



# Unusual pattern of recurrence and atypical visceral metastases in extremity soft tissue sarcoma: a case report

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**Abstract:** Soft-tissue sarcomas (STS) are a rare group of tumors, commonly arising in the extremities. For extremity STS, the main treatment strategy is limb sparing surgery followed by neoadjuvant radiotherapy. Patterns of disease relapse after multimodal treatment have been analyzed in the past decades, being the lung the first recurrence site. Non-pulmonary metastases are uncommon and are associated with worse prognosis. Local recurrences are less frequent and usually develop after a longer period of time. Local control depends on tumor grade and size, surgical margins and adjuvant radiotherapy. Here, we describe the case of an extremity STS fibrosarcoma in a 30-year-old male that in the course of the disease developed multiple marginal recurrences followed by gastric, lung and soft-tissue metastases. All local recurrences were identified by the patient himself and confirmed by magnetic resonance imaging (MRI). Limb marginal recurrences were treated with a multidisciplinary approach consisting of radical surgery and radiotherapy. Metastatic lesions were initially resected and adjuvant chemotherapy was considered after the last distant failure. STS can have an unpredictable pattern of recurrence, therefore follow-up protocols should be tailored to individual risk. Multimodal management for primary site is the key to achieve higher local control rates, and it should also be considered as an approach for secondary sites in selected patients.

**Keywords:** Case report; soft-tissue sarcomas (STS); visceral metastases; recurrence

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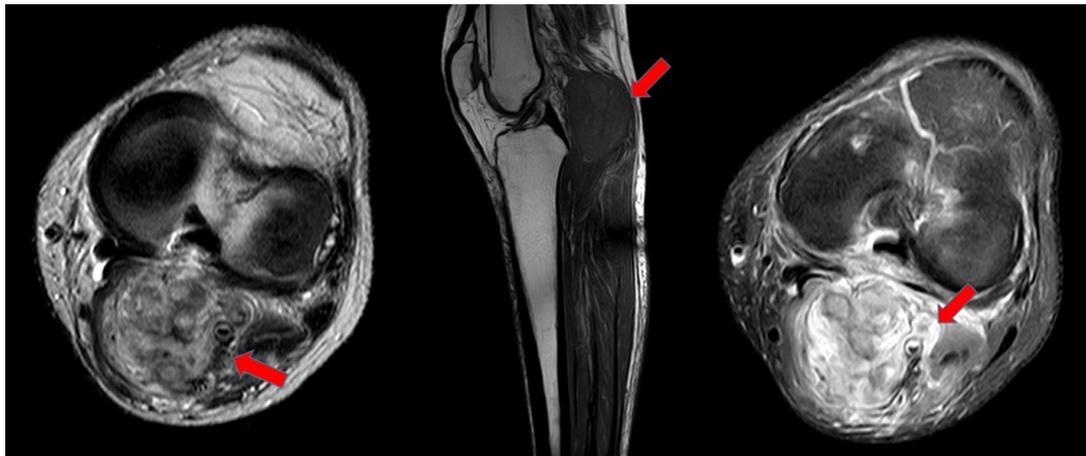
## Introduction

Soft-tissue sarcomas (STS) are a rare and heterogeneous group of malignancies with different prognosis depending on histological subtype, stage and anatomic location (1). Commonly, STS arise in the extremities, predominantly in the lower limbs, accounting for up to 50% of all STS, and the most frequent histological subtypes are liposarcoma and leiomyosarcoma followed by fibrosarcoma. Fibrosarcoma is composed of malignant spindle-cell fibroblasts and represents up to 5.2% of adult's STS (2).

Multimodal treatment with limb sparing surgery

combined with pre- or post-operative radiotherapy can lead to 5-years local control rates of up to 85–90% (3). Prognostic factors have been related to local failure risk and development of distant metastases, including increasing tumor size (>5 cm), high grade, positive surgical margin or depth to muscular fascia (4,5). The 5-year distant failure rate for patients with lower extremity STS is 30% being the most common site the lungs (6-9). Nonetheless, STS dissemination may also involve lymph nodes, the bone or the abdominal cavity. Intra-abdominal metastases from STS are extremely rare and occur mainly in the liver, being

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**Figure 1** Axial T2 weighted fast spin echo magnetic resonance imaging (MRI). MRI demonstrates high-signal-intensity sarcomatous mass (arrow) located within the calf muscle.

frequently observed in leiomyosarcoma (10-12).

Herein, we report the case of a patient diagnosed with lower extremity fibrosarcoma that underwent multimodal treatment, and then presented a series of loco-regional, outfield recurrences, followed by contralateral limb failure along with lung and gastric metastases.

We present the following article in accordance with the CARE reporting checklist (available at <http://dx.doi.org/10.21037/pcm-20-49>).

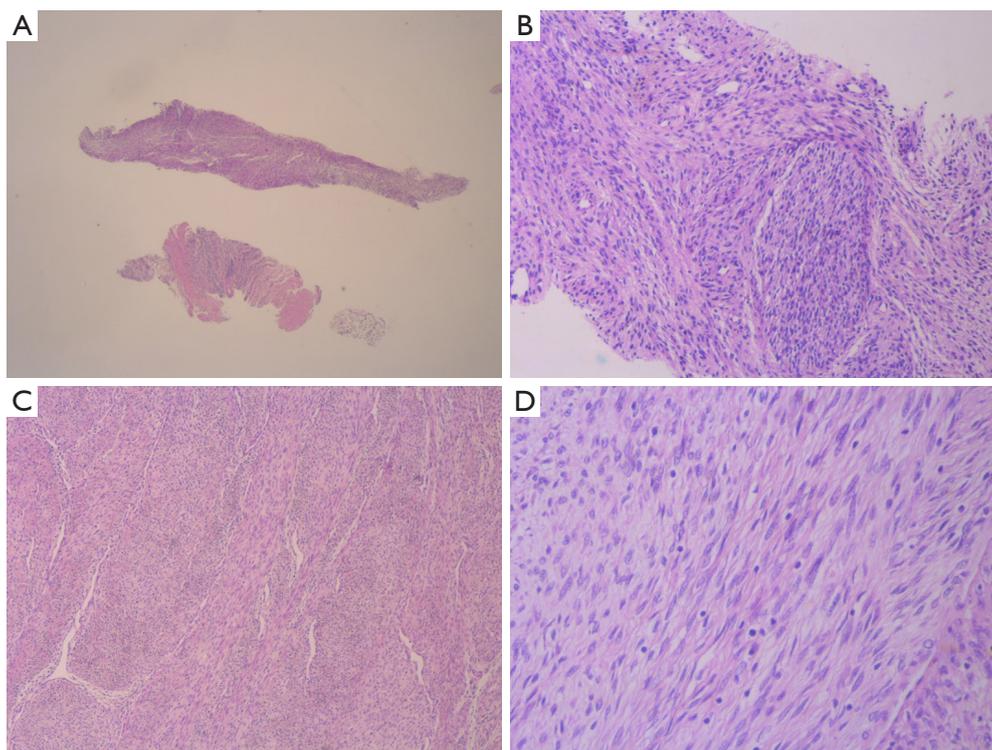
### Case presentation

At the time of initial diagnosis, the patient was a 30-year-old male with no medical history of interest. He initially noticed a painful mass on the left calf, consulting an orthopedic, who ordered a magnetic resonance imaging (MRI) revealing a lesion within the left limb (*Figure 1*). In February 2013, patient underwent gross total resection with clear margins. Histological sections of the specimen showed spindle cell proliferation with two areas of tumor necrosis (5%). Immunohistochemical (IHC) analysis confirmed the presence of cells with positive only Vimentin marker (*Figure 2*). Based on these features the diagnosis established was Adult Fibrosarcoma (pT2b). Following the tumor board decision, the patient then completed treatment with adjuvant radiotherapy, up to a total dose of 66 Gy. First follow-up MRI, performed after 12 weeks of treatment, showed post-treatment changes with no findings suggestive of malignancy. Patient at this time was asymptomatic and follow-up was continued during the next year every 6 months.

In September 2014, patient consults again after noticing a second mass, in the same limb, but in the left popliteal fossa area. A core needle biopsy of such node was performed and it was informed as a grade II fibrosarcoma. Case was presented in the multidisciplinary musculoskeletal tumor board, deciding neo-adjuvant radiotherapy up to 46 Gy, followed by total resection and intraoperative radiotherapy as a tumor bed boost.

After 17 months of this last approach, a third marginal recurrence presents on left thigh with a maximum diameter of 3 cm and aggressiveness criteria by MRI. Patient underwent total resection of the lesion with clear margins, followed by adjuvant radiotherapy and in addition, adjuvant chemotherapy, epirubicin and ifosfamide regimen. Histological specimen showed grade III fibrosarcoma with necrosis (80%). In the IHC analysis, positive Vimentin marker, Desmine, CD68 and factor XIIIa marker, with a Ki-67% of 20%. Patient received last cycle on December 2016, and initiated surveillance with lower extremities MRI and total body computed tomography (CT) every 4 months.

MRI of June 2018 described a new solid nodular lesion within the contralateral extremity soleus muscle. The total body CT also revealed recent increase in the size of pulmonary lesions described in previous imaging as nonspecific nodes. Patient received multidisciplinary management with neo-adjuvant radiotherapy followed by surgery and intraoperative radiotherapy tumor bed boost. In a second time, a wedge resection of the superior and inferior right pulmonary lobes was performed. The histological examination revealed no evidence of malignancy of



**Figure 2** Histological sections of the first tumor resected in February 2013. Staining method: Hematoxylin and Eosin (H&E). (A) H&E, 2.5 $\times$ . Core biopsy with fusiform neoplasm, without necrosis and relatively monomorphic spindle cells. (B) H&E, 10 $\times$ . Low power view shows the characteristically arranged in long sweeping fascicles with collagen stroma and spindle cells with scanty cytoplasm. (C) H&E, 4 $\times$ . Dense hypercellular neoplasm with monomorphic spindle cell showing with herringbone growth pattern. (D) H&E, 20 $\times$ . Low grade fusiform sarcoma showing scanty cytoplasm with bland zones, increased stromal collagen and lesser degree of nuclear atypicity.



**Figure 3** Positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated ( $^{18}\text{F}$ -FDG PET/CT) shows a focal uptake of fluoro-D-glucose (FDG) (Standardized Uptake Value (SUV<sub>max</sub>) 3.96) within the right gluteus medius, without a clear morphological correlation in the computed tomography (CT) scan (arrow).

pulmonary nodes but confirmation of recurrent high grade fibrosarcoma in the lower right extremity. With this final pathological anatomy report, and after radical treatment of the soft-tissue recurrence site, systemic treatment was not recommended at this time.

In July 2019 patient presents to the emergency room with clinical features suggestive of upper gastrointestinal bleeding with minimum blood test alteration. Patient was under study for a new suspicious lesion within the contralateral gluteus, with hypermetabolic activity on PET-CT (*Figure 3*). Study was completed with a panendoscopy examination, revealing a gastric mass suggestive of primary malignancy versus secondary disease (*Figure 4*). In August 2019, surgeons performed a total gastrectomy with Roux-en-Y reconstruction, and in parallel, orthopedic surgeon performed a total resection of the gluteal lesion. Finally



**Figure 4** Panendoscopy shows the presence of a metastasis with a lobulated surface, 70 mm in diameter, located in the minor curvature. Indocyanine green marking used. Other findings: abundant food remains in the gastric cavity.

the pathology report informed of a fibrosarcoma gastric metastasis with no lymph node involvement (25 nodes), necrosis <5% and a right gluteal metastasis. In the IHC analysis, positive Actin ML and HHF35, Desmine, and negative for Myogenin, with a Ki-67% of 80%. Prior to initiate systemic treatment, re-staging imaging revealed evidence of lung progression and a suspicious pancreatic lesion. Patient starts chemotherapy in October 2019, initially with adriamycin followed then by liposomal doxorubicin.

On his last visit, patient remains asymptomatic and at the time has received 5 cycles of doxorubicin. Last PET-CT (6<sup>th</sup> of February 2020) shows stability of bilateral pulmonary nodes with no evidence of new lesions and describes the pancreatic lesion as a possible pseudocyst. Therefore, treatment is discontinued for now, and patient initiates new follow-up plan with imaging studies every 3–4 months.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient. A patient perspective letter is added as [supplementary file](#). In the attached file, the patient explains how he has experienced his disease during the 7 years of evolution, his mindset on the diagnostic tests and treatments, and the significant impact on his quality of life.

## Discussion

Soft tissue sarcomas (STS) represent less than 1% of

all neoplasms and include a wide variety of histological subtypes (2). Anatomically, extremities are the most common primary site, and generally lesions are found in deep soft tissue or adjacent to the bone (1,2). Local control depends on tumor grade and size, surgical margins and adjuvant radiotherapy. Extremity STS can achieve 5-year local control rates of up to 85–90%, ideally after a multimodal approach with radiotherapy followed by limb sparing surgery (3,13,14). There is no statistical difference in terms of local control between the different STS histological subtypes, nor is there evidence in the literature of a greater risk of marginal recurrences along the extremity in fibrosarcoma (2).

Previous series of extremity STS, document a mean time to local failure that may vary from 9 to 53 months (7,9,14). In the present case, as the patient had a high grade, deep tumor, with dimensions greater than 5 cm, the risk of local recurrence was higher. He received multimodal treatment with surgery and radiotherapy. Despite this, within a period of time shorter than 48 months, he developed three recurrences along the limb distal-proximal axis (*Figure 5*). These were considered marginal recurrences, outside the previous irradiation field, in the immediately superior area, allowing surgical salvage therapy and delivery of optimal doses of radiotherapy without field overlap.

Leibel *et al.* carried out a study which included 81 patients with extremity STS. Patients were treated with surgery, radiotherapy or both (13). With a mean time of 17 months, local failure was 41% after surgery alone, 100% after radiotherapy alone and 16% after surgery and radiotherapy (1/3 infield recurrence). Distant metastases



**Figure 5** Limb's patient with three surgery scars and radiotherapy dermatitis in left extremity.

occurred during the first two years after treatment for the majority of patients, being the most common site the lung (90%).

In a more recent study, that included 174 patients with localized extremity STS, patterns of recurrence were analyzed in order to establish routine follow-up (14). After multimodal treatment with surgery (n=172), radiotherapy (n=145) and chemotherapy (n=25) the 5-year local control rate was 51%. With a mean time of 9 months, 31 patients presented local failure, having 5 of them synchronous metastases. Distant disease occurred in 51 patients, with a mean time of 5 months for lung failure and 11 months for non-pulmonary metastasis.

Similarly, Dogan et al, studied long-term outcomes in 114 patients with primary extremity STS all treated with surgery and radiotherapy followed by adjuvant chemotherapy in 43 cases (9). The 5-year and 10-year local control rates were 77% and 70% respectively with a mean time of 53 months to local recurrence. Five-year and 10-year disease-free survival was 60% and 52% respectively, with up to 27% of distant relapse, more frequently in lungs.

In the reviewed literature, there is no evidence of the effect of local control on the development of distant metastases. Smith *et al.* analyzed the patterns of relapse in extremity STS, observing that up to 80% of patients with distant failure presented lung metastasis and these appeared after a mean time of 20.5 months (7). In the case we have reported, distant failure wasn't observed until 60 months after primary site treatment, and presented with a synchronous contralateral limb metastases.

Although the majority of patients with distant failure developed lung metastases, other sites of dissemination such as bone or abdominal cavity have also been described.

Within STS, intra-abdominal metastases may develop more frequently in myxoid liposarcoma, but for other histological subtypes the incidence is low, ranging from 1–6% (15,16). The overview of previous studies reporting for STS abdominal metastases is provided in *Table 1*.

Smolle *et al.* carried out a multicenter study that included up to 796 patients with localized STS mainly of the extremities (11). Up to 202 patients presented distant failure, but just 24 of these had intra-abdominal metastasis. The mean time to abdominal recurrence was 2.4 years, and the most common site was the liver. Myxoid liposarcoma followed by pleomorphic liposarcoma were the histological subtypes with higher abdominal affinity. Undifferentiated tumors also presented higher risk of developing primary abdominal metastases, although this was not significant in multivariate analysis (P=0.277).

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 (12,19). 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 (10,15,17).

Little is known about gastric metastases from STS, as they are mainly documented in case reports or as isolated cases in larger studies (15,20). 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 (12,19).

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 (16,17). 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).

**Table 1** Original articles documenting abdominal metastases in soft tissue sarcoma

Study (year of publication)	Patients with AM from STS	AM location (n)	Patients with previous or synchronous non-AM	Mean time to AM	Management (n)	Prognosis
Ogose <i>et al.</i> (10), 2000	Primary site: Extremities [14]; Trunk wall [1]; Abdomen/pelvis * [8]	Visceral: Liver [14]; Jejunum [2]; Pancreas [1]; Colon [1]; Jejunum and pancreas [1]; Other: Peritoneum [4];	22; Lung [19]; Other: Bone, soft tissue and brain	Liver: 17.6 months; Other: 19.4 months	Conservative treatment [18]; Surgery [1]; RT [1]	23 pts DOD; Mean time to event: 8.2 months
Behranwala <i>et al.</i> (15), 2004	Primary site: Extremities [18]; Trunk wall [1]	Visceral: Gastric [1]; Small bowel [4]; Large bowel [1]; Liver [1]; Spleen [1]; Adrenal [2]; Other: Omentum [3]; Mesentery [9]; Retroperitoneal [8];	13; Lung [6]; Other: Soft tissue	27 months	Surgery [16]; Plus adjuvant RT and CT [3]	2-year post-AM; survival was 54% surgical treatment; and 0% for unresected patients
Sheah <i>et al.</i> (17), 2008	Primary site: Extremities [6]; Abdomen/pelvis * [1]	Visceral: Liver [4]; Other: Retroperitoneal [1]; Mesentery/soft-tissue [2];	4; Lung [2]; Other: Bone and soft tissue	2.7 years	N/A	N/A
King <i>et al.</i> (16), 2009	Primary site: Extremities [10]	Visceral: Liver [2]; Adrenal [1]; Other: Intraabdominal [3]; Retroperitoneal [2]; Abdomen wall [1]; Widespread [1]	9; All lung	19.8 months; *4 patients AM at diagnosis;	N/A	At time of study: 7 pts DOD; 3 pts. AWD
Rehders <i>et al.</i> (12), 2009	Primary site: Extremities [5]; Abdomen/pelvis * [22]	Liver [27]	4; Lung [2]; Nodal [2]	44 months	All surgery; Plus adjuvant CT [4]	5-year and 10-year post-AM survival were 49% and 33%, respectively
Thompson <i>et al.</i> (18), 2015	Primary site: Extremities [7]	Visceral: Liver [4]; Other: Abdominal [1]; Mesenteric [1]; Peritoneal [1]	5; All lung	27.9 months	N/A	N/A
Grimme <i>et al.</i> (19), 2019	Primary site: Extremities [5]; Abdomen/pelvis* [22]; Head&neck [2]; Other [9];	Liver [38]; 51% solitary	12	N/A; 11 pts. Synchronous with primary tumor	All surgery;	3-year and 5-year post-AM survival were 53.9 and 41.1% respectively
Smolle <i>et al.</i> (11), 2020	Primary site: Extremities [24];	Visceral: Liver [13]; Intestinal [7] Pancreatic [2]; Other: Peritoneal [2]	14	2.4 years	CT [19]; Surgery and CT [2]; Supportive care [1]	2-year post-AM survival was 60–65%

\*, Abdomen/pelvis: viscera, retroperitoneum, gynaecologic, pelvis, AM, abdominal metastases; DOD, dead of disease; AWD, alive with disease.

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 (14,21,22). 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 (21).

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 (22). 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. Surveillance strategies should therefore focus on the individual risk of each patient.

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. However, there are some limitations inherent 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 STS after local and distant failure.

## Conclusions

The case reported highlights the importance of patient's self-examination for local recurrence detection. Multimodal management for primary site is the key to achieve high rates local control and long disease-free survival. Local radical approaches to secondary sites should be considered for selected patients with STS.

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## Footnote

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient. Patient was offered the opportunity to read the manuscript.

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## Patient disease perspective

To start from the beginning, we would have to go back to the end of 2012 when I noticed a lump in my left leg. After several visits to the Primary Health Center and the Hospital's Emergency Room, I was prescribed ice and anti-inflammatory medication. Finally, I was referred to the orthopedist at the Specialty Center, and after asking for an MRI I was referred to the Hospital's Emergency Room, where I was told the probable diagnosis of my disease.

From the diagnosis, everything went very quickly and in February 2013 I had my first operation to remove the tumor and the surrounding area to ensure a sufficient margin. After recovering from the operation, I had several sessions of radiation therapy with immobilization devices, which ensured tumor wouldn't relapse in the radiated area, but unfortunately, I also had a lot of deterioration in the adjacent normal tissue. These sequels are the most important ones I have, since they cause me a muscular deterioration, and muscular fibrosis along with a chronic venous insufficiency and a chronic neuropathic pain, which limit my daily life.

Over the next few years I had four relapses in different areas of my legs, which were detected by myself when I noticed lumps of the same characteristics as the initial tumor. All of them were managed with surgery and different treatments before, during and after the operations, with less aggressive side effects. Probably due to not using a cast or to being areas with more muscle mass. Preoperative radiotherapy produced a reduction in the tumor in one of the operations, which also meant that it was not necessary to remove such a large safety margin. These operations have also caused me loss of muscular mass in both legs, which, together with the initial operation, limit my movements and require me to lie down for part of the day.

I have also undergone right lung surgery due to the appearance of several nodules, which in the end were reported as benign lesions. However, I currently have metastases in my lungs with new nodules, which is confusing for me.

The last surgery was due to a gastric relapse and after months of slow recovery, I have now hardly any sequelae.

After the following 3 cycles with the new treatment, I

have been told that the disease is stable (it has not grown, but neither has it diminished) and I am going to continue with another 3 cycles before the next revision.

In summary, after 8 years with the disease:

- ❖ I think there is a lack of screening tests to detect this type of tumor earlier or in very early stages for the first time.
- ❖ Once you are already suffering from it, I believe it is difficult to control its expansion, since the imaging tests for controlling the disease are carried out mainly on the affected areas. In my case, I had recurrences in areas close to the areas that were being followed-up, but they were not detected since the MRIs did not include such new areas.
- ❖ My type of cancer is rare or infrequent, so its behavior is not very predictive. I think this is due to the lack of research or information on similar cases.
- ❖ Regarding the lack of information about my type of cancer, I believe that chemotherapy does not have specifically targeted drugs, since after different types of chemotherapy, it is not having the expected effect on me.
- ❖ On the other hand, I am very satisfied with the proactive response of all the hospital staff, with a rapid response to the initial diagnosis and the subsequent relapses, the quality of the different surgeries and treatments available so far.
- ❖ I would also like to highlight the humane treatment and the accessibility when needing any consultation.
- ❖ Physically, I have a 35% disability and soon I will have a permanent total disability. The consequences of the surgical and adjuvant treatments allow me to live a normal sedentary life with certain mobility limitations.
- ❖ My attitude, despite receiving bad news after bad news over the years, has always been very positive. Nowadays, being at stage IV and the fact that the disease has spread to other parts of the body, lead to pessimistic thoughts about whether I will be able to recover from it. However, there is no other choice than to move forward with positive attitude and follow the advice and treatments of professionals to fight and defeat this disease.