggested a high risk of residual disease). Improvement in the quality of external beam therapy has led to irradiation now being reserved for the postoperative period.

Therefore, for the surgically fit, the accepted first line of management is TAH and BSO followed by irradiation for high risk patients.[33] This basic principle still leaves some uncertainties, which remain to be resolved. In 1988, FIGO changed the staging criteria to include surgical observations (intra- and retro-peritoneal assessment, uterine inspection for cervical involvement and tumour invasion of the myometrium). Photopoulos[34] in 1994 asked, 'What is gained by preoperative evaluation? What is the best technique of surgical staging? What are the hazards to the patient? How is staging incorporated into clinical management?'.

These questions remain relevant and additionally one may ask whether standard surgical management needs to be reviewed. As modern techniques render surgery safer, more patients will be accepted for surgery. Many surgeons now routinely take biopsies from the pelvic and para-aortic nodes or even perform a pelvic lymphadenopathy as well as obtaining peritoneal washings for cytology.[35] So far, published results do not appear to show a significant increase in morbidity but if such surgery is to become standard management then it is crucial that it be performed by experienced, designated gynaecological oncologists.

Whether or not pelvic lymphadenectomy is more effective in controlling involved lymph nodes and produces less morbidity than pelvic irradiation is unknown but these questions should be answered by the ASTEC trial. This multicentre UK trial began in 1998. Patients with Stage I disease who are fit for some form of surgery are divided into those who are judged fit enough to undergo lymphadenectomy in addition to TAH and BSO and those who are not – this latter group simply having surgery according to local practice, generally TAH and BSO alone (Group 2). Those fit for lymphadenectomy (Group 1) are randomised to have either TAH and BSO or TAH, BSO and lymphadenectomy. Post-operatively, any patients with either low risk pathology or macroscopic disease remaining are treated according to standard local practice. Further information available from the Medical Research Council (MRC).**1**

All the remaining patients (high risk pathology but no macroscopic disease) underwent a second randomisation either to external beam irradiation of the pelvis or no external beam. Vaginal vault brachytherapy was allowed in either group at the discretion of the treating oncologist. A minimum of 400 and a maximum of 1000 patients will be required for the surgical component. The radiotherapy arm will include additional patients not undergoing the surgical randomisation and it is planned to recruit a minimum of 1000 patients for this arm. Preliminary results should be available within 2 to 3 years of trial closure.

5.1. Role of Radiotherapy in Surgically Operable Disease

Although radiotherapy has for most oncologists an established role in the management of endometrial cancer, evidence in support of a survival benefit from adjuvant radiotherapy is unsatisfactory because there have been so few prospective randomised trials. This problem was well reviewed by Blake and Thomas in their paper on adjuvant loco-regional therapy for uterine cancer published in Clinical Oncology in 1996.[36] The old practice of preoperative intracavity irradiation no longer has a place in the management of this disease. Currently accepted practice is that surgery, minimally TAH and BOS, should come first with any postoperative treatment recommended on the basis of the surgical and histopathological findings. There are 3 separate lymph node areas at risk – pelvis, para-aortic chain and inguinal nodes. In addition vaginal vault and upper vaginal seeding can occur. Transperitoneal spread usually occurs only when deeply penetrating tumours have gained access to the serosal covering of the fundus. However, there is a route to the peritoneal cavity via the fallopian tubes, although this route is uncommon. The incidence of blood borne metastases increases with tumour grade. Factors associated with a relatively high risk of residual disease after surgery have already been reviewed,[37,23] the difficulty is in marshalling evidence for the optimisation of postoperative irradiation.

In 1998 the American Gynaecological/Oncology Group published the results of a Phase III randomised study of surgery versus surgery plus adjunctive radiation therapy in the management of intermediate risk endometrial adenocarcinoma. Patients with endometrial cancer corresponding to FIGO Stages 1b, 1c, 2a (occult) and 2b (occult) [table 1] were included in the study and after they had undergone radical surgery they were randomised to either whole pelvic irradiation or no additional therapy. 390 women were evaluated,

1. MRC Cancer Trials Office, 5 Shaftesbury Road, Cambridge CB2 2BW; Fax 01 223 311 844.

and radiation treatment was allowed for those patients who had surgery alone and then relapsed. They found that the use of adjunctive radiotherapy decreased the risk of recurrence but had a negligible effect on overall survival.[38]

More recently the Post-Operative Radiation Therapy in Endometrial Carcinoma (PORTEC) study group published the results of a similar randomised study comparing surgery plus postoperative radiotherapy with surgery alone. All patients underwent TAH and BOS without routine lymphadenectomy. Patients with Stage I endometrial carcinoma (Grade I) with deep (more than 50%) myometrial invasion, Grade II with any invasion or Grade III with superficial (less than 50%) invasion were enrolled into the study. They were then randomised to receive either whole pelvic irradiation or no further treatment. This study also showed that irradiation reduced local regional recurrences but without any impact on survival. More worryingly, it suggested that radiotherapy increased treatment-related morbidity. They identified a group of patients (those with Stage I endometrial carcinoma below 60 years of age and/or with Grade II tumour with only superficial muscle invasion) for whom radiotherapy was not indicated.[39]

However, postponing radiotherapy until a recurrence is identified in those patients that do have a local relapse may render the radiotherapy less effective. If it is the effect of additional morbidity which is counter balancing a potential survival benefit from the radiotherapy, then perhaps attempting to reduce radiation morbidity may be more productive than dismissing radiotherapy as a useful post-operative entity. For adjuvant therapy to be utilised effectively there are also other considerations such as –

- What is the distribution of the treatment failure sites in the prognostic groups?
- What constitutes effective adjuvant therapy at each relapse site after surgery?
- Is an effective systemic treatment available?

In the case of postoperative irradiation there are 3 options available – external beam irradiation of the pelvis, intracavity irradiation of the vagina, and a combination of both. To this could be added a fourth option of para-aortic chain irradiation.

Available evidence shows reasonably conclusively that vaginal vault brachtherapy is effective in reducing local relapse at that site; the risk varies between 4 to 8% depending on the tumour grade. However, even if vaginal brachytherapy is deferred until a relapse occurs, providing the patients have been followed up carefully, it is still possible to salvage a proportion of them. In those groups where the risk of local failure is low anyway, surgery alone maybe sufficient therapy. These groups are defined by Partridge[33] and Bond[37] as Ia and as Stage Ia Grade I by Bliss and Cowie.[40] Allowing for changes in Staging, these would now be defined as Stage Ia GI.

Where the histological grade is more advanced, vaginal brachytherapy may still improve local control[41-43] but in these Grade III tumours or indeed Stage II disease there is still insufficient evidence to clarify the role of pelvic irradiation. If radiotherapy is to be given postoperatively then whether or not pelvic irradiation and vaginal vault brachytherapy should be combined and in which situations and for which group of patients remains unclear. DeCruze et al.[44] reported the results of a retrospective study in which a series of patients with Stage I poor risk endometrial cancer were treated postoperatively with vaginal vault brachytherapy and the outcome from these patients was compared with 13 similar patients (matched for stage and grade) treated with both external beam and vaginal vault irradiation postoperatively. They found no significant differences in survival. However, the patient numbers in this study were small. The recently opened multicentre ASTEC trial in the UK is designed to show whether or not postoperative pelvic irradiation has a place in the management of endometrial cancer and since the trial allows vaginal vault brachytherapy at the discretion of the clinician it may help define the place of brachytherapy also.

5.2 Place of Cytotoxic Chemotherapy

While endometrial cancer cell lines can be demonstrated to respond to a number of cytotoxic drugs,[45-47] there is no evidence to show any benefit from neoadjuvant or adjuvant cytotoxic chemotherapy in the primary management of endometrial cancer. However, it may have some limited benefits for patients with metastatic disease. Doxorubicin (adriamycin), cyclophosphamide, flurouracil, cisplatin and paclitaxel all have activity with some combinations of these drugs producing a reported response rate of around 50%.

5.3 Place of Adjuvant Hormone Therapy

About one-third of endometrial cancers will respond to progesterone, with Grade I tumours showing the highest response rate. Occasionally, this response will be dramatic with patients who have widespread disease, including multiple lung metastases, going into complete remission for up to 5 years (unpublished observations). This potential for response created enthusiasm for the adjuvant use of progesterone and led to the COSA study 'Evaluation and Role of Progesterone in High Risk Disease'.[48,49] Analysis of the results has not shown significant long term benefit and in many women the treatment produced problems related to bodyweight gain and exacerbation of hypertension. Although some clinicians continue to advocate a period of treatment with progesterone after primary surgery for uterine cancer, justification for this practice is slim.

5.4 Management of Inoperable Disease

A small number of patients may have very early disease (Stage Ia) but are not fit enough to undergo any form of surgery. For these patients, simple intra-cavity irradiation using a uterine canal source may be sufficient to produce local control. 10% of patients will have locally advanced disease or metastases, and these, along with patients with less advanced disease but who are surgically unfit, must be managed with radiotherapy matched to the specifics of the disease at the time of presentation.

For patients with relatively early disease, radical radiotherapy has the potential to cure but the results are inferior to surgery or surgery combined with radiotherapy.[50-52] Inability to control local disease in the fundas is a significant cause of local failure. Patients who have advanced local disease or metastatic spread in the pelvis may benefit from adjuvant progesterone therapy added to the radiotherapy. In the very small number of patients presenting in relatively young women who are otherwise fit, neoadjuvant chemotherapy should be considered on an individual basis.

5.5 Management of Involved Para-Aortic Nodes

Apart from a small role for hormone and cytotoxic chemotherapy (see sections 5.2, 5.3 and 5.4) the management of endometrial cancer is local to the pelvis and vagina rather than systemic. The presence of involved pelvic nodes is associated with a 60% risk of para-aortic node involvement and in this situation computed tomography scanning of the para-aortic nodes immediately after primary treatment is completed and again at 4 to 6 months should pick up an enlarging mass in the para-aortic chain. Local irradiation for such metastases can produce a complete and durable response in up to 50% of patients where this is the only site of relapse (unpublished observations).

5.6 Management of Recurrent Disease and Distant Metastases

Disease relapsing in the pelvic or para-aortic nodes after surgical treatment alone can be treated with some success with local irradiation at the time of relapse. Disease relapsing in the vaginal vault can be safely and effectively treated with intracavity brachytherapy. There are no randomised trials to show whether or not delaying radiotherapy until relapse occurs decreases the chances of controlling the disease.

Blood borne metastases may occur at any site, although the lung is the most common.[53-57] Most endometrial cancers have sufficient radiosensitivity for local palliative irradiation to produce a

worthwhile response if the site is accessible to treatment.

6. Conclusion

The curability of low risk endometrial cancer should not be allowed to mask the potential for aggressive behaviour by high grade tumours. The fact that a significant number of patients have done, and continue to do, well with available treatments has led to a paucity of randomised controlled clinical trials. As surgical and radiotherapeutic techniques continue to be refined, and perhaps as other cytotoxic agents become available, further clinical trials will undoubtedly be necessary.

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