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The added value of chest imaging after neoadjuvant radiotherapy for soft tissue sarcoma of the extremities and trunk wall: A retrospective cohort study

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ABSTRACT

Introduction: There is no clear evidence regarding the benefit of restaging for distant metastases after neoadjuvant radiotherapy (RTX) in patients with soft tissue sarcoma (STS) of the extremities and trunk wall. This study aimed to determine how often restaging of the chest identified metastatic disease that altered management in these patients.

Methods: We performed a single-centre retrospective study from 2010 to 2020. All patients with non-metastatic STS of the extremities and trunk wall who were treated with neoadjuvant RTX and received a staging and restaging chest CT scan or X-ray for distant metastasis were included. The outcome of interest was change in treatment strategy due to restaging after neoadjuvant RTX.

Results: Within the 144 patients who were staged and treated with neoadjuvant RTX, a restaging chest CT or X-ray was performed in 134 patients (93%). A change in treatment strategy due to new findings at restaging after RTX was observed in 26 out of 134 patients (19%). In 24 patients the scheduled resection of the primary STS was cancelled at restaging (24/134, 18%), given the findings at restaging. The other two patients did receive the intended local resection, but either with palliative intent, or as a part of a previously unplanned multimodality treatment.

Conclusion: In approximately one in five patients restaging results in a change in treatment strategy. This underlines the added value of routine restaging for distant metastases with chest CT or X-ray after neoadjuvant RTX in patients with STS.

1. Introduction

Approximately 30% of the patients with primary high-grade soft tissue sarcoma (STS) develop metastatic disease within 5 years after diagnosis or primary treatment [1–3]. In addition, 7–14% of the STS patients have distant metastases at presentation [4,5]. STS mainly metastasize to the lungs [6–8]. Median time to pulmonary metastasis is around 11 months [8,9]. Extrapulmonary metastases seem to occur later in time (median 22 months) [8]. Metastatic STS is usually treated in a palliative setting. Especially patients with a metastatic-free interval <1 year are treated palliatively as they have a poor prognosis [7,10–14]. In this metastatic setting, the right balance between life expectancy and quality of life is considered to be very important.

Therefore, patients with primary sarcoma are usually staged with a Computed Tomography (CT) scan of the chest and/or abdomen to rule out distant metastases [10,15]. If no metastases are found, patients are usually treated surgically with curative intent [10,15]. (Neo)adjuvant radiotherapy (RTX) is typically indicated after multidisciplinary discussion in high-grade lesions considering risk factors for local recurrence, anticipated surgical margins,

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tumour size, grade and histological subtype [10,15,16]. Historically RTX was mainly delivered postoperatively. However, over the last few years a shift has occurred from adjuvant to neoadjuvant RTX [17]. The oncological outcomes between neoadjuvant and adjuvant RTX are comparable but neoadjuvant RTX results in less long-term morbidity due to fibrosis, oedema and, joint stiffness [16,18–20]. The higher short-term wound complications of neoadjuvant RTX are often well managed in a specialized sarcoma centre or prevented with the use of reconstructive surgery [16,18–20]. Due to the shift to neoadjuvant RTX, surgery is usually delayed with 12–15 weeks. Therefore, there has been an increasing interest in the need to accurately assess disease progression after neoadjuvant therapy.

Taking into consideration that the median time to pulmonary metastasis is 11 months, that patients with a metastatic-free interval of <1 year have a worse prognosis, and that patients with metastatic disease are treated differently, restaging after neoadjuvant RTX could influence the planned treatment strategy if formerly non-detectable distant metastasis appear in the time between staging and definitive surgery. However, to our best knowledge, restaging for distant disease is not standard practice in multiple sarcoma centres across Europe, and none of the current international clinical guidelines (European Society for Medical Oncology [ESMO] and National Comprehensive Cancer Network [NCCN]) have incorporated restaging for distant disease in their recommendations [10,15]. Furthermore, there are no studies in STS that support the added value of restaging chest CT or X-ray. Therefore, the aim of this study was to assess the value of distant restaging with chest CT or X-ray after neoadjuvant RTX by determining how often restaging identified metastatic disease that altered treatment management in patients with localized STS of the extremity and trunk wall.

2. Methods

2.1. Study design

Patients with localized STS of the extremities or trunk from a tertiary referral centre in The Netherlands (Erasmus MC Cancer Institute) were included in this retrospective single centre cohort study. This study was approved by the local Ethical Committee. Patients were identified from the centre's pathology database and from the radiotherapy department. The inclusion period was from January 2010 until December 2020.

The primary outcome of interest was change in treatment strategy after restaging chest CT or chest X-ray for distant metastases.

2.2. Study population

Adults (≥18 years) with histologically proven STS of the extremity or trunk wall treated with neoadjuvant RTX with curative intent who received a staging CT or X-ray of the chest at presentation and after RTX were included in this study. Patients were excluded if they had synchronous distant metastases, received neoadjuvant CTX or ILP, had a Kaposi's sarcoma or alveolar rhabdomyosarcoma, or if they had a concurrent primary malignancy at staging.

2.3. Study procedure

All patients received the standard work-up for soft tissue sarcoma that included an MRI scan of the primary site for local staging, and a CT scan (or X-ray) of the chest (and abdomen) for distant staging. All diagnoses were assessed by a specialized sarcoma pathologist according to the WHO classification [21]. All newly diagnosed patients were discussed during the multidisciplinary tumour board (MDT) meetings consisting of dedicated surgical oncologists, medical oncologists, radiation oncologists, radiologists and pathologists.

All patients within our centre were treated in accordance with the ESMO guidelines [10]. RTX was preferably delivered in the preoperative setting in our centre within the study period. This treatment generally consisted of long-course RTX with a total dose of 50 Gy delivered in 25 fractions of 2 Gy in 5 weeks. RTX was followed by surgery after ±10 weeks.

2.4. Data collection

To investigate the value of restaging after neoadjuvant RTX, patients and tumour characteristics, staging and restaging imaging findings before and after neoadjuvant RTX, the planned treatment before RTX and the ultimate treatment after restaging, and the intention of the treatment (curative/palliative) were collected. A detailed description of the definitions used in this study for each variable can be found in appendix A1.

2.5. Staging and restaging

Staging chest CT or X-ray was defined as a chest CT, chest-abdomen CT, or chest X-ray made before neoadjuvant RTX at either the referring hospital or at our institution. Restaging chest CT or X-ray was defined as a chest CT, chest-abdomen CT, or chest X-ray made in the period between the last week of RTX administration and surgery, or start of any other treatment, or within 3 months after RTX if no additional treatment was offered.

All staging and restaging images were assessed by dedicated radiologists and discussed in sarcoma MDTs. The reports from the radiologists and the MDTs were retrospectively evaluated. The findings at staging and restaging were classified as not suspected, indeterminate or metastases. A detailed description for the classification of lesions found at staging and restaging can be found in appendix A2.

2.6. Statistical analysis

Descriptive statistics were used for the analyses of the data. Patient demographics, baseline characteristics and all outcomes were described with numbers and percentages for categorical variables and means with standard deviations (SD) or medians with interquartile ranges (IQR) for continuous variables. All analyses were performed in the statistical program R, version 4.0.5 [22].

3. Results

After removal of the duplicates from the pathology and radiotherapy database, 1061 patients with STS of the trunk wall and extremity were eligible. A total of 927 patients did not meet the selection criteria, resulting in 134 patients who were included in this study. Ten patients were excluded in this analysis since they did not receive a restaging chest CT/X-ray after neoadjuvant RTX. Fig. 1 depicts the flow diagram of patient selection. Median time between the first staging scan and start of RTX was 4.9 weeks (IQR 3.8-6.78). The median time between start of RTX and restaging was 9.4 weeks (IQR 8.9-10.4) (Fig. 2).

3.1. Imaging techniques

Primary staging for distant disease with a CT scan was performed in 131/134 patients (98%). The other 3 patients were staged with a chest X-ray (2%, 3/134). One hundred thirty patients were

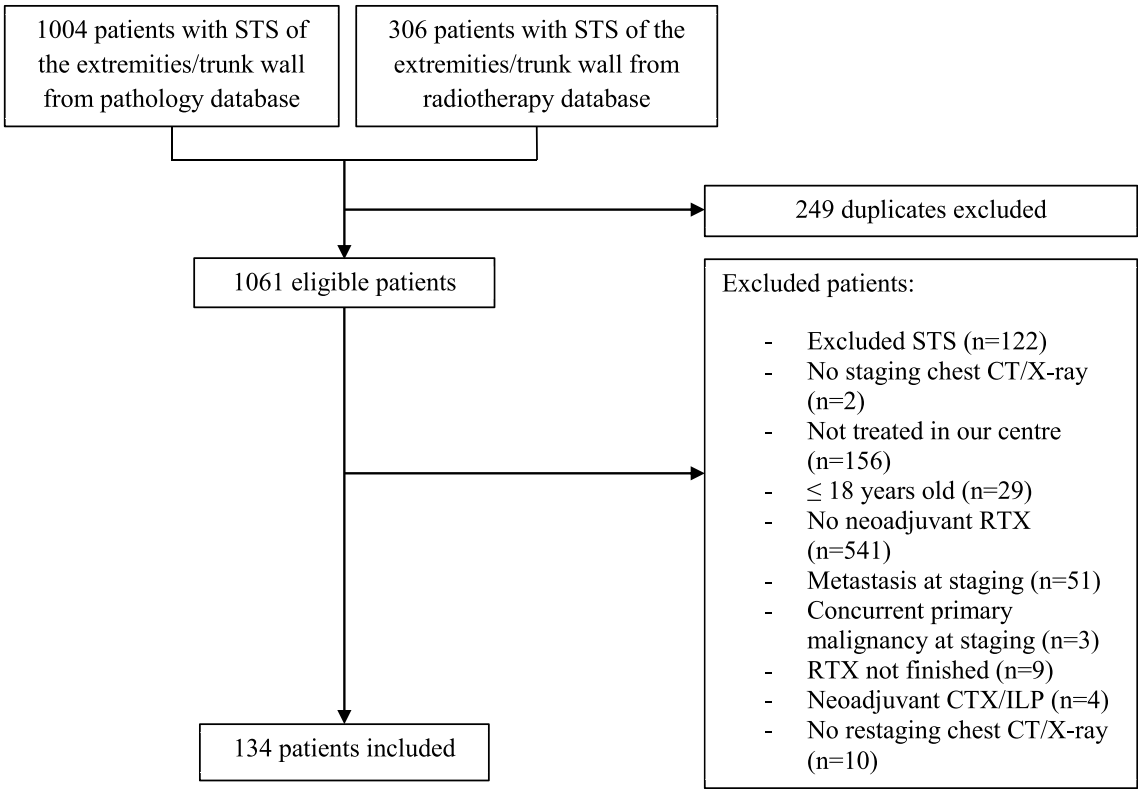

Fig. 1. Study flow diagram.

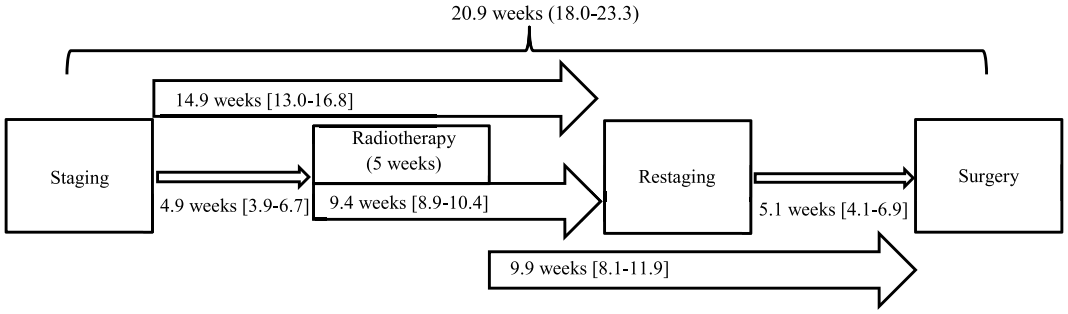

Fig. 2. *Timeline.* Median time (IQR).

restaged with a CT scan (130/134, 97%). Four patients were restaged with a chest X-ray (3%, 4/134). The median age of the study population was 66 [IQR 52–74]. Baseline characteristics are depicted in Table 1.

3.2. Imaging findings

Of the 134 patients who were restaged after neoadjuvant RTX, 91 patients did not have a suspected lesion at restaging (91/134, 68%). Twenty-four out of 134 patients (24/134, 18%) had metastases at restaging and 19 out of 134 patients (19/134, 14%) had an indeterminate lesion for which additional diagnostic tests or surveillance was needed (Fig. 3).

3.2.1. Restaging findings after unsuspected staging CT/X-ray

Of the 96 patients with an unsuspected staging scan, 20 patients had newly emerging lesions on the restaging scan after neoadjuvant RTX (20/96, 21%). Fifteen patients had lesions suspected for metastases (15/96, 16%) and 5 patients had indeterminate lesions at restaging (5/96, 5%) (Fig. 3). One patient with a newly emerging indeterminate lesion in the liver at restaging turned out to have a cholangiocarcinoma. Only two patients with a lesion suspected for metastasis received a biopsy after restaging which confirmed distant metastases (1 lung metastasis, 1 retroperitoneal metastasis both found on CT-thorax/abdomen).

3.2.2. Restaging findings after indeterminate lesions at staging CT/X-ray

Of the 38 patients with indeterminate lesions at staging, 9 patients had metastases at restaging (9/38, 24%) (none were confirmed by biopsy) (Fig. 3). Fourteen patients still had an indeterminate lesion at restaging, which means that the pre-existing lesion did not decrease in number and in size and did not show an obvious progression in number and or in size, or that there were no newly developed nodules suspected for metastases. One patient with an indeterminate lesion in the pancreas at restaging turned

Table 1
Baseline characteristics.

	Overall (N = 134)
Sex	
Female	53 (39.6%)
Male	81 (60.4%)
Age (years)	
Median [IQR]	66 [52–74]
ASA physical status	
ASA 1	25 (18.7%)
ASA 2	54 (40.3%)
ASA 3	31 (23.1%)
ASA 4	3 (2.2%)
Missing	21 (15.7%)
Presentation	
Primary disease	124 (92.5%)
Recurrent disease	10 (7.5%)
Staging modality of chest	
X-ray	3 (2.2%)
Chest CT	78 (58.2%)
Chest/abdomen CT	53 (39.6%)
Restaging modality of chest	
X-ray	4 (3.0%)
Chest CT	94 (70.1%)
Chest/abdomen CT	36 (26.9%)
Size (mm)	
Median [IQR]	89 [61–130]
Missing	9 (6.7%)
Histological subtype	
LMS	12 (9.0%)
MPNST	4 (3.0%)
MFS	28 (20.9%)
SS	3 (2.2%)
Other	7 (5.2%)
LPS	31 (23.1%)
UPS and NOS	49 (36.6%)
Grade	
Low grade	3 (2.2%)
High grade	96 (71.6%)
Missing	35 (26.1%)
Depth	
Superficial	8 (6.0%)
Deep	126 (94.0%)

IQR: interquartile range, CT: computed tomography, mm: millimetres, LMS: leiomyosarcoma, MPNST: malignant peripheral nerve sheath tumour, MFS: myxofibrosarcoma, SS: synovial sarcoma, LPS: liposarcoma, UPS: undifferentiated pleomorphic sarcoma, NOS: soft tissue sarcoma – not otherwise specified.

out to have an adenocarcinoma in the head of the pancreas.

3.3. Change in strategy

Of the 134 patients who received a restaging chest CT scan or X-ray, 26 patients had a change in treatment strategy due to findings at restaging (19%). In 24 patients resection of the primary STS was not indicated due to the findings at restaging (24/134, 18%).

3.3.1. Treatment of patients with metastatic lesions at restaging

Twenty-four patients were newly diagnosed with metastatic disease at restaging with CT scan or X-ray (24/134, 18%). Due to the metastatic findings, the treatment strategy was adjusted for 23 out of 24 patients (96%). The treatment intention changed for 22 out of 24 patients (92%). The majority of patients received best supportive care (9/24, 38%), or palliative chemotherapy (9/24, 38%) after the metastatic findings. Three out of 24 patients received multimodality treatment with chemotherapy and surgery for the primary tumour and/or distant metastases. One patient received multimodality treatment with curative intent. Two patients received multimodality treatment because of pain caused by the primary tumour or the distant metastases (Table 2).

One patient had two newly developed nodules of <5 mm at restaging which were classified in de radiology report as suspected for metastases. This is in accordance with the criteria in Fig. 1 of appendix A2. Nevertheless, this patient received local surgery with curative intent. After surgery, follow-up CT scans revealed progression of the lung lesions to ≥10 mm and newly developed lung nodules.

3.3.2. Treatment of patients with indeterminate lesions at restaging

Of the 19 patients with indeterminate lesions at restaging, 17 patients had no change in treatment strategy. In two patients the indeterminate lesion turned out to be another primary malignancy after additional diagnostics (cholangiocarcinoma and adenocarcinoma in the head of the pancreas, respectively). Both patients did not receive any treatment for the STS after the finding (Table 2).

4. Discussion

We evaluated the value of restaging with chest imaging for distant metastases after neoadjuvant RTX in patients with localized soft tissue sarcoma of the extremities and trunk wall. The study showed a change in treatment strategy in 19% of the patients due to new findings at restaging after neoadjuvant RTX. In 18% of the patients the intended local resection of the primary tumour was not indicated after findings at restaging.

Local staging of STS has important implications for the choice of optimal treatment. Local control could be improved with (neo) adjuvant RTX in patients with large, high-grade, deep-seated tumours if a compartmental resection is not indicated [10,16]. Distant staging has important implications on treatment options and intention of treatment. International clinical guidelines recommend screening for distant metastases by staging patients with contrast-enhanced chest, abdomen, and pelvis CT [10,15]. However,

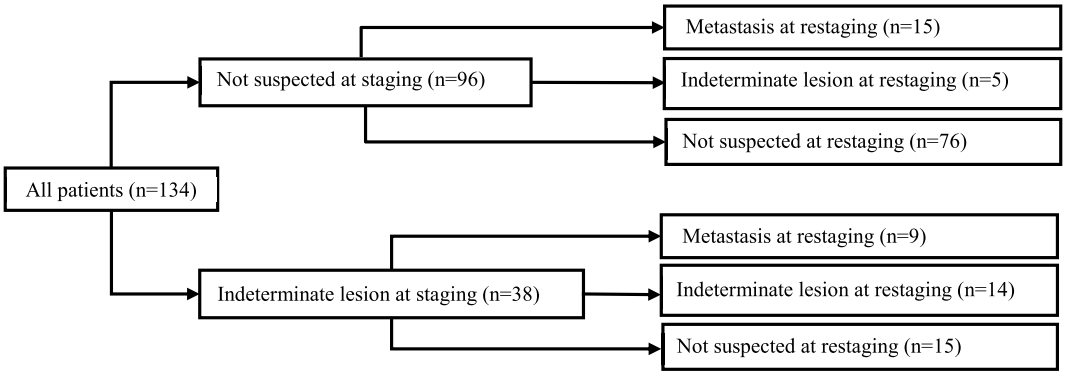

Fig. 3. Findings on staging and restaging chest CT/X-ray.

Table 2
Diagnostic findings of restaging after radiotherapy and change in treatment strategy.

Staging	Restaging	N	Treatment	Curative intention	Change in treatment strategy	N (%)
Not Suspected	Not Suspected	75				
			Curative surgery	Yes	No	75 (100%)
Not Suspected	Indeterminate	5				
			Curative surgery	Yes	No	4 (80%)
			No treatment[a]	No	Yes	1 (20%)
Not Suspected	Metastases	15				
			No treatment	No	Yes	6 (40%)
			Local surgery	Yes	No	1 (7%)
			Palliative chemotherapy	No	Yes	5 (33%)
			Palliative chemotherapy + metastasectomy lymph nodes inguinal	No	Yes	1 (7%)
			Chemotherapy + local surgery + metastasectomy solidary retroperitoneal metastasis	Yes	Yes	1 (7%)
			Palliative intent − treatment unknown	No	Yes	1 (7%)
Indeterminate	Not Suspected	15				
			Curative surgery	Yes	No	15 (100%)
Indeterminate	Indeterminate	14				
			No treatment[b]	No	Yes	1 (7%)
			Curative surgery	Yes	No	13 (93%)
Indeterminate	Metastases	9				
			No treatment	No	Yes	3 (33%)
			Palliative chemotherapy + local surgery	No	Yes	1 (11%)
			Palliative chemotherapy	No	Yes	4 (44%)
			Palliative intent − treatment unknown	No	Yes	1 (11%)

[a] Not due to STS, but due to cholangiocarcinoma found at restaging.
[b] Not due to STS, but due to pancreatic cancer found at restaging.

restaging for distant metastases after neoadjuvant RTX is not incorporated in these guidelines [10,15].

The local control, distant metastasis rates and progression-free survival between neoadjuvant and adjuvant RTX are comparable, indicating that delaying surgery because of neoadjuvant RTX does not influence oncological outcomes. Therefore, the standard of care of STS has evolved in most centres from surgical resection followed by RTX to RTX followed by surgery, taking the short- and long-term morbidity of adjuvant and neoadjuvant RTX into consideration. Surgery is usually planned 6–10 weeks after finishing neoadjuvant RTX. During this period previously undetectable or new metastases could develop, which could influence further management of the disease. Therefore, with the shift to neoadjuvant RTX the need to accurately assess distant disease is becoming increasingly important.

Restaging for distant metastases after neoadjuvant RTX has several advantages. In case of unresectable metastatic disease, resection of the primary tumour is likely not beneficial from an oncological point of view in most cases [10]. Through restaging, patients might therefore not undergo an often extensive operation. Nevertheless, in some cases resection of the primary tumour might still be beneficial and improve quality of life, for example in case of an ulcerating, bleeding, or painful tumour. Moreover, through restaging, some patients could benefit from metastasectomy of the timely detected metastases [12,23]. Also, in case of indeterminate lesions, a restaging scan could help to differentiate between metastases and benign lesions. However, there are also some disadvantages of restaging such as the costs, radiation exposure, the prolonged uncertainty due to the finding of indeterminate lesions, and false-positive findings.

To our knowledge, this study is the first study to date that assessed the value of restaging for distant metastases in patients with STS of the extremities and trunk wall. However, the value of restaging for distant metastases has been evaluated within other types of cancer, such as gastric cancer and locally advanced rectal cancer (LARC) [24–35]. The results of restaging after neoadjuvant (chemo)radiotherapy in patients with LARC seem conflicting with a change in strategy rate varying from 0 to 15% [26–35]. A possible explanation of the conflicting results within these studies might be selection bias. It could be that restaging was not offered routinely in these studies and therefore only patients with a high likelihood of developing distant metastases or patients with complaints that could be caused by distant metastases received a restaging CT scan resulting in an overestimation of the value of routine restaging for distant metastases. Most of the studies did not report how many patients were restaged [26–30], however in some studies only 44–65% of the patients were restaged, suggesting some form of selection for restaging [31–33]. Contrary to these studies, the change in strategy rate in our centre for STS was 19% with a restaging rate of 93%, suggesting that selection bias in this study was limited. Nevertheless, in our centre neoadjuvant RTX was mainly indicated in patients with high-grade, large (>5 cm), deep-seated tumours in which the members of the MDT meetings considered the estimated risk for local relapse as high. Therefore, restaging after neoadjuvant RTX might only be beneficial in these high-risk patients, who might also have a higher risk for the development of distant metastases.

A potential source of misclassification bias is the accuracy of chest CT and X-ray for the detection of distant metastases. Pulmonary nodules are frequently encountered on chest CT. However, there are no uniform definitions to distinguish from indeterminate and metastatic pulmonary lesions. Also, the Fleischner criteria for the evaluation of pulmonary nodules are not recommended for the use in patients with known primary cancers [36]. Furthermore, in literature a wide variety of definitions are used for indeterminate and metastatic pulmonary lesions [37–40]. In this study the investigators reviewed all radiology reports after an extensive literature search. Afterwards, the investigators designed a list of criteria to define indeterminate and metastatic lesions (Appendix A2). This was reviewed by a dedicated radiologist. Based on these criteria all staging and restaging reports were reviewed and classified by the investigators. In our study only 2 out of 24 patients had a pathology

confirmed metastasis. Both patients had a large solitary lesion suspected for distant metastasis. All other patients diagnosed with metastases at restaging had multiple lung lesions suspected for metastatic disease. In all these patients follow-up CT scans showed (further) progression of the pulmonary nodes, which increases the likelihood of being truly metastatic lung lesions.

This study has some limitations due to its retrospective design. Besides the abovementioned limitations of our study, we were unable to find out why some patients were not restaged with chest CT or X-ray (n = 10). Therefore, selection bias could not be ruled out entirely. Furthermore, owing to the selected indication of neoadjuvant RTX, the findings of this study might not be generalizable to low-risk patients with small, superficial, low-grade tumours. Due to loss of follow-up, mainly because of referral of patients to secondary care in palliative setting, the received treatment after restaging was missing for some patients. Also, staging and restaging scans were not reassessed for this study by a blinded dedicated radiologist. Due to the relatively small numbers of patients we were unable to assess risk factors that are associated with change of treatment strategy after restaging. Furthermore, we were unable to assess whether change of treatment strategy results in better quality of life compared to patients who did not receive restaging imaging for distant disease. However, this study is the first to date that shows that restaging for distant disease in STS results in a notable number of new findings which influences the clinical and patient's decision for further treatment and care. These findings should be further validated in prospective controlled studies to assess whether the change in treatment strategy due to findings on restaging improves quality adjusted life years. Furthermore, future studies are needed to assess which patients are most likely to benefit from restaging.

In conclusion, this study showed the value of routine restaging for distant metastases with chest CT or X-ray after neoadjuvant RTX in patients with STS of the trunk wall and extremities. Restaging imaging reveals a notable number of formerly unknown metastases and results in 19% of the patients in a change in treatment strategy.

Declaration of competing interest

The authors have no competing interests to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2022.03.231.

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