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REVIEW

Management of metastatic retroperitoneal sarcoma: a consensus approach from the Trans-Atlantic Retroperitoneal Sarcoma Working Group (TARPSWG)†

Trans-Atlantic Retroperitoneal Sarcoma Working Group (TARPSWG)*

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Introduction: Retroperitoneal sarcoma (RPS) is a rare disease accounting for 0.1%–0.2% of all malignancies. Management of RPS is complex and requires multidisciplinary, tailored treatment strategies at all stages, but especially in the context of metastatic or multifocal recurrent disease. Due to the rarity and heterogeneity of this family of diseases, the literature to guide management is limited.

Methods: The Trans-Atlantic Retroperitoneal Sarcoma Working Group (TARPSWG) is an international collaboration of sarcoma experts from all disciplines convened in an effort to overcome these limitations. The TARPSWG has compiled the available evidence surrounding metastatic and multifocally recurrent RPS along with expert opinion in an iterative process to generate a consensus document regarding the complex management of this disease. The objective of this document is to guide sarcoma specialists from all disciplines in the diagnosis and treatment of multifocal recurrent or metastatic RPS.

Results: All aspects of patient assessment, diagnostic processes, local and systemic treatments, and palliation are reviewed in this document, and consensus recommendations provided accordingly. Recommendations were guided by available evidence, in conjunction with expert opinion where evidence was lacking.

Conclusions: This consensus document combines the available literature regarding the management of multifocally recurrent or metastatic RPS with the practical expertise of high-volume sarcoma centers from multiple countries. It is designed as a tool for decision making in the complex multidisciplinary management of this condition and is expected to standardize management across centers, thereby ensuring that patients receive the highest quality care.

Key words: sarcoma, retroperitoneal sarcoma, recurrence, metastasis, surgery, chemotherapy, outcome

Introduction

Retroperitoneal sarcomas (RPS) represent a heterogeneous group of rare malignancies with an overall expected incidence of 0.5–1/100 000. Patterns of recurrence vary by histologic subtype, with biologic behavior spanning a broad spectrum from no metastatic potential to a propensity for local recurrence to predominantly distant relapse [1]. Metastatic RPS includes both systemic disease, with lung and liver being the most common sites of distant failure, and multifocal intra-abdominal disease, or

sarcomatosis. Despite multimodal treatment, outcomes for metastatic RPS are poor with median overall survival of 16 months [2] and a dismal 5% 5-year survival [3]. Nonetheless, the possibility of long-term survival or even cure remains. Therefore, each case must be considered individually by a multidisciplinary team of sarcoma specialists in order to tailor an appropriate treatment strategy, taking into account a variety of disease- and patient-specific factors.

The existing literature regarding the multidisciplinary management of RPS is limited by the rarity and heterogeneity of this disease, as well as the evolution in histologic classification over time. Investigation of optimal management strategies in a prospective, randomized fashion is constrained by the low incidence of RPS overall, and the applicability of available data to specific histologic subtypes is unclear. The Trans-Atlantic RPS Working Group (TARPSWG) was established in 2013 in an effort to address these challenges, bringing together high-volume sarcoma centers to generate a combined experience of the multidisciplinary management of RPS and to establish consensus regarding various aspects of the approach to this family of diseases. From an original 8 institutions, membership has now expanded across Europe and North America to 35 institutions and consensus documents have been published concerning the management of primary and locally recurrent RPS [4, 5]. The current work addresses the management of metastatic RPS and represents a collation of published literature and expert opinion. The objective of this document is to guide sarcoma specialists, including surgeons, medical and radiation oncologists, pathologists, and radiologists in the diagnosis and treatment of metastatic RPS. Due to the paucity of high-level evidence in this domain, the management of metastatic RPS is heavily nuanced by the experience and expertise of high-volume sarcoma specialists. For this reason, a consensus document reflecting the current practices and recommendations of these opinion leaders and the evidence underpinning them is of great value. Of note, these recommendations were developed with a unanimous consensus. This is reflected by the level of recommendations, which is often high even in the absence of strong data. The importance of an experienced multidisciplinary team for the treatment of metastatic RPS underscores the need for referral of these patients to specialist centers.

Methods

A comprehensive literature search of the PubMed database was carried out encompassing the topics of metastasectomy, ablative therapies, and systemic therapies for soft tissue sarcoma (STS). On the basis of available evidence, a series of best practice recommendations was generated. The first version of the document was drafted and circulated in advance of the 2016 Connective Tissue Oncology Society Annual Meeting in Lisbon, Portugal where it was discussed at the meeting of the TARPSWG. The document was revised in the following months and the second iteration debated at the 2017 Society of Surgical Oncology Annual Meeting in Seattle, Washington. Once informal consensus was achieved, the final version was circulated for approval by all group members. To further validate the document, the 'Appraisal of Guidelines for Research and Evaluation II instrument' (AGREE II) was employed [6, 7]. The overall scores of the different domains after review by four independent experts are shown in the supplementary Table S1, available at *Annals of Oncology* online.

The recommendations that follow apply to select subtypes of RPS in the metastatic setting (Table 1).

Results

Principles of recommended practice from diagnosis to follow-up are summarized in 43 statements. Each statement has been attributed a level of evidence according to the scale reported in Table 2.

1. Patients with metastatic RPS should be evaluated in specialized sarcoma centers by multidisciplinary teams with expertise and experience in the full range of treatments of this complex and rare family of diseases. If appropriate, care may then be administered at local centers to minimize patient inconvenience. (VA)

Pretreatment assessment

Clinical history and prior treatment. Details regarding the patient's clinical history and treatment(s) of RPS to date should be procured and reviewed, with particular attention to time course and response to therapy.

2. Operative reports from all prior procedures should be obtained and details of resection(s) undertaken to date understood. (VA)

3. If systemic therapy was previously administered, details regarding agent(s), dose (including cumulative dose for anthracyclines), regimen, toxicities, and response to treatment should be ascertained. (VA)

4. If radiotherapy was previously administered, the dose, regimen, volumes, and boundaries of the radiation field should be determined. (VA)

Imaging. Suspected metastases should be characterized using appropriate imaging modalities for the anatomic location(s) in question.

5. Imaging from the time of initial presentation and diagnosis to completion of treatment as well as postoperative baseline, if applicable, should be reviewed. (VB)

6. Computed tomography (CT) is the standard imaging modality for staging of the chest [4, 5, 8]. (IVA)

7. Contrast-enhanced CT of the abdomen and pelvis is the preferred imaging modality for intra-abdominal/retroperitoneal disease [8]. (IVA)

8. If the anatomic relationship of metastases to specific neurovascular structures requires clarification in order to initiate treatment, magnetic resonance imaging (MRI) can be a useful adjunct [9]. (IVB)

9. Suspected liver metastases can be further imaged with triphasic CT, contrast-enhanced MRI, or targeted liver ultrasound if the nature of the liver lesions is in question or if precise

Table 1. Subtypes of retroperitoneal sarcoma included and excluded from consideration in this consensus document

Included	Excluded
Well-differentiated/dedifferentiated liposarcoma (WD/DD LPS)	Ewing sarcoma and EWS-negative small round blue cell sarcoma
Leiomyosarcoma (LMS)	Alveolar/embryonal rhabdomyosarcoma
Solitary fibrous tumor (SFT)	Sarcoma arising from teratoma
Malignant peripheral nerve sheath tumor (MPNST)	Carcinosarcoma
Synovial sarcoma (SS)	Sarcomatoid carcinoma
Undifferentiated pleomorphic sarcoma (UPS)	Clear cell sarcoma and clear cell-like sarcoma of the gastrointestinal tract
	Desmoplastic small round cell sarcoma
	Gastrointestinal stromal tumors (GIST)
	Visceral sarcomas
	Sarcomas arising from the uterus, cervix, prostate, testis, and spermatic cord
	Benign entities, such as fibromatosis and classic angiomyolipoma

Table 2. Level of evidence and grade of recommendation adapted from the Infectious Diseases Society of America–United States Public Health Service Grading System

I	Evidence from at least one large randomized control trial of good methodologic quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodologic quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs,), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

determination of burden of disease is necessary for initiation of treatment (e.g. consideration of resection/local therapies) [10]. (IVB)

10. Additional imaging is recommended only as clinically indicated:

a. Suspected brain and soft tissue metastases are best characterized with MRI. (VA)
b. Suspected bone metastases can be investigated with bone scan or [18]FDG-PET, but routine bone imaging is unnecessary, with the exception of solitary fibrous tumor (SFT) which entails a higher likelihood of bone metastases than other sarcoma subtypes [11]. (VA)
c. [18]FDG-PET may be helpful in differentiating metastatic disease from benign processes if other imaging modalities are equivocal, or to evaluate treatment response [12, 13]. (IVB)

Pathology. 11. Pathology review of the primary tumor should be carried out, including those cases where the original diagnosis was made at a sarcoma center, as variability among institutions and expert sarcoma pathologists is not uncommon. (VA) The diagnosis of histologic subtypes marked by specific chromosomal alterations should be confirmed by molecular genetic testing [14]. (IVA)

12. Lung and liver lesions with a radiographic appearance consistent with metastatic disease in the context of a biopsy-proven primary RPS do not necessarily require tissue diagnosis. However, lesions with radiographic features atypical for STS metastases, in unusual anatomic locations, or those occurring in the context of a known second malignancy or a hereditary syndrome (e.g. Li–Fraumeni) should be sampled before treatment. If ablative therapies [i.e. radiotherapy, radiofrequency ablation (RFA), etc.] are planned where tissue destruction will preclude pathologic diagnosis, biopsy should be considered before initiating treatment. Tissue sampling can also be undertaken for the purposes of enrolment in clinical trials, tissue banking for research, and potential future use for personalizing treatment. (VB)

13. For subcutaneous or soft tissue lesions suspicious for metastases, core needle or open biopsy can be carried out. (VB)

14. Intra-abdominal/retroperitoneal masses in keeping with multifocal recurrence or metastases do not require confirmation with tissue sampling if they are widespread and the pattern and distribution are radiographically consistent with metastases.

However, biopsy should be considered to rule out alternative pathology (e.g. fibromatosis) when the radiographic appearance is less characteristic. Solitary lesions contralateral to the primary site should be confirmed with tissue diagnosis if feasible as these have a broad differential diagnosis (e.g. lymphoma, germ-cell tumor, schwannoma, paraganglioma, gastrointestinal stromal tumor (GIST), metastasis from another primary). (VB)

15. Biopsies of retroperitoneal and abdominal masses should be obtained under image guidance, ideally without transgressing the peritoneal cavity, and should be carried out by expert radiologists with experience in soft tissue neoplasms. (VA)

16. To ensure adequate tissue sampling, a minimum of four large gauge cores (14G–16G) is advised [15]. There is no role for fine-needle aspiration biopsy in initial diagnostic evaluation for connective tissue neoplasms; however, recurrences of known sarcomas can be accurately detected using fine-needle aspiration. (IVA)

Patient evaluation. 17. Patients should be evaluated with respect to the nature and severity of symptoms as well as performance status in order to guide decisions regarding appropriate treatment modalities and sequencing thereof. This should include a comprehensive assessment of comorbidities and conditions affecting candidacy for multimodal treatment (e.g. geriatric comorbidity indices [16]), nutritional and functional status, physiologic sequelae of prior treatment (e.g. cardiomyopathy, impaired kidney function), and pain or other disability resulting from metastatic disease. (IVA)

18. Consideration for metastasectomy must take into account the likelihood of achieving a macroscopically complete resection as well as the number and extent of prior operations and complications thereof in order to estimate operative risk and counsel patients regarding anticipated morbidity. (VA)

19. All newly referred patients and patients with a first presentation of metastatic sarcoma should be presented at a multidisciplinary tumor board with sarcoma specialists from surgical, medical, and radiation oncology, radiology, and pathology. Patients relapsing or progressing after treatment of metastases should be re-reviewed at a multidisciplinary tumor board, as should patients exhibiting a favorable response to treatment who might be eligible for resection. A tailored treatment strategy should be formulated on an individual basis taking into consideration disease biology, patient performance status, likelihood of disease control or symptom relief with eligible treatment modalities and risks thereof, as well as patient preference and goals of care. (VA)

20. Patients with suspected synchronous metastases based on equivocal lesions on imaging should not be precluded from appropriate treatment of their primary tumor, but short-term follow-up imaging should be obtained in an attempt to clarify tumor stage. (VA)

21. Early involvement of palliative care specialists is encouraged for symptom management and coordination of services with a view to maintaining active treatment and supportive care within an outpatient environment for as long as possible[17]. (IA)

22. An understanding of patient goals of care should be established before initiation of therapy. (VB)

Treatment

Local therapies. It is widely believed that the best possibility for long-term survival with metastatic RPS involves complete extirpation of disease, with metastasectomy considered the preferred treatment strategy for resectable oligometastatic disease in appropriately selected patients. In recent years, other local therapies such as RFA and stereotactic body radiotherapy have been shown to achieve similar rates of disease control for hepatic and pulmonary metastases and are thus considered acceptable alternatives [18–28]. Microwave ablation has supplanted RFA as the preferred ablative modality in many centers, based on evidence from other disease sites. These less invasive treatment modalities may offer the benefit of lower complication rates, shortened disruption of systemic treatment, and expanded application to patients deemed unsuitable for major operative intervention. In addition, they can be combined with surgery to achieve complete disease eradication [19, 29, 30]. Although multiple retrospective series demonstrate prolonged survival in patients who have undergone pulmonary or hepatic metastasectomy [18, 30–45] (Tables 3 and 4), there is no level 1 evidence to show that any apparent benefit of either metastasectomy or ablative therapies is due to the treatment itself rather than a consistent selection of patients with favorable disease biology. The available literature is further limited by the inclusion of both bone and soft tissue sarcomas, as well as STS of extremity/trunk and retroperitoneal origins, and in the case of hepatic metastasectomy, by the inclusion of metastatic GIST and visceral sarcomas. Prognostic factors consistently shown to be associated with improved overall survival after metastasectomy include a prolonged disease-free interval between treatment of the primary tumor and detection of metastases, and complete resection of all metastatic disease [26, 30–32, 35–41, 46–49]. Resection of synchronous metastases has not been associated with improved survival and thus metastasectomy is typically restricted to the setting of metachronous disease [48, 50].

23. Following the diagnosis of potentially resectable metastatic disease, a period of observation without any therapy may be considered to establish disease biology, provided the resectability of existing disease is unlikely to be compromised by a planned delay. (VB)

24. Patients being considered for metastasectomy should, in general, meet the following criteria: [51] (IVA)

a. The primary tumor should be completely resected.
b. All metastatic disease should be completely resectable or controllable with local ablative therapies, unless palliative resection is being considered for symptom relief or control of progressing foci.
c. The patient should have a suitable performance status and the planned procedure should entail acceptable anticipated morbidity for the individual patient.

25. Selection of patients with favorable tumor biology requires consideration of prognostic features including: (IVA)

Table 3. Overview of the literature for pulmonary metastasectomy for soft tissue sarcoma

Reference	Institution	*N*	5y OS (%)	Median OS (mo)	Proportion RPS (%)
Roth 1985 [98]	NCI, Bethesda, USA	67	15 (est, for DFI>12 mo)	30 (est, for DFI>12 mo)	N/A
Jablons 1989 [99]	NIH, Bethesda, USA	63	–	–	N/A
Lanza 1991 [100]	MDACC, Houston, USA	24	18.5	22	15
Casson 1992 [52]	MDACC, Houston, USA	65	25.8	25	N/A
Verazin 1992 [40]	RPCI, Buffalo, USA	61	22	21	N/A
Gadd 1993 [101]	MSCKK, New York, USA	135	18	19	0
Mentzer 1993 [102]	BWH, Boston, USA	34	21 (4YS)	26	N/A
Saltzman 1993 [103]	UMH, Minnesota, USA	23	71	–	N/A
Ueda 1993 [104]	Osaka, Japan	23	24.8	–	N/A
Van Geel 1994 [105]	Rotterdam, Netherlands	9	–	–	N/A
Choong 1995 [106]	Mayo clinic, Rochester, USA	214	40	–	0
Van Geel 1996 [38]	Multi-institutional	255	38	–	5.2
Pastorino 1997 [37]	Multi-institutional	1917	31	–	N/A
Billingsley 1999 [39]	MSKCC, New York, USA	138	46 (3YS)	33	N/A (9% of all sarcoma patients in used database)
Weiser 2000 [36]	MSKCC, New York, USA	86 (repeated resections)	36	42.8	N/A
Canter 2007 [35]	MSKCC, New York, USA	138	29 (DSS)	30	N/A
Rehders 2007 [30]	Hamburg, Germany	61	25	33	N/A
Liebl 2007 [107]	Hamburg, Germany	42	40.5	66	N/A
Chen 2009 [108]	Kyoto, Japan	23	43	24 (est)	9
Smith 2009 [34]	RPCI, Buffalo, USA	94	18	16	6
Blackmon 2009 [33]	MDACC, Houston, USA	147	26	35.5	N/A
Stephens 2011 [32]	MDACC, Houston, USA	81 (after chemotherapy)	32	35.5	N/A (44% non-extremity)
Nakamura 2011 [109]	Mie, Japan	45	10.6	N/A	N/A
Casiraghi 2011 [110]	Milan, Italy	80	39	N/A	N/A
Predina 2011 [111]	JKCC, Philadelphia, USA	48	52	20.4 (DFS)	N/A
Hornbech 2011 [112]	Copenhagen, Denmark	32	21.7	25.5	N/A
Kim 2011 [113]	MGH, Boston, USA	62	50.1 (including bone sarcoma)	25 (including bone sarcoma)	N/A
Burt 2011 [31]	BWH, Boston, USA	82	52 (LMS)	70 (LMS)	8.5
Treasure 2012 [114]	Thames Registry, UK	6256	15	N/A	N/A
Schur 2014 [43]	Vienna, Austria	46	32	45.3	19.6 (abdomen/pelvis)
Dossett 2015 [44]	Moffitt Cancer Center, Tampa, USA	120	–	48	N/A
Lin 2015 [41]	UCLA, Los Angeles, USA	108	61 (LMS), 17 (LPS)	35.4	6.5
Chudgar 2017 [45]	MSKCC, New York, USA	539	34%	33.2	12 (RP/abdomen/pelvis)

GISTs and bone sarcomas were excluded when possible.
OS, overall survival; RPS, retroperitoneal sarcoma; N/A, not available.

a. low volume disease [32, 36, 37, 45, 52, 53];
b. disease-free interval of 12 months or longer [32, 35–41, 45, 53, 54];
c. confirmed response to or prolonged stable disease (≥6 months) on systemic therapy [32].

26. Minimally invasive approaches to metastasectomy may be safely undertaken provided both the surgeon and the treating center have appropriate expertise and experience with these techniques [45, 55, 56]. (IVB)

Pulmonary metastases: 27. When considering definitive treatment of pulmonary metastases, the possibility of extrapulmonary metastatic disease should be investigated using CT of the abdomen and either bone scan or [18]FDG-PET [57]. (IVA)

28. In selected patients, the presence of concomitant pulmonary and extrapulmonary metastases is not an absolute contraindication to curative treatment, and occasionally prolonged survival can be achieved with complete extirpation of multiorgan disease [33]. (IVB)

29. Lung function should be optimized in advance of pulmonary metastasectomy. Patients should have preoperative pulmonary function tests before planned extensive resection [58] and should achieve complete smoking cessation at least 3 weeks in advance of pulmonary metastasectomy [42]. (IVA)

Table 4. Overview of the literature for hepatic metastasectomy for soft tissue sarcoma

Reference	Institution	N	5y OS (%)	Median OS (mo)	Proportion RPS (%)
Harrison 1997 [115]	MSKCC, New York, USA	27	26	31	22
Chen 1998 [116]	Johns Hopkins, Baltimore, USA	11	–	39	45
Lang 2000 [117]	Hannover, Germany	26	20 (after R0-resection)	32 (after R0 resection)	19
DeMatteo 2001 [46]	MSKCC, New York, USA	22	30	39	N/A
Ercolani 2005 [118]	Bologna, Italy	10	36	44	N/A
Yedibela 2005 [119]	Erlangen, Germany	15	–	–	N/A
Adam 2006 [120]	Multi-institutional	125	31	32	N/A
Pawlik 2006 [121]	MDACC, Houston, USA	53	27	47	42 (abdomen/RP)
Rehders 2009 [30]	Dusseldorf, Germany	27	49	44	30 (RS/pelvis)
Marudanayagam 2011 [122]	Birmingham, UK	36	31.8	24	5.5
Groeschl 2012 [123]	Multi-institutional (four centers)	98 (excluding GIST)	32	72	N/A
Brudvik 2015 [26]	MDACC, Houston, USA	47 LMS, 50 other subtypes	48.4 LMS 44.9 other subtypes	42.1 LMS 45.5 other subtypes	21 (LMS)

GISTs and bone sarcomas were excluded when possible.
OS, overall survival; RPS, retroperitoneal sarcoma; N/A, not available.

30. Patients with compromised pulmonary function may be candidates for local ablative therapies as these result in less tissue destruction than resection [18, 19, 21, 22, 24, 28]. (IVB)

Hepatic metastases: 31. For patients with large-volume liver metastatic disease and limited extrahepatic disease, liver-directed therapies such as transarterial embolization and transarterial chemoembolization may be considered. The evidence for these techniques in metastatic sarcoma is limited [59, 60], but their documented efficacy in other malignancies has prompted some centers to extrapolate their use to this setting. (IVC)

Intra-abdominal metastases: 32. The role of surgery for multifocal intra-abdominal metastases is limited to palliative intervention as dictated by symptoms (e.g. intestinal obstruction, pain control). Incomplete resection confers no survival benefit and can lead to significant morbidity [5]. (IVB)

33. The role of hyperthermic intraperitoneal chemotherapy in sarcomatosis has been investigated, with no evidence of benefit [2] [61–67]. (IIIB)

Recurrent metastases: 34. Surveillance with imaging every 3–6 months is warranted after resection of metastatic disease, as many patients will develop recurrent metastases and some will be candidates for further local or systemic treatment [68–70]. (IVA)

35. Local ablative therapies should be considered in the treatment of recurrent metastatic disease, taking into account the likelihood of disease control and the anticipated morbidity of these modalities compared with repeat resection. (VB)

36. Repeated metastasectomy for recurrent metastatic disease may be appropriate in patients with evidence of favorable tumor biology (Figure 1). High-grade histology, high tumor volume, and short disease-free interval (i.e. <1 year) are associated with poor outcomes after re-resection and should discourage further surgery [31, 36]. (IVB)

Palliation: 37. Radiotherapy can be used for palliation of symptoms, in particular for pain, dyspnea due to post-obstructive atelectasis or pneumonia, and symptoms of spinal compression. (VA)

Systemic therapy. Systemic therapy is the preferred first-line approach in patients presenting with synchronous primary and metastatic disease or when complete extirpation of metastatic disease is not possible with surgery or other local techniques [71–73]. In the event of a favorable response to systemic therapy, defined as either clear regression or stable disease over 6 months, these patients may eventually be considered for resection (Figure 2). First-line systemic therapy may also be considered in patients with resectable metastatic disease in order to observe disease biology and determine appropriateness of aggressive local therapy. In the setting of clearly unresectable metastatic disease, the goal of systemic treatment should be maximal prolongation of an acceptable quality of life, balancing the potential benefits of systemic treatment against expected toxicity.

Although the evidence for individual histologic subtypes is limited, a number of prospective, randomized trials are available to guide treatment [74] (Table 5). Additional potential therapeutic agents are currently under investigation in pre-clinical and early clinical trials. The following recommendations are based on currently approved therapies for metastatic sarcoma, often guided by histologies and molecular alterations.

38. For patients with indolent or limited disease, an active surveillance policy can be adopted. (VB)

39. Given the poor outcomes and limited options available to patients with metastatic RPS, inclusion in clinical trials is encouraged. Referral to appropriate academic centers for this purpose is recommended. (VA)

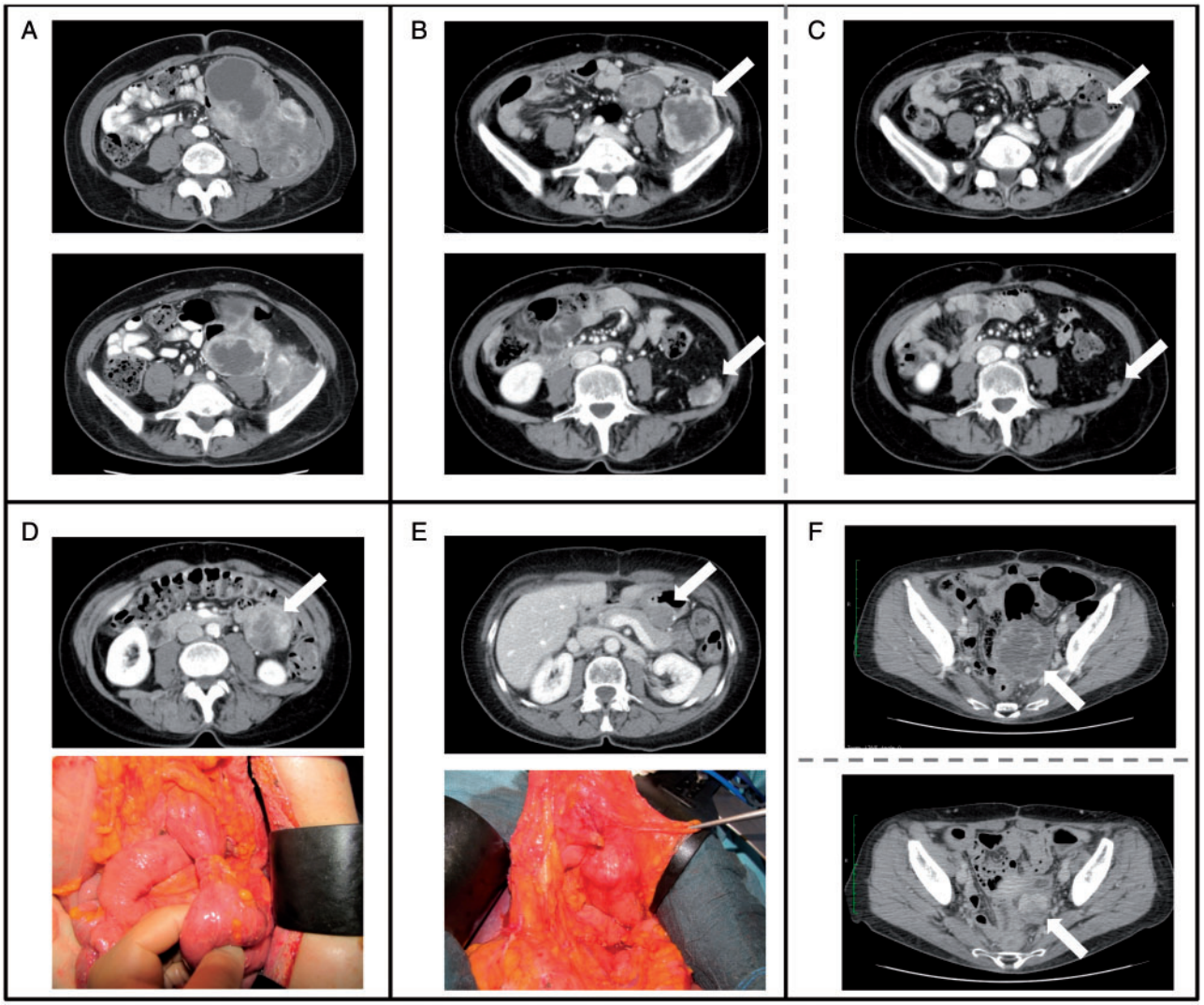

Figure 1. A 59 year-old patient presented with a recurrent multifocal grade 3 dedifferentiated liposarcoma originating from the left retroperitoneum (B). The primary tumor (A) had been resected 6 months prior in a peripheral hospital with microscopically positive margins. At recurrence (B), the patient presented with ipsilateral retroperitoneal nodules (arrows), the largest in the iliac muscle, and limited intraperitoneal nodules (maximum diameter 3cm). She was treated with epirubicine + ifosfamide (5 cycles) with major response (C) at all tumor sites. She then underwent complete surgical resection of multiple peritoneal nodules, en bloc with a 20cm tract of small bowel, and the left retroperitoneal masses. After surgery, two additional cycles of epirubicine and ifosfamide were administered. Twenty months later the patient was diagnosed with a second intraperitoneal recurrence (D). She was treated with 6 cycles of high-dose ifosfamide with dimensional response and then with surgery (D). The single abdominal nodule was resected en bloc with a small bowel loop and a small wedge of stomach. One year later (E) she developed a third recurrence on the stomach that was treated with surgery (partial gastrectomy). Four months later the patient developed a pelvic recurrence that was treated with high-dose ifosfamide for 2 cycles with progression (F, upper figure), then with Trabectedin for 6 cycles with dimensional response (F, lower figure) and then with surgery (excision of the pevic mass en bloc with sigmoid colon, uterus and adnexa). The patient died two years later due to other causes. Arrows, tumor; Dotted line, pre/post-operative imaging; Continuous line, oncological event.

40. For first-line systemic treatment in the palliative setting, an anthracycline-based regimen (doxorubicin or epirubicin) either alone or in combination is recommended [75–79]. (IA) The combination of doxorubicin and olaratumab was shown to be superior in a randomized phase II trial and should be considered for patients with doxorubicin-sensitive histologies [80]. (IIB)

41. If the goal of treatment is tumor downsizing, either for symptomatic relief or possible resection, a combination of doxorubicin with other agents, including high-dose ifosfamide or dacarbazine (DTIC), can be considered [75, 76, 81]. (IA) The combination of doxorubicin and DTIC is preferred in leiomyosarcoma (LMS) and SFT, as ifosfamide may have limited activity in these subtypes [82, 83]. (VA)

42. A multicenter trial randomizing patients with metastatic STS to receive either doxorubicin or gemcitabine/docetaxel in the first-line setting has reported equivalent efficacy but more toxicity with the combination [79]. (IA)

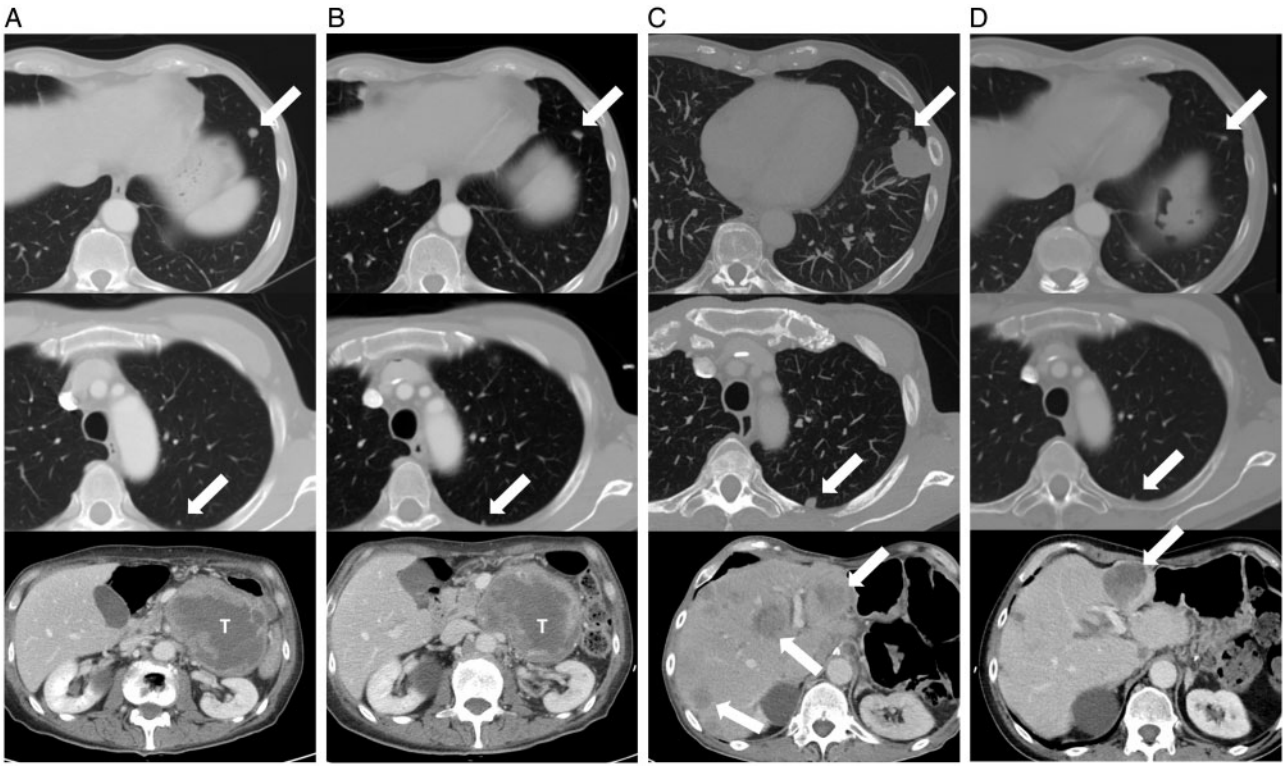

Figure 2. A 66 year-old patient presented with a primary localized 10cm grade 2 leiomyosarcoma of the left retroperitoneum and was scheduled for surgery. Preoperative triphasic CT scan (A) performed one month after initial imaging revealed two synchronous pulmonary metastases (12mm in the left lower lobe and 4mm in the left upper lobe, arrows) and progression of the abdominal mass (10cm to 12cm, T). The patient was treated with upfront Adriamycin + Dacarbazine (DTIC). After two courses the abdominal mass and major lung nodule were stable while the minor lung nodule showed mild progression (4mm to 6mm). The chemotherapy regimen was altered to Gemcitabine 900 mg/m^2 + DTIC 750 mg/m^2 and after 5 courses the CT scan (B) showed partial response of the lung nodules (12mm to 8mm, 6mm to 3mm, arrows) and stable disease of the primary tumor. The patient then underwent resection of the primary tumor en bloc with the pancreatic tail, spleen, duodenojejunal flexure and part of the portal vein. Two months after surgery the CT scan (C) showed dimensional and numerical progression of the lung nodules and appearance of bilateral liver metastases. Gemcitabine + Vinorelbine were started with major response in the lungs and partial response in the liver. Eighteen months after the first course of Gemcitabine (D) the lung disease burden was limited and, due to the progression of a single liver nodule, the patient was treated with transarterial chemoembolization with Adriamycin. Twenty-seven months after disease onset the patient is alive with limited disease in the lungs and stable liver metastases.

43. There is no clear agent of choice for second-, third- and higher-line treatment, or in the event that anthracycline-based therapy is contraindicated, but the following agents can be considered based on histologic subtype:

a. Single-agent ifosfamide can be used for selected subtypes [84]. An infusional schedule of ifosfamide (1 g/m^2 for 14 days followed by 14 days off) may be particularly effective for dedifferentiated liposarcoma (LPS), synovial sarcoma, and malignant peripheral nerve sheath tumor [85]. For synovial sarcoma in particular, high-dose (>10 g/m^2) ifosfamide can be effective [86]. (IB)
b. Trabectedin can be considered in sensitive histologies, such as LMS and LPS [87, 88]. (IB)
c. Eribulin has been shown to confer a survival advantage over treatment with DTIC in advanced pre-treated liposarcoma [89]. (IB)
d. For non-LPS, pazopanib can be considered based on the results of a randomized placebo-controlled trial in pre-treated STS [90]. (IB)
e. Gemcitabine can be used alone or in combination with docetaxel or DTIC for all subtypes, but especially LMS and undifferentiated pleomorphic sarcoma [79, 91–94]. (IB)
f. DTIC can be used alone or in combination with anthracyclines for LMS and SFT [72, 92, 95]. (IB)
g. Antiangiogenics, such as sunitinib, pazopanib, or temozolomide, can be considered for SFT [95]. (IVB)
h. Sirolimus and other mTOR inhibitors can be considered in PEComa [96]. (VB)
i. Crizotinib and other ALK inhibitors can be considered for inflammatory myofibroblastic tumor, although they are not yet approved for this application [97]. (VB)

Table 5. Randomized trials investigating the use of systemic therapy in the treatment of locally advanced or metastatic soft tissue sarcoma

Trial	Study design	*N*	Objective response rate	Progression-free survival	Overall Survival	Conclusions
Maki 2007 [92]	Phase II: Gemcitabine + docetaxel versus gemcitabine	122	16% versus 8%	6.2 versus 3 mo	18 versus 12 mo	Combination superior but has increased toxicity (prohibitive of long-term use)
Lorigan 2007 [84]	Phase III: Two investigational schedules of ifosfamide versus doxorubicin	326	8.4% versus 5.5% versus 11.8% NS	3.0 versus 2.16 versus 2.52 NS	10.92 versus 10.92 versus 12.0 NS	Increased toxicity with ifosfamide with no benefit over doxorubicin alone
Garcia-Del-Muro 2011 [94]	Phase II: Gemcitabine + dacarbazine versus gemcitabine	113	49% versus 25% *P*=0.009	4.2 versus 2 mo *P*=0.005	16.8 versus 8.2 mo *P*=0.014	Combination superior and well tolerated, no increased toxicity
PALETTE van der Graaf 2012 [90]	Phase III: Pazopanib versus placebo in non-adipocytic STS	369	6% versus 0%	4.6 versus 1.6 mo *P*<0.0001	12.5 versus 10.7 mo *P*=0.25	Superior disease control with pazopanib, acceptable toxicity
TAXOGEM Pautier 2012 [93]	Phase II: Gemcitabine + docetaxel versus gemcitabine in LMS	44 (non-uterine LMS only)	5% versus 14%	3.4 versus 6.3 mo NS	13 versus 15 NS	Increased toxicity with combination with no difference in disease control
EORTC 62012 Judson 2014 [81]	Phase III: Doxorubicin + ifosfamide versus doxorubicin	455	26% versus 14% *P*<0.0006	7.4 versus 4.6 mo *P*=0.03	14.3 versus 12.8 mo *P*=0.076	No benefit to combination for palliation of advanced STS unless the goal of treatment is tumor shrinkage
GeDDiS Seddon 2015 [79]	Phase III: Gemcitabine + docetaxel versus doxorubicin	257	N/A	5.5 versus 5.4 mo *P*=0.07	14.5 versus 16.4 mo *P*=0.67	Increased toxicity with combination with no difference in disease control
Demetri 2016 [87]	Phase III: Trabectedin versus dacarbazine in LPS and LMS	518	9.9% versus 6.9% *P*=0.33	4.2 versus 1.5 mo*P* <0.0001	12.4 versus 12.9 mo *P*=0.37	Superior disease control with trabectedin. Led to FDA approval
Ryan 2016 [77]	Phase III: Doxorubicin + palifosfamide versus doxorubicin	447	28.3% versus 19.9%	6.0 versus 5.2 mo*P*=0.19	15.9 versus 16.9 mo *P*=0.74	Increased toxicity with combination with no difference in disease control
Tap 2016 [80]	Phase II: Doxorubicin + olaratumab versus doxorubicin	133	18.2% versus 11.9% *P*=0.3421	6.6 versus 4.1 mo *P*=0.06	26.5 versus 14.7 mo *P*=0.0003	Highly significant 11.8-mo survival benefit with olaratumab
Schoffski 2016 [89]	Phase III: Eribulin versus dacarbazine in LPS and LMS	452	4% versus 5% *P*=0.62	2.6 versus 2.6 mo *P*=0.229	13.5 versus 11.5 mo *P*=0.0169	Survival benefit with eribulin in LPS and LMS

STS, soft tissue sarcoma; LPS, liposarcoma; LMS, leiomyosarcoma; NS, not significant; mo, months.

Conclusions

The probability of cure in the context of metastatic RPS is low, but long-term survival has been achieved with metastasectomy in carefully selected patients, often as part of a multimodal treatment strategy. The literature surrounding the management of metastatic RPS is limited in multiple respects. Although level 1 evidence exists for the selection of systemic therapies, and does suggest a limited survival benefit, these trials include sarcomas arising from a variety of primary sites as well as multiple histologic subtypes with widely variable tumor biology. The data in support of metastasectomy consist largely of retrospective, single-institution case series with relatively small numbers, and these are similarly limited in their generalizability due to inclusion of multiple histologic subtypes and anatomic sites of origin. Published reports for local therapies such as RFA and stereotactic body radiotherapy in the treatment of oligometastatic disease demonstrate good efficacy; however, literature with respect to

RPS is scant and further work is needed to clarify the role of non-surgical local management.

This consensus document is intended to add to the limited available literature the practical expertise of multiple high-volume sarcoma centers and to serve as a tool for decision making in the complex, multidisciplinary management of this family of diseases. Implementation of the recommendations contained herein may be limited by lack of approval or availability of the described treatment modalities in certain jurisdictions or centers. Referral to specialist centers is strongly encouraged to ensure that patients have access to the full armamentarium of therapeutic options, including experimental therapies.

A prospective registry has been established to improve the quality of evidence going forward and to afford a better understanding of metastatic RPS in order to optimize the complementarity of survival and quality of life. This registry may also allow for investigation of adherence to the recommendations put forth here.

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