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T4 retroperitoneal liposarcoma. Challenges of big size sarcomas surgical treatment

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Abstract

Our article presents some of the challenges of the surgical treatment of T4 (>15 cm) retroperitoneal liposarcomas (up to 65/56/30 cm, 25.5 kg) series of cases treated by the Department of Surgical Oncology, Prof. Dr. Ion Chiricuţă Oncology Institute, Cluj-Napoca (IOCN), Romania, with illustrations, insisting on important blood vessels and nerves dissection and preservation and discussions of strategies with references to important articles from the last 10 years specialty literature. Challenges do not come only from intraoperative difficulties but also from establishing the right attitude from the extent of resection and oncological safety point of view, the role of the pathologist being very important because histological subtype and completeness of the resections are the most important prognostic factors for such tumors. Despite all today available aids in decision making, like nomograms or high-resolution imagery, sometimes this decision is to be taken intraoperative based on surgeon's expertise and skills. That is why is strongly advised that such cases to be treated in high-volume specialized tertiary centers of surgical oncology.

Keywords: retroperitoneal, liposarcoma, giant tumor, well differentiated, dedifferentiated.

Introduction

With an incidence of less than 1/100 000/year, liposarcomas are the most frequent subtype of sarcomas, rare type of malignancies accounting more than 80 subtypes [1, 2]. One of the most common presentation of the liposarcomas is the retroperitoneal liposarcoma (liposarcomas represent about 40% of all retroperitoneal sarcomas) [3]. Most common histological type of liposarcoma (even in retroperitoneal presentation) is the well-differentiated liposarcoma followed by dedifferentiated liposarcoma, myxoid and pleomorphic type [4]. Well-differentiated liposarcoma usually stays as grade 1 liposarcoma [5]. Recent, retroperitoneal presentation has gathered a specific staging in *American Joint Committee on Cancer/Union for International Cancer Control* (AJCC/UICC) tumor–node–metastasis (TNM) staging system, with T category divided in T1: <5 cm, T2: 5–10 cm, T3: 10–15 cm, T4: >15 cm, and elimination of the notice about tumor depth [6].

Well-differentiated liposarcomas [grade 1 *Fédération Nationale des Centres de Lutte Contre Le Cancer* (FNCLCC) – *French Federation of Cancer Centers Sarcoma Group*] [5] trend to grow slowly, with no or few symptoms and often they are diagnosed when they are big sized (T3 or T4).

Main treatment of retroperitoneal liposarcoma is surgery [2, 3, 7–9]. Complete excision of the tumor is the main goal of the treatment and most important therapeutic factor for patient's prognosis. Extension of the surgery is yet to be discussed as is the use of neoadjuvant or adjuvant treatments even if important, valuable helping tools such as postoperative nomograms are now available as aids in therapeutic decision making [2, 3, 7–12] and high-resolution imagery can help us to distinct a lipoma from a well-differentiated liposarcoma [13] or to distinct dedifferentiated areas in well-differentiated liposarcomas [14].

Well-differentiated liposarcomas almost never gives metastasis but may have a high rate of loco-regional recurrence, even with dedifferentiation. Dedifferentiated liposarcoma often is more aggressive with an important metastatic capacity. Yet, at least for T4 retroperitoneal liposarcomas this is a very challenging decision. Where is cut-off limit for the oncological safety/postoperative complications ratio for aggressive surgery? How many healthy organs may be sacrificed and does it worth? A special situation is that of tumors encountering both abdominal aorta and inferior vena cava. Is it justified to

sacrifice healthy organs if big abdominal vessels can't be resected?

Aim

The aim of the study was to present challenges of the surgical treatment of T4 retroperitoneal liposarcoma cases as they emerge from our Service experience, Department of Surgical Oncology, Prof. Dr. Ion Chiricuţă Oncology Institute, Cluj-Napoca (IOCN), Romania.

Materials and Methods

T4 retroperitoneal liposarcoma cases from January 1, 2017 to April 1, 2020 were extracted from IOCN Institutional Cancer Registry database.

As inclusion criteria, we imposed to the followings: (*i*) surgical procedure/procedures performed in our Service; (*ii*) pathological diagnosis of retroperitoneal liposarcoma established in IOCN; (*iii*) T4 stage (>15 cm).

Exclusion criteria were: (*i*) procedure performed for a relapse after a surgical procedure performed prior to January 1, 2017; (*ii*) coexistence of retroperitoneal liposarcoma with other malignancy types; (*iii*) grossly macroscopic positive margins (R2) or biopsy only.

After applying the imposed inclusion and exclusion criteria there were 11 cases who remained in our database constituting the series of cases studied by this article. Medical files of the 11 cases were reviewed, sourcing present study.

Ethics Committee approval was obtained for this study and a copy is available at the Editor.

All data presented in the study was obtained from IOCN Institutional Cancer Registry.

All patients had signed informed consents regarding the use of their medical files in medical studies and publication of data from their medical files with respect to the *General Data Protection Regulation* (GDPR) rules. Although no identification can be made in any way from the intraoperative pictures, a special written consent was obtained from the patients whose intraoperative pictures are presented in the article and copies are available at the Editor.

Results

From the over 90 cases of retroperitoneal tumors, which underwent a surgical procedure in our Service between January 1, 2017 and April 1, 2020, 11 were primary T4 retroperitoneal, non-metastatic, liposarcoma, with a curative visa surgery.

Table 1 shows the descriptive features of our series.

Table 1 – ***Descriptive features of the studied series***

Case No.	Age [years]	Gender [F/M]	Dimension [cm]	Symptoms	Date of procedure [mm/yy]	Follow-up [months]	Recurrence [Yes/No]	DFS [months]
1.	68	M	65	Abdominal growing; moderate dyspnea	03/2020	1	No	1
2.	68	M	28	Weight loss; mild dyspnea	10/2019	5	No	5
3.	71	M	20	GI habitus change; fatigability	05/2019	11	No	11
4.	48	F	28	Abdominal growing; moderate dyspnea	10/2018	17	No	17
5.	64	F	21	Weight loss; GI habitus change	07/2018	20	No	20
6.	56	F	24	Fatigability; abdominal growing	03/2018	24	No	24
7.	60	M	30	Abdominal growing; mild dyspnea	12/2017	27	No	27
8.	64	M	20.5	GI habitus change	11/2017	28	Yes	20
9.	59	F	17	Fatigability	09/2017	30	No	30
10.	56	M	22	GI habitus change	06/2017	31	No	31
11.	68	F	29	Moderate dyspnea	01/2017	37	No	37

DFS: Disease-free survival; F: Female; GI: Gastrointestinal; M: Male; mm: Month; yy: Year.

Average age of our series was 62 years (56 to 71 years). Average tumor greatest dimension was 27.68 cm (17–65 cm). To note that mentioned dimensions are those obtained from the pathological report as they were specified there, not from computed tomography (CT) measurements and represent strictly tumor size not specimen size (which obviously is greater).

No important symptomatology was noted, most important dyspnea especially in big size tumors.

Average follow-up period was 21 months (1–37 months), there was only one recurrence (local) with a disease-free survival (DFS) of 20 months.

There was no fatality during the studied period nor malignancy linked, neither from other reason.

All cases have had the last follow-up visit during last two months.

Our follow-up schedule supposes visits every three months in the first two years, every six months from two to five years after the surgery and yearly follow-up visit after five years.

All cases have had CT scan thorax–abdomen–pelvis prior to the surgical procedure. Figure 1 presents the CT scan of the most impressive case from the series.

Large tumor mass located retroperitoneal, incompletely included in the scan area (see anterior and lateral marginal artefacts), well delimited, with predominantly fat densities (-80 UH), with fine septa inside and hyperdense, heterogeneous areas (arrow from Figure 1b) with values between -20 and -40 UH. The lesion extends cranially from the subhepatic level (Figure 1a) to the lower pole of the formation located in the pelvis, in relation to the sigmoid colon, which it moves to the left (Figure 1b). There is an important mass effect with the movement of the intra-abdominal structures: the right kidney is ascended and rotated (Figure 1, a and e), the inferior vena cava is compressed (Figure 1e), and the mesentery and intestinal loops are displaced to the anterior (Figure 1a) and to the left (Figure 1b). Several intra-lesion vascular structures are detected, the largest originating at the superior mesenteric vessels level (arrow from Figure 1d).

Most important pathological features of the cases are presented in Table 2.

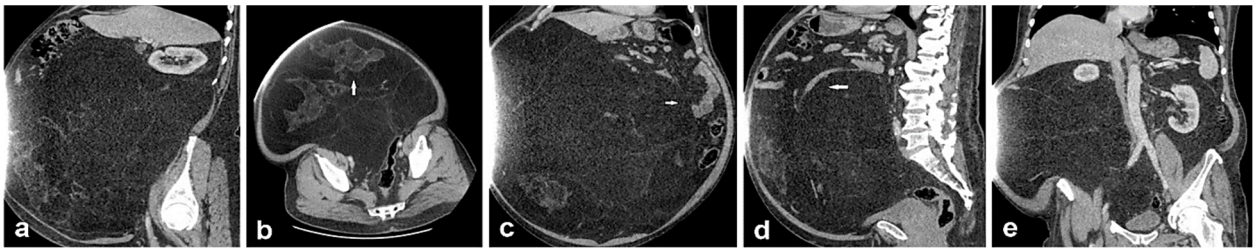

Figure 1 – *(a–e) CT scan of one case from the series. CT: Computed tomography.*

Table 2 – *Pathological features of the cases from studied series*

Case No.	Histological subtype	G	Histological G	Necrosis G	Mitosis G	Angiolymphatic invasion	Perineural invasion	Organs on specimen	Invaded organs	Margins status
1.	WD	1	1	1	1	0	0	No		1
2.	Myxoid	1	2	0	1	0	0	No		1
3.	DD	3	3	2	2	0	0	Left kidney, ureter	No	0
								Adrenal gland	No	
								Colon	Yes	
								Spleen	No	
								Pancreas tail	No	
								Abdominal anterior wall	Yes	
4.	WD	1	1	0	1	0	0	Right kidney, ureter	Yes	2
								Adrenal gland	No	
								Colon	No	
								Right uterine adnexa	No	
5.	Myxoid	1	1	0	1	0	0	Right kidney, ureter	Yes	0
6.	WD	1	1	0	1	0	0	No		2
7.	WD	1	1	0	1	0	0	No		1
8.	DD	3	3	1	3	0	0	Left kidney, ureter	No	1
								Adrenal gland	No	
								Colon	Yes	
9.	WD + DD	3	3	1	3	0	0	Right kidney, ureter	Yes	2
								Adrenal gland	No	
								Colon	Yes	
10.	WD	1	1	0	1	0	0	No		2
11.	WD + DD	2	3	0	1	0	0	Left kidney, ureter	Yes	1
								Adrenal gland	No	
								Colon	Yes	

DD: Dedifferentiated; G: Grade; WD: Well-differentiated. Margins status: 0 – tumor in contact with the margins (R1); 1 – 0 < margins ≤10 mm; 2 – margins >10 mm.

Immunohistochemical (IHC) features of the series are shown in Table 3.

A special attention was paid to Case No. 8, which initial was thought to be, based on microscopy and IHC profile [alpha-smooth muscle actin (*α*-SMA) negative; caldesmon negative; desmin negative; cluster of differentiation (CD)34 positive; CD99 positive; p53 positive; CD57 negative; cytokeratin (CK) AE1/AE3 negative; delay of germination 1 (DOG1) negative; murine double minute 2 (MDM2) negative], a G3 *FNCLCC* fusocellular sarcoma, with the need of fluorescence *in situ* hybridization (FISH) testing of *MDM2* gene amplification for differential diagnosis of a liposarcoma. *MDM2* gene amplification was FISH tested and amplification of *MDM2* gene was confirmed [10.54 copies (average)/nucleus, 100 non-overlapping tumor cell nuclei were examined]. Based on this, the final diagnosis was in favor of G3 dedifferentiated liposarcoma. Cases Nos. 3, 4 and 11 had no need for IHC tests.

Table 3 – *IHC features of studied series*

Immunomarker	Case No.										
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*
CD34	+	+			+	+	+	+	+	+	
S100	+	+			+	+	+		+	+	
Vimentin	+	+			+	+	+		+	+	
MDM2	+	x			+	+	+		+	+	

CD34: Cluster of differentiation 34; IHC: Immunohistochemical; MDM2: Murine double minute 2. IHC score: + – weakly positive; ++ – positive; +++ – intensely positive; x – non-contributory; empty case – not tested.

Surgical treatment consisted in every case in curative visa excision with removal of tumor-infiltrated organs or a more aggressive approach, with removal of unaffected close to tumor organs. Strategy depended on surgeon and local intraoperative conditions. Table 4 presents the main features of surgical treatment for every case in our series.

Table 4 – ***Main features of surgical treatment for studied series***

Main features	Case No.										
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*
Monoblock excision	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Resected organs	No	No	Left kidney ureter; adrenal gland; colon; spleen; pancreas tail; abdominal anterior wall	Right kidney ureter; adrenal gland; colon; right uterine adnexa	Right kidney ureter	No	No	Left kidney ureter; adrenal gland; colon	Right kidney ureter; adrenal gland; colon	No	Left kidney ureter; adrenal gland; colon
Intraoperative complications	IVC	No	IVC	No	No	No	No	Left CIV	IVC	No	No
Intraoperative transfusion	No	No	2 U	1 U	No	No	No	2 U	1 U	No	1 U
Postoperative complications	ARF	No	No	No	No	No	No	ARF	SSI	No	SSI

ARF: Acute renal failure (reversible in both cases); CIV: Common iliac vein; IVC: Inferior vena cava; SSI: Site surgical infection; U: Unit.

There were three intraoperative inferior vena cava lesions resolved by suture and one left common iliac vein lesion also resolved by suture. Postoperative complications were represented by two surgical site infections conservatively treated and two cases of reversible acute renal failure. All patients were discharged with normal renal function. No ileostomy or colostomy was made and there was no anastomotic fistula in the series. Also, in follow-up period two patients developed incisional hernia (Cases Nos. 9 and 11) (Figures 2–6).

Pathological report showed a 65/56/30 cm surgical specimen, all in one piece, partially covered by serosa, on section with a heterogeneously appearance alternating solid and cystic areas, with a yellow liquid leaking at cystic areas section together with a gelatinous, yellow, polynodular content (fat tissue). There also were cystic areas with a creamy, yellow content, covering about 10% of section surface. Necrosis areas interested under 50% of section surface.

Microscopically, the tumor was characterized as an adipose differentiated mesenchymal tumor formed by variable dimension adipocytes, rare hypocellular conjunctival septa with extensive necrosis areas and dystrophic calcifications. The tumor was interpreted as a well-differentiated grade 1 liposarcoma (lipoma-like), *FNCLCC* 1 (differentiation grade 1, mitotic grade 1, necrosis grade 1) (Figures 7–11).

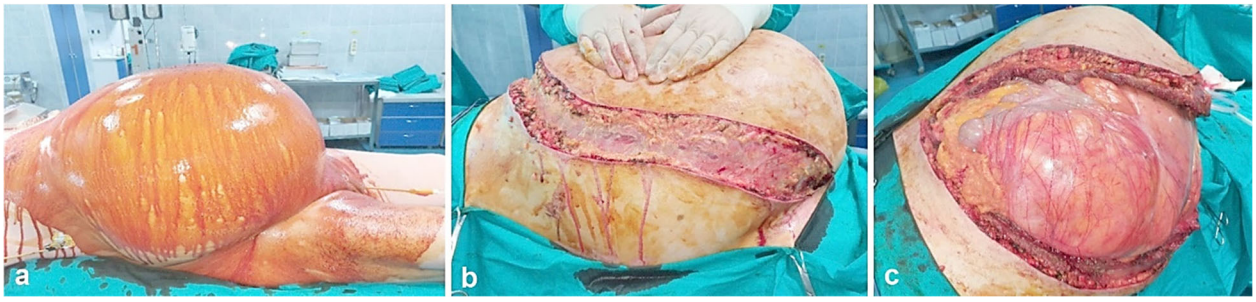

Figure 2 – ***(a) Patient laying on the operating table, view from right side – to note tumor dimensions; (b) Incision line – right pararectal, extended inferiorly to right iliac fossa and superiorly extended with right and left subcostal incision; (c) Tumor arising immediately after abdominal wall incision; right colon and transverse colon centrally displaced by the tumor; all abdominal organs were displaced in the right upper quadrant of the abdomen.***

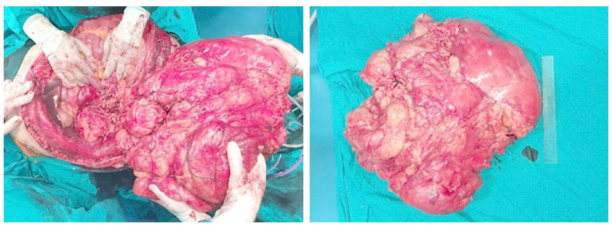

Figure 3 – ***Intraoperative aspect: tumor dissected and detached from the retroperitoneal structures, right and transverse colon preserved and mobilized up and right, with exposure of the main vascular pedicle of the tumor, ligated, arising from the superior mesenteric artery.***

Figure 4 – ***Surgical specimen, 60/56/30 cm – 25.5 kg. To note the 30 cm transparent plastic ruler.***

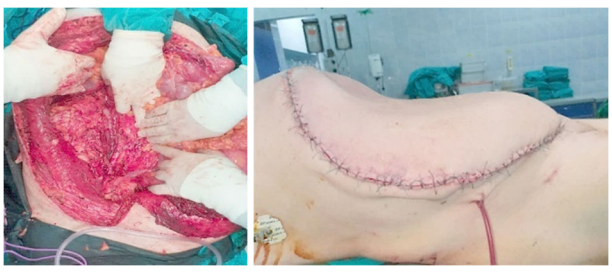

Figure 5 – ***Post-excisional aspect: inferior vena cava, aorta, and right common iliac vessels in the middle of the image. Right ureter dissected on all length evident crossing the common iliac vessels.***

Figure 6 – ***Immediate postoperative aspect of the patient.***

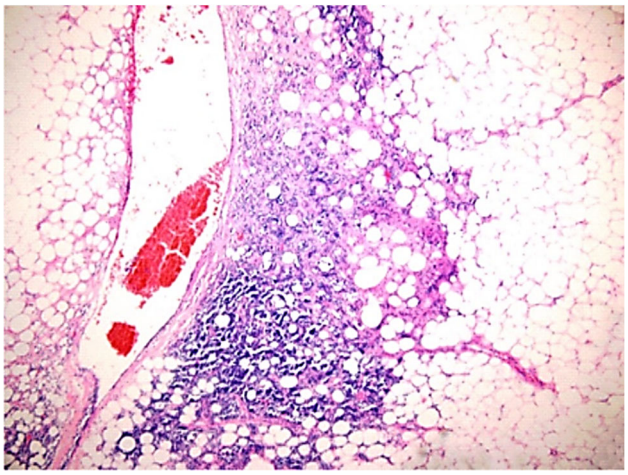

Figure 7 – ***Mesenchymal tumor with adipose differentiation and adipocytes with variable dimensions and inflammatory infiltrates [Hematoxylin–Eosin (HE) staining, ×40].***

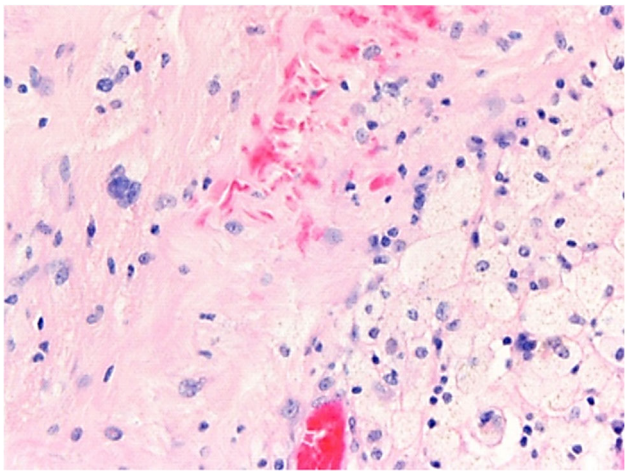

Figure 8 – ***Isolated atypical multinucleated cells (HE staining, ×600).***

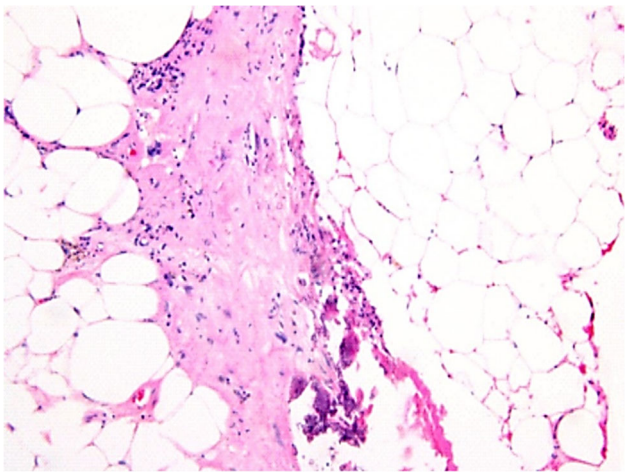

Figure 9 – ***Hypocellular thick fibrotic septa (HE staining, ×100).***

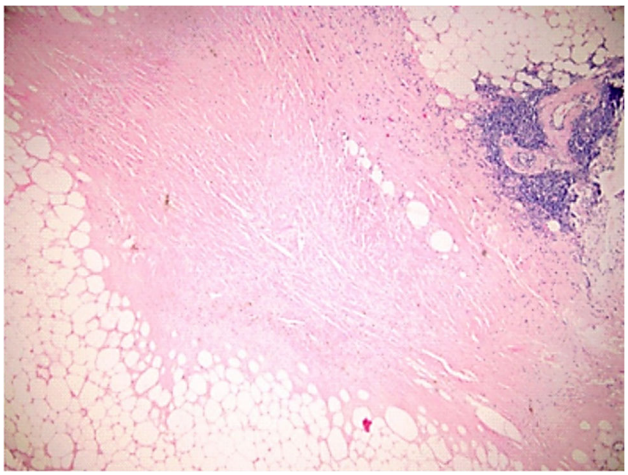

Figure 10 – ***Mesenchymal tumor with adipocyte differentiation, thick fibrotic septa and inflammatory infiltrates and necrosis (right upper corner) (HE staining, ×40).***

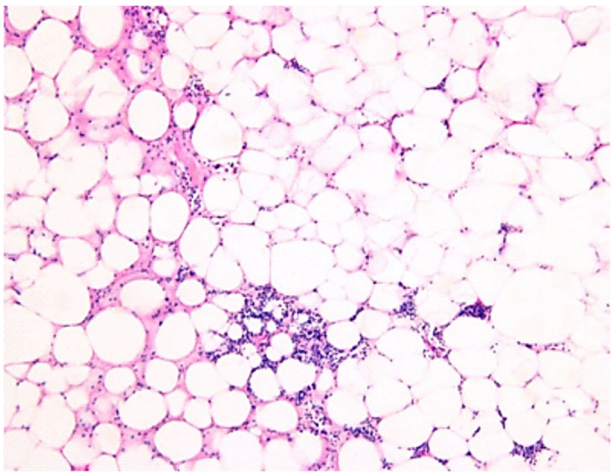

Figure 11 – ***Adipocytes with variable dimensions and interstitial lymphocytes infiltration (HE staining, ×100).***

Discussions

Soft tissue sarcomas represent rare malignancies, their incidence being of about 4.76/100 000/year, according to the *Surveillance of Rare Cancers in Europe* (RARECARE) project cited by Stiller *et al.* (2013), with a five-year survival of 58% [1]. Representing about 75% of all sarcomas, soft tissue sarcomas have more than 80 histological subtypes among which the liposarcoma and leiomyosarcoma are the most frequent subtypes both with an incidence of less than 1/100 000/year [1, 2].

Liposarcomas usually affect limbs or retroperitoneum. Retroperitoneal liposarcomas are the most common type of retroperitoneal sarcomas (about 40% of all retroperitoneal sarcomas) with an estimated account of 0.07–0.2% of all malignancies [3]. According to 2013 *World Health Organization* (WHO) Classification, liposarcomas are classified in four groups: well-differentiated, dedifferentiated, myxoid and pleomorphic liposarcomas [4]. Retroperitoneal liposarcomas usually consist in well-differentiated (most common type) and dedifferentiated types [4]. To note that according to this latest 2013 *WHO* Classification of soft tissue tumors, the mixed type' class of sarcomas was removed [4].

In our series there were five cases of well-differentiated liposarcoma, four cases of dedifferentiated liposarcoma (entire tumor or associating a dedifferentiated component

to the well-differentiated component) and two cases of myxoid liposarcoma.

Most used grading system is the *FNCLCC* system which, using differentiation grade, presence of the necrosis and mitotic rate, stratifies sarcomas upon three degrees [5]. Grading of the peritoneal liposarcomas is a critical issue as grade of a sarcoma is a very important prognostic factor also included in sarcomas staging. This is, at the same time, a great challenge but also a great responsibility for the pathologist.

In our series, there were seven cases of grade 1 *FNCLCC* liposarcoma, one case of grade 2 *FNCLCC* liposarcoma and three cases of grade 3 *FNCLCC* liposarcoma. The only recurrence occurred to a grade 3 *FNCLCC* case.

The *AJCC*/*UICC* TNM staging is the staging system widely used today, its last (8th) version seeming to be the most accurate sarcoma staging system [6]. In this latest edition, specific staging for retroperitoneal sarcomas is presented with T category divided in four subgroups (T1: ≤5 cm; T2: >5 cm – ≤10 cm; T3: >10 cm – ≤15 cm; T4: >15 cm), and removal of depth tumor notation [6].

Retroperitoneal liposarcomas often are silent-growing tumors until they reach big dimensions. In this time, the tumor remains with no or few symptoms [2, 3, 8]. This is also the case of all our patients who presented only slowly growing of the abdomen in four cases, modification of the gastrointestinal habits in four cases, fatigability in three cases and mild to moderate effort dyspnea in five cases.

CT scan is largely used to characterize both the tumor and metastatic status of the illness. Thorax–abdomen–pelvis scan is probably the most used imagistic investigation, with excellent results [2, 3, 8, 9, 12], not only in revealing the tumor size and relations with nearby organs but, due to big amount ok knowledge achieved, it can even predict well-differentiated liposarcoma type thanks to specific features of the tumor [13]. Moreover, recent studies try to distinguish dedifferentiated liposarcoma components in well differentiated liposarcomas [14]. Magnetic resonance imaging (MRI) is also an alternative to CT scan, sometimes with identic accuracy (retroperitoneal sarcomas) [2], sometimes with better results in describing the tumor and its relations (pelvic tumors) [2, 3, 8, 12].

Usually, once with the CT scan tumor biopsy is performed, with care taken to place the core-guided biopsy paths in an area incorporable in the future excision line and to avoid possible perforation or bleeding. The guided biopsy may be performed also under ultrasound guidance with almost similar accuracy meanwhile open biopsy remains as the last option [2, 3, 8, 12]. But there are also voices saying that not always the biopsy is conclusive, especially in big size tumors, due to possibility that the biopsy to be taken from a part of the tumor and other parts to present other features (there were well-differentiated liposarcomas on the biopsy specimens meanwhile dedifferentiated liposarcoma was revealed on excision specimen) [15, 16].

Combining the excellent results of CT scan characterization of the tumors with these errors of the biopsies we can understand why some authors say that biopsy prior to surgical excision is not entirely necessary [17–19]. But what can you do when the patient denies biopsy? (One personal case, the one with a 65/56/30 cm tumor).

Regarding the management of retroperitoneal liposarcoma cases, complete surgical resection remains the "golden standard" of the treatment, obtaining R0 being the most important prognostic factor for the patient [2, 3, 7–10, 12]. In our series, two cases were considered R1 (tumor focally in contact with the margins), nine cases had completeness of resection, five cases with margins not touching the tumor and under or equal to 10 mm and four cases with margins larger than 10 mm.

Several recent studies referred to neoadjuvant treatment, especially radiotherapy but the results are contradictory and neoadjuvant treatment is not included yet in the Guidelines [20, 21]. In our series, no cases had neoadjuvant chemo- or radiotherapy.

Entire management of these cases is strongly recommended to be assured by multidisciplinary teams with treatment decisions taken in specialized boards including surgeons, medical oncologists (chemotherapy and radiotherapy specialists), pathologists, radiologists [2, 8, 12].

First used to obtain postoperative prognostic information about liposarcoma cases and to help with decision-making of adjuvant therapy, nomograms have evolved and now are used even in establishing surgical strategy [7, 11, 22, 23]. An important observation is that these nomograms admit that over 30 cm in grater dimension is a good prognostic factor for a less aggressive tumor in the case of well-differentiated retroperitoneal liposarcomas [2].

Returning to surgical treatment today recommendations are that surgical treatment of these cases to be done in high-volumes specialized centers with surgeons trained in large, aggressive surgery [2, 3, 7–10, 12, 24]. Regarding the extent of the surgery, the need for R0 excision is very clear and this is one the factors impacting patient's prognostic, beside histological type, grade, size. More and more groups of surgeons are in favor of a more aggressive attitude, including sacrifice of nearby organs even if they are not macroscopically invaded to ensure enough surgical margins [2, 3, 9, 10, 12] but this attitude is not adopted yet by all guidelines [7]. The main idea is to tailor the surgical treatment to the patient with an optimal balance of benefit from an aggressive surgical procedure *versus* mutilating or permanent side effects of such surgery [25]. This was the toughest decision, also, for our cases.

Our series of cases comprises retroperitoneal liposarcomas surgically treated in our Service between 2017 and 2020. We selected only cases from 2017 or newer because that was the moment when the new (8th edition) *AJCC/UICC* staging system appeared, introducing site-specific staging categories among which the retroperitoneal sarcoma staging system [6].

A special emphasis in this article is on one case, the last case we treated, first case in our series, presenting with a giant 65/56/30 cm retroperitoneal well-differentiated liposarcoma. Being trained to be as aggressive as possible with such tumors the first idea was always an *en bloc* resection including organs like: right kidney, right ureter, right, transverse, and sigmoid colon, and an enteral segmental resection. Based on CT scan aspect typical for well-differentiated liposarcoma, slow growing rate, over 30 cm dimensions (in all three dimensions), which

seems to be an indicator of a less aggressive tumor and is treated so in current nomograms [7] and with the awareness of a huge surgical front affecting in fact all abdominal infragastric, infrahepatic and pelvic structures, our judgment was in favor of a complete *en bloc* excision through an extraperitoneal approach but sparing non-macroscopically invaded structures, with a rim of normal tissue even from the mesenteries or with serosa cover. Surprising, although on the CT scan the right kidney appeared displaced and malrotated, we had an at least 1 cm rim of normal tissue on the specimen in that area, allowing us to spare the kidney. No doubt closest margin was the inferior vena cava, aorta, and superior mesenteric vessels area. Very careful, close follow-up is the key to our strategy, allowing us to early discover possible relapses.

Regarding the intraoperative and perioperative complications, in our series was no intraoperative or perioperative death. There were three cases of inferior vena cava lesion resolved by suture, one case of common iliac vena lesion also treated by suture. Postoperative important complications, stratified as grade IVa Dindo complications [26] were the two reversible acute postoperative renal failures (remitted after fluid and Furosemide administration). According to their medical files, four patients needed postoperative transfusions during the postoperative intensive care unit period, classified as grade II Dindo complications [26]. The two surgical site infections were bedside opened, grade I Dindo complications [26].

There was only one recurrence in our series, in a 64-year-old man (at the moment of first operation) with a G3 dedifferentiated liposarcoma invading the colon, treated by an aggressive primary surgical procedure including left kidney, ureter, adrenal gland, and colon. It is the case who needed *MDM2* gene amplification FISH testing to establish the diagnosis. Recurrence occurred 20 months after the primary operation, was intra-abdominal, involving enteral loops and mesentery and was treated by another operation in July 2019, followed by adjuvant chemotherapy. Also, after primary surgery the patient underwent adjuvant chemotherapy. In total, in our series, six patients underwent adjuvant chemotherapy.

Conclusions

Retroperitoneal liposarcoma, despite its rarity, is one of the most challenging topic in current oncological surgery. Apart from technical difficulties during their removal procedures, tailoring the procedure to the patient remains the most difficult challenge to face for the surgeon involved in treating this continuously evolving pathology. Aggressive surgery is a good solution, in fact is the solution for such cases, with the awareness of the point of no return.

Conflict of interests

All authors have no conflict of interests to declare.

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