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Uterine Sarcomas – Review of Literature

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1. Summary

Uterine sarcomas are rare and comprise only 3% of all uterine cancers, 8% of malignant uterine tumors. Within the group of soft tissue sarcomas they occure in 7% of all cases. They consist of different histological subtypes as leiomyosarcoma, endometrial stromal tumor, undifferentiated sarcoma, pure heterologous sarcoma and mixed epithelial and mesenchymal tumors. Standard treatment in localized disease is abdominal hysterectomy. Bilateral salping-oophorectomy and lymphonodectomy have no proven value in leiomyosarcoma and undifferentiated sarcomas. However in endometrial stromal tumors is salpingo-oophorectomy recommended according to their hormonal responsiveness. Therapy of carcinosarcomas is according to current recommendations as in treatment of epithelial uterine tumors - standard is hysterectomy, salpingo-oophorectomy, pelvic and paraaortal lymphonodectomy and omentectomy [1].

2. Introduction

Uterine sarcomas are rare type of uterine cancer [2]. Appointed nomenclature – sarcomas – is historically used for tumors with sarcoma component and this group has common mesodermal origin. The group of sarcomas includes many histological types according to the types of the tissue which they include. They are divided into homologous and heterogeneous sarcomas. Homologous tumors are formed by tissue which we can commonly find in uterus / soft tissue, endometrial stromal, blood and lymphatic veins. In heterogeneous types there is striated muscle, fat tissue, cartilage and bones [3]. According the the presence only mesodermal component or combination of epithelial and mesodermal component we call these as clear or mixed sarcomas [4]. The type with best prognosis is leiomyosarcoma. This type occurred in 60%, then endometrial stromal tumor, non-differentiated sarcoma and heterogeneous sarcomas. Mixed epithelial and mesenchymal tumors are adenosarcomas [with sarcomatous invasion or without invasion at all] or carcinosarcomas [mixed Mullerian tumors]. Among tumors with unfavorable prognosis – high-grade types – there belongs leiomyosarcoma, non-differentiated endometrial sarcoma and carcinosarcoma. Among tumors with better prognosis – low-grade types – there are endometrial stromal sarcomas and adenosarcomas [5].

3. Staging

Staging is according to system FIGO/AJCC for classification of uterine sarcomas according to it's difference comparing to endometrial carcinomas (Table 1).

Table 1:

Stage		Definition
Leiomyosarcomas and endometrial stromal sarcomas		
T1	I	Tumor invades only uterus
T1a	IA	≤5cm
T1b	IB	>5cm
T2	II	Tumor disseminates around uterus, still locate in pelvis
T2a	IIA	Invades adnexal parts
T2b	IIB	Invades other tissue located in pelvis
T3	III	Tumor invades abdominal tissue
T3a	IIIA	Tumor invades unilaterally
T3b	IIIB	Tumor invades tissue in different directions
N1	IIIC	Tumor metastasis do pelvic and/or paraaortal lymph nodes
T4	IVA	Tumor invades urinary bladder and/or rectum
M1	IVB	Distant metastasis
Adenosarcomas		Definition
T1	I	Tumor invades only uterus
T1a	IA	Tumor infiltrates endometrium/ endocervix but doesn't invade myometrim
T1b	IB	Infiltration less than ½ thickness of myometrium
T1c	IC	Infiltration more than ½ thickness of myometrium
T2	II	Tumor infiltrated extrauteral in pelvis
T2a	IIA	Tumor invades adnexal parts
T2b	IIB	Tumor spreads into extra uterine pelvic tissue
T3	III	Tumor infiltrated abdominal tissue
T3a	IIIA	Is unilateral
T3b	IIIB	Invades in different directions
N1	IIIC	Metastasis into pelvic and/or paraaortal lymph nodes
T4	IVA	Tumor invades urinary bladder and/or rectum
M1	IVB	Distant metastasis
Carcinosarcomas		
Carcinosarcomas should be classified as endometrial carcinomax		

4. Survival Rate

Survival rate in uterine sarcomas depends on:

- Stage of the tumor
- Type of the tumor
- Grading [high-grade or low -grade type]
- Overall health of the patient
- Medical treatment

Statistics of the survival rate are collected from National Cancer Institute SEER program and they are based on the statistic of women diagnosed with uterine sarcoma in years 2004 – 2010. SEER doesn't use FIGO classification but uses classification according to tumor localization.

- Localized form means that the tumor is limited only in uterus, which is FIGO classification stadium T1
- Regional form means that the tumor invaded close tissue or lymph nodes, which is FIGO classification T2, T3
- Distant form means that the tumor spreaded to distant tissue, which is FIGO classification T4 [1] (Table 2-4).

Table 2: Leiomyosarcom

Form	5-year survival rate
Localized	63%
Regional	36%
Distant	14%

Table 3: Non differentiated sarcoma

Form	5-year survival rate
Localized	70%
Regional	43%
Distant	23%

Table 4: Endometrial stromal sarcoma

Form	5-year survival rate
Localized	99%
Regional	94%
Distant	69%

5. Treatment of Uterine Sarcomas

Basic therapeutic approaches are:

- Surgical treatment
- Radiotherapy
- Chemotherapy
- Hormonal therapy

5.1. Surgical Treatment

Surgical intervention is the primary treatment for uterine sarcomas. The main goal is the removal of tumor tissue. First of all surgical approach includes hysterectomy, in some cases salpingo-oophorectomy and partial vaginal resection. There may be local lymphonodectomy performed for eventual assessment of spreading the disease extrauterinal. The range of surgical intervention depends on the type, stage or disease and also on overall health of the patient and her age [2].

5.2. Radiotherapy

There are X-rays with high energy used for radiotherapy. Either it is applicated as outer radiation or used as brachytherapy by placing radioactive material close to the tumor.

Brachytherapy is applicated for 4 to 6 weeks before performing hysterectomy and in two types: low-dose or high-dose. In cases where the tumor invades through cervical tissue, the radiotherapy is used before surgery – adjuvant radiotherapy- for easier removal of the tumor during surgical procedure.

There are short term unwanted effects of radiotherapy such as fatigue, nausea, vomiting, diarrhea, or decrease in blood work. Long term unwanted effects include radiation cystitis, vaginal stenosis or lymphedema [6].

5.3. Chemotherapy

Chemotherapy is considered as a systematic treatment and is applied in per oral form, intramuscular or intravenous form. It can be applied before surgery – neoadjuvant chemotherapy – or after the surgery as adjuvant chemotherapy.

The most commonly used chemotherapeutics are: cisplatin, decarbazin, docetaxel, doxorubicin, gemcitabin, ifosfamid, paclitaxel, or in combination, for example, gencitabin and docetaxel in therapy of leiomyosarcoma. Severity of unwanted effects depends on the specific drug, it's dosage and time of application [7].

5.4. Hormonal Treatment

Hormonal treatment is used mostly in endometrial stromal sarcomas with good response of hormonal receptors.

In hormonal treatment we usually use:

- Progestins – Medroxyprogesterone
- Gonadotropine-releasing hormonal agonist – Gosereline
- Aromatasis inhibitors – Letrosole [1]

5.5. Possibilities of Treatment of Uterine Sarcomas According to the Disease Stage

Leiomyosarcoma and non-differentiated sarcoma

Leiomyosarcoma is the most common type of uterine sarcoma. In general the treatment of leiomyosarcoma, non-differentiated sarcomas and heterogeneous uterine sarcomas is subject to treatment guidelines of soft tissue uterine sarcomas.

5.5.1. Stage I and II: Surgical approach is the primary therapeutic modality. Local therapy includes total abdominal hysterectomy. Bilateral salpingo-oophorectomy is suggested in menopausal and post-menopausal patients. In case or pre-menopausal patients in early stages of disease there is suggestion of leaving and not respecting of ovaries. Dissection of pelvic and paraaortal lymph nodes is not recommended while the lymph nodes are affected in less than 3%. Lymphonodectomy is therefore not a standard treatment in these stages. Uterine leiomyosarcoma in I.stage still has high risk of recurrence in for of distant metastasis.

In leiomyosarcomas with metastasis there is suggested radiotherapy according to reconsideration of risk factors as size of the tumor and it's invasion to uterine myometrium [2].

Currently there isn't adjuvant chemotherapy considered as standard care in soft tissue sarcomas in adults, with exclusion of Ewing tumor and embryonal rabdomyosarcoma because the benefit is not clearly confirmed [8].

5.5.2. Stage III: In surgical treatment there is suggested not only hysterectomy, bilateral salpingo-oophorectomy but also sampling and/or dissection of lymph nodes. In stage IIIb when the tumor had invaded vaginal tissue there is need to extend the surgical treatment to partial vaginal resection. After surgery there should be treatment continued by radiotherapy and chemotherapy. In patients when their health status doesn't recommend surgical treatment there should be radiotherapy and chemotherapy suggested [1].

5.5.3. Stage IV: Stage IVa when the tumor disease spreaded to distant organs and tissues [urinary bladder, rectum] should these be removed surgically with follow-up radiotherapy and chemotherapy.

In case of stage IVb with generalization of the disease outside the pelvis, mostly lungs, liver and bones there is no standard approach of the treatment. Neoadjuvant chemotherapy is suggested for down-staying of the disease, but not for it's completely cure [9].

5.6. Endometrial Stromal Sarcoma

5.6.1. Stage I and II: Therapy of stages I and II include surgical treatment: hysterectomy and bilateral salpingo-oophorectomy.

Followed therapy is not standard, there women should stay dispensarised by oncogynecologist or can be treated by hormonal supplementation to decrease the risk of tumor disease recurrence. Low-grade sarcomas and endometrial stromal sarcomas which express hormonal receptors have usually good reaction on post-operative hormonal therapy. Mostly used hormonal preparates are progestins or aromatase-inhibitors [10].

Post-operative radiotherapy didn't show higher survival rates but showed decrease percentage of local recurrence in endometrial stromal sarcomas [11].

5.6.2. Stage III: Following hysterectomy and bilateral salpingo-oophorectomy there is suggested also lymp node dissection, or partial vaginal resection in case that the tumor disease had spreach to vagina in stage IIIb. In these patients there should be hormonal therapy or/and radiotherapy or combination of hormonal and radiotherapy [12].

5.6.3. Stage IV: In stage IVA should be besides standard gynecological surgical intervention also included surgical removal of affected distant tissue [urinary bladder, rectum] followed by radiotherapy or radiotherapy with combination of chemotherapy [11].

5.7. Recurrent Uterine Sarcomas

In case of recurrence of tumor disease we have to differentiate between local or distant recurrence when the tumor occurs again but in different regions such as liver or lungs. Unfortunately the uterine sarcomas have showed the habit of recurrence in first years after primary treatment. The choice of treatment is identical as in stage IV of primary tumors. In case of possibility of removing the tumor lesion the surgical intervention is strongly suggested. There is suggested radiotherapy to down-stage of the tumor and releasing symptoms of disease recurrence [13].

5.8. Carcinosarcomas

In carcinosarcomas there is a crucial role of their metastasis to lymph node system. Therefor not only hysterectomy and adnexectomy, but also pelvic and paraaortal dissection, lymphonodectomy, omentectomy, peritoneal excision and lovage of abdominal cavity, debulcisation of tumor and secondary lesions is recommended.

In carinosaroomas there is shown higher survival rate after applying adjuvant chemotherapy and therefore it is considered as standard treatment. In mono therapy there is the most effective use of Ifosfamid [14].

6. Conclusion

Despite of increasing occurrence of uterine sarcomas there is not enough information in literature and group studies include little number of women which leads to non-unity and controversies about treatment approaches and guidelines.

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