Endometrial cancer

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Each year, endometrial cancer develops in about 142 000 women worldwide, and an estimated 42 000 women die from this cancer. The typical age-incidence curve for endometrial cancer shows that most cases are diagnosed after the menopause, with the highest incidence around the seventh decade of life. The appearance of symptoms early in the course explains why most women with endometrial cancer have early-stage disease at presentation. For all stages taken together, the overall 5-year survival is around 80%. There is a substantial prognostic difference between the histological types of endometrial cancers. The most common lesions (type 1) are typically hormone sensitive and low stage and have an excellent prognosis, whereas tumours of type 2 are high grade with a tendency to recur, even in early stage. The cornerstone of treatment for endometrial cancer is surgery, which not only is important for staging purposes but also enables appropriate tailoring of adjuvant treatment modalities that benefit high-risk patients only. We review current concepts about epidemiology, pathology, pathogenesis, risk factors and prevention, diagnosis, staging, prognostic factors, treatment, and follow-up of endometrial cancer.

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Worldwide, endometrial cancer is the seventh most common malignant disorder, but incidence varies among regions.[1] In less developed countries, risk factors are less common and endometrial cancer is rare, although specific mortality is higher.[2,3] The incidence is ten times higher in North America and Europe than in less developed countries; in these regions, this cancer is the commonest of the female genital tract and the fourth commonest site after breast, lung, and colorectal cancers.[1,4] The incidence is rising as life expectancy increases.[5] Age-adjusted incidence is increasing even when corrected for hysterectomy.[6] The rise has been associated with an epidemic of obesity and physical inactivity.[5,7] As an example, in the year 2000 in the Flemish region of Belgium, with a female population of just over 3 million, 743 women were diagnosed as having endometrial cancer. In Flanders, this cancer is the third commonest in the female population, after breast and colon cancers. The incidence of 24·7 per 100 000 women in this region is much the same as that in other western European countries. The incidences per 100 000 women in the same region for cervical, ovarian, and breast cancers were 13·6, 20·8, and 161·9. The cumulative risk of endometrial cancer up to age 75 years has been estimated as 1·7%.[8]

In North America, endometrial cancer is the eighth commonest cause of death from cancer in the female population.[4] Each year, in Europe, an estimated 9000 women die of endometrial cancer. Substantial decreases in the incidence and mortality of endometrial cancer are unlikely in the next few years, because early detection and treatment modalities have not had a major influence on mortality.[9]

Pathology

Pathological examination is the cornerstone of diagnosis of endometrial cancer (figure 1). About 80% of all endometrial carcinomas are of the endometrioid type (figure 2); this term refers to endometrial-type glands of varying differentiation easily recognisable on microscopy.[10] Several subtypes or variants of endometrioid carcinoma have been described, such as secretory carcinoma and villoglandular carcinoma (panel 1). The former resembles a secretory endometrium, because glycogen vacuoles are present in most of the tumour cells; the latter has a striking papillary growth pattern with bland nuclei (figure 3).[11] Squamous differentiation is a common finding in endometrioid carcinoma. Previously, endometrioid carcinomas with apparently benign squamous differentiation were distinguished

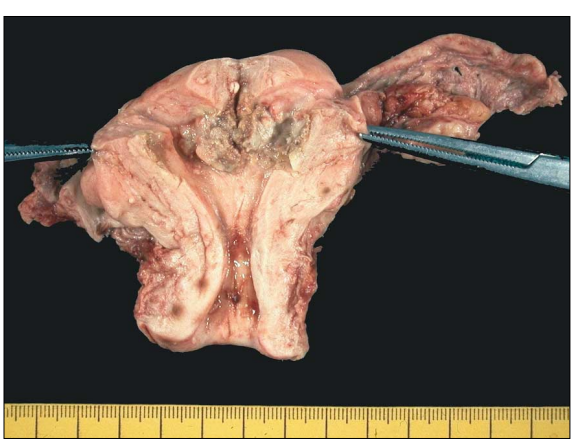

Figure 1: **Opened fresh hysterectomy specimen**
An endometrial adenocarcinoma forms a friable polypoid mass, protruding into the uterine fundus.

Search strategy and selection criteria

We searched PubMed with the term "endometrial cancer" in combination with the terms "epidemiology", "pathology", "pathogenesis", "risk factors", "prevention", "diagnosis", "staging", "prognostic factors", "tamoxifen", "surgery", "radiotherapy", "hormonotherapy", and "chemotherapy". We mainly included results from randomised trials undertaken by large groups such as the Gynaecological Oncology Group and the European Organisation for Research and Treatment of Cancer. We also refer to current trials for unresolved issues. We generally selected papers published in English or French during the past 5 years, up to date reviews, and highly regarded older papers.

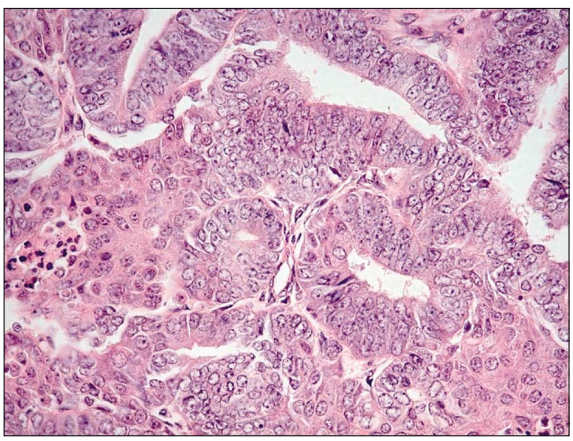

Figure 2: **Well-differentiated endometrioid adenocarcinoma**

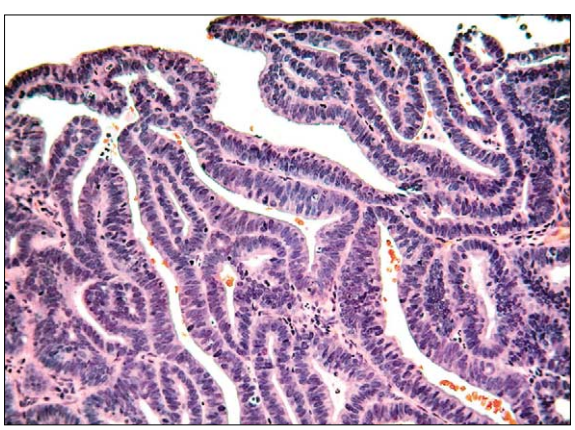

Figure 3: **Villoglandular variant of endometrioid adenocarcinoma**
Note the bland cytology.

from carcinomas with a frankly malignant squamous component. The former tumours were designated as adenoacanthoma, the latter as adenosquamous carcinoma. More recent studies have shown that these types are actually part of a range.[12]

Histological grading applies only to endometrioid carcinomas; serous and clear-cell carcinomas are classed as high grade by definition. According to the system of the International Federation of Gynecology and Obstetrics (FIGO), an endometrioid carcinoma of grade 1 consists of well-formed glands, with no more than than 5% solid non-squamous areas (areas of squamous differentiation are not deemed to be solid tumour growth).[13] Carcinomas of grade 2 consist of 6–50% and those of grade 3 of more than 50% solid non-squamous areas.[14] The tumour is upgraded from grade 1 to 2, or from grade 2 to 3, if there is striking cytological atypia. An alternative binary architectural grading system has lately been proposed and validated.[15,16] An endometrioid carcinoma is classified as low grade or high grade by use of low-magnification assessment of the amount of solid growth (with no distinction between squamous and non-squamous epithelium), the pattern of invasion, and the presence of tumour necrosis. A tumour is classed as high grade if at least two of the following three criteria are met: more than 50% solid growth; diffusely infiltrative growth, rather than expansive; and tumour-cell necrosis.

Most endometrioid carcinomas are well to moderately differentiated and arise on a background of endometrial hyperplasia. These tumours, also known as type 1 (low-grade) endometrial carcinomas, have a favourable prognosis.[17] They are associated with long-duration unopposed oestrogenic stimulation. About 10% of endometrial cancers are type 2 (high-grade) lesions. Women with such tumours are at high risk of relapse and metastatic disease. These tumours are not oestrogen driven, and most are associated with endometrial atrophy; surgery is commonly followed by adjuvant therapy. The histological type is either poorly differentiated endometrioid or non-endometrioid.

Serous carcinoma is the most aggressive type of non-endometrioid endometrial carcinoma.[18–20] The histological diagnosis is based on the presence of papillae, covered by highly pleiomorphic tumour cells with frequent mitoses and necrosis (figure 4). Myometrial invasion is prominent in most cases, and vascular invasion is common. Nearly all serous carcinomas show strong, diffuse immunohistochemical staining for TP53 antigen, reflecting intranuclear accumulation of mutant TP53; the mutant protein has increased stability, whereas the wild-type is unstable and undetectable.[21] Clear-cell carcinoma is another type of non-endometrioid endometrial carcinoma.[22] Up to 40% of non-endometrioid endometrial cancers are mixed, with an endometrioid component.[20] In endometrial carcinomas of high nuclear but low architectural grade, use of a panel of immunohistochemical stains can facilitate the distinction between serous and endometrioid endometrial cancers.[23] The probable precursor lesion of invasive serous carcinoma is endometrial intraepithelial carcinoma (EIC).[24] In this

***Panel 1:* WHO histological classification of endometrial carcinoma**

Endometrioid adenocarcinoma
Variants: with squamous differentiation
villoglandular
secretory
with ciliated cells

Other adenocarcinomas
Mucinous carcinoma
Serous carcinoma
Clear-cell carcinoma
Mixed carcinoma
Squamous-cell carcinoma
Transitional-cell carcinoma
Small-cell carcinoma
Undifferentiated carcinoma

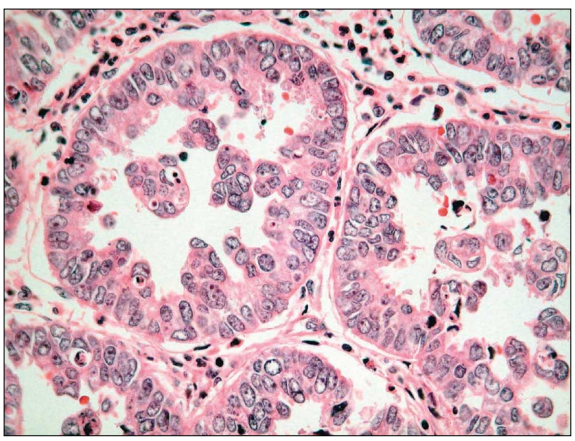

Figure 4: **Serous (papillary) adenocarcinoma of the endometrium**
Note the high-grade nuclear atypia.

lesion, the epithelium of the endometrial surface and underlying glands is replaced by pleiomorphic tumour cells resembling invasive serous carcinoma, but without stromal invasion. The lesion commonly involves the surface of a benign endometrial polyp.[25] EIC is a rare finding, but it can be associated with extensive transtubal intraperitoneal spread.[26]

With the exception of EIC, endometrial adenocarcinoma-in-situ is believed not to be a valid concept. This term is misleading and should be avoided. It should certainly not be confused with intramucosal or intraendometrial adenocarcinoma, in which there is invasion of the endometrial stroma (FIGO stage IA), but not of the underlying myometrium. Atypical endometrial hyperplasia is the term of choice for intraendometrial neoplasia without stromal invasion, and severe atypical hyperplasia has been equated with adenocarcinoma-in-situ. Admittedly, and despite many publications on this subject, the differential diagnosis on curettage between atypical hyperplasia and well-differentiated endometrioid adenocarcinoma remains difficult. It is less important on a hysterectomy specimen, because the decision on further treatment will not be affected.

About 8% of endometrial carcinomas are associated with the simultaneous presence of an ovarian carcinoma with the same histology. In most instances, especially when both tumours are well differentiated and the endometrial tumour is only superficially invasive in the myometrium, these are independent primary tumours.[27] The only circumstances in which the ovarian tumour should be considered as metastatic are when it is small, bilateral, or multinodular with surface implants and angiolymphatic invasion in the ovarian cortex.[28] A molecular-genetic and statistical approach for the diagnosis of dual-site endometrial and ovarian cancers has been proposed.[29]

Endometrial carcinosarcoma has lately been considered a special subtype of endometrial cancer, since epidemiological, clinicopathogical, immunohistological, in-vitro, in-vivo, and molecular-genetic research has lent support to the monoclonal nature of carcinosarcoma that points to an endometrial origin.[30] Given a tendency to lymphatic and transperitoneal spread with a 50% recurrence rate, surgical therapy is as for type 2 endometrial cancers. There is currently no proof that adjuvant treatment in endometrial carcinosarcomas results in a better outcome after primary surgery.

Pathogenesis

The endometrium undergoes structural modification and changes in specialised cells in response to fluctuations of oestrogen and progesterone during the menstrual cycle. Long-lasting unopposed oestrogen exposure leads to endometrial hyperplasia, which increases the chance of development of atypical hyperplasia and eventually type-1 endometrial cancer. The molecular basis of this process is still not known, since the involvement of only a minority of factors is reproducible.[10] Endometrial cancers, from a molecular viewpoint also, resemble proliferative rather than secretory endometrium.[31] *PTEN* is a tumour-suppressor gene that is expressed most highly in an oestrogen-rich environment; progestagens affect *PTEN* expression and promote involution of *PTEN*-mutated endometrial cells in various histopathological settings.[31–34] These observations are consistent with the well-documented clinical effect of progestagen-mediated suppression of human endometrial precancer and even ablation of some cancers.[35] Apart from mutations of *PTEN* typically seen in type-1 endometrial cancers, there are other gene alterations that are specific for cancers of types 1 and 2, which supports a dualistic model of endometrial carcinogenesis.[36–38] Carcinomas of type 1 are associated with mutations in *KRAS2* oncogene, *PTEN* tumour-suppressor gene, defects in DNA mismatch repair, and near-diploid karyotype; by contrast, those of type 2 are associated with mutations in *TP53* and *ERBB-2* (HER-2/neu) expression, and most are non-diploid.[39–44] Although some inconsistencies between single-gene and the whole-genomic approach have been observed, gene-array studies should be useful to disentangle molecular pathways and to identify potential targets for molecular-based treatments.

Risk factors and primary prevention

Women with type-1 endometrial cancer are likely to have been exposed to unopposed oestrogens (panel 2). Oestrogen-producing tumours are an uncommon risk factor. Unopposed oestrogens should no longer be used to treat postmenopausal symptoms in women who have not had hysterectomy. Excessive fat consumption and overweight (defined as body-mass index [BMI] of at least 25 kg/m^2) are important risk factors present in

Panel 2: Risk factors for endometrial cancer

Factors increasing risk
Increasing age
Long-term exposure to unopposed oestrogens
Residence in North America or Europe
High concentrations of oestrogens postmenopausally
Metabolic syndrome (obesity, diabetes)
Years of menstruation
Nulliparity
History of breast cancer
Long-term use of tamoxifen
HNPCC family syndrome
Hormone-replacement therapy with less than 12–14 days of progestagens
First-degree relative with endometrial cancer

Factors decreasing risk
Grand multiparity
Smoking
Oral-contraceptive use
Physical activity
Diet of some phyto-oestrogens

almost 50% of women with endometrial cancer.[45–50] In premenopausal women, overweight causes insulin resistance, ovarian androgen excess, anovulation, and chronic progesterone deficiency. In postmenopausal women, it causes higher circulating concentrations of bioavailable oestrogens from extraglandular conversion of androgens (figure 5). This change stimulates endometrial-cell proliferation, inhibits apoptosis, and promotes angiogenesis. A BMI above 25 kg/m^2 doubles a woman's risk of endometrial cancer, and a BMI above 30 kg/m^2 triples the risk.[50] A high BMI at a young age and BMI gain are also associated with endometrial cancer.[7] Obesity remains a risk factor for endometrial cancer even when circulating concentrations of oestrogen are normal.[46] It alters concentrations of insulin-like growth factor and its binding proteins. This pathway can be stimulated by oestradiol and suppressed by progestagens. Oestrogen-receptor transcriptional activity can be induced by signalling by insulin-like growth factor 1 even in the absence of oestradiol, which provides evidence of cross-talk between these pathways.[51–55]

Physical inactivity, high energy intake, blood pressure above 140/90 mm Hg, and high serum glucose concentrations are BMI-independent risk factors, whereas the presence of polycystic ovaries depends on the BMI.[7,56–60] A substantial proportion of endometrial cancers could be avoided with the maintenance of a normal weight and physical activity throughout life, an inexpensive way to lower bioavailable oestrogens.[61] Individual differences in biosynthesis, sensitivity, and metabolism of oestrogens could also be important.[62]

There have been suggestions of a protective effect of increasing phyto-oestrogen consumption on risk of endometrial cancer among postmenopausal women, even if they are obese.[63–65] The effect of eating a diet rich in soy throughout a lifetime cannot be compared with use of soy extracts given after the menopause. Furthermore, a daily intake of 150 mg isoflavones consisting of genistein (40–45%), daidzein (40–45%), and glycitein (10–20%), for 5 years has lately been associated with endometrial hyperplasia.[66] Smoking reduces risk of endometrial cancer because it affects oestrogen production and metabolism.[67,68] Alcohol use is associated with raised oestrogen concentrations. Epidemiological studies, however, do not support a positive association between alcohol use and endometrial cancer as shown for breast cancer.[69,70]

Pregnancy, with intense placental production of progestagens, protects against endometrial cancer. Nulliparity is a risk factor that is more important if infertility is also present; grand multiparity protects.[71–73] The use of an intrauterine device and tubal ligation have also been associated with a lower risk.[74,75] Whether a levonorgestrel-containing intrauterine device further protects is unclear.[51]

Contraceptive pills containing oestrogens and progestagens lower the endometrial-cancer risk.[76] After menopause for women taking hormone-replacement therapy, addition of progestagens to oestrogen, generally for 10–14 days per month or daily, counteracts the adverse effects of oestrogens on the endometrium; this approach

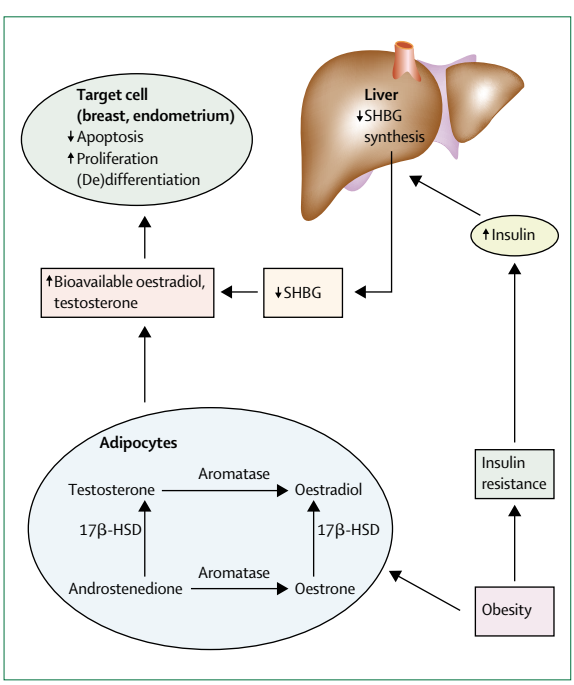

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Figure 5: **Relation in postmenopausal women between hormones and obesity affecting endometrial growth**
SHBG=sex-hormone binding globulin; 17β-HSD=17β-hydroxysteroid dehydrogenase.

lowers the endometrial-cancer risk especially if the two hormones are continuously combined and particularly in obese (BMI ⩾30 kg/m²) women.[77–79] Clinical studies are currently testing the uterine safety of tibolone, but an increased endometrial-cancer risk has been reported.[79,80]

Women with breast cancer are at increased risk of endometrial cancer. Breast cancer can rarely metastasise to the endometrium, and primary endometrial cancers are more likely in breast-cancer survivors because of common risk factors.[81] In women with breast cancer who subsequently developed endometrial cancer, the risk of developing a serous endometrial cancer was 2·6 times higher than the risk of developing an endometrioid carcinoma.[82] An additional endometrial-cancer risk has been related to the use of tamoxifen for breast cancer. This drug triples the risk of endometrial cancer and also increases the chance of developing benign endometrial lesions.[83] Endometrial cancers appear sooner than in non-tamoxifen users.[83–86] Pre-existing endometrial pathology, high BMI, and use of hormone-replacement therapy are associated risk factors.[87,88] Although most reported cases are low-risk lesions, type-2 lesions such as carcinosarcomas have also been described in long-term users of tamoxifen.[89] The mechanism behind this action is unclear, but tissue-specific coregulators have a role.[90] Whether continuous local administration of progestagens or oral administration of aromatase inhibitors after or instead of tamoxifen in breast-cancer patients lowers the risk of endometrial cancer is unclear.[91–93] Raloxifene, like tamoxifen, is a selective oestrogen-receptor modulator licensed for prevention of osteoporotic fractures; it does not have the stimulatory effect on the endometrium that tamoxifen has.[94] Many new drugs of this class are in clinical trials, and uterine effects are being monitored. Pelvic radiotherapy as a treatment modality for cervical cancer does not exclude the risk of endometrial cancer, and such cancers can be more advanced at diagnosis.[95]

The proportion of cases of endometrial cancer on a background of familial risk is low but having a first-degree relative with this cancer is a risk factor.[96,97] Endometrial cancer can also be part of a hereditary cancer syndrome as described in the mid-1960s.[98] Hereditary non-polyposis colon cancer (HNPCC) is a mendelian dominant syndrome of right-sided colon, endometrial, and other cancers; it results from germline mutations in mismatch-repair genes. HNPCC is diagnosed on molecular grounds by a combination of mutation screening, microsatellite instability, and immunohistochemistry.[99] Guidelines have been published for selection of families for molecular investigation of HNPCC; endometrial cancer before age 45 years is one of the criteria.[99]

Secondary prevention

There is no point in screening for endometrial cancer; screening is unlikely to decrease mortality from the disorder. It will mainly detect women with low-risk tumours.[100] Furthermore, minimally invasive modalities potentially suitable for mass screening, including transvaginal ultrasonography (TVU) and cytology from a Pap smear or endometrial brush, have limited accuracy for the diagnosis of endometrial cancer in an asymptomatic population.[101,102] Education about the importance of investigation if any vaginal bleeding occurs in postmenopausal women should be given to health-care workers and women themselves; such education is also important for tamoxifen users. Ultrasonographic screening before initiation of tamoxifen treatment has been recommended to prevent growth of pre-exisiting lesions.[103] Women with an HNPCC syndrome have lifetime risks of endometrial and ovarian cancers of 40–60% and 12%, respectively; these are sentinel cancers, preceding the development of colon cancer in half of cases.[104] Apart from prophylactic surgery beyond age 45–50 years, gynaecologists and gynaecological oncologists have a crucial role in the identification of such women.[104,105]

Symptoms and diagnosis

Abnormal uterine bleeding is the most frequent symptom of endometrial cancer, but many other disorders give rise to the same symptom. All postmenopausal women with vaginal bleeding and those with abnormal uterine bleeding associated with risk factors for endometrial cancer or hyperplasia (eg, polycystic ovaries, obesity, age over 40 years, erratic cycles, hormone-replacement therapy, tamoxifen use) should undergo further diagnostic endometrial assessment. The probability of endometrial cancer in women presenting with postmenopausal bleeding is 5–10%, but the chances increase with age and risk factors.[106] The probability also determines which diagnostic strategy is best from a health-economic viewpoint.[106,107]

Endometrial cancer is mostly diagnosed histologically from endometrial tissue obtained with miniature endometrial biopsy devices (generally based on the plastic disposable Pipelle de Cornier prototype). A meta-analysis on the value of Pipelle biopsy for the diagnosis of atypical hyperplasia or endometrial cancer calculated sensitivity of 81–99% and specificity of about 98%. These findings were confirmed by a systematic quantitative review of 11 published studies.[108,109] The accuracy estimates of the endometrial biopsy are better in symptomatic (bleeding) and postmenopausal women and for the diagnosis of endometrial cancer as opposed to atypical endometrial hyperplasia.[110]

The strategy starting with endometrial biopsy is most cost-effective when the prevalence of endometrial carcinoma is over 15%. The strategy with TVU followed by endometrial biopsy if abnormality is detected is the most cost-effective for populations in which the prevalence of endometrial carcinoma is lower.[111] We therefore consider TVU as the first step in any woman presenting with abnormal uterine bleeding.[112]

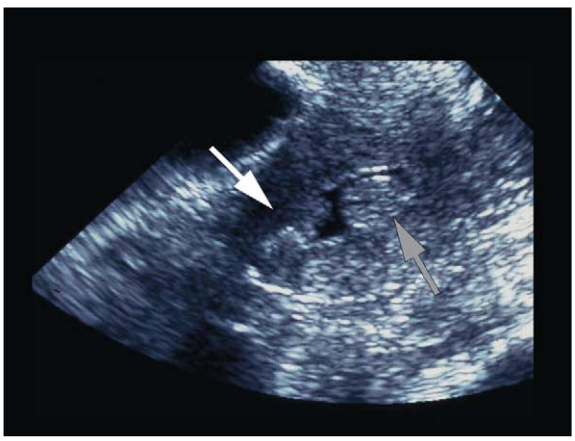

Figure 6: **TVU showing how saline-infusion sonography can differentiate between normal and intracavitary uterine pathology**
There was a regular and benign polyp in this woman's uterus (grey arrow) and a small endometrial carcinoma (FIGO stage 1A) in the fundus (white arrow).

Normality for TVU is defined as a thin symmetrical endometrial line of less than 4–5 mm double endometrial thickness.[113,114] For assessment by an experienced observer, a thin and regular endometrial line is associated with a very low risk of endometrial cancer as long as the endometrium is clearly visualised throughout the uterus. Above this threshold, we judge an endometrial biopsy to be a priority because a normal hysteroscopic image does not always exclude malignancy.[115,116] If the biopsy sample shows endometrial cancer, treatment is needed. If the biopsy sample is normal or non-diagnostic or if the uterine cavity is inaccessible in a woman with an abnormal endometrium on TVU, we advise colour doppler TVU and saline-infusion sonography (figure 6) or outpatient hysteroscopy. This method will exclude intracavitary lesions such as submucous fibroids and endometrial polyps that might also contain endometrial cancers.[116–118] Limitations of saline-infusion sonography or hysteroscopy in endometrial cancer include a small risk of spread of malignant cells to the peritoneal cavity.[119] Since the prognostic importance of such peritoneal spread is unknown, neither saline-infusion sonography nor hysteroscopy should be used when the Pipelle biopsy sample includes malignant cells or when TVU strongly suggests endometrial cancer.[120] If uterine bleeding persists when there is no abnormality on TVU or endometrial biopsy, the same diagnostic investigations are advised because normal findings on both diagnostic tests do not exclude endometrial cancer with certainty.

The value of TVU in symptomatic premenopausal women and those using hormone-replacement therapy is lower because the "normal" endometrial thickness varies with circulating concentrations of female steroid hormones.[121]

The diagnosis of endometrial cancer is established with an abnormal cervical smear or treatment for presumed benign uterine disease in only a minority of cases. A cervical smear is only of value when it is abnormal. A normal result is not sufficient to exclude endometrial cancer in symptomatic women, and an abnormal result frequently points to advanced disease.[122] Endometrial cytology from an endometrial brush has a lower sensitivity to detect endometrial cancer than endometrial biopsy, and up to 33% of endometrial carcinomas are falsely classified as hyperplasia.[122,123]

Stage and grade	Features
Stage IA; grade 1, 2, or 3	Tumour limited to endometrium
Stage IB; grade 1, 2, or 3	Invasion of less than half the myometrium
Stage IC; grade 1, 2, or 3	Invasion of more than half the myometrium
Stage IIA; grade 1, 2, or 3	Endocervical glandular involvement only
Stage IIB; grade 1, 2, or 3	Cervical stromal invasion
Stage IIIA; grade 1, 2, or 3	Tumour invading serosa or adnexa, or malignant peritoneal cytology
Stage IIIB; grade 1, 2, or 3	Vaginal metastasis
Stage IIIC; grade 1, 2, or 3	Metastasis to pelvic or para-aortic lymph nodes
Stage IVA; grade 1, 2, or 3	Tumour invasion of the bladder or bowel mucosa
Stage IVB	Distant metastases including intra-abdominal or inguinal nodes

Table: **Surgical staging of carcinoma of the uterus (1988)**

Staging

Endometrial cancer is a surgically staged disease, because clinical estimates and preoperative imaging of the extent are incorrect in over 20% of cases.[13] The depth of myometrial invasion and extrauterine disease (uterine serosa, adnexal involvement, peritoneal cytology, intra-abdominal, and lymph nodes) have all been incorporated into the FIGO staging scheme (table). Although the preoperative assessment of extent cannot replace FIGO staging, and it does not lead to better survival, it enables clinicians to tailor treatment. Useful preoperative assessments include clinical examination, Pap smear, TVU, and CT of lungs, liver, and retroperitoneal lymph nodes. The sensitivity to detect retroperitoneal lymph nodes is better for CT than for MRI. If overt metastatic disease is found, extensive surgery will not be undertaken. If we expect advanced-stage disease, we instead undertake laparotomy to avoid port-site metastasis from laparoscopic surgery, which is the approach we generally use in early stages. Preoperative and peroperative assessment of myometrial invasion can help to select patients with type-1 endometrial cancer for lymphadenectomy.

TVU is simple and readily available and has reasonable accuracy in predicting cervical and myometrial invasion from endometrial cancer. A logistic regression model based on several variables was as accurate as most other proposed methods for measuring depth of myometrial invasion including frozen section of the hysterectomy specimen and CT.[124–126] It was almost as accurate as contrast-enhanced MRI, which is currently seen as the best method for

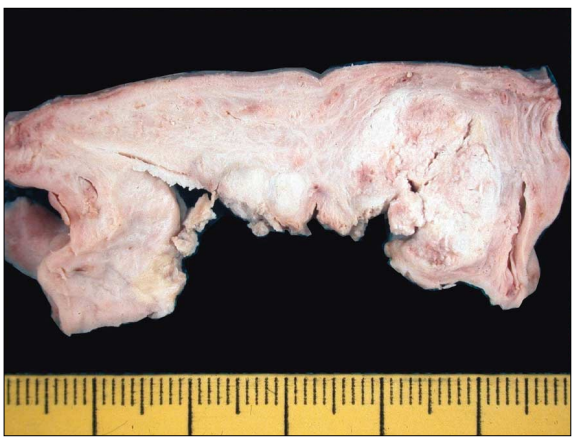

Figure 7: **Sectioned uterine corpus after formalin fixation, showing invasion in the outer half of the myometrium (FIGO stage 1C)**
The pathologist can be asked to assess the depth of invasion by frozen section. However, this should always be preceded by skilled gross examination.

myometrial assessment.[127] However, MRI is costly, is not so widely available, can induce contrast allergies, and is not appropriate for all patients (eg, those who are extremely obese or who have claustrophobia).

Although the histological assessment of the hysterectomy specimen remains the gold standard, we always ask our pathologist to assess the myometrial and endocervical invasion peroperatively (figure 7). Intraoperative visual estimation of the depth of myometrial invasion is accurate in 90% of cases.[124,128] When no pathologist is available during surgery or when time is a limiting factor, the combination of a preoperatively known tumour grade and visual estimation of the depth of myometrial invasion will enable the experienced surgeon to select candidates for lymphadenectomy.

Positron emission tomography with fluorine-18-labelled 2-fluoro-2-deoxy-D-glucose is costly and only moderately sensitive in predicting extrauterine disease. It should therefore not be used for routine staging.[129]

CA125 is a potential tumour marker. Its concentration is more likely to be raised in type-2 or advanced-stage cancers than earlier-stage cancers, but a normal value does not exclude more advanced tumours.[130]

Prognostic factors and survival

The most important prognostic features in endometrial cancer are the surgical FIGO stage, myometrial invasion, histological type, and differentiation grade; most are independent of each other (panel 3).[131–135] Whether the 5–15% of patients with positive peritoneal cytology in the absence of extrauterine disease also classified as having stage IIIA lesions have a different outcome from those with negative cytology remains controversial.[136,137] Apart from this uncertainty, the FIGO stage reflects the 5-year survival, which varies according to series but is around 85% for stage I, 75% for stage II, 45% for stage III, and 25% for stage IV disease.[138–140] The 5-year survival for FIGO (1988) surgical stage IA–IC based on the depth of myometrial invasion is further affected by the tumour grade, ranging from over 95% for low-grade stage IA lesions to only 42% for high-grade stage IC endometrial cancers.[19,140,141] The distance from the serosa might be a better prognostic factor than myometrial invasion from the cavity.[142] Vascular-space invasion, although associated with tumour grade and depth of myometrial invasion, has been an independent prognostic factor in some studies.[143] It is present in about 37% of endometrial cancers, but more than one vascular cross-section should be involved for it to be a prognostic indicator. Non-endometrioid endometrial cancers such as serous and clear-cell carcinomas make up about 10% of all endometrial cancers but account for more than 50% of recurrences and deaths from endometrial cancer.[18,20,134,135] The effects of other non-pathological prognostic factors such as race, age, diabetes, and parity have been reviewed elsewhere.[144]

Treatment options

Surgery

The most important therapy for endometrial cancer is surgery. The procedures include acquisition of peritoneal fluid or washings for cytology, total hysterectomy including the uterine cervix, and bilateral salpingo-oophorectomy; in selected cases, there is a place for omentectomy and a thorough retroperitoneal lymph-node dissection.

Although the results of randomised trials are still lacking, in experienced hands, laparoscopy-assisted vaginal hysterectomy is feasible when operating for endometrial cancer; fluid for cytology, peritoneal biopsy samples, lymph nodes, and omentum can be obtained in a single procedure.[145] We compared clinical outcomes in women who had surgical staging for early-stage endometrial cancer by laparoscopy (n=80) or by laparotomy (n=105) during the same period.[146] Exclusion criteria for laparoscopy included poor uterine descensus, largest uterine diameter from ultrasonography of more than 10 cm, BMI more than 35 kg/m^2, and history of previous laparotomy or pelvic radiotherapy. The mean age (62 [SD 10] *vs* 66 [9] years; p=0·012) and BMI (26 [4] *vs* 31 [7] kg/m^2; p<0·001)

***Panel 3*: Poor prognostic histopathological factors for 5-year overall survival in women with endometrial cancer of surgical stage I**

High tumour grade and non-endometrioid-type lesions
Depth of myometrial invasion or distance between serosa and tumour
Involvement of lower segment
Vascular-space involvement
Aneuploidy

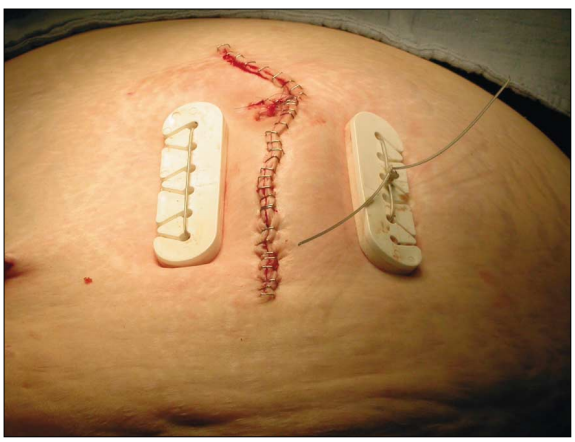

Figure 8: **Surgical prevention of wound morbidity in an obese woman**
Metal transabdominal traction sutures (Ventrofil).

were lower in the laparoscopy group than in the laparotomy group. Although the operation was slightly longer for patients in the laparoscopy group (169 [59] *vs* 152 [57] min; p=0·063), they had less blood loss (344 [195] *vs* 505 [390] mL; p=0·0002) and a shorter hospital stay (5·6 [2·6] *vs* 10·1 [9·4] days; p<0·001). After follow-up of 55 months, multivariate analysis showed no difference in progression-free survival (odds ratio 0·89; p=0·52) or overall survival (0·96; p=0·63). In the absence of randomised trials on this issue, we believe that laparoscopy is a valuable alternative to laparotomy in a selected group of patients. Manipulation of tumour, including macroscopically involved lymph nodes, should be avoided to prevent the rare occurrence of port-site metastasis. Furthermore, the use of an intrauterine manipulator should be avoided, since it results in a high frequency of positive peritoneal cytology and might contribute to vaginal-cuff recurrence.[147–149] Conversion to a midline laparotomy is advocated if macroscopic extrauterine disease or macroscopically positive pelvic lymph nodes are found. Maylard incision or metal transabdominal traction sutures (Ventrofil) for midline incisions are frequently used in obese women and aim to decrease wound morbidity (figure 8).

Type-1 endometrial cancer has a primarily lymphatic spread in most cases limited to pelvic nodes. If there are positive lymph nodes, those around the obturator nerve are more likely to be involved than those around the external and common iliac vessels, whereas the nodes in the presacral area are rarely involved. Isolated involvement of the para-aortic nodes is rare. Complete excision of the nodes located around the iliac vessels and above the obturator nerve allows identification of 90% of node-positive patients.[150] Endometrial cancer presenting with grossly positive pelvic nodes, grossly positive adnexal metastasis, or serosal infiltration is associated with positive inframesenteric para-aortic lymph nodes. We consider para-aortic lymphadenectomy for such patients.[150] Whether lymphadenectomy is curative in endometrial cancer remains controversial. Recent findings suggested that it was curative in women with grade-3 endometrial cancer, when more than 11 nodes were removed.[151,152] Furthermore, in a study in Scotland including 703 patients with endometrial cancer, deficient staging was associated with poorer survival.[153] The first multicentre randomised trial to investigate the curative value of standard lymphadenectomy for endometrial cancer of stages 1 and 2 is the recently closed UK MRC ASTEC trial. Patients with endometrial cancer thought preoperatively to be confined to the uterus were randomly assigned hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy. Women with high-risk surgical and pathological findings were subsequently assigned pelvic radiotherapy or not. Anticipating the results of this trial, we currently select our patients for lymphadenectomy on the basis of the risk of lymph-node involvement. Patients with endometrioid cancer, grade 1 with deep myometrial invasion, grade 2 with any myometrial invasion, and any grade 3 endometrioid endometrial cancer have at least a 5% risk of having positive pelvic lymph nodes.[131,154] In our current treatment protocol, all such patients undergo full pelvic lymphadenectomy. The decision on whether to undertake lymphadenectomy should not be based on palpation of the nodal area, because less than 10% of patients with nodal metastases have grossly enlarged nodes.[13] A less aggressive surgical approach has been proposed by Mariani and colleagues.[155] In their series, pelvic lymphadenectomy and radiotherapy were abandoned in patients with endometrioid cancer of grade 1 or 2 with greatest surface dimension of 2 cm or less, myometrial invasion of 50% or less, and no intraoperative evidence of macroscopic disease. Among 328 patients, 5-year overall cancer-related survival was 97% and recurrence-free survival 96%.

Stage-IV type-1 endometrial cancer can be optimally debulked in 44–72% of patients; it seems to be associated with improved survival but data are from small studies only.[156–158] We advise surgical cytoreduction only in patients with good performance status and for whom this procedure can be accomplished without organ resection.

Different surgical management is needed for type-2 endometrial cancers because the pattern of spread is different from that in type 1, with a higher likelihood of extrauterine disease. Given the propensity for lymphatic spread, a thorough lymphatic dissection is recommended in women with such tumours.[20,159,160] The transperitoneal spread of type-2 endometrial cancer resembles that of ovarian cancer.[161] Women with such lesions therefore need the same surgical management as those with ovarian cancer, including a midline abdominal skin incision, peritoneal biopsy samples, total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and biopsy of any suspect lesions.[20,156,161–165]

Maximum surgical cytoreduction for type-2 endometrial cancer with transperitoneal spread (stage IV) has been recommended.[164–167] However, there are few sound data to support this recommendation as scientifically proven. Another approach is to administer cytotoxic systemic treatment in these cases. Neoadjuvant chemotherapy might be a compromise. Complete remission of advanced-stage type-2 endometrial cancer can apparently be obtained by use of neoadjuvant chemotherapy followed by interval debulking surgery.[168] Women with such disease not responding to neoadjuvant chemotherapy might also not benefit from cytoreductive surgery and do not need to be exposed to major surgery. This strategy of selecting patients for surgery should lower unnecessary costs related to postoperative care.

Radiotherapy

Radiation can be delivered externally to the pelvis, as vaginal brachytherapy (colpostats, mould, or cylinder), or as a combination. Treatment can also be directed to the whole abdomen or to an extended field that includes the pelvis and para-aortic region.

Indications for radiotherapy are generally in the adjuvant setting. Radical radiotherapy with intrauterine brachytherapy is curative but should be applied only in medically inoperable patients.[169] The practice of preoperative radiotherapy has been abandoned because it interferes with adequate surgical staging and there is no proven benefit over postoperative radiotherapy.

The goal of adjuvant radiotherapy is to treat the pelvic lymph-node regions that might contain microscopic disease, as well as the central pelvic region including the upper vagina. There is a general consensus that patients with lesions of surgical stage IA or IB and grade 1 or grade 2 (low risk) can be treated without postoperative radiotherapy.[155] Isolated pelvic and vaginal recurrences of low-risk endometrial cancers can successfully be treated at the time of recurrence.

The precise benefit of adjuvant radiotherapy in other stage-I endometrial cancers is not clear. Three randomised phase III trials that studied the value of postoperative radiation in surgical stage-I endometrial cancer showed a reduction only in pelvic recurrences; overall survival was not improved.[170–172] Pelvic-node sampling was done in only one study.[172] In the Portec study,[171] which included 715 patients with lesions of stage IB grade 2–3 or stage IC grade 1–2 and in which lymphadenectomy was not done, the investigators concluded that pelvic radiotherapy is not indicated in patients with lesions of stage IB grade 2 who are younger than 60 years. In that study, the locoregional relapse rate and 5-year survival in the radiotherapy group were 5% and 85% compared with 18% and 81% in the control group. Therefore, according to this subgroup analysis, pelvic radiotherapy should be considered for local control if lymphadenectomy is not done and if two of the three risk factors—stage IC, grade 3, or age over 60 years—are present.[171] Given the absence of pelvic side-wall recurrences in women with such risk factors, a lymph-node-negative status from a formal lymphadenectomy, and the cumulative adverse effects of surgery and radiotherapy, node-negative patients can be spared further radiotherapy.[160] The subset of patients found to be node positive at lymphadenectomy might also benefit locally from further radiotherapy. In our centre, this strategy is applied irrespective of the type of endometrial cancer. The randomised trial ASTEC will further define the role of external radiotherapy in women with high-risk lesions confined to the uterus. Vault brachytherapy was optional in the trial, and patients were randomly assigned external-beam radiotherapy or no external-beam radiotherapy. Assessment was made independently of nodal status, but high-risk pathology was defined as one or more of: grade 3 endometrioid, more than 50% invasion, serous or clear-cell type, and stage-IIA disease. The first results are expected soon, since accrual is complete and the first analysis is expected by the end of this year.

As an intermediate between no further irradiation and external pelvic radiation, and since a substantial proportion of isolated pelvic recurrences occur in the vagina, postoperative treatment with vaginal brachytherapy is efficient for local control in surgically staged node-negative patients.[173] Because there is no difference in overall survival between prophylactic radiotherapy and radiotherapy given at the time of local relapse, this practice is not common in our centre.[174]

The combination of surgery and postoperative radiotherapy is not without risk of serious complications. They occur in 1–10% of women, depending on the patient's status, irradiated volume of bowel, bladder, or vagina, radiation dose, fraction size, dose rate (low, pulsed, or high), and especially in combination with lymph-node resection. Modern radiotherapy techniques with belly board and multiple fields or three-dimensional conformal radiotherapy are recommended to limit side-effects. Prophylactic brachytherapy should be restricted to the upper third of the vagina, and contact doses should not exceed 60 Gy low-dose-rate equivalent to limit long-term side-effects.[175]

Systemic treatment of endometrial cancer

In surgical stage I–II type 1 or 2 endometrial cancer, there is currently no proof that adjuvant hormone therapy or chemotherapy results in a better outcome. Adjuvant cytotoxic chemotherapy has been studied in only one large randomised trial.[176] Patients were surgically staged and received postoperative radiotherapy if nodes were positive. Subsequently, patients were assigned intravenous doxorubicin or no further therapy. After follow-up of 5 years, there was no difference in survival between the groups. Pilot studies showed improved outcome after the combination of both local and systemic treatment in early-stage

***Panel 4:* Areas of controversy and current research**

Assessment of the role of three-dimensional ultrasonography in the diagnosis of endometrial cancer
Cost-benefit analysis of tests done in women with abnormal uterine bleeding
Microarray analyses and proteomics are likely to further disentangle molecular pathways
Distillation of prognostic and predictive factors from molecular findings
Conservative management with antioestrogens or local progestagens to conserve fertility
Long-term safety in relation to local and port-site metastases of laparoscopically assisted vaginal hysterectomy
Accuracy of sentinel procedure for lymph-node staging
Pelvic versus local radiotherapy to decrease local relapses
Survival benefit of correct surgical staging (lymphadenectomy) and mode of radiotherapy
Role of adjuvant chemotherapy in endometrial cancer of surgical stage I–II, type 2
Role of pure antioestrogens (fulvestrant) and newer selective oestrogen-receptor modulators
Tibolone and endometrium
Role of ultrasonography in detection of recurrent disease

carcinosarcoma and type-2 endometrial cancer but this finding must be confirmed.[177–179] In a Japanese randomised study,[179] adjuvant treatment of intermediate-risk endometrial carcinoma with cyclophosphamide, doxorubicin, and cisplatin resulted in similar survival to pelvic radiotherapy. Also the adjuvant administration of progestagens does not appear to increase survival in patients with endometrial cancer predominantly of type 1 stage I–II.[180] In the metastatic or advanced setting, systemic treatment is palliative, and objective responses to treatment are generally partial and last for an average of 3–6 months, resulting in median survival of 7–10 months. Progestagens have been the cornerstone of hormonal treatment of metastatic endometrial cancer, and response is related to the presence of steroid-hormone receptors. The ideal dose is 200 mg medroxyprogesterone acetate daily; it is as effective as but less toxic than the 1 g dose.[181] Response rates range from 15% to 20%. Tamoxifen also has a small benefit in this setting; alternation of this drug with progestagens can result in a longer-lasting response.[182] Locally released progestagens could be an option in women with inoperable cancers or those wishing to preserve fertility if they have an early-stage low-grade lesion.[183] In the absence of long-term data, however, this treatment option is experimental.

In advanced-stage disease, phase II studies that included both endometrioid and non-endometrioid endometrial cancer have shown that cisplatin and doxorubicin are active agents in this cancer.[184–187] Carboplatin in doses of 300–400 mg/m^2 every 4 weeks has been associated with similar response rates to cisplatin.[188–190] In a randomised trial, in which the type of endometrial cancer studied was not specified, the addition of cisplatin to doxorubicin resulted in only a slight survival benefit (9 *vs* 7 months), despite greater toxic effects (mainly haematological and nausea/vomiting) in the combination group.[191,192] For serous endometrial cancer, small non-randomised trials have found response rates to cisplatin-based therapy of 10–33%, whereas the reports show response rates of only up to 30% in salvage settings for doxorubicin; objective response rates of 77% to single-agent paclitaxel are promising.[193–195] In 273 cases of mainly type-1 advanced endometrial carcinoma, the addition of paclitaxel to doxorubicin and cisplatin resulted in a gain in overall survival of 3 months (overall survival 15·3 *vs* 12·3 months), but resulted in more patient-reported peripheral neurotoxicity.[196] A good therapeutic index (effective but low toxicity) was obtained by the combination of carboplatin and paclitaxel in endometrial cancer of both types 1 and 2.[197] On the basis of the low toxicity, ease of administration, and efficacy, the combination of carboplatin and paclitaxel has become standard in many centres in the treatment of advanced or recurrent endometrial cancer. Chemotherapy has been compared in a randomised setting with whole-abdominal radiotherapy, but the results are available only in abstract form so far.[198] After surgery for endometrial cancer of stage III–IV with the maximum size of residual disease limited to 2 cm, 388 patients were randomly assigned cisplatin and doxorubicin chemotherapy for seven courses or whole-abdominal radiotherapy with 30 Gy in 20 fractions and a pelvic boost of 15 Gy. Although recurrences were frequent (55%) in the pelvis and abdomen in both groups, 2-year progression-free survival was better with chemotherapy (59% *vs* 46%) as was overall survival (70% *vs* 59%; $p<0·01$).[198]

Follow-up

Weight loss, pain, and vaginal bleeding can suggest recurrent disease, which mostly occurs during the first 3 years after primary treatment. Although follow-up visits are organised in most settings, retrospective data suggest that there is no difference in survival between symptomatic and asymptomatic recurrences, or between women with recurrences detected during routine follow-up visits and those with recurrences detected during the interval between routine visits.[199] Furthermore, follow-up of patients treated for endometrial cancer based on routine Pap smears and systematic radiography does not permit earlier detection of recurrences.[200] Also, since about two-thirds of the cost was due to Pap smears and radiography, there appears to be no economic or clinical justification for these examinations during routine follow-up.[199,200] However, these calculations do not take into account the psychological benefit for most patients, who were reassured that they did not have recurrent disease.

Centres advocating surveillance should focus on the detection of potentially curable vaginal recurrences, since isolated vaginal-vault recurrence of endometrial cancer is curable in up to 87% of cases, in patients previously not exposed to radiation.[174] Therefore, women should be counselled to contact their physician in the case of vaginal bleeding.

Several non-randomised studies have addressed the safety of oestrogen replacement after therapy for early-stage endometrial cancer, and safety was confirmed in a large randomised GOG-137A study. However, the number of events was too low to permit any firm conclusions.[201]

Controversial or unresolved issues

Issues that remain controversial or unresolved in relation to endometrial cancer are listed in panel 4.

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