PCM PRECISION CANCER MEDICINE
A JOURNAL AIMING TO DELIVER A LASTING BLOW TO CANCER

Peer Review File

Article information: http://dx.doi.org/10.21037/pcm-20-49

Reviewer A

Comment 1: Manuscript could have been made a lot more succinct by presenting a case report with a brief summary of the literature review on the "unusual pattern of recurrence" as the title suggests. The discussion could be a lot shorter and leave out the last two paragraphs.

Reply 1: We thank the reviewer for his comment. We have simplified the discussion as recommended.

Changes in the text 1:

Regarding primary site location, extremities STS tend to have more abdominal distant failure compared to trunk wall or head and neck sites. Two retrospective series analyzing surgical treatment for liver metastases from STS, found that by far the most common primary site was the abdomen and pelvis (12,17). However, other series that analyze the presence of intra-abdominal metastases, predominantly include extremities STS with secondary tumor sites such as liver, bowel, spleen and also non-visceral abdominal spread (10,15,18).

~~There is no agreement or protocol in terms of treatment for abdominal STS metastases; therefore, it is important to individualize each patient according to metastatic extent and previous systemic therapy.~~

Little is known about gastric metastases from STS, as they are mainly documented in case reports or as isolated cases in larger studies (15,19). To the best of our knowledge, our case report is the first one to document a gastric lesion from an extremity fibrosarcoma. As shown in Table 1, the treatment of choice for abdominal metastases tends to be surgery followed in some cases by adjuvant therapy. This radical approach in patients with distant disease provides a greater disease-free interval and 2-year post-metastasis survival rate (12,17). ~~In the case reported, eight months after~~

~~surgical resection of gastric metastasis, the patient is still alive with stable pulmonary disease.~~

Myxoid liposarcomas differ from other subtypes, as they show a tendency toward extrapulmonary spread and therefore seem to benefit from a more rigorous follow-up with whole body CT or MRI, for early detection of abdominal dissemination (16,18). However, this intensified follow-up regimen has not been considered for other STS subtypes such as fibrosarcoma. Regular surveillance strategies for extremity STS, consists of a 3-monthly physical examination and involved extremity MRI or ultrasound and a chest CT or X-ray, every 3-6 months for the first 2-3 years as the majority of STS relapse occur within the first 3 years after completion of treatment (8). Nonetheless, some doubts arise regarding the utility of MRI of the primary involved area during follow-up, as more than 95% of local recurrences are noted clinically by physician or the patient themselves (14,20,21). This is consistent with our findings, as all of the repeated recurrences located in the left limb and in the contralateral limb, were identified by the patient. Regarding chest imaging, a randomized trial comparing standard follow-up showed non-inferiority of chest X-ray compared to CT scan. Although CT scans offer an earlier detection of pulmonary lesions, this does not lead to an improvement in terms of survival compared to chest X-ray (20).

~~Regarding STS follow-up after treatment, it is important that they are tailored to the individual risk of recurrence; therefore, patients with intermediate or high-grade STS should be followed more regularly (every 3-4 months the first 2-3 years) with a clinical examination focus on local recurrence (plus consideration on MRI scanning where indicated) and routine chest X-ray (8). A randomized trial comparing standard follow-up showed non-inferiority of chest X-ray compared to CT scan. Although CT scans offer an earlier detection of pulmonary lesions, this does not lead to an improvement in terms of survival compared to chest X-ray (20). A six monthly regimen with physical examination and imaging along with patient education about self-examination appear to be a safe approach.~~ In relation to STS follow-up after distant failure, there is no consensus, however based on synchronous stage IV STS follow-up recommendations, we can conclude that chest, and other known sites of metastatic disease, imaging (CT preferred) every 2-6 months for 2-3 years and then every 6 months

for the next 2 years, seems a safe approach (21). However, there is no evidence, of the benefit of routine abdominal-pelvic imaging for fibrosarcoma STS.

In summary, high-risk STS patients generally relapse within the first 2-3 years, usually with pulmonary metastases or/and local recurrence, however gastric dissemination is uncommon. To our knowledge, this is the first case of STS fibrosarcoma with gastric metastases published in the literature. ~~although some histological subtypes like myxoid liposarcomas, may show a higher affinity for other sites such as abdominal cavity~~. Surveillance strategies should therefore focus on the individual risk of each patient. ~~Thus, our experience of this case indicates that STS can have an unpredictable pattern of recurrence and therefore it is sometimes necessary to intensify follow-up protocols regarding mode of imaging.~~

One of the main strengths of this study, is its long clinical evolution of more than five years, revealing the therapeutic effort with local treatments such as surgery or radiotherapy, ~~despite the multiple recurrences, achieving long-term survival along with acceptable quality of life~~. However, there are some limitations inherit to the type of publication, single case study, not being therefore able to recommend what would be the ideal follow-up strategy in patients with soft-tissue sarcomas after local and distant failure. ~~Taking into account the recurrence pattern of this case, it would have been interesting to include the final long-term outcomes after the last chemotherapy regimen.~~ (Page 7-8, Discusion, from line 203 to 243).

Comment 2: Was the histopathology reviewed in comparison to the original pathology when the marginal recurrence occurred? Different terminology is used to describe the diagnosis each time - was this a WHO classified adult fibrosarcoma or undifferentiated spindle cell sarcoma?

Reply 2: We thank the reviewer for his comment, and we agree that the way it is written in the manuscript may lead to confusion. We confirm that all the surgical specimens were revised by the Pathological Anatomy Department and informed as Adult Fibrosarcoma.

Changes in the text 2:

- Based on these features the diagnosis established was Adult Fibrosarcoma (pT2b). (Page 3, line 101).
- A core needle biopsy of such node was performed and it was informed as a grade II fibrosarcoma. (Page 3, Line 108).

Comment 3: Non-pulmonary metastases from soft tissue sarcoma are uncommon but NOT extremely uncommon.

Reply 3: We thank the reviewer for his comment. We agree that we could maybe not say they are extremely uncommon, however to our knowledge, within STS, intra-abdominal metastases may be more frequent for myxoid liposarcoma, but for other histological subtypes, such as fibrosarcoma, the incidence is low, ranging from 1-6%. What is more, the updated version of the NCCN guidelines, just recommend abdominal-pelvic CT for myxoid/round cell liposarcoma, epithelioid sarcoma, angiosarcoma and leiomyosarcoma subtypes; but not for fibrosarcoma.

Changes in the text 3: Non-pulmonary metastases are uncommon and are associated with worse prognosis. (Page 2, Line 41-42).

Reviewer B

Comment 1: Interesting subject is the treatment of a slow oligo progression visceral metastatic disease for fibrosarcoma.

Main problem to my mind: I am uncomfortable about the way the discussion is on the follow up:

- you cited the RCT on Chest X-ray follow-up... does early diagnosis of lung metastatic relapse has the same consequence than appearance of a solitary visceral metastasis? It is not the same problem here: the success of your treatment is not based on the early detection but on the slow progression. More than being critical of eventual futility of systematic local RMI and requirement of CT scan or not, discussion could be focused

on the utility of a distant metastatic follow up, that could be proposed for myxoid liposarcoma and fibrosarcoma, by body CT or RMI, with which frequence... anually? (if patient does not present other recurrence)

Reply 1: We thank the reviewer and agree that maybe more than focusing just on primary localized limb follow-up we should focus also on a distant metastatic follow-up proposal. As mentioned it is important that STS follow-up is tailored according to risk and also to histological subtypes; but in general terms, a six monthly regimen with physical examination and imaging along with patient education about self-examination appear to be a safe approach for primary STS follow-up.

For metastatic disease there is no clear follow-up strategy and normally the recommendations are an assessment of metastatic lesions on CT or MRI with an individual plan of follow-up visits whilst for primary disease follow-up the regular time-line is set on every 3-6 months for the first 2-3 years. In 2002, the Expert Panel of the American College of Radiology recommended chest CT scans as the most optimal follow-up imaging for very high-risk patients, but also for those patients after metastasectomy. The NCCN-2020 guidelines recommend for synchronous stage IV STS, imaging of chest and other known sites of metastatic disease (X-Ray or CT) every 2-6 months for 2-3 years, then every 6 months for the next 2 years, then annually if no evidence of disease. However, abdominal-pelvic CT is just recommended for myxoid/round cell liposarcoma, epithelioid sarcoma, angiosarcoma and leiomyosarcoma subtypes. For our patient, stage IV STS, follow-up was carried out with PET-CT imaging also to evaluate functional response to chemotherapy treatment. Nonetheless, based on guidelines recommendations, a surveillance strategy for patients with stage IV STS with stable disease or non-evidence of disease after treatment, could be chest CT and imaging of other known metastatic disease every 3-4 months the first 2-3 years. There is no evidence however, of the benefit of routine abdominal-pelvic imaging for fibrosarcoma STS.

Changes in the text 1: In relation to STS follow-up after distant failure, there is no consensus, however based on synchronous stage IV STS follow-up recommendations,

we can conclude that chest, and other known sites of metastatic disease, imaging (CT preferred) every 2-6 months for 2-3 years and then every 6 months for the next 2 years, seems a safe approach. However, there is no evidence, of the benefit of routine abdominal-pelvic imaging for fibrosarcoma STS. (Page 8, Lines 230-234).

Comment 2: Other point that is not discussed is managment of a visceral recurrence: why deciding a surgery+radiation first instead of a chemotherapy, for a visceral metastasis: size? location? delay? other? For example, you should discuss/argue why you decided a surgery in 2018 without any chemotherapy, although you though it was a triple recurrences (2 lung nodes and 1 lesion of soleus muscle).

Reply 2: We thank the reviewer for his very important comment. According to guidelines, metastasectomy is the historical standard for patients with oligometastatic disease when feasible. Following this, the contralateral limb recurrence in 2018, was managed with a radical primary approach (surgery+radiotherapy). On the other hand, the suspicious lung lesions, where planned for surgery +/- chemotherapy, however as the final histological exam revealed no evidence of malignancy, no systemic treatment was initiated. Decision making was based on patient PS, young patient with good PS, feasibility of surgical treatment as treatment morbidity and mortality and final pathological anatomy report.
In 2019 when distant abdominal progression and lung failure was confirmed, once again the treatment was surgery to the feasible sites (gastric lesion and soft tissue recurrence site), but this time followed by chemotherapy for systemic control.

Changes in the text 2: With this final pathological anatomy report, and after radical treatment of the soft-tissue recurrence site, systemic treatment was not recommended at this time. (Page 5, Line 126-128)

Comment 3: Few remarks:
abstract: "sparing surgery followed by radiotherapy": i prefer: with (neo)adjuvant radiotherapy

INTRODUCTION "intra abdominal metastases from STS are extremely rare and occur mainly in the liver": liver metastases are frequently observed in leiomyosarcoma

CASE REPORT: "MRI revealing a lesion with sarcomatous component": biopsy revealing sarcomatous lesion not MRI

Reply and changes in the text 3: We thank the reviewer for pointing out this remarks. We have corrected them in the text as follows:

- Page 2, Line 39: neoadjuvant radiotherapy
- Page 3, Line 88: Intra-abdominal metastases from STS are extremely rare and occur mainly in the liver, being frequently observed in leiomyosarcoma
- Page 4, Line 97: (MRI) revealing a lesion within the left limb (Figure 1)