ACCSCIENCE PUBLISHING

Tumor Discovery

CASE REPORT

Stereotactic radiotherapy with simultaneous integrated protection planning technique for synovial sarcoma with stomach abutment: A case report of a complete response

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Abstract

Here, we report the clinical case of a 44-year-old lady, affected by synovial sarcoma (SS) of the mediastinum which was treated in 2014, and relapsed in the upper abdomen in 2020. SS is a relatively radioresistant disease, radiotherapy (RT) is routinely reserved for the neoadjuvant/adjuvant or palliative context. In our scenario, stereotactic RT consisting in 45Gy in 6 fractions was proposed to manage the upper abdominal relapse. Exploiting simultaneous integrated protection, a deliberated reduction in the dose prescription in area of planning target volume overlapped with stomach was achieved, obtaining reasonable dosimetric goals. Acute toxicity in the patient was acceptable, and she did not experience late toxicity and was still free from disease, as noted in last follow-up, 15 months after treatment.

Keywords: Synovial sarcoma; Radiotherapy; Stereotactic body radiotherapy; Stereotactic radiotherapy (RT); Simultaneous integrated protection

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1. Introduction

Synovial sarcoma (SS) is a malignant mesenchymal neoplasm with partial epithelial differentiation that occurs predominantly in older children and young adults[1]. The designation SS has become historically established but is known to be incorrect as this tumor does not originate from intra-articular synovium, but from primitive mesenchymal cells[2,3]. SS has been classically described as occurring in the soft tissues of the extremities (80%), especially near large joints[4] but can develop in almost any anatomic site (20%)[5-10]. The most common non-extremity sites of primary disease include the trunk (8%) followed by retroperitoneum/abdomen (7%).

SS is generally considered a high-grade malignant sarcoma, with 5- and 10-year survival rates between 24% – 68% and 11% – 56%, respectively[11]. The natural history of primary SS is best predicted by a combination of patient, tumor, and treatment factors. The most important prognostic factors identified are age, primary tumor size, stage, grade, margin of resection, mitotic activity, bone or neurovascular invasion, histologic subtype, p53 overexpression, Ki67 proliferative index, and SYT-SSX fusion

type[11-15]. Some studies have stratified the patients into low-risk (patient age <25 years, tumor size <5 cm, and no histologic evidence of poorly differentiated tumor) and high-risk groups (age ≥25 years, tumor size ≥5 cm, and poorly differentiated tumor)[11]. Backbone therapy for SS is represented by radical surgery, with polychemotherapy with ifosfamide-adriamycin before or after surgical treatment. Classically, RT is used in neoadjuvant and adjuvant context, with the aim of maximizing local control and possibly increasing overall survival (OS)[16,17]. Prognosis in case of Rx/1 resection is worse, with a possible impact of RT to reduce the risk of local relapse[18-20].

Due to the relative radio-resistance and often large size of sarcoma lesions, conventionally fractionated palliative RT may be inadequate to provide effective palliation or durable tumor control. To eradicate microscopic disease, RT doses at range of 60 – 70 Gy are needed to be delivered[21]. The potential radioresistance of sarcomas was attributed to tumor cell capacity for sublethal damage repair, as implied by the initial large shoulder on their survival curve[22,23]. One of the radiobiological characteristics of sarcoma cells is their relatively low (0.5 – 5.4) α/β ratio, suggesting that such tumors may be more vulnerable to higher dose per fraction. This ratio, theoretically, may justify the use of larger-than-standard fractionation to achieve significant cell-kill by RT[24]. Stereotactic RT (SRT) technique enables delivery of high dose to the tumor in a relatively small number of fractions (generally from 1 to 8), potentially overcoming radioresistance of some histological cancer subtypes. In SRT, the therapeutic ratio is optimized through delivery of highly conformal dose distributions with steep dose fall-off with the aim of optimal absorbed dose in the target volume combined with minimal normal-tissue irradiation. Despite these considerations, the impact of RT in the context of unresectable or macroscopically positive resection is poorly understood and classically considered for palliative intent. The relevance of our case report is manifold. Our analysis applies cutting-edge technique together with innovative planning technique to maximize therapeutic index and to minimize side effects. Our considerations involve the analysis of the choices on the clinical and radiobiological point of view, contributing to enrich the evolving literature in the field.

2. Case presentation

In August 2014, a 36-year-old lady experienced worsening of dyspnea and upper back pain after childbirth. In November 2014, a thorax and abdomen computed tomography (CT) scan with and without contrast agent was performed on her, which showed a huge thoracic/posterior mediastinum right mass infiltrating lung, diaphragm and with contact to the hearth structures, as shown in Figure 1. The lady denied any previous significant medical illnesses and she had no family history of malignancy. Differential diagnosis was performed, ruling out various neoplastic entities, such as sarcomatoid carcinoma, leiomyosarcoma, spindle cell rhabdomyosarcoma, solitary fibrous tumor, and malignant peripheral nerve sheath tumor (MPNST).

Transthoracic core-needle biopsy was used to obtain tissue biopsy that described a neoplastic process (huge necrosis with limited diagnostic accuracy). Considering this data together with the imaging results, differential diagnosis was restricted to sarcomatoid carcinoma and small round blue cell tumors. In March 2015, the patient underwent surgical operation consisting in resection of mediastinal mass, inferior right lobectomy, and partial resection of right diaphragm with bovine patch reconstruction. No major perioperative complications occurred.

Results of pathologic examination were consistent with the diagnosis of poorly differentiated SS with invasion of costal muscle, visceral pleura, and mediastinum, in close proximity to the pericardial sierosa. Margin status was R1 with microscopic positivity in the right costal muscle. The diagnosis was supported by immunochemistry that showed positivity for Bcl2 and negativity for CD34, CD99, Ckpan S100, and SOX10. The molecular profile of disease showed translocation of locus SS18 (SYT-18q11.2). Figure 2A and B show histologic image and positive stain for Bcl2.

All nodes analyzed were negative for disease dissemination. The patient progressively recovered

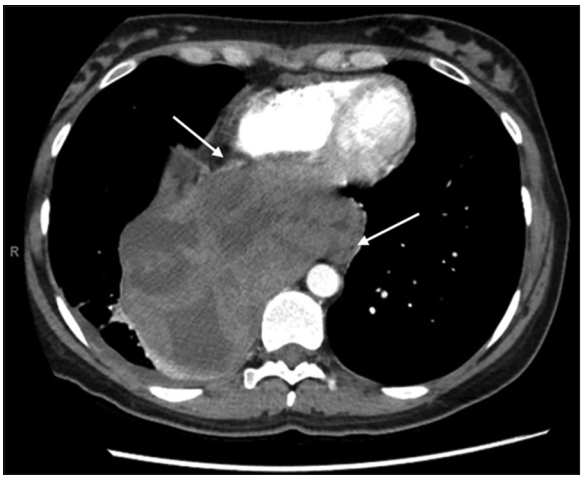

Figure 1. Thorax and abdomen computed tomography scan showing a huge thoracic/posterior mediastinum right mass infiltrating lung and diaphragm and with contact to the hearth and esophageal structures (white arrows).

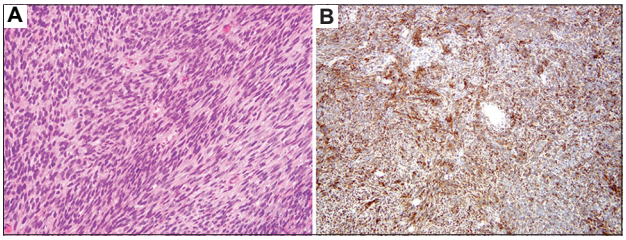

Figure 2. (A) Histologic image of synovial sarcoma and (B) immunohistochemistry for Bcl2.

without perioperative major complication (dyspnea G1, dyspepsia G1) and was discharged the 10th day after surgery.

After a whole-body CT scan performed in May 2015 that did not show evidence of disease, the patient underwent, from June 2015 to September 2015, four cycles of adjuvant chemotherapy with ifosfamide and adriamycin without major complications (alopecia and nausea, both G2). High dose normo-fractionated RT was then administered to tumor bed, with a schedule consisting of 1.8 Gy per fraction up to a total dose of 59.4 Gy in 33 fractions. Treatment was delivered with intensity modulated RT technique (IMRT) from October 27, 2015, to December 17, 2015. The treatment was well tolerated. At the end of treatment, she experienced mild radiation-induced esophagitis (G2); 3 months after the end of the treatment, the patient experienced mild radiation-induced pneumonitis (G2) that resolved in 6 months.

Then, the patient started on regular follow-up with CT scan every 4 months in the first 2 years and every 6 months thereafter, without evidence of disease until November 2020. An ultrasound scan was performed when the patient felt abdominal discomfort, which showed a mass close to stomach and celiac axis with more than 4 cm in length.

A complete staging consisting of whole-body contrast enhanced CT scan was performed. The study described a huge abdominal-retroperitoneal disease relapse, with the maximum diameter of 8 cm, characterized by an infiltrating behavior, in contact with hepatic parenchyma, lesser gastric curvature and body of stomach, clearly encasing celiac axis, superior mesenteric artery, left gastric, and common hepatic arteries (Figures 3 and 4).

After a third level multi-disciplinary team discussion, on February 5, 2021, the patient started chemotherapy with high-dose ifosfamide q21. Contrast-enhanced CT scan performed after two cycles described an increase in the maximum volume of the mass, reaching a maximum diameter of more than 8 cm, with a more necrotic aspect, suggesting a partial response to chemotherapy. The patient later underwent one more cycle of high-dose ifosfamide at the end of March 2021.

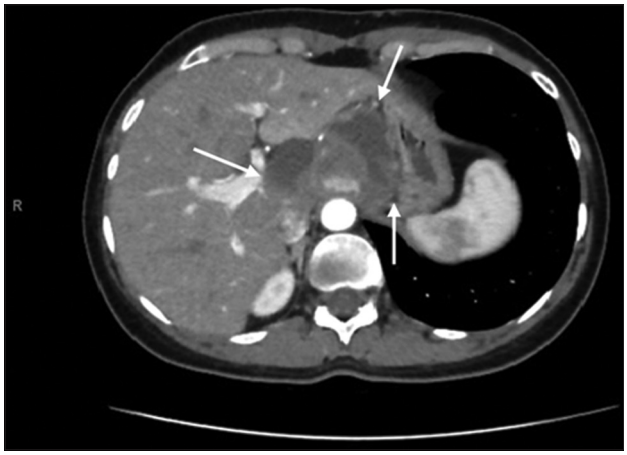

Figure 3. Computed tomography scan showing the abdominal-retroperitoneal disease relapse, with the maximum diameter of 8 cm, in contact with hepatic parenchyma, lesser gastric curvature and body of stomach, and encasing common hepatic arteries (white arrows).

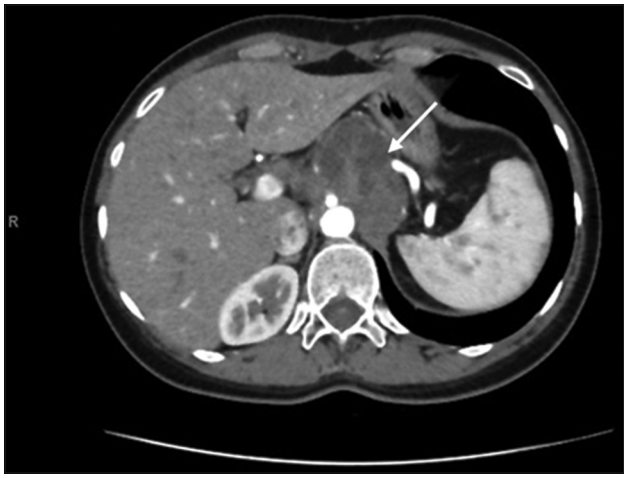

Figure 4. Computed tomography scan showing the abdominal-retroperitoneal disease relapse in an axial plane passing through the celiax axis, encasing celiac axis, superior mesenteric, left gastric, common hepatic arteries, and proximal splenic artery (white arrow).

On April 15, a new multi-disciplinary team discussion evaluated the therapeutic options, pre-operative RT or surgery followed by post-operative RT. The discussant decided to perform another CT scan and to re-evaluate the two options on the basis of the results, which showed stable disease.

On May 25, a laparotomic resection/debulking of the mass was performed, intraoperative evaluation showed infiltration of the left gastric artery that was dissected at the origin; moreover, during the mobilization of the mass, a rupture occurred, with loss of necrotic material in the upper abdomen. The left adrenal gland, the pancreatic gland, the diaphragm, and the aortic plane were in close contact with the mass, and a careful dissection was

performed. Celiac axis and common hepatic artery were clearly infiltrated by tumor and a surgical clip was left for post-operative guidance purposes. Pathologic examination confirmed an SS relapse, with a vital cellularity of 40%, and also confirmed the specimen translocation of locus SS18 (SYT-18q11.2). All four lymph nodes removed resulted negative for tumor involvement. Moreover, pathologic report confirmed the presence of invasive tumor at surgical margin (extensively R2 resection). The patient recovered without major complication and was discharged in good clinical conditions; acute toxicity was represented by limitation of solid oral intake determined by G2 dyspepsia in the following 2 months.

Taking into account the macroscopic persistence of disease, at the end of June 2021, the patient was evaluated by a radiation oncologist that proposed a normofractionated treatment consisting of 59.4 Gy in 33 fractions versus 60 Gy in 30 fractions on the sites of persistent disease. A second approach was performed at our center, with the propose to study the feasibility of an hypofractionated schedule, optimally stereotactic body RT in 5 – 6 fractions. Our choice for hypofractionation was aimed at maximum tumor control probability, given the well-known intrinsic radioresistance of the histologic subtype to standard normofractionated regimens.

A new diagnostic CT scan was performed prior RT, showing a persistent disease along the celiac axis and hepatic artery, and with tissue contact to stomach and the left margin of the liver (Figure 5).

Considering all these aspects, a planning CT scan was acquired in supine position with arms above the head, compressing Belt (CIVCO®) and a Monarch (CIVCO®) was exploited for patient immobilization purpose. First, a 4D was acquired thanks to a respiratory belt (Philips®); second, a triphasic contrast-enhanced CT study was performed. Both the studies used a slice thickness of 1.5 mm.

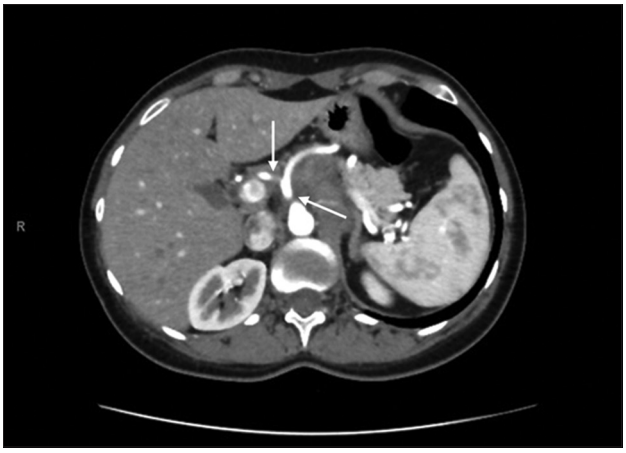

Figure 5. Computed tomography scan performed before radiotherapy showing the persistent disease along the celiac axis and hepatic artery (white arrows).

Planning was performed on average CT to take into account tumor and organs at risk (OARs) motion. In details, on Velocity (Varian®) treatment planning system (TPS), each of the ten respiratory phases was exploited to define the position of the tumor, the stomach, duodenum, jejunum, and colon.

As a result, ten regions of interest were created for the stomach, duodenum, and the critical area of jejunum proximal to target. Moreover, internal margin (IM) representing the maximum position of the stomach, duodenum, and jejunum was created. For stomach and jejunum near to the target, a planning respect volume (PRV) was crated with an isotropic expansion of 2 mm.

For target definition, exploiting all the information derived from diagnostic CT and contrast-enhanced planning CT, after co-registration to each respiratory phase, a gross tumor volume (GTV) was defined on each respiratory phase. The sum of GTV of each phase formed the internal target volume (ITV) that virtually represents the area, in which GTV moves during the respiratory cycle. A margin accounting for set-up errors and unpredictable organ motion was added to obtain the planning target volume (PTV_Full). Thereafter, the area of overlap between PRV_stomach, PRV_duodenum, PRV_jejunum, and PTV was created by intersection and was called PTV_simultaneous integrated protection (PTV_SIP). Inside the PTV, the area which is at least 7 mm from PRV_Stomach, PRV_duodenum, and PRV_jejunum was called PTV_SIB dose.

The dosimetric objectives and results for targets and critical structures are reported in Tables 1 and 2.

Concerning technique, 6 Mev photons beams delivered by a volumetric-modulated arc therapy (V-MAT) with 5-mm jaws (Versa HD, Elekta®) was used; for RT plan Pinnacle (Philips®), TPS was used.

2.1. Acute and late toxicity and assessment of tumor response

On the 5th day of RT, the patient was admitted to our department for nausea and dyspepsia. She was treated with supportive therapy with the administration of fluids (1000 mL of saline e.v. in 24 h) for 2 days, antagonist of 5-HT3 receptors (ondansetron 8 mg e.v. q24 h) and protonic pump inhibitors (PPI; 40 mg e.v. q24 h). RT continued without interruption during supportive therapy and the patient was discharged from hospital 5 days after the admission with the indication to maintain PPI

for 6 months at 40 mg q24 h. Treatment was ended as planned on July 20, and the full planned schedule was delivered. After 30 days from the end of RT, the patient was visited for monitoring acute toxicity. She was in good clinical condition (ECOG PS1) and complained of only G1 dyspepsia, whereas her body weight remained stable. After 3 months, restaging CT scan described partial response (RECIST 1.1 criteria), and she was found negative for disease relapse during clinical visit.

The last patient follow-up was in January 2023. She was in excellent performance status (PS0), clinical examination, and whole-body CT scan showed the absence of disease (RECIST 1.1 criteria) 15 months after treatment (Figure 6).

Table 1. Dosimetric objectives (in black) and results (in blue) concerning PTV

Target	Dosimetric objectives
PTV_FULL	D80% > 40 Gy
	36 Gy
PTV_SIP	D70% > 32 Gy
	27 Gy
PTV_SIB	D95% > 42.75 Gy
	45 Gy

PTV_FULL: Planning target volume obtained by adding a margin to internal target volume accounting for set-up errors and unpredictable organ motion; PTV_SIP: PTV simultaneous integrated protection, obtained by intersection between PTV and planning respect volumes of stomach, duodenum, and jejunum; PTV_SIB: The area inside the PTV distant at least 7 mm from planning respect volumes of stomach, duodenum, and jejunum

Table 2. Dose constraints (in black) and dosimetric results (in blue) for organs at risk

OAR	D 0,1cc (Gy)	D 2cc (Gy)	D 20cc (Gy)
IM_DUODENUM	≤38	≤32	≤24
	34	31.8	15
IM_STOMACH	≤38	≤32	≤24
	38	32	26
IM_JEJUNUM	≤38	≤32	≤24
	38	28	18
PRV IM_DUODENUM/IM_ STOMACH/IM_JEJUNUM/IM_COLON	≤40	≤36	≤28
	met	met	met
OAR	**Dmax (Gy)**	**D 0.2cc (Gy)**	**D 10cc (Gy)**
Spinal chord	<30	<22.5	-
	met	met	
Great vessels	<55	-	<47
	met		met
OAR	**CONSTRAINT (Gy)**		
Vascular axis of kidney D66%		<23	
		Met	
Kidney at least 200cc <15 Gy (rV15):		<15	
		Met	
Liver at least 700cc <21 Gy (rV21):		≤21	
		Met	

OAR: Organ at risk; IM: Internal margin; PRV: Planning respect volume; met means that the dose constraint was respected

3. Discussion

3.1. Radiobiological and dosimetric considerations

The intrinsic radioresistant phenotype, the site of tumor spread, and the possible consequences of a locoregional progression suggested us to attempt the maximization of tumor control probability through extreme hypofractionation. Another keypoint was represented by the relatively paucity of other effective therapeutic options in case of disease progression. Unfortunately, the upper abdomen represents a paradigm for planning complexities, given the presence of frequent tumor abutment near critical OARs, tumor motion, and OARs motion, and despite cutting-edge SRT techniques, the intrinsic radiosensitivity of most of the visceral OARs in the upper abdomen limits the delivery of therapeutic doses.

Taken these aspects together, we decided to perform a feasibility study exploiting a relatively new concept of RT planning. SIP was defined by Brunner *et al.* as a deliberated and calculated reduction in the dose prescription in area of PTV overlapped with critical OARs[25]. First published experiences seem to show a fair toxicity profile and a promising local control result for radioresistant histological tumor types[26-30].

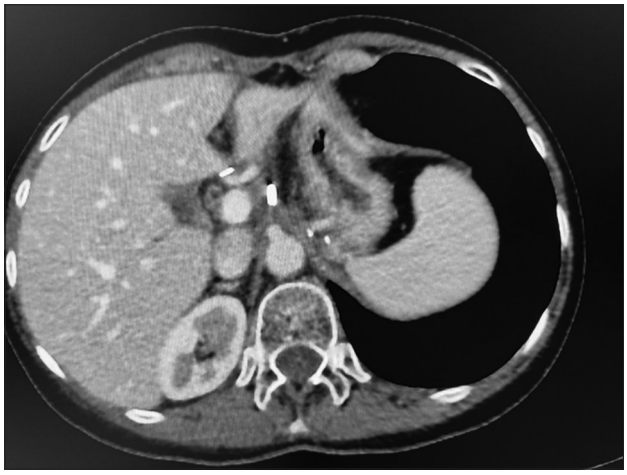

Figure 6. The last follow-up computed tomography at 15 months from treatment showing complete regression of the mass and the free plane of the lesser gastric curvature.

One of the advantages in SIP is represented by the formalization of dosimetric goals in overlap area, with the possibility of quantifying and comparing the amounts of dose trade-off. On the other hand, one of the most critical aspects of SIP planning is represented by the uncertainty in tumor control in area of dose reduction.

This scenario planning was particularly challenging due to the high volume of overlap between PTV and internal margin (IM) of the stomach (33 mL). Such a high-volume overlap was explained by the diffuse tumor abutment to the stomach and also by the high respiratory motion of the stomach itself, despite the high-quality abdominal compression used and the indication of fasting for solid and liquids.

3.2. Clinical considerations

Management of relapsed SS in a single site generally aims, whenever possible, to maximize radical probability through chemotherapy and surgery. RT in such a context classically presents an ancillary role. Thanks to the new advances previously described, SRT is now an emerging treatment in the management of metastatic sarcomas, due to a relatively higher response rate compared to normofractionated and moderately hypofractionated RT. Early report showed that response rate is related to smaller lesion size (<5 cm) and low grade (G1). Limitations of the available studies include the small sample size, the heterogeneity concerning histological subtypes, and the target sites that limit the applicability of study conclusions to all the pathologic entities in soft tissue sarcomas[31]. In fact, no studies have considered the role of SRT in the context of SS, and especially in critical sites such as upper abdomen.

The treatment outcome of complete response achieved in our case is clinically significant because the mass at first presented poor prognostic factors (size >5 cm, poorly differentiated, and critical site). In this case study, SIP planning proved to be safe and, despite the relatively short follow-up time, effective in achieving local tumor control. The results are particularly important given the huge area of tumor-OAR overlap and the consequent low minimum doses delivered to some area of PTV.

4. Conclusions

In this case report, a SS relapsed in a critical abdominal site was managed with SRT. SIP planning ensured safety concerning acute and late toxicity and achieved complete tumor control, despite the huge trade-off between target coverage and the achievement of dose constraints objectives. This case underlines the importance of better clarification of the major determinants of tumor control in RT planning. More data are needed to confirm SIP as a safe and effective planning modality. Moreover, given the surprising result achieved, there is also an important need to better understand the biological mechanisms impacting tumor control in the context of SIP planning.

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Conflict of interest

The authors declare no conflicts of interest.

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Ethics approval and consent to participate

Not Applicable.

Consent for publication

The patient signed an informed consent to use anonymized data for publication.

Availability of data

Data are fully available under explicit request to the corresponding author.

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