LISBOA
UNIVERSIDADE DE LISBOA

FACULDADE DE MEDICINA LISBOA

TRABALHO FINAL
MESTRADO INTEGRADO EM MEDICINA

Clínica Universitária de Cirurgia I

The key role of surgery in the management of retroperitoneal sarcomas: a case report of a rare undifferentiated pleomorphic sarcoma

Manuel Murteira Damásio Boieiro Cotovio

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Abstract

Retroperitoneal sarcomas are rare, complex neoplasms that comprise approximately 15% of all soft tissue sarcomas and less than 1% of all adult cancers. These rare tumors often involve adjacent organs and major blood vessels. Due to its rarity, it is essential that the approach to these patients must be performed in the multidisciplinary setting of high-volume sarcoma reference centers. Complete surgical resection is so far the only treatment-related factor that exert a strong influence on overall survival. Here, we report the case of a patient with a large, rare undifferentiated pleomorphic sarcoma with vascular and ureteral involvement that required resection as well as major vascular resections and arterial reconstruction. We address the key role of surgery and the role of other treatment options in the approach of these patients. In conclusion, complete *en bloc* surgical resection of the tumor is the gold-standard for the management of retroperitoneal sarcomas and there is still no consensus about the extension of resection and whether radiotherapy can complement or not the role of surgery.

Keywords: retroperitoneal sarcomas; surgery; multidisciplinary approach; resection; undifferentiated pleomorphic sarcoma; radiotherapy

Resumo

Os tumores retroperitoneais são neoplasias raras e complexas que constituem 15% dos sarcomas de tecidos moles e menos de 1% das neoplasias em adultos. Estes tumores frequentemente invadem órgãos adjacentes e estruturas vasculares major. Devido à sua raridade, é essencial que a abordagem a este tipo de doentes seja realizada em contexto multidisciplinar em centros de referência com um elevado volume de casos. A resseção cirúrgica completa é, até ao momento, o único fator relacionado com o tratamento que exerce uma forte influência na sobrevida global. Pretende-se, então, descrever o caso de um doente com um raro sarcoma pleomórfico indiferenciado com com envolvimento vascular e ureteral, tendo sido necessária resseção tumoral bem como ressecções vasculares major e reconstrução arterial. Pretende-se também avaliar o papel chave da cirurgia e o papel de outras opções terapêuticas na abordagem a estes

doentes. Em conclusão, a resseção cirúrgica *en bloc* do massa tumoral é o *gold-standard* na gestão dos sarcomas retroperitoneais e não existe ainda consenso acerca de qual extensão da resseção completa e se a radioterapia pode ou não ter um papel complementar à cirurgia.

Palavras-chave: sarcomas retroperitoneais; cirurgia, abordagem multidisciplinar, resseção; sarcoma pleomórfico indiferenciado; radioterapia.

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List of Abbreviations

ACOSOG - Alliance for Clinical Trials in Oncology

AJCC - American Joint Committee on Cancer

CT scan - Computed Tomography scan

DD-LPS - Dedifferentiated Liposarcoma

DM - Distant Metastasis

DR - Distant Recurrence

DSS - Disease Specific Survival

ECG - Electrocardiography

ESBL - Extended Spectrum Beta Lactamases

ICU - Intensive Care Unit

IV - Intravenous

IVC - Inferior Vena Cava

LMS - Leiomyosarcoma

LR - Local Recurrence

LRFS - Local Recurrence Free Survival

MPNST - Malignant Peripheral Nerve Sheath Tumor

MRI - Magnetic Resonance Imaging

NCCN - National Comprehensive Cancer Network

NCT - Number of the Clinical Trial

OS - Overall Survival

RCT - Randomized Clinical Trial

RPS - Retroperitoneal Sarcoma(s)

RT - Radiotherapy

SEER - Surveillance, Epidemiology, and End Results Program

SFT - Solitary Fibrous Tumor

STS - Soft Tissue Sarcoma

UPS – Undifferentiated Pleomorphic Sarcomas

WD-LPS - Well-differentiated Liposarcoma

Resumo

Introdução

Os sarcomas retroperitoneais correspondem a cerca de 15% de todos os sarcomas de partes moles, o que representa menos de 1% de todos os tumores em adultos, com uma incidência estimada de 4-5/100000/ano na Europa. Estes tumores surgem a partir de células mesenquimatosas da cavidade retroperitoneal, como o músculo, gordura e tecido conjuntivo. A reduzida incidência destes tumores bem como a ausência de de ensaios prospectivos randomizados e a consequente falta de consenso na abordagem destes doentes, evidencia a importância de uma abordagem multidisciplinar e da existência de centros de referência.

Caso clínico

Indivíduo do sexo masculino, 70 anos de idade, hipertenso e com antecedentes de adenocarcinoma da próstata em 2014, que recorre ao nosso centro, vindo de um outro centro, com o diagnóstico prévio de sarcoma retroperitoneal pleomórfico, tendo previamente realizado ressecção parcial do tumor e onde lhe foi colocado um catéter urinário em duplo J. Quando o doente recorreu ao primeiro centro, o tumor já invadia os vasos ilíacos direitos e também apresentava ureterohidronefrose à direita. O primeiro estadiamento patológico era pT2 N0 M0, classificando o tumor como Grau 3 e a margem cirúrgica era R2 (macroscopicamente positiva). Quando o doente finalmente recorreu à nossa instituição (Centro Hospitalar Lisboa Norte), o caso foi discutido na reunião multidisciplinar do Centro de Referência de Sarcomas. Nessa reunião, oncologistas, radioterapeutas, radiologistas, cirurgiões gerais e anátomo-patologistas procederam a novo estadiamento, avaliação da ressecabilidade e do estado geral (performance status). O estadiamento foi realizado analisando lâminas do tumor ressecado no primeiro centro e realizando Tomografia Computorizada tóraco-abdómino-pélvica, que não demonstrou qualquer evidência de metástases.
Para avaliar a possibilidade de ressecção, foi realizada uma Ressonância Magnética, um Ecodoppler dos membros inferiores e uma AngioTC e as imagens foram discutidas com cirurgiões vasculares.

Finalmente, foi avaliado o performance status e o resultado foi de 80% na escala de Karnofsky. Foram ainda realizados exames pré-operatórios e o doente foi avaliado em Consulta de Anestesiologia, sem que o doente tivesse contraindicações para cirurgia major.

O SRP foi considerado potencialmente ressecável e foi tomada a decisão de realizar cirurgia seguida de radioterapia adjuvante.

O doente foi submetido a ressecção em bloco do tumor bem como a excisão dos dos vasos ilíacos direitos e do ureter direito. Além disso, foi construído um bypass femoro-femoral, foi ainda realizada uma ressecção ileocecal e uma ureterostomia.

O pós-operatório imediato decorreu na UCI onde o doente recebeu suporte ventilatório e aminérgico durante o primeiro dia de pós-operatório. No dia seguinte, o doente teve alta para a enfermaria.

Durante a permanência no serviço, o doente teve uma infeção profunda da ferida operatória, com o consequente isolamento de *Escherichia coli* ESBL e *Streptococcus gallolyticus*, tendo sido administrado ertapenem IV durante 14 dias. Mais tarde, foram *Streptococcus haemolyticus*, *Pseudomonas aeruginosa* e *Enterococcus faecalis* foram isolados em urocultura e foi administrada ceftazidima IV e gentamicina IV durante 7 dias.

O doente iniciou fisioterapia e teve alta cerca de 1 mês após a admissão, clinicamente restabelecido com consultas de reavaliação marcadas para Cirurgia Geral, Cirurgia Vascular, Urologia e Oncologia

O tumor e as estruturas ressecadas foram analisadas e caracterizadas no Laboratório de Anatomia Patológica, tendo as seguintes características: 478g de peso e 13x9x7cm de dimensões, tendo sido classificado como um sarcoma desdiferenciado pleomórfico de alto grau, com veias de médio e alto calibre. Um nódulo linfático foi identificado, mas estava era negativo.

Foi realizado um novo estadiamento patológico, que classificou o tumor como Grau III, pT2 N0 M0. A margem cirúrgica foi considerada R2, tendo em conta a primeira cirurgia. Após o estadiamento, o doente iniciou um protocolo de radioterapia adjuvante.

Discussão

Os SRP representam menos de 1% de todos os cancros em adultos, com apenas 73 casos identificados no nosso centro entre Janeiro de 2007 e Dezembro de 2013. Os doente são mais comummente diagnosticados na sexta década de vida, com uma distribuição equitativa entre géneros. O tamanho mediano era de 15-20cm.

Os SRP contém um espectro de tipos/subtipos histológicos com comportamento biológico e história natural distintos. Os lipossarcomas correspondem a 40-50% dos casos, em grandes séries, o que é consistente com os resultados do nosso centro (prevalência de 50%). Os lipossarcomas classificam-se habitualmente em bem diferenciados ou desdiferenciados. Os lipossarcomas bem diferenciados estão habitualmente associados a recidiva local mas não a metastização à distância. Por outro lado, os lipossarcomas desdiferenciados têm um risco mais elevado e precoce de recidiva local (dentro de 2 anos), mas têm um risco de recidiva local a longo prazo sobreponível ao do lipossarcomas bem diferenciados. Os lipossarcomas desdiferenciados podem também metastizar à distância. Leiomiossarcomas correspondem ao segundo tipo mais frequente de SRP e podem ter origem em estruturas vasculares major como a veia cava inferior, sendo na quase totalidade de alto grau. A sobrevida específica de doença para doentes com leiomiossarcomas de alto grau é semelhante à de doentes com lipossarcomas desdiferenciados, mas como uma menor taxa de recidiva local (RL) e uma taxa mais elevada de metastização à distância. Existem ainda dois subtipos de SRP menos frequentes, como os tumores malignos da bainha do nervo periférico, que constituem cerca de 5% dos casos e que surgem a partir das células de Schwann. Com uma prevalência semelhante ao subtipo anteriormente mencionado, existem os tumores fibrosos solitários.

No que diz respeito à apresentação clínica, os SRP apresentam-se frequentemente como uma massa retroperitoneal assintomática descoberta acidentalmente em exames de imagem. Quando o tumor é sintomático, tal acontece habitualmente devido a compressão de estruturas abdominais adjacentes: o intestino, causando desconforto ou dor abdominal, saciedade precoce, perda de peso ou oclusão intestinal; grandes vasos (como a veia cava inferior ou vasos ilíacos), causando edema dos membros inferiores; nervos, originando dor ou parésia dos membros inferiores.

A RL, mais do que a recidiva à distância, é o outcome major de maior importância, por causa das complexidade anatómica da cavidade retroperitoneal e o grande tamanho dos tumores, sendo responsável por cerca de 75-80% da mortalidade dos doentes. A RL é extremamente frequente com uma taxa que varia de 44 a 85%. Por outro lado, a taxa de recorrência à distância a 5 anos é de 13-20%. Contudo, no caso em análise, tendo em conta que se tratava de uma Grau III lipossarcoma diferenciado, metástases à distância devem ser uma preocupação no follow up do doente, particularmente através de disseminação hematogénea. A sobrevida global permanece baixa, mas tem aumentado ao longo das últimas décadas, variando entre 47 e 70% a 5 anos com uma sobrevida mediana de 45 a 60 meses.

No que diz respeito ao diagnóstico, o gold standard é a tomografia computorizada, pois permite confirmar a localização e origem da massa e, frequentemente, a composição da mesma. Tendo em conta que o grau é um importante fator prognóstico, é importante obter um diagnóstico histológico e uma biópsia percutânea ecoguiada deve ser encorajada, uma vez que se trata do método de diagnóstico mais preciso e pode ajudar no planeamento de tratamento neoadjuvante.

A qualidade de cirurgia é, até ao momento, o factor relacionado com o tratamento que demonstrou exercer a maior influência nos resultados oncológicos e todos os esforços devem ser envidados no sentido de a melhorar. No presente caso, a qualidade da primeira cirurgia (incompleta, com margens tumorais positivas macroscopicamente) comprometeu certamente os resultados e o prognóstico, mas é difícil determinar a extensão dessa contribuição negativa, tendo em conta a ausência de literatura relativa a situações em que a abordagem cirúrgica inicial foi incompleta, mas em que houve, em segunda intenção, uma nova intervenção, com resseção completa. No que diz respeito à morbilidade, houve certamente um importante incremento tendo em conta a necessidade de uma reintervenção major num centro de referência. A resseção completa é um preditor de sobrevida livre de doença e deve ser o objetivo da terapêutica cirúrgica. A evidência recentemente publicada é clara na demonstração que uma extensiva abordagem cirúrgica de primeira linha, com a remoção de órgãos adjacentes, é crítica na obtenção de taxas de resseções R0, com aumento de controlo local e, consequentemente prognóstico. Tal não sucedeu no caso apresentado.

Por outro lado, esta tendência não deve ser aplicada para cada subtipo de SRP (como no caso apresentado), no qual a morbilidade adicional de resseções extensas pode

não beneficiar doentes com altas taxas de mortalidade por doença metastática. Assim, pretende-se demonstrar a importância da decisão multidisciplinar tomada em centros de referência.

Tendo em consideração o reduzido volume de casos deste tipo específico de tumores, o número de casos de cada centro ou cirurgião é, habitualmente, muito baixo. Considerando a alta variabildade biológica de cada subtipo histológico entre SRP, é sugerido na literatura que este tipo de tumores menos frequentes deve apenas ser tratado em centros com um grande volume de casos e, por conseguinte, mais especializados.
No caso em análise, o doente recorreu inicialmente a um centro com pequeno volume de casos, onde procedeu a uma excisão parcial da massa tumoral, deixando margens cirúrgicas positivas.

A evidência disponível mostra que volume do hospital foi um fator independente de terapêutica cirúrgica, ressecção R0 e ressecção R0/R1. Os doentes tratados em centros com grande volume de casos têm uma probabilidade superior (OR) de serem submetidos a tratamento cirúrgico e de uma ressecção R0. Também em hospitais com maior volume de casos se observou uma maior probabilidade de submeter o doente a radioterapia neoadjuvante. Apesar da melhoria em outcomes cirúrgicos em hospitais de grande volume de casos, permanece por verificar, de forma estatisticamente significativa, que a melhoria dos referidos outcomes se traduz num benefício em termos de sobrevida, o que se poderá dever a follow-up insuficiente. Também o volume de casos do cirurgião parece ser um importante fator que influencia a realização de cirurgia completa (com margens negativas), recidiva local e sarcomatose abdominal. Para além disso, desde que as decisões terapêuticas de um doente com SRP são tomadas em reunião multidisciplinar, a influência do volume de casos de um cirurgião poderá estar a ser sobrevalorizada. O volume de casos do patologista, do imagiologista e do radio-oncologista devem ser avaliados em estudos futuros.

No que diz respeito a resseções vasculares elas são cada vez mais necessárias à medida que se promove um tipo de cirurgia cada vez mais extenso, no entanto, o envolvimento vascular dificulta a própria resseção completa. A necessidade de resseção vascular não se associa a um pior prognóstico. Associa-se por outro lado, a uma maior morbilidade do que quando essa necessidade não existe. O envolvimento venoso é mais frequente que o envolvimento arterial e o envolvimento secundário é mais frequente que o envolvimento primário (por ex.: leiomiossarcoma). Na maioria das séries já realizadas

em sarcomas de tecidos moles, a resseções vasculares são raras (cerca de 4% dos casos) e as reconstruções vasculares ainda mais.

A resseção arterial é frequentemente extensa e a anastomose primária é raramente exequível, sendo necessária a reconstrução! Por outro lado, no que às veias diz respeito, essa reconstrução é menos vezes necessária, tendo em conta a circulação venosa colateral já estabelecida.

Em suma, embora as resseções vasculares sejam ainda pouco frequentes em contexto de sarcomas retroperitoneais, estas são cada vez mais necessárias para preservação da função dos membros inferiores e para a obtenção de resseções tumorais completas.

No que diz respeito a outras opções terapêuticas, como a quimioterapia, a sua utilização é infrequente e a evidência que suporte a sua utilização é escassa e que deriva, na sua grande maioria, de sarcomas das extremidades. Além disso, existe a noção de que os sarcomas retroperitoneais (nomeadamente lipossarcomas e leiomiossarcomas) são pouco quimiossensíveis.

Quanto à radioterapia, a sua utilização é frequente, quer em contexto neoadjuvante quer em contexto adjuvante e o seu racional da sua utilização advém do elevado risco de recidiva local destes tumores, enquanto maior ameaça ao prognóstico. Também no caso apresentado, a sua utilização justificou-se tendo em conta a disseminação tumoral que ocorreu, necessariamente, na primeira intervenção a que o doente foi submetido pois de acordo com alguns estudos retrospetivos, esta opção terapêutica parece estar associada à diminuição da recidiva local, no entanto, desconhecem-se para já, benefícios em termos de sobrevida. Para isso, aguardam-se com expectativa os resultados do ensaio clínico multicêntrico randomizado STRASS que compara radioterapia neoadjuvante seguida de cirurgia completa com cirurgia completa (apenas).

O follow up destes doentes está cada vez melhor definido em diversas guidelines de diversas entidades, com ligeiras variações entre elas. Todas estas orientações sugerem um follow up mais apertado nos primeiros dois anos, tendo em conta o risco elevado de recidiva local precoce, com a realização de TC Tóraco-abdómino-pélvica (ou eventualmente RM) a cada 3-6 meses nos primeiros dois anos sendo o follow up, a partir daí, anual. No entanto, todos estes algoritmos falham em levar em conta os diferentes comportamentos biológicos dos diferentes subtipos histológicos.

NOTA 1: A leitura deste resumo não substitui nem pretende substituir, de forma alguma, a leitura do texto integral em língua estrangeira.

NOTA 2: O presente trabalho expressa a opinião do autor e não a opinião da FMUL.

Introduction

Retroperitoneal sarcomas (RPS) comprise approximately 15% of all soft tissue sarcomas (STS)[1], which represent less than 1% of all adult cancers[2] with an estimated incidence of 4-5/100.000/year in Europe[3]. These tumors arise from mesenchymal cells of the retroperitoneum, such as muscle, fat and connective tissue[4]. The low incidence of these tumors as well as the absence of prospective randomized trials and the consequent lack of consensus on how to approach these patients demonstrate the importance of a multidisciplinary approach in reference centers. The present case report pretends to demonstrate the importance of surgery on the approach of RPS. The surgical approach to a RPS often requires the resection of adjacent organs. However, major vascular resections and, even more, major vascular reconstructions are rarely described, even in respect to leiomyosarcomas arising from the inferior vena cava (IVC). To our knowledge, this is the second case report in literature where an extra-anatomical femoro-femoral cross-over bypass was performed in the context of the surgical approach to a RPS.

Case report

A 70-year-old male was admitted to our center with a recent diagnosis of pleomorphic retroperitoneal sarcoma, from another hospital. The patient had a history of hypertension and history of a Gleason 8 prostate adenocarcinoma in 2014, submitted to brachytherapy and radiotherapy. The patient was medicated with low molecular weight heparin due to a right iliac vein thrombosis. He had previously undergone partial resection of the tumor and a right double J stent was placed due to ureterohydronephrosis in the first hospital. As observed in the first surgery, the tumor was already involving right iliac vessels and he also presented right ureterohydronephrosis. The first pathologic staging of the tumor classified it as a high grade (G3), pT2b undifferentiated pleomorphic sarcoma[1]

[1] According to Edge, S., Byrd, D.R., Compton, C.C., Fritz, A.G., Greene, F.L., Trotti, A. (2009) AJCC Cancer Staging Manual | Stephen Edge | Springer. *Springer*, 2009. 7th Ed.

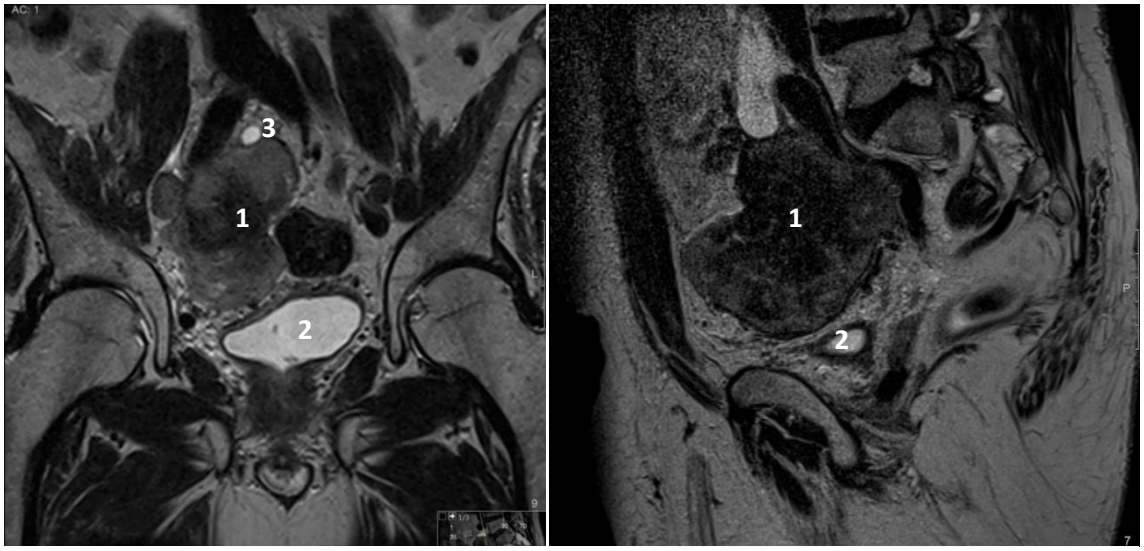

Figure 1 – Coronal oblique (A) and sagittal (B) sections of preoperative abdominal and pelvic MRI (T2 sequence) where the tumor (1), bladder (2) and right ureter (3) are shown.

and the surgical margin was R2 (macroscopically positive). When the patient was admitted to our institution (Centro Hospitalar Lisboa Norte), the patient's approach was discussed at the multidisciplinary meeting of the Sarcoma Reference Center. At this meeting, oncologists, radiotherapists, radiologists, surgeons and pathologists assessed restaging, resectability and performance status.

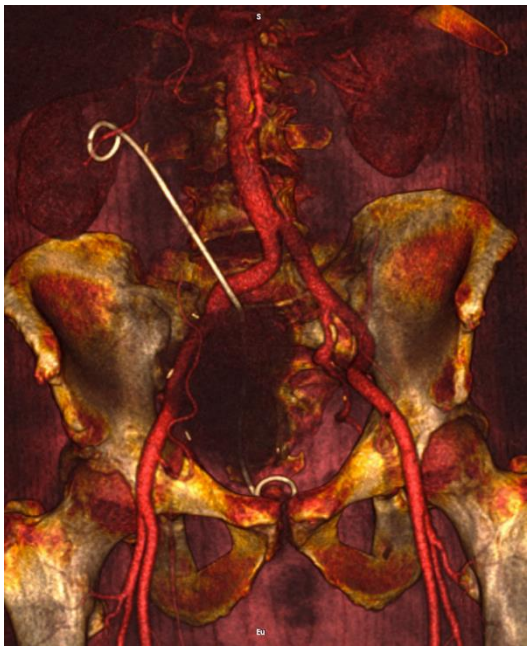

Figure 2 – Preoperative pelvic 3D CT Angiography.

Restaging was performed by reviewing surgical specimens of the tumor resected in the first center and performing CT scan. The pathologists confirmed the previous diagnosis and there was no evidence of distant metastases.

To assess resectability, a pelvic MRI (Figures 1-2), a Doppler ultrasound of the lower limbs and a CT Angiography were performed.

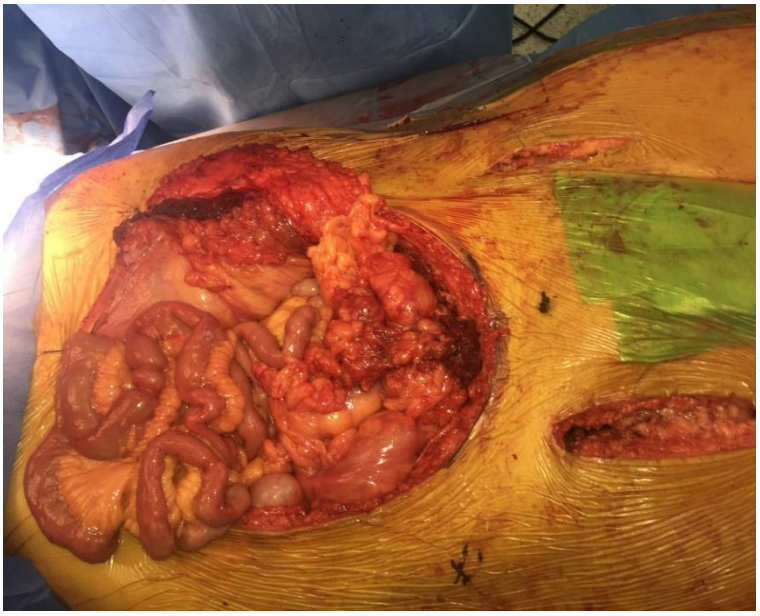

Figure 3 – Intraoperative view after resection of the tumor.

The performance status was also assessed.

The patient's score was 80% in the Karnofsky Performance Status Scale – "Normal activity with effort; some signs or symptoms of disease". ECG, blood tests and a cardiac ultrasound were also performed. The patient was observed by the anaesthesiology team that found no contraindication for major procedure.

The tumor was considered potentially resectable and it was decided to perform upfront surgery with a multidisciplinary surgical team followed by postoperative radiotherapy.

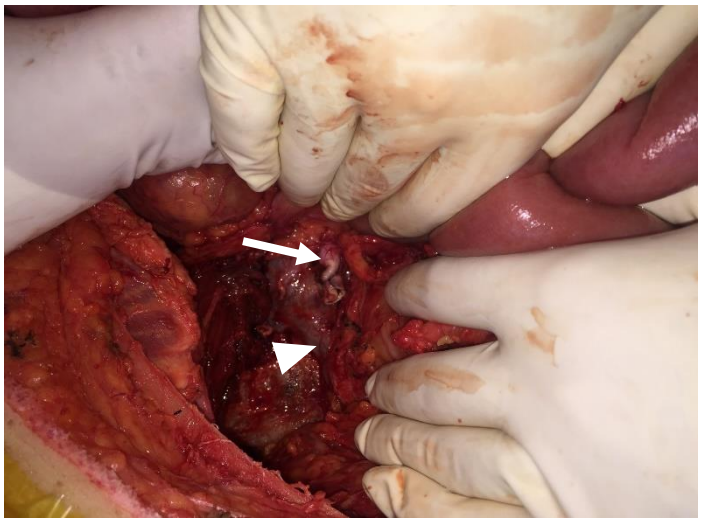

Figure 4 – Right Iliac Primitive Artery (arrow), Inferior Vena Cava (arrowhead).

The patient underwent *en bloc* resection of the tumor with resection of the right iliac vessels and right ureter. Furthermore, an extra anatomical femoro-femoral cross-over bypass was built (Figure 3) and a ureterostomy was performed.

Surgery took 10 hours in total, requiring 10 units of erythrocyte concentrate, 9 units of fresh frozen plasma and 4 units of platelet concentrate.

During surgery, the patient also needed aminergic support with administration of norepinephrine Immediately after surgery, the patient was admitted to the ICU under ventilatory and aminergic support. On the second postoperative day, the patient no longer needed organ support and urinary output returned to normal values so he was discharged to the ward of the department of surgery.

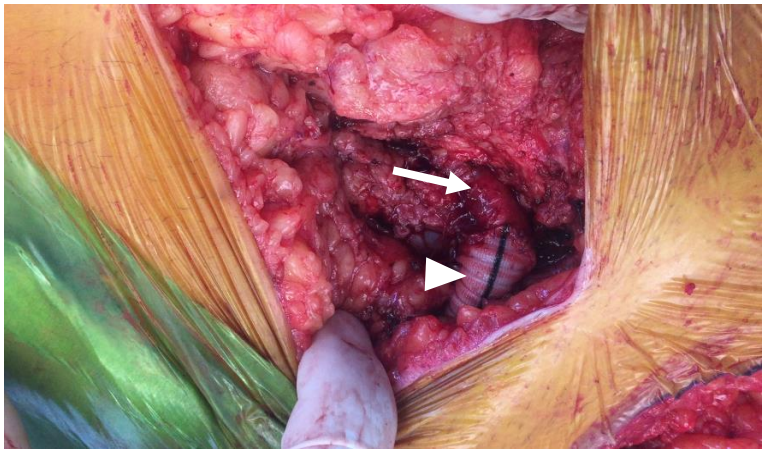

Figure 5 – Intraoperative picture of the femoral artery and the femoro-femoral cross-over. Femoral artery (arrow) and the cross-over (arrowhead) are visible.

During the admission at the department he had a deep infection of the surgical wound. *Escherichia coli* ESBL + *Streptococcus gallolyticus* were isolated and he was administered ertapenem IV for 14 days. Later, the patient had a urinary infection (ureterostomy) as well as a superficial surgical wound infection. *Streptococcus haemolyticus, Pseudomonas aeruginosa* and *Enterococcus faecalis* were isolated and ceftazidime and gentamicin IV were administered to the patient for 7 days.

A physical rehabilitation program was established and the patient was discharged home clinically well slightly about 1 month after admission. Outpatient appointments for general surgery, vascular surgery, urology and oncology were scheduled.

The tumor and adjacent tissues resected were analysed and characterized by pathologists (its weight was 478g and its dimensions were 13x9x7cm) (Figure 6). The tumor was classified as a high-grade dedifferentiated pleomorphic sarcoma with a high and medium calibre veins.

Figure 6 – The RPS and adjacent tissue after resection.

A new staging was performed by the pathologists that considered the tumor to be a Grade 3, high grade, pT2b tumor. Since the surgical margin from the first surgery was R2 (macroscopic tumor in margin) it was considered as a Stage IV[2]. After restaging, the patient started post-operative adjuvant pelvic radiotherapy for 30 sessions. The ureteric double J stent was removed 5 months after surgery. Approximately 6 months after surgery, he was admitted to our center due to intestinal obstruction, which was successfully managed with conservative medical treatment.

After 22 months of follow up, the patient remains alive. A recent bone scintigraphy showed a secondary lesion in the wing/ala of ilium, not yet characterized by biopsy but considered as a distant metastasis of the prostate adenocarcinoma since there was an increase of serum Total PSA levels.

Discussion

Retroperitoneal sarcomas represent less than 1% of all adult cancers which make them extremely rare, with 73 cases identified in our center from January 2007 to December 2013. Patients are most commonly diagnosed within the sixth decade of life, with an equal sex incidence. Median tumor size is 15-20cm [1].

RPS comprise a spectrum of histological types/subtypes with distinct biologic behaviour. Liposarcomas account for 62% of all RPS in large series by Gronchi *et al* [5], which is similar to our results with a prevalence within the period from 2007 to 2013 of 50%. Retroperitoneal liposarcomas are typically either of the well-

[2] Staging accoding to Edge, S., Byrd, D.R., Compton, C.C., Fritz, A.G., Greene, F.L., Trotti, A. (2009) AJCC Cancer Staging Manual | Stephen Edge | Springer. *Springer*, 2009. 7th Ed.

differentiated/dedifferentiated subtype. Well-differentiated liposarcomas recur locally but not distantly. Dedifferentiated liposarcomas have a higher early risk of local recurrence (within two years), but have an equivalent long-term cumulative risk of local recurrence compared with the well-differentiated liposarcoma[1]. Dedifferentiated liposarcomas can also spread to distant sites. Leiomyosarcomas are the second most common histologic type of RPS with an estimated incidence of 19.3%. These tumors can arise from major vessels like the inferior vena cava. Almost all leiomyosarcomas are high grade. The disease-specific survival (DSS) for patients with high grade leiomyosarcomas is almost identical to those with dedifferentiated liposarcomas, but with a lower rate of local recurrence (LR) and higher rate of distant metastasis (DM). There are also three less frequent subtypes, such as the malignant peripheral nerve sheath tumors (MPNST), constituting around 3.3% of RPS, solitary fibrous tumors (SFT), comprising approximately 5.9% of RPS[5] and undifferentiated pleomorphic sarcomas (UPS) with an estimated incidence of 2.2%[5], although incidence can vary from 1% to 6.4%. [6]

In what concerns to the clinical presentation, RPS often presents as an asymptomatic retroperitoneal mass or as an incidental discovery in imaging studies[1]. When the tumor is symptomatic, usually it is due to the compression of adjacent abdominal structures like the bowel, high calibre veins and/or nerve leading to abdominal discomfort, early satiety, weight loss or bowel obstruction, leg swelling and lower extremity pain or weakness, respectively. In a series of 500 patients[7], 80% of patients presented an abdominal mass, 42% with lower neurologic symptoms and 37% with pain.

LR, rather than distant recurrence (DR), is the major postoperative oncological concern because of the anatomical restraints of the retroperitoneum and the large size of tumors, with around 75-80% of patients dying from the local recurrence[8]. LR is extremely frequent with a 5-year LRR that varies from 25.9% [5] to 85%[8]. On the other hand, the rate of occurrence of distant metastasis at 5 years is only 13-21%[5][9].

Risk factors for LR are patients' age, size of the tumor, completeness of surgical resection, malignancy grade, tumor rupture, multifocality, administration of RT, and histological subtype. [5]

Overall survival (OS) is still low but has increased along the last decades. 5-year OS ranges from 47% to 70% and median overall survival ranging from 45 to 60

months[4]. Significant risk factor for OS are patients' age, size of the tumor, completeness of surgical resection, malignancy grade and multifocality. Despite the lack of data concerning undifferentiated pleomorphic sarcoma, the largest recent series by Gronchi *et al*[5], clearly shows that both LR and DM must be taken into consideration in the management of these patients. UPS show the highest premature LRR and when it comes to the rate of DM, these tumors are only surpassed by LMS.

Failure in recognizing RPS on imaging may lead to inadequate management. Thus, contrast-enhanced computed-tomography (CT) is the most useful primary imaging investigation, allowing confirmation of site and origin of the mass and often tissue composition. A histological diagnosis may be established, therefore image-guided percutaneous coaxial core needle biopsy (12-16 gauge) is the most accurate diagnostic modality and since it is safe and reliable should be encouraged unless imaging is pathognomonic and if no preoperative treatment is planned. The reported needle tract seeding is almost negligible[10][11]. Fine-needle aspiration is not recommended anymore since samples are usually insufficient to distinguish the histologic subtypes or to confirm the diagnosis of sarcoma.[12] Surgical biopsies were abolished in RPS mainly due to the risk of tumor seeding.

Staging stands as an important step for the management of RPS. The 7th edition of the American Joint Committee on Cancer (AJCC) TNM classification was derived from the analysis of soft tissue sarcomas of the extremities, with some authors questioning its applicability because it does not include histologic type or subtype[1]. However, the 8th edition of the *AJCC Cancer Staging Manual* endorses finally normograms to predict postoperative survival and DSS for patients with RPS[13].

RPS are rare, complex neoplasms with frequent involvement of multiple organs and/or vascular structures. Regarding the low volume of this specific type of tumors, individual hospitals and surgeons usually manage very few cases[14]. Considering the highly variable biological behaviour of each histological type among the retroperitoneal sarcomas, it has been suggested that RPS should only be managed at high-volume centers[14]. Hospital volume was an independent factor of surgical management, R0 resection and R0/R1 resection. Patients treated at high-volume centers (defined as hospitals in the top 10th percentile for volume in a 3141 RPS cases from the National Cancer Database, with a median annual volume of 19.4 cases) had 1.9-fold higher odds of undergoing surgical management and 1.8-fold higher odds of an R0 resection.

Despite the improvement in surgical outcomes related to high-volume hospitals, they failed to confer a statistically significant OS benefit on RPS patients, maybe due to insufficient follow-up[14]. However, when the large series of 1007 patients from sarcoma reference centers affiliated to Trans-Atlantic RPS Working Group[5] compared their results with the population-based SEER results[15], the first series shows a 20% improvement in OS at the 5, 8, and 10-year time points.

Plus, according to the French Sarcoma Group[16] a specialized sarcoma surgeon predicts a higher R0/R1 resection rate, a lower LRR and a lower rate of abdominal sarcomatosis[16]. Moreover, since the management of RPS is a multidisciplinary team work, surgeon volume analysis can also overestimate surgeon's influence on outcome. Radiation oncologist volume and pathologist volume and its impact on outcomes need to be addressed in further studies.

An extended resection how it is nowadays proposed often requires resection of multiple organs (such as kidneys, pancreas, colon, spleen), vascular structures (such as the inferior vena cava, iliac vessels and some major or minor vascular structures) and other structures and tissues (psoas muscle, for example) but there is an absence of literature on whether to resect one and/or another structure in case of involvement to obtain a wider negative margin. Again, not only the importance of the surgeon specialization should be considered but also vascular surgeons and urologists.

Quality of surgery is so far the only treatment-related factor that has been proved to exert a strong influence on the oncological outcome and every effort should be made to optimize it[3]. In the case we present, outcomes and prognosis may have been compromised by the quality of the first surgery, but it is hard to determine to which extent. There is a consensus on complete gross resection as a clear predictor of DSS and should be the therapeutic goal of surgical therapy[1]. However, the extent of resection for RPS is controversial. Recently, two European centers (French and Italian Sarcoma Groups) proposed a more aggressive surgical approach. Since LR is the main cause of death of these patients, a more aggressive approach was tried to obtain safer margins and reduce LRR. This "extended compartmental resection" includes the resection of uninvolved organs to obtain a rim of normal tissue around the tumor. Classically a complete resection was the standard procedure in which only the tumor and involved organs were resected.

Compared to “classical” complete resection, the new strategy demonstrated a notorious 3.29-fold decrease in LRR. Surprisingly a significant benefit in OS was not observed. Not that surprisingly, some criticism was raised against the alleged selection of adjacent organs to resect. Other authors argued that some adjacent organs were frequently resected while others were not, usually those with higher morbidity (such as major blood vessels or pancreas). They also argue that the critical endpoint in order to decrease LR is to obtain macroscopically negative margins (R0/R1) and avoidance of R2 margins. Converting R1 to R0 margins seems to be questionable especially when this conversion is obtained at the expense of an increase in morbidity.

As these neoplasms have some variability between each other in what concerns to their biological behaviour perhaps one standardized approach is not equally valid for all histological subtypes. There is a trend towards a more tailored approach according to the natural history of each histological subtype. For the rare UPS subtype, since it is known for its high rate of DM and LR, an aggressive approach is likely adequate but it is questionable if this strategy may be applied to LMS bearing in mind its low LRR. There is an urgent need for more investigation regarding different treatment approaches for different histological subtypes.

In the present case report, prognosis is maybe compromised from the first step since a frontline piecemeal resection[16] was performed with consequent tumor seeding. It is possible to speculate on how a second procedure with complete resection after partial resection can provide the patient a similar outcome as if a frontline complete resection was performed. There is also a need for further studies showing the burden of a frontline partial resection when followed by a complete resection.

In what concerns to vascular structures there are also no standard algorithms about reconstructions or even about the best techniques to perform it.

Major vascular involvement is challenging when the goal of surgery is to achieve negative tumor margins and to this purpose vascular resection is often needed.

In an era when tumor margins are becoming wider following the trend towards extended compartmental resection, it is surprising to note that vascular resections are quite infrequent. According to Gronchi *et al*[5], resection of iliac vein/IVC and iliac artery and/or aorta were performed in only 14.1% of patients. There are several reasons that may help to explain this fact such as inexistence of major vascular structures surrounding the tumor, increased morbidity, lack of data supporting the decision to

resect as well as lack of tools to assess margins *in loco,* presence of collateral vein circulation making venous reconstruction unnecessary. Finally, a major arterial resection often requires an arterial reconstruction and, consequently, the need of an intervention of a surgeon with experience in performing vascular anastomosis or a vascular surgeon.

The secondary involvement or encasement of major vessels (like in this case report) is much more common than a primary sarcoma of the aorta, for example.

Moreover, resected veins are more often involved by tumor than resected arteries but again there is no link between the type of vascular invasion and OS.

The OS of patients with RPS with secondary vascular involvement is not affected by the need for vascular resection or by surgical morbidity. In all retrospective series, major vascular resection for RPS were associated with increased morbidity. In a series of 249 patients with primary RPS retrospectively analysed, morbidity was not substantially affected in resections of three or fewer organs but increased in resections of more than three organs. Three of the patterns of resection were associated with an increased risk for severe adverse events as follows: vascular resection, pancreaticoduodenectomy and the combination of colon, kidney, spleen and pancreas. Surprisingly, no association between surgical morbidity and long-term oncological outcomes was observed[17][18].

Due to the length of resection it is rarely possible to perform a primary anastomosis, when an arterial resection is necessary. Arterial reconstructions are usually performed using synthetic prostheses in an anatomical or extra-anatomical position. In this case report, both vein and artery required resection. There was a need to perform a femoro-femoral cross-over bypass in order to maintain functionality of the right lower limb. To our knowledge, this case report is the second in literature of a femoro-femoral cross-over in the context of retroperitoneal sarcoma and the first in the context of an UPS.

As an example, surgical reconstruction of the IVC is still controversial. The criteria for the decision of reconstruction are not defined yet. However, the major factor influencing the need for vascular replacement when a complete resection is necessary is the presence of a well-established collateral venous system and it is important to preserve these vessels. Other factors that are considered before taking a decision of performing a vascular resection are distant metastasis, performance status, renal

function, evaluation of cumulative visceral resection and risk for mortality. In many cases, however, the tumor is only pushing against major vessels and its resection in order to obtain clear margins probably increases risks more than potential benefits. It should be considered that a vascular adventitia may prevent better a LR than a margin of fat. There is no indication that a systematic vascular resection strategy would increase the local control and, ultimately, the overall survival. On the other hand, the advantages of not reconstructing the IVC are that pulmonary embolism following thrombosis of the prosthesis is prevented and that it results in no potential lifelong anticoagulation complications or graft infection[18].

When it comes to LR involving major vessels, a vascular resection strategy is usually restricted to candidates that present low grade tumors, good performance status, long duration between the primary tumor and LR and possibility of a complete resection[18].

In addition to surgery and despite the fact that it is so far the only treatment with chances of cure, there are other therapeutic options that when combined with surgery seem to improve local control, namely radiotherapy.

Radiotherapy *latu sensu* is a term that gathers essentially different techniques of administration and different points in time when it is administered in the management of a patient with cancer. Several trials on this particular topic have already been published but there is still need of a prospective randomized multicenter trial that compares different types of radiotherapy combined with surgery *versus* surgery alone and its impact in different outcomes such as LR and OS.

Preoperative (neoadjuvant) radiotherapy, which apparently seems to be effective when combined to surgery, has also shown some advantages when compared to postoperative radiotherapy.

Some advantages of the preoperative radiotherapy are[19]:

1. Preoperatively, the gross tumor volume can be more precisely defined on the CT images with smaller safety margins. Potentially the tumor can be downsized with RT (by devitalisation of tumor cells) to facilitate surgical resection
2. The tumor displaces adjacent normal tissues out of the high-dose region thereby minimising RT-related toxicities of adjacent of radiosensitive organs.
3. Prior to surgery, the tumor is better oxygenated and RT is probably more effective in killing neoplastic cells.

4. The tumor is treated *in situ* thereby reducing risk of peritoneal seeding at the time of surgery.
5. Due to the lower incidence of surgical adhesions, higher doses can be delivered to the tumor bed preoperatively. On the contrary, postoperative radiotherapy may be problematic or hazardous in patients with small bowel adhesions.
6. May avoid treatment delay due to postoperative complications.

On the other hand, it is argued that preoperative radiotherapy may delay surgery which is the only treatment with a curative intent. Radiotherapy can improve local control and LRFS but it has shown to improve OS when combined in surgery just in some trials but not all of them. Radiotherapy (apparently preoperative) when combined with extended surgery with negative margins is the therapeutic combination that has shown the best results so far.

For RPS, as previously mentioned, prospective studies that unequivocally define the optimal extent of surgical resection, the need for RT and the ideal sequencing of radiotherapy, are lacking. The American College of Surgeons Oncology Group (ACOSOG) started a phase III randomized trial that compared preoperative RT and surgery with surgery alone. Unfortunately, the trial had to be prematurely closed due to poor accrual. This subject is currently being studied in a randomized, controlled trial through the European Organization for the Research and Treatment of Cancer (EORTC), the STRASS Trial (NCT 01344018), which is accruing well, with excellent international collaboration and which, if completed, will significantly advance our approach to RPS. Preliminary results are expected by late 2018 to early 2019[20].

Chemotherapy emerges as another therapeutic line available. However, its apparent efficacy is largely based on randomized trials and meta-analysis where the primary sites were the extremities. Very few patients with RPS were included in the RCTs and RPS may have a unique biology and response to treatment compared to sarcomas at other sites. To sum up, the use of chemotherapy has not been conclusively shown to provide significant downsizing or benefit in RPS[1].

There is an urgent need of initiation of additional clinical trials to address the unanswered questions in RPS management and advancing our approach to these neoplasms[21, 22]. Most of the literature now available is retrospective which is associated with several limitations and selection bias is one of them. Since there is an absence of high evidence level literature and there is a low level of evidence on some

therapies available, there is a lack of protocols and guidelines on this topic. For that reason, there is still enough flexibility and room for experts' opinions. Taking this into consideration, a multidisciplinary approach is of utmost importance.

In what is related to follow up, again there is some data lacking on how often physicians should follow patients. Nevertheless, the National Comprehensive Cancer Network (NCCN) guidelines recommend physical exam and CT scan of the abdomen and pelvis every 3 to 6 months for two years, then annually. Chest CT should be added for those patients with high grade tumors, since there is also a bigger risk of distant metastasis in those cases[1]. Different national and international cancer institutions suggested similar but still slightly different approaches. A recent review by Zaidi *et al*[13], in which different international guidelines were taken into consideration, authors argued that once different histological subtypes have totally different natural histories as well as distinct patterns of recurrence, tumor-specific, tailored surveillance strategies are essential and a closer monitoring for locoregional recurrences in WD/DD-LPS and for distant metastasis in DD-LPS and LMS is suggested. It was raised awareness about the risk of radiation from frequent CT scans in younger patients with some arguing that MRI should be the modality of choice to assess local recurrence in abdomen and pelvis[13]. Furthermore, since management of these patients should be done in a reference center, the standard must be the same in what concerns to follow up.

Conflicts of interest

The author declares no potential conflicts of interests for the topic of this publication.

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