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review

Retroperitoneal sarcomas: from diagnosis to treatment. Case series and review of the literature

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SUMMARY: **Retroperitoneal sarcomas: from diagnosis to treatment. Case series and review of the literature.**

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Background. *Retroperitoneal sarcoma is a rare malignancy arising from mesenchymal cells, most commonly presented as an abdominal mass and is associated with poor prognosis. The most effective treatment modality for retroperitoneal sarcomas is complete surgical resection, including sometimes adjacent organs infiltrated by the tumor. Radiotherapy is frequently applied and has shown some benefit, while the role of chemotherapy and molecular-targeted agents is still not clear. Local recurrence is common for retroperitoneal sarcomas and still remains the main cause of death. The major factors associated with the overall survival are tumor grade, histological subtype, complete macroscopic excision and multifocality.*

Aim. *To report our experience via the presentation of patients with retroperitoneal sarcomas managed in our department during the period 2014-18; and to review the current literature.*

Patients and methods. *Eight patients appeared with chronic non-specific complaints including abdominal distension and changes in bowel or bladder habit, while one patient presented with acute abdominal pain due to mass rupture. All of the patients underwent surgical resection of the tumor.*

Results. *Among the patients, seven were operated for primary disease and one only for recurrent. The most common histologic type was liposarcoma (well-differentiated, dedifferentiated), found in five patients; followed by leiomyosarcoma found in two cases. Fibrous histiocytoma was found in only one case. The masses were removed with macroscopically clear margins (R0 and R1 resections) in four cases. In five patient cases adjuvant therapy was required. Three patients are still alive and free of disease.*

Conclusions. *Retroperitoneal sarcomas present to be a therapeutic challenge based on their location, their extent at the time of diagnosis and the high risk of local recurrence or distant metastasis. Their management requires a multidisciplinary approach, with the surgical resection remaining the mainstay of curative treatment, combined with surveillance for early detection of recurrence or metastases.*

KEY WORDS: Retroperitoneal - Tumor - Mass - Sarcoma - Resection.

Introduction

Retroperitoneal sarcomas (RPSs) consist uncommon malignant masses arising from mesenchymal cells, accounting for 0,1%-0,2% of all malignant tumors (1) and they are associated with poor prognosis because of the absence of early clinical symptoms, involvement of adjacent structures and difficulty in obtaining sufficient resection margins. If symptomatic, patients often suffer from abdominal distension, altered bowel motions, abdominal discomfort and occasionally weight loss and anemia. They may also be diagnosed incidentally, during imaging for unrelated symptoms. The most effective treatment modality for RPSs is complete surgical resection, including sometimes adjacent organs that have been tumor infiltrated (2). Radiotherapy is frequently applied and has shown some benefit, while the role of chemotherapy and molecular-targeted agents is still not clear. Local recurrence is common for RPSs and

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still remains the main cause of death (2, 3). The major factors associated with the overall survival (OS) are tumor grade, histological subtype, complete macroscopic excision and multifocality.

The purpose of this study is to report our experience in the management of RPSs, to point out the role of surgical resection in the survival benefit and to compare our results to the existing references.

Case series

Patients and methods

During the period 2014-2018, eight cases of RPSs were operated in our Department. Among them, five were women and three men. The patients' age was 40-79 years (mean age: 64 years), and two of them were under 50. Patients were analyzed for survival and prognostic factors such as demographic characteristics (sex, age), symptoms, diagnostic procedures, type of surgical excision (R0, R1 or R2 resection), tumor characteristics (primary or recurrent, infiltration of adjacent organs, histological type, grade), post-operative course, recurrence and mortality. Table 1 summarizes the clinical-pathological characteristics and the treatment results of our patients.

Clinical presentation - Diagnosis

An extensive medical history and physical examination was performed in all patients. Diagnosis was achieved in four cases by abdominal computed tomography (CT), in order to investigate unclear symptoms as vomiting, weight loss, anemia and mild persistent abdominal pain. In one of our cases the sarcoma was an incidental finding in a CT undergone for microscopic hematouria. Another patient presented with abdominal distention mainly at the lower part of the abdomen and the radiologic investigation revealed the sarcoma.

One young male patient was admitted in the hospital due to acute abdomen and septic condition and had an urgent laparotomy that revealed a rupture to the lower right abdomen of a large retroperitoneal neoplasm.

The last case presented with abdominal pain and had a history of surgical management of a retroperitoneal leiomyosarcoma (LMS) 6 years earlier. Her CT revealed relapse of the disease with at least 3 large masses invading left kidney and parts of small bowel.

Surgical treatment

Beside the patient with the acute abdomen needing immediate intervention, all remaining seven cases were informed about the severity of their disease, the proper treatment and their prognosis. All patients preferred to have their treatment in our Hospital.

All patients were operated by the same surgeon. Laparotomy was done in all the cases; 7 (87,5%) for primary RPSs and 1 (12,5%) for recurrent RPS. The masses were removed with macroscopically clear margins (R0 and R1 resections) in four cases, while in the rest four cases this was impossible due the extend of the disease (R2 resection). The median tumors size was 14,71cm, while mean weight was 1869g.

In one case, the left kidney and spleen were removed due to organ invasion, while another patient required new surgical exploration with masses removal along with spleen, left kidney, left colon and a part of invaded small bowel due to tumor relapse 6 years later her primary tumor removal (in another institution).

The duration of the operations was among 150-270 min (mean time: 190 min); median blood loss was 1.100 ml and in 5 cases blood transfusion was given (1-3 units). Only one case was transferred to Intensive Care Unit (ICU) postoperatively for 1 day due to severe concomitant diseases (diabetes, coronary disease and obstructive pulmonary disease).

All patients had a good postoperative course and the median duration of hospitalization was 6 days (range: 5 to 9 days).

Histology reports

Among our cases, the most common histologic type was liposarcoma (LPS), found in five patients, with only two of them having a well-differentiated LPS (WDLPS) and the others dedifferentiated LPS (DDLPS). Leiomyosarcoma (LMS) of low to moderate differentiation was found in two cases, followed by malignant fibrous histiocytoma (MFH) found in only one case. By immunohistochemistry, WDLPSs were positive MDM2, p16 and CDK4; DDLMSs were positive for MDM2 and CDK4;

TABLE 1 - Clinical-pathological characteristics and the treatment results of patients.

Pt	Age	Sex	Clinical Presentation	Diagnosis	P/R	Operation	Excision	Pathology	Immunohisto-chemistry	Adjuvant therapy	Follow-up	DFS	OS	CS
1	48	M	Weight loss	CT	P	Mass removal	R0	WDLPS	MDM2, p16, CDK4	None	47	47	47	A
2	70	F	Anemia	CT	P	Mass removal	R1	DDLPS	MDM2, CDK4	Radiotherapy	11	11	11	D
3	79	F	None	CT	P	Mass removal	R2	LMS	SMA, desmin, H-caldesmin	None	30	24	30	D
4	66	F	Abdominal distention	CT	P	Mass removal	R2	DDLPS	MDM2, CDK4	Chemotherapy, Radiotherapy	26	15	26	D
5	40	M	Acute abdominal pain, Sepsis	Laparotomy	P	Mass removal along with left kidney and spleen	R2	DDLPS	SMA, desmin, H-caldesmin	Chemotherapy, Radiotherapy	6	4	6	D
6	62	M	Vomit	CT	P	Mass removal	R0	WDLPS	MDM2, p16, CDK4	None	19	19	19	A
7	76	F	Abdominal pain	CT	R	Mass removal along with left kidney, spleen, left colon and a part of small bowel	R2	LMS	MDM2, CDK4	Chemotherapy, Radiotherapy	10	4	10	D
8	73	F	Abdominal pain	CT	P	Mass removal	R0	MFH	CD68, CD 34, α1-antitrypsin, α1-antichymotrypsin, factor XIII	Chemotherapy	5	5	5	A

LMSs were positive for muscle actin (SMA), desmin and H-caldesmin, but negative for CD117, DOG1, Melan-A, HMB-45 and MDM2; and MFH was positive for CD68, CD 34, α1-antitrypsin, α1-antichymotrypsin and factor XIII.

Postoperative assessment

The decision of administration of radiotherapy and/or chemotherapy was taken by the surgeon and the oncologist taking into consideration the extent of the disease and the high possibility of tumor relapse. In four cases adjuvant therapy was required: one patient had radiotherapy, one chemotherapy and two both modalities. The results of those treatments were quite satisfactory in three of the patients in short term follow up checked by radiologic tests.

Outcomes

Three of the patients are still alive and well (follow up 5, 19 and 47 months post-surgically). One patient has minor tumor abdominal relapse, presented 26 months after the sarcoma excision and was referred to another Surgical Department.

Four patients died 6 to 30 months postoperatively, three of them due to the disease and one of irrelevant reason. In details, one patient 70 years old died due to myocardial infraction 11 months postoperatively. Her last investigations were clear of disease.

The patient with the ruptured mass, which was an aggressive grade 3 LPS, presented relapse of the disease with multiple masses 4 months later. No response to adjuvant chemotherapy or radiotherapy was achieved and unfortunately the patient died 6 months after the surgery.

Another 79-year-old female patient with a grade 3 LMS presented a metastatic lesion on her neck 2 years later, which was removed and has been identical to the excised primary retroperitoneal lesion. The patient did not receive any adjuvant treatment due to her age and developed pulmonary metastatic disease 5 months later and died within 4 weeks.

A 66-year-old patient presented tumor relapse 15 months postoperatively and had a second surgery. She received both chemotherapy and radiotherapy. She was in good condition for about 9 months, but she had a new massive tumor relapse that caused her death 2 months later.

Discussion

Soft tissue sarcomas (STS) are rare malignant tumors of mesenchymal origin accounting for 1% of all solid tumors. These tumors can be found anywhere in the body, with 50% arising in the extremities, 10% to 15% from the trunk, less than 10% from the head and neck, and 15% in the retroperitoneum (4). RPSs consist a heterogeneous group of malignant tumors with very low incidence; and very little is known about their biological behavior and no specific causative compounds have been identified. In general, RPSs are sporadic cancers; however, there are several hereditary cancer syndromes associated with STS including Li-Fraumeni and neurofibromatosis type 1 (Table 2). Radiation-associated sarcomas are rare and can arise as a late complication of treatment with a median onset of 10 years (5, 6). If symptomatic, patients often suffer from abdominal distension, altered bowel motions, abdominal discomfort and occasionally weight loss and anemia. They may also be diagnosed incidentally, during imaging for unrelated symptoms (2). While many studies have attempted to demonstrate factors influencing prognosis after surgical excision of RPSs in order to identify patient groups that may benefit from frequent follow-up and adjuvant therapies, controversies exist (7). RPSs and their management continue to pose a challenge and the gold-standard therapy is surgical resection with microscopically free of disease margins (R0 resection) (8). However, R0 resection isn't always feasible because of the massive size of the tumor or possible tumor infiltration

TABLE 2 - GENETIC SYNDROMES ASSOCIATED WITH RETROPERITONEAL SARCOMAS (63).

Syndrome	Mutation	Chromosome	Retroperitoneal sarcoma
Li-Fraumeni	TP53, hCHK2	17p13.1	LPS, LMS
Neurinomatosis type 1	NF1	17q11.2	MPNST

of adjacent structures, all within the confined space in the retroperitoneum (9). Radiotherapy is frequently applied and has shown some benefit, while the role of chemotherapy and molecular-targeted agents is still not clear. Local recurrence is common for RPSs and still remains the main cause of death (2, 3). The major factors associated with the OS are tumor grade, histological subtype, complete macroscopic excision and multifocality.

Epidemiology

RPSs account for 0.1%-0.2% of all malignant tumors and the overall incidence is 0.3%-0.4% per 100.000 of the population (10). RPSs occur equally in men and women; they may present at any age, but the peak incidence is in the 5th decade of life (11).

Clinical presentation

RPSs are often asymptomatic and are incidentally identified in imaging for unrelated reasons. Symptoms are non-specific and appear late in the course of the disease caused by compression of the organs and obstructive phenomena, when they have reached a substantial size and they are located adjacent to vital organs and structures (e.g., the aorta, inferior vena cava, duodenum, and head of the pancreas) (12, 13).

Most patients with a RPS present with abdominal swelling or increase in abdominal girth developing over months or years, early satiety and abdominal discomfort and most patients on clinical examination have a palpable mass (14). Other clinical presentations may include an inguinal or umbilical hernia, femoral nerve irritation, testis swelling or bilateral lower limb swelling. Although the gastrointestinal and urinary tracts are often displaced, they are rarely invaded, and gastrointestinal or urinary symptoms are unusual (15). Nevertheless, in our study, one case was discovered as an incidental finding during CT scan following investigation for microscopic hematouria.

Physical examination

On physical examination, a large abdominal mass is often found. The differential diagnosis should include other malignancies such as lymphomas (16) and the physical examination should be supplemented with checking lymph nodes and testicles for men, in order to exclude them.

Imaging

Shortly after a physical examination, patients presenting with the above symptoms and signs, are evaluated with imaging investigation. Contrast enhanced CT of the abdomen and pelvis is the most useful tool in the evaluation of retroperitoneal tumors, since it allows to determine not only the tumor's size and location and its relationship to adjacent organs, neurovascular and skeletal structures; but also reveals the presence of metastatic disease, if it exists (17) (Figure 1 A-B). CT also provides us with information about the status of the kidneys. This is necessary as the required resection of a kidney during the surgical operation for RPSs is frequent (18). From the aforemen-

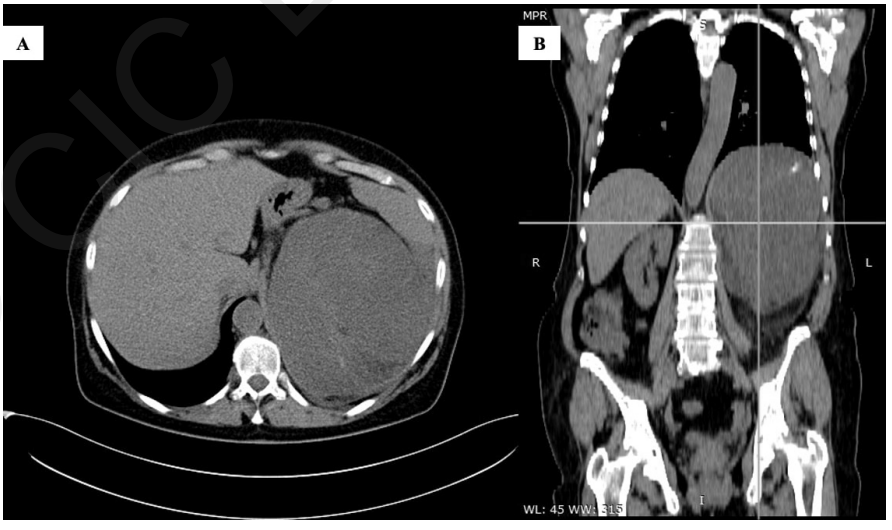

Figure 1 - Contrast enhanced computed tomography (CT) findings for a retriperitoneal sarcoma. A) Cross section; B) Coronal section.

tioned, it is clear that CT evaluation is required for planning surgical excision of RPSs.

CT imaging is not reliable in predicting the histological subtype of RPSs, except LPS which demonstrate a characteristic appearance with a predominantly fatty component causing displacement of the kidney, colon and other organs. As far as LPS is concerned, the CT attenuation reflects the histological subtype, specifically the amount of fat in the mass, with lower grade, WDLPS entirely or predominantly fatty while higher grade lesions show increased density with solid attenuation and contrast enhancement (2).

Magnetic resonance imaging (MRI) offers no additional advantage over CT scan in evaluation of RPSs except for the management of lesions involving vascular structures such as aorta, iliac vessels, superior mesenteric vessels and inferior vena cava; and to further characterize solid, cystic, necrotic, and enhancing areas.

Chest X-ray is required with patients with RPSs (19). If X-ray seems suspicious, these patients should undergo a CT scan of the thorax.

Core needle and incisional biopsies are also important, especially when the tumor is inoperable or metastatic; and chemotherapy of radiotherapy is being planned (2, 4). Biopsy is also useful for differential diagnosis from other diseases (lymphoma) with different therapeutic approaches (3).

Fluorodeoxyglucose positron emission tomography (FDG PET/CT) does not play a significant role in the diagnosis of RPTs (20). However, FGD PET/CT may be useful in order to guide biopsies for heterogenous masses (21). FDG PET/CT is useful to identify malignant peripheral nerve sheath tumors in patients with neurofibromatosis (22) and to diagnose recurrent or metastatic disease (23).

Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is useful for differential diagnosis from gastrointestinal stromal tumors (GIST) (24).

Differential diagnosis

Once a mass in the retroperitoneum is identified, the etiology must be determined. There are several mimics of RPSs, which must be considered. Benign fat content in renal angiomyolipoma or adrenal myelolipoma can be misinterpreted as LPS; however, the presence of enlarged vessels, aneurysms and hemorrhage can be helpful and most commonly, although not exclusively can be seen to arise from the kidneys with a renal cortical defect (12). Another LPS mimic is retroperitoneal myelolipoma that is a benign tumor comprising hematopoietic tissue and mature adipose tissue that tends to be better defined than LPS and often arise from the adrenals.

Other retroperitoneal neoplasms include non-lipomatous sarcomas, primary lymphoproliferative tumors (Hodgkin's and non-Hodgkin lymphoma) and epithelial tumors (renal, adrenal and pancreas) or might represent metastatic disease from known or unknown primary sites (germ cell tumors, carcinomas and melanomas) (2). Metastatic testicular neoplasm should be considered in younger male patients with a midline retroperitoneal lesion and investigated by testicular ultrasound and tumor markers. Lymphoma can present as a retroperitoneal mass and homogeneous enhancement, absent necrosis, presence of enlarged nodes and encasement of vessels without effacement must raise suspicion for a lymphoproliferative process. Many benign lesions are discovered as an incidental finding during imaging for unrelated symptoms (25). Benign neurogenic tumors can occur in the retroperitoneum and can grow to a significant size before becoming palpable or symptomatic. Most schwannomas are well-circumscribed masses with smooth, regular margins with central cystic degeneration, displacing rather than invading local structures. In the abdominal retroperitoneum, nerve sheath tumors may be located anterior to the psoas muscle arising from the sympathetic chain or femoral nerve while those located in the presacral space arising from the sacral nerve roots often show expansion of the exit foramina (26). Figure 2 represents a proposed differential diagnostic algorithm for the management of RPSs.

Histological subtypes

Despite the fact that there are more than 60 different histological subtypes of STS, 5 main subtypes account for 90% of RPSs (27).

The most commonly encountered histologic subtypes of RPSs are LPS (WDLPS, DDLPS), LMS, MFH, solitary fibrous tumor (SFT) and malignant peripheral nerve sheath tumors (MPNST) (1, 27, 28). WDLPS and SFTs tend to have more favorable outcomes with a 7-year OS of over 80 %, in contrast with DDLPS, LMS and

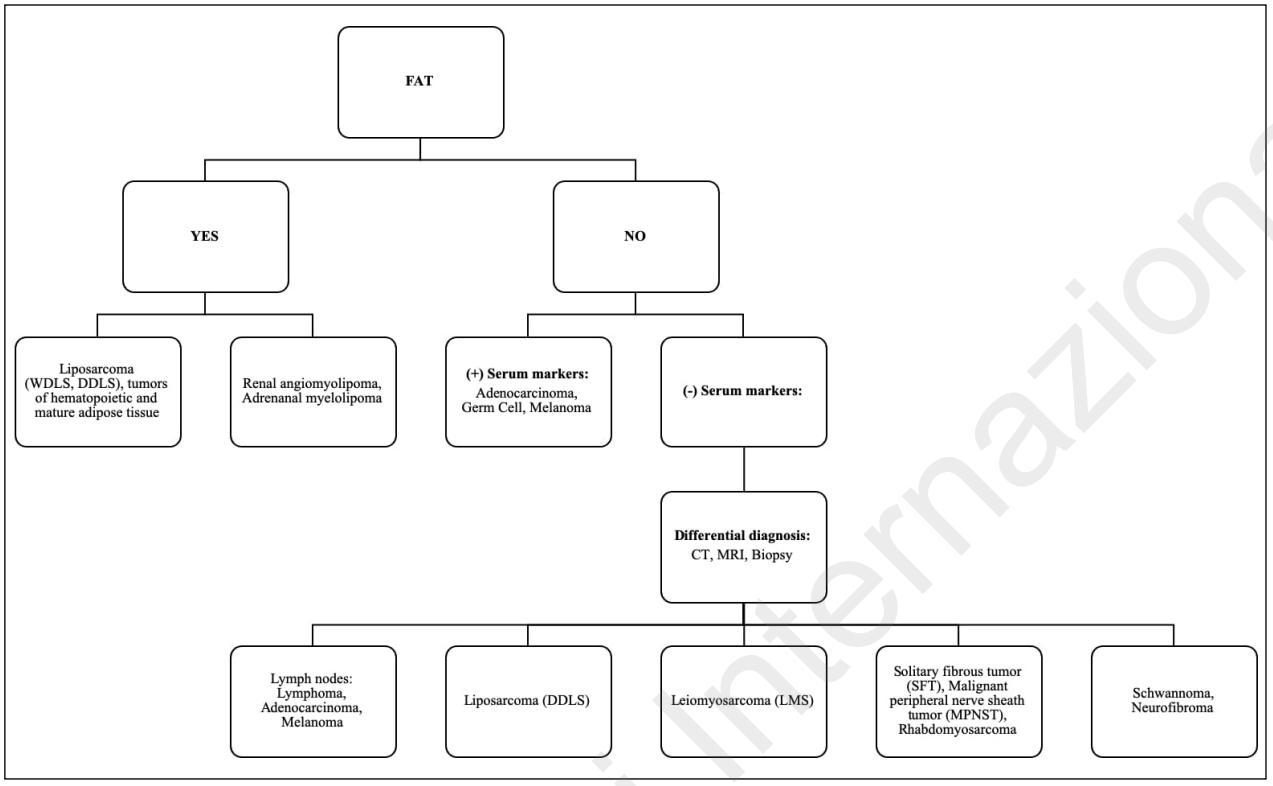

Figure 2 - Proposed differential diagnostic algorithm for the management of retroperitoneal sarcomas.

MPNST who are considered to be high-risk histological subtypes (27). Table 3 summarizes all the subtypes of RPSs, while Table 4 summarizes the most common of them alongside their diagnostic markers.

Liposarcoma

LPSs are the commonest histology found in the retroperitoneum comprising 50% of tumors; WDLPS account for 25% of these (27). WDLPS are low grade tumors, that often recur locally several years after surgery and therefore require long-term follow up (27, 29, 30). Microscopically, while WDLPS resembles normal fat cells, is characterized from nuclear atypia in adipocytes and stromal cells. There are adipocytic sheets with fibrous septa and hyperchromatic spindle cells (31). WDLPSs are divided into three subtypes: adipocytic (lipoma-like), sclerosing and inflammatory (32). By immunohistochemistry, WDLPSs reveal positive expression of MDM2, CDK4 and p16 (31).

DDLPS can be subdivided according to whether they are intermediate or high grade. Intermediate grade DDLPS tends to recur locally (40% at 7 years), but the risk of metastasis is low (10% at 7 years). High grade DDLPS has the same risk of local recurrence, but a much higher risk of distant metastasis (30% at 7 years). Intermediate grade DDLPS and high grade DDLPS have a 7-year OS of 50% and 30%, respectively (27). Microscopically, DDLPS (Figure 3 A, B) is appeared with yellow-tan fatty foci. It contains both well differentiated lipogenic areas and non-lipogenic solid fleshy and tan areas. DDLPSs are divided in many subtypes, such as undifferentiated spindle-pleomorphic sarcoma and myxofibrosarcoma (Figure 3 C, D, E). Other subtypes are pleomorphic liposarcoma-like, myxoid liposarcoma-like and meningothelial-like patterns. Other morphologic patterns of heterologous differentiation such as osteosarcoma, rhabdomyosarcoma, leiomyosarcoma and round cell morphologies have been described. Immunohistochemically, DDLPSs are characterized by over-expression of MDM2 and CDK4 (31).

TABLE 3 - HISTOLOGICAL SUBTYPES OF RETROPERITONEAL SARCOMAS (64).

Subtype
Liposarcoma Well differentiated - Dedifferentiated - Myxoid/round cell - Pleomorphic
Leiomyosarcoma
Malignant fibrous histiocytoma - Undifferentiated pleomorphic sarcoma
Sarcoma not otherwise specified
Malignant peripheral nerve sheath tumor
Solitary fibrous tumor - Hemangiopericytoma
Fibrosarcoma (nondesmoid)
Rhabdomyosarcoma
Schwannoma
Angiosarcoma
Anaplastic sarcoma
Adenosarcoma
Chondrosarcoma
Desmoplastic small-round cell tumor
Epithelioid sarcoma
Extraskeletal osteosarcoma
Fibromyxosarcoma
Giant cell sarcoma
Mesenchymoma
Primitive neuroectodermal tumor - Extraskeletal Ewing sarcoma
Small cell - Embryonal - Synovial - Undifferentiated sarcoma
Spindle cell sarcoma
Undifferentiated round-cell sarcoma
Other

TABLE 4 - MOST COMMON RETROPERITONEAL SARCOMAS SUBTYPES AND THEIR DIAGNOSTIC MARKERS.

Histology	**Immunohistochemistry**	**Molecular**
Liposarcoma (6)	MDM2, CDK4, p16	MDM2 amplification
Leiomyosarcoma (6, 31)	Smooth muscle actin (SMA), desmin, H-caldesmin, smooth muscle-myosin heavy chain (SM-MHC)	Not applicable
Solitary fibrous tumor (6)	CD34, CD99, BCL2, STAT6	NAB2-STAT6 fusion product
Malignant peripheral nerve sheath tumor (6, 31)	S100, H3K27me3, SOX10, CD56, CD57, PGP9.5	Not applicable
Undifferentiated pleomorphic sarcoma (31, 35)	TLE1, CD56, CD99, CD68, lysozyme	SS18-SSX1, -SSX2, -SSX4, SS18L1-SSX1 fusion product

Leiomyosarcoma

LMS represent 20% of RPSs and usually arise from major veins such as the IVC, gonadal veins or renal veins. They have a high risk of metastasis (50% at 5 years), but a lower risk of local recurrence (10% at 5 years) (27, 29). LMS (Figure 3 F, G, H, I) may be infiltrative or circumscribed and it is characterized by smooth muscle differentiation with areas of cystic and necrotic changes. Grossly, in these tumors microscopically we recognize cells with central "cigar shaped" nucleus, eosinophilic cytoplasm and perinuclear vacuole (31). By immunohistochemistry, LMS presents positive expression of myoid differentiation markers such as smooth muscle actin (SMA), desmin, H-caldesmin, smooth muscle-myosin heavy chain (SM-MHC); but negative expression of MDM2, CD117, DOG1, HMB-45 and Melan-A (31, 32).

Malignant fibrous histiocytoma

Malignant fibrous histiocytoma (MFH) which is also named undifferentiated pleomorphic sarcoma, while is rarely observed in retroperitoneum, account 19% of RPSs (33). Recurrence occurs in 25% and metastasis in 34% (34). There are five histological subtypes of MFH (Figure 3 J): storiform-pleomorphic (65%), myxoid (15%), giant cell (10%), inflammatory (8%), and angiomatoid (2%) (35). Microscopically, their morphology varies but there are grossly characterized by round and spindle-shaped

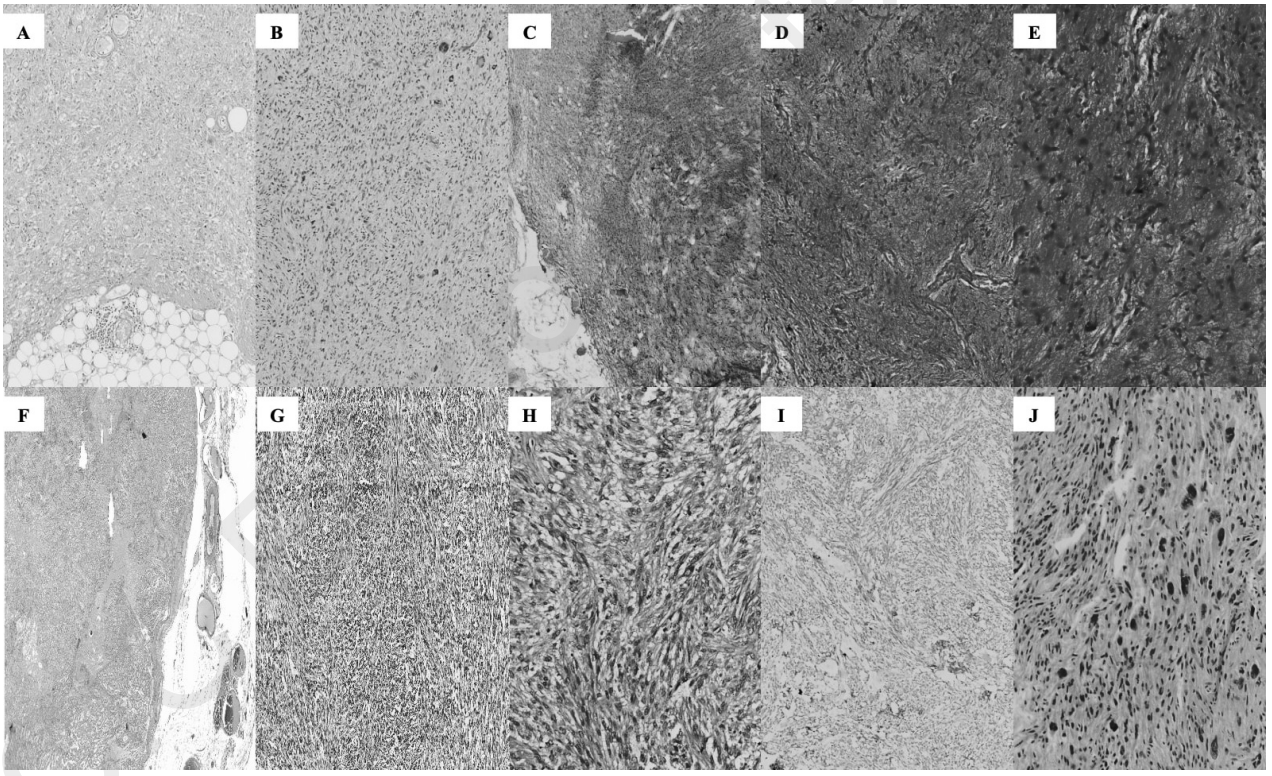

Figure 3 - Histological characteristics of most common retroperitoneal sarcomas. A) Section of dedifferentiated liposarcoma showing the coexistence of well-differentiated and poorly differentiated non-lipogenic areas (hematoxylin-eosin, original magnification x40); B) Section of dedifferentiated liposarcoma consisting of spindle cells with eosinophilic cytoplasm and small or medium sized nuclei in an admixture with giant cells. (hematoxylin-eosin, original magnification x100); C) Section of myxofibrosarcoma. Tumor composed of pleomorphic spindle cells in myxoid background (hematoxylin-eosin, original magnification x40); D) Section of myxofibrosarcoma. Curvilinear vessels with condensation of cells around them in a myxoid stroma (hematoxylin-eosin, original magnification x100); E) Section of myxofibrosarcoma. Higher magnification of a myxofibrosarcoma with moderate nuclear atypia as well as rare neoplastic cells with anaplastic features and hyperchromatic nuclei (hematoxylin-eosin, original magnification x200); F, G) Sections of a leiomyosarcoma with a multinodular growth pattern consisting of spindle cells with moderate atypia (hematoxylin-eosin, original magnification x20 and x100 respectively); H) Higher magnification of a leiomyosarcoma showing groups of cigar-shaped spindle cells with cytoplasmic vacuoles at both ends of nucleis (hematoxylin-eosin, original magnification x200); I) Sections of a leiomyosarcoma. Tumor cells are immunoreactive for h-caldesmon (h-caldesmon, original magnification x200); J) Malignant fibrous histiocytoma - like dedifferentiated liposarcoma with moderate cellular spindle-cell proliferation with anaplastic features focally (hematoxylin-eosin, original magnification x200).

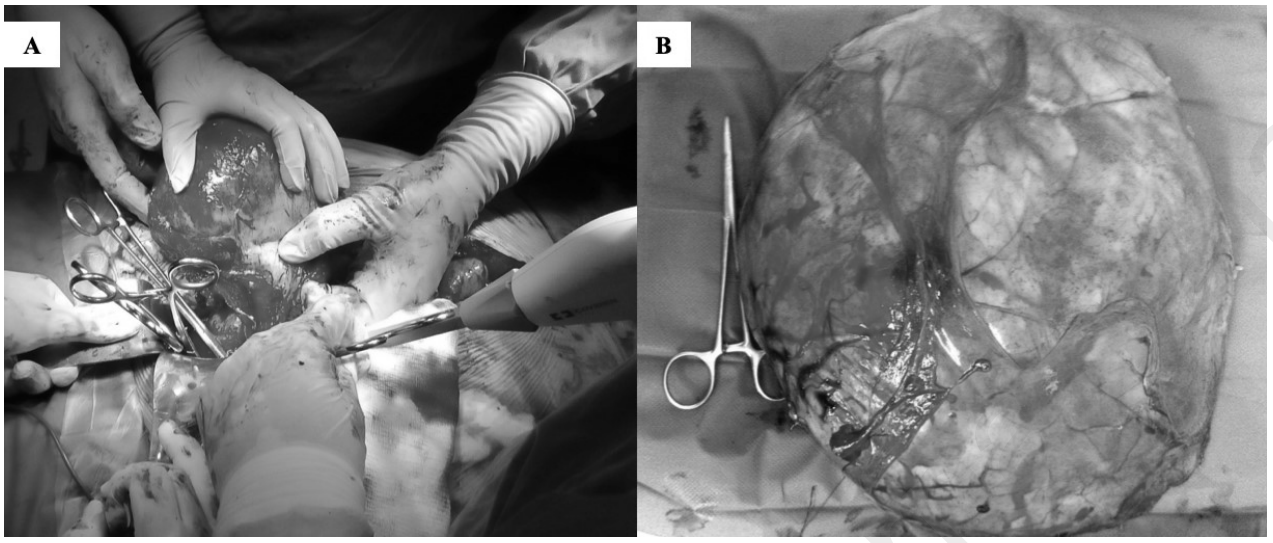

Figure 4 - Retroperitoneal sarcoma. A) Surgical resection; B) Surgical specimen.

histiocytes which are arranged in storiform (36). By immunohistochemistry, MFH presents positive expression of TLE1, CD56, CD99, CD68, lysozyme; but negative expression of S-100 and SMA (31, 35).

Solitary fibrous tumor

Solitary fibrous tumors (SFTs) also known as hemangiopericytoma, account for 6% of all RPSs (27). More than 90% of these tumors are cured by surgical resection, however a small minority are particularly aggressive and can metastasize. Local recurrence is rare with a rate of 10% at 7 years (27, 29, 37). Microscopically SFTs present a "patern-less" structure characterized by spindle-ovoid cells, scant eosinophilic cytoplasm and low mitotic activity ovoid and monomorphic nuclei. Stroma usually is collagenous while the wall of the vessels is hyalinized (31). By immunohistochemistry, SFTs express positive CD34, CD99, BCL2 and STAT6 (38).

Malignant peripheral nerve sheath tumor

While malignant peripheral nerve sheath tumors (MPNSTs) account for only 3% of RPSs, they are aggressive and high risk for both early local recurrence and distant metastases (27). They consist a heterogeneous group of tumors with "fish-flesh" appearance, poor differentiation and necrotic and hemorrhagic areas. Microscopically MPNSTs have areas with hyper- and hypo-cellularity and they are characterized by spindle cells with herringbone structure, ovoid nuclei, eosinophilic cytoplasm and epithelioid cells surrounding the blood vessels (31). By Immunohistochemistry, MPNSTs may positively express markers such as S100, H3K27me3, SOX10, CD56, CD57, PGP9.5 (31, 38).

Staging

Staging has an important role in determining the appropriate surgery and the (neo)adjuvant therapy and establishes the prognosis. Several staging systems have been reported but currently, the most common used systems are: the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) Staging System; The French Federation Nationale des Centers de Lutte Contre le Cancer (FNCLCC) Grading System; and the Dutch/Memorial Sloan-Kettering Cancer Centre Classification System (D/MSKCCCS).

American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) Staging System

The main staging system used for patients with STS has recently undergone transformation. The 7th edition of the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) Staging Manual had limited ability to categorize RPS patients into meaningful prognostic groups (6).

Firstly, all patients with STSs were categorized into stages according to tumor grade, size, depth, lymph node involvement and distant metastasis

(39). Secondly, anatomical site or histological subtype were not considered as prognostic variables by the staging system. Finally, tumor size was subdivided into two categories; below 5cm and above 5cm. Most RPSs are over 5cm and frequently there is no lymph node involvement or distant metastasis. This meant that tumor grade was the only prognostic variable within the staging system relevant to the prognosis of RPS. High tumor grade is associated with a higher recurrence rate and have a high rate of distant metastasis, and as a result carries a poor prognosis compared to low grade tumors (3).

The recent 8th edition of the AJCC Staging Manual was published with three major changes. Firstly, patients with STS were sub-categorized according to the anatomical site of the tumor (trunk and extremity, retroperitoneum, head and neck, abdomen and visceral organ system). Tumor size was also changed to incorporate four categories, instead of two previously (less than 5cm, 5-10cm, 10-15cm, 15cm and above) (40). The aforementioned classification is depicted in Tables 5, 6, 7.

In addition, the new staging system took into account the need for tools to predict individual prognosis and therefore incorporated Gronchi's nomograms. These nomograms have enabled clinicians to predict the 7-year OS and disease-free survival (DFS) for primary resected RPS patients based on clinical variables. Unfortunately, there still isn't a validated predictive tool available for patients with recurrent or metastatic RPS (41).

The French Federation Nationale des Centers de Lutte Contre le Cancer (FNCLCC) Grading System

The French Federation Nationale des Centers de Lutte Contre le Cancer (FNCLCC) grading system includes three parameters: Tumor differentiation, mitotic count and tumor necrosis. Tumor differentiation and mitotic index are scored 1 to 3 while tumor necrosis is scored 0 to 2. A 3-grade system is derived from the sum of the above scores, as it is described in Table VIII. Despite it is a simple system, it may not be used for recurrent or previously treated with radiotherapy or chemotherapy RPSs (28).

The Dutch/Memorial Sloan-Kettering Cancer Centre (D/MSKCC) Classification System

The Dutch/Memorial Sloan-Kettering Cancer Centre (D/MSKCC) Classification System consists a post-surgical 4-stage system has including histological grade, completeness of surgical resection and presence of metastases (42) (Table 9).

Treatment

Resection of primary disease

Retroperitoneal soft tissue sarcomas present challenges that distinguish them from the more common soft tissue sarcomas of the extremities. Difficulty in the management of RPSs relates to their large size and the complexity of the retroperitoneal anatomy. Complete margin-negative resections (R0 resection) is often difficult to achieve. While the most common site of first recurrence for patients with extremity sarcomas is a distant site, patients with RPSs are more likely to develop recurrences within the abdominal cavity. The OS for patients with extremity sarcomas is superior to that of patients with RPSs. Local failure is evident in nearly 90% of patients who die of RPSs, a fact that reflects the large tumor size on presentation, the inability to achieve wide surgical margins, and the limitations of adjuvant radiation and chemotherapy (43). Local failure continues to occur beyond 5- and 10-years following resection, leading some to estimate that the long-term recurrence rate for resectable RPSs exceeds 70% (44, 45).

Surgery is the treatment standard for retroperitoneal sarcomas (Figure 3 A, B). Complete resection of all gross disease is significant in improving local control and disease-specific survival. In most cases, complete excision is achieved less than 70% of the time, with local recurrence occurring in approximately half of patients undergoing complete resection (46-48). The impact of local recurrence is reflected in diminished OS despite attempts at further resections (46, 49, 50). Recurrent disease confers a decrease in the ability to resect all disease and achieve long-term DFS in those who have their recurrence completely resected.

With the possible exception of low-grade retroperitoneal LPS, no survival benefit has been observed when incomplete resection is undertaken. However, major complication rates are identical for partial and complete resections. Thus, patients undergoing incomplete resection are exposed to the morbidity of the procedure but without the poten-

TABLE 5 - TNM CLASSIFICATION OF SARCOMAS OF THE RETROPERITONEUM, ACCORDING TO THE 8TH EDITION OF AMERICAN JOINT COMMITTEE OF CANCER (AJCC).

	Primary Tumor (T)
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 5cm or less in greatest dimension
T2	Tumor more than 5cm and less than or equal to 10cm in greatest dimension
T3	Tumor more than 10cm and less than or equal to 15cm in greatest dimension
T4	Tumor more than 15cm in greatest dimension
	Regional Lymph Node (N)
N0	No regional lymph node metastases or unknown lymph node status
N1	Regional lymph node metastasis
	Distant Metastasis (M)
M0	No distant metastasis
M1	Distant metastasis

TABLE 6 - DEFINITION OF HISTOLOGIC GRADE OF RETROPERITONEAL SARCOMAS ACCORDING TO THE 8TH EDITION OF AMERICAN JOINT COMMITTEE OF CANCER (AJCC).

	Histologic Grade (G)
GX	Grade cannot be assessed
G1	Total differentiation, mitotic count and necrosis score of 2 or 3
G2	Total differentiation, mitotic count and necrosis score of 4 or 5
G3	Total differentiation, mitotic count and necrosis score of 6, 7 or 8

Differentiation Score	
1	Sarcomas closely resembling normal adult mesenchymal tissue
2	Sarcomas for witch histologic typing is certain
3	Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, soft tissue osteosarcoma, Ewing sarcoma/primitive neuroectodermal tumor of soft tissue

Mitotic Count Score	
1	0-9 mitoses per 10 HPF
2	10-19 mitoses per 10 HPF
3	≥20 mitoses per 10 HPF

Necrosis Score	
0	No necrosis
1	<50% tumor necrosis
2	≥50% tumor necrosis

TABLE 7 - PROGNOSTIC STAGE GROUPS OF RETROPERITONEAL SARCOMAS ACCORDING TO THE 8TH EDITION OF AMERICAN JOINT COMMITTEE OF CANCER (AJCC).

Stage	T	N	M	G
IA	T1	N0	M0	G1 or GX
IB	T2, T3, T4	N0	M0	G1 or GX
II	T1	N0	M0	G2 or G3
IIIA	T2	N0	M0	G2 or G3
IIIB	T3 or T4	N0	M0	G2 or G3
	or			
	Any T	N1	M0	Any G
IV	Any T	Any N	M1	Any G

TABLE 8 - THE FRENCH FÉDÉRATION NATIONALE DES CENTERS DE LUTTE CONTRE LE CANCER (FNCLCC) GRADING SYSTEM (65).

Tumor Differentiation (TD)	
Score 1	Sarcomas that closely resemble normal adult mesenchymal tissues
Score 2	Sarcomas for which histologic typing is certain
Score 3	Embryonal and undifferentiated sarcomas, synovial sarcoma, and sarcomas of uncertain differentiation

Mitotic Count (MC)	
Score 1	0-9 mitoses/10 hpf
Score 2	10-19 mitoses/10 hpf
Score 3	≥20 mitoses/10 hpf

Tumor Necrosis (TN)	
Score 0	No necrosis
Score 1	<50% tumor necrosis
Score 2	≥50% tumor necrosis

Histologic Grade (HG)		
HG = TD + MC + TN	**Grade 1**	Total score: 2 or 3
	Grade 2	Total score: 4 or 5
	Grade 3	Total score: 6, 7, or 8

TABLE 9 - THE DUTCH/MEMORIAL SLOAN-KETTERING CANCER CENTRE (D/MSKCC) CLASSIFICATION SYSTEM (42

Classification	**Definition**		
	Grade	*Resection*	*Metastases*
Stage I	Low	Complete	No
Stage II	High	Complete	No
Stage III	Any	Incomplete	No
Stage IV	Any	Any	Distant

tial survival benefit achieved by their counterparts who undergo complete excision. This emphasizes the need for careful preoperative planning as well as determination of unresectability early in the operative procedure so that incomplete resections are not mandated because the surgeon has passed "the point of no return" (46, 49, 51-54).

Retroperitoneal LPS represent a distinct situation that may justify a more aggressive surgical approach, including multiple resections for repeated recurrences and even occasionally incomplete resections. LPS in this location have been observed to have a lower incidence of distant metastases (7%) than that of other histologic subtypes (15-34%) (50, 51).

Radiotherapy and Chemotherapy

The size and complexity of RPS often result in microscopic residual disease after surgery and consequently a multidisciplinary therapy including pre- and/or post-operative radiotherapy and chemotherapy are implemented in order to improve the survival (55). The decision of administration of radiotherapy and/or chemotherapy is individualized.

Regarding the role of radiotherapy after surgery, there are controversies: On the one hand, there are studies showing the benefit of pre-, intra- and post-operative radiation, improving the OS; but on the other hand, other studies fail to confirm these results (56, 57). Other studies (e.g. STRASS, SEER) re-

ported the association between radiotherapy results and histological subtypes (58). More clinical trials are needed.

The role of chemotherapy in the treatment of RPS is not clear. Neo-adjuvant chemotherapy with agents such as doxorubicin, while remains under dispute; should be applied in cases of incomplete surgical resection (59). Neoadjuvant chemotherapy in combination with pre-operative radiotherapy may have promising results (60). The role of adjuvant chemotherapy remains under discussion; however, patients with high-grade RPS such as DDLPS and LMS may benefit. Histology-driven chemotherapy is also applicable (58). More clinical trials in order to develop new therapeutic strategies are required.

Novel strategies such as targeted therapies consist agents with promising future therapeutic role (61).

Recurrent disease

Surgical excision - if feasible - is also indicated for patients with a local relapse of the disease. There are studies that indicate that full resection in recurrent sarcoma increases survival rates. However, it is of particular importance to decide on surgical resection at the right time and for possible combination with other treatments such as radiotherapy and/or chemotherapy. The operation for recurrent disease is technically more difficult than the operation for the primary RPS. This is because there are now postoperative lesions and an increased risk of complications. For this reason, any subsequent surgery is associated with lower rates of complete resection and increased morbidity. That's why patients with recurrent RPS should be properly selected to undergo surgery. In patients whose re-operation is not feasible, treatment may include radiotherapy and/or chemotherapy and/or minimal invasive techniques such as percutaneous radiofrequency ablation (56).

Metastatic disease

Metastasectomy - if possible - consists the treatment of RPS metastases. Patients with metastatic RPS should be properly selected to undergo surgery. Minimal invasive techniques with less complication such as radiofrequency ablation (RFA), Microwave ablation and stereotactic body radiotherapy therapies; can be applicable as monotherapy or in combination with surgical resection of metastases (56). There are still controversies about treatment of metastatic disease.

Palliative resection

Palliative resection is indicated to relieve the patient of very serious symptoms. Thus, surgical excision may not be complete. Properly selection of patients should be made taking into account possible complications and the fact that possible interruption of systemic therapy prior to surgery, may lead to progression of the disease and metastases (56).

Prognosis

Despite complete resections, 5- and 10-year survival rates are poor, being 51% and 36% respectively (62). Most tumor recurrences occur within 2 years of initial surgical resection and could be as high as 50-85%. The main prognostic factors that are associated with the local recurrence (LR) and the OS complete macroscopic excision, tumor grade, multifocality and histological subtype (2). Specifically, researches have shown that unresectable disease, positive surgical margins, high tumor grade and recurrent tumors carry a poor OS and may present with metastatic disease (lung, liver, bone, lymph nodes) (11).

Because the main clinical challenge in RPS is LR, determining whether adjuvant radiotherapy is beneficial in patients with RPS has been an area of ongoing investigation. In contrast to extremity STS, where the role of adjuvant RT has been established in clinical trials, evidence to support its routine use in patients with RPS is limited (38). After RPS recurs, the lifetime chance of cure is considered limited. Approximately 9% to 27% of recurrences present with synchronous LR and DR, which is associated with poor (median 12 months) survival (27).

Conclusion

RPSs present to be a therapeutic challenge based on their location, their extent at the time of diagnosis and the high risk of local recurrence or distant metastasis. Their management requires a multidisciplinary approach, with the surgical resection remaining the mainstay of curative treatment, combined with surveillance for early detection of recurrence or metastases.

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