RESPONSES TO THE REVIEWERS

Reviewer 1

Thank you very much for the constructive observations about the submitted article. I hope I will be able to exhaustively replay to them, one by one.

1. **A picture of the histological aspect of the post-surgical piece of the case described**

Thank you for the suggestion; the pictures have been added at page 25 and 26.

Since the picture has been provided by the Pathology Unit, the name of Iacopo Panarese has to be added to the Authors list.

2. **Delve deeper into the description of the different histological types of liposarcomas (myxoid, pleomorphic, round cell, dedifferentiated, well differentiated)**

Sarcomas are an heterogeneous family of malignant tumors stemming from connective tissue cells (Tab. 1); since they can rise from any mesenchymal cell line, more than 70 different histological subtypes of sarcomas are known, often with peculiar clinical behaviour and response to therapy. The WHO classification is based both on the specific interested cellular line, with a wide range of different histotypes for each stem category, and on the cell differentiation (G), with different strictly related biological behaviour. According to the histological grading, these tumors are recognized as stage I (Low grade), and stage II or more (High grade), with different prognosis and different outcome. Soft tissue sarcomas are ubiquitous tumors, more frequent in male sex, with a peack of incicedence in 5th-6th decade.

Table 1

CLASSIFICATION OF SOFT TISSUE SARCOMAS
- Adipocytic tumors - Fibroblastic/Myofibroblastic tumors - Fibrohistiocytic tumors - Vascular tumors - Smooth muscle tumors - Skelethal muscle tumors - Gastrointestinal Stromal Tumors - Chondro-osseous tumors - Peripheral Nerve Sheat Tumors - Tumors of uncertain differentiation

WHO histopathological classification

Table 2

LIPOSARCOMA HISTOTYPES
- Well differentiated Liposarcoma (Lipoma-like) - Indifferentiated Liposarcoma - Myxoid Liposarcoma - Pleomorphic Liposarcoma - Myxoid pleomorphic Liposarcoma

WHO histopathological classification of Liposarcoma

Despite the wide range of histotypes, liposarcoma, leiomyosarcoma, and undifferentiated pleomorphic sarcoma, are the most common varieties of soft tissue sarcomas; limbs, trunk, and retroperitoneum are the most frequent site of onset.

Radical surgery is the cornerstone of the therapeutic strategy, consisting in the complete removal of the tumor with free resection margins; however, since the infiltrating nature of the tumor with possible spreading into different surrounding organs, sometimes radical resection becomes a daunting challenge. Distant metastases are relatively common (20-25%), but local recurrence, even after 10 years from radical resection, appears with a frequence of 35% conditioning a cumulative 10-Y survival of 46%, and it is strictly depending from the anatomical site of origin and the histopathological type.

Your suggestions have been added at page 3 and 4.

3**. the explanation of the probability that this patient will have local recurrence and what would be its management if this occours**

In our case, tumor was capsulated and completely removed by an R0 resection; nevertheless, since the concrete possibility of a local recurrence, the patient entered a strict follow-up program by bi-annual computed tomography and ultrasonograpy. If local recurrence would be suspected, MRI could be useful to resolve the doubt; in that case, as the patient relatively young age, a re-resection will have been offered, even for local and distant recurrence, if it is feasible.

I added this clarification at page 9 and 10.

Reviewer 2

Even if the Reviewer 2 rejected the article, his judgment has been important, in my opinion, because gave me the opportunity to further highlight some interesting aspects of the case we presented.

1. **The author report a case of a large retroperitoneal tumor that was treated surgically. This case report does not provide sufficient reference for clinical practice. And this case is not unique enough.**

The onset of a giant liposarcoma in the retroperitoneal space is definitely a rare event, since this condition accounts less than 0.2% of all malignant tumors. Apart from its dimension, we judged this case interesting because it had a peculiar modality of onset: a sudden inguinal hernia that was confirmed at ultrasonography. If the patient would have been operated, two negative events will be occurred: the patient won't have received the appropriate treatment, and the surgeon will have made an unforgivable mistake. Then, if a soft tissue mass, more than 5 cm in size, suddenly appears in a tipical body area (retroperitoneum, trunk, limbs), the suspicion of a sarcoma is mandatory.

This clarification has been added at page 11.

Reviewer 3

Thank you very much for your constructive observations that hopefully will improve the quality of the article. I will answer each hoping your suggestions will be satisfied.

1**. You mentioned the miltidisciplinary team reccomended surgery upfront, but you did not mention the metastatic workup, which is mandatory before aggressive surgical resection with curative intent. Did you have a whole body scan; especially did you image the lung for any metastatic lesions**

A thorax-abdomen contrast enhanced CT scan was performed; nor lesion suspected as metastasis was found in lung, or lymphnodal localization, as well.

The paragraph has been added at page 8.

2. **You mentioned MDM2 amplification very brifly, in fact this is one tumor marker specific for liposarcoma and you should describe a bit more on this tumor marker for the readers.**

The positivity of MDM2 amplification is an interesting diagnostic aspect in the liposarcoma management. MDM2 (Murine Double Minute clone 2), an oncogene located at 12q15, is the most important negative regulator of p53, a tumor suppressor gene whose mutation is frequently found in many human cancers. MDM2 amplification is frequently seen in soft tissue sarcomas, and it can specifically be a hallmark for WDL, even if a lack of this marker doesn't necessarily exclude that diagnosis; currently, MDM2 amplification by FISH is considered sensitive and specific for WDL diagnosis. When p53 is mutated, MDM2 can promote cancer growth by enhancing the cell cycle; in absence of p53 mutation, the overexpression of MDM2 by the tumor cells can induce p53 degradation and inactivity. In the presented case, MDM2 amplification was found at FISH, confirming a diagnosis that can be difficult, sometimes. Nutlin, an anti-MDM2 drug, is a promising targeted therapy for liposarcoma.

The above paragraph has been added at page 12.

3. **Further you mentioned this was well differentiated tumor, addition of pathologic slides will also benefit the readers specially when describing a rare tumor**.

The slides were added at page 25 and 26.

4. **Further what was the final staging for sarcoma? That is important for readers and for this patient too, to determine the need for follow up adjuvant radiation or surveillance, as these sarcomas have a very high recurrence rates.**

Liposarcoma pathological stage was IIIB TNM (T4N0M0, G1). This advanced stage was exclusively due to the dimension of the tumor (> 15 cm); otherwise, both the histotype and the differentiation configured a low grade sarcoma with a limited risk of recurrence; furthermore, both the absence of any surrounding organ invasion and the complete capsular lining of the tumor make us confident in a less negative prognostic judgment. The decision of a strict follow-up program should allow to detect possibile recurrence in early stage.

This observation has been added at page 12.

5. **You could also add a brief discussion on the latest types of neoadjuvant or adjuvant therapies for these tumors.**

Radiotherapy is mainly indicated in adjuvant settings, in order to improve local control rate, when tumor size is > 5 cm and an incomplete surgical resection (R1) has been performed. In the examinated case, apart from the completeness of the resection and the lack of any histological sign of other organs invasion, the area occupied by the tumor was so wide that radiotherapy should have invested a too large field with the real danger of a kidney chronic disease.

The role of peroperative chemotherapy is still controversial; it could be proposed in high risk patients (comorbidities, R1 resection, organ infiltration, cellular dedifferentiation) with more benefits in limb and chest sarcomas than in retroperitoneal ones, or in metastatic disease. Neoadjuvant chemotherapy with

Anthracyclines plus Ipofosfamide may represent a therapeutic option in high risk patients for the disease downstaging; on the other hand, Doxorubicin is indicated in palliative therapy of stage IV disease.

As the excellent results of Imatinib in gastrointestinal stromal tumors, immunotherapy may represent a concrete therapeutic chance in the next future.

This discussion has been added at page 6 and 11.

6. **In addition for surgical management of these tumors, it is generally described to use peri-operative ureteral stents to identify the ureters and prevent risk of injury tu ureters during dissection. Did you consider that in preoperative planning and preparation?**

The bilateral check of the ureters in every major abdominal operation is a mandatory surgical step in order to avoid a possible ureteral iatrogenic damage; conceptually, we disagree with the ureteral profilactic stenting, because we think the possible risks and complications of the procedure itself must be avoided. The ureteral stenting is reserved to the cases in which intraoperative ureteral research is unsuccessful or the ureter is so involved in tumoral spreading that its integrity couldn't be preserved. In our case, the individuation of both ureters and their continue control during the operation were easy and complete and any further method was not required.

The above suggestion has been added at page 9.

7. **You could also add a brief discussion on the differential diagnosis on abdomino-inguinoscrotal swelling**

Usually, the diagnosis of inguinal hernia is quite easy: patient presents with a not sore reducible mass in corresponcence of the external inguinal ring; if complications, such as strangulation or hernial clogging, occour, pain and/or peritonitic simptomatology complete the clinical presentation. In the case we presented, a sudden inguino-scrotal swelling appeared: the hernial content was of hard consistency and irreducible. In a such case, a correct anamnestic harvesting and a complete clinical evaluation could have immediately demonstrated the contemporary presence both of an inguinal and an abdominal mass and the diagnostic mistake could have been avoided. The important teaching of this clinical case is also the need of a whole clinical approach to each patient, despite strumental exams lead towards a locally sited disease.

The paragraph has been added at page 10.

Reviewer 4

Did not show the Figure 2 Preoperative computed tomography scan, and the intraoperative picture.

Done