

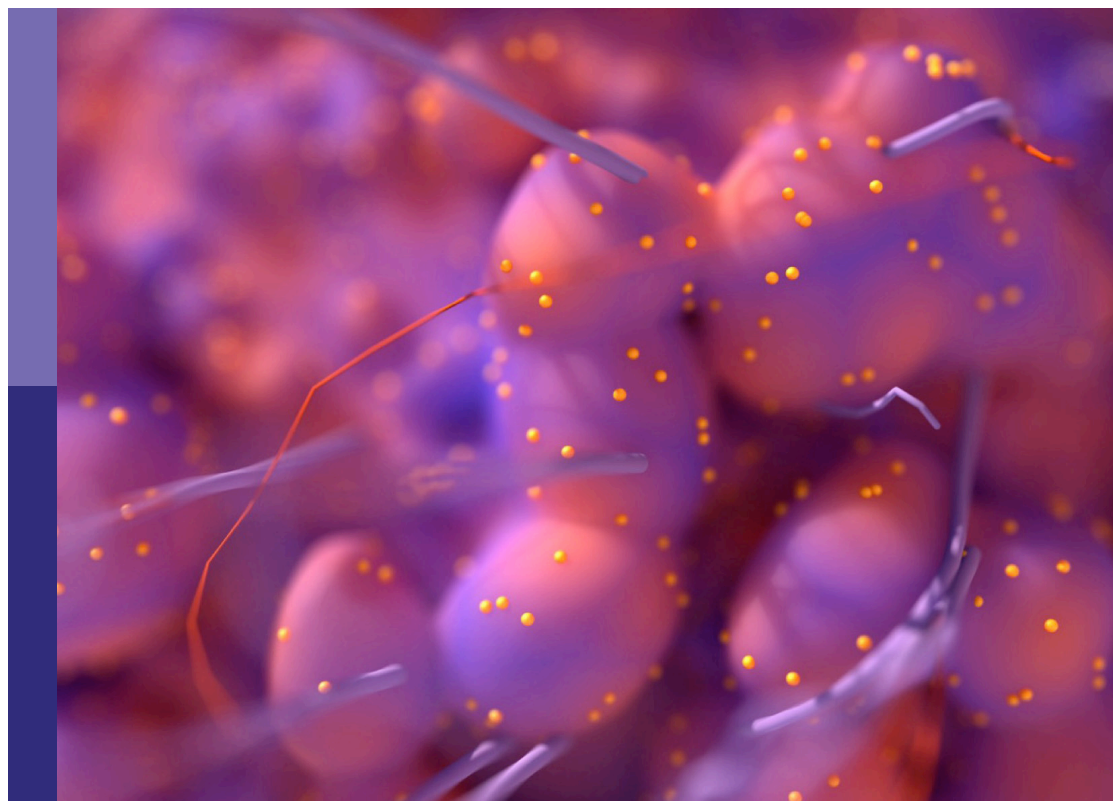
Comprehensive treatment strategy for improving surgical resection rate of retroperitoneal sarcomas

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and Yong Zhang

Published in

Frontiers in Oncology
Frontiers in Surgery



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ISSN 1664-8714
ISBN 978-2-8325-6904-7
DOI 10.3389/978-2-8325-6904-7

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Comprehensive treatment strategy for improving surgical resection rate of retroperitoneal sarcomas

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Citation

Tong, H., Cananzi, F. C. M., Zhang, Y., eds. (2025). *Comprehensive treatment strategy for improving surgical resection rate of retroperitoneal sarcomas*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-6904-7

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OPEN ACCESS

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RECEIVED 18 August 2025

ACCEPTED 29 August 2025

PUBLISHED 11 September 2025

CITATION

Tong H (2025) Editorial: Comprehensive treatment strategy for improving surgical resection rate of retroperitoneal sarcomas. *Front. Oncol.* 15:1687933. doi: 10.3389/fonc.2025.1687933

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Editorial: Comprehensive treatment strategy for improving surgical resection rate of retroperitoneal sarcomas

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KEYWORDS

retroperitoneal sarcomas, diagnosis, surgical technique, perioperative care, systemic therapy

Editorial on the Research Topic

Comprehensive treatment strategy for improving surgical resection rate of retroperitoneal sarcomas

Retroperitoneal sarcomas (RPS) present a formidable challenge in surgical oncology. Their rarity, anatomical complexity, frequent involvement of critical structures, and pronounced histological heterogeneity contribute to high rates of local recurrence and significant morbidity, despite aggressive treatment. This Research Topic brings together a collection of insightful studies that collectively advance our understanding of RPS management, highlighting significant progress and persistent challenges across the spectrum of diagnosis, surgical technique, perioperative care, staging, and systemic therapy. The contributions underscore the critical importance of a multidisciplinary, histology-tailored approach to this complex disease.

The cornerstone of curative intent for localized RPS remains complete surgical resection with negative margins (R0). Achieving this goal often necessitates complex, extended procedures. The case series by Al-Makassed Hospital powerfully illustrates this reality, demonstrating successful R0 resection in three patients with locally advanced sarcomas invading major vessels, kidneys, and other viscera (Bael et al.). These successes were unequivocally attributed to meticulous preoperative planning and the indispensable role of a dedicated, highly specialized multidisciplinary surgical team encompassing vascular, urologic, and hepatobiliary expertise. This reinforces the paradigm that complex RPS surgery demands a collaborative effort far beyond the scope of a single surgeon. Complementing this, the comparative study on Total Retroperitoneal Lipectomy (TRL) provides compelling evidence that extending the resection beyond the tumor mass itself, specifically in primary retroperitoneal liposarcoma (RPLS) involving the removal of ipsilateral retroperitoneal fat, improves recurrence-free survival (RFS) and overall survival (OS) compared to traditional complete resection (CR), particularly in dedifferentiated subtypes, without significantly increasing severe morbidity (Gao et al.). This suggests a potential shift towards more extensive compartmental resections for specific histologies.

Technological advancements continue to refine surgical approaches. The large single-center experience with Da Vinci robot-assisted retroperitoneal tumor resection (RRTR) demonstrates the safety and efficacy of this minimally invasive technique in selected

patients (Hao et al.). Their analysis identified a maximum tumor diameter ≤ 64 mm and benign pathology as key predictors of successful robotic resection, offering valuable practical guidance for patient selection and setting the stage for further refinement of robotic applications in RPS. While successes in R0 resections and robotic approaches are well highlighted, a brief acknowledgment of limitations, as most existing reports are single-center, retrospective, or small sample sizes. Therefore, future exploration through large-scale cohort studies or even prospective studies is warranted.

The complexity of RPS surgery inherently carries significant perioperative risks. The study on anesthetic management in patients requiring massive blood transfusion (MBT) during RPS resection provides crucial insights into mitigating these risks (Wang et al.). It highlights the profound blood loss encountered (median 7000ml) and the extensive transfusion requirements, while identifying elevated lactate levels at surgery's end as the sole significant risk factor for perioperative mortality. This underscores the critical importance of meticulous intraoperative hemodynamic monitoring, aggressive resuscitation strategies, and vigilant postoperative care in this high-risk cohort.

Accurate diagnosis and prognostication are of utmost importance. The analysis of retroperitoneal unicentric Castleman disease (UCD) resected as sarcomas serves as a crucial reminder of diagnostic pitfalls in the retroperitoneum (Gao et al.). Although UCD is exceptionally rare, its potential to mimic sarcoma necessitates awareness, as complete surgical resection offers excellent long-term survival. Conversely, the comprehensive evaluation of the AJCC staging system and proposal of a novel stage grouping system (nTNM) for RPLS addresses the limitations of current staging (Fan et al.). This large study, which combines institutional and SEER data, convincingly demonstrates that the revised T-stage and nTNM system provide superior risk stratification compared to the 7th and 8th AJCC editions. Furthermore, the developed nomogram offers a valuable tool for individualized prognostic assessment and treatment planning.

The role of adjuvant and neoadjuvant therapies in RPS remains an area of active investigation and debate. The population-based propensity score-matched study on intraoperative radiotherapy (IORT) delivers a sobering message, finding no significant improvement in overall survival for patients with RPLS receiving IORT compared to those who did not (Zhou et al.). This suggests IORT should not currently be considered a standard therapy outside of clinical trials, emphasizing the need for more effective local control strategies. In the realm of systemic therapy for advanced disease, the retrospective study on Anlotinib combined with Envafolelimab shows promising activity in unresectable or metastatic liposarcoma, achieving a disease control rate of 73.3% and a median progression-free survival of 14.2 months, with manageable toxicity (Liu et al.). This adds to the growing armamentarium of targeted and immunotherapeutic options being explored for specific sarcoma subtypes.

Looking towards the future, understanding the molecular drivers of RPS is essential for developing novel therapeutics. The review “*Targeting Liposarcoma: Unveiling Molecular Pathways and Therapeutic Opportunities*” synthesizes the critical molecular heterogeneity across liposarcoma subtypes, detailing distinct

genetic alterations and signaling pathways (Liu et al.). This knowledge is foundational for the rational design and application of histology-specific targeted therapies, moving beyond a one-size-fits-all approach (Garcia-Ortega). Similarly, the development and validation of the Comprehensive Hematological Scoring System (CHSS) represents a step forward in prognostication (Qiu et al.). By integrating multiple pre-treatment hematological markers, CHSS outperforms established ratios like NLR and PLR in predicting overall survival for soft tissue sarcoma patients, offering a potentially more robust tool for risk assessment.

In conclusion, the studies presented in this Research Topic paint a picture of a field in evolution. Significant strides are being made in refining surgical techniques, from the imperative of multidisciplinary radical resection to the exploration of minimally invasive robotics and extended compartmental procedures like TRL, guided increasingly by histological subtype. Perioperative care is being better defined, particularly for high-risk scenarios like massive transfusion. Diagnostic accuracy and prognostication are improving through awareness of mimics like UCD and the development of superior staging systems (nTNM) and prognostic scores (CHSS). While challenges remain, particularly in defining the optimal role for radiotherapy and overcoming the limitations of current systemic therapies, promising avenues are emerging, exemplified by the activity of anlotinib plus envafolimab and the growing understanding of subtype-specific molecular vulnerabilities. The overarching theme resonating throughout these contributions is the necessity for personalized, histology-driven management strategies delivered within a framework of close multidisciplinary collaboration. Continued research focusing on the molecular underpinnings of RPS subtypes and innovative therapeutic combinations holds the key to further improving outcomes for patients facing this challenging group of malignancies.

Author contributions

HT: Writing – original draft, Writing – review & editing.

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RECEIVED 22 November 2023

ACCEPTED 02 January 2024

PUBLISHED 22 January 2024

CITATION

Bael P, Alqtishat B and Alshawwa K (2024)
Case Report: Successful R0 resection in locally
advanced retroperitoneal sarcomas.
Front. Surg. 11:1343014.
doi: 10.3389/fsurg.2024.1343014

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Case Report: Successful R0 resection in locally advanced retroperitoneal sarcomas

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We present a case series of three successfully resected tumors in our center at Al-Makassed Hospital in Jerusalem, Palestine, all of which primarily involved or invaded adjacent structures and needed a multidisciplinary approach to achieve R0 resection. Our first patient is a 42-year-old previously healthy female with intermittent attacks of dull aching abdominal pain. Her tumor was a leiomyosarcoma that involved major vessels and other adjacent vital structures. Ultimately, she needed major highly advanced surgery necessitating the need for vascular reconstruction of the IVC, as well as R0 resection. The surgery was performed by a multidisciplinary team of highly specialized surgeons in related fields. Our second case is a 75-year-old female patient with a well-differentiated liposarcoma invading the upper pole of the right kidney, necessitating a nephrectomy. Consequently, this case demanded the interdisciplinary involvement of nephrology. Our third patient is a 59-year-old male with dedifferentiated liposarcoma that involved the spleen, pancreas, and splenic flexure while engulfing the left kidney and ureter. Beyond the removal of the tumor, multiorgan resection was imperative to achieve microscopic margin-free resection. This extensive local spread needed broad collaboration from the medical team and other surgical subspecialties. All surgeries went well, and their outcomes were promising. All patients had an uneventful follow-up and, to date, no recurrence. Invasive retroperitoneal sarcomas of different histological types and clinical stages represent a technical challenge. Careful preoperative investigation and an experienced, dedicated multidisciplinary team of surgeons and non-surgeons from related fields, including vascular, urologic, and hepatobiliary surgeons, are usually needed for a safe and successful R0 resection despite extensive tumor involvement in light of difficulty achieving early diagnosis.

KEYWORDS

retroperitoneal sarcomas, IVC graft, R0 resection, liposarcoma, leiomyosarcoma, multidisciplinary involvement, case report

1 Introduction

Retroperitoneal malignancies are rarer than their extremity counterparts and are among the rarest soft-tissue malignancies, representing only 12%–15% (1, 2). Their placement in the retroperitoneum makes their presentation vague, their diagnosis hard, and their excision tricky (1). Surgical management, though it is first-line treatment, is impeded and complicated when the tumor involves surrounding structures and vasculature, generating a high recurrence rate due to incomplete excision (1, 3).

This is especially true in the case of retroperitoneal liposarcoma, which calls for specialist management in centers with experience in management, and a multi-disciplinary team integrating surgery, radiology, and oncology, along with case-specific involvement from other fields. Diagnostic imaging is complex requiring multiple modalities, and post-operative follow-up is exhausting necessitating consistent imaging to detect recurrence (4).

R0 resection is defined as resection resulting in microscopically and macroscopically margin-negative resection, whereas R1 resection is restricted to macroscopic remission. Classically, R1 resection has been the mainstay of surgical treatment for retroperitoneal sarcomas, except in cases of invasion. Recent studies have challenged this concept and suggested compartmentalization as a method to decrease tumor recurrence, which, in the case of retroperitoneal sarcomas, is the leading cause of death (2). R0 excision has now become the gold standard of management of retroperitoneal sarcomas, with consistent improvement in survival rates (3, 4).

In our case series, we present multiple large sarcomas involving different, multiple, and obscure organs, causing various changes in their presentations and requiring multidisciplinary management. Nevertheless, in the end, they were successfully resected with R0 resection and have yet to recur.

Our first case is of a 42-year-old female whose leiomyosarcoma involved the inferior vena cava, ultimately demanding vascular reconstruction, and yet was managed successfully, with an uneventful postoperative course. The second case is of a 75-year-old female with liposarcoma invading the right kidney and thus requiring nephrectomy, with close renal observation postoperatively.

Our third and final case is of a 59-year-old male, whose dedifferentiated liposarcoma arose from the mesentery, which occurs in 2% of cases and involved varied structures, requiring multiorgan excision.

2 Case presentation

2.1 Case 1

A 42-year-old female patient presented to our department complaining of intermittent attacks of dull aching abdominal pain localized at the top and upper right side of her abdomen. On examination, she had right upper quadrant tenderness but no palpable masses. An abdominal ultrasound revealed a heterogeneous lesion at the upper pole of her right kidney. Computerized tomography (CT) showed a heterogeneous lesion at the upper pole of the right kidney that measured 7.5 × 7 cm, invading adjacent liver parenchyma without clear cleavage (Figure 1—CT).

Abdominal MRI was performed next and showed a heterogeneously enhanced soft tissue mass in the upper pole of the right kidney measuring 6.8 × 9.5 cm, mainly involving segment VII of the liver and a small part of segment VIII. The mass abutted the inferior vena cava (IVC) and severely narrowed



FIGURE 1
Ct, CT findings for case 1.

it, causing it to appear slit-like. The mass was circumferentially compressing the vein and surrounding it, and even stimulated a chronic inflammatory reaction with focal mural thrombosis, though it didn't seem to invade or penetrate the inferior vena cava itself. Furthermore, the mass seemed to involve the lower wall of the IVC. An ultrasound-guided tru-cut biopsy showed evidence of leiomyosarcoma with many mitotic figures.

Due to the complexity of the mass anatomy, a multidisciplinary team was formed, involving oncologists, surgeons, radiologists, and pathologists, who opted for surgical management aiming for R0 resection of the tumor, which involved drastic vascular, hepatic, and renal resection, and significant risk of morbidity and mortality. The combined efforts of all involved parties was essential, especially considering the high risk of bleeding, surrounding organ injury, and the importance of achieving negative margins.

Surgery was performed through the modified Makuuchi incision, in the supine position. Once the underlying tissue was separated to achieve access to the peritoneal cavity, we ligated and excised the falciform ligament. We divided the hepatocolic ligament, and carefully dissected any remaining attachments to the retroperitoneum, diaphragm, and IVC, allowing us to freely mobilize the liver. We kocherized and dissected the duodenum until the IVC was exposed and isolated. We could then visualize a large solid retroperitoneal mass, circumferentially engulfing the IVC to the level of the left renal vein and extending upwards to the hepatic veins while compressing the right liver lobe (segment VII). We dissected, separated, and isolated the IVC segment from the insertion of the hepatic vein to the level of the left renal vein. Subsequently, we performed the Pringle's maneuver for 5 min. The mass extension into segment VII of the liver was resected. The remaining parenchyma showed no involvement or abnormal changes. We then placed two stitches to secure hemostasis.

We then attempted to carefully separate the mass surrounding the IVC by fine sharp dissection; however, we were only partially successful due to the apparent involvement of the IVC wall. The left renal vein was isolated and controlled via a vessel loop. We

applied two vascular clamps, one inferior to the left renal vein, and one superior to the right suprarenal vein. The right gonadal vein was dilated, though we managed to isolate and protect it as well. We applied three staples to the renal pedicle and performed a nephrectomy. We then clamped the right ureter.

A 10-cm segment of the IVC was obliquely resected along with the mass, up to the origin of the left renal vein. We then reconstructed the IVC by implementing a 22 mm Dacron graft, first sutured at the level of the liver hilum, and then above the renal vein. This was when we released the vascular clamps, with no detectable leakage, and we secured hemostasis.

Urine output was checked after 15 min and showed 15 cc of clear urine. Intraoperative blood loss was approximately 3 L, and required 6 L of crystalloids, 7 packs of packed red blood cells, 6 packs of fresh frozen plasma and platelets, and 4 packs of cryoprecipitate. The surgery lasted for approximately 7 h, and there were no intraoperative complications (Figure 2—IVC Graft).

Histopathology of the specimen showed a 9 cm leiomyosarcoma pushing into the renal sinus and ipsilateral adrenal gland, with a negative ureteric margin. The mass was superiorly limited by a thin fibrous capsule. Separated wall pieces with chronic inflammation and focal mural thrombosis were negative. The margins were negative all around. Immunohistochemistry revealed that the tumor cells were positive for SMA and desmin.

Postoperatively, the patient was kept for 48 h in the intensive care unit (ICU) for close observation and then transferred to the general ward. In the following hours, she developed intra-abdominal bleeding with hematoma formation and bloody drain output, managed conservatively with blood product transfusion. She was discharged 2 weeks later in good general condition. A week after discharge, she complained of abdominal pain and distention. Imaging revealed intraperitoneal fluid accumulation. An ultrasound-guided drain was inserted, draining old blood and successfully resolving her symptoms.

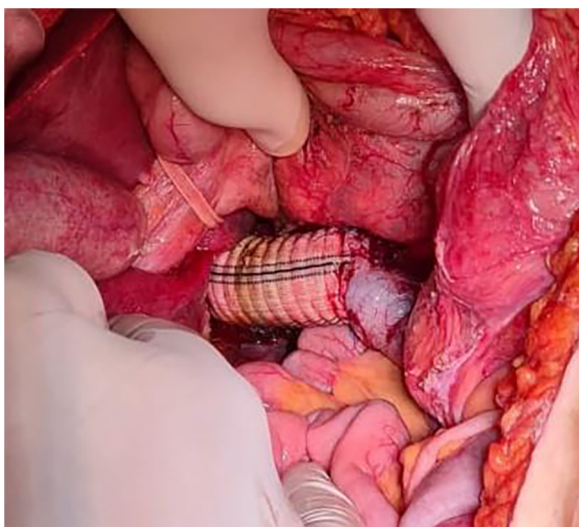


FIGURE 2
IVC graft, intraoperative image of IVC graft placement.

A 2-month CT scan follow-up showed only postoperative changes, with no evidence of metastatic disease or local recurrence. The patient was followed up closely for 4 months after surgery, and her condition showed an uneventful course. She was sent to an oncological center and started on a radiotherapy course.

2.2 Case 2

A 75-year-old female patient was referred to our hospital for an excisional biopsy of a retroperitoneal mass. She had a past medical history of diabetes mellitus and hypertension. She previously underwent bilateral knee replacement and hip replacement surgery. The patient's history dates back to 2016 when she noticed a lump on the front of her head. Following medical consultation, the mass was excised but recurred thrice in 2016, 2020, and 2021.

Histopathological examination following its third recurrence revealed squamous cell carcinoma. A positron emission tomography (PET) scan following oncological referral revealed various masses, including a mildly hypermetabolic heterogeneous fat-containing mass lesion in the right retroperitoneal region, pushing the right kidney antero-inferiorly, measuring approximately 10 cm in the longest axial diameter with fluorodeoxyglucose (FDG) uptake up to 3, with a similar 1.8 mass in the left upper quadrant of the mesentery, although with insignificant FDG uptake. There was also a hypermetabolic nodule in the right adrenal gland measuring 2.2 cm axially with a maximum standardized uptake value of up to 3.9.

On abdominopelvic CT, there was a large heterogeneous fat containing a retroperitoneal-retrorenal relatively well-defined mass measuring $11 \times 9.5 \times 7.5$ cm.

The mass showed fat haziness and increased vascularity, mainly arising from the right renal artery while abutting the whole upper posterior renal surface without definite invasion. Another small heterogeneous focal lesion measuring 1.7 cm was also observed, anterior to the lower pole of the left kidney, and two right adrenal gland nodules measuring 2.4 cm and 1 cm were suspicious of pathological activity.

Following high suspicion of liposarcoma, considering the typical presentation of recurrent malignancies, and multiple resections, the patient was referred to our department for an excisional biopsy. Upon admission and review of her reports, it was decided to perform a laparotomy with retro-peritoneal mass excision and right adrenalectomy. She had no complaints at this point.

Upon examination, she had no palpable abdominal masses other than a small umbilical hernia. Preoperatively, she was prepared for surgery and had no abnormalities on the echocardiogram. She underwent resection of a right-sided retroperitoneal mass with a right nephrectomy. Intraoperatively, a large right-sided retroperitoneal mass, approximately 10×7 cm, was found invading the upper pole of the right kidney, which was completely resected with no immediate complications.

The resected mass was sent for histopathological examination. It consisted of kidney tissue and a hemorrhagic necrotic mass at the

upper pole measuring $7 \times 5 \times 5$ cm and was surrounded by a thin capsule. Upon opening, the kidney parenchyma was almost unremarkable, with mild chronic interstitial nephritis, and the vessel margins were negative. The viable areas of the mass showed a white and yellow cut surface. The histopathological examination of the mass showed a well-differentiated liposarcoma. Perinephric fat measuring 2 cm in thickness is identified. Unremarkable adrenal gland tissue was also present. An incidental adrenal mass measuring $2.5 \times 1.5 \times 1$ cm was also identified as an adrenocortical adenoma.

Following surgery, after recovery with stable vital signs, the patient was transferred to the ICU for 24 h for close observation. Postoperatively, renal ultrasound was performed and showed no abnormalities. However, the patient's creatinine was rising, and acute kidney injury was suspected. Thus, she was maintained on IV fluids and closely monitored by the nephrology team. They reported steady improvement and normalization over the next 3 days.

Prior to discharge, the patient was well and had her drain removed. She had no further complications. She was then referred to a specialist oncology center for further management, where she did not receive adjuvant chemotherapy. To date, the tumor has not recurred, despite high rates of recurrence concerning retroperitoneal liposarcomas.

2.3 Case 3

A 59-year-old male patient presented to our department complaining of a lump on the left side of his abdomen he had noticed a year and a half beforehand. The patient had a history of diabetes mellitus for 25 years, ischemic heart disease, and a COVID-19 infection a month and a half ago. He previously underwent 4 cardiac catheterizations with stenting, the last of which was a year ago. He also underwent an open appendectomy 25 years ago.

The patient had initially noticed the mass by accident but neglected it, as it had no associated symptoms. Since then, the lump has grown, causing the patient to develop constipation 6 months ago and preventing him from passing stool more than once every 4 days. The patient also mentioned that he had recently become anorexic and lost 3 kg in the past 3 months. The culmination of these symptoms prompted him to seek medical attention 20 days ago.

Thus, he underwent an abdominal ultrasound, which revealed a well-defined large heterogeneously enhanced soft tissue mass with few calcific foci in the left side of the abdomen, located antero-inferiorly to the left kidney measuring approximately $16 \times 14 \times 11$ cm.

The seemingly mesenteric mass was surrounded by mesenteric fat stranding, a mild amount of free fluids, and loculated fluid superior to the mass, which measured $8 \times 12.5 \times 9.5$ cm. Although there was no evidence of invasion of surrounding structures, it was visualized compressing the transverse and descending colon. Multiple mildly enlarged para-aortic lymph

nodes, the largest measuring 2.2×1.2 cm on the left side (Figure 3—CT Angio).

The right kidney showed mild hydronephrosis with perinephric free fluid and fat stranding. The liver and spleen were also enlarged. Furthermore, the urinary bladder wall was thickened with a visible urachus.

On examination, his abdomen was distended with full flanks and a palpable, irregular, slightly tender left-sided abdominal mass of approximately 10×15 cm extending from the left costal margin to the left iliac crest. He also had a visible appendectomy scar at the McBurney point. Thus, the patient was admitted to excise the mass.

A multidisciplinary team of pulmonologists, cardiologists, and urologists provided their recommendations following spirometry, abdominal CT angiography, and echocardiography.

Pulmonary function tests showed no abnormalities. CT findings suggest post-COVID changes, although PCR testing for COVID-19 was negative. Echocardiography findings were significant for mild diastolic dysfunction and pleural effusion. Thus, the patient was started on antiplatelet therapy and high doses of statins. Upon urologic recommendations, a double J stent was used, and the procedure was performed via a retroperitoneal approach.

The patient thus underwent midline laparotomy and layer dissection to afford access to the peritoneal cavity. We attempted to bypass the peritoneum from the left side, however we were unable to. Subsequently, we dissected the peritoneum. A huge mass was apparent in the retroperitoneum attached to the spleen, distal pancreas, splenic flexure, and engulfing the left kidney and ureter. The mass was severely adherent to surrounding structures. There was also an enlarged para-aortic and mesenteric lymph node.

We began to carefully dissect the peritoneal covering of the mass starting from the inferolateral border. We attempted medial dissection to separate the mass from the splenic flexure, however we were unsuccessful.



FIGURE 3
Ct angio, CT findings for case 2.

We were able to afford access to the inferior border of the mass and continued dissection from there. We resected the splenophrenic ligament and managed to free the spleen laterally. Since the distal pancreas was adherent to the mass, we had to maneuver with careful dissection and suction, to identify the splenic vein and artery. We ligated the splenic artery and dissected the distal pancreas and splenic vein. We then resected the descending colon and splenic flexure.

We identified, ligated, and cut the renal artery, vein, and ureter, and then proceeded to do *en bloc* nephrectomy. Despite being adherent to the iliopsoas muscle, the mass was separated from it with fine dissection. We performed para-aortic lymphadenectomy extending to lymph nodes surrounding the left common iliac artery. The sigmoid mesentery and enlarged mesenteric lymph node were hard, and so were included in the resection under high suspicion of involvement. We concluded with colo-colic anastomosis and securing hemostasis.

The patient then received 2 units of packed red blood cells. He also had drains, a nasogastric tube, and a Foley catheter.

On histopathological examination, the specimen consisted of a large mass measuring $25 \times 20 \times 18$ cm attached to multiple viscera. Sectioning of the mass showed a mucoid and gray cut surface attached to the mass, and the left kidney measured $9 \times 4 \times 2$ cm. The colon part measured 12×5 cm, the splenic part measured $12 \times 6 \times 3$ cm, and the pancreatic tail measured $7 \times 7 \times 3$ cm. The neoplastic margin was circumferentially 2 mm away from the margins, including the mesentery. The extent of necrosis extended to up to 20%.

The mass was determined to be a dedifferentiated liposarcoma, with a high mitotic rate and necrotic tissue. The mass was invading adjacent structures, including the colon, kidney, pancreas, and hilum of the spleen, along with three reactive lymph nodes. The tumor cells showed focal positivity for S100 and MDM2 markers on immunohistochemistry.

Postoperatively, he was transferred to the ICU for close observation. His Foley catheter was changed as he was anuric, and he was administered furosemide, after which his urine output improved. He was also started on antibiotic therapy. He also developed sudden onset dysarthria, difficulty speaking, and transient left upper and lower limb weakness for 1 min. There were, however, no abnormalities on brain CT.

During his second postoperative day, he developed acute kidney injury and was oliguric but was successfully managed with furosemide. All catheter lines and the NGT tube were removed upon leaving the ICU. His Foley catheter was removed 1 day later. The patient then developed hypertension, which was started on aminocaproic acid and kept on carvedilol. However, his hypertension persisted. Thus, he was successfully managed with nifedipine, and previous medications were stopped.

The patient complained of dyspnea on mild exertion but showed no new abnormalities on echocardiography. Electrocardiography showed no acute changes. Chest CT revealed moderate right-sided pleural effusion. By the evening, the patient's symptoms had resolved, and his left drain was removed. His right drain was removed 1 day later, and the patient was discharged in good condition.

3 Discussion

Among retroperitoneal sarcomas, well-differentiated liposarcomas are the most commonly presented, followed by dedifferentiated liposarcomas and leiomyosarcomas (1, 2, 5, 6). Both types of liposarcomas show amplification of MDM2, while leiomyosarcomas are negative for S100 and express desmin (5). Retroperitoneal sarcomas and liposarcomas, in particular, do not show symptoms until they grow to massive sizes, through which they compress surrounding structures that generate a variety of vague neurological, musculoskeletal, gastrointestinal, and urinary symptoms. In most cases, they remain asymptomatic. These symptoms are commonly thought to be the result of other less serious pathologies, which further delay proper management (6, 7).

In retroperitoneal sarcoma cases, diagnosis and treatment are of utmost importance and intricacy. Due to their rarity and the vagueness of their presentation, in concomitance with their poor prognosis, it is crucial to identify leading trends concerning their diagnosis and appearance on imaging modalities. Especially in the case of retroperitoneal liposarcoma, delayed imaging may lead to a large unresectable tumor, inevitably worsening outcomes (1, 3, 7, 9). Other neoplasms may mimic the presentation of retroperitoneal sarcomas, thus demanding definitive differentiation, especially in the face of different treatment protocols (7, 9).

Despite the efficacy of percutaneous biopsy, it is not always possible due to difficulty in attaining the specimen. Thus, CT offers an excellent solution for first-line imaging. A mixture of MRI and CT is beneficial in a mutually compensatory manner, especially when CT is not entirely conclusive (1, 5, 6, 7, 9). PET scans, although not routinely used, play a pivotal role in problem-solving or incidental findings, as in our second case (1). Although biopsy offers a definitive diagnosis, it is still important to act promptly under high suspicion of retroperitoneal sarcomas, as in 2 of our cases. Furthermore, liposarcomas predominate the fat tissue masses in the retroperitoneum, which guides management upon detection (6, 9).

It is also essential to consider the implications of undetermined extensions of masses obscured by viscera, especially in liposarcomas. This plays a significant role in determining the surgical approach and decreasing complications (1, 5).

The mainstay of treatment is surgical resection. Previous studies have shown that R0 resection reduces abdominal recurrence to approximately 10% in contrast to 50% in R1, which is the main predictor of mortality in retroperitoneal sarcoma. Multidisciplinary involvement is also a vital determinant of outcomes (1, 2, 5, 8, 9).

Extra care must be placed into the tumor's extension into multiple organ systems. Multiple disciplines inevitably involve renal involvement, alimentary invasion, or encirclement of the vasculature. In the case of resected organs, which account for 75% of cases, the importance of this multidisciplinary approach reaches its peak (1, 5, 8, 9).

Possible paths to resection include wide local excision, compartmental, and complete multiorgan evisceration, with emphasis on removal from the first try, to prevent further seeding

and recurrence. Compartmental resection, which involves the removal of unaffected soft tissue within the vicinity of the tumor, was shown to be marginally more effective at reducing recurrence, while acceptably compromising morbidity. This plays into the risk of non-apparent infiltration, especially in cases where invasion is likely, including vascular supply, or organ encasement, adjacency, or adherence to the tumor. It is important to acknowledge the removal of major vessels or nerves only if the tumor involves them as well. Palliative and distant metastasis options are available though somewhat controversial (10).

Despite trends in R0 resection, recurrence is still a problem. According to some accounts, it may even approach 85%, involving both local and distant recurrence. Certain low-risk recurrences may be followed up, or alternatively undergo salvage surgery, though it is also debatable due to the risk of a scarred abdomen. The latency in deciding to operate is also controversial as the risk of recurrence grows beyond 3 times, but also enables the finding of distant or alternative foci of recurrence (10).

It is especially important to take into account leiomyosarcomas involving or arising from major vessels, the chief of which is IVC (9). Not only does it account for 0.5% of retroperitoneal sarcomas, but the involvement of the vessel may be complicated with further extension of the tumor or compression, influencing morbidity and presentation (9, 10). Under the decision of vascular resection is a background of risk vs. reward. Despite limited studies concerning Dacron grafting and venous reconstruction in retroperitoneal sarcomas, the outlook is promising as a readily available method of IVC reconstruction, especially in low-resource settings, considering the difficulty of procuring donor parts (11). Though vascular resection plays an important role in R0 resection, it carries significant risk and high morbidity rates, irrespective of reconstruction modality. Despite this, most complications can be dealt with, with relatively low risk. This makes them effective and relatively safe options to achieve R0 resection (11).

Several points contribute to the ultimate surgical plan. How much of the vessel should be removed, is it an artery or a vein, and what should it be replaced with? In the case of the aorta, the sheer amount of tissue that needs to be resected in such a vital place rules out the procedure. Usually, prostheses are reserved for arterial grafts. In the case of superior mesenteric involvement, the tumor is likely unresectable, though there are reports of select cases in which segmental resection and prosthesis placement are a viable option (11, 12).

In the case of IVC involvement, tumor site, size, adequate collaterals, and lumen patency are the most important deciding factors. Several options are available. Primary repair is useful in cases of partial resection where lumen patency may be compromised to less than 50%. In greater resections, or when ligation is not an option, grafts are more useful, though also come at the cost of lifelong anticoagulation and greater post-operative complications. One problem with biological grafts such as aortic grafts is that they are in short supply in low income areas, such as our case. Should the lumen be obliterated, IVC

ligation is viable if sufficient collaterals are available. In all cases of IVC involvement, renal vascular intricacy is advised, especially when preserving the right kidney, as it lacks sufficient collaterals and must therefore be re-implanted (11, 12).

Although evidence shows that renal artery embolization before radical nephrectomy for renal masses seems to be a valuable tool in the surgical management of a large mass and advanced disease, as it induces preoperative infarction and facilitates surgical intervention (13), this was not possible in our first case, as radiological evaluation did not confirm the renal vs. hepatic origin of the tumor. There was no single specific feeding vessel.

4 Conclusion

Invasive retroperitoneal sarcomas of different histological types and clinical stages represent a technical challenge. Careful preoperative investigation and an experienced, dedicated multidisciplinary team of surgeons from related fields, including vascular, urologic, and hepatobiliary surgeons, are usually needed for a safe and successful R0 resection despite extensive tumor involvement.

Data availability statement

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

Ethics statement

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

PB: Conceptualization, Validation, Visualization, Writing – original draft, Writing – review & editing. BA: Conceptualization, Validation, Visualization, Writing – original draft, Writing – review & editing. KA: Conceptualization, Data curation, Project administration, Resources, Supervision, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

We acknowledge the support of the Medical Research Club at Al-Quds University.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial

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OPEN ACCESS

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RECEIVED 30 November 2023

ACCEPTED 19 February 2024

PUBLISHED 05 March 2024

CITATION

Wang J, Chen J, Liu K, Zhang H, Wei Y,
Suo L, Lan S, Wang Y, Luo C and Yao L (2024)
Anesthetic managements, morbidities and
mortalities in retroperitoneal sarcoma
patients experiencing perioperative
massive blood transfusion.
Front. Oncol. 14:1347248.
doi: 10.3389/fonc.2024.1347248

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Anesthetic managements, morbidities and mortalities in retroperitoneal sarcoma patients experiencing perioperative massive blood transfusion

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Objective: Given high risks of major bleeding during retroperitoneal sarcoma (RPS) surgeries, severe complications and deaths are common to see perioperatively. Thus, effective anesthetic management is the key point to ensuring the safety of patients. This study aimed to introduce anesthesia management and mortalities in RPS patients receiving massive blood transfusions during surgeries.

Methods: Records of RPS surgeries under general anesthesia from January 2016 through December 2021 were retrospectively retrieved from our database. Patients who received massive blood transfusions (MBT) exceeding 20 units in 24h duration of operations were finally included in this study. Demographics, modalities of anesthesia management, blood loss, transfusion, peri-anesthesia biochemical tests as well as morbidities and mortalities were collected. Risk factors of postoperative 60d mortality were determined through logistic regression in uni- and multi-variety analysis using the statistics software STATA 17.0.

Results: A total of 70 patients (male 31) were included. The mean age was 50.1 ± 15.8 years. All patients received combined resections of sarcoma with involved organs under general anesthesia. Mean operation time and anesthesia time were 491.7 ± 131.1 mins and 553.9 ± 132.6 mins, respectively. The median intraoperative blood loss was 7000ml (IQR 5500,10000ml). Median red blood cells (RBC) and fresh frozen plasma (FFP) transfusion were 25.3u (IQR 20,28u), and 2400ml (IQR 2000,3000ml), respectively. Other blood products infusions included prothrombin complex concentrate (PCCs), fibrinogen concentrate (FC), platelet(plt) and albumin(alb) in 82.9% (58/70), 88.6% (62/70), 81.4% (57/70) and 12.9% (9/70) of patients. The postoperative severe complication rate(Clavien-Dindo grade $\geq$ 3a) was 35.7%(25/70). A total of 7 patients (10%) died during the postoperative 60-day period. BMI, volumes of crystalloid infusion in anesthesia, and hemoglobin and lactate levels at the termination of operation were found

significantly associated with postoperative occurrence of death in univariate analysis. In logistic multivariate analysis, extended anesthesia duration was found associated with postoperative venous thrombosis embolism (VTE) and severe complication. The lactate level at the immediate termination of the operation was the only risk factor related to perioperative death ($p < 0.05$).

Conclusion: RPS patients who endure MBT in surgeries face higher risks of death postoperatively, which needs precise and effective anesthesia management in high-volume RPS centers. Increased blood lactate levels might be predictors of postoperative deaths which should be noted.

KEYWORDS

retroperitoneal sarcoma, massive blood transfusion, anesthesia management, morbidity, mortality

Introduction

Retroperitoneal sarcoma (RPS) represents a heterogeneous group of malignant mesenchymal neoplasms with an annual incidence of less than 0.5 per 100,000 population (1, 2). RPS often presents as an enlarged mass involving multiple organs or major vessels. Surgery remains the mainstay treatment for localized RPS (3, 4). An extended resection of the sarcoma with adherent structures and organs has been introduced and advocated for achieving better local control and longer overall survival (5, 6). However, this approach poses significant challenges for surgeons and anesthesiologists due to the deep anatomical sites, wide excisions, and intraoperative hemodynamic instabilities (7, 8). Perioperative major bleeding in RPS surgery has been reported as the leading cause and independent factor associated with surgical mortality (9, 10). Meanwhile, major bleeding that occurs intraoperatively remains a significant challenge to handle, not only for surgeons but also for anesthesiologists. Intraoperative blood loss (IBL) exceeding 2000ml, followed by massive blood transfusion (MBT), can result in a significant increase in severe complications such as coagulation disorders, secondary hemorrhages, renal dysfunctions, thrombosis, cardiovascular events, and more (11). Nevertheless, blood transfusion was also reported as an independent risk factor associated with severe complications either in primary or recurrent RPS surgeries, according to the largest case series of 1007 cases from Transatlantic Australasian RPS Working Group (TARPSWG) (10, 12). To ensure the safety of RPS surgeries, hybrid surgical techniques are key. Nevertheless, proactive and effective anesthetic managements, applied with a damage-control principle also plays an utmost important role. Immediate hemorrhage control, limited intravenous crystalloid, early administration of warmed blood products, balanced massive transfusion, and permissive hypotension are the mainstay approaches for

managing hemorrhage in surgical patients. Appropriate components and ratios of blood products have been reported to be associated with lower 24-hour mortality in massively transfused patients (13–15). However, to date, no data have been reported on the anesthetic strategies and related outcomes in the RPS area. This study was conducted at a high-volume RPS referral center in China, which performs over 400 surgeries annually for retroperitoneal tumors. The study aims to introduce the anesthetic management and experiences, and analyze the risk factors associated with postoperative morbidity and mortality.

Patients and methods

Study design and patients

It was a retrospective study, conducted in accordance with the Declaration of Helsinki (as revised in 2013), following the STROBE retrospective cohort guideline. It was approved by the institutional review board of Peking University International Hospital (PKUIH-NO.2022-KY-0032-01) and individual consent for this retrospective analysis was waived. Medical records of consecutive patients undergoing resection surgeries under general anesthesia for RPS at PKUIH from January 2016 through December 2021 were retrieved from our prospectively collected database. Patients who received transfusion ≥ 20 units of packed red blood cells (RBCs) in perioperative 24 hours were defined as MBT and included in this study. Patients with histological subtypes of retroperitoneal tumors other than RPS were excluded from this study. Patients who underwent tumor biopsy through laparotomy only instead of radical resections were also excluded. Data collection included demographics, perioperative variables, detailed anesthesia managements with intraoperative dynamic blood cell and biochemical tests, operative outcomes as well as postoperative 60-d survivals.

Surgical and anesthesia protocols

All surgeries were performed by the same surgical team after careful MDT discussion. The extended resection policy was applied in most patients with localized or uni-focal tumors. Major vessels involved by tumors were often isolated, repaired, or transected/ligated with or without reconstruction. Decisions were made according to the surgeons' discretion. Patients with metastasis, multifocal tumors or obstructive symptoms in the digestive tract or urinal tract were also operated under the palliative surgical policy. A novelty ipsilateral lipectomy was performed in patients with primary retroperitoneal liposarcoma in order to decrease the localized recurrence rate.

All patients were treated with general anesthesia through endotracheal intubation. Central and peripheral venous accesses were built for infusions. Continuous infusion of Remifentanyl, Propofol and Dexmedetomidine with occasional inhalation of Sevoflurane or Desflurane were normally used for maintaining anesthesia effects. Speeding bolus or transfusion of blood products, crystalloids with vasoactive agents such as norepinephrine were administered when dealing with intraoperative major bleeding. Recording the amounts of IBL, blood components and crystalloid infusions as well as values of blood glucose, creatinine, and blood gas analysis at the entry and exit of the operating room (OR) was also the routine process of anesthesia management.

Statistics

Categorical variables were reported as frequency (%) and continuous variables were reported as mean with standard deviation (SD) or median with interquartile range (IQR). Morbidities were evaluated by Clavien-Dindo grading system. Logistic regression was used to determine risk factors of postoperative VTE and deaths in univariate and multivariate analysis. Variables acquired P value less than 0.1 in univariate analysis were included and calculated in the multivariate analytic equation. A P value of less than 0.05 was considered statistically significant. The software of STATA Version 17.0 was used for statistics.

Results

Patient characteristics

There were 70 RPS patients (male 39) experiencing MBT over 20u in peri-operative 24 hours finally included in this study. The flow chart was introduced in Figure 1. The mean age was 50.1 ± 15.8 years old. Seventeen out of 70 (24.3%) patients were primary RPS cases, while other 53 patients were recurrent RPS, including 33 (47.1%) patients who had over 3 times of histories of surgeries. Preoperatively, 37.1% (26/70) of patients had miscellaneous comorbidities, consisting 8 diabetes, 7 hypertension and 7

cardiovascular diseases. Patients' characteristics were described in Table 1.

Anesthesia and operative outcomes

Preoperatively, the general health status of all patients was assessed using the ASA classification system, resulting in the following distribution: 4 patients were classified as ASA I, 30 as ASA II, and 36 as ASA III. No patients were classified as ASA IV. All patients received combined resections of sarcoma with involved organs under general anesthesia. A total of 99 organs or major vessels were resected in 70 surgeries, with 12 surgeries combining resection of three or more organs and five surgeries with major vessel resections, either with or without reconstructions. The average operation and anesthesia durations were 491.7 ± 131.1 mins and 553.9 ± 132.6 mins, respectively. The median intraoperative blood loss was 7000ml (interquartile range [IQR] 5500,10000), with 19 cases (27.1%) exceeding 10000ml. Table 2 showed the details of anesthesia and operative outcomes.

Infusions in anesthesia

All patients received transfusions of blood products and fluids, as well as vasoactive medications such as norepinephrine, dopamine, or epinephrine, to maintain stable circulation during anesthesia (Table 3). The median red blood cell (RBC) transfusion volume was 25.3 units (IQR 20, 28), and fresh frozen plasma (FFP) transfusion volume was 2400 ml (IQR 2000, 3000). Prothrombin complex concentrate (PCCs), fibrinogen concentrate (FC), platelets, and albumin were administered to 82.9% (58/70), 88.6% (62/70), 81.4% (57/70), and 12.9% (9/70) of patients, respectively. Additionally, crystalloid and artificial colloid fluids were transfused with a median volume of 6200 ml (IQR 4000, 7450) and 2250 ml (IQR 1500, 3000), respectively. In the postoperative

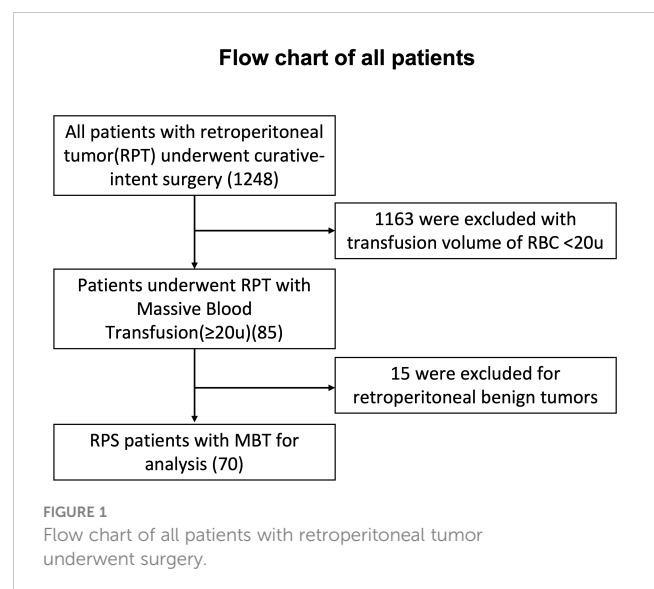


TABLE 1 Characteristics of all patients experiencing MBT≥20u in peri-operative 24 hours.

Variables	N	%
Total	70	100
Age(mean±SD)	50.1 ± 15.8	–
Male gender	39	55.7
BMI (mean±SD)	22.2±3.2	–
RPS		
Primary	17	24.3
Recurrent	53	45.7
2 nd recurrence	20	28.6
≥3 rd recurrence	33	47.1
Comorbidities		
Diabetes	8	11.4
Hypertension	6	8.6
Cardiovascular disease	6	8.6
Anemia	6	8.6
Renal Dysfunction	3	4.3
Venous Thrombosis	3	4.3
RPS subtypes		
Liposarcoma	42	60
Leiomyosarcoma	4	5.7
Solitary fibrous tumor	11	15.7
Other	13	18.6

24-hour period, 39 patients received additional RBC transfusions, and 47 patients received additional plasma infusions.

Blood tests in anesthesia

During the entire anesthesia procedure, comprehensive assessments such as complete blood count, blood chemistry analysis, coagulation profiling, and arterial blood gas analysis were conducted for all patients. These tests encompass the preoperative, intraoperative, and postoperative phases, spanning a duration of 24 hours. Details were listed in [Table 4](#).

Morbidities and mortalities

Postoperatively, a total of 52 patients (74.3%) were admitted to the Intensive Care Unit (ICU), and they required a median duration of mechanical ventilation of 3.9 days. The overall postoperative complication rate was 65.7% (46/70) with 35.7%(25/70) of patients experiencing severe morbidities(Clavien-Dindo grade≥3a). Anesthesia duration was the only risk factors associated to

TABLE 2 Anesthesia and operative outcomes of all subjects.

Variables	N	%
Total	70	100
ASA Score		
1	4	5.7
2	30	42.9
3	36	51.4
Operation time(mean ± SD, min)	491.7 ± 131.1	–
Anesthesia time(mean ± SD, min)	553.9 ± 132.6	–
Blood loss (median, IQR)(ml)	7000 (5500,10000)	–
Patients No underwent organs resection	46	65.7
1	14	20.0
2	20	28.6
≥3	12	17.1
Organs resected in all patients		
Stomach & Duodenum	6	8.6
Intestine	12	17.1
Colon & Rectum	26	37.1
Kidney	15	21.4
Ureter	6	8.6
Spleen & Pancreas	9	12.9
Liver	3	4.3
Major Vessels resected in all patients		
Inferior Vena Cava	3	4.3
External Iliac Vein	1	1.4
External Iliac Artery	2	2.8
Morbidities	46	65.7
Venous thrombosis	16	22.9
Acute renal dysfunction	13	18.6
Infectious	9	12.9
Acute lung Injury	7	10.0
ARDS	6	8.6
Miscellaneous fistular (intestine, urinary, gastric)	12	17.1
Cardiac events	4	5.7
Complication Classification		
I-II	21	30.0
III-IV	18	25.7
V(Death)	7	10.0
Postoperative Day in hospital (median, IQR)	29.5(20,44)	–

TABLE 3 Details of infusions during anesthesia in all MBT patients.

Infusions	N (%)	Median	InterQual Range
RBC(unit)	70(100)	22	22,28
FFP(ml)	70(100)	2400	2000,3000
PCCs(ml)	58(82.9)	600	400,1200
FC(unit)	62(88.6)	1.5	1,2
Platelet	9(12.9)	0	0,0
Albumin(g)	57(81.4)	400	150,500
Crystalloid(ml)	70(100)	6200	4000,7450
Artificial colloid fluids(ml)	70(100)	2250	1500,3000

postoperative severe morbidity in logistic multivariate analysis, though there were lots of anesthesia related factors associated with severe morbidity in univariate analysis, like infusion volume of RBC and FFP, intraoperative blood loss, hemoglobin and lactate level at the termination of operation, etc. (Table 5). The most common complications observed were venous thrombosis (16 cases) and acute renal dysfunction (13 cases). Three patients underwent salvage reoperations due to hemostasis (2 cases) and intestinal fistula (1 case). During the postoperative 60-day period, there were 7(10%) patients deceased. The main causes of death included 1 immediate intraoperative bleeding, 4 delayed bleeding, and 2 septic shocks with severe abdominal infections. In univariate analysis, durations of operation and anesthesia, and repairing/ resection of major vessels were significant related to postoperative onset of VTE (Table 6). Factors such as body mass index (BMI), volumes of crystalloid infusion during anesthesia, and hemoglobin and lactate levels at the termination of operation were significantly associated with postoperative mortality. However, in logistic multivariate analysis, lactate level at the termination the operation was identified as the only risk factor related to perioperative mortality. The anesthesia time and was found significant associated to postoperative VTE (p<0.05) (Table 6).

Discussion

Patients with retroperitoneal tumors often present with large tumor sizes and involvement of surrounding blood vessels and organs, which increases the difficulty of surgical treatment. Prolonged compression of the retroperitoneal space by the tumor can lead to adhesion formation between the tumor and vascular walls, resulting in vascular occlusion and compensatory formation of extensive collateral circulation vessels supplying the tumor (16, 17). Besides, extended surgical resection with adjacent/infiltrated major vessels and organs in order to achieve better local controls also poses challenges for intraoperative bleeding control, and significant intraoperative bleeding frequently occurs (7, 18). In this study, an average of 1.5 organs were resected in whole patients, including 12 patients with 3 or more organs resected and 5 patients with major vessel resections. The intraoperative

TABLE 4 Blood tests in different time phases of anesthesia.

Tests	Values		P Value
	Median/Mean	IQR/ $\pm$ SD	
Pre-anesthesia term			
Hemoglobin(g/dl)	110.0	17.2	
Lactate(mmol/l)	0.8	0.6, 0.9	
Platelet(10^9 /L)	260.5	200, 368	
Albumin(g)	34.6	5.0	
Fibrinogen(mg/dl)	399	325,459	
PT(s)	11.7	11.2, 12.9	
APTT(s)	30.73	3.35	
INR	1.1	1,1.2	
FDP	4.4	2.7, 8.4	
D-Dimer	429	238, 776	
Creatine	61	51, 89	
Terminal time of anesthesia*			
Hemoglobin(g/dl)	88	20.8	0.000
Lactate(mmol/l)	2	1.1, 3.9	0.000
24-hours post anesthesia*			
Hemoglobin(g/dl)	93.8	26.9	0.000
Platelet(10^9 /L)	66	46, 110	0.000
Albumin(g)	29.4	7.0	0.210
Fibrinogen(mg/dl)	217.5	192,279.5	0.000
PT(s)	12.95	12.1, 14.2	0.004
APTT(s)	31.4	28.8, 36.6	0.015
INR	1.2	1.1, 1.3	0.002
FDP	7.3	3.92, 14	0.15
D-Dimer	734	392, 1545	0.185
Creatine	80	57, 102	0.991

*Compared with correspondent variables in pre-anesthesia term.

blood loss ranged from 3000ml to a devastated volume of 25800 ml. Therefore, sufficient blood supply, precise and efficient anesthesia managements should be administered perioperatively, especially for those elderly, multiple comorbidities or recurrent cases with multiple surgical histories (19). Throughout the entire anesthesia process, goal-directed fluid treatment has been strongly recommended and implemented using various hemodynamic monitoring methods, including arterial pressure or central venous pressure monitoring, pulse contour analysis, and transesophageal echocardiography (20, 21). Instead of crystalloid resuscitation, damage control resuscitation with balanced components in a 1:1:1 fashion or whole blood (WB) has been advocated as a crucial component in the resuscitation of major bleeding (22–24). Transfusion of FFP, platelets, and RBC at a higher

TABLE 5 Univariate and multivariate analysis of postoperative severe morbidities in all patients.

Variables	N	Severe Morbidities		Uni-variate	Multivariate		
		Yes	No	P	OR	95% CI	P
Total	70	25	45				
Age(mean±SD)	50.1 ± 15.8			0.618			
Male gender	31	12	19	0.641			
BMI(mean±SD)	22.2±3.2			0.704			
ASA Score							
1	4	1	3	0.569			
2	30	10	20				
3	36	14	22				
Comorbidities							
Diabetes	8	3	5	0.911			
Hypertension	6	1	5	0.329			
Cardiovascular disease	6	4	2	0.120			
Preoperative blood tests							
Hb (mean ± SD, g/l)	110.0 ± 11.2			0.652			
Alb(median, g/l)	34.1			0.673			
Plt(median, 10^9/l)	260.5			0.797			
Fg(median, mg/dl)	399			0.529			
PT(median, s)	11.7			0.464			
APTT(mean ± SD, s)	30.73±3.35			0.064	1.193	0.980-1.453	0.079
INR(median)	1.1			0.844			
FDP(median, mg/l)	4.4			0.222			
D-dimer(median, mg/l)	429			0.293			
Anesthesia time(mean ± SD, min)	553.9 ± 132.6			0.034	1.007	1.000-1.012	0.025
Repairing/Resection of major vessels during surgeries	12	6	6	0.637			
Organ resections							
No	24	7	17	0.410			
Yes	46	18	28				
Blood tests at the end of operation							
Hb (mean ± SD, g/l)	88.0 ± 20.8			0.004	0.973	0.935-1.013	0.181
Lactate(median, mmol/l)	2.0			0.033	1.060	0.785-1.431	0.703
IBL(median, ml)	7000			0.015	1.000	1.000-1.000	0.903
Blood products infusions during operation							
RBC(median, U)	22			0.012	1.053	0.888-1.250	0.551
FFP(median, ml)	2400			0.049	1.000	0.999-1.000	0.605
PCC(median, u)	600			0.124			
FC(median, mg/dl)	1.5			0.103			
PLT(median, range, u)	0(1-10)			0.063	4.101	0.605-27.80	0.148

(Continued)

TABLE 5 Continued

Variables	N	Severe Morbidities		Uni-variate	Multivariate		
		Yes	No	P	OR	95% CI	P
Blood products infusions during operation							
Crystalloid infusion during anesthesia(mean ± SD, ml)	6254.8 ± 1923.5			0.054	1.000	1.000-1.000	0.971
Colloid infusion during anesthesia(median, ml)	2250			0.072	1.000	1.000-1.000	0.465

TABLE 6 Univariate and multivariate analysis of postoperative VTE in all patients.

Variables	N	VTE		Uni-variate	Multivariate		
		+	-	P	OR	95% CI	P
Total	70	16	54				
Age(mean±SD)	50.1 ± 15.8			0.193			
Male gender	31	2	29	0.409			
BMI(mean±SD)	22.2±3.2			0.489			
ASA Score							
1	4	1	3	0.903			
2	30	8	22				
3	36	8	28				
Comorbidities							
Diabetes	8	2	6	0.960			
Hypertension	6	2	4	0.589			
Cardiovascular disease	6	2	4	0.589			
Preoperative blood tests							
Hb (mean ± SD, g/l)	110.0 ± 11.2			0.704			
Alb(median, g/l)	34.1			0.365			
Plt(median, 10^9/l)	260.5			0.726			
Fg(median, mg/dl)	399			0.946			
PT(median, s)	11.7			0.214			
APTT(mean ± SD, s)	30.73±3.35			0.476			
INR(median)	1.1			0.127			
FDP(median, mg/l)	4.4			0.568			
D-dimer(median, mg/l)	429			0.414			
Operative time(mean ± SD, min)	491.7 ± 131.1			0.004	0.978	0.956,1.000	0.060
Anesthesia time(mean ± SD, min)	553.9 ± 132.6			0.001	1.031	1.007,1.058	0.013
Repairing/Resection of major vessels during surgeries	12	6	6	0.022	5.053	1.066,23.964	0.041
Use of Tranexamic acid during anesthesia	40	10	30	0.872			
Blood tests at the end of operation							
Hb (mean ± SD, g/l)	88.0 ± 20.8			0.430			
Lactate(median, mmol/l)	2.0			0.691			

(Continued)

TABLE 6 Continued

Variables	N	VTE		Uni-variate	Multivariate		
		+	-	P	OR	95% CI	P
Blood tests at the end of operation							
IBL(median, ml)	7000			0.543			
Blood products infusions during operation							
RBC(median. U)	22			0.222			
FFP(median, ml)	2400			0.436			
PCC(median, u)	600			0.778			
FC(median, mg/dl)	1.5			0.831			
PLT(median, range, u)	0(1-10)			0.578			
Crystalloid infusion during anesthesia(mean ± SD, ml)	6254.8 ± 1923.5			0.248			
Colloid infusion during anesthesia(median, ml)	2250			0.191			
Total RBC infusion within 24h	24			0.224			
Total plasma infusion within 24h	2800			0.295			

1:1:1 ratio, compared to the conventional 1:1:2 ratio, is associated with a lower incidence of complications and mortality in patients with severe trauma (15, 25, 26). In this particular study, the median transfusion volume of FFP and RBC was 2573ml and 25.2 units, resulting in a ratio of 1:1. Based on this fluid treatment approach, the case series observed a severe morbidity rate of 35.7% and a 30-day mortality rate of 7%, which is notably lower than the reported ranges of 20% to 60% in patients with acute trauma (22, 27). In addition, whole blood (WB) has been considered as an ideal and beneficial option for patients undergoing massive blood transfusion (MBT). However, one of the challenges associated with WB transfusion is the time required to conduct safety tests on the blood, which can lead to significant depletion of coagulation factors. Otherwise, WB transfusion was also associated with higher platelet-to-red blood cell (PLT : RBC) and plasma-to-red blood cell (plasma: RBC) ratios, which warrants further discussion and investigation (28).

In situations of significant blood loss, the depletion of blood components is not uniform. The concentrations of coagulation factors are insufficient to adequately increase or maintain the already low plasma concentrations in bleeding patients. The median fibrinogen level was dropped with PT and APTT extended significantly from preoperative to postoperative term ($p < 0.05$). Studies on surgical patients receiving massive blood transfusions have also shown that higher fibrinogen levels at the end of surgery are associated with increased patient survival rates. However, administration of PCC or FC was reported associated with an increased risk of thrombotic events in trauma patients according to several earlier studies (29, 30). On the opposite, Florian et al. discovered that 68% out of 1630 patients experiencing severe hemorrhage at 6h and 72% at 24h co-administration of FFP and FC in that complied with recommendations, mortality was systematically lower than expected in contrast to non-compliant

without FFP and FC using subgroups (31). In this study, 82.9% and 88.6% out of 70 patients underwent PCC and FC transfusions respectively. Instead of the PCC and FC using, the anesthesia duration was the only risk factors found significantly associated to VTE and severe morbidity ($P < 0.05$) (Table 6, 7). Thus, whether PCC/FC administration in patients with MBT remains further exploration through high-quality data. Point of Care Testing (POCT), Rotational thromboelastometry (ROTEM), thrombelastography (TEG), might be useful tools recommended in monitoring the real-time deficiencies of concentrates of blood cells and coagulation factors, decreasing transfusion related complications and mortalities (32–34). Therefore, individual use of laboratory test-based approach with coagulation factor concentrates is essential for fast and goal-directed therapy to address bleeding-induced coagulation factor deficiency (35).

RPS surgeries pose persistent challenges for surgeons and anesthesiologists, carrying elevated risks of severe postoperative complications and mortalities, despite the implementation of comprehensive management strategies. The need for transfusion of blood products during RPS surgeries has been a significant predictor of severe postoperative adverse events in previous reports from TARPSWG (10, 12). However, in our study, statistical significance was not achieved. Notably, only anesthesia durations were found to be associated with postoperative severe complications. This finding may be attributed to the case selection in our study, which focused on patients in extremely emergent situations requiring major transfusions, excluding those who did not require blood product transfusions. Owing to the extensive volume of retroperitoneal sarcoma (RPS) surgical experiences, coupled with the meticulous application of surgical and anesthesiologic interventions, as well as sustained postoperative blood transfusions, postoperative bleeding did not emerge as a primary complication, contrary to previous cases reported by

TABLE 7 Univariate and multivariate analysis of postoperative deaths in all patients.

Variables	N	Death		Uni-variate	Multivariate		
		+	-	P	OR	95% CI	P
Total	70	7	63				
Age(mean±SD)	50.1 ± 15.8			0.263			
Male gender	31	2	29	0.452			
BMI(mean±SD)	22.2±3.2			0.032	0.830	0.464,1.488	0.533
ASA Score							
1	4	1	3	0.404			
2	30	2	28				
3	36	4	32				
Preoperative blood tests							
Hb (mean ± SD, g/l)	110.0 ± 11.2			0.883			
Alb(median, g/l)	34.1			0.857			
Plt(median, 10^9/l)	260.5			0.252			
FC(median, mg/dl)	399			0.368			
PT(median, s)	11.7			0.213			
APTT(mean ± SD, s)	30.73±3.35			0.074	1.852	0.981,3.495	0.057
INR(median)	1.1			0.216			
FDP(median, mg/l)	4.4			0.941			
D-dimer(median, mg/l)	429			0.583			
Lactate(median, mmol/l)	0.8			0.085	1.491	0.588,3.776	0.400
Glucose(median,mmol/l)	5.2			0.229			
Operative time(mean ± SD, min)	491.7 ± 131.1			0.857			
Anesthesia time(mean ± SD, min)	553.9 ± 132.6			0.724			
Organ resections during surgeries							
0	24	1	23	0.399			
1	14	1	13				
≥2	32	5	27				
Repairing/Resection of major vessels during surgeries	12	2	10	0.595			
Blood tests at the end of operation							
Hb (mean ± SD, g/l)	88.0 ± 20.8			0.010	0.988	0.891-1.096	0.823
Lactate(median, mmol/l)	2.0			0.002	2.401	1.021-5.651	0.045
Glucose(median,mmol/l)	10.2			0.558			
IBL(median, ml)	7000			0.095	1.000	1.000-1.000	0.775
Blood products infusions during operation							
RBC(median. U)	22			0.138			
Plasma(median, ml)	2400			0.499			
PCC(median, u)	600			0.085	1.001	0.998-1.005	0.475
FC(median, mg/dl)	1.5			0.065	0.544	0.078-3.793	0.539

(Continued)

TABLE 7 Continued

Variables	N	Death		Uni-variate	Multivariate		
		+	-	P	OR	95% CI	P
Blood products infusions during operation							
Alb(median, g)	300			0.109			
Plt(median, range, u)	0(1-10)			0.252			
Crystalloid infusion during anesthesia(mean ± SD, ml)	6254.8 ± 1923.5			0.031	1.000	0.999-1.000	0.896
Colloid infusion during anesthesia(median, ml)	2250			0.926			
Total RBC infusion within 24h	24			0.063	0.979	0.824-1.163	0.807
Total plasma infusion within 24h	2800			0.380			

ASA, American Society of Anesthesia; RBC, Red blood cell; Hb, Hemoglobin; Alb, Albumin; Plt, Platelet; PCC, Prothrombin complex concentrate; FC, Fibrinogen concentrate; PT, Prothrombin time; APTT, Activated partial thromboplastin time; INR, International normalized ratio; FDP, Fibrin degradation product; IBL, Intraoperative blood loss.

TARPSWG. Conversely, venous thrombosis emerged as the most prevalent adverse event after massive blood transfusion (MBT), potentially associated with prolonged anesthesiologic durations. In the examination of mortality factors, the singular factor correlated with postoperative 60-day death was lactate levels. Elevated lactate levels have been consistently reported as a robust risk factor linked to increased mortality in patients experiencing septic shock, cardiac arrest, hemorrhagic shock, and major surgeries (36–39). A lactate level of ≥ 2.5 mmol/L has been identified as the optimal threshold for predicting 28-day mortality in severe sepsis and septic shock patients (40). In our study, the lactate levels in the seven deceased patients rose to an average of 6.01 mmol/L at the conclusion of surgeries, compared to the preoperative mean value of 2.26 mmol/L ($p < 0.001$). This value of 6.01 mmol/L was also significantly higher than the level of 2.55 mmol/L in the other 63 surviving patients at the same juncture, indicating a substantial increase in postoperative mortality.

This study has several intrinsic limitations. Due to the rarity and unavailability of platelet, the ratio of FFP: PLT: RBC were not fully compliant to recommendations according to some MBT guidelines and protocols. The exact effects of more PLT application in perioperative mortality and VTE need further exploration. This study is a retrospective analysis with limited numbers of subjects. And the severity and complexity of the RPS remains diverse. Selective bias was not avoidable as no significant statistical relationship were found between fluid/blood product infusion and postoperative morbidities and mortalities.

In general, precise and effective anesthesia managements using goal-directed and blood test guided strategy during RPS surgeries are utmost important which may arrive at acceptable postoperative morbidities and mortalities in MBT patients. Patients with higher lactate level at the termination of operation with extended anesthesia duration deemed to have higher possibilities of postoperative VTE and deaths which should be alerted.

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 authors.

Ethics statement

The studies involving humans were approved by Peking University International Hospital Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because It was a retrospective study without any interventions of the subjects.

Author contributions

JW: Data curation, Project administration, Writing – original draft. JC: Funding acquisition, Methodology, Resources, Writing – review & editing, Writing – original draft, Formal analysis. KL: Data curation, Investigation, Validation, Writing – review & editing. HZ: Formal analysis, Software, Writing – original draft. YWe: Data curation, Methodology, Writing – original draft. LS: Data curation, Methodology, Writing – original draft. SL: Data curation, Methodology, Writing – original draft. YWa: Data curation, Methodology, Writing – original draft. CL: Resources, Supervision, Validation, Writing – review and editing. LY: Investigation, Project administration, Supervision, Validation, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. The present study was kindly supported by both grants from Beijing Municipal Science & Technology Commission, Administrative Commission of Zhong-Guancun Science Park (No. Z221100007422042) and Peking University International Hospital Research Funds (2023-KY-0059).

Acknowledgments

Partial results were previously presented as poster in 2022 Connective Tissue Oncology Society (CTOS) Annual Conference.

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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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OPEN ACCESS

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RECEIVED 20 January 2024

ACCEPTED 18 March 2024

PUBLISHED 27 March 2024

CITATION

Fan P, Tao P, Wang Z, Wang J, Hou Y, Lu W,
Ma L, Zhang Y and Tong H (2024) Evaluation
of AJCC staging system and proposal of a
novel stage grouping system in
retroperitoneal liposarcoma: the Fudan
Zhongshan experience.
Front. Oncol. 14:1373762.
doi: 10.3389/fonc.2024.1373762

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Evaluation of AJCC staging system and proposal of a novel stage grouping system in retroperitoneal liposarcoma: the Fudan Zhongshan experience

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Background: Overall survival (OS) varies significantly among individuals with heterogeneous retroperitoneal liposarcoma (RPLS), even among those with the same clinical stage. Improved staging of RPLS is a critical unmet need, given the disappointing results of external validations of the 8th American Joint Committee on Cancer (AJCC) TNM staging system.

Methods: The cohort study included 220 consecutive patients who underwent surgical resection for primary RPLS at the largest sarcoma centre of Fudan University in China from September 2009 to August 2021, combined with 277 adult patients with RPLS in the SEER database from 1975 to 2020. Data analysis was performed from December 2021 to December 2022. Patients were retrospectively restaged according to the 8th and 7th editions of the TNM staging system as well as the new TNM (nTNM) staging system. The primary endpoint was overall survival (OS). Comparative analysis of postoperative survival was performed using the Kaplan-Meier method, and differences between subgroups were tested using the log-rank test. The OS prediction nomogram was generated based on baseline variables and tumour characteristics. Harrell's consistency index (C-index), area under the curve (AUC) of receiver operating characteristic curves (ROC), and calibration curves were used to evaluate the performance of the nomogram.

Results: A total of 497 patients were enrolled in the study, including 282 (56.7%) male patients. The median follow-up was 51 months (interquartile range, IQR, 23–83), and the OS rates at 1, 3, and 5 years were 87.9%, 75.3%, and 64.9%, respectively. According to the staging distribution of the AJCC 7th edition, 6 patients were stage IA (1.2%), 189 patients were stage IB (38%), 12 patients were stage IIA (2.4%), 150 patients were stage IIB (30.1%), 131 patients were stage III (26.3%), and 9 patients were stage IV (1.8%). With the 8th edition staging, this

distribution changed: 6 patients (1.2%) were stage IA, 189 patients (38%) were stage IB, 12 patients (2.4%) were stage II, 24 patients (4.8%) were stage IIIA, 257 patients (51.7%) were stage IIIB, and 9 patients (1.8%) were stage IV. 182 patients (36.6%) were reclassified according to the nTNM staging system with the new T stage classification. The C-index and log-rank score improved after implementation of nTNM implementation. The nTNM system was associated with improved identification of high-risk patients compared with the AJCC 7th and 8th TNM. The FNCLCC stage proved to be highly prognostic with significant intergroup differences in OS. The calibration curve shows a high degree of agreement between the actual OS rate and the nomogram estimated OS rate.

Conclusion: Compared with 8th AJCC TNM, 7th AJCC TNM staging system showed a more homogeneous staging distribution and a slight improvement in the prognostic accuracy of RPLS. The revised T-stage and nTNM systems showed better risk stratification performance. The FNCLCC stage was found to have high prognostic value, further emphasising histological grade is the least negligible prognostic factor in predicting patient survival. The constructed nomogram model enables individualized prognostic analysis and helps to develop risk-adapted therapy for RPLS patients.

KEYWORDS

revised T stage, modified TNM system, os, RPLS, FNCLCC

Introduction

The relative rarity and biological heterogeneity of soft tissue sarcoma (STS), especially in retroperitoneal sarcoma (RPS) (1), contributes to the potential diversity and complexity of the disease, thereby limiting the development of robust histotype-specific or site-specific evidence to guide clinical management. However, the increasing recognition of RPS over the past few decades has led to standard classification, grading and staging systems (2).

The most commonly used grading system is the (Fédération Nationale des Centres de Lutte Contre le Cancer) FNCLCC grading system for STS, and the most commonly used nomograms are derived from Sarculator, Memorial Sloan-Kettering Cancer Center (MSKCC) (3), and Gronchi A (4). However, all of these nomograms are not specific for retroperitoneal liposarcoma (RPLS), as only 13% of patients in the development and validation cohorts of the MSKCC database were RPLS patients (5, 6), whereas primary extremity sarcomas in Sarculator (7) and RPS in Gronchi A (4). Notably, STS with different pathologic types and anatomic sites exhibit an extremely high degree of tumour heterogeneity and biological behavior (8). Furthermore, most of these models have not been included in the TNM staging system, and the external validation power of these models is limited (9, 10). Therefore, histology-type-specific clinical staging and nomograms are needed to stratify patients with STS, especially for RPLS.

At the same time, the latest 8th edition of the AJCC STS staging system recognizes the importance of the anatomic location of the sarcoma and establishes a site-specific staging system that

distinguishes RPS from other sarcomas (11), based primarily on tumour size without any clinical experience or published evidence, but completely ignoring the important predictive information tumour invasion of adjacent organs (12), tumour multifocality (13), and histologic subtype (14). A recent evaluation of the performance of the 8th edition of the AJCC staging system for RPS using a large national database showed that its overall prognostic performance remains unsatisfactory (12). Therefore, the ability of the new staging system to risk stratify specific types (e.g., liposarcoma) among RPS needs to be investigated.

The aim of this study was to compare the clinical presentation of AJCC 7th TNM staging system and AJCC 8th TNM staging system in RPLS using data extracted from the SEER database in conjunction with the Fudan University database. Meanwhile, we aimed to propose a revised T staging algorithm based on our clinical experience and also to construct a novel nomogram incorporating several indispensable clinical factors for personalized risk assessment in RPLS.

Methods

Retrospective patient cohort

Patients undergoing radical resection for RPLS were identified retrospectively from the SEER and Fudan databases. This is a population-based study of subjects from a publicly available de-

identified patient database that does not require institutional review board approval. This study was reviewed and approved by the Institutional Review Board (ID: B2022-586R) of Zhongshan Hospital, Shanghai, China. All studies were guided by the principles of the Declaration of Helsinki.

Variables downloaded from the SEER database (www.seer.cancer.gov) included age, sex, year of diagnosis, tumour site, tumour diameter, lymph node metastasis, distant metastasis, histological subtype of sarcoma, histological grade, survival information, and follow-up data.

For the sarcoma centre at the ZSFD, a dynamically updated big data database has been developed includes daily electronic medical record data. Sarcoma patients treated at the ZSFD since September 2009 were included in the database. Each patient's data were collected from 10 electronic health record systems, including the outpatient work system, pathology system, electronic medical record, the follow-up system, laboratory information system, electrocardiogram system, anaesthesia information management system, hospital information system, physical examination information system, tumour tissue biobank.

Inclusion criteria included the following: (1) RPLS on pathologic examination; (2) complete TNM staging information ([Supplementary Table 1](#)); (3) complete clinical information; (4) no history of other malignant tumours; (5) effective postoperative follow-up information.

Clinical end point and follow-up

The endpoint of the current study was OS, defined as the time from surgery to death from any cause (15). OS was prospectively collected from the sarcoma centre database. Patients were followed up over time through medical records and telephone calls. Follow-up time was defined as the interval between the date of surgery and the time of the last follow-up or death.

Follow-up consisted of a physical examination, laboratory tests, and at least one radiological imaging test [abdominal computed tomography (CT) and/or magnetic resonance imaging (MRI)] every 3 months for the first 2 years after surgery, then every 6 months, and once a year after 5 years, depending on the specific pathological subtype. PET-CT was not routinely performed. Patients were also contacted by telephone if necessary.

nTNM staging system

Patients were restaged based on pathological tumour size, nodal status and metastatic spread to distant sites according to the 7th (16) and 8th edition staging systems (11). The nTNM system incorporated a modified T-stage (21cm, the median value from tumour diameter in the ZSFD database) into the 7th and 8th editions, respectively, and patients were also restaged according to sub-stage re-grouping based on prognostic performance on surveillance.

Statistical analysis

Continuous variables were expressed as mean with standard deviation (SD). Categorical variables were expressed as frequencies and percentages. Fisher's exact test and chi-squared test were used for categorical data. All tests were 2-tailed.

Kaplan-Meier curves were plotted to estimate median OS. Cox proportional hazards regression models were applied to identify OS-related prognostic factors. The assumptions of the Cox model were tested by partial residual analysis.

The accuracy of the 7th TNM and 8th TNM staging systems in predicting postoperative OS was compared using concordance index, ROC and AUC.

The nomogram predicting postoperative OS was generated from the results of Cox regression analysis. The corresponding calibration curves were used to compare the predicted probabilities of the nomograms with the agreement between the observations.

This study was conducted using statistical software including SPSS (version 26.0), R software (version 4.0.3), and GraphPad Prism (version 8.0), and a two-sided p-value of less than 0.05 was considered statistically significant. All methods followed relevant guidelines and regulations.

Results

Baseline characteristics

A total of 497 consecutive RPLS were retrospectively included in the follow-up analysis, with 277 patients from the SEER database and 220 patients from the ZSFD database ([Supplementary Figure 1](#)). Baseline and tumour characteristics are demonstrated in [Table 1](#). 282 (56.7%) were male and the median age at diagnosis was 48 years (range, 19-85 years). The median tumour size was 21 cm (IQR, 15-30 cm). Of note, only 1% of patients had lymph node metastases in the overall cohort and 1.8% had distant metastases.

Due to the time span of the study, 7th or even 6th edition of AJCC TNM staging was applied before 2017 and 8th edition after 2017, in order to effectively evaluate the usability of 7th and 8th edition, therefore all patients were restaged to obtain their respective 7th and 8th edition staging. As shown in [Table 2](#), when the 7th edition of the TNM staging system was applied, the numbers of patients with stage IA, IB, IIA, IIB, III, and IV were 6 (1.2%), 189 (38%), 12 (2.4%), 150 (30.1%), 131 (26.3%) and 9 (1.8%), respectively. This distribution changed after the application of the 8th edition of the classification: 6 patients (1.2%) were in stage IA, 189 patients (38%) were in stage IB, 12 patients (2.4%) were in stage II, 24 patients (4.8%) were in stage IIIA, 257 patients (51.7%) were in stage IIIB, and 9 patients (1.8%) were in stage IV. Using the 8th edition classification, 293 patients (58.9%) were reclassified to another stage.

Due to the time span of the study, 7th or even 6th edition of AJCC TNM staging was used before 2017 and 8th edition after

TABLE 1 Baseline characteristics of SEER and ZSFD cohorts.

Characteristics	No. (%)	SEER Cohort (N=277)	ZSFD Cohort (N=220)
	Total Cohort		
	(N=497)		
Age, median (IQR)	61 (52-68)	64 (55-70)	56 (50-65)
Sex			
Male	282 (56.7%)	156 (56.3%)	126 (57.3%)
Female	215 (43.3%)	121 (43.7%)	94 (42.7%)
Tumor size, median (IQR), mm	210 (150-300)	200 (130-270)	245 (170-300)
AJCC 7th T Stage			
T1	19 (3.8%)	15 (5.4%)	4 (1.8%)
T2	478 (96.2%)	262 (94.6%)	216 (98.2%)
AJCC 8th T Stage			
T1	19 (3.8%)	15 (5.4%)	4 (1.8%)
T2	38 (7.6%)	28 (10.1%)	10 (4.6%)
T3	79 (16%)	46 (16.6%)	33 (15%)
T4	361 (72.6%)	188 (67.9%)	173 (78.6%)
N Stage			
N0	492 (99%)	272 (98.2%)	220 (100%)
N1	5 (1%)	5 (1.8%)	0
M Stage			
M0	488 (98.2%)	270 (97.5%)	218 (99.1%)
M1	9 (1.8%)	7 (2.5%)	2 (0.9%)
FNCLCC Grade			
1	201 (40.4%)	104 (37.5%)	97 (44.1%)
2	159 (32%)	75 (27.1%)	84 (38.2%)
3	137 (27.6%)	98 (35.4%)	39 (17.7%)
Histologic subtypes			
WDLPS	192 (38.6%)	82 (29.6%)	110 (50%)
DDLPS	221 (44.5%)	154 (55.6%)	67 (30.5%)
MLPS	23 (4.6%)	10 (3.6%)	13 (5.9%)
PLS	9 (1.8%)	6 (2.2%)	3 (1.4%)
Mixed liposarcoma	21 (4.2%)	2 (0.7%)	19 (8.6%)
Liposarcoma, NOS	31 (6.2%)	23 (8.3%)	8 (3.6%)

WDLPS, well-differentiated liposarcoma; DDLPS, dedifferentiated liposarcoma; MLPS, myxoid Liposarcoma, PLS, pleomorphic liposarcoma; NOS, Not specified.

2017, in order to effectively evaluate the performance of 7th and 8th edition, therefore all patients were restaged to obtain their respective 7th and 8th edition staging.

Regarding other pathological variables, a total of 201 patients had a G1 tumour (40.4%), 159 patients had a G2 tumour (31.9%) and 137 patients had a G3 tumour (27.5%). The proportion of each

histological subtype was 38.6% (WDLPS), 44.5% (DDLPS) and other LPS (16.9%).

Clinical outcomes by TNM staging system

At the last follow-up, 336 patients (67.6%) were alive and the median follow-up for the entire cohort was 51 (IQR, 23-83) months. The median OS for the entire cohort was 85 (95%CI, 73-97) months, with the 1-, 3-, and 5-year OS estimates of 87.9%, 75.3%, and 64.9%, respectively. Kaplan-Meier curves for OS were examined according to the 7th and 8th editions of the AJCC TNM (Figure 1).

Based on Kaplan-Meier survival analysis, the 5-year survival rates changed from 83.2% for stage I, 64.7% for stage II, 40.5% for stage III and <25.9% for stage IV (log-rank, p<0.001) under the 7th AJCC TNM to 83.1% for stage I, NA for stage II, 52.2% for stage III and <25.9% for stage IV (log-rank, p<0.001) under the 8th AJCC TNM. Similar results were found in the SEER and ZSFD cohorts (Supplementary Figure 2).

In the subgroup of patients, neither 7th or 8th edition T stage was discriminative for survival (Supplementary Figure 3). Furthermore, no significant changes in N and M stage were observed between the 7th and 8th editions (data not shown).

When assessing the prognostic accuracy for OS, the C-index reached 0.694 (95% CI, 0.673-0.715) for 7th AJCC TNM and 0.654 (95% CI, 0.635-0.672) for 8th AJCC TNM staging system (Table 3). The AUC value at 1, 3 and 5 years were 74.5%, 72% and 70.7% for the 7th edition and 70.2%, 68.5% and 67.7% for the 8th edition for OS as shown in Supplementary Figure 4. The time-dependent AUCs indicated that 7th has higher AUCs compared to 8th of the OS. Consistent with the overall cohort, similar results were found in the SEER and ZSFD cohorts, respectively (Supplementary Figure 5).

Taken together, these results demonstrate that the 7th edition has a more even staging distribution and a slightly improved prognostic accuracy for RPLS compared to the 8th edition.

Proposed modifications to the 7th and 8th edition

Accumulating evidence has shown that RPLS, unlike other solid tumours, is located in the retroperitoneal space without any obvious clinical features during tumour progression (17, 18). In addition, patients were always diagnosed with a large tumour volume and an overloaded tumour burden (2). We then estimated the value of T stage in prognostic accuracy for OS. Interestingly, patients with tumour diameters of less than 5 cm were extremely rare, both in the 7th edition of stage IA and IIA and the 8th edition of stage IA and II (Figure 2), which had greatly attracted our attention.

Patients were restaged according to the newly proposed tumour size staging, which is based on median and quartile of the entire cohort. For the 8th edition staging criteria, T1: ≤15 cm maximum diameter, T2: >15 to 21 cm maximum diameter, T3: >21 cm to 30 cm maximum diameter, and T4: >30 cm. Meanwhile, for the 7th

TABLE 2 Staging reclassification by the 7th and 8th Edition of the TNM and nTNM staging system for RPLS.

Overall Stage	Patients, No. (%)	TNM 8th Edition	nTNM 7th Edition	nTNM 8th Edition
	TNM 7th Edition			
Stage I				
IA	6 (1.2)	6 (1.2)	94 (18.9)	48 (9.6)
IB	189 (38)	189 (38)	101 (20.3)	147 (29.6)
Stage II				84 (16.9)
IIA	12 (2.4)	12 (2.4)	153 (30.8)	
IIB	150 (30.2)	NA	83 (16.7)	NA
Stage III	131 (26.4)	NA	57 (11.5)	NA
IIIA	NA	24 (4.8)	NA	69 (13.9)
IIIB	NA	257 (51.7)	NA	140 (28.2)
Stage IV	9 (1.8)	9 (1.8)	9 (1.8)	9 (1.8)

NA, not applicable; TNM, tumor node metastasis; RPLS, retroperitoneal liposarcoma.

edition staging criteria, T1: ≤21 cm maximum diameter, T2: >21 cm maximum diameter.

Using the new modified T-stage classification and regrouping the TNM staging, the distribution of patients was optimised for stage IA in 48 patients (9.6%), stage IB in 147 (29.5%), stage II in 84 (16.9%), stage IIIA in 69 (13.8%), stage IIIB in 140 (28.1%) and stage IV in 9

(1.8%) in the 8th edition. Meanwhile, according to the AJCC 7th TNM, stage IA was found in 94 patients (18.9%), stage IB in 101 (20.3%), stage IIA in 153 (30.7%), stage IIB in 83 (16.7%), stage III in 57 (11.4%), and stage IV in 9 (1.8%) (Supplementary Table 2).

When assessing the prognostic accuracy of the new T stage on OS, the C-index was 0.675 (95% CI, 0.655-0.696) for the modified

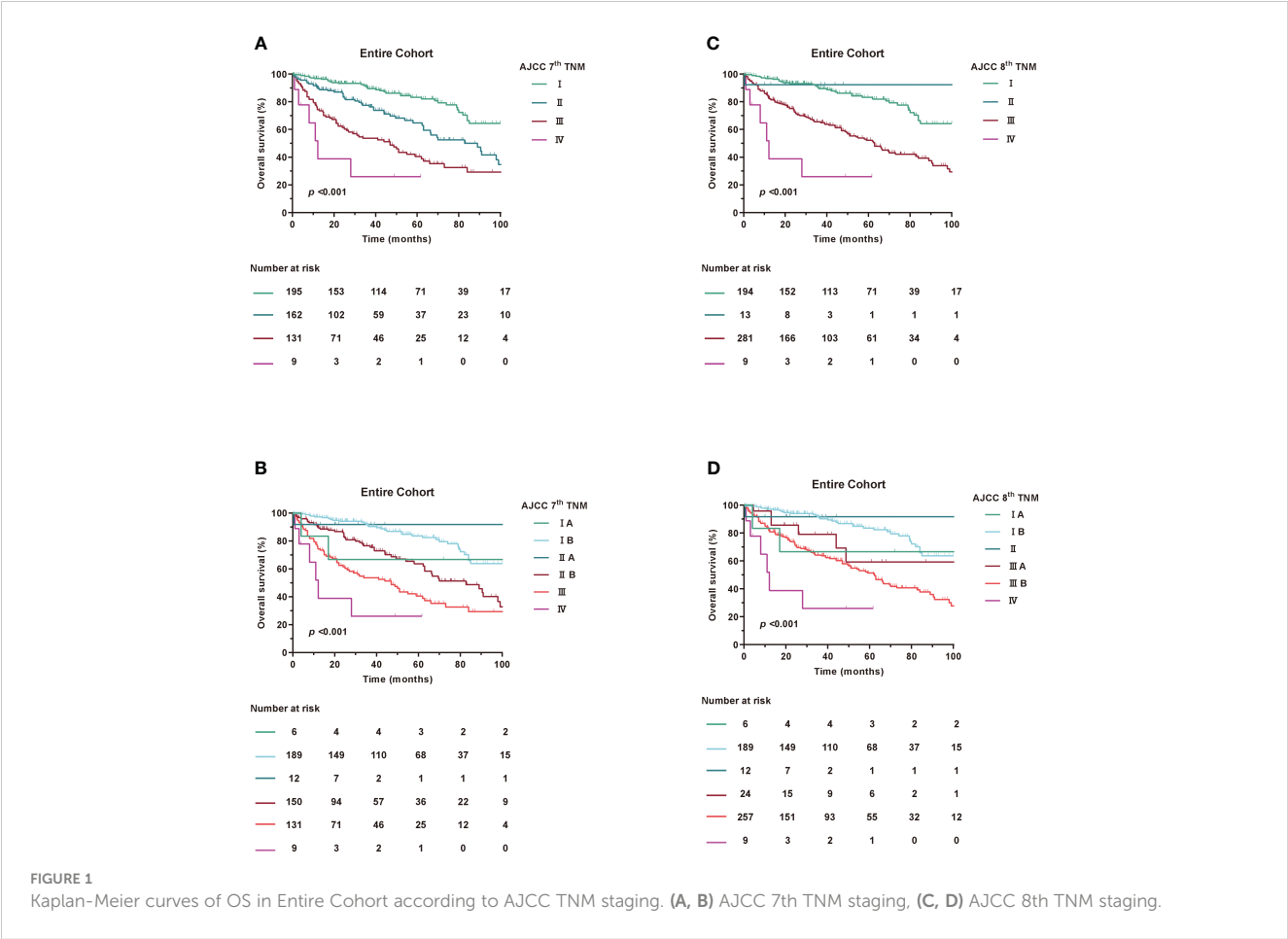


TABLE 3 Summary of the C-index of prognostic models for OS in patients with RPLS.

Models	C-index (95% CI)	p value
7th TNM Stage	0.696 (0.675-0.717)	< 0.001
8th TNM Stage	0.664 (0.645-0.683)	< 0.001
7th nTNM Stage	0.677 (0.656-0.699)	< 0.001
8th nTNM Stage	0.676 (0.655-0.696)	< 0.001
FNCLCC Grade	0.683 (0.662-0.704)	< 0.001

TNM, tumor node metastasis; FNCLCC, French Fédération Nationale des Centres de Lutte contre le Cancer.

7th edition and 0.673 (95% CI, 0.653-0.693) for the modified 8th edition (Table 3). The ROC curve for predicting OS at 1, 3 and 5 years showed an AUC of 73.3%, 70.7% and 69% for the modified 7th edition and an AUC of 72.6%, 69.5% and 68.4% for the modified 8th edition, as shown in Supplementary Figure 6.

To further explore the prognostic predictive power of the nTNM staging in different histological subtypes of RPLS, we performed further analyses. Since the main component was on WDLPS and DDLPS, we empirically divided the WDLPS, mixed liposarcoma and 'liposarcoma, NOS' into a group named H1, and the remaining into a group named H2. The results of the study showed that the C-indexes of H1 in 7th nTNM and 8th nTNM

staging 0.632 and 0.643, whereas the C-indexes of H2 were 0.607 and 0.590. The ROC curves for the 7th nTNM and 8th nTNM staging in H1 and H2 predicting 1-, 3-, and 5-year postoperative survival are shown in the Supplementary Figure 7.

Taken together, these results suggest that the overall model fit of the nTNM staging is better compared with 7th TNM and 8th TNM staging and that the new T staging can be used as a powerful tool for RPLS risk stratification.

FNCLCC grade in prognosis

Since histologic grading has been shown to be one of the factors most strongly associated with postoperative prognosis in patients with RPLS (12, 19, 20), we also examined the association between the modified 7th and 8th edition histological grades. Notably, histological grade analysis based on FNCLCC grading remained unchanged. In addition, the C-index for FNCLCC grade alone was 0.683 (95% CI, 0.662-0.704) for prognostic accuracy (Table 3). Furthermore, the FNCLCC grade showed a statistically significant survival difference in risk stratification compared with the TNM staging system (Figure 3), as confirmed by the results of the SEER and ZSFD cohorts. However, when assessing the prognostic accuracy for OS in the combination of FNCLCC grade and TNM, the C-index reached 0.710 (95% CI, 0.688-0.732).

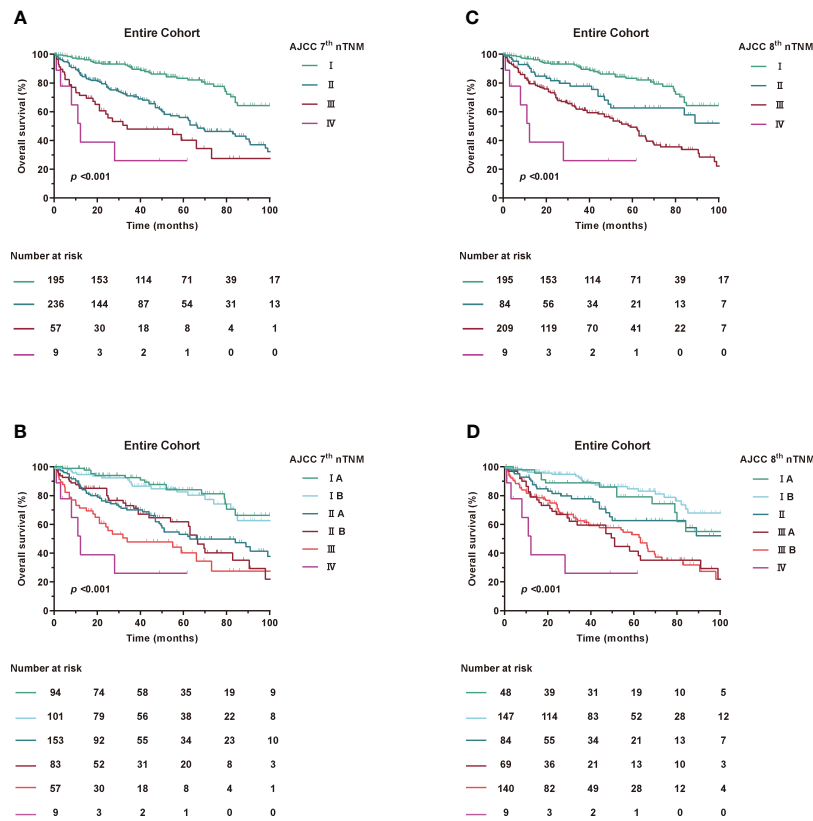


FIGURE 2 Kaplan-Meier curves of OS in Entire Cohort according to modified AJCC TNM staging. (A, B) AJCC 7th nTNM staging, (C, D) AJCC 8th nTNM staging.

Taken together, these results showed that the TNM staging system had some advantages over FNCLCC grade alone, but needed to be improved in a larger RPLS cohort.

Nomogram development and validation

Nomogram is a concise graphical model that integrates multiple prognostic-related factors and is an effective tool for personalized risk assessment of cancer patients (21, 22). To further explore the significant differences in baseline variables and tumour characteristics, we constructed the OS-related nomogram, including sex, age, tumour size, FNCLCC grade pathological subtypes, lymph node metastasis and distant metastasis (Figure 4A). Of note, the C-index reached 0.726 (95% CI, 0.705–0.748) and the AUC values at 1, 3, and 5 years postoperatively were 77.2%, 75%, and 77.1%, respectively (Figure 4B). The calibration curve showed that the actual OS rate was highly consistent with the nomogram estimated OS rate (Figure 4C).

Discussion

Tumour heterogeneity requires personalised cancer therapy (23–26). However, RPLS is one of the most heterogeneous types of solid tumours (27). Determining a patient's postoperative risk can assist oncologists in developing the most appropriate personalized treatment plan (28). However, the broad nature of the TNM staging system and the heterogeneity of patients with

tumours in the same stage make its widespread use for risk stratification still imperfect.

Furthermore, RPLS was particularly influenced by anatomical location, tumour biological behaviour, histological grade and pathological subtype (12, 29–31). Given its rarity, heterogeneity and heterogeneous therapeutic response, the true predictors of survival and staging system for RPLS are still under investigation.

Relative to the 7th AJCC TNM, the 8th AJCC TNM addresses this issue by providing separate staging algorithms according to the anatomic location of the sarcoma, such as limbs and trunk, retroperitoneum, or head and neck (11). However, no significant improvement was found, which may be related to the behaviour of different histological types of sarcomas (32).

Several studies have now evaluated the 8th AJCC TNM staging system (33, 34). However, categorizing continuous data generates regression coefficients that are weighted according to the distribution of data within each category, which almost always fails to capture the true nonlinear relationship between a continuous variable and its log hazard (35). In any case, risk stratification for lymph node metastasis (LNM) is unlikely to play a major determining role in prognostic model performance, as less than 5% of sarcoma patients develop nodal metastases (32).

To the best of our knowledge, studies that have modified the T-staging in the TNM staging system and developed a comprehensive nomogram for estimating OS are lacking. This study proposes a nomogram that combines the TNM staging system and other widely assessed clinical characteristics to accurately assess the optimal stratification of patients with RPLS.

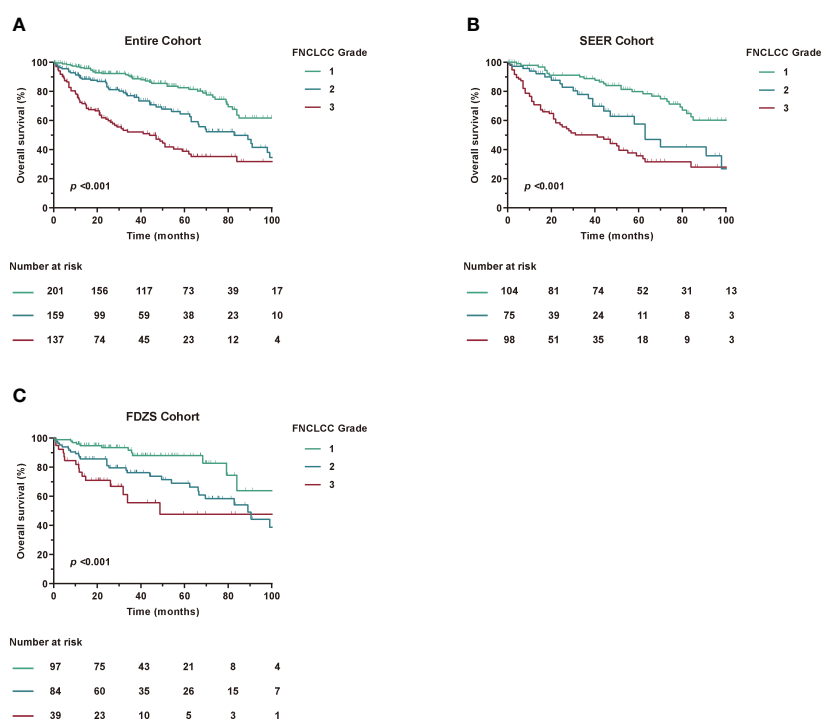


FIGURE 3
Kaplan-Meier curves of OS according to FNCLCC Grade among different cohorts. (A) Entire Cohort, (B) SEER Cohort, (C) FDZS Cohort.

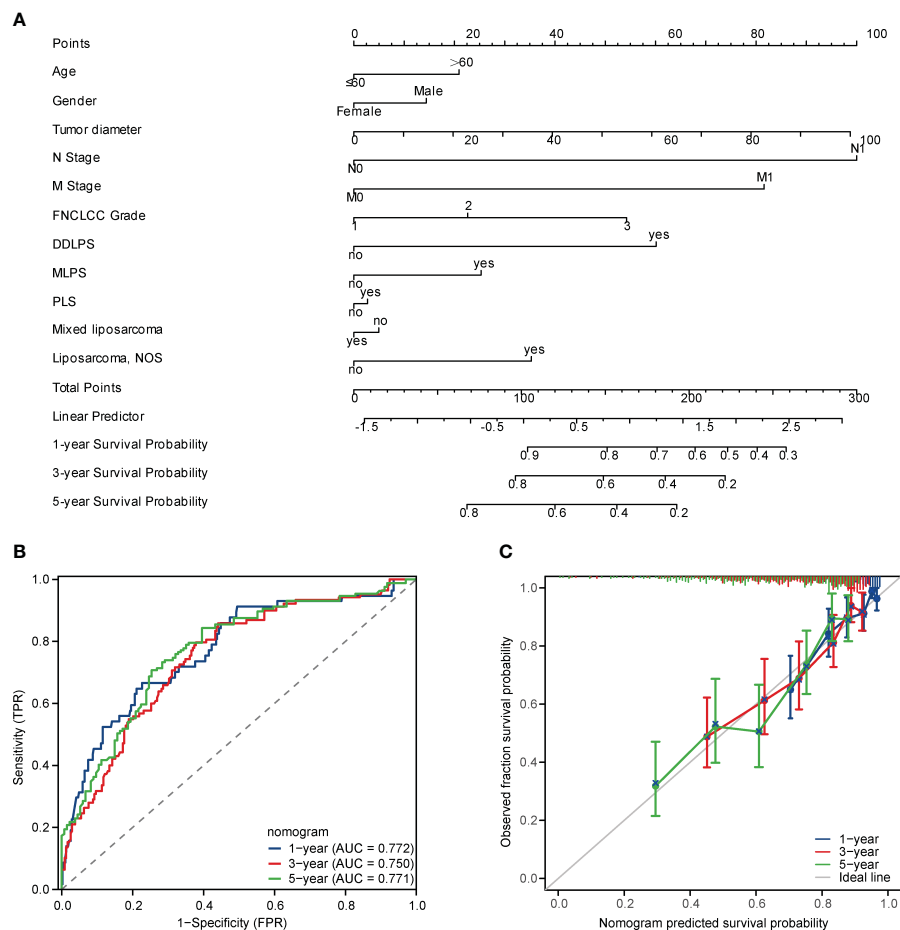


FIGURE 4

(A) A nomogram for predicting the 1-, 3-, 5-year OS in RPLS after resection, (B) Receiver operating characteristic (ROC) curves of the nomogram in predicting 1-, 3-, 5-year OS in RPLS after resection, (C) Calibration plots of the nomogram in predicting 1-, 3-, 5-year OS in RPLS after resection.

Compared with the widely used Sarculator (3) and the multicentre nomogram proposed by Gronchi A (4), the nomogram proposed in this study has comparable predictive performance and is unique to RPLS. The C index of the sarculator and the multicentre nomogram proposed by Gronchi A in RPS is 0.73 (6) and 0.68 (4), respectively. The nomogram proposed in this study had excellent discriminatory power (C index 0.726; 95% CI 0.705-0.748) and the actual OS was highly consistent with the probability of OS estimated by the nomogram, which was confirmed by the calibration curves, which represents a reliable model with strong predictive performance for OS estimation in RPLS.

A number of nomograms for predicting survival in STS or RPLS have been available in the published literature since 2002 (36–38), but unfortunately most of them were not covered by the TNM staging system. To fill this gap, we conducted a large real-world study including 220 primary RPLS patients from the ZSFD database and 277 RPLS from the SEER database to develop and validate a nomogram for estimating OS.

Limitations

There exist some limitations of the research that cannot be ignored. Firstly, selection bias may be unavoidable due to the retrospective cohort study design. Second, although the internal validation cohort of the SEER database showed excellent discriminatory power with a high degree of concordance between the actual OS and the estimated OS probability of the nomogram, which was confirmed by the calibration curves, we did not perform external validation in China or the United States (United State of America). Third, this study was conducted in a high-flow sarcoma centre and may not be generalizable to a small population of RPLS patients.

Conclusions

Compared with 8th AJCC TNM, 7th AJCC TNM staging system showed a more homogeneous staging distribution and a slight

improvement in the prognostic accuracy of RPLS. The revised T-stage and nTNM systems showed better risk stratification performance. The FNCLCC stage was found to have high prognostic value, further emphasising histological grade is the least negligible prognostic factor in predicting patient survival. The constructed nomogram model enables individualized prognostic analysis and helps to develop risk-adapted therapy for RPLS patients.

Data availability statement

The data that support the findings of this study are available on request from corresponding author.

Ethics statement

The studies involving humans were approved by Institutional Review Board of Zhongshan Hospital, Shanghai, China (ID: B2022-586R). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

PF: Conceptualization, Data curation, Formal analysis, Methodology, Validation, Writing – original draft, Writing – review & editing. PT: Conceptualization, Formal analysis, Methodology, Validation, Writing – original draft. ZW: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. JW: Conceptualization, Data curation, Supervision, Writing – original draft. YH: Supervision, Writing – review & editing. WL: Resources, Supervision, Writing – review & editing. LM: Conceptualization, Formal analysis, Methodology, Resources, Supervision, Writing – original draft, Writing – review & editing. YZ: Conceptualization, Methodology, Resources, Supervision, Writing – review & editing. HT: Conceptualization, Formal analysis, Methodology, Resources,

Supervision, Validation, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by grants from Scientific Research Project of Shanghai Municipal Health Commission (20214Y0087, 20204Y0409); Hongkou District "Outstanding Young Talents in Clinical Medicine" Training Program (No. HKLCYQ2024-01); "Young Talents" Training Plan of Shanghai TCM-integrated Hospital (No. RCPY0063); Scientific Research Project of Shanghai TCM-integrated Hospital (No. 18-01-03); Scientific Research Project of Hongkou District Health Committee (No. 2003-02); Fujian Natural Science Foundation (No. 2023J011698); Xiamen Natural Science Foundation (No. 3502Z20227280).

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/fonc.2024.1373762/full#supplementary-material>

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OPEN ACCESS

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RECEIVED 09 April 2024

ACCEPTED 08 July 2024

PUBLISHED 23 July 2024

CITATION

Hao Q, Cha L, Zhou B, Li X, Gong M, Li Q,
Dong G, Song M, Wu Z, Guo Z, Qiu F, Wang X
and Tian L (2024) Da Vinci robot-assisted
retroperitoneal tumor resection in 105
patients: a single-center experience.
Front. Oncol. 14:1414780.
doi: 10.3389/fonc.2024.1414780

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Da Vinci robot-assisted retroperitoneal tumor resection in 105 patients: a single-center experience

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Background: The Da Vinci Surgical System (DVSS) has the advantages of minimal invasion, rapid recovery, safety, and reliability. Although the DVSS has been widely used in various abdominal surgeries, descriptions of its use in robot-assisted retroperitoneal tumor resection (RRTR) are limited to case reports; large-sample systematic studies are lacking. The present study was performed to analyze the data of RRTR in our center, summarize our experience, and provide a reference for other retroperitoneal tumor centers.

Methods: We retrospectively analyzed the clinical data of 105 patients who underwent RRTR at the Affiliated Hospital of Qingdao University from January 2015 to December 2022. Logistic univariate and multivariate analyses were performed to identify independent risk factors affecting RRTR. A receiver operating characteristic curve was used to find the cut-off value, which was then included in the logistic multivariate analysis for verification.

Results: Among the 105 patients, 87 successfully underwent RRTR (DVSS group) and 18 underwent conversion to open surgery (conversion group). There was no significant difference in sex, age, body mass index, history of abdominal surgery, or tumor location between the two groups ($P > 0.05$). The maximum tumor diameter [odds ratio (OR), 1.041; 95% confidence interval (CI), 1.015–1.067; $P = 0.002$] and pathological property (OR, 8.646; 95% CI, 2.370–31.544; $P = 0.001$) were independent risk factors for conversion to open surgery. Further analysis confirmed that the success rate of RRTR was higher for tumors with a maximum diameter of ≤ 64 mm and benign tumors. Based on our experience and statistical results, we believe that retroperitoneal tumors that meet the following criteria have a higher success rate of DVSS resection: maximum tumor diameter of ≤ 64 mm, benign tumors, the tumor has relatively clear boundary, no obvious invasion of surrounding tissues and organs, and no need for combined organ resection.

Conclusions: RRTR is safe and effective in the treatment of RPT, and the clinical prognosis is similar to that of open surgery. The success rate of RRTR in patients with appropriate surgical indications for this procedure is higher.

KEYWORDS

retroperitoneal tumor, robotic surgery, minimally invasive technique, Da Vinci surgery system, robot-assisted retroperitoneal tumor resection

1 Introduction

A retroperitoneal tumor (RPT) arises from fat, muscle, lymph, nerve, and residual embryonic tissue. These tumors may be located anywhere within the retroperitoneal space, which extends from the plane of the diaphragm to the potential retroperitoneal space above the pelvis (1). Statistical data indicate that the incidence of RPT ranges from 0.5 to 1.0 per 100,000 individuals (2). Malignant retroperitoneal tumors constitute approximately 70% of all RPTs and account for 0.1%–0.2% of all human malignancies (3). Despite their rarity, about one-third of RPTs are sarcomas, which are associated with an extremely poor prognosis and high recurrence rates (4). Surgical intervention remains the primary treatment modality for RPT and is a crucial factor in determining patient outcomes (5, 6). The main surgical techniques for RPT include traditional open surgery, laparoscopic approaches, and robot-assisted procedures [including the use of the Da Vinci Surgical System (DVSS) (Intuitive Surgical, Sunnyvale, CA, USA)]. The challenges presented by the limited surgical space, narrow surgical field, restricted surgical range, deep tumor location, various pathological types, and proximity to blood vessels in the retroperitoneal space have been addressed by increasing numbers of surgeons specializing in retroperitoneal tumors. These surgeons have demonstrated the safety and effectiveness of open surgery for RPT resection through good exposure of the surgical field and the ability to identify tumors by intraoperative palpation. Therefore, traditional open surgery is widely performed for retroperitoneal tumor resection. However, traditional open surgery cannot avoid the need for a large surgical incision, intraoperative manipulation of organs, slow postoperative recovery, and potential complications; thus, clinicians still face many challenges in perioperative management. With the development of minimally invasive techniques in recent years, successful laparoscopic treatment of RPT has been reported, and many retroperitoneal tumor surgeons continue to progress in this field (7, 8). For example, Chatelet et al. (9) laparoscopically removed a large schwannoma measuring $17 \times 8 \times 6$ cm. Laparoscopic RPT resection is feasible even when the tumor is large or attached to adjacent vascular structures, and although several challenges remain (10), laparoscopic surgery is technically safe, improves patients' prognosis, and is a viable surgical option (11). The development of robot-assisted surgical systems is

one of the greatest advances in laparoscopic technology. Several reports have confirmed that the DVSS is safe and effective for RPT resection and that it can significantly reduce surgical trauma and promote patient recovery (12–19). However, no systematic, large-sample studies have been performed to evaluate the application of DVSS robot-assisted RPT resection (RRTR). The present study was performed to analyze the clinical data of patients who underwent RRTR in our hospital, identify the risk factors affecting RRTR, and provide a reference for the application of RRTR in other retroperitoneal tumor centers.

2 Materials and methods

This study involved 105 patients who underwent RRTR at the Affiliated Hospital of Qingdao University from January 2015 to December 2022. Preoperative color Doppler ultrasound, contrast-enhanced computed tomography or magnetic resonance imaging, endoscopic ultrasonography, and three-dimensional imaging were used to comprehensively diagnose and evaluate the resectability of RPT. All patients were evaluated by a multidisciplinary treatment team before surgery, and the surgical plan was formulated. Preoperatively, patients were informed in detail of the surgical plan and the possibility of conversion to open surgery. This study was approved by the Institutional Review Board of the Affiliated Hospital of Qingdao University.

2.1 Patient selection

The inclusion criteria for the study were relatively clear tumor boundaries observed during preoperative examinations, indicating that complete resection was feasible based on preoperative assessments, absence of preoperative anesthetic or surgical contraindications, no evidence of metastasis, and no prior exposure to preoperative chemoradiotherapy or targeted therapy. The exclusion criteria were severe uncontrolled infection; tumor recurrence; unsuitability for surgery because of severe cardiovascular or cerebrovascular disease, hematological disease, immune system disease, or diabetes; and pregnancy or lactation.

2.2 Perioperative data

The basic data, perioperative information, and pathological reports of all patients who had successfully undergone RRTR, recovered, and been discharged were obtained from the electronic medical records. The operation time, estimated blood loss, blood transfusion volume, and postoperative complications were analyzed.

Data on the tumor location, number of tumors, pathological properties, maximum tumor diameter, and adhered to major blood vessels were obtained from imaging and pathology reports. Tumor adhered to major vessels was defined as tumor contact with the great vessels, including the aorta, inferior vena cava, portal vein, renal artery and vein, splenic artery and vein, and superior mesenteric artery and vein. Postoperative complications were graded according to the Clavien–Dindo classification.

2.3 Surgical technique and follow-up

All procedures were performed with the DVSS by the same team of surgeons who had received standardized training in robotic surgery and were certified to perform the procedure. The surgical position varied according to the patient’s body size, body mass index, and tumor location. The supine position or the contralateral 70° lateral decubitus position was chosen to establish pneumoperitoneum, insert a trocar, and install a robotic arm. After ensuring that no metastasis was present, the tumor was exposed, carefully separated along the tumor capsule, completely removed, and loaded into a specimen bag. The specimen was then removed for routine examination. All patients were followed up at the outpatient clinic 1 month after discharge and every 3 months thereafter.

2.4 Statistical analysis

SPSS 24 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Continuous variables are expressed as mean ± standard deviation and were compared using the t test. Categorical variables are expressed as count ratio and were compared using the chi-square test. In total, 105 patients who underwent RRTR were divided into the DVSS group and the conversion group according to whether they had undergone conversion to open surgery. Correlations between parameters were analyzed. Logistic univariate and multivariate analyses were performed to identify independent risk factors affecting the need for conversion to open surgery. Logistic multivariate analysis was used to verify the results. A P value of <0.05 was considered statistically significant.

3 Results

3.1 Patient characteristics

Among the 105 patients, 87 successfully underwent RRTR (DVSS group) and 18 underwent conversion to open surgery

(conversion group). The 105 patients comprised 40 men and 65 women. The baseline characteristics of the study population are shown in Table 1.

3.2 Pathological outcomes

The pathological results were based on the final histopathology, which revealed 37 malignant tumors and 68 benign tumors. As shown in Figure 1, schwannoma (n = 27) was the most common, followed by paraganglioma (n = 13), cystic lesion (n = 11), pheochromocytoma (n = 11), extragastrointestinal stromal tumor (n = 7), lymphangioma (n = 7), hemangioma (n = 6), ganglioneuroma (n = 5), leiomyosarcoma (n = 5), bronchogenic cyst (n = 4), gangliocytoma (n = 4), neurofibroma (n = 2), ganglioneuroblastoma (n = 1), myelolipoma (n = 1), and aggressive fibromatosis (n = 1).

3.3 Comparison of DVSS group and conversion group: perioperative outcomes

The patients’ perioperative characteristics are shown in Table 2. No intraoperative complications occurred in the DVSS group. One patient received 4 U red blood cells during the operation, and one patient developed a postoperative complication (unilateral atelectasis). One patient in the conversion group had intraoperative blood loss of 2400 mL, received an intraoperative transfusion of 8 U red blood cells and 840 mL plasma, and received a postoperative transfusion of 570 mL plasma. One patient developed a postoperative complication (pancreatic fistula, which healed after nonsurgical treatment).

There were no significant differences in sex (P = 0.253), age (P = 0.449), body mass index (P = 0.738), history of abdominal

TABLE 1 Comparison of DVSS group and conversion group: demographic outcomes.

Parameter	DVSS group	Conversion group	P
	N=87	N=18	
Sex			0.253
Male, n (%)	31 (35.6)	9 (50)	
Female, n (%)	56 (64.4)	9 (50)	
Age, mean± SD	48.64 ± 10.52	51.33 ± 16.40	0.449
BMI, mean± SD	24.43 ± 2.86	24.10 ± 3.46	0.738
History of abdominal surgery, n (%)	20 (23.0)	3 (16.6)	0.555
Adhered to major vessels, n (%)	46 (52.9)	9 (50)	0.824
Tumor number, mean± SD	1.0 ± 0	1.0 ± 0	
Maximum tumor diameter (mm), mean± SD	46.45 ± 16.08	62.56 ± 23.42	0.006

BMI, body mass index; SD, standard deviation.

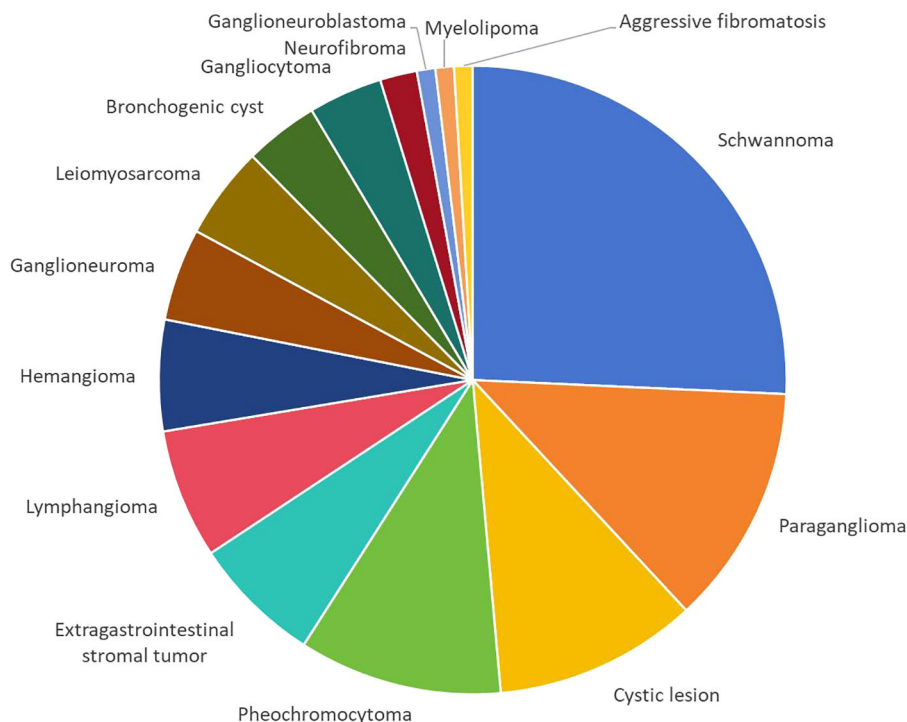


FIGURE 1
Pathological findings of the study population.

surgery ($P = 0.555$), or tumor adhesion to large vessels ($P = 0.824$) between the DVSS group and conversion group. However, there were significant differences in the maximum tumor diameter ($P = 0.006$), pathological property ($P = 0.002$), blood loss ($P = 0.002$), operation time ($P = 0.037$), and postoperative hospital stay ($P = 0.026$). There was no significant difference in the frequency of blood transfusion between the two groups (1.1% vs. 5.6%, $P = 0.281$). The operation time in the DVSS group was significantly shorter than that in the conversion group (163.28 ± 47.76 vs. 212.22 ± 88.39 min, $P = 0.037$). Additionally, the blood loss volume was lower (31.69 ± 32.56 vs. 230.00 ± 556.35 mL, $P = 0.002$) and the postoperative hospital stay was shorter (3.62 ± 1.11 vs. 6.11 ± 6.16 days, $P = 0.026$) in the DVSS group. The hospitalization cost was higher in the conversion group (60441.33 ± 7047.89 vs. 68230.22 ± 10168.35 yuan, $P = 0.046$).

No patient required reoperation or readmission, and the 90-day mortality rate was 0%. The median follow-up time was 19 months (range, 13–36 months) and there was no imaging evidence of tumor recurrence in any patient.

3.4 Regression analysis

To evaluate the influence of various factors on the need for conversion to open surgery, relevant parameters were included in the univariate logistic regression analysis to screen out risk factors and further included in the multivariate logistic regression analysis. The results showed that the independent risk factors for conversion to open surgery were the pathological property of the tumor [odds ratio (OR),

8.646; 95% confidence interval (CI), 2.370–31.544; $P = 0.001$] and maximum tumor diameter (OR, 1.041; 95% CI, 1.015–1.067; $P = 0.002$) (Figure 2, Table 3). These findings indicate that a larger maximum tumor diameter is associated with a higher probability of conversion to open surgery and that the probability of conversion to open surgery is higher for malignant than benign tumors. Figure 3 shows the receiver operating characteristic curve generated according to the maximum tumor diameter, with a determined cut-off value of 64 mm for conversion to open surgery. The classification variable and pathological property were used as covariates, and the decision to convert to open surgery served as the dependent variable for logistic regression analysis. The Hosmer test indicated a good fit for the model ($P = 0.787 > 0.05$). The pathological property of the tumor (OR, 9.805; 95% CI, 2.403–40.003; $P = 0.001$) and a maximum tumor diameter of >64 mm (OR, 14.228; 95% CI, 3.504–57.774; $P < 0.001$) were independent risk factors for conversion to open surgery (Table 4, Figure 4). These findings indicate that RRTR has a higher success rate for retroperitoneal benign tumors with a maximum diameter of ≤ 64 mm.

3.5 Tumor location and intraoperative status of the conversion group

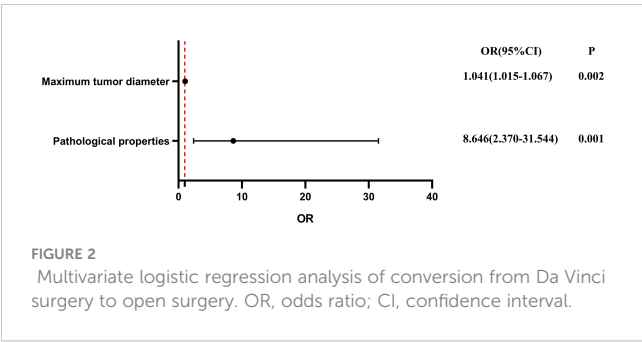
In this study, the total conversion rate was 17.14%. As shown in Table 5, the reasons for conversion included poor vision (7 cases), uncontrolled bleeding (4 cases), difficulties in achieving radical resection with DVSS (5 cases), and the occurrence of hypertensive crisis during surgery (2 cases). In the conversion group, there were 8

TABLE 2 Comparison of DVSS group and conversion group: perioperative outcomes.

Parameter	DVSS group	Conversion group	P
	N=96	N=18	
Operative time (minutes), mean ± SD	163.50 ±62.91	212.22±88.39	0.006
Estimated blood loss (mL), mean± SD	30.28±84.27	230.00±556.35	0.001
Blood transfusion, n (%)	1 (1.0)	1 (5.6)	0.292
Pathological property			
malignant tumor, n (%)	27 (28.1)	12 (66.7)	0.002
ASA score, n (%)			0.373
1	74 (77.1)	14 (77.8)	
2	21 (21.9)	3 (16.7)	
3	1 (1.0)	1 (5.6)	
4	0 (0)	0 (0)	
Tumor location, n (%)			0.7121
Right upper area	26 (27.1)	5 (27.8)	
Left upper area	45 (46.9)	6 (33.3)	
Right lower area	9 (9.4)	3 (16.7)	
Left lower area	14 (14.6)	3 (16.7)	
Pelvic	2 (2.1)	1 (5.6)	
Intraoperative complications, n(%)	0 (0)	1 (5.6)	
Postoperative complications, n(%)			
Clavien I-II	1 (1.04)	0 (0)	
Clavien ≥III	0 (0)	1 (5.56)	
Postoperative hospital stay (days), mean± SD	3.36±2.03	6.11±6.16	0.001
Surgical margins, n (%)			
Positive margin	0 (0)	0 (0)	
Negative margin	96 (100)	18 (100)	
Hospitalization expenses, mean ± SD	59940.43 ±9243.68	68230.22±20168.35	0.006
90-day readmission	0 (0)	0 (0)	
90-day mortality	0 (0)	0 (0)	
Reoperation	0 (0)	0 (0)	

ASA, American Society of Anesthesiologists; SD, standard deviation.

cases of combined organ resection. Given the proximity to the inferior vena cava (IVC), 2 cases of right upper abdominal RPT were challenging to separate, leading to partial resection and repair of the IVC during surgery. One case of right upper abdominal RPT required partial duodenectomy because of its extensive invasion into the duodenum. Another case of left upper abdominal RPT, situated



between the left kidney and pancreas and closely associated with the tail of the pancreatic body and left kidney, necessitated distal pancreatectomy. Additionally, 1 case of left upper abdominal RPT involved the gastric antrum and was managed with partial gastrectomy. One case of RPT in the right lower abdominal mesenteric region required partial small intestine resection and enterostomy. The left lower abdominal RPT in 2 cases was challenging to separate from the left psoas major muscle, resulting in partial resection of this muscle during surgery.

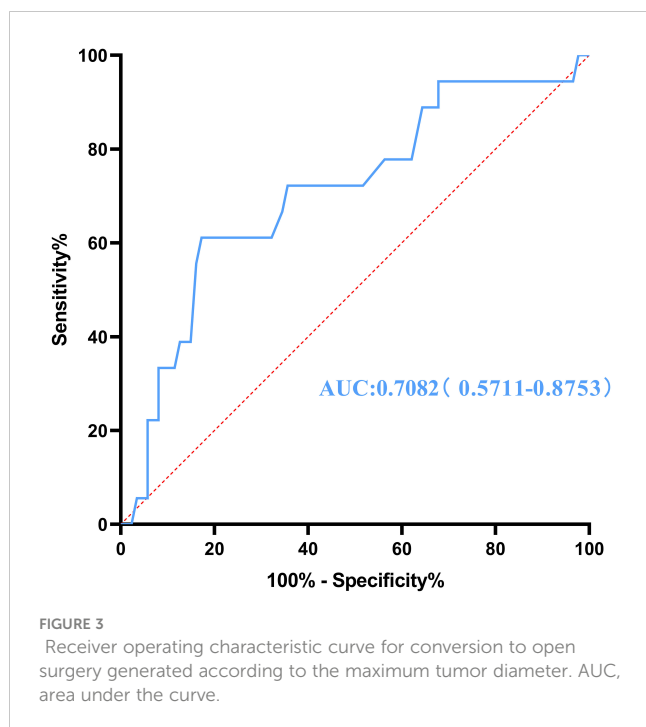
4 Discussion

The DVSS is currently the most widely used robotic system. It has the advantages of magnified and stable three-dimensional stereovision, multidimensional robotic arm movement, elimination of hand tremor, flexible instruments to enhance tactile feedback, no need for reverse operation or intensive training of operators and assistants, and the potential for use in remote surgery. It has the same surgical efficacy as laparoscopic techniques in the treatment of various diseases, and it overcomes

TABLE 3 Univariate and multivariate logistic regression analysis of conversion from Da Vinci robotic surgery to open surgery.

Parameter	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
Sex	2.537 (0.740-8.704)	0.139		
Age	1.017 (0.970-1.065)	0.490		
BMI	0.903 (0.760-1.072)	0.242		
History of abdominal surgery	1.455 (0.334-6.341)	0.617		
Maximum tumor diameter	1.047 (1.018-1.077)	0.001	1.041 (1.015-1.067)	0.002
Adhered to major vessels	1.068 (0.302-3.774)	0.919		
Pathological property	8.382 (2.220-32.882)	0.002	8.646 (2.370-31.544)	0.001

BMI, body mass index; OR, odds ratio; CI, confidence interval.

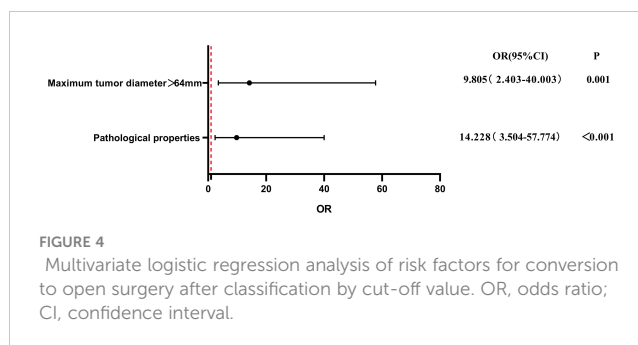


several limitations of laparoscopic surgery such as the lack of three-dimensional depth perception in two-dimensional imaging, high technical difficulty, and a steep learning curve (20–23). Widespread use of the DVSS can also reduce reliance on surgical assistants, thereby reducing the number of assistants and saving medical resources (24). At the same time, competition between hospitals and increased patient expectations have contributed to the popularity of robot-assisted surgery (25). Surgical resection of RPT is often accompanied by a variety of postoperative complications due to the limited working space and rich, fine structures within the retroperitoneal space, which prompts retroperitoneal tumor surgeons to attempt resection with minimal trauma and the shortest possible operation time. It is quite helpful to use robotic techniques that are finer, safer, and more stable than traditional laparoscopic surgery. Such techniques can significantly reduce damage to the surrounding tissues and the occurrence of complications (19, 26). However, no systematic large-sample case study on RRTR has been performed to date. To further explore the feasibility of RRTR and promote safer use of robotic technology, we analyzed the data of 105 patients who underwent RRTR in our hospital and identified risk factors for conversion to open surgery.

TABLE 4 Multivariate logistic regression analysis of risk factors for conversion to open surgery after classification by cutoff value.

Parameter	OR	95% CI		P
		Lower limit	Upper limit	
Pathological property	9.805	2.403	40.003	0.001
Maximum tumor diameter > 64mm	14.228	3.504	57.774	<0.001

OR, odds ratio; CI, confidence interval.



With this study, we aim to provide a preliminary basis for preoperative evaluation of surgical indications and guide clinical practice. To the best of our knowledge, this is the first large-sample study of RRTR.

In total, 105 patients who underwent RRTR were included in this study. Among them, 87 patients successfully underwent RRTR (DVSS group) and 18 patients underwent conversion to open surgery (conversion group). There were no significant differences in sex ($P = 0.253$), age ($P = 0.449$), body mass index ($P = 0.738$), history of abdominal surgery ($P = 0.555$), or tumor adhered to major vessels ($P = 0.824$) between the DVSS group and conversion group, although patients with a history of abdominal surgery inevitably had different degrees of intestinal adhesion. Changes in the normal anatomical structure of the abdomen and tumor adhesion to large abdominal blood vessels will also increase the difficulty of the operation, but these are not key reasons for conversion of robotic to open surgery. Using the DVSS, the main blood vessels around the tumor can be accurately dissected and bleeding can be controlled. This approach is beneficial in terms of the tumor anatomy and may be more suitable for RRTR. This is consistent with the results reported by Liu (12). In our study, the procedure time was shorter in the DVSS than conversion group (163.28 ± 47.76 vs. 212.22 ± 88.39 min, $P = 0.037$). Additionally, the blood loss volume was lower (31.69 ± 84.27 vs. 230.00 ± 556.35 mL, $P = 0.002$) and the postoperative hospital stay was shorter (3.62 ± 1.11 vs. 6.11 ± 6.16 days, $P = 0.026$) in the DVSS group. The dexterity and precision of the DVSS can reduce surgical trauma (27, 28), and minimally invasive surgery can reduce postoperative pain (29, 30); both of these factors promote faster patient recovery after RRTR. Conversion to open surgery requires a change of surgical instruments, which may have contributed to the increased operation time in the conversion group; however, this longer operation time may not be clinically significant.

This study revealed that the pathological property of the tumor (OR, 9.805; 95% CI, 2.403–40.003; $P = 0.001$) and maximum tumor diameter of >64 mm (OR, 14.228; 95% CI, 3.504–57.774; $P < 0.001$) were independent risk factors for conversion to open surgery. Higher success rates are observed in benign retroperitoneal tumors with a maximum diameter of ≤ 64 mm. Therefore, the pathological property and size of the tumor should be determined according to preoperative imaging examination or biopsy, which is helpful for evaluating the difficulty of the operation and provides a preliminary basis for clinical and surgical decision-making. A study by the Transatlantic Australasian Retroperitoneal Sarcoma Working Group showed that schwannomas increase in size at a

TABLE 5 Tumor location and intraoperative status of conversion group.

Tumor location	Specific location	Maximum tumor diameter (mm)	Pathological outcome	Pathological property	Conversion reason	Combined organ resection
Right upper area	Behind the IVC	23	Pheochromocytoma	Malignant tumor	Hypertensive crisis occurred during the operation	Partial resection and repair of the IVC
	Below the horizontal part of the duodenum	36	Extragastrointestinal stromal tumor	Malignant tumor	Radical resection is difficult with DVSS	Partial duodenectomy
	Below the right renal hilum	70	Pheochromocytoma	Malignant tumor	Uncontrolled bleeding	
	Behind the IVC	34	Paraganglioma	Malignant tumor	Poor visualization	
	Right side of the IVC	66	Leiomyosarcoma	Malignant tumor	Radical resection is difficult with DVSS	Partial resection and repair of the IVC
Left upper area	Below the left renal hilum	40	Pheochromocytoma	Malignant tumor	Poor visualization	
	Below the bifurcation of the abdominal aorta	66	Pheochromocytoma	Malignant tumor	Uncontrolled bleeding	
	Between the left kidney and the pancreas	66	Leiomyosarcoma	Malignant tumor	Radical resection is difficult with DVSS	Distal pancreatectomy
	Left side of gastric antrum	36	Extragastrointestinal stromal tumor	Malignant tumor	Radical resection is difficult with DVSS	Partial gastrectomy
	Left side of the IVC	50	Pheochromocytoma	Malignant tumor	Hypertensive crisis occurred during the operation	
	Behind the tail of the pancreas	74	Hemangioma	Benign tumor	Uncontrolled bleeding	
Right lower area	Mesenteric area	89	Aggressive fibromatosis	Malignant tumor	Poor visualization	Small intestinal resection-anastomosis
	Behind of ascending colon	87	Hemangioma	Benign tumor	Uncontrolled bleeding	
	Mesenteric area	90	Lymphangioma	Benign tumor	Poor visualization	
Left lower area	Right side of the psoas major muscle	75	Cystic lesion	Benign tumor	Poor visualization	
	In front of the psoas major muscle	65	Leiomyosarcoma	Malignant tumor	Radical resection is difficult with DVSS	Partial resection of the psoas muscle
	In front of the psoas major muscle	110	Neurilemmoma	Benign tumor	Poor visualization	Partial resection of the psoas muscle
Pelvic	In front of the sacrum	49	Neurilemmoma	Benign tumor	Poor visualization	

rate of 10.5% per year (31). If the tumor size increases by $\geq 20\%$ per year, surgical resection is recommended regardless of the presence or absence of symptoms, and the success rate of R0/R1 resection for benign RPT is as high as 91.6% (32). Therefore, patients with asymptomatic retroperitoneal tumors detected by physical examination should be actively treated with surgery because of the unpredictability of tumor growth and the possible progression to malignancy. The present study indicates that minimally invasive surgery is preferable for benign tumors measuring ≤ 64 mm in diameter, with RRTR being the treatment of choice for these lesions.

In the present study, the total conversion rate was 17.14%, with the rate of conversion to open surgery for malignant tumors standing at 32.43%. Moreover, two-thirds of the tumors treated by conversion to open surgery were malignant. The reasons for conversion to open surgery, consistent with findings from other studies (33), included poor visibility (seven cases), uncontrolled bleeding (four cases), difficulty achieving radical resection with DVSS (five cases), and the occurrence of hypertensive crisis during surgery (two cases). In instances where malignant tumors could not be radically cured through RRTR, our team promptly performed conversion to open surgery. Retroperitoneal malignant tumors, noted for their invasiveness, necessitate a wider resection margin to ensure negative margins, thereby increasing the risk of damage to surrounding tissues and the possibility of incomplete resection. Given these considerations and the implications for patient prognosis, open surgery remains the recommended approach because of its safety (34). The need for combined organ resection often arises under several circumstances: 1. suspected tumor invasion; 2. tumor involvement in the peripheral vascular supply of organs; 3. tumors encasing or adhering to organs, making separation difficult; and 4. iatrogenic injuries necessitating organ resection. In our study, the Da Vinci group, consisting of 96 cases, did not report any intraoperative combined organ resections. However, in the conversion group, which included 18 cases, 8 required intraoperative combined organ resections. Of these, five involved tumors in the upper abdomen, where vital organs such as the liver, kidneys, pancreas, spleen, and duodenum are located alongside major vessels like the inferior vena cava (IVC), abdominal aorta, hepatic hilum, and renal hilum, presenting complex anatomical challenges and surgical difficulties. There were three cases of combined organ resection for tumors in the lower abdomen, which includes structures such as the colon, small intestine, mesentery, psoas major, and related vessels. During surgical dissection in these cases, it is crucial to protect the ureter, mesenteric vessels, and iliac vessels. Additionally, in cases where pheochromocytoma is suspected, preparations to convert to open surgery should be made intraoperatively, as approximately 15% of patients may experience hemodynamic instability or crisis despite adequate preoperative preparation (35).

We recommend conversion to open surgery when complications occur during RRTR, the clinician suspects incomplete tumor resection, or the intraoperative pathology suggests malignancy requiring wide resection. Especially for malignant tumors, the following principles of radical tumor treatment must be followed: complete resection of the tumor and surrounding tissue, minimization of direct physical manipulation of

the tumor (non-contact principle of tumor surgery), achievement of adequate margins, and complete lymph node dissection (36).

Retroperitoneal tumors with a diameter of >64 mm will have a limited surgical field, narrow surgical space, and increased difficulty of surgery; thus, they are more suitable for open surgery. However, tumor size is not an absolute contraindication for minimally invasive surgery (37). For example, a retroperitoneal tumor with a maximum diameter of 131 mm was removed by RRTR in our center. Thus, even if the tumor is large, RRTR can still be considered based on factors such as whether the tumor is easy to expose. Notably, for huge or malignant tumors, the increased operation time may introduce additional risks such as anesthetic complications, pulmonary infections, and postoperative nursing challenges. From doctors' perspective, striving for high rates of minimally invasive procedures is valuable but should not be done at the expense of patient safety.

Although the learning curve of RRTR is unknown, it should not be ignored. Mastering RRTR is indeed a challenging undertaking, and surgeons are advised to proceed with great caution even if they are already very familiar with open and laparoscopic RPT procedures.

The DVSS has the disadvantages of a long training time, long setup time, long operation time, and high cost, all of which limit its application. The high costs associated with using the DVSS are mainly related to the purchase and maintenance of the equipment, the high cost of the instruments, and the long operating time. Although the main limitation of using the DVSS is the additional cost to the patient, this may be offset by the benefits of reduced trauma and bleeding, a shorter hospital stay, and an earlier return to work. With the emergence of increasingly more new robotic systems, such as the avatera[®] robotic system (avateramedical GmbH, Jena, Germany) and the hinotori[™] robotic system (Medicaroid, Kobe, Japan), the cost and limitations of robotic surgery will gradually decrease (38, 39). Its wide applicability is likely to facilitate further substantial progress over the next decade. Reasonable selection of surgical methods can improve resource utilization and reduce costs for patients and the medical system. As a complex surgical method, RRTR must be explored in detail to help clinicians make informed decisions and benefit more patients.

This was a retrospective study and has certain inherent limitations. First, this study involved a single-center retrospective analysis. To the best of our knowledge, this is the first large-sample study of RRTR; nevertheless, the number of cases was limited, increasing the risk of statistical bias. Multicenter prospective studies are needed to confirm the conclusions drawn in this study. Second, retroperitoneal tumors are clinically rare, and the sample size of this study is low; this may reduce the reliability of the final results to some extent. Third, there may have been errors in the data obtained from the medical records, such as the anesthetic details, operation time, and blood loss, and such errors may have affected the statistical results. Fourth, younger patients with a higher socioeconomic status or better health status may be more inclined to choose robot-assisted surgery, which may lead to selection bias. Fifth, patients who received neoadjuvant therapy before surgery were not included in this study; therefore, whether neoadjuvant chemotherapy or radiotherapy affects the DVSS procedure remains unclear.

5 Conclusion

RRTR is safe in experienced centers, and its clinical prognosis is similar to that of open surgery. Patients with retroperitoneal tumors who undergo RRTR have a higher chance of surgical success when the maximum tumor diameter is ≤ 64 mm, the tumor is benign, the tumor has relatively clear boundary, there is no obvious invasion of surrounding tissues and organs, and there is no need for combined organ 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 authors.

Ethics statement

The patients involved in the database have obtained Medical Ethics Committee of The Affiliated Hospital of Qingdao University approval (QYFY WZLL 28271). 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), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

QH: Data curation, Formal analysis, Software, Writing – original draft. LC: Writing – original draft, Writing – review & editing. BZ: Methodology, Resources, Writing – review & editing. XL: Data curation, Writing – original draft. MG: Data curation, Writing – original draft. QL: Data curation, Investigation, Writing – original

draft. GD: Validation, Writing – original draft. MS: Investigation, Project administration, Writing – review & editing. ZW: Methodology, Project administration, Validation, Writing – review & editing. ZG: Data curation, Formal analysis, Writing – review & editing. FQ: Funding acquisition, Resources, Supervision, Writing – review & editing. XW: Methodology, Supervision, Writing – review & editing. LT: Funding acquisition, Resources, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the National Natural Science Foundation of China (No.82073078).

Acknowledgments

We would like to thank our colleagues at the Affiliated Hospital of Qingdao University for their support and assistance in this study.

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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RECEIVED 17 January 2024

ACCEPTED 27 August 2024

PUBLISHED 05 September 2024

CITATION

Gao H, Li W, Zou B, Liu S and Miao C (2024)
Clinical features and outcomes of
retroperitoneal unicentric Castleman disease
resected as sarcomas: insights from a high-
volume sarcoma center.
Front. Surg. 11:1371968.
doi: 10.3389/fsurg.2024.1371968

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Clinical features and outcomes of retroperitoneal unicentric Castleman disease resected as sarcomas: insights from a high-volume sarcoma center

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Background: Castleman disease (CD) is a rare lymphoproliferative disorder that can occur anywhere along the lymphatic pathway. Retroperitoneal unicentric Castleman disease (UCD) is an extremely rare manifestation. This study aims to explore the clinical features and surgical treatment of retroperitoneal UCD.

Methods: We retrospectively reviewed patients who underwent retroperitoneal tumor surgery and were diagnosed with CD based on postoperative pathology before December 31, 2022. Data from these patients were collected and analyzed.

Results: A total of 15 patients were included in the final analysis. All patients underwent radical resection under general anesthesia. Two out of 15 patients (13.3%) experienced serious complications but recovered well. There were no perioperative deaths. The median follow-up time was 78.5 months (range: 18–107.5 months), and no deaths or recurrences occurred during this period.

Conclusions: Surgical treatment for retroperitoneal UCD is safe. Patients with retroperitoneal UCD can achieve long-time survival through complete resection.

KEYWORDS

unicentric Castleman disease, retroperitoneal, surgery, complications, prognosis

1 Introduction

Castleman disease (CD) comprises a group of heterogeneous disorders involving lymphoid tissue and is considered very rare. Based on the number of lymph node stations involved, CD can be classified into unicentric CD (UCD) and multicentric CD (MCD) (1, 2). Histologically, CD can be further divided into hyaline-vascular, plasma cell, and mixed types. However, our understanding of the epidemiology and etiology of CD remains limited (3, 4).

The treatment and prognosis of MCD are complex and significantly differ. Although consensus exists that surgical resection should be considered for UCD patients whenever feasible, managing UCD occurring in the retroperitoneum remains challenging (5–7). The deep location, complex surrounding organs, and blood vessels make surgical treatment of retroperitoneal UCD high-risk. Additionally, distinguishing this disease from primary retroperitoneal sarcomas based on imaging examinations (such as lymphoma, leiomyoma, and paraganglioma) poses difficulties (8–12).

As a high-volume center specializing in retroperitoneal sarcoma treatment, we observed that some patients initially diagnosed with retroperitoneal tumors were

pathologically confirmed to have CD after surgery. Given the rarity of this disease, we conducted a retrospective analysis of retroperitoneal CD patients treated in our center to gain insights into the disease's characteristics, treatment strategies, and prognosis.

2 Materials and methods

2.1 Patient selection

We retrospectively reviewed patients treated at our center from January 1, 2014 to December 31, 2022. Among them, 20 patients had a definitive pathological diagnosis of Castleman disease (CD), confirmed either by needle biopsy or surgical resection. Exclusion criteria included patients with a history of other malignancies, those who underwent needle biopsy only and declined surgery, and one patient diagnosed with multicentric Castleman disease (MCD) after thorough examination. Ultimately, 15 patients with retroperitoneal unicentric Castleman disease (UCD) were included in the final analysis.

2.2 Imaging and diagnostic criteria

All patients underwent contrast-enhanced computed tomography (CT) scans of the neck, chest, abdomen, and pelvis, or ultrasound examinations of the involved regions/organs and superficial lymph nodes. Additional systemic positron emission tomography (PET) scans were performed as needed. UCD was defined as a solitary site of mass without other suspicious lesions.

2.3 Data collection and statistical analysis

We established a comprehensive database from medical records, including patient demographics (gender, age), body mass index (BMI), presenting symptoms, blood test results, radiological lesion size, and pathology subtype. Surgical details, such as the surgical approach, operative time, estimated blood loss, length of postoperative stay, and postoperative complications, were also recorded. Patients were followed up via telephone conversations, with the last follow-up date set at November 1, 2023. The primary endpoint was disease-related death or disease recurrence. Survival analysis was conducted based on the occurrence of endpoint events during follow-up.

Categorical variables were expressed as frequencies and percentages, while continuous variables were presented as means with standard deviation (SD) or medians with ranges or interquartile ranges (IQRs), depending on the distribution normality. Data analyses were performed using SPSS v22 statistical software (Chicago, IL, USA).

TABLE 1 Clinicopathological characteristics of 15 patients with retroperitoneal unicentric Castleman disease.

Item	Number	Proportion (%)
Age (years)		
<40	12	80
≥40	3	20
Gender		
Female	4	26.7
Male	11	73.3
B symptoms	2	13.3
Ascites and/or pleural effusion	1	6.7
Splenomegaly	1	6.7
Pathology		
HV	10	66.7
Mix	5	33.3
PC	0	0
Item		
IQR/mean ± SD		
HGB (g/L)	142 ± 26	
WBC (10 ⁹ /L)	4.93 ± 0.65	
Platelet (10 ⁹ /L)	209 (156, 268)	
Albumin (g/L)	42.97 ± 5.71	
CRP (mg/L)	1.27 (0.86, 2.40)	
eGFR (ml/min)	115.98 ± 16.10	
Size (cm)	6.9 ± 2.3	

HV, hyaline-vascular; PC, plasma cell; HGB, hemoglobin; WBC, white blood cell count; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; IQR, interquartile range.

TABLE 2 Details of surgical treatment for 15 retroperitoneal unicentric Castleman disease patients.

Item	Number	Proportion (%)
Approach		
Open	13	86.7
LAP	2	13.3
Postoperative complications (Grade III/IV)		
Yes	2	13.3
No	13	86.7
Item		
IQR/mean ± SD		
Operation time (min)	186 ± 57	
Estimated blood loss (ml)	625 ± 477	
LOS (day)	11.2 ± 3.6	

LAP, laparoscope; LOS, length of stay after operation.

TABLE 3 Post-operative complications (grade III/IV) and the treatment outcome.

Patient	Complication	Treatment	Outcome
No. 1	Seroperitoneum	Abdominocentesis under local anesthesia	Recovered
No. 2	Hydronephrosis	Ureteral stenting through cystoscope under local anesthesia	Recovered

2.4 Ethics approval and informed consent

This study adhered to the ethical standards outlined by the responsible committee on human experimentation (both institutional and national) and followed the principles of the Declaration of

Helsinki (1964 and subsequent revisions). The Institutional Review Board of Peking University International Hospital approved the study, and informed consent (or an appropriate substitute) was obtained from all patients before their inclusion.

3 Results

3.1 Clinical features

The clinical characteristics of 15 retroperitoneal UCD patients are summarized in Table 1. The ratio of male to female patients was 2.75:1.00. The median age was 31 years (range, 24–58 years), with 80% patients younger than 40 years. The histology subtype was hyaline-vascular for 10 patients (66.7%), mixed type for 5 patients (33.3%), and 0 plasma cell type. B symptoms (fever, night sweats, and weight loss) were present in 2 patients (13.3%). Pleural effusion was found in 1 patient (6.7%). Splenomegaly was found in 1 patient (6.7%). Most lesion sizes were smaller than 10 cm (6.9 ± 2.3 cm) (showed in Table 1). The laboratory tests were generally normal for all patients, including blood routine examination, serum biochemical indicators, C-reactive protein and renal function (showed in Table 1). Only one patient had suspected TAFRO syndrome, with splenomegaly and pleural effusion.

3.2 Surgical details

Patients were admitted to hospital for retroperitoneal lesions suspected of malignant sarcomas. The surgical strategy aimed for radical resection with adjacent tissue dissection, ensuring negative margins.

Thirteen patients underwent traditional open surgery, while two patients received laparoscopic surgery. The average operation time was 186 min (186 ± 57 min). Estimated intraoperation blood loss ranged from 50 ml to 1,500 ml, and median volume was 400 ml (showed in Table 2). Two patients experienced severe postoperative complications and recovered well after treatment (details in Table 3). All patients were discharged with satisfactory recovery. There were no perioperative deaths or readmissions within 30 days. The average length of stay after surgery was 11.2 days (11.2 ± 3.6 days).

3.3 Follow-up results

The median follow-up time for all retroperitoneal UCD patients was 78.5 months (range, 18–107.5 months). Regular follow-up visits were conducted until the last recorded visit. Encouragingly, all patients remained alive during the follow-up period, and no

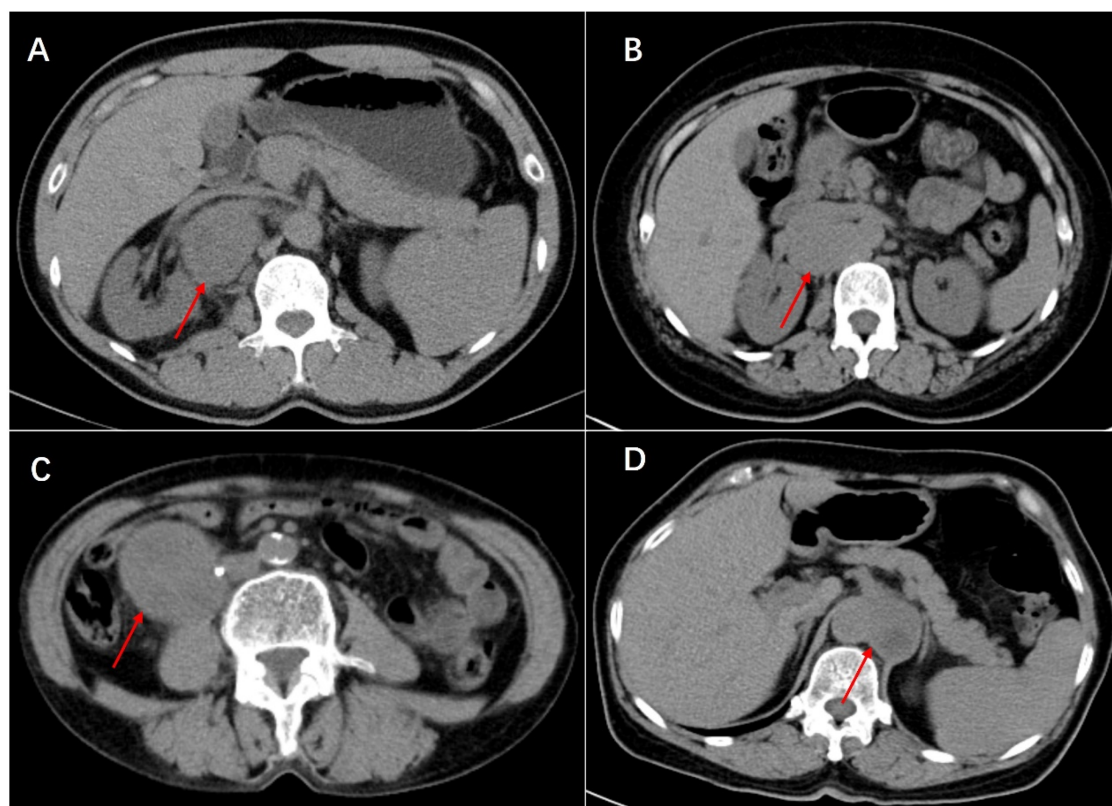


FIGURE 1

Plain scan of Castleman disease (A), lymphoma (B), leiomyosarcoma (C) and paraganglioma (D) in enhanced CT scan. Multiple enlarged small lymph nodes can be seen around lesion of Castleman disease and lymphoma. In the image, the leiomyosarcoma can be seen invading the right ureter, resulting in secondary hydronephrosis (not shown in the image), which was managed with a ureteral stent placement before surgery. In particular, splenomegaly can be seen in Castleman disease. They are all cases that have been definitely diagnosed by postoperative pathology.

evidence of disease recurrence was observed. Given the absence of endpoint events, survival analysis was omitted.

4 Discussion

Retroperitoneal Castleman disease cases are exceedingly rare worldwide. Existing literature primarily consists of case reports, often involving fewer than two cases (8–11). As a specialized center focused on the surgical management of retroperitoneal sarcomas, we present a comprehensive analysis of unicentric Castleman disease occurring in the retroperitoneum based on a cohort of patients.

4.1 Clinical characteristics and diagnostic challenges

Unlike multicentric Castleman disease (MCD), which frequently manifests with symptoms such as polyneuritis, organomegaly, endocrinopathy, and skin changes, most patients with unicentric Castleman disease (UCD) remain asymptomatic except for the localized mass. In our study, only one patient had suspected TAFRO syndrome, which was considered as a

special subtype of multicentric Castleman disease (13). This patient presented with splenomegaly and pleural effusion but did not have fever or abnormal hematological markers. The remaining patients showed no significant symptoms, and objective laboratory tests and examinations revealed no abnormalities. This subtle presentation underscores the challenge of early diagnosis (14). In the case of retroperitoneal UCD, patients often lack symptoms until abdominal ultrasound or computed tomography is performed during routine physical examinations (5, 12).

Histologically, Castleman disease encompasses three main subtypes: hyaline-vascular (accounting for 90%–91% of cases), plasma cell, and mixed type. The hyaline-vascular subtype is associated with UCD, while the plasma-cell subtype is linked to MCD (6). Definitive diagnosis of retroperitoneal UCD hinges on histological analysis of the mass. However, differential diagnosis remains challenging due to the absence of characteristic symptoms. Preoperative fine-needle aspiration is not recommended due to its low specificity and risk of tumoral seeding (15, 16, 22). Furthermore, fine-needle aspiration has limited utility in CD diagnosis, as it relies on cell architecture rather than cell morphology (15). When encountering patients with isolated retroperitoneal masses exhibiting contrast kinetics along the midline adjacent to the inferior vena cava and

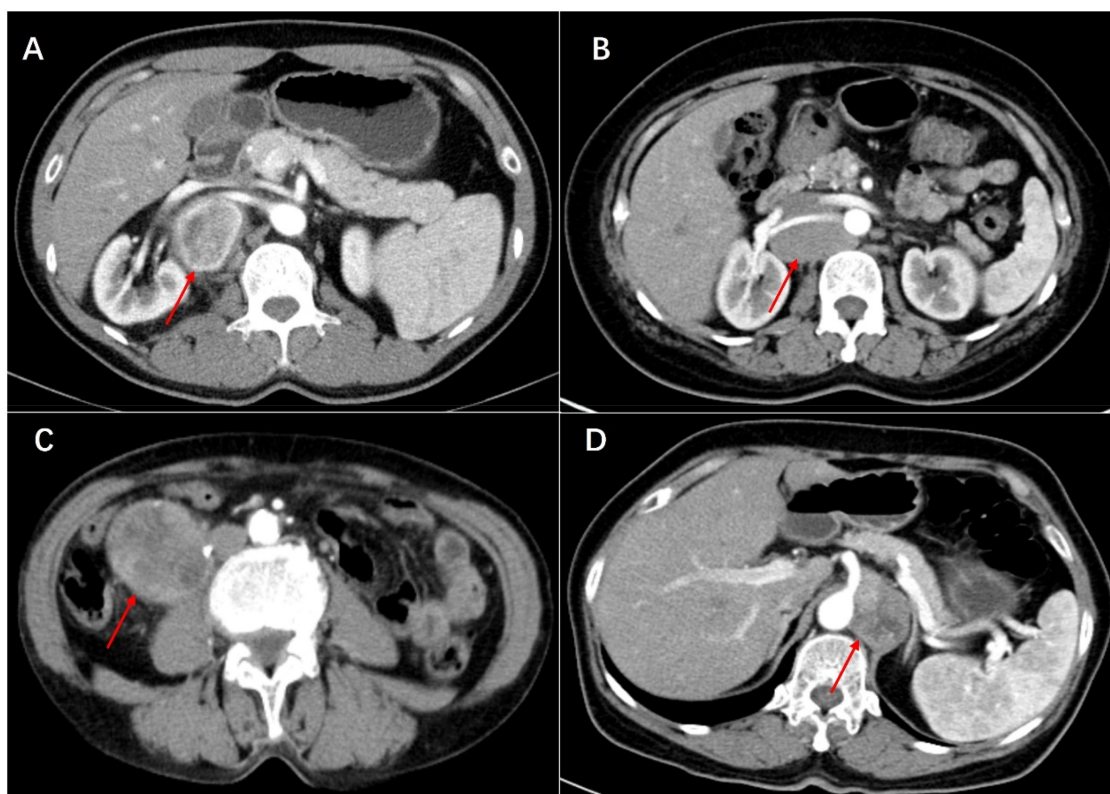


FIGURE 2
Artery phase of castleman disease (A), lymphoma (B), leiomyosarcoma (C) and paraganglioma (D) in enhanced CT scan. The tumors show heterogeneous enhancement in the arterial phase. All tumors are closely related to the blood vessels in the retroperitoneum, even encircling the renal artery or celiac trunk.

abdominal aorta, UCD should be considered, and differential diagnoses should include other highly hypervascular retroperitoneal tumors (e.g., lymphoma, leiomyosarcoma, and paraganglioma, et al.) (see [Figures 1–3](#)) ([17–19](#)). The imageological distinctions of retroperitoneal UCD and other retroperitoneal tumors are listed in [Table 4](#).

4.2 Surgical approach and prognosis

Complete surgical resection remains the gold standard for treating UCD, including retroperitoneal UCD. The prognosis for retroperitoneal UCD is generally favorable. Most patients achieve long-term survival following R0 resection. Systematic reviews

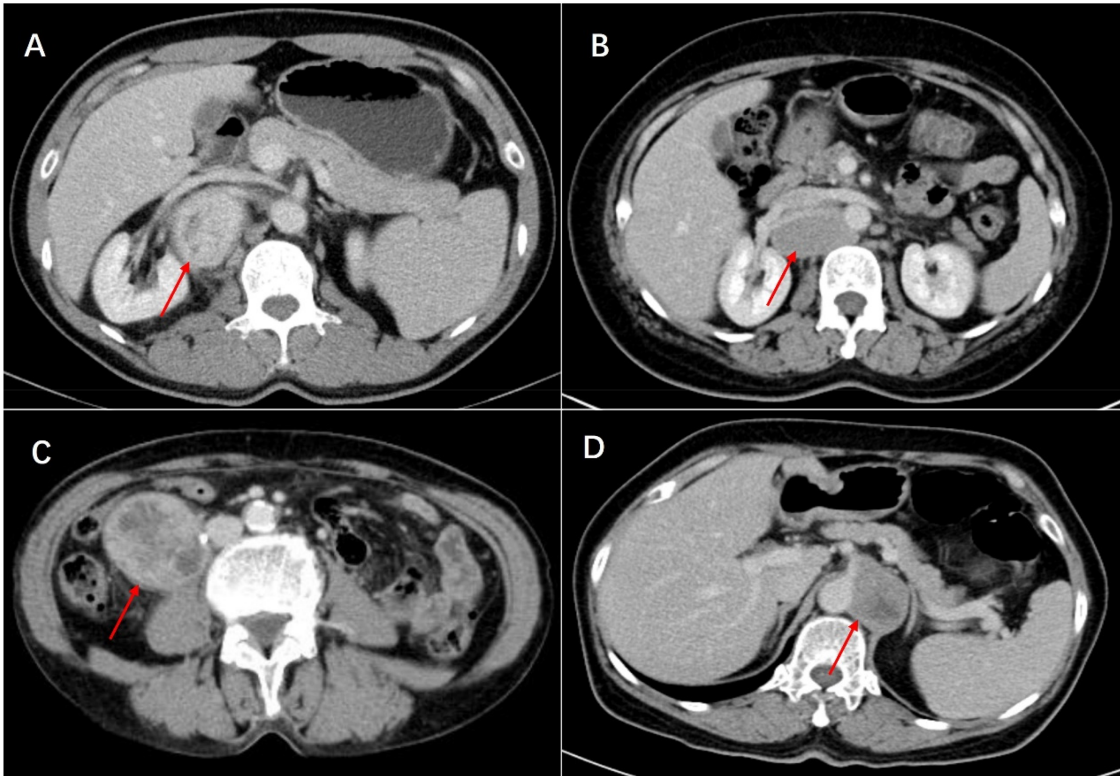


FIGURE 3
Venous phase of castleman disease (A), lymphoma (B), leiomyosarcoma (C) and paraganglioma (D) in enhanced CT scan. This lymphoma is highly similar to Castleman disease and surrounds the renal vessels, leading to a high risk of needle biopsy. Ultimately, surgical resection was performed, and postoperative pathology revealed invasive B-cell lymphoma.

TABLE 4 Imageological distinctions between retroperitoneal UCD and other tumors.

Parameter	rUCD	Lymphoma	Leiomyosarcoma	Paraganglioma
CT	• Uniform enhancement during the arterial phase and sustained enhancement during the venous phase • Multiple small lymph nodes around the lesion	• Multiple enlarged lymph nodes, which may fuse together, forming a mass-like appearance. • Mild to moderate enhancement after contrast administration. • Fused lymph nodes can encase the mesenteric vessels, abdominal aorta, and inferior vena cava, namely distinctive “vascular encasement sign”	• Solitary soft tissue mass • Moderate to high enhancement during the arterial phase, consistent during the venous phase • Typically, no evidence of lymph node metastasis	• Uneven density • Often with hemorrhage, necrosis, calcification and cystic changes • Heterogeneous enhancement in artery phase
PET	• Significant variability in FDG uptake, usually lower than lymphoma • Used to evaluate the number and distribution of lesions in MCD	• Increased uptake of FDG, indicating high metabolic activity • Used to evaluate the number and distribution of lesions	• Increased uptake of FDG • Used to evaluate distant metastasis	• Increased uptake of FDG • Used to evaluate distant metastasis

rUCD, retroperitoneal unicentric Castleman disease; FDG, fluorodeoxyglucose; MCD, multicentric Castleman disease; CT, computed tomography; PET, positron emission tomography.

indicate that complete resection alone, without additional treatment, yields excellent outcomes, with 5-year disease-free survival (DFS) rates exceeding 80% and overall survival (OS) rates surpassing 90% (5, 6).

In our study, all 15 patients with retroperitoneal UCD underwent complete resection of the primary lesion as the initial treatment, without additional therapies. Remarkably, all patients remained alive during the follow-up period, and no evidence of disease recurrence was observed. Although our patient cohort was small, our surgical strategy—favoring extended resection margins to ensure radical cure—may have contributed to these positive outcomes. This finding underscores the importance of radical resection with negative margins in patients suspected of having UCD but lacking definitive diagnosis. Longer follow-up and larger patient cohorts are needed to validate the impact of extended resection on retroperitoneal UCD. Currently, no standardized follow-up protocol exists for resected UCD. Based on existing literature, we recommend CT scans every 6 months during the first 3 years postoperatively, followed by annual scans thereafter.

4.3 Surgical challenges and strategies

Our experience highlights the significant challenge posed by intraoperative bleeding during resection of retroperitoneal UCD. The adjacent and surrounding blood vessels, primarily branches of the abdominal aorta and inferior vena cava, contribute to this complexity. To mitigate operative risks and ensure safety, comprehensive radiographic examinations play a crucial role. These examinations should include:

- Color Ultrasonography: Provides real-time visualization of blood flow patterns and helps assess vascular relationships.
- Contrast-Enhanced Computed Tomography (CT): Offers detailed anatomical information, aiding in precise evaluation of lesion-to-vessel proximity.
- Angiography (if necessary): Allows direct visualization of vascular structures and assists in surgical planning.

By meticulously assessing the relationship between lesions and adjacent vessels, surgeons can navigate the retroperitoneal space safely. Notably, laparoscopic surgery emerged as a viable option for selected patients. In our cohort, two patients underwent laparoscopic procedures without perioperative complications, and long-term follow-up revealed no recurrences.

4.4 Study limitations

First, as a retrospective study, inherent biases in patient selection and data collection may exist. Second, Patients were often screened by other hospitals and departments before seeking our specialized team's expertise, potentially introducing additional selection bias. Besides, the rarity of retroperitoneal UCD limited the number of patients available for final analysis. Due to the small sample size, we could not directly compare different treatment strategies (e.g., incomplete resection vs. radiotherapy). As patients were initially managed as

malignant sarcomas, certain Castleman disease-related details (e.g., human herpes virus 8 status, serum immunoglobulin G, interleukin-6 levels) were lacking (20, 21).

5 Conclusion

Our findings underscore that complete resection remains the gold standard for treating retroperitoneal UCD. Achieving excellent survival outcomes with minimal surgery-related morbidity validates this approach. Furthermore, experienced surgeons can safely explore laparoscopic surgery in carefully selected patients. Future studies should validate our results and deepen our understanding of this rare disease.

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 Institutional Review Board of Peking University International 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 individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

HG: Data curation, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing. WL: Data curation, Software, Writing – review & editing. BZ: Data curation, Writing – review & editing. SL: Data curation, Writing – review & editing. CM: Funding acquisition, Supervision, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Peking University International Hospital Research Fund (No. YN2021ZD04).

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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OPEN ACCESS

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RECEIVED 14 May 2024

ACCEPTED 09 September 2024

PUBLISHED 07 October 2024

CITATION

Garcia-Ortega DY (2024) Comprehensive
treatment strategy for improving surgical
resection rate of retroperitoneal sarcomas: a
histology-specific approach narrative review.
Front. Oncol. 14:1432900.
doi: 10.3389/fonc.2024.1432900

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Comprehensive treatment strategy for improving surgical resection rate of retroperitoneal sarcomas: a histology-specific approach narrative review

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Retroperitoneal sarcoma (RPS) represents a rare and heterogeneous group of malignancies, posing significant challenges in evaluation and management. Surgery, the cornerstone of RPS treatment, critically depends on complete resection for a favorable prognosis. The extent of resection is a crucial determinant of local control and survival. This review delves into the evolution of multidisciplinary management of localized RPS, highlighting the imperative to adapt surgical strategies to tumor histology, location, and patient functional status. We explore the principles of compartmental surgery—an extended first-line approach that involves resecting adjacent viscera for wide negative margins—and its effectiveness across different histological subtypes of RPS and more limited resections for other types. Particular emphasis is placed on the heterogeneity of the disease, as various histological subtypes exhibit distinct biological behaviors. This necessitates a shift away from a one-size-fits-all treatment approach. The review analyzes the role of different surgical strategies, focusing on histological type and location. Additionally, the potential benefits of (neo)adjuvant treatments, such as radiotherapy and chemotherapy, are examined, recognizing their specific histological indications and limitations. This comprehensive review consolidates recent data on surgical strategies and complementary therapies, advocating for a personalized approach tailored to histology. As understanding of the molecular and genetic underpinnings of RPS continues to evolve, so will strategies for its effective management, underscoring the need for global collaboration among specialists in this field to enhance our collective knowledge and treatment methodologies.

KEYWORDS

retroperitoneal sarcoma, extended resection, histology-specific approach, reference center, multidisciplinary tumor board (MDTB)

Introduction

Retroperitoneal sarcomas (RPS) are rare malignant neoplasms, constituting less than 1% of all cancers in adults but accounting for approximately 15% of soft tissue sarcomas (STS) (1–4). The incidence of RPS is estimated at 2.7 cases per million people per year, with an equal prevalence among men and women, typically diagnosed between the fifth and sixth decades of life (5). These tumors arise from the retroperitoneal space, an area without defined anatomical boundaries and surrounded by vital structures, which significantly complicates surgical interventions and increases the risk of recurrence even in low-grade tumors (6, 7). RPS are characterized by their histological heterogeneity, with predominant types such as liposarcoma and leiomyosarcoma, representing more than 80% of cases. This variability directly impacts the biological behavior of the tumor and the applicable therapeutic strategies since there are no “low-risk histologies,” even tumors classified as low-grade have high rates of local failure that compromise long-term survival (7, 8). Surgery is the cornerstone of treatment for RPS, being the only curative modality in localized disease. Complete resection (R0/1) has been consistently identified in retrospective historical series as the most important prognostic factor, with recent advances in surgical techniques increasing the R0/1 resection rates to a range of 70–95%. The implementation of compartmental surgery, inspired by principles used for STS of the extremities, has allowed for minimizing incomplete resections (R2) and is currently the recommended approach by leading expert groups. This approach involves en-bloc resection of the tumor and adjacent organs, improving oncological outcomes and reducing recurrence rates; however, it is not a strategy applicable to all sarcomas (8–12).

Despite these advances, the management of RPS continues to face challenges due to the anatomical complexity of the retroperitoneum and the diversity of histological subtypes. This requires a personalized approach based on the specific characteristics of the tumor and the patient. This review discusses these surgical and oncological principles, evaluates existing literature, and outlines strategies to optimize the treatment and survival of patients with RPS.

Historical perspective

The history of surgical treatment for retroperitoneal sarcomas has evolved remarkably since 1761 when Italian anatomist Giovanni Battista Morgagni first described a lipomatous tumor in his treatise “*De Sedibus et causis morborum per anatomen indagatis*.” Later, in 1829, Lobstein provided a more comprehensive description of these tumors, using the term “sarcoma” for the first time. During the 19th and early 20th centuries, cases were recorded sporadically, often as autopsy findings or during surgical procedures, primarily focusing on pathological descriptions rather than treatment.

Throughout the first half of the 20th century, surgery began to gain recognition as the standard treatment, although techniques and knowledge of the disease were still developing. At the turn of

the century, researchers such as J. Dutton Steele and Howard Williams expanded the literature, though with limited cases and infrequent complete resections. It was not until 1933 that, thanks to a series of 46 patients by Judd and Larson at the Mayo Clinic, surgery was established as the primary treatment. However, complete removal was achieved in only a third of these cases (13).

During the 1950s and 1960s, awareness of retroperitoneal sarcomas (RPS) increased, with more extensive case series reported by prominent institutions such as Columbia Presbyterian Hospital and Memorial Hospital in New York. However, the frequency of complete resections remained low, and operative mortality, although reduced, continued to be a challenge. In 1973, a study at Memorial Hospital in New York revealed that only 32.4% of patients with retroperitoneal sarcoma (RPS) underwent complete resection, while 44.1% had partial resection, and 23.5% received only biopsy and radiotherapy. By 1984, another study reported that 38% of RPS patients at the Medical College of Virginia underwent complete resection, with multivisceral resection being necessary in 68% of cases. In 1998, an analysis of 500 patients demonstrated that complete resection significantly reduced the risk of local recurrence compared to incomplete resection, with a postoperative mortality rate of 4%. Finally, in the 2000s, European studies confirmed that extended resection improved recurrence-free survival compared to standard resection, with 5-year recurrence rates of 28% versus 48% (14, 15). Current discussion on resection in retroperitoneal sarcomas focuses on the appropriate extent. Although R0 and R0/1 resections show similar oncologic outcomes, there is evidence suggesting that R0 resection might be superior in some instances; Paik et al (16), in a systematic review, found that R0 margins reduce the recurrence rate (45.5%–52.3% for R0 vs. 66.7%–91.7% for R1). However, the relationship between tumor biology and the extent of resection remains uncertain due to limited data.

In the 1980s and 1990s, advances in surgical techniques and an accumulation of clinical experience led to significant improvements in complete resection rates. The Memorial Sloan Kettering Cancer Center (MSKCC) reported an increase in complete resection rates from 21% to 56% and a notable reduction in operative mortality from 11% to 2%. However, disease recurrence remained high, demonstrating the continued difficulty of managing these tumors even after successful resection (17).

Towards the end of the 20th century, an analysis of 500 patients by Lewis et al. in 1998 at MSKCC underscored the critical importance of complete resection in optimizing outcomes. It highlighted the increasing difficulty of achieving complete resections with each recurrence. This study also emphasized the need to evaluate non-surgical therapies and to develop a more systematic and cooperative approach to studying these rare and complex tumors (6).

Today, the Transatlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG), established in 2013, brings together specialists from various disciplines. Starting with eight institutions, the group has expanded its reach to 128 international institutions, fostering global collaboration and translational research in managing retroperitoneal sarcomas. The group has published consensus guidelines and promotes the creation of prospective

clinical trials, highlighting a worldwide effort to improve outcomes in this field (18, 19).

Initial evaluation of primary disease

Patients diagnosed with retroperitoneal sarcomas (RPS) may either exhibit nonspecific symptoms or remain entirely asymptomatic. Tumors are frequently detected incidentally during imaging studies conducted for unrelated reasons. High-quality contrast-enhanced computed tomography (CT) of the abdomen and pelvis is essential for initial evaluation, providing crucial details for surgical planning. In some cases, magnetic resonance imaging (MRI) may offer additional relevant information for delineating the involvement of soft tissues (20–22).

Image-guided core needle biopsy, targeting solid, non-necrotic areas that enhance with contrast using a coaxial technique and an 18-gauge needle to maximize the tissue available for pathological analysis. This biopsy is crucial for ruling out benign pathologies and confirming the histological type of RPS, a necessary step to plan neoadjuvant therapies and other specific management of the tumor histology (22). Although needle biopsy can provide information on the tumor grade, the accuracy of this assessment may be limited, and a detailed pathological evaluation of the resection specimen is recommended. Surgical incisional biopsy is discouraged due to the risk of altering tissue planes for subsequent resection and potential tumor dissemination, as evidenced by a detailed systematic review that examined studies from 1990 to June 2022. This study focused on assessing the incidence of local recurrence and overall survival, comparing patients who underwent preoperative biopsy with those who did not (23). Out of 3192 studies examined, five retrospective cohort studies from the United Kingdom, the Netherlands, and Japan were selected, providing data on biopsy tract seeding. Two of these studies, with a combined size of 572 patients (24, 25), reported no recurrence along the biopsy tract. However, the third study, conducted by Van Houdt et al. (26), which included 498 patients undergoing RPS resection at the Royal Marsden NHS Foundation Trust and The Netherlands Cancer Institute, found a biopsy tract recurrence rate of 2% (5 of 255 patients who underwent preoperative biopsy). These recurrence cases included three grade 2 leiomyosarcomas and two grade 3 liposarcomas. Notably, all recurrences occurred in patients whose biopsies were performed using a transabdominal approach and not a coaxial technique, suggesting a higher risk associated with non-coaxial methods ($p = 0.02$).

These studies found no significant differences in local recurrence or overall survival between patients who underwent biopsy and those who did not. This finding supports the safety and utility of preoperative biopsy in RPS for appropriate clinical decision-making without negatively impacting long-term outcomes. However, it is crucial to note that the Van Houdt et al. (26) study had a relatively short median follow-up of 38 months, and biopsy tract recurrences occurred between 6 months and seven years after biopsy, indicating the need for prolonged follow-up for a more accurate assessment of long-term risks. These findings suggest that while preoperative biopsy is a safe tool for managing RPS, the

technique can significantly influence the risk of complications, particularly biopsy tract seeding, and methods such as the coaxial technique should be considered to minimize this risk.

Preoperative management of retroperitoneal sarcomas

In the preoperative phase of retroperitoneal sarcoma treatment, it is critical to perform a detailed evaluation in three key areas: the extent of the disease, the patient's functional performance (including their nutritional status), and the healthcare responsible for the treatment. Staging is crucial for determining the tumor's extent and planning the surgery effectively. Chest, abdominal, and pelvic computed tomography (CT) is essential for identifying possible visceral metastases, especially in the liver and lungs, which are the most common sites of dissemination for these tumors. Further cross-sectional imaging is also suggested for certain histologic types of retroperitoneal sarcoma that have a propensity to metastasize to the liver, such as leiomyosarcoma. Although positron emission tomography (PET) is not standard for staging these sarcomas, it is being evaluated as a potential tool to provide additional prognostic information about the primary tumor. New technologies such as radiomics and augmented reality are currently under investigation, promising to transform the evaluation of these patients in the future (22, 27–30).

The involvement of a multidisciplinary team with experience and access to adequate facilities is essential for ensuring optimal patient management. Patients with RPS should be assessed and treated by surgical oncologists with specific expertise in sarcomas. These specialists, often part of multidisciplinary teams that include medical oncologists, radiation oncologists, pathologists, and radiologists, significantly enhance patient outcomes. It has been suggested that a minimum volume of 10 to 13 RPS cases annually is necessary to maintain competency in managing these complex and rare tumors (22, 27, 28).

RPS surgery, typically performed after confirming the absence of metastatic disease, presents unique challenges due to the often large size of these tumors and their proximity to critical organs and structures. Therefore, preoperative planning is an integral component of the surgical process, with preparations ranging from consultations with other surgical specialists to coordination with anesthesiology to anticipate intraoperative needs such as transfusions and venous access (8, 12, 20, 22, 24, 31, 32).

Particular attention must be given to the patient's comorbidities. Comprehensive medical evaluations are necessary to determine the viability of extensive procedures, such as ipsilateral nephrectomy in patients with compromised renal function or interventions to enhance cardiopulmonary function in those with significant preexisting conditions. Moreover, careful nutritional evaluation and optimizing the patient's protein-caloric status are essential to improve postsurgical outcomes. This meticulous and personalized preparation not only facilitates the execution of the surgery but also maximizes the chances of a successful outcome, minimizing complications and enhancing the patient's quality of life after the intervention (33–35).

Surgical approach

In the surgical management of retroperitoneal sarcomas, selecting the appropriate surgical technique is essential to ensure optimal access to both the neoplasm and adjacent critical anatomical structures. Generally, an extensive midline laparotomy is preferred because it effectively exposes the tumor and critical vascular structures, including the aorta and inferior vena cava (IVC). However, depending on the tumor's location and size, adjustments to the surgical approach may be necessary. This could include considering lateral or thoracoabdominal incisions to accommodate the surgeon's preferences and the unique aspects of the case (8, 13, 20, 22).

The main objective of surgery for retroperitoneal sarcomas is the en-bloc resection of the tumor along with affected organs, aiming for a complete resection. Resections are classified as R0, with total excision and margins free of disease at a microscopic level; R1, where the margins are microscopically positive; and R2, where the resection is incomplete. Studies indicate that a partial or R2 resection, which often leads to tumor rupture or leaves visible tumor residue, significantly worsens oncological outcomes and increases mortality compared to complete resections; achieving R0 margins is ideal, though it presents a significant challenge in practice, especially considering the size of the tumors and the anatomical complexity of the retroperitoneal space. The complete evaluation of margins in large tumors is challenging, and while R0 resections are associated with better oncological outcomes, this advantage may be influenced by the presence of smaller tumors (7, 22, 27, 36).

In an aim of R0 resection, preoperative planning should include anticipation of tumor involvement in organs and structures, which may require simultaneous resections. Recent studies from sarcoma centers show that in 58-87% of primary PRS cases, surgeons perform resections of one or more organs, commonly including ipsilateral nephrectomy and partial colectomy. Resections of major vascular structures, such as the IVC, although less common, are feasible with appropriate planning and support (7, 37, 38).

For tumors on the left side, surgeons may need to perform a distal pancreatectomy and splenectomy. Conversely, tumors on the right may require a pancreaticoduodenectomy, though this procedure is rare. Tumor laterality and specific characteristics dictate these surgical decisions, underscoring the need for a personalized and meticulously planned approach in RPS surgery. For right upper retroperitoneal tumors that displace the liver, we recommend a thoracoabdominal incision. This technique allows exhaustive control from the inferior vena cava to the right atrium. During surgery, access can be improved by placing a rolled towel under the tumor side of the patient or by positioning the patient partially on their side, with the arm on the same side elevated on support (39, 40).

The first surgical step involves the release of the root of the mesentery, followed by separation of the omentum from the colon and division of the transverse colon, which facilitates access to the major vessels. It is essential to initiate tumor release from the center outward to adequately prepare vascular structures and minimize tension, thereby reducing the risk of vascular tears. It is most

effective to begin vascular dissection from the iliac vessels to the proximity of the aorta or vena cava using a subadventitial technique. The adventitial layer is preserved on the tumor side as an anatomical barrier. The primary vascular branches are ligated near the edge of the tumor, including the gonadal and renal vessels. If the renal artery cannot be divided before the renal vein due to the size of the tumor, clamping can be used to stop the flow temporarily. At the same time, access is improved, dividing and then ligating the renal vein. An endoscopic stapling device with vascular clips may be helpful when exposure is limited.

Regarding nerve management, the femoral nerve is located just above the inguinal ligament, accessing through the fascia of the psoas muscle. If the psoas is compromised, it is resected while preserving the femoral nerve. Other sensory nerves, such as the genitofemoral, ilioinguinal, iliohypogastric, and lateral femoral cutaneous nerves, are preserved to the extent possible to reduce the risk of postoperative dysesthesias. Finally, the tumor is removed en bloc along with adjacent structures such as the kidney, the colon on the same side and its mesocolon, and the psoas aponeurosis or the entire muscle. The inner part of the lateral abdominal wall and the peritoneum of the diaphragm are also preserved on the side of the tumor and are resected if infiltrated. After removing the tumor, the diaphragm is reconstructed, and the greater omentum can be used to fill the surgical bed, avoiding displacement of the abdominal viscera (39, 41).

Compartmental resection

The surgical approach should be tailored to each case's specific, considering factors such as tumor boundaries, recurrence patterns, and the risk of systemic failure. Compartmental resection is the standardized surgical technique for managing retroperitoneal sarcomas; this is particularly applicable in well-differentiated liposarcoma (WDLPS), dedifferentiated grade 2 (DDLPS G2), and grade 3 (DDLPS G3) surgical methods may vary significantly for other histotypes, such as leiomyosarcoma, solitary fibrous tumor, or malignant peripheral nerve sheath tumor (MPNST).

The compartmental resection technique involves the removal of the visible tumor and potentially compromised nearby organs, structures, and surfaces, such as the psoas fascia, to ensure circumferential soft tissue-free margins (8, 20, 22, 39–41). While this method has faced controversy and has not been universally adopted, studies have shown its effectiveness (42). For instance, Gronchi et al. reported that compartmentectomy reduces recurrences threefold at three years (10% vs. 50%) (43). Similarly, Bonvalot et al. noted a reduction in local recurrence from 48% to 28% at five years (44). Recent studies also indicated that compartmentectomy can decrease recurrence rates from 42.3% to 20% ($p = 0.007$) (12).

This procedure is particularly suitable for treating liposarcoma, thoroughly considering the patient's clinical status, including comorbidities and expected oncological outcomes, before determining the extent of resection required. If the organs do not show clear evidence of tumor involvement, the decision to resect

them depends on whether they can be preserved without significant risks of complications. For example, the rate of Acute Kidney Injury (AKI) post-nephrectomy is 14.8% versus 4.3% without nephrectomy, with a notable reduction in the first postoperative days and only 0.3% of patients requiring permanent dialysis (45). The complication rate of post-colectomy intestinal anastomotic/fistula is 6% (46).

Recent studies on the frequency of microscopic infiltration in resected organs have informed surgical decisions, finding that histological invasion is frequent and varies by organ and histological type (absent (HOI-0), perivisceral (HOI-1), initial (HOI-2), advanced (HOI-3)). It is also associated with a higher risk of recurrence and death, as demonstrated by the study by Improtta et al., where patients with HOI-3 had significantly shorter overall survival (HOI-3 vs HOI-0/HOI-1 HR 2.92; $p = 0.012$) and disease-free survival (HOI-3 vs HOI-0/HOI-1 HR 2.23; $p = 0.045$) (47). Surgical decisions must balance potential morbidity against essential oncologic principles, such as maintaining tumor integrity to ensure complete en-bloc resection.

Adopting a histology-based surgical approach has gained recognition for soft tissue sarcoma surgery in primary disease, particularly when anticipating the tumor's origin and local extent based on its histological type. For instance, a leiomyosarcoma originating in the inferior vena cava (IVC) will require a surgical strategy focused on this structure. Regarding liposarcomas, the necessity of performing an extended resection of adjacent "at risk" fat continues to be debated, especially distinguishing between well-differentiated liposarcomas, which are less invasive, and those with dedifferentiated components, which are more aggressive. The surgical strategy for treating retroperitoneal sarcoma (RPS) must be tailored individually, considering the histology of the tumor and its specific risk of recurrence, which varies significantly among different types. For instance, leiomyosarcoma often does not require extensive resection due to its tendency to metastasize distally rather than recur locally.

In contrast, tumors such as solitary fibrous tumors, which have a low risk of recurrence, may be managed with less invasive surgical approaches. The surgical approach for RPS focuses on removing the visible tumor and includes a detailed assessment of the risk for multifocal disease and potential future recurrences. This comprehensive evaluation helps define the necessary extent of resection based on each tumor's unique characteristics and behavior (20, 22, 27, 40).

A study published in EJSO by Willis (48) demonstrates that patients with retroperitoneal sarcoma (RPS) report a relatively high quality of life, even after undergoing multiple and multivisceral resections. The study by Zhuang et al. showed that while aggressive surgical approaches may impair quality of life within the first six months post-operation, long-term quality of life is similar to that of patients who underwent simple tumor resection. Additionally, the study found that as the postoperative interval increased, all indicators improved in patients who underwent multivisceral resection, whereas no significant improvement was observed in patients without MVR (49).

Sarcomas from the right side

Surgical treatment of retroperitoneal sarcoma located on the right side requires special considerations, particularly regarding the possible involvement of the inferior vena cava (IVC), pancreas, and duodenum. The main goal of this intervention is to achieve adequate exposure to the tumor. This is accomplished by performing meticulous dissection through the connective tissue and carefully separating the tumor from these vital organs. Extensive resections are avoided unless there is clear macroscopic involvement. Additionally, it may be necessary to mobilize the right liver by dividing the coronary and falciform ligaments and rotating the liver to the left; subsequent steps include performing a coloepiploic separation and dividing the transverse colon to the right of the middle colic artery and the distal ileum. The right colic vessels are isolated proximally from the superior mesenteric vessels, and the mesocolon is separated from the main vessels. A Kocher maneuver is performed to free the duodenum and head of the pancreas, facilitating complete IVC access. This process is especially critical for right-sided tumors, as the duodenum and head of the pancreas often adhere closely to the tumor surface, sometimes leaving only a thin layer over the tumor, if any margin at all (39, 41).

Preservation of the duodenum and pancreas is prioritized and occurs in only 1.4% of cases. Given that pancreaticoduodenectomy has not shown significant improvements in disease-free survival and is associated with a high rate of complications—including a third of cases developing pancreatic leaks and up to a mortality rate of 3.4%—it is generally avoided. However, if duodenal perforation occurs during dissection at the pancreaticoduodenal junction due to wall thinning—a result of compression or tumor invasion—partial resection may be considered. In exceptional cases of severe infiltration, a pancreaticoduodenectomy could be justified, and in these cases, imaging can demonstrate up to 80–85% invasion microscopically (50). In cases where resections require vascular involvement, morbidity increases significantly (54% vs 25%; $p < 0.0001$). This is also associated with longer surgical times (480 minutes vs 330 minutes; $p = 0.001$), a higher risk of relapse (local: 45% vs 24%, $p = 0.05$; distant: 20% vs 0%, $p = 0.04$), and an increased risk of death (60% vs 81%; $p = 0.05$) (51).

Sarcomas from the left side

In the management of retroperitoneal sarcomas located on the left side, the process begins with coloepiploic separation. Subsequently, the transverse colon is divided on the left side of the middle colic artery. The inferior mesenteric vein is ligated along the lower edge of the pancreas. When the tumor is confined to the left superior retroperitoneum, the left superior colic artery is ligated, and the descending colon is divided at its junction with the sigmoid colon. This technique possibly preserves the inferior mesenteric artery. The inferior mesenteric artery is ligated for tumors primarily located in the lower part of the left retroperitoneum, and the sigmoid colon is divided at the rectosigmoid junction. The left mesocolon is then separated from

the main vessels and preserved as an anterior resection margin. The duodenojejunal junction may be displaced but not constantly invaded; it may detach from the tumor surface, which usually remains covered by the root or medial edge of the left mesocolon. If the tumor has invaded or is tightly adhered, the third and fourth portions of the duodenum and the proximal jejunum just distal to the ligament of Treitz are divided. This leaves the duodenojejunal junction attached to the surface of the tumor. During reconstruction, a side-to-side anastomosis is performed between the second portion of the duodenum and the remaining proximal jejunum. For tumors confined to the left lower retroperitoneum (i.e., below the transverse mesocolon), the distal pancreas and spleen are separated from the top of the tumor. The tumor remains covered by the transverse mesocolon and the lateral wall and is rotated medially to achieve good exposure. For tumors extending into the left upper retroperitoneum, the distal pancreas is divided. The splenic artery and vein are ligated, and the aorta is dissected up to the diaphragmatic hiatus. The spleen is mobilized en bloc with the upper portion of the tumor. A segment of the posterior aspect of the diaphragm may be resected to facilitate safer tumor mobilization. In such cases, the distal pancreas and spleen form part of the anterior margin of the specimen, and up to 42.4% demonstrate microscopic invasion in the absence of frank macroscopic invasion. It is important to note that grade B pancreatic fistulas have been documented in 18.2% of cases. These structures, including the diaphragm, can serve as the upper margin of the specimen (39–41, 52).

Management of pelvic retroperitoneal sarcomas

Management of pelvic retroperitoneal sarcomas, which constitute approximately 18% of all retroperitoneal sarcomas, requires meticulous evaluation of tumor characteristics and the complex network of anatomical structures of the pelvis. Comprehensive staging, using abdominopelvic computed tomography (CT) or pelvic MRI, is crucial, especially for histological subtypes such as well-differentiated (WD-LPS), dedifferentiated (DD-LPS) liposarcoma, leiomyosarcoma (LMS), and solitary fibrous tumors. This detailed staging is essential for personalized surgery to preserve the anatomy and function of the pelvic organs while achieving optimal tumor resection (53, 54).

The extraperitoneal pelvic cavity, bounded by the parietal peritoneum, pelvic floor, pubis, inguinal ligaments, and sacrum, presents unique challenges in obtaining wide surgical margins due to the proximity of vascular, bony, and visceral structures. Pelvic sarcomas often exert pressure on organs such as the bladder, prostate, seminal vesicles, or ureters. Although joint resection of these organs with the tumor is rarely justified due to the infrequency of direct invasion, partial resection of the bladder may be necessary to preserve its functionality when bladder invasion occurs. Involvement of the mesorectum may require including the rectum in the resection, and in severe cases, abdominoperineal resection may be necessary. Pelvic recurrences, often more complicated, tend to require more extensive visceral resections (36, 54).

Intraoperative identification of ureters is complex, and preoperative ureteral catheters or nephrostomies are frequently required to manage obstructive hydronephrosis. This is followed by resection of the distal part of the ureter and bladder reimplantation. Tumor fragmentation increases the risk of local recurrence and reduces survival; therefore, large, recurrent, or tumors adherent to the bony pelvis may benefit from neoadjuvant or intraoperative chemotherapy and radiotherapy. This integrated and meticulous approach is crucial for managing pelvic retroperitoneal sarcomas, combining advanced surgical techniques with adjuvant treatment strategies to maximize survival and preserve the patient's quality of life. In the TARPSWG RPS report, the series demonstrated a local recurrence-free period of 74.1%, a distant recurrence-free period of 79%, and an overall survival (OS) of 67% (55). The upcoming PELVISARC results show an OS of 69.6%, a local recurrence-free period of 62.7%, and a distant recurrence-free period of 66.5%, with leiomyosarcoma being the most reported histology, prompting considerations for a differentiated approach to maximize outcomes.

For RPS with pelvic extension, adhesion to structures such as the rectum and bladder peritoneum and possible extension into the sciatic or obturator notches demands a detailed preoperative evaluation for optimal surgical planning. Preservation of pelvic organs and nervous structures is crucial unless they are directly invaded by the tumor. Sarcomas arising from the psoas muscle and parietal sarcomas present unique challenges due to their deep location within muscle tissue, where the fascia acts as a natural protective barrier. In some instances, an extraperitoneal approach may be appropriate. However, adopting a transperitoneal approach that ensures meticulous vascular control is crucial for more aggressive histologies, such as undifferentiated pleomorphic sarcoma (UPS) (36, 53, 54, 56).

Why adopt a position based on histology?

The adaptation of surgical strategies based on histology is critical in the treatment of retroperitoneal sarcomas (RPS) because overall survival (OS) heavily depends on local control, especially for low- and intermediate-grade tumors where extended surgery offers significant benefits. However, the approach becomes more complex with high-grade tumors, which have a higher propensity for distant metastases (DM). In these cases, the primary goal is to achieve a complete resection (R0), often supplemented with systemic treatments to minimize DM risks (16, 51). This strategy has been detailed in studies by A. Gronchi and others in 2016 (55) and Callegaro et al. in 2021 (57). These studies differentiate the recurrence patterns between well-differentiated liposarcoma (WDLPS) and grade 2 dedifferentiated (DDLPS G2) versus grade 3 dedifferentiated (DDLPS G3) and leiomyosarcoma (LMS), underscoring that DM critically impacts OS. In LMS, the delineation of tumor borders and the relationship with neighboring organs are more defined, making the quality of the

initial surgery crucial for safely preserving non-infiltrated structures and maintaining the radical nature of the procedure. Thus, implementing first-line extended surgery in treating RPS should consider the histological subtype and the tumor's expected biological behavior and recurrence patterns. Moreover, assessing the tumor in the context of the patient's overall health is essential, as it influences the feasibility of undergoing extensive surgeries and adjuvant treatments (36, 40, 56, 58, 59).

The treatment of retroperitoneal sarcomas (RPS) is significantly enhanced by a multidisciplinary team (MDT) approach, mainly when patients are treated within specialized sarcoma centers (NSC) (60). A study involving 2,945 patients revealed that those who underwent their first surgery at an NSC had notably better outcomes than those treated at out-of-network centers. Specifically, 41.9% of patients in NSCs achieved first R0 resections, a stark contrast to the 12.3% in out-of-network centers. Additionally, the overall survival (OS) was significantly superior for patients treated within NSCs, with a 2-year OS of 87% compared to 70% for those treated elsewhere ($p < 0.001$). Multivariate analysis confirmed that surgery within an NSC independently predicted better OS, showing a twofold reduction in the odds of death (61). Beyond clinical benefits, the multidisciplinary approach also optimizes healthcare resources, reducing treatment costs by approximately 10-15% due to better therapeutic planning and avoiding unnecessary procedures. These findings underscore the critical importance of MDTs in improving oncological outcomes and enhancing the efficiency of healthcare for RPS patients (22, 27, 28, 60) Table 1; Figure 1.

Liposarcoma

Retroperitoneal liposarcomas are the most common type of sarcoma in this location. Among these, well-differentiated

liposarcoma (WDLPS) represents 50–60% of cases, followed by dedifferentiated liposarcoma (DDLPS) at 30-37%, and other liposarcoma subtypes comprising the remaining 7% (62–64).

WDLPS is a low-grade tumor primarily composed of proliferating mature adipocytes. Despite its relatively indolent behavior, WDLPS has a high propensity for local recurrence, with rates reaching up to 43% at 8 years. Although it rarely metastasizes, approximately 20% of cases may dedifferentiate into a higher-grade liposarcoma. The overall survival (OS) at 5 years for WDLPS is 87%. DDLPS is a high-grade tumor that can arise *de novo* or as a progression from a WDLPS. This subtype is significantly more aggressive and has a high metastatic potential. DDLPS can exhibit heterologous components, such as osseous, muscular, or neurogenic differentiation, although these components do not significantly impact the prognosis. The local recurrence rate for DDLPS is 40%, and the rate of distant metastasis ranges from 15-20%. The overall 5-year survival rate for DDLPS varies between 44% and 53%, with worse outcomes in retroperitoneal cases. Specifically, the 5-year OS is 54% for grade 2 dedifferentiated liposarcoma (G2 DDLPS) and 41% for grade 3 dedifferentiated liposarcoma (G3 DDLPS) (55).

Myxoid liposarcoma (MLS) is rare in the retroperitoneum. Some authors suggest that due to its rarity in this location, these tumors should be considered metastatic until primary lesions are ruled out, particularly in the extremities. When MLS presents in the retroperitoneum, its prognosis is variable, depending on the presence of a round cell component, which increases the metastasis rate to between 30-40% (65).

Pleomorphic liposarcoma (PLS) is the rarest and most aggressive liposarcoma subtype, with the retroperitoneum being an unusual site of occurrence. At diagnosis, PLS may present with metastases in 30-50% of cases, most commonly to the lungs (66).

The diagnosis of retroperitoneal liposarcomas relies on a combination of imaging studies and histopathological evaluation. The treatment of these tumors requires a highly specialized

TABLE 1 The histological type of retroperitoneal sarcoma, with its associated dissemination pattern, 5-year disease failure rate, and surgical implications.

RPS Histology	Proportion	Relapse pattern	Surgical Management	5-Year OS	5-Year LR	5-Year DR
WDLPS	23%-28%	Local	Extended en bloc resection requires resection of ipsilateral retroperitoneal fat	87%	19%-39%	0%
DDLPS G2 G3	32%-43%	Mixed	Extended en bloc resection requires resection of ipsilateral retroperitoneal fat	54% 41%	44% 33%	10% 44%
LMS	18-23%	Distant metastasis from early stages of the disease	En bloc resection with vascular structures may preserve adjacent critical structures	58%	6%-16%	56%
SFT Risk class Low Moderate High	5%-6%	Mixed None Mixed Mixed	Simple resection	85%	5%-8%	17%
MPNST	3%-23%	Mixed	En-bloc resection with associated neurovascular structures may preserve adjacent critical structures	67%	20%-35%	13%

OS, overall survival; LR, locoregional recurrence; DR, distant recurrence.

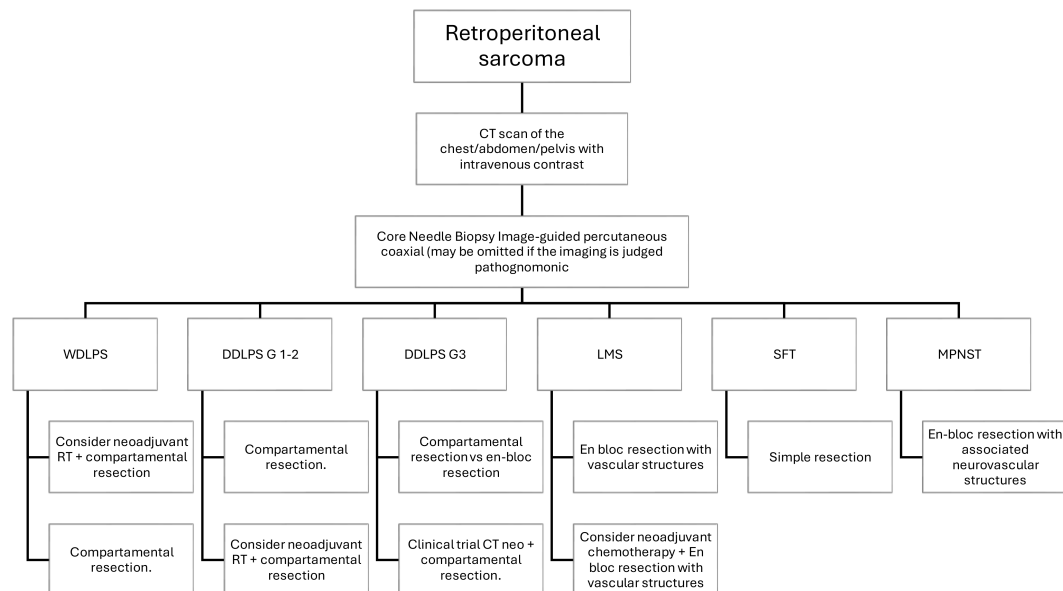


FIGURE 1

Proposed algorithm for evaluation and management of localized retroperitoneal sarcoma according to histology.

multidisciplinary approach. Surgery remains the cornerstone of management to achieve complete resection. However, the anatomical complexity of the retroperitoneum often makes it challenging to obtain negative margins, highlighting the importance of surgical expertise and intraoperative decision-making informed by tumor biology. Preoperative radiotherapy is the preferred modality for reducing local recurrence, although the proximity of vital organs limits its use. Chemotherapy, while not a standard treatment, may be considered in specific cases, particularly in more aggressive subtypes or in tumors that are not fully resectable. Oncological outcomes in retroperitoneal liposarcomas are closely related to the histological subtype, tumor grade, and the effectiveness of local control. Although WDLPS has a relatively high survival rate, the dedifferentiated and pleomorphic subtypes present a significantly worse prognosis, with high morbidity associated with local recurrence and metastatic progression. Local recurrence remains the most significant clinical challenge and the leading cause of death in patients with retroperitoneal liposarcomas (22, 27, 28).

As discussed in previous sections, the management of these cases requires a personalized therapeutic strategy based on the tumor's clinical and molecular characteristics, with the goal of optimizing long-term outcomes for patients.

Leiomyosarcoma

Retroperitoneal leiomyosarcoma is a rare mesenchymal tumor with an inferior prognosis, occurring predominantly in women with a ratio of 3:1 (67). These tumors are more common in the fifth or sixth decade of life, but they can affect any age group. IVC leiomyosarcomas, which arise predominantly in this vein and constitute 50% of all venous leiomyosarcomas, are classified according to the affected segment of the IVC: inferior, middle,

and superior, with the middle segment being the most frequently involved. The renal vein is a critical anatomical landmark for this classification (68).

These are slow-growing tumors that exhibits three patterns of growth: extraluminal (62%), intraluminal (5%), and a combination of both (33%). Multiplanar computed tomography (CT) with sagittal and coronal reconstructions is essential to reveal the craniocaudal extent of the tumor. Typical CT features include an irregularly distended IVC containing a lobulated soft tissue mass with heterogeneous enhancement, reflecting the internal hemorrhage and necrosis these tumors often exhibit (69).

Differentiating IVC leiomyosarcomas with an extraluminal growth pattern from other retroperitoneal venous leiomyosarcomas can be diagnostically challenging. Preoperative imaging should detail the tumor's size, location, relationship to surrounding structures, degree of IVC involvement, relationship to the renal and retrohepatic veins, and any intraluminal tumor components. Defining the lumbar vessels and collateral veins in the retroperitoneum is crucial to anticipate possible blood loss during surgery (69, 70).

Due to the rarity of these tumors, data to guide optimal oncologic treatment are limited; however, a multidisciplinary approach is generally recommended. Surgical resection of the primary tumor is considered the only potentially curative treatment, with 5- and 10-year survival rates of 49.4% and 29.5%, respectively. The surgical strategy depends on the location and extent of the tumor. Several important surgical considerations must be considered for primary leiomyosarcomas of the inferior vena cava (IVC) located below the renal vessels. In many patients, collateral venous pathways develop, which should ideally be identified preoperatively using imaging modalities such as CT or MRI venography. Ligation of the IVC is typically performed after tumor excision. However, if there is significant preoperative venous flow, reconstruction may be required using a prosthetic graft, such

as polytetrafluoroethylene (PTFE). The graft size varies depending on the native IVC, usually between 16 and 22 mm. In cases where the surgical site is potentially contaminated, such as when bowel resection is necessary, cadaveric tissue and autologous tissue grafts offer distinct advantages. These materials may reduce the risk of infection, particularly in a contaminated field, as reported in multiple surgical series. For leiomyosarcomas located above the renal vessels and involving the renal vein ostia, surgical exposure can be achieved by mobilizing the right lobe of the liver or via an anterior approach by cutting the caudate lobe. The anesthesia team should be alerted before surgery, and clamping of the IVC above the tumor is necessary to assess the patient's hemodynamic response. If the patient tolerates this maneuver, segmental resection of the IVC can be performed without reconstruction. In cases where the right kidney is resected, the left renal vein should be divided proximally to the left gonadal vein to preserve venous drainage. Studies have shown no significant differences in complication rates, postoperative morbidity, or 5-year overall survival between patients undergoing IVC reconstruction versus those with ligation. However, patients requiring IVC reconstruction were more likely to need ICU admission (83% vs. 33%; $p = 0.0257$). Those with IVC ligation tended to develop postoperative lymphedema (35% vs. 0%; $p = 0.1615$), which resolved in most cases (71, 72).

Kidney autotransplantation can also be utilized to preserve renal function, especially in situations where the renal hilum is involved, as highlighted in studies demonstrating the feasibility and success of this approach. For leiomyosarcomas extending above the hepatic veins, hepatic resection may be necessary if the tumor involves the retrohepatic IVC. This procedure requires total hepatic vascular exclusion and venovenous bypass, which are complex but can be lifesaving. The retrohepatic IVC can then be exposed using a liver suspension technique, particularly useful in avoiding liver congestion. Tumors in the upper segment may necessitate extracorporeal circulation to ensure complete resection and reduce intraoperative blood loss. Studies indicate that despite the complexity of these procedures, with proper patient selection and surgical expertise, long-term outcomes can be favorable (70, 71, 73).

Postoperative complications occur in 18% to 30% of patients and commonly include lower extremity edema and renal failure. Leiomyosarcomas of the lower segment of the IVC is associated with a lower incidence of postoperative complications than those of the upper segment. Additionally, in patients with advanced disease, surgical resection of metastatic disease, such as pulmonary metastasectomy or liver resection, may improve overall survival (68, 71, 73). Although surgery is technically demanding, it remains the primary treatment approach for all patients with localized disease. Recognizing the significant risk of distant metastasis is critical, especially in larger or higher-grade tumors. A recent study also highlights that, in patients with tumors originating in the inferior vena cava, the degree of macroscopic vascular invasion is a crucial clinical predictor of MD (74).

The role of neoadjuvant chemotherapy and radiotherapy in reducing tumor size and increasing resectability remains uncertain, although their use is advised. Chemotherapeutic agents used include dacarbazine, doxorubicin, cyclophosphamide, ifosfamide,

and cisplatin, although there is no standard regimen, and management varies depending on patient characteristics. The 5-year disease-free survival for patients with leiomyosarcoma of the IVC is 6%, while the overall survival rate reaches 55% (68).

Solitary fibrous tumors

Solitary fibrous tumors (SFTs) were described morphologically in 1931 by Klemperer and Rabin as pleural neoplasms (75). Initially termed "solitary (localized) mesothelioma of pleura" by Stout and Murray in 1942, these tumors were later renamed "solitary fibrous tumor" in 1951 by Stout and Hamidi. The term "Hemangiopericytoma" (HPC) was introduced by Stout and Murray in the same year while describing a similar tumor series. These terms reflected the evolving understanding of these tumors, which were considered part of a histomorphological spectrum until their unifying molecular signature was discovered. The defining molecular feature, identified as the recurrent fusion of NAB2 and STAT6 genes on chromosomal region 12q13, solidified the classification of SFT and HPC as ends of a spectrum of a single tumor entity (76). This was officially recognized in the 4th edition of the World Health Organization (WHO) Classification of Tumors of Soft Tissue and Bone, which consolidated these tumors into a single entity. The WHO classifies SFT as a fibroblastic neoplasm with intermediate (rarely metastasizing) behavior. Interestingly, the WHO Classification of Tumors of the Central Nervous System describes extra meningeal SFT and HPC as a single group. Still, different histologic grades are retained along with their distinct names (77).

SFTs can occur across a wide range of ages but are more common in the fifth and sixth decades of life and are rare in children and adolescents. The mean age of presentation for extrapleural tumors is 50.3 years. There are no known specific risk factors for the development of SFTs. SFTs are generally slow-growing, asymptomatic tumors, often discovered incidentally in imaging studies. They can vary in size from 1 to 40 cm, with an average length of 5 to 8 cm. Some may present with Doege-Potter syndrome, a paraneoplastic hypoglycemic syndrome due to the excessive production of insulin-like growth factor II (IGF2) (18, 76).

According to Demicco et al., predictors of time to metastasis and tumor-related death include patient age, tumor size, mitosis rate, and necrosis. The Demicco model classifies risk as follows: patient age (score 0 for <55 years; 1 for ≥55 years), tumor size (score 0 to 3, from <5 cm to ≥15 cm), mitotic frequency of tumor cells (score 0 to 2, from 0/mm² to ≥4/mm²), and tumor necrosis (score 0 for <10%; 1 for ≥10%). Patients are classified into low risk (0–3 points), intermediate risk (4–5 points), and high risk (6–7 points) (78).

The primary treatment for SFTs is surgical excision; adjuvant radiotherapy or chemotherapy is usually unnecessary. Due to the rarity of SFTs and the need for randomized clinical trials, there is no global consensus on management, and a multidisciplinary treatment approach is recommended. In managing retroperitoneal SFTs specifically, the goal is to achieve negative margins and complete tumor excision, ideally including an adjacent adipose tissue margin, to ensure complete resection and minimize morbidity. Approximately

10% of cases that present more aggressive characteristics, such as a size greater than 10 cm or histological markers of malignancy, may require a more aggressive surgical approach, including the resection of adjacent organs (46, 76).

Malignant peripheral nerve sheath tumors

Malignant peripheral nerve sheath tumors (MPNST) account for approximately 10% of all soft tissue sarcomas and develop in 8–13% of patients with neurofibromatosis type 1 (NF1), representing one of the primary causes of mortality in these patients. MPNSTs can also arise sporadically or following radiation exposure. These tumors are known for their aggressiveness and invasiveness, with a high rate of local and systemic recurrence, often exhibiting characteristics similar to leiomyosarcomas (LMS). Genetic instability, a hallmark of MPNSTs, includes nucleotide sequence mutations, microsatellite instability, and significant chromosomal alterations such as gains, losses, and rearrangements leading to DNA copy number changes (CNAs). Recurrent losses in numerous chromosomal regions, such as 1p, 9p, 11, 12p, 14q, and 22q, are expected, while typical gains occur on chromosomes 7, 8q, 9q, 13q, 15q, and 17q (79). Diagnosis is supported by imaging techniques such as magnetic resonance imaging (MRI), which is used to locate the tumor, determine its size, and assess its invasiveness. Although MRI and computed tomography (CT) are not entirely reliable in detecting malignant transformation, 18-fluorodeoxyglucose positron emission tomography (FDG-PET) can identify increased metabolism in malignant tumors, facilitating discrimination between MPNST and benign plexiform neurofibromas (pNF). FDG-PET, when combined with CT or MRI, offers superior capability in differentiating benign from malignant lesions and estimating the degree of malignancy in heterogeneous lesions (79, 80).

The primary treatment for MPNST is complete resection with negative margins (R0), which aims to preserve adjacent structures and minimize associated morbidity. However, resection of MPNSTs typically involves removal of the nerve of origin, entailing significant surgical morbidity. Despite these challenges, R0 resection remains the standard of care and the only option with curative potential, given the limited efficacy of available alternative therapies. These tumors, often originating in neural structures such as the femoral nerve in the retroperitoneum, present significant post-resection functional loss. It is crucial for physicians to discuss the potential impact of surgery with patients beforehand (56, 79).

The recommended approach for treating MPNST is multimodal. Although there is no evidence that extended, resections improve outcomes, complete surgical resection offers the best chance of cure. Indeed, 80% of patients who achieve complete removal survive at ten years, compared to 14% of those with incomplete removal. Overall survival varies based on several factors; it is lower in the presence of NF1, decreases with incomplete surgical resection, and is affected by synchronous metastases. Furthermore, larger primary tumors are associated with lower survival. In managing these high-risk tumors, the surgical approach is frequently combined with other treatment

modalities, such as radiotherapy and chemotherapy, to improve both local and systemic disease control. This integrated approach is essential, given that local recurrence and distant metastases are the leading causes of morbidity and mortality in patients with high-grade RPS (56, 79, 81).

Table 1, which details the surgical management and outcomes associated with each significant RPS histology, underscores the need to adopt a therapeutic strategy based on the tumor's specific biology, aiming to maximize both survival and postoperative quality of life.

Morbidity in the management of RPS

The management of RPS involves a significant profile of morbidity and mortality, mainly due to the need for extensive multivisceral surgery. Case series have documented a severe 30-day postoperative morbidity (Clavien-Dindo ≥ 3) of 16.4% and a mortality of 1.8%, with hemorrhages, anastomotic leaks, and abscesses being the most common complications. Identified risk factors include the patient's advanced age, the need for intraoperative transfusions, and the number of organs resected. Interventions that carry higher risks include caudal pancreaticoduodenectomy, significant vascular resections, splenectomies, and pancreatectomies. Despite the association of surgical morbidity with complex procedures, recent studies have shown a decrease in postsurgical morbidity, even with an increase in the number of organs resected. This improvement could reflect advancements in perioperative care and patient selection. However, surgical morbidity has not demonstrated a direct correlation with local or distant recurrence or overall survival (34).

In terms of long-term morbidity, research has evaluated consequences such as renal failure, chronic pain, and functional deficiencies, finding that serious complications related to femoral nerve resections are infrequent. No significant differences were observed in postoperative creatinine levels between patients with and without nephrectomy, indicating minimal impact on renal and adrenal function from nephrectomy and adrenalectomy. Surgical treatment of RPS may require resection of iliac or femoral vessels to achieve negative margins, often followed by prosthetic vascular reconstructions. These interventions increase postoperative morbidity and mortality but are essential for maintaining vascular integrity. In cases where the involvement of prominent pelvic veins has generated robust collateral venous circulation, resection without reconstruction may be appropriate, thus avoiding the need for venous stents. Lymphadenectomy is justified only in the presence of evidence of lymphatic spread. Interventions involving significant vessels or pancreaticoduodenectomy are linked with the highest risk of serious complications. Patients undergoing these procedures have shown increased ICU admissions (83% vs. 33%; $p=0.0257$) and higher incidence of significant complications, most frequently pancreatic fistula, associated with a mortality rate of 3.4%. Other long-term complications include the development of incisional hernias (16.8%), alterations in excretion (41%), changes in urinary habits (9%), erectile dysfunction (27.3%), retrograde ejaculation (9%), and dyspareunia (22%). The selection of therapeutic strategies must be individualized,

weighing the balance between the benefits of radical resection and the risks of associated morbidity to preserve the patient's quality of life (33, 35, 46, 71).

Radiotherapy

The role of radiotherapy in treating primary RPS remains a topic of intense debate despite its recognized benefit in locally controlling extremity sarcomas. The application of RT in RPS is particularly complicated by anatomical and biological differences specific to the retroperitoneum. Preoperative radiotherapy is preferred because it allows better delineation of the target volume, takes advantage of greater tissue oxygenation, and facilitates tumor detachment from vital organs, thus reducing the risk of local recurrence—a significant cause of therapeutic failure (81, 82). The STRASS-1 study, a multicenter randomized phase III trial, showed no improvement in abdominal recurrence-free survival (ARFS) with the addition of preoperative RT compared to surgery alone. However, additional analyses indicate that in specific subgroups, such as patients with low-grade well-differentiated and dedifferentiated liposarcoma, RT may significantly reduce local recurrence. These findings underscore the importance of considering particular histology when evaluating the potential benefits of RT. Technical challenges of RT include precision in tumor volume delineation, which is essential for its effectiveness. Common planning errors, such as deviations in the delineation of the macroscopic tumor volume, could have compromised the results of the STRASS study (83).

Additionally, the trial needed to adequately stratify patients by histology, which may have affected the interpretation of the results. The results were revealed in a follow-up study with quality-adjusted analysis derived from STRASS-1, where treatments were classified as radiotherapy-compliant (RC) or non-radiotherapy-compliant (NRC) for patients with unacceptable deviations. The 3-year ARFS rate was 66.8% (95% CI, 55.8%–75.7%) for the RC group and 49.8% (95% CI, 32.7%–64.8%) for the NRC group, respectively (adjusted hazard ratio, 2.32; 95% CI, 1.25–4.32; $P = .008$); local recurrence after macroscopic complete resection occurred in 13 of 89 patients (14.6%) in the RC group versus 2 of 36 patients (5.6%) in the NRC group (84).

More recent studies, such as STRASS and STREXIT, which employed propensity-adjusted analyses, found a significant improvement in ARFS for patients with low-grade dedifferentiated liposarcoma treated with preoperative RT, suggesting that RT may have a more prominent role in specific histological subtypes. Although RT remains vital in managing RPS, its application must be carefully considered and tailored according to tumor histology. Future clinical trials should focus on stratifying patients by histologic type and prospectively examining the benefits of RT, especially in subgroups that may derive more significant benefits. This will help refine the role of RT and optimize outcomes for patients with RPS, leading toward more personalized and effective treatment. Furthermore, RT for RPS has shown potential benefits in local control in multiple retrospective series, although these results have been questioned due to possible selection biases. Unfortunately, the difficulty in enrolling patients in randomized trials was confirmed with the premature closure of the ACSOG Z9031 trial 2014. The most

robust evidence comes from the phase III STRASS trial, which evaluated radiotherapy in a neoadjuvant setting. The final results were negative, with no difference in ARFS between the surgery arms with and without preoperative RT (28, 81, 85, 86).

Proponents of RT for RPS highlight that RT was associated with a significant reduction of more than 50% in local relapse in all patients. However, approximately 25% of RT plans had significant deviations related to inadequate delineation of the macroscopic tumor volume, which may have affected the results. Furthermore, the lack of robust stratification by histology in the trial could have influenced the interpretation of the data. A *post hoc* exploratory sensitivity analysis found that patients with WDLS and DDLS G1-2 improved abdominal recurrence-free survival (HR 0.62, 95% CI: 0.38–1.02) with statistical significance. Using a propensity-matched analysis, a recent study combined patients treated under the STRASS protocol and those not treated in a study known as STREXIT. This analysis showed significantly improved abdominal recurrence-free survival with preoperative RT in patients with liposarcoma (83, 87).

Systemic therapy

In the neoadjuvant or adjuvant setting, and even in combination with radiotherapy, chemotherapy has an established role in the treatment of soft tissue sarcomas (STS). In RPS management, chemotherapy remains an area of notable uncertainty, mainly due to anatomical and biological differences that complicate the direct extrapolation of data from soft tissue sarcomas of the extremities and trunk (27, 46). Given this uncertainty, patient participation in available clinical trials is recommended. The ongoing phase III randomized controlled trial, STRASS 2, estimated to be completed by 2029, evaluates a histology-tailored chemotherapy regimen in patients with leiomyosarcoma and dedifferentiated liposarcoma at high risk for distant metastatic recurrence. This study compares neoadjuvant chemotherapy followed by surgery to surgery alone, aiming to improve disease control and survival. Preliminary findings and previous retrospective studies have shown conflicting results, reflecting the complexity of chemotherapy's impact on these patients (40).

The development of systemic treatments in the field of sarcomas faces the challenge of histological heterogeneity, with varied biologies and responses to treatment. Tseng et al. observed that tumor responses varied depending on the histological type and the chemotherapy regimen. Specifically, patients with leiomyosarcoma (LMS) who received doxorubicin and dacarbazine showed a partial response rate of 37%, compared with only 16% for those who received another chemotherapy combination. This finding aligns with other retrospective studies indicating that ifosfamide has limited activity in LMS compared to dacarbazine (88).

In some reference centers, neoadjuvant chemotherapy is standard for histologies such as high-grade dedifferentiated liposarcoma and leiomyosarcoma, which present high-risk criteria for distant recurrence. For cases of resectable but high-risk RPS (SARCULATOR OS < 60% at ten years), neoadjuvant

chemotherapy is considered with the primary goal of increasing overall survival (OS) and, secondarily, of reducing tumor size to facilitate surgery (89). A recent multi-institutional retrospective study revealed that 23% of patients with RPS had a RECIST partial response (>30% tumor reduction) to neoadjuvant chemotherapy. In comparison, 21% showed disease progression associated with significantly worse survival. This suggests that response to treatment could be a criterion for evaluating the appropriateness of proceeding with resection (40).

Finally, the combination of chemotherapy and preoperative radiotherapy (chemoradiation) in patients with RPS remains an experimental approach. Prospective studies are required to determine whether preoperative chemoradiation offers advantages over radiotherapy alone.

The specific application of chemotherapy in RPS needs to be clarified. The treatment strategy for RPS must be carefully evaluated and personalized, prioritizing participation in clinical trials that can provide additional insights and optimize interventions for this complex disease.

Conclusions

Over the past few years, significant advances have been made in understanding the biology and treatment modalities of RPS. Surgery remains the fundamental pillar and the only curative treatment for localized disease. Meticulous surgical planning is crucial and must be personalized based on specific factors such as tumor histology, location, extension, high-risk characteristics, patient age, comorbidities, and tumor biology. The goal is to standardize the surgical approach to optimize the chances of achieving a complete resection. Global collaboration and specialization of sarcoma teams have increased disease-free and overall survival rates for patients with resected RPS. These advances have facilitated a better understanding of the disease and the development of more personalized treatment strategies, marking a paradigm shift in patients' prognosis and quality of life. Improvements in the quality of oncologic surgery, appropriate patient selection, and enhancements in perioperative management, including neoadjuvant therapy and intraoperative radiotherapy, are crucial in this progress.

Managing this diverse group of tumors is complex and requires recognizing the multifaceted aspects of surgical management, which must extend beyond mere resection. The goal is always to achieve a complete en-bloc resection, maximizing disease clearance while

balancing the associated morbidity and thoroughly understanding the expected post-surgery outcomes based on the tumor's histologic type. The treatment of RPS is constantly evolving, and new research findings will influence future guidelines and clinical practices, providing a more substantial basis for decision-making. Continued research is essential to further our understanding and management of RPS. Basic and translational research focused on RPS biology and global collaborative efforts are crucial to accelerate progress in this field. The Australasian Transatlantic Retroperitoneal Sarcoma Working Group (TARPSWG) has catalyzed critical retrospective and prospective studies, demonstrating the value of multicenter collaboration in advancing the knowledge and treatment of this rare and challenging disease.

Author contributions

DG-O: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Funding

The author declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The author declares 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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OPEN ACCESS

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RECEIVED 13 May 2024

ACCEPTED 07 October 2024

PUBLISHED 25 October 2024

CITATION

Zhou X, Zhuang A, Li X, Xi Z, Cheng Y, Yan G,
Wang Y, Zhang G, Huang Y, Zhang C, Xie F,
Ma X, Wu T and Li W (2024) Intraoperative
radiotherapy might not serve as a standard
therapy for retroperitoneal liposarcoma:
insights from a population-based propensity
score-matched study.
Front. Oncol. 14:1431920.
doi: 10.3389/fonc.2024.1431920

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Intraoperative radiotherapy might not serve as a standard therapy for retroperitoneal liposarcoma: insights from a population-based propensity score-matched study

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Background: Difficulty in achieving complete resection leads to a poor prognosis for retroperitoneal soft tissue sarcoma, hence emphasizing the significance of adjuvant treatment. The benefit of preoperative radiotherapy for retroperitoneal liposarcoma was initially demonstrated by the STRASS trial. However, the impact of intraoperative radiotherapy (IORT) on retroperitoneal liposarcoma remains unexplored.

Method: Patients with retroperitoneal liposarcoma were identified in the Surveillance, Epidemiology, and End Results (SEER) database, treated between 2000 and 2019. Subsequently, a 1:1 propensity score-matched (PSM) analysis was conducted based on variables identified from a multivariate analysis. T-tests were used to assess differences in normally distributed continuous variables, while the rank-sum test was applied to variables that did not follow a normal distribution. The chi-squared test was utilized to evaluate differences in categorical variables. Ultimately, survival analysis was performed using SPSS to evaluate patient prognosis.

Result: A total of 2129 patients with retroperitoneal liposarcoma were included in our study. Age, sex, histology, grading, chemotherapy, and tumor size as independent prognostic risk factors for these patients through multivariate Cox regression analysis. Subsequently, 66 patients were included in the survival analysis through PSM, with 33 patients receiving IORT. Finally, the survival analysis revealed that there was no difference in overall survival among patients with retroperitoneal liposarcoma, regardless of whether they received IORT or not ($p = 0.711$).

Conclusion: As an exploratory study, our findings suggest that patients may not derive benefit from intraoperative radiotherapy. These observations are intended to lay the groundwork for future prospective clinical studies.

KEYWORDS

retroperitoneal liposarcoma, intraoperative radiotherapy, SEER, propensity score matching, overall survival

Background

Soft tissue sarcomas (STS) are heterogeneous tumors that arise from mesenchymal cells, including muscle, fat, cartilage, nerve, and vascular tissue. Consequently, STS occur in all body parts, with a higher prevalence in the lower and upper limbs, and a comparatively lower prevalence in the retroperitoneum, chest wall, and head and neck (1). STS accounts for approximately 1% of all newly diagnosed malignant solid tumors, equating to approximately 12,000 cases annually in the United States (2). Despite the low incidence rate of STS, retroperitoneal sarcoma (RPS) still contributes to approximately 15% of all STS cases, with an average annual incidence of 2.7 per million people (3). Among adults, the most common histological type is liposarcoma (approximately 50-70%), which is further subdivided into well-differentiated liposarcoma (WDLPS) (synonymous with atypical lipoma tumors [ALT] when diagnosed in the extremities) and dedifferentiated liposarcoma (DDLPS) (4).

Local area recurrence (LAR) is the dominant form of recurrence in patients with RPS and often leads to death (5). Therefore, reducing LAR is an important goal for patients with RPS (5). The primary and only treatment for localized RPS is surgical excision, with the major oncological goal being to achieve complete resection (R0+R1) (6).

Although many people have undergone multiple sequential excisions of multiple organs, the outcomes of RPS are generally less satisfactory than those of other soft tissue sarcomas (7). Hence, adjuvant treatment with surgery holds significance; nonetheless, there is insufficient evidence to support the effectiveness of chemotherapy in retroperitoneal liposarcoma (RPL) (6). Surgeons have, therefore, begun to experiment with radiotherapy. Multiple randomized trials have confirmed that preoperative or postoperative radiotherapy during limb-sparing surgery significantly reduces the risk of local recurrence (LR) in patients with STS in the extremities (5). In recent years, there has been a growing trend among academics and experts to utilize preoperative radiotherapy as a prominent approach in the treatment of RPS. The STRASS trial was also the first to demonstrate the benefits of preoperative radiotherapy for RPL (8).

An advantage of intraoperative radiotherapy (IORT) is the ability of surgeon to remove critical organs and attempt to irradiate only the tumor bed. This advantage allows the dose to

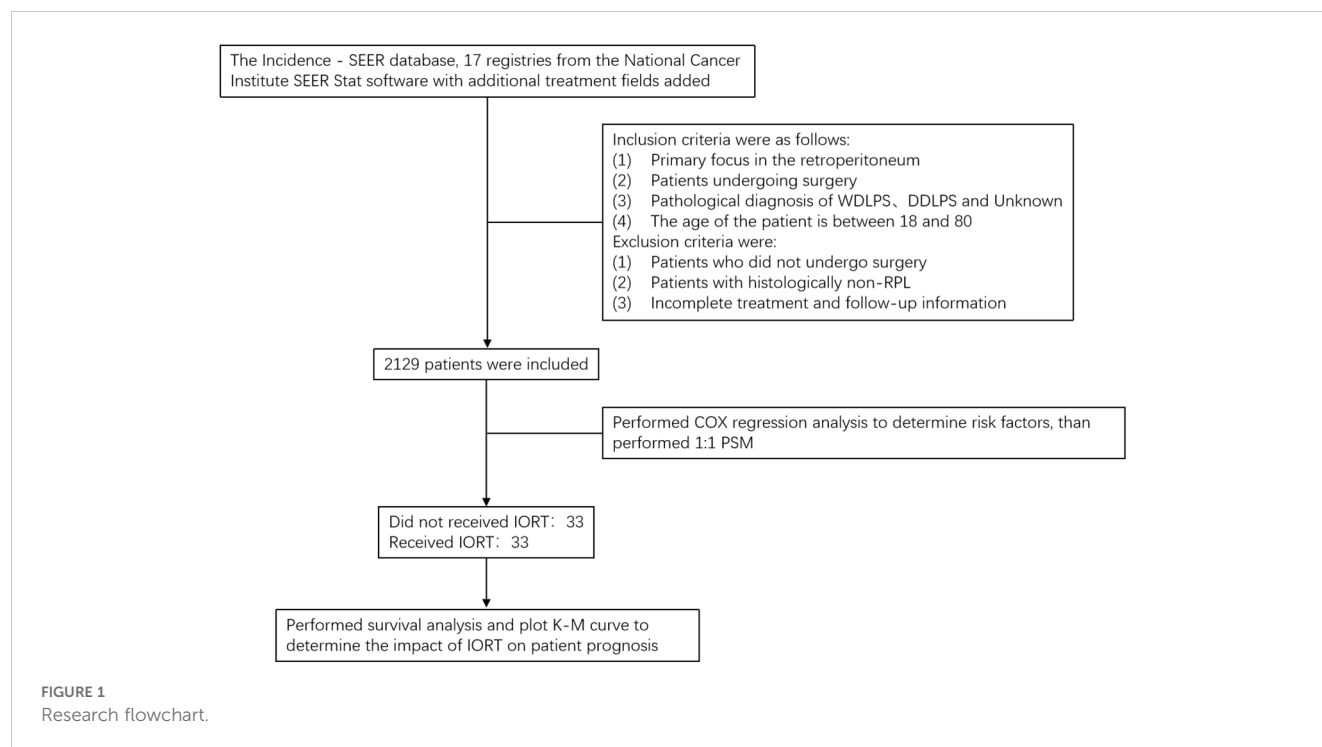
be selectively increased in the risk area, thereby increasing the treatment ratio between target and normal tissues (5). However, research into IORT in patients with retroperitoneal soft tissue sarcoma needs to be improved, and the number of patients included in the prospective only studies must be expanded (5).

Although the STRASS trial demonstrated that patients with RPL may benefit from neoradiotherapy, there are currently no studies on the prognostic impact of IORT in patients with RPL. Therefore, we conducted the exploratory study by reviewing bulk data through searching the Seer database to address the gaps in IORT of RPL patients and provide direction for further prospective clinical research.

Method

According to the [Figure 1](#), patient data were collected from the Incidence - SEER database, 17 registries from the National Cancer Institute SEER Stat software with additional treatment fields added. According to the third edition of the International Classification of Diseases for Oncology (ICD-O-3), patients diagnosed with RPL and underwent surgery in 2000 and 2019 were incorporated into the study cohort. Inclusion criteria were as follows: (1) primary focus in the retroperitoneum; (2) patients undergoing surgery; (3) pathological diagnosis with well-differentiated liposarcoma, dedifferentiated liposarcoma, and unknown; (4) The age of the patient is between 18 and 80. Exclusion criteria were: (1) patients who did not undergo surgery; (2) patients with histologically non-RPL; (3) incomplete treatment and follow-up information. The variables chosen for analysis include the year of diagnosis, age, sex, race (Caucasians, African-Americans, or other), site code ICD-0-3, tissue grade, histology record ICD-0-3, radiotherapy (sequence of radiotherapy with surgery), status of lymph node dissection, chemotherapy (whether or not), month of survival, COD to site rec KM, and vital status record.

The characteristics that are extracted include year of diagnosis, age, sex, race, histology, grade, radiotherapy, lymph node dissection status, chemotherapy, and tumor size. Univariate Cox regression analysis is conducted on the entire cohort, and multivariate Cox regression analysis is performed on statistically significant variables to evaluate the impact of variables on the prognosis of RPL patients.



As this study is a retrospective analysis using the SEER database, the implementation of IORT may be subject to selection bias and potential confounding factors. To address this issue, we balanced the baseline characteristics between different treatment groups through 1:1 propensity score matching (PSM), making the cohorts more comparable and the results more reliable. Using the Cox regression model, we identified key prognostic factors affecting the prognosis of patients with retroperitoneal liposarcoma, such as tumor size, grade, histological type, and patient baseline characteristics (e.g., age, gender, race). Based on these variables, we calculated the propensity score for each patient and employed a 1:1 nearest neighbor matching algorithm, setting the maximum allowable propensity score difference (caliper width) at 0.01, and divided the patients into two groups based on the treatment methods. Subsequently, we validated the matching quality by performing comparative analysis on the matched characteristics to ensure that the baseline features of the two groups were similar.

Overall survival (OS) of RPL is defined as the duration between the initial diagnosis and the occurrence of death from any cause or the most recent follow-up. Using survival status as the dependent variable and treatment modality as the independent variable, 1:1 PSM was performed with a clamp value of 0.01 to calibrate for the effect of baseline clinicopathological differences. The normality test was used to test whether the continuous variables fit the normal distribution (e.g., age, tumor size), the t-test was used to assess whether there were differences between groups for the continuous variables that fit the normal distribution while the rank sum test is used for variables that do not conform to a normal distribution, and the chi-squared test was used to assess whether there were differences between groups for categorical variables (e.g., gender, race, sex, histology, grade,

chemotherapy, treatment). Survival analysis was performed by plotting the Kaplan-Meier curve to compare whether there were differences in OS between groups. To eliminate the confounding effects of adjuvant radiotherapy, patients were stratified into two groups based on their exposure to adjuvant radiotherapy (which included preoperative, postoperative, and combined IORT with pre- and postoperative treatments). Subsequently, within these two groups, patients were further matched on a 1:1 PSM based on whether they received IORT as the independent variable. Following this matching, survival analyses were conducted once more to evaluate the outcomes. SPSS (Version 27.0. Armonk, NY: IBM Corp) statistical software was used for statistical analysis and presentation. Double-tailed $p < 0.05$ was considered statistically significant.

Result

As shown in Table 1, 2129 patients who met the inclusion criteria were included, the age distribution exhibited a median value of 63 (IQR: 54, 71) years and the tumor size distribution had a median value of 208 (IQR: 130, 300) mm. The patient population exhibited minimal disparity in terms of sex, with 1199 male patients and 930 female patients. The most common histological type was dedifferentiation (960 cases, 45.09%), followed by well-differentiation (787 cases, 36.97%), and the most common tumor grade was FNCLCC I (976 cases, 45.84%). Most patients did not receive chemotherapy (1914 cases, 89.9%) and most were Caucasians (1786 cases, 83.89%). There were 18 cases (0.85%) of IORT, 15 cases (0.71%) of Intraoperative radiation with other radiation before/after surgery, 9 cases (0.42%) of preoperative and

TABLE 1 Characteristics of included patients.

Characteristic	Total: 2129
Age	63 (IQR: 54, 71) years
Tumor Size	208 (IQR: 130, 300) mm
Sex:	
Male	1199 (56.32%)
Female	930 (43.68%)
Histology:	
Dedifferentiated	960 (45.09%)
Well-differentiated	787 (36.97%)
Unknown	382 (17.94%)
Grade:	
FNCLCC I	976 (45.84%)
FNCLCC II	396 (18.60%)
FNCLCC III	757 (35.56%)
Chemotherapy:	
Yes	215 (10.1%)
No/unknown	1914 (89.9%)
Race:	
Caucasians	1786 (83.89%)
Other (American Indian/AK Native, Asian/ Pacific Islander)	219 (10.27%)
African-Americans	113 (5.31%)
Unknown	11 (0.53%)
Treatment:	
Intraoperative radiation	18 (0.85%)
Intraoperative radiation with other radiation before/ after surgery	15 (0.71%)
Radiation before and after surgery	9 (0.42%)
Radiation prior to surgery	138 (6.48%)
Radiation after surgery	281 (13.20%)
Non radiotherapy	1666 (78.25%)
Sequence unknown	2 (0.09%)

postoperative radiotherapy, 138 cases (6.48%) of preoperative radiotherapy, 281 cases (13.20%) of postoperative radiotherapy and 1666 cases (78.25%) of no radiotherapy.

As shown in Table 2, univariate Cox regression analysis was conducted using variables including year of diagnosis, age, sex, race, histology, grade, radiotherapy, lymph node dissection status, chemotherapy, and tumor size. The study revealed that patients' prognosis were affected by age ($p<0.001$), sex ($p<0.001$), histology ($p<0.001$), grade ($p<0.001$), chemotherapy ($p<0.001$), and tumor size ($p=0.003$). Upon inclusion of all aforementioned variables in the multivariate Cox regression analysis, the findings revealed that age (HR

= 1.041, 95% CI 1.035-1.047, $p<0.001$), sex (HR = 1.230, 95% CI 1.080-1.402, $p<0.001$), histology ($p=0.029$), grade ($p<0.001$), chemotherapy (HR = 1.947, 95% CI 1.608-2.357, $p<0.001$), and tumor size (HR = 1.001, 95% CI 1.000-1.001, $p<0.001$) were identified as independent risk factors for the prognosis of patients.

Due to the significant disparity in the number of patients undergoing IORT relative to the entire cohort, we implemented a 1:1 PSM strategy to eliminate potential confounders by using independent risk factors derived from the previous step of the analysis. After matching, there were no statistically significant differences between the two groups.

Baseline characteristics of the population after PSM are shown in Table 3. The median age of patients who underwent IORT was 61 years old, while the median tumor size was 200 mm. The patient population consisted predominantly of individuals exhibiting both well-differentiated and dedifferentiated characteristics, with comparable frequencies observed for each group. The majority of patients exhibited a tumor grade of FNCLCC I. A limited number of patients received chemotherapy. The majority of patients were Caucasians.

The survival analysis was conducted using SPSS software and a survival curve was plotted. According to the Kaplan-Meier analysis, there was no statistically significant disparity in OS between patients who received IORT and those who did not (Figure 2: $P=0.711$). To eliminate the confounding effects of adjuvant radiotherapy, patients were stratified into two groups based on their exposure to adjuvant radiotherapy (which included preoperative, postoperative, and combined IORT with pre- and postoperative treatments). Subsequently, patients were further matched on a 1:1 PSM based on whether they only received IORT as the independent variable. Following this matching, survival analyses were conducted once more to evaluate the outcomes. And as shown in Figures 3, 4, IORT did not affect patient prognosis, regardless of whether the patient receives adjuvant radiotherapy ($P=0.45$, $P=0.899$).

Discussion

Retroperitoneal sarcomas (RPS) frequently lead to local recurrences, which are the primary cause of mortality in affected patients, complete resection is the only means of radical cure, but the effect is not satisfactory (3, 9, 10). There is also a lack of substantial evidence supporting the efficacy of adjunctive chemotherapy (6). And the prognosis of radiotherapy for these patients is also controversial (11–15). In response to these challenges, our study aimed to evaluate the effectiveness of IORT in the treatment of RPL. Our findings revealed that IORT did not significantly improve treatment outcomes.

The effectiveness of preoperative radiotherapy was first demonstrated in the RPL subgroup in the recently published randomized STRASS trial (EORTC 62092/STRASS). This trial reported a notable improvement in 3-year abdominal relapse-free survival in patients who received preoperative radiotherapy (71.6% vs. 60.4%). However, patients diagnosed with leiomyosarcoma

TABLE 2 Univariate and Multivariate COX regression analysis.

Characteristics	Univariate analysis		Multivariate analysis	
	P-value	HR (95%CI)	P-value	HR (95%CI)
Age	<0.001	1.040 (1.035-1.046)	<0.001	1.041 (1.035-1.047)
Sex (male vs. female)	<0.001	1.521 (1.337-1.731)	0.002	1.230 (1.080-1.402)
Histology:				
Well-differentiated liposarcoma	<0.001	Reference	0.029	Reference
Dedifferentiated liposarcoma	<0.001	2.615 (2.257-3.029)	0.009	1.362 (1.080-1.718)
Unknown	<0.001	1.477 (1.225-1.780)	0.053	1.227 (0.997-1.510)
Grade:				
FNCLCC I	<0.001	Reference	<0.001	Reference
FNCLCC II	<0.001	1.790 (1.486-2.155)	0.003	1.406 (1.123-1.759)
FNCLCC III	<0.001	2.904 (2.524-3.341)	<0.001	1.979 (1.584-2.472)
TumorSize	0.003	1.000 (1.000-1.001)	<0.001	1.001 (1.000-1.001)
Received chemotherapy	<0.001	2.150 (1.787-2.588)	<0.001	1.947 (1.608-2.357)
Race:				
African-Americans	0.750	Reference		
Other	0.921	1.017 (0.724-1.430)		
Unknown	0.317	0.364 (0.050-2.638)		
Caucasians	0.779	1.042 (0.783-1.386)		
Type of radiotherapy:				
IORT with radiotherapy before/after surgery	0.662	Reference		
IORT	0.460	1.490 (0.517-4.294)		
No radiotherapy	0.295	1.536 (0.688-3.431)		
Radiotherapy after surgery	0.230	1.649 (0.729-3.729)		
Radiotherapy before and after surgery	0.436	0.529 (0.107-2.623)		
Radiotherapy prior to surgery	0.301	1.565 (0.670-3.658)		
Sequence unknown	0.657	1.616 (0.194-13.427)		
Year of diagnosis	0.272	1.007 (0.995-1.019)		
Lymph node dissections:				
0	0.749	Reference		
1	0.905	1.022 (0.713-1.465)		
1~3	0.978	0.997 (0.812-1.225)		
>4	0.170	1.168 (0.936-1.459)		
Unknown	0.975	0.994 (0.699-1.415)		

(LMS) and high-grade sarcoma were not found to have an increased LR rate when administered preoperative radiotherapy. The findings suggest that preoperative radiotherapy provides a favorable prognosis for patients with this RPL subtype (8).

Callegaro et al. then compared the abdominal relapse-free survival (ARFS) of patients with primary RPS. The study

compared the outcomes of patients who were treated with RT in EORTC-STBSG-62092 (STRASS) Phase 3 randomized controlled trial (STRASS cohort) with those who were treated with RT off-trial (STREXIT cohort). The results indicated that the use of radiotherapy improved ARFS in patients with liposarcoma, especially well-differentiated liposarcoma and G1-G2

TABLE 3 Result of 1:1 propensity score matching.

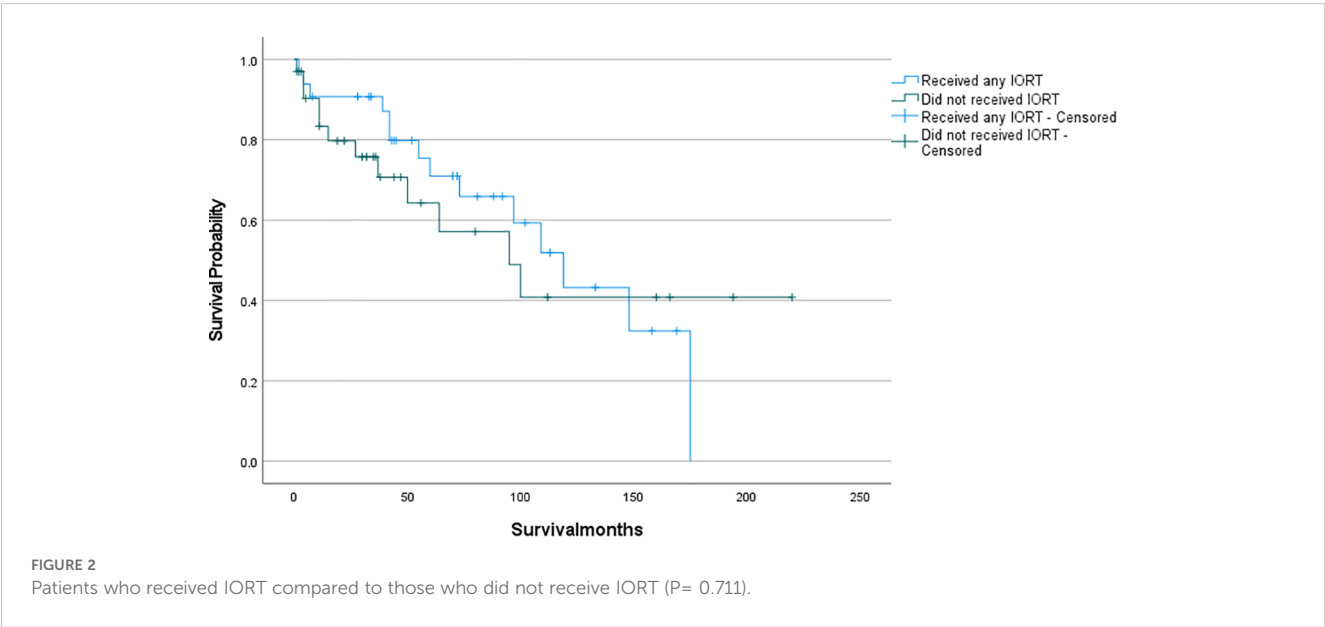
Characteristics	Did not received IORT (33)	Received any IORT (33)	P-value
Age (years)	62 (IQR: 53-70)	61 (IQR: 53-70)	0.894
Tumor Size (mm)	180 (IQR: 130-260)	200 (IQR: 150-260)	0.572
Sex	Male:16	Male:13	0.323
Histology:			0.439
Well-differentiated	11	15	
Dedifferentiated	16	15	
NOS	6	3	
Grade:			0.393
FNCLCC I	13	17	
FNCLCC II	8	4	
FNCLCC III	12	12	
Chemotherapy:			0.689
Yes	3	4	
No/unknow	30	29	
Race:			0.458
Caucasians	26	29	
Unknown	1	0	
Other	6	4	
African-Americans	0	0	

dedifferentiated liposarcoma. However, radiotherapy did not benefit patients with leiomyosarcoma or G3 dedifferentiated liposarcoma (16).

IORT is a procedure that allows for the administration of high doses of radiation during surgery while the surgeon is removing vital organs and exposing the tumor site (5). The application of IORT has demonstrated prognostic benefits for patients in cases of breast cancer (17). It is a reasonable option to increase the dose and improve local control (LC). The risk of wound healing disorder or gastrointestinal toxicity is minimal. Delivering sufficient radiation over a significant retroperitoneal area without harming other organs poses a considerable challenge regarding RPL. Radiation treatment can have adverse effects on overall survival. Nonetheless, the impact of IORT on the prognosis of patients with RPL remains unknown.

The initial prospective randomized trial aimed to evaluate IORT for retroperitoneal soft tissue sarcoma. A total of 35 patients were enrolled in the trial, with 15 patients received IORT at 20Gy in combination with postoperative radiotherapy at 35-40Gy, and with 20 patients received postoperative radiotherapy at 50-55Gy alone. The results indicated a decrease in local relapses and radiation-related abdominal complications among patients who underwent IORT together with postoperative radiotherapy (18). Their findings is similar to ours, however, there was no significant improvement in overall survival (OS) or cancer-specific survival (CSS) among the patients. Although their study only compared the efficacy of intraoperative radiotherapy (IORT) combined with postoperative radiotherapy versus postoperative radiotherapy alone, and failed to distinguish between the various histologic types. Nonetheless, their research presents novel strategies for implementing IORT in RPS patients.

There has been ongoing debate regarding the efficacy of IORT for sarcoma treatment in previous studies. Wang L. B. et al. found that IORT benefits the OS of liposarcoma patients, which is contrary to our results. This discrepancy may stem from differences in baseline characteristics such as tumor size, race, and grade among patients receiving different treatments in their cohort, as well as a smaller sample size. Our study increased comparability



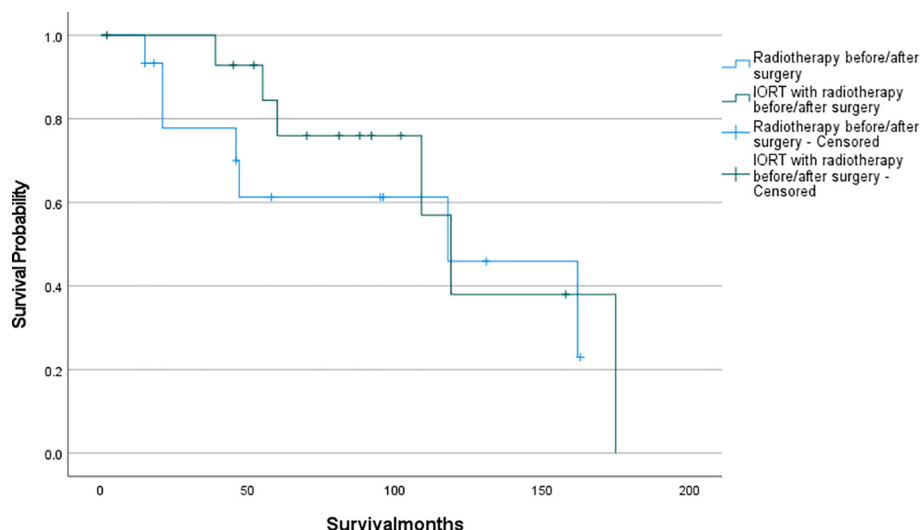


FIGURE 3

Patients who received IORT with radiotherapy before/after surgery compared to those who received radiotherapy before/after surgery ($P = 0.45$).

by balancing baseline characteristics between different groups through 1:1 PSM and included a larger sample size, which may explain the differing results (19). Similarly, Gieschen H. L. et al. reported that IORT benefits OS in patients with retroperitoneal sarcoma, but their inclusion of various histological types and a smaller sample of patients receiving IORT (only 16 cases) may have led to different outcomes. Although they found that IORT benefits disease-free survival (DFS) and local control (LC), the differences did not reach statistical significance, possibly due to the small sample size (20). J.-P.E.N. Pierie et al. compared preoperative radiotherapy with combined preoperative and intraoperative radiotherapy and found that the combined treatment improved disease-specific survival and recurrence. Their cohort included 103 patients but did not analyze the effects of using IORT alone, so the

benefits of IORT alone in their cohort were still unknown (21). Timothy M. Pawlik et al. analyzed the results of preoperative radiotherapy combined with either IORT or other radiotherapy, finding a 5-year LC rate of 60% and a 5-year OS of 61%, higher than many studies, but similarly did not clearly evaluate the pros and cons of using IORT alone (22). Robert Krempien et al. also found benefits of IORT for retroperitoneal sarcoma patients but noted a higher risk of complications. They included various histological types and had a small sample size, and did not clearly balance baseline characteristics between different treatment groups, which may have led to different results from ours (23). Falk Roeder et al. demonstrated the benefits of IORT, and although their sample size was larger (156 patients), they only compared IORT with combined treatment (IORT combined with additional radiotherapy), without

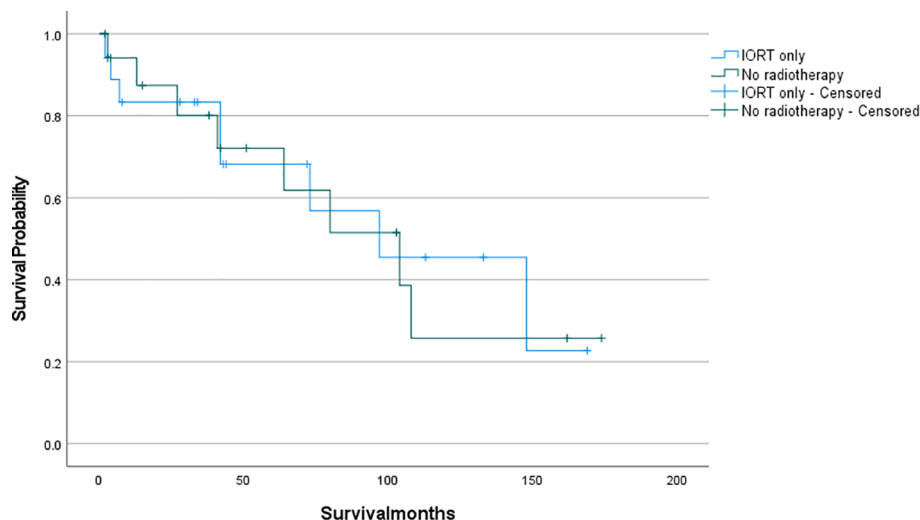


FIGURE 4

Patients who only received IORT compared to those who did not received radiotherapy ($P = 0.899$).

analyzing the group of patients not receiving IORT, leaving the benefits of IORT unclear (24).

Previous studies often included multiple histological types such as liposarcoma, leiomyosarcoma, malignant fibrous histiocytoma, etc. and did not specifically analyze liposarcoma. Most studies had limitations such as small sample sizes and unbalanced baseline characteristics. Additionally, some studies had design flaws, making it difficult to clearly distinguish between the effects of using IORT and not using IORT. Our study used a larger cohort specifically focusing on liposarcoma and balanced baseline characteristics through 1:1 PSM, making the cohorts more comparable. Additionally, we conducted a detailed analysis of the effects of IORT by comparing patients who received IORT to those who did not, those who received only IORT to those who received no radiotherapy at all, and those who received IORT in combination with other adjuvant radiotherapies to those who received only other adjuvant radiotherapies, eliminating interference from preoperative/postoperative adjuvant radiotherapy. However, the results indicated that receiving intraoperative radiotherapy had no impact on patient prognosis, regardless of whether adjuvant radiotherapy was administered.

This investigation aimed to examine the effects of IORT on the prognosis of RPL patients and suggest novel approaches for managing the entire process for these patients. Regrettably, our findings imply that IORT does not hold significant value for the prognosis of these patients. Based on the outcomes of numerous retrospective studies and the STRASS experiment, it is not recommended to use IORT as a routine treatment for RPL patients, because the effect of combined or single use of IORT is the same as that of other radiotherapy modalities. What's more, preoperative radiotherapy has the advantage that the target (tumor volume [GTV]) is clearly visible and can be more precisely defined to ensure repeatability and accuracy of the radiotherapy plan, and lower and, therefore, safer radiation doses are used before surgery (5). In conclusion, preoperative radiation might be the best option.

Moreover, previous studies have mainly reported LC as the primary endpoint for the benefit of IORT. While it is possible that IORT enhances LC, it may not translate into better OS due to some factors, leading our results to contradict some previous results. It is important to note, however, that our study results were influenced by a selection bias in the patients chosen for IORT. Our study is a retrospective exploratory research, and the results offer insight into future radiotherapy methods for RPL patients. Further prospective experiments could provide a better analysis of IORT's efficacy.

The subsequent generation of STRASS 2 trials will assess the influence of neoadjuvant chemotherapy in leiomyosarcoma and high-risk liposarcoma patients, thereby promoting the integrated treatment of RPS (25).

Our study has several limitations. The SEER database only includes U.S. data, potentially introducing selection bias by excluding patients treated elsewhere. It also lacks key treatment details such as surgical margins, resection extent, and radiotherapy doses, limiting our analysis, especially given the importance of surgical margins. Additionally, SEER's limited survival data prevents assessment of local control and recurrence rates, and the absence of TNM staging restricts patient staging analysis. As a retrospective study, inherent selection biases exist despite using 1:1

PSM to mitigate these. Nevertheless, SEER remains valuable for studying rare tumors and overcoming sample size limitations.

Conclusion

Our results suggest that IORT alone or combined with pre - or post-operative radiotherapy does not improve patients' OS. As an exploratory study, although the sample size is small and public data is used, we have conducted the first global exploration of the efficacy of IORT in RPL, which is expected to provide references for further prospective clinical research. Future studies should include prospective and randomized controlled trials. Additionally, further multicenter studies could not only increase the sample size but also enhance the representativeness and external validation of the research.

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 authors.

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

XZ: Writing – original draft. AZ: Writing – original draft. XL: Writing – original draft. ZX: Writing – original draft. YC: Writing – original draft. GY: Writing – original draft. YW: Writing – original draft. GZ: Writing – original draft. YH: Writing – original draft. CZ: Writing – original draft. FX: Writing – original draft. XM: Writing – review & editing. TW: Writing – review & editing. WL: Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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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OPEN ACCESS

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RECEIVED 29 August 2024

ACCEPTED 18 November 2024

PUBLISHED 04 December 2024

CITATION

Gao H, Liu S, Li W, Zou B and Miao C (2024)
Total retroperitoneal lipectomy improves
prognosis in patients with primary
retroperitoneal liposarcoma:
a comparative study.
Front. Oncol. 14:1488143.
doi: 10.3389/fonc.2024.1488143

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Total retroperitoneal lipectomy improves prognosis in patients with primary retroperitoneal liposarcoma: a comparative study

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Background: Retroperitoneal liposarcoma (RPLS) is the most common soft tissue sarcoma originating in the retroperitoneal space. Although surgery is the standard treatment, recurrence remains frequent. In this study, we aimed to explore the safety and efficacy of total (ipsilateral) retroperitoneal lipectomy (TRL) compared to traditional complete resection (CR) for primary RPLS.

Methods: We retrospectively analyzed patients with primary RPLS treated at our center between January 2014 and December 2020. Univariate and multivariable Cox regression analyses assessed the impact of demographic, operative, and clinicopathological variables on recurrence-free survival (RFS) and overall survival (OS). Kaplan-Meier plots illustrated RFS and OS, and the log-rank test compared time-to-event distributions.

Results: A total of 81 patients were included in the final analysis: 37 in the CR group and 44 in the TRL group. Demographic and clinicopathologic parameters were comparable between the two groups. Post-operative morbidity occurred in 30.9% of cases, with 15 (40.5%) in the CR group and 10 (22.7%) in the TRL group ($P=0.086$). There were 9 cases of severe complications at grade 3 or higher, with 5 cases in the CR group and 4 cases in the TRL group. There was no significant difference between the two groups ($P=0.314$). The TRL group demonstrated improved RFS and OS, particularly among dedifferentiated liposarcoma (DDLs) patients.

Conclusions: Total retroperitoneal lipectomy (TRL) appears to be a safe procedure that enhances survival outcomes in patients with primary RPLS. Further studies are needed to validate these findings.

KEYWORDS

retroperitoneal liposarcoma, total retroperitoneal lipectomy, complete resection, prognosis, complication

1 Introduction

Retroperitoneal liposarcoma (RPLS) is the most prevalent malignancy among retroperitoneal sarcomas (RPS), which accounts for approximately 0.15% of all adult cancers and has an incidence of 0.5–1 case per 100,000 (1, 2). RPLS poses significant challenges for treatment due to its potential of adjacent organ involvement and frequent recurrence. The role of radiation and systemic therapy in RPLS is not well defined, and surgery is currently the only potentially curative treatment choice (3, 4). Macroscopic complete resection (CR) combined with the resection of involved adjacent organs has been recommended for the treatment of RPLS. However, local recurrence remains common (40–85%) (4).

The inability to achieve a true R0 resection with the susceptible microscopic involvement of adjacent organs, structures, and surfaces might contribute to the high rate of postoperative recurrence in RPLS (5). Multiple satellite tumor foci may exist in the perceived normal adipose tissue that can be separated from the visible tumor (5, 6). Complications arising from recurrence, such as ileus, cachexia, and multiple organ dysfunction are the main cause of tumor related death. Many surgical oncologists recommend extended resection for RPLS to improve prognosis based on experience or clinical research (7, 8). However, Controversy exists over whether normal adipose tissue adjacent to the tumor should be removed in addition to combined resection of organs invaded by the tumor and abnormal adipose tissue.

In this regard, we reviewed primary RPLS patients treated with CR or TRL in our department, a center focused on the treatment of retroperitoneal tumors, to further clarify the effect of TRL in treating primary RPLS compared with traditional CR.

2 Materials and methods

2.1 Patient selection

Patients with unilateral primary RPLS who underwent resection with curative intent between January 2014 and December 2020 were identified from prospectively maintained sarcoma databases at our hospital. Only patients with well-differentiated liposarcoma (WDLPS) or dedifferentiated liposarcoma (DDLPS) who were treated with R0/R1 resection were included in this study. Patients with central (mesenteric) or primarily pelvic tumors, grossly incomplete (R2) resection, missing clinical information or history of other malignancies were excluded from this study.

Electronic medical records were retrieved to extract data on the following variables: (I) preoperative variables [i.e., age, gender, preoperative hemoglobin (Hb), albumin (ALB), receipt of neoadjuvant or adjuvant therapy, tumor size (maximum diameter), tumor site, and number of tumors (unifocal vs. multifocal)]; (II) intraoperative variables [i.e., type of surgery (TRL vs. CR), organs resected, operation duration, and estimated blood loss]; and (III) postoperative variables [i.e., histologic subtype, length of hospital stay, complications according to Clavien-Dindo

classification, dates of recurrence, and death]. To assess these variables, patients' medical history, radiologic imaging, operative notes, and pathological reports were reviewed and integrated by experienced multidisciplinary sarcoma specialists. A unifocal tumor was defined as 1 solitary tumor in the retroperitoneum, while multifocal tumors were defined as the presence of 2 or more non-contiguous tumors in the retroperitoneum, as determined by preoperative computed tomography (CT) scans and confirmed by intraoperative findings. Patients who had both WDLPS and DDLPS components in their tumors were classified as DDLPS.

2.2 Standard of CR and TRL

CR was defined as the surgical resection of the total tumor mass with grossly negative margins (R0/R1). To achieve this goal, *en-bloc* resection of the tumor with grossly involved adjacent organs and/or major vessels was carried out. In TRL, in addition to CR, all the ipsilateral retroperitoneal adipose tissue was removed, regardless of normal or abnormal fat. The anatomic extent of lipectomy in TRL was demarcated by the following 6 borders: anterior (the posterior surface of abdominal viscera); posterior (the psoas, iliopsoas, and other muscle surfaces); superior (the diaphragm surface); inferior (the iliac vascular surface); medial [the inferior vena cava surface (to the right) or abdominal aorta surface (to the left)]; and lateral (the lateral abdominal wall surface at mid-auxiliary line level). The aforementioned borders are shown in Figure 1.

2.3 Follow-up

Postoperative baseline CT scans were performed to ensure the complete removal of gross visible adipose tissue in all RPLS patients. Patients continued to receive CT scans of the abdomen/pelvis every 3 months for 2 years, and then every 6 months for 5 years as recommended by the National Comprehensive Cancer Network (NCCN, United States of America) and The Trans-Atlantic Retroperitoneal Sarcoma Working Group (TARPSWG). For patients with high-grade DDLPS tumors, contrast-enhanced CT of the chest was added as a form of surveillance imaging.

All patients were followed up by outpatient records or telephone conversations.

2.4 Statistical analysis

The TRL- and CR-related parameters were compared by independent sample t-tests for the numerical variables and Wilcoxon rank-sum test for the categorical variables. Recurrence-free survival (RFS) and overall survival (OS) were defined as the time from the date of surgery to the date of recurrence, or to death/last at follow-up, respectively. Survival curves were obtained by means of Kaplan-Meier plots to estimate the RFS and OS. The log-rank test was used to compare the survival outcomes. To identify the patient population that would benefit the most from TRL,

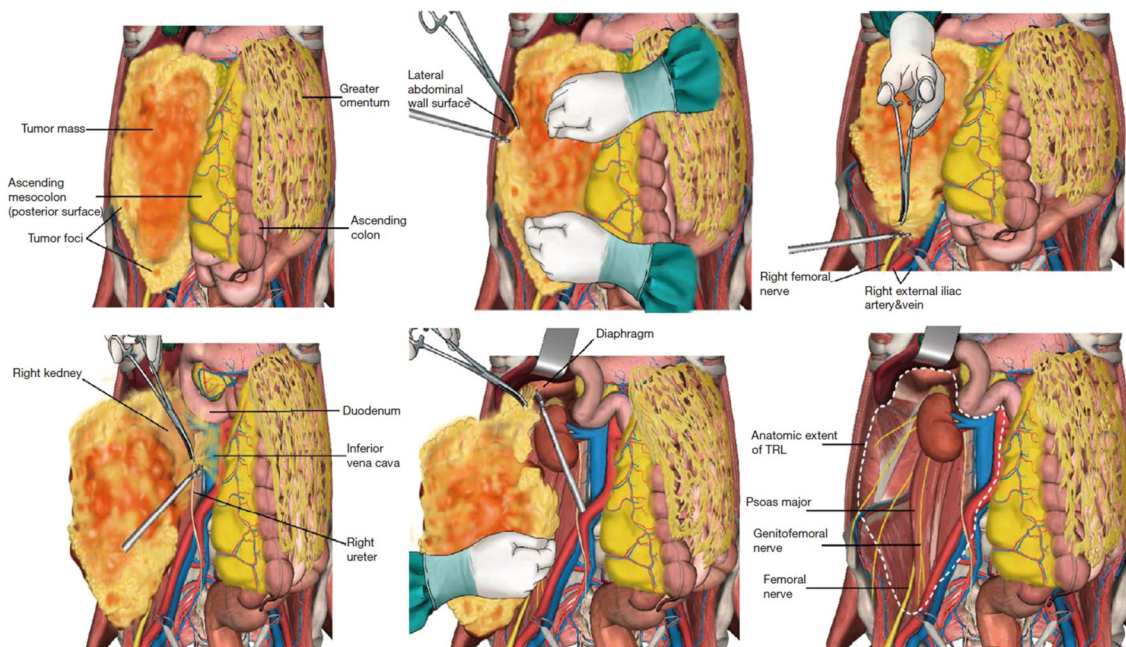


FIGURE 1

Schematic diagram of the six borders in the TRL procedure. Reproduced with permission from Miao et al. (8), licensed under CC BY-NC-ND 4.0.

univariable and multivariable Cox proportional-hazards regression models were used. Variables with P-values less than 0.1 in univariate Cox regression analysis are included in multivariate Cox regression analysis. All the statistical analyses were carried out using SPSS software (version 22.0), and a P value <0.05 was considered statistically significant.

3 Results

3.1 Baseline characteristics and surgery details

In total, 81 patients met the inclusion criteria for this study and were included in the final study, with 37 patients in the CR group and 44 patients in the TRL group. Clinicopathologic features of patients were listed in Table 1. As shown, there was no significant difference in gender, age, tumor size, tumor location, number of tumors, preoperative hemoglobin and albumin, adjuvant therapy or surgical details.

3.2 Post-operative morbidity

A total of 25 patients (30.9%) had postoperative complications. Among them, there were 15 cases (40.5%) in the CR group and 10 cases (22.7%) in the TRL group, with no significant difference between the two groups ($P=0.086$). Severe complications of grades 3 and 4 occurred in a total of 8 cases, with a rate of 9.9%. Among these, 5 cases (13.5%) were in the CR group and 3 cases (6.8%) were

in the TRL group, with no significant difference between the groups ($P=0.317$). There were no perioperative deaths, and no readmissions within 30 days after discharge.

3.3 Follow-up results

Patients were followed up by telephone or outpatient visits. The average follow-up duration was 61.5 months (range: 11–107). No patients were lost to follow-up, and all patients were included in the final survival analysis.

3.3.1 RFS

In the entire patient cohort, TRL group patients had significantly better recurrence-free survival (RFS) compared to CR group patients ($P=0.002$). The 1-year RFS rates were 80.2% and 59.5%, respectively ($P<0.001$), while the 3-year RFS rates were 46.9% and 32.4% ($P<0.001$). Subgroup analysis revealed that TRL improved RFS in DDLS patients ($P<0.001$), whereas in WDLS patients, there was no significant difference in RFS between TRL and CR groups ($P=0.443$). Additionally, TRL improved RFS in unifocal patients ($P=0.004$), while for multifocal patients, there was no significant difference in RFS between the two surgical approaches ($P=0.123$). (see Figures 2–6) In multivariate analysis, histology and post-operative complications were confirmed as independent factors correlated with tumor recurrence (Table 2).

3.3.2 OS

In the entire patient cohort, TRL group patients had significantly better overall survival (OS) compared to CR group

TABLE 1 Baseline characteristics of the 81 patients with primary retroperitoneal liposarcoma.

Variable		ALL	CR	TRL	P value
Gender					0.111
	Male	47	25	22	
	Female	34	12	22	
Age, years			54.7 ± 12.1	52.4 ± 12.7	0.409
Tumor size, cm					0.498
	≤10cm		6	4	
	10~20cm		10	10	
	≥20cm		21	30	
Location					0.934
	center		18	21	
	Right		19	23	
Number of tumors					0.570
	Unifocal		20	21	
	Multifocal		17	23	
Hemoglobin, g/L			118.7 ± 20.5	120.7 ± 22.2	0.681
Albumin, g/L			34.3 ± 5.6	36.5 ± 6.0	0.088
Adjuvant therapy					0.700
	Yes		4	6	
	No		33	38	
Combined evisceration					0.089
	Yes		23	19	
	No		14	25	
Operation duration, minutes			309 ± 129	315 ± 89	0.813
Estimated blood loss, ml, IQR		800 (400, 1625)	1000 (450, 1900)	650 (400, 1500)	0.152
Histology					0.371
	WDLS		14	21	
	DDLs		23	23	
Post-operative complications					0.084
	Yes		15	10	
	No		22	34	
Severe complications					0.314
	Yes		5	4	
	No		32	41	
Length of hospital stay, day			26.0 ± 14.5	22.0 ± 8.8	0.129

patients (P=0.030). The 1-year OS rates were 96.3% and 91.9%, respectively (P=0.015), while the 3-year OS rates were 91.4% and 83.8% (P=0.026). Subgroup analysis revealed that TRL improved OS in DDLS patients (P=0.033), while in WDLS patients, there was no significant difference in OS between the two surgical approaches (p=0.654). For both multifocal and unifocal patients, there was no significant difference in OS, with P-values of 0.082 and 0.119, respectively. (see [Figures 2–6](#)) In multivariate analysis, only histology was confirmed as independent factors correlated with tumor related death ([Table 3](#)).

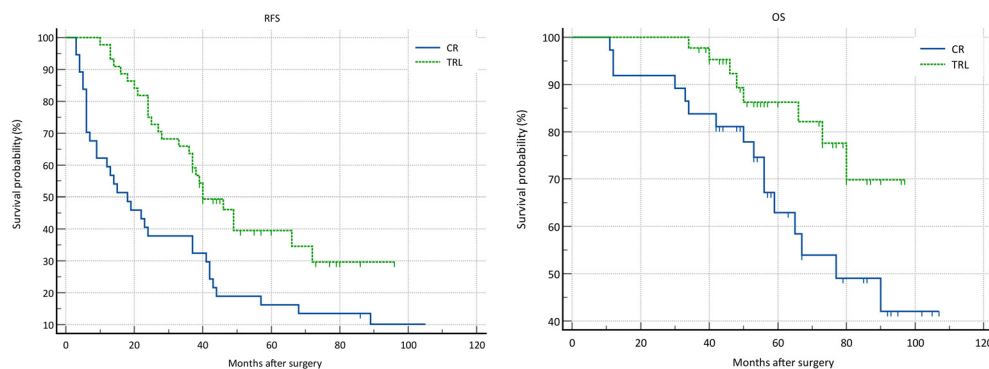


FIGURE 2
Comparison of RFS ($P=0.002$) and OS ($P=0.030$) Between CR and TRL group in all patients.

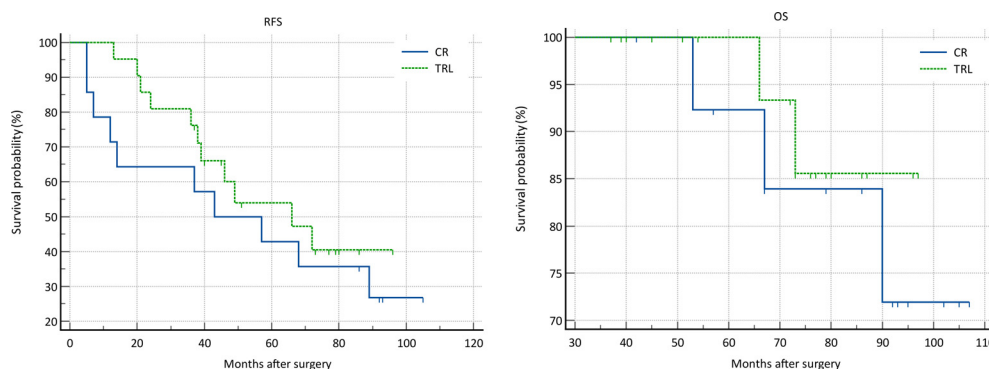


FIGURE 3
Comparison of RFS ($P=0.443$) and OS ($P=0.654$) between CR and TRL group in WDLS patients.

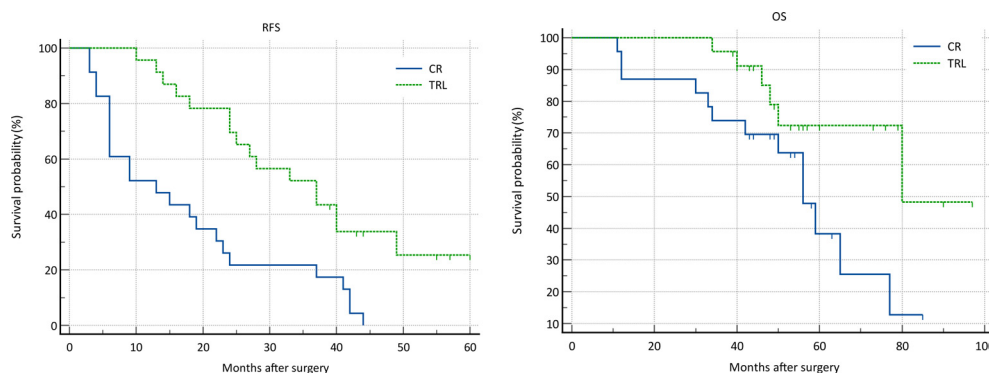


FIGURE 4
Comparison of RFS ($P<0.001$) and OS ($P=0.033$) between CR and TRL group in DDLS patients.

4 Discussion

Retroperitoneal liposarcoma (RPLS) is a relatively rare malignant tumor with four distinct histological subtypes. The most common subtypes are well-differentiated liposarcoma and dedifferentiated liposarcoma. Other less common types include

myxoid liposarcoma and pleomorphic liposarcoma. Well-differentiated liposarcomas (LPS) are characterized by low-grade malignancy, slow growth, and minimal symptoms. These tumors can reach a substantial size before diagnosis, and achieving R0 resections (complete removal) is often challenging (9). Notably, the rate of local recurrence for retroperitoneal LPS is significantly

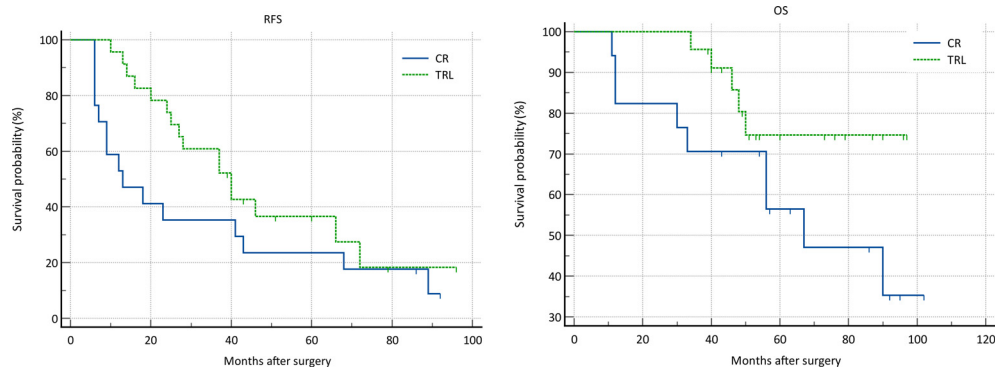


FIGURE 5
Comparison of RFS ($P=0.123$) and OS ($P=0.082$) between CR and TRL group in multifocal tumor patients.

higher than that for LPS with distant metastasis. In contrast, dedifferentiated LPS can exhibit extreme aggressiveness. Multifocal disease is common in retroperitoneal LPS. At initial presentation, 34% of patients have multifocal disease, and 57% of patients with unifocal disease progress to multifocal disease upon recurrence after chemotherapy or radiation (5, 10, 11). Therefore, when treating patients with retroperitoneal liposarcoma, both the extent of surgical resection and tumor biology must be carefully considered (6).

The current standard of care for treating RPLS involves complete resection (CR). However, CR is associated with a high rate of recurrence, necessitating more extensive resections (12–14). A novel surgical technique, known as total (ipsilateral) retroperitoneal lipectomy (TRL), has emerged. In TRL, the surgeon removes the ipsilateral retroperitoneal adipose tissue en bloc with the tumor, aiming not only for complete resection but also to address multifocal disease while preserving organs rather than performing aggressive resections. Despite being proposed by sarcoma surgeons, clinical studies evaluating the safety and efficacy of TRL remain limited. In our study, patients who underwent TRL surgery showed no significant difference in overall complication rates and rates of severe complications (Grade 3 or higher) compared to patients who underwent traditional CR surgery. These findings demonstrate excellent

safety. Furthermore, when compared to other studies, our results also indicate satisfactory safety (15, 16).

In all enrolled patients, TRL significantly improved patients' recurrence-free survival (RFS) and overall survival (OS). Notably, subgroup analysis revealed that this survival benefit was only present in patients with dedifferentiated liposarcoma (DDLs). This suggests that due to the generally milder and less aggressive nature of WDLS, satisfactory treatment outcomes can be achieved with CR surgery alone. However, it is common for tumors in the same patient to contain both well-differentiated and dedifferentiated components (17). Histologic type has long been considered the most important factor affecting the prognosis of retroperitoneal soft tissue sarcomas, including its impact on overall survival, recurrence-free survival, and distant metastasis (18–20). The impact stems from poorly differentiated sarcomas, known for their high invasiveness and indistinct margins, often infiltrating nearby structures. This can result in microscopic residual tumors at the surgical margin, even when an R0 resection appears successful macroscopically, thereby increasing recurrence risk and reducing disease-free survival. There is currently no established method for effectively assessing pathological margins and the extent of infiltration in retroperitoneal soft tissue sarcomas, either preoperatively or intraoperatively. Surgeons must depend on their experience to determine tumor borders or the depth of invasion into nearby organs, which guides decisions on the extent of resection. The

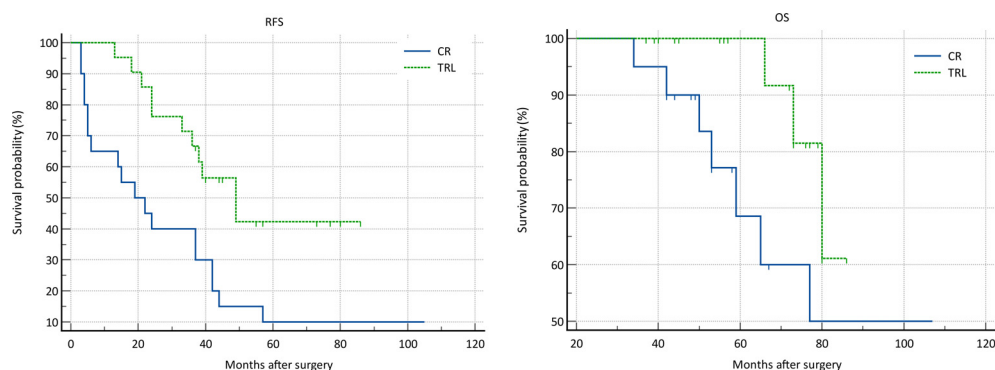


FIGURE 6
Comparison of RFS ($P=0.004$) and OS ($P=0.119$) between CR and TRL group in unifocal tumor patients.

TABLE 2 Univariable and multivariable analysis of associations between clinicopathological factors and RFS.

Variable	Univariate analysis			Multivariate analysis		
	HR	95%CI	P value	HR	95%CI	P value
Gender (female vs. male)	0.7018	0.4179-1.1785	0.177	–	–	–
Age, year	1.0025	0.9823-1.0230	0.811	–	–	–
Tumor size, cm						
10~20 vs. <10	1.1065	0.4668-2.6224	0.818	–	–	–
>20 vs. <10	1.0349	0.4785-2.2385	0.931	–	–	–
Location (left vs. right)	0.5610	0.3333-0.9441	0.028	0.5873	0.3396-1.0033	0.051
Number of tumors (multifocal vs. unifocal)	1.1070	0.6666-1.8384	0.694	–	–	–
Hemoglobin, g/L	0.9951	0.9832-1.0073	0.434	–	–	–
Albumin, g/L	0.9621	0.9206-1.0055	0.091	1.0001	0.9518-1.0509	
Adjuvant therapy (yes vs. no)	1.7815	0.8639-3.6734	0.142	–	–	–
Combined evisceration (yes vs. no)	1.8467	1.0320-3.0931	0.019	1.2497	0.6694-2.3331	0.484
Operation duration, min	1.0023	0.9997-1.0050	0.086	1.0000	0.9969-1.0031	0.991
Estimated blood loss, ml	1.0002	1.0000-1.0003	0.138	–	–	–
Histology						
DDLS vs. WDLS	2.9811	1.6572-5.3627	<0.001	2.9121	1.5603-5.4351	0.001
Post-operative complications (yes vs. no)	2.5136	1.4687-4.3021	0.001	2.4418	1.0992-5.4239	0.028
Severe complications (yes vs. no)	1.4190	0.6067-3.3188	0.440	–	–	–
Length of hospital stay, day	1.0193	0.9978-1.0412	0.094	0.9870	0.9561-1.0189	0.419
TRL vs. CR	0.4588	0.2746-0.7665	0.003	0.4631	0.27310.7850	0.004

TABLE 3 Univariate and multivariate analysis of associations between clinicopathological factors and OS.

Variable	Univariate analysis			Multivariate analysis		
	HR	95%CI	P value	HR	95%CI	P value
Gender (female vs. male)	0.2949	0.1099-0.7911	0.015	0.4936	0.1631-1.4942	0.212
Age, year	1.0260	0.9914-1.0618	0.142	–	–	–
Tumor size, cm				–	–	–
10~20 vs. <10	0.5714	0.1573-2.0755	0.395	–	–	–
>20 vs. <10	0.5867	0.1898-1.8139	0.355	–	–	–
Location (left vs. right)	0.6901	0.3014-1.5800	0.374	–	–	–
Number of tumors (multifocal vs. unifocal)	1.5181	0.6712-3.4337	0.313	–	–	–
Hemoglobin, g/L	0.9719	0.9536-0.9906	0.003	0.9754	0.9467-1.0051	0.103
Albumin, g/L	0.8966	0.8381-0.9592	0.002	1.0171	0.9066-1.1410	0.773
Adjuvant therapy (yes vs. no)	1.8869	0.6398-5.5652	0.250	–	–	–
Combined evisceration (yes vs. no)	2.3810	1.0230-5.5034	0.043	0.8485	0.2850-2.5262	0.768
Operation duration, min	1.0033	0.9999-1.0067	0.059	0.9981	0.9932-1.0031	0.464
Estimated blood loss, ml	1.0002	1.0000-1.0004	0.020	1.0000	0.9998-1.0003	0.723

(Continued)

TABLE 3 Continued

Variable	Univariate analysis			Multivariate analysis		
	HR	95%CI	P value	HR	95%CI	P value
Histology						
DDLS vs. WDLS	6.1106	2.2131-16.8721	<0.001	4.3936	1.3598-14.1964	0.013
Post-operative complications (yes vs. no)	4.2402	1.8759-9.5840	<0.001	2.9746	0.8703-10.1668	0.082
Severe complications (yes vs. no)	2.1589	0.6335-7.3577	0.219	–	–	–
Length of hospital stay, day	1.0269	0.9930-1.0618	0.121	–	–	–
TRL vs. CR	0.4017	0.1714-0.9413	0.036	0.4168	0.1638-1.0609	0.0663

possibility of postoperative complications affects the decision-making process regarding combined organ resection to secure clear margins. For instance, removing organs like the colon, kidney, and psoas generally poses a low risk of severe postoperative complications, whereas resections involving the pancreas, duodenum, or major blood vessels are associated with higher risks of severe complications. Assessing tumor differentiation based solely on imaging and gross examination is unreliable. Therefore, relying solely on imaging to determine the differentiation type and depth of tumor invasion for retroperitoneal liposarcomas (LPS) when deciding between CR or TRL surgery is not feasible (8, 21–23). Studies by Singer et al. indicates that the condition of the surgical margin independently influences the prognosis of RPLS (24–26). Therefore, on the basis of controlling the risk of complications, adopting more aggressive surgical techniques to achieve negative margins becomes essential. Unfortunately, due to the lack of description of margin status in the postoperative pathological results of most patients, we were unable to incorporate and analyze data on margins in this study. Nevertheless, considering the similar safety profiles observed in the study for both surgical approaches, we still recommend TRL surgery for all retroperitoneal LPS cases.

Multifocal disease has profound effects on the oncological outcomes of retroperitoneal liposarcoma (RPLS) patients. In a recent study, 20% of patients presented with multifocal disease, and the 5-year overall survival (OS) rate was significantly lower in the multifocal group than the unifocal group (11). Another study found that 25% of RPLS patients presented with multifocal disease, which was associated with curtailed OS (23). Additionally, a clinical study that included both primary and recurrent RPLS cases showed that the proportion of multifocal disease at initial presentation was 45% (23% for primary cases and 22% for first-recurrent RPLS). Interestingly, the 3-year OS rate after TRL was significantly higher than the 3-year OS rate after CR in patients with multifocal disease (27). Our own research findings indicate that although TRL did not demonstrate improved RFS and OS compared to CR surgery for multifocal liposarcomas among primary RPLS patients, it also did not perform worse than CR. Therefore, our results are consistent with the recommendation of TRL for multifocal RPLS based on the previous study.

Our study had several limitations. First, due to its retrospective nature, our study had inherent biases. Second, the low incidence rate of RPLS results in a scarcity of specialized centers dedicated to diagnosing and treating this disease. Patients are often dispersed across various

surgical specialties such as gastrointestinal surgery and urology. Conducting standardized, multicenter clinical studies specifically targeting this condition becomes challenging, which in turn limits the number of patients included in our research. Nevertheless, the critical clinicopathological characteristics were comparable between the two groups. Notably, the proportion of patients receiving adjuvant therapy was relatively low. This allowed us to more accurately compare the effectiveness of the two surgical approaches while minimizing interference from nonsurgical therapies.

5 Conclusion

Total (ipsilateral) retroperitoneal lipectomy (TRL) is a relatively safe surgical approach for primary retroperitoneal liposarcoma (RPLS) patients. It has been associated with significantly better recurrence-free survival (RFS) and overall survival (OS) in particular subsets of patients. Further clinical research is needed, particularly in experienced sarcoma centers, to design more standardized and larger-scale studies that can validate the therapeutic efficacy of TRL for RPLS.

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 Institutional Review Board of Peking University International 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.

Author contributions

HG: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. SL: Data curation, Investigation,

Software, Validation, Writing – review & editing. WL: Conceptualization, Data curation, Validation, Visualization, Writing – review & editing. BZ: Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – review & editing. CM: Funding acquisition, Project administration, Resources, Supervision, Validation, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Peking University International Hospital Research Fund (No. YN2021ZD04).

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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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OPEN ACCESS

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RECEIVED 21 August 2024

ACCEPTED 25 November 2024

PUBLISHED 11 December 2024

CITATION

Liu H, Wang X, Liu L, Yan B, Qiu F and Zhou B (2024) Targeting liposarcoma: unveiling molecular pathways and therapeutic opportunities.
Front. Oncol. 14:1484027.
doi: 10.3389/fonc.2024.1484027

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Targeting liposarcoma: unveiling molecular pathways and therapeutic opportunities

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In recent years, an increasing number of studies have utilized molecular biology techniques to reveal important molecular heterogeneity among different subtypes of liposarcoma. Each subtype exhibits distinct genetic patterns and molecular pathways, which may serve as important targets for molecular therapy. In the present review, we focus on the molecular characteristics, molecular diagnostics, driver genes, and molecular mechanisms of liposarcoma. We also discuss the clinical research progress of related targeted therapies, with an aim to provide a reference and crucial insights for colleagues in the field.

KEYWORDS

liposarcoma, driver genes, molecular pathogenesis, targeted therapy, outlook

1 Introduction

Liposarcoma (LPS) is the most common soft tissue sarcoma (STS) in adults, accounting for 15%–20% of STS, and can also occur in adolescents and children. It is a malignant tumor derived from adipose cell differentiation (1). According to the fifth edition of the World Health Organization Classification of Tumors of Soft Tissue and Bone, published in 2020 (2), the LPS subtypes comprise atypical lipomatous tumor (ATL)/well-differentiated LPS (WDLPS), dedifferentiated LPS (DDLPS), myxoid LPS (MLPS), pleomorphic LPS (PLPS), and myxoid pleomorphic LPS. The main treatment for all LPS subtypes is surgical resection; however, for patients with unresectable, advanced, or metastatic LPS, treatment options are currently limited and often ineffective, resulting in a generally poor prognosis. New drugs are therefore urgently needed to improve the current state of treatment. In recent years, the continuous development of molecular biology techniques has resulted in the stratification of genetic subgroups within LPS. Concurrently, an increasing number of clinical and research-oriented treatments have been tested based on an understanding of the specific molecular pathology of each subtype; these studies have yielded good progress and results. In the present review, we discuss the molecular characteristics, molecular

diagnostics, driver genes, and molecular pathogenesis of LPS. We also explore the corresponding therapeutic targets and downstream pathways, and summarize progress toward targeted therapies for several subtypes of LPS.

2 Molecular characteristics of LPS

The LPS subtypes differ in their clinical behaviors, treatment sensitivities, and underlying biological characteristics. In the following sections, the detailed molecular characteristics of each subtype are described in terms of genomics, proteomics, and epigenetics.

2.1 Genomics

The different STS subtypes exhibit molecular heterogeneity. Nacev et al. identified specific somatic mutations and copy number alterations in some subtypes via the genetic sequencing of STS samples, and compared tumor mutational burden and microsatellite instability across the different subtypes (3). STS can be divided into two genomic categories. One category (80%) consists of tumors with complex karyotypes, such as leiomyosarcoma, undifferentiated pleomorphic sarcoma, DDLPS, and anigosarcoma. These tumors are characterized by many gene rearrangements and chromosomal gains or losses that often include cell cycle-related genes such as *TP53*, *MDM2*, *RB1*, and *CDK4* (4). The other category (20%) consists of tumors with specific genetic alterations, such as gene translocations and activating point mutations (5). Importantly, tumors with specific genetic alterations can also develop complex karyotypes as the tumor progresses. Taylor et al. reported that different subtypes of retroperitoneal liposarcoma (RPL) have distinct genomic landscapes, and discussed the genomic differences between RPL and extremity LPS (6).

WDLPS and DDLPS share several common genetic features. Research by Wagner and his team indicates that WDLPS and DDLPS evolve from common precursors into distinct patterns (7). The molecular signatures of both subtypes are characterized by amplifications in the 12q13-15 region on the long arm of chromosome 12 (8). Molecular testing indicates that approximately 90% of WDLPS/DDLPS cases have confirmable *MDM2* and *CDK4* gene amplifications, which are the primary driver genes (9). In recent years, an increasing number of whole-genome sequencing studies have identified that additional gene amplifications within the 12q13-15 region in WDLPS/DDLPS (such as the amplification of *HMG2*, *TSPAN31*, *FRS2*, *GLI1*, *YEATS4*, *YEATS2*, *NAV3*, and *CPM* in WDLPS), new genes outside the 12q13-15 region (such as *DDR2* and *SDHC* in WDLPS, and *FGFR3* in DDLPS), and receptor tyrosine kinase (RTK)-related signaling pathways are closely associated with the occurrence and progression of WDLPS/DDLPS (10–12).

Given the shared genetic characteristics between DDLPS and WDLPS, and the observation of both well-differentiated and poorly

differentiated areas in many DDLPS samples, DDLPS is commonly believed to evolve from WDLPS. However, these two sarcomas differ substantially. During dedifferentiation, ongoing DNA damage leads to genomic instability and the further accumulation of complex genomic aberrations. In DDLPS, pathways related to cell proliferation and the DNA damage response are upregulated, whereas in WDLPS, pathways related to adipocyte differentiation and metabolism are upregulated (13). Studies have also reported that the loss of 11q23 and the amplification of 6q23 or 1q32 (or the co-amplification of 6q23 and 1q32) are DDLPS-specific genomic abnormalities. Additionally, intrachromosomal and interchromosomal gene rearrangements and gene fusions (such as *C15orf7::CBX3*, *CTDSP1::DNM3OS*, and *CTDSP2::DNM3OS*) have been identified in DDLPS but not in WDLPS. *DDIT3* is also amplified in DDLPS patients (14). Furthermore, a study that comprehensively analyzed the molecular characteristics of retroperitoneal sarcoma-WDLPS revealed that *FOXD4L3* has periodic mutations that interact with the PAX pathway to promote tumorigenesis. Moreover, the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) and mitogen-activated protein kinase (MAPK) pathways, as well as genes associated with the transition from an adipose to a “tumor” phenotype, are all dysregulated (15). Pollock et al. reported that Aurora A kinase (AURKA) is significantly overexpressed in retroperitoneal sarcoma-DDLPS and is strongly associated with metastasis and recurrence (16). Combined, large-scale whole-exome and RNA sequencing in Japan has revealed that somatic copy number alterations are the most common genomic mutations in DDLPS (17). The frequency of mutations varies for each chromosome, ranging from 0.114 (chromosome 21) to 0.482 (chromosome 12). In this study, DDLPS was then divided into the following three groups based on the associations between somatic copy number alterations and clinical features: cluster 1, with only 12q15 high magnification; cluster 2, with 12q15 and 1p32.1 high magnification; and cluster 3, without 12q15 high magnification. A survival analysis conducted after the genomic clustering revealed that, compared with cluster 1 patients, cluster 2 DDLPS patients had better progression-free survival (PFS) rates. Multivariate regression analysis revealed that cluster 1 was a significant predictor of poor PFS, independent of the surgical margin and primary tumor site. Furthermore, a comparative analysis of WDLPS and DDLPS components revealed that the gene sets associated with cell cycle progression, including the G2/M checkpoint and *E2F* target genes, were significantly enriched in DDLPS. By contrast, a gene set associated with adipocyte differentiation or lipid metabolism, including adipogenesis and fatty acid metabolism, was significantly enriched in WDLPS.

Lago et al. reported that DNA G-quadruplexes (G4s) in the promoters of lipopolysaccharide-treated cells are associated with high transcription levels in open chromatin, indicating that promoter G4s and related transcription factors work in concert to form cell-specific transcriptional programs (18). Moreover, Richter et al. reported that mouse double minute 2 homolog (MDM2) induces the formation of stable G-quadruplexes, which are specifically recognized by cellular helicases. The targeting of G-

quadruplexes can reduce MDM2 expression and p53 degradation, thereby promoting cell cycle arrest and apoptosis in cancer cells (19).

MLPS is genetically characterized by the translocation of t (12;16)(q13;p11) in more than 95% of cases; this results in the *FUS-DDIT3* fusion gene, which stimulates cell proliferation and disrupts adipogenic differentiation (20). The remaining 5% of MLPS cases are genetically characterized by the translocation of t (12;22)(q13;q12), which results in the *EWSR1-DDIT3* fusion gene (20). These features are considered unique to MLPS. Additionally, high *RET* expression has been observed in MLPS, and approximately 25% of all cases have mutations that activate the PI3K/AKT/mammalian target of rapamycin (mTOR) signaling pathway (21). Moreover, over 50% of MLPS cases carry mutations in the *TERT* promoter (22).

PLPS is characterized by marked chromosomal abnormalities, including chromosomal deletions and duplications (23). Although related molecular research is limited, studies have reported that mutations or inactivation of *RB1* are associated with PLPS development (24). Furthermore, genetic testing of a metastatic lesion in a patient with uterine PLPS with liver metastasis revealed an *IQGAP-NTRK3* gene fusion (25).

Myxoid pleomorphic LPS exhibits complex chromosomal changes; however, it lacks the *FUS-DDIT3* gene fusion that is characteristic of MLPS and the *MDM2/CDK4* gene amplification found in DDLPS (2). Molecular research in this area is also limited.

2.2 Proteomics

Proteomic technologies and strategies are increasingly being applied to the study of STS. Huang et al. conducted proteomic analyses of different STS subtypes. By mining the proteomic data of cluster of differentiation 3 (CD3)⁺ tumor-infiltrating lymphocyte (TIL) groups in patients with DDLPS, these authors revealed that the high CD3⁺ TIL group was enriched in aspects such as T-cell activation, T-cell receptor signaling, leukocyte proliferation, cell adhesion, and the interferon response. By contrast, the low-CD3⁺ TIL group was enriched in the complement cascade, with an active complement system. These findings support the future evaluation of combination therapy with anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) checkpoint inhibitors and complement inhibitors to treat DDLPS patients in the low CD3⁺ TIL group (26, 27). Moreover, the data from this study suggest that, at the protein level, cyclin-dependent kinase 4 (CDK4) is expressed at a relatively high level in DDLPS. This finding is consistent with the amplification of *CDK4* in many DDLPS, although no enriched ontology was observed in an overexpression analysis of DDLPS. It has also been reported that vesicular trafficking proteins are an independent prognostic factor for distant metastasis. In addition, through the joint analysis of proteomic and phosphorylation data, a team led by Ding demonstrated STS subtypes with different molecular characteristics and clinical outcomes, and identified the key driving molecules for STS metastasis and proliferation (28). Fat

metabolism-related pathways, peroxisome proliferator-activated receptor (PPAR) pathways, and vitamin metabolism pathways are significantly upregulated in DDLPS and MLPS. Furthermore, the PI3K/AKT/mTOR signaling pathway was significantly upregulated in DDLPS. Numerous molecular markers associated with pathological subtypes were also validated, including CDK4 in DDLPS. Notably, this study conducted an integrated analysis of histopathological subtypes, a hierarchical clustering of pathological subtypes, a proteomic analysis of subtypes, and an analysis of immune subtypes. The findings revealed the relationships between STS subtypes under different classification criteria, as well as their respective molecular, pathway, and clinical characteristics. In this integrated analysis, a detailed division of STS was noted, and STS heterogeneity was explored in great detail.

Together, these findings indicate that LPS has extensive molecular heterogeneity. Further exploration and discoveries of molecular differences and unique molecular characteristics will provide a wide range of ideas and directions for the experimental design and treatment of LPS.

3 Driver genes and molecular mechanisms

The generation of different LPS subtypes is caused by their relatively unique driver genes and molecular mechanisms, which ultimately lead to large differences between subtypes. In the following sections, the main driver genes and molecular pathways of each LPS subtype are described.

3.1 Molecular mechanisms related to WDLPS/DDLPS

3.1.1 Molecular mechanisms associated with MDM2 amplification in WDLPS/DDLPS

The most important function of MDM2 is to control p53 activity, by acting as a negative regulator of p53 (29). MDM2 amplification is mutually exclusive with p53 gene mutation; when MDM2 is amplified, p53 is not mutated, and only wild-type p53 is present (30). The cellular tumor antigen p53 (TP53) pathway in cancer cells can be reactivated by inhibiting MDM2–TP53 interactions, thereby inducing apoptosis and inhibiting tumorigenesis.

MDM2 may also promote tumor growth through other mechanisms. Cyclin-dependent kinase inhibitor 2A (CDKN2A, also known as P14ARF or p16INK4a) is a tumor suppressor protein encoded by *CDKN2A*, which is overexpressed in WDLPS/DDLPS. CDKN2A causes MDM2 to be localized in the nucleolus, thus preventing TP53 degradation (31). Furthermore, MDM2 regulates serine metabolism and redox homeostasis independently of TP53 to drive tumor growth, and targeting the function of MDM2 in serine metabolism can inhibit DDLPS growth (32). Chen et al. reported that panhistone deacetylase 2 (HDAC2) is co-expressed with MDM2 in DDLPS, and that specific targeting of HDAC2 can reduce the expression of MDM2, which plays a role in antitumor activity (33).

3.1.2 Molecular mechanisms associated with CDK4 amplification in WDLPS/DDLPS

CDK4 plays a role in LPS progression by negatively regulating the retinoblastoma protein (Rb) signaling pathway. However, CDK4 can also promote tumor growth through mechanisms that are independent of the Rb pathway. For example, CDKN2A overexpression can inhibit the Rb pathway-dependent function of CDK4 (34).

3.1.3 Role of the fibroblast growth factor/FGF receptor signaling pathway in LPS

In LPS, studies have identified activating mutations, amplifications, and the overexpression of genes related to the FGFR pathway (35–37). FGFR1 and FGFR4 overexpression is observed in approximately 30% of DDLPS cases and is associated with a poor prognosis (38). In approximately 90% of DDLPS cases, *FRS2* is coamplified with *MDM2* and plays a role in tumor progression. Additionally, FGFR2 is overexpressed in MLS, where it regulates cell proliferation, apoptosis, and migration (39).

3.1.4 Possible molecular mechanisms of dedifferentiation

Although up to 10% of WDLPS can progress to DDLPS, molecular research on the progression from WDLPS to DDLPS remains limited. Amplification events, such as c-Jun amplification during dedifferentiation, play a role in the occurrence and development of LPS. In DDLPS, transcription factor Jun (JUN) and apoptosis signal-regulating kinase 1 (ASK1)/mitogen-activated protein kinase 5 (MAP3K5) are coamplified; these are located in the regions of chromosomes 6q23 and 1p32. By contrast, these changes have never been reported in WDLPS. JUN amplification is strongly associated with DDLPS, although it is also observed in some cases of ATL and WDLPS. Approximately 91% of DDLPS cases express c-Jun, whereas its amplification or expression is rare in pure WDLPS. Both the *JUN* and *ASK1/MAP3K5* products are involved in the c-Jun N-terminal kinase (JNK) signaling pathway. *JUN* encodes a protein that regulates the activity of transcription-related factors in adipocytes, and *ASK1* encodes a kinase that activates the JNK pathway, leading to JUN activation. *JUN* or *ASK1* amplification suggests that the dedifferentiation of WDLPS ultimately leads to changes in the tissue type and the development of DDLPS (10).

In a study of exome and transcriptome sequencing data from 17 patients diagnosed with both WDLPS and DDLPS, DDLPS samples generally had a slightly greater mutational burden than matched WDLPS samples; however, this apparent difference did not reach significance. When the overall differences in gene expression between WDLPS and DDLPS samples were compared, 357 genes were highly expressed in WDLPS tumors compared with DDLPS tumors; *FABP4*, *ADIPOQ*, *LPL*, *LEP*, and *PTGER3* had the highest gene expression. The 395 genes that were less highly expressed in WDLPS tumors included the genes that were upregulated in DDLPS. In addition, among the known markers of adipocyte differentiation, *PPARG*, *CEBPB*, *CEBPD*, *FOXO1*, *FOXO3*, *FOS*, *JUN*, *MYC*, and *CDKN1A* were also expressed at higher levels in WDLPS than in DDLPS.

In nine frozen pairs of WDLPS and DDLPS samples, 933 gene fusion transcripts were identified, with a median of 39 fusion transcripts per sample. Notably, the number of fusions in DDLPS samples was significantly greater than that in matched WDLPS samples. In DDLPS samples, only 17% of fusions were shared with homologous WDLPS samples, on average. This finding suggests that, after detachment from the clonal origin, new chromosomes in DDLPS tumors may experience more break-fusions than those in WDLPS tumors. *HMGA2* and *CPM* fusions on Chr12q occurred more frequently and were more prevalent in DDLPS samples than in WDLPS samples. In addition, *HMGA2* was significantly overexpressed in DDLPS samples. Shared somatic mutations indicated the clonal origin of matched WDLPS and DDLPS tumors, with early differentiation and genomic instability caused by the continued production and selection of new chromosomes. The random generation and expression of fusion transcripts of new chromosomes, such as *HMGA2* and *CPM*, may influence subsequent tumor differentiation status (40).

The amplification of genes located at chromosome 12q13-15 differs significantly between WDLPS and DDLPS, and may be related to progression and dedifferentiation. Amplification of the following genes in the 12q region was confined primarily to DDLPS: *MAP3K12*, *TBX5*, *CDK2*, *GLI1*, and *ALX1*. Moreover, DDLPS had a significantly higher average amplification rate than WDLPS. A key component of dedifferentiation is the loss or downregulation of adipogenesis, which leads to the formation of nonadipogenic masses that are histologically indistinguishable. Various genes are involved in fat cell metabolism. Some of these genes, including *PLIN*, *PLIN2*, and *LIPE*, are uniquely absent in DDLPS, suggesting that these cells have lost their ability to function as fat.

Bouزيد et al. reported that *HMGA2* amplification is significantly associated with ATL/WDLPS but not DDLPS (10). Furthermore, Wood et al. speculated that several potential parallel signaling pathways may be involved in the dedifferentiation process of WDLPS/DDLPS (41). The Wnt signaling pathway reportedly inhibits preadipocyte differentiation (42). Moreover, Wnt signaling plays an important role in LPS occurrence and development (11). The Wnt antagonist Frzb reduces c-Met expression and inhibits Met-mediated signaling, which may be a new therapeutic strategy for STS (43). MiR-193b targets the Hippo signaling effector YAP1 to indirectly inhibit Wnt/ β -catenin signaling, resulting in the inhibition of LPS cells (44). Hedgehog signaling is also involved in the regulation of adipogenesis, with one study suggesting that the aberrant activation of Hedgehog signaling during adipose tissue development leads to myogenic cell-derived rhabdomyosarcoma (45). Gli is reported to be commonly coamplified with *MDM2* and *CDK4*, and Gli-mediated upregulation of the Hedgehog signaling pathway is enriched in dedifferentiated adipose progenitor cells and DDLPS tumor cells, resulting in undesirable immune cell infiltration of the tumor (46). Notch signaling also plays a role in the adipocyte differentiation process. A recent study reported that Notch signaling activation is associated with DDLPS occurrence through the inhibition of lipid metabolism (47).

Notably, a synthetic PPAR- γ ligand reverses DDLPS dedifferentiation and blocks LPS formation. Moreover, activation

of the autophagy and phosphatase and tensin homolog (PTEN)/PI3K/AKT/mTOR pathways can inhibit Notch signaling, thereby promoting the adipogenic differentiation of mesenchymal stem cells (48). Activation of the Notch/platelet-derived growth factor receptor beta (PDGFR β) signaling pathway can also inhibit the differentiation of brown adipose progenitor cells in mice (49). Furthermore, the synthesis of PPAR- γ ligands reverses DDLPS cell dedifferentiation and prevents LPS formation (47).

3.1.5 Changes in microRNA expression in WDLPS/DDLPS

The differential expression of multiple miRNAs has been identified in WDLPS/DDLPS and may have an important effect on WDLPS/DDLPS growth. In one study, more than 40 dysregulated miRNAs were identified in DDLPS, and restoring the expression of downregulated miR-143 inhibited DDLPS cell proliferation and induced apoptosis (50). In another study, compared with normal adipose tissue, miR-155 expression was upregulated in all LPS subtypes except WDLPS, and the knockdown of overexpressed miR-155 inhibited DDLPS proliferation and growth (51). A later study revealed 35 miRNAs (four with high expression and 31 with low expression) that were able to distinguish between WDLPS/DDLPS and normal fat (52). The targeting of these aberrantly expressed miRNAs may have therapeutic potential for patients with WDLPS/DDLPS; however, their exact roles and mechanisms of action in WDLPS/DDLPS remain to be clarified.

3.2 Preclinical research advances in determining the molecular mechanisms of MLS

3.2.1 Role of the Hippo/YAP1 pathway in MLS

Hartmann et al. reported that MLS occurrence and development depend on the Hippo/YAP1 pathway, and that the *FUS-DDIT3*-driven tyrosine-protein kinase receptor (IGF-IR)/PI3K/AKT signaling pathway promotes the stability and nuclear accumulation of YAP1 by “turning off” the Hippo signal. *FUS-DDIT3* and YAP1/TEAD colocalize in mesenchymal stem cells and MLS cells to jointly regulate proliferation, cell cycle progression, apoptosis, and adipogenic differentiation (53, 54). Moreover, an increasing body of research emphasizes the importance of dysregulated Hippo signaling in MLS (55).

3.2.2 Key functional interactants of *FUS-DDIT3* in chromatin remodeling complexes in MLS

Nelson et al. reported that several members of chromatin remodeling complexes, including NuRD (Nucleosome Remodeling and Deacetylase) and SWI/SNF (SWItch/Sucrose NonFermenting), are present in the *FUS-DDIT3* interactome and play key roles in regulating genomic structure and gene expression (56). Kadoch et al. confirmed that, in MLS, *FUS-DDIT3* inhibits the targeting and activity of the BAF complex, thereby suppressing DNA accessibility and failing to activate the target gene *CEBPB* (an

adipogenic transcription factor), which ultimately reduces adipogenesis (57). Additionally, *FUS-DDIT3* activates the SRC/focal adhesion kinase (FAK)/RHOA/C GTPases (RHO)/Rho-associated coiled-coil-containing protein kinases (ROCK) signaling axis in MLS to increase the invasive capacity of MLS cells (58).

3.2.3 Others

The bromodomain and extraterminal domain (BET) family is a group of epigenetic regulatory proteins that can modulate gene expression and are involved in tumor occurrence and development. Chen et al. reported that BET proteins promote core transcriptional regulatory programs in DDLPS (59). Furthermore, Xu et al. reported that the absence of MAPK-interacting serine/threonine protein kinases 1 and 2 (MNK1/2) inhibits STS occurrence (60).

3.3 Roles of long noncoding RNAs in LPS

Kirtonia et al. reported that many oncogenic long noncoding RNAs, including *MALAT1*, *PVT1*, *SNHG15*, *LINC00152*, and *MIR210HG*, are differentially expressed in LPS (61). Similarly, Yuhong et al. reported that *LINC00423* expression is downregulated in retroperitoneal sarcoma; this is primarily caused by the disruption of *NFATC3* stability, thus activating the MAPK signaling pathway (62).

3.4 Interaction of extracellular vesicles in the tumor microenvironment of LPS

Cancer-derived extracellular vesicles facilitate intercellular communication and transport bioactive molecules within the tumor microenvironment to impact tumor occurrence, progression, and metastasis. In RPL-DDLPS, extracellular vesicles carrying “cargo” MDM2 are released into the microenvironment, and MDM2 DNA from RPLPS is transferred to target recipient cells—preadipocytes—in the tumor microenvironment. This transfer leads to impaired p53 activity and increased matrix metalloproteinase 2 (MMP2) production in preadipocytes, which is involved in tumor cell dissemination and recurrence (63, 64).

3.5 Cancer stem cells

3.5.1 Notch signaling in tumor-initiating LPS cells

Shihua et al. enriched tumor-initiating cells to obtain cells with sustained Notch activation (mLPS1) and cells with normal Notch activity (mLPS2). When transplanted into mice, only mLPS1 gave rise to LPS; these cells highly expressed tumor stem cell markers (CD133) and mesenchymal stem cell markers (CD73, CD90, CD105, and Delta-like homolog 1 [DLK1]). Moreover, the clustered regularly interspaced short palindromic repeats (CRISPR)-mediated destruction of Notch signaling inhibited mLPS1 tumorigenicity (65).

3.5.2 Role of the Janus kinase/Signal transducer and activator of transcription signaling pathway in cancer stem cells in MLS

Steinberg et al. reported that a subpopulation of MLS cells with cancer stem cell characteristics possess an activated JAK/STAT signaling pathway, which controls and monitors the number of cells with cancer stem cell properties (66).

3.5.3 Role of the PIK3R3/Extracellular signal-regulated kinase/Nanog signaling pathway in sarcoma stem-like DDLPS cells

Yoon et al. reported that the PIK3R3/ERK/Nanog signaling pathway promotes the cancer stem cell phenotype in DDLPS, and identified PIK3R3 as a potential therapeutic target for DDLPS. In addition, Nanog knockdown and AKT inhibition can reduce the formation of spheroid cells and reverse drug resistance to doxorubicin and radiation (67, 68).

To date, progress in research into driver genes and molecular pathways has elucidated the mechanisms of LPS in a stepwise manner. These studies have also provided insights and guidance regarding the content and direction of clinical research.

4 Molecular targeted therapies

Genes and their expression products, related molecular pathways, and intermolecular interactions all play important roles in LPS occurrence and development. On the basis of these findings, the corresponding possible therapeutic targets have been explored in clinical practice.

4.1 Targeting MDM2: selective MDM2 inhibitors

A phase I study of the MDM2 inhibitor milademetan included 48 patients with recurrent or refractory WDLPS/DDLPS, with a median PFS (mPFS) of 6.3 months; one DDLPS patient achieved a partial response (69). The MANTRA study compared the efficacy of milademetan with that of trabectedin in 178 patients with unresectable or metastatic DDLPS who had failed to respond to prior treatments. No significant differences in mPFS were observed (3.6 months vs. 2.2 months, respectively), the median overall survival was comparable (9.5 months vs. 10.2 months, respectively), and the objective response rate did not significantly differ (4.7% vs. 3.4%, respectively) between the two treatments. On the basis of these findings, the MDM2 inhibitor failed as a second-line treatment for DDLPS (70).

4.2 Brigimadlin, an MDM2-p53 antagonist

A phase Ia study evaluated the efficacy of the MDM2-p53 antagonist brigimadlin in the treatment of 54 patients with advanced/metastatic MDM2-amplified and TP53 wild-type solid

tumors. The overall objective response rate was 11.1% (6 of 54), the disease control rate was 74.1% (40 of 51), and the mPFS was 8.1 months. These findings indicate that brigimadlin has potential antitumor activity in patients with DDLPS and WDLPS. In the phase Ib (dose expansion) study, the number of evaluable DDLPS patients increased to 76 cases, with a preliminary mPFS of 8.1 months (95% confidence interval: 5.7–13.6 months), an objective response rate of 19%, and a disease control rate of 85%. Moreover, in the five evaluable WDLPS patients, the disease control rate was 100% (71). A phase II/III global multicenter study comparing brigimadlin with doxorubicin as first-line treatments for advanced DDLPS patients is currently underway (Clinical Trial: NCT05218499).

4.3 Targeting CDK4: CDK4/6 inhibitors

A phase II clinical study of palbociclib in 59 patients with WD/DDLPS revealed an mPFS of 17.9 weeks, with one patient achieving a complete response that lasted over 2 years. Thirty-six percent of the patients experienced grade 3–4 neutropenia (72). In 61 patients with retroperitoneal WDLPS/DDLPS treated with the single agent palbociclib, the practical application and surgical outcomes were as follows. The mPFS for WDLPS and DDLPS patients were 9.2 and 2.6 months, respectively. In addition, 12 patients ultimately underwent surgical resection, with half of the patients achieving R0/R1 resection; however, surgery did not improve overall survival (73).

Higuchi et al. reported that a combination of palbociclib and recombinant methioninase enhanced the efficacy of palbociclib against DDLPS in a patient-derived orthotopic xenograft mouse model of LPS (74). Moreover, a phase II clinical study of patients with recurrent or metastatic DDLPS treated with abemaciclib reported an mPFS of 30.4 weeks, with two patients achieving a partial response (75).

4.4 Combination of MDM2 inhibitors and CDK4/6 inhibitors

A phase Ib study combined siremadlin (a p53-MDM2 inhibitor) with ribociclib (a CDK4/6 inhibitor) in 74 patients with advanced WDLPS and DDLPS. Three patients achieved a partial response and 38 patients had stable disease, thus demonstrating the good antitumor activity of this combination treatment (76).

4.5 Targeting PARP1: PARP1 inhibitors

PARP1 expression is heterogeneous across subtypes. High PARP1 expression is mostly found in leiomyosarcoma, is often found in Grade 3 CINSARC (Complexity INDEX in SARComas) and high-risk tumors, and is associated with a shorter MFS. By contrast, low PARP1 expression is mostly found in LPS and MFS (77). A multicenter, randomized, controlled phase II clinical study

(TOMAS2) explored the efficacy of trabectedin combined with the PARP inhibitor olaparib versus trabectedin alone in 130 adult patients with STS whose previous treatments had failed. Of these, 67 patients had an L-sarcoma (LPS/leiomyosarcoma) subtype. The subgroup analysis did not yield positive results for mPFS or overall survival (78).

4.6 Targeting the nuclear export protein exportin 1

Zaffaroni et al. reported that selinexor (a selective XPO1 inhibitor) has stronger antitumor activity than doxorubicin against retroperitoneal DDLPS patient-derived xenografts (79). A phase Ib study of selinexor in the treatment of advanced STS included 15 DDLPS patients. Six patients experienced a reduction in the target lesion size and seven patients achieved stable disease as the best response; this was maintained for at least 4 months (80). A subsequent study, SEAL, included 285 patients with advanced DDLPS who had previously received two to three lines of treatment, and reported an mPFS of 2.8 months. The most common grade 3–4 adverse events associated with selinexor use were nausea (80.7%), decreased appetite (60.4%), and fatigue (51.3%) (81). Another study demonstrated that selinexor treatment can help to control pain and improve quality of life in patients with advanced DDLPS (82).

4.7 Targeting vascular endothelial growth factor

In the ALTER-0202 study, 13 patients with recurrent/metastatic advanced LPS were treated with anlotinib. This treatment resulted in a 12-week progression-free rate of 63%, and mPFS and median overall survival times of 5.6 and 13 months, respectively (83). The ALTER-S006 study revealed that anlotinib maintenance treatment resulted in an mPFS of 9.1 months in 49 STS patients who achieved a partial response or stable disease after at least four cycles of first-line anthracycline-based chemotherapy; LPS patients had an mPFS of 12.5 months (84). In another retrospective study, 17 patients with metastatic/recurrent WDLPS/DDLPS who were treated with anlotinib had an mPFS of 27.9 weeks, a 24-week progression-free rate of 58.8%, and an overall survival of 56.6 weeks (85). The aforementioned studies indicate the good efficacy of anlotinib for LPS, and the use of anlotinib as a second-line treatment for patients with STS is included in the Chinese Society of Clinical Oncology guidelines.

4.8 Multitarget tyrosine kinase inhibitors

The National Comprehensive Cancer Network guidelines recommend pazopanib as a second-line treatment option for patients with STS (86). In a phase II study, pazopanib was used to treat 41 patients with LPS (27 with DDLPS). This treatment resulted in a 12-week progression-free rate of 68.3%, and for

DDLPS patients, the mPFS was 6.24 months (87). A multicenter phase II randomized controlled trial in Germany compared the efficacy of combined pazopanib and gemcitabine with pazopanib alone in the treatment of 90 patients with refractory STS (19% with LPS). There was a 12-week PFS of 74% vs. 47%, an mPFS of 5.6 months vs. 2.0 months, and an overall survival of 13.1 months vs. 11.2 months, respectively. However, the objective response rate was generally low, at 11% vs. 5%, respectively (88). Similarly, a previous study revealed that preoperative pazopanib treatment for nonmetastatic, resectable, high-risk STS did not benefit patients (89). In addition, in the SARC024 study, regorafenib treatment did not yield positive results for mPFS or overall survival in 48 patients with advanced LPS (90).

In summary, many types of targeted drugs have been used in the exploration of clinical treatments, and have achieved different results. Nonetheless, through continuous in-depth research, more accurate targets are expected to be obtained. The ultimate goal is to develop new drugs and novel solutions to improve the quality of life and survival of patients.

5 Research progress in immunotherapy for LPS

Multiple studies have shown broad heterogeneity in the tumor immune microenvironment of LPS based on tumor subtype, grade, size, multifocality, and primary or recurrent status (91, 92). Regarding immune microenvironments, research has mainly focused on DDLPS and MLPS; WDLPS and PLPS are therefore less understood. DDLPS is characterized by a greater abundance of TIL and a higher expression of PD-L1, whereas MLPS displays the opposite characteristics, and WDLPS is likely positioned between the two (93, 94). In terms of treatment, immune checkpoint inhibitors, therapeutic antibodies, and tumor vaccines (95), immunomodulators (96), adoptive cell therapy, and T-cell receptor–genetically engineered T-cells may become new options for patients with advanced unresectable LPS. At present, the initial efficacy of immune checkpoint inhibitor monotherapy in LPS patients is poor (97). Nonetheless, the combination of immune checkpoint inhibitors with other strategies—such as chemotherapy (98), VEGF blockers (99), cytokines, immunomodulators, radiotherapy, and other regimens—is being actively explored, and is expected to improve the oncological prognosis of LPS.

6 Discussion

With the rapid development of medical science and technology and the continuous innovation of research methods, important progress has been made in the research and treatment of LPS. Clinical studies related to LPS targeted therapy have been collected by the authors and presented in table form. Information on clinical trials that have been completed can be found in Table 1. Information on ongoing clinical trials can be found in Table 2. In terms of LPS occurrence and the mechanisms of LPS development, extensive heterogeneity and unique characteristics exist at the

TABLE 1 Clinical trials related to LPS-targeted therapy.

Clinical trial	Medication regimen	Pathway target	Phase	Objective	Primary endpoint	Secondary endpoints	Primary outcome	Author	Year of publication	References
NCT01877382	DS-3032b	Disrupts the MDM2-p53 interaction	I	94 pts: WD/DD LPS (40, 43%)	MTD, PK, PD, efficacy	–	47(60%)SD; Median duration of SD:6.7 (1.6 to 36.4) m; 1 PR in DDLPS.	Todd Michael Bauer	2018	(69)
MANTRA (RAIN-3201; NCT04979442)	Trabectedin +milademetan vs. Trabectedin	A selective, potent, small molecule inhibitor of the MDM2-p53 interaction	III	175 DDLPS pts	PFS	OS; ORR	M-follow-up:2.1m (range 0–13m). mPFS was numerically higher. mOS and ORR was comparable in the two arms.	R.L. Jones	2023	(70)
NCT03449381	Brigimadlin (BI 907828)	An oral MDM2–p53 antagonist	Ia	28 (51.9%) sts pts: 12 DDLPS and 7 WDLPS	MTD、Pk、Pd、Activity	–	WD/DDLPS ORR:100%; WD/DDLPS DCR:75%; DDLPS with duration of SD 1.5~22 m	Patricia LoRusso	2023	(71)
NCT01209598	Palbociclib	The selective CDK4 and CDK6 inhibitor	II	60 WD/DDLS pts	PFS	PFR12 weeks	PFR12 weeks:57.2%; mPFS:17.9 weeks; 1 CR; Toxic effects:hematologic、neutropenia.	Mark A. Dickson, MD	2016	(72)
NCT02846987	abemaciclib	A newer and more potent CDK4 inhibitor	II	30 DDLS pts	PFR12 weeks	–	PFR12 weeks:76%; mPFS:30.4 weeks; one PR; Grade 3-4 toxicity:anemia、neutropenia、thrombocytopenia、diarrhea.	Mark Andrew Dickson	2019	(75)
NCT02343172	Siremadlin + ribociclib	A p53–MDM2 inhibitor;a CDK4/6 inhibitor	Ib	74 WDLPS or DDLPS pts	MTD、RDE	–	RDE: siremadlin 120 mg every 3 weeks +ribociclib 200 mg QD; 3 PR, 38 SD.	Albiruni R. Abdul Razak	2022	(76)
TOMAS2 (NCT03838744)	Trabectedin +Olaparib	PARP1 Inhibitor	II	130 STS pts (L–sarcoma 67)	PFS6m	PFS, OS, ORR, DOR, safety.	m-follow-up:10.2 mo; T+O PFS6mo:32%; T+O mPFS:4.0 mo; T+O PFS12mo:20%	L D'Ambrosio	2023	(78)
NCT01607905	selinexor	Selective inhibitor of nuclear export compound	Ib	54 sts pts (WD/DD 16;MLS 3)	PK, PD,efficacy	–	none ORR; SD (≥ 4 months):17 (33%), including 7 (47%) DDLPS.	Mrinal M. Gounder	2016	(80)
SEAL (NCT02606461)	S (Selinexor) vs.placebo (P)	Selective inhibitor of nuclear export compound	II/III	51 DDLS pts	PFS by WHO	–	PFS (WHO):no difference; mPFS (R v1.1): 5.6 mo vs.1.8 mo, hr0.64. Grade 3/4 AEs: hyponatremia, anemia, thrombocytopeniam	Mrinal M. Gounder	2018	(81)
ALTER-0202 (NCT01878448)	Anlotinib	A multikinase angiogenesis inhibitor	II	166 STS pts , LPS (n = 13)	PFR12 weeks	–	LPS PFR 12weeks:63% LPS mPFS:5.6m LPS mOS:13 m LPS ORR:7.7%	Yihebalı Chi	2018	(83)

(Continued)

TABLE 1 Continued

Clinical trial	Medication regimen	Pathway target	Phase	Objective	Primary endpoint	Secondary endpoints	Primary outcome	Author	Year of publication	References
ALTER-S006 (NCT03890068)	Anlotinib as a maintenance treatment	multikinase angiogenesis inhibitor	II	49 STS pts, 17 lps (35%)	PFS	OS, ORR, DCR and safety.	M-follow-up:17.1 mo; mPFS:9.1 mo; LPS mPFS:12.5 mo(95% CI 7.1–18.0); WDLS (n= 4) and DDLS (n = 11) mPFS:19.1 mo、9.0 mo; Overall ORR and DCR:16%(8/49)、94% (46/49); Lps ORRs and DCRs:12% (2/17)、100% (17/17) ; WDLS ORRs and DCRs:25%(1/4)、100%; DDLS ORRs and DCR:9% (1/11)、100%; MLPS:2 SD, DCR 100%.	Bushu Xu	2023	(84)
EORTC 62043	Pazopanib	multityrosine kinase	II	142 STS pts: LPS (19)	PFR12 weeks	response, safety,os	LPS PFSR 12 weeks :26% (5/19); LPS mPFS:80 d; LPS mOS:197; AEs:hypertension, fatigue, hypopigmentation, nausea	Stefan Sleijfer	2009	(100)
NCT01506596	Pazopanib	multitargeted TKI with activity against VEGF and PDG	II	41 lps pts:DDLPS 27 (65.9) ;MLS 12 (29.3) ;PLPS 2 (4.9)	PFR12 weeks	–	PFR12:68.3%; mPFS:4.4mo; mOS:12.6mo; AEs:nausea (39%), hypertension (36.6%), diarrhea (34.1%), and fatigue (29.3%)	Brian L. Samuels	2017	(87)
DRKS00003139	Pazopanib +gemcitabine (A) vs. gemcitabine (B)	multityrosine kinase	II	90 STS pts:LPS (16, 19%).	PFSR 12 weeks	Toxicity, os, ORR	M-follow-up:12.4mo;PFSR 12 weeks :74% (A) vs 47% (B) (HR, 1.60; P = .01). mPFS:5.6 vs 2.0 mo(HR, 0.58;P = .02) mOS:13.1 vs 11.2 mo(HR, 0.98; P = .83). ORR:11% (A) vs 5% (B) (P = .10).	Hans-Joachim Schmoll	2021	(88)
NCT01900743	Regorafenib vs. placebo	A multitargeted kinase inhibitor with a kinase profile overlapping	II	37 STS pts: LPS (20)	PFS	OS	mPFS:1.1m; mOS:4.7m; ORR:0%	Nicolas Penel	2019	(101)
SARC024 (NCT02048371)	Regorafenib vs. placebo	A multitargeted kinase inhibitor with a kinase profile overlapping	II	48 LPS pts(34 DDLPS, 12 MLPS, 2 PLPS)	PFS	–	mPFS:1.87 mo vs. 2.07mo, HR=0.85, p = .62. No responses on regorafenib. mOS:6.46mo vs. 4.89mo, HR=0.66, p = .28.	Richard F. Riedel	2023	(102)

TABLE 2 Clinical trials of LPS-targeted and immunotherapy are currently underway.

Regision number	Pathway target	Study Status	Phase	Objective	Intervention	Primary outcome	Location	Years study Started
NCT06414434	a type of kinase inhibitor	RECRUITING	I	LPS	DRUG: BTX-A51	Safety and tolerability	America	2024/9/1
NCT06389799	combination of an FGFR inhibitor, pemigatinib, with a PD-1 inhibitor, retifanlimab	RECRUITING	II	advanced DDLPS	DRUG: Pemigatinib、 Retifanlimab	OS、 ORR	Europe	2024/6/20
NCT05580588	the CDK4/6 Inhibitor, a selective enzyme blocker	RECRUITING	II	Locally Advanced or Metastatic LPS	DRUG: SPH4336	PFS at 12 weeks	America	2023/8/31
NCT05496569	the CDK4/6 Inhibitor	NOT_YET_RECRUITING	II	DDLPS	DRUG: TQB3616 capsule	PFS	China	2022/12/1
NCT06058793	a so-called MDM2 inhibitor	ACTIVE_NOT_RECRUITING	III	DDLPS	DRUG: Brigimadlin (BI 907828)	TEAEs	America	2023/12/12
NCT05218499	a so-called MDM2 inhibitor	ACTIVE_NOT_RECRUITING	II/III	DDLPS	DRUG: Brigimadlin (BI 907828)、 Doxorubicin	PFS	America	2022/3/25
NCT00969917	HSP90 inhibitor	WITHDRAWN	II	DDLPS	DRUG: IPI-504	safety profile and ORR	America	2010/1/1
NCT04967521 (SARC041)	the CDK4/6 Inhibitor	RECRUITING 108	III	DDLPS	DRUG: Abemaciclib、 Placebo	PFS	America	2021/11/11
NCT02846987	the CDK4/6 Inhibitor	ACTIVE_NOT_RECRUITING	II	DDLPS	DRUG: Abemaciclib	PFS	America	2016/7/1
NCT05886634	the A2AR/A2BR Inhibitor;PD-1 Inhibitor	RECRUITING	II	DDLS	DRUG: Etrumadenant、 Zimberelimab	ORR	America	2023/5/23
NCT03074318	Immunotherapy with monoclonal antibodies、 chemotherapy	TERMINATED	I/II	Liposarcoma or Leiomyosarcoma	DRUG: Avelumab、 Trabectedin	Adverse Events, ORR	America	2017/9/28
NCT04785196	APG-115 Combination With PD-1 Inhibitor(toripalimab)	RECRUITING	Ib/II	Advanced LPS or Advanced Solid Tumors	DRUG: APG-115、 Toripalimab	Dose Limiting Toxicity (DLT)、 MTD、 ORR	Britain	2021/5/26
NCT04438824	PD-1 Inhibitor;the CDK4/6 Inhibitor	ACTIVE_NOT_RECRUITING	II	DRUG: INCMGA00012、 Palbociclib	Advanced LPS	RP2D、 DLTs、 orr	America	2020/6/17
NCT02571829	the CDK4/6 Inhibitor	–	II	DRUG: ribociclib	Advanced WD/DDLPS	Response	Jerusalem、 Israel	2016/5/1
NCT03096912	the CDK4/6 Inhibitor	–	II	DRUG: Ribociclib	Advanced WD/DDLPS	Response	Be’er Ya’aqov, Israel	2016/7/1
NCT02587169	the BCR-ABL Inhibitor	–	I/II	DRUG: Nilotinib、 adriamycin	LPS and LMS of Retroperitoneum	RFS at 5 years、 OS	Spain	2012/1/1

(Continued)

TABLE 2 Continued

Regision number	Pathway target	Study Status	Phase	Objective	Intervention	Primary outcome	Location	Years study Started
NCT03307616	Immunotherapy with monoclonal antibodies	ACTIVE_NOT_RECRUITING Ii 32	II	Ipilimumab、Nivolumab、 Radiation therapy when given before surgery works	undifferentiated pleomorphic sarcoma or ddtps	Pathologic response	America	2017/10/4
NCT05694871	blocking some of the enzymes;PD- 1 Inhibitor	RECRUITING	II	DRUG: Palbociclib、 Cemiplimab	Advanced Dedifferentiated Liposarcoma	PFS;Efficacy analyses; PFS rates at 12, 24, 36, and 48 months	America	2023/5/30
NCT01876043	–	TERMINATED	II	DRUG: plitidepsin	Advanced Unresectable or Metastatic, Relapsed/ Refractory, DLPS	Percentage of Patients Remaining Alive and Progression Free at 3 Months	France	2012/2/1
NCT02609984	Vaccine;PD-L1 Inhibitor	TERMINATED	II	CMB305、 atezolizumab	sarcoma (synovial or mrlps) expressing the NY- ESO-1 protein	PFS、 OS	America	2015/4/29
NCT03114527	the CDK4/6 Inhibitor;the mTOR Inhibitor	ACTIVE_NOT_RECRUITING	II	DRUG: Ribociclib、 Everolimus	advanced LMS or DDL	Tumor response、 Progression free rate, 16 weeks	America	2017/8/8
NCT04356872	PD-1 immune check point inhibitor, sintilimab, in combination of stand of care chemotherapy	–	II	DRUG: Sintilimab、 Doxorubicin 、 Hydrochloride、 Ifosfamide	Select Type of Metastatic/ Unresectable Soft Tissue Sarcoma	ORR	China	2020/4/8
NCT02059850	Vaccin	WITHDRAWN	I	Autologous NY-ESO-1-specific CD8-positive T Lymphocytes、 Cyclophosphamide	advanced synovial sarcoma or myxoid/round cell liposarcoma.	toxicity	America	2014/7/1
NCT06498648	kinase inhibitors	NOT_YET_RECRUITING	1/2	DRUG: Abemaciclib、 Docetaxel、 Gemcitabine	STS(LMS、 DDLPS)	Time course of blood thymidine kinase activity (TKa)		2024/9/30
NCT04242238	the CSF1R Inhibitor;PD-L1 Inhibitor	ACTIVE_NOT_RECRUITING	I	DRUG: DCC-3014、 Avelumab	Advanced or Metastatic Sarcomas (DDLPS)	MTD、 ORR	America	2020/1/22
NCT03880123	the XOP1 Inhibitor	WITHDRAWN	I	DRUG: Selinexor、 Ixazomib	Advanced Sarcoma	MTD、 ORR	America	2020/11/1
NCT06116578	Immunotherapy、 DNA repair inhibitor	NOT_YET_RECRUITING	II	DRUG: Pembrolizumab、 Olaparib	tertiary lymphoid structures (TLS) Positive Selected Resectable STS	Rate of CD8+ T-cell tumor infiltration density at surgery compare to baseline	France	2024/9/1
NCT05813327	–	RECRUITING	I/II	DRUG: Neoadjuvant ADI PEG20、 Ifosfamide、 Radiotherapy、 Mesna	STS	SAE rate、 RP2D、 efficacy	America	2024/3/14

(Continued)

TABLE 2 Continued

Regision number	Pathway target	Study Status	Phase	Objective	Intervention	Primary outcome	Location	Years study Started
NCT05497843	kinase inhibitors		II	DRUG: Chiauranib	Advanced or Unresectable STS	PFS12w	China	2022/8/2
NCT03064243	a kinase inhibitor of receptor tyrosine with VEGFR2.	–	II	DRUG: apatinib	STS	6 months PFS rate	China	2017/3/1
NCT01878448	a kinase inhibitor of receptor tyrosine with multi-targets, especially for VEGFR2 and VEGFR3.	COMPLETED	II	DRUG: Anlotinib	STS	effectiveness	China	2017/4/30
NCT03121846	TKI		II	DRUG: Apatinib	PFS	STS	China	2017/5/1
NCT02449343 (ALTER0203)	TKI		II/III	DRUG: Anlotinib、 Placebo	PFS	STS	China	2015/5/12
NCT00276302	HSP90 inhibitor	COMPLETED	I	IPI-504	safety and MTD of IPI-504 in GIST and STS	GIST or STS	America	2005/12/1
NCT03217266	blocking some of the enzymes needed for cell growth	ACTIVE_NOT_RECRUITING	Ib	DRUG: Navtemadlin、 Radiation Therapy	STS	Mtd	America	2018/6/20
NCT01995981	multitargeted TKI with activity against VEGF and PDG	COMPLETED	IV	DRUG: Pazopanib	STS	evaluate whether early metabolic response is correlated to clinical benefit:FDG uptake	Britain	2013/12/1
NCT02636725	multitargeted TKI with activity against VEGF1-3;PD-1 Inhibitor	COMPLETED	II	DRUG: Axitinib、 Pembrolizumab	STS	PFS at 3 Months	America	2016/4/19
NCT01418001	TKI	TERMINATED	Ib/II	DRUG: Neoadjuvant Pazopanib、 Gemcitabine、 Docetaxel	STS	ORR	America	2011/8/1
NCT05926700	PD-1/CTLA-4 Inhibitor	RECRUITING	II	DRUG: Candonilimab	Advanced STS	ORR	China	2024/2/28
NCT03138161	Immunotherapy	RECRUITING	I/II	DRUG: Trabectedin、 Ipilimumab、 Nivolumab	Advanced STS	MTD	America	2017/4/13
NCT05448820	CTLA-4 Inhibitor;PD-L1 Inhibitor	ACTIVE_NOT_RECRUITING	I/II	DRUG: YH001、 Envafohimab、 Doxorubicin	Advanced or Metastatic Sarcoma	RP2D、 ORR	America	2022/11/14
NCT02451943	A PDGFRa Inhibitor	COMPLETED	III	DRUG: Olaratumab、 Doxorubicin、 Placebo	Advanced or Metastatic STS	OS	America	2015/9/14
NCT01975519	Anti-endoglin antibody	COMPLETED	I/II	DRUG: TRC105 and Pazopanib	Advanced STS	RP2D、 PFS、 DLT、 ORR	America	2013/12/10
NCT00626704	a DR5 agonistic antibody	COMPLETED	I/II	DRUG: AMG 655、 Placebo、 Doxorubicin	Unresectable STS	PFS	–	2007/11/1

molecular level. Notably, the rapid development of molecular diagnostic technology is opening the door to understanding these molecular mechanisms in a stepwise manner. Moreover, “targeted therapy” has been launched at the molecular level.

Ongoing research into LPS has led to important advancements in understanding its molecular biology. The identification of numerous genes, their RNA products, and associated downstream pathways has presented many potential targets for therapeutic intervention. In the future, the development of targeted treatment strategies based on these insights will be paramount.

Given the diversity of STS subtypes and their relatively low incidence compared with other malignancies, the research community faces the challenge of addressing a “rare” tumor with a dispersed pathology. The trajectory of future LPS research should therefore focus on two main avenues: identifying specific histological subtypes to reveal subtype-specific therapeutic opportunities, and discovering precise biomarkers to identify patient populations that are most likely to benefit from targeted therapies. Personalized medicine—crafted according to the intricate interplay of histological and molecular profiles—holds great promise for the treatment of LPS.

The progress made thus far lays a solid foundation for the next steps in LPS research. As we continue to unravel the complexities of this disease, the integration of molecular insights with clinical practice will be essential. Through this collaborative and targeted approach, we hope to improve the outcomes for patients with LPS.

Author contributions

HL: Investigation, Writing – original draft. XW: Formal analysis, Writing – original draft. LL: Writing – original draft.

BY: Writing – review & editing. FQ: Writing – review & editing. BZ: Formal analysis, Funding acquisition, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

We thank Bronwen Gardner, PhD, from Liwen Bianji (Edanz) (www.liwenbianji.cn/) for editing the English text of a draft of this manuscript.

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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OPEN ACCESS

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RECEIVED 27 September 2024

ACCEPTED 19 December 2024

PUBLISHED 10 January 2025

CITATION

Liu H, Hao Q, Wang X, Cheng M, Qiu F and
Zhou B (2025) Efficacy and safety of the
combination of anlotinib and envafolelimab in
the treatment of unresectable or metastatic
liposarcoma: findings from a single-center
retrospective study.
Front. Oncol. 14:1502945.
doi: 10.3389/fonc.2024.1502945

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Efficacy and safety of the combination of anlotinib and envafolelimab in the treatment of unresectable or metastatic liposarcoma: findings from a single-center retrospective study

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Objective: To evaluate the efficacy and safety of anlotinib combined with envafolelimab in the treatment of unresectable or metastatic liposarcoma.

Methods: This single-center, retrospective study enrolled 15 patients with unresectable or metastatic liposarcoma, who were treated at the Retroperitoneal Tumor Surgery Research Center of Qingdao University Affiliated Hospital between April 2022 and November 2023. The treatment regimen consisted of anlotinib combined with envafolelimab. Treatment efficacy was evaluated using the Response Evaluation Criteria in Solid Tumors version 1.1. Treatment-related adverse events (TRAEs) were assessed using Common Terminology Criteria for Adverse Events version 5.0.

Results: A total of 15 patients with unresectable or metastatic liposarcoma were included; among them, seven were male (46.7%) and eight were female (53.3%), with a median age of 55 years. The pathological subtype distribution was as follows: three (20.0%) patients with well-differentiated liposarcoma, 11 (73.3%) patients with dedifferentiated liposarcoma, and one (6.7%) patient with myxoid liposarcoma. At 12 weeks post-diagnosis, none of the patients achieved a complete response. The objective response rate was 6.7%, with one patient (6.7%) achieving a partial response. Disease stability was observed in 10 (66.6%) patients, which corresponded to a disease control rate of 73.3%. Disease progression occurred in four (26.7%) patients. The median follow-up time was 16.9 months and the median progression-free survival time was 14.2 months. Seven patients experienced TRAEs, of whom three (42.2%) had grade 3–4 TRAEs.

The most common TRAEs were liver function abnormalities, hypertension, and fatigue.

Conclusion: Anlotinib combined with envafolimab demonstrates promising efficacy and manageable safety in treating unresectable or metastatic liposarcoma.

KEYWORDS

liposarcoma, targeted therapy, immunotherapy, efficacy, safety

1 Introduction

Liposarcoma is a rare and complex soft tissue malignancy. While surgery remains the primary treatment modality, local recurrence rates exceed 50% following surgical resection, resulting in poor patient prognosis (1). Anthracycline-based systemic chemotherapy remains the standard treatment for unresectable or metastatic disease. However, existing data suggest that targeted therapy or immunotherapy represent promising treatment alternatives. This study retrospectively investigated the efficacy and safety of anlotinib combined with envafolimab in the treatment of advanced liposarcoma.

pathological liposarcoma subtype, was collected. All the patients were pathologically diagnosed at our hospital and had complete clinical and follow-up data. The pathological diagnoses were confirmed by two senior pathologists. Representative pathology images are shown in Figure 1. Discussions with the multidisciplinary team led to the establishment of the following treatment protocol: 1) administer oral anlotinib (10 mg) on days 1–14; 2) administer intravenous envafolimab (200 mg) on day 1; 3) repeat the treatment cycle every 3 weeks. This study was approved by our hospital's ethics committee (approval number: QYFY-WZLL-29433). All the patients provided informed consent.

2 Materials and methods

2.1 Clinical data and treatment protocol

This single-center, retrospective study included 15 patients with unresectable or metastatic liposarcoma, who were treated at the Retroperitoneal Tumor Surgery Research Center of Qingdao University Affiliated Hospital between April 2022 and November 2023. Patient information, including sex, age, treatment history, and

2.2 Treatment efficacy evaluation

Both short-term and long-term treatment efficacy was evaluated. Short-term efficacy, including the complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), objective response rate (ORR), and disease control rate (DCR), was evaluated at 12 weeks after treatment initiation. Long-term efficacy, including the above indicators plus progression-free survival (PFS) and overall survival (OS), was assessed at the end of the follow-up period. ORR was calculated as: $(CR + PR) / \text{total number of cases} \times 100\%$. DCR was calculated as: $(CR + PR + SD) / \text{total number of cases} \times 100\%$. PFS was defined as the time from treatment initiation to disease progression or the last follow-up date if progression had not occurred. OS was defined as the time from treatment initiation to death from any cause or the last follow-up date for surviving patients. All patients underwent imaging examinations at baseline (prior to treatment initiation) and after every two treatment cycles. Treatment efficacy was assessed according to the RECIST 1.1 criteria.

2.3 Safety assessment

Treatment tolerance was evaluated by monitoring adverse events. Patients who tolerated the treatment continued to adhere to the original protocol; those that experienced adverse events, discontinued the treatment. All adverse reactions were graded according to the Common Terminology Criteria for Adverse Events (CTCAE version 5.0).

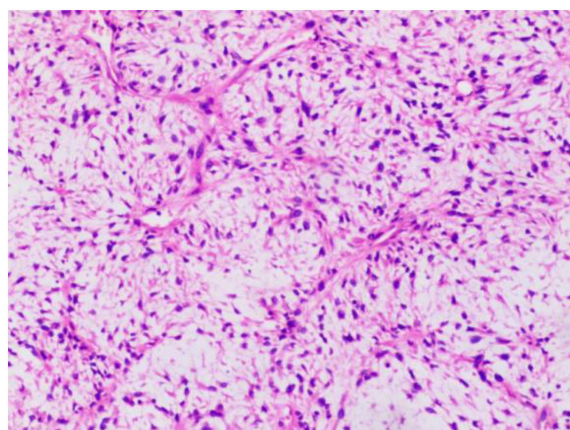


FIGURE 1
HE staining of liposarcoma.

2.4 Follow-up

Regular telephone follow-up interviews were conducted to collect PFS and OS data.

2.5 Statistical analysis

Data analysis was performed using SPSS 24.0 statistical software. All 15 eligible patients were included in the analyses. Continuous variables were reported as median (range). Categorical variables were presented as frequency counts and percentages. Survival analysis was performed using the Kaplan-Meier method, with a significance level of $\alpha < 0.05$.

3 Results

3.1 Patient characteristics

A total of 15 patients were enrolled in this study; among them, three patients had WDLPS, 11 patients had DDLPS, and one patient had MLPS. Seven of the patients were male and eight were female. The median age at diagnosis was 55 years (range: 41–75 years). All patients had primary tumors that were located in the retroperitoneal space. Four patients had unresectable disease at initial diagnosis, six had local recurrence, and five had distant metastases. Of the 15 patients, 11 had a history of previous liposarcoma resection.

In terms of previous treatment history, four patients received anlotinib monotherapy, three received anlotinib combined with chemotherapy, and four received anlotinib combined with radiotherapy. The remaining four patients had no prior treatment history. All three patients who previously received chemotherapy had DDLPS and were treated with ifosfamide (7.5 mg/m²/cycle) combined with doxorubicin (75mg/m²/cycle). Of the four patients who received radiotherapy, three had DDLPS and one had MLPS. Radiation was administered to the retroperitoneal region, with external beam radiation doses of 95% PTV 45–50 Gy (1.8–2.0 Gy/fraction). The patient baseline characteristics are summarized in [Table 1](#).

3.2 Treatment efficacy and patient prognosis

After 12 weeks of treatment with anlotinib plus envafolimab, none of the patients achieved a CR; however, one patient (6.7%) achieved a PR, 10 patients (66.6%) had SD, and four patients (26.7%) had PD. The DCR reached 73.3%, and the ORR was 6.7%. Among the 11 patients in the DDLPS group, one (9.1%) achieved a PR, seven (63.6%) had SD, and three (27.3%) had PD. Of the three patients in the WDLPS group, two had SD and one had PD. The individual patient responses are shown in [Figure 2](#). As of April 2024, four patients had died. The median follow-up time was 16.9 months (range: 4.1–22.3 months), with a median PFS (mPFS)

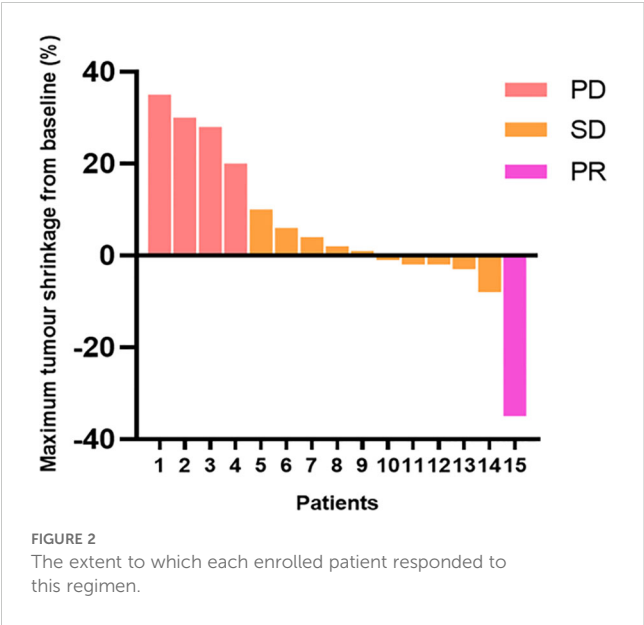
TABLE 1 Basic information and clinical features of enrolled liposarcoma patients.

Clinical features	Proportion (%)
Age	
Range of variation	41–75
Median age	55
Sex	
Male	7 (46.7%)
Female	8 (53.3%)
Pathological classification	
WDLPS	3 (20%)
DDLPS	11 (73.3%)
MLPS	1 (6.7%)
Previous liposarcoma surgery history	
Yes	11 (73.3%)
No	4 (26.7%)
Invading surrounding organs	
Yes	10 (66.7%)
No	5 (33.3%)
History of previous drug treatment	
Without antitumor therapy	4 (26.7%)
Anlotinib monotherapy	4 (26.7%)
Anlotinib combined with chemotherapy	3 (20%)
Anlotinib combined with radiotherapy	4 (26.7%)
Single or multiple lesion	
Single lesion	6 (40%)
Multiple lesion	9 (60%)
Pathological characteristics	
MDM2 (+)	14 (93.3%)
CDK4 (+)	14 (93.3%)
FUS-DDIT3 (+)	1 (6.7%)

of 14.2 months (95% confidence interval [CI]: 11.1–17.4 months). The median OS (mOS) was 26 months (95% CI: 22.2–29.7 months) ([Figures 3A, B](#)).

3.3 Adverse events

During treatment, seven patients experienced treatment-related adverse events (TRAEs); three of whom (42.2%) had grade 3–4 TRAEs ([Table 2](#)). The most common TRAEs were liver function abnormalities, hypertension, and fatigue. As all of the adverse reactions were manageable, no dose adjustments or treatment interruptions were required.



4 Discussion

Liposarcoma accounts for ~15%–20% of soft tissue sarcomas (STTs) (2). It is a rare malignant tumor that arises due to dysregulated lipocyte differentiation, and develops primarily in the extremities and retroperitoneum (representing 41% and 36% of cases, respectively) (3). According to the WHO Classification of Soft Tissue Tumors (5th edition, 2020) (4), liposarcoma subtypes include: atypical lipomatous tumor (ALT)/well-differentiated liposarcoma (WDLPS), dedifferentiated liposarcoma (DDLPS), myxoid liposarcoma (MLPS), pleomorphic liposarcoma (PLPS), and myxoid pleomorphic liposarcoma (MPLPS), which has been newly added to this latest edition.

While surgical resection remains the primary treatment for all liposarcoma subtypes, therapeutic options are limited and outcomes are inconsistent for patients with advanced/unresectable disease. Current first-line systemic therapy consists of doxorubicin, ifosfamide, or their combination (5). However, treatment response varies significantly among liposarcoma subtypes. Moreover, the

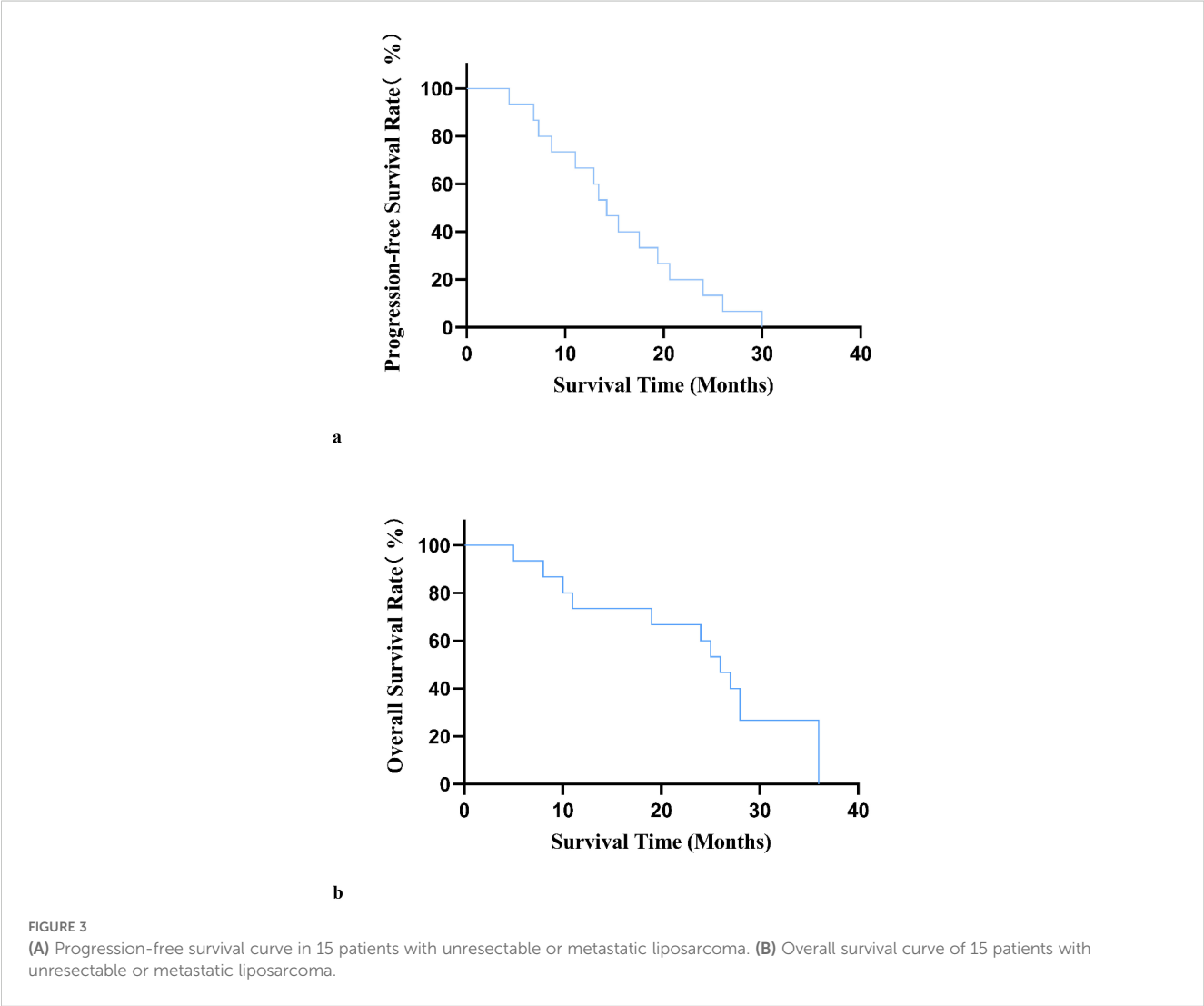


TABLE 2 General situation of adverse reactions.

Adverse reaction	Level I	Level II	Level III	Level IV	Total
Abnormal liver function	2	1	1	1	5
Hypertension	2	2	1	0	5
Fatigue	1	0	1	2	4
Gastrointestinal reaction	1	0	2	0	3
Pneumonia	1	1	0	0	2
Oral mucositis	1	1	0	0	2
Albuminuria	1	1	0	0	2
Anemia	0	0	1	0	1
Thrombocytopenia	0	0	1	0	1
Hypothyroidism	0	0	0	0	0
Hyperthyroidism	0	0	0	0	0

median survival time of patients with advanced, albeit, chemotherapy-sensitive subtype, is only 2 years (6). Novel agents such as trabectedin have shown promise in 3D culture models (7); however, they are still in the exploratory phase of development. Therefore, there is an urgent need for new drugs or therapeutic strategies with the potential to improve the current treatment landscape.

Existing data suggest that targeted therapy or immunotherapy may increase treatment responses. Studies involving DDLPS patients have shown that the sequential administration of the CDK4 inhibitor palbociclib combined with lenvatinib can achieve synergistic effects (8). Additionally, research indicates that liposarcoma has a denser microvascular network than other sarcoma subtypes, suggesting that it may be especially sensitive to anti-angiogenic therapy (9). In a study by Li et al., anlotinib was used to treat 40 patients with STS who were not eligible for chemotherapy. The median PFS was 6.83 months, and the median OS was 27.40 months. One patient achieved a PR and 26 patients had SD, which resulted in a DCR of 67.5% (27/40) (10). In the ALTER-0202 study, 13 patients with recurrent/metastatic advanced liposarcoma receiving anlotinib had a 12-week PFS rate (PFR) of 63%, with an mPFS and an OS of 5.6 and 13 months, respectively (11). Meanwhile, in the ALTER-S006 study, 49 STS patients who achieved a PR or SD after receiving at least four cycles of first-line anthracycline-based chemotherapy underwent maintenance therapy with anlotinib. The over cohort had an mPFS of 9.1 months, with liposarcoma patients having an mPFS of 12.5 months (12). In another retrospective study of 17 patients with metastatic/recurrent liposarcoma who were treated with anlotinib, the mPFS was 27.9 weeks, with a 24-week PFR of 58.8% and an OS of 56.6 weeks (13). These studies consistently demonstrate the favorable efficacy of anlotinib as an anti-angiogenic treatment for liposarcoma. These promising results have led to the inclusion of anlotinib in the CSCO guidelines as a second-line treatment option for STSs (14).

Beyond anti-angiogenic agents, immunotherapy has shown proven efficacy against various solid tumors, including STSs. STSs are traditionally considered as “immunologically inert or cold”

tumors, characterized by low-level immune infiltration and poor immune reserves. As such, STSs generally respond poorly to immunotherapy. However, recent biomarker studies have revealed significant immune heterogeneity among different sarcoma subtypes, meaning that immunotherapy tailored to specific biomarker profiles and tissue subtypes shows promise in improving the treatment outcomes of patients with STSs (15). From an immunogenomics perspective, sarcomas with complex karyotypes are more likely to be “immunologically hot”. This genomic complexity translates to increased tumor mutational burden (TMB) and a tumor microenvironment (TME) that facilitates immune cell infiltration. These characteristics may increase the responsiveness of sarcomas to immunotherapy. Multiple clinical trials have investigated various immunotherapeutic approaches, including immune checkpoint inhibitors (ICIs), therapeutic antibodies, cancer vaccines, immunomodulators, adoptive cell therapy, and T-cell-receptor-engineered T cell therapy, for the treatment of STSs. Among these, ICIs are the most widely used. However, clinical trials of ICI monotherapy have yet to demonstrate convincing clinical benefits for patients with STSs. The initial results of a multicenter phase II study (SARC028) of pembrolizumab (200 mg every 3 weeks) in patients with advanced STS were encouraging, with 2/10 liposarcoma patients achieving a PR (16). However, in the expanded liposarcoma cohort, the ORR was only 10%, with an mPFS of 2 months and a 12-week PFR of 44%; these low response rates led to the study failing to meet its predetermined endpoint (17). A 2020 meta-analysis of clinical trials investigating the utility of PD-1 or PD-L1 antagonists in the treatment metastatic STS. In the nine trials included, the 153 patients (39.8%) who received PD1/PD-L1 antagonist monotherapy had an ORR of 15.1% (18). Furthermore, among the 61 patients with retroperitoneal DDLPS, the ORR was only 7.3% (19). In the Alliance A091401 study, no DDLPS patients responded to treatment in either the nivolumab monotherapy group or the nivolumab plus ipilimumab combination group (20).

Given the limited efficacy of anti-angiogenic drugs as a monotherapy for liposarcoma, and the similarly disappointing results generated with immunotherapy alone, optimizing treatment strategies remains a key focus for researchers in this field. Combining immunotherapy with chemotherapy, radiotherapy, or targeted therapy can potentially transform “cold” liposarcoma tumors into “hot” ones (21). Multiple studies have demonstrated the synergistic effects of combining anti-angiogenic drugs with chemotherapy and immunotherapy. For instance, anti-angiogenic targeted drugs that block the VEGF signaling pathway can be used to address the challenge of suboptimal anti-tumor immune responses in patients with sarcomas. Such a strategy aims to reduce hypoxia, while promoting drug delivery and immune cell infiltration into the TME, which ultimately modulates host immunity and sensitizes it to immunotherapy (3, 22). Furthermore, using a combination therapy can overcome tumor resistance (which is a common limitation of monotherapy) and achieve higher response rates through synergistic effects. The success of combination therapies has been demonstrated in the context of lung cancer, hepatocellular carcinoma, and renal cancer (23).

Several clinical studies have investigated combination therapies against liposarcoma. For instance, one study treated 47 patients with retroperitoneal liposarcoma using a combination of eribulin, anlotinib and camrelizumab over a median follow-up period of 21.8 months (24). The ORR and DCR were 18.2% and 75%, respectively. In another study by the same team, 57 patients with RST received a combination of anlotinib and camrelizumab. Two (3.5%) patients achieved a CR and 13 (22.8%) patients a PR, with an ORR and a DCR of 26.3% and 80.7%, respectively (25). A retrospective study of 24 patients with advanced DDLPS receiving chemotherapy combined with a PD-1 inhibitor and anlotinib, reported an ORR of 20.8% and a DCR of 83.3% over a median follow-up time of 7.7 months (26). The multicenter, single-arm phase I/II ALTER-S007 clinical trial evaluated the efficacy of penpulimab combined with anlotinib and epirubicin as a first-line treatment for unresectable/metastatic STS. The recommended phase II dose was determined as: anlotinib (10 mg, days 1–14), epirubicin (60 mg/m², day 1), and penpulimab (200 mg, day 1), repeated every 3 weeks. The grade 3–4 adverse events were primarily epirubicin-related hematological toxicities, with no increased TRAE risk observed on addition of anlotinib and penpulimab. Among the seven evaluable patients in the early phase of the trial, three achieved a PR and four achieved SD, with all patients reaching the goal DCR (27). A retrospective study of camrelizumab combined with anlotinib and eribulin in 60 patients with metastatic retroperitoneal LPS/LMS (including 38 liposarcoma cases: nine with WDLPS, 24 with DDLPS, five with MLPS) reported an ORR and a DCR of 19.4% and 72.2%, respectively (28). These data demonstrate the promising potential of combining targeted therapy and immunotherapy for the treatment of liposarcoma, particularly DDLPS. However, significant variations exist among studies in terms of patient populations and treatment protocols. Moreover, the inherent heterogeneity of liposarcoma contributes to the variability of the results. Further studies are needed to determine the optimal therapeutic combinations and their value in clinical practice.

In the present study, we conducted a preliminary investigation into the efficacy and safety of anlotinib combined with envafoimab in patients with unresectable/metastatic liposarcoma at our treatment center. The results showed that only one (6.7%) patient achieved a PR, yielding an ORR of 6.7%. Meanwhile, 10 (66.6%) patients achieved SD, which corresponded to a DCR of 73.3%. These results were consistent with previous findings. Although the ORR was not satisfactory, the combination of targeted therapy and immunotherapy appeared to show advantages over the respective monotherapies at improving disease control. Moreover, in view of the fact that this study is an exploration of a new combination therapy regimen in clinical practice and the common drug intolerance in patients with advanced tumors, in order to minimize the incidence of serious adverse reactions, the dose specification of 10mg was selected. In terms of results, the safety

profile of the combination therapy was similar to that reported by previous studies (29–31), with all adverse events being manageable. Patients ultimately benefited, and we can explore larger sized drug dosages in patients in the future.

The present study had several limitations. Due to its single-center, retrospective nature, this study provides only preliminary insights into the efficacy and safety of anlotinib combined with envafoimab in treating unresectable or metastatic liposarcoma. The rationale for focusing specifically on liposarcoma rather than several STS types was to reduce the influence of confounding factors. However, due to the rarity of this disease, our sample size was relatively small, which may have introduced some bias into the results. Moreover, the evaluation was limited to clinical efficacy. Future multi-center, large-sample, prospective clinical trials are warranted to validate our findings and identify specific prognostic biomarkers.

In conclusion, as liposarcoma research continues to advance, differences in TME characteristics and pathogenic mechanisms among the STS subtypes will be revealed. Therefore, subtype-specific treatment approaches will likely become the primary focus of future research endeavors. Ultimately, as it seems unlikely that a single, universal therapy for STS will emerge, patient selection based on factors such as histological subtype, TME characteristics, immune category, and tumor-infiltrating lymphocyte profile, will be essential.

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 authors.

Ethics statement

The studies involving humans were approved by Ethics Committee of the Affiliated Hospital of Qingdao 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. The animal study was approved by Ethics Committee of the Affiliated Hospital of Qingdao University. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

HL: Writing – original draft. QH: Writing – original draft. XW: Formal analysis, Investigation, Writing – original draft. MC: Formal

analysis, Writing – original draft. FQ: Writing – review & editing. BZ: Funding acquisition, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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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OPEN ACCESS

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RECEIVED 02 October 2024

ACCEPTED 07 May 2025

PUBLISHED 01 August 2025

CITATION

Qiu Y, Liu J, Chai S, Liu L, Li L and Zhang Y
(2025) Development and validation of a
Comprehensive Hematological Scoring
System for predicting overall survival in
patients with soft tissue sarcomas:
a comparison with NLR and PLR.
Front. Oncol. 15:1505485.
doi: 10.3389/fonc.2025.1505485

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Development and validation of a Comprehensive Hematological Scoring System for predicting overall survival in patients with soft tissue sarcomas: a comparison with NLR and PLR

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Background: Soft tissue sarcomas (STS) are rare malignancies with high relapse/metastasis risks and limited treatment efficacy. Current biomarkers like neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) lack comprehensive prognostic value due to their reliance on limited hematological parameters.

Methods: This retrospective study analyzed 206 STS patients (2016–2023) to develop a Composite Hematological Scoring System (CHSS) integrating 19 pretreatment markers. LASSO regression selected key variables (glucose, CRP, LDL-C, HDL-C, albumin, platelets, hemoglobin, lymphocytes), weighted by coefficients. CHSS's prognostic performance was compared to NLR/PLR via Kaplan-Meier, time-dependent ROC, and Cox regression analyses. A nomogram combining CHSS with clinical variables was validated using C-index, calibration, and decision curves.

Results: CHSS outperformed NLR/PLR in predicting overall survival (OS) across all timepoints. High CHSS patients had significantly worse OS (HR=6.197, $P<0.001$). Multivariate analysis confirmed CHSS, age, tumor size, and FNCLCC grade as independent predictors. The CHSS-based nomogram achieved a C-index of 0.79, with accurate 3-/5-year OS calibration.

Conclusion: CHSS integrates inflammation, metabolism, and nutrition markers to provide superior prognostic stratification for STS patients compared to NLR/PLR. Its integration into a nomogram supports personalized management, though multicenter validation is needed.

KEYWORDS

soft tissue sarcoma (STS), Comprehensive Hematological Scoring System (CHSS), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), prognosis

1 Introduction

Soft tissue sarcomas (STS) are rare solid cancers originating from mesenchymal tissues—including muscle, adipose, bone, and fibrous tissues—comprising approximately 1% of adult malignancies and exhibiting an annual incidence of 4–5 per 100,000 individuals (1). Liposarcoma (LPS), leiomyosarcoma (LMS), and undifferentiated pleomorphic sarcoma (UPS) represent the most prevalent subtypes, although the WHO classification system recognizes over 70 distinct histopathologic subtypes (2–4). A critical clinical challenge lies in the high rates of local recurrence and distant metastasis, occurring in 25–50% of patients, with risk stratification dependent on tumor stage and histologic subtype (5). For locally advanced and metastatic STS, first-line chemotherapies such as doxorubicin and ifosfamide remain standard-of-care, yet demonstrate limited efficacy, yielding a median overall survival (OS) of merely 10–15 months in metastatic cases (6, 7). Over the past decade, therapeutic paradigms have evolved from uniform protocols to histology-driven algorithms, incorporating tumor subtype- and stage-adjusted surgical and multimodal interventions (8).

Advances in tumor biology have established that systemic inflammation, metabolic dysregulation, and nutritional status are intrinsically linked to tumor aggressiveness and clinical outcomes (9–11). This understanding has catalyzed the emergence of prognostic biomarkers, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), prognostic nutritional index (PNI), and Controlling Nutritional Status Score (CONUT) (12–15). While these hematologic indices reflect inflammatory or nutritional derangements and enable partial prediction of oncologic prognosis and therapeutic responses, most rely on limited parameter combinations—for instance, NLR is derived solely from absolute neutrophil and lymphocyte counts—thereby limiting their ability to fully exploit hematologic data (16). It is reasonable to speculate that a multidimensional scoring system integrating comprehensive laboratory parameters may offer superior prognostic predictive capacity.

In this study, we retrospectively analyzed 19 pretreatment hematologic parameters spanning inflammation, nutrition, metabolism, and coagulation, constructing a composite prognostic score via Least Absolute Shrinkage and Selection Operator (LASSO) COX proportional hazards regression analysis. This novel scoring system was benchmarked against

two conventional hematologic markers (NLR and PLR) to evaluate the comparative prognostic utility of multidimensional versus simplified biomarker approaches.

2 Patients and methods

2.1 Patients

This retrospective cohort study analyzed the clinical data of patients with STS treated at the Musculoskeletal Tumor Center of Zhengzhou University First Affiliated Hospital from June 2016 to June 2023. The inclusion criteria for patients were as follows: 1. Histopathologically confirmed STS; 2. Complete pretreatment hematologic profiles; 3. receipt of institutionally approved standard therapies. The exclusion criteria: 1. Postsurgical recurrence; 2. Concurrent hematologic disorders; 3. Secondary malignancies. All enrolled patients underwent surgical treatment and were followed up regularly until death or June 2023. The ethics committee of Zhengzhou University First Affiliated Hospital approved this study, and each participant signed a written informed consent form.

2.2 Data collection and analysis

Nineteen pretreatment laboratory parameters were collected: neutrophils, lymphocytes, monocytes, red blood cells, red cell distribution width, platelets, hemoglobin, albumin, globulin, glucose, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), activated partial thromboplastin time (APTT), prothrombin time (PT), fibrinogen, thrombin time (TT), and C-reactive protein (CRP). The optimal cutoff values for each indicator were calculated using receiver operating characteristic (ROC) curves, converting all indicators into binary variables. Clinical variables including age, gender, body mass index (BMI), tumor size, tumor location, and the French Federation Nationale des Centres de Lutte Contre le Cancer sarcoma grade (FNCLCC) were extracted from electronic medical records. Overall survival (OS) was defined as the interval from diagnosis to death or last follow-up.

2.3 Comparison of prognostic value of NLR/PLR/CHSS in STS patients

NLR = Neutrophil/Lymphocyte; PLR = Platelet/Lymphocyte. The construction method of the CHSS score is as follows: first, variables with prognostic value in STS patients were screened using logistic regression ($P < 0.05$). Subsequently, LASSO regression analysis was performed to reduce dimensionality of the selected variables and assign a coefficient to each variable. The CHSS score is the sum of all variables multiplied by their respective coefficients. The optimal cutoff value for the CHSS score was calculated using ROC analysis. Kaplan-Meier survival curves were plotted to

Abbreviations: STS, Soft tissue sarcoma; CHSS, Comprehensive Hematological Scoring System; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; LPS, Liposarcoma; LMS, leiomyosarcoma; UPS, undifferentiated pleomorphic sarcoma; OS, overall survival; PNI, prognostic nutritional index; CONUT, Controlling Nutritional Status Score; LASSO, Least Absolute Shrinkage and Selection Operator; HDL, high-density lipoprotein; LDL, low-density lipoprotein; APTT, activated partial thromboplastin time; PT, prothrombin time; TT, thrombin time; CRP, C-reactive protein; ROC, receiver operating characteristic; FNCLCC, French Federation Nationale des Centres de Lutte Contre le Cancer sarcoma grade; DCA, Decision curve analysis; HR, Hazard ratio; CI, confidence interval.

evaluate the prognostic value of the three biomarkers in predicting overall survival in STS patients. The predictive capabilities of the three biomarkers were compared using time-dependent ROC curves. Subgroup analyses were conducted to compare the stability of the predictive abilities of the three biomarkers.

2.4 Construction and evaluation of the CHSS-based nomogram for STS

CHSS was integrated with clinical covariates to identify independent OS predictors via multivariable Cox regression. A prognostic nomogram was constructed using significant predictors, with discriminative performance evaluated by Harrell’s concordance index (C-index) and calibration curves. Decision curve analysis (DCA) and clinical impact curves quantified clinical net benefit.

2.5 Statistical analysis

The Kolmogorov-Smirnov test was used to determine whether continuous variables follow a normal distribution. Based on the normality, either the t-test or the Mann-Whitney U test was used to assess differences between continuous variables. The chi-squared test or Fisher’s exact test was used to evaluate differences in categorical variables, depending on the sample size in each group. All statistical analyses were performed using R software version 4.4.0 (Vienna Institute of Statistics and Mathematics, Austria). A P value of < 0.05 was considered statistically significant.

3 Results

3.1 Patient characteristics

The cohort comprised 206 STS patients (108 males, 98 females) with a mean age of 49.7 ± 13.2 years (range: 26–77). FNCLCC grading classified 145 patients (70.4%) as grade 3 and 61 (29.6%) as grade 2. Tumor distribution included upper limbs (n=31, 15.0%), lower limbs (n=138, 67.0%), and trunk (n=37, 18.0%). Tumor size stratification revealed 27 patients (13.1%) with lesions <5 cm, 99 (48.1%) with 5–10 cm tumors, and 80 (38.8%) with tumors >10 cm. At final follow-up (June 2023), 44 deaths (21.4%) were recorded (Table 1).

3.2 Comparison of prognostic value of NLR/PLR/CHSS in STS patients

The optimal cutoff values for 19 test results in STS patients are shown in Table 2. Eight parameters—glucose, CRP, LDL-C, HDL-C, albumin, platelet count (PLT), hemoglobin (HB), and lymphocyte count—were significantly associated with prognosis and incorporated into CHSS. Table 3 presents the coefficients of the aforementioned

TABLE 1 Patients demographics.

Variable	CHSS Low Risk (N = 141)	CHSS High Risk (N = 65)	P-value
Overall survival			
Mean (SD)	1600 (734)	1180 (812)	< 0.001
Gender			
Female	66 (46.8%)	32 (49.2%)	0.862
Male	75 (53.2%)	33 (50.8%)	
Age			
Mean (SD)	49.4 (13.7)	50.2 (12.3)	0.665
FNCLCC			
Stage 2	33 (23.4%)	8 (12.3%)	0.0957
Stage 3	108 (76.6%)	57 (87.7%)	
TumorLocation			
Upper extremity	22 (15.6%)	9 (13.8%)	0.429
Lower extremity	97 (68.8%)	41 (63.1%)	
Trunk	22 (15.6%)	15 (23.1%)	
TumorSize			
T<5 cm	17 (12.1%)	10 (15.4%)	0.593
5 cm<T<10 cm	71 (50.4%)	28 (43.1%)	
T>10cm	53 (37.6%)	27 (41.5%)	
BMI			
Abnormal	45 (31.9%)	22 (33.8%)	0.908
Normal	96 (68.1%)	43 (66.2%)	

test results in the CHSS score. The CHSS cutoff (0.189) stratified patients into high- versus low-risk groups (Figure 1A), with significantly worse OS in high-CHSS patients (log-rank P < 0.001). Similarly, patients in the high NLR group and high PLR group had lower overall survival than their respective controls (P < 0.001) (Figures 1B–D). The time-dependent ROC curve results indicated that the predictive ability of CHSS was superior to that of NLR/PLR at all time points, and in most instances, it outperformed the constituent indicator CRP (Figure 2A). Subgroup analysis results showed that CHSS demonstrated significant predictive ability in the majority of subgroups, whereas NLR/PLR showed limited generalizability (Figures 2B–D).

3.3 Univariate analysis and multivariate analysis

Cox regression analysis was used to explore independent prognostic factors in STS patients. Univariate analysis revealed

TABLE 2 Univariate logistic results under best roc cutoff.

Variable	Auc	Cutoff	Logistic.Pvalue	Logistic.OR
NLR	0.605	2.851	<0.001	3.643 (1.825-7.271)
PLR	0.633	148.792	0.001	3.129 (1.573-6.227)
LMR	0.538	4.448	0.121	0.560 (0.269-1.166)
PLT	0.601	213	0.019	2.252 (1.145-4.431)
Neutrophil	0.525	4.01	0.183	1.577 (0.807-3.082)
Lymphocyte	0.589	2.08	0.032	0.364 (0.145-0.917)
Monocytes	0.516	0.44	0.265	0.684 (0.350-1.335)
RBC	0.543	3.98	0.082	0.551 (0.282-1.079)
HB	0.527	95	0.022	0.339 (0.134-0.857)
Albumin	0.578	41.3	0.018	0.428 (0.211-0.865)
RDW	0.548	13.7	0.086	1.840 (0.918-3.688)
Globulin	0.584	23.6	0.058	2.029 (0.975-4.222)
Glucose	0.568	5.93	0.001	3.733 (1.675-8.322)
Triglycerides	0.528	1.78	0.057	0.238 (0.054-1.043)
Cholesterol	0.555	4.71	0.052	0.134 (0.018-1.017)
HDL-C	0.573	1.35	0.014	0.316 (0.126-0.793)
LDL-C	0.612	1.97	0.009	2.667 (1.283-5.542)
APTT	0.554	30.4	0.081	1.826 (0.929-3.589)
PT	0.565	11.3	0.09	1.861 (0.907-3.815)
TT	0.515	17.2	0.154	1.839 (0.796-4.251)
FIB	0.528	4.04	0.114	1.845 (0.864-3.943)
CRP	0.629	9.1	0.004	3.080 (1.427-6.649)

that age (hazard ratio (HR) = 1.036 (95% confidence interval (CI) 1.014–1.060), $P = 0.002$), FNCLCC (HR = 3.222 (1.361–7.631), $P = 0.008$), tumor size (HR = 1.942 (1.188–3.172), $P = 0.008$), and CHSS (HR = 6.119 (3.238–11.561), $P < 0.001$) were associated with OS in STS patients (Figure 3A). The results of the multivariate analysis

indicated that age (HR = 1.041 (1.017–1.066), $P < 0.001$), FNCLCC (HR = 3.044 (1.276–7.264), $P = 0.012$), tumor size (HR = 1.749 (1.080–2.833), $P = 0.023$), and CHSS (HR = 6.197 (3.242–11.845), $P < 0.001$) were all independent prognostic factors for STS patients (Figure 3B). CHSS consistently outperformed other variables in time-dependent ROC comparisons (Figure 3C).

3.4 Construction and validation of CHSS-based nomogram

A prognostic nomogram integrating four independent predictors (CHSS, age, FNCLCC grade, tumor size) was developed (Figure 4A). The model demonstrated excellent discrimination (C-index=0.79) and calibration accuracy for 3-/5-year OS predictions (Figure 4B). Decision curve analysis revealed greater net clinical benefit for Model 2 (CHSS + clinical variables) versus Model 1 (clinical variables alone) across threshold probabilities (Figures 4C, D).

4 Discussion

This single-center retrospective study evaluated two biomarker development paradigms in 206 STS patients. While both conventional biomarkers (NLR/PLR) and the CHSS demonstrated prognostic utility, time-dependent ROC analyses revealed CHSS’s superior predictive accuracy and stability across follow-up intervals. CHSS was identified as an independent prognostic factor for STS patients, and the nomogram based on CHSS could reliably predict 3-year and 5-year overall survival in STS patients.

In the past decade, accumulating evidence has validated the prognostic value of NLR and PLR in various cancers, including lung cancer, breast cancer, thyroid cancer, and liver cancer (17–22). Furthermore, these inflammatory makers demonstrate prognostic relevance in STS subtypes, particularly liposarcoma (23–28). Emerging evidence further highlights their potential in predicting therapeutic responses, as exemplified by trabectedin outcomes in STS patients (29). NLR’s role as a marker for predicting cancer patient survival may be attributed to its reflection of the balance between the body’s inflammatory and immune status (30). Neutrophils are key effector cells in the inflammatory response and are often elevated in cancer patients, indicating a significant inflammatory reaction. Neutrophils promote tumor progression by releasing cytokines and growth factors, which enhance tumor angiogenesis, suppress immune surveillance, and promote the growth and invasiveness of tumor cells (31, 32). On the other hand, lymphocytes are crucial cells in the immune system responsible for anti-tumor responses (33). A decrease in lymphocytes usually reflects a state of immunosuppression, indicating impaired immune surveillance (34, 35). This immunosuppressive state hinders the body’s ability to effectively eliminate tumor cells, increasing the risk of tumor recurrence and metastasis. A high NLR reflects a combination of increased neutrophils and decreased lymphocytes, indicating a state of both

TABLE 3 Univariate logistic results under best roc cutoff.

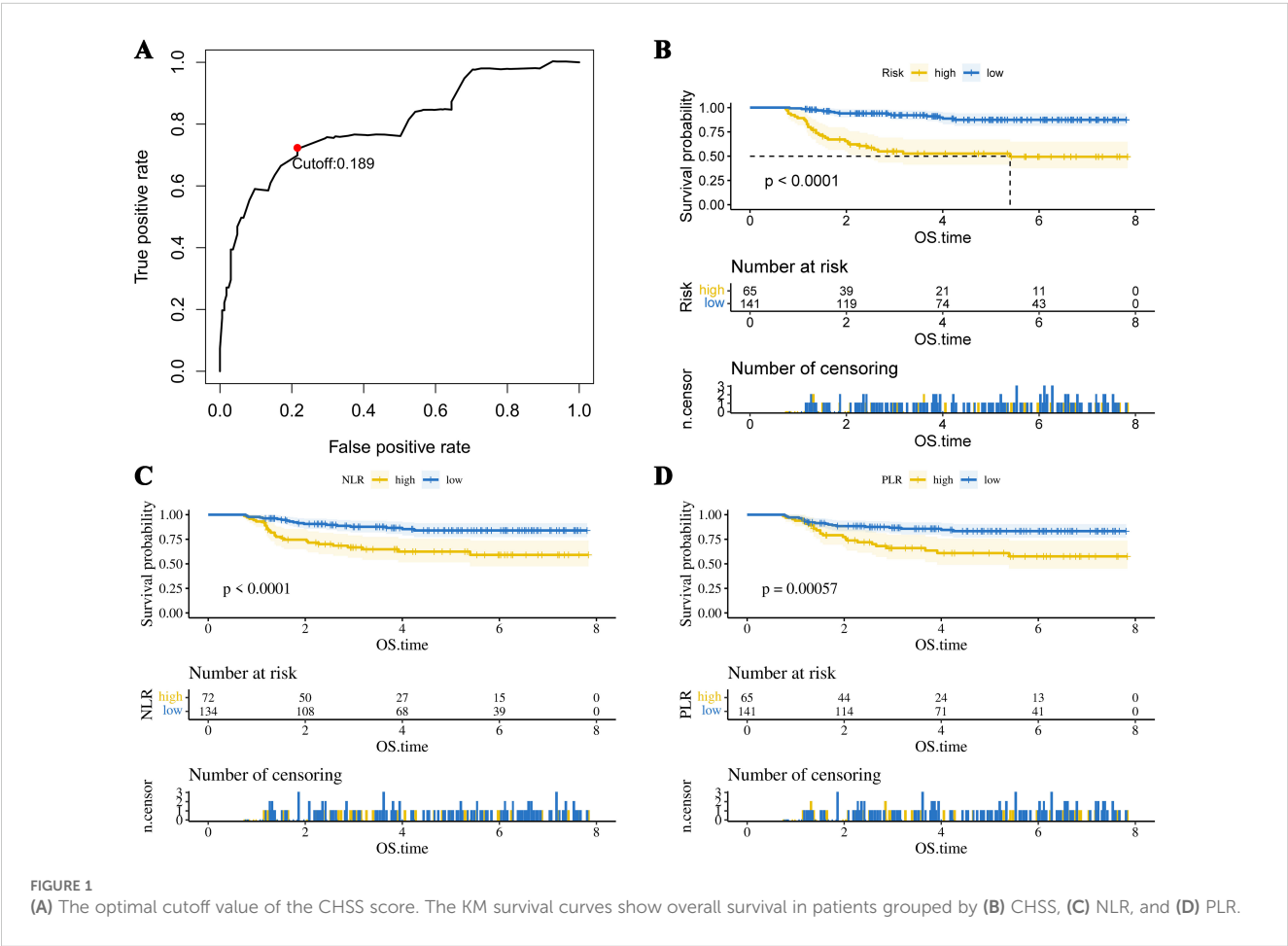
Variable	Coef
PLT	0.567091
Lymphocyte	-0.47881
HB	-0.5132
Albumin	-0.78245
Glucose	0.708249
HDL-C	-0.60477
LDL-C	0.498902
CRP	0.971148

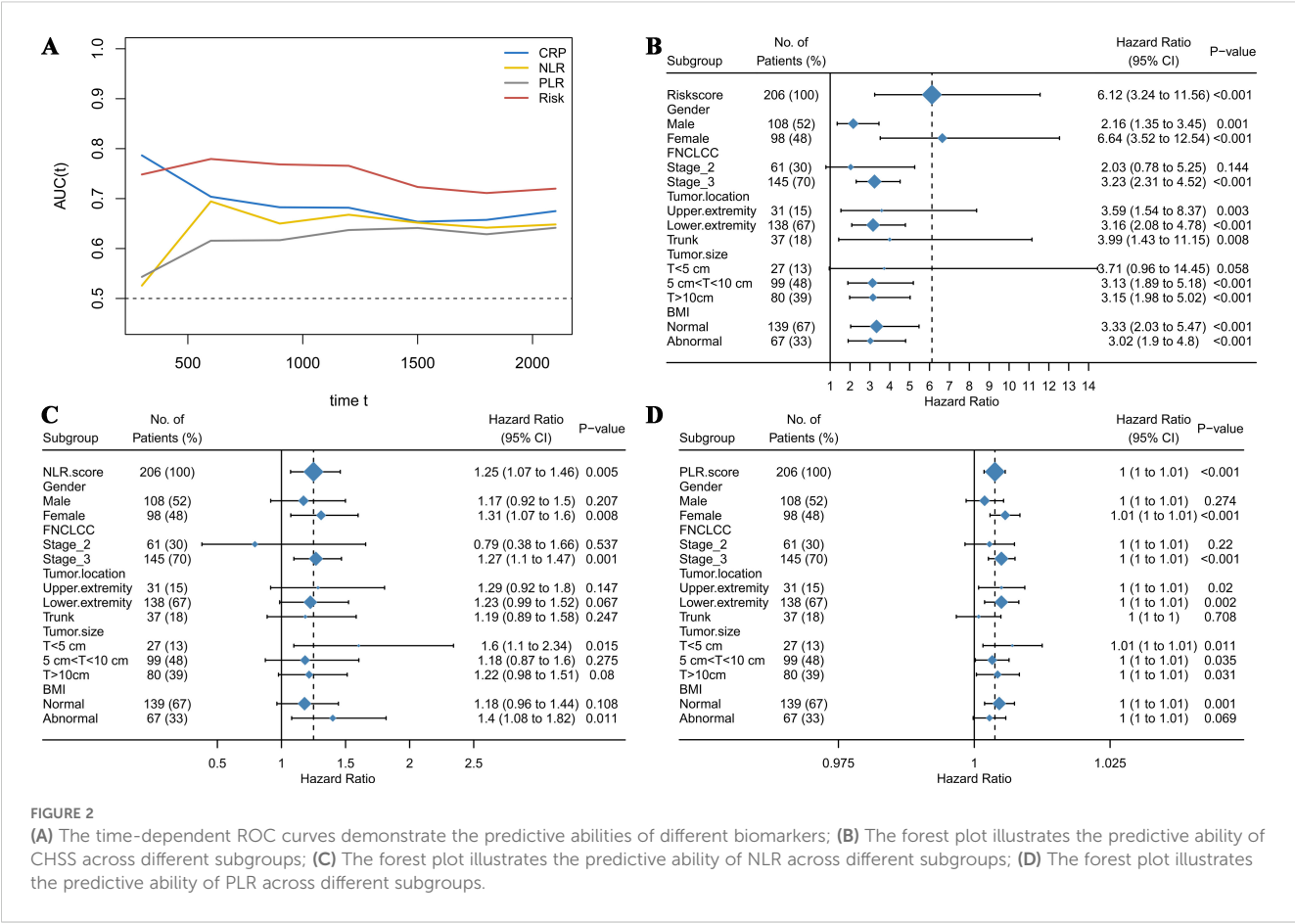
heightened inflammation and weakened anti-tumor immunity. Additionally, experimental tumor therapies that reduce neutrophil counts have further solidified the association between elevated neutrophils and poor prognosis in cancer patients (36, 37).

Similar to NLR, a high PLR also reflects an imbalance between tumor-promoting factors and anti-tumor immune responses (23, 38). For example, platelets can release pro-angiogenic factors such as vascular endothelial growth factor to promote tumor growth (39, 40). However, these biomarkers only incorporate a very limited portion of the hematological test results, making it difficult to fully

capture the true value of these tests. In our study, we collected up to 19 blood test results, including neutrophil count, lymphocyte count, monocyte count, and C-reactive protein, which are related to inflammation and immunity; glucose, albumin, triglycerides, HDL-C, LDL-C, and other indicators associated with nutritional status and metabolism; as well as APTT, PT, TT, which are related to coagulation status. Through dimensionality reduction of these results, we constructed the CHSS prognostic score to comprehensively reflect the value of the patients' blood test results. As we predicted, CHSS demonstrated superior predictive ability and stability compared to NLR and PLR. CHSS is composed of CRP, lymphocytes, HB, albumin, glucose, HDL-C, LDL-C, and PLT, and it comprehensively reflects the patient's inflammatory, immune, nutritional and metabolic status. The response of CHSS to the body's inflammation and immune balance primarily comes from CRP, PLT and lymphocyte count. CRP is an acute-phase reactive protein synthesized by the liver when stimulated by inflammatory factors. Elevated CRP indicates the presence of a persistent inflammatory state, which can promote tumor growth and metastasis by enhancing angiogenesis, supporting tumor cell survival, and increasing invasiveness (41, 42).

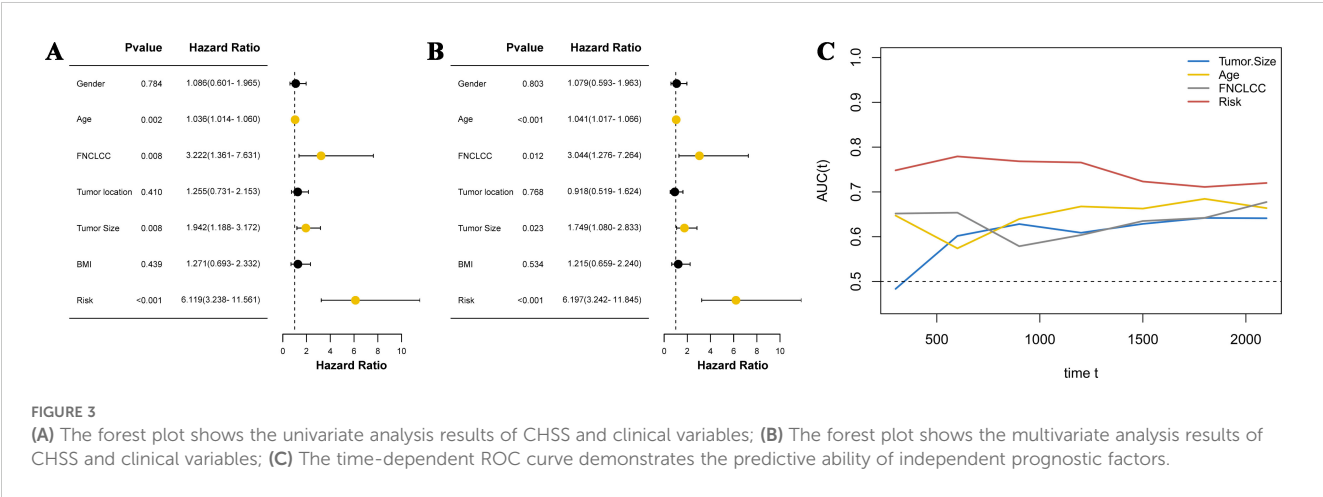
Beyond inflammation, CHSS can also reflect the body's lipid metabolism balance. The coefficients of LDL-C and HDL-C in CHSS are 0.498 and -0.605, respectively, with elevated LDL-C and reduced HDL-C associated with poor prognosis in STS patients. LDL-C is the





lipoprotein primarily responsible for distributing cholesterol to extrahepatic tissues and body cells, while HDL-C is the smallest and densest lipoprotein in the blood, functioning to clear excess cholesterol through reverse transport (43, 44). Abnormally elevated LDL-C and reduced HDL-C may indicate an abnormal lipid metabolism, where tumor cells uptake and synthesize more cholesterol and fatty acids to support their growth and proliferation (45). Similarly, the glucose coefficient in CHSS is 0.708, suggesting that elevated blood glucose is

associated with a worse prognosis in STS patients. This aligns with previous research showing that elevated blood glucose, even below the diagnostic threshold for diabetes, is related to poor outcomes in cancer patients (46). This may be due to the high-glucose environment upregulating the pathways related to the Warburg effect in tumor cells, promoting tumor growth and metastasis. Additionally, glucose can activate various signaling pathways involved in tumor cell proliferation, metastasis, and therapy resistance, promoting



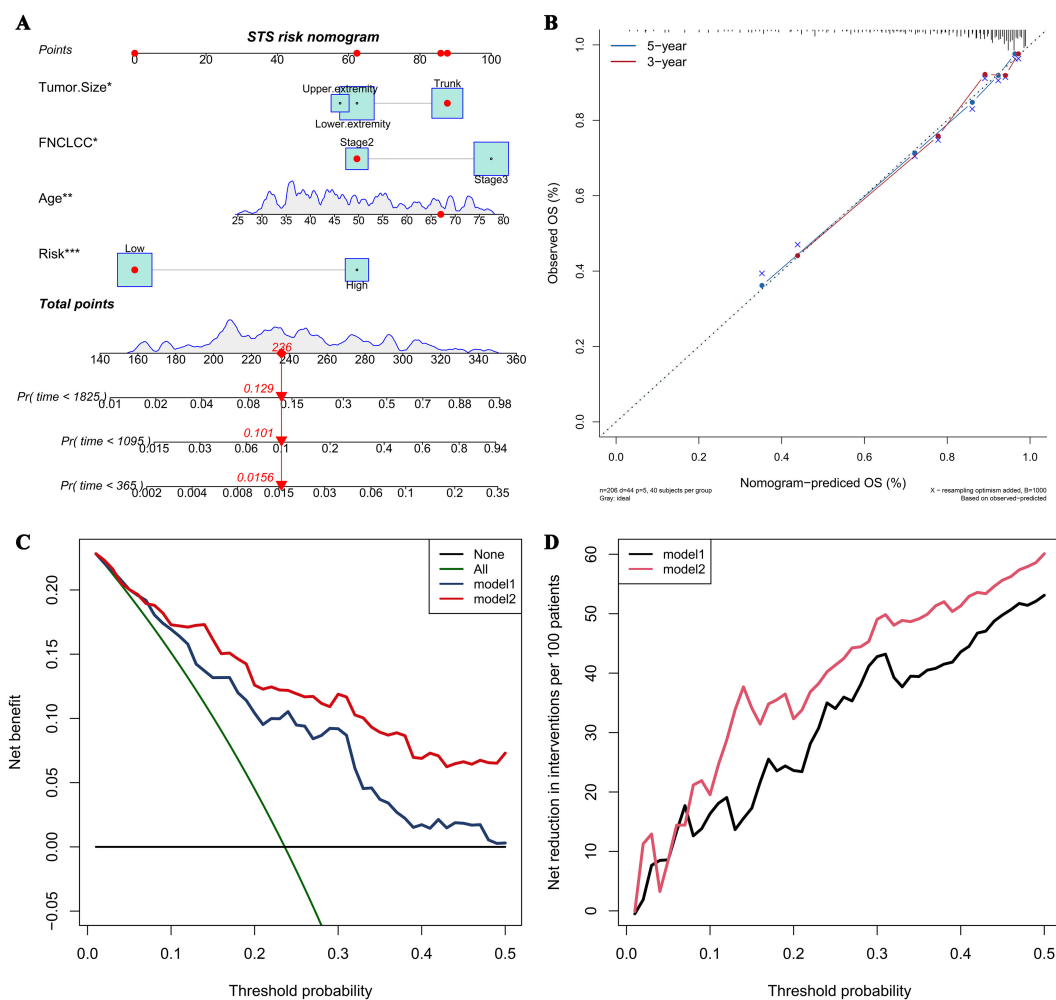


FIGURE 4

(A) The nomogram predicting overall survival in soft tissue sarcoma patients based on independent risk factors; (B) The calibration curve of the nomogram; (C) The net benefit curve of the nomogram; (D) The net reduction curve of the nomogram.

malignant phenotypes (47). Experimental results show that cancer cells exposed to supraphysiological glucose concentrations become more aggressive, further confirming this (46, 48).

Lastly, CHSS may also reflect the body's nutritional status. The nutritional status of patients is also closely related to the prognosis of tumor patients (49). The coefficients for albumin and hemoglobin (HB) in CHSS are -0.513 and -0.782, respectively. Albumin is a chronic-phase protein commonly used to assess a patient's nutritional status and the body's protein synthesis capacity (15). An abnormal decrease in albumin indicates poor nutritional status and may weaken the body's antitumor immune function and response to treatment (50). HB is the primary carrier responsible for transporting oxygen from the lungs to tissues throughout the body. Anemia may reflect a state of insufficient oxygen supply to tissues, and in a hypoxic environment, tumor tissues adapt by activating a series of survival-promoting mechanisms, such as inducing angiogenesis, which in turn promotes further tumor growth and metastasis (51, 52). Additionally, a decrease in HB may also indicate systemic malnutrition and cachexia in cancer patients.

In conclusion, we believe that CHSS utilizes the patient's test results more comprehensively, reflecting the overall status of the body, and thus has a stronger predictive capability for patient prognosis. However, it must be acknowledged that our study has certain limitations. First, our study is a single-center retrospective study, which may introduce some selection bias. Secondly, although the CHSS exhibits stronger predictive capabilities, its computational complexity exceeds that of NLR and PLR, and the optimal coefficients for individual markers may vary across different cohorts, potentially limiting its clinical applicability. However, the enhanced stability of CHSS predictions provides a novel direction for developing next-generation biomarkers: integrating comprehensive indicators reflecting systemic inflammatory, immune, and nutritional statuses can circumvent the risk of prediction failure inherent to single-marker reliance. Future studies should focus on identifying the optimal balance between computational complexity and predictive performance in multicenter, large-scale cohorts. Furthermore, the development of standardized assays analogous to Oncotype DX is critical to advancing the clinical translation of CHSS (53). Lastly, our study

only included the most common laboratory test results, and some novel test results with prognostic value, such as cytokines test, may have been overlooked.

5 Conclusion

The CHSS, composed of multiple test results, demonstrates superior predictive ability and stability for overall survival in STS patients compared to NLR/PLR. CHSS is an independent risk factor for OS in STS patients. The nomogram based on CHSS aids in the personalized management of patients.

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 ethics committee of Zhengzhou University First Affiliated Hospital approved this study, and each participant signed a written informed consent form.

Author contributions

YQ: Writing – original draft, Writing – review & editing. JL: Writing – review & editing. SC: Writing – review & editing. LLL: Writing – review & editing. LQL: Writing – review & editing. YZ: Supervision, Visualization, Writing – original draft, Writing – review & editing.

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Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Acknowledgments

Thanks to the support of The First Affiliated Hospital of Zhengzhou University, Zhengzhou University for the research.

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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