

Radiotherapy in uterine sarcoma: a narrative review of international guidelines

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Background and Objective: Uterine sarcomas (US) are a rare heterogeneous disease and their management is controversial, probably due to lack of strong evidence. The aim of this review was to summarize the available international guidelines on radiotherapy (RT) of uterine sarcoma.

Methods: In this review we collected all available international clinical practice guidelines and consensus conference from PubMed database and other medical oncology societies. Analyzing the included documents, we collected, for each of them, indications for primary, adjuvant, and neoadjuvant treatment, based on the histological subtype.

Key Content and Findings: In total four international guidelines on RT in uterine sarcoma were identified. Surgery is considered as the first approach in early stages uterine sarcoma. Lymphadenectomy is suggested in carcinosarcoma and, for the other subtypes, only if enlarged nodes are observed. In advanced or metastatic US, the first approach is systemic treatment. In primary therapy, all guidelines exclude RT. Considering adjuvant therapy, in no histological type there are uniform indications among the different guidelines regarding RT. The use of neoadjuvant therapy, based on RT or systemic therapies, is not considered by any guideline.

Conclusions: Therefore, the results of our analysis show clear uncertainty about the role of RT in uterine sarcoma. Further trials are needed to define the best treatment for each patient, mainly in high-risk local relapse patients where RT increases local control but benefit on survival is uncertain.

Keywords: Uterine sarcomas (US); radiotherapy (RT); clinical guidelines; carcinosarcoma

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Introduction

Uterine sarcomas (US) are rare and heterogeneous malignant mesenchymal tumors. They account for 3% to 7% of uterine cancers. The annual incidence is almost

2 cases/100,000 inhabitants and the age at diagnosis ranges between 50 and 70 years (1,2).

Main histotypes include: leiomyosarcoma (LM), low-grade endometrial stromal sarcoma (LG-ESS), high-

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grade endometrial stromal sarcoma (HG-ESS) and undifferentiated endometrial sarcoma (UES) according to last WHO classification (3). Carcinosarcomas (CS) were categorized as US until 2000s but now they are included in high-grade epithelial tumors, being that they contain a malignant epithelial component (4). Nevertheless, we included them in this review because they are still included in many retrospective studies on US and in some guidelines, together with the other subtypes.

The diagnosis of US is often made after surgery, even if ultrasound and magnetic resonance imaging (MRI) could give the suspicion of mesenchymal malignant tumor, above all in patients with rapidly growing uterine mass. Pathological examination should be performed in centers with established expertise in this field.

LM is the most common US (60%), arising from myometrial muscle, occurring at the median age of 50 years (1,5). LMs are aggressive tumors with dismal prognosis, depending above all on stage (2). LG-ESS represents almost 10% of US and arises from endometrial stroma. It is a slow-growing indolent disease, that usually affects 45–58 years old women (1,6). A prolonged follow up is mandatory because of the risk of long-term recurrences, also after decades. HG-ESS and UES, always originating from endometrial stroma, account for 5% of all US. They have an aggressive behavior and poor prognosis, with a median age at diagnosis among 55 and 60 years (1,7). Most patients present with advanced disease at diagnosis, with 1–2 years median overall survival (OS) (2,7). Lastly, CS are high grade aggressive tumors, typically arising in postmenopausal women, with both malignant epithelial and mesenchymal components. Two third of patients are diagnosed with advanced stage disease (8).

Standard local treatment of US and CS, in patients without metastases, is total hysterectomy with or without bilateral salpingo-oophorectomy (9,10) avoiding laparoscopic morcellation due to the higher risk of recurrence and metastasis (11,12). Systematic lymphadenectomy has not been demonstrated to be useful and therefore is not routinely indicated (1,9,10), except for CS where the risk of nodal involvement is relatively high and an impact on survival has been hypothesized (8). Locally advanced or metastatic disease are usually treated with systemic therapies, such as chemotherapy (CHT) or hormonal therapy (HT) according to the histological type. In this setting, local therapies as surgery or radiotherapy (RT) may have a palliative role.

Neoadjuvant CHT has no evidence to date, and it is only considered in some guidelines with the aim of cytoreduction in locally advanced but potentially resectable disease (1,13).

Adjuvant CHT is always recommended in CS, also in early stages, while in other US it is proposed only in advanced stages or in patients with high-risk features (large tumors or deep myometrial invasion mainly) (1,4,14,15). The more effective drugs are doxorubicin, gemcitabine, docetaxel, ifosfamide, and paclitaxel.

In LG-ESS, and in other US with hormonal receptors expression, HT is suggested after surgery, mainly based on progestogens but also aromatase inhibitors (1,4,13).

In patients with high risk of local relapse (tumor rupture, large tumors or with involvement of cervix, parametria, uterine serosa) RT is suggested after surgery above all in CS, LM, HG-ESS, and UES (4,5,10).

US are a rare heterogeneous disease and their management it is itself heterogeneous, probably due to the lack of strong evidence. In this review we collected all available international clinical practice guidelines and consensus conference about US and CS from PubMed database and other oncological societies, in order to focus on the RT role in all settings. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://gpm.amegroups.com/article/view/10.21037/gpm-20-65/rc>).

Material and methods

We searched for available clinical guidelines about US treatments, without time restrictions, in PubMed database and from other oncological societies. The search strategy in PubMed was: ((uterine sarcoma) OR (uterine carcinosarcoma)) AND (guideline). We decided to also cover guidelines about CS, because some authors included them in US guidelines and many retrospective studies included patients with CS among US. We included international guidelines only if an English version was available.

Two authors independently examined full text of all articles potentially useful in this analysis. In case of disagreements in this selection, a final decision was taken through a discussion with a third author.

Analyzing the included papers, we collected, for each of them, indications for primary, adjuvant and neoadjuvant treatment, divided by histological subtype. If available, we also reported the design of the studies on which the

Table 1 CS guidelines

Guideline [year]	Primary treatment	Adjuvant treatment	Scientific basis (level of evidence)
Gynecologic Cancer InterGroup (GCIG) Consensus [2014]	Localized disease: surgery Advanced/metastatic disease: CHT (ifosfamide-paclitaxel or carboplatin-paclitaxel)	CHT (carboplatin-paclitaxel or cisplatin-ifosfamide); consider RT for LC	Randomized (level 1b) and retrospective (level 3) studies
PDQ [2019]	Stage I–II: surgery Stage III: surgery Stage IV: clinical trials	Pelvic RT; CT with cisplatin and doxorubicin Under clinical evaluation	Prospective non-randomized studies for adjuvant treatments (level 2b)
NCCN [2020]	Surgery	CHT in advanced disease (ifosfamide-Paclitaxel); consider RT	Randomized (level 1b), prospective non-randomized (level 2b), and retrospective (level 3) studies

CS, carcinosarcoma; CHT, chemotherapy; LC, local control; RT, radiotherapy.

Table 2 LM guidelines

Guideline [year]	Primary treatment	Adjuvant treatment	Scientific basis (level of evidence)
Gynecologic Cancer InterGroup (GCIG) Consensus [2014]	Early stages: surgery Advanced stages: surgery if feasible, metastasectomy for selected patients or CHT	Consider RT and CHT case by case	Retrospective (level 3) and randomized (level 1b) studies
ESMO-EURACAN [2018]	Localized disease: surgery Advanced disease: CHT (doxorubicin, dacarbazine, trabectedin and pazopanib)	RT in selected high-risk cases (cervical, parametrial or serosal involvement); CHT is not standard	Prospective uncontrolled (level 2c) and retrospective studies (level 3)
PDQ [2019]	Stage I–II: surgery Stage III: surgery Stage IV: clinical trials	Pelvic RT; CT with cisplatin and doxorubicin Under clinical evaluation	Prospective non-randomized studies for adjuvant treatments (level 2b)
NCCN [2020]	Stage I: surgery Stage II–III: surgery Stage IVA: surgery Stage IVB: consider surgery or palliative RT and CHT	Consider CHT (doxorubicin) and RT in high-risk patients (if large tumor or deep myometrial invasion)	Randomized (level 1b), prospective non-randomized (level 2b), and retrospective (level 3) studies

LM, leiomyosarcoma; CHT, chemotherapy; RT, radiotherapy.

guidelines were based.

Discussion

We performed a review of international guidelines on US treatment, mainly focusing on RT. In total, seven international guidelines were identified (4-9,16). The Gynecologic Cancer InterGroup (GCIG) published four different papers for each different histological US type (6-8,16). CS treatment was described in three international

guidelines (4,5,8), and LM and LG-ESS were included in all of them (4-6,9,16), HG-ESS and UES were included in three guidelines (4,7,9). *Tables 1-4* summarize the indications of guidelines for CS, LM, LG-ESS and HG-ESS/UES, respectively.

CS treatment

Three guidelines described CS treatment (4,5,8) with different indications for early and advanced stages only in

Table 3 LG-ESS guidelines

Guideline [year]	Primary treatment	Adjuvant treatment	Scientific basis (level of evidence)
Gynecologic Cancer InterGroup (GCIg) Consensus [2014]	Early stages: surgery Advanced ore metastatic disease: cytoreductive surgery or HT—consider CHT	HT and consider RT	Case series and retrospective studies (level 3)
ESMO-EURACAN [2018]	Localized disease: surgery Advanced disease: HT or CHT [above all with t(10;17)]	HT	Prospective uncontrolled (level 2c) and retrospective studies (level 3)
PDQ [2019]	Stage I–II: surgery Stage III: surgery Stage IV: clinical trials	Consider pelvic RT and CHT with cisplatin and doxorubicin Under clinical evaluation	Prospective non-randomized studies for adjuvant treatments (level 2b)
NCCN [2020]	Stage I: surgery Stage II–III–IVA: surgery Stage IVB: surgery or palliative RT	HT (aromatase inhibitors preferred) and consider RT	Randomized (level 1b), prospective non-randomized (level 2b), and retrospective (level 3) studies

LG-ESS, low grade-endometrial stromal sarcomas; CHT, chemotherapy; HT, hormonal therapy; RT, radiotherapy.

Table 4 HG-ESS and UES guidelines

Guideline [year]	Primary treatment	Adjuvant treatment	Scientific basis (level of evidence)
Gynecologic Cancer InterGroup (GCIg) Consensus [2014]	Early stages: surgery Advanced stages: surgery if feasible, also on distant metastases	Consider RT and CHT	Retrospective (level 3) and randomized (level 1b) studies
ESMO-EURACAN [2018]	Surgery	Pelvic RT and consider CHT	Prospective uncontrolled (level 2c) and retrospective studies (level 3)
NCCN [2020]	Stage I: surgery Stage II–III: surgery Stage IVA: surgery Stage IVB: surgery and CHT or palliative RT	Consider CHT and RT in high-risk patients (if large tumor or deep myometrial invasion)	Randomized (level 1b), prospective non-randomized (level 2b), and retrospective (level 3) studies

HG-ESS, high-grade endometrial stromal sarcoma; UES, undifferentiated endometrial sarco; CHT, chemotherapy; RT, radiotherapy.

two of them (5,8). The primary treatment is usually total hysterectomy with bilateral salpingo-oophorectomy, pelvic and para aortic nodal dissection, and omentectomy.

There is not a clear consensus on adjuvant therapies but considering the high rate of local recurrences and of distant metastases, all guidelines suggest adjuvant CHT, also in early stages due to the benefit on progression free survival (PFS) and OS, as reported in one phase III trial (17) and one Cochrane metanalysis (18).

RT

RT has to be considered in high-risk local relapse patients (myometrial invasion, advanced stage, lymphadenectomy

not performed), possibly with concomitant or sequential CHT (8).

Palliative RT can improve quality of life in advanced/inoperable disease, and in recurrent or metastatic patients.

LM treatment

All the included guidelines (4,5,9,16) considered LM therapy. Surgery as total hysterectomy with bilateral resection of the adnexa is always the first treatment when feasible based on tumor stage.

Conflicting opinions exist about adjuvant treatments. One guideline suggests CHT in all patients after surgery (5),

others only in selected high-risk patients with advanced stage, micro or macroscopic residual after surgery, morcellation, and high mitotic index (4). Some guidelines did not suggest CHT as standard adjuvant approach (9,16).

RT

Adjuvant RT increases LC but there is no benefit on OS, therefore some guidelines suggested to consider it in high-risk patients with tumor rupture during surgery, residual disease after surgery, higher stages, and cervical/parametrial/serosal involvement (4,9,16).

Palliative RT has to be considered in patients with local relapses or metastases.

LG-ESS treatment

All guidelines (4-6,9) included LG-ESS treatment. The first approach in localized disease remains surgery based on total hysterectomy with bilateral salpingo-oophorectomy. Systematic lymphadenectomy did not demonstrate a benefit in retrospective studies and so it is not routinely recommended, unless enlarged nodes are evident at surgical exploration (6).

For the high rate of hormone receptor positivity in this specific histological subtype, adjuvant treatment is usually based on HT with progestogens, aromatase inhibitors, megestrol acetate, or gonadotropin releasing hormone analogues (GnRH). Adjuvant HT is recommended in all patients in some guidelines (6,9), and from stage II in NCCN guideline (4).

Among LG-ESS there is a subtype with a particular genetic alteration, that is t(10;17), with a more aggressive behavior and an increased risk of metastases. It is usually HT resistant and therefore it is suggested to consider CHT for these patients, particularly in the metastatic setting (9).

RT

In LG-ESS, the incidence of distant metastases is higher compared to the rate of local recurrences, and therefore RT has a minor role in this setting, though some retrospective studies suggested improved LC after RT (6,9). Moreover, the paucity of published data suggest that RT is not offered as a standard adjuvant therapy.

Some guidelines suggest RT in high risk for local relapse patients, mainly those with stage III–IV or with cervical and parametrial involvement (4-6).

Pelvic recurrences or symptomatic patients could be

considered for palliative RT (4).

HG-ESS/UES treatment

These subtypes, that for similarities and brevity we describe together, represent a small percentage of US. Their prognosis is poor, also due to the low response-rate to systemic therapies (2,15). Three international guidelines (4,7,9) presented their treatment.

Surgery is the only treatment that can impact on patients' prognosis (total hysterectomy with bilateral salpingo-oophorectomy). Lymphadenectomy is recommended if clinical or radiological suspected lymph nodes are detected (7).

The poor response also to CHT raises relevant doubts about its prescription, though a phase III study showed a positive trend for OS with undifferentiated sarcomas being only a minor subgroup (19). However, the included guidelines suggest adjuvant CHT for all patients (4,7,9).

RT

Like all poorly differentiated tumors, HG-ESS and UES have high local and distant relapse rates. Therefore, RT can be an option in selected high-risk patients: advanced stage or bulky tumors, positive resection margins and deep myometrial invasion (4).

Palliation remains an important field of application for RT in these patients (4).

Conclusions

Our findings show contradictions between the analyzed guidelines probably explained by the rarity and heterogeneity of these neoplasms. Not all histological types were included by all guidelines. Moreover, some of them focused only on one or few USs but with a more extensive discussion (5-8,16). On the contrary several authors described USs within the more general topic of soft tissue sarcomas or of uterine neoplasms, with obvious lack of details (4,9). RT details were not described in the included guidelines. The lack of homogeneity and sometimes the contradictory statements make it difficult to summarize clear suggestions for the daily practice.

However, trying to summarize, we can propose the following observations. All reviewed guidelines exclude RT from primary treatments, in all histological subtypes. In terms of adjuvant therapy, RT is considered in CS as a primary treatment together with CHT by one guideline (5).

On the contrary, it is considered only as an optional treatment by two other guidelines (4,8). Similarly, in LM, only one guideline (5) considers RT (and CHT) as a treatment option, while the others suggest RT only in selected cases (4,9,16). In LG-ESS, one guideline excludes RT (9) while the other three only suggest to “consider it” (4-6). Finally, in HG-ESS and UES, one guideline (9) proposes RT as adjuvant therapy (\pm CHT), while two other guidelines define RT as optional (4,7).

Although cited by some national guidelines (1,13), none of the analyzed international guidelines include neoadjuvant therapy, whether based on RT or systemic treatments.

Finally, only one guideline (4) considers RT as a therapeutic option in the symptomatic treatment of all “true” US (LM, LG-ESS, HG-ESS and UES).

Despite the role of adjuvant RT is not strongly defined in the reviewed guidelines, some recent studies report positive results. The French Sarcoma Group (20) retrospectively described the effect of adjuvant RT and CHT in HG-ESS and UES patients, with improved OS and DFS, despite the small sample size (39 patients in total, 22 patients treated with RT). Moreover, Malouf *et al.* reported the positive impact of adjuvant RT on OS and PFS in univariate analysis, mainly in locally advanced UES (21).

In summary, in primary therapy, all guidelines exclude RT, regardless of the histological type, both in early and advanced disease, except in those patients where surgery for medical reasons is contraindicated and RT can be taken into account. Considering adjuvant therapy, in no histological type there are uniform indications among the different guidelines regarding RT, moreover, high-risk criteria are not uniformly defined. The use of neoadjuvant therapy, based on RT or systemic therapies, is not considered by any guideline. Surprisingly enough, only one guideline mentions RT as a palliative treatment.

Therefore, the results of our analysis show evident uncertainty about the role of RT in the US. Therefore, there is a clear need for trials evaluating the possible impact of RT in these aggressive tumors. Considering the rarity of these neoplasms, and in particular of some subtypes, randomized studies in this field would require the involvement of several centers. Moreover, as reported also by Ferrandina *et al.* in an Italian recent review (22), treatment of these patients in referral centers is essential considering the rarity of the disease and the heterogeneity of the available evidence to date. Furthermore, based on the difficulties in carrying out randomized trials in rare

diseases such as US, alternative ways of generating scientific evidence in this field should be evaluated. For example, multi-center collaborations with the aim of designing large databases could allow the development of predictive models that can guide the prescription of RT in individual patients with US. Finally, considering the growing role of neoadjuvant therapy in other sarcomas (especially those of the limbs) (23,24), the role of RT should be tested also in this setting.

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