

Uterine Cancer

Cancer of the endometrium is the most common gynaecologic malignancy in Australia. It is the fourth most common malignancy found in women after breast, colorectal, and lung cancer, and is predominantly a disease of affluent, obese, postmenopausal women of low parity.

The risk factors associated with the development of carcinoma of the endometrium are listed below. Any factor that increases the exposure to estrogen unopposed by progesterone increases the risk of endometrial cancer. Oestrogen causes endometrial proliferation, and if its proliferative effects are not counteracted by progesterone, endometrial hyperplasia and possibly adenocarcinoma can result.

Obesity results in an increased production of oestrogen. Granulosa-theca cell tumours of the ovary produce estrogen, and up to 15% of patients with these tumours have an associated endometrial cancer.

Unopposed estrogenic stimulation from failure to ovulate occurs in patients who have polycystic ovarian syndrome and in patients with a late menopause. In post-menopausal women taking estrogen replacement without a progestin for menopausal symptoms, the risk of cancer developing appears to be both dose-dependent and duration-dependent. Women taking tamoxifen for breast cancer have a twofold to threefold increased risk of endometrial cancer. Young women who use oral contraceptives have been shown to have a lower incidence of subsequent endometrial cancer.

Risk factors for endometrial cancer

- Obesity
 - Having no children
 - Late menopause
 - Diabetes mellitus
 - Hypertension
 - Breast, colon, or ovarian cancer
 - Chronic failure to ovulate
 - Chronic tamoxifen use
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SCREENING OF ASYMPTOMATIC WOMEN

Population screening for endometrial cancer is not feasible, because there is no simple method of cancer detection available. However, screening may be justified for high risk women, including those with a family history of Lynch II Syndrome (hereditary nonpolyposis colorectal cancer syndrome), those with polycystic ovarian disease, and any woman with an intact uterus taking unopposed estrogen. Only about 50% of women with endometrial cancer will have malignant cells on a pap smear.

Transvaginal ultrasonography, to measure the thickness of the endometrium, is the best way to screen for endometrial cancer.

SYMPTOMS

The most common symptom of endometrial cancer is abnormal vaginal bleeding, which is present in 90% of patients. Postmenopausal bleeding is always abnormal and must be investigated. Most postmenopausal bleeding is not due to cancer, but rather to HRT or lack of hormones causing atrophic vaginitis. In the premenopausal patient, especially after age 35 years, heavy periods or bleeding between periods may signal an endometrial malignancy.

DIAGNOSIS

Any woman who presents with postmenopausal bleeding should have a transvaginal ultrasound. If the endometrial thickness is greater than 5mm, endometrial biopsy is necessary. Outpatient techniques for endometrial sampling include the use of the Pipelle cannula. This technique has a diagnostic accuracy of about 90%. If the endometrial biopsy reveals endometrial cancer, definitive treatment can be arranged. If the endometrial biopsy is negative for cancer or reveals endometrial hyperplasia, a hysteroscopy and uterine curettage should be performed under general anaesthesia.

STAGING

The International Federation of Gynaecology and Obstetrics (FIGO) is shown in the table below.

1988 FIGO staging of endometrial carcinoma

Stage

Stage Ia	Tumour limited to endometrium
Stage Ib	Invasion through less than one half of the myometrium
Stage Ic	Invasion equal to or more than half of the myometrium
Stage IIa	Endocervical glandular involvement only
Stage IIb	Cervical stroma invasion
Stage IIIa	Tumour invades serosa or adnexa, or both, or positive peritoneal cytologic findings, or both
Stage IIIb	Vaginal metastases
Stage IIIc	Metastases to pelvic or para-aortic lymph nodes, or both
Stage IVa	Tumour invasion of bladder or bowel mucosa, or both
Stage IVb	Distant metastases including intraabdominal or inguinal lymph nodes, or both

Histologic grade does not change the stage

Grade 1	Well differentiated
Grade 2	Moderately differentiated
Grade 3	Poorly differentiated

PREOPERATIVE INVESTIGATIONS

The only radiologic study necessary is a chest x-ray.

PATTERN OF SPREAD

Endometrial cancer spreads by (1) direct extension, (2) shedding of cells that are spread through the fallopian tubes, (3) the lymphatic vessels to the lymph nodes, and (4) the blood stream.

The most common route of spread is direct extension of the tumour to adjacent structures. The tumour may invade through the uterine muscle and eventually penetrate the serosa (outer covering). It may also grow downward and involve the cervix.

Exfoliated cells may pass through the fallopian tubes and implant on the ovaries, the peritoneum, or the omentum.

Lymphatic spread occurs most commonly in patients with deep muscle (myometrial) penetration. Dissemination through the blood stream is less common, but it results in distant metastases, particularly in the lungs or liver, or both.

TREATMENT

STAGE I

Surgery

Total abdominal hysterectomy and removal of both tubes and ovaries is performed on all patients. Surgical staging, including at least removal of the pelvic lymph nodes, should be performed on high risk patients, including those with serous, clear cell or grade 3 tumours; outer half muscle invasion; or cervical extension. Laparoscopic surgery, including laparoscopic-assisted vaginal hysterectomy and laparoscopic lymph node dissection, is currently under investigation.

Radiation Therapy

Radiation is sometimes given 6 – 8 weeks after surgery.

Recommendations are as follows.

1. Patients with grade 1 or 2 endometrioid carcinomas confined to the inner half of the myometrium may be followed without adjuvant therapy (i.e., stage Ia or Ib, grade 1 or 2).
2. Patients with high risk carcinomas with negative pelvic nodes (i.e., any stage Ic cancer; any grade 3, clear cell or serous cancer; or any stage II cancer) may have vault brachytherapy (without external beam pelvic radiation).
3. Patients with positive pelvic nodes or proven positive paraaortic nodes should receive extended field radiation (i.e., pelvic and paraaortic).
4. Whole abdominal radiation may be considered for patients with ovarian or omental metastases completely resected.

In patients medically unfit for surgery, radiation therapy alone may be employed. A combination of intracavitary plus external beam radiation is used. The overall 5-year survival rate is about 20% lower than for patients treated with hysterectomy.

STAGE II

If the cervix is involved with endometrial cancer, primary radical hysterectomy, bilateral removal of the tubes and ovaries, removal of the pelvic lymph nodes, and postoperative external beam therapy for positive lymph nodes is the treatment of choice.

ADVANCED STAGES

For advanced disease, treatment is individualized. The uterus, tubes, and ovaries should be removed, if possible, for palliation of bleeding and other pelvic symptoms. If gross disease is present in the upper abdomen, tumour metastases that are operable, should be removed in an attempt to improve the patient's quality of life. In addition to preoperative or postoperative radiation, patients with advanced disease also require hormonal therapy, and/or chemotherapy.

RECURRENT DISEASE

Seventy-five percent of recurrences develop within 2 years of treatment. Careful follow-up is particularly important for patients treated without adjuvant therapy. The majority of recurrences in these patients are at the vaginal vault, and 70% to 80% of patients can be salvaged by radiation therapy.

Metastases in other sites, such as the upper abdomen, lungs, or liver, are treated initially with high-dose progestins or antiestrogens. As with breast cancer, the likelihood of a patient responding to progestin treatment is increased in patients whose tumour contains estrogen and progesterone receptors. Approximately 80% of such patients respond to progestin therapy, compared with fewer than 10% of patients whose tumour is receptor negative.

Provera, 200 mg twice daily; may be given. If disease progresses while the patient is receiving progestins, chemotherapy may be offered. The combination of Carboplatin and paclitaxel (Taxol) gives a response rate of about 50%.

Prognosis

Prognosis is dependent on several variables, including uterine size, histologic type, grade of tumour, depth of myometrial penetration, status of lymph nodes, status of peritoneal cytologic features, and presence or absence of ovarian or upper abdominal metastases. Stage I endometrial cancers have a very good prognosis. Serous and clear cell endometrial carcinomas have a particularly bad prognosis, and both of these histologic types are prone to early dissemination. Five-year survival rates for these tumour types are less than 50%, even for patients with stage I disease.

Follow-Up

Follow-up examinations should be performed every 3 months for 2 years, every 6 months for 3 years, and then annually. It is important to take a vault pap smear on patients who have not had radiation therapy.

UTERINE SARCOMAS

Uterine sarcomas account for about 4% of uterine cancers. They arise from the stromal components of the uterus, either the endometrial stroma or the muscle tissues. As a group, sarcomas are more likely to disseminate through the blood stream, and have much lower 2- and 5-year survival rates.

LEIOMYOSARCOMA

Leiomyosarcomas are malignancies of the uterine muscle. They may be associated with a benign fibroid of the uterus, but the risk of malignant transformation in a benign fibroid is less than 1%.

Clinically, the mean age of patients with leiomyosarcoma is about 55 years. Patients with this disease may present with pelvic pain, abnormal uterine bleeding, or a pelvic or lower abdominal mass. A sensation of pressure on the bladder or rectum may also be noted.

Most cases are not diagnosed preoperatively but are discovered at the time of surgery for a probable fibroid. Curettings are usually normal. If a known fibroid uterus appears to be rapidly enlarging, especially postmenopausally, malignancy should be suspected.

The treatment of a uterine leiomyosarcoma consists of total abdominal hysterectomy and removal of both tubes and ovaries. Adjuvant pelvic radiation appears to decrease local pelvic recurrence but does not prolong survival because most patients die with distant spread.

Response rates to chemotherapy are very low.

ENDOMETRIAL STROMAL TUMOURS

Endometrial stromal sarcoma is a low-grade lesion. These patients usually present with abnormal vaginal bleeding and often with pelvic pain.

Most patients are cured with total abdominal hysterectomy and removal of the tubes and ovaries. Local and distant recurrences may occur even 10 to 20 years later and require re-exploration and resection of disease. Prolonged survival is possible after resection of recurrent disease, and response to progestins is good. Pelvic disease may respond to radiation therapy.

High-grade endometrial sarcoma generally causes abnormal uterine bleeding, and more than half the patients are premenopausal. The diagnosis can often be made by endometrial biopsy or uterine curettage. Aggressive myometrial invasion occurs, and hematogenous spread is common at the time of diagnosis.

The treatment of high grade endometrial sarcoma is total abdominal hysterectomy and removal of the tubes and ovaries. Postoperative pelvic irradiation improves local control but does not improve survival. In patients with metastatic disease, progestogens or chemotherapy may be offered.

MALIGNANT MIXED MÜLLERIAN TUMOUR (MMMT)

Malignant mixed müllerian tumours account for about 40% of uterine sarcomas. Most patients are postmenopausal and present with vaginal bleeding or discharge. About one-third of patients have tumour

growing through the cervix into the vagina as a polypoid mass. Up to 50% of patients with this lesion have evidence of metastatic disease at the time of diagnosis if surgically staged.

These tumours aggressively invade the uterine muscle and disseminate via the lymphatics and the blood stream.

The primary treatment of mixed müllerian sarcoma is the same as that for high-grade endometrial stromal sarcomas. Prophylactic cisplatin and epirubicin may improve survival for patients with stage I or II disease.

Prognosis

The prognosis for leiomyosarcomas and uterine sarcomas is poor because of the propensity for dissemination via the blood stream. The overall 5-year survival rate is about 35%. Patients with malignant mixed müllerian tumours have a much better prognosis.