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Cancer of the Uterine Corpus

Robbert Soeters

INTRODUCTION

Malignancies affecting the uterine corpus are endometrial adenocarcinoma and uterine sarcomas.

ENDOMETRIAL ADENOCARCINOMA

Endometrial adenocarcinoma is the most common gynecological malignancy in industrialized countries. However, incidences vary among regions. In industrialized countries the incidence maybe four to six times higher than in low-resourced countries. A number of reasons may explain this discrepancy. In industrialized countries there has been a sharp increase of the life expectancy and a subsequent risk of exposure to causative factors of endometrial cancer. Secondly, it has been shown that obesity is reaching epidemic levels in industrialized areas. Obesity, due to increasing levels of estrogens from peripheral conversion of androgens is closely associated with the occurrence of endometrial cancer.

For patients with serous, clear cell and other non-endometrioid cancers there is no clear association with obesity and other hormonal conditions, but the association with increased life expectancy seems on the other hand to be stronger. The patients with non-endometrioid cancer seem to be older compared to those patients with endometrioid cancers.

In South Africa with a mixed economy, the number of patients with endometrial cancer also has increased over the past 10 years (Figure 1).

The mortality of endometrial cancer is higher in low-resourced countries compared to industrialized regions. It may well be, that a lack or at least sub-standard treatment options in low-resource regions are the cause for this discrepancy. Furthermore, it may be that the population in those areas with co-morbid conditions such as HIV/AIDS, tuberculosis and malnutrition is in a worse state compared to that of high-resource areas. Although exact figures are not known, it may well be that patients in low-resource areas present more often with advanced-stage disease (due to a lack of knowledge and less access to health resources) compared to patients in other areas. In Figure 2 the incidence rates are displayed.

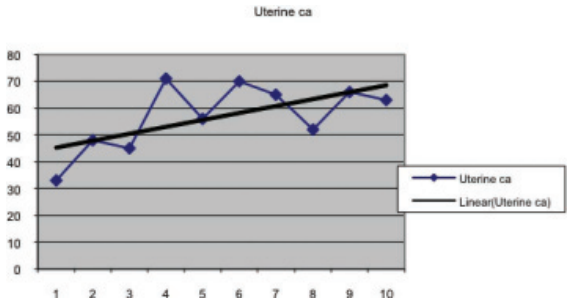

Figure 1 Number of new patients with uterine cancer at Groote Schuur Hospital, Cape Town

Endometrial cancer is a malignancy, which is most commonly found in postmenopausal women. The peak incidence is found in patients aged between 60 and 69 years. Age-adjusted incidence shows mainly an increase of the incidence in this age group without an increase in premenopausal patients.

The age distribution nevertheless has consequences for the management of the elderly patients with a diagnosis of endometrial cancer with co-morbid conditions such as hypertension, diabetes and most importantly obesity and metabolic syndrome. Patients with these conditions are at more risk for postoperative morbidity such as wound sepsis and thromboembolic events with possible grave consequences.

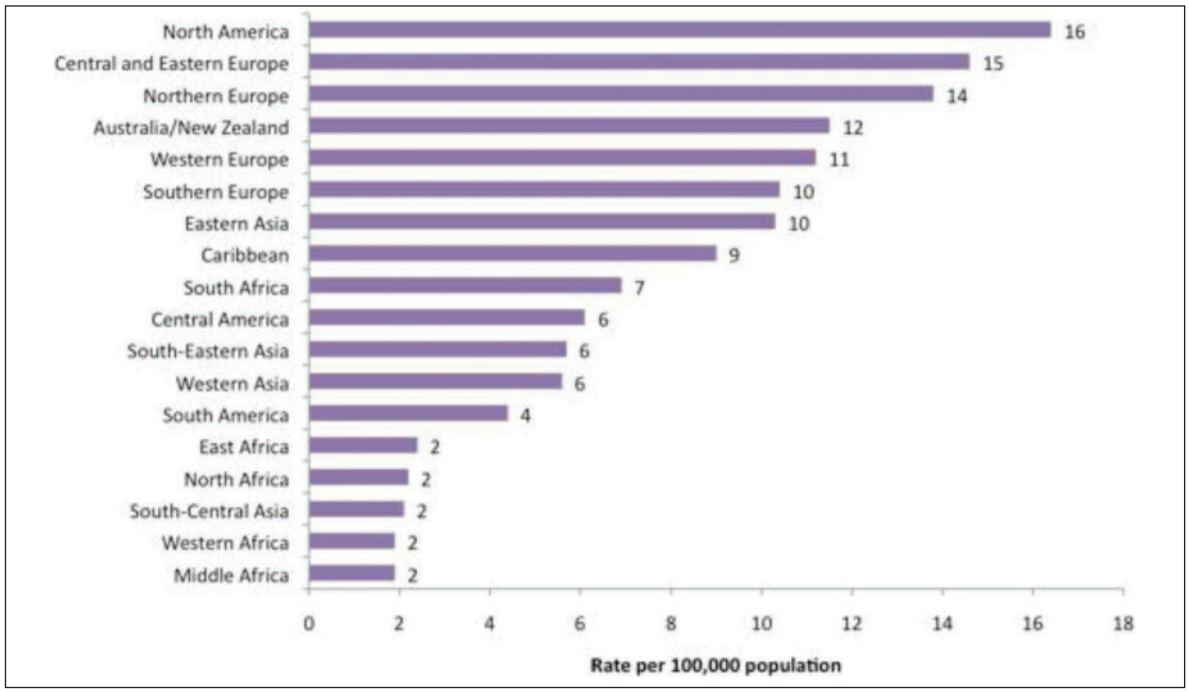

Figure 2 Age-standardized incidence rates for endometrial cancer for 2008. Source: World Cancer Research Fund International

Pathology

The majority of patients (80%) who present with endometrial carcinoma are found to have an endometrioid-type adenocarcinoma or a variant thereof (Figure 3a). The remainder of patients have a variety of histological abnormalities. The most important types of this group are the serous and clear cell carcinomas (10%), which are aggressive tumors and account for 50% of patients who die from the whole group of endometrial carcinomas.

The World Health Organization (WHO) histological classification of endometrial cancer is commonly used as a guideline to the histological diagnosis of endometrial carcinoma (Table 1).

The histological examination of endometrioid endometrial carcinomas shows endometrial-type glands. The International Federation of Gynecology and Obstetrics (FIGO) has sub-classified these carcinomas in varying differentiation; cases of carcinoma of the endometrium should be grouped with regard to the degree of differentiation of the adenocarcinoma as follows:

- G1: ≤5% of solid non-squamous or non-morular solid growth pattern.

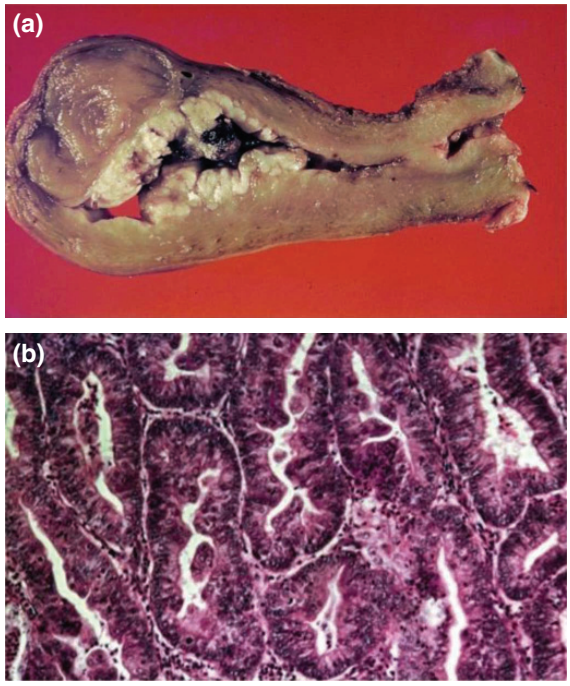

Figure 3 (a) Endometrial endometrioid adenocarcinoma; (b) well-differentiated endometrioid adenocarcinoma. Courtesy of Dr Judy Whittaker

Table 1 WHO histological classification of endometrial cancer

Endometrial adenocarcinoma
Typical: endometrioid
Variants: villoglandular; with squamous differentiation; secretory; with ciliated cells
Other adenocarcinomas
Serous carcinoma
Clear cell carcinoma
Mucinous carcinoma
Squamous-cell carcinoma
Undifferentiated carcinoma
Small-cell carcinoma
Mixed carcinoma
Large-cell and small-cell carcinoma

- G2: 6–50% of solid non-squamous or non-morular solid growth pattern.
- G3: >50% of solid non-squamous or non-morular solid growth pattern.

Further notes on pathological grading include:

- Notable nuclear atypia, inappropriate for the architectural grade, raises the grade of a grade I or grade II tumor by one.
- In serous adenocarcinoma, clear cell adenocarcinoma and squamous-cell carcinoma, nuclear grading takes precedence.
- Adenocarcinoma with squamous differentiation is graded according to the nuclear grade of the glandular component.

Serous and clear cell carcinomas are by definition graded grade III carcinomas. Bokhman[1] should be credited with a further, mainly prognostic, classification of two distinct groups of patients presenting with an adenocarcinoma of the endometrium (Table 2):

- *Type I* patients present with a typical endometrioid carcinoma arising against a background of endometrial hyperplasia. Type I is associated with a prolonged exposure to estrogens such as a late menopause, incessant ovulation and representing about 80% of the cases. These malignancies usually show a low or moderate differentiation. The prognosis for these patients is usually good.
- Patients with a *type II* cancer on the other hand, account for up to 20% of cases, and are found against a background of atrophic endometrium. Serous and clear cell carcinomas (high grade) are most commonly found in this group of patients. Patients with type II carcinomas are at high risk for extrauterine disease and recurrence. The prognosis for these elderly patients is usually poor.

Table 2 Clinical sub-classification of endometrial cancer according to Bokhman,1983[1]

Type I	*Type II*
Endometrioid carcinoma	Serous carcinoma/clear cell carcinoma
<65 years	65 years
Estrogen dependent	Estrogen independent
Associated with endometrial hyperplasia	Associated to atrophic endometrium
Low/moderate grade	High grade
Good prognosis	Aggressive behavior and poor prognosis

Type I carcinomas are associated with endometrial hyperplasia. Several classifications for hyperplasia have been suggested. The most important variable is the presence of cytological atypia, which put the patient at risk for the development of frankly invasive endometrioid endometrial carcinoma. In up to 40% of patients with atypical hyperplasia, a concomitant frankly invasive endometrioid endometrial carcinoma is found. This has consequences for the management of patients in which a hyperplasia with cytological atypia is found insofar that these patients should be considered for a simple hysterectomy and bilateral salpingo-oophorectomy (see Chapter 20 on how to perform a vaginal hysterectomy and Chapter 19 for simple abdominal hysterectomy). For diagnosis and treatment of all other endometrial hyperplasia see Chapters 9 and 10 on pre- and postmenopausal bleeding disorders.

In about 10% of endometrial carcinoma a synchronous ovarian primary is found which in most cases is an endometrioid carcinoma.

Screening

There is currently no generally accepted method for screening for endometrial carcinoma in asymptomatic patients. Screening of the general population is neither efficient nor cost-effective[2]. There are nevertheless women at risk for developing endometrial cancer. These include:

- Increasing age
- Long-term exposure to unopposed estrogen (i.e. the use of estrogens without progesterone)
- Obesity (with or without co-existing diabetes and hypertension)
- Patients without children
- Anovulation such as is found in polycystic ovarian disease
- Late menopause
- Patients with previously diagnosed breast cancer
- Long-term use of tamoxifen
- Hereditary non-polyposis colon cancer (HNPCC)
- Family history of endometrial, ovarian and breast carcinoma

Methods for screening in these patients include serial transvaginal ultrasound (TVU) and endometrial sampling. In the postmenopausal patient who is not taking hormone replacement treatment the endometrial thickness (ET) found on TVU should be <4 mm (Figure 4).

Above this threshold of 4 mm an endometrial sampling in the symptomatic patient (with vaginal bleeding) is indicated. Endometrial sampling should render a histological specimen. A cytological specimen, if abnormal, needs to be followed by an endometrial sampling for histological analysis. Currently, many devices for out-patient histological endometrial sampling are available. The most popular are the Pipelle®, manual vacuum aspiration (MVA; smallest cannula) and the Endosampler® (Figure 5). All these devices work on the principle of scraping and subsequent suction of endometrial tissue and can be used during an office procedure. Non-disposable instruments such as small curettes work just on the principle of scraping tissue and are often painful for the patient when used during an office procedure.

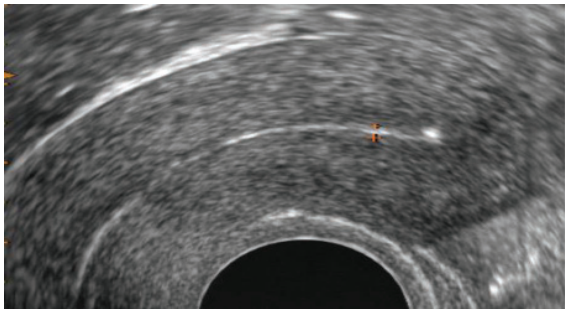

Figure 4 Thin normal endometrial line. Courtesy of Dr Douglas Dumbrill

Symptoms and diagnoses

Most patients present with abnormal bleeding or at least bloody discharge after menopause. The age distribution should however at the same time alert the medical attendant when a premenopausal patient presents with intermenstrual or heavy prolonged bleeding. There are several causes of postmenopausal bleeding (see Chapter 10); in approximately 5–20%, carcinoma of the endometrium is diagnosed[3].

A TVU for a patient presenting with abnormal bleeding, after a lower genital tract cause (vulval, vaginal, cervical abnormality) has been excluded, is mandatory to visualize the endometrial cavity. The ET should be measured and an increased ET should alert the medical attendant of the presence of an endometrial carcinoma (Figure 6).

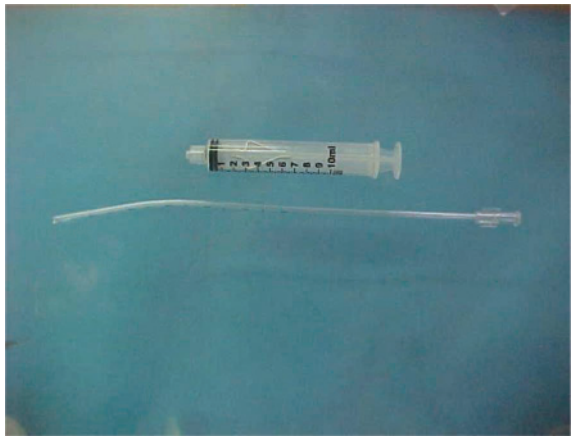

Figure 5 An Endosampler

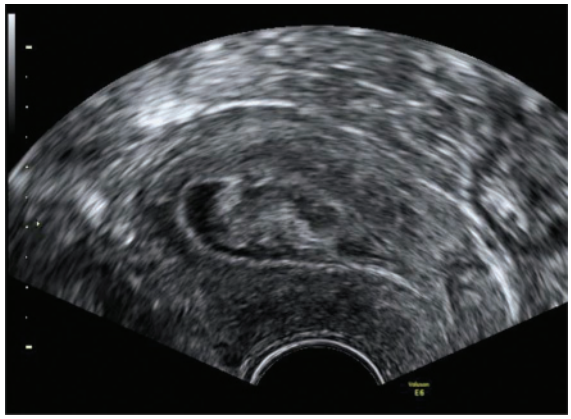

Figure 6 Endometrial carcinoma. Courtesy of Dr Douglas Dumbrill

In postmenopausal patients where the ET is <4 mm other causes for postmenopausal bleeding should be entertained. In postmenopausal patients where the ET is >4 mm the index of suspicion should be high for an endometrial carcinoma. An endometrial biopsy is indicated to confirm or exclude the diagnosis of an endometrial carcinoma. In cases where access to the uterine cavity is not possible, a hysteroscopy (if available) together with endometrial sampling under a general anesthetic is mandatory.

Staging

Endometrial carcinoma spreads according to a number of routes:

1. Direct extension to adjacent structures such as myometrium, fallopian tubes and cervix.
2. Spread of cancer cells through the fallopian tubes may explain ovarian metastasis and the presence of malignant cells in the peritoneal washings.
3. Lymphatic spread to pelvic and para-aortic lymph nodes.
4. Hematogenous spread occurs which is less common and may include spread to liver, brain and lungs.

Until 1988, the FIGO staging classification for endometrial cancer was clinical. In 1987 a study performed by the American Gynecologic Oncology Group (GOG) published results of the surgical pathologic spread patterns of endometrial cancer. The study evaluated 621 patients with clinical stage I carcinoma of the endometrium. Patients with endocervical involvement were excluded from the study. All patients had a total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) in addition to a selective pelvic and para-aortic lymphadenectomy and collection of peritoneal cytology. It was shown that high-risk groups for lymph node metastases (and therefore systemic disease) could be identified. The grade of the tumor and depth of myometrial invasion were shown to be independent significant factors for pelvic lymph node involvement. In patients with a grade 1 tumor and no invasion of the myometrium, no involvement of pelvic lymph nodes was found. However, patients with grade 3 endometrial cancer and infiltrating into the outer one-third of the myometrium had a 34% incidence of pelvic lymph node metastasis. Patients with a grade 1 cancer, which was limited to the endometrium had no involvement of para-aortic nodes, while patients with a grade 3 tumor and where the tumor was infiltrating into the outer one-third of the myometrium had a 23% incidence of para-aortic lymph node metastasis. As a consequence, the FIGO staging changed in 1988 from a clinical stage to a surgical staging including for the first time assessment of the pelvic and para-aortic lymph nodes. A further refinement took place in 2009 when the latest FIGO staging was published (Table 3).

Table 3 Staging for carcinoma of the endometrium (FIGO 2009)

Stage I	Tumor confined to the corpus uteri
IA	No or less than half myometrial invasion
IB	Invasion equal to or more than half of the myometrium
Stage II	Tumor invades cervical stroma, but does not extend beyond the uterus
Stage III	Local and/or regional spread of the tumor
IIIA	Tumor invades the serosa of the corpus uteri and/or adnexae
IIIB	Vaginal and/or parametrial involvement
IIIC	Metastases to pelvic and/or para-aortic lymph nodes
IIIC1	Positive pelvic nodes
IIIC2	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA	Tumor invasion of bladder and/or bowel mucosa
IVB	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

Either G1, G2, or G3. Endocervical glandular involvement only should be considered as stage I and no longer as stage II. Note: positive cytology has to be reported separately without changing the stage.

Preoperative work-up

After a histological diagnosis of endometrial carcinoma has been made a number of relatively simple preoperative investigations should be done. These include:

Laboratory:

- Full blood count

- Liver function tests
- Renal function test (including urea and creatinine)
- Baseline CA-125 (if available)
- Random glucose.

Radiological:

- X-ray chest
- Pelvic ultrasound if that has not been done yet
- Where available, advanced imaging like a contrast enhanced magnetic resonance imaging (MRI) of abdomen and pelvis may be considered.

The patient should be counseled on the extent of the operation and possible complications. The typical patient with endometrial carcinoma is often obese, with co-morbid disease such as diabetes and hypertension, and elderly. These patients often have a postoperative course complicated by wound sepsis. Factors that will influence the incidence of postoperative wound sepsis are: body mass index (BMI), low albumin, pre-existing pulmonary disease and previous abdominal surgery. In these patients extra care should be given to prolonged antibiotic cover and wound draining. Several factors (surgery for malignant disease, obesity, diabetes and hypertension) put these patients at risk for postoperative thromboembolic complications and adequate anticoagulation is indicated if available.

Treatment

The cornerstone for treatment of patients with endometrial cancer is surgery. The most commonly used incisions are a Pfannenstiel or a low transverse incision. However, if there is a suspicion or a diagnosis of an advanced-stage cancer or a high-grade tumor such as serous papillary or clear cell carcinoma a mid-line incision may be indicated for better access. This incision will facilitate an omentectomy and/or a para-aortic lymphadenectomy and/or removal of abdominal metastatic deposits. In extremely obese patients with a BMI >35 it may be necessary to do a so-called panniculectomy for better access to the abdominal cavity. After entering the abdomen careful exploration of the abdomen is indicated. This is followed by washings of the pouch of Douglas for cytological examination. If the tumor is resectable a (extra-fascial) TAH-BSO should be performed (see Chapter 19 on uterine fibroids on how to do a TAH-BSO).

Worldwide there is much debate whether or not to perform a pelvic and para-aortal lymph node dissection. Where indicated and experts to perform surgery are available, a pelvic lymphadenectomy including the common iliac nodes may be performed. The indications for a pelvic lymphadenectomy include known high-risk factors:

- Grade 3 with or without >50% myometrial invasion
- Grades 1 or 2 with >50% myometrial invasion
- Type of histology (uterine serous papillary carcinoma and clear cell carcinoma)
- In stage II disease a radical hysterectomy is advised.

The role of pelvic and para-aortic lymphadenectomy in patients with endometrial cancer remains controversial. There is randomized evidence that the lymph node dissection itself is not curative. The reasoning behind lymphadenectomy, however, is that such a procedure should identify the patients with systemic disease. In cases of positive lymph nodes one may consider local as well as systemic treatment such as pelvic radiotherapy and chemotherapy. Alternatively, in patients with high-risk factors who are found to have negative lymph nodes after a full lymphadenectomy can be reassured and only brachytherapy may be considered. The use of pelvic radiotherapy may result in long-term side-effects such as radiation induced cystitis and proctitis.

If a facility for frozen section is available, frozen section should be done in patients with a preoperative diagnosis of complex atypical hyperplasia, and grade 1 and 2 endometrioid adenocarcinoma. The pathologist should assess the histological type, the grade, the depth of myometrium invasion and cervical involvement. If frozen section indicates >50% myometrium invasion, grade 3 and/or cervical stromal involvement, a pelvic lymphadenectomy may be performed. If a frozen section facility is not available the uterus may be bivalved after removal on the operating table and the depth of invasion and cervical involvement may be assessed macroscopically to judge whether the patient is at risk for lymph node metastases.

In patients with extrauterine disease cytoreduction to no residual disease should be attempted as this may result in a significant prolonged survival time.

Patients with early-stage clear cell carcinoma or patients with uterine serous papillary carcinoma are

staged the same as for early ovarian cancer: peritoneal washings, TAH, BSO, omentectomy, pelvic and para-aortic lymph node sampling and biopsies.

An omentectomy and cytoreduction are recommended in patients with advanced-stage endometrioid cancer, clear cell carcinoma or patients with uterine serous papillary carcinoma. If there is locally advanced disease an attempt should be made for cytoreductive surgery. A lymphadenectomy is indicated in these patients In cases where bulky nodes are found removal of bulky lymph nodes should be attempted.

Occasionally, a vaginal hysterectomy may be indicated in patients with co-morbid disease where a laparotomy maybe hazardous. Several (retrospective) studies have demonstrated that a vaginal hysterectomy does not have a negative effect on prognosis. Laparoscopic-assisted vaginal hysterectomy (LAVH) and BSO with or without pelvic lymphadenectomy has been shown to be an excellent alternative for an open procedure, but unfortunately is not yet available in many low-resource settings. Several studies have demonstrated that a laparoscopic approach does not compromise the prognosis of patients with endometrial cancer, with probably a more rapid recovery period and less postoperative complications, which is, considering the profile of these patients, a distinct advantage. A number a limiting factors such as obesity and an enlarged uterus may be contraindications for laparoscopic surgery. A laparoscopic approach requires special training and skills. Lastly, the operating time is longer compared to an open approach and it is still shown to be the more expensive procedure.

Histological evaluation of specimens is mandatory to determine possible adjuvant treatment. The histopathologist should report on grade or differentiation, size of the tumor, depth of myometrium invasion, lymph–vascular space invasion, cervical involvement and adnexal involvement. Although in the latest 2009 FIGO staging classification positive washings do not change the stage, the presence of malignant cells in the pouch of Douglas washing should be reported (Table 4).

Adjuvant treatment

Although in many low-resource countries, radiotherapy is not easily available, it may be considered for certain high-risk patients. The adjuvant treatment should be individually tailored. Low-risk patients have a favorable prognosis and do not need adjuvant treatment. The most relapses in early stages are located in the vagina. This is a favorable location for salvage therapy with external and intracavitary radiotherapy, surgery, or both, but this can often only be done in special centers in resource-poor settings[4].

Patients with stage I disease without high-risk factors may be followed up only, as in this group the prognosis is very good (Table 5).

Patients with high-intermediate-risk factors may be treated with brachytherapy only when this is available. The PORTEC 2 study demonstrated that pelvic external beam radiotherapy (EBRT) did not render a better survival or disease-free survival compared to vaginal brachytherapy only[5]. Of interest is that the patients in the PORTEC 2 study did not undergo a lymphadenectomy, which suggests that rate of positive nodes in patients with high-intermediate-risk factors is relatively low.

Table 4 Based on the latest FIGO 2009 staging classification risk groups have been identified for stage I endometrial cancer

Low risk: stage IA, grade 1 and 2, endometrioid adenocarcinoma

Intermediate risk:
1. Stage I:
   - moderate to poorly differentiated tumor (grade 3)
   - presence of lympho-vascular invasion
   - outer third myometrial invasion (stage IB)
2. Age ≥50 years with any two risk factors listed above; *or*
3. Age ≥70 with any risk factor listed above

High risk: stage IB plus grade 3, non-endometrioid histology

Table 5 Overview of treatment in stage I endometrial cancer risk according to groups in Table 4[7]

Risk group	*Adjuvant treatment*
Low risk	No adjuvant treatment
Intermediate risk • With 2 high-risk factors (age >50 years) • With 1 risk factor (age >70 years)	Brachytherapy
High risk	External beam radiotherapy and brachytherapy

Risk factors for recurrent disease in stage I endometrial cancer include grade 3 tumors with infiltration into the outer half of the myometrium. These patients are certainly at risk for positive pelvic and or para-aortic lymph nodes. If the lymph node status is known and positive the patients should receive full pelvic radiation maybe including the para-aortic lymph node groups.

Patients with grade 3 tumors and involvement of the outer half of the myometrium without positive pelvic and para-aortic lymph nodes can be adequately treated with vaginal brachytherapy[6].

For adjuvant treatment in stage III disease, EBRT is recommended. The role of systemic treatment, i.e. chemotherapy, is still controversial in patients with high stage endometrioid cancers.

Several agents had been studied but no conclusive evidence of benefit has been published. In patients with a non-endometrioid cancer such as uterine serous papillary carcinoma and clear cell carcinomas it has become common practice to give intravenous chemotherapy including carboplatinum and paclitaxel (see Chapter 28). A number of studies have suggested an increased progression-free survival in patients who received external pelvic radiotherapy (EPRT) in combination with chemotherapy compared with only EBRT. We have to wait for further studies.

Recurrence of endometrial cancer

In a limited number of patients the disease will recur. When the recurrence is local (vagina or vagina top) surgery by an experienced doctor or radiotherapy can still cure the patient. In cases of distant recurrence the prognosis is poor and only palliative chemotherapy (with carboplatin and paclitaxel) or hormone therapy in patients with a tumor with positive progesterone receptors (medroxyprogesterone 200 mg daily orally) are possible. Palliative care is described in Chapter 32.

Community sensitization

There are two important points in health promotion activities around endometrial cancer. First, as already mentioned, type I endometrial cancer is linked to exposure to excess estrogens, which is often related to obesity and metabolic syndrome (obesity, type 2 diabetes and hypertension). Only recently, the WHO has acknowledged the importance of chronic disease prevention and cure including cancer, hypertension and diabetes. In transitional but increasingly also in low-resource settings a large proportion of society tend to be obese. Communities need to be sensitized about this link and the dangers associated with metabolic syndrome. Secondly, endometrial cancer has its peak incidence in postmenopausal women. They usually hide genital symptoms, such as bleeding from their kin for a long time due to being ashamed of talking about their genitals. As a consequence it is not sufficient to sensitize men and women about signs and symptoms of cervical and endometrial cancer. It is more frequently recognized that reproductive healthcare should be provided along a continuum of care, meaning from adolescent age to postmenopausal status, which gives enough opportunities for such a sensitization.

UTERINE SARCOMAS

Uterine sarcomas represent only 3–8% of all uterine malignancies. The low occurrence precludes any prospective studies and most published data concern retrospective studies and case histories. The latest classification of uterine sarcomas includes leiomyosarcoma, endometrial stromal sarcoma and undifferentiated or unclassifiable sarcomas. Carcinosarcoma (previously known as malignant mixed Müllerian tumors or MMMT) are now seen as poorly differentiated epithelial carcinomas. In this chapter, carcinosarcoma is discussed together with the uterine sarcomas.

Carcinosarcoma

These tumors represent <5% of all uterine cancers. These tumors are mainly seen in postmenopausal patients, who usually present with postmenopausal bleeding. A polypoid tumor on macroscopic examination is shown in Figure 7.

These are biphasic neoplasms involving malignant epithelial as well as mesenchymal (homologous and heterologous) tumors, i.e. sarcoma. The epithelial component is adenocarcinoma. The sarcomas may be heterologous with histological evidence of tissue not normally found in the uterus such as cartilage and bone (Figure 8).

Because these tumors are considered to be poorly differentiated epithelial carcinomas, the staging is according to that of epithelial (endometrioid) uterine malignancies as described above. It is at present not clear whether the 2009 FIGO

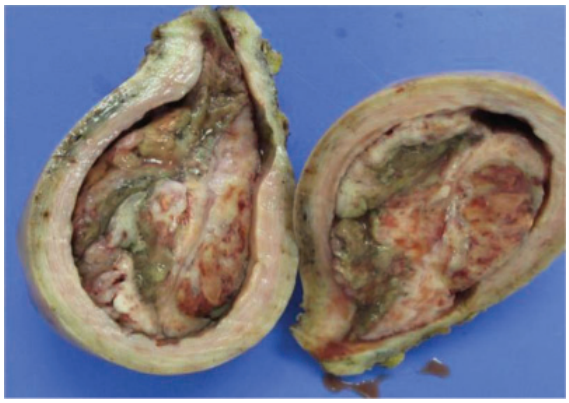

Figure 7 Carcinosarcoma filling the uterine cavity. Courtesy of Dr Judy Whittaker

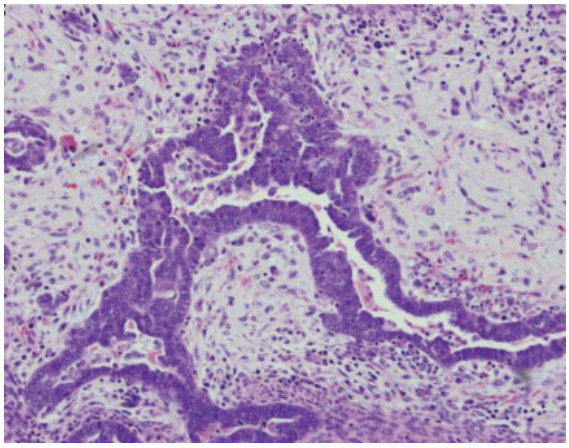

Figure 8 Heterologous carcinosarcoma of the uterus. Courtesy of Dr Judy Whittaker

staging classification is appropriate for these highly malignant tumors.

Carcinosarcomas show a tendency for lymphatic as well as transperitoneal spread. The cornerstone of treatment is surgical and the metastatic pattern has obvious consequences for the extent of a surgical procedure. Preoperative work-up should include (if available) a full blood count, liver function and renal function tests. Imaging should include a chest X-ray [and a chest computed tomography (CT) scan, if indicated and available]. An ultrasound maybe useful and, if available, MRI or CT scan of the abdomen and pelvis may be considered in order to determine the extent of intraperitoneal disease.

Surgery should be done by an experienced surgeon only and should at least include a TAH-BSO. The procedure should also include a full pelvic lymphadenectomy and an omentectomy[8]. A para-aortic lymphadenectomy may be considered although this would most likely represent a staging procedure without proven survival benefit[8]. If there is extrauterine spread, i.e. pelvic and/or upper abdominal peritoneal, an attempt should be made to remove these deposits although it is not clear whether this would improve the prognosis.

Postoperatively, adjuvant treatment may be recommended if there is extrauterine disease, residual disease or nodal disease, but the prognosis remains poor. Cytotoxic agents may play a role and active agents include carboplatinum, paclitaxel and anthracyclines. Due to infrequent occurrence of carcinosarcomas it is difficult to assess the true efficacy of adjuvant chemotherapy. The same goes for postoperative radiotherapy where mainly retrospective data are available. One prospective randomized trial found better local control in patients receiving adjuvant pelvic radiotherapy compared to patients who did not receive radiotherapy. Radiotherapy did however not result in a better progression-free survival or overall survival.

Leiomyosarcoma

For leiomyosarcoma, because of its classification as a true uterine sarcoma from a histological perspective a different FIGO staging classification is used (Table 6).

Although leiomyosarcoma is the most common uterine sarcoma accounting for 40% off all sarcomas it still only accounts for 1–2% of all uterine malignancies. In most patients a preoperative diagnosis is uncommon as these patients undergo surgery for what is perceived as a fibroid uterus (Figure 9).

Table 6 FIGO staging of uterine sarcomas, 2009 (leiomyosarcoma, endometrial stromal sarcoma and adenosarcoma)

IA	Tumor limited to uterus <5 cm
IB	Tumor limited to uterus >5 cm
IIA	Tumor extends to the pelvis, adnexal involvement
IIB	Tumor extends to extra-uterine pelvic tissue
IIIA	Tumor invades abdominal tissues, one site
IIIB	More than one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis

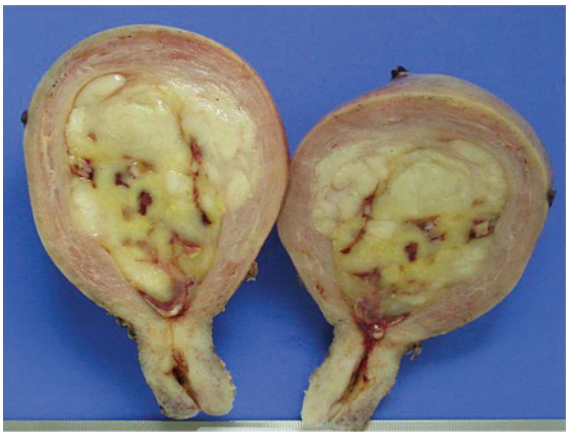

Figure 9 Leiomyosarcoma. Courtesy of Dr Judy Whittaker

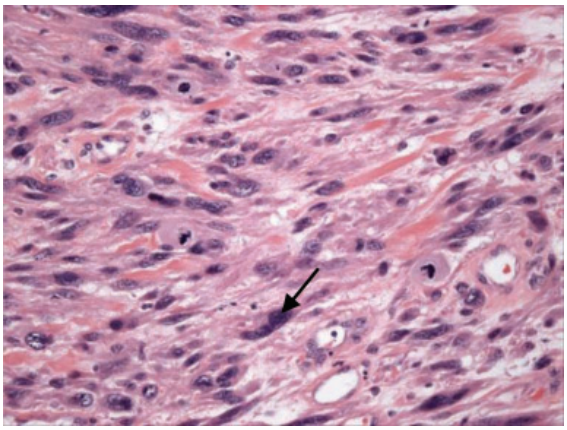

Figure 10 Leiomyosarcoma showing a malignant spindle cell (arrow). Courtesy of Dr Judy Whittaker

Histologically, leiomyosarcoma are characterized by spindled cells, nuclear atypia, and a high mitotic rate per high-power field (HPF) (Figure 10). Leiomyosarcoma with fewer than 10 mitoses/10 HPF are considered to be low risk while more than 10 mitoses/10 HPF are considered to be high risk with consequences for adjuvant treatment after surgery.

Smooth muscle tumors of uncertain malignant potential (STUMP) do not have all the diagnostic criteria of leiomyosarcoma, but show histological features such as pleomorphism, nuclear atypia and mitotic figures which are concerning. The prognosis is considered to be favorable. Leiomyosarcomas are sometimes estrogen receptor (ER) and/or progesterone receptor (PR) positive and this has obvious consequences for possible adjuvant treatment and management of recurrent disease although the efficacy may be disappointing.

The most common preoperative signs and symptoms are pelvic pain in the presence of a pelvic mass. Some patients may present with abnormal vaginal bleeding. Preoperative investigations are similar to those for carcinosarcomas and should include a full blood count, renal and liver function test. Imaging should at least include a routine chest X-ray. Ultrasound imaging which is commonly done preoperatively will not often give relevant information.

The metastatic pattern of leiomyosarcoma is mainly transperitoneal and hematogenic and if there is metastatic disease it is commonly distant. Lymphatic disease is uncommon and this has consequences for surgical management of these tumours. A TAH-BSO (see how to do a TAH in Chapter 19 on uterine fibroids) is the surgical treatment of choice. Pelvic lymphadenectomy is not indicated as the involvement of pelvic nodes is very rare.

In early and/or low-risk leiomyosarcoma there is no evidence in the literature to suggest a proven benefit of adjuvant therapy. For high-risk, metastatic and recurrent disease the systemic treatment of choice remains single agent Adriamycin® with a response rate varying between 15% and 25%. In tumors which are ER and/or PR positive, hormonal treatment may be considered in recurrent disease. Solitary metastases may be resected to improve prognosis. The role of radiotherapy in leiomyosarcoma is not clear, but may be considered in incompletely resected tumor confined to the pelvis or in isolated metastases and/or recurrent disease.

Endometrial stromal tumor

These tumours account for <10% of all uterine sarcomas. The tumors are typically characterized by cells resembling endometrial stromal cells of the proliferative endometrium. According to the WHO sub-classification endometrial stromal tumors include endometrial stromal nodules, low-grade endometrial stromal sarcomas (Figure 11) and undifferentiated endometrial sarcomas.

Endometrial stromal tumors occur in women during reproductive and later years. An endometrial stromal nodule is commonly an incidental finding as there are no signs and symptoms, while in the patients with sarcomatous de-differentiation abnormal bleeding is frequently found. Endometrial stromal nodules have an excellent prognosis and a simple hysterectomy is the treatment of

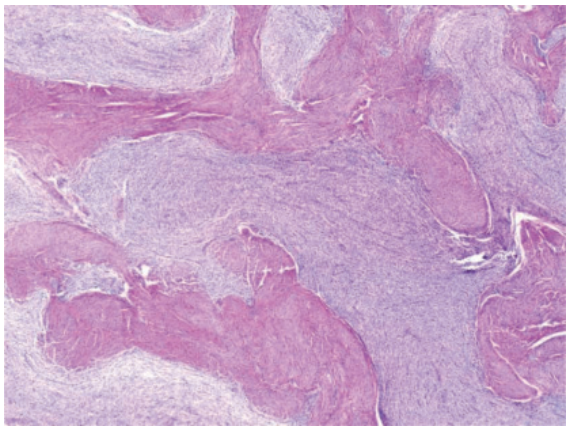

Figure 11 Low-grade stromal sarcoma. Courtesy of Dr Judy Whittaker

choice. Endometrial stromal sarcomas frequently display an infiltrative growth pattern with irregular margins with worm-like growth filling myometrial veins. The preoperative work-up for endometrial stromal sarcoma is similar to the work-up for other uterine sarcomas.

In patients with an endometrial stromal sarcoma and extrauterine extension the ovaries are commonly involved. A TAH-BSO is the surgical treatment of choice. Postoperative treatment may be considered in patients with extrauterine extension and high-dose progesterone or aromatase inhibitors (if available; for more information see Chapter 30) may be used depending on the ER and PR of the tumor. The tumors frequently show an indolent pattern and life-long follow-up is indicated.

Other uterine sarcomas

Undifferentiated sarcomas and adenosarcomas form the remainder of the uterine sarcomas.

Undifferentiated sarcomas are highly malignant rare tumors. The histological features include myometrial invasion, nuclear pleomorphism, necrosis and high mitotic activity. These tumors often present with distant metastases. The surgical treatment should at least include a TAH and BSO. There is no evidence to suggest that adjuvant treatment (either chemotherapy or radiotherapy) has any benefit, but may still be considered.

Adenosarcomas are mixed tumors with a benign epithelial component and a low-grade endometrial stromal-like sarcoma. The cervix is frequently involved. The treatment options are comparable to that of endometrial stromal sarcoma.

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