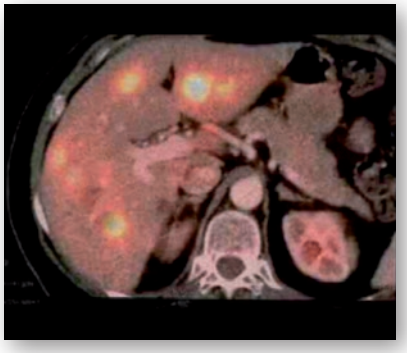

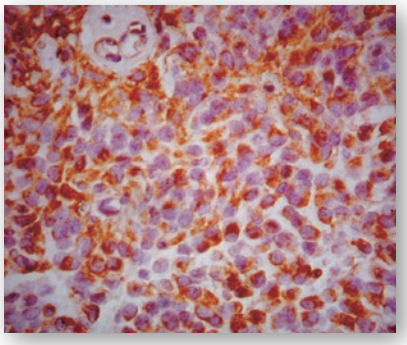

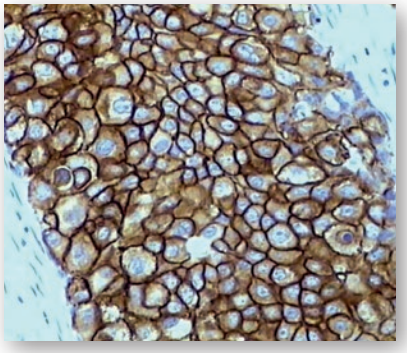

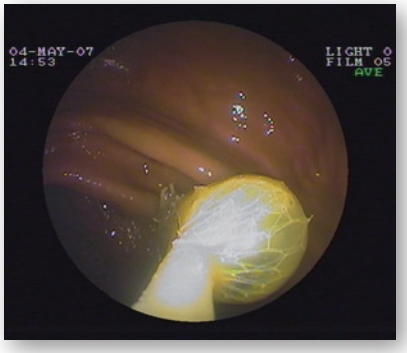

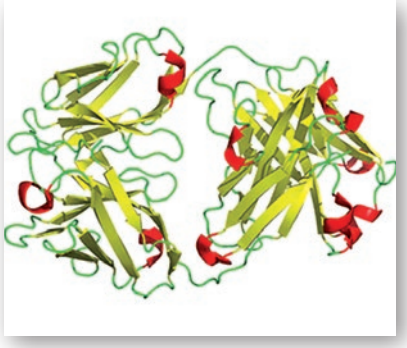

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Managing advanced soft tissue sarcoma in these unprecedented times: looking into different scenarios through practice cases

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Introduction

The coronavirus disease-2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected many areas of people's daily lives, including the healthcare environment. Healthcare professionals have had to adapt and change the way they care for patients, and cancer patients have been no exception. During this pandemic, telemedicine has become a widely used tool[1,2]. However, the real impact of SARS-CoV-2 on cancer patients is still unknown. Many have suffered significant delays in their treatment, interruptions to treatment, or have been lost to follow-up. Despite the fact that the risk of morbidity and mortality is higher in cancer patients than in COVID-19 infected patients (only 5% estimated fatality rate from COVID-19), virus precautionary principles have prevailed over the continuation of curative cancer treatment in many cases[3,4]. Thus, during this pandemic, 30% of cancer patients have reported consequences for their oncologic treatment or follow-up[5].

Oncology patients, including patients with soft-tissue sarcoma, constitute a high-risk group who suffer higher morbidities and mortality than other patients. Results from Europe's largest prospective dataset of patients with cancer and COVID-19 revealed an adverse impact of malignancy on prognosis of COVID-19, with a hazard ratio of 1.62 (95% confidence interval 1.56-1.68; $p < 0.001$) for mortality in patients with cancer versus patients without cancer[6]. These results may be due, at least in part, to the inability to receive necessary medical services for cancer. Decisions on whether or not to delay cancer treatment and clinical trials should be made on an individual patient basis and according to the inherent tumor risk and the prevailing situation, as delays could lead to tumor progression and poorer outcomes[7].

Thanks to the cooperation of numerous networks and medical societies during this pandemic and the knowledge that has been acquired about SARS-CoV-2 infection, consensus and recommendations for the care of sarcoma patients have been developed, providing a tool for multidisciplinary tumor committees during the COVID-19 pandemic[8,9].

This compilation of clinical cases aims to provide an example of patients with soft-tissue sarcomas during the COVID-19 pandemic. The first case series describes patients with leiomyosarcoma or osteosarcoma with a diagnosis of COVID-19 during their follow-up, adjuvant chemotherapy, or chemotherapy for advanced disease. The second clinical case addresses the change from oral to intravenous treatment during this health crisis. The third and last clinical case deals with the prioritization of treatment selection in a liposarcoma patient.

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When coronavirus is suspected

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Introduction

According to recent guidelines for clinical practice published about the management of sarcoma during the coronavirus disease-2019 (COVID-19) pandemic, patients with a suspected infection should be screened for the presence of the virus. If confirmed or strongly suspected (clinically or by computed tomography [CT] scan), any cancer treatment must be postponed for at least 15 days after the start of symptoms and until the patient has recovered[1]. We present three clinical cases of patients with suspected COVID-19 in different situations.

Clinical case 1: diagnosis during follow-up thoracic CT scan in a leiomyosarcoma patient

A 54-year-old female patient was diagnosed in November 2019 with leiomyosarcoma of the distal right thigh G2T1a (4.5 cm) N0M0. The sarcoma committee recommended surgery and then to evaluate for radiation therapy. In December 2019, the patient underwent wide surgery (0.5 cm in deep margin but with fascia of muscle as a boundary). Radiation therapy was considered but was eventually interrupted by COVID-19 infection. Figure 1 shows magnetic

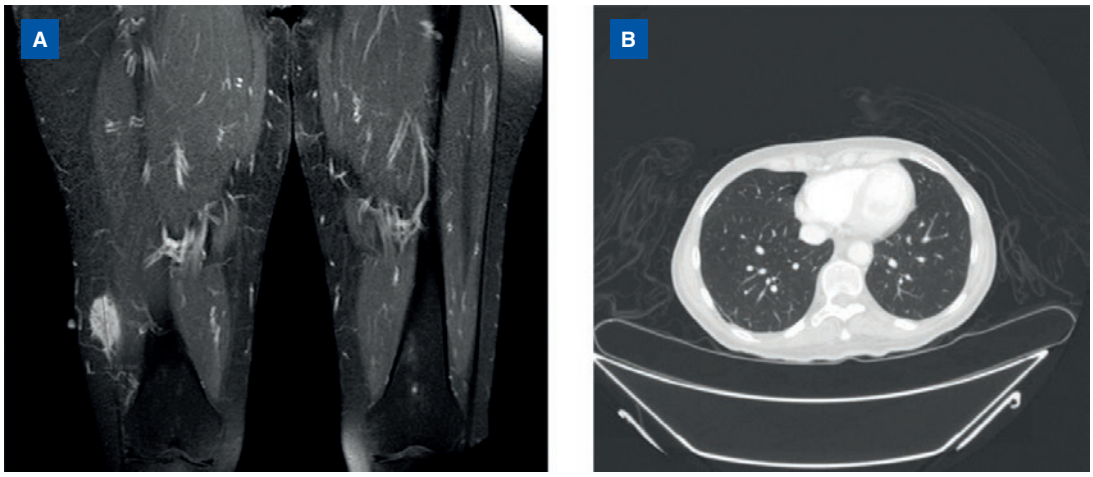

Figure 1. ***(A)*** *Magnetic resonance imaging (MRI) of the thighs and* ***(B)*** *CT scan of the thoracic region (December 2019).*

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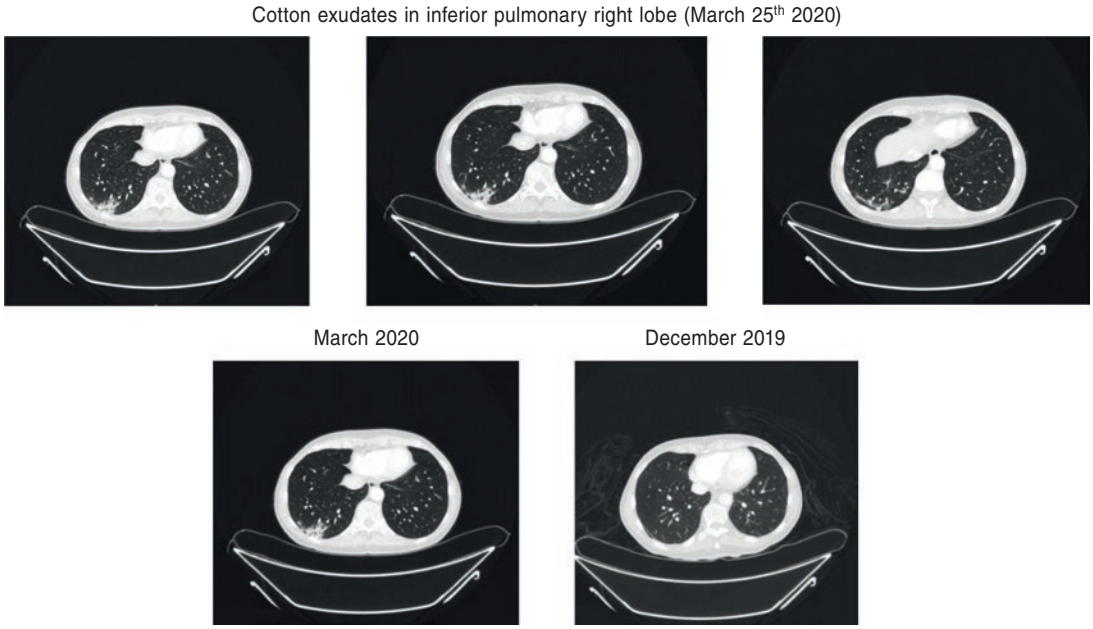

Figure 2. *Cottony exudates in the inferior pulmonary right lobe.*

resonance imaging (MRI) of the thighs, with evidence of the tumor in the distal right thigh, and a CT scan of the thoracic region without any suspicious finding. In March 2020, the patient developed odynophagia, sore throat, bilateral otalgia, and low-grade fever, for which she visited primary care, where the general practitioner prescribed general antibiotics. In the meantime, she underwent a thoracic CT scan as a follow-up that showed cottony exudate opacities in the inferior right basal lobe of the lung (Fig. 2), leading to the suspicion of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection.

It is important to take into consideration that findings of some CT scans could be confused or associated with other presentations. For instance, what used to be called bronchiolitis obliterans or constrictive bronchiolitis can be related to chemotherapy, as happened in this case, in which there were ill-defined opacities that were considered as bronchiolitis (Fig. 3). After stopping chemotherapy, a normal CT scan was observed. Something similar can be seen in vascular sarcomas, for instance, in angiosarcoma, a "ground-glass" imaging can be seen in the lungs indicating metastatic spread (Fig. 4). These ill-defined opacities can be difficult to distinguish from pneumonia or bronchiolitis. Similarly, in retiform hemangioendothelioma, "ground-glass" imaging can also be seen.

Returning to our case, because of a suspicion of SARS-CoV-2 infection, a polymerase chain reaction (PCR) test of pharyngeal exudate was requested, which was positive for SARS-CoV-2. However, the patient improved and became asymptomatic in 5 days. She continued to be followed up by phone since it was considered to be a mild coronavirus infection.

Clinical case 2: diagnosis during adjuvant chemotherapy for localized osteosarcoma

A 20-year-old female patient was diagnosed in February 2020 with osteosarcoma of the fibula T2b (7.8 cm) N0M0. A lesion on the cortical bone was observed in a plain radiograph of the fibula (Fig. 5). In addition, an MRI image showed a large component of soft tissue lesion of the tumor (Fig. 6). The tumor committee recommended two courses of induction multi-agent chemotherapy (MAP – doxorubicin, cisplatin, and high-dose methotrexate). After that, the patient underwent surgery followed by adjuvant chemotherapy. As the patient was negative for P-glycoprotein, mifamurtide (liposomal muramyl tripeptide phosphatidylethanolamine; Mepact) was not prescribed in the adjuvant setting.

On March 16, 2020, she received the first MAP cycle, and on April 7, 2020, the second cycle of high dose methotrexate was administered. However, she reported then that she had symptoms associated

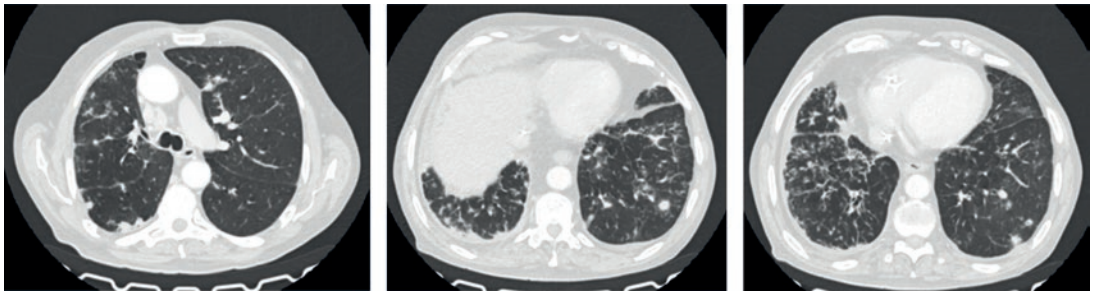

Figure 3. *Computed tomography scan showing bronchiolitis obliterans related to chemotherapy.*

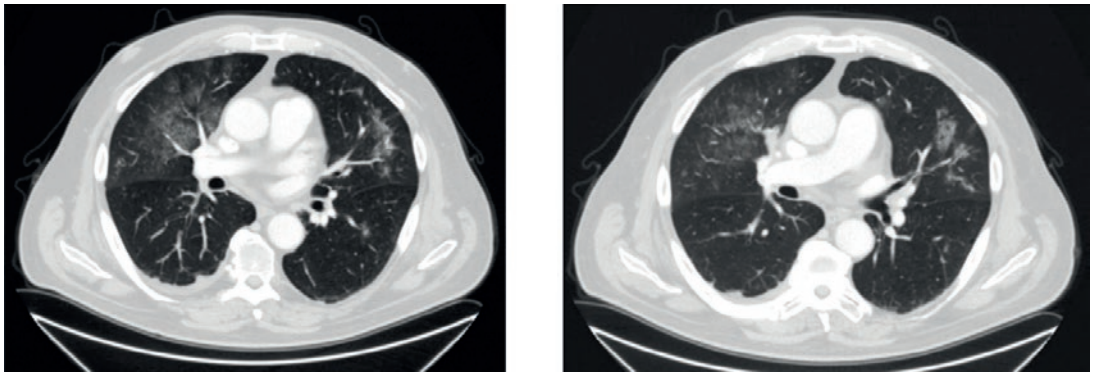

Figure 4. *Computed tomography scan of an angiosarcoma case with metastatic spread.*

with COVID-19 since March 24, in particular, low-grade fever and cough. Being in good general condition, the patient was diagnosed with SARS-CoV-2 infection (PCR negative, IgM positive).

On April 7, 2020, laboratory findings showed the usual effects of methotrexate on liver function (lactic dehydrogenase [LDH] 463 international units [IU]/L, gamma-glutamyl transferase 53 IU/L, aspartate aminotransferase 154 IU/L, and alanine aminotransferase 291 IU/L). However, C-reactive protein (CRP) levels returned to normal in a few days: From 6.2 mg/L on April 7 to 3 mg/L on April 11. The levels of other acute-phase inflammatory mediators were also normalized.

We waited two additional weeks before prescribing cisplatin and doxorubicin (second MAP) until we were sure that the PCR was negative in two different samples. During this time, the patient remained in good condition. Figure 7 shows a comparative MRI at baseline (February 12, 2020) and after two cycles of MAP induction therapy (May 18, 2020).

The main concern, in this case, was the administration of high-dose methotrexate while the patient was positive for COVID-19. However, no impairment in the clinical status nor in the biochemistry parameters was detected.

Clinical case 3: diagnosis during chemotherapy for advanced well-differentiated liposarcoma

A 79-year-old male patient was diagnosed with a well-differentiated retroperitoneal liposarcoma in October 2017. At the time of diagnosis, the mass measured 24.6 cm × 20.2 cm × 17.6 cm. To differentiate it from angiomyolipoma, a presurgical biopsy was performed and confirmed the final diagnosis of well-differentiated liposarcoma with MDM2 positive amplification. In November 2017, the patient underwent surgery with some doubts of complete resection in the inferior pole of the tumor. There was a relapse one year later and a new resection was performed. According to the pathologist and the radiologist, the liposarcoma included de-differentiated areas. A second recurrence took place in March 2019. Subsequently, treatment with eribulin was started.

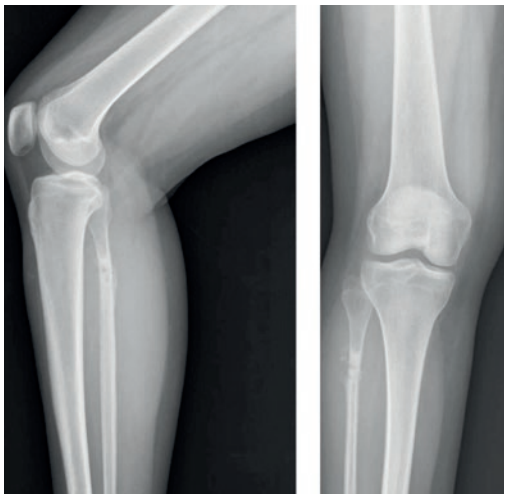

Figure 5. *Plain radiographs of the fibula at baseline (February 2020).*

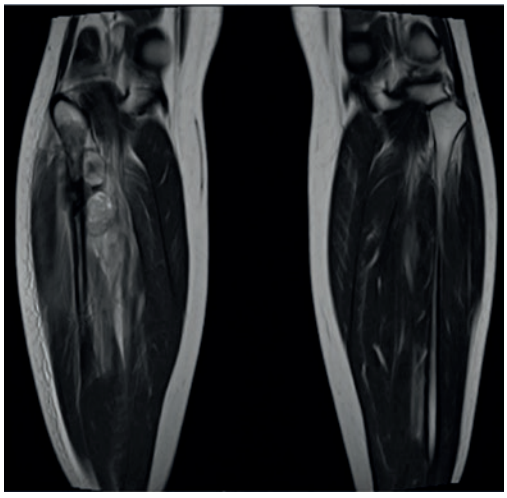

Figure 6. *Magnetic resonance imaging of the legs (February 12, 2020).*

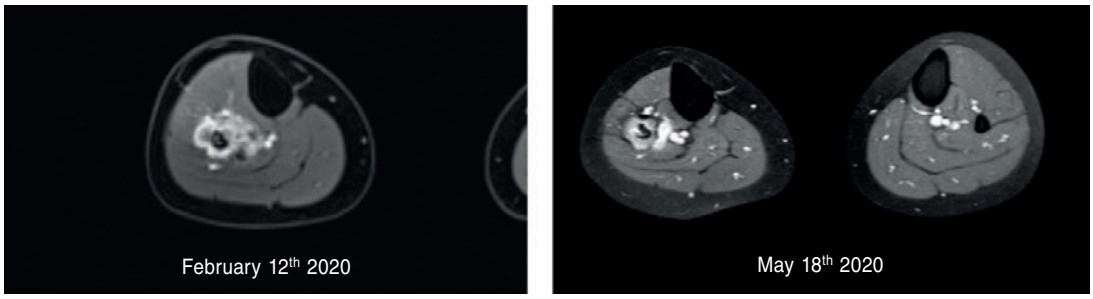

Figure 7. *Comparative magnetic resonance imaging at baseline (February 12, 2020) and after two cycles of induction therapy with methotrexate, doxorubicin, and cisplatin (May 18, 2020).*

On March 11, 2020, the patient presented to the emergency department with a fever (38.2°C) and cough with whitish expectoration. The results of the PCR for SARS-CoV-2 were positive. The most important laboratory findings during patient admission were D-dimer 752 ng/mL, hemoglobin 14.2 g/dL, hematocrit 41.6%, mean corpuscular volume 88.1 fL, leukocytes 1310/µL, and platelets 201,000/µL. Chest X-rays were normal and the general condition of the patient was good. The last eribulin administration was 6 days before admission but was resumed on April 14, 2020, after a negative PCR result for coronavirus.

Diagnosis of SARS-CoV-2 infection

The incubation period for SARS-CoV-2 is thought to be within 14 days following exposure. In a study on patients with confirmed infection, the median incubation period was 4 days (interquartile range 2-7 days)[2]. Symptoms appeared within 2 days after infection in 2.5% of subjects and within 11.5 days in 97.5%[3].

The severity of symptoms ranges widely from mild to critical. According to a study by the Chinese Center of Disease Control and Prevention on 44,500 confirmed infected patients, 81% developed mild symptoms that could include mild pneumonia; 14% had severe disease, usually with dyspnea and hypoxia, or more than 50% of lung involvement; 5% had critical disease with respiratory failure, shock, or multiorgan dysfunction; and 2.3% died[4]. Higher overall fatality rate has been documented in Italy (7.2%) and in Spain (8.9%). However, it should be considered that results of mortality rates depend on the number of tests available at the time these statistics were calculated.

The main symptoms in patients diagnosed with SARS-CoV-2 include fever, cough, dyspnea (new or worsening over baseline), and smell or taste

abnormalities among others. Symptoms in hospitalized infected patients include fever (99%), fatigue (70%), dry cough (59%), anorexia (40%), myalgias (35%), dyspnea (31%), and sputum production (27%)[5,6].

Comorbidities associated with SARS-CoV-2 infection are cardiovascular disease, diabetes mellitus, hypertension, chronic lung disease, cancer (in particular, hematologic malignancies, lung cancer, and metastatic disease), chronic kidney disease, obesity, and smoking[7].

Clinical suspicion and criteria for testing for SARS-CoV-2 should be based on the identification of symptoms such as fever, cough, dyspnea, myalgias, diarrhea, smell/taste disturbance, or severe lower respiratory tract illness. The suspicion should be increased if the patient is resident in or has traveled to a high incident population in the last 14 days or if the patient has been in contact with a confirmed case. The most common laboratory findings include lymphopenia or increased levels of aminotransaminases, LDH, and inflammatory markers (i.e., ferritin, CRP, and erythrocyte sedimentation rate). For patients with a severe condition, there is an increase in D-dimer (>1 µg/ml), elevated prothrombin time, and elevated troponin. Although there is still some controversy regarding elevated D-dimer, many articles report that the elevation of these markers indicates the severity of the condition of the patient. Procalcitonin levels are also increased in cases of severe pneumonia[6].

Microbiologic tests include reverse transcription PCR (RT-PCT) or serology. RT-PCR is used to diagnose current infection by detecting viral RNA. The procedure consists of the detection of two or more genes, including nucleocapsid, envelope, spike genes, and regions in the first open reading frame. Samples are collected from the nasopharynx, oropharynx, and nasal cavity. False-negative result rate is <10% on days 1-3 of illness, > 20% at day 6, and >50% after day 14. Serology is used for detecting IgM and/or IgG. Median time from symptoms to seropositivity is 12 days for IgM and 14 days for IgG[8].

Conclusions

Suspicion of SARS-CoV-2 infection should be based on clinical and epidemiological data. For the recent onset of symptoms or contact with a confirmed case, detection of virus RNA by PCR in pharyngeal exudate is recommended. However, for patients with symptoms lasting at least 12 days, assessment of serologic immunoglobulin IgM or IgG in blood could be the best option. If the result is negative and the infection is still suspected, then the test should be repeated. Although the main recommendation is to delay cancer treatment in virus-confirmed cases, it has been observed that chemotherapy or other systemic therapies administered within 4 weeks from testing positive for COVID-19 did not have a significant effect on mortality from COVID-19. Indeed, mortality in infected cancer patients appears to be principally driven by age, gender, and comorbidities[9]. Therefore, it can be argued that delaying effective cancer treatment could increase the risk of cancer morbidity or mortality, perhaps leading to worse consequences than those generated by COVID-19 infection. In all cases, multidisciplinary tumor boards (with virtual discussion if needed) will be always the best option, especially when complex cases have to be discussed[1].

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The use of rare cancer network during the COVID-19 pandemic

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Case presentation

In February 2007, a 50-year-old male patient was diagnosed with well-differentiated/dedifferentiated liposarcoma by biopsy of a retroperitoneal mass. He underwent surgery with *en bloc* excision of the mass and of the surrounding tissue (right colon, kidney, adrenal glands, and psoas muscle). Three years later, the patient experienced an abdominal relapse with a single nodule treated with surgery. However, 1 year later, a new multifocal abdominal relapse was detected.

Treatments evaluation and case evolution

Surgery for abdominal relapse of retroperitoneal dedifferentiated liposarcoma is extensively used and many patients can undergo several consecutive resections especially in case of isolated and single nodule progressive disease. In this case, it was preferred to offer medical treatment mainly due to the multifocality of the disease and the progressive shortening of time between the second and third surgery. The patient was treated with the standard front line treatment with doxorubicin with the addition of ifosfamide, but unfortunately, the disease progressed after three cycles (Fig. 1). Second-line treatment with trabectedin was then delivered, achieving stabilization of the disease after four cycles. After the seventh cycle of treatment patient underwent progression (Fig. 2). In our experience, high-dose continuous-infusion ifosfamide can be effective in patients who have already progressed to the combination of doxorubicin and ifosfamide. For this reason, high-dose ifosfamide was selected as further treatment, followed by eribulin that was administered as fourth-line therapy. Unfortunately, the patient progressed on both therapies.

As we commonly observe in sarcoma patients, the patient had an optimal performance status despite all the previous lines of treatment and was willing to receive active therapy. Thus, in January 2020, he was enrolled into a clinical trial with an oral targeted therapy. Conveniently, the study drug was administered orally and, according to the study promoter, could be delivered to the patient's home and monitored by phone during the COVID-19 crisis. In this way, the patient did not have to expose himself to the high risk of going to the hospital on those critical days. The patient progressed again after 5 months of treatment (Fig. 3).

Rechallenge with trabectedin was proposed for the following line, as the previous administration of this treatment provided a disease stabilization. At that time, by the end of April, the COVID-19 crisis in Italy was beginning to improve and the patient could be referred to a hospital close to his home in Verona. It was agreed with the medical team of Verona to continue with the same treatment schedule of trabectedin. The follow-up of the patient was carried out through the virtual platform of the Italian Rare Cancer Network (*Rete Tumori Rari,* [RTR]) that allows sharing clinical decisions among physicians treating sarcoma (or other rare cancers). After three cycles of trabectedin, the patient achieved a good clinical response. At present, the patient is still receiving trabectedin with good tolerability. The previous reports have indicated that trabectedin retains its efficacy when patients are rechallenged after a treatment break, with a similar safety profile to that during the original administration[1,2].

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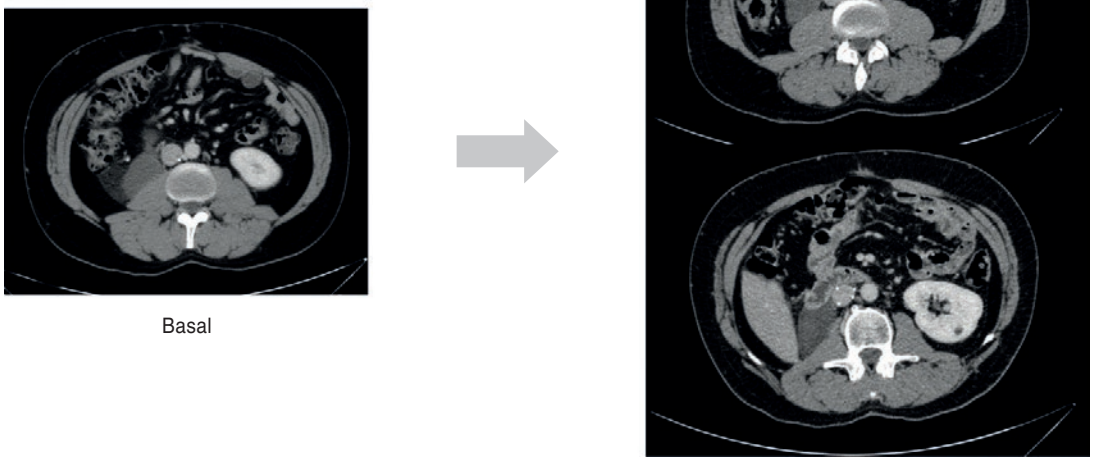

Figure 1. *Progression after three cycles with doxorubicin and ifosfamide.*

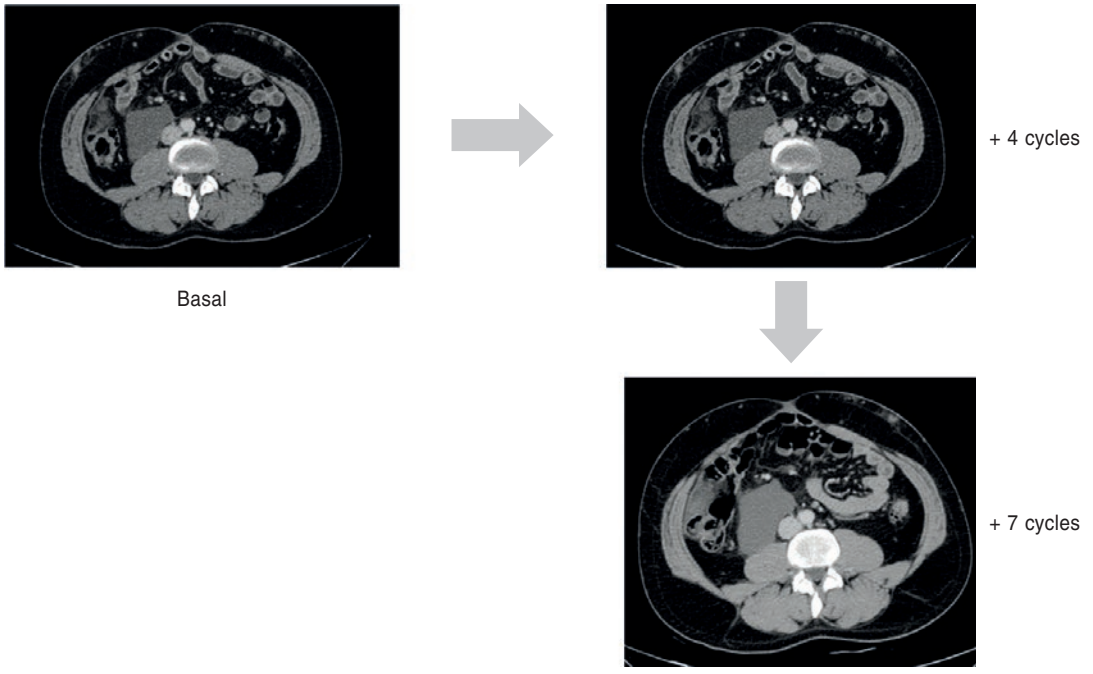

Figure 2. *Treatment with trabectedin.*

Conclusions

One of the main recommendations that have been established during the COVID-19 pandemic has been to limit the movement of patients to hospitals or outpatient centers as much as possible[3,4]. For this reason, efforts have been made to give priority to those therapies that do not require medical intervention, such as oral treatments[3,4]. However, this type of treatment is quite limited in

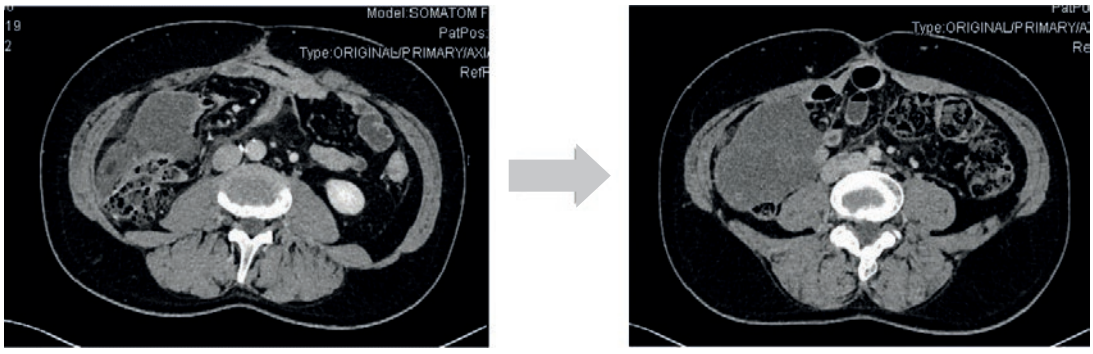

Figure 3. *Oral targeted therapy in clinical trial.*

dedifferentiated liposarcoma and does not always offer the best results. As this clinical case with trabectedin re-exposure illustrates, a return to intravenous treatment after oral therapy is feasible and offer to the patient the possibility of long-term disease stabilization with convenient tolerability.

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Prioritizing treatment selection: management of an advanced liposarcoma in the COVID-19 era

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Case presentation and initial considerations

In April 2013, a 34-year-old female patient was referred to Gustave Roussy Cancer Institute with good condition. Of note, she was a research scientist, working on cell lines and different cellular pathways, including liposarcoma models. She had been experiencing abdominal pain for 2-3 months, and a huge, heterogeneous intra-abdominopelvic mass developed from mesosigmoid/mesorectum was discovered. Based on the hypothetical radiological diagnosis, it could be a teratoma, liposarcoma, or paraganglioma. A computed tomography (CT) scan was performed in February 2013 and confirmed a huge mass of 20 cm × 10 cm (Fig. 1). Subsequently, core needle biopsy revealed a non-gastrointestinal stromal tumor soft-tissue sarcoma (STS), including spindle cells, fibrotic cells, and myxoid cells. Immunohistochemistry detected smooth muscle actin, desmin, caldesmon, MDM2, and p16. Fluorescence *in situ* hybridization (FISH) detected the expression of MDM2. It was concluded that the tumor was a grade 2 dedifferentiated liposarcoma with a leiomyosarcoma component.

Once the diagnosis was confirmed, there were several treatment alternatives that could be proposed for this patient, such as induction chemotherapy followed by surgery, surgery alone, radiation therapy followed by surgery, or inclusion in a clinical trial.

It is always important to take into consideration that the management of sarcoma patients in reference centers has been associated with a better prognosis. A large nationwide study performed in France showed that compliance with clinical practice guidelines and relapse-free survival of sarcoma patients are significantly better when the initial treatment is guided by a pre-therapeutic specialized multidisciplinary tumor board[1]. Moreover,

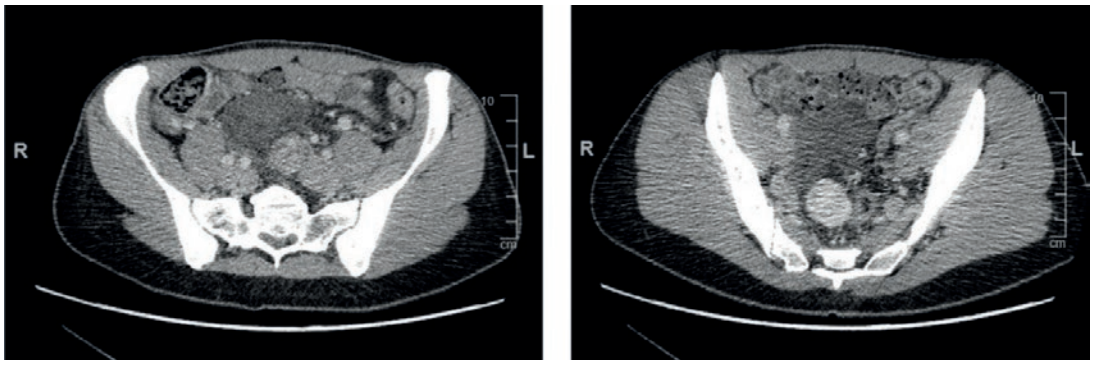

Figure 1. *Baseline computed tomography scan (February 2013).*

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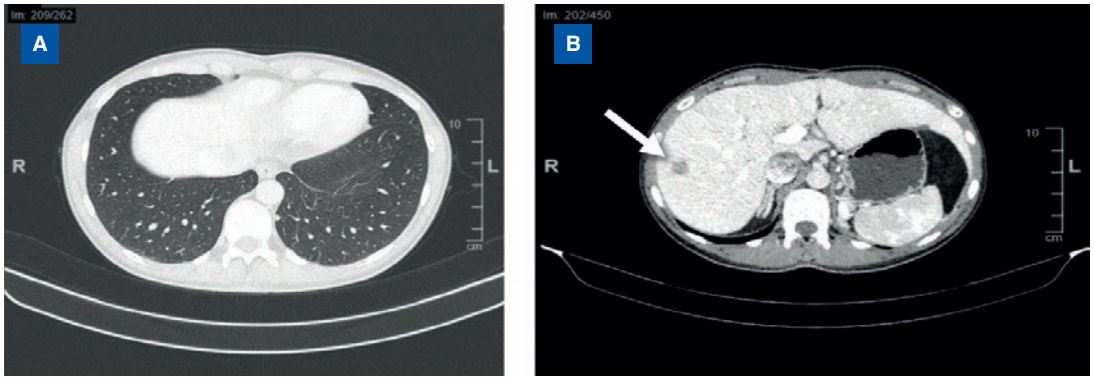

Figure 2. *Computed tomography scans showing nodules in the lungs* ***(A)*** *and mass in the liver (****B****, arrow) after three cycles of doxorubicin plus dacarbazine, three surgeries, and 12 sessions of radiotherapy (November 2019).*

subsequent analysis allowed to conclude that surgical treatment in referral centers with specialized multidisciplinary tumor boards reduces the risk of relapse and death of sarcoma patients[2]. Of course, if surgery is chosen as the next step for the patient, it is essential to ensure that it is performed in a sarcoma referral center.

Regarding radiation therapy, an important trial comparing radiation therapy followed by surgery versus surgery alone failed to demonstrate a benefit of pre-operative radiotherapy for retroperitoneal sarcoma[3]. However, in the exploratory analysis, it was found that pre-operative radiotherapy may benefit the liposarcoma subgroup[3].

Finally, if the decision is to use chemotherapy preoperatively, a local benefit may be gained facilitating surgery[4]. One study demonstrated that three cycles of neoadjuvant doxorubicin plus ifosfamide can be an option in high-risk individual patients[5]. For leiomyosarcoma, in which the activity of ifosfamide is far less convincing, the combination of doxorubicin plus dacarbazine has shown favorable activity in terms of both overall response rate and progression-free survival (PFS)[6].

Management of locoregional disease

Due to the leiomyosarcoma component and the patient's reluctance to experience alopecia, preoperative doxorubicin plus dacarbazine was proposed. The disease was stabilized after the administration of three treatment cycles. In September 2013, the patient underwent *en bloc* resection of the tumor plus left colectomy, left ovariectomy, resection of the left hypogastric artery, resection of the left iliac vein, and left nephrectomy. There was a poor histological response with 98% of residual identifiable tumor cells. Confirmation by immunohistochemistry showing overexpression of MDM2 and CDK4, confirmed by FISH. Final diagnosis was R1 resection (200 mm × 100 mm × 45 mm) for retroperitoneal dedifferentiated liposarcoma.

The patient relapsed in March 2015. The CT scan showed a well-differentiated liposarcoma component of 50 mm that was operated in October 2015, after several months of surveillance. One year later, there was a new sarcomatosis relapse with few nodules in the abdominal cavity, the patient was asymptomatic and followed up by surveillance. A third surgery was carried out in May 2018 with the resection of macroscopic lesions, including well and dedifferentiated liposarcoma. In May 2019, an 8 cm mass was detected in the left iliac psoas region and 12 sessions of radiotherapy (36 Gy) were administered, achieving a minor response. In November 2019, the patient developed small nodules in the lungs and liver (Fig. 2), suspicious for metastatic relapse.

Management of advanced/metastatic disease

In advanced disease, the decision-making is often complex, depending on diverse presentations and histologies, and should always be multidisciplinary[4].

The main systemic treatments available after the failure of doxorubicin-based chemotherapy (this patient had been previously treated with doxorubicin-dacarbazine combination) are trabectedin (for all sarcomas in Europe and L-sarcoma in the United States), pazopanib (for all sarcomas except liposarcoma), eribulin (for liposarcoma), and gemcitabine-based therapy (for leiomyosarcoma)[4]. Several factors must be taken into account for the

selection of treatment that is related both to the drugs (type of compound, safety profile, route of administration, available clinical trials) and to the patient (age, comorbidities, whishes, activities, lifestyle). The treatment plan should be shared with patients together with accurate and easy to interpret the quality of life data or any additional information they may need or request. Of note, it has been estimated that around 70% of the information given during a consultation is forgotten by patients.

Interestingly, the patient moved to Heidelberg for next-generation sequencing analysis. Results suggested the use of CDK4 and MDM2 inhibitors with level of evidence 1A and 1C, respectively, a Hedgehog inhibitor with level of evidence 3 and a poly (ADP-ribose) polymerase (PARP) inhibitor plus chemotherapy with level of evidence 4.

We proposed to the patient a "wait and see" attitude in November 2019, but in January 2020, there was an increase of lung nodules together with a rapid increase in liver mass (Fig. 3). However, the patient was in good condition. This kind of aggressive progression is not rare and has been previously described in advanced sarcoma patients receiving placebo: in three randomized studies comparing trabectedin or pazopanib versus best supportive care, the vast majority of patients in the non-active arm relapsed after the first evaluation[7-9]. Therefore, it is very important that patients are aware of the high risk of progression associated with a "wait and see" attitude in the advanced setting.

In February 2020, the COVID-19 outbreak started, and the French Sarcoma Group recommended the use of oral compounds for advanced STS to limit visits to the hospital during this period. However, recommendations maintained the indication of trabectedin or eribulin for liposarcoma patients[10]. The efficacy of trabectedin in advanced liposarcoma has been evaluated in both clinical trials and real-life studies. In a randomized phase III study comparing trabectedin versus dacarbazine, 154 liposarcoma patients were included in the study. A higher median PFS was observed with trabectedin (PFS 3 months vs. 1.5 months, $p < 0.009$), along with an increased proportion of patients benefiting from long-term treatment (40% of patients received ≥6 trabectedin cycles vs. 16% with dacarbazine), and a statistically superior rate of clinical benefit maintained for at least 18 weeks (trabectedin 28% vs. dacarbazine 15%; $p = 0.096$)[11]. In daily clinical practice, median overall survival (OS) values ranging from 15 to 20 months have been reported in several studies that included, in total, more than 300 pre-treated liposarcoma patients[12]. Furthermore, trabectedin has been shown to provide longer PFS and OS when administered in the second-line compared to more advanced lines[13]. Importantly, second-line treatment with trabectedin also provides the greatest potential for long-term benefit, with more than 50% of patients remaining on treatment for at least six cycles[14]. According to this evidence, STS guidelines recommend trabectedin as a global second-line treatment[4].

In January 2020, the patient started to receive trabectedin 1.5 mg/m^2 for 24 h by continuous infusion. On March 11, the patient attended the consultation to evaluate the first two cycles of treatment. There was a reduction in the lung nodes and a response in the liver mass (stable disease according to RECIST Criteria, and partial response according to CHOI criteria) (Fig. 4). On March 16, the specialist who attended the patient a few days before (the author) tested polymerase chain reaction (PCR)-positive for SARS-CoV-2, showing no symptoms, and subsequent serological tests showed very high levels of antibodies. Therefore, the patient underwent the PCR test with fortunately negative results.

In the following two cycles, the dose of trabectedin was reduced to 1.2 mg/m^2 due to alkaline phosphatase increase grade 1 and to the COVID-19 situation. After 5 cycles of trabectedin, a stabilization of the liver mass was observed according to RECIST criteria; however, a 50% reduction was detected by evaluation under CHOI criteria. It is important to note that the high antitumor activity of trabectedin observed in the early phase of tissue changes preceding tumor shrinkage has been described previously in myxoid liposarcoma tumors but rarely in dedifferentiated liposarcoma[4,15]. Regarding lung nodules, a 60% reduction by RECIST criteria was observed after 5 cycles of trabectedin. In view of the evolution of the patient and the available evidence, it was decided to continue with the administration of trabectedin. In fact, a randomized phase II trial assessing the clinical benefit of trabectedin continuation until progression versus interruption after six cycles in patients with advanced STS showed a significant advantage with trabectedin maintenance until disease progression (median PFS 7.2 vs. 4.0 months)[15].

In the event of future relapse, there are several treatment alternatives to consider, such as MDM2/CDK4 inhibitors, eribulin, salvage surgery, or locoregional non-surgical treatment on residual disease:

- A phase II study with a CDK4 Inhibitor has shown interesting tumor response with manageable toxicity in dedifferentiated liposarcoma[16]
- Eribulin represents an important option for advanced lines of liposarcoma since its approval in 2016 by the U.S. Food and Drug Administration and the European Medicines Agency. Approval was based on a randomized phase III study that showed an improvement in PFS and OS over dacarbazine in the subgroup of

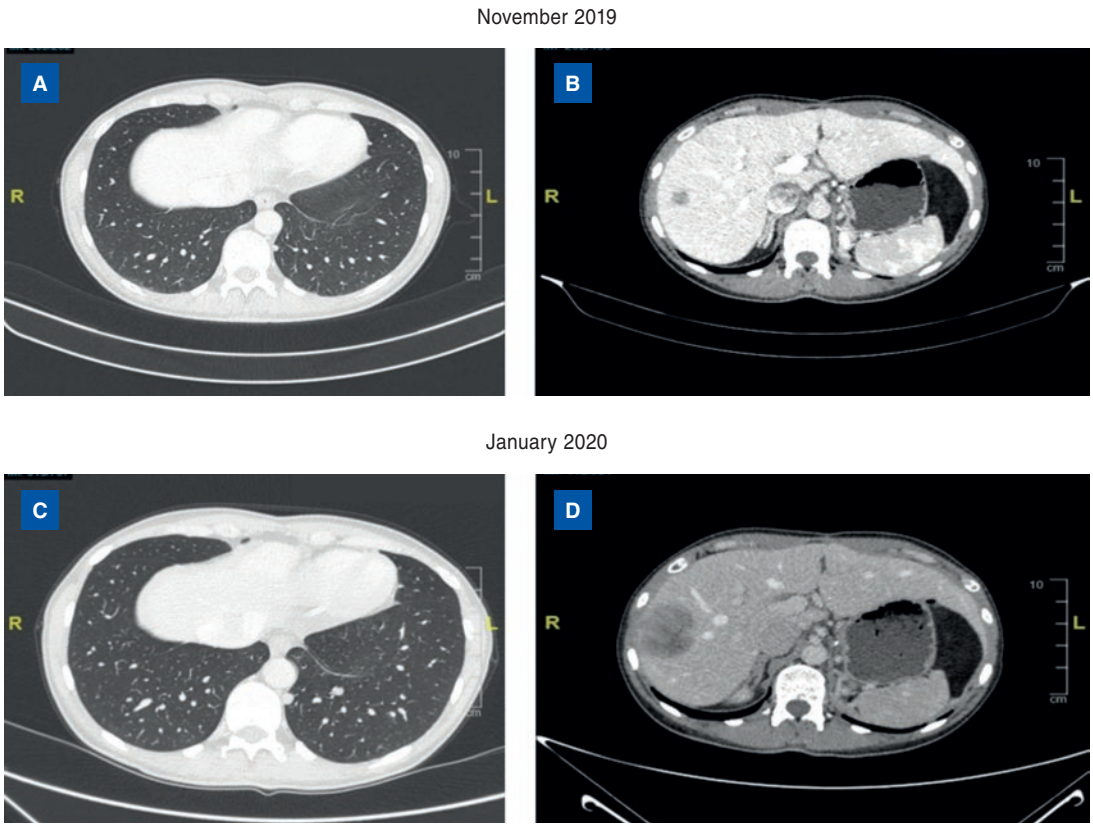

Figure 3. *"Watch and wait" from November 2019 to January 2020. Computed tomography scan of nodules in the lungs* ***(A, C)*** *and mass in the liver* ***(B, D)****.*

liposarcoma patients[17]. Preplanned OS analysis based on previous cancer therapies revealed greater survival benefit with eribulin compared to dacarbazine when administered as post-trabectedin therapy[18].

– A retrospective analysis performed by the French Sarcoma Group in 281 oligometastatic sarcoma patients (1-5 metastasis in lung, liver, and other) showed that the combination of systemic treatment plus loco-regional therapies provides longer OS than systemic treatment alone[19]. Accordingly, this therapeutic strategy was proposed to the patient, aiming to combine the ongoing systemic treatment and stereotactic radiotherapy in the liver.

Conclusions

Over a 7-year period, this young dedifferentiated liposarcoma patient underwent three consecutive surgeries and received radiotherapy and two different chemotherapy regimens, always maintaining a good condition. As illustrated by this case, sarcoma patients with consecutive oligometastatic recurrences and in good condition must be treated with a curative approach. Moreover, presenting these cases at tumor boards is absolutely mandatory; since surgery is not the only option and there are several alternatives, such as partial surgery of a nodule alongside stereotactic radiotherapy or cryoablation, that need to be multidisciplinary evaluated.

Despite the COVID-19 pandemic, this patient continued to receive trabectedin after failure of doxorubicin-based therapy without complications and achieving prolonged tumor control. When selecting treatments for our sarcoma patients, the potential benefit and tolerability that treatment can bring must continue to be considered, even in times of pandemic.

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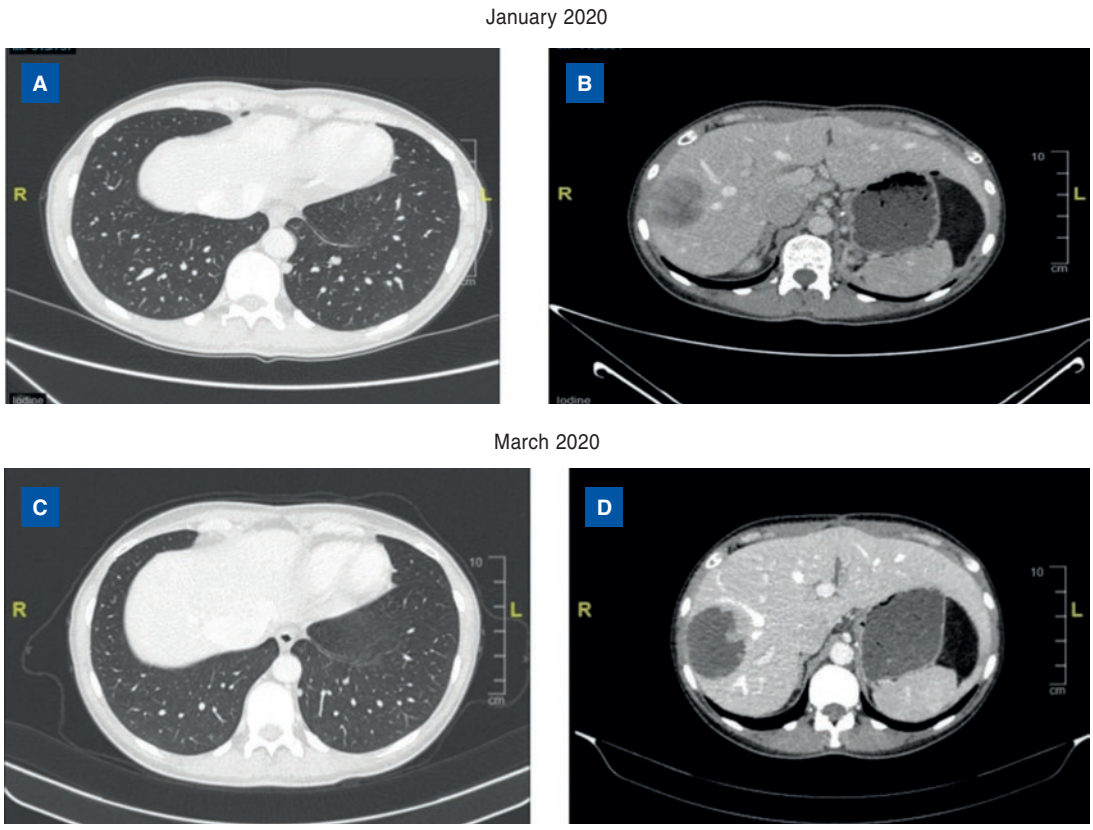

Figure 4. *Computed tomography scan of nodules in the lungs* ***(A, C)*** *and mass in the liver* ***(B, D)*** *at baseline (January 2020) and after two cycles with trabectedin (March 2020).*

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