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# What is the role of routine follow-up for localised limb soft tissue sarcomas? A retrospective analysis of 174 patients

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**Background:** There are neither prospective data nor agreement on the optimal routine follow-up procedures in patients treated for soft tissue sarcoma of the limb.

**Methods:** Data on 174 consecutive patients with a soft tissue sarcoma of the limb undergoing follow-up by oncologists at a single centre from 2003 to 2009 were included in this analysis. The rate and site of recurrence and mode of detection were analysed. Outcome of the patients was assessed.

**Results:** Eighty-two patients (47%) experienced relapse of any type. Isolated local recurrence occurred in 26 patients and local relapse with synchronous pulmonary metastases in five patients. Local recurrences were detected clinically in 30 of these 31 patients; magnetic resonance imaging identified only one local recurrence. Twenty-eight patients developed isolated lung metastases; in nine patients these were amenable to resections, seven of whom are currently free of disease after treatment. Lung metastases were detected by chest x-ray (CXR) in 19 patients, computed tomography scanning in 3 patients, and clinically in 11 patients. Twenty-three patients developed non-pulmonary metastases. More than 80% of relapses occurred in the first 2 years of follow-up; however, later recurrences were also observed.

**Conclusions:** Routine follow-up CXR can detect lung metastases suitable for surgical resection, although the optimal interval of imaging has yet to be defined. Local relapse is almost always detected by patients or physicians, and routine scanning of the primary site is of doubtful benefit. Patient and physician education to detect local relapse may be helpful. Prospective evaluation of follow-up is recommended.

Sarcomas are a rare and heterogeneous group of malignant tumours of mesenchymal origin. They account for <1% of all new cancer cases diagnosed in the UK each year. The number of new cases diagnosed in England between 2000 and 2009 was 2626 (National Cancer Intelligence Network, 2012). Approximately 80% of all sarcomas arise from soft tissue and the remaining from bone. Soft tissue sarcomas (STS) most frequently originate within an extremity (70%), followed by the trunk, retroperitoneum, and head and neck (Zagars *et al*, 2003). The standard treatment of localised STS of the extremities is limb-preserving surgery (Rosenberg *et al*,

1982; Potter *et al*, 1986), frequently in combination with adjuvant or neoadjuvant radiotherapy in intermediate- and high-grade disease (Barkley *et al*, 1988; Wilson *et al*, 1994; Wanebo *et al*, 1995; Yang *et al*, 1998; O'Sullivan *et al*, 2002). This combined modality treatment achieves 5-year local control rates of 80–90% and 5-year disease-specific survival rates of >70% (Zagars *et al*, 2003). Local recurrences have been documented to mostly occur up to 5 years after completion of treatment (Ballo *et al*, 2004), and in synovial sarcomas metastatic relapse has been shown to occur as late as 16.3 years after primary treatment (Krieg *et al*, 2011). A recent analysis

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of outcome in intermediate- and high-grade myxofibrosarcomas showed local recurrences in 31% of patients and distant recurrences in 17%, indicating a more aggressive local behaviour compared with other STS (Haglund *et al*, 2012).

Surveillance strategies in cancer are adopted for the following: detection of local or distant recurrences based on the supposition that early detection and treatment prolongs survival; detection of secondary tumours or other relevant medical conditions, which might have been caused by previous anti-cancer treatment; and as a source of reassurance to the patient. However, there is concern about the negative effects of using excessive radiation in surveillance imaging of cancer survivors (Brenner and Hall, 2007; Tarin *et al*, 2009) and about causing anxiety by frequent investigations (Thompson *et al*, 2010).

There have been few prospective studies evaluating follow-up strategies in common cancer types, and none in STS. In breast cancer, survival has been shown to be equivalent with either intensive or routine follow-up (Palli *et al*, 1999). In stage I non-seminomatous germ cell tumours, the number of computed tomography (CT) scans during post-treatment surveillance was prospectively assessed and could be safely reduced from five to two with equivalent patient outcomes (Rustin *et al*, 2007). Treating patients with recurrent ovarian cancer on the basis of a rise in CA125 levels alone did not achieve superior outcomes when compared with deferring treatment to symptomatic relapse (Rustin *et al*, 2010). In colorectal cancer there is evidence that follow-up programmes for patients with curatively resected tumours improve survival, although which tests or frequencies of visits are optimal remains unclear (Figueredo *et al*, 2003). Recent data on surveillance in diffuse large B-cell lymphoma demonstrated that scanning detected diffuse large B-cell lymphoma relapse prior to clinical manifestations in only 8 out of 537 patients (1.5%) (Thompson *et al*, 2013).

Because of the lack of prospective data, follow-up recommendations for STS after primary curative treatment are based on expert opinions and vary in frequency and modality. All include regular chest imaging and some include routine imaging of the primary site (Grimer *et al*, 2010; ESMO/European Sarcoma Network Working Group, 2012; NCCN, 2014). A 2004 survey in UK cancer centres illustrates wide variations in follow-up practices, with little consistency on imaging, follow-up intervals, or duration of follow-up (Gerrand *et al*, 2007). An ideal surveillance schedule should meet the criteria of easy implementation, efficiency in detection of recurrence, and cost effectiveness.

The aim of this study was to describe the presentation of relapse, the modality of detection of recurrence, and patient outcomes, and to assess the effectiveness of current unit follow-up guidelines. We retrospectively assessed all patients who presented with STS of the limb between December 2003 and December 2009 at a large regional specialist non-surgical sarcoma unit who had undergone resection of the primary tumour. Most patients were referred for evaluation for radiotherapy and chemotherapy, thus representing a high-risk group of patients.

## PATIENTS AND METHODS

This retrospective analysis includes data on 174 patients with localised STS of the limbs who presented as new patients at the London Sarcoma Service at University College London Hospital (UCLH) between December 2003 and December 2009. Patient and tumour data were collected from hospital records.

Follow-up guidelines (Table 1) were implemented within the London Sarcoma Service in April 2007; previously, post-treatment surveillance was not standardised and was performed at the discretion of the treating physician. However, follow-up practice

did not change substantially in the period prior to guideline implementation.

The median follow-up duration of all patients was 32 (range 1–91) months. For patients still alive median follow-up was 37 (range 1–91) months, and for those who had died it was 18 (range 7–70) months.

Information retrieved included age at surgery, tumour site, histological subtype, histological tumour grade (Coindre *et al*, 1988), treatment modalities, date of recurrence, location of recurrence (local, local and lung, lung only, non-pulmonary), mode of detection of relapse, and treatment for recurrence. Time to relapse was calculated from the date of completion of treatment to the date of relapse, with the exception of patients who relapsed following surgery and prior to starting adjuvant radiotherapy, when date of surgery to the date of relapse was used. The method of Kaplan and Meier was used for relapse-free survival analysis (Kaplan, 1958). Statistical calculations were performed with R version 3.0.1 (CORE TEAM R, 2013) and confidence intervals (CI) for median survival were calculated (Brookmeyer and Crowley, 1982).

Data collection was in accordance with local ethical standards.

## RESULTS

In total, 174 patients were assessed. Patient and tumour characteristics are summarised in Table 2.

Of the 174 patients, 172 underwent surgery; two patients received definitive combination chemo-radiation and underwent no surgery. The mean age at surgery was 51 (range 13–88) years. Radiotherapy was delivered to 145 of the 174 patients (83%) in addition to surgery: 25 patients received preoperative radiotherapy, and 118 patients received postoperative radiotherapy; two patients received pre- and postoperative radiotherapy. Twenty-five (14%) patients received neo- or adjuvant chemotherapy.

At the time of last follow-up, 116 patients (67%) were alive, 43 patients (25%) had died, and 15 (9%) were lost to follow-up (as defined by no follow-up information within the last 12 months). At the time of last follow-up, 112 patients (64%) were disease free.

**Site of relapse.** Tumour recurrence was experienced by 82 patients (47%). Sites of relapse are summarised in Table 3. Among patients who received radiotherapy (147 patients), the overall relapse rate was 42%, with a local relapse rate of 14%. In patients treated with surgery alone (27 patients), the overall relapse rate was 78%, with a local relapse rate of 37%.

**Time of relapse.** The median relapse-free survival for the entire group was 43.9 months (95% CI, 29.9 – infinity) (Figure 1). Disease-free survival at 2 years was 61% (95% CI 53–68) and that at 5 years was 42% (95% CI 32–51). Local relapse-free survival at 2 years was 75% (95% CI 67–81) and that at 5 years was 51% (95% CI 39–62). Median time from end of treatment to relapse was 9 (range 0–49) months for local recurrence, 3 (range 0.6–15) months for local relapse and synchronous lung metastases, 5 (range 1–66) months for lung metastases only, and 11 (range 3–52) months for non-pulmonary metastases (Figure 2). In some of these patients local as well as systemic relapse occurred prior to initiation of adjuvant radiotherapy.

During the first year 48 (59%) of 82 patients relapsed (13 local, 4 local with synchronous lung metastases, 18 lung relapses only), and a further 18 patients relapsed during the second year of follow-up (6 local, 1 local with synchronous lung metastases, and 5 lung recurrences). There was one relapse beyond 5 years; however, median follow-up was only 32 months.

### Detection of relapse

**Local relapse.** Thirty of 31 local recurrences (97%) were detected clinically. In 22 patients detection was by self-examination, and

Table 1. London Sarcoma Service follow-up guidelines

Exam	Grade	Year 1			Year 2		Year 3–4		Year 5–10	
		Clinical	CXR	MRI of the primary site	Clinical	CXR	Clinical	CXR	Clinical	CXR
Interval (months)	Low	6			6		12		12	
Interval (months)	Intermediate/high	3	3	at 6 months	3	3	6	6	12	12

Abbreviations: CXR = chest X-ray; MRI = magnetic resonance imaging.

Table 2. Patient and tumour characteristics

Characteristics total, n = 174		
Age (range)	51 (13–88)	
Gender	94 male	80 female
<b>Grading</b>	<b>n</b>	<b>%</b>
Low grade	1	1
Intermediate grade	15	9
High grade	156	90
No grade	2	1
<b>Histologic subtype</b>	<b>n</b>	<b>%</b>
Myxofibrosarcoma	37	21
Liposarcoma	34	20
Synovial sarcoma	29	17
Leiomyosarcoma	10	6
Others	64	37
<b>Localisation</b>	<b>n</b>	<b>%</b>
Upper extremity	40	23
Lower extremity	134	77
<b>Resection status</b>	<b>n</b>	<b>%</b>
R0	158	91
R1	13	7
R2	1	1
No surgery	2	1

in 8 cases recurrence was noted on physical examination by the physician at routine follow-up. Only one patient had an asymptomatic local relapse detected on magnetic resonance imaging (MRI), when repeat imaging was performed to reassess a postoperative seroma.

Our current practice is to routinely perform an MRI of the primary tumour site 6 months after completion of adjuvant radiotherapy, to act as a post-treatment baseline for future comparison. However, some patients underwent additional scans routinely for local surveillance. In 16 patients with a local relapse who had had a previous MRI not suspicious for recurrence, the median time from MRI to clinical detection of relapse was 6 (range 3–19) months. This indicates that, despite recent normal imaging, local recurrences were still detected clinically in this group of patients. The median time from previous normal follow-up to local relapse was 3 (range 1–28) months, which highlights the fact that local relapses were noted between regular 3-monthly appointments by the patient in the majority of cases.

**Lung metastases.** Twenty-eight patients (16%) developed isolated lung metastases. Asymptomatic lung metastases were discovered on routine chest X-ray (CXR) in 19 patients and by CT scanning in 3 patients at a median of 8 (range 1–66) months after completion

Table 3. Site of relapse

Relapse total, n = 82 (47%)		
Site	n	%
Lung	28	16
Local and lung	5	3
Local	26	15
Non-pulmonary	23	13
Bone	6	3
Abdominal	4	2
Chest wall	2	1
Mediastinum	2	1
Pelvis	2	1
Soft tissue	2	1
Diffuse	2	1
Epigastrium	1	1
Groin	1	1
Subcutaneous	1	1

of initial treatment. Of the three patients who had CT scans, one had indeterminate lung nodules on an original staging CT scan at first diagnosis, and a repeat CT scan after 3 months confirmed progression of the nodules, thereby diagnosing lung metastases; two patients underwent CT scans for other reasons (to exclude an axillary nodal recurrence; to reassess pelvic lymph nodes that had been irradiated as part of primary treatment), and the lung metastases were an incidental finding. As such, none of these three patients represent a deviation from our defined follow-up guidelines. Symptomatic lung metastases occurred in 6 patients at 2, 3, 5, 5, 5, and 40 months after the end of primary sarcoma treatment (median 5 months). The short time from initial treatment to symptomatic relapse in five of these patients suggests aggressive tumour biology. Relapse was detected at a median of 2 (range 1–5) months after the last routine follow-up and normal imaging. The patient with disease recurrence more than 3 years after surgery developed symptoms of a pleural effusion secondary to lung metastases, <3 months after a routine follow-up appointment.

**Non-pulmonary metastases.** Eighteen of 23 non-pulmonary recurrences (lymph node, soft tissue, subcutaneous, bone, or multiple sites) were discovered by the patients, one chest wall recurrence was detected on physical examination, and one pelvic and one mediastinal recurrence was noted on MRI and CT scans, respectively. In two of the patients, routine CXR was suggestive of lung metastases and further staging revealed additional non-pulmonary metastases. Median time from last routine follow-up to relapse with non-pulmonary metastases was 3 (range 1–9) months (Figure 3).

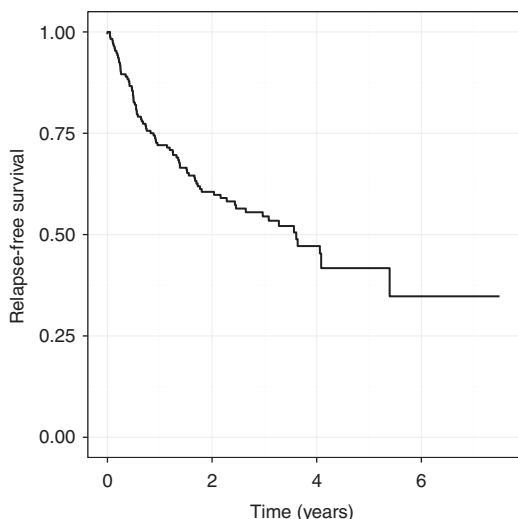


Figure 1. Relapse-free survival. Time (years).

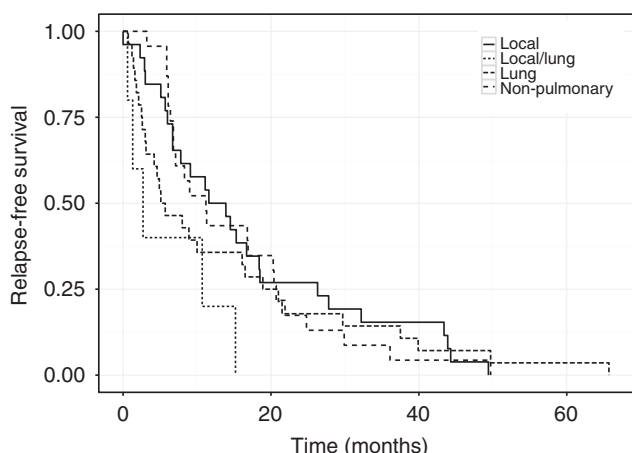


Figure 2. Relapse-free survival by site. Time (months).

**Outcomes of relapsed patients**

*Local relapse.* Fifteen of the 26 patients (58%) who experienced an isolated local recurrence are alive, and 12 of those patients (46%) are disease free with a median follow-up time of 22 (range 4–57) months after the last recurrence. Nine patients are deceased, and two are lost to follow-up.

In 20 of 26 patients, curative treatment for local tumour recurrence was undertaken: surgery alone in 10 patients, surgery and radiotherapy in 8 patients, surgery and chemotherapy in a patient with synovial sarcoma, and chemotherapy alone in a patient with extraosseous Ewing sarcoma. Eight patients did not have a further relapse. However, 12 patients had another recurrence: five were local (four of which were successfully salvaged — 2 with further local resections and two with subsequent limb amputation), four developed lung metastases, two developed local relapse with synchronous lung metastases, and one patient relapsed with non-pulmonary metastases (Figure 4).

*Lung metastases.* Nine of the 22 (41%) patients with imaging-detected asymptomatic lung metastases (seven on CXR, two on CT scan) underwent pulmonary metastatectomy with curative intent. Eight of these patients are alive and seven are currently disease free with a median follow-up time of 14 (range 6–38) months. In these seven patients, the interval between primary sarcoma treatment and detection of lung metastases was more than 6 months. Patients

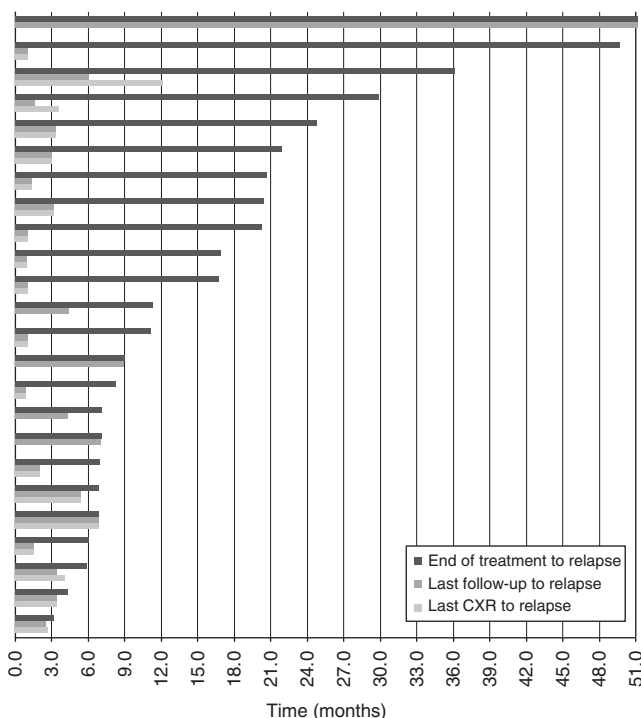


Figure 3. Patients with non-pulmonary metastases: Time from treatment, last follow-up, and last CXR to relapse. Time (months).

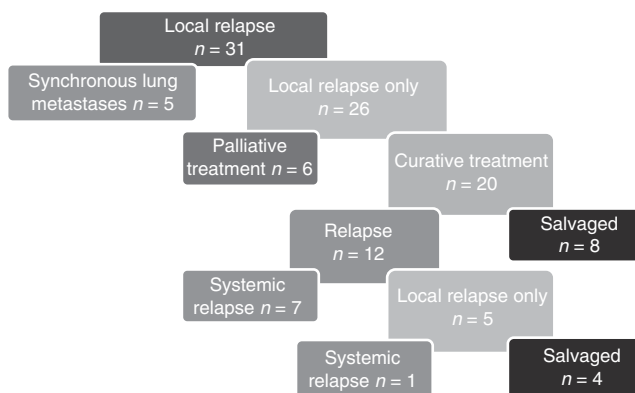


Figure 4. Treatment of local relapse and outcome.

had one to four metastases on preoperative scanning, and a maximum of four metastases were removed at surgery. One patient developed lung metastases shortly after initial primary treatment. Whereas on the preoperative CT scan only 3 metastases were visible, at surgery more than 20 metastases were resected. This patient subsequently relapsed rapidly and died. Two patients were treated with radiofrequency ablation for recurrent lung metastases; one remains disease-free, while the other patient has relapsed again.

Thirteen patients with CXR- or CT-scan-detected lung metastases were considered unsuitable for pulmonary metastatectomy owing to the extent of disease, and were treated with palliative intent. Twelve patients have died since, and one patient was lost to follow-up and has presumably died. Median time from relapse to death was 13 (range 4–39) months.

The six patients with symptomatic lung relapse all had advanced disease without curative treatment options. Five patients died of



metastatic sarcoma and one was lost to follow-up. The short interval from end of treatment to relapse indicates aggressive disease with rapid progression.

In summary, 41% of patients with lung metastases detected on routine imaging were treated with curative intent and 32% remain free of disease at present. Of note, the seven patients who underwent curative metastectomy and are disease free had a longer relapse-free interval from primary treatment of 30 (range 9–66) months compared with patients who had a subsequent relapse or were not deemed suitable for surgical intervention with a median relapse-free interval of 3 (range 1–22) months.

**Non-pulmonary metastases.** Thirteen of the 23 patients with non-pulmonary metastases have died from metastatic sarcoma. Median time from relapse to death was 8 (range 1–33) months. Two patients were lost to follow-up and nine patients are still alive, two of whom are currently disease free. Both of them had soft tissue metastases amenable to resection at relapse.

## DISCUSSION

The aim of this study was to assess the mode and effectiveness of detection of relapse in patients undergoing surveillance for extremity STS, and to identify optimal follow-up schedules. We retrospectively analysed data from 174 patients who were treated at a single centre over a period of 6 years. In our patient group with mostly high-grade and therefore high-risk STS, the rate of local relapse of 18% is consistent with other data sets in extremity STS (Lawrence *et al*, 1987; Lewis *et al*, 1997; Eilber *et al*, 2003), as is the rate of metastatic spread of 32% (Pisters *et al*, 1996; Huth and Eilber, 1988; Billingsley *et al*, 1999b). The aim of any surveillance programme is to identify relapses at such a time that the relapses can be successfully treated, achieving long-term survival. In our series, of the 31 patients with local recurrence, 46% are disease free at a median follow-up of 22 months after recurrence, and of the 28 patients with lung metastases 32% who underwent metastectomy are disease free at a median follow-up of 14 months.

Of the 31 patients in our series with a local relapse, 97% of relapses were detected clinically, 22 by the patients themselves and 8 by physicians in clinic. Only one local recurrence was asymptomatic and detected on an MRI scan. This is consistent with a study that evaluated the role of routine surveillance MRI scanning in the detection of local recurrence for limb STS (Labarre *et al*, 2009). One hundred and twenty-four patients underwent 663 planned MRI scans according to a defined follow-up protocol. Of 11 local recurrences (9%), nine were detected clinically and only two were asymptomatic MRI-detected recurrences. This low screen detection rate came at a cost of 11 false-positive MRI scans. Overall, the authors concluded that clinical examination was a more effective method of surveillance compared with routine MRI scanning.

A proportion of patients with STS who develop isolated relapse in the lungs can be potentially cured by resection of lung metastases (Billingsley *et al*, 1999a). In a series of 719 STS patients with lung metastases, the median interval between the treatment of the primary tumour and the development of metastatic disease was 10 months. Relapse-free interval was a prognostic indicator, with an interval of 1 year or less being associated with poorer prognosis. In another series, the number of nodules detected by CT scanning preoperatively was found to have significant prognostic value, with poorer outcomes for patients with four or more nodules (Casson *et al*, 1992). Our patients with lung metastases who underwent subsequent resection and are disease free had a median relapse-free interval from primary treatment of 30 months, and had up to four nodules removed. Patients in our series with symptomatic lung metastases had a median time to relapse of 5 months, and none of these patients were suitable for surgery. It seems unlikely that more

frequent surveillance would have altered outcomes in this patient group, which probably reflects aggressive tumour biology.

The challenge of early detection of local relapse and metastatic spread with a view to curative salvage treatment while preventing unnecessary and even harmful investigations is yet to be solved. Follow-up recommendations differ substantially in modality and intensity and routine practice is even more diverse (Sakata *et al*, 2003; Gerrand *et al*, 2007). In a small retrospective analysis of children diagnosed with relapsed soft tissue and bone sarcomas, regular imaging studies (chest CT, MRI, and PET) did not lead to earlier recognition of relapse and did not influence overall survival (Postovsky *et al*, 2008).

Previously, Whooley *et al* published data on the efficacy of their surveillance strategy in 174 patients with primary extremity STS and provided a cost-effectiveness analysis (Whooley *et al*, 1999, 2000). Importantly, only 49% of sarcomas were high grade compared with 90% in our series. They concluded differently in their two publications: whereas they advocated physical examination, clinical assessment of patient symptoms, and CXR imaging as effective strategies for follow-up of primary extremity STS in the first publication (Whooley *et al*, 1999), they subsequently postulated that more aggressive observation during the first 2 years after treatment with a 3-monthly physical examination and CXR and cross-sectional imaging every 6 months where indicated for 2 years would be appropriate in high-risk tumours with high grade, large size, and deep localisation in the second publication (Whooley *et al*, 2000). However, the accompanying editorial (Brennan, 2000) raised several appropriate still unanswered questions: 'Is routine physician-directed follow-up justified if 50% of relapses are detected between regular visits? Is any imaging of the primary tumour required if 86% of local relapses were resectable and 19 of 20 were noticed on physical examination? Furthermore, taking into account the negative impact on outcome for a short interval from initial sarcoma treatment to pulmonary relapse, this could be an argument against frequent scanning during the first year of follow-up.'

The benefit and cost-effectiveness of chest CT as compared with CXR for staging at initial sarcoma diagnosis was evaluated in two studies (Fleming *et al*, 2001; Porter *et al*, 2002). However, these results cannot be extrapolated to the follow-up situation and do not inform on the best imaging modality. Recently a retrospective analysis of 176 patients who were followed up with CT scans or plain CXR for pulmonary metastasis monitoring after surgery for STS was reported (Cho *et al*, 2011). As expected, there was a trend towards unilaterality of lung metastases, smaller size, and management with metastectomy in the CT cohort. The 2- and 4-year survival rates after detection of pulmonary metastasis were 20% and 0% in the plain radiograph cohort and 47% and 32% in the chest CT cohort, respectively. These results should be interpreted with caution because of the small number of patients in each cohort (26 and 28, respectively). In our series of patients with lung relapses that were mostly detected on CXR, outcomes appear broadly comparable to other reports (Billingsley *et al*, 1999a), although our patient numbers are small and follow-up is short for some patients.

There has been only one randomised trial of follow-up strategies in sarcoma patients (Puri *et al*, 2014). This compared modality of chest imaging (CXR and CT scans) and frequency of follow-up (3-monthly and 6-monthly visits) in 500 patients with extremity sarcomas (359 bone and 151 soft tissue sarcomas) in a two-by-two factorial design. The results demonstrated non-inferiority of CXR as compared with CT scans (3-year OS 67% and 66%, respectively; DFS 54% and 49%, respectively). Three year OS was similar for 3-monthly and 6-monthly visits (69% and 64%, respectively); yet the trial could not conclusively demonstrate non-inferiority for less frequent follow-up visits. Interestingly, almost 90% of local recurrences were found by patients themselves, which is very consistent with our findings.

ESMO guidelines for sarcoma acknowledge the lack of published data on the optimal routine follow-up of patients with localised disease treated by surgery (ESMO/European Sarcoma Network Working Group, 2012). Imaging of the lungs is advocated, in addition to clinical assessment of the primary site. Follow-up intervals of 3–4 months in the first 2–3 years, 6-monthly up to the 5th year, and annually thereafter are suggested.

Overall, regular CXR seems to be a feasible method of chest surveillance considering the positive and negative predictive values of surveillance CXR in STS of 92% and 97%, respectively (Whooley *et al*, 2000). In a review on surveillance strategies for patients following surgical resection of STS, the additional benefit of CT scans of the lung was considered low, and the importance of thorough history and physical examination was emphasised (Kane, 2004).

There are several limitations to our analysis: it was performed retrospectively and follow-up was not performed according to defined guidelines before April 2007. However, on comparing patients who underwent treatment during the years 2003–2006 and 2007–2009, the recurrence-free survival curves appeared similar and no significant changes in the relapse pattern could be observed ( $P = 0.76$ , log-rank test). We only included STS of the limb in this study and therefore no conclusions for surveillance strategies in STS of other locations can be drawn, especially for retroperitoneal sarcomas, where clinical assessment is difficult. Another limitation of our study is in the heterogeneity of STS and the diverse biological behaviour of the >50 histological subtypes, which makes generalisations difficult. Furthermore, we are unable to present an optimal schedule for the follow-up of soft tissue sarcomas of the limb. However, we can conclude that regular physical examination of the primary tumour site detects the vast majority of local relapses. Moreover, in the light of our results and the recent prospective randomised trial comparing radiological modalities in the follow-up of extremity sarcomas (Puri *et al*, 2014), it appears that CXR may well be sufficient to detect lung metastases amenable to resection, and that regular CT scans of the lungs are unlikely to yield better results.

## CONCLUSION

Patients with recurrent STS of the limb can potentially be salvaged either by resection of local recurrence or by resection of distant (usually lung) metastases. Surveillance should be directed at detection of local relapse or lung metastases. Patient education and awareness to detect local relapse should be encouraged. As a minimum, regular CXR to detect lung metastases amenable to resection should be performed, although the optimal interval of imaging is not known, and it seems that patients developing lung metastases during the first year after primary treatment have particularly poor outcomes. The definition of a rational evidence-based follow-up programme based on the risk of recurrence remains to be established and needs prospective evaluation in clinical trials.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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