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Uterine sarcomas

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1. Introduction

Uterine sarcomas account for approximately 1% of all female genital tract malignancies and 3%–7% of all uterine cancers [1]. Their rarity and histopathological diversity have contributed to the lack of consensus on risk factors for poor outcome and optimal treatment [2].

Histologically, uterine sarcomas were classified initially into carcinosarcomas (malignant mesodermal mixed tumors), accounting for 50% of cases, leiomyosarcomas (30%), endometrial stromal sarcomas (15%), and undifferentiated sarcomas (5%). Subsequently, carcinosarcoma has been reclassified, largely based on its spreading pattern, as a dedifferentiated or metaplastic form of endometrial carcinoma. However, as it behaves more aggressively than the usual type of endometrial carcinoma, carcinosarcoma is still included in most retrospective studies of uterine sarcomas, as well as in the separate section of "mixed epithelial and mesenchymal tumors" of the 2014 WHO classification [3].

Tumor stage is the single most important prognostic factor. In the past, uterine sarcomas were staged using a staging system proposed in 1988 for endometrial carcinoma. This has not proven satisfactory and, in 2009, a new FIGO staging system was developed for uterine sarcomas (Table 1) [4]. The new staging system has two divisions, one for leiomyosarcoma and endometrial stromal sarcoma (ESS), and one for adenosarcoma. Carcinosarcoma is still staged using the endometrial carcinoma staging system [4].

Prolonged use of tamoxifen, a uterine estrogen receptor agonist, is associated with a three times risk of sarcoma development [5]. There have been reported cases of radiation-induced sarcomas occurring long after treatment for other cancers [6].

Neither preoperative imaging with ultrasonography nor PET scans are capable of differentiating between benign or malignant smooth muscle masses. The use of diffusion weighted magnetic resonance imaging (DWI) for tumor location and characterization has been suggested, but is yet to be validated.

Patients with carcinosarcomas and adenosarcomas tend to be much older than patients with other sarcomas.

2. Leiomyosarcomas

Leiomyosarcomas are considered true sarcomas.

2.1. Clinical features

After excluding carcinosarcoma, leiomyosarcoma has become the most common subtype of uterine sarcoma even though it accounts for only 1%–2% of uterine malignancies [2]. Approximately 1 in every 800 smooth muscle tumors of the uterus is a leiomyosarcoma [2]. It occurs in women over 40 years of age who usually present with abnormal vaginal bleeding (56%), a palpable pelvic mass (54%), and/or pelvic pain (22%) [2]. Signs and symptoms resemble those of the far more common leiomyoma and preoperative distinction between the two tumors may be difficult. Malignancy should be suspected by the presence of tumor growth in postmenopausal women who are not using hormonal replacement therapy, although it is rare for a leiomyosarcoma to present as a rapidly growing tumor.

2.2. Pathological features

Leiomyosarcomas are either single masses or, when associated with leiomyomas, the largest mass. They are typically voluminous tumors with a mean diameter of 10 cm (only 25% of cases measure less than 5 cm). The cut surface is typically soft, bulging, fleshy, necrotic, hemorrhagic, and lacks the prominent whorled appearance of leiomyomas. The histopathologic diagnosis of leiomyosarcoma is usually straightforward as most clinically malignant smooth muscle tumors of the uterus exhibit the constellation of hypercellularity, severe nuclear atypia, and high mitotic rate generally exceeding 15 mitotic figures per 10 high-power-fields (MF/10 HPF) (Fig. 1) [3]. Moreover, one or more supportive clinicopathologic features such as peri- or postmenopausal age, extrauterine extension, large size (over 10 cm), infiltrating border, necrosis, and atypical mitotic figures are frequently present. However, epithelioid and myxoid leiomyosarcomas are two rare variants that may be difficult to recognize microscopically as their pathologic features differ from those of ordinary spindle cell leiomyosarcomas. In both tumor types nuclear atypia is usually mild and the mitotic rate often less than 3 MF/10 HPF [3]. Necrosis may be absent in epithelioid leiomyosarcomas and myxoid leiomyosarcomas are often hypocellular. In the absence of severe cytologic atypia and high mitotic activity, both tumors are diagnosed as sarcomas based on their infiltrative borders.

The minimal pathological criteria for the diagnosis of leiomyosarcoma are more problematic and, in such cases, the differential diagnosis

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Table 1
FIGO staging for uterine sarcomas.

	Stage	Definition
Leiomyosarcomas and endometrial stromal sarcomas		
I		Tumor limited to uterus
	IA	Less than 5 cm
	IB	More than 5 cm
II		Tumor extends beyond the uterus, within the pelvis
	IIA	Adnexal involvement
	IIB	Involvement of other pelvic tissues
III		Tumor invades abdominal tissues (not just protruding into the abdomen).
	IIIA	One site
	IIIB	More than one site
	IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	IVA	Tumor invades bladder and/or rectum
	IVB	Distant metastasis
Adenosarcomas		
I		Tumor limited to uterus
	IA	Tumor limited to endometrium/endocervix with no myometrial invasion
	IB	Less than or equal to half myometrial invasion
	IC	More than half myometrial invasion
II		Tumor extends to the pelvis
	IIA	Adnexal involvement
	IIB	Tumor extends to extrauterine pelvic tissue
III		Tumor invades abdominal tissues (not just protruding into the abdomen).
	IIIA	One site
	IIIB	More than one site
	IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	IVA	Tumor invades bladder and/or rectum
	IVB	Distant metastasis
Carcinosarcomas		
Carcinosarcomas should be staged as carcinomas of the endometrium.		

Note: Simultaneous tumors of the uterine corpus and ovary/pelvis in association with ovarian/pelvic endometriosis should be classified as independent primary tumors.

includes, not only benign smooth muscle tumors that exhibit variant histologic features and unusual growth patterns (Boxes 1 and 2), but also atypical smooth muscle tumors (so-called smooth muscle tumors of uncertain malignant potential [STUMPs]) (Box 3). Application of the WHO diagnostic criteria [3] has allowed distinguishing these unusual histologic variants of leiomyoma frequently misdiagnosed as "well-differentiated" or "low-grade" leiomyosarcomas in the past. In a population-based study of uterine sarcomas from Norway [7], of 356 tumors classified initially as leiomyosarcomas, the diagnosis was confirmed in only 259 (73%) cases, whereas 97 (27%) were excluded on review and reclassified, according to WHO criteria, as leiomyomas or leiomyoma variants

2.3. Immunohistochemistry and molecular biology

Leiomyosarcomas usually express smooth muscle markers such as desmin, h-caldesmon, smooth muscle actin, and histone deacetylase 8 (HDCA8). However, epithelioid and myxoid leiomyosarcomas may show lesser degrees of immunoreaction for these markers [3]. Also, leiomyosarcomas are often immunoreactive for CD10 (mainly considered a marker of endometrial stromal differentiation) and epithelial markers including keratin and EMA (the latter being more frequently positive in the epithelioid variant) [3]. Conventional leiomyosarcomas express estrogen receptors, progesterone receptors, and androgen receptors in 30%–40% of cases. Whereas a variable proportion of uterine leiomyosarcomas has been reported as being immunoreactive for c-KIT, no *c-KIT* mutations have been identified [3].

The levels of Ki67 are higher in uterine leiomyosarcomas compared with benign smooth muscle tumors. Overexpression of p16 has been described in uterine leiomyosarcomas and may prove to be a useful adjunct immunomarker for distinguishing between benign and malignant uterine smooth muscle tumors [8].

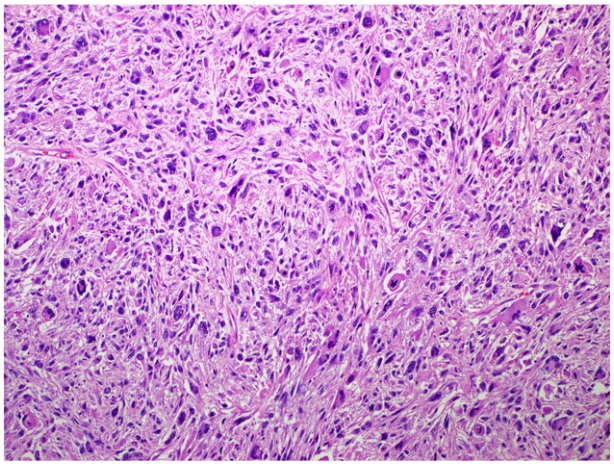

Fig. 1. Leiomyosarcoma.

The vast majority of uterine leiomyosarcomas are sporadic. Patients with germline mutations in fumarate hydratase are believed to be at increased risk for developing uterine leiomyosarcomas as well as uterine leiomyomas [9]. The oncogenic mechanisms underlying the development of uterine leiomyosarcomas remain elusive. Overall, uterine leiomyosarcoma is a genetically unstable tumor that demonstrates complex structural chromosomal abnormalities and highly disturbed gene regulation, which likely reflects the end-state of accumulation of multiple genetic defects.

2.4. Prognosis

Leiomyosarcomas diagnosed according to the WHO criteria [3] are associated with poor prognosis even when confined to the uterus at the time of diagnosis [7,10]. Recurrence rate ranges from 53% to 71% [11,12]. First recurrences occur in the lungs in 40% of patients and in the pelvis in only 13% [13]. Overall five-year survival rate ranges from 15% to 25% with a median survival of only 10 months in one study [14]. In the Norwegian series, 148 patients with leiomyosarcomas limited to the uterus had a five-year survival of 51% at Stage I and 25% at Stage II (by the 1988 FIGO staging classification). All patients with tumor spread outside the pelvis died within 5 years [7].

Box 1
Leiomyoma variants that may mimic malignancy.

- Mitotically active leiomyoma
- Cellular leiomyoma
- Hemorrhagic leiomyoma and hormone-induced changes
- Leiomyoma with bizarre nuclei (atypical leiomyoma)
- Myxoid leiomyoma
- Epithelioid leiomyoma
- Leiomyoma with massive lymphoid infiltration

Box 2
Smooth muscle proliferations with unusual growth patterns.

- Disseminated peritoneal leiomyomatosis
- Benign metastasizing leiomyoma
- Intravenous leiomyomatosis
- Lymphangioleiomyomatosis

Box 3
Atypical smooth muscle tumors (so-called smooth muscle tumors of uncertain malignant potential [STUMP]).

- Tumor cell necrosis in a typical leiomyoma
- Necrosis of uncertain type with ≥ 10 MF/10 HPFs, or marked diffuse atypia
- Marked diffuse or focal atypia with borderline mitotic counts
- Necrosis difficult to classify

There has been no consistency among various studies regarding correlation between survival and patient age, clinical stage, tumor size, type of border (pushing versus infiltrative), presence or absence of necrosis, mitotic rate, degree of nuclear pleomorphism, and vascular invasion [3]. However, one study [15], found tumor size to be a major prognostic parameter: 5 of 8 patients with tumors less than 5 cm in diameter survived, whereas all patients with tumors greater than 5 cm in diameter died. In a series of 208 uterine leiomyosarcomas [2], the only other parameters predictive of prognosis were tumor grade and stage. In the report from Norway [7], including 245 leiomyosarcomas confined to the uterus, tumor size and mitotic index were significant prognostic factors and allowed for separation of patients into three risk groups with marked differences in prognosis.

Ancillary parameters including p53, p16, Ki 67, and Bcl-2 have been used in leiomyosarcomas to try to predict outcome [10]. It is not clear whether they act independently of stage. However, a recent study revealed that the combination of tumor size, mitotic index, Ki67, and Bcl-2 protein expression allows two groups of leiomyosarcomas to be distinguished, with different survival: tumors greater than or equal to10 cm in diameter, with greater than or equal to 20 MF/10 HPF, greater than or equal to10% immunoreactive nuclei for Ki67, and negative for Bcl-2 had worse prognosis than smaller leiomyosarcomas with less than or equal to 20 MF/10 HPF, less than or equal to10% immunoreactive nuclei for Ki67, and positive or negative for Bcl-2 [15].

2.5. Treatment

Treatment of leiomyosarcomas includes total abdominal hysterectomy and debulking of the tumor if present outside the uterus. Removal of the ovaries and lymph node dissection remain controversial as metastases to these organs occur in only a small percentage of cases and are frequently associated with intra-abdominal disease [2]. Ovarian preservation may be considered in premenopausal patients with early-stage leiomyosarcomas [2]. Lymph node metastases have been identified in 6.6% and 11% in two series of patients with leiomyosarcoma who underwent lymphadenectomy [2,16]. In the first series, the five-year disease-specific survival rate was 26% in patients who had positive lymph nodes compared with 64.2% in patients who had negative lymph nodes ($P < 0.001$) [16]. The influence of adjuvant therapy on survival is uncertain. Radiotherapy may be useful in controlling local recurrences and chemotherapy with doxorubicin or docetaxel/gemcitabine is now used for advanced or recurrent disease with response rates ranging from 27% to 36% [17]. Some tumors may respond to hormonal treatment [18]. Targeted therapies such as trabectedin have been investigated as treatment in advanced stage or metastatic leiomyosarcoma with some appreciable disease control [19].

3. Atypical smooth muscle tumors (smooth muscle tumors of uncertain malignant potential) (STUMP)

Uterine smooth muscle tumors that show some worrisome histological features (i.e. necrosis, nuclear atypia, or mitoses), but do not meet all diagnostic criteria for leiomyosarcoma, fall into the category of atypical smooth muscle tumors (STUMP) (Box 2) [3]. This diagnosis, however, should be used sparingly and every effort should be made to classify a smooth muscle tumor into a specific category when possible [3]. Most tumors classified as atypical smooth muscle tumors (STUMP) have been associated with favorable prognosis and, in these cases, only follow-up of the patients is recommended.

4. Endometrial stromal tumors

Endometrial stromal tumors account for less than 1% of all uterine tumors [1]; nevertheless, they represent the second most common category of mesenchymal uterine tumors. They are predominantly or exclusively intramural neoplasms and are divided into benign and malignant based on the type of tumor margin: well-circumscribed tumors are benign stromal nodules, whereas those exhibiting myometrial invasion and permeation of myometrial lymphovascular spaces are sarcomas [3]. Endometrial sarcomas are further classified by the latest WHO classification, based on resemblance to (or lack of) proliferative-type endometrial stroma, into the following three main categories: (1) low-grade endometrial stromal sarcoma; (2) high-grade endometrial stromal sarcoma; and (3) undifferentiated endometrial sarcoma [3].

4.1. Low-grade endometrial stromal sarcoma

Low-grade endometrial stromal sarcomas frequently occur in women between 40 and 55 years of age and more than 50% of patients are premenopausal [19]. Some cases have been reported in women with ovarian polycystic disease, and after estrogen use or tamoxifen therapy [19]. Patients commonly present with abnormal uterine bleeding, pelvic pain, and dysmenorrhea, but as many as 25% are asymptomatic [15]. At presentation, extrauterine pelvic extension, most commonly involving the ovary, is found in up to one-third of patients [19,20].

Microscopically, endometrial stromal sarcomas consist of well-differentiated endometrial stromal cells exhibiting only mild nuclear atypia and characteristically invade the lymphovascular spaces of the myometrium (Fig. 2). Tumor cell necrosis is rarely seen.

The tumor cells are strongly immunoreactive for CD10, usually positive for smooth-muscle actin and less frequently for desmin (30%), but they are negative for h-caldesmon and HDAC8. Estrogen receptors (only alpha isoform), progesterone receptors, androgen receptors, and WT-1 are typically positive. Nuclear beta-catenin expression has been shown in up to 40% of low-grade endometrial stromal sarcomas. The most common cytogenetic abnormality of low-grade endometrial stromal sarcomas is a recurrent translocation involving chromosomes 7 and 17 t(7;17)(p15;q21)], which results in a fusion between *JAZF1* and *SUZ12* (formerly designated as JJAZ1) [21]. The fusion can be detected by fluorescence in situ hybridization as well as by reverse transcriptase–polymerase chain reaction.

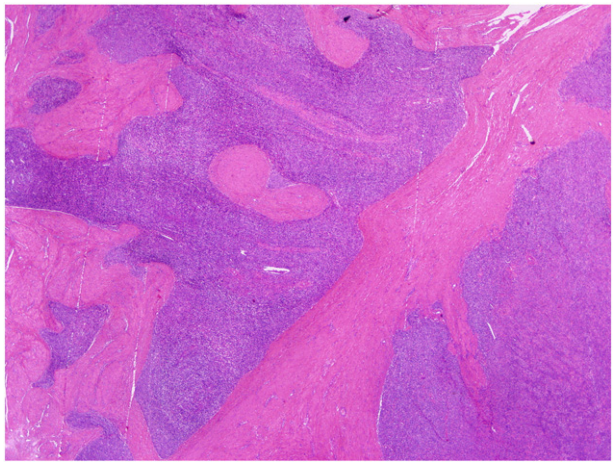

Fig. 2. Low-grade endometrial stromal sarcoma.

Low-grade endometrial stromal sarcomas are indolent tumors with a favorable prognosis [19]. Tumor behavior is characterized by late recurrences even in patients with Stage I disease; thus, long-term follow-up is required. About one-third of patients develop recurrences, most commonly in the pelvis and abdomen, and less frequently in the lungs and vagina [19]. Stage of the tumor is the most significant prognostic factor. Surgical stage higher than Stage I is a univariate predictor of unfavorable outcome. Five-year survival for patients with Stages I and II tumors is 90% compared with 50% for Stages III and IV [22].

Treatment of low-grade endometrial stromal sarcomas is largely surgical in the form of hysterectomy and bilateral salpingo-oophorectomy. The tumors are often sensitive to hormones and it has been shown that patients retaining their ovaries have a much higher risk of recurrence (up to 100%) [23]. Lymph node dissection does not seem to have a role in the treatment of these tumors. Patients may also receive adjuvant radiation or hormonal treatment with progestational agents or aromatase inhibitors. Hormone replacement therapy is discouraged.

4.2. High-grade endometrial stromal sarcoma

These rare tumors have features that are intermediate between low-grade endometrial stromal sarcomas and undifferentiated sarcomas [24]. Patients range in age from 28–67 years (mean 50 years) and usually present with abnormal vaginal bleeding, an enlarged uterus, or a pelvic mass [25].

The tumors may appear as intracavitary polypoid or mural masses. They range in size up to 9 cm (median 7.5 cm) and often show extra-uterine extension at the time of diagnosis. The cut surface is fleshy with extensive areas of necrosis and hemorrhage. Microscopically, they consist predominantly of high-grade round-cells that are sometimes associated with a low-grade spindle cell component that is most commonly fibromyxoid [25]. Mitotic activity is striking and typically greater than 10 per 10 HPF. Necrosis is usually present. Rarely, areas of conventional low-grade endometrial stromal sarcoma are seen. High-grade endometrial stromal sarcomas are CD10, estrogen receptor, and progesterone receptor negative but show strong diffuse cyclin D1 immunoreactivity (>70% nuclei). They are also typically c-Kit positive but DOG1 negative. High-grade endometrial stromal sarcoma typically harbors the *YWHAE-FAM22* genetic fusion as a result of t(10;17) (q22;p13).

These tumors appear to have a prognosis that is intermediate, between low-grade endometrial stromal sarcomas and undifferentiated uterine sarcomas [25]. Compared with low-grade endometrial stromal sarcomas, patients with high-grade endometrial stromal sarcomas have earlier and more frequent recurrences (often <1 year) and are more likely to die of disease. Advanced or recurrent tumors (10;17) should be treated aggressively with a combination of radiation and chemotherapy as they do not respond to conventional treatment for low-grade endometrial stromal sarcomas [25].

4.3. Undifferentiated endometrial sarcoma

This tumor is rare. Patients are typically postmenopausal (mean age is 60 years) and have postmenopausal bleeding or signs/symptoms secondary to extra-uterine spread [26]. Approximately 60% of patients present with high-stage disease (Stage III/IV). The diagnosis of undifferentiated endometrial sarcoma is applied to tumors that exhibit myometrial invasion, severe nuclear pleomorphism, high mitotic activity and/or tumor cell necrosis, and lack smooth muscle or endometrial stromal differentiation [3]. The histological appearance of this tumor is more like the mesenchymal elements of a carcinosarcoma than a typical endometrial stromal tumor. It is variably CD10 positive and typically estrogen receptor and progesterone weakly positive or negative. Undifferentiated endometrial sarcomas are highly aggressive tumors that are associated with a very poor prognosis (less than 2 years' survival) [26]. Patients should be treated by hysterectomy and bilateral salpingo-oophorectomy and adjuvant radiation and/or chemotherapy.

5. Adenosarcoma

Müllerian adenosarcoma is a mixed tumor of low malignant potential that shows an intimate admixture of benign glandular epithelium and low-grade sarcoma, usually of endometrial stromal type. It represents between 5% and 10% of all uterine sarcomas. The tumor occurs mainly in the uterus of postmenopausal women (average 58 years) but also in adolescents and young adults (30%) [27]. Most adenosarcomas arise from the endometrium, including the lower uterine segment, but rare tumors develop in the endocervix (5%—10% of cases) and in extrauterine locations [28].

Adenosarcomas are polypoid tumors of approximately 5–6 cm in maximum diameter (range, 1–20 cm) that typically fill and distend the uterine cavity. Adenosarcomas with sarcomatous overgrowth tend to be larger with a fleshy, hemorrhagic, and necrotic cut surface. They invade the myometrium more often than conventional adenosarcomas.

Microscopically, the stroma typically concentrates around the glands forming periglandular cuffs (Fig. 3). Well-differentiated tumors may exhibit only mild nuclear atypia and very few or no mitoses in the stromal component. However, the presence of hypercellular periglandular cuffs helps to distinguish adenosarcoma from its rarer benign counterpart, the adenofibroma [28]. Heterologous mesenchymal elements, usually rhabdomyosarcoma, are found in 10%—15% of cases. Vaginal or pelvic recurrence occurs in approximately 25%—30% of cases at 5 years and is associated almost exclusively with myometrial invasion and sarcomatous overgrowth [27,28]. Myometrial invasion is found in approximately 15% of cases, but deep invasion in only 5% [27,28]. Sarcomatous overgrowth, defined as the presence of pure sarcoma, usually of high-grade and without a glandular component, occupying at least 25% of the tumor, has been reported in 8% to 54% of uterine adenosarcomas [27,28].

Whereas immunoreactions for cell proliferation markers (Ki-67 and P53) are stronger in adenosarcomas with sarcomatous overgrowth than in typical adenosarcomas, the expression of markers of cell differentiation (CD10 and PR) is higher in typical adenosarcomas than in adenosarcomas with sarcomatous overgrowth [28].

Except when associated with myometrial invasion or sarcomatous overgrowth, the prognosis of adenosarcoma is far more favorable than that of carcinosarcoma; however, about 25% of patients with adenosarcoma ultimately die of their disease [27]. Recurrences are usually composed exclusively of mesenchymal elements. Distant metastases, which occur in 5% of cases, are almost always composed of pure sarcoma (70%). The treatment of choice is total abdominal hysterectomy with bilateral salpingo-oophorectomy.

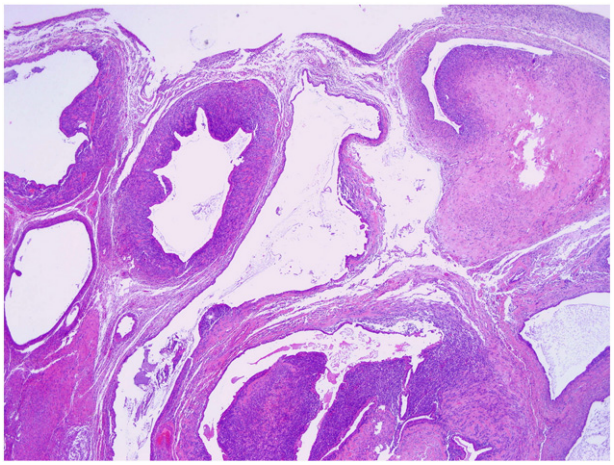

Fig. 3. Adenosarcoma.

6. Carcinosarcoma

Carcinosarcoma, also referred to as "malignant müllerian mixed tumor," is a biphasic neoplasm composed of distinctive and separate, but admixed, malignant-appearing epithelial and mesenchymal elements (Fig. 4). The mean age of patients with carcinosarcoma is in the seventh decade, but the age range spans from the fourth through the ninth decades [29]. The disease usually presents like other endometrial cancers with vaginal bleeding. Another typical presentation of carcinosarcoma is in the form of a polypoid mass that protrudes through the cervical os.

The epithelial component is serous, or high-grade carcinoma not otherwise specified, in about two-thirds of cases, and endometrioid carcinoma in approximately one-third [29]. In a recent study, 10% of the carcinomatous components were FIGO grade 1, 10% grade 2, and 80% grade 3 [29]. The homologous components of carcinosarcoma are usually spindle cell sarcoma without obvious differentiation; many resemble fibrosarcomas or pleomorphic sarcomas. Almost all are high-grade sarcomas. The most common heterologous elements are malignant cartilage or skeletal muscle constituting something that resembles either pleomorphic rhabdomyosarcoma or embryonal rhabdomyosarcoma [1].

Carcinosarcomas are highly aggressive tumors—far more aggressive than usual endometrial carcinomas. The overall five-year survival for patients with carcinosarcoma is around 30% and for those with Stage I disease (confined to the uterus) it is approximately 50% [1,6,30,31]. This is in contrast with other high-grade endometrial cancers for which five-year survival in Stage I disease is approximately 80% or higher [32,33]. This has led to toxic treatment protocols that usually include ifosfamide and cisplatin along with whole pelvic irradiation.

In carcinosarcomas, there is general agreement that surgical stage is the most important prognostic indicator regardless of how the patient was staged. A recent study found that the presence of heterologous elements is a poor prognostic factor in patients with FIGO Stage I tumors [29]. Other factors proposed include the histologic grade of the carcinomatous and sarcomatous elements, the percentage of tumor with sarcomatous differentiation, depth of myometrial invasion, and presence of lymphovascular invasion [1,6,30,31].

6.1. Treatment of carcinosarcomas

Primary surgery for early disease includes a hysterectomy, bilateral salpingo-oophorectomy, and pelvic node dissection as the tumor spread pattern is similar to high-grade endometrial carcinomas. Omentectomy is also advocated by some. Complete cytoreduction should be the aim of surgery, as this may be associated with an overall survival benefit.

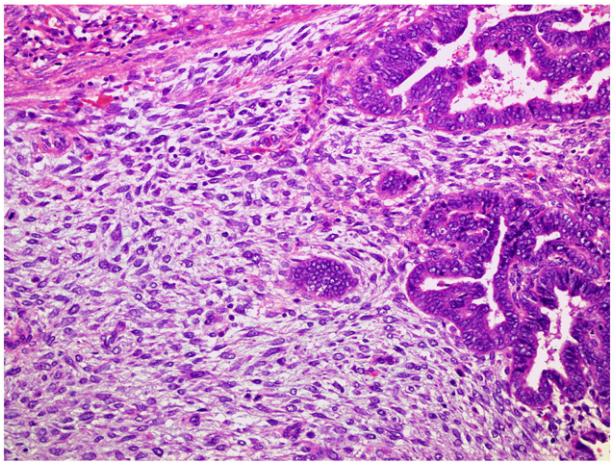

Fig. 4. Carcinosarcoma.

Combination chemotherapy seems to result in fewer recurrences than whole body irradiation [34]. Patients with carcinosarcomas, however, tend to be elderly with co-morbidities. The ideal agents still need to be established. The results of the Gynecologic Oncology Group 261 study, which aims to compare ifosfamide/paclitaxel versus carboplatin/paclitaxel combinations in patients with advanced stage or recurrent carcinosarcoma, are awaited. Radiotherapy is only able to control pelvic disease [35].

6.2. Follow-up of sarcomas

Follow-up should be determined by risk of recurrence. As metastasis to the lungs is common, efforts must be made to rule these out remembering that early lesions tend to be asymptomatic but resectable. Low-grade sarcoma patients may be followed for local relapse every 4–6 months for the first 3–5 years, then yearly. High-grade tumors can be followed-up every 3–4 months for the first 2–3 years, twice a year for the next 2–3 years, and then annually.

Conflict of interest

The authors have no conflict of interest.

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