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Advances in surgical management of abdominal and retroperitoneal sarcoma: Where do we stand, and where do we go?

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Advances in surgical management of abdominal and retroperitoneal sarcoma: Where do we stand, and where do we go?

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Editorial: Advances in surgical management of abdominal and retroperitoneal sarcoma: where do we stand, and where do we go?

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KEYWORDS

sarcoma, retroperitoneal tumor, abdominal tumor, evidence based medicine (EBM), surgical approach

Editorial on the Research Topic
Advances in surgical management of abdominal and retroperitoneal sarcoma: where do we stand, and where do we go?

The article series on "Advances in Surgical management of abdominal and retroperitoneal sarcoma" describes real-world clinical problems, current challenges, and new management options of sarcomas in these anatomical locations. Examples of real-world clinical problems in the article series are the occurrence of sarcoma types at uncommon locations, and the occurrence of very rare sarcoma types, like primary osteosarcoma of the kidney (Yu et al.), and retroperitoneal undifferentiated pleomorphic sarcoma (Chen et al.). Another frequently-faced problem is a very large tumor-size at presentation. Hence, surgical treatment requires an extensive and major surgical procedure, and sometimes an alternative surgical approach. An example of this in the article series is a thoracotomy for a giant retroperitoneal tumor with diaphragmatic hernia (Hu et al.). In addition, patients happen to present with metastatic disease and new non-surgical treatment options need to be applied. An example of this in the article series is PD-1 inhibitor treatment combined with chemotherapy for metastatic follicular dendritic cell sarcoma of the spleen (Li et al.). Furthermore, a major problem in clinical practice is the very high risk of recurrence after surgical resection of retroperitoneal liposarcoma as reported in two articles in the series (Gao et al., Wang et al.). New treatment strategies are urgently required to reduce the recurrence risk of retroperitoneal sarcomas. These strategies may include more precise surgery, more extensive surgery, (neo)adjuvant chemo and radiation therapy, and other new treatment options. One article in the series reports on the results of preoperative radiotherapy for retroperitoneal liposarcoma, showing that radiotherapy is well-tolerated, though an increase in postoperative blood transfusions and intensive care stay was observed (Jo et al.). However, no effect on local recurrence and survival was observed, which is in accordance with the randomised STRASS-1 trial (1).

The articles series also include systematic reviews on solitary fibrous tumors and leiomyosarcomas (Tolstrup et al., Øines et al.). Prediction of the risk of recurrence in patients with solitary fibrous tumors is a major clinical problem, and proper

identification of risk factors for disease recurrence is of utmost importance and summarized in the systematic review on solitary fibrous tumours (Tolstrup et al.). Especially, high mitotic index, Ki67 index and presence of necrosis in surgically resected solitary fibrous tumor increased the risk of recurrence, while TERT promoter mutation appears to be promising component in future risk stratification models (Tolstrup et al.).

The systematic review on abdominal and retroperitoneal leiomyosarcoma in the article series summarizes all available evidence on treatment and diagnosis of these tumors. Of special interest is that the review points out the importance of genetic subtype classification of leiomyosarcomas, as molecular subtype may be more important for tumor behavior and prognosis than tumor location (e.g., abdomen, retroperitoneal, gynecological, extremities) (Øines et al.).

Our article series illustrate the lack of high-quality evidence for the management of abdominal and retroperitoneal sarcoma. There is a great need for well-designed and well-performed prospective studies with relevant clinical and patient reported outcomes. Abdominal and retroperitoneal sarcomas are rare tumors, and special actions are required to establish firm evidence for these seldom cancer types. High-quality evidence can be achieved by performing international multicenter randomised studies. These studies should aim at reducing the risk of recurrence and increase survival. Recent international multicenter RCTs on the effect of neoadjuvant radiotherapy (STRASS-1, completed and published) and neoadjuvant chemotherapy (STRASS-2, currently recruiting) in patients with retroperitoneal sarcomas are excellent examples of how to establish evidence (1–3). In addition, all patients should be registered in national and international clinical registries.

Furthermore, there is a great need for more projects on molecular subtyping and protein expression of different sarcoma tumor types. This will allow for applying individual target treatment approaches. Personalised medicine in sarcoma patients may improve treatment results, reduce recurrence risk and improve survival. An example of this is molecular subtyping for tyrosine kinase inhibitor treatment in patients with gastrointestinal stromal cell tumors (GIST). Personalised medicine will also mean that we can avoid treatments in patients who have no or limited benefits of the treatment. This will reduce adverse treatment effects and improve quality of life. Identification of proper biomarkers may add further to individual-tailored approaches.

Further progress is needed in application of new surgical modalities in sarcoma surgery. Application of fluorescense-guided surgery, irreversible electroporation (Nanoknife®), and microwave ablation are examples of techniques which should be further investigated in the treatment of abdominal and retroperitoneal sarcomas (4–6). Similar to other surgical fields, the benefits and harms of minimal invasive (robotic, laparoscopic and endoscopic) surgery in sarcoma patients should be explored, and Enhanced Recovery After Surgery (ERAS) principles should be fully applied and improved (7, 8). We can conclude that advances are made in the surgical management of abdominal and retroperitoneal sarcoma, though further research is certainly needed to improve outcomes.

Author contributions

LuP: Conceptualization, Writing – original draft, Writing – review & editing. LoP: Writing – original draft, Writing – review & editing. JH: Writing – original draft, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effect of pre-operative radiation therapy on surgical outcome in retroperitoneal sarcoma

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Background: A high rate of locoregional recurrence is one of the major difficulties in successful treatment of retroperitoneal sarcoma (RPS). Although pre-operative radiation therapy (RT) is considered a potential way to improve local recurrence, concerns about the associated treatment toxicity and risk of peri-operative complications need to be addressed. Hence, this study investigates the safety of pre-operative RT (preRTx) for RPS.
Methods: A cohort of 198 patients with RPS who had undergone both surgery and RT was analyzed for peri-operative complications. They were divided into three groups according to the RT scheme: (1) preRTx group, (2) post-operative RT without tissue expander, and (3) post-operative RT with tissue expander.
Results: The preRTx was overall well tolerated and did not affect the R2 resection rate, operative time, and severe post-operative complications. However, the preRTx group was associated with higher incidence of post-operative transfusion and admission to intensive care unit ($p = 0.013$ and $p = 0.036$, respectively), where preRTx was an independent risk factor only for the post-operative transfusion ($p = 0.009$) in multivariate analysis. The median radiation dose was the highest in preRTx group, although no significant difference was demonstrated in overall survival and local recurrence rate.
Conclusion: This study suggests that the preRTx does not add significant post-operative morbidity to the patients with RPS. In addition, radiation dose elevation is achievable with the pre-operative RT. However, a meticulous intra-operative bleeding control is recommended in those patients, and further high-quality trials are warranted to evaluate the long-term oncological outcomes.

KEYWORDS

retroperitoneal sarcoma, preoperative radiation therapy, saftey and effectiveness, morbididty, surgical outcome

Abbreviations

CD, Clavien-Dindo; COPD, Chronic obstructive pulmonary disease; CT, Computed tomography; CTV, Clinical target volume; FNCLCC, French Federation of Cancer Centers Sarcoma Group Grading System; LRFS, Local recurrence free survival; OS, Overall Survival; preRTx, Pre-operative radiotherapy; postRTx, Post-operative radiotherapy without tissue expander; postRTx + TE, Post-operative radiotherapy with tissue expander; PTV, Planning target volume; RT, Radiation therapy; RPS, Retroperitoneal sarcoma; NSQIP, National Surgical Quality Improvement Program.

Introduction

Soft tissue sarcomas are uncommon malignancy, comprising approximately 1% of all solid malignancies (1). Between 15% and 20% of them originate from the retroperitoneal space, representing a rare tumor of heterogenous histological subtypes. The backbone of curative treatment is *en bloc* resection of the primary tumor (2). However, complete resection with adequate microscopic margin is difficult or even impossible at times, due not only to the confined anatomic characteristics of the retroperitoneum, but also to the proximity of the adjacent vital structures (2–4). Consequently, the rate of complete resection, which is the most dominant predictor of long-term survival outside of tumor biology, is only achieved in 40%–60% of cases (5, 6). Unfortunately, even in completely resected retroperitoneal sarcomas (RPS), the rate of locoregional recurrence is unacceptably high, occurring in up to 50% of cases. This has been a major barrier to successful management of RPS, with five-year survival for all subtypes being about 60% at best (3, 7).

In an attempt to resolve this issue and obtain better local control of the disease, multimodal treatment approach involving radiation therapy and/or chemotherapy has been endeavored, but concrete evidence for their benefit is currently lacking (8). Chemotherapy has minimal effect, and RT to the retroperitoneum is complex with potential adverse effects to the surrounding vital organs (9). Various publications, largely of small retrospective studies, have demonstrated potential roles of pre-operative RT in improving local control and survival in RPS, including better defined target volume with more oxygenated tumor cells, reduced tumor seeding, improved tumor resectability, and minimization of unnecessary irradiation to adjacent radiosensitive tissues, especially small bowel, and thus better tolerability of RT at higher dose (8, 10, 11). Moreover, a review by Diamantis et al. suggested a potential survival benefit from peri-operative RT in RPS (12). Recently, The STRASS trial, the first and only randomized multicenter study to date, has been published. Unfortunately, however, the trial failed to demonstrate the role of pre-operative RT in improving recurrence free survival as well as overall survival in retroperitoneal sarcoma, except for the liposarcoma group in an unplanned subgroup analysis (13).

Nonetheless, RT has been increasingly utilized for RPS over the past decade, influenced largely by its established role in extremity sarcoma. Its use is still center-dependent, and more high-quality randomized controlled trials are warranted to reach a consensus and form a treatment guideline (8, 14). With the uncertainty about the long-term oncologic benefits of neoadjuvant RT, a significant concern has been raised about the treatment toxicity from the radiation and associated peri-operative morbidity by making the operation difficult. This has contributed to limiting widespread adoption of pre-operative RT (10, 15). Despite the general view that the pre-operative RT can be safely administered to the retroperitoneum, there are limited data on the short-term post-operative outcomes (6, 16). Therefore, we aim to investigate the contribution of pre-operative RT to the short-term surgical morbidity associated with RPS resection as well as its effect on survival.

Materials and methods

Ethics approval

This study was approved by the Samsung Medical Center Institutional Review Board (SMC IRB 2022-08-135). The need for informed consent was waivered by the board as the study did not involve any patient contact.

Inclusion and exclusion criteria

This retrospective study included adult patients who underwent both RT and surgery for retroperitoneal sarcoma between October 2001 and February 2020 at Samsung Medical Center, Seoul, Korea. Patients were excluded if they received neither pre-operative RT nor post-operative RT. Patients treated with palliative intent were also excluded from the study.

Patients

A cohort of 198 patients was reviewed and analyzed. The diagnosis of sarcoma and its subtypes were confirmed by reviewing the final histopathology report of the resected specimen. We then searched their medical records to confirm that those patients received peri-operative radiation therapy. They were then divided into three groups according to the RT scheme: Group (1) pre-operative RT group (preRTx), Group (2) post-operative RT without tissue expander group (postRTx), and Group (3) post-operative RT with tissue expander group (postRTx + TE). The tissue expander insertion was intraoperatively inserted at the SMC to overcome the radiation vulnerability of surrounding normal organs and deliver optimal RT doses post-operatively (3, 17, 18).

The decision to administer preoperative RT was made by a dedicated multidisciplinary sarcoma team. Pre-operative RT was only considered for patients after 2019, and the main consideration was local control of the posteromedial margin rather than cytoreduction or R0 resection. The decision was made based on the location of the tumor rather than the size of the tumor and the consent of patient for the pre-operative biopsy. Following the completion of pre-operative RT, patients were re-staged, and the surgery was performed on average 5 weeks later. All patients in this study underwent surgical resection with curative intent (R0 or R1), an *en bloc* resection of the tumor and involved adjacent organs without tumor fragmentation. After the surgery, follow-up surveillance with abdominopelvic and chest CT scans was performed every three months for the first two years, every six months for the next three years, and then yearly, to evaluate for locoregional and distant metastasis.

Study outcomes

Our primary outcome measures were post-operative morbidity related to pre-operative RT detected during the follow-up period.

The variables reflecting the morbidity entailed post-operative complication graded by Clavien-Dindo classification, length of hospital stay, need for transfusion and re-operation, and unexpected admission to intensive care unit (ICU). The secondary outcomes of interest entailed the rate of R2 resection, dose of radiation given and its tolerability, local recurrence, and survival. Local recurrence was defined as recurrence in the retroperitoneal space, as demonstrated on imaging, excluding distant metastasis. The final histopathology was reviewed to assess microscopic margins of the resection specimen and was subsequently classified as R0, R1, or R2.

Radiation therapy protocol

In terms of the RT, the following protocol and dose escalation was uniformly implemented. Simulation computed tomography (CT) scans using contrast agent were performed for all patients. Patients were positioned supine with both arms raised and vac-lok system was used during the simulation. CT scans were obtained with slice thickness of 2.5 mm and were registered in Pinnacle (Philips, Madison, WI, USA) system to delineate the target volume. The delineated clinical target volume (CTV) included the area expanded from gross tumor volume (GTV)—the gross tumor on simulation CT or other diagnostic images—with 5–10 mm and additional subclinical disease extent decided by radiation oncologists. The planning target volume (PTV) was generated as low-risk PTV by expansion of CTV with 5–10 mm and high-risk PTV by extraction from the low-risk PTV by the volume expanded from bowel with 10 mm. The simultaneous intensity boost was applied to prescribe 62.5–70 Gy in 25 fractions to high-risk PTV and 55.0 Gy in 25 fractions to low-risk PTV.

The risk-adapted RT planning was achieved by reducing the CTV accordingly based on the proximity of adjacent radiosensitive organs such as bowel, muscle, and bony structures. The Accuray Precision^{TM} and Pinnacle (Philips, Madison, WI, USA) were used for the RT planning of helical Tomotherapy and volumetric modulated arc therapy, respectively. Image-guided RT was performed for every session of RT using mega-voltage CT or cone-beam CT in the treatment room.

Statistical analysis

Descriptive statistics were examined. Univariate analysis was performed using the *t*-test for continuous variables and the chi square or Fisher's exact test for categorical data, as appropriate. Multivariate odds ratios and 95% confidence intervals were calculated using logistic regression to estimate the relative odds of post-operative morbidity and outcomes by radiation therapy and the factors identified as significantly associated in the univariate analysis.

Local recurrence free survival (LRFS) and overall survival (OS) were measured from the date of surgical resection to the date of event detection or date of last follow-up visit. The Kaplan-Meier method was used to estimate survival rates. All statistical analyses were conducted using the R version 4.0.4 software program (R Foundation for Statistical Computing, Vienna, Austria) and a p-value of <0.05 was considered statistically significant.

Results

Of 198 patients, pre-operative RT was performed in 23 patients (11.6%), while the remainder of the patients received post-operative RT with or without tissue expander.

Patient demographics

When comparing the three groups based on the mode of RT, the mean age in the pre-operative RT group was the highest (64.5 ± 12.2 years), which was statistically significant ($p = 0.008$). Two patients in the preRTx group and six patients in the postRTx group received pre-operative chemotherapy, while the tissue expander group did not have anyone who received chemotherapy. Patients receiving pre-operative RT were more likely to have a pre-operative albumin <3 g/dl. There was no other significant difference in the patient characteristics including male-to-female ratio, BMI, underlying disease, as illustrated in Table 1. There was no patient with chronic obstructive pulmonary disease.

Histopathology

The predominant final histopathology was liposarcoma across all groups, as shown in Table 2. There was no significant difference in tumor grade between the groups ($p = 0.133$), and Grades I–III were all present in each group. Since the significance of microscopic margin is unclear despite some evidence for better outcomes with R0 than with R1 resections (19), we have selected the rate of R2 resection as a meaningful marker of resection margin. R0/1 resection was achieved in more than 85% of the cases in all groups, and the rate of R2 resection showed no statistically significant difference between the groups. Intraoperatively, the most frequently resected adjacent organs were kidney, followed by large bowel and spleen, and there was no statistically significant difference in the number of resected organs between the groups ($p = 0.949$). In terms of the operative time, estimated blood loss and intra-operative transfusion requirement, there was no statistically significant difference.

Radiation therapy

The median dose of the RT delivered in the preRTx group was 62.5 Gy (range 60.0–62.50), and it was significantly higher than that of postRTX and postRTx + TE groups ($p < 0.001$). The RT was overall well tolerated in all three groups and did not require

TABLE 1 Patient characteristics.

	Group 1 preRTx ($n = 23$)	Group 2 postRTx ($n = 89$)	Group 3 postRTx + TE ($n = 86$)	p-value
Tumor type				
Primary tumor (%)	16 (69.6)	63 (70.8)	63 (73.3)	0.909
Recurrent tumor (%)	7 (30.4)	26 (29.2)	23 (26.7)	
Age (years)	64.49 ± 12.20	55.67 ± 11.78	55.70 ± 12.65	0.008
Sex = M (%)	15 (65.2)	45 (51.1)	37 (43.0)	0.149
BMI	22.73 ± 3.04	23.58 ± 3.08	23.10 ± 2.81	0.393
BMI category (%)				0.169
<18.5	3 (13.0)	4 (4.5)	1 (1.2)	
<25	15 (65.2)	59 (67.0)	67 (77.9)	
<30	5 (21.7)	24 (27.3)	17 (19.8)	
≥30	0 (0.0)	1 (1.1)	1 (1.2)	
DM = Yes (%)	5 (21.7)	6 (6.7)	9 (10.5)	0.095
HTN = Yes (%)	10 (43.5)	24 (27.0)	27 (31.4)	0.307
Previous Abdominal surgery = Yes (%)	6 (26.1)	25 (28.1)	23 (26.7)	0.971
Pre-operative chemotherapy = Yes (%)	2 (8.7)	6 (6.7)	0 (0.0)	0.02
Hb below 10 g/dl = Yes (%)	5 (21.7)	9 (10.1)	10 (11.6)	0.302
Albumin below 3 g/dl = Yes (%)	4 (17.4)	2 (2.2)	3 (3.5)	0.017
PLT below 100 = Yes (%)	0 (0.0)	1 (1.1)	1 (1.2)	1
Follow up (days)	624.26 ± 358.44	1,360.58 ± 979.82	1,705.93 ± 1,031.74	<0.001

TABLE 2 Tumor and treatment characteristics.

	Group 1 preRTx ($n = 23$)	Group 2 postRTx ($n = 89$)	Group 3 postRTx + TE ($n = 86$)	p-value
Tumor size (mm)	209.13 ± 111.89	147.20 ± 103.07	189.16 ± 116.51	0.013
Liposarcoma = Yes (%)	22 (95.7)	59 (66.3)	73 (84.9)	0.001
FNCLCC grade (%)				0.133
Grade I	5 (22.7)	26 (29.5)	23 (27.7)	
Grade II	10 (45.5)	28 (31.8)	41 (49.4)	
Grade III	7 (31.8)	34 (38.6)	19 (22.9)	
Resection = R2 (%)	1 (4.3)	12 (13.5)	11 (12.8)	0.557
Number of resected organ [median (IQR)]	1.00 [1.00, 2.00]	1.00 [0.00, 2.00]	1.00 [1.00, 2.00]	0.949
Large bowel = Yes (%)	8 (34.8)	33 (37.1)	15 (17.6)	0.014
Kidney = Yes (%)	15 (65.2)	53 (59.6)	59 (69.4)	0.396
Spleen = Yes (%)	1 (4.3)	12 (13.5)	13 (15.1)	0.459
Pancreas = Yes (%)	1 (4.3)	10 (11.2)	12 (14.0)	0.492
Small bowel = Yes (%)	3 (13.0)	11 (12.4)	5 (5.8)	0.263
Vascular = Yes (%)	1 (4.3)	4 (4.5)	1 (1.2)	0.386
Operative time [median (IQR)]	266.00 [224.50, 340.00]	321.00 [233.00, 412.00]	323.00 [273.00, 402.00]	0.056
Intraoperative transfusion = Yes (%)	8 (34.8)	28 (31.5)	24 (27.9)	0.775
Estimated blood loss [median (IQR)]	400.00 [275.00, 850.00]	400.00 [200.00, 1,200.00]	500.00 [262.50, 800.00]	0.994
Radiotherapy (gray)	62.50 [60.00, 62.50]	54.00 [50.10, 60.00]	58.75 [54.00, 60.00]	<0.001

dose limitation. Only one patient in the preRTx group did not complete the RT due to intolerance.

Peri-operative outcomes

The post-operative complications are summarized in Table 3, and they were recorded until the time of recurrence or the last follow up. The average length of hospital stay was 22 days and was comparable between the groups ($p = 0.728$). The Clavien-Dindo (CD) complication ≥3 was defined as severe post-operative complications, and three out of five patients with severe complications in the preRTx group required operative intervention under general anesthesia (CD IIIb) for wound dehiscence, diaphragmatic hernia, and anastomotic leakage of large bowel. In the postRTx + TE cohort, there were two patients with CDIIIb; one required explantation of infected TE due to peritonitis and the other underwent repair of wound dehiscence. The rate of severe complications was statistically insignificant between the pre-operative and post-operative RT groups ($p = 0.334$). In patients with severe post-operative complications, univariate analysis was performed on various patient factors, operative factors, and tumor factors for their association (Table 4). The following factors were significantly associated with severe post-operative morbidity: BMI < 18.5 (OR = 3.49, 95% CI = 0.05–0.98, $p = 0.047$), number of resected organs (OR = 1.76,

TABLE 3 Post-operative complications.

	Group 1 preRTx ($n = 23$)	Group 2 postRTx ($n = 89$)	Group 3 postRTx + TE ($n = 86$)	p-value
Length of hospital stay (days)	21.78 ± 11.94	21.70 ± 15.38	20.33 ± 10.05	0.728
Post-operative transfusion = Yes (%)	7 (30.4)	7 (7.9)	7 (8.1)	0.013
Clavien-Dindo complication ≥3 (%)	5 (21.7)	11 (12.4)	9 (10.5)	0.334
Unplanned ICU Admission = Yes (%)	2 (8.7)	1 (1.1)	0 (0.0)	0.036
Need for re-operation = Yes (%)	3 (13.0)	4 (4.5)	8 (9.3)	0.215
Mortality within 30 days	0 (0)	0 (0)	0 (0)	

TABLE 4 Risk factor analysis for severe post-operative complications.

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Age	1.03 (1, 1.07)	0.065		
BMI < 18.5	4.55 (1.02, 20.39)	0.047	3.49 (0.7, 17.4)	0.127
DM	0.75 (0.16, 3.44)	0.71		
Hb < 10 g/dl	1.46 (0.45, 4.68)	0.527		
PLT < 100 K	7.17 (0.43, 118.39)	0.169		
Albumin <3 g/dl	2.06 (0.4, 10.53)	0.384		
Previous abdominal operation	0.63 (0.22, 1.78)	0.386		
Pre-operative radiotherapy	2.15 (0.72, 6.43)	0.17	2.61 (0.78, 8.76)	0.12
Pre-operative chemotherapy	0.99 (0.12, 8.39)	0.991		
Tumor size	1 (1, 1.01)	0.057		
Liposarcoma	2.28 (0.65, 8)	0.199		
FNCLCC Grade III	1.05 (0.43, 2.59)	0.916		
Number of resected organs	1.76 (1.27, 2.42)	<0.001	1.59 (1.12, 2.27)	0.01
Operative time	1 (1, 1)	0.024	1 (1, 1)	0.089

95% CI = 1.27–2.42, $p < 0.001$), and operative time ($p = 0.024$). However, in a multivariate logistic regression model including the factors significantly associated on univariate analysis, the number of resected organs was the only independent variable that was significantly associated with increased risk of major morbidity (OR = 1.59, 95% CI = 1.12–2.27, $p = 0.01$) while the tumor factors including tumor size (OR = 1, 95% CI = 1–1.01, $p = 0.057$), FNCLCC Grade III (OR = 1.05, 95% CI = 0.43–2.59, $p = 0.916$) and liposarcoma subtype (OR = 2.28, 95% CI = 0.65–0.80, $p = 0.199$) did not. Moreover, the use of pre-operative RT did not impact on the post-operative complication (OR = 2.15, 95% CI = 0.72–6.43, $p = 0.17$).

The need for post-operative transfusion and unplanned ICU admission were significantly higher in the preRTx group ($p = 0.013$ and $p = 0.036$, respectively). Subsequently in the multivariate analysis, albumin <3 g/dl ($p = 0.029$) was the only significant independent risk factor for the post-operative ICU admission while the pre-operative RT ($p = 0.242$) did not demonstrate a meaningful association (Supplementary Table S1). On the other hand, the need for post-operative transfusion was significantly associated with the use of pre-operative RT in both univariate and multivariate analysis ($p = 0.002$, $p = 0.009$, respectively) (Supplementary Table S2). Despite these differences, there was no statistically significant difference in mortality between all groups.

Survival and local recurrence rate

The OS and LRFS rates are illustrated in Figure 1. The OS until the last follow up was compared between the three groups, and there was no significant difference ($p = 0.634$). In addition, there was no evidence of statistically significant difference in LRFS

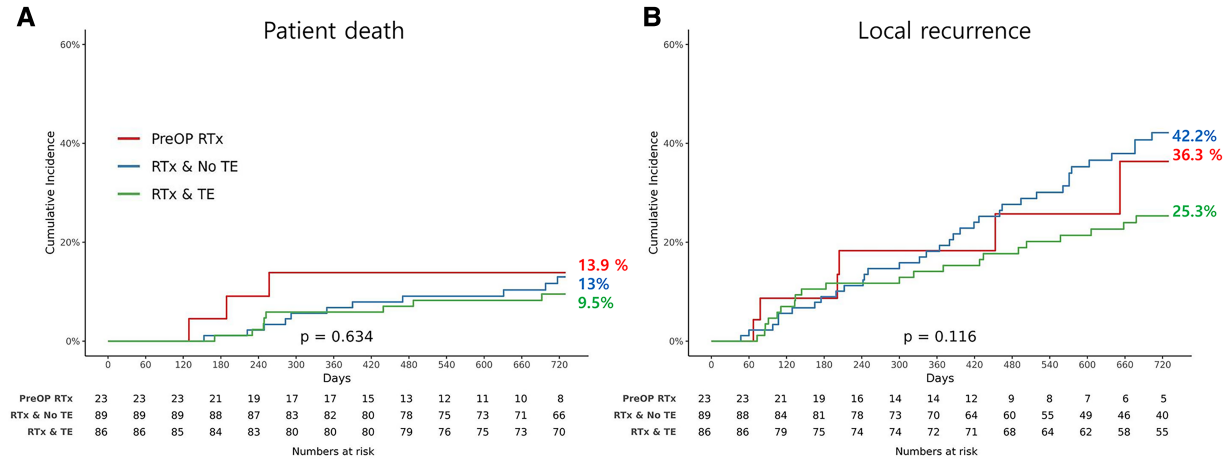

FIGURE 1
Kaplan-Meier graph for (A) overall survival and (B) incidence of local recurrence for each group.

between the groups ($p = 0.116$). However, the patients in the preRTx cohort had a shorter follow-up duration with an average of 625 days, as compared to the other two groups: 1,361 days for postRTx, and 1,706 days for postRTx + TE group.

Discussion

Most of the evidence for neoadjuvant RT in sarcoma are derived from multiple randomized trials in extremity sarcoma (20). However, at the same time, it is well recognized that those patients are at increased risk of post-operative complications including poor wound healing and surgical site infections, as shown in a randomized trial, where the rate of wound complication was twice as common in the neoadjuvant group (35%) when compared to the adjuvant radiation cohort (17%) (21). Using the database at Samsung Medical Center, we have found that the patients in the neoadjuvant group for retroperitoneal sarcoma were older and the primary tumor was significantly larger, consisting largely of G2 liposarcoma. In contrast to concerns about adverse effects of RT, the use of pre-operative RT did not demonstrate any significant impact on the operative time, the length of hospital stay, the need for intra-operative transfusion and re-operation, and severe post-operative complications defined as CD $\geq$3. The rate of concomitant adjacent organ resection was similar between the groups. However, a statistically significant increase was observed in the need for post-operative transfusion and unplanned admission to ICU in the preRTx patients. The age and tumor size did not show any significant association, but pre-operative RT was an independent risk factor for the post-operative transfusion ($p = 0.009$). Therefore, we recommend that a meticulous bleeding control is accomplished during operation in those patients. However, multivariable analysis revealed that preoperative RT was not independent risk factor for severe post-operative complication. Therefore, these findings suggest that the use of pre-operative RT seems to be safe, and this is in keeping with previous analysis from NSQIP data. Nussbaum et al. investigated a total of 785 patients undergoing RPS resection, where 71 patients (9%) received pre-operative RT and reported that the pre-operative RT did not increase 30-day morbidity or mortality (7). Bartlett et al. also used the NSQIP data, analyzing 696 patients where 70 patients (10%) received pre-operative RT, and reported similar findings (16).

In terms of the radiation therapy, previous studies have reported that RT dose escalation resulted in improved local control, tumor response, and even cancer-specific survival in various solid tumors (22–26). With the advancement of RT techniques, considerable efforts have been directed towards delivery of higher dose radiation, especially in the radiation-resistant solid tumors (27). Currently suggested dose-fractionation regimen in the neoadjuvant RT for RPS is 50 Gy in 25 fractions or 50.4 Gy in 28 fractions as the guideline from American Society for Radiation Oncology recommended based on the STRASS trial (28). However, the quality of evidence for the recommendation is moderate and some reports of dose escalation with IMRT and SIB were discussed in the guideline as showing acceptable toxicity and encouraging early local control (28–31). One of the studies, by Tzeng et al., investigated the feasibility and outcomes of dose escalation in the pre-operative RT with selective dose escalation to the margin at risk for the patients with retroperitoneal sarcoma (31). In that study, 45 Gy in 25 fractions was delivered to the entire tumor bed and surrounding margin and the boost dose up to 57.5 Gy to the volume predicted as high risk for positive surgical margins. Despite the reports of tolerability of such RT regimen and high rates of tumor response and complete resection, subsequent analysis of the relevant clinical outcomes from dose escalation in neoadjuvant setting has not been conducted. Instead, intraoperative RT boost with dose escalation has been attempted for the at-risk area in addition to the neoadjuvant RT, the results of which demonstrated improved local control and overall survival (5, 32, 33). In our cohort, we have found that higher dose of radiation was possible in the pre-operative RT group with median dose of 62.5 Gy, which was even higher than that in the TE group (median dose of 58.8 Gy), and it was overall well tolerated. This is helpful as the pre-operative RT is often preferred over adjuvant RT for the protective effect from the primary retroperitoneal sarcoma on the adjacent radiosensitive organs (34).

The overall survival and local recurrence free survival did not demonstrate statistically significant difference between the three groups. However, it requires a careful interpretation as the analysis is limited by the short-term follow up period in the preRTx group, where the other two groups had 2–3 times longer follow up duration, and this difference was statistically significant ($p < 0.001$). The authors are planning to conduct subsequent analysis with longer follow up to better assess the oncological and survival benefit of the pre-operative RT. This study has other limitations to note. Most importantly, the retrospective nature of the study conducted at a single institution entails potential selection bias, and our findings may not be generalizable to other cohorts of patients. In addition, a small sample size, particularly in the pre-operative group, further limits the study, although the issue of overall small sample size is somewhat attributed to the low incidence of retroperitoneal sarcoma. Nonetheless, our study demonstrates that the addition of pre-operative RT to curative resection of retroperitoneal sarcoma does not appear to increase the peri-operative morbidity and mortality, and that it is safe and feasible.

Conclusion

In conclusion, this study describes a single institution cohort of patients undergoing curative resection of retroperitoneal sarcoma with peri-operative RT at a dedicated sarcoma center. Despite presenting with older age and larger tumors, the use of pre-operative RT did not add any statistically significant morbidity to the peri-operative outcomes, except for the post-operative transfusion requirement. Therefore, we recommend a meticulous intra-operative bleeding control in those patients having undergone pre-operative RT. However, exaggerated concern for

increased peri-operative complications should not exclude appropriately selected patients from receiving potentially valuable pre-operative RT. Further study is warranted to better define the long-term sequelae of radiation as well as its oncologic efficacy in patients with RPS.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Samsung Medical Center Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conceptualization, SJJ, KWL; methodology, GSY, JIY, KWL; software, JK; validation, KWL, JBP; formal analysis, JK; investigation, SHL, KDK; resources, KWL, MJK, JBP, KDK; data curation, SHL; writing—original draft preparation, SSWP, SJJ; writing—review and editing, SJJ, SSWP, MJK, GSY, JIY, KWL, JBP; visualization, SJJ, JK; supervision, JBP; project administration, JBP, KWL; funding acquisition, KWL. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2023.1209698/full#supplementary-material

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Retroperitoneal undifferentiated pleomorphic sarcoma with total nephrectomy: a case report and literature review

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Background: Undifferentiated pleomorphic sarcoma (UPS) is a highly malignant soft tissue sarcoma with a poor prognosis and no clear effective clinical means for treatment, and there has been no significant progress in research within this field in recent years. This study aimed to investigate the epidemiology, etiology, clinical features, diagnostic modalities, various treatment modalities, and prognosis of retroperitoneal undifferentiated pleomorphic sarcoma and to contribute to the clinical management of this type of disease. In this study, we report a case of undifferentiated pleomorphic sarcoma with a primary origin in the retroperitoneum. Undifferentiated pleomorphic sarcoma occurring in the retroperitoneum is rarely reported.

Case description: A 59-year-old man with abdominal distension and pain for 4 months presented to our hospital after the failure of conservative treatment. A 9.6 cm by 7.4 cm mass in the left retroperitoneum was found on a CT scan of the whole abdomen with three degrees of enhancement. After surgical treatment, the tumor and the left kidney were completely removed, and pathological examination and genetic sequencing showed an apparent undifferentiated pleomorphic sarcoma. The patient subsequently declined follow-up treatment and is currently alive and well.

Conclusions: At the current level of clinical technology, the treatment of undifferentiated pleomorphic sarcoma is still in the exploratory stage, and the scarcity of clinical cases of this disease may have hindered the acquisition of clinical trials and research data for this disease. At present, the first choice of treatment for undifferentiated pleomorphic sarcoma is still radical resection. In the existing clinical studies, there are no strong data to support the effect of preoperative neoadjuvant chemoradiotherapy and adjuvant chemoradiotherapy in clinical practice. Similar to other diseases, the use of radiotherapy and chemotherapy before and after surgery may be a potential treatment for this disease in the future. Targeted therapy for this disease still needs further exploration, and we need more reports on related diseases to promote future treatment and research on this disease.

KEYWORDS

treatment, case report, pleomorphic undifferentiated sarcoma, diagnosis, retroperitoneum

Introduction

Undifferentiated pleomorphic sarcoma (UPS), a malignant soft tissue tumor of mesenchymal origin, occurs in middle-aged and elderly people, more often in men than in women. The disease occurs mainly in the extremities and only rarely in the retroperitoneum (1, 2), and its pathogenesis is unclear. The disease was first reported in 1964 as malignant fibrous histiocytoma (3), which has since been renamed undifferentiated pleomorphic sarcoma (4). The occurrence of this tumor in the retroperitoneum is less reported, and only eight cases have been described, of which five tumors originated in the kidney (5–9), two were documented in a clinical study by A. Pirayesh (10), and one was a paraspinal primary (11). We report a case of undifferentiated pleomorphic sarcoma arising in the retroperitoneum in a 59-year-old man and review the available medical literature on undifferentiated pleomorphic sarcoma to summarize the epidemiology, etiology, clinical presentation, radiologic features, diagnosis, and treatment options, including radiotherapy, chemotherapy, and targeted therapy for this rare tumor.

Case report

History and examination

The patient, 59 years old, had pain in the left upper abdomen after eating before April and lost 15 kg in the past 2 months, with no relief after taking oral gastric medication. In order to seek further treatment, he consulted our outpatient clinic.

Imaging findings

A mass-like, dense soft tissue shadow was seen in the left upper abdomen, measuring approximately 9.6 cm by 7.4 cm, with a CT value of about 41 HU. On enhancement scan, the mass was inconsistent enhancement and poorly demarcated from the tail of the pancreas, the left adrenal gland, and the left kidney, and the pancreatic duct was not dilated. Intraoperatively, the patient's mass was found to be located on the dorsal side of the pancreas, adjacent to the abdominal aorta and to the right of the splenic hilum, with unclear demarcation from the left kidney, as shown in Figure 1.

Surgery

The patient's preoperative imaging tended to indicate malignancy, and the tumor had certain boundaries with the kidney, but the anatomical location of the tumor was complicated, and the physician suggested a puncture biopsy. However, the family refused, considering factors such as possible kidney injury and bleeding, so this preoperative procedure was not performed. The general appearance of the tumor was observed intraoperatively, and it was found to be soft and irregular in shape, adhering more closely to the renal vessels, which made separation difficult. To achieve a complete resection of the tumor and to reduce the possibility of tumor recurrence after surgery, it was therefore decided to remove the ipsilateral kidney intraoperatively. The patient was preoperatively diagnosed with a retroperitoneal mass and underwent a combined left nephrectomy, left adrenalectomy, and mass removal. The tumor was solid, bloody yellowish, and the visible perirenal fat capsule was largely visible as shown in Figure 2.

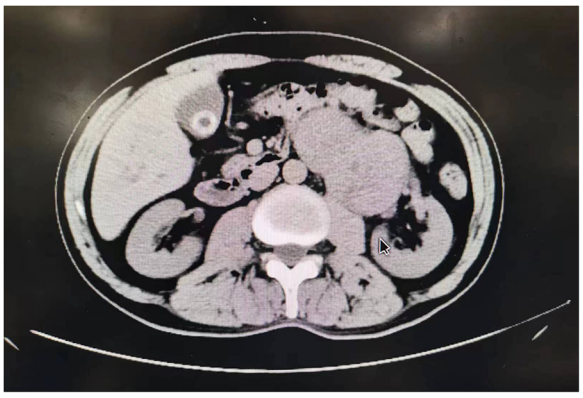

FIGURE 1
The patient's retroperitoneal undifferentiated pleomorphic sarcoma.

Histopathologic findings

The pathological findings were undifferentiated pleomorphic sarcoma, not excluding dedifferentiated liposarcoma, as jointly diagnosed by two senior pathologists at our hospital. The left kidney and retroperitoneal mass had a total weight of 816.5 g.

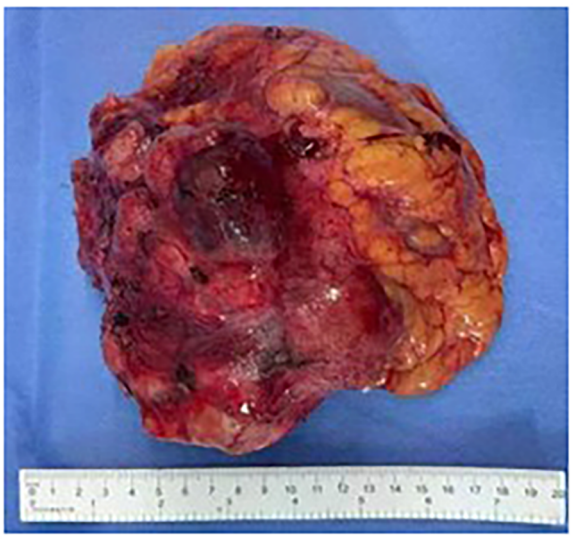

FIGURE 2
Gross observation of undifferentiated pleomorphic sarcoma.

The volume of the mass was 12.0 cm by 9.5 cm by 6.5 cm, the surface was slightly stringy, the cut surface was grayish white, firm, and hard, and two tough nodules, both 0.3 cm in diameter, were palpated in the adipose tissue around the mass. The renal pelvis and ureteral mucosa were not abnormal. No lymph nodes were seen in the renal hilum. The adrenal gland was 4.5 cm by 1.0 cm by 0.8 cm in size, golden yellow in color, firm, and tough in texture. The tumor volume was 12 cm by 9.5 cm by 6.5 cm, and the nuclear schizophrenia was about 10 nuclei/10 HPF. Local tumors necrosis, local invasion of the adrenal parenchyma, and renal peritoneal adhesions did not invade the renal parenchymal vasculature and nerves, tumor infiltration of the ureter and blood vessels were visible, and tumor infiltration was visible at the end of the cut edge. A metastasis was visible in the lymph nodes around the tumor (3/3), as shown in Figure 3A.

Immunohistochemistry: CD34(−), Desmin(−), Ki-67(+40%), SMA(partial +), S-100(scattered +), CD117(−), Dog-1(−), HMB45(−). TFE3(+), CK-pan(−), H-caldesmon(−), β-catenin (membrane +). STAT6(−), CK-pan(−), Vimentin(+), CK5/6(−), WT-1(weak+), Calretinin(−), D2-40(−).

Examination findings

Diagnosis: retroperitoneal (including left kidney) malignant tumor of mesenchymal origin consistent with undifferentiated pleomorphic sarcoma; it was recommended that genetic testing was attempted to further exclude dedifferentiated liposarcoma, as shown in Figure 3B.

Gene sequencing

The tumor mutational burden (TMB) was 2.922.92 Muts/Mb (ModerateModerate), microsatellite instability (MSI) was detected as microsatellite stable (MSS), positive gene (1): TP53 p.I332M; negative gene (1): PTEN copy number was decreased in tumor tissues. The HLA-I-like molecular genotype was detected as HLA-I (A, B, C); heterozygous secondary variants were detected as PTEN copy number reduction only; the evidence level was C, which may be sensitive to platinum-based chemotherapy modalities; and no hereditary tumor-related genetic variants were detected. The genetic diagnosis also excluded the possibility of dedifferentiated liposarcoma.

Postoperative course

The patient recovered well after surgery with only transient renal insufficiency. After consultation with the Department of Nephrology and the Department of Urology I, relevant symptomatic treatment was performed, and the patient was discharged 7 days after the surgical intervention, with the renal function returning to normal at the time of discharge. After the postoperative joint consultation with several specialists, the combination of the targeted therapy drug anlotinib and the immunotherapy drug pablizumab was recommended. The patient was informed about his condition but did not indicate his attitude toward the next treatment. However, according to the current follow-up results, the patient is currently in good health with no significant abnormalities, and we are continuing to follow up with him.

Discussion

Epidemiology and etiology

Soft tissue sarcomas (STSs) are rare malignant tumors of mesenchymal origin that account for approximately 1% of adult malignancies (12), with a large number of approximately 50 subtypes, of which the less differentiated ones that can exhibit multiple cellular forms are called undifferentiated pleomorphic sarcomas. Undifferentiated pleomorphic sarcomas can occur in any part of the body, with the extremities being the most common site (50% in the lower extremities and 20% in the upper extremities) (13), with only a few occurring in the retroperitoneum. This case is that of a 59-year-old man with undifferentiated pleomorphic sarcoma occurring in the retroperitoneum, which is consistent with the age (around 60 years) and gender (male) of onset reported in the literature (13). The incidence of the disease is extremely low, but there is an increasing trend year by year, with only three cases per 100,000 in 2013 (14) and three cases per 45,000 to date (15). Metastatic foci of the disease are mostly found in the lungs and, to a lesser extent, in the liver (16). The odds ratio (OR) of smoking for UPS is 2.05 (95% confidence interval, 1.78–2.37; $p < 0.01$) (17), and more than 30% of patients with undifferentiated pleomorphic sarcoma were found to have a family history in a previous study (18, 19). Approximately 3%–5% of patients may develop locally more harmful RA-UPS as a result of radiation

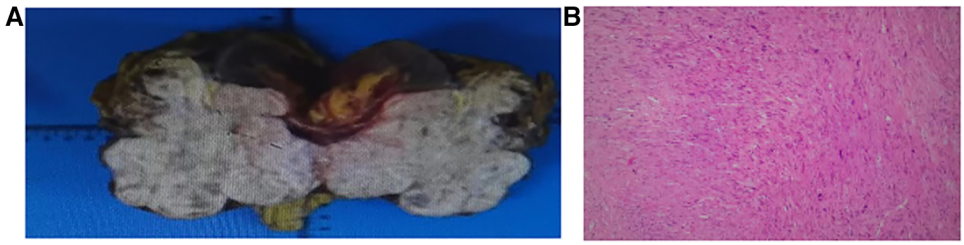

FIGURE 3
(A) Macroscopic tumor. (B) HE staining of tumor.

therapy, which is commonly referred to as radiation-associated undifferentiated pleomorphic sarcoma (RA-UPS) (20, 21).

Clinical presentation

Patients with undifferentiated pleomorphic sarcoma usually have no obvious specific symptoms, and clinical symptoms are usually related to the location and size of the tumor.

Patients typically present with clinical indications that are signs of tumor compression. In this case, the patient presented with gastritis because the mass was located in the posterior peritoneum and pressed forward on the stomach, and some patients may report to the clinic with respiratory symptoms due to tumor metastasis in the lungs. In similar cases and this case report, common symptoms included abdominal pain (lumbago) in five cases (83.3%) (5, 6, 8, 9), weight loss in four cases (66.7%) (5, 6, 8), anemia in three cases (50%) (6, 8, 9), fever in two cases (33.3%) (8, 9), and difficulty urinating in one case (16.7%) (8).

Diagnosis and radiological characteristics

Radiological details about UPS are scarce in the literature because of how uncommon it is. Imaging of this disease is usually non-specific, and exclusionary diagnostic methods are mostly used (22). The majority of well-differentiated liposarcomas contain adipose tissue within the tumor, and some poorly differentiated liposarcomas have calcifications (23); smooth muscle sarcomas have vascular invasion and hemorrhagic necrosis as the main imaging features (24); and undifferentiated pleomorphic sarcomas have calcifications that typically appear at the edge of the lesion (23). Imaging is of great importance for surgical treatment, and normally the surgical margins are selected 2–3 cm outside the tumor infiltration shown on imaging; with the development of imaging techniques, the preoperative diagnosis and postoperative pathologic diagnosis of the extent of infiltration have become more consistent. A "tail sign", a frequent curvilinear signal extension of the mass, can be found in some MRIs of infiltrative UPS and can be used as a potential diagnostic basis for the disease (25, 26). However, generally speaking, the diagnostic imaging modality is more limited in its ability to identify the disease. The main gold standard for the diagnosis of this disease is still pathology, and imaging is typically only used as a reference and for auxiliary evaluation. In pathological examination, care should be taken to protect the specimen and to avoid cross-sectioning, which may affect the assessment of tumor depth and infiltration. There are no specific histochemical markers for undifferentiated pleomorphic sarcoma in clinical practice, and positive or negative endosialin (27) is commonly used as a basis for diagnosis.

Treatment

Due to the rarity of UPS, standard management guidelines have not yet been established. Despite a multimodal approach including surgery, radiotherapy, and chemotherapy, targeted therapy is the predominant therapy. In addition, surgical resection is the leading treatment for performing gross tumor resection (GTR), and the achievement of negative surgical margins due to the extension of the resection is one of the most frequently reported predictors of recurrence and survival. Surgical treatment has removed the gross tumor cells, but potentially smaller lesions or tumor cells in circulating cells are still alive, and a combination of other treatments is needed to effectively control tumor recurrence.

Radiotherapy

Regarding the effect of radiation therapy, most researchers believe that local radiotherapy is more effective in tumors that have not infiltrated. Especially in undifferentiated pleomorphic sarcomas located in the extremities and superficial occurrences (28), radiotherapy can induce increased antigen expression at the tumor site, promote immune cell infiltration and antigen cross-presentation, and, to some extent, alter the tumor microenvironment, thereby affecting tumor cell proliferation (29, 30). However, no significant effect has been seen in tumors with infiltrative metastases (31, 32). In our patient, radiotherapy was often ineffective because the patient's tumor was located in the retroperitoneum, as per the observations in previous studies (33).

As for the timing of radiation therapy application, some studies have shown that radiation therapy in the perioperative period, preoperatively, can prolong the patient's survival time (34). With respect to the type of radiation therapy used, heavy ion radiation therapy, which can cause irreparable DNA cluster damage in tumor cells, has gradually become a key technology in tumor radiation (35), which was better validated in Zaixing Wang's study. At the same time, however, we need more randomized controlled trials for in-depth studies on the development of technology in this field (36). However, radiation therapy also has certain side effects, and some patients have developed RA-UPS after receiving radiotherapy, which has an incidence of about 0.16% (37) and a poor prognosis. Patients should receive radiation therapy with controlled radiation doses to avoid the occurrence of RA-UPS as much as possible.

Chemotherapy

For the treatment of deep tumors in several parenchymal organs and RA-UPS, chemotherapy performs better compared to radiation therapy (38). The effectiveness of chemotherapy in this disease is controversial, and there are no clear clinical guidelines for its description. Different case reports and studies have shown that chemotherapy may extend the survival time of patients to some extent (39, 40). In the application of chemotherapeutic agents, the effectiveness of adriamycin alone is still being investigated (41), and the combination of adriamycin with cyclophosphamide is still the drug of choice for chemotherapy of this disease in clinical practice (42). In a study by Paul Lorigan, the combination of

doxorubicin and cyclophosphamide was also employed, with comparatively good results (43). Due to the large size of the tumor and the structural similarity of the core to the central region of the parenchymal organ, chemotherapy is typically more effective in larger tumors (>8 cm) (44), and secondary tumor side effects are less severe than with radiation (45). In studies on the timing of drug application, neoadjuvant chemotherapy before surgery can also be used with good results (46).

Targeted therapy

Undifferentiated pleomorphic sarcoma (UPS) is an aggressive adult soft tissue sarcoma characterized by low tumor mutational burden (TMB) and high copy number alterations (47). In recent years, PD-1 and PD-L1 have been identified as novel antitumoral targets. PD-1/PD-L1 interaction is the main pathway of immune control of tumor suppression, and PD-1 has gradually become a hot topic for research (48). PD-1/PD-L1-related immune responses are more common in UPS (49, 50), but more as a differential diagnosis, one of the methods that has limitations for the prognosis prediction of the disease (51). In a study by YangYou et al., anti-angiogenesis inhibitors combined with PD-1 inhibitors had a good effect on UPS (52), and in a study by Zhichao Tian et al., paclitaxel combined with PD-1 inhibitors also had a significant effect on UPS (53), but some patients had poor results with PD-1 inhibitors (54). PD-1 may be a potential therapeutic target for UPS in the future, and its expression is important in influencing CD8+ T lymphocyte infiltration and patient prognosis (55). Using a comparative oncology approach, researcher Ashley M. Fuller identified DNMT3B, which leads to DNA methylation patterns in human undifferentiated pleomorphic sarcoma, as a potential therapeutic target (56). However, anti-methylation drugs currently in clinical use have not yet been able to provide effective treatment for this disease due to poor drug uptake or systemic toxicities, and future studies on hENT1 (SLC29A1) may enhance drug uptake to treat the disease (57). Christina L. Roland found that cyclin D1, pEGFR, pIGF-1R, and PTEN deletion ($p < 0.001$) and AXL overexpression ($p = 0.015$) were associated with reduced disease-specific survival (DSS) (58). In addition, neurotensin receptor 1 (NTSR1) (59), anti-human tumor endothelin 1 (TEM-1) (60), and various other targeted therapeutic targets are under progressive research by related scholars and may become effective for the treatment of this disease in the future.

Prognosis

The survival rate of this condition is related to the site of disease onset, with a 5-year survival rate of more than 70% for tumors in the trunk and extremities and less than 50% for tumors in the head and neck (61), which may be related to the richer blood supply and more important anatomical sites in the head and neck. Currently, the American Joint Committee on Cancer (AJCC) staging system (62) is used to evaluate the main clinical prognosis of UPS, and patient prognosis is mainly related to recurrence and distant metastases. Among them, tumor recurrence is mainly related to size (>5 cm), tissue infiltration (>5.5 mm), and whether the margins are positive, with more than 30% of patients likely to experience recurrence (63, 64). The presence of a "tail sign" in preoperative imaging may also represent a high likelihood of recurrence (64). Risk factors for distant metastases are related to the tumor site (trunk and extremities), tumor size (>2 cm), and infiltration (invasion of subcutaneous fat and lymphatic vessels). Risk factors for all-cause mortality were gender (male), ethnicity (white), age (>55 years), immunosuppression, tumor size >2 cm, and lymphovascular invasion (65–67). However, the prognosis of patients with this disease is usually highly variable, and a prognostic evaluation criterion called the nomogram is emerging as a novel method for the evaluation of this disease (13, 68). Radiation-associated undifferentiated pleomorphic sarcoma patients usually have a worse prognosis (69), and the disease's strong PD-1 expression in immunohistochemistry represents a poor prognosis and IDO-1 expression a better prognosis (70).

Conclusion

In the patient described here, the tumor adhered to the renal hilum and adhered more tightly to the renal vessels, making separation more difficult and showing obvious infiltration. There were some surrounding lymph node metastases, but no distant metastases for the time being. The tumor, left kidney, and left adrenal gland were completely removed during surgery. After follow-up, the patient is in good mental and physical condition but did not express a clear opinion on the future treatment.

In conclusion, retroperitoneal undifferentiated pleomorphic sarcoma is rare and difficult to diagnose. There are no obvious specific signs in the early clinical stage, and most patients come to the hospital with non-specific symptoms such as tumor compression. For this disease, we should classify and summarize the imaging manifestations and actively perform tumor puncture biopsy if the benign and malignant tumors cannot be clearly determined. In accordance with the pathological results of tumor puncture, relevant radiotherapy and chemotherapy should be performed during the perioperative period to reduce the risk of surgery and postoperative recurrence. Currently, there are no clear guidelines for the treatment of this disease, and more in-depth research is needed regarding chemotherapy and comprehensive treatment.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Ethical review and approval was not required for the animal study because do not need. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

KY: project development, data collection, manuscript writing. FB: project development, data collection, manuscript writing. RH: data collection. LW: data collection. JZ: data collection. ZL: data collection. YH: data collection. XS: data collection. LJ: project development, data collection, manuscript writing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Surgical approach for complete resection of giant retroperitoneal liposarcoma with diaphragmatic hernia via ninth rib thoracotomy

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Background: Resection of a giant retroperitoneal liposarcoma is difficult and technically demanding, especially for large retroperitoneal tumors accompanied by a diaphragmatic hernia. Technically, the open abdominal approach can be time-consuming and difficult to perform, with possible intraoperative complications and other factors bringing psychological and physical difficulties to the patient. This study reports a safe and feasible approach for the complete resection of a large retroperitoneal tumor complicated by a diaphragmatic hernia.

Methods: A 58-year-old male patient with persistent upper abdominal pain and distension was treated at a local hospital on 4 July 2022. Computed tomography showed a mixed-density mass on the right retroperitoneum, and liposarcoma was considered. On 6 July 2022, the patient was transferred to our hospital for further treatment. Computed tomography showed a mass with low-density fatty shadow in the right adrenal region. The boundary with the right adrenal gland was unclear. The mass was 102 mm × 74 mm, and the right lobe of the liver was compressed. Insufficiency of the right middle lobe of the liver was seen due to a right diaphragmatic hernia and left mediastinal deviation. We considered the traditional approach for tumor resection via laparotomy, but we opted to perform a comprehensive evaluation first. The tumor was close to the back of the right kidney and liver, causing the diaphragm to rise because of its proximity to these organs. Exposing the tumor through laparotomy would be difficult, making it challenging to remove. The patient had a diaphragmatic hernia and moderate pulmonary dysfunction; therefore, we decided to enter the abdomen through a thoracotomy of the ninth rib.

Results: Using our technique, the tumor was easily visualized and completely removed in approximately 30 min. The intraoperative blood loss was 100 ml, and no postoperative bleeding, pneumothorax, intestinal fistula, infection, or other complications occurred.

Conclusion: The transthoracic approach may be a safer and more feasible resection method than the traditional open approach for patients with giant retroperitoneal liposarcoma with a diaphragmatic hernia.

KEYWORDS

retroperitoneal liposarcoma, diaphragmatic hernia, approach, treatment, surgery

1 Introduction

Retroperitoneal tumors occur in the peritoneal space and originate from tissues such as fat, muscle, lymph, blood vessels, and nerves (1). Retroperitoneal tumors are relatively rare, especially giant retroperitoneal liposarcomas. These tumors can show expansile growth in their early stage with no apparent symptoms. Most symptoms are caused by the increase in tumor volume and compression of surrounding tissues, requiring patients to seek medical attention (2). Large retroperitoneal tumors, generally larger than 10 cm, are rare, especially when complicated by a diaphragmatic hernia. These large tumors are difficult to resect, can cause many symptoms in patients, and can impact breathing and blood flow. A skilled and experienced surgeon is required with clear requirements for the anatomy of the abdominal tissue to operate on these large tumors. When the tumor is large, spatial visualization concerning the surrounding tissue is difficult during the operation, posing certain challenges to the surgeon (3, 4). The traditional operation approach used to treat retroperitoneal liposarcoma requires entering the abdominal cavity via laparotomy and exposing the tumor and surrounding tissue from different angles. For large tumors, the surgery is more invasive and has added risks for the patients. For example, the space is smaller, and tissue injury and increased bleeding may occur (5, 6). Therefore, it is important to find a safe and feasible way to reduce the operation time, expose the tumor tissue for complete resection, and alleviate the patient's symptoms. The traditional method of laparotomy to remove retroperitoneal liposarcoma presents surgeons with certain challenges. These challenges include long procedure times, increased bleeding, and the possibility of incomplete resection. In our case, the patient had retroperitoneal liposarcoma with a diaphragmatic hernia. A thoracotomy was considered after a comprehensive evaluation of the patient. The tumor was completely exposed during the operation, the procedural time was short, and the patient recovered well postoperatively.

2 Methods and results

2.1 Description of the patient's condition

A 58-year-old male patient with persistent pain in the upper abdomen and abdominal distension after eating presented to a local hospital on 4 July 2022. The patient had no nausea, vomiting, dizziness, fatigue, or other symptoms. Computed tomography (CT) showed a defect in the right diaphragm, herniation of the right inferior bowel, mesentery, gallbladder, and part of the liver into the right thoracic cavity. A mass of mixed density was observed in the right retroperitoneum, approximately 102 mm × 74 mm, with clear edges. An additional scan showed moderate enhancement in the parenchyma, compression of the right adrenal gland, and unclear visualization of the right kidney boundary. No obvious fluid in the abdominal cavity was observed, and liposarcoma was first considered. However, it was decided not to perform surgery at that time, and the patient was discharged after being treated conservatively for abdominal pain.

On 16 July 2022, a day after the patient was discharged from our hospital, CT showed a mass in the right suprarenal area near the right kidney, and it was highly likely to be a myeloid liposarcoma. Insufficiency of the right middle lobe of the liver was seen due to the right diaphragmatic hernia and left mediastinal deviation (Figure 1). Physical examination revealed the following: body temperature, 36.4° C; respiration rate, 20 breaths/min; blood pressure, 122/80 mmHg; pulse, 98 beats/min; and epigastric distention and tenderness, with no rebound tenderness. Other laboratory tests, including routine blood tests, biochemical tests (including liver and kidney function and electrolytes), and evaluation of the coagulation function were normal. Pulmonary function tests showed moderately restrictive ventilatory dysfunction, and maximum ventilation accounted for 51% of the expected moderate reduction. According to the CT, liposarcoma was the diagnosis, and we used that information to determine the best treatment options for the patient. At that time, we communicated with the patient and his family following the traditional surgical method protocol and planned to perform a laparotomy to remove the tumor.

However, we carefully evaluated the CT and the patient before surgery. Owing to the diaphragmatic hernia (caused by trauma in 1998), there was a diaphragmatic defect and some herniation of the abdominal organs into the right thoracic cavity. The tumor location was carefully evaluated, which was behind the right kidney and liver and close to the diaphragm. The visualization of the abdomen between the tumor and surrounding tissues was difficult. Resection could be difficult and time-consuming, with an increased risk of intraoperative bleeding and injury to the peripheral organs. Therefore, we opted to use the upper chest as the entry point to the abdomen through the diaphragm, which could better expose the tumor. Finally, the patient and his family were informed of the possible complications during and after the operation. After

Abbreviations: CT, computerized tomography.

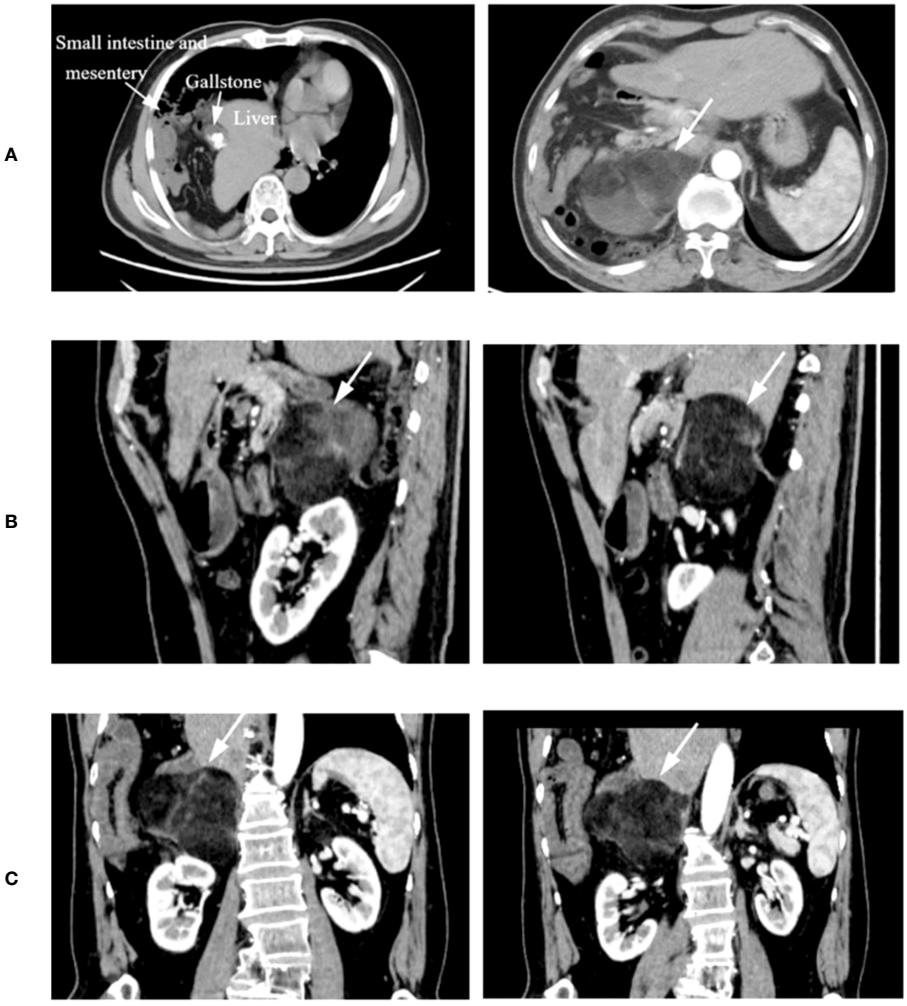

FIGURE 1
Representative CT images. **(A)** Cross-sectional CT showing part of the liver and small intestine and mesentery herniated into the thoracic cavity. **(B, C)** CT sagittal and coronal scans, with the tumor location indicated by the finger.

obtaining consent, the operation was performed using the ninth rib as the incision point, which reduced the procedural time and the impact on the patient.

2.2 Surgical intervention

Routine blood preparation was performed before surgery, and the patient was transferred to the operating room. The patient was in the left lateral decubitus position on the operating table, and the surgeon, nurse, and anesthesiologist checked the patient's data. The patient received general anesthesia with endotracheal intubation. After successful anesthetizing, routine disinfection and draping were performed. An incision of approximately 20 cm in length was made at the ninth intercostal space. The skin, subcutaneous tissue, aponeurosis, muscle, and pleura were incised sequentially, and the bleeding point was carefully coagulated. Intraoperative exploration revealed that the liver herniated into the thoracic cavity, the right diaphragm was defective, and the bilateral diaphragms were atrophied. A mass of approximately 10 cm × 8 cm was seen above the right adrenal gland, which had adhered to the surrounding tissues. The adhesions around the mass were carefully separated, the bowel was opened to expose the mass, and the mass was abruptly dissected. Careful separation of the mass from the adhesions of the right kidney and adrenal gland did not damage the mass. The adhesions and nourishing blood vessels were gradually separated, and the blood vessels were sutured and checked for bleeding. The mass was slowly removed in its entirety, and a drainage tube was placed in the right abdomen (Figure 2).

The diaphragmatic hernia repair was the final part of the procedure. Visualization of the ninth rib in the thoracic cavity showed that the right lung and liver had adhered to the pleura, liver, and part of the intestine and had herniated into the thoracic cavity, making it difficult to repair the defect from the ninth rib incision. We decided to make a 20-cm incision in the seventh intercostal space to enter the chest and push the herniated thoracic organs into the abdominal cavity. We found the stumps on both sides of the diaphragm and sutured the edges of both ends with No. 7 silk

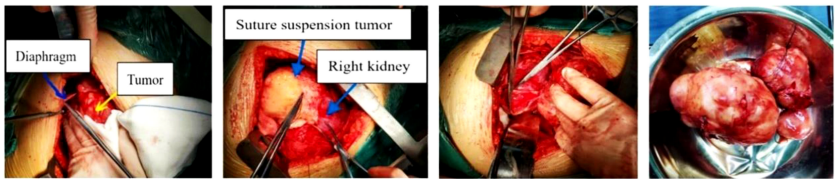

FIGURE 2
Intraoperative tumor resection.

thread for traction. A 15 cm × 9 cm patch (American Medtronic Self-Adhesive Patch, Pp1509g) was trimmed to fit the size of the diaphragm defect. The area around the stump of the diaphragm was sutured to repair the defect and restore the integrity of the diaphragm (Figure 3). After the patch was fixed and checked for active bleeding, the abdominal cavity was flushed with normal saline, and a chest drainage tube was inserted to connect to the water-sealed bottle. After checking the gauze, the chest cavity was closed layer by layer, and the lungs and water bottle were sealed again. After the fluctuations in the bottle were normalized, the operation was complete. The operation went smoothly; the procedure for tumor resection required approximately 30 min, and the intraoperative blood loss was 100 ml. Surgical specimens were sent for pathological examination after being inspected by family members. The patient was sent to the recovery room accompanied by the medical staff. Pathological examination revealed that the tumor comprised mature fat and bone marrow components, hemorrhage in some areas, and fibrous necrosis with hyalinization. The pathological diagnosis was myeloliposarcoma, with no tumor involvement at the resection margins.

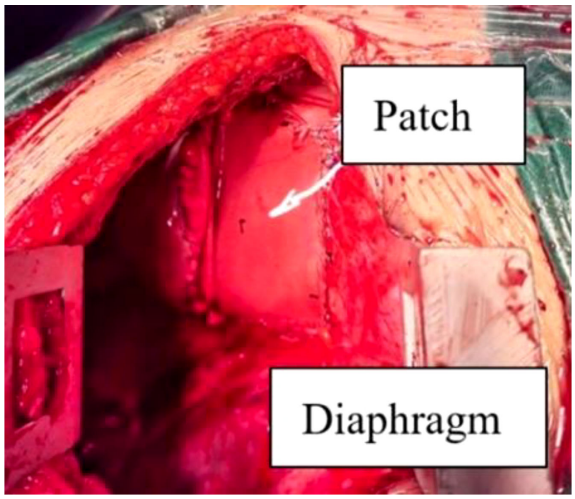

FIGURE 3
Diaphragmatic defect patch repair. After the tumor was completely removed, the patch was placed on the diaphragm defect and sutured to make up the defect and repair the integrity of the diaphragm.

2.3 Postoperative outcomes

After the operation, the patient fasted and was administered fluid replacement, nutritional support, nebulization, anticoagulation, pain relief drugs, and other comprehensive treatments. Routine blood tests, liver and kidney function, and electrolytes were regularly checked. The patient recovered well after the operation; the chest and abdomen drainage tubes were unobstructed and gradually decreased, and there were no complications such as anastomotic leakage, abdominal distension, or pain. On postoperative day 10, the patient underwent CT to visualize the reduction of the abdominal organs and the changes in pleural effusion. The CT showed that the abdominal organs that herniated into the thoracic cavity had been reset, but a small amount of fluid in the thoracic cavity persisted (Figure 4). Because of the preoperative complexity of this case, pleural effusion always exists after tumor resection and repair of a diaphragmatic hernia. We recommended the patient be hospitalized to facilitate postoperative recovery and avoid complications. During postoperative management, the pleural effusion was gradually absorbed, and the thoracic drainage tube was removed. No other related complications were observed postoperatively. The patient recovered well, and the incision healed. The patient returned to a normal diet and was discharged on postoperative day 28.

3 Discussion

Liposarcoma originates from mesenchymal cells, occurs in adult malignant soft tissue sarcomas, and has multiple satellite lesions beyond its boundaries (7). Liposarcomas are usually divided into four subtypes: highly differentiated/atypical, dedifferentiated, myxoid/round cell, and pleomorphic liposarcoma (8). Dedifferentiated liposarcoma is more common in late adulthood and has no sex predisposition. The retroperitoneum is the most common site of liposarcoma (> 80% of cases). Other areas include the limbs, spermatic cord, torso, head and neck, and subcutaneous tissues (9). A study reported a dedifferentiated liposarcoma with a 3 cm × 2 cm diameter on the medial side of the left thigh in a 24-year-old woman (10). Leiomyoma is a rare myoma of the extremities that originates from smooth muscle cells and is mainly divided into skin, blood vessels, and deep soft tissue leiomyoma. However, myomas are more common in the lower extremities than in the upper limbs (11, 12).

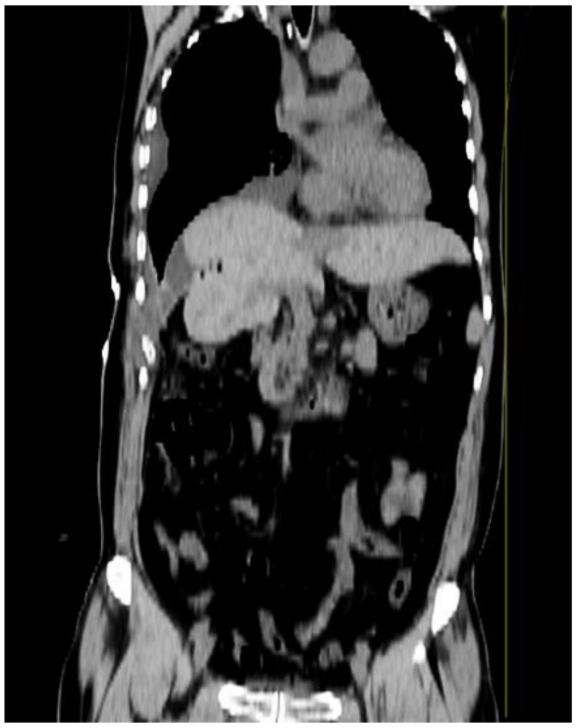

FIGURE 4
Representative images of abdominal CT after 10 days. Coronal CT showed that there was a small amount of fluid in the pleural cavity and that the liver had been repositioned into the abdominal cavity.

Therefore, the possibility of this type of lesion should be considered in the differential diagnosis of solitary pain with slowly growing masses in the extremities.

Giant retroperitoneal liposarcoma causes severe complications, such as abdominal pain, distension, and compression of adjacent tissues and organs. For those with a diaphragmatic hernia induced by a large tumor, it can affect breathing and blood flow, resulting in serious consequences (13, 14). Although chemoradiotherapy can reduce tumor size and slow tumor growth, there are side effects, and survival and recurrence rates also increase accordingly. Therefore, surgical resection is still the first and only way to cure retroperitoneal tumors (2, 15). In particular, for fast-growing malignant tumors, resection improves the survival rate and overall quality of life of patients. Postoperative radiotherapy and chemotherapy are options that can significantly improve the symptoms of patients if needed.

Giant retroperitoneal liposarcoma is a passive condition. If a patient has symptoms such as low protein and anemia, it is necessary to adjust their general health status to improve their suitability for surgery. However, in this case, the patient was well-nourished, without anemia, and could tolerate surgery well. Because of the relatively abundant blood supply of retroperitoneal giant lipoma, 1,000 ml–3,000 ml of blood should be prepared for the operation. Preoperative preparations for unexpected events during the operation are also necessary (16, 17). Resection of a retroperitoneal giant lipoma requires an experienced and skilled surgeon with a superior anatomical understanding of tissue structure. Choosing the appropriate incision site to expose the tumor tissue is crucial to improving the tumor resection rate. Because a large retroperitoneal liposarcoma occupies a large amount of space in the abdominal cavity, the surrounding tissues and organs are compressed, and the exposed space is small, making the operation difficult (18). Based on previous experience in retroperitoneal tumor resection, we found that the scope and selection of the surgical incision site are crucial to the complete resection of the tumor, which can reduce the operation time and the possibility of injury. While performing a comprehensive evaluation of the patient and the tumor, we abandoned the idea of the traditional transabdominal incision approach. We opted to use a method that could better expose the tumor. We entered the abdomen through the chest, and the tumor was visualized entirely and then removed. The postoperative results showed complete resection of the tumor, the operation time was short, and the intraoperative blood loss was small, thereby reducing the surgical impact on the patient and achieving satisfactory results. Exposing the tumor tissue through an abdominal incision is relatively difficult, usually taking 2–4 h or longer. In this case, complete tumor resection took only 30 min via the thoracic approach.

For the resection of large retroperitoneal tumors, attention should be paid to several aspects during surgery. First, the relationship between the tumor tissue and surrounding tissues and organs should be carefully evaluated, especially the large blood vessels, to determine whether it can be completely removed and to avoid damage and massive bleeding. In a large blood vessel injury, a gauze block can compress the bleeding. If the bleeding is considerable, fluid and blood can be transfused through the open channel simultaneously, and changes in vital signs, such as urine volume and blood pressure, can be closely monitored. Second, when peeling the tumor tissue, ensuring the integrity of its envelope, avoiding residual tumor tissue, and trying to achieve abrupt separation, working from the easy to the difficult separation without forcing separation, is of utmost importance. Attention should be paid to the existence of variable structures to avoid unnecessary damage during the operation. Large tumors that invade large blood vessels or surrounding tissues should not be rashly removed. Therefore, a better field of vision should be sought. Determining the spatial relationship between the tumor and surrounding tissues is particularly important. Palliative surgery or combined organ resection is possible. Finally, complete removal of the tumor tissue, checking for any remaining tumors, and complete hemostasis of the wound should be achieved. The abdominal cavity should be washed and soaked with chemotherapy drugs, washed with a large amount of normal saline, counted with gauze, and check again to confirm no bleeding. Importantly, although knot tying is a basic surgical technique, the need for firm and stable knot tying plays a significant role in preventing postoperative complications. In diaphragm repair and thoracic closure, if there are difficulties, it is recommended that a thoracic surgeon assist in suturing the diaphragm during closure to avoid the recurrence of diaphragmatic hernias and affecting the function of the diaphragm. Compared with a single abdominal incision or a right median incision, there are some disadvantages to making two 20-cm incisions through the chest. For example, it may increase the risk of pleural effusion, lung injury, and pneumothorax. It can also increase the incidence of postoperative pain,

pulmonary infections, and incision-related infections and prolong the hospitalization and recovery time of patients. However, we comprehensively considered these factors during the preoperative evaluation. Given the overall condition of the patient and the prospect of better tumor exposure, complete resection, and diaphragmatic hernia repair, we implemented this feasible and safe method. Intraoperatively, the patient was given indwelling thoracic drainage. Postoperatively, the patient was given comprehensive care such as fluid replacement, nutritional support, anti-infection medications, atomization, tracheal management, and instructions to try small movements and resume their activities of daily living. It is suggested that a rehabilitation doctor be consulted and that lung and diaphragm function training be provided to patients. All of these aspects can optimize healing.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical approval has been exempted by the Ethics Committee of the Second Affiliate Hospital of Nanchang University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

B-EH: Completed patient data collection and references. C-LW: Completed this data collation and drafted this article. J-PL: Completed the drawing and revised the references. W-JZ: Designed this study, completed the writing and revision of the article, and received funding. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Favorable response to PD-1 inhibitor plus chemotherapy as first-line treatment for metastatic follicular dendritic cell sarcoma of the spleen: a case report

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Follicular dendritic cell sarcoma (FDCS) is an uncommon low-grade malignant sarcoma. For localized FDCS, surgery is the most commonly recommended therapy option. However, there is no standard treatment protocol for metastatic FDCS. Here, we present a 68-year-old female with primary spleen FDCS who had multiple peritoneal metastases. She was treated with sintilimab (PD-1 inhibitor) plus chemotherapy (epirubicin plus ifosfamide) as first-line treatment achieving partial response (PR) and a relatively long progression-free survival (PFS) of 17 months. This case suggests that PD-1 inhibitor plus chemotherapy as first-line therapy seem to be a promising treatment option for metastatic FDCS.

KEYWORDS

PD-1 inhibitor, immunotherapy, follicular dendritic cell sarcoma, sintilimab, chemotherapy

Introduction

Follicular dendritic cell sarcoma (FDCS) is an extremely rare low-grade malignant sarcoma that originates from follicular dendritic cells. Most FDCS arises from lymph nodes, with the cervical, axillary and intra-abdominal lymph nodes being the most frequently affected. Less than one-third of cases occur in extra-nodal sites, such as the liver, lung, tonsil, nasopharynx, pancreas and spleen (1, 2).

Due to the rarity of this disease, no standard treatment protocol exists. For patients with localized disease, most received surgery with or without adjuvant therapy. In clinical practice, chemotherapy is mostly used for patients with metastatic FDCS. Commonly used chemotherapy regimens have included CHOP (cyclophosphamide, vincristine, doxorubicin, prednisolone), ICE (ifosfamide, carboplatin, etoposide), ABVD

(doxorubicin, bleomycin, vincristine, dacarbazine) and gemcitabine plus taxane (2–4). However, the efficacy of chemotherapy is limited, and the 2-year survival rate for distant metastatic diseases is approximately 40% (2). Therefore, more effective drugs need to be found.

Programmed death-1 (PD-1)/programmed death factor ligand-1 (PD-L1) checkpoint inhibitors are the main strategies of immunotherapy and have made breakthrough progress in the treatment of various cancers (5–9). However, there are only a few studies on the use of PD-1/PD-L1 inhibitors in patients with FDCS (10–13). Here, we present the first case of metastatic FDCS with high tumor PD-L1 expression and abundant tumor-infiltrating lymphocytes (TILs) in the tumor microenvironment that achieved partial response (PR) and a long progression-free survival (PFS) of 17 months after receiving PD-1 inhibitor plus chemotherapy as first-line treatment.

Case presentation

A 67-year-old female presented with recurrent episodes of fever for 20 days in July 2020. She went to the hospital, and a computed tomography (CT) scan showed a mass lesion with a size of 8.1 cm*7.2 cm in the spleen. On August 28, 2020, she underwent splenectomy. Postoperative pathology showed that the tumor was positive for CD35, CD21, CD23 and CD20 (Figures 1A-C). The Ki-67 expression index was 20-30%, and EBER1/2-ISH was positive. Pathological diagnosis confirmed it to be follicular dendritic cell sarcoma of the spleen. She did not receive adjuvant chemotherapy or radiation after surgery. On the follow-up after one year, CT in October 2021 (Figures 2A1-A3) indicated extensive intraperitoneal metastases, including in the original splenic zone and beside the left-side colon (the largest nodule size was 3.2*2.6 cm). Surgical debulking of the lesions was not considered feasible by the surgeons.

To help establish the treatment for her, immunohistochemical (IHC) staining of PD-L1 (Figure 1D) and multiple immunofluorescences to evaluate the tumor microenvironment (TME) of this patient in both spleen FDCS cells and tumor stromal cells (Figure 3) were carried out. The tumor proportion score (TPS) was 1%, and the combined positive score (CPS) was 10. The data indicated that the tumor cells expressed a high level of PD-L1. Moreover, a relatively high density of infiltrating CD8+ T cells was also observed in tumor cells (2.20%) and stromal cells (3.82%), indicating tumor-infiltrating lymphocyte (TIL) positivity. The analysis revealed that the tumor of this patient expressed both PD-L1 and TILs, indicating the presence of “adaptive immune resistance”. Meanwhile, the low levels of PD-1+CD8+ (0.12% in tumor cells and 0.04% in tumor stromal cells) and CD4+FoxP3+ (0% in both tumor and tumor stromal cells) showed that the inhibitory function of Treg cells was weak. Furthermore, tumor-associated macrophages (TAMs) mainly include two functional states, M1 (anti-tumour) and M2 (tumor-promoting), and for this patient, the proportion of M1-type macrophages (1.59%) was higher than that of M2-type macrophages (0.75%). The above information demonstrated that this patient might be more likely to benefit from immune checkpoint therapies. Next-generation sequencing (NGS) testing results showed low tumor mutation burden (TMB-L) (0.96 Muts/Mb, 8%) and microsatellite stability (MSS).

The patient decided to undergo immunotherapy combined with chemotherapy as palliative first-line treatment. On Oct 12, 2021, she received her first cycle of the AI (epirubicin plus ifosfamide) chemotherapy regimen plus sintilimab (anti-PD-1) every 3 weeks thereafter. After 5 cycles of combined treatment, a CT scan on

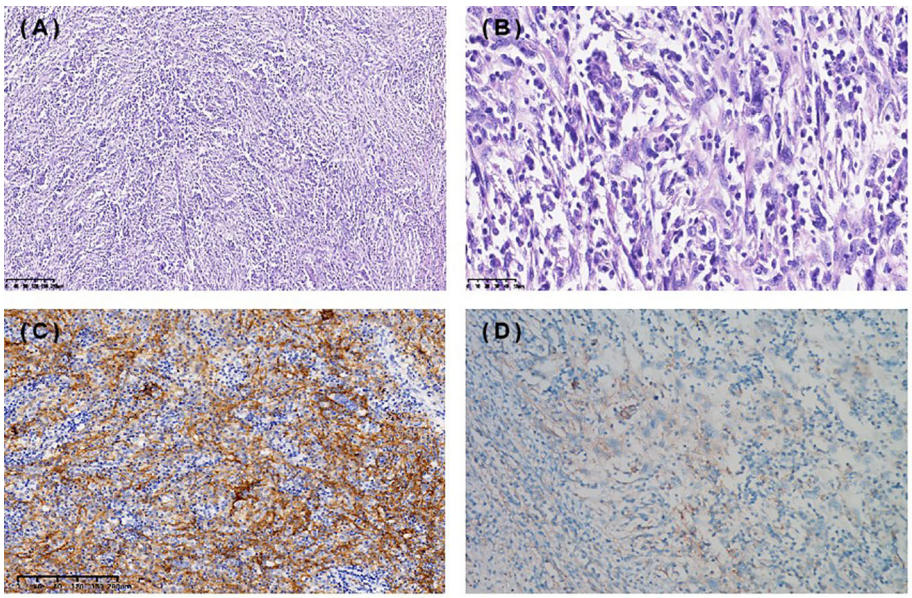

FIGURE 1
Immunohistochemical staining (IHC) of spleen follicular dendritic cell sarcoma (FDCS). Hematoxylin and eosin staining 10X **(A)**, 40X **(B)** . **(C)** Tumor cells were positive for CD35. **(D)** PD-L1 TPS 1%, CPS 10.

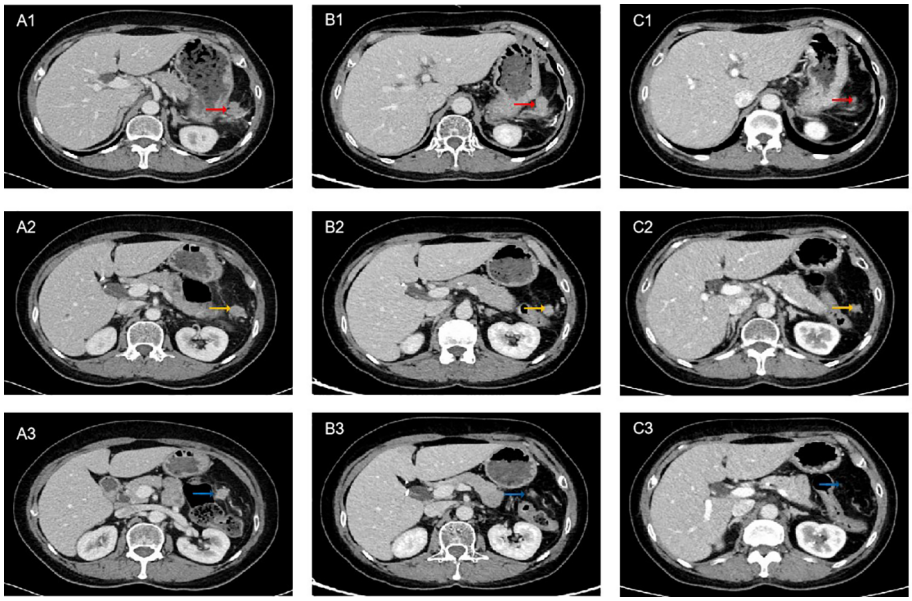

FIGURE 2
Computed tomography (CT) scan of the patient on treatment. **(A1-A3)** Pretreatment. **(B1-B3)** After 5 cycles of PD-1 inhibitor plus chemotherapy, CT showed partial response (PR). **(C1-C3)** After 8 cycles of PD-1 inhibitor plus chemotherapy combined with radiotherapy, CT showed sustained PR. The red arrows indicate lesion 1, yellow arrows indicate lesion 2, and blue arrows indicate lesion 3.

March 5, 2022 (Figures 2B1-B3) showed a decrease in the size of the nodules (the largest nodule size was 2.5*2.4 cm). The efficacy was partial response (PR) based on Response Evaluation Criteria In Solid Tumors (RECIST) v1.1. After eight cycles of PD-1 inhibitor plus chemotherapy, the patient continued to receive maintenance sintilimab monotherapy once every 3 weeks. After achieving PR, the surgeons considered there was still no indication for surgery. To achieve better local tumor control, radiotherapy was administered to her from June 17, 2022, to August 8, 2022 (60 Gy/30 f). Persistent PR was observed after 8 cycles of immunotherapy combined with chemotherapy plus radiotherapy (Figures 2C1-C3). Until March 2023, the follow-up CT scan showed disease progression in the hepatic hilar lymph node. The progression-free survival (PFS) was 17 months following sintilimab plus chemotherapy as first-line treatment. During the treatment period, the patient experienced treatment-related adverse events of grade 2 leukopenia and grade 2 hypothyroidism, and her general condition was good.

Discussion

To the best of our knowledge, this is the first report that metastatic FDCS had a good response and long PFS to a combination of anti-PD-1, chemotherapy, and radiotherapy as first-line treatment.

FDCS was first described by Monda in 1986 (14). Gatta G documented the incidence of FDCS as 0.05/10,0000/year (15). It occurred mainly in adults, and there was no sex difference (2). The etiopathogenesis of FDCS remains unclear. It often manifests as slow-growing, asymptomatic or painful masses. The diagnosis of

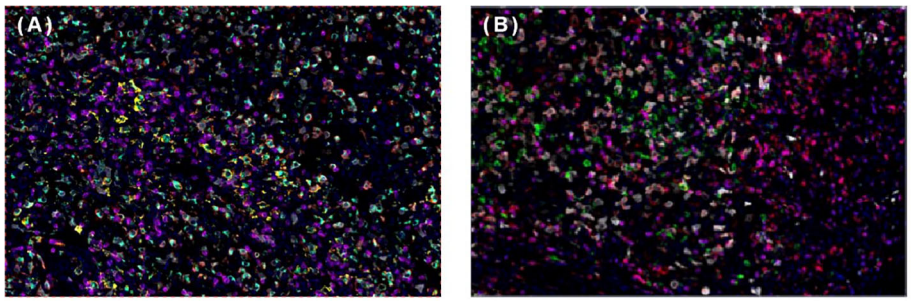

FIGURE 3
Multiplex immunofluorescence of spleen follicular dentritic cell sarcoma (FDCS). **(A)** Immunofluorescence staining of PD-1 (green), PD-L1 (yellow), CD8 (magenta), CD68 (cyan), and CD163 (red). **(B)** Immunofluorescence staining of CD3 (magenta), CD4 (red), CD20 (green), CD56 (cyan), and FoxP3 (yellow).

FDCS is mainly dependent on IHC features. Tumor cells typically express one or more of the following markers: CD21, CD35, CD23, clusterin and CXCL13. CD21, CD35 and CD23 were positive in our patient. Therefore, the definite diagnosis of FDCS was made based on IHC and histologic microscopic findings for this patient.

FDCS is considered to be a low- or intermediate-grade malignancy (16). Local recurrence was observed in 28% of patients, and 27% of cases experienced distant metastasis (2, 3). Unfortunately, our patient developed distant metastases 1 year after surgery. For patients with metastatic disease, the 2-year survival rate was only 42.8%, and the median survival was 9 months (range 0.25-72 months) (2). There is no standard treatment protocol for FDCS even today. Surgical treatment is the most often used therapy for localized FDCS. The role of adjuvant chemotherapy or radiotherapy is debatable (2, 17–19). For patients with unresectable, recurrent and metastatic disease, therapies are diverse. Chemotherapy with or without radiotherapy is the most frequently used treatment. Chemotherapy regimens for aggressive lymphoma are commonly used, such as CHOP, ABVD or ICE, but there is still no consensus.

The therapeutic landscape of tumors has significantly changed over the last years with the rise of immune therapy, especially the immune checkpoint PD-1/PD-L1-based immunotherapy. Xu et al. reported that 50% of FDCS patients were positive for PD-L1 (20). Seven (54%) of 13 assessable FDCS cases showed moderate to strong membranous staining for PD-L1 (21). About 40-60% FDCS cases exhibited neoplastic PD-L1 expression (22). Over 60% of FDCS cases showed conspicuous reactivity for PD-L1 (23). The expression of PD-L1 in each study is shown in Supplemental Table 1. The results above revealed FDSC patients as rational candidates for immunotherapy. Moreover, the role of immunotherapy was explored with variable responses in a few FDCS cases. A patient with primary small intestine FDCS received sintilimab (anti-PD-1) plus lenvatinib (antiangiogenic agent) as third-line treatment, achieving a PFS of 7 months (10). A trial of salvage nivolumab (anti-PD-1) was attempted to treat a patient with liver metastases without any success (11). Lee et al. reported two patients with FDCS who received nivolumab (anti-PD-1) and ipilimumab (anti-PD-L1) with evidence of tumor response (12). A man with FDCS received pembrolizumab (a PD-1 inhibitor) monotherapy as second-line treatment and achieved a good response (13). However, due to the rarity of FDCS, there remains insufficient evidence on the effectiveness of emerging treatment modalities. At present, no metastatic spleen FDCS receiving multimodal treatment, including immunotherapy, chemotherapy and radiation as first-line treatment has been reported.

Our patient had high expression levels of PD-L1 and TILs. Studies have shown that high PD-L1 may be a predictive biomarker for the efficacy of PD-1/PD-L1 therapy (5, 24, 25). Patients with higher TIL density predict favorable outcomes (26). Moreover, PD-L1+/TIL+ tumors are most likely to respond to PD-1/PD-L1 blockade therapy (27). Furthermore, TME analysis revealed the weak Treg cells and a high proportion of tumor-associated macrophage M1 type cells. Treg cells suppress effective tumor immunity, being associated with poor prognosis in cancer patients (28) and can be used as a predictor of the clinical efficacy of anti-PD-1 therapies (29). Increasing levels of M1 macrophages indicate a better prognosis (30). Considering the above factors, this patient was treated with sintilimab. The findings in phase III clinical trials have already confirmed the efficacy of immunotherapy combined with standard-of-care chemotherapy to treat tumors (31–34). The underlying mechanisms of these synergetic results include immunogenic tumor cell death, antiangiogenesis, selective depletion of myeloid immunosuppressive cells, and lymphopenia, which decreases regulatory T cells and makes room for proliferation of effector T cells (35, 36). Therefore, she received immunotherapy combined with chemotherapy. In addition, radiation was reported to be used to control local lesions in patients with FDCS (12, 13). Therefore, radiotherapy was also used for her. Through multiple treatment modalities, this patient achieved PR and a long PFS of 17 months.

Conclusion

To the best of our knowledge, this is the first case of metastatic spleen FDCS with high expression of PD-L1 and TILs receiving PD-1 inhibitor plus chemotherapy as first-line treatment obtained a long PFS. This case suggests that a combination of immunotherapy and chemotherapy as first-line treatment might be a new therapeutic option for metastatic FDCS patients. We also highlight that PD-L1 and TME analyses are important technologies to assist in treatment choice. Further large prospective studies are warranted to confirm the results.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee of West China Hospital, Sichuan University, China. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

JL, MR, FB, YC, and ZL were responsible for the treatment of this patient. JL was responsible for drafting the article. YC was responsible for article revising. All authors commented on previous versions of the manuscript and approved the final manuscript. All authors contributed to the article.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2023.1228653/full#supplementary-material

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Case Report: Primary osteosarcoma of the kidney

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Extraosseous osteosarcoma is a rare malignant tumor, most commonly occurring in the thigh, upper limbs, and retroperitoneum. However, there are only a few reported cases of renal osteosarcoma. Herein, we present the case of a 54-year-old woman with malignant extraosseous osteosarcoma of the left kidney. CT and MR imaging revealed a soft tissue mass originating from the left kidney.

KEYWORDS

osteosarcoma, extraosseous, kidney, MRI, CT

Introduction

Primary renal osteosarcoma is an uncommon extraosseous malignant tumor that arises in the kidneys. While there have been sporadic cases reported in the literature, there's still limited understanding of the variations in clinical presentations and prognoses. Our report provides a unique case with specific imaging and genetic findings, adding to the existing pool of knowledge. Primary renal osteosarcoma mostly affects adults and has a poor overall prognosis (1). Nonspecific features and intra-abdominal location make detection difficult until late into disease progression (2). Here, we present a case of primary osteosarcoma of the kidney and review its clinical features, diagnosis, and treatment options.

Case report

A 54-year-old female farmer presented with a 6-month history of abdominal pain, and 4 months of weight loss of approximately 5 kg. She had left abdominal pain with no tenderness, accompanied by a mass for 6 months. Physical examination revealed no tenderness in the abdomen. Abdominal computed tomography (CT) (Figure 1A) revealed a mixed-density mass in the left kidney. The mass displayed heterogeneous attenuation with clear boundaries, measuring approximately 8 × 6 cm in size. Magnetic resonance imaging (MRI) revealed a mixed solid cystic mass in the left kidney (Figure 1B). The mass had unclear boundaries,

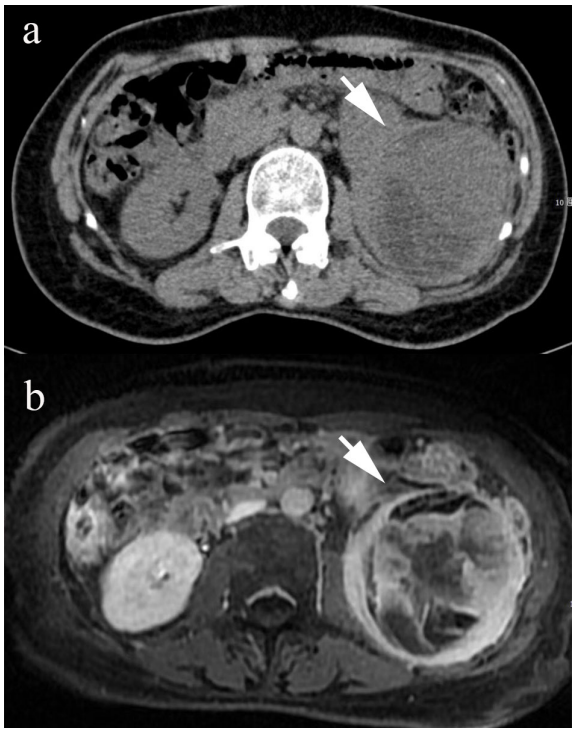

FIGURE 1
The CT image shows a mixed-density mass in the left kidney ((**A**), arrow). The MR examination shows a mixed solid-cystic mass with unclear boundaries in the left kidney ((**B**), arrow).

possibly indicating local invasion. A routine urine examination revealed an NWBC count of 5 U/L. All other biochemical profiles were within normal limits. The patient has no significant family history of any malignancies or known genetic predispositions. Her occupation as a farmer did not expose her to any known risk factors associated with renal osteosarcoma. We surgically excised the lesion, which measured approximately 8 × 6 × 5 cm. There were no enlarged retroperitoneal lymph nodes. Postoperative pathology revealed a left renal primary osteosarcoma. No recurrence was observed 1 year after surgery.

Pathological findings: After gross examination, the kidney revealed an 8 × 6 cm tumor replacing the lower part of the left kidney. The surface cut showed cystic and solid masses with hemorrhagic areas. Microscopic examination using hematoxylin–eosin staining revealed numerous spindle cell proliferations with interspersed osteoid calcifications (Figure 2). Immunohistochemistry: vimentin+, CD4+, CD34, CD99, CD117, desmin, myogenin, S-100, EMA, Fly-1, and Dog-1 were negative, and the Ki-67 positivity rate was approximately 40%. Therefore, the patient was diagnosed with osteosarcoma. Genetic tests identified three variants (PIK3CA, CTCF, and RASA1) among the 733 genes tested; The patient had an uneventful postoperative recovery. Regular follow-up was conducted to monitor the patient's condition, which included CT scans and MR scans. This comprehensive follow-up schedule allowed for close observation of any potential recurrence or complications. No recurrence was observed after 13 months of diligent follow-up. The patient provided informed consent for the publication of her clinical and radiological data.

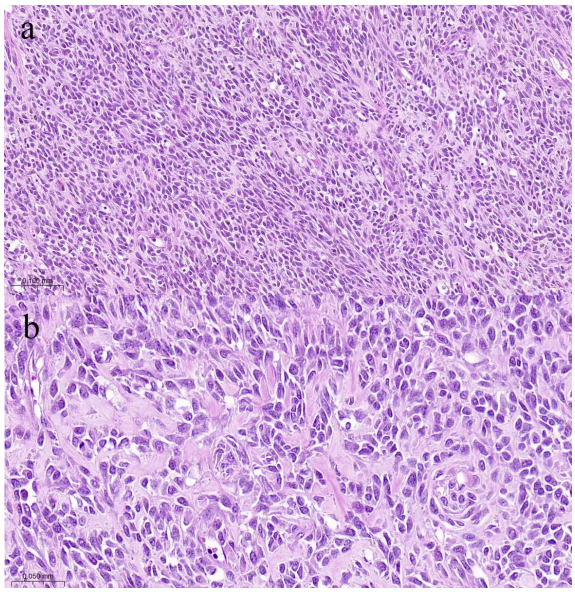

FIGURE 2
Photomicrograph shows many densely distributed invasive tumor cells are arranged in bundles and braided shapes, with collagen-rich interstitial fluid ((**A**), HE×100). The size of tumor cells varies, while the cytoplasm and chromatin are coarse, and partial mitosis is present ((**B**), HE×200).

Discussion

Extraosseous osteosarcoma (EOS) is a rare malignant subtype of osteosarcoma that accounts for about 1% of all soft tissue sarcomas (1) and shares histological features with primary bone osteosarcoma. EOS occurs in all age groups and the male-to-female ratio is 1.9:1 (2). The pathological subtypes of extraosseous osteosarcoma can be divided into telangiectasis, chondroblasts, fibroblasts, osteoblasts, and small cell types. Flank pain and hematuria are the most common complaints in renal osteosarcoma (3).

The exact etiology of EOS remains unclear. According to Virchow's theory (4), the risk factors include exposure to X-rays and radioactive substances. Under certain circumstances, such as radiation, metaplastic transformation occurs from the connective tissue to the embryonic mesenchyme, which can differentiate into osteoblasts and bones.

Common symptoms of renal osteosarcoma are flank pain and hematuria, with weight loss and a progressively enlarged soft tissue mass in the hypochondrium. Some patients experience an occult onset and pain. In most cases, by the time patients go to a clinic, the mass would have grown quite large (5). Hence, patients often have a concealed symptom onset.

Historically, EOS in kidneys has been an elusive diagnosis with only 28 cases documented, including this case reported here. The manifestation in our patient, particularly the imaging and genetic findings, aligns yet somewhat differs from previous reports, emphasizing the heterogeneity of this disease. Flank pain and hematuria, as observed in our patient, are the most common complaints in renal osteosarcoma (6). However, a comprehensive

review of the existing literature, including a notable study in the American Journal of Clinical Pathology (6), showcased a range of clinical presentations and outcomes. Such variations underscore the need for a consolidated case table, which we provide below, contrasting our findings against the historical cases (Table 1) (3, 7–26).

In general, osteosarcoma in the kidney grows aggressively and is extremely fatal, and the contiguous structures of the kidney, such as the spleen, liver, and adrenal gland, can easily be infiltrated. The prognosis of EOS in the kidney or other locations is poor, with approximately 86% of patients with EOS in the kidney having metastases (27). In our case, it was difficult to detect EOS because all biochemical blood test results were often normal, except serum alkaline phosphatase, which has a relatively poor diagnostic specificity. CT scans are considered to be relatively characteristic because most of the renal EOS presents as a mass in the kidney, which resembles a "sunburst" space-occupying lesion. Clinical manifestations, imaging such as CT and MR, and pathological examinations are necessary for the diagnosis of EOS. Allen et al. reported 26 patients with EOS and summarized the points of diagnosis for EOS. First, the mass appeared in soft tissue but did not adhere to the bone or periosteum; Second, pathological examination showed that the mass manifested as a sarcoma pattern; Third, the mass-produced a bone-like cartilage matrix (28). No definitive osseous matrix was observed in this case. Consequently, a multitude of diagnostic challenges have arisen in this particular instance.

Our patient underwent genetic testing after surgery. We analyzed 755 tumor-associated genes and identified three associated genes (*PIK3CA*, *CTCF*, and *RASA1*). *PIK3CA* has been reported in colorectal, ovarian, and breast cancers; a study by Ian G (29) showed that *PIK3CA* is an oncogene in ovarian cancer, greatly extending recent findings in breast cancer, and encodes a highly conserved zinc finger protein that has been implicated in diverse regular functions (30). Mutations in *RASA1* can cause capillary malformations, which may result from the loss of functional proteins produced by the genes (31). Since there was no clinical evidence to support the suspicion that she was sensitive to chemotherapy, the patient did not receive chemotherapy after surgery.

TABLE 1 Summary of clinical and pathologic features of 29 primary renal osteosarcoma cases.

Characteristic	Value
Age range (mean; median), y	47-81 (59; 59)
Sex	
Male	17 (59)
Female	12 (37)
Initial symptoms	
Weight loss	5 (17)
Palpable mass	8 (28)
Flank pain, weight loss	7 (24)
Flank pain, palpable mass	2 (7)
Pelvic and back pain	1 (3)
Back pain	1 (3)
Flank pain	3 (10)
Flank pain, gross hematuria	2 (7)
Histotype	
Classic (NOS)	12 (41)
Pleomorphic	11 (38)
Osteoblastic	3 (10)
Chondroblastic	2 (7)
Low grade	1 (3)
TNM stage	
pT1a N0M0	1 (3)
pT1b N0M0	1 (3)
pT2aN0M0	1 (3)
pT3a N0M1	9 (27)
pT3aN1M1	1 (3)
pT4N0M1	1 (3)
pT4N1M1	15 (52)
Treatment	
RN	15 (52)
RN + ChT	10 (34)
RN + RT	9 (31)
Side	
Left	18 (62)
Right	11 (39)
Follow-up, mo	
DOD (range, 2 wk to 32 mo; mean, 15 mo)	21 (76)
AWD (both at 6-mo follow-up)	3 (10)
NED (range, 13-72 mo; mean, 27 mo)	4 (7)
DOC (range, 9-10 mo; mean, 9.5 mo)	2 (7)

AWD, alive with disease indicates metastases; ChT, chemotherapy; DOC, died of other causes; DOD, died of disease; NED, no evidence of disease; NOS, not otherwise specified; RN, radical nephrectomy; RT, radiation therapy. Values are presented as numbers (%) unless otherwise indicated.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by The ethics committee of Zhuhai People's Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

JD, GW, and JZ: manuscript writing. QZ: pathological review. JC, HL and RZ: manuscript revision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Analysis of recurrence and metastasis patterns and prognosis after complete resection of retroperitoneal liposarcoma

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Objective: To analyze the recurrence and metastasis patterns and prognosis after complete resection of retroperitoneal liposarcoma.

Methods: The clinical postoperative follow-up data and results of patients who underwent complete resection of retroperitoneal liposarcoma from September 10, 2014, to September 8, 2021, at Hebei Medical University hospital were collected retrospectively.

Results: A total of 60 patients with complete resection of retroperitoneal liposarcoma, including 33 cases of retroperitoneal liposarcoma recurrence, 2 cases of liver metastasis, and 1 case of lung metastasis, were included. The results showed that 100% of the recurrent sites were located in the primary region of the tumor, with most recurrences located near the kidney, paracolic sulci, and iliac vessels. Three patients had distant metastasis without obvious recurrence on imaging examination. The pathological type of retroperitoneal liposarcoma, Ki67 expression, and presence of serum albumin were risk factors for recurrence and metastasis after complete resection of retroperitoneal liposarcoma. The malignancy and Ki67 expression were independent risk factors for recurrence and metastasis as well as for overall survival of patients undergoing complete resection of retroperitoneal liposarcoma.

Conclusion: Complete resection remains the most effective method to treat retroperitoneal liposarcoma. Patients with pathological types of retroperitoneal liposarcoma showing dedifferentiation, pleomorphism, mixed type, and high Ki67 expression should be closely monitored and observed after complete resection, especially for imaging changes in the primary tumor area.

KEYWORDS

retroperitoneal liposarcoma, complete resection, prognosis, recurrence, metastasis

1 Introduction

Liposarcoma is a rare malignancy derived from mesenchymal cells; retroperitoneal liposarcoma (RPLS), which occurs in the retroperitoneal region and is the most common retroperitoneal tumor, accounts for approximately 1% of all malignancies, 25% of all soft tissue sarcomas, and 45% of primary retroperitoneal soft tissue sarcomas (1–3). RPLS refers to a kind of soft tissue malignant tumor originating from adipose tissue and occurring in the retroperitoneal space. It is rare, with a global prevalence rate of approximately 3–4 cases/million per year (4). Although RPLS can occur at all ages, it is rare in teenagers. RPLS peaks at the age of 40–60 years and is slightly more common in men than in women. RPLS includes different histological types of tumors, accounting for approximately 19% of all liposarcomas (5). RPLS occurs in the wide retroperitoneal space, where it is anatomically deep and relatively obscure. Early diagnosis of RPLS is difficult, and most diagnoses are through physical examination. Small tumors show no obvious clinical symptoms or signs; however, as the tumor grows in size, it often compresses and infiltrates adjacent vital organs, blood vessels, and nerves. Most of the symptoms are caused by tumor compression, and the most common symptoms are nonspecific clinical symptoms such as abdominal pain and distension, changes in stool traits, intraperitoneal effusion, and paresthesia of the lower limbs (6). A large mass can occupy much of the abdomen and pelvis and drive the bowel, easily wrapping around the large blood vessels and abdominal and pelvic organs, and growing aggressively along each tissue space. At present, chemoradiotherapy and targeted therapy have limited efficacy in retroperitoneal tumors, and surgery is still the optimal treatment option (7). Initial complete resection with a negative endoscopic margin (R0) is the surgical goal and key to reducing recurrence.

Currently, surgery is known to be the main treatment for RPLS, but postoperative recurrence is common (8). Even after complete capsulectomy and radical resection of the tumor, a complete cure is rarely achieved, which is an important diagnostic and treatment problem associated with the disease (9). A discussion on the recurrence and metastasis patterns of RPLS is scarce in the literature. Therefore, we retrospectively analyzed the clinical and pathological data of patients after RPLS surgery and statistically analyzed the risk factors, patterns of recurrence and metastasis, and impact on survival outcomes of patients with RPLS who underwent complete resection.

2 Methods

2.1 Clinical data

Cases of 60 patients with RPLS, who were treated by surgery at Hebei Medical University from September 10, 2014, to September 8, 2021, were analyzed retrospectively. The inclusion criteria were as follows: (1) diagnosed with retroperitoneal tumors preoperatively through imaging examinations such as computed tomography (CT) scans and absence of a history of other malignant tumors (10). In addition, the availability of complete clinical and pathological data as well as postoperative follow-up data of the patients; (2) the retroperitoneal tumor was completely removed by surgery with the naked eye, and the negative surgical resection margin was pathologically confirmed; and (3) liposarcoma was confirmed by pathological examination after the operation. The exclusion criteria were as follows: (1) a history of other malignant tumors and other serious diseases; and (2) incomplete clinical, pathological, and follow-up data.

2.2 Methods

2.2.1 Treatment methods

Preoperative imaging, such as CT, confirmed the retroperitoneal tumor and the operation was radical (gross complete resection of R1 including combined organ resection) or pathology confirmed the negative surgical margin. Each patient will undergo regular follow-up examinations after complete resection, with a follow-up period of 1 month, 3 months, 6 months, and 1 year. Dedifferentiated patients will receive adjuvant chemotherapy, with a chemotherapy regimen of pirarubicin combined with amitripramide.

2.2.2 Clinical data collection

General clinical data (sex and age), CT image data (tumor size and location), pathological data (resected tumor size and pathological type (high differentiation, dedifferentiation, mucus type, polymorph, and mixed type), tumor margin after radical surgery (gross complete resection, pathological result of surgical margin), and intraoperative data (simple tumor resection and combined organ resection) of patients who underwent complete resection of RPLS included in the study were collected.

2.2.3 Follow-up

The patients were followed up by telephone, outpatient re-examination, and examination upon hospitalization. The follow-up examination methods were mainly through CT, magnetic resonance imaging, and other imaging examinations. The follow-up ended on January 1, 2023, with a median follow-up of 54 months.

2.3 Statistical analysis

Statistical analysis was performed using SPSS27.0 software. The enumeration data were compared using the $\chi 2$ test, expressed as percentage. In this study, we performed a univariate analysis of the factors likely to affect the recurrence and metastasis of RPLS. Multivariate logistic regression was included for variables that significantly differed in the recurrence of RPLS to analyze independent influencing factors for recurrence. The factor analysis of influencing factors of prognosis was performed using

the Cox regression model, and the difference with P<0.05 was statistically significant.

3 Results

3.1 Basic characteristics

Sixty patients (32 men and 28 women), with maximum, minimum, and average ages of 71 years, 26 years, and 50.75 years, respectively, were included in the study, Among them, 18 patients were found to lack clear symptoms during a physical examination. During medical consultation, the main symptoms manifested as abdominal pain in 8 patients, abdominal distension in 16, palpable abdominal mass in 12, changes in stool frequency and traits in 2, lumbago and leg pain in 1, frequent micturition and urgent urination in 1, and gross intermittent hematuria in 1 case. Preoperative CT showed that the minimum, maximum, and average diameters were 4.8 cm, 60 cm, and 21.54 cm, respectively. The presence of a single mass, multiple masses, simple mass resection, and combined organ resection was observed in 40, 20, 40, and 20 patients, respectively. According to abdominal quartering, the primary site was located in 6, 14, 6, and 8 patients in the right upper abdomen, left upper abdomen, right lower abdomen, and left lower abdomen, respectively. In 12 patients, the tumors were located in the left abdomen, both left upper and left lower abdomen; 10 patients had tumors in the right abdomen; and 2 patients had tumors located in the lower abdomen, both left lower and right lower abdomen. The tumors were larger than those in the four abdominal regions where they were distributed.

3.2 Recurrence and metastasis patterns of RPLS after complete resection

In this study, 60 patients who underwent complete resection of RPLS were included. According to the abdominal quartering method, the primary site was located in the right upper abdomen, left upper abdomen, right lower abdomen, and left lower abdomen in 6, 14, 6, and 8 patients, respectively. Twelve patients had tumors located in the left abdomen, both left upper and left lower abdomen, and ten patients had tumors in the right abdomen. Two patients had tumors in the lower abdomen where tumors were located in both the left lower and right lower abdomen, and the tumors were larger than those in the four abdominal regions. The primary site was located in the left abdomen (56.7%). There were 33 cases of recurrence, with a recurrence rate of 55% and the recurrence site was 100% located in the primary area. Distant metastasis occurred directly after surgery in three cases at a metastasis rate of 5%, of which liver metastasis was 3.33% and lung metastasis was 1.67%, as shown in Figure 1. Fourteen cases underwent more than 2 surgeries, and 2 patients received three-dimensional conformal radiotherapy after recurrence.

3.3 Factors affecting recurrence and metastasis of RPLS after complete resection

In this study, 36 of the 60 patients who underwent complete resection of RPLS showed recurrence and metastasis; of these 21 had pathologically dedifferentiated liposarcoma, 5 had mucinous, 3 had mixed, 4 had highly differentiated, and 3 had pleomorphic pathological types. Univariate analysis showed that recurrence and metastasis of RPLS after complete resection were related to the pathological type, Ki67 expression, and serum albumin level but not to sex, age, height, weight, body mass index, hemoglobin level, tumor diameter, single and multiple tumors, or whether the tumor was partitioned or lobulated by CT (Table 1). Logistic regression analysis showed that malignancy and Ki67 expression were independent risk factors for the recurrence and metastasis of RPLS after complete resection, as shown in Table 2.

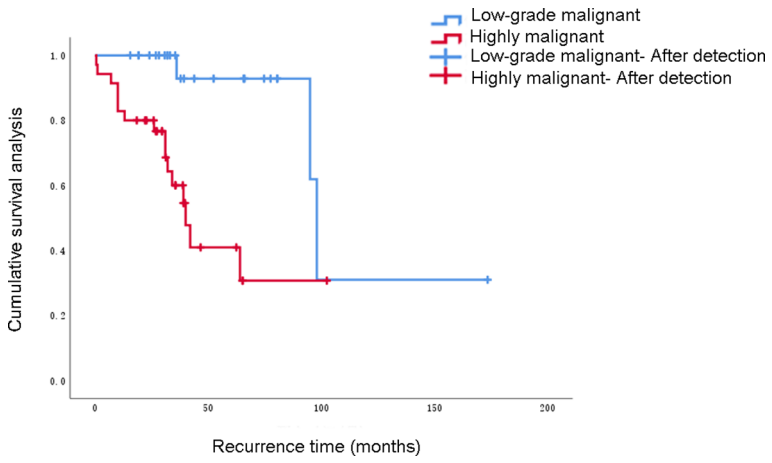

FIGURE 1
Recurrence and metastasis pattern of retroperitoneal liposarcoma after complete resection.

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TABLE 1 Single-factor analysis of recurrence and metastasis of retroperitoneal liposarcoma after complete resection.

Clinical features	No recurrence (n=24)	Recurrence (n=36)	χ2/t	P
Sex				
Male	12 (50.00%)	20 (55.56%)	0.044	0.833
Female	12 (50.00%)	17 (44.44%)		
Age, y	50.75 (11.51)	55.69 (10.54)	1.716	0.092
Height, cm	165.92 (7.73)	164.97 (7.88)	0.458	0.648
Weight, kg	64.88 (13.16)	66.35 (10.55)	0.483	0.632
BMI	22.87 (4.87)	24.58 (2.87)	1.536	0642
Hemoglobin, g/L	130.42 (21.4)	121.88 (20.86)	0.469	0.130
Albumin, g/L	40.20 (6.07)	33.5 (7.11)	3.733	0.000
Tumor diameter, cm	17.38 (11.06)	21.43 (12.69)	0.831	0.410
Ki67, %	6.505 (9.27)	16.37 (14.82)	3.713	0.002
Pathological type				
Pleomorphic LPS	1 (4.17%)	3 (8.33%)	18.929	0.001
Well-differentiated LPS	12 (50.00%)	4 (11.11%)		
Mixed LPS	0 (0%)	3 (8.33%)		
Myxoid LPS	6 (25.00%)	3 (8.33%)		
Dedifferentiated LPS	5 (20.83%)	23 (63.89%)		
CT imaging				
Single shot	19 (79.17%)	27 (75.00%)	0.140	0.709
Multiple shot	5 (20.83%)	9 (25.00%)		
Surgical resection range				
Simple tumor resection	18 (75%)	21 (58.33%)	1.758	0.185
Combined organ resection	6 (25%)	15 (41.67%)		
Blood transfusion volume	410.00 (1351.86)	768.19 (811.85)	1.283	0.204
Neutrophils/ lymphocytes	3.50 (2.50)	4.03 (2.89)	0.724	0.471

(Continued)

TABLE 1 Continued

LPS, liposarcoma.

3.4 Factors affecting the overall survival rate and progression-free survival rate of patients undergoing complete resection of RPLS

In this study, 60 patients who underwent complete resection of RPLS survived from 0.5 to 196 months as of the follow-up date, and 41 patients were still alive. The 1-, 3- and 5-year OS rates were 91.7%, 71.1%, and 46.6%, respectively. The PFS rates were 76.7%, 54.3%, and 27.8%, respectively. The survival curve was drawn using the Kaplan–Meier method, and the influencing factors were analyzed by the Cox risk regression model. The results showed that the degree of malignancy, Ki67-positivity expression rate, and albumin level were risk factors for PFS in patients undergoing complete resection of RPLS. Among them, the degree of pathological OS factors for progression-free survival of PFS in patients undergoing complete resection of RPLS (Figures 2–4, Table 3). Malignancy and Ki67 expression were also risk factors for OS in patients undergoing complete resection of RPLS (Figure 5, Table 4).

4 Discussion

Patients with multiple recurrences have progressively shorter recurrence intervals, and approximately 75% of patients die from recurrent tumor recurrence (11), the rate of which has been reported as 55%. According to the abdominal quartering method, 100% of recurrence sites are located in the primary abdominal subregion, mostly near the perinephric region, paracolonic groove, and iliac blood vessels. RPLSs are prone to relapse in situ, which, we believe, may be because of the following reasons: (1) Because most RPLSs have a complete capsule, most surgeons probably consider that it is not aggressive, and aim to ensure the integrity of the capsule during the operation. However, the invasive ability of RPLS may exceed that established previously by the surgical community. The Dana-Farber Institute of Oncology found that the endoscopic infiltration depth of both highly differentiated and poorly differentiated liposarcoma was more severe than that indicated by a macroscopic evaluation during the operation (12). Gronchi et al. found that a positive surgical strategy combined with the resection of organs 1–2 cm around the tumor could significantly reduce the local recurrence rate (61–36%) (13). In addition, different histological types of RPLS have different biological characteristics and different invasive abilities, which are related to their recurrence (14). Whether the surgical resection range can be determined

TABLE 2 Logistic regression results.

Clinical pathological factors	β	SE	95%CI	P
Albumin	0.720	0.290	0.276	0.860
Ki67A	0.048	0.068	0.918	1.198
Low-grade malignant	0.411	1.456	0.087	26.202
Highly malignant	5.594	2.149	0.000	0.251

according to the invasive ability of different histological types has not yet been studied. (2) RPLS usually has no specific clinical manifestation in the early stage; it is generally large-sized when discovered and easily invasive, growing in the interstitial spaces of tissues, often easily compressing, encapsulating, or invading adjacent vital organs and blood vessels. The operation is difficult, which means that residual tumor cells are more likely to be present when examined under the microscope. Moreover, due to the infiltrative extent of RPLS and the particularity of histopathology, intraoperative frozen section examination is almost impossible to achieve. With pathological advancements, a more effective method is expected to be developed for evaluating the intraoperative margin of RPLS in the future. (3) In addition, RPLS is large in size, and surgical operation often results in tumor capsule rupture. A previous study has shown that approximately 20% of tumors rupture during RPLS surgery (15), which may also be the reason for *in situ* recurrence of RPLS. RPLS often recurs near the kidney, paracolonic groove, and iliac blood vessels. The authors suggest that there may be several reasons for this: (1) There are more adipose tissues around the kidney, paracolonic groove, and iliac blood vessels. RPLS arises from the malignant transformation of adipose tissues in these regions; (2) There is relatively more soft tissue and relatively deeper infiltration of malignant cells in these areas; (3) There are relatively more important tissues and organs in these regions, which makes the operation more difficult; and (4) the probability of tumor rupture is higher, which is associated with an increased number of residual tumor cells. Future studies are expected to prove this hypothesis.

In the Transatlantic Australasian Retroperitoneal Sarcoma Working Group consensus, for patients with first local recurrence of RPS, a nomogram to predict survival is available to assist in this decision (16). Clinicopathologic variables to be considered in the decision-making process for patients with first recurrence include histologic type, grade, multifocality, and expected completeness of the second resection, among others (16). At present, extended resection mainly includes combined resection of the organs 1–2 cm around the tumor and resection of the adjacent organs without tumor invasion to ensure a negative margin. Relevant studies have shown that although extended resection can effectively reduce the recurrence rate, it is not conducive to long-term survival and reduces the quality of life of patients after surgery. There is currently no consensus on a detailed definition of extended-scope resection. The current relatively accepted surgical approach is simple and complete resection of the tumor, combined with full excision of the affected organ when organs are involved, the most common being one side of the kidney, adrenal gland, and colon (17, 18). These excisions are all aimed at improving the complete resection rate of the tumor, prolonging the survival time, and reducing the recurrence rate. According to the data obtained in this study, it remains to be further investigated whether surgical resection of the perirenal vessels, paracolonic vessels, and soft tissue near the iliac vessels, where possible, can reduce the recurrence rate of RPLS.

The most important characteristic of RPLS is that it easily recurs *in situ* after surgical resection. In this study, a total of 30 patients relapsed, with a recurrence rate of 72.2% over five years. Univariate analysis showed that Ki67 expression, tumor malignancy, and albumin level were important factors for the recurrence of the tumor after surgery (all P values < 0.05); the results of logistic regression analysis were consistent with the above results ($P < 0.05$). The results indicate that the differentiation degree of RPLS is closely related to the clinical features, that high-grade

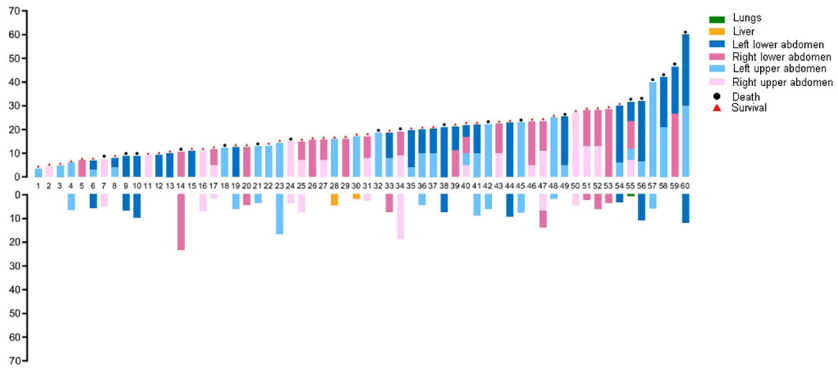

FIGURE 2
Progression-free survival.

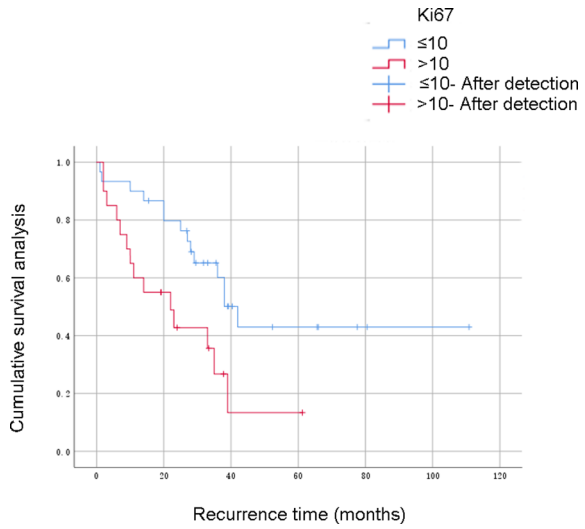

FIGURE 3
Progression-free survival.

malignant tumors are related to local recurrence and distant metastasis, and that the pathological type and surgical margin are closely related to prognosis (19). The higher the malignancy of RPLS, the faster the growth rate of general tumors and the stronger their invasiveness. Tumors easily invade or surround the surrounding organs, blood vessels, and other tissues, which increases surgical difficulty. The higher the probability of intraoperative endoscopic tumor residue and intraoperative tumor rupture, the more likely these patients with RPLS are to have local recurrence after surgery. The more active the tumor cells are, the more likely the patients will experience recurrence. In addition, owing to the large size of retroperitoneal tumors, the nutritional status of a significant percentage of patients is deficient, as indicated by body mass index alone. A prospective study showed that 46% of patients with retroperitoneal tumors had protein malnutrition (20), with a 43.3% hypoproteinemia rate. Malnutrition may affect the production and release of inflammatory mediators, thus reducing the immune response, as well as reducing the antioxidant and direct antitumor effects (21, 22), thereby increasing the tumor recurrence rate. Ki67 is an essential tumor cell proliferation marker, which reflects the proliferative activity of tumor cells. Most studies have shown that a higher Ki67 expression represents a greater proliferative activity of tumors. Based on existing literature from China and other countries, and the current study results, we believe that the degree of RPLS malignancy, Ki67 expression positivity, and nutritional status of patients are important factors affecting postoperative recurrence. Patients with these high-risk factors for recurrence need close follow-up after surgery to reduce their risk of recurrence of RPLS and improve their prognosis. Moreover, low serum albumin may mirror a poor performance status of cancer patients who are at increased risk of death. Albumin helps to maintain intravascular oncotic pressure and acts as a radical scavenger (23). It is not known whether the association is a general oncogenic effect or attributed to a specific cancer. Previous studies have also proved that serum albumin could be used for individual risk estimation and integrated in existing prognostic models for soft tissue sarcoma (24, 25).

In this study, univariate analysis showed that tumor malignancy, Ki67 expression, and serum albumin levels were important influencing factors of the PFS time of the patient (*P* values were all < 0.05). Multivariate analysis showed that tumor malignancy and positive Ki67 expression were independent risk factors for the patient's PFS time. Malignancy was an independent risk factor for the OS of patients with RPLS ($P < 0.05$). The 1-, 3-, and 5-year OS rates of patients in this group were 91.7%, 71.1%, and 46.6%, respectively. Recurrent episodes were the leading cause of death. Studies have shown that, compared with patients with low-grade differentiated liposarcoma, those with polymorphous liposarcoma and mixed liposarcoma with higher malignancy, high-grade differentiated liposarcoma and myxoid liposarcoma with lower malignancy had better prognoses (26). Therefore, we believe that tumor malignancy is an important factor affecting the OS of patients with RPLS. A previous study demonstrated the potential role of ECM in the mechanism of action of trabectedin in

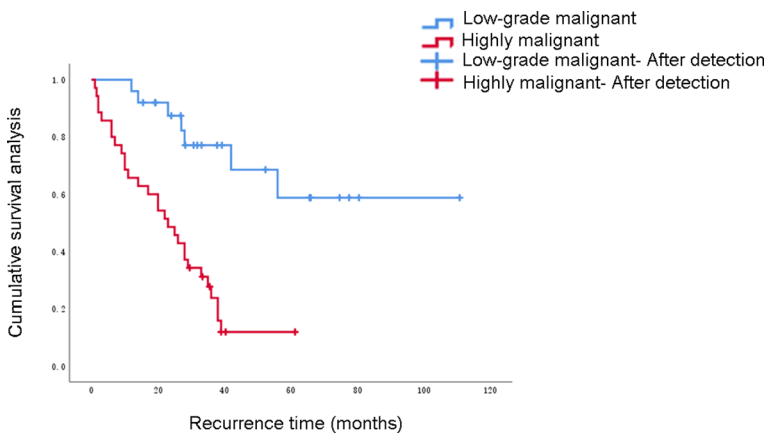

FIGURE 4
Progression-free survival.

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TABLE 3 Factors influencing disease-free survival rate.

Category	Grouping	Cases	Univariate analysis	Multivariate analysis
Tumor diameter (grouped by median)	<=17	31	0.633	
	>17	29		
Malignancy degree			<0.001	0.001
	High	25		
	Low	35		
Ki67 (grouped by median)	<=10	35	0.002	0.017
	>10	25		
Single shot CT imaging	1	46	0.605	
	2	14		
Surgical resection range	1	39	0.096	
	2	21		
Albumin grouping	<=35.9	32	0.012	0.918
	>35.9	28		

some of most frequent STS histotypes in adults. It underlines the involvement of tumor microenvironment component in predicting response to trabectedin and provide the rationale for better stratifying patients which would be candidate for this drug (27).

In the present series, the risk of local recurrence after primary resection was 2.5 percent at 3 years (28). Strategies aimed at improving outcomes for well-differentiated liposarcoma should primarily focus on enhancing the quality of surgery. The extent of surgical intervention should be tailored based on tumor location and characteristics, while minimizing the associated morbidity rate associated with extensive resection (29). It is important to consider that tumor biology may contribute to recurrence, and there could be a potential field change in the retroperitoneal and intra-abdominal fat that contributes to recurrence development (30). Future strategies to improve outcomes in dedifferentiated liposarcoma should not only concentrate on optimizing local therapy but also explore the potential of new medical treatments. A phase III multicenter randomized trial is currently underway to compare surgery alone with preoperative radiotherapy followed by surgery. The goal is to determine whether the addition of preoperative radiotherapy can reduce the risk of local recurrence. However, preliminary evidence suggests that the addition of preoperative radiotherapy may not provide significant benefits for patients with retroperitoneal sarcoma (31). Another ongoing randomized study, the STRASS 2 trial, is an international multicenter phase 3 trial that includes only high-grade dedifferentiated liposarcoma (DDLPS) and leiomyosarcoma (LMS)

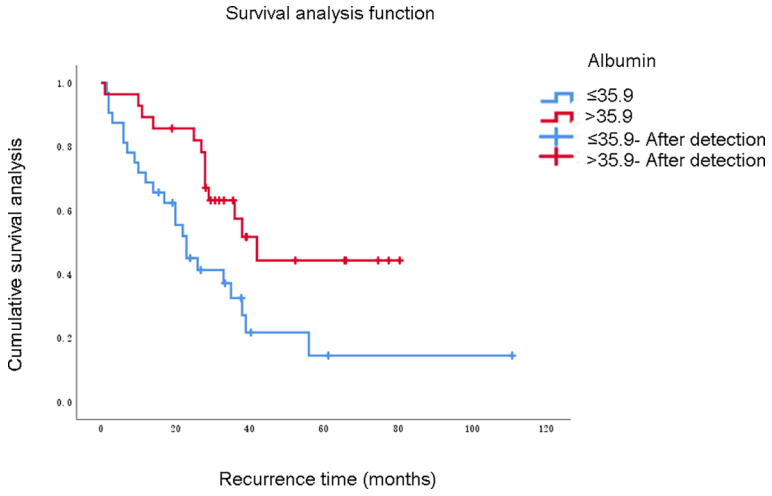

FIGURE 5
Total survival.

TABLE 4 Factors influencing overall survival rate.

Category	Grouping	Cases	Univariate analysis	Multivariate analysis
Tumor diameter (grouped by median)	<=17	31	0.209	
	>17	29		
Malignancy degree			0.004	0.007
	Low	25		
	High	35		
Ki67 (grouped by median)	<=10	35	0.073	0.223
	>10	25		
Single shot CT imaging	1	46	0.202	
	2	14		
Surgical resection range	1	39	0.063	
	2	21		
Albumin grouping	<=35.9	32	0.071	0.408
	>35.9	28		

cases, with stratification based on specific tumor histology. The objective is to evaluate whether neoadjuvant chemotherapy can reduce the development of distant metastasis in these well-defined histological subtypes (31). This trial will be the first of its kind to include only high-grade retroperitoneal sarcoma cases and focus on two specific histological subtypes. The neoadjuvant setting offers valuable insights into tumor response *in situ*, providing opportunities for better understanding of clinical consequences, prognostic information, and research opportunities. The main limitation of our current study is that the sample size of this study is small. Moreover, HOI of the tumor has not been recorded.

In conclusion, the recurrence rate after complete resection of RPLS remains high, with the majority of recurrences located in the primary abdominal compartment. The degree of tumor malignancy, positive Ki67 expression, and serum albumin levels are important factors for the recurrence of imaging tumors. Tumor malignancy is an important factor affecting the OS of patients with RPLS undergoing complete resection. such patients should be closely followed up, with a focus on the imaging changes in the primary area of the tumor. Furthermore, the nutritional status of patients should be closely monitored to reduce the incidence of hypoproteinemia, reduce the risk of recurrence and metastasis, and improve the prognosis of patients.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

XG: Writing – review & editing. PD: Writing – original draft. ZZ: Writing – review & editing. YLi: Writing – review & editing. QZ: Writing – review & editing. DW: Writing – review & editing. XZ: Writing – review & editing. YLiu: Writing – review & editing. BT: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Risk factors for recurrent disease after resection of solitary fibrous tumor: a systematic review

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Introduction: Solitary fibrous tumor (SFT) is a rare soft tissue tumor found at any site of the body. The treatment of choice is surgical resection, though 10%–30% of patients experience recurrent disease. Multiple risk factors and risk stratification systems have been investigated to predict which patients are at risk of recurrence. The main goal of this systematic review is to create an up-to-date systematic overview of risk factors and risk stratification systems predicting recurrence for patients with surgically resected SFT within torso and extremities.
Method: We prepared the review following the updated Prisma guidelines for systematic reviews (PRISMA-P). Pubmed, Embase, Cochrane Library, WHO international trial registry platform and ClinicalTrials.gov were systematically searched up to December 2022. All English studies describing risk factors for recurrence after resected SFT were included. We excluded SFT in the central nervous system and the oto-rhino-laryngology region.
Results: Eighty-one retrospective studies were identified. Different risk factors including age, symptoms, sex, resection margins, anatomic location, mitotic index, pleomorphism, hypercellularity, necrosis, size, dedifferentiation, CD-34 expression, Ki67 index and *TP53*-expression, APAF1-inactivation, TERT promoter mutation and *NAB2::STAT6* fusion variants were investigated in a narrative manner. We found that high mitotic index, Ki67 index and presence of necrosis increased the risk of recurrence after surgically resected SFT, whereas other factors had more varying prognostic value. We also summarized the currently available different risk stratification systems, and found eight different systems with a varying degree of ability to stratify patients into low, intermediate or high recurrence risk.
Conclusion: Mitotic index, necrosis and Ki67 index are the most solid risk factors for recurrence. TERT promoter mutation seems a promising component in future risk stratification models. The Demicco risk stratification system is the most validated and widely used, however the G-score model may appear to be superior due to longer follow-up time.

Systematic Review Registration: CRD42023421358.

KEYWORDS

solitary fibrous tumor, risk factor, prognosis, pathology, sarcoma

Introduction

Solitary fibrous tumor (SFT) is a rare soft tissue tumor. Morphologically the cells typically appear with oval to spindle-shaped nuclei surrounded by scarce cytoplasm and intervening collagen fibres arranged in a "patternless" pattern (Figure 1). Different SFT variants such as giant-cell containing, dedifferentiated, myxoid, fat-forming and

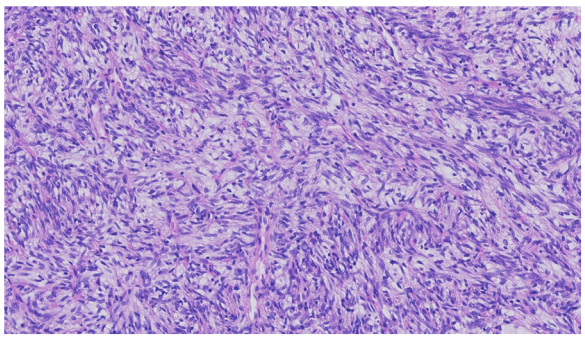


FIGURE 1
SFT with charcteristics "Patternless pattern" predominantly spindle cell morphology with cellular atypia (HE 22X).

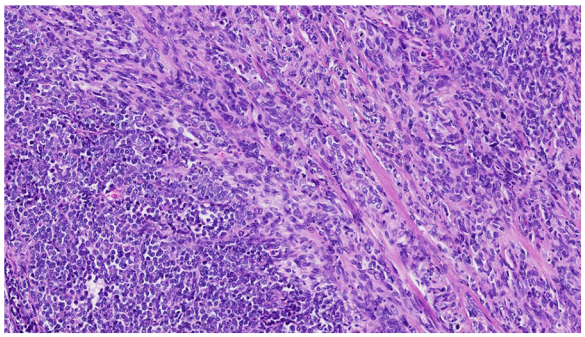


FIGURE 2
Malignant SFT with both spindle cell areas and round cell areas (HE 14X).

pleomorphic forms have been described. The final diagnosis of SFT is based on the immunohistochemical detection of a fusion between *NAB2::STAT6* genes, in practice by using STAT6 immunochemical stain (1, 2) (Figure 2).

The most common tumor location is within the thoracic cavity and abdomen, but SFT can be found throughout the whole body (3). Surgical resection with negative margins is the recommended treatment. SFTs can be benign or malignant, typically based on the criteria by England et al. (4), but even benign SFTs can metastasize, and this unpredictable nature poses a clinical challenge and questions the follow-up after treatment. Recurrence rates are varying and have been estimated to approximate 10%–20% (5, 6), but in studies with longer follow-up time recurrence rates of more than 30% have been reported (7).

Multiple risk factors have been proposed to predict which patients are at risk of recurrence (5, 8–11). In addition, numerous risk stratification systems (RSS) have been developed to predict recurrence risk. In an extra-meningeal cohort, Demicco et al. found age, size, necrosis and mitotic index to be predictive of recurrence (12), however Georgiesh et al. found, in their RSS, that mitotic index, necrosis and sex better identified the low-risk patients (11). Some models, like Diebold et al, developed a RSS specifically for pleural SFT and found mitotic index, size, Ki-67 index and necrosis to be the best predictive variables (10). Hence, there exist controversies regarding risk factors, and in addition, the development in molecular and genetic techniques has made it possible to investigate new potential risk factors for patients with SFT (13, 14). These factors create a need for an up-to-date systemic review of the current knowledge in this field.

Methods

Study design

This systematic review followed the PRISMA extension guidelines for systematic reviews (PRISMA-P). The protocol was registered in the Prospero Database with registration number: CRD42023421358.

Participants

Inclusion criteria were: randomized controlled trials (RCTs), reviews, observational studies ($n \geq 5$) reporting on children or adults, who were treated for histologically confirmed SFT, and reported data on risk factors or potential risk factors for adverse outcome such as local recurrence, metastasis, reduced disease-free survival, disease-specific mortality, etc.

Also, we included studies assessing performance of risk-stratification models.

We excluded studies where patients were treated exclusively for SFT in CNS (and meninges) as well as in the oto-rhino-laryngology region, since these anatomic sites were out of scope for this systematic review. Studies where patients only received radio- or chemotherapy were also excluded.

Search strategy

A systematic search was made in the following databases: PubMed, Embase, and the Cochrane Library. Furthermore, the WHO international trial registry platform and ClinicalTrials.gov were searched to identify ongoing studies. We restricted inclusion from the year 2000 until December 2022.

The search strategy was created with help from an information specialist. Search terms were: "Solitary fibrous tumor" and "hemangiopericytoma". No efforts were made to find "grey" literature.

Data extraction

References were screened by two researches (JT and LP), initially on title and abstract level, to exclude studies clearly out of scope. Disagreements were solved by discussion. A second screening process was carried out, and the full-text articles were

read in order to make a final inclusion of studies. Again, consensus was obtained after discussion. Data was extracted by predefined data-charts: title, author, year of publication, demographic data, setting, follow-up, results regarding risk-factors or risk stratification models.

Risk of bias

Due to the fact that included studies only comprised retrospective cohorts and case-series, the "JBI Critical Appraisal Tool" was found appropriate to assess risk of bias. It contains 10 questions and assesses internal validity, risk of selection and information bias as well as the quality of reporting of results. This tool has been used in various studies (15).

Briefly, question 1, 2 and 3 address the inclusion of patients, and if the condition is measured in a standardized and valid way. Question 4 and 5 address whether or not the inclusion was consecutive and complete. Question 6, 7 and 8 address reporting of demographics, clinical information and follow-up. Question 9 addresses the geographic location of the clinic in which the study is carried out. Question 10 addresses the statistical methods used.

Results

A total of 3,289 studies were initially identified, 829 duplicates were removed, and 2,460 studies were eligible for title and abstract screening. A total of 2,323 studies were excluded leaving 137 studies for full text assessment. Due to inappropriate study design (reviews, conference abstracts, editorial comments, etc.), or studies which did not full-fill the inclusion criteria (no prognostic data or risk factors included) another 63 studies were excluded. Finally, we identified 7 relevant references from other reference lists, and included these in the total number of 81 included studies. Inclusion is summarized in Table 1.

Study characteristics

We did not find any randomized controlled trials, nor did we find prospective cohort studies, thus all included studies were retrospective cohort studies. The numbers of cases in the included studies ranged between 11 and 549 (16, 17). Median and mean patient age ranged from 50 to 67 years (18, 19) and 57% of studies had a slight predominance of female patients. Follow-up time was not clearly reported for 14 studies, the remaining 67 studies reported mean or median follow-up time between 12 months to 168 months (20, 21).

In all 81 studies, patients were diagnosed with SFT either by biopsy or based on resection specimens, and almost all patients were treated with surgical resection. The vast majority of studies included patients with primary, localized SFT, however a minority of case-series included locally advanced or metastatic SFT. Twenty-nine studies reported SFT at any anatomic site of the body, twenty-five pleuro-pulmonary or in the chest/thorax (mediastinum, lung and pleura), eleven extra meningeal, three extra-thoracic and extra-meningeal, two in the urogenital tract, one in bones, one in extremities, one in retroperitoneum, one in the mesentery and liver, one in the retroperitoneum and pelvis, and one in pelvis.

Relapse from SFT was typically measured as either time to local recurrence or metastasis [disease-free survival (DFS), recurrence-free survival (RFI) event-free survival (EFS)]. Overall survival (OS) and disease-specific death (DSD) were also calculated for some studies.

Clinical and demographic risk factors

Age

Many studies have investigated age as an independent risk factor for adverse outcome after resected SFT. As expected, age is often correlated to inferior OS (8, 12), however, Demicco et al. found a significant correlation between higher age and metastasis in two large cohorts of patients with extra-meningeal SFT (5, 12), and this is why age was included in their risk stratification model. The largest cohort to date, with 613 SFT cases, also found reduced disease-free survival (DFS) for patients above 51 years, however this study was characterized by missing data, i.e., 70% of the SFT patients lacked proper staging (3). Furthermore, Ghanim found positive associations between age ≥59 and reduced event free survival (EFS) in a cohort of intrathoracic SFT (22). Opposite to this, numerous studies did not find such correlations (23–34), and recently a Norwegian group with a long follow-up time (median of 84 months), did not find association between age and recurrence free interval (RFI) (11).

Symptoms

Only a minor fraction of studies has investigated the prognostic role of symptoms vs. no symptoms. We only found studies without association between symptoms and adverse outcome (25, 33, 35).

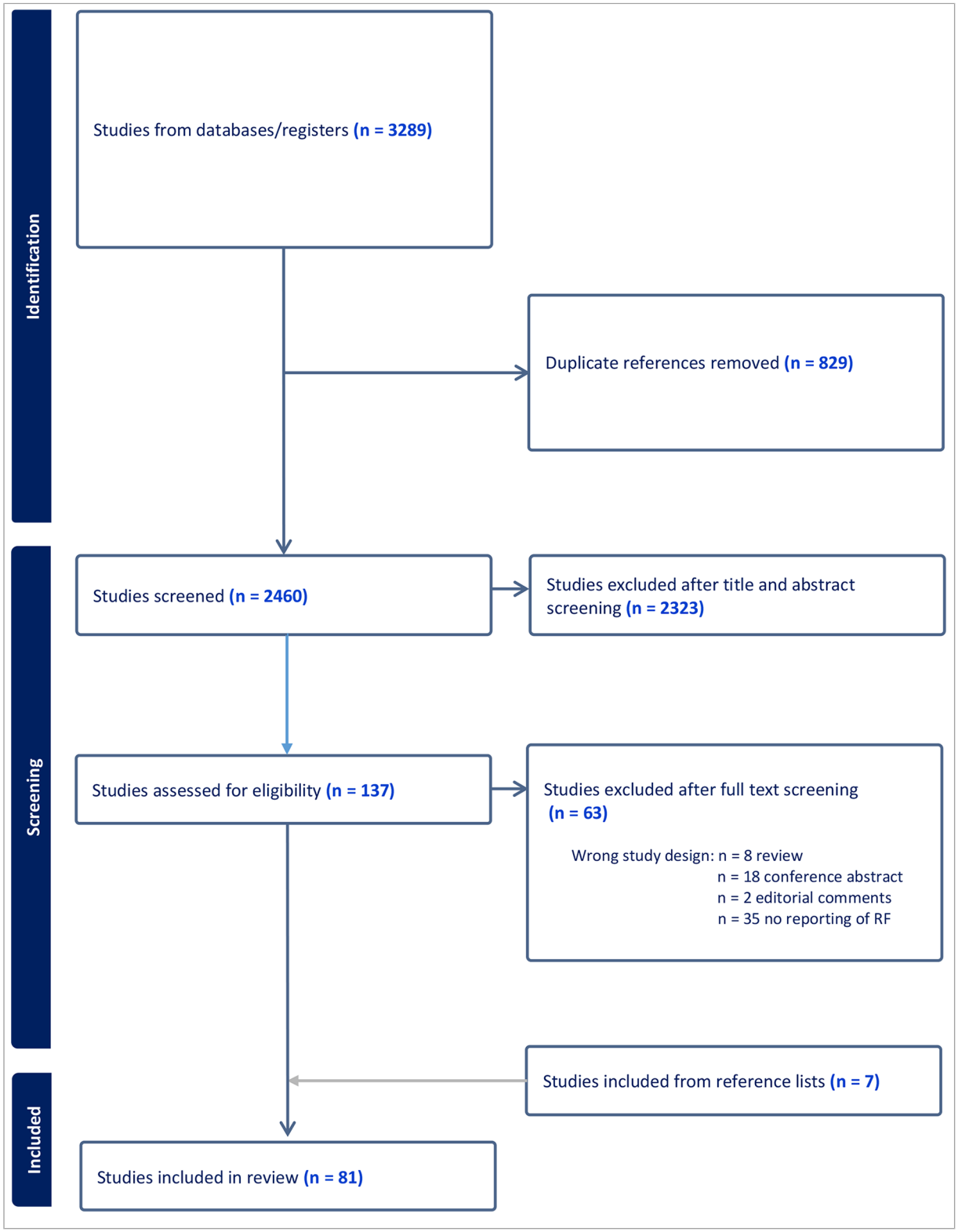
Sex

Most studies find no relation between sex and risk of recurrence or reduced OS (3, 22, 28, 30, 31, 33, 36–38), however, one study by Reisenauer et al. found worse OS for male patients in a univariate analysis (39). Interestingly, Georgiesh et al. found that male gender was associated with increased risk of late recurrence (11), and thus added male gender to their risk score (G-score).

Resection margins

Surgical removal of the SFT is the cornerstone in the treatment, but the significance of radical resection is still not clear. Most series, however demonstrate adverse outcome (LR, metastasis, shorter event-free survival, etc.) after positive resection margins (6, 12, 19, 22, 40, 41). One of the largest cohorts with 303 SFT patients found a marked increased risk of local recurrence (HR = 10.0) in the cohort with positive margins (12). Surprisingly, a large study with 162 patients with extra

TABLE 1 Inclusion process.



meningeal SFT, did not find positive resection margins (R0 vs. R1) as risk factor of neither OS, local recurrence or metastatic recurrence in univariate or multivariate analysis (8), and neither did Deanna Wand et al. find any significant association between R0 vs. R1 resection and local recurrence, metastasis or OS in their cohort of 59 SFT patients (36).

Anatomic location

The most frequent location for SFT is believed to in thorax followed by the abdomen/retroperitoneum (3). Numerous studies have found anatomic location to be a prognosticator for recurrence, however results are conflicting. Gholami et al. found location to be an independent predictor for recurrence and

disease-specific death, and in their cohort of 219 patients, thoracic SFTs had the highest risk of local recurrence (5- and 10-year cumulative risk of 10% and 18%, respectively, compared to 4% and 7% for the total population consisting of SFT throughout the body). Regarding metastasis, SFTs in the abdomen/retroperitoneum had the highest risk with 10-year cumulative risk of 27% compared to SFT in thorax and in the head-neck region where 10-year cumulative risk was 16% and 15%, respectively (38). Also, Cranshaw et al. found intraabdominal, retroperitoneal and pelvic SFTs to have the highest risk of local recurrence (42). Wilky et al. found extra thoracic SFTs to be independently associated with recurrence (26), and O'Neil also found higher rate of malignancy in extra-thoracic SFTs (43). Luo et al. also found extra thoracic SFTs to be more aggressive (28), and in accordance with these results Akaike et al. found the extra thoracic location to be associated with lower disease-free survival rate (44). The largest cohort to date found SFT in thorax/abdomen/pelvis to be favorably associated with DFS compared to SFT in CNS or head-neck region (3). Salas et al. found SFT in the limbs to be associated to increased risk of metastasis in both uni- and multivariate analysis (8). Finally, 4 studies did not find any correlation between anatomic location and risk recurrence (7, 31, 36, 41).

Pathological risk factors

Mitotic index

Number of mitosis [≥4 mitosis/high-power fields (HPFs)] has traditionally been a central criteria in the distinction between malignant and benign SFT (4). Indeed, mitotic index seems to be higher in malignant SFT, and it is found to be prognostic for recurrence or metastasis regardless the anatomic location (3, 5–8, 10–12, 14, 17, 22, 23, 25, 26, 29, 32, 36, 37, 39–42, 44–52).

Three studies did not find mitotic index to be a significant prognostic risk factor (31, 38, 53).

Pleomorphism

Pleomorphism is often referred to as variation in shape and form of the nuclei in the tumor. We found 8 studies where pleomorphism was found to be a risk factor of adverse outcome (6, 10, 11, 37, 40, 44, 54, 55). Four studies did not find any significant prognostic value of pleomorphism (5, 25, 49, 56).

Hypercellularity

Hypercellularity can be seen as excessive amount of crowded cells and overlapping nuclei with minimally intervening collagen (39), and this feature has been investigated for its prognostic value. We found 7 studies which proved hypercellularity to be significantly associated with recurrence or other measures of adverse outcome (6, 37, 39, 40, 49, 52, 56), however, 5 studies could not find similar results (5, 11, 27, 30, 32).

Necrosis

We found 15 studies which found a significant higher risk of recurrence, metastasis or reduced OS when necrosis was present in the tumor (5, 6, 10, 11, 19, 32, 36, 37, 39, 40, 48, 49, 54, 55, 57). Demicco et al. added necrosis to their original 3-item score, thus making it better to identify low risk patients (32). However, 7 studies did not find necrosis to be prognostic of adverse outcome (25, 27, 30, 31, 41, 45, 57).

Size

Whether tumor size is a risk factor for tumor recurrence is a subject of debate, and results are very conflicting. Demicco and Gholami both found that tumor size was an independent risk factor for disease-specific death and risk of metastasis, respectively (5, 38), which explains the inclusion of tumor size in the original 3-tiered risk assessment model by Demicco et al. Also, a number of other studies found similar correlations (10, 12, 17, 25, 28, 32, 37, 39, 41, 49, 55, 56). Opposite to the above mentioned studies, we found 16 studies which could not find any significant correlation between size and recurrence (7, 8, 21, 26, 27, 29–31, 33, 34, 36, 46, 48, 57, 58). Surprisingly, we even found an inverse correlation between tumor size and DFS and OS in a study based on 243 patients with resectable extra-meningeal, extra-pleural SFT (6). Of note, a series with pleural SFTs by Woodard et al. included nine giant SFTs with a mean diameter of more than 20 cm, and none of these experienced recurrence (48).

Dedifferentiation

Morphologically, dedifferentiation in SFT is described as an abrupt transition from areas with conventional SFT to areas resembling a high-grade sarcoma (59). Dedifferentiation is very rare and the available evidence is scarce, however some studies indicate a worse prognosis for patients with dedifferentiated SFT. In a case-series from 2009, three out of eight patients with dedifferentiated SFT died from their disease (60), and in a case-series of 10 dedifferentiated SFT, seven of ten patients died because of their disease within a median of 73 months from diagnosis. Also, Yamada et al. found dedifferentiation to be an independent risk factor of recurrence (61). Finally, Sugita et al. found dedifferentiation to be significantly associated with worse 5 year metastasis-free survival, however only 2 of 43 patients had dedifferentiated SFT in their study (31).

Immunohistochemical risk factors

CD34

The expression of CD34 glycoprotein on the cell membrane is common in SFT, yet not specific, when diagnosing SFT (62), and some studies have investigated its prognostic potential. Franzen et al. found no difference in CD34 expression between malignant and benign SFT, and no prognostic value of this marker (25). In accordance with these results, DeVito et al. did not find CD34 status to predict OS in a cohort of 82 patients (46). Diebold et al. graded CD34 staining from weak to strong (4 categories), but found no correlation to adverse outcome (10). Interestingly, a minor fraction of SFTs are CD34 negative, and in a study by Lahon et al. CD34 negativity was significantly associated with

recurrence of malignant SFT (21). Similarly, Dermawan et al. also found that CD34 negative SFTs were more likely to metastasize than CD34 positive tumors (20).

Ki67-index

The Ki67 protein is present on the cell nucleus, and it reflects the proliferative potential of the tumor cells, thus high percentage of Ki67 is known to be a prognosticator in many malignant conditions. Sugita et al. found that the Ki67 LI (labeling index) ranged from <1% to 72%, and they divided their samples in low (Ki67 < 1%) with 35% of the patients, intermediate (Ki67 1%–10%) with 56% of the patients and high (Ki67 ≥ 10%) with 9% of the patients. Patients with high Ki67 had a significantly higher risk of metastasis within 5 years of surgery and furthermore, the authors substituted mitotic index with Ki67-index in Demiccos RSS, and found it to be potentially superior (31). We found more studies in which high Ki67 was associated with adverse outcome (63, 64), however Ki67 cut-off values differed from ≥2% (39), ≥5% (30), ≥10% (10, 19, 65) and ≥12% (25).

TP53 expression

Mutations in *TP53* may lead to dysfunction of the tumor suppressor gene P53. Traditionally, *TP53* status is measured by immunohistochemistry (IHC), but DNA-sequencing, PCR and other techniques are also available. Machado et al. found a low prevalence of *TP53* mutations (15 out of 97 samples), and no clear correlation to adverse outcome was found, but *TP53* was more common in high risk SFT (14). Park et al. found *TP53* immuno-positivity to be significantly associated with local recurrence and metastasis (13), which is in accordance with findings from Schirosi, Akaike and Rodriguez-Gonzalez (37, 44, 63), however these results were disputed by others (10, 57, 66).

APAF1

APAF1 (apoptotic protease-activating-factor1) is involved in the process of apoptosis, and some researchers have proposed, that inactivation of APAF1 could be involved in malignant transformation of SFT. Park et al. found a correlation between APAF1 inactivation and malignancy, but not with local recurrence or metastasis (13). Machado et al. found no correction between APAF1 status (positive or negative) and clinical outcome (14).

Molecular risk factors

TERT promoter mutation

Mutations in the TERT promoter region may promote aggressive behavior in SFT, and it is present in about 20%–40% of SFTs (14, 67). In a large series with 172 patients Demicco demonstrated an increased risk of metastasis when TERT promoter mutation was present (HR = 2.9), however no correlation to OS or disease-specific death was found (67). Bahrami and Akaike found likewise TERT promoter mutation to be associated with lower event-free survival (44, 68). Park and Lin however, only found TERT promoter mutation to be associated with malignancy, but not with local recurrence or metastasis (13, 69). Bianchi studied 41 patients with SFT in the extremities and found TERT promoter mutation to be associated with risk of metastasis (57). Salguero-Aranda found that TERT promoter mutation was associated with reduced progression-free survival and OS (66). Machado et al. found TERT promoter mutation was more frequent in patients with high and intermediate risk stratification, thus speculating that this feature could be particularly useful in risk stratification of the "intermediate" group of SFT patients (14). Finally, a recent study by Krsková et al. fount TERT promoter mutation to be associated with malignant behavior, but not strictly with risk of recurrence (64).

NAB2::STAT6 fusion variants

In 2013 two research groups discovered the *NAB2::STAT6* gene-fusion to be diagnostic for SFT (65, 70), and now more than 40 different fusion variants have been discovered. Many studies have investigated whether these different fusion variants have different malignant potential.

We found two studies which proved *NAB2::STAT6* fusion variants to have a clear prognostic significance. Barthelmess discovered 12 different fusion variants in 52 patients. *NAB2ex4::STAT6ex2* ($n = 25$), *NAB2ex6::STAT6ex16* ($n = 7$), and *NAB2ex6::STAT6ex17* ($n = 4$), were the most frequent events. They found significantly higher risk of recurrence in the *NAB2ex6::STAT6ex16/17* group. Georgiesh studied 39 patients and found 12 different fusion variants. They divided the fusion variants into two groups based on the length of the STAT6 gene, the so-called *STAT6-TAD* and *STAT6-full*. Patients with *STAT6-TAD* had an increased risk of local recurrence, distant recurrence and OS in the univariate analysis (71).

Park et al. discovered 3 different fusion variants in 68 cases: 1b (*NAB2*ex4::*STAT6*ex2) in 56%, 2a (*NAB2*ex6::*STAT6*ex16) in 13%, 2b (*NAB2*ex6::*STAT6*ex17) in 6%, but found no association to malignant potential (13). Machado found the most common fusion variants to be *NAB2-exon4::STAT6-exon2* followed by *NAB2-exon6::STAT6-exon16/17*, but failed to find them to be predictive of aggressive behavior (14). Akaike found 7 types *of NAB2::STAT6* fusion variants in 40 cases, the most frequent being *NAB2exon4::STAT6exon2*. They found *NAB2exon4::STAT6exon2-3* to be associated with less aggressive phenotype, but correlation with lower DFSR was not present (44). Likewise, seven other studies with SFT from various anatomic sites, did not find significant correlation between fusion variants and adverse outcome (57, 61, 64, 72–76).

Risk stratification models

SFT is an unpredictable tumor, making it notoriously difficult to estimate recurrence risk and plan surveillance. Therefore, many different research groups have made great efforts to develop risk stratification systems (RSS), which have clearly improved prognostication for patients with primary SFT (Table 2). As seen from the examples below, RSS are typically based on various

TABLE 2 Risk stratification systems.

Risk stratification score	Anatomic site	Prognostic factors
Georgiesh et al. (11)	Extra-meningeal	- Gender - Mitotic index - Necrosis
Demicco et al. (12)	Extra-meningeal	- Mitotic index - Size - Age - Necrosis
Demicco et al. (5)	Extra-meningeal	- Mitotic index - Size - Age
Salas et al. (8)	Extra-meningeal	- Mitotic index - Age - Anatomic site
Tapias (2012)	Pleural	- Pleural origin (parietal or visceral) - Morphology (pedunculated or sessile) - Size - Hypercellularity - Necrosis/hemorrhage - Mitotic index
Diebold et al. (10)	Pleural	- Mitotic index - Size - Ki67 index (MIB-1) - Necrosis
De Perrot et al. (9)	Pleural	- Hypercellularity - Mitotic index - Pleomorphism - Hemorrhage - Necrosis - Invasion - Morphology (pedunculated or sessile)
Pasquali et al. (6)	Extra-thoracic Extra-meningeal	- Mitotic index - Cellularity - Pleomorphism

combinations of clinical and histomorphological variables which have been identified as independent risk factors in multivariate analyses.

RSS can be separated into three different groups, according to the anatomic location of the SFT from which they are developed:

We identified four RSS developed and validated in extra-meningeal SFT:

Three-variable risk score from Demicco (original D-score) including age, size and mitotic rate (5). Four-variable risk score from Demicco including age, size, mitotic rate, necrosis (modified D-score) (32). Three-variable risk score from Salas 2017 (separated in Salas overall survival ($Salas^{OS}$), Salas metastasis ($Salas^{MET}$), Salas local recurrence ($Salas^{LR}$)) including mitotic rate, age and anatomic site (8). Three-variable G-score by Georgiesh based on male sex, necrosis and mitotic count (11).

We found three RSS developed and validated in pleura-pulmonary SFT:

The six-variable risk score by Tapias based on pleural origin, morphology, size, hypercellularity, necrosis/hemorrhage, mitotic rate (49). The four-variable risk score by Diebold based on mitotic rate, size, Ki67 index (MIB-1) and necrosis (10). Finally, de-Perrot who staged from 1 to 4 based on 6 different histological malignancy signs (hypercellularity, mitotic rate, pleomorphism, hemorrhage, necrosis, invasion) and morphology (pedunculated or sessile) (9).

We found one RSS based on extra meningeal and extra pleural SFT, namely a study by Pasquali, they made a scoring system based on: mitotic rate, cellularity and pleomorphism (6).

Comparison of RSS

Georgiesh collected data from 318 patients with primary, extra meningeal SFT. G-score could be calculated for 211 patients, 23% low risk, 43% intermediate risk and 34% high risk. The modified D-score was used to calculate risk for 224 patients, 56% low risk, 26% intermediate risk and 18% high risk. $Salas^{OS}$ were calculated for 248 patients, 36% low risk, 44% intermediate risk and 19% high risk. There was a surprisingly poor correlation between the three models. The modified D-score performed best to identify high-risk patients, however the G-score was best to identify low-risk patients (7). These results were in accordance with previous work from Georgiesh et al, where 6 and 7 patients from the low-risk groups in the revised D-score and $Salas^{OS}$ score developed recurrence of disease, respectively. Only one patient from the G-score low-risk group developed recurrence. Of interest, many of the recurrences occurred several years after treatment, in fact median time to recurrence was >5 years (11).

Demicco performed a comparison between their own modified D-score, $Salas^{OS}$, $Salas^{MET}$, $Salas^{LR}$ and Pasquali on a cohort of 303 SFT patients. Modified D-score, $Salas^{MET}$ and $Salas^{OS}$ were better than Pasquali to predict the risk of metastasis and RFS, however none of the RSS were able to significantly predict local recurrence. The modified D-score was best to identify the patients at lowest- and highest risk (12).

Ricciardi tested the Tapias-score, the modified D-score and de Perrot RSS and found that Tapias better predicted OS and DFS compared to the others in a cohort of 34 SFT patients with metastatic, pleuro-pulmonary SFT (19).

Reisenauer found that both the original and modified D-score, Tapias and de Perrot predicted progression-free survival, but only the D-scores and Tapias predicted OS, with a slightly better discrimination in the modified D-score (39).

A recent study of patients with intraabdominal SFT compared the modified D-score, Salas and Pasquali. None of the RSS were able to predict LR, however, the modified D-score and $Salas^{OS}$ had the best performance (54).

Silverwood tested the revised D-score and Pasquali-score on a small cohort of 12 patients with extra-thoracic and extra-meningeal SFT, and found the Pasquali model to perform better than the D-score (77).

Bellini collected a patient cohort with 107 pleural SFT. They found Tapias and Diebold to be independently associated with tumor recurrence, however, de Perrot was not. Tapias

had the highest reliability with a highly significant p-value ($p < 0.0001$) (29).

Diebold et al. developed their own scoring system for SFT, and found it superior to the Tapias score. As much as 44% of the patients in their cohort could not be scored according to de Perrot due to missing data (10).

Finally, Tapias validated their own score on a population of 113 pleural SFTs. They found a score sensitivity of 78% and specificity of 74% compared to 100% and 92% in the development cohort. However, they outperformed both the scoring system by de Perrot, and the classic malignancy criteria by England (52).

Risk of bias

Overall, only retrospective studies were identified, and no prospective studies have been performed, which increases the risk of bias. We found that nearly all studies reported well-established inclusion criteria (histological diagnosis of SFT), however many studies did not perform an extra (central) pathological confirmation of the samples.

The vast majority of studies did not report whether the inclusion was consecutive or complete, usually the authors denounced that a number of SFT-cases were identified, typically from a pathological database with no further details.

In general, the studies thoroughly reported demographics, clinical information and follow-up, and most studies also provided estimates of "missing data".

We only found scarce information on geographic characteristics on the clinic or clinics responsible for the treatment. Often, it was stated, that it was a tertiary centre.

All studies had a proper description about the applied statistical methods, however, with varying level of detail.

Discussion

We have provided a systematic, up-to-date review regarding risk factors and risk stratification systems after treatment of SFT. We found 81 retrospective studies investigating both clinical, demographic, histological, immunohistochemical and molecular risk factors. The most reliable prognostic marker was the mitotic index, typically measured as ≥4 mitosis/high-power fields. Furthermore, the presence of necrosis appeared to be a solid risk factor. Other histological markers, such as pleomorphism and hypercellularity were generally regarded as signs of malignancy (4), but results were not clear in this review. Possibly, this might be due to low numbers of included patients in the cohorts and failure to reach statistical significance. Another weakness in the histological assessment of tumor tissue, is the risk of inter-observer differences. This is why some authors have explored the possibility to replace mitotic index with Ki67 LI in Demiccos' RSS, thus making measures of proliferative potential more objective (31). In this review we found elevated K-67 LI to be a clear risk factor for recurrence.

Surgical resection of SFT is the best treatment option, and many studies find, that a radical resection (R0) was associated with a better prognosis. Surprisingly, some studies did not find such associations, which may reflect the more aggressive nature of the tumor, or simply, that the cohorts lacked statistic power.

New molecular techniques have been applied in investigations of SFT, and in our review the most promising item was the TERT promoter mutation. Several studies found an association with either risk of recurrence or other malignant characteristics, and of particular interest, was the finding that TERT promoter mutation might ease risk stratification of patients who have intermediate risk of recurrence (14). In 2013 it was discovered, that *NAB2::STAT6* mutation was diagnostic for SFT, yet often the STAT6 staining was used as a surrogate marker (78). This invention is obviously extremely useful in the diagnostics of this rare and complex tumor, but there is no consensus regarding its prognostic value. More research is needed to elucidate this question.

Risk stratification of patients with SFT is also debated, and we found eight different RSS. The most validated RSS's are the models by Demicco (32, 34, 36), and they are the most widely used (12, 24, 39, 54). The revised D-score has more advantages. It is based on age, mitotic rate, size and necrosis, variables that are typically part of a histological report, thus making it easy to use. Furthermore, it can be used for SFT in all extra-meningeal sites, making it more universally applicable than for instance the model by Tapias (pleural) or Pasquali (extra-meningeal and extra-pleural). Nevertheless, the G-score seems to be a very promising tool as well, including male sex, necrosis and mitotic count, making it likewise easily calculated. It was published in 2020 (11), and validated in 2022 in a very large multinational cohort with promising results (7). The indisputable strength in the G-score is the long follow-up time (median 84 months) which is important, since SFT is able to relapse after several years, even after 15–16 years from initial treatment (38). More studies are needed clarify which RSSs are superior.

We did not find any RSS incorporating molecular findings, a possible future approach could be integration of TERT promoter mutation. It might be interesting to see if proteomics can be of any help in triaging SFT's into different categories. But so far, there haven't been any study utilizing proteomics.

Limitations

This review has some weaknesses. The included studies are all retrospective cohorts with great heterogeneity and an inherent risk of selection-bias. Also, SFTs are treated at tertiary centers from which these publications proceed, and this may cause a selection bias towards more advanced and potentially aggressive SFTs. Furthermore, some studies include SFTs removed 30–40 years ago enhancing the risk of a wrong diagnosis, especially since the majority of patients in these studies were included before the discovery of *NAB2::STAT6* gene-fusion in 2013. These reservations make it difficult to draw firm conclusions and recommendations. Publication-bias may also influence the results of this review, favoring publication of significant associations.

Initially, our ambition was to describe all risk factors or potential risk factors, however we had to omit a few. For instance, we encountered a study investigating fibrinogen (22), microRNA (79) or hemorrhage (30), and due to very scarce data, we chose not to describe these in detail.

Finally, there is a risk that all relevant studies may not be identified and included in this review. Even though we developed a thorough search strategy, strictly followed the PRISMA guidelines, and two authors selected studies, both the search strategy and screening process may lead to inappropriate exclusions.

Conclusion

Several risk factors are known to predict recurrence after surgical resection of SFT. In this systematic review based on 81 retrospective studies, we found mitotic index, necrosis, KI67 index and possibly TERT promoter mutations to be the most valid risk factors. Of the numerous published risk stratification systems, the modified Demicco score is the most validated and widely used, however the G-score seems promising too. Even though, some studies did not find radical resection (R0) to be important for the prognosis, the corner-stone in treatment of SFT remains radical surgical resection.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

JT: Writing – original draft. AL: Writing – review & editing. NA: Writing – review & editing. LoP: Writing – review & editing. LuP: Conceptualization, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Recurrent retroperitoneal liposarcoma with multiple surgeries: a case report

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Retroperitoneal liposarcoma (RPLPS) is a rare malignant tumor that is typically treated with surgical resection. However, RPLPS often has a high rate of local recurrence, making it crucial to explore new treatment options. In this report, we present the case of a middle-aged woman who experienced seven recurrences and underwent seven surgeries following the initial resection. Currently, the patient's condition remains stable after the eighth surgery. Although there have been numerous reports of RPLPS cases both domestically and internationally, instances of repeated recurrence like this are exceptionally rare. Therefore, we have gathered the patient's case data and conducted a retrospective analysis, incorporating relevant literature, to enhance the understanding of this disease among clinical practitioners.

KEYWORDS

retroperitoneal liposarcoma, recurrence, surgical treatment, auxiliary treatment, case report

1 Introduction

Liposarcoma (LPS) is the most common subtype of soft tissue sarcomas (STSs), accounting for 20% of all STSs (1). Pathologically, LPS is divided into five types (2): well-differentiated liposarcoma (WDLPS), dedifferentiated liposarcoma (DDLPS), myxoid liposarcoma (MLS), pleomorphic liposarcoma (PLPS), and myxoid pleomorphic liposarcoma (MPLPS). LPS originates from primitive mesenchymal cells differentiated from adipocytes (3) and is most commonly found in the extremities (52%) and retroperitoneum (13%) (4). It is worth noting that due to the large retroperitoneal space, retroperitoneal liposarcoma (RPLPS) can often grow to extremely large sizes. Consequently, RPLPS is typically asymptomatic in the early stages until the tumor enlarges and compresses surrounding organs, leading to noticeable symptoms (5). This characteristic makes early diagnosis and subsequent effective treatment challenging. Currently, surgical resection is the primary treatment method for RPLPS (6). However, even after successful tumor resection, most patients still require additional treatment

modalities due to the higher recurrence rate of RPLPS compared to LPS in other locations. These additional treatment modalities may include surgery, radiotherapy, chemotherapy, or targeted therapy (7, 8). In this study, we present a case of RPLPS with repeated recurrence and multiple surgeries, and provide a comprehensive overview of the current treatment methods for RPLPS.

2 Case description

The patient, a 37-year-old female, presented to our hospital on January 9, 2017 with a history of retroperitoneal tumor resection 8 months prior. She had noticed an abdominal mass for the past month. The initial tumor resection had taken place at the Retroperitoneal Tumor Surgery Department of the People's Liberation Army General Hospital in Beijing in April 2016. The tumor weighed approximately 4.6kg and was diagnosed as liposarcoma based on the postoperative pathology report. One month before her current visit, the patient discovered a palpable mass on the right side of her abdomen, along with a mild bloating sensation. The patient reported no prior instances of hypertension, diabetes mellitus, coronary heart disease, or any allergies to drugs or food. During the physical examination, a flat abdomen was observed along with a scar from a previous surgical incision in the upper abdomen's center. Additionally, a hard, irregular mass was identified on the right side of the abdomen. An enhanced CT scan of the abdomen revealed a space-occupying lesion measuring 9.3×6.4×11.3cm in the right abdominal cavity. It also showed slight dilation of the right renal pelvis and compression of the right ureter. Based on the patient's medical history, physical examination, and CT findings, the clinical team diagnosed the mass as recurrent retroperitoneal tumor. On January 16, 2017, the patient underwent right retroperitoneal tumor resection and right hemicolectomy. The size of the resected tumor was approximately 20×15×15cm. The postoperative pathological diagnosis confirmed the presence of retroperitoneal dedifferentiated liposarcoma, localized myxoid liposarcoma, and involvement of the mesentery, right renal fat sac, and adrenal nodular hyperplasia. There was no involvement of the omentum or appendix. The stump and periintestinal lymph nodes showed no evidence of tumor spread with 0/9 lymph nodes affected. As the surgical resection was deemed complete, the patient did not receive postoperative radiotherapy or chemotherapy.

The patient was regularly followed up after surgery until the local recurrence of the tumor was discovered on October 19, 2018. Subsequently, the patient's RPLPS has relapsed multiple times on the following dates: October 30, 2018; December 31, 2019; December 5, 2020; July 31, 2021; September 22, 2022; and December 14, 2023. Tumor resection was performed through open surgery. In January 2020, the patient underwent a comprehensive gene test, which revealed an insertion-deletion mutation in the patient's somatic KMT2D gene, with a mutation frequency of 1.3%. Chemotherapy was initially considered for the patient, however, their financial constraints posed a challenge in affording long-term treatment. Furthermore, due to the frequent tumor recurrences and the limited interval between them, it was uncertain whether chemotherapy would yield the desired outcomes. Consequently, after thorough deliberation, the patient decided to forgo the treatment plan. Despite undergoing several courses of anlotinib targeted therapy during the patient's seventh relapse, there was no significant improvement in their condition. Throughout the course of the disease, the patient has experienced a total of 7 recurrences and has undergone 8 surgeries. Figure 1 displays the abdominal CT scan since the seventh recurrence, illustrating the presence of multiple tumors. The eighth operation revealed the largest tumor measuring 32 × 26 cm, with a total weight of 12 kg (Figure 2). During the second surgery, the patient underwent a right hemicolectomy due to colon involvement, and in the fifth surgery, the right kidney was removed due to tumor invasion into the right renal parenchyma. All postoperative pathological diagnoses primarily indicated DDLPS, with local WDLPS, MLS, and PLPS also present (Figure 3). The timeline of this case is depicted in Figure 4.

3 Discussion

RPLPS is a rare mesenchymal tumor, accounting for approximately 0.07% to 0.2% of all tumors (9). It typically affects individuals aged 40 to 60 years, with a relatively equal gender distribution (10). The American Cancer Society (ASC) has identified several risk factors for LPS, including radiation (especially radiation therapy for other malignancies), certain familial cancer syndromes, lymphatic system damage or trauma, and exposure to toxic chemicals (11). According to the classification of STSs by the World Health Organization, the subtypes of LPS include WDLPS, DDLPS,MLPS, PLPS, and MPLPS (2). Among these subtypes, PLPS and MLPS are more commonly found in the extremities, while WDLPS and DDLPS are more commonly found in the retroperitoneum (12).

The clinical manifestations of early RPLPS are usually not significant and are often detected at an advanced stage, characterized by a large abdominal mass (13). Many patients do not experience any symptoms, but if present, they may include nonspecific symptoms like flank pain, early satiety, or general discomfort (14). In this case, the patient did not exhibit any obvious physical signs initially, but a palpable abdominal mass was identified.

Computed Tomography (CT) is widely used for the diagnosis and preoperative evaluation of Retroperitoneal Liposarcoma (RPLPS) (15). However, Magnetic Resonance Imaging (MRI) offers higher resolution of soft tissues, enabling more accurate diagnosis of retroperitoneal tumors. MRI also provides clear visualization of tumor blood vessels, allowing for the identification of tumor characteristics and assessment of tumor invasion. As a result, MRI is gradually replacing CT scans in the radiological evaluation of LPS (16, 17). In this particular case, the patient underwent abdominal CT or contrast-enhanced CT scans every 3 months for follow-up evaluations. This approach effectively tracks the recurrence and development of retroperitoneal tumors.

Surgical resection with negative margins is widely recognized the primary treatment for RPLPS (18). Studies have demonstrated that resection with clean margins under microscopy (R0 resection)

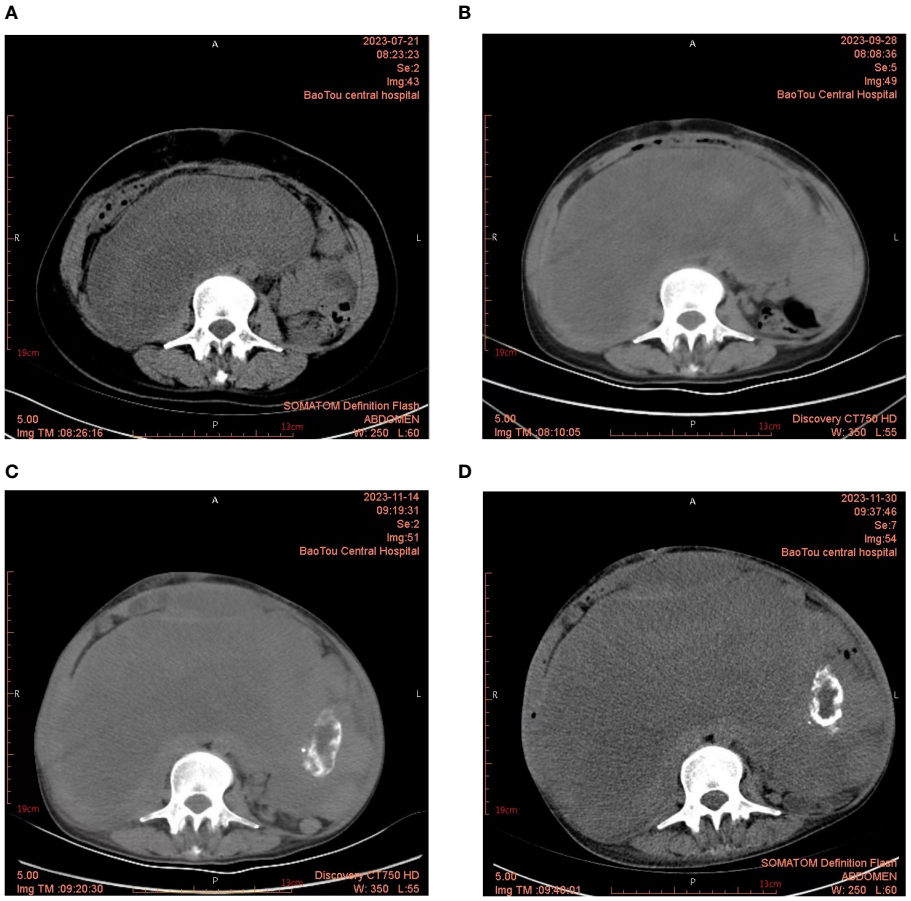

FIGURE 1
(A–D) Abdominal CT showed multiple huge masses in the abdominal cavity. By the eighth surgery, the larger masses had grown to 23x12 cm.

leads to longer postoperative survival compared to resection with positive tumor margins under microscopy (R1 resection) (19). The scope of surgical resection for RPLPS remains controversial. Some studies suggest a method called 'extended resection or septal resection' to achieve radical resection. This involves removing adjacent organs and structures such as the kidney, colon, pancreas, spleen, psoas muscle, diaphragm, and retroperitoneal fat tissue vessels on the iliac side, even if they are not directly impacted by the tumor (20, 21). However, even with complete tumor removal, approximately 50% of patients still experience tumor recurrence within 5 years (22). For recurrent RPLPS, multiple reoperations may significantly improve long-term survival rates (23), although some studies suggest that an increase in recurrence and surgical frequency could lead to a higher recurrence rate (24). Our patient experienced 7 recurrences and underwent 8 complete resections. Remarkably, the patient's survival period has reached nearly 8 years, which is exceptionally rare. The patient's compliance with follow-up consultations has been exemplary, allowing for timely detection and treatment of each recurrence.

The efficacy of radiotherapy and chemotherapy in RPLPS remains controversial. According to a study by Littau MJ et al., adjuvant radiotherapy has been shown to improve survival rates in patients with tumors larger than 10 cm, but caution should be exercised when using it in patients with smaller tumors (25). Some studies have suggested that neoadjuvant radiotherapy (NART) combined with radical resection may result in better local control and prolonged survival compared to surgical resection alone. However, the long-term benefits of NART have not been thoroughly evaluated (26). As for adjuvant chemotherapy (AC) in RPLPS, anthracycline-based chemotherapy regimens, such as doxorubicin, are currently considered the first-line treatment for advanced or metastatic LPS (27). The combination of doxorubicin and ifosfamide appears to be more effective than doxorubicin alone, with doxorubicin showing greater benefit (28). However, a large phase III randomized controlled trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) found that this combination regimen did not improve overall survival (OS) or recurrence rates (29). In conclusion, the effectiveness and long-term benefits of radiotherapy and chemotherapy for RPLPS still require higher-level evidence to be established.

Targeted therapy is currently a major focus of research in the treatment strategies for RPLPS. The amplification of MDM2 and the inhibition of p53 are recognized as key mechanisms contributing to the growth and progression of RPLPS. Therefore, targeting the MDM2-p53 axis has emerged as an appealing therapeutic approach (30). The first selective and potent MDM2 inhibitors discovered were Nutlins (Nutlin-1, -2, and -3), followed

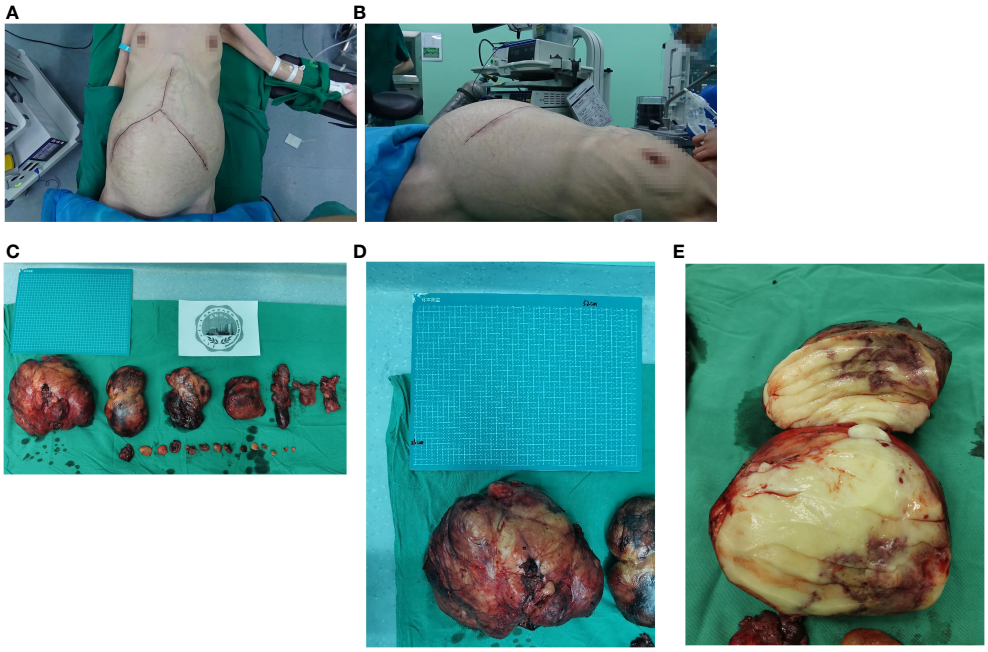

FIGURE 2
(A, B) Frontal and lateral appearance of the patient's abdomen before the eighth surgery. **(C)** A total of 21 retroperitoneal tumors were removed in the eighth operation. **(D, E)** The maximum size of the tumor is 32×26cm, and the cut surface is fish-shaped.

by RG7112, Idasanutlin, and SAR405838 (31). CDK4 is also identified as a potential therapeutic target for LPS. Zhang and his team have demonstrated that continued treatment with a CDK4 inhibitor (CDK4i) as a single agent leads to reduced proliferation of DDLPS cell lines and inhibits tumor growth in an *in vivo* xenograft model (32). Palbociclib, ribociclib, and abemaciclib are currently approved CDK4 inhibitors for clinical use, and they have shown promising results as single agents in the treatment of solid tumors (33). Anlotinib is an alternative treatment strategy for unresectable or advanced LPS, which has been shown to improve progression-free survival (PFS) and overall survival (OS) in patients with advanced STSs (34, 35). This patient was treated with anlotinib after experiencing a recurrence for the seventh time. However, the treatment did not yield positive results. Furthermore, ongoing investigations are exploring other therapeutic targets for retroperitoneal liposarcoma (RPLPS). Xu et al. conducted a study where they isolated and identified tumor-associated fibroblasts (TAFs) from retroperitoneal dedifferentiated liposarcoma (DDLPS). They discovered that the Tsp2 protein encoded by THBS2 promotes the formation of TAFs and tumor progression, suggesting that Tsp2 could be a significant component in the context of RPLPS and a promising therapeutic target for patients (36). Additionally, the research conducted by Yi et al. suggests that histone lysine N-methyltransferase 2D (KMT2D) is closely associated with the clinicopathological characteristics and unfavorable prognosis of gastric cancer, making it a potential biomarker for predicting the prognosis of gastric cancer (37). In our case, the comprehensive gene test results revealed a KMT2D mutation in the patient's tumor. However, it remains to be determined whether this indicates a correlation between KMT2D and the poor prognosis of RPLPS, and whether KMT2D could serve as a novel therapeutic target for RPLPS. Further investigation is needed to verify these possibilities.

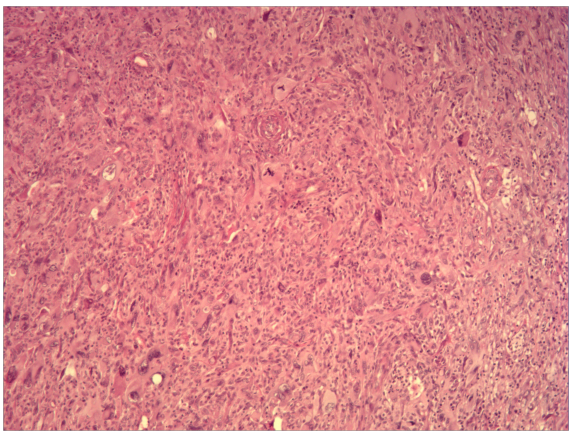

FIGURE 3
The patient's eighth postoperative pathological analysis (hematoxylin and eosin staining, ×100 magnification) showed dedifferentiated liposarcoma, with localized pleomorphic liposarcoma.

4 Conclusion

In summary, RPLPS is a rare malignant tumor with a high recurrence rate. CT and MRI are valuable auxiliary examination methods. Currently, surgery is the preferred treatment approach. The effectiveness of radiotherapy and chemotherapy in treating RPLPS has yet to be determined, but targeted therapy shows promise as a treatment strategy and a new avenue for future exploration. In cases of relapse after surgery, further surgical treatment may be considered,

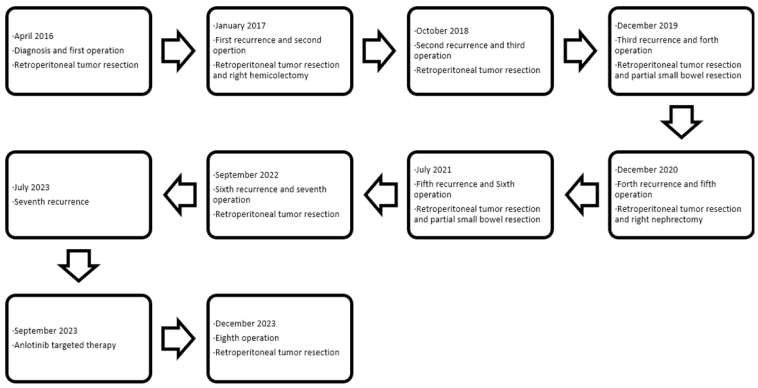

FIGURE 4
Timeline of this case.

as multiple surgical resections have shown success in providing symptom relief. If complete removal of the tumor is not feasible, post-surgery options such as radiotherapy, chemotherapy, and targeted therapy can be utilized to achieve favorable outcomes. Regular monitoring, early detection, and prompt treatment are crucial in enhancing the quality of life and extending the survival time of patients with RPLPS. In this particular case, we will continue to monitor the patient closely and implement appropriate adjunctive treatments as needed to maximize the patient's survival time.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

XW: Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Validation. XS: Formal analysis, Validation, Writing – review & editing. QS: Data curation, Formal analysis, Writing – review & editing. JW: Formal analysis, Validation, Writing – review & editing. JC: Data curation, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1363055/full#supplementary-material

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Leiomyosarcoma of the abdomen and retroperitoneum; a systematic review

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Background: Intraabdominal and retroperitoneal leiomyosarcomas are rare cancers, which cause significant morbidity and mortality. Symptoms, treatment and follow up differs from other cancers, and proper diagnosis and treatment of intraabdominal and retroperitoneal leiomyosarcomas is of utmost importance. We performed a systematic review to collect and summarize available evidence for diagnosis and treatment for these tumours.
Methods: We performed a systematic literature search of Pubmed from the earliest entry possible, until January 2021. Our search phrase was (((((colon) OR (rectum)) OR (intestine)) OR (abdomen)) OR (retroperitoneum)) AND (leiomyosarcoma). All hits were evaluated by two of the authors.
Results: Our predefined search identified 1983 hits, we selected 218 hits and retrieved full-text copies of these. 144 studies were included in the review.
Discussion: This review summarizes the current knowledge and evidence on non-uterine abdominal and retroperitoneal leiomyosarcomas. The review has revealed a lack of high-quality evidence, and randomized clinical trials. There is a great need for more substantial and high-quality research in the area of leiomyosarcomas of the abdomen and retroperitoneum.

Systematic Review Registration: PROSPERO, identifier, CRD42023480527.

KEYWORDS

leiomyosarcoma, retroperitoneal tumours, retroperitoneal sarcoma, abdominal sarcoma, abdominal tumours

Introduction

Soft tissue sarcomas are rare tumours that represent a broad and diverse type of cancers that can occur nearly anywhere in the body. These tumours account for less than 1% of all cancers (1). They originate from mesenchymal stem cells, which are present in muscles, fat and connective tissue (1). Soft tissue sarcomas are most frequently located in the extremities, though about 40% are located intraabdominally or retroperitoneally (2). The most common intraabdominal and retroperitoneal soft tissue sarcomas are gastrointestinal stromal tumours (GIST), leiomyosarcomas (LMS) and liposarcomas (LS) (1, 3).

Leiomyosarcoma account for up to 25% of all newly diagnosed soft tissue sarcomas (4, 5). Other types of leiomyosarcoma include those of cutaneous origin, vascular origin, of bone, and in the immunocompromised host. Leiomyosarcomas of vascular origin are also found in the abdomen and retroperitoneum, e.g., leiomyosarcoma of the caval vein. In a Danish prospective cohort study of intraabdominal and retroperitoneal

sarcomas, 11% of the tumours were leiomyosarcomas, 39% were GIST, 18% were liposarcomas and 30% had a different histological origin (1).

Intraabdominal and retroperitoneal leiomyosarcomas are rare cancers, which cause significant morbidity and mortality. Symptoms, treatment and follow up differs from other cancers, and proper diagnosis and treatment of intraabdominal and retroperitoneal leiomyosarcomas is of utmost importance. We performed a systematic review to collect and summarize the available evidence for diagnosis and treatment of these tumours.

Methods

Study design

This systematic review followed the PRISMA extension guidelines for systematic reviews (PRISMA-P). We prepared a protocol, which was registered in the Prospero Database with registration number: CRD42023480527.

Participants

Inclusion criteria were: randomized controlled trials (RCTs), reviews, prospective studies, observational studies and case series ($n \geq 2$) reporting on adults treated for histologically confirmed leiomyosarcoma in the abdomen and retroperitoneum. We excluded case reports.

Outcome measures

We assessed the following outcomes: different aspects of diagnosis and treatment of abdominal and retroperitoneal leiomyosarcoma. This included diagnostic accuracy, treatment modalities and their effect on survival, cancer-related survival, recurrence of disease, adverse effects and harms of treatment, and quality of life.

Search method for identification of studies

We searched PubMed and Cochrane for relevant studies from the earliest entrance date possible up until January 2021, using the search phrase; (((((colon) OR (rectum)) OR (intestine)) OR (abdomen)) OR (retroperitoneum)) AND (leiomyosarcoma), including mesh terms to obtain titles and abstracts that could be relevant for the review.

Data extraction

Using Covidence, each hit was systematically reviewed by two of the authors (MØ and LuP) on title and abstract level to exclude irrelevant studies. A second screening process was carried out, where full-text articles were read in order to make a final decision on inclusion of studies. Data was extracted by predefined data-charts: Title, author, year of publication, demographic data, setting, follow-up and results. Inclusion criteria were applied independently by two reviewers, and in case of disagreement, a consensus was reached. Relevant references from included studies were also included. References were managed using Mendeley®.

Results

Our predefined search identified a total of 1,983 publications, of which 218 were selected and retrieved in full-text (Figure 1). 144 were ultimately included in the review. The studies are summarized in Supplementary Material Table S1 (see Supplementary Material). There are 108 publications regarding leiomyosarcoma of the abdomen, of which 75 were abdominal tumours only, while the rest included multiple locations. There are 64 publications regarding retroperitoneal leiomyosarcomas, of which 22 were retroperitoneal tumours only. 55 studies reported on leiomyosarcomas only, while the rest included multiple histologies, both malignant and benign. The primary reason for study exclusion were case reports, leiomyosarcoma of other locations than the abdomen and retroperitoneum (uterine e.g.,), non-human studies and *in vitro* trials.

Study characteristics

We found 1 randomized controlled trial investigating neoadjuvant radiotherapy in patients with resectable leiomyosarcoma/soft tissue sarcoma (6), and 1 prospective study reporting the incidence of sarcoma in a population (7). All other included studies were retrospective cohort studies, review articles, case series and guidelines.

Analysis and statistics

We performed a systematic literature review of publications concerning leiomyosarcoma of the abdomen and retroperitoneum to write this systematic review. The literature was evaluated and reported in a systematic fashion in our review. We intended to pool data from included studies if possible, though the available studies were too diverse to pool results and perform a meta-analysis, because they mostly describe leiomyosarcomas of multiple anatomical locations or multiple types of sarcomas in the same anatomical location (i.e., abdomen or retroperitoneum). Furthermore, interventions and outcomes differ between studies, which also make in depth comparison difficult. This is why there is no metaanalysis, further statistical analysis or description of additional statistics.

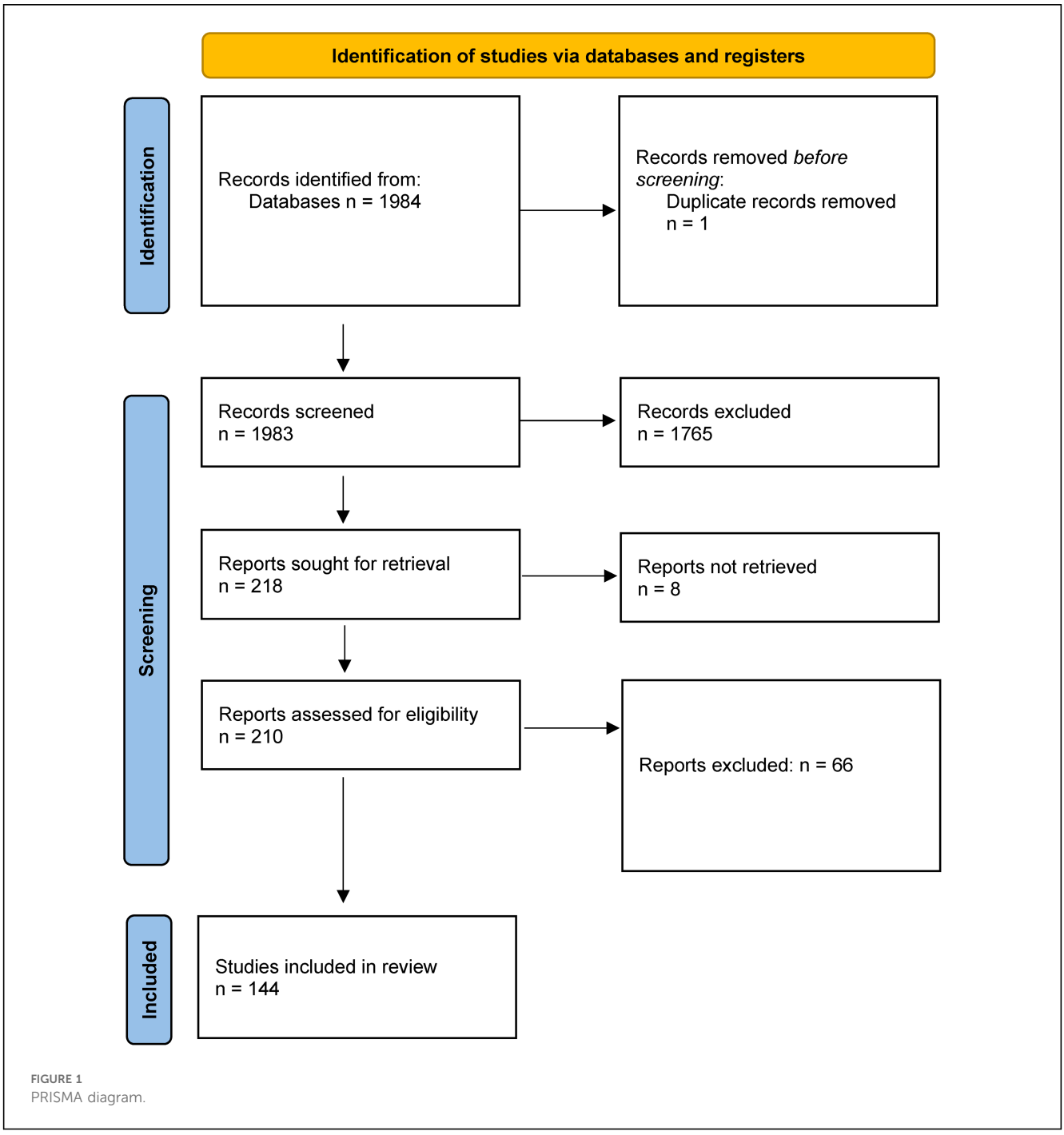

FIGURE 1
PRISMA diagram.

Epidemiology

The most common sites of leiomyosarcoma are the abdomen or retroperitoneum, uterus and extremities (5). Approximately 50% of all leiomyosarcomas are located in either the abdomen or retroperitoneum (2).

In a French register study of sarcoma incidence from 2000 to 2013, the male to female ratio of leiomyosarcoma was 0,6, while the overall male to female ratio of sarcomas in intestinal organs was 1,0 (8). In a Danish study from 2011, 53% of abdominal and retroperitoneal sarcomas were found in men, and 47% in women (1). According to the latest annual report of the Danish Sarcoma Database, 50,8% of all sarcomas were found in men, and 49,2 in women (9).

Sarcomas most commonly occur after 40 years of age. According to the French register study, sarcoma incidence was highest in the age-group 40–64 years (35,7%), followed by those aged 75 and above (27,4%) and 65–74 (19,2%) (8). In Denmark in 2019, the sarcoma incidence was 21,4% among both patients of 61–70 years and 71–80 years, while those aged 51–60 years had an incidence of 14%, and 41–50 years and 80 + an incidence of 10,7% (9).

Abdominal leiomyosarcoma

The predominant intraabdominal locations of leiomyosarcoma are the small and large intestine, but the tumour can also be oesophageal or gastric (10). In addition, a whole range of rare locations have been described in published cases, including the gallbladder, liver, Meckel's diverticulum, porta hepatis, pancreas, spleen, appendix, and various blood vessels like the iliac vein.

Only 0,1% of colorectal malignancies are sarcomas (11), and of these, some 90% are leiomyosarcomas (12). There is a connection between previous radiation therapy and the development of anorectal leiomyosarcoma, and a review of published cases showed an incidence of 11,7% of radiation-induced leiomyosarcoma in this subpopulation (13).

Retroperitoneal leiomyosarcoma

Leiomyosarcoma is the second most common type of retroperitoneal sarcomas, with an incidence of approximately 20%, while liposarcoma, the most common type of retroperitoneal sarcoma has an incidence of 64% (14, 15).

As mentioned above, leiomyosarcoma can occur in various blood vessels, and is common in retroperitoneal located blood vessels like the caval vein, and occasionally in the iliac vein. Leiomyosarcomas of the caval vein are classified in three groups according to Mingoli et al. Segment 1 caval vein LMS are located from the aortic bifurcation to the infrarenal veins. Segment 2 LMS are located from the interrenal or suprarenal veins to, but not involving the main hepatic veins, while Segment 3 LMS involve the main hepatic veins and extends to the right atrium or extends into the heart (16). Approximately 25%–37% of intravascular cases involve segment 1. Segment 2 is the most common site of disease, accounting for 43%–69% of intravascular cases. Segment 3 is the least commonly affected segment, representing 6%–20% of intravascular cases (17, 18).

Clinical presentation

Symptoms of leiomyosarcoma of the abdomen and retroperitoneum vary greatly depending on tumour site. There might be diffuse symptoms or no symptoms at all. Depending on tumour location, there might be haemorrhage, pressure symptoms, pain or ascites (1). According to Clark et al., the most common finding at diagnosis is a painless, gradually enlarging mass (19). Some patients primarily present with weight loss and abdominal pain, other with intestinal obstruction and dysphagia. While unspecific, anaemia is also a possible symptom (20).

Diagnosis

The definitive diagnosis of leiomyosarcoma, and other sarcomas, should involve a broad multidisciplinary team of pathologists, radiologists, surgeons, radiation therapists and medical oncologists, preferably at specialist centres (3, 14).

The National Comprehensive Cancer Network (NCCN) guidelines for intraabdominal and retroperitoneal soft tissue sarcoma, recommends CT of the chest, abdomen and pelvis with intravenous contrast for diagnosis, occasionally supplemented by MRI of lesions in the pelvis or abdomen. PET/CT can be considered in order to detect distant metastases, or to help determine the site of biopsy (21).

According to the European Society for Medical Oncology-European Reference Network for rare adult solid cancers (ESMO-EURACAN) report on soft tissue and visceral sarcomas from 2018, all retroperitoneal tumours should be biopsied. The risk of needle track seeding is minimal, if the biopsy is thoroughly planned, and not performed transperitoneally (3). Similarly, a consensus statement on retroperitoneal sarcoma from 2021 strongly recommends image-guided core needle biopsy to secure the reliability of the diagnosis, and allow for histologic and molecular subtyping and grading. The risk of needle tract seeding during this procedure is not zero, but very low, and the benefits of proper preoperative diagnostics are considered to greatly outweigh the risks (14).

Recommendations from the NCCN argue that image guided core needle biopsy should be performed if preoperative treatment is planned, or if non-sarcoma malignancies are suspected. If the tumour is a well differentiated liposarcoma, biopsy is unnecessary. The rationale for biopsy is to determine whether the tumour is malignant or benign, provide a specific diagnosis if possible, and determine tumour grade where appropriate. For some non-sarcoma malignancies, like lymphoma or germ cell tumours, first choice of treatment is not surgical, and a preoperative biopsy can prevent unnecessary surgical procedures. Furthermore, biopsies should be examined by pathologists with special expertise in sarcomas (21).

Histopathology

Leiomyosarcoma is a malignant mesenchymal tumour of smooth muscle origin. Histologically, it is characterized by the presence of spindle cells with abundant eosinophilic cytoplasma and hyperchromatic nuclei. There can be necrotic areas in the tumour, and areas of pleomorphism (22). The criteria for malignancy are mitotic activity of more than 2 MF/50 HPF (mitotic figures/high power field) and nuclear atypia (22).

Immunohistochemistry is necessary to obtain an accurate diagnosis of leiomyosarcoma. Leiomyosarcoma can be differentiated from other soft tissue sarcomas by the presence of smooth muscle cell actin and desmin on immunohistochemistry. To differentiate leiomyosarcoma from myofibroblastic sarcoma, heavy-caldesmon and smooth muscle myosin can be useful markers (23).

According to the NCCN guidelines on soft tissue sarcoma, there is no ancillary technique to support the morphological diagnosis of leiomyosarcoma (21).

Staging

Leiomyosarcoma can be more or less aggressive, and are classified as malignancy grade 1–3 based on differentiation (1–3),

mitoses (1–3) and necrosis (0–2) according to the French Federation of Cancer Centres Sarcoma Group (FNCLCC)-system (24–26). See Figure 2.

A combination of TNM classification and malignancy grade results in a categorization of retroperitoneal tumours in stage 1–4 (3).

Furthermore, tumour size, site, resectability and the presence of metastases are of relevance for proper staging (3). Pathological diagnosis is categorized according to the 2020 WHO classification of Soft Tissue and Bone Tumours (27).

Genetic subtypes

Gene expression patterns play a role, and may affect tumour characteristics, how sensitive the tumour is for chemotherapy and also affects prognosis (28, 29). Whole-Exome and RNA sequencing of leiomyosarcomas has been performed, and three mRNA expression subtypes have been identified. These subtypes may or may not vary with anatomical location (30–32). Genetic subtype 1 is primarily found in the extremities and gynaecological tumours. Subtype 2 is primarily found in the abdomen, and to a lesser degree in the extremities. While subtype 3 primarily is found in gynaecological leiomyosarcomas, to a lesser degree in the abdomen, but not in the extremities (31, 32).

The distribution of these three genetic subtypes may be explained by the following: Subtype 1 &2 comprises extremity and abdominal leiomyosarcoma, which resembles vascular smooth muscle; Subtype 2 comprises abdominal leiomyosarcoma, which resembles digestive smooth muscle. Subtype 3 comprises gynaecological leiomyosarcoma, which resemble uterine smooth muscle (30).

Genetic studies have also showed a near-universal inactivation of TP53 and RB1 genes, while a homologous recombination (HR)-deficiency signature (SBS3) was present in 98% of all specimens (33).

Another genomic finding is that alteration in muscle related genes differs in the three leiomyosarcoma subtypes. Myocardin (MYOCD) amplifications occur frequently in subtypes 2 and 3, while dystrophin (DMD) gene deletions occur predominantly in subtype 1, and to a lesser degree in subtype 3.

In addition, a high immune infiltration expressed as enrichment of Macrophage M2 is associated with LMS subtype 1, and subtype 1 has also been called inflammatory LMS. In a gene-expression study, Hemming et al. called subtype 1 inflammatory LMS, with a high ARL4C gene expression, and detected a worse disease-specific survival (34). Subtype 2 was called conventional LMS, was muscle-associated with a high Insulin-like growth factor 1 receptor (IGF1R) expression, and subtype 3 was called uterogenic LMS with an uterine-like gene expression profile, and high prolactin expression. Worse survival was associated with subtype 1 compared to subtype 3 for gynaecological cancers, and subtype 2 appears to have the best survival of the three subtypes. It appears that LMS subtypes may play a more important role than LMS location to predict prognosis and survival. This also raises the question whether further trials should be designed based on molecular LMS

Histological grading according to FNCLCC	
Tumour differentiation	
Score 1	Closely resembling normal tissue
Score 2	Histological typing is certain
Score 3	Embryonal or undifferentiated sarcomas
Mitotic score	
Score 1	0-9 mitoses per 10 HPF
Score 2	10-19 mitoses per 10 HPF
Score 3	> 19 mitoses per 10 HPF
Tumour necrosis	
Score 0	No necrosis
Score 1	≤ 50% tumour necrosis
Score 2	> 50% tumour necrosis
Histological grade:	
	Grade 1: total score 2-3
	Grade 2: total score 4-5
	Grade 3: total score 6-8

FIGURE 2
Histological grading.

subtype, and not on LMS location. An argument for this is that DNA-damage response inhibition (DDRi) has been demonstrated to be effective across different locations. Knowledge on the three genetic subtypes also indicates that immunotherapy possibly is most effective in the inflammatory LMS subtype 1.

Treatment

Treatment options are complex, and a treatment plan should be discussed at a multidisciplinary team conference (3, 21). A recent consensus statement by the Transatlantic Australasian Retroperitoneal Sarcoma Working Group provides evidence of increased survival, reduced postoperative morbidity and mortality, significantly higher adherence to guidelines, and reduced risk of relapse and sarcoma-related death when patients are treated for retroperitoneal sarcoma at sarcoma reference centres (14). Many of the below treatment principles applies to both abdominal and retroperitoneal sarcomas.

The indisputable first line of treatment for localized leiomyosarcoma, is surgery with liberal excision and negative margins (3, 14, 21). The minimal margin considered acceptable might vary depending on preoperative treatment and presence of anatomical barriers limiting the excision (3). A review of anorectal leiomyosarcomas comprising 51 cases, described both wide local excision and radical resection as treatment options. Local recurrence was more common after wide local excision (30%) compared with radical resection (20%), though the total rate of metastasis was just over 50% regardless of the operative treatment option (13).

Wide excision refers to a dissection plane through unaffected normal tissue within the involved compartment. Radical or compartmental resection refers to *en bloc* excision of the entire involved compartment with no reactive tissue or tumor cells at the margin. For retroperitoneal leiomyosarcomas, there is a tendency towards radical or compartmental resection, and some evidence that retroperitoneal liposarcomas should be treated with radical resection (35).

The aim of a complete resection is to achieve negative margins in the histological sample. The width of these margins are not ultimately defined in the literature, but some suggests a margin of 1 cm, or a layer of intact fascia (36). Excessive lymph node resection does not seem to be necessary, as leiomyosarcoma rarely are metastatic to local lymph nodes (37). If the tumour involves or originate from a blood vessel, the proximal and distal end of the resection should have negative margins. Furthermore, it's recommended to resect tumour thrombosis if present, but the evidence grade of this is unknown.

Resections are categorised as R0-2, where R0 represents margins with no residual microscopic disease, R1 shows residual microscopic disease and R2 ushows macroscopic residual disease. According to the NCCN guidelines on soft tissue sarcoma, resection of a whole anatomical compartment is not usually necessary to obtain oncologically appropriate margins, but evidence is inconclusive. While the NCCN guidelines state that the biopsy site should, if possible, always be included in the resection (21), biopsy sites of retroperitoneal sarcomas are usually left *in situ* (38). This makes it even more important to perform the biopsy with a coaxial technique, and with a retroperitoneal approach rather than intraabdominal.

If the pathologist examining the surgical specimen finds a positive margin after primary surgery of soft tissue sarcoma, re-resections are recommended to achieve negative margins, but only if there is no significant impact on functionality, and if the structures adjacent to the margins are not bone, major vessels or nerves (21).

Similar to abdominal leiomyosarcomas, treatment of retroperitoneal leiomyosarcomas is complete surgical tumour resection with negative margins. Whole anatomical compartment resection is a topic of debate, and more recent management of primary retroperitoneal sarcomas is histology-tailored. For leiomyosarcomas, preservation of adherent organs without direct involvement is preferred, while compartment resection including resection of adherent organs is advised for liposarcomas (35).

However, every surgical procedure entails an individual assessment of extensiveness vs. consequence, and consideration of postoperative morbidity due to damage or resection of retroperitoneal structures. The retroperitoneal space is a confined compartment with multiple large vessels and nerve bundles, limited by bone on multiple sides. This makes radical resection more difficult in some cases of retroperitoneal sarcoma, and marginal surgical resections more frequent. Some structures in the retroperitoneal spaced are more readily sacrificed during surgery, like one kidney, parts of the colon, the adrenal gland and the psoas muscle, while other retroperitoneal structures are more frequently spared due to morbidity if resected, like the bladder, pancreas, duodenum, and major vessels or nerves (14, 38).

Retroperitoneal leiomyosarcomas are usually more well-defined than other retroperitoneal tumours, and closely adjacent organs and structures, provided they are not inseparably adherent or invaded, may be spared if the surgeon can still achieve negative margins (14). When leiomyosarcoma arises from a major vein, special attention should be directed to achieve microscopically negative longitudinal margins of the vein of origin. The use of intra-operative frozen sections to achieve this can be advised (16).

The surgical approach to resect leiomyosarcoma of the caval vein depends on the segment involved. Segment 1 and 2 LMS (below the hepatic veins) can be treated by a midline laparotomy or right subcostal abdominal incision. The retroperitoneum is exposed by mobilizing away non-involved organs like the duodenum, pancreatic head, and the right colon. Proximal and distal control of the inferior caval vein should be achieved including lumbar and renal veins. Finally the involved part of the caval vein should be resected (16). After resection the caval vein can be managed with primary repair, ligation, patch repair, or graft reconstruction. Whether the caval vein can be ligated or should be reconstructed depends on the degree of caval obstruction (presence of thrombus and collateral veins), the degree of cardiac stability when clamping the caval vein, and the complexity of the reconstruction. Ligation of the caval vein is often well tolerated. In the beginning the patient may suffer from lower limb oedema, but often aften a few weeks sufficient collaterals have developed, and symptoms disappear.

Surgical resection of segment 3 LMS of the caval vein is very challenging. Resections are associated with a high mortality risk, and these tumours are considered unresectable by traditional surgical techniques (39). Liver explantation, ex-vivo resection of the retro-and suprahepatic LMS, graft reconstruction of the retrohepatic caval vein, and reimplantation of the liver are amongst the highly specialized surgical options for these tumours. During surgery, venovenous bypass, cardiopulmonary bypass, or portocaval shunting may be required (40). This procedure should be performed at a liver transplant unit, and in the literature only 100 cases have been reported. A ringed polytetrafluoroethylene (PTFE) is the most applied graft for caval reconstruction with good long-term patency (41).

Resection rates of abdominal and retroperitoneal leiomyosarcoma are not readily reported in the published literature. A review of 76 cases of abdominal leiomyosarcoma reported resection rates between 93% - 100% depending on location (20). A Danish register study of abdominal and retroperitoneal soft tissue sarcoma reported a resection rate of 89% for primary sarcomas over a 10-year period. 79% of patients with first recurrence of sarcoma were resectable. Only 11% of the tumours were leiomyosarcomas (1).

A referral centre in Italy published data on patients with inoperable primary retroperitoneal sarcomas, and reasons for not performing surgery. They reported a resection rate of 88,5% over a 4-year period. The primary reason for not performing surgery was a technically non-resectable tumour. The second reason was patient factors such as poor performance status and comorbidities. Approximately 25% of the non-resectable patients had leiomyosarcoma, while 50% had liposarcoma (42). A similar study reported a resection rate of 74% on patients with primary retroperitoneal sarcomas. The reasons for not performing surgery were non-resectability, rapid progression before/under radiotherapy, and poor performance status or comorbidity (43).

There has been an increase in use of adjuvant radiotherapy in some soft tissue sarcomas, including retroperitoneal sarcomas, over the last 5–7 years, while chemotherapy usually has been reserved for stage 4 (metastatic disease) (44, 45). A review of 51 patients with anorectal leiomyosarcomas found that neoadjuvant radiotherapy was associated with a lower risk of local recurrence compared to adjuvant radiotherapy, and also that neoadjuvant radiotherapy facilitates R0 resection of the tumour (13).

In a retrospective review of prognostic factors, 42 patients with intraabdominal or retroperitoneal leiomyosarcoma were included. The patients underwent surgical resection with curative intent, and amongst other prognostic factors, the authors found no impact of adjuvant therapy on survival (46).

In a large retrospective study of more than 7,000 patients with leiomyosarcoma in the National Cancer Database, Gootee et al. found decreased mortality when comparing adjuvant or neoadjuvant radiotherapy in combination with surgery, to surgery alone (4). More than 1,500 patients had leiomyosarcoma of the abdomen, but separate analyses of the effects of chemotherapy on these patients were not performed.

The NCCN guidelines from 2021 on soft tissue sarcoma of the abdomen and retroperitoneum, state that postoperative radiotherapy is not routinely recommended for R0-2 resections. If anything, the surgeon should consider a re-resection if a R0 resection is possible. If surgery leaves a margin close to soft tissue, or a microscopically positive margin, and a R0 resection is not feasible due to anatomical constraints, radiotherapy should be considered. In patients that have received neoadjuvant radiotherapy, a booster dose might be considered postoperatively (21).

In patients with stage IV intraabdominal or retroperitoneal sarcoma, watchful waiting is recommended if the patient is asymptomatic. In symptomatic cases, chemotherapy and/or radiotherapy can be administered, and surgery can be an option to relieve symptoms (21).

There are few randomized trials that explore whether there is an auxiliary effect of concomitant therapy in patients with resectable leiomyosarcoma. Trans-Atlantic Retroperitoneal Sarcoma Working Group (TARPSWG) refers to analyses from the STRASS-1 trial, where 266 resectable patients with retroperitoneal sarcomas from 31 institutions and 13 countries were randomized to either preoperative radiation therapy (RT) followed by surgery, or surgery alone. The RCT showed that there is no evidence that neoadjuvant RT has an impact on local disease control or overall survival, when all histological subgroups are considered. Thus, RT is not routinely recommended for high grade retroperitoneal sarcomas.

Subgroup analysis further revealed that RT was without effect on retroperitoneal leiomyosarcoma, but might play a role in treatment of well differentiated and low-grade dedifferentiated lipomyosarcoma (6, 14).

Neoadjuvant chemotherapy targeted towards specific histological subgroups have shown an increased survival in extremity sarcomas, but these results cannot be extrapolated directly to other soft tissue sarcomas. It is however suggested that neoadjuvant chemotherapy can be facilitated for individual use in patients with chemosensitive histological subtypes, such as retroperitoneal leiomyosarcoma (14). Currently the role of neoadjuvant chemotherapy in patients with retroperitoneal leiomyosarcomas and dedifferentiated liposarcomas is investigated in a multicentre randomized controlled trial in which patients are randomized to neoadjuvant chemotherapy and surgery vs. surgery alone (STRASS-2 trial) (47).

A subgroup analysis of patients receiving perioperative chemotherapy and hyperthermia, showed that this might be beneficial for abdominal sarcomas undergoing R0-1 resections. This treatment is however currently not available in many facilities (14). Postoperative chemotherapy has no beneficial effect after complete en-bloc resection (14).

Postoperative adjuvant chemotherapy can be considered for patients with sarcomas of histological subtypes which have a high tendency for metastatic disease, like leiomyosarcoma. Hypothetically, it makes sense to administer chemo to these patients, since disease relapse is due to hematogenic spread (48).

Previously, Doxorubicin has been the preferred single line treatment for soft tissue sarcoma. Only one trial has demonstrated superiority of treatment with a more extensive regime than single line doxorubicin for metastatic leiomyosarcoma. That trial administered Trabectedine and

Doxorubicin in combination, had a median follow up of more than 7 years, but out of 108 patients, only 16 had retroperitoneal sarcoma. Results were reported as progression free survival, which was 12.9 months in the extremity/retroperitoneal group, and overall survival, which was 38,7 months (29).

According to the NCCN guidelines, doxorubicin in combination with ifosfamide is the chemotherapy regimen with the highest response rate in patients with unresectable soft tissue sarcoma (21).

Prognosis

The 5-year survival of patients in Denmark with primary intraabdominal or retroperitoneal sarcoma is 70,2%. Not surprisingly R0 resections result in a higher 5 year survival of 76,8%, while patients with R1 and R2 resections have a survival rate of 43,5% (1).

Intraabdominal and retroperitoneal leiomyosarcomas have a shorter disease-free survival (DFS) and overall survival (OS), than leiomyosarcomas at other anatomical locations. One study found a 5-year DFS of 39,1% and 35,3% for abdominal and retroperitoneal leiomyosarcomas respectively (46). It also found a 10-year OS of 63,4% for patients with leiomyosarcoma in the abdomen and retroperitoneum, compared to an OS of 79,2% for disease outside the abdomen. Recurrent disease was more often due to metastases in the abdominal/retroperitoneal group (59,5%), than in patients with primary leiomyosarcoma located elsewhere 32,2% (46). The outcome for retroperitoneal leiomyosarcomas may be worse due to large tumour size at diagnosis (median 20 cm), high recurrence rates, and anatomical constraints of retroperitoneal surgery (49).

Other studies have suggested worse outcome for metastatic or recurrent disease with uterine leiomyosarcomas compared to non-uterine leiomyosarcomas, even though uterine leiomyosarcomas were thought to be more sensitive for chemotherapy.

Tumour grade, size, depth and primary site are significant prognostic markers for survival and recurrence. Size and margin status is significant for the rate of local recurrence, while size and grade are relevant for distant recurrence (4, 50).

In a retrospective review of 144 patients with abdominal or retroperitoneal leiomyosarcoma from New York, the 5-year disease free survival of patients was 67%, significantly lower than leiomyosarcomas at other anatomical locations (50). There was a recurrence rate of 51%, which also was higher than for leiomyosarcomas located elsewhere. Distant recurrence was the most common recurrence for leiomyosarcoma at all anatomical sites (53%), but local recurrence was more common amongst patients with intraabdominal or retroperitoneal tumours (30%), than at other anatomical locations (50).

When compared to more common cancers, such as colorectal adenocarcinoma, colorectal leiomyosarcoma has a significantly lower overall 5 year survival rate of 43,8% against 52,3% (11).

Depending on the study, the reported 5 year disease-free survival ranges from 39,1% (46) to 67% for abdominal leiomyosarcoma (50) [56.4% (4)] Given this discrepancy, the reader will appreciate the degree of divergence in published articles on the subject. Reported data is retrospective, sometimes incomplete, and occasionally confounded by inclusion of other sarcomas in the material (predominantly GIST). Furthermore, publications are heterogenous in the sense that some group abdominal and retroperitoneal leiomyosarcomas, while others include uterine and non-visceral sarcomas in their statistics.

In a study of more than 7,000 patients with leiomyosarcoma from the National Cancer Database, age was identified as an independent prognostic factor. The younger the patient was at the time of diagnosis, the better the survival statistics. The authors reported a 3% increase in mortality per additional year of age (4). The patient group was homogenous, and there were no subgroup analysis of the effect of age on abdominal leiomyosarcoma specifically.

Surveillance

The NCCN guidelines recommend periodical follow up by imaging of the primary site after neoadjuvant therapy, postoperatively and periodically based on the risk of recurrence. Chest imaging by x-ray, CT scan, or PET-CT scan is a necessity due to risk of pulmonary metastases.

In patients without radiographic evidence of disease, imaging of the primary tumour site, chest and other sites at risk of metastases (e.g., the liver) is recommended every 3–6 months the first 2–3 years, every 6 months for the next 2 years, and then annually (21).

27% of patients with intraabdominal or retroperitoneal leiomyosarcoma succumb to disease more than 5 years after they are diagnosed (6% disease-specific mortality after 8 years) (50). This strongly suggests that follow up should be more than 5 years for patients with intraabdominal or retroperitoneal leiomyosarcoma.

Despite complete surgical resection of RPS, the risk of recurrence never plateaus. Consequently, these patients should have lifelong follow-up, which is a burden for patients and healthcare resources. Recurrence might be visible on imaging from months to years prior to any symptoms, and follow up should include CT scans as well as a clinical evaluation. Chest scans may be omitted, particularly in patients with low-grade histology (14).

The median time to recurrence is less than 5 years for high grade RPS, and follow up should probably be performed every 3–6 months the first 5 years, and then every year (14).

Future perspectives

This systematic review has summarized current knowledge and evidence on non-uterine abdominal and retroperitoneal leiomyosarcomas. The review has revealed a lack of high-quality evidence, and a lack of randomised trials. Little is known, but we are gradually building knowledge through increasing data and subclass definition of soft tissue sarcoma, clinical presentation, histological and genetic sarcoma subtypes, surgical strategies,

individualized treatment approaches, adjuvant therapy, follow-up and recurrent disease. There is a great need for more substantial and high-quality research in the area of leiomyosarcomas of the abdomen and retroperitoneum. Consensus statements and publications from global sarcoma associations often lack high quality evidence (14). Abdominal and retroperitoneal leiomyosarcomas are rare tumours, and rare tumours require special actions to acquire evidence. There is a great need for prospective studies with relevant clinical and patient reported outcomes. If possible, these studies should be international multicentre randomised studies. Recent international multicentre RCTs on the effect of neoadjuvant radiotherapy (STRASS-1, completed and published) and neoadjuvant chemotherapy (STRASS-2, currently recruiting) in patients with retroperitoneal sarcomas are excellent examples of how to establish firm evidence. Furthermore, all patients should be registered in international clinical registries.

Conclusions

- Abdominal and retroperitoneal leiomyosarcomas are difficult to diagnose due to vague symptoms, these tumours are therefore often quite advanced or large when diagnosed.
- Adjuvant therapy for abdominal and retroperitoneal leiomyosarcomas is less effective than with other cancer diseases.
- These tumours have a high risk of distant or local recurrence, also after 5 years of disease-free survival.
- Treatment of sarcoma patients by multidisciplinary teams, and with adherence to guidelines, is important for their survival. Thus, updated knowledge of current best practice is essential for any facility treating sarcoma patients.
- Although based on thorough literature review and expert discussions, most consensus articles, guidelines and reports do not focus specifically on abdominal and retroperitoneal leiomyosarcoma. Thus, some of the above recommendations are more general, and covers a broader group of soft tissue sarcomas, or sarcomas also located at other anatomical sites.
- Classification of LMS in three genetic subtypes is a breakthrough, and should cause future trials to be based on molecular subtype, rather than tumour localisation (abdomen/retroperitoneum, extremities, and gynaecological).

144 studies were eventually included in this systematic review from our search (1, 2, 4, 6–8, 10, 11, 13, 16, 20, 39, 41, 42, 50–54, 55–64, 65–73, 74–83, 84–93, 94–103, 104–113, 114–123, 124–133, 134–143, 144–153, 154–163, 164–173, 174–177).

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

Author contributions

MØ: Conceptualization, Data curation, Formal Analysis, Investigation, Validation, Writing – original draft, Writing – review & editing. HS: Formal Analysis, Validation, Writing – review & editing. LPR: Conceptualization, Validation, Writing – review & editing. LPE: Conceptualization, Data curation, Formal Analysis, Investigation, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2024.1375483/full#supplementary-material

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