Lung Surveillance Strategy for High-Grade Soft Tissue Sarcomas: Chest X-Ray or CT Scan?

Check for updates

Adriana C Gamboa, MD, Cecilia G Ethun, MD, Jeffrey M Switchenko, PhD, Joseph Lipscomb, PhD, George A Poultsides, MD, FACS, Valerie Grignol, MD, FACS, J Harrison Howard, MD, FACS, T Clark Gamblin, MD, FACS, Kevin K Roggin, MD, FACS, Konstantinos Votanopoulos, MD, FACS, Ryan C Fields, MD, FACS, Shishir K Maithel, MD, FACS, Keith A Delman, MD, FACS, Kenneth Cardona, MD, FACS

BACKGROUND: Given the propensity for lung metastases, National Comprehensive Cancer Network guidelines recommend lung surveillance with either chest x-ray (CXR) or CT in high-grade soft tissue sarcoma. Considering survival, diagnostic sensitivity, and cost, the optimal modality is unknown.

METHODS: The US Sarcoma Collaborative database (2000 to 2016) was reviewed for patients who underwent resection of a primary high-grade soft tissue sarcoma. Primary end point was overall survival (OS). Cost analysis was performed.

RESULTS: Among 909 patients, 83% had truncal/extremity and 17% had retroperitoneal tumors. Recurrence occurred in 48%, of which 54% were lung metastases. Lung surveillance was performed with CT in 80% and CXR in 20%. Both groups were clinically similar, although CT patients had more retroperitoneal tumors and recurrences. Regardless of modality, 85% to 90% of lung metastases were detected within the first 2 years with a similar re-intervention rate. When considering age, tumor size, location, margin status, and receipt of radiation, lung metastasis was independently associated with worse OS (hazard ratio 4.26; p < 0.01) and imaging modality was not (hazard ratio 1.01; p = 0.97). Chest x-ray patients did not have an inferior 5-year OS rate compared with CT (71% vs 60%; p < 0.01). When analyzing patients in whom no lung metastases were detected, both cohorts had a similar 5-year OS rate (73% vs 74%; p = 0.42), suggesting CXR was not missing clinically relevant lung nodules. When adhering to a guideline-specified protocol for 2018 projected 4,406 cases, surveillance with CXR for 5 years results in savings of $5 million to $8 million/year to the US healthcare system.

CONCLUSIONS: In this large multicenter study, lung surveillance with CXR did not result in worse overall survival compared with CT. With considerable savings, a CXR-based protocol can optimize resource use for lung surveillance in high-grade soft tissue sarcoma; prospective trials are needed. (J Am Coll Surg 2019;229:449−457. © 2019 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Abbreviations and Acronyms

CXR   = chest x-ray
HR   = hazard ratio
NCCN = National Comprehensive Cancer Network

Soft tissue sarcomas are rare tumors that account for 1% of adult malignancies. In 2018, approximately 13,000 people were diagnosed with soft tissue sarcomas in the US.[1] During the past 3 decades, a multimodality approach has been used in the treatment of primary, high-grade soft tissue sarcomas, leading to improvements in survival. Despite this, distant recurrences are common, with up to 60% of high-grade soft tissue sarcomas recurring in the lungs.[2,3] The rate of metastases depends predominantly on tumor grade, and 70% of high-grade soft tissue sarcoma lung metastases will occur within the first 2 years after resection.[4-7]

Considering this rapid progression of high-grade soft tissue sarcomas, prompt detection of lung metastases can improve prognosis, given therapeutic interventions currently available. Surgical metastasectomy remains the primary treatment modality for isolated lung metastases, and although no randomized controlled trial has evaluated its benefit over medical therapy, several retrospective series have demonstrated 3-year survival rates of 40% to 50% after complete metastasectomy.[2,3,7-18] Even when resection is not feasible, other lung-directed strategies, such as radiofrequency ablation or stereotactic body radiotherapy have demonstrated acceptable local control rates.[19-21]

Due to the availability of salvage therapy and its association with improved survival, postoperative lung surveillance is crucial. However, consensus is lacking about the optimal imaging modality. Current National Comprehensive Cancer Network (NCCN) guidelines for high-grade soft tissue sarcomas recommend imaging with either chest x-ray (CXR) or chest CT.[22] Although CXR is easily accessible and minimizes radiation, the enhanced resolution of CT can improve the sensitivity of detection for lung nodules as small as 3 to 4 mm.[23,24] However, patients with <5-mm nodules have been shown to have survival equivalent to those with normal CT scans.[25] Additionally, the higher false-positive rate for CT can result in costly, unnecessary assessments and procedures with potential increased morbidity and patient anxiety.[26] In addition, the cost between CXR and CT differs by an order of magnitude. Intuitively, elimination of unnecessary CT scans for lung surveillance of high-grade soft tissue sarcoma would result in significant savings to the US healthcare system.

Considering the potential variability in diagnostic sensitivity, and known differential cost of each modality, the preferred modality of lung surveillance in high-grade soft tissue sarcoma remains unknown. Therefore, the primary objective of this study was to evaluate the difference between CXR and CT lung surveillance after curative resection of high-grade soft tissue sarcoma with regard to overall survival and cost to the US healthcare system.

METHODS

Data source and study variables

The US Sarcoma Collaborative is a consortium formed to investigate outcomes in soft tissue sarcoma and comprises 8 academic centers (Emory University, Stanford University, Wake Forest University, Medical College of Wisconsin, University of Wisconsin, University of Chicago, The Ohio State University, Washington University). All patients who underwent resection of a primary soft-tissue sarcoma (2000 to 2016) were identified. To mitigate selection bias, this study was limited to high-grade tumors, as pathologic grade can affect selection of modality for lung surveillance. High-grade was defined as grade 2 or 3 using the French Federation of Cancer Centers Sarcoma Group or as determined in the pathology report by the National Cancer Institute system. The analysis was further limited to patients with R0 or R1 resections, without metastatic disease at the time of resection or 30-day operative mortality, and those with lung surveillance data available. Clinicopathologic variables and postoperative outcomes were collected through chart review. As the study was conducted by 8 academic institutions, NCCN guidelines for lung surveillance frequency were followed. However, there were no institutional protocols to guide selection of modality of surveillance, and this decision was based largely on physician preferences. Patients were considered to have CXR surveillance if they exclusively underwent imaging with CXR throughout the surveillance period. If a patient was transitioned from CXR surveillance to CT at any point during the lung surveillance period and before detection of lung metastases, they were included in the CT surveillance cohort. Once a suspicious lesion was identified with either modality, additional diagnostic workup (cross-sectional imaging, percutaneous biopsy, or wedge resection) was pursued at the discretion of the treating physician and there were no institutional protocols or algorithms to guide this decision making. IRB approval was confirmed at each institution before data collection.

Statistical analysis

All statistical analyses were performed using SPSS statistical package, version 25.0 (IBM Corp). Statistical significance
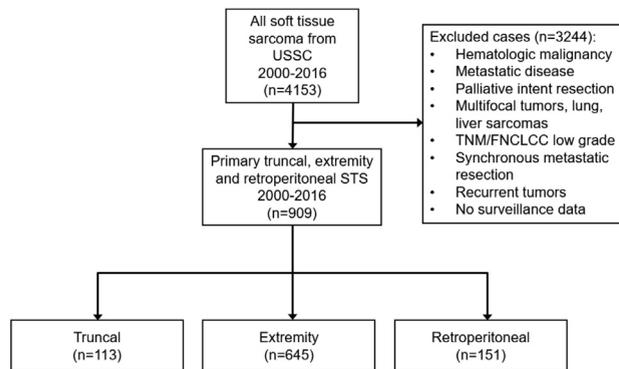
Figure 1. Patient population flow diagram. FNCLCC, French Federation of Cancer Centers Sarcoma Group; STS, soft tissue sarcoma; USSC, US Sarcoma Collaborative.

was predefined as 2-tailed (p < 0.05). Nominal variables were analyzed with chi-square or Fisher's exact test. Continuous variables were analyzed using t tests or the Wilcoxon signed-rank test. Survival was estimated using the Kaplan-Meier method, and log-rank test was used for comparison of survival between CXR and CT cohorts. Cox-regression analysis was used to determine the association of clinicopathologic factors with overall survival. A multivariable model was constructed using sequential regression entry with variables statistically associated (p < 0.05) with overall survival on univariate analysis.

Cost model comparing chest x-ray and CT

A cost model was developed to estimate total cost to the US healthcare system during a 5-year period using either a CXR or CT-based surveillance protocol. The 2018 incidence data of non-metastatic, high-grade soft tissue sarcoma were determined based on published estimates. This hypothetical cohort was simulated to enter a CXR or CT-based protocol at low-frequency (every 6 months for 4 years, then annually) or high-frequency (every 3 months for the first 2 years, then every 6 months for 2 years, then annually). At each imaging time point there were 3 potential probabilities: no lung metastases, true lung metastases (true positive), or false lung metastases (false positive). The probability of a true positive was calculated as the modality sensitivity multiplied by the true recurrence rate among those who did not die before the imaging time point. The probability of a false positive is the modality false-positive rate (1-specificity) multiplied by 1 minus true recurrence rate plus the death rate among those who did not die before the imaging time point. The cost of each imaging modality or intervention was derived by using the 2018 Medicare Physician Fee Schedule and each service was identified using the CPT code. If a recurrence was detected, the downstream cost of histologic

confirmation via wedge resection was also included. Each model was simulated 1,000 times and the average cost to the US healthcare system at 5 years is reported.

RESULTS

Demographic and clinicopathologic characteristics

Among 4,153 patients, 1,093 patients with high-grade soft tissue sarcoma underwent curative-intent resection and, of these, 909 had lung surveillance data available. Tumor location included extremities in 71% (n = 645), trunk wall in 12% (n = 113), and retroperitoneum in 17% (n = 151) (Fig. 1). Tumor size was <5 cm in 15% (n = 137), 5 to 10 cm in 40% (n = 366), >10 cm in 39% (n = 351), with a median of 9 cm (interquartile range 5.5 to 14.5 cm). Tumors were classified into 6 main histologic categories as follows: undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma 39% (n = 355), leiomyosarcoma 12% (n = 106), myxofibrosarcoma 8% (n = 75), dedifferentiated liposarcoma 4% (n = 40), synovial sarcoma 5% (n = 48), pleomorphic liposarcoma 5% (n = 44), and others 27% (n = 241). Median follow-up was 33 months.

Among those patients who underwent curative resection (R0/R1), 48% (n = 432) had a recurrence and, of these, 34% were local/locoregional (n = 149), 55% were distant (n = 239), and 10% were synchronous locoregional/distant (n = 42). Of all recurrences, 54% were in the lungs (n = 232). Lung surveillance was performed with CXR in 20% (n = 197) and CT in 80% (n = 771).

Patients who underwent surveillance with CT had more retroperitoneal tumors, a higher proportion of dedifferentiated liposarcoma, and were more likely to have lung metastases (p < 0.05). Importantly, both imaging modalities detected the majority of the lung metastases within the first 2 years (CXR 91%, CT 85%; p = 0.88). Definitive therapy for these included ablation (CXR 0%, CT 0.4%), radiation (CXR 9%, CT 5%), operation (CXR 18%, CT 40%), and chemotherapy (CXR 18%, CT 40%), and both groups had similar intervention rates to treat lung metastases (p = 0.77; Table 1).

Lung metastases and survival

On univariate Cox regression analysis, older age, retroperitoneal tumors, tumor size ≥5 cm, positive margin status, presence of lymphovascular invasion, and positive lymph node status were associated with worse overall survival. Lung metastasis was also strongly associated with worse overall survival (hazard ratio [HR] 3.91; 95% CI 3.11 to 4.92; p < 0.01), and lung surveillance with CXR was not associated with inferior overall survival compared with CT (HR 0.62; 95% CI 0.45 to 0.85; p < 0.01). On multivariable Cox

Table 1. Demographic and Clinicopathologic Factors of Patients with High-Grade Soft Tissue Sarcoma

Variable	All patients (n = 1,093)	Surveyed patients (n = 909)	CXR (n = 192)	CT (n = 717)	p Value (CXR vs CT)
Demographic					
Age, y, median (IQR)	61 (49−72)	60 (48−71)	62 (51−76)	59 (48−71)	0.02*
Sex, n (%)					0.34
Male	582 (53)	480 (53)	95 (49)	385 (54)	
Female	511 (47)	429 (47)	97 (51)	332 (46)	
Missing	0 (0)	0 (0)	0 (0)	0 (0)	
Race, n (%)					0.87
White	818 (75)	679 (75)	144 (75)	535 (75)	
Black	123 (11)	102 (11)	22 (11)	80 (11)	
Other	112 (10)	100 (11)	19 (10)	81 (11)	
Missing	40 (4)	28 (3)	7 (4)	21 (3)	
Primary location, n (%)					<0.01*
Truncal	131 (12)	113 (12)	18 (9)	95 (13)	
Extremity	762 (70)	645 (71)	157 (82)	488 (68)	
Retroperitoneal	200 (18)	151 (17)	17 (9)	134 (19)	
Missing	0 (0)	0 (0)	0 (0)	0 (0)	
Clinicopathologic factor					
Tumor size, n (%)					0.13
<5 cm	174 (16)	137 (15)	38 (20)	99 (14)	
5−10 cm	422 (39)	366 (40)	74 (39)	292 (41)	
>10 cm	434 (40)	351 (39)	70 (36)	281 (39)	
Missing	63 (5)	55 (6)	10 (5)	45 (6)	
Histopathology, n (%)					
UPS/malignant fibrous histiocytoma	424 (39)	355 (39)	79 (41)	276 (39)	0.56
Leiomyosarcoma	133 (12)	106 (12)	18 (9)	88 (12)	0.33
Myxofibrosarcoma	86 (8)	75 (8)	23 (12)	52 (6)	0.05
Liposarcoma, dedifferentiated	56 (5)	40 (4)	3 (2)	37 (5)	0.03*
Synovial	53 (5)	48 (5)	11 (6)	37 (5)	0.89
Liposarcoma, pleomorphic	46 (4)	44 (5)	10 (5)	34 (5)	0.94
Other	295 (27)	241 (27)	48 (25)	193 (27)	0.66
Lymph node metastasis, n (%)					0.69
Negative	121 (11)	95 (10)	9 (5)	86 (12)	
Positive	25 (2)	20 (3)	3 (2)	17 (2)	
Missing	947 (87)	794 (87)	180 (93)	614 (86)	
Lymphovascular invasion, n (%)					0.12
Negative	625 (57)	551 (61)	130 (68)	421 (59)	
Positive	54 (5)	41 (5)	5 (3)	36 (5)	
Missing	414 (38)	317 (35)	57 (29)	260 (36)	
Final resection status, n (%)					0.82
R0	888 (81)	755 (83)	161 (84)	594 (65)	
R1	205 (19)	154 (17)	31 (16)	123 (17)	
Missing	0 (0)	0 (0)	0 (0)	0 (0)	
Adjuvant multimodal treatment, n (%)					
Chemotherapy	346 (32)	513 (35)	65 (34)	254 (36)	0.78
Radiation	582 (53)	513 (57)	105 (55)	410 (57)	0.55
Mode of lung surveillance, n (%)					
CXR	192 (18)	192 (21)	—	—	
CT	717 (66)	717 (79)	—	—	

(Continued)

Table 1. Continued

Variable	All patients (n = 1,093)	Surveyed patients (n = 909)	CXR (n = 192)	CT (n = 717)	p Value (CXR vs CT)
First recurrence, n (%)	455 (43)	432 (48)	33 (17)	399 (56)	<0.01*
Local/locoregional	156 (34)	149 (34)	16 (48)	133 (33)	0.3
Distant	249 (55)	239 (55)	15 (45)	224 (56)	0.3
Both (locoregional + distant)	48 (11)	42 (10)	2 (6)	40 (10)	0.3
Lung metastasis[†]	234 (79)	232 (83)	11 (65)	221 (83)	<0.01*
Median follow-up, months	41	33	48	43	0.128
Lung metastasis					
Timing of detection, n (%)	—	—			0.88
<2 y	—	—	10 (91)	188 (85)	
2−5 y	—	—	1 (9)	27 (12)	
>5 y	—	—	0 (0)	1 (0.4)	
Intervention type, n (%)	—	—			0.77
Ablation	—	—	0 (0)	1 (0.4)	
Radiation	—	—	1 (9)	12 (5)	
Surgery	—	—	5 (45)	94 (43)	
Chemotherapy	—	—	2 (18)	88 (40)	

*Significant.

[†]Percentage in parentheses calculated with distant metastases (either distant alone or locoregional + distant) as the denominator.

CXR, chest x-ray; IQR, interquartile range; UPS, undifferentiated pleomorphic sarcoma.

regression analysis, when controlling for age, tumor location, tumor size, margin status, and receipt of radiation, lung metastasis remained an independent predictor of worse overall survival (HR 4.26; 95% CI 3.28 to 5.53; p < 0.01), and lung surveillance modality had no effect on overall survival (HR 1.01; 95% CI 0.71to 1.43; p = 0.97) (Table 2).

Survival analysis by lung surveillance modality

On log-rank analysis, patients in the CXR cohort did not have a worse 5-year lung-specific recurrence-free survival (CXR 93% vs CT 62%; p < 0.01; Fig. 2A) and 5-year overall survival (CXR 71% vs CT 60%; p < 0.01) (Fig. 2B). However, when analyzing patients in whom no lung metastases were detected, both imaging cohorts had identical 5-year overall survival (CXR 74% vs CT 73%; p = 0.42) (Fig. 2C), suggesting that patients undergoing surveillance with CXR were not subjected to false-negative imaging for clinically relevant lesions that would otherwise have resulted in decreased overall survival.

Cost analysis of lung surveillance modalities

Estimated 2018 incidence data for non-metastatic, high-grade soft tissue sarcoma are shown in Tables 3 and 4. During a 5-year surveillance period, a CXR-based protocol compared with CT results in a savings of $5,525,413 to $7,853,732 to the US healthcare system based on the 2018 Medicare Physician Fee Schedule, depending on whether a low- or high-frequency strategy is used, respectively (Table 5).

DISCUSSION

Lung metastases after curative-intent resection will develop in nearly 60% of patients with high-grade soft tissue sarcoma, with the risk of recurrence being greatest within 2 years of operation.[29,30] This study's findings are concordant with those in the literature, with an lung metastasis rate of 52% (Table 1). Additionally, as previously known, our results demonstrate that lung metastasis is associated with a worse prognosis. Given this high rate of recurrence, the associated impact on survival, and the availability of salvage therapy, NCCN guidelines provide clear recommendations for lung surveillance. However, the optimal modality is unknown and either CXR or CT is accepted. Our results demonstrate that lung surveillance with CXR is not associated with inferior overall survival compared with CT. In addition, depending on the frequency of imaging, a CXR-based protocol affords a potential cost savings of $5 million to $8 million during a 5-year period to the US healthcare system.

Several small studies and a randomized controlled trial have evaluated the optimal modality of lung surveillance in soft tissue sarcoma.[30-33] In a prospective, single-institution study, Puri and colleagues[32] demonstrated that at a median follow-up of 42 months, surveillance with CXR after resection of extremity soft tissue sarcoma did not lead to worse survival compared with CT. Additionally, a retrospective study by Whooley and colleagues[34] evaluated the effectiveness of follow-up testing for detecting distant recurrences of extremity soft tissue sarcoma

Table 2. Clinicopathologic Factors Associated with Overall Survival in R0/R1 Resections

Variable	Univariable Cox regression		Multivariable Cox regression	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age, y	1.02 (1.01–1.03)	<0.01*	1.02 (1.01–1.03)	<0.01*
Sex				
Male	ref	—	—	—
Female	1.06 (0.85–1.34)	0.60	—	—
Race				
White	ref	—	—	—
African American	1.05 (0.73–1.51)	0.78	—	—
Other	0.90 (0.61–1.33)	0.60	—	—
Primary location				
Truncal/extremity	ref	—	ref	—
Retroperitoneal	0.64 (0.48–0.83)	<0.01*	1.32 (0.97–1.80)	0.08
Tumor size				
<5 cm	ref	—	ref	—
5–10 cm	1.79 (1.156–2.77)	<0.01*	1.38 (0.87–2.18)	0.11
>10 cm	3.03 (1.98–4.62)	<0.01*	2.13 (1.36–3.34)	<0.01*
Histopathology				
UPS/malignant fibrous histiocytoma	0.86 (0.68–1.10)	0.23	—	—
Leiomyosarcoma	1.06 (0.75–1.49)	0.74	—	—
Myxofibrosarcoma	0.81 (0.51–1.29)	0.37	—	—
Liposarcoma, dedifferentiated	1.29 (0.79–2.11)	0.31	—	—
Synovial	0.79 (0.46–1.35)	0.39	—	—
Liposarcoma, pleomorphic	1.16 (0.73–1.85)	0.53	—	—
Other	1.18 (0.92–1.51)	0.20	—	—
Lymph node metastasis				
Negative	ref	—	—	—
Positive	2.61 (1.37–4.98)	<0.01*	—	—
Lymphovascular invasion				
Absent	ref	—	—	—
Present	1.94 (1.25–3.03)	<0.01*	—	—
Final margin status				
Negative (R0)	ref	—	ref	—
Positive (R1)	1.64 (1.25–2.15)	<0.01*	1.79 (1.34–2.39)	<0.01*
Multimodal treatment				
Radiation	0.79 (0.63–0.99)	0.04*	0.75 (0.58–0.96)	0.11
Chemotherapy	0.91 (0.72–1.16)	0.44	—	—
Recurrence				
No recurrence	ref		ref	
Recurrence	7.1 (5.22–9.66)	<0.01*	—	—
Lung metastasis	3.91 (3.11–4.92)	<0.01*	4.26 (3.28–5.53)	<0.01*
Lung surveillance modality				
CXR	ref	—	ref	—
CT	1.61 (1.17–2.21)	<0.01*	1.01 (0.71–1.43)	0.97

*Significant.
CXR, chest x-ray; HR, hazard ratio; UPS, undifferentiated pleomorphic sarcoma.

and showed that 83% of asymptomatic lung metastases were detected by CXR. The current study differs from the existing literature in that it further establishes the utility of CXR for lung surveillance after resection of high-grade soft tissue sarcoma, a subset of sarcoma that has been deemed high-risk for lung metastases. On Kaplan-Meier
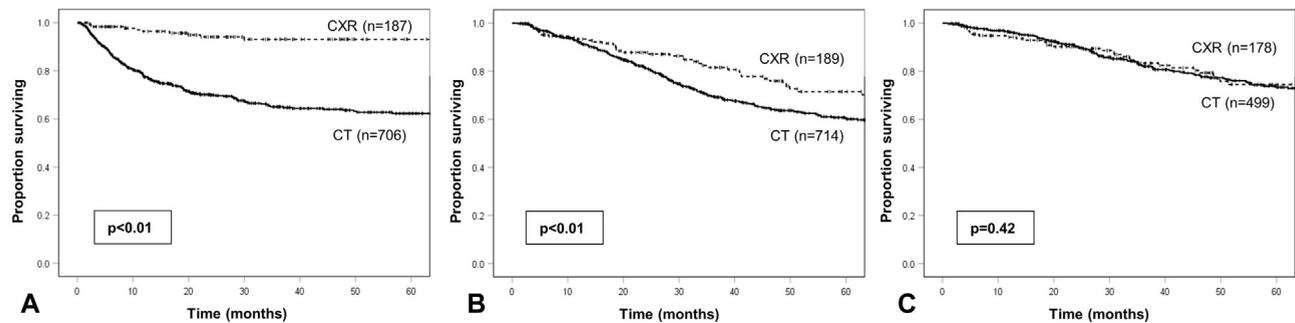
Figure 2. Kaplan-Meier curves of patients with pulmonary metastasis compared according to chest imaging modality. (A) Lung-specific recurrence-free survival, (B) overall survival, and (C) overall survival excluding patients with documented lung metastases. CXR, chest x-ray.

analysis, patients in the CXR cohort had a superior 5-year lung-specific recurrence-free survival (Fig. 2A). It naturally follows to question whether this observation in recurrence-free survival is related to a decreased diagnostic sensitivity of the CXR modality, and a higher false-negative rate and inability to detect a metastasis. However, if patients surveyed with CXR had lung metastases that were not detected and therefore not treated, this cohort would likely have had a decreased overall survival compared with the CT cohort. In contrast, the CXR cohort had an improved 5-year overall survival (Fig. 2B). To further investigate this observation, survival analysis was repeated after excluding patients in whom no lung metastases was detected, which demonstrated near identical 5-year overall survival rates between imaging cohorts (CXR 73% vs CT 74%; p = 0.42) (Fig. 2C). Given the known poor prognosis of untreated lung metastases, this finding suggests that CXR is not associated with a high false-negative rate of clinically significant nodules, which would otherwise have led to worse overall survival compared with CT. These results were further supported with multivariable Cox regression, which demonstrated that surveillance modality was not associated with decreased overall survival (HR 1.01; 95% CI 0.71 to 1.4; p = 0.97) when considering age, tumor size, tumor location, margin status, and receipt of adjuvant radiation. It appears that CXR provides an adequate detection threshold for clinically significant lung nodules.

The decreased survival observed in the CT cohort is a result of selection bias, specifically unidentified factors that influenced the decision to survey with CT vs CXR. Given this study's retrospective design, these factors cannot be identified accurately. One potential explanation is that patients in the CT cohort were more likely to have primary retroperitoneal soft tissue sarcomas. It is well established that retroperitoneal sarcomas have a high propensity for early local recurrence, and that this local progression can be the main driver of disease-specific death.[28] Given that these patients generally undergo local abdominopelvic

surveillance with CT, it is likely that lung surveillance would have been pursued with the same modality.

Notably, for both imaging cohorts, the majority of lung metastases were detected within the first 2 years (Table 1), a finding that is in accord with other series.[35] In addition, there was no difference in the intervention frequency and type pursued, including ablation, radiation, operation, or chemotherapy, for these lung metastases (p > 0.05). Therefore, it does not seem that CT surveillance results in an earlier diagnosis of lung metastases and more prompt treatment, particularly because the overall survival was not superior to CXR surveillance.

Although cost should not be the primary driver of our decision making, the importance of being thoughtful about the cost of each intervention is ever-increasing. Cost-effectiveness is commonly cited in studies on surveillance strategies for soft tissue sarcoma. However, few have examined the actual costs to the US healthcare system of follow-up surveillance according to NCCN guidelines, which recommend chest imaging with either CXR or CT every 3 to 6 months for 2 to 3 years, then every 6 months for the next 2 years, and then annually.[22] A review by Goel and colleagues[36] in 2004 summarized the literature on the topic from 1982 to 2003 and found wide disparity in costs of 54 methods of following soft tissue sarcoma patients. The financial analysis in our study,

Table 3. Cost Model Assumptions

STS incidence	n	%
Incidence of STS (2018)	13,040[1]	—
Non-metastatic STS	10,432[27]	80
High-grade STS	6,676[28]	64
Retroperitoneal STS	2,671[28]	40
Trunk STS	668[28]	10
Extremity STS	1,068[28]	16
Final cohort	4,406	—

STS, soft tissue sarcoma.

Table 4. Cost Data

Modality	CPT code	Cost, $
Chest x-ray	71046	30.96
CT	72178	183.96
Video-assisted thoracoscopic wedge resection	32666	904.31

Cost of each imaging modality or intervention was derived by using the 2018 Medicare Physician Fee Schedule.

which is based on current NCCN guidelines and takes into account sensitivity and specificity of each modality, demonstrates that a CXR-based protocol could lead up to $5 million to $8 million in savings to the US healthcare system per 5-year surveillance period, depending on whether a low- or high-frequency surveillance strategy is used. Notably, compared with CT, CXRs provide decreased radiation exposure and are more readily available, particularly at smaller community-based practices.

The limitations of this work stem from its retrospective design and lack of granular data about frequency of surveillance. It should also be noted that this study includes only patients who were selected for surveillance with either CXR or CT. This decision is inherently subject to bias, as patients chosen to undergo surveillance with CT might have been deemed to be higher risk for distant recurrence. Indeed, in 2003, Sakata and colleagues[37] examined whether tumor grade and size accounted for variation in follow-up of soft tissue sarcoma. The authors found that office visits, laboratory tests, and imaging were ordered more frequently with increasing tumor size and grade. In an effort to reduce this selection bias, this study was limited to high-grade soft tissue sarcoma. However, it is difficult to account for all clinicopathologic differences between each group that could introduce bias. In addition, there are several limitations to our cost model resulting from our assumptions. The incidence data are derived from published estimates. Additionally, cost data were estimated using Medicare payments as a proxy, given the interest in estimating cost to the US healthcare system. Although these costs can change over time and certainly vary per institution, the economic impact of a surveillance protocol using CXR is nonetheless compelling. The results of this study are not attempting to propose a protocol for generalized acceptance, but simply suggesting that the modality of lung surveillance in high-grade soft tissue sarcoma can include CXR with no associated decrease in survival. A prospective clinical trial is being developed to identify whether CXR is the optimal lung surveillance modality after resection of high-grade soft tissue sarcoma by providing non-inferior survival compared with CT at a reduced financial burden to the US healthcare system.

CONCLUSIONS

In this large multicenter study, lung surveillance with CXR did not result in worse overall survival compared with CT. Considering a potential cost savings of $5 million to $8 million per 5-year surveillance period, a CXR-based protocol can optimize resource use for lung surveillance in patients after resection of high-grade soft tissue sarcoma.

Author Contributions

Study conception and design: Gamboa, Switchenko, Lipscomb, Maithel, Delman, Cardona

Acquisition of data: Ethun, Poultsides, Grignol, Howard, Gamblin, Roggin, Votanopoulos, Fields

Analysis and interpretation of data: Gamboa, Switchenko, Lipscomb, Maithel, Delman, Cardona

Drafting of manuscript: Gamboa, Switchenko, Lipscomb, Maithel, Delman, Cardona

Critical revision: Gamboa, Ethun, Switchenko, Lipscomb, Poultsides, Grignol, Howard, Gamblin, Roggin, Votanopoulos, Fields, Maithel, Delman, Cardona

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7–30.
2. Feig BW, Ching CD. The MD Anderson Surgical Oncology Handbook. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health; 2012.
3. Cariboni U, De Sanctis R, Giaretta M, et al. Survival outcome and prognostic factors after pulmonary metastasectomy in sarcoma patients: a 18-year experience at a single high-volume referral center. Am J Clin Oncol 2019;42:6–11.
4. Markhede G, Angervall L, Stener B. A multivariate analysis of the prognosis after surgical treatment of malignant soft-tissue tumors. Cancer 1982;49:1721–1733.
5. Mandard AM, Petiot JF, Marnay J, et al. Prognostic factors in soft tissue sarcomas. A multivariate analysis of 109 cases. Cancer 1989;63:1437–1451.
6. Coindre JM, Terrier P, Guillou L, et al. Predictive value of grade for metastasis development in the main histologic types of adult soft tissue sarcomas: a study of 1240 patients from the French Federation of Cancer Centers Sarcoma Group. Cancer 2001;91:1914–1926.

Table 5. Cost Model Results for a 5-Year Surveillance Period for High-Grade Soft Tissue Sarcoma

Surveillance protocol	Low-frequency surveillance	High-frequency surveillance
Chest x-ray, $, mean ± SD	2,333,224 ± 32,057.71	2,985,268 ± 33,626.64
CT, $, mean ± SD	7,858,637 ± 62,783.94	10,839,000 ± 77,141.49
Savings, $	5,525,413	7,853,732

7. Rehders A, Hosch SB, Scheunemann P, et al. Benefit of surgical treatment of lung metastasis in soft tissue sarcoma. Arch Surg 2007;142:70−75; discission 76.

8. Casson AG, Putnam JB, Natarajan G, et al. Five-year survival after pulmonary metastasectomy for adult soft tissue sarcoma. Cancer 1992;69:662−668.

9. Billingsley KG, Burt ME, Jara E, et al. Pulmonary metastases from soft tissue sarcoma: analysis of patterns of diseases and postmetastasis survival. Ann Surg 1999;229:602−610; discussion 610−612.

10. Garcia Franco CE, Algarra SM, Ezcurra AT, et al. Long-term results after resection for soft tissue sarcoma pulmonary metastases. Interact Cardiovasc Thorac Surg 2009;9:223−226.

11. Pastorino U, Buyse M, Friedel G, et al. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. J Thorac Cardiovasc Surg 1997;113:37−49.

12. Jablons D, Steinberg SM, Roth J, et al. Metastasectomy for soft tissue sarcoma. Further evidence for efficacy and prognostic indicators. J Thorac Cardiovasc Surg 1989;97:695−705.

13. Gadd MA, Casper ES, Woodruff JM, et al. Development and treatment of pulmonary metastases in adult patients with extremity soft tissue sarcoma. Ann Surg 1993;218:705−712.

14. Verazin GT, Warneke JA, Driscoll DL, et al. Resection of lung metastases from soft-tissue sarcomas. A multivariate analysis. Arch Surg 1992;127:1407−1411.

15. Roth JA, Putnam JB Jr, Wesley MN, Rosenberg SA. Differing determinants of prognosis following resection of pulmonary metastases from osteogenic and soft tissue sarcoma patients. Cancer 1985;55:1361−1366.

16. Mentzer SJ, Antman KH, Attinger C, et al. Selected benefits of thoracotomy and chemotherapy for sarcoma metastatic to the lung. J Surg Oncol 1993;53:54−59.

17. Saltzman DA, Snyder CL, Ferrell KL, et al. Aggressive metastasectomy for pulmonic sarcomatous metastases: a follow-up study. Am J Surg 1993;166:543−547.

18. Choong PF, Pritchard DJ, Rock MG, et al. Survival after pulmonary metastasectomy in soft tissue sarcoma. Prognostic factors in 214 patients. Acta Orthop Scand 1995;66:561−568.

19. Nakamura T, Matsumine A, Yamakado K, et al. Lung radiofrequency ablation in patients with pulmonary metastases from musculoskeletal sarcomas [corrected]. Cancer 2009; 115:3774−3781.

20. Navarria P, Ascolese AM, Cozzi L, et al. Stereotactic body radiation therapy for lung metastases from soft tissue sarcoma. Eur J Cancer 2015;51:668−674.

21. Dhakal S, Corbin KS, Milano MT, et al. Stereotactic body radiotherapy for pulmonary metastases from soft-tissue sarcomas: excellent local lesion control and improved patient survival. Int J Radiat Oncol Biol Phys 2012;82:940−945.

22. National Comprehensive Cancer Network. The Complete Library of NCCN Oncology Practice Guidelines. Rockledge, PA: National Comprehensive Cancer Network; 2000.

23. Patel DB, Matcuk GR Jr. Imaging of soft tissue sarcomas. Chin Clin Oncol 2018;7:35.

24. Peloschek P, Sailer J, Weber M, et al. Pulmonary nodules: sensitivity of maximum intensity projection versus that of volume rendering of 3D multidetector CT data. Radiology 2007; 243:561−569.

25. Rissing S, Rougraff BT, Davis K. Indeterminate pulmonary nodules in patients with sarcoma affect survival. Clin Orthop Relat Res 2007;459:118−121.

26. Marten K, Engelke C, Seyfarth T, et al. Computer-aided detection of pulmonary nodules: influence of nodule characteristics on detection performance. Clin Radiol 2005;60:196−206.

27. Italiano A, Mathoulin-Pelissier S, Cesne AL, et al. Trends in survival for patients with metastatic soft-tissue sarcoma. Cancer 2011;117:1049−1054.

28. Brennan MF, Antonescu CR, Moraco N, Singer S. Lessons learned from the study of 10,000 patients with soft tissue sarcoma. Ann Surg 2014;260:416−421; discussion 421−412.

29. Kane JM 3rd. Surveillance strategies for patients following surgical resection of soft tissue sarcomas. Curr Opin Oncol 2004; 16:328−332.

30. Miller BJ, Carmody Soni EE, Reith JD, et al. CT scans for pulmonary surveillance may be overused in lower-grade sarcoma. Iowa Orthop J 2012;32:28−34.

31. Chou YS, Liu CY, Chen WM, et al. Follow-up after primary treatment of soft tissue sarcoma of extremities: impact of frequency of follow-up imaging on disease-specific survival. J Surg Oncol 2012;106:155−161.

32. Puri A, Gulia A, Hawaldar R, et al. Does intensity of surveillance affect survival after surgery for sarcomas? Results of a randomized noninferiority trial. Clin Orthop Relat Res 2014;472: 1568−1575.

33. Johnson FE, Sakata K, Sarkar S, et al. Patient surveillance after treatment for soft-tissue sarcoma. Int J Oncol 2011;38: 233−239.

34. Whooley BP, Gibbs JF, Mooney MM, et al. Primary extremity sarcoma: what is the appropriate follow-up? Ann Surg Oncol 2000;7:9−14.

35. Tseng WW, Amini B, Madewell JE. Follow-up of the soft tissue sarcoma patient. J Surg Oncol 2015;111:641−645.

36. Goel A, Christy ME, Virgo KS, et al. Costs of follow-up after potentially curative treatment for extremity soft-tissue sarcoma. Int J Oncol 2004;25:429−435.

37. Sakata K, Johnson FE, Beitler AL, et al. Extremity soft tissue sarcoma patient follow-up: tumor grade and size affect surveillance strategies after potentially curative surgery. Int J Oncol 2003;22:1335−1343.