Rare uterine cancers

Sheetal Acharya, Martee L Hensley, Anthony C Montag, Gini F Fleming

The most common malignant tumour of the uterus is endometrioid endometrial cancer. However, many less common malignant diseases also develop in the uterus, including both carcinomas and sarcomas. Most notable of these tumours are papillary serous carcinomas, clear-cell carcinomas, carcinosarcomas, stromal sarcomas, and leiomyosarcomas. These less common cancers can be aggressive, and account for a greatly disproportionate amount of deaths from uterine cancers. Because they are uncommon, physicians will usually have seen only a few cases, and randomised data to guide treatment often do not exist. This review summarises the epidemiology, clinical characteristics, and prognoses of the less common malignant diseases of the uterus, and presents the information available to guide the clinician about treatment options.

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UP Hematology Associates, Marquette, MI, USA (S Acharya MD)**; Gynecologic Medical Oncology Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA** (M L Hensley MD)**; and Department of Pathology** (A C Montag MD) **and Department of Medicine, Section of Hematology and Oncology** (Prof G F Fleming MD)**, University of Chicago, Chicago, IL, USA**

Correspondence to:
Prof Gini Fleming, Section of Hematology and Oncology, University of Chicago Medical Center, 5841 South Maryland Ave MC2115, Chicago, IL 60637, USA
gfleming@medicine.bsd.uchicago.edu

Introduction

The most common uterine cancer is endometrioid endometrial carcinoma. In the initial report that described the results of the National Surgical Adjuvant Breast and Bowel Project P-1 tamoxifen chemoprevention trial, the investigators stated "An endometrial cancer should not be considered the equivalent of a breast cancer, since the majority of cases are diagnosed early and cured with surgery."[1] However, an overall view that endometrial carcinoma is a harmless tumour is not warranted. In particular, unusual endometrial carcinomas, of which uterine papillary serous carcinoma is the prototype, are histologically distinct tumours that usually have a much worse prognosis than do grade 1–2 endometrial cancers of endometrioid histology. Uterine carcinosarcomas and uterine sarcomas are also aggressive tumours with a poor prognosis.

Endometrial carcinomas

Unusual endometrial carcinomas include uterine papillary serous carcinoma (figure 1), clear-cell carcinoma, mixed tumours, tumours with undifferentiated histology, mucinous tumours, and squamous-cell carcinomas. Uterine papillary serous carcinoma and clear-cell carcinoma are high-grade tumours by definition and are not graded further. Such tumours have a high rate of extrauterine involvement, even without deep myometrial invasion, and a high rate of recurrence even when there is no extrauterine involvement. Recommendations for primary treatment remain controversial and include pelvic radiotherapy or vaginal brachytherapy, or both; whole abdominopelvic radiotherapy, combinations of radiotherapy with chemotherapy, and chemotherapy alone.

More than 15 years ago, Bokhman[2] classified endometrial carcinomas into two types. Although this classification is an oversimplification, it is of use conceptually. Type I, oestrogen-related carcinomas, usually arise in the setting of endometrial hyperplasia and have endometrioid histology with low grade, and tend to be biologically indolent. Type II cancers are not oestrogen driven, have a higher grade, have various histologies, particularly serous carcinomas and clear-cell carcinomas, and have a poorer prognosis. Table 1 lists the classic features of the two categories.[3] Black women have substantially more aggressive tumour types than do white non-Hispanic women, including serous carcinoma and clear-cell carcinoma, and have a worse overall survival for all tumour types.[4] Although they are not discussed in this review, grade-3 endometrioid cancers, which constitute a minority of endometrial cancer, also behave aggressively.

Uterine papillary serous carcinoma

Histopathological characteristics

In 1982, Hendrickson and colleagues[5] described uterine papillary serous carcinoma as a highly malignant subtype of endometrial carcinoma that is characterised by complex papillary architecture with tufted stratification of the epithelial lining, high nuclear to cytoplasmic ratio, notable nuclear pleiomorphism, macronuclei, and a high rate of mitosis. This carcinoma almost always stains positively for P53 (figure 1). Histologically, uterine papillary serous carcinoma

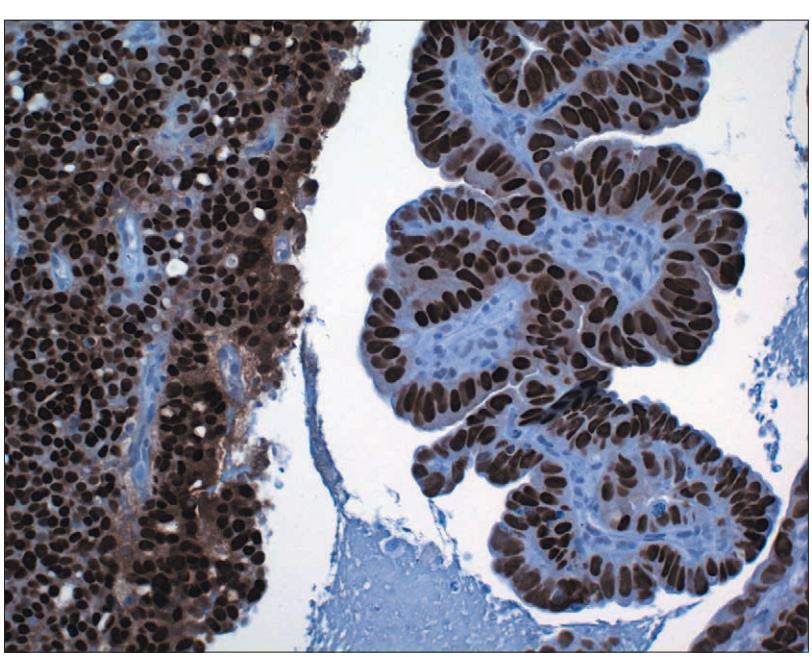

Figure 1: **Papillary serous carcinoma of endometrium**
P53 immunostain, magnification ×400.

	Type I	Type II
Menopausal status	Premenopausal and perimenopausal	Postmenopausal
Oestrogen-related*	Yes	No
Oestrogen or progesterone receptors	Present	Absent
Histological characteristics	Atypical hyperplasia	Atrophy
Obesity	Yes	No
Parity	Nulliparous	Multiparous
Grade	Low	High
Histological subtype	Endometrioid	Uterine papillary serous carcinoma, clear-cell carcinoma
Clinical behaviour	Indolent	Aggressive

*Caused partly by high concentrations of oestrogen (eg, from granulosa-cell tumours or unopposed oestrogen in hormone-replacement therapy).

Table 1: **Classic types of endometrial carcinoma**

closely resembles ovarian papillary serous carcinoma, and psammoma bodies might be present.[5] Serum cancer antigen (CA)125 concentrations are frequently raised in patients with uterine papillary serous carcinoma, and raised concentrations usually correlate well with both disease recurrence and response to treatment.[6] Spread of uterine papillary serous carcinoma is commonly intra-abdominal, in a manner resembling ovarian cancer. Like endometrioid cancer, it usually presents with vaginal bleeding.

Histological diagnosis can often be made from dilation and curettage samples. The name papillary serous carcinoma should not be confused with the term papillary carcinoma, which describes the architectural pattern seen in various cell types, and generally applies to villoglandular tumours, which are a low-grade subset of endometrioid endometrial cancers. Uterine papillary serous carcinomas, unlike uterine endometrioid carcinomas, tend not to express oestrogen and progesterone receptors.[7]

	n	Staging method	5-year overall survival	Ref
Stage I	11	Surgical*	82%	10
Stage II	7	Surgical*	64%	
Stage III	8	Surgical*	31%	
Stage I or II	12/2	Surgical†	84%	11
Stage III	13	Surgical†	69%	
Stage IV	9	Surgical†	10%	
Stage I–II	10	Variable‡	79%	12
Stage III–IV	20	Variable‡	25%	
Stage I	52	Surgical§	63%	13
Stage II	5	Surgical§	100%	
Stage III	41	Surgical§	37%	
Stage IV	31	Surgical§	20%	
Stage I	148	Surgical¶	72%	14

*Vertical incision, total abdominal hysterectomy and bilateral salphingo-oophorectomy, peritoneal cytology, omental biopsy, peritoneal biopsy, lymph-node sampling. †Total abdominal hysterectomy and bilateral salphingo-oophorectomy, lymph-node dissection, peritoneal cytology. ‡Total abdominal hysterectomy and bilateral salphingo-oophorectomy, pelvic or para-aortic lymphadenectomy, cytology. §All patients had total abdominal hysterectomy and bilateral salphingo-oophorectomy, cytology. 89% had at least pelvic-lymph-node sampling. ¶Federation of Gynaecology and Obstetrics (FIGO) staging.

Table 2: **Prognosis of surgically staged uterine papillary serous carcinoma treated with various treatments**

Epidemiological features

In a study of Norwegian patients by Trope and co-workers,[8] clear-cell carcinoma and uterine papillary serous carcinoma made up only about 10% of endometrial carcinomas but were associated with about 50% of relapses. Patients with clear-cell carcinoma and uterine papillary serous carcinoma are a median of 5 years older than those with endometrioid cancers, and like other tumours with a poor prognosis, uterine papillary serous carcinoma is more common in black women than in non-hispanic white women.

Prognosis and survival

Patients with uterine papillary serous carcinoma have a very poor 5-year overall survival of only 18–27%.[8,9] Most uterine papillary serous carcinomas (69–87%) have spread outside of the uterus by the time of presentation and even in cases apparently confined to the uterus, 31–80% of patients develop recurrent disease.[10] Many investigators have shown that survival is 35–50% for patients with clinical or pathological stage I–II uterine papillary serous carcinoma and 0–15% for stage III–IV disease.[11]

Few studies have assessed the survival of patients with uterine papillary serous carcinoma who have been surgically staged in detail, but these studies have shown improved survival (about 80%) for patients with fully surgically staged stage I disease compared with clinical stage I disease (table 2).[10–14]

Molecular changes and precursor lesions

Although microsatellite instability and mutations in *PTEN* have been commonly associated with endometrioid carcinoma, these changes are rarely seen in uterine papillary serous carcinoma.[3] *P53* mutations, which are not usually seen in endometrioid cancers, have been identified in most uterine papillary serous carcinomas.[15] Positive staining for P53 (showing the longer survival of the mutated protein) can be used clinically to lend support to the diagnosis of uterine papillary serous carcinoma. Overexpression of ERBB2 is more common in uterine papillary serous carcinoma than in endometrioid carcinomas; about 20% of uterine papillary serous carcinoma will stain strongly (3+ on standardised immunohistochemical grading) for ERBB2.[16]

The typical precursor lesion in endometrioid carcinoma is complex atypical hyperplasia, whereas serous endometrial intraepithelial carcinoma has been identified as the precursor lesion in uterine papillary serous carcinoma. Endometrial intraepithelial carcinoma has also been called surface serous carcinoma or endometrial carcinoma in situ. It usually arises in a background of

atrophy, and replaces the surface epithelium with atypical cells that resemble serous carcinoma, with a high ratio of nucleus to cytoplasm, irregular nuclear membranes, abnormal chromatin texture, and atypical mitotic figures. Endometrial intraepithelial carcinoma has been identified in up to 90% of uteri that have uterine papillary serous carcinoma.[17]

Staging

In 1988, the International Federation of Gynecology and Obstetrics (FIGO) surgical staging system (panel) replaced the previous clinical staging system, and since then surgical stage has been the most important predictor of overall survival for patients with endometrial carcinoma and possibly also for patients with uterine papillary serous carcinoma (table 2).[10–14] However, the discordance between clinical and surgical staging for uterine papillary serous carcinoma is much greater than it is for type I endometrial cancer.

For endometrioid endometrial cancers, depth of invasion into the myometrium is the strongest predictor of nodal involvement and extrauterine disease. Many centres do not dissect lymph nodes routinely in patients with low-grade, superficially invasive endometrioid endometrial cancer. However, absence of myometrial invasion does not predict the absence of lymph-node involvement or of extrauterine metastases in women with uterine papillary serous carcinomas. Therefore, routine extended surgical staging is usually recommended, as it is for ovarian carcinoma, when uterine papillary serous carcinoma pathology is suspected.[11] Several groups[12,18–20] have reported that up to 57% of patients with clinical stage I uterine papillary serous carcinoma are upstaged at the time of laparotomy. Chan and colleagues[19] did comprehensive surgical staging on 12 patients with lesions that had not invaded the myometrium (pathological stage IA). Six of these patients had disease beyond the uterine corpus.

The outlook for patients with uterine papillary serous carcinoma who have disease that seems to be localised after surgical staging is controversial, partly because some surgeons are more or less aggressive in the extent of staging, and less aggressive staging can sometimes miss spread of disease. The prognostic importance of depth of myometrial invasion in patients who are well-staged without evidence of lymph-node involvement or intraperitoneal spread is also uncertain. Studies have had varying lengths of follow up, and most give more aggressive treatment to patients with more deeply invasive lesions than to those with less invasive tumours. However, most investigators find that patients with well-staged stage I uterine papillary serous carcinoma that has no myometrial invasion (stage IA) will do better than will those who have myometrial invasion (stage IB and IC); (table 3).[10,11,13,21] Series[10,11,13,19,20,22–24] of patients with stage IA disease who did not receive adjuvant chemotherapy gives about 14% recurrence; several of which were only in the pelvis (table 4), which suggested that radiotherapy could be of benefit in this situation.

Treatment

Most studies have been small and retrospective investigations of patients from one institution who have been variably staged, and have received various combinations of adjuvant treatments. However, it is clear that in most patients, the disease will have spread by the time of diagnosis, and systemic chemotherapy should be a part of the treatment.

Surgery

In addition to its value in staging apparently limited disease, surgery might have a role in patients who present with bulky intraperitoneal uterine papillary serous carcinoma. Bristow and co-workers[25] retrospectively reviewed patients with stage IV uterine papillary serous carcinoma

***Panel:* FIGO staging system**

Stage	Description
IA (grades 1–3)	Tumour confined to endometrium
IB (grades 1–3)	Invasion to less than half of myometrium
IC (grades 1–3)	Invasion to more than half of myometrium
IIA (grades 1–3)	Endocervical glandular involvement
IIB (grades 1–3)	Cervical stromal involvement
IIIA (grades 1–3)	Tumour invades serosa or adnexae, has positive peritoneal cytology, or a combination of these
IIIB (grades 1–3)	Vaginal metastases
IIIC (grades 1–3)	Metastases to pelvic or para-aortic lymph nodes
IVA (grades 1–3)	Tumour invades bladder or bowel mucosa
IVB	Distant metastases with intra-abdominal or inguinal lymph-node involvement

	n	Outcome*	Ref
Stage IA	4	One recurrence	10
Stage IB	7	One DOC and one recurrence	
Stage IA	4	No recurrences	11
Stage IB	4	One DOC	
Stage IC	4	Two recurrences and one DOC	
Stage IA	19	82%†	13
Stage IB	26	59%†	
Stage IC	7	34%†	
Stage IA	32	78%†	19
Stage IB	67	81%†	
Stage IC	49	55%†	
Stage IA	NS	100%‡	21
Stage IB	NS	71%‡	
Stage IC	NS	40%‡	

DOC=dead from other causes. NS=not stated. *In most series, patients with deeper invasion received more treatment. †5-year overall survival. ‡5-year disease-free survival in 21 patients.

***Table 3:* Importance of depth of invasion in surgical stage I uterine papillary serous carcinoma**

who underwent cytoreductive surgery. Median survival of the 16 patients who were optimally debulked (maximum dimension of residual disease ⩽1 cm) was 26·2 months, compared with 9·6 months for the 15 patients left with suboptimum residual disease ($p<0·001$). Other researchers have confirmed that survival of patients with microscopic residual disease is better than that for those with macroscopic residual disease after primary surgical cytoreduction. However, as is the case for ovarian cancer, no data are available from prospective randomised trials, and the relative contributions of disease biology and surgical effort cannot be distinguished.

Radiotherapy

Early-stage (I–II) uterine papillary serous carcinoma has traditionally been treated like other forms of endometrial carcinoma, with primary surgery possibly followed by radiotherapy. Because uterine papillary serous carcinoma and other aggressive variants have a propensity to relapse in the upper abdomen, adjuvant whole-abdominal radiotherapy might provide a survival benefit. Small single-institution studies have suggested good results with this approach. However, in a multicentre US Gynecologic Oncology Group (GOG) study (GOG 94),[26] the 5-year disease-free survival of 31 patients with stage I/II uterine papillary serous carcinoma, who were treated with whole abdominopelvic radiotherapy, was only 35%.

Chemotherapy

Randall and colleagues[27] reported results from the GOG 122 study in which 396 patients with stage III or optimally debulked (<2 cm largest residual disease) stage IV endometrial cancer were randomised to receive either whole-abdominal radiotherapy or chemotherapy with doxorubicin and cisplatin chemotherapy. 83 (21%) of 396 had uterine papillary serous carcinoma and 17 (4%) had clear-cell carcinoma. Overall, patients who received chemotherapy had better disease-free and overall survival (hazard ratio for death 0·67, 95% CI 0·51–0·89).[27] Use of adjuvant chemotherapy in women with early-stage uterine papillary serous carcinoma has become more widespread. Approaches that combine whole-abdominal radiotherapy and chemotherapy have been investigated, but cannot be regarded as standard. Pelvic radiotherapy or vaginal brachytherapy, as discussed above, could offer benefit in these patients, and these methods are easier to combine with chemotherapy than is abdominal radiotherapy. However, no randomised trials of such chemoradiotherapy have been done

For advanced or recurrent disease, chemotherapy is the mainstay of treatment, and should be similar to that given to women with high-grade endometrioid carcinomas. An overview analysis[28] of large randomised trials by the GOG suggest that, despite the apparent biological differences between endometrioid and serous endometrial carcinomas, the overall response rates (40–50%) to taxane, doxorubicin, and platinum chemotherapy, and survival after such treatment is similar for women with advanced or recurrent uterine papillary serous carcinoma as for those with advanced or recurrent endometrial carcinoma of other histologies.

n	Radiotherapy	Comment	Ref
4	None	One pelvic recurrence	10
4	One received whole-abdomen radiotherapy. Three received surgery only	No recurrences	11
19	Four received brachytherapy. One received whole-abdomen radiotherapy	Two abdominal recurrences and one pelvic recurrence in patient who did not receive radiotherapy. One lung recurrence in patient receiving brachytherapy	13
4	None	One lung recurrence	19
5	Uncertain number received radiotherapy	No recurrences	20
23	Five received pelvic radiotherapy. 18 received surgery only	One vaginal-vault and one pelvic recurrence, both in patients who did not receive radiotherapy	22
6	None	Two recurrences in vagina	23
3	Two received pelvic radiotherapy. One received no radiotherapy	No recurrences	24

Table 4: **Number of patients with stage 1A papillary serous carcinoma (reasonably surgically staged) receiving no adjuvant chemotherapy**

Clear-cell carcinoma

5% or fewer endometrial cancers reported in the USA have clear-cell histology. Clear-cell tumours, like uterine papillary serous carcinoma, are an aggressive subtype of endometrial carcinoma that have a tendency to relapse outside of the pelvis. Cirisano and colleagues[29] showed that up to 40% of patients with clear-cell carcinoma that was clinically confined to the uterus had extrauterine spread and that, similar to patients with uterine papillary serous carcinoma, extrauterine spread occurred even without deep myometrial invasion.

The term clear-cell carcinoma was first defined by Scully and Barlow[30] who described tumours that originated from the Mullerian epithelium. Under microscopy, the tumours show tubulocystic, papillary, or solid patterns,[31] can have a clear appearance because of their high glycogen content (and not intracellular mucin), and sometimes include eosinophilic cells and hobnail cells (figure 2). All cases are graded as poorly differentiated, and unlike clear-cell carcinoma of the cervix, clear-cell carcinoma of the uterus is not associated with maternal exposure to diethylstilbestrol.

Clear-cell carcinoma has epidemiological features similar to those of uterine papillary serous carcinoma. It develops more frequently in postmenopausal patients who are not obese, is not associated with oestrogen use, and is more common in black women.

Survival of women with clear-cell carcinoma is generally worse than that of those with endometrioid tumours, but seems to be somewhat better than that of women with uterine papillary serous carcinoma. Abeler and co-workers[32] reviewed 97 patients with clear-cell carcinoma and reported a crude 5-year survival for all stages as 42%, compared with 27% for uterine papillary serous carcinoma, 59% for pathological stage I disease and 27% with stage II disease; myometrial infiltration and vessel invasion were important prognostic factors. Notably, 90% patients with no myometrial invasion survived for 5 years. Carcangiu and Chambers[33] reviewed 29 cases of pathological FIGO stage I and II clear-cell carcinoma (only 11 had retroperitoneal nodal sampling) and 47 stage I and II uterine papillary serous carcinoma (only 17 underwent retroperitoneal nodal sampling). They recorded a 5-year survival for stage I clear-cell carcinoma of 73% and for uterine papillary serous carcinoma of 44%. 5-year survival was 59% for patients with stage II clear-cell carcinoma and 32% for those with uterine papillary serous carcinoma.

As with uterine papillary serous carcinoma, surgical staging refines the prognosis: Creasman and co-workers[14] reviewed the FIGO annual report data and found a 5-year survival of 81% for surgically staged stage I clear-cell carcinoma compared with 72% for uterine papillary serous carcinoma, and 76% for grade 3 endometrioid cancers.

Like uterine papillary serous carcinoma, clear-cell carcinoma has low expression of oestrogen and progesterone receptors. P53 expression is intermediate between those reported in uterine papillary serous carcinoma and those in endometrioid cancers.[34] The rarity of clear-cell carcinoma precludes randomised data on treatment outcomes; however, these tumours sometimes respond to chemotherapy.

Tumours of mixed histology

Endometrial carcinomas of mixed histology are not unusual. Craighead and co-workers[22] reported that 11% of their patients had tumours of mixed histology including some combination of endometrioid carcinoma, clear-cell carcinoma, and uterine papillary serous carcinoma. Many pathologists have used an approach similar to that used in ovarian cancers, in which the term mixed-cell type is used if two or more histological

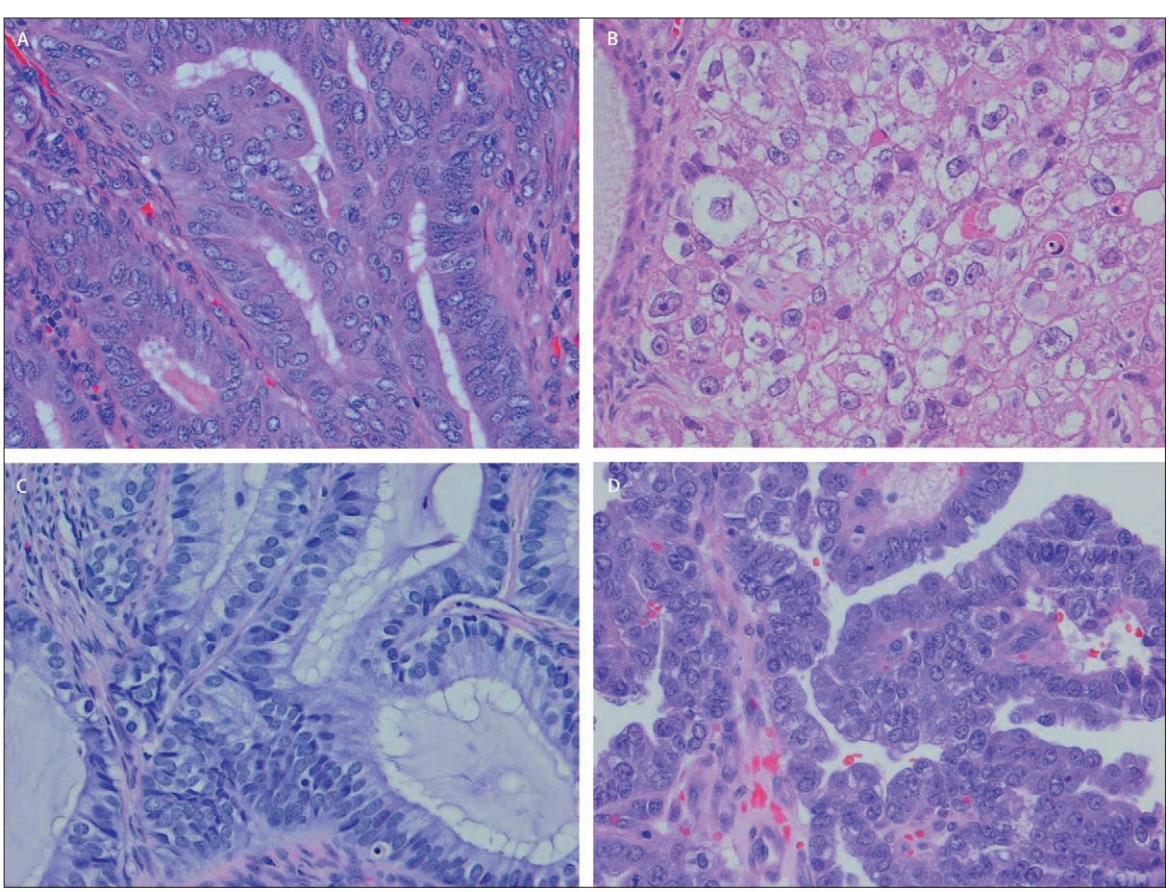

Figure 2: **Unusual epithelial tumours of uterus**
(A) Endometrioid carcinoma. (B) Clear-cell carcinoma. (C) Mucinous carcinoma. (D) Papillary serous carcinoma of endometrium. All sections stained with haematoxylin and eosin with magnification ×400.

cell types exist, each of which constitute at least 10% of the tumour volume. Cirisano and colleagues[29] reported that tumours with mixed histology (at least 25% of uterine papillary serous carcinoma or clear-cell carcinoma) had a clinical behaviour comparable to that of uterine papillary serous carcinoma. The amount of unusual histology needed in a mixed carcinoma to confer a poor prognosis is unclear; some investigators believe that any amount of poor-prognosis histology (uterine papillary serous carcinoma or clear-cell carcinoma) is sufficient, whereas others think that a small focus of poor histology might not drive overall prognosis. Therefore, treatment approaches for tumours of mixed histology, when an aggressive variant is present, are similar to those for uterine papillary serous carcinoma and clear-cell carcinoma.

Adenosquamous carcinoma of the endometrium was traditionally regarded as a mixed histology and was thought to be very aggressive with a poor response to radiotherapy and a 5-year survival of less than 20%. Pekin and co-workers,[35] showed that 172 (72%) of 240 endometrial carcinomas were adenocarcinomas, 50 (21%) were adenoacanthomas (a term used for adenosquamous carcinoma in which the squamous component is very well differentiated), and 14 (6%) were adenosquamous carcinomas (in which the squamous component resembles a squamous carcinoma). All had similar prognoses, which suggested that adenocarcinomas with and without squamous differentiation should be approached in a similar way. The prognosis is dependent on the grade of the glandular component.

Undifferentiated carcinomas

Such carcinomas of the endometrium consist of only 1% of endometrial carcinomas. They have no glandular, squamous, or sarcomatous differentiation, and most can be stained for epithelial antigens.[36] Undifferentiated carcinomas are regarded as high grade and have a propensity for metastatic spread.

Mucinous carcinomas

This carcinoma (figure 2C), when the mucinous component is identified as the main histological feature (>50% of volume), constitutes 5% of all cases of uterine carcinoma; it is rarely found as a pure cell type.[36] Nuclear atypia and high mitotic rates are not typical and most mucinous tumours are well-differentiated. This cell type is more common in endocervical carcinomas than in endometrial carcinomas and the origin of these tumours should be established before the diagnosis is made. Unlike uterine papillary serous carcinoma and clear-cell carcinoma, early-stage mucinous carcinomas seem to have a similar prognosis to more common endometrioid endometrial carcinomas, and are managed similarly. No data are available for the sensitivity of mucinous endometrial carcinomas to chemotherapy.

Squamous-cell carcinomas

Primary squamous-cell carcinoma of the endometrium is quite uncommon. To diagnose this carcinoma, primary cervical squamous carcinoma must be ruled out, the tumour should have no connection with benign stratified squamous epithelium of the cervix, and glandular carcinoma should not be present.[37] Primary squamous-cell carcinoma of the endometrium might be associated with chronic inflammation or irritation either from an intrauterine device, pyometra, uterine prolapse, cervical stenosis, or previous pelvic radiation.[38] Whether these tumours arise from squamous metaplasia, a fairly common phenomenon in the endometrium, is not clear.

In a retrospective review[39] of 1182 patients with corpus cancers, six (0·5%) had squamous-cell carcinomas. The investigators analysed these six patients, two additional patients were seen in consultation, and 56 patients that had been previously reported. They found that patients with squamous-cell carcinoma tended to be older than 67 years, and noted no association with oestrogen or obesity. 44 (69%) patients had vaginal bleeding. Tumour grade was not associated with survival, but all patients with vascular space invasion died, and all those without vascular space invasion survived. 21 of 26 patients with stage I disease survived, compared with two of ten with stage III, and none of six patients with stage IV disease. Because, by definition, the cervix cannot be involved, surgical stage II does not exist for this disease. Diagnosis based on curettage samples can be difficult because the squamous elements can seem benign. Adjuvant radiotherapy has been used, but its effectiveness is not known.

Carcinosarcomas

Also called malignant mixed Mullerian tumours, carcinosarcomas have both epithelial and mesenchymal differentiation. Mesenchymal components could be homologous, with endometrial stromal or muscle differentiation, or heterologous, with malignant cartilaginous, osteoid, rhabdomyosarcomatous, or other differentiation (figure 3). Although heterologous differentiation has long been thought to be associated with a more aggressive clinical course, it has no independent prognostic relevance.[40] Clinical, pathological, and molecular evidence supports the idea that most of these tumours are monoclonal, rather than a combination of two uterine tumours.[41] Until recently, carcinosarcomas were thought to be a subtype of uterine sarcoma and were treated more as a sarcoma than as a carcinoma. Evidence[41,42] now suggests that these tumours are metaplastic carcinomas. The pattern of metastasis of carcinosarcomas is more similar to that of aggressive endometrial carcinomas than to that of sarcomas, with the mode of spread being mainly through the lymphatic system rather than through the blood.[43] Furthermore, assessment of the histology of

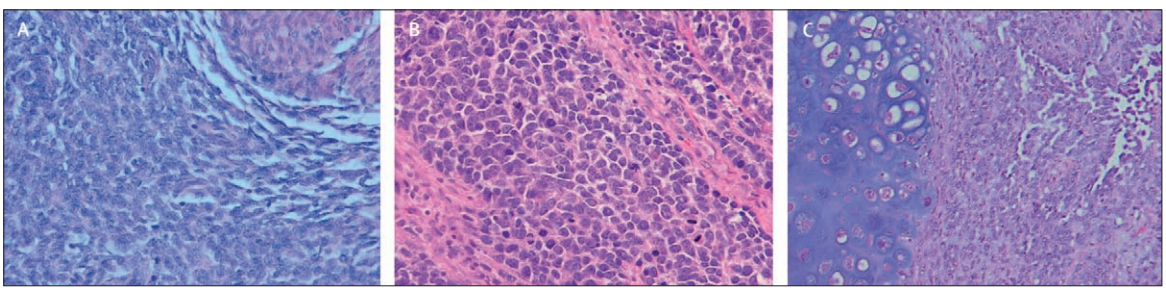

Figure 3: **Stromal sarcomas and carcinosarcoma**
(A) Endometrial stromal sarcoma (haematoxylin and eosin, magnification ×400). (B) High-grade endometrial stromal sarcoma (haematoxylin and eosin, magnification ×400). (C) Carcinosarcoma with heterologous (chondroid) elements (haematoxylin and eosin, magnification ×200).

tumour emboli and metastases show that these elements usually contain carcinoma (with or without sarcomatous differentiation), with pure sarcoma being uncommon.[44] Sreenan and Hart[43] showed that 43 of 62 metastases of uterine carcinosarcoma contained carcinomas, 15 contained both carcinoma and sarcoma, and four contained sarcoma alone.

Unlike uterine papillary serous carcinoma and clear-cell carcinoma, epidemiological features of carcinosarcomas include obesity, nulliparity, and exogenous use of oestrogen (eg, hormone-replacement therapy). Furthermore, uterine carcinosarcomas sometimes develop in association with tamoxifen treatment.[45]

However, carcinosarcomas are aggressive cancers, and their poor prognosis is similar to that of leiomyosarcomas, with an overall 5-year survival (all stages) of about 35%.[46,47] Carcinosarcomas usually arise in women older than 65 years[46] and commonly present at an advanced stage.

Dinh and colleagues[46] found no association between survival and tumour size or depth of myometrial invasion in 47 patients with stage I–IV malignant mixed Mullerian tumours. As is the case with sarcomas, carcinosarcomas that arise in previously irradiated fields have a particularly poor prognosis and the three patients died at 6 months (stage I), 15 months (stage III), and 7 months (stage IV) after treatment. George and co-workers[47] found that only 12 of 32 patients had pathological stage I disease, and these patients had a 5-year survival of 46%.

Adjuvant radiotherapy is thought to reduce recurrence in the pelvis.[48] The only large randomly assigned trial of adjuvant chemotherapy, GOG #150, randomly assigned women with optimally debulked stage I–IV carcinosarcomas to a combination of ifosfamide and cisplatin chemotherapy or to whole-abdominal radiotherapy; this trial has completed accrual, and results should be available shortly.

Chemotherapeutic agents tested in advanced or recurrent disease have traditionally been used for sarcomas, and active single agents include ifosfamide (response rate 36%), doxorubicin (response rate 10%), and cisplatin (response rate 18%). However, such treatment produces low response rates with substantial toxic effects.[49–51] Since these trials, paclitaxel has also shown activity, and complete responses have been reported with the combination of paclitaxel and carboplatin.[52]

Sarcomas

Endometrial sarcomas account for between 3% and 7% of uterine corpus malignant diseases.[53] Most sarcomas have a poor prognosis, with an estimated 2-year overall survival of less than 50%, even when discovered at an early stage. Uterine sarcomas are classified broadly into those that arise from endometrial stroma and those that arise from the smooth muscle of the myometrium. Although no specific staging system is available for uterine sarcomas, clinicians often use the surgical staging system for endometrial cancers. Prognostic factors include stage, grade, mitotic index, and DNA ploidy.[54] Surgery is the mainstay of treatment for all sarcomas. No adjuvant treatment has yet been proven to clearly improve overall survival.[55,56]

Endometrial stromal tumours

These tumours (figure 3B) account for 7–15% of all uterine sarcomas. They are composed exclusively of cells that resemble the endometrial stroma and include both benign stromal nodules and malignant stromal tumours. Malignant endometrial stromal tumours are separated into low-grade and high-grade tumours. The high-grade tumours were called high-grade endometrial stromal sarcoma, but are now referred to as undifferentiated stromal sarcomas. They have a growth pattern unlike that of the low-grade sarcomas, with marked cellular pleiomorphism, high mitotic activity, and no oestrogen or progesterone receptors.

Treatment of endometrial stromal sarcomas includes whole-abdominal hysterectomy and bilateral salpingo oophorectomy. Data from a retrospective study[57] have shown a decrease in local recurrence with adjuvant pelvic radiation, although the number of patients treated was small, and no randomised trials have been done to assess the effect of adjuvant radiation on progression-free survival or overall survival.

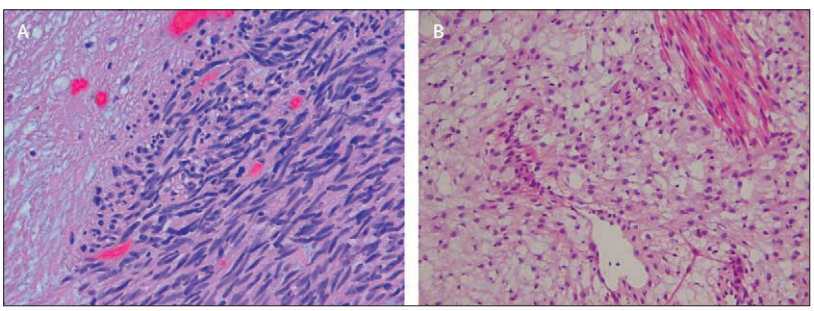

Figure 4: **Leiomyosarcoma**
(A) Leiomyosarcoma. Note area of tumour necrosis. (B) Myxoid leiomyosarcoma. Both sections stained with haematoxylin and eosin, magnification ×400.

Low-grade endometrial stromal sarcomas have a good prognosis with an indolent growth pattern. Overall survival at 5 years is about 60%.[58,59] In a study by Chang and colleagues,[60] the median time between hysterectomy and relapse was 5·4 years for stage I disease and 9 months for stages III and IV. Low-grade endometrial stromal sarcomas generally express oestrogen receptors and progesterone receptors, and responses have been documented to various hormonal treatments including oophorectomy in premenopausal women, aromatase inhibitors,[61] progestins,[62] and gonadotrophin-releasing-hormone agonists.[63] Because of the indolent growth of metastatic disease, resection of recurrent disease is a reasonable treatment option.[64]

Undifferentiated endometrial sarcomas have a poor prognosis, similar to that of leiomyosarcoma, with 5-year overall survival of about 25%.[59] These tumours rarely express hormone receptors, and recurrent or advanced disease is usually treated with systemic chemotherapy. Responses have been reported to doxorubicin[57] and ifosfamide (33%),[65] and a case report has shown a response to paclitaxel and carboplatin.[66] Patients with metastatic undifferentiated endometrial sarcomas are appropriate candidates for participation in clinical trials for soft-tissue sarcoma.

Histological diagnosis of leiomyosarcoma

Leiomyosarcomas (figure 4) are the most common uterine sarcoma. Smooth-muscle tumours of uncertain potential have intermediate histology between that of benign leiomyoma and leiomyosarcoma, occasionally recur, and rarely metastasise. The typical therapeutic dilemma arises when tumours of intermediate histology are identified after myomectomy in a young woman who wishes to preserve childbearing potential. Whereas previous criteria for malignant disease in uterine smooth-muscle tumours relied mainly on mitotic activity, current criteria give greater weight to the presence of coagulative tumour necrosis and cytological atypia in addition to mitotic activity.[67] Tumours with no atypia, no coagulative necrosis, and low mitotic activity are classified as leiomyomas. In a well-circumscribed tumour that has no coagulative tumour-cell necrosis or cellular atypia, as many as 20 mitoses per ten high-power microscopic fields could be present and still be consistent with a diagnosis of benign mitotically active leiomyoma; such cases would have been diagnosed as leiomyosarcomas under the earlier criteria. Both leiomyomas and mitotically active leiomyomas can be treated with myomectomy alone. Tumours with necrosis, atypia, or both, but without mitotic activity are generally termed atypical leiomyomas and have some risk of recurrence.[68] A study by Mayerhofer and colleagues[69] suggests that expression of Ki67 could be a useful immunohistochemical variable to help predict the potential for malignant disease and that significantly high concentrations of Ki67 antigen correlate well with rapid growth.

Benign leiomyomas are not thought to develop into malignant leiomyomas, but leiomyosarcomas frequently coexist in the uterus with benign leiomyomas.[70] About 0·5% of patients who have hysterectomy for presumed benign leiomyoma will be found to have leiomyosarcoma.[71]

Uterine myxoid leiomyosarcoma is a rare variant of leiomyosarcoma that is characterised by low cellularity, abundant ground substance, and very low mitotic activity (figure 4). Despite the absence of necrosis and the low proliferative activity, most cases metastasise.[72]

Prognosis for leiomyosarcoma

Uterine leiomyosarcomas usually present as solitary, poorly demarcated, intramural masses. Reported 5-year overall survival ranges from 50% to 65%, but is strongly dependent on tumour grade.[56,69] In women with stage I and II, high-grade uterine leiomyosarcomas, recurrence rates at 2 years are 60–70%.[73]

Treatment for leiomyosarcoma

Whole-abdominal hysterectomy and bilateral salpingo-oophorectomy is the standard surgical procedure. Routine lymph-node dissection is not usually done for patients with disease that is confined to the uterus and with lymph nodes that seem healthy on observation and palpation, since lymph-node involvement is highly unlikely in the absence of extrauterine disease.[74] Results of adjuvant pelvic radiation reported in retrospective series suggest some beneficial effect of radiotherapy on pelvic control. For example, in a retrospective, case-control study by Giuntoli and colleagues[56] of 208 patients with uterine leiomyosarcoma, external-beam radiotherapy significantly reduced local recurrence (p=0·011) but produced only a non-significant trend towards increased survival.

To date, no randomised controlled trials have shown that adjuvant chemotherapy improves survival in completely resected high-grade leiomyosarcomas. The GOG did a prospective phase III trial[75] of eight cycles of adjuvant doxorubicin versus observation after resection

of stage I or stage II leiomyosarcomas or malignant mixed Mullerian tumours. Pelvic radiation was allowed at the discretion of the physician. With only 156 patients available for assessment and with various histologies, the study was underpowered to show significant differences between the treatment groups. Of the 25 patients with uterine leiomyosarcomas in the doxorubicin group 11 (44%), recurred compared with 14 of 23 (61%) patients with leiomyomas in the observation group. In another study,[76] 18 patients with stage I–III gynaecological sarcoma (13 leiomyosarcomas, two malignant mixed Mullerian tumours, one adenosarcoma, and two high-grade stromal sarcoma) were treated with doxorubicin, ifosfamide, and cisplatin followed by radiotherapy. Survival outcomes were compared with matched controls who had received only radiotherapy. 3-year disease-free survival was 43% in women who received radiotherapy only, and 76% in those treated with chemotherapy followed by radiotherapy.[76] Well-designed, adequately-powered, phase III studies that assess agents with clear activity in advanced disease are needed to establish the role of adjuvant treatment in completely resected, high-grade uterine leiomyosarcomas.

Some patients with recurrent or metastatic leiomyosarcoma (like other soft-tissue sarcomas) could benefit from resection. In a study[77] of 41 patients with recurrent uterine leiomyosarcomas (17 local pelvic, 18 distant, and six both), resection at the time of first recurrence resulted in a disease-specific 2-year survival of 71%. These results should be interpreted in light of the subgroup of patients for whom resection can be recommended.

For patients with multifocal metastatic disease, treatment is usually systemic. Negligible activity was seen in phase II trials that tested cisplatin,[78] mitoxantrone,[79] and oral etoposide.[80] Single agents that have shown moderate activity in leiomyosarcomas include ifosfamide (17%),[81] intravenous etoposide (11%),[82] doxorubicin (25%),[50] and gemcitabine (response rate 21%).[83] Combination chemotherapy regimens with activity in previously untreated patients include hydroxycarbamide, dacarbazine, etoposide (18%),[84] and doxorubicin plus ifosfamide (30%).[85] In a single-institution study at Memorial Sloan Kettering Cancer Center, patients with unresectable leiomyosarcomas of uterine (n=29) or other (n=5) primary sites who had not responded to up to two previous chemotherapy regimens were enrolled on a phase II study[86] of dose-rate-based 900 mg/m^2 gemcitabine given intravenously on days 1 and 8 and 100 mg/m^2 docetaxel given intravenously on day 8 every 21 days, with filgrastim support on days 9–15. Patients who had received previous pelvic radiation received 25% lower doses of both agents. Three patients had a complete response and 15 patients had a partial response, giving an overall response of 53% (95% CI 35–70%). This regimen is being tested in multi-institution studies through the GOG as second-line (GOG 131G) and as first-line (GOG 87L) treatment for advanced or recurrent disease. Dose-rate-based gemcitabine alone and in combination with docetaxel are also being compared in terms of objective response rates in patients with soft-tissue sarcomas, including leiomyosarcomas, in a randomised phase III trial.

Advances in the management of uterine leiomyosarcoma will probably come with better understanding of the molecular biology of the disease, which could lead to the identification of appropriate therapeutic targets. Tissue microarray has shown that 40% of high-grade uterine leiomyosarcomas express oestrogen receptors, progesterone receptors, and androgen receptors,[87] which suggests that these could be potential treatment targets. However, prospective data are needed on whether hormonal approaches achieve objective responses in advanced disease. The roles of inhibitors of the cell cycle, tyrosine kinase inhibitors, and vascular growth factors are also unknown. Cooperative efforts between institutions and well-designed correlative translational investigations done in conjunction with treatment trials should help elucidate appropriate targets and interventions, which should ultimately improve outcomes for women with this high-risk disease.

Search strategy and selection criteria

Recent textbooks were searched for a comprehensive list of unusual uterine cancers; those to be discussed were selected on the basis of being rare, but with enough information, as judged by the senior author. Relevant references from the textbooks were retrieved. PubMed was searched (no date restrictions) using headings for each of the histologies, with more specific searches for prognosis, epidemiology, and therapies. References cited in reviews were retrieved as needed. Furthermore, the past 3 years of abstracts from the American Society of Clinical Oncology and the Society of Gynecologic Oncology were reviewed. Where relevant, the US National Cancer Institute clinical trials website was used to search for open trials.

Conflict of interest

We declare no conflicts of interest.

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