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Limbs and trunk soft tissue sarcoma systematic local and remote monitoring by MRI and thoraco-abdomino-pelvic scanner: A single-centre retrospective study

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ABSTRACT

Introduction: Soft tissue sarcomas (STS) are rare malignant tumors that require management by an expert center. Monitoring modalities are not consensual. The objective of our study is to report systematic radiological monitoring data obtained by local MRI and by thoracic-abdominal-pelvic computed tomography (TAP CT).

Material and methods: 113 consecutive patients managed at "Centre Georges François Leclerc, Dijon", between 2008 and 2016, for an initially localized STS were included. Patient follow-up consisted of a local MRI and a TAP CT. Follow-up exams schedule was initially every 4 months during 2 years, followed by every 6 months during 3 years and finally every year during 5 years.

Results: Median follow-up time was 37.2 months [min = 2.4 – max = 111.6]. After 5 years of surveillance, local recurrence (LR) rate was 8.8% and diagnosed by imaging in 60% of cases. No deep LR was clinically found. Median LR diagnosis time was 23.9 months [min = 2.0 – max = 52.4]. 50% of patients locally treated for their LR were alive without recurrence. Metastatic recurrence (MR) rate was 31%. 42.8% had extra-pulmonary involvement and 17.1% had exclusive extrathoracic metastases. The median time to diagnosis of MR was 17.4 months [min = 2.7- max = 77.2]. High-grade tumors relapsed more (20.4%) and earlier (all before the 5th year) than low grade.

Conclusion: Local MRI seems particularly suitable for monitoring deep tumors. In addition, the systematic monitoring by TAP CT highlighted a limited number of cases of exclusive extrathoracic metastases. The schedule of local and remote monitoring should primarily be adjusted to tumor grade.

Introduction

Soft tissue sarcomas (STS) are rare malignant tumors with an estimated incidence averaging 4–5/100 000/year in Europe [1] [–] [4].

Initial clinical and radiologic characteristics can be falsely reassuring and/or not specific [1,5,6] and lead to an inadequate initial care [4,5,7,8]. Current recommendations endorse diagnosis and therapeutic care in expert sarcoma's centers (NetSarc in France)

Abbreviations: CGFL, Centre Georges François Leclerc; LR, local recurrence; MR, metastatic recurrence; MPNST, malignant peripheral nerve sheath tumor; STIR, short tau inversion recovery; STS, soft tissue sarcomas; TAP CT, thoraco-abdomino-pelvic computed tomography; TSE, turbo spin echo; US, ultrasound.

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upon initial clinical or radiological suspicion [8–14]. Diagnosis must be confirmed by a core needle biopsy controlled by a radiological device (US scan or CT scan) and the histological analysis should be systematically read (or reread) in a RePPS expert center [12,15] (French sarcoma pathological reference network). Wide surgical excision with negative margins (R0, *in sano*) is the standard treatment of STS [1,13,14,16], followed by radiotherapy (excepted for low grade, superficial and less than 5 cm lesions) to reduce the local recurrence (LR) risk [13,14,17–22]. Optionally, a neoadjuvant treatment (chemotherapy and/or radiotherapy) can be discussed in multidisciplinary team meeting [13]. Nevertheless, Heudel et al. have shown that only 36% of STS patient management, between 2005 et 2007, was in total conformity with French clinical practice recommendations [7]. The quality of initial disease management impacts global prognosis [9,23,24] and local disease control [23,25,26], which is a risk factor for metastatic recurrence (MR) [27] and death [21]. Neither the surgical re-resection [25,28–30], nor the adjuvant radiotherapy [29,31] can replace an optimal initial surgery.

Delay of LR and MR essentially depend on the grade and quality of initial surgery [13,14].

Lung is the most common organ of MR [14]. Few data are available to propose an optimal follow-up [14,32,33]. French national standards only recommend a clinical exam and a chest CT-scan [13], no available study addressed the relevance of STS follow-up by magnetic resonance imaging (MRI) and by thoracic-abdominal-pelvic computed tomography (TAP CT).

The primary objective of our study is to report data from STS systematic radiological monitoring by local MRI and TAP CT. The secondary objectives are to evaluate survival without LR and MR, overall survival and to propose a schedule and modalities of follow-up in agreement with imaging data and recurrence risk factors.

Materials and methods

Inclusion criteria

113 patients managed for initially localized trunk or limb STS at CGFL-Dijon, sarcoma's reference center of the NetSarc network, and operated between 01/01/2008 and 21/12/2016, were retrospectively recruited.

Non-inclusion criteria

Patients diagnosed with breast sarcomas and malignant phyllodes tumors, desmoids tumors, Kaposi sarcomas and sarcomas which initially required amputation (no local follow-up can be performed), were not included.

Surgical margins

Surgical margins were defined according to the following criteria:

- R0: *in sano* resection;
- R1: microscopic residuals or enucleation (excision without capsular effraction but without margin at tumor periphery);
- R2: macroscopic residual disease, capsular effraction or fragmented excision.

Follow-up

Clinical follow-up included a local and a general examination.

Radiological follow-up included a local MRI and a TAP CT with iodinated contrast every 4 months during 2 years, every 6 months during the following 3 years and finally every year during 5 years, in agreement with recent international recommendations [14].

MRI was performed in CGFL (MRI Siemens 1,5 T). At least 2 orthogonal incidences (including one axial plan) centered on the operative zone were performed: T1 TSE, T2 TSE (optional), T2 fat saturation (STIR) and T1 fat saturation (FAT-SAT) and gadolinium injection as contrast.

Statistical analysis

Qualitative variables were described using percentage and compared with Chi2 or Fisher tests. Quantitative variables were described using median with range, Survival rates with their 95% confidence intervals (95% CI) were obtained using the Kaplan Meier method. The median follow up was determined using the reverse Kaplan Meier method. Factors independently associated with metastatic relapse free survival and overall survival were identify in univariate and multivariate Cox's models. Patients alive without metastases and patients lost of follow up were censored at the date of last follow up for metastatic relapse free survival analyzes. Patients alive and patients lost of follow up were censored at the date of last follow up. All variables with a p value less than 0.20 in univariate analysis were entered into the multivariate model. Final models include all variables with a p value less than 0.10 in multivariate analyses. Hazard ratios (HR) were presented with their 95% CI. Correlations between variables eligible for the multivariate models were tested. Time to local free recurrence was analyzed using univariate Cox model. Patients without local free recurrence and patients who died were censored at the date of last follow up. Due to the low number of events (n = 10), multivariate analyzes were not performed. all tests were 2-sided. The significance level was set at 5%. All analyses were performed using SAS 9.4.

Results

Epidemiological data and tumor characteristics

65 men (57.5%) and 48 women (42.5%) were included. Median age at diagnostic was 63 years [min = 20 - max = 91]. 73 (64.6%) tumors were located in the lower limb, 25 (22.1%) in the trunk and 15 (13.3%) in the upper limb. Tumor size, histological type, grade and depth were presented in Table 1.

Initial surgery and patient follow-up

Initial surgery was performed at CGFL for 82 patients (72.6%) and outside a sarcoma's reference center for 31 patients (27.4%). Of patients initially operated at CGFL, 56 (68.3%) were R0, 26 (31.7%) were R1 and none was R2. Of patients initially operated outside a sarcoma reference center, none was R0, 20 (66.7%) were R1, 10 (33.3%) were R2 and the surgical margin was unknown for 1 patient.

Concerning R1 patients, 14 (30.4%) underwent a re-resection (including 6 (42.9%) with a tumoral residue) and 3 (6.5%) were re-operated for a relapse. All R2 patients were re-operated. For the 27 patients (23.9%) re-operated at CGFL, 21 (77.8%) were R0, 6 (22.2%) were R1 and none was R2.

The median follow-up was 37.2 months [min = 2.4–max = 111.6]. 43 (38.1%) patients relapsed: 10 (8.8%) presented a LR; 35 (31%) presented a MR and 2 (1.8%) presented both LR and MR.

Overall survival rate at 5 years was 71.0%; 95%CI [59.2%–80.0%].

5 years survival rate [95%CI] for LR patient group was 87.1%; 95% CI [76.3%–93.2%] and 65.9% [54.9 %–74.7%] for MR patient group. Survival's median were not reached.

Table 1
Initial tumor characteristics.

Tumoral size (mm)	
Median [min - max]	93.5 [7.0–410.0]
Unknown	1
Histological type	
Undifferentiated sarcoma	30 (26.6%)
Myxofibrosarcoma	21 (18.6%)
Well differentiated liposarcoma	19 (16.8%)
Dedifferentiated liposarcoma	10 (8.9%)
Myxoid liposarcoma	9 (8.0%)
Darier and Ferand dermatofibrosarcoma	6 (5.3%)
Others:	18 (15.9%)
LEIOMYOSARCOMA	4
SYNOVIALOSARCOMA	4
FIBROMYXOID SARCOMA	2
ALVEOLAR RHABDOMYOSARCOMA	1
PLEOMORPHIC RHABDOMYOSARCOMA	1
EWING LIKE SARCOMA	1
SOFT TISSUE OSTEOBLASTIC OSTEOSARCOMA	1
MALIGNANT MYOEPITHELIOMA	1
SOLITARY FIBROUS TUMOR	1
OSSIFYING FIBROMYXOID TUMOR	1
MALIGNANT PERIPHERAL NERVE SHEATH TUMOR (MPNST)	1
Grade	
1	29 (28.4%)
2	30 (29.4%)
3	43 (42.2%)
Unknown	11
Deep tumor	
No	33 (29.2%)
Yes	80 (70.8%)

Local recurrence (LR)

Over the 10 LR (8.8%), 6 (60%) have been identified by imaging (4 (40%) by MRI and 2 (20%) by TAP CT) and 4 (40%) by clinical examination (but 2 (50%) did not have a MRI follow-up because of a contra-indication).

The median delay between initial surgery and LR highlighting was 23.9 months [min = 2.0 − max = 52.4]. This delay was shorter when LR was identified by imaging (median: 20.1 months [min = 5.3-max = 35.7]) than by clinical examination (median: 28.6 months [min = 2.0-max = 52.4]).

Clinically identified LR were exclusively superficial tumors. Median size was 28 mm [min = 12.0-max = 62.0]. Imaging identified LR were almost exclusively deep tumors, except a small superficial recurrence (2 nodules of 8 mm and 4 mm). Median size was 40.5 mm [min = 8.0-max = 40.0].

12.9% of patients operated outside an expert center relapsed as compared to 7.3% of patients initially operated at CGFL.

The higher the grade, the earlier the LR was observed, as shown in Fig. 1. No LR arose after the fifth year of follow-up. Median tumor size was larger (155 mm [min = 14- max = 350]) than in our global population (93.5 mm [min = 7- max = 410]). Histological types are shown in Table 2.

7 patients had no adjuvant radiotherapy: 2 lipoma-like liposarcomas treated with enucleation, 1 low-grade superficial myxofibrosarcoma, 1 large myxofribrosarcoma with an initial fragmented R2 resection with early recurrence after resection, 1 myxofibrosarcoma with delayed healing not allowing radiotherapy, 1 poorly differentiated grade 3 sarcoma with a rapid metastatic progression prior to local recurrence, and a poorly differentiated pleiomorphous sarcoma with initial R1 resection. The other 2 other patients had adjuvant radiotherapy and the median delay was 40 days after surgery.

5 patients (50%) were treated and lived without relapse after a median follow-up of 45 months after relapse [min = 7.0-max = 81.0]. 2 patients (20%) had relapses, including 1 only followed-up for a liposarcoma lipoma-like and 1 who was still treated for a unique bone metastases.

3 patients (30%) died after local recurrence: 1 presented a synchronous MR, 2 presented a MR shortly after LR (including 1 with a surgical margin R2 with a voluminous tumor residue and 1 with lymph node initially invaded).

In univariate analysis, administration of neoadjuvante chemotherapy (HR = 3.18; 95%CI[1.23–18.60]; p = 0.0238), R1-R2 surgical margins, (HR = 8.50; 95%CI[1.08–67.17]; p = 0.0424) were associated with poorer time to local progression. On the contrary

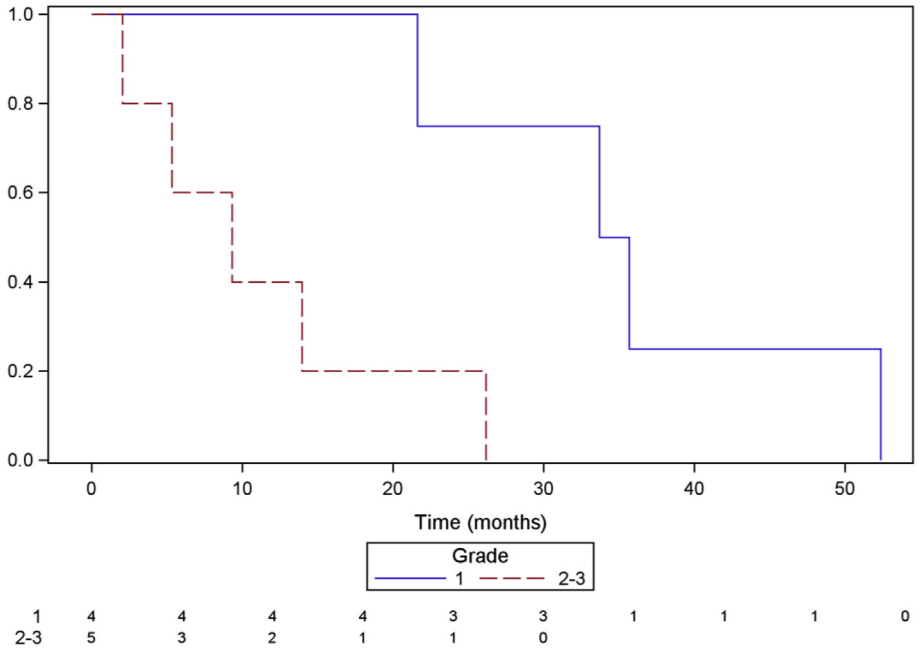

Fig. 1. Time to local recurrence according to tumor grade.

Table 2
Tumor Histological types of local and metastatic recurrences.

	Histological types	N (%)
Local recurrencesrowhead	Myxofribrosarcoma	3 (14.3%)
	Undifferentiated sarcoma	2 (6.7%)
	Well-differentiated liposarcoma	2 (10.5%)
	Dedifferentiated liposarcoma	1 (10.0%)
	Alveolar rhabdomyosarcoma	1 (100%)
	Fibromyxoid sarcoma	1 (50.0%)
Metastatic recurrences	Undifferentiated sarcoma	15 (50.0%)
	Myxofibrosarcoma	7 (33.3%)
	Dedifferentiated liposarcoma	6 (60.0%)
	Myxoid liposarcoma	3 (33.3%)
	Others:	4 (22.2%)
	- LEIOMYOSARCOMA	1 (25.0%)
	- PLEOMORPHIC HABDOMYOSARCOMA	1 (100%)
	- SYNOVIALOSARCOMA	1 (25.0%)
	- MALIGNANT PERIPHERAL NERVE SHEATH TUMOR (MPNST)	1 (100%)

adjuvant radiotherapy administration tend to be associated with better time to progression (HR = 0.26; 95%CI[0.07–1.03]; p = 0.0545).

Metastatic recurrence (MR)

35 patients (31%) presented metastases. All MR (100%) have been identified by TAP CT.

Main histological types (Table 2) were: 15 undifferentiated sarcomas (50% of all undifferentiated sarcomas), 7 myxofibrosarcomas (33% of all fibromyxosarcomas), 6 dedifferentiated liposarcomas (60% of all dedifferentiated liposarcomas) and 3 myxoid liposarcomas (33% of all myxoid liposarcomas).

Undifferentiated sarcomas and dedifferentiated liposarcomas were statistically more at risk of MR than others (HR = 3.183; 95%CI [1.656–6.120]; p = 0.0005) in univariate analysis.

No metastases were observed in patients with a well differentiated liposarcoma nor a Darier Ferrand dermatofibrosarcoma.

15 patients (42.8%) had pulmonary extra-parenchymal metastases. 6 patients (20%) had exclusively extra-thoracic metastases (2 myxoid liposarcomas, 1 undifferentiated sarcoma, 1 malignant peripheral nerve tumor (MPNST), 1 dedifferentiated liposarcoma and 1 myxofibrosarcoma). Metastatic locations are listed in Table 3.

Extra-pulmonary involvement was found in 100% of myxoid liposarcoma metastases (p = 0.0695), 50% of dedifferentiated liposarcoma metastases (p = 1.000) and 40% of undifferentiated sarcoma metastases (p = 0.7674) (Table 4).

Independent correlates of metastatic relapse or death were: having 65 years old or more (HR = 2.13; 95%CI[1.02–4.44]; p = 0.0441), a tumor size bigger than 9 cm (HR = 2.98; 95%CI [1.42–6.22]; p = 0.0037) and high grade tumor (2–3 versus 1) (HR = 9.16; 95%CI[2.06–40.71]; p = 0.0036). In addition, undifferentiated sarcoma and dedifferentiated sarcoma histological types had a tendency to be associated to metastatic relapse free survival (HR = 1.90 IC95%[0.95–3.80], p = 0.00710).

Median delay between initial surgery and the first MR was 17.4 months [min = 2.7–max = 77.2]. MR was more frequent during the first two years. Recurrence rate during the first two years was 68.6% versus 31.4% in the 5 following years. (Fig. 2).

Time to MR varied with initial tumor grade: high grade tumors relapsed more frequently (recurrence rate 20.4%) and earlier (all before the fifth year after initial surgery), whereas low-grade tumors relapsed less frequently (recurrence rate 9.7%) and later, until 6.4 years after initial surgery.

9 patients (25.7%) were treated by a curative therapy (surgery or radiotherapy). 1 patient had previous chemotherapy and another had adjuvant chemotherapy. 6 (66.6%) were alive at the end of our study, after a median follow-up of 19 months after recurrence [9.0–85.0], 4 (44.4%) were recurrence-free and 2 (22.2%) had MR. The median survival time of patients treated for their MR by a curative therapy was greater than the median survival time of all patients who had recurrences (19 months [9.0–85.0] versus 14 months [0.3–34.1]).

24 patients (21.2%) died. Median time between first relapse and death was 14 months [0.3–34.1]. Age equal or superior to 65 year-old was the main risk factor (HR = 3.83; 95%CI[1.373–10.665]; p = 0.0103) in multivariate analysis. High grade (2–3 versus 1) (HR = 5.33; 95%CI[1.248–22.780]; p = 0.0239) and undifferentiated sarcoma and dedifferentiated sarcoma histological types (HR = 3.14, 95%CI[1.393–7.094]; p = 0.0058) were also significant risks factors in univariate analysis. Both factors tended to persist in multivariate analysis, but not significantly.

Table 3
Metastatic recurrences location.

METASTATIC RECURRENCES	N = 35
Pulmonary parenchymatous only	**20 (57.2%)**
Extra-pulmonary parenchymatous	15 (42.8%)
- Bone	2 (5.7%)
- Peritoneum	2 (5.7%)
-Soft tissue	1 (2.9%)
-Liver	1 (2.9%)
-Pleura	1 (2.9%)
-Pleura and liver	1 (2.9%)
-Lung and bone	2 (5.7%)
-Lung and liver	1 (2.9%)
-Lung, peritoneum and liver	1 (2.9%)
-Lung and intra-cardiac	1 (2.9%)
-Lung and pleura	1 (2.9%)
-Lung and cerebral	1 (2.9%)

Discussion

STS of limbs and trunk LR was frequent in the 90's and short-term survival remained poor [34]. It became rarer in our study (8.8%) as in literature (6.5% according to Cheney and al. [35], 18% according to Rothermundt et al. [32], 21% according to Posch and al. between 1998 and 2015 [27], and 26% according to Zhao and al [21]). Initial surgery with margins other than R0 was the main LR risk factor found in both our study and available literature [24,26,36]. Indeed, according to Levy et al., LR rate at 10 years was: 44% after R2 resection, 21% after R1 resection and 8% after R0 resection [22].

Imaging revealed 60% of LR in our study. LR were detected

Table 4
Metastases location according to tumor histological type.

Histological type	Extra-pulmonary metastases (+/− pulmonary) N = 15	Pulmonary metastases only N = 20	p-value (Chi-2 or Fisher)
Undifferentiated sarcoma	6 (40.0%)	9 (60.0%)	0.7674
Myxofibrosarcoma	2 (28.7%)	5 (71.4%)	0.6722
Myxoid liposarcoma	**3 (100.0%)**	**0 (0.0%)**	0.0695
Dedifferentiated liposarcoma	3 (50.0%)	3 (50.0%)	1.000
Others	1 (25.0%)	3 (75.0%)	0.6190

Bold indicates the main result of the table.

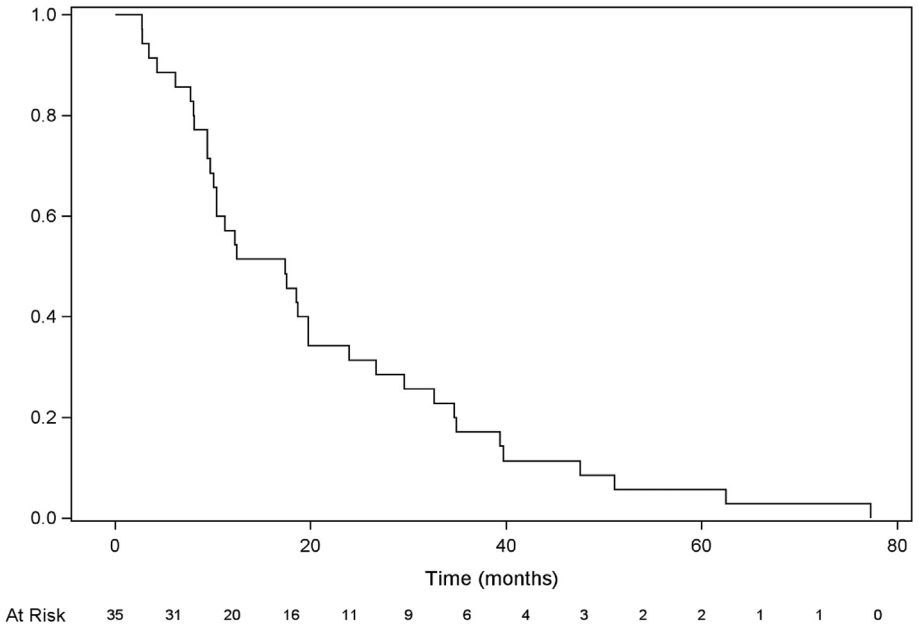

Fig. 2. Time to metastatic recurrence.

earlier than clinically diagnosed recurrences. Deep LR were never clinically found, all clinical identified LR's were superficial, therefore MRI seems to play a significant role in LR's early detection, in particular for deep LR. Its usefulness in the context of superficial STS is less clear.

All LR occurred before the fifth year of follow-up and before the third year for high grade tumors, suggesting that MRI follow-up could be spaced out of 3 years for high grade tumors.

LR rate was less important when initial surgery was performed in a sarcoma's expert center (7.3%) as compared to outside (12.9%), confirming the importance of initial management in a sarcoma's expert center.

In our study, 2 liposarcomas lipoma-like well differentiated locally relapsed after enucleation surgery (surgical margin R1), suggesting that identical surgical management (surgical margin R0 one-piece) should be performed even if these tumors have a better prognosis when compared to other sarcomas.

31% of patients presented a MR, consistent with literature's data (32% according to Rothermundt et al. [32]).

The main metastatic site in our study was the pulmonary parenchyma, data consistent with available literature. Standard follow-up consists of thoracic CT or even chest x-ray [14]. Systematic TAP CT monitoring in our study showed that 17% of metastatic patients had exclusively extra-thoracic metastases.

In our study, all myxoid liposarcoma's metastases were extra-pulmonary, as previously described in literature [37]. A follow-up using body-MRI is proposed by some teams to increase bone and soft tissue MR's detection of this histological type. Indeed, Seo et al. show a sensitivity and a specificity respectively of 80% and 97% for soft tissue metastases and 99% for bone metastases [38]. Stevenson et al. showed that for 38 metastases found by MRI, 29 were in the acquisition field of TAP CT but only 5 out of 8 soft tissue metastases were visible and none of 21 bone metastases were detected [39]. In Noble et al. study, 8 patients developed bone metastases, all were visible by MRI but 2 out of 4 were not visible in bone scintigraphy and 6 out of 7 were not visible by CT-scan [40]. TAP CT or whole-body MRI are justified for mixoid liposarcomas follow-up. For other histological forms, our data do not demonstrate a major interest of TAP CT.

Risk factors found in our study are similar to the ones previously identified in the literature such as undifferenciated histological type, high grade, big tumor size and age [27,34,41].

MR occurred frequently during the first two years of follow-up, independently tumor grade. First metastases appeared 2.7 months after initial surgery. All high grade MR appeared before the fifth year of follow-up whereas low grade MR appeared until 6.5 years after initial surgery. These results suggest that an extended follow-up is required for lower grade tumours as compared to high grade tumours.

Of the 31 metastatic patients, 9 patients could be submitted to a curative treatment. The median survival time of curatively treated MR patients was greater than the median survival time of all patients presenting a recurrence. This result suggests a potential benefit of early metastases detection on survival, allowing a curative treatment of some patients. Thoracic CT is much more sensitive than chest x-ray to early detection of metastases. The detection of

pulmonary metastases requires extension assessment, with at least one TAP CT to ensure the absence of extra-pulmonary metastases. A curative strategy, as proposed to 9 patients of our study, can be considered in selected patients: metastatic pauci, delay of occurrence greater than one year, slowly progressive disease after possible first chemotherapy according to time of occurrence of recurrence, grade and histological type.

Our study has several limits such as its retrospective and monocentric nature and the reduced statistic power due to population small size and to the reduced number of LR's and MR's.

Our data suggest that neoadjuvant chemotherapy could be a LR risk factor, this result is probably linked to the small size of the population and to confusion factors not included in our data collection (rapid tumor progression, skin inflammation, risk of incomplete initial excision due to contact with a noble structure) which are well-known LR risk factors.

Conclusion

Our study shows the interest of imaging in local and remote monitoring of limb and trunk STS. Imaging allows a faster detection of recurrences that can undergo a curative treatment.

Local MRI monitoring seems particularly appropriate for deep STS. End of monitoring after 5 years can be envisaged, in particular for high-grade tumors that usually recur earlier (before 3 years in our study).

For remote monitoring, our study reports 17% of exclusive extrathoracic metastases in metastatic patients. The small size of the population in our study do not allow, apart from the mixoid liposarcomas, to propose in systematic monitoring by TAP CT. Nevertheless, a complementary abdominopelvic CT is necessary if pulmonary metastases are detected, given the frequency of associated extrathoracic metastases.

In high-grade tumors, all metastases occurred before 5 years. End of monitoring at 5 years can be envisaged.

However, given the small population size in our study, these results need to be confirmed by a national multicenter study within NETSARC network centers. On the other hand, these medical exams represent a significant public health cost for which the effect on patient survival remains to be proven. Only a comparative cost-effectiveness study (clinical monitoring and thoracic CT versus clinical monitoring, TAP CT and local MRI) would answer this question.

Ethical approval

Ethical approval was not required.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

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