UTERINE SARCOMAS – CURRENT THERAPEUTIC OPTIONS

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Abstract Uterine sarcomas are rare but very aggressive uterine malignancies originating from mesenchymal elements of the uterine wall. They are classified by the “Gynecologic Oncology Group” in non-epithelial neoplasms and mixed epithelial-nonepithelial tumors, each category presenting different features and prognostic factors. In this review we present the main characteristics and the current therapeutic options for each type of primary uterine sarcoma and for their recurrences.

Key words: uterine sarcoma, surgery, recurrence

Introduction

Uterine sarcomas are rare tumors accounting for 3-7% of all uterine neoplasms (1), with poor prognosis. Uterine sarcomas originate from mesenchymal elements at the level of the uterine wall: endometrial stroma and myometrium smooth muscle tissue.

Classification of uterine sarcomas

Uterine sarcomas were histologically classified by the “Gynecologic Oncology Group” as it follows: (1,2)

I. Nonepithelial neoplasms

A. Endometrial stromal tumors

1. Stromal nodule

2. Low-grade stromal sarcoma

3. High-grade stromal sarcoma

B. Smooth muscle tumor of uncertain malignant potential

C. Leiomyosarcoma

1. Epithelioid

2. Myxoid

D. Mixed endometrial stromal and smooth muscle tumor

E. Poorly differentiated (undifferentiated) endometrial sarcoma

F. Other soft tissue tumors

1. Homologous

2. Heterologous

II. Mixed epithelial-nonepithelial tumors

A. Adenosarcoma

1. Homologous

2. Heterologous

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3. With high-grade stromal overgrowth (see notes)

B. Carcinosarcoma (malignant mixed mesodermal tumor or malignant mixed müllerian tumor)

1. Homologous

2. Heterologous

Homologous histological types contain elements that are specific to uterine tissue (Spindle cell sarcoma, stromal sarcoma, leiomyosarcoma, Fibrosarcoma) while heterologous ones contain histological elements that usually do not exist at this level (osteosarcoma, chondrosarcoma, rhabdomyosarcoma). (1)

The incidence of uterine sarcomas in the United States is 2.68 / 100 000. The most common types of uterine sarcomas are in order of frequency carcinosarcoma, leiomyosarcoma, endometrial stromal sarcoma and adenosarcoma. Both type and incidence of uterine sarcomas are dependent on age and race. Carcinosarcoma rarely occurs before age 40, the mean age of patients with this type of tumor being 65 while leiomyosarcoma occurs in younger patients, the mean age being 55 years. (1)

FIGO staging for uterine sarcomas (2009)

Stage I (tumor limited to uterus)

IA: <5 cm tumor size

IB: ≥5 cm tumor size

For Leiomyosarcoma

IA: tumor limited to endometrium/ endocervix without myometrial invasion

IB: tumor invades < 50% myometrium

IC: tumor invades > 50% myometrium

For Endometrial Stromal Sarcoma and Adenosarcoma

Stage II (tumor extension into the pelvis)

IIA: adnexal involvement

IIB: other extrauterine pelvic disease

Stage III (tumor invades abdominal tissues)

IIIA: one site involvement

IIIB: >1 site involvement

IIIC: metastasis to pelvic and/or para-aortic lymph nodes

Stage IV (tumor invades bladder and/or rectum, and/or distant metastasis)

IVA: involvement of bladder and/or rectum

IVB: distant metastasis

Uterine carcinosarcomas

Carcinosarcoma contains both malignant epithelial and mesenchymal elements. Epithelial

component is usually represented by serous and endometrioid cells, and rarely, mucinous or squamous cells while mesenchymal component is heterogeneous. The most important prognostic factor in carcinosarcoma is tumor stage; the 5 year overall survival is 59%, 22% and 9% for stages I, II and III respectively. Other prognostic factors are the cell type, presence or absence of lymphatic spread, grade of differentiation and number of mitoses, sarcomatous component, depth of myometrial invasion, peritoneal cytology. (3,4)

Surgical treatment for patients with uterine carcinosarcoma is total hysterectomy with bilateral adnexectomy with pelvic and para-aortic lymph node dissection. Staging is performed according to the FIGO staging system for endometrial cancer. Carcinosarcomas are tumors with a high capacity of extension: 37% of patients present myometrial invasion, 17% present nodal involvement and almost 21% of patients present malignant cells in the peritoneal lavage cytology. (3,4,5)

In almost all cases the presence of the distant metastases is due to the epithelial component of the carcinosarcoma.

In a study conducted on 3962 cases diagnosed histopathologically with carcinosarcoma, lymph node dissection was performed in 53% of cases. 5-year survival rate in cases without extrapelvic extension, was 59% for IA stage, 54% for IB stage and only 38% for IC stage. In another study of the Gynecologic Oncology Group, 53% of all patients with carcinosarcoma and 40% of those with stage I carcinosarcoma had a recurrence in the first 3 years after diagnosis. The prognosis depends on the presence of lymph node metastasis, depth of myometrial invasion and impaired uterine segment or cervix. (6)

Adjuvant therapy is represented by adjuvant radiotherapy or chemotherapy in order to obtain a good local control of the disease. Radiation therapy is usually used to reduce the frequency of pelvic recurrences. Several studies have shown a decrease in local recurrence, but no evidence of any benefit in terms of survival. Recently, a study made by the European Organization for Research and Treatment of Cancer (EORTC) on 224 patients diagnosed with uterine sarcoma (91 cases of carcinosarcoma) showed that pelvic radiotherapy after surgery does not improve survival, but in cases of carcinosarcoma, decreases the risk of pelvic recurrence. (1)

Uterine leiomyosarcomas

Leiomyosarcoma is a malignant tumor originating from the smooth muscle cells of the myometrium. In these cases preoperative diagnosis is usually difficult to be established; they are often categorised as benign leiomyomas; the only preoperative examination which could differentiate the two histopathological types is the tumor tissue biopsy. Macroscopically, quite often the tumor borders are irregular, infiltrating the surrounding tissue. The main histopathological features necessary to diagnose leiomyosarcoma are: cellular atypia, a large number of mitoses and the presence of areas of coagulation necrosis. (1)

The most common way of dissemination is the hematogenous route, approximately 10% of patients presenting lung metastases at the moment of presentation. (5,6)

The correlation between mitotic index, tumor type and metastatic potential is shown in the table 1. (7)

The standard treatment of uterine leiomyosarcomas in premenopausal women is total interadnexial hysterectomy; unfortunately there are cases in which the right diagnosis is not known preoperatively and a myomectomy is performed for the preoperative suspicion of benign tumor. In these cases most authors opiate for a second surgery in order to perform a complete hysterectomy.

Prognostic factors - the most important prognostic factor in leiomyosarcoma is the stage of the disease. The 5 year survival rate is about 50% for stage I-II. (table 2)

Lymph node metastases have a low incidence in leiomyosarcomas (2.7 to 4%). In the study of Giuntoli et al on 208 patients with leiomyosarcoma, lymph node metastasis were found in 4 of 36

patients who underwent lymph node dissection, while three of these patients presented multiple metastases. There seems to be a significant difference in survival in patients with stage I leiomyosarcoma with or without lymph node metastases. (8,9)

Older age at diagnosis is a poor prognostic factor. In a retrospective study conducted in Italy, patients aged over 50 years old had a risk of progression of the disease 2.07 times higher than patients younger than 50 years while Wu et al showed that patients over 50 years old had a risk of death of 7.11 times when compared to younger patients. (10)

Tumor size is another important prognostic factor, especially in stage I disease. Abeler et al reported a 5-year survival rate of 64% in cases presenting a tumor smaller than 50 cm, 56% in cases with tumors measuring between 50 and 100 mm -, and only 29% in cases with tumors larger than 100 mm. Combining size tumor with the mitotic index, led to the classification of patients into three risk groups: low risk group (tumor size less than 100 mm and less than 10 mitoses / 10 high-resolution fields), medium-risk group (whether the tumor is larger than 100 mm, and no more than 10 mitoses / 10 fields) - risk of death 1.9 times higher, and high-risk group (tumor greater than 100 mm or a high index of mitosis) - risk of death by 5.3 times higher. (3,11,12)

Endometrial stromal sarcomas

Endometrial stromal tumors are tumors arising from mesenchymal cells from the uterine mucosa. The macroscopic aspect of the tumors can be soft, fleshy, smooth and sometimes polypoid. These tumors are classified in two groups according to

Table 1

Mitotic figures/10 hfh	Atypia	Tumor type	Metastatic potential
1-4	Any degree	Leiomyoma	Very low
5-9	None	Leiomyoma with high mitotic activity	Very low
5-9	Grade 1	Smooth muscle tumor of uncertain malignant potential („STUMP“)	Low
5-9	Grade 2 or 3	Leiomyosarcom	Moderate
≥10	Grade 1	Leiomyosarcom	High
≥10	Grade 2 or 3	Leiomyosarcom	Very high

Table 2

Mitotic figures/10 hff	Atypia	Tumor type	Metastatic potential
1-4	Any degree	Leiomyoma	Very low
Clinical trial	Stage	Number of patients	Survival rates after 5 years
Kapp (3)	I	951	75,8%
	II	43	60,1%
	III	99	44,9%
	IV	303	28,7%
Mayerhofer (11)	I	49	75%
	II	5	14%
	III-IV	17	0%
Salazar Dunne (4)	I	113	53%
	II-IV	50	8%
Gadducci (2)	I-II	90	54%
	III	16	6%
	IV	20	0%
Kahanpaa (5)	I	23	74%
	II-IV	45	39%
Blom (13)	I-II	29	52%
	III-IV	20	0%

their potential for metastasis: stromal nodules - benign tumors that can not be differentiated from the endometrial stroma and stromal sarcomas – tumors presenting a local invasiveness with vascular and lymphatic extension. (2,14)

Endometrial stromal sarcomas are classified on the basis of mitotic activity in sarcomas with low mitotic index ("low-grade"), and sarcomas with increased mitotic index or high-grade sarcomas. Tumors with low mitotic activity have an infiltrative pattern of development, their macroscopic appearance is a sinuous route being developed in the myometrium or in the pelvic blood vessels. Microscopically, these tumors present cellular atypia, with low mitotic index; although metastasis might appear, endometrial stromal sarcomas have a rather favorable clinical outcome. Recurrence usually appears after a long disease free period, of over 5 years although relapse can occur even at 25 years after the initial diagnosis. Survival at 80 months after diagnosis is about 90%. (1)

Endometrial stromal sarcomas with high rate of cell mitosis ("high grade") have a more aggressive evolution. In a study conducted on a sample of 109 cases, Kempson et al demonstrated that the tumor stage is a more precise prognostic factor than the rate of mitosis. (15)

In another study, on 114 patients with endometrial stromal sarcoma, enrolled from 1990 to 2012, showed that in the premenopausal patients bilateral salpingo-oophorectomy was independently

associated with longer recurrence-free survival. Patients who underwent cytoreductive resection of recurrent tumor demonstrated longer survival after recurrence than patients without this surgery. The incidence of nodal metastasis among patients with endometrial stromal sarcomas with lymphadenectomy was 6,6%. Endometrial stromal sarcomas show a higher incidence of estrogen and progesterone receptors compared with other uterine sarcomas. Based on the hormonal sensitivity of endometrial stromal sarcomas and risk for recurrence, treatment of endometrial stromal sarcoma consist of performing bilateral salpingo-oophorectomy. Bilateral salpingo-oophorectomy should be considered a primary surgical treatment for improving the recurrence free survival. (2)

Cytoreductive procedures of recurrent endometrial stromal sarcoma is an independent predictor of survival after recurrence. Of the 28 patients who underwent cytoreductive surgery, 6 patients died and 22 were successfully salvaged. Aggressive and repeated surgical resection of recurrent tumors seemed to be valuable. The 5 years overall survival rate for all the patients was 92,6%. In FIGO stage I was 96,1% and in FIGO II-IV 76%. The recurrence was 28,9% and the death rate was 8,7%. (7,8,15,16,17)

Conclusion

Uterine sarcomas are relatively uncommon

tumors that usually have an aggressive clinical behaviour and a poor prognosis. The only curative treatment remains surgical – total abdominal hysterectomy and bilateral salpingo-oophorectomy. Pelvic and para-aortic lymphadenectomy is indicated for carcinosarcoma but not for leiomyosarcoma and undifferentiated endometrial sarcoma. Adjuvant pelvic radiotherapy appears to improve local control without any significant impact on overall survival. Uterine sarcomas have a high tendency to develop distant recurrences. The treatment of recurrent disease often requires the integration of different therapeutic modalities. No curative therapeutic option is currently available except surgery for isolated pulmonary metastases or association between hormone therapy and debulking surgery. (2,14)

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