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REVIEW ARTICLE

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Current therapy of retroperitoneal sarcomas

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ABSTRACT

The location of soft tissue sarcoma (STS) in the retroperitoneal space (about 15% of all STS) is a special therapeutic challenge, which is why these cancers should be strictly treated in specialised centres. The most common subtypes in this area are liposarcoma (mainly well-differentiated liposarcoma WD LPS and dedifferentiated liposarcoma DD LPS), leiomyosarcoma, and solitary fibrous tumour. The specificity of retroperitoneal sarcomas (RPS) is based on a high potential for local recurrence, less frequent occurrence of lung metastases (more often to the liver), and greater difficulty in achieving adequate tissue margins (extra compartmental locations, invasion of vital organs). The main prognostic factors include the size of the tumour, histological subtype, histological malignancy, multifocality, and radicalism of the resection. Nomograms can be used to assess the prognosis. Extensive resections that include the adjacent organs (kidney, intestine, muscles, liver) along with the tumour are the only way to cure these cancers and are particularly justified in cases where no macroscopic tumour fragments are left. When planning the treatment preoperative radiotherapy should be considered and also (in high-grade cases) chemotherapy based on doxorubicin and ifosfamide. During the surgery together with the tumour are often removed: kidneys/adrenal glands (in about 50% of patients), large intestine — right or left-sided hemicolectomy (over 20%), part of the pancreas (15%), and spleen (10%). Block resections of retroperitoneal STS together with infiltrated peripheral organs improves patients' survival (especially in the case of liposarcoma). Some authors propose operating RPS in a "compartmental" manner, removing also the unoccupied surrounding organs, such as the spleen, pancreatic tail, kidney, and lumbar muscle, which may improve the patient outcome because microscopic infiltration of adjacent organs, which macroscopically are not occupied by sarcoma in over 60%. A liberal approach to resection of adjacent organs that are not involved by cancer should always be considered when the scope of surgical treatment is selected. The quality of the margins should be taken into account, as well as the histological type and the expected complications. Surgical complications after extensive MPZ operations concern about 12–15% of patients. Determination of infiltration of the inferior vena cava in the imaging tests requires special analysis because some of the operated cases of leiomyosarcoma may develop from its wall.

Key words: sarcoma, retroperitoneal space, liposarcoma

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Introduction

The location of soft tissue sarcoma (STS) in the retroperitoneal space (about 15% of all STS) is a special therapeutic challenge, which is why these cancers should be strictly treated in specialised centres [1, 2]. This location is generally associated with worse prognosis than for tumours localised on the limbs. The specificity of retroperitoneal sarcomas (RPS) is based on a high potential for local recurrence, less frequent occurrence of lung metastases (more often to the liver), and greater difficulty in achieving adequate tissue margins (extra-compartmental location, invasion of vital organs). Extensive resections that include adjacent organs (kidney, intestine, muscles, liver) along with the tumour are the only way to cure these cancers and are justified in cases in which macroscopic tumour fragments are not left behind.

Diagnosis and differentiation

Proper pre-operative diagnostics with the collection of histological material (preferably with a core needle biopsy) and radiological evaluation is an essential ele-

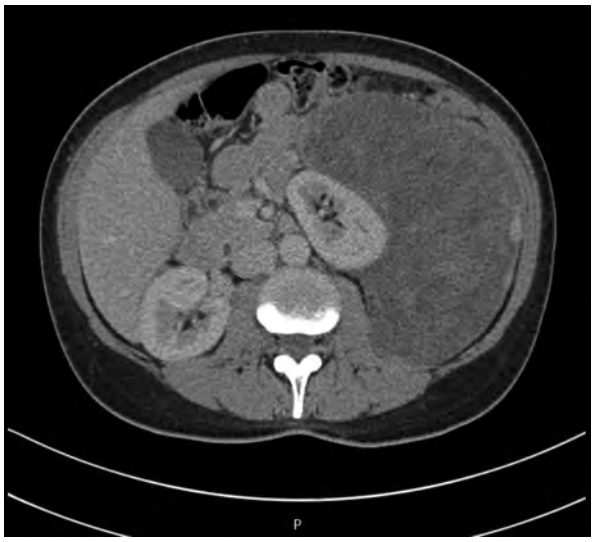

Figure 1. Image of the CT scan of an extensive left retroperitoneal liposarcoma that relocates the kidney

ment in the management of retroperitoneal sarcomas [2]. The diagnosis is usually late (delayed when compared to limb localisation) because the symptoms of RPS are very uncharacteristic: often asymptomatic tumours in the abdominal cavity, sometimes weight loss, lumbar region pain, lower limb oedema, or gastrointestinal symptoms (such as obstruction or bleeding). Differential diagnosis should include epithelial tumours of the kidneys, pancreas, adrenal glands, germ cell tumours, lymphomas, and metastases of testicular cancer. Assessing the levels of serum tumour markers (gonadotropin and alpha-fetoprotein) may be helpful.

The basic imaging technique of choice is a spiral computed tomography (CT) scan with contrast of the abdomen and pelvis (Figure 1, 2) [2].

Research shows that the magnetic resonance (MR) test has not been proven superior to CT in the diagnosis of retroperitoneal lesions; MR is applicable in the case of STS located in the pelvis. The CT scan of retroperitoneal liposarcoma is so characteristic that it is possible to undertake an attempt of surgical treatment without prior histopathological verification (it is necessary to obtain such verification if multiorgan resections or preoperative treatment are considered as part of the planned operation) (Figure 2).

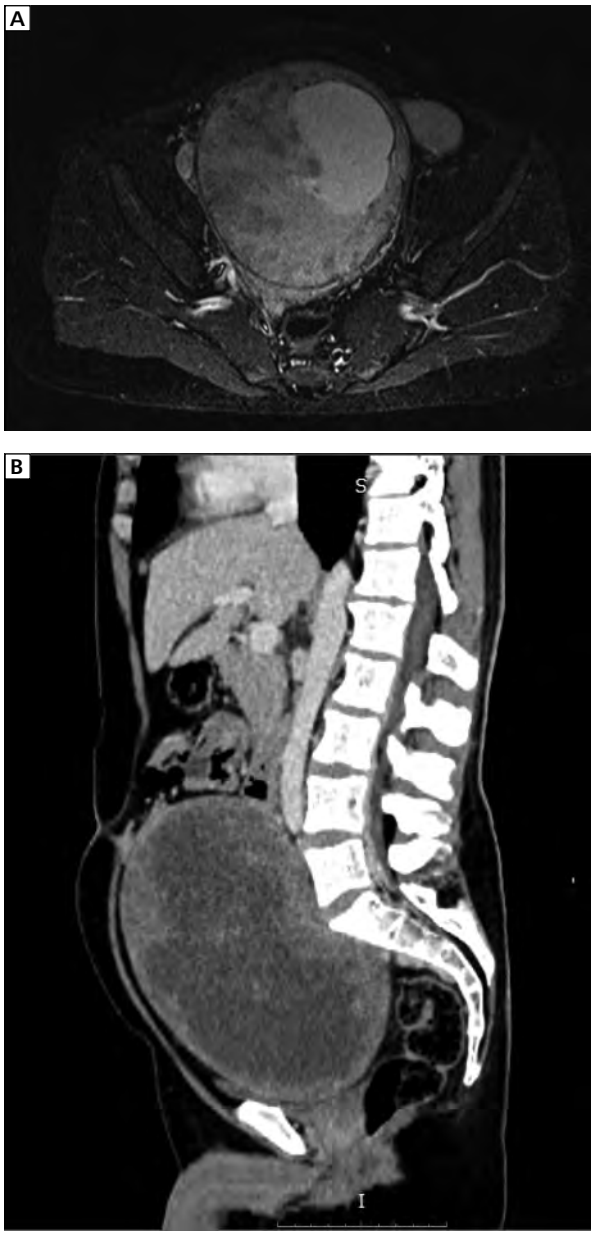

Figure 2. Magnetic resonance image of the pelvis MPNST (**A**) and reconstruction of the same sarcoma in the CT scan (**B**)

Prognostic factors and staging

Rates of five-year survival of patients with retroperitoneal STS is 36–70%, and better results are obtained in reference centres (Table 1) [1–14]. Most common in this area are liposarcoma (mostly well-WD LPS differentiated liposarcoma and dedifferentiated liposarcoma DD LPS), leiomyosarcoma, and solitary fibrous tumour (SFT) (Table 2).

Independent, unfavourable prognostic factors are: incomplete surgical treatment, high histological grade, histological type of sarcoma (other than WD LPS and SFT), multifocal tumour, and patient's age (the last factor for overall survival) [1, 3, 15]. For staging of primary RPS, TNM AJCC edition 8 is used, taking into account the size of the tumour (T1 ≤ 5 cm, T 2 > 5 cm and ≤ 10 cm, T3 > 10 cm ≤ 15 cm, T4 > 15 cm), tumour grade (G1–G3), and the presence of metastases. Currently, a nomogram is also used to assess the prognosis of these cancers [16–19].

Table 1. Results of treatment of patients with retroperitoneal soft tissue sarcoma (STS)

Study	Number of patients	Percentage of patients who underwent radical resection	5-year local recurrence-free survival	5-year overall survival
Jaques et al. (1990) [4]	114	65%	49%	Not given
Stoeckle et al. (2001) [5]	165	65%	48%	46%
Hassan et al. (2004) [6]	97	78%	44%	51%
Dziewirski et al. (2006) [7]	87	66%	51%	55%
Gronchi et al. (2009) [8]	152	90%	71%	60%
Bonvalot et al. (2009) [9]	382	90%	51%	57%
Bremjit et al. (2014) [10]	132	90%	35%	71%
Toulemonde et al. (2014) (multicentre) [11]	537	76%	46%	66%
Smith et al. (2015) [12]	362	100%	3-year LFRS: 98% WD LPS, 57% DD LPS, 80% LMS	3-year OS: 97% WD LPS, 78.5% DD LPS, 79% LMS
Gronchi et al. (2015) [13]	377	96%	76%	64%
Tan et al. (2016) [14]	632	85%	61%	69%
Gronchi et al. (2016) (multicentre) [15]	1007	95%	74%	67%

LFRS — local relapse-free survival; WD LPS — well-differentatied liposarcoma; DD LPS — dedifferentiated liposarcoma; LPS — liposarcoma; LMS — leiomyosarcoma

Table 2. Distribution of histopathological subtypes of primary retroperitoneal sarcomas on the basis of the two largest contemporary patient cohorts: 1007 cases (Gronchi et al. [15]) and 675 cases (Tan et al. [14])

Histological subtype	Percentage of all patients (%)	
	Gronchi et al. [15]	Tan et al. [14]
DD LPS	36.7	32
WD LPS	26.1	28
LMS	19.3	23
SFT	5.9	5
MPNST	3.3	3
UPS	2.2	Not given
Other	6.6	10

DD LPS — dedifferentiated liposarcoma; WD LPS — well-differentatied liposarcoma; LMS — leiomyosarcoma; SFT — solitary fibrous tumour; MPNST — malignant peripheral nerve sheath tumour; UPS — undifferentiated pleomorphic sarcoma

Surgical treatment

Radical surgery is the primary and only method that gives a chance to cure patients with retroperitoneal STS. An operation with the intention of cure should be done in macro- and microscopically radical resection margins, preferably in a reference centre. Recently, the international rules for surgical treatment of RPS have been published [2, 20, 21].

In most cases, the operation starts with a median incision (from the xiphoid process to pubic symphysis). In cases of localisation in the upper retroperitoneal space (above the renal vessels), thoracoabdominal incision is sometimes performed. In the pelvic position (including the smaller one) it is recommended to use the abdominal-inguinal incision (retroperitoneal access from the so-called Karakousis incision). The abdominal cavity is evaluated for the presence of possible liver metastases and intraperitoneal implants. Then the possibility to remove the tumour within the limits of macroscopically normal tissue is evaluated. The most common reason for withdrawal from surgery is infiltration of the aorta, inferior vena cava, portal vein, upper mesenteric vessels, and celiac trunk (less frequently — duodenal infiltration, pancreas head and liver in the case of STS location in the upper retroperitoneal space). Multiple implants into the peritoneum (*peritonitis sarcomatosa*) are a contraindication for attempts to resect the primary sarcoma lesion (i.e. cytoreductive surgery).

The most desirable is a block resection (in a block of adjacent organs), which is possible in 55–90% of patients. The radicalism of surgical treatment is hindered by anatomical relations, lack of real muscle compartments, asymptomatic growth of the tumour to large sizes, and frequent infiltration of vital organs. Most often together with the tumour the following are removed: kidney/adrenal (about 50% of patients), large intestine — right or left-sided hemicolectomy (over 30%), lumbar muscle or its fascia (over 20%), spleen (15%),

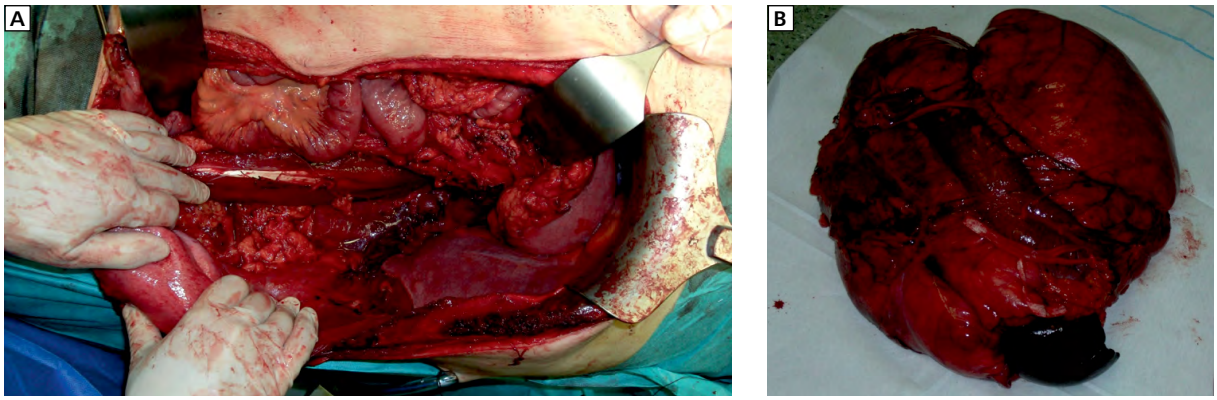

Figure 3. Image of post-operative bed and preparation (**A**, **B**) including the RPS (WD LPS) en-bloc of the ilio-lumbar muscle fascia, left kidney, left half of the colon, diaphragm section, spleen, and pancreatic tail

and pancreas (15%). The retroperitoneal STS block resection with infiltrated peripheral organs improves survival of patients. Some authors propose operating RPS in a "compartmental" manner, also removing unoccupied surrounding organs such as the spleen, pancreatic tail, kidney, and lumbar muscle, which may affect the improvement of distant results, as microscopic infiltration of adjacent organs, which macroscopic are not occupied by sarcoma in over 50% [8, 9, 20, 22, 23] (Figure 3). The liberal approach to resection of adjacent organs not involved with the cancer should always be considered when the scope of surgical treatment is selected. The quality of the margins, the histological type, and the expected complications should also be taken into account. Liposarcomas are characterised by a greater tendency for local recurrences, so multiorgan surgery is the most indicated in this type of tumour [13, 14, 16]. Surgical complications after extensive RPS operations affect about 12–16% of patients, and perioperative mortality is about 2–3% [24, 25].

Determination of infiltration of the inferior vena cava in the imaging tests requires special analysis, because some of the operated cases of leiomyosarcoma may develop from its wall. In the section below the origin of the renal vein the inferior vena cava can be cut or tied without serious complications. Cavities in the upper part (especially above the renal veins) require reconstruction of the inferior vena cava.

As in the case of other STS locations, metastases to the lymph nodes are extremely rare and there is no need to perform lymphadenectomy of the retroperitoneal space at the same time with the excision of RPS.

Retroperitoneal sarcomas metastases to distant organs are relatively rare. The most frequent cause of treatment failure is local recurrence, which explains the paradox of worse prognosis of these tumours despite the biologically slower natural course than sarcomas in the limb location. In more than half of these patients, a radical resection of the sarcoma may be performed during the second operation, which is associated with prolonged survival compared to patients treated with palliative care. However, the results of treatment of patients operated on for primary sarcomas are definitely better than those due to recurrence. For example, in a group of 167 patients with retroperitoneal sarcomas treated at the Istituto Nazionale Tumori in Milan, 10-year survival rates were below 30% and were significantly better in the group of patients operated for primary tumours than for relapses [26].

The macroscopically non-radical excision of RPS (primary or recurrent lesions) does not prolong the survival of patients compared to patients undergoing only laparotomy and diagnostic biopsy. In some of these patients, the following are used to improve the quality of life: urinary tract surgery (e.g. nephrostomy), avoiding anastomosis in gastrointestinal obstruction, and neurolysis in cases of severe pain. In general, in the case of multifocal recurrence, surgical treatment is rarely effective, in the case of an isolated recurrence of well-differentiated liposarcoma, especially after primary radical resection, the first option is to observe the tumour growth rate [27, 28].

Adjuvant therapy

There are no results of prospective trials that would indicate clearly reduction in the incidence of local recurrence in the RPS with the use of adjuvant tele-radiotherapy (preoperative, postoperative), although there is increasing evidence from retrospective studies indicating improvement in local control with the combination of radiotherapy (especially preoperative) with surgery in RPS [29, 30]. The location in the retroperitoneal space due to the presence of critical organs often makes unable the safe use of optimal doses of radiation in patients with sarcomas (50 Gy and more) and complicates the planning of adjuvant treatment. Unproven benefits of

adjuvant radiotherapy should be critically compared with the possibility of radiation-induced complications, mainly from the gastrointestinal tract (e.g. chronic and difficult to treat inflammatory bowel disease, gastrointestinal sub ileus). The EORTC STRASS protocol is currently undergoing comparing surgical treatment with combined surgery with preoperative irradiation from external fields.

Another option is the use of external-beam radiotherapy (EBRT) and intraoperative radiotherapy (IORT). The theoretical advantages of IORT include direct visualisation of the treated area, allowing greater control over the dose distribution and delivery of a larger dose per target volume/sarcoma operating bed (with an estimated biological effect two to five times greater than that of traditional fractions from external fields). In the only prospective clinical study in patients undergoing radical surgery IORT (20 Gy) and EBRT (35–40 Gy) were used, or only postoperative EBRT (50–55 Gy), and the patients had similar overall survival and lower incidence of local recurrence in the group irradiated during surgery [30–32]. Similar results were obtained in non-randomised and retrospective studies. Research conducted at the Oncology — Institute Centre in Warsaw confirms the possibility of using supplemental high-dose intraoperative brachytherapy after removal of sarcoma along with post-operative radiotherapy, which allows five-year relapse-free survival exceeding 50%, but this method was associated with a significant percentage of complications [7]. Nowadays, preoperative radiotherapy is applied more often in selected cases, which is connected with the possibility of more precise planning of irradiated volume and with reduction of toxic complications, because the sarcoma fills the space by pushing the intestines out of the irradiated field. Preliminary prospective results and retrospective analyses indicate the safety of this therapeutic method and the improvement of local control after preoperative EBRT.

The role of adjuvant chemotherapy in the treatment of retroperitoneal sarcomas remains uncertain, although it may be used in individual cases and histological types. High hopes lie in new molecularly targeted agents (e.g. Inhibitors of MDM2 and CDK4 in well-differentiated and dedifferentiated liposarcoma). Preoperative treatment with three cycles of anthracyclines with ifosfamide may be justified in sarcomas of high histological grade (like dedifferentiated liposarcoma or leiomyosarcoma) according to the results of the ISG-STS 10-01 study, which, however, did not include retroperitoneal sarcomas [33].

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