Original Article

Defining the Role of Neoadjuvant Systemic Therapy in High-Risk Retroperitoneal Sarcoma: A Multi-Institutional Study From the Transatlantic Australasian Retroperitoneal Sarcoma Working Group

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BACKGROUND: In patients with retroperitoneal sarcoma (RPS), the incidence of recurrence after surgery remains high. Novel treatment approaches are needed. This retrospective study evaluated patients with primary, high-risk RPS who received neoadjuvant systemic therapy followed by surgery to 1) determine the frequency and potential predictors of radiologic tumor responses and 2) assess clinical outcomes. **METHODS:** Clinicopathologic data were collected for eligible patients treated at 13 sarcoma referral centers from 2008 to 2018. Univariable and multivariable logistic models were performed to assess the association between clinical predictors and response. Overall survival (OS) and crude cumulative incidences of local recurrence and distant metastasis were compared. **RESULTS:** Data on 158 patients were analyzed. A median of 3 cycles of neoadjuvant systemic therapy (interquartile range, 2-4 cycles) were given. The regimens were mostly anthracycline based; however, there was significant heterogeneity. No patients demonstrated a complete response, 37 (23%) demonstrated a partial response (PR), 88 (56%) demonstrated stable disease, and 33 (21%) demonstrated progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors, version 1.1. Only a higher number of cycles given was positively associated with PR ($P = .005$). All patients underwent complete resection, regardless of the tumor response. Overall, patients whose tumors demonstrated PD before surgery showed markedly worse OS ($P = .005$). An indication of a better clinical outcome was seen in specific regimens given for grade 3 dedifferentiated liposarcoma and leiomyosarcoma. **CONCLUSIONS:** In patients with high-risk RPS, the response to neoadjuvant systemic therapy is fair overall. Disease progression on therapy may be used to predict survival after surgery. Subtype-specific regimens should be further validated. ***Cancer* 2020;0:1-10**. © *2020 American Cancer Society*.

KEYWORDS: leiomyosarcoma, liposarcoma, neoadjuvant, retroperitoneal sarcoma, systemic therapy.

INTRODUCTION

Retroperitoneal sarcoma (RPS) is a rare malignancy and represents an anatomic subset (20%) of soft-tissue sarcomas (STSs) that develop in the back of the abdomen and adjacent to the kidneys.[1,2] The vast majority of patients with RPS present with localized disease, and surgery is the mainstay of treatment. However, because tumors are frequently massive

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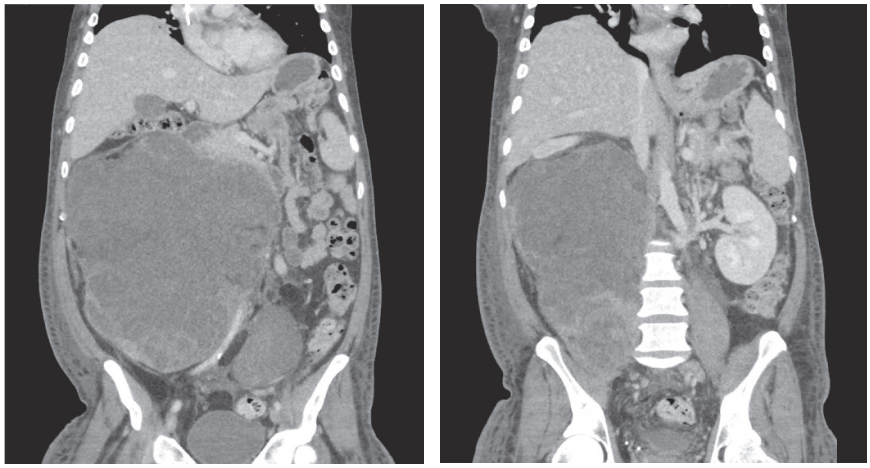

Figure 1. Example of a high-risk retroperitoneal sarcoma.Cross-sectional imaging studies demonstrate potential involvement of multiple organs and critical structures as shown by two representative coronal views. According to preoperative needle biopsy, this was a grade 3 dedifferentiated liposarcoma.

in size and can involve adjacent organs and critical structures (eg, major vessels), complete resection can be challenging. Even at major referral centers, the incidences of 5-year local recurrence (LR) and distant metastasis (DM) after RPS surgery are as high as 30% to 50%.[3,4] Novel treatment approaches are needed.

Similarly to STS arising at other sites, a variety of histologic subtypes exist for RPS, and biological factors alone dramatically affect the patterns of recurrence and clinical outcomes.[3,4] In the retroperitoneum, well-differentiated (WD)/dedifferentiated (DD) liposarcoma and leiomyosarcoma are the most common subtypes. Other subtypes such as undifferentiated pleomorphic sarcoma (UPS), malignant peripheral nerve sheath tumor, and solitary fibrous tumor can also occur.[5] Recognition of the specific subtype in a patient with RPS is important to guide management, including the extent of surgery and consideration of nonsurgical therapies (eg, systemic therapy).[6]

Although there are emerging data on the role of radiation therapy in RPS (eg, the STRASS trial),[7] there is a severe paucity of data for assessing the benefit of systemic therapy. Most published studies have explored systemic therapy in the setting of unresectable and metastatic disease, and they often have included patients with RPS within a large group of patients with STS at other anatomic sites (eg, an extremity).[8] There are clear clinical and likely biological differences based on location, even within the same histologic subtype (eg, WD/DD liposarcoma), that merit study.[9]

Systemic therapy given before surgery (neoadjuvant) has several hypothetical advantages in the management of RPS.[10] For patients who respond to therapy, a decrease in tumor size may facilitate resection and, in exceptional cases, convert an unresectable situation into a resectable one. For RPS patients with high-risk disease, systemic therapy may reduce or eliminate both local and distant microscopic disease, and this could lead to improved clinical outcomes. Because of the frequently challenging nature of RPS surgery and the potential for a prolonged recovery, which may delay or even preclude adjuvant therapy, the neoadjuvant approach seems ideal. In addition, for nephrotoxic regimens, the neoadjuvant approach would be better tolerated before unilateral nephrectomy, which is performed in up to half of patients at the time of surgery.[3,4]

To begin to define the role of neoadjuvant systemic therapy in RPS, we sought to retrospectively evaluate a cohort of patients with primary, high-risk disease (for an example, see Fig. 1) who underwent this approach followed by surgery at a sarcoma referral center. Our primary objectives were to 1) determine the frequency and potential predictors of radiologic tumor responses to therapy and 2) assess the clinical outcomes in these patients. Our secondary objectives were to explore differences in these data based on histologic subtype and the systemic therapy regimen given. Overall, this work was intended to help to guide daily practice and optimize the design of a planned prospective, randomized clinical trial (STRASS2).

This study leveraged the multi-institutional resources of the Transatlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG). Established in 2013, TARPSWG is an international collaboration of sarcoma referral centers that treat a high volume of patients

with RPS and have a specific research interest in this rare disease.[11,12] The group has published consensus guidelines for the management of RPS as well as several original research studies (eg, STRASS).[7,13-15]

MATERIALS AND METHODS

Patient Selection

To be eligible for this study, patients were required to have 1) primary RPS, 2) unifocal disease, 3) 1 of 5 histologic subtypes (liposarcoma [WD/DD], leiomyosarcoma, UPS [MDM2-negative], malignant peripheral nerve sheath tumor, or solitary fibrous tumor), and 4) complete resection (R0/R1) after neoadjuvant systemic therapy. Patients with metastatic disease at the time of their initial presentation and those who did not undergo surgery or had incomplete (R2/debulking) resection were excluded. All patients were treated with curative intent.

Clinicopathologic data were retrospectively collected for eligible patients treated at 13 institutions within TARPSWG from 2008 to 2018. Institutional research board approval was obtained at each site. For each patient, the best preoperative objective response to therapy (Response Evaluation Criteria in Solid Tumors, version 1.1 [RECIST 1.1])[16] was reported by each institution. This assessment was made through a comparison of computed tomography (CT) at the initial presentation and subsequent CT(s) before surgery. The final histologic subtype and grade were determined on the basis of a pathology examination of the surgical resection specimen as reported by each institution.

Statistical Analysis

Univariable and multivariable logistic models were performed to assess the associations between demographic, clinical, and pathologic characteristics, including the following: sex (male vs female), age, number of cycles of neoadjuvant systemic therapy, tumor size after neoadjuvant systemic therapy, histologic subtype, neoadjuvant radiotherapy (yes vs no), completion of neoadjuvant systemic therapy (intended course: yes vs no), tumor size at the final pathologic evaluation, anthracycline plus ifosfamide (A + I) treatment in patients with grade 3 DD liposarcoma (yes vs no), anthracycline plus dacarbazine (A + DTIC) treatment in patients with leiomyosarcoma (yes vs no), and radiologic tumor response (RECIST 1.1) combining stable disease (SD) and progressive disease (PD) responses.

Fisher exact tests were performed to assess the association between radiologic tumor response and histologic subtype and A + DTIC treatment in patients with leiomyosarcoma. Other objectives of the study were overall survival (OS) and the crude cumulative incidence (CCI) of LR and DM. Survival and incidence times started from the date of surgery. OS was defined as the time to death due to any cause. The CCI of LR (DM) was estimated in a competing risk setting, and death without recurrence and DM (LR) were considered as competing events. The OS curves were estimated with the Kaplan-Meier method and compared with the log-rank test. The CCI curves, based on cumulative incidence estimates, were compared with the Gray test. The median follow-up was estimated with the reverse Kaplan-Meier method on the basis of OS data.[17] Continuous variables were modeled with 3-knot restricted cubic splines to obtain a flexible fit.[18] Statistical analyses were conducted with SAS (Cary, North Carolina) and R software programs (http://www.r-project.org/).

RESULTS

Patient and Tumor Characteristics

Thirteen centers contributed 162 patients; 4 patients were excluded from the study (3 did not have tumor response data, and 1 had metastatic disease at the time of surgery). In total, 158 patients were included in the study (Table 1). All patients received neoadjuvant systemic therapy (median, 3 cycles; the distribution of cycles given is shown in Fig. 2), and in addition, almost half (73 patients [46%]) also received neoadjuvant radiation therapy. The proportions of histologic subtypes were representative of what is typically encountered in the retroperitoneum, with WD/DD liposarcoma being the most common (54%); it was followed by leiomyosarcoma (32%). Most patients (88%) had intermediate- or high-grade disease. This was also reflected specifically within the liposarcoma subset, in which 71 of the 85 patients (84%) had high-grade (DD) disease.

The systemic therapy regimens are shown in Table 2. Although most (140 of 160 [87.5%]) were anthracycline based, there was significant heterogeneity. Patients with DD liposarcoma and leiomyosarcoma were most commonly given dual combination therapy, although single-agent and other nonstandard combination regimens were also given.

All patients included in this study underwent complete resection after neoadjuvant systemic therapy, regardless of tumor response. In the vast majority of patients (94%), surgery included adjacent organ resection. Postoperative complications of any severity were seen in 57 patients (36.1%); these were graded as major

TABLE 1. Demographic, Clinical, and Pathologic Characteristics (n = 158)

Characteristic	All
Sex, No. (%)	
Female	76 (48.1)
Male	82 (51.9)
Age, median (IQR), y	58.5 (48.0-64.0)
No. of cycles of neoadjuvant systemic therapy, median (IQR)	3 (2-4)
Neoadjuvant radiation therapy, No. (%)	
Yes	73 (46.2)
No	85 (53.8)
Histologic subtype, No. (%)	
DD	71 (44.9)
LMS	50 (31.6)
WD	14 (8.9)
UPS	11 (7.0)
MPNST	6 (3.8)
SFT	6 (3.8)
Tumor size at final pathologist evaluation, median (IQR), cm	17.0 (11.0-25.0)
FNCLCC grade, No. (%)[a]	
1	18 (11.9)
2	56 (37.1)
3	77 (51.0)
Adjacent organ resection, No. (%)[b]	
Yes	145 (93.5)
No	10 (6.5)
Any complications after surgery, No. (%)	
Yes	57 (36.1)
No	101 (63.9)
Major complications after surgery, No. (%)	
Yes	37 (23.4)
No	121 (76.6)
Adjuvant systemic therapy, No. (%)	
Yes	19 (12.0)
No	139 (88.0)
Adjuvant radiation therapy, No. (%)	
Yes	5 (3.2)
No	153 (96.8)

Abbreviations: DD, dedifferentiated liposarcoma; FNCLCC, French Federation of Centers for the Fight Against Cancer; IQR, interquartile range; LMS, leiomyosarcoma; MPNST, malignant peripheral nerve sheath tumor; SFT, solitary fibrous tumor; UPS, undifferentiated pleomorphic sarcoma; WD, well-differentiated liposarcoma.
[a]Seven missing values.
[b]Three missing values.

(Clavien-Dindo grade ≥ 3) in 37 patients (23.4%). Reoperation for surgical complications was required in 14 patients (8.9%). A minority of patients also received further adjuvant systemic (12%) and radiation therapy (3%). Overall, the 90-day mortality incidence was 0%.

Tumor Response to Neoadjuvant Systemic Therapy

For the entire cohort, before surgery, no complete radiographic responses were observed. According to RECIST 1.1 criteria, a partial response (PR) was seen in 37 of the 158 patients (23%), SD was seen in 88 (56%), and PD was seen in 33 (21%). Differences in the proportions of tumor responses were seen according to the histologic subtype (Table 3); for example, a PR was seen in 5 of 11 patients (45%) with UPS ($P = .358$ [Fisher exact test]).

Predictors of Tumor Response

In univariable and multivariable logistic modeling, only a higher number of cycles of neoadjuvant systemic therapy given was positively associated with PR (vs SD/PD; see Supporting Table 1). No other clinicopathologic factors, including the receipt of neoadjuvant radiation therapy ($P = .620$) and histologic subtype ($P = .920$), were predictive of PR.

Clinical Outcomes by Tumor Response

The median follow-up for the entire cohort was 42.5 months (interquartile range, 21.4-82.9 months). When patients were stratified according to tumor response type, those who had PD had significantly worse OS than those with a PR or SD ($P = .005$; Fig. 3). At 5 years, OS was 26% (95% confidence interval [CI], 13%-54%) for patients with PD, 56% (95% CI, 39%-81%) for those with a PR, and 58% (95% CI, 45%-73%) for those with SD. No clear differences in the CCIs of LR and DM were observed according to response type (data not shown).

Subgroup Analyses for DD Liposarcoma and Leiomyosarcoma

Previously published data have demonstrated distinctly worse clinical outcomes (eg, a higher incidence of DM) for grade 3 DD liposarcoma and leiomyosarcoma.[3,19] These 2 subgroups were separately analyzed to investigate the hypothesis that the optimal systemic therapy regimens are A + I for patients with grade 3 DD liposarcoma and A + DTIC for patients with leiomyosarcoma. Patients with grade 3 DD liposarcoma who received A + I and those who received another regimen had similar proportions of PRs (5 of 22 [23%] vs 3 of 12 [25%]; Table 4); conversely, those with leiomyosarcoma who received A + DTIC versus another regimen had a higher proportion of PRs (7 of 19 [37%] vs 5 of 31 [16%]; $P = .170$ [Fisher exact test]). Although it was not statistically significant, we found that an indication of better outcomes was observed particularly for the leiomyosarcoma subgroup when the hypothesized optimal regimens were given (Fig. 4).

DISCUSSION

Surgery is the mainstay of treatment for RPS; however, complete resection can be challenging. Recurrence remains a major issue for these patients, and its extent is affected by both technical factors (eg, surgical) and biological factors (eg, histologic subtype).[1,2] Several

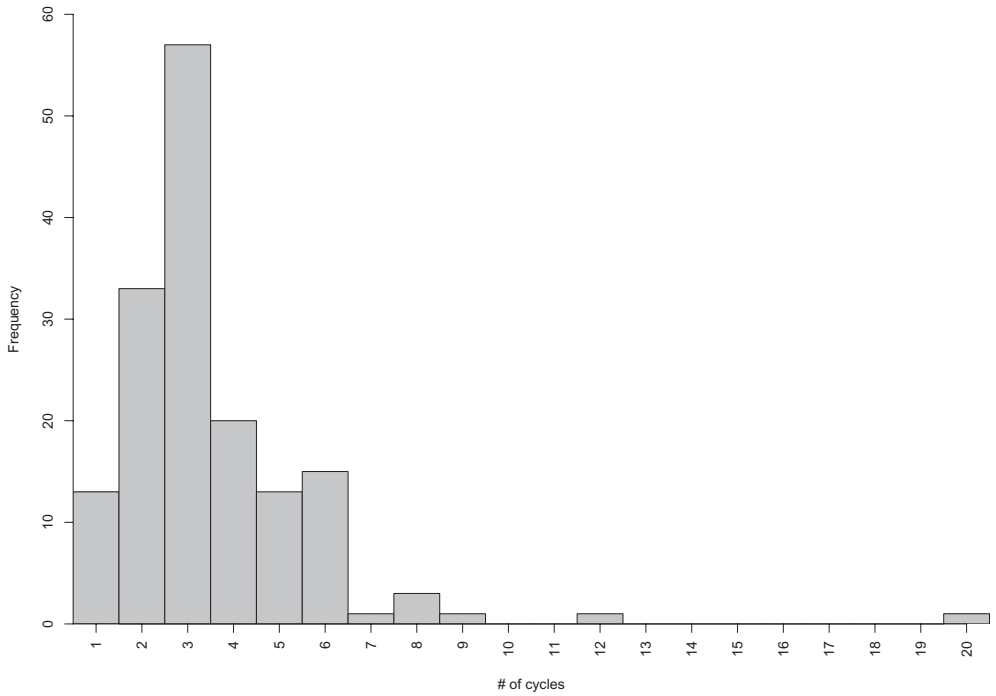

Figure 2. Histogram demonstrating the distribution of the number of cycles of neoadjuvant systemic therapy given.

TABLE 2. Systemic Therapy Regimens by Histologic Subtype

	A + I	A	I	A + DTIC	G + T	Other
DD	49	1	9	3	4	7
LMS	15	2	7	19	3	4
WD	5	2	7	0	0	0
UPS	5	1	2	1	0	2
MPNST	4	0	2	0	0	0
SFT	4	0	1	1	0	0

Abbreviations: A, anthracycline; A + DTIC, anthracycline plus dacarbazine; A + I, anthracycline plus ifosfamide; DD, dedifferentiated liposarcoma; G + T, gemcitabine plus docetaxel; I, ifosfamide; LMS, leiomyosarcoma; MPNST, malignant peripheral nerve sheath tumor; SFT, solitary fibrous tumor; UPS, undifferentiated pleomorphic sarcoma; WD, well-differentiated liposarcoma.

TABLE 3. RECIST 1.1 Tumor Responses by Histologic Subtype

	PR, No. (%)	SD, No. (%)	PD, No. (%)
DD	14 (19.7)	37 (52.1)	20 (28.2)
LMS	12 (24.0)	28 (56.0)	10 (20.0)
WD	3 (21.4)	11 (78.6)	0 (0.0)
UPS	5 (45.5)	5 (45.5)	1 (9.1)
MPNST	1 (16.7)	4 (66.7)	1 (16.7)
SFT	2 (33.3)	3 (50.0)	1 (16.7)

Abbreviations: DD, dedifferentiated liposarcoma; LMS, leiomyosarcoma; MPNST, malignant peripheral nerve sheath tumor; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SD, stable disease; SFT, solitary fibrous tumor; UPS, undifferentiated pleomorphic sarcoma; WD, well-differentiated liposarcoma.

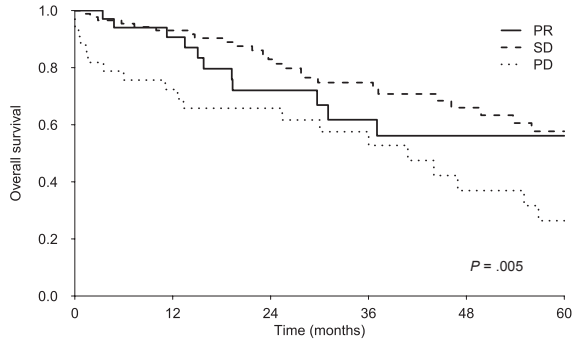

Figure 3. Kaplan-Meier curves of overall survival for patients with retroperitoneal sarcoma according to the radiologic tumor response to neoadjuvant systemic therapy (Response Evaluation Criteria in Solid Tumors, version 1.1). PD indicates progressive disease; PR, partial response; SD, stable disease.

large retrospective studies suggested that radiation therapy may improve local control in RPS.[20,21] This led to the first prospective study (STRASS/European Organization for Research and Treatment of Cancer [EORTC] 62092) in which patients with RPS were randomized to neoadjuvant radiation therapy followed

TABLE 4. RECIST 1.1 Tumor Responses by Regimen

	PR, No. (%)	SD, No. (%)	PD, No. (%)
Grade 3 DD			
A + I	5 (22.7)	10 (45.5)	7 (31.8)
Other	3 (25.0)	7 (58.3)	2 (16.7)
LMS			
A + DTIC	7 (36.8)	10 (52.6)	2 (10.5)
Other	5 (16.1)	18 (58.0)	8 (25.8)

Abbreviations: A + DTIC, anthracycline plus dacarbazine; A + I, anthracycline plus ifosfamide; DD, dedifferentiated liposarcoma; LMS, leiomyosarcoma; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SD, stable disease.

by surgery or surgery alone.[7] The results of this large, multicenter, phase 3 trial, presented in 2019, demonstrated no benefit to surgery with the addition of radiation therapy: the 3-year LR-free survival rates were equivalent in the 2 groups (60.4% vs 58.7%; $P = .954$). Patients who received neoadjuvant systemic therapy were excluded from the STRASS trial.

Although there are several hypothetical advantages to neoadjuvant systemic therapy in the management of RPS,[10] to date, there is a severe paucity of adequate data to assess its potential benefit for these patients. Previously, single-institution series from sarcoma referral centers have had at most 73 patients who received neoadjuvant systemic therapy before curative-intent resection for RPS.[4] In that study, these patients represented only 11% of the entire cohort, and this highlights the fact that this approach is not routinely used at some centers. The multicenter EORTC 62961 trial compared neoadjuvant chemotherapy plus hyperthermia with chemotherapy alone and enrolled 149 patients with retroperitoneal and abdominal sarcoma; however, 44.3% of the patients had "other sarcomas" not commonly seen in the retroperitoneum, and a minority of the patients included (10.7%) had recurrent disease.[22] Another study used the US National Cancer Database to try to assess the benefit of systemic therapy (chemotherapy) in RPS; it included 163 patients who were treated in the neoadjuvant setting.[23] The study concluded that chemotherapy does not confer a survival benefit and, in fact, discouraged routine use for RPS. This analysis, however, included both patients with primary and recurrent disease, those who underwent incomplete resection (R2/debulking) and those with a variety of histologic subtypes which are not as relevant in the retroperitoneum, including 33% with an "unspecified" sarcoma. Most importantly, in this study, it is unclear whether these patients were evaluated and managed at sarcoma referral centers, which would include multidisciplinary discussion and evaluation by an experienced sarcoma surgeon, a medical oncologist, and a radiation oncologist. This is critical for optimizing outcomes in RPS and ideal for research purposes, especially in patients with this rare disease.[24,25]

The current study of neoadjuvant systemic therapy is one of the largest series to date of patients treated at 13 sarcoma referral centers within a dedicated RPS working group (TARPSWG). The enrolled patients all met strict inclusion criteria, which included primary (not recurrent) disease and a diagnosis of 1 of 5 specific histologic subtypes representative of what is commonly seen at this anatomic site. Our study for the first time, to our knowledge, has specifically examined RPS tumor responses to neoadjuvant systemic therapy in general and according to histologic subtype and regimen given. The intent of our work was to begin to define the role of neoadjuvant systemic therapy in RPS to help to guide daily practice and to use these retrospective data to optimize the design of a planned prospective clinical trial (STRASS2).

Our findings show that neoadjuvant systemic therapy can result in a radiographic tumor response in almost a quarter of patients with RPS (PR proportion, 23%). The majority of patients (79%), in fact, can experience a clinical benefit (PR + SD) with this approach. Therefore, our results suggest that in clinical practice, neoadjuvant systemic therapy may be helpful in the management of RPS. Specifically, the clinicopathologic data (Table 1) highlight the high-risk nature of our cohort of patients, with an anticipated increased risk for local and/or distant recurrence. The vast majority had intermediate- to high-grade tumors and underwent aggressive surgery that in almost all cases (94%) required adjacent organ resection. It is these patients with RPS who are deemed to be high risk by multidisciplinary discussion that are most likely to benefit from neoadjuvant systemic therapy. Importantly, disease progression (PD) on therapy was observed in 21% of the study patients who still underwent complete resection, and this suggests that surgery is possible in this situation during neoadjuvant systemic therapy. This interpretation should be cautioned, however, by the fact that we did not evaluate patients who received neoadjuvant systemic therapy and then did not undergo resection. In daily practice, the decision making to initiate and continue with neoadjuvant systemic therapy should be multidisciplinary with continual input from the surgical oncologist to assess for the risk of unresectability with PD.

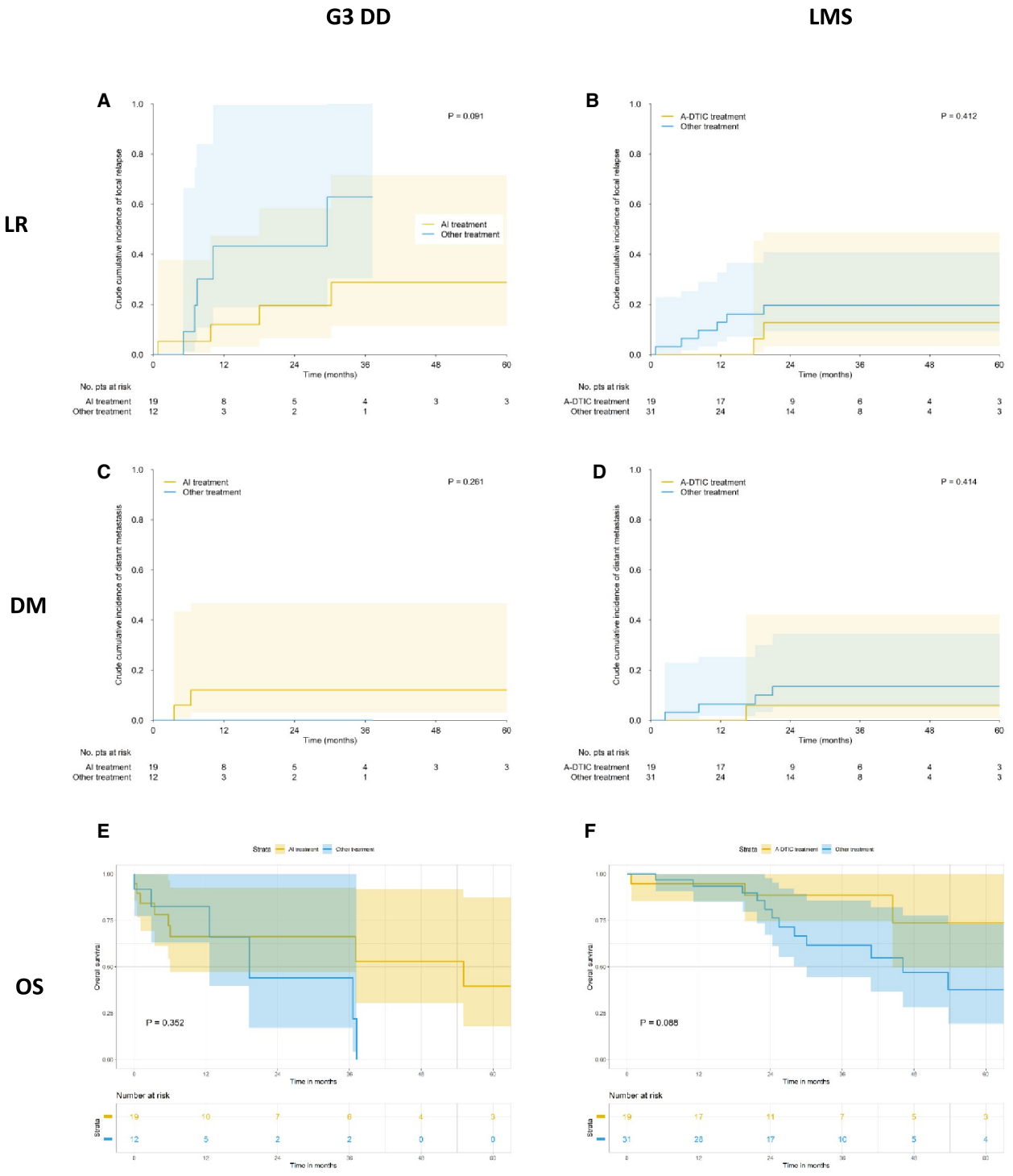

Figure 4. Crude cumulative incidence curves of (A,B) local recurrence and (C, D) distant metastasis and (E, F) Kaplan-Meier curves of overall survival for patients with (Left Column) grade 3 dedifferentiated liposarcoma or (Right Column) leiomyosarcoma according to the treatment received (AI, A-DTIC, or other). Shaded regions represent the 95% confidence intervals. A-DTIC indicates anthracycline plus dacarbazine; AI, anthracycline plus ifosfamide; DM, distant metastasis; G3 DD, grade 3 dedifferentiated liposarcoma; LMS, leiomyosarcoma; LR, local recurrence; OS, overall survival.

In our analysis for predictors of response (Supporting Table 1), only a higher number of cycles of neoadjuvant systemic therapy given was positively associated with PR. This is likely due to the fact that patients with an initial PR would continue therapy to achieve the maximal response, whereas those with PD, in contrast, would discontinue therapy and proceed to surgery. In support of this, a post hoc analysis showed that the median number of cycles by tumor response group was 4, 3, and 2 for PR, SD, and PD, respectively. No other factors were predictive of PR, including the receipt of neoadjuvant radiation therapy, which did not appear to augment tumor response. Differences in tumor response were seen according to histologic subtype (Table 3), including a higher proportion of tumor response (46%) in undifferentiated pleomorphic sarcoma (UPS, n = 11) which deserves further investigation. This specific finding is consistent with published data supporting the benefit of systemic therapy in UPS at all anatomic locations.[8] Overall, however, histologic subtype was not found to be predictive of PR in our study.

Although we could not identify any factors predictive of a response to neoadjuvant systemic therapy, the type of response itself is important and appears to predict survival after surgery (Fig. 3). Specifically, it is notable that patients whose tumors demonstrated PD had an almost 2-fold worse 5-year OS rate of 26% in comparison with those with a PR or SD (56%-58%). For comparison, the 5-year survival probability for all patients with RPS from previously published series ranges from 67% to 69%.[3,4] The clearly worse clinical outcome for these RPS patients with PD despite complete resection is likely a reflection of aggressive disease biology, and such patients should be counseled regarding their prognosis. It remains to be determined whether in these patients there may be a benefit to trying a second-line systemic therapy regimen in an attempt to achieve a PR or SD before surgery or in the adjuvant setting after surgery. In daily practice, this again requires input from the surgical oncologist to assess the immediate need for surgery in a patient with PD. Importantly, equivalent survival was seen in our study patients with tumors that demonstrated a PR and in those with SD. It is not known whether patients with SD (eg, after 2 consecutive CT scans) derive additional benefit from continued therapy in an attempt to achieve a PR. Continuing therapy after SD also carries the danger of progression to unresectability.

The optimal regimen or regimens of systemic therapy in RPS need to be defined; however, there are very little data in the published literature in this regard.[26] Consistent with this, in our study, there was notable heterogeneity in the regimens used according to histologic subtype (Table 2). For liposarcoma, combination therapy with an anthracycline (eg, doxorubicin) plus ifosfamide (A + I) is commonly given as first-line therapy: the tumor response rate specifically for retroperitoneal disease has been reported to vary from 0% for WD disease to up to 21% for DD disease.[27,28] In our study, the response proportion for this regimen in DD was similar (PR = 23%, Table 5). For leiomyosarcoma, a recent multicenter study suggests that combination therapy with doxorubicin and dacarbazine (A + DTIC) may be the most effective regimen as first-line therapy.[29] The authors reported a tumor response rate of 31% to A + DTIC in all patients, 34% of whom had retroperitoneal disease. In the current study, we found that the PR rate for patients with leiomyosarcoma who received this regimen was also similar (37%). To further test the hypothesis that the A + I and A + DTIC regimens are optimal for DD liposarcoma (specifically grade 3) and leiomyosarcoma, respectively, we performed subgroup analyses of outcomes in comparison with patients with these subtypes who received other regimens. Although limited by low numbers, our results (Fig. 4) do support the need for continued investigation (eg, in a prospective trial). Notably, the proportion of leiomyosarcoma patients with disease progression on A + DTIC versus other regimens was also lower (10.5% vs 25.8%; Table 4), suggestive of better activity with this regimen. Although recent data for extremity/truncal soft sarcomas suggests that histology-tailored neoadjuvant systemic therapy regimens may not be superior to A + I,[30] this remains to be determined in RPS.

The current study does have limitations. The retrospective design and relatively low numbers of events, particularly for histologic subtype analyses, conferred limited power to the statistical tests. There was also inherent bias within our collaborative group (TARPSWG) because several sarcoma referral centers did not have any patients to contribute. For these centers, upfront surgery is still considered the preferred approach, even for high-risk RPS. Furthermore, among the 13 centers that did contribute patients to the study cohort, some used neoadjuvant systemic therapy more frequently than others (data not shown). In addition, for the final study cohort, TARPSWG centers contributed a range of 2 to 74 patients (1%-47%; median, 5) per institution, with a preponderance of cases from 1 center (Istituto Nazionale dei Tumori Milano). With the data submitted by participating centers, although we were able to determine the regimens of systemic therapy given (Table 2), we could not capture the rationale(s) for regimen

selection and the inclusion of neoadjuvant radiation therapy (given to 46% of patients) or details such as the sequencing of multimodality therapies. The precise reasons for discontinuation of systemic therapy, which can be multifactorial in daily practice, were also not readily available.

Although retrospective, the current study does help to optimize the design of a planned prospective study of neoadjuvant systemic therapy in RPS (STRASS2), which could answer the most important question of efficacy. Analogous to the STRASS trial[7] (radiation therapy), in STRASS2, patients will be randomized to neoadjuvant systemic therapy followed by surgery versus surgery alone. Patients who receive neoadjuvant radiation therapy will not be included. Importantly, study patients will be limited to DD liposarcoma (grade 3) and leiomyosarcoma, the 2 RPS subtypes previously shown to have a high DM rate.[3,18] Patients will receive A + I or A + DTIC, respectively, in line with the data from our current subgroup analysis. Three cycles of systemic therapy will be given; this is inferred from previous prospective trials of neoadjuvant systemic therapy in extremity/truncal STS[30-32] but is also concordant with the median number of cycles (3) given to patients with RPS in this study. We also observed that the median number of cycles in the PD group was 2; as such, interval imaging (eg, CT) in STRASS2 will performed at this time point as a safety measure before the third cycle is given. Overall, although the tumor response by RECIST criteria will be assessed, the primary endpoint for STRASS2 will be disease-free survival.

In summary, in this series of patients with RPS treated with neoadjuvant systemic therapy over a 10-year time span, PRs were possible in almost a quarter of the cases, whereas most tumors demonstrated SD. Disease progression on systemic therapy was clearly associated with worse outcomes. The current analysis provides data to begin defining the role of neoadjuvant systemic therapy in RPS and help to optimize the design of an upcoming prospective trial. Henceforth, the current study can also serve as a reference for future studies in RPS focused on specific systemic therapies (eg, eribulin and immunotherapy) or those with combination multimodality therapies (eg, systemic and radiation).

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AUTHOR CONTRIBUTIONS

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