Journal of Pediatric Surgery 56 (2021) 282–285

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Current surgical management of children with osteosarcoma and pulmonary metastatic disease: A survey of the American Pediatric Surgical Association☆

Timothy B. Lautz [a,*], Mark D. Krailo [b], Ruxu Han [b], Todd E. Heaton [c], Roshni Dasgupta [d], John Doski [e]

[a] Division of Pediatric Surgery, Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University, Chicago, IL
[b] COG Children's Oncology Group, Arcadia, CA, USA
[c] Division of Pediatric Surgery, Memorial Sloan Kettering Cancer Center, New York, NY
[d] Division of Pediatric General and Thoracic Surgery, Cincinnati Children's Hospital Medical Center, Cincinnati, OH
[e] Department of Surgery, UT Health Science Center San Antonio, San Antonio, TX

ARTICLE INFO

Article history:
Received 13 June 2020
Received in revised form 1 September 2020
Accepted 24 September 2020

Key words:
Osteosarcoma
Pulmonary
Metastasis
Metastasectomy
Pediatric
Thoracoscopy
Thoracotomy

ABSTRACT

Background: Rates of long-term survival for children with pulmonary metastatic osteosarcoma are low, and complete surgical resection of all visible pulmonary metastases is necessary for long term survival. Surgical approaches for metastasectomy include thoracotomy and thoracoscopy, with the approach chosen influenced by training and institutional bias. Thoracotomy with manual palpation of lung surfaces can identify nodules not seen on preoperative imaging, but no clear survival benefit has been demonstrated compared to complete thoracoscopic resection of all visible nodules.
Methods: All member of the American Pediatric Surgical Association were surveyed, and 204 members responded.
Results: Thoracoscopy was the preferred approach of 34% of surgeons for patients with 3 unilateral nodules but only 21% for those with 5 unilateral nodules. Hospital volume did not correlate with operative approach. Localization strategies are used by 37% of surgeons who prefer thoracotomy and 64% who prefer thoracoscopy. Importantly, the vast majority of responding surgeons (84%) expressed a willingness to participate in a randomized controlled trial of thoracotomy versus thoracoscopy.
Conclusion: Findings of this survey of North American pediatric surgeons confirm both the need for, and interest in, a prospective trial to define optimal surgical management of children with osteosarcoma with limited pulmonary metastasis.
Level of evidence: V.

Pulmonary metastases are present at diagnosis in approximately 20% of patients with osteosarcoma, and another 20% at relapse [1–3]. In the European and American Osteosarcoma Study (EURAMOS) of more than 2000 patients, 12.5% had pulmonary metastasis at diagnosis, and 92% of relapses involved the lungs [3]. Survival for patients with pulmonary metastatic disease is poor, with long term survival <40% consistently reported [4]. A prerequisite for cure is complete surgical clearance of all known metastatic disease. Open thoracotomy has been the standard approach for pulmonary metastasectomy and manual palpation of all lung surfaces frequently identifies additional small nodules not seen on preoperative imaging. Furthermore, some institutions advocate contralateral exploration in patients with unilateral disease on preoperative imaging, owing to the risk of nonvisualized contralateral lesions. However, the oncologic benefit of removing these "occult" nodules has not been established, and the potential benefit should be weighed against the morbidity of open thoracotomy. Improvements in imaging and localization techniques, along with advances in thoracoscopic technology now allow for successful minimally invasive excision of pulmonary metastases.

Given the importance of complete resection of pulmonary metastatic disease in osteosarcoma, optimizing surgical management has the potential to impact outcomes for these patients. While retrospective multi-institutional data have demonstrated equivalent survival with open and thoracoscopic pulmonary metastasectomy, the findings are limited by significant selection bias [5]. These retrospective data do suggest clinical equipoise for a randomized clinical trial (RCT) to definitively establish the optimal surgical approach. Considerable effort has been undertaken to design and implement an RCT in the Children's Oncology Group comparing pulmonary disease-free

☆ Funding: Funding support for this study was provided by The Mason Chandler Allen Memorial Foundation.

* Corresponding author at: Division of Pediatric Surgery, Ann and Robert H. Lurie Children's Hospital of Chicago, 225 East Chicago Avenue, Box 63, Chicago, Illinois 60611. Tel.: +1 312 227 4210.
E-mail address: tlautz@luriechildrens.org (T.B. Lautz).

https://doi.org/10.1016/j.jpedsurg.2020.09.060
0022-3468/

survival in patients undergoing pulmonary metastasectomy by open surgery versus thoracoscopy. However, a major barrier to conducting such a trial is determining patient and provider willingness to undergo randomization. Given the relative rarity of the problem, adequate accrual is dependent on a strong majority of surgeons believing in the equipoise of the surgical question. A survey of the American Pediatric Surgical Association (APSA) membership was thus undertaken to obtain current practice information and willingness to participate in an RCT.

1. Methods

A survey on preferred surgical approach to patients with osteosarcoma pulmonary metastasis, as well as willingness to participate in an RCT, was distributed electronically to members of the American Pediatric Surgical Association. The study was approved through the Institutional Review Board of Christus Health and authorized through the APSA Outcomes and Evidence based practice committee. The survey was sent to all 1197 active and associate members of APSA during the month of November 2016. This included an initial email invitation followed by 3 reminder emails sent over the course of the month to those who did not respond. The median response rate for surveys administered through the APSA Outcomes and Evidence Based Practice committee is 27%. Survey questions and response options are listed in Appendix 1. Questions investigated surgeon's practice type, preferred surgical approach based on disease burden, utilization of localization techniques, willingness to participate in a randomized controlled trial, and annual volume of patients meeting potential inclusion criteria for a randomized trial. Questions about surgical approach for different scenarios were all based on patients with synchronous pulmonary metastatic disease at the time of osteosarcoma diagnosis. The pulmonary operation in these scenarios typically occurs after induction chemotherapy and definitive local control, but while the patient remains on chemotherapy. Recognizing that surgical approach for an individual patient is based on many factors besides simply the number and laterality of the nodules (including central vs peripheral location, relationship to major structures, etc), the intent of this analysis was to capture general practice trends. Analyses were conducted eliminating missing data; a no imputation strategy for such data was employed. For cross tabulated answers, the p-value for the test of hypothesis that the row characteristic was not associated with the column characteristic was calculated using the exact conditional method [6].

2. Results

The survey was completed by 204 pediatric surgeons from North America, 78% ($n = 149$) of whom practice at academic children's hospitals. Complete responses are summarized in Appendix 2. Respondents reported treating a median of 3 patients per year with newly diagnosed osteosarcoma and limited metastatic disease burden in the lungs. Sixteen percent ($n = 28$) reported that their institutions cared for more than 5 of these patients per year. One hundred and sixty-five participants, representing the vast majority of respondents (85%, confidence interval 79%–89%) expressed a willingness to participate in a randomized trial comparing thoracoscopy to thoracotomy for these patients.

In describing their surgical approach for patients with pulmonary metastases from osteosarcoma, practice patterns differed depending on the extent of metastatic disease (Table 1). Thoracoscopy was the preferred approach for 34% of surgeons for patients with newly diagnosed osteosarcoma (synchronous disease present at diagnosis) with limited unilateral (3 on one side) and for 35% of patients with bilateral (3 on one side, 1 on the other) disease. However, for a patient with newly diagnosed osteosarcoma with more extensive (5 nodules) unilateral disease, only 21% expressed a preference for thoracoscopy. For patients with unilateral disease on imaging, 29% of surgeons perform a routine contralateral exploration.

Table 1
Survey responses with confidence intervals for preferred operative approach and willingness to participate in randomized trial.

	Thoracotomy	Thoracoscopy
Unilateral disease: 3 nodules	134 (66%; CI 59%–72%)	69 (34%; CI 28%–41%)
Unilateral disease: 5 nodules	160 (79%; CI 73%–84%)	43 (21%; CI 16%–27%)
Bilateral disease: 3 + 1 nodules	131 (65%; CI 58%–72%)	69 (35%; CI 28%–42%)
	Yes	**No**
Willingness to participate in randomized trial	165 (85%; CI 79%–89%)	30(15%; CI 11%–21%)

CI, confidence interval.

Hospital volume did not correlate with surgical approach for any of the three patient scenarios. For the scenario of a patient with 3 unilateral nodules, 22% (6 of 27) at high volume (>5 per year) centers prefer thoracoscopy compared to 36% (52 of 145) at lower volume centers ($p = 0.19$). Likewise, there was no difference in utilization of routine contralateral exploration at high volume (10 of 28, 36%) or lower volume centers (40 of 143, 28%; $p = 0.50$).

Localization strategies are utilized by 46% ($n = 90$) of surgeons when resecting osteosarcoma pulmonary metastases. The preferred localization approach was a wire in 26% ($n = 23$), methylene blue injection in 14% ($n = 13$), intraoperative sonography in 8% ($n = 7$), the combination of a wire and methylene blue in 28% ($n = 25$), and another combination of the above modalities in 19% ($n = 17$). Five respondents did not identify their preferred approach for localization. There was no difference in utilization of localization strategies at high volume (13 of 28, 46%) or lower volume (68 of 143, 48%, $p = 1$) centers. However, there was a significantly greater utilization of localization techniques by respondents who perform a thoracoscopic approach for 3 unilateral nodules (41 of 64, 64%) compared to those who perform thoracotomy (48 of 129, 37%, $p = 0.0007$).

3. Discussion

The lung is the most common metastatic site in osteosarcoma, both at initial presentation and recurrence. Pulmonary metastasectomy is believed to play a crucial role in the care of these patients, with complete surgical resection of all known metastatic disease shown to be a consistent prerequisite for survival in published studies [2,7–10]. However resection of “occult” nodules – microscopic nodules identified by manual palpation but not seen on imaging – has never been shown to influence recurrence or survival. Specifically, patients with unilateral disease who underwent unilateral thoracotomy with manual palpation of just that one lung were equally likely to have ipsilateral and contralateral recurrence [11]. While reports document statistically significant survival benefit in those who had pulmonary metastasectomy for osteosarcoma, two recent systematic literature reviews have shown that most data come from single institution case series, with few cooperative group trials [12,13]. Survival data are obscured by the rarity of the problem, advances in imaging and surgical technique, varying chemotherapy regimens, and institutional biases. As a result, it has been difficult to establish a consensus for optimal surgical management. Findings from this survey confirm the heterogeneity of current practice, including the preferred operative technique, preference for contralateral exploration and utilization of localization techniques. Most importantly, however, the survey reveals widespread support

for a randomized trial to more definitively determine optimal surgical management.

While diagnostic imaging is employed to define extent, location, and laterality of disease to inform surgical strategy, manual palpation is believed necessary to ensure complete resection of all lesions. One study demonstrated that the number of lung lesions seen on preoperative CT scan correlated poorly with operative findings and underestimated the number of viable metastases in 26% of patients [14]. An additional study of patients presenting with unilateral disease within 2 years of diagnosis who underwent contralateral exploration identified contralateral disease in 86% of patients [15]. However in a similar group of patients with unilateral metastatic disease from another institution managed with unilateral thoracotomy and no contralateral exploration, the incidence of recurrence was similar in the ipsilateral and contralateral lung [11]. The advent of thoracoscopy further complicates surgical strategy. One recent investigation utilizing high resolution CT found that thoracoscopic resection of solitary metachronous metastasis did not compromise survival [16]. Without tactile feel, thoracoscopy relies on preoperative and intraoperative nodule identification, and in many cases intraoperative localization techniques with wires, coils, dye or intraoperative ultrasound [17]. While thoracotomy remains the mainstay of pediatric practice, thoracoscopy is more widespread in adult patients owing to findings of comparable survival with decreased morbidity in selected patients with various sarcoma histologies [18]. However, no direct comparisons of the two surgical techniques have been performed in adult patients with osteosarcoma, and selection bias complicates interpretation because thoracoscopy is utilized more frequently for patients with better prognostic features (solitary, peripheral, and/or unilateral nodules). Furthermore, with increased utilization of muscle-sparing techniques for thoracotomy, the extent to which surgical morbidity differs between the two approaches is unclear.

The inconclusive evidence on optimal surgical practice manifests with wide variety in clinical practice for the management of these patients. A survey of the membership of the Connective Tissue Oncology Society (CTOS), a multidisciplinary sarcoma focused organization, demonstrated that management of a 2 cm unilateral lung nodule present at initial diagnosis varies widely between medical providers [19]. Treatment strategies ranged from resection at initial diagnosis, delayed resection during chemotherapy, to resection after completion of chemotherapy. Surgical approach in this survey ranged from unilateral thoracoscopic resection to bilateral thoracotomies to median sternotomy. The management of nodules present at diagnosis that resolved with chemotherapy was also found to be variable, and the natural history of such patients, in the absence of attempted resection, is poorly understood.

Findings from our survey confirm the heterogeneity of current practice but indicate a willingness to participate in an RCT limited to patients with oligometastatic disease in one or both lungs to optimally compare surgical and oncologic outcomes between surgical approaches. Our survey suggests that in those scenarios, approximately one-third of pediatric surgeons prefer thoracoscopy, while two-thirds prefer thoracotomy. While the use of thoracoscopy for patients with 3 or fewer nodules by a substantial minority of surgeons was expected, the preference for thoracoscopy even in patients with 5 nodules by 21% of surgeons was surprising. While this may represent response bias, the use of newer localization techniques such as fluorescence-guided surgery with ICG may in fact make this feasible in very select circumstances. The survey suggests that many but not all surgeons have experience with the localization techniques necessary for reliable and successful thoracoscopic excision. That experience has increased further since this survey was administered, and new techniques including microcoil localization and fluorescence-guided metastasectomy have gained some use.

Although limited by a survey response rate < 20%, our results do include broad representation of different types of pediatric surgical practice across North America and are thus likely representative of current practice. Furthermore, in the event that surgeons who have increased specialization in pediatric surgical oncology or who care for more patients with metastatic osteosarcoma were more likely to respond to the survey, the findings would actually better correlate with anticipated participation in the proposed randomized trial. Additionally, in extensive discussions with oncologists in the COG bone tumor committee, strong support for a randomized trial has been repeatedly demonstrated. Finally, support was obtained from patients at an osteosarcoma patient advocacy meeting (The MIB FACTOR Conference) in 2019, with 69% of respondents expressing willingness to enroll in a randomized trial [20].

In conclusion, this survey of the American Pediatric Surgical Association membership highlights the need for, and the average pediatric surgeon's interest in a randomized controlled trial to define optimal surgical management of children with osteosarcoma with limited pulmonary metastasis.

Appendix A. Appendix 1: survey questions

What is your surgical approach for a patient with newly diagnosed osteosarcoma and 3 unilateral radiographically diagnosed pulmonary metastases?

Open Thoracotomy Thoracoscopy

What is your surgical approach for a patient with newly diagnosed osteosarcoma and 5 unilateral radiographically diagnosed pulmonary metastases?

Open Thoracotomy Thoracoscopy

What is your surgical approach for a patient with newly diagnosed osteosarcoma and 3 unilateral radiographically diagnosed pulmonary metastases, 2 on the right, one on the left?

Open Thoracotomy Thoracoscopy

Do you perform a staged contralateral procedure for a patient with newly diagnosed osteosarcoma and 3 unilateral radiographically diagnosed pulmonary metastases?

Yes No

Would you be willing to participate in a study of patients with newly diagnosed osteosarcoma and pulmonary metastases where you could be asked to perform thoracoscopy when your traditional approach would be open thoracotomy (or vice versa)?

Yes No

Do you use localization strategies when resecting pulmonary nodules in osteosarcoma?

Yes No

IR Wire placement is a localization strategy when resecting pulmonary nodules in osteosarcoma utilized Yes

IR injection of methylene blue is a localization strategy when resecting pulmonary nodules in osteosarcoma utilized Yes

Intraoperative sonography is a localization strategy when resecting pulmonary nodules in osteosarcoma utilized Yes

Number of patients with newly diagnosed osteosarcoma and <3 pulmonary metastases treated at your institution per year _____

Type of practice Academic Children's Hospital Community Children's Hospital Community Hospital

Zip Code/Province of practice _____

Appendix B. Appendix 2: complete survey results

What is your surgical approach for a patient with newly diagnosed osteosarcoma and 3 unilateral radiographically diagnosed pulmonary metastases?	Count	%
Unknown/Missing	1	.
Thoracotomy	134	66.0%
Thoracoscopy	69	34.0%
Frequency missing = 1		
What is your surgical approach for a patient with newly diagnosed osteosarcoma and 5 unilateral radiographically diagnosed pulmonary metastases?	Count	%
Unknown/Missing	1	.
Thoracotomy	160	78.8%
Thoracoscopy	43	21.2%
Frequency missing = 1		
What is your surgical approach for a patient with newly diagnosed osteosarcoma and 3 radiographically diagnosed pulmonary metastases, 2 on right, 1 on left side?	Count	%
Unknown/Missing	4	.
Thoracotomy	131	65.5%
Thoracoscopy	69	34.5%
Frequency missing = 4		
Do you perform a staged contralateral procedure for a patient with newly diagnosed osteosarcoma and 3 unilateral radiographically diagnosed pulmonary metastases?	Count	%
Unknown/Missing	10	.
No	138	71.1%
Yes	56	28.9%
Frequency missing = 10		
Would you be willing to participate in a study of patients with newly diagnosed osteosarcoma and pulmonary metastases where you could be asked to perform thoracoscopy when your traditional approach would be open thoracotomy (or vice versa)?	Count	%
Unknown/Missing	9	.
No	30	15.4%
Yes	165	84.6%
Frequency missing = 9		
Do you use localization strategies when resecting pulmonary nodules in osteosarcoma?	Count	%
Unknown/Missing	10	.
No Localization	104	53.6%
Localization	90	46.4%
Frequency missing = 10		
Localization strategy	Count	%
Missing: not answered	10	.
Missing: do not apply (answered "no localization")	104	.
None identified	5	5.6%
IR wire placement	23	25.6%
IR injection of methylene blue	13	14.4%
Intraoperative sonography	7	7.8%
IR wire placement; IR injection of methylene blue	25	27.8%
IR injection of methylene blue; intraoperative sonography	3	3.3%
IR wire placement; intraoperative sonography	5	5.6%
IR wire placement; IR injection of methylene blue; intraoperative sonography	9	10.0%
Frequency missing = 114		
Number of patients with newly diagnosed osteosarcoma and <3 pulmonary metastases treated at your institution per year.	Count	%
.	31	.
0	4	2.3%
1	35	20.2%
2	29	16.8%
3	26	15.0%
4	10	5.8%
5	41	23.7%
6	3	1.7%
8	5	2.9%
10	10	5.8%
12	4	2.3%
15	2	1.2%
20	3	1.7%
30	1	0.6%
Frequency missing = 31		
Type of practice	Count	%
Not answered/missing	14	.
Academic children	149	78.4%
Community children	34	17.9%
Community	7	3.7%
Frequency missing = 14		

(continued on next page)

References

[1] Duffaud F, Digue L, Mercier C, et al. Recurrences following primary osteosarcoma in adolescents and adults previously treated with chemotherapy. Eur J Cancer. 2003; 39:2050–7.

[2] Kager L, Zoubek A, Potschger U, et al. Primary metastatic osteosarcoma: presentation and outcome of patients treated on neoadjuvant Cooperative Osteosarcoma Study Group protocols. J Clin Oncol. 2003;21:2011–8.

[3] Smeland S, Bielack SS, Whelan J, et al. Survival and prognosis with osteosarcoma: outcomes in more than 2000 patients in the EURAMOS-1 (European and American Osteosarcoma Study) cohort. Eur J Cancer. 2019;109:36–50.

[4] Mirabello L, Troisi RJ, Savage SA. Osteosarcoma incidence and survival rates from 1973 to 2004: data from the Surveillance, Epidemiology, and End Results Program. Cancer. 2009;115:1531–43.

[5] Doski JJ, Faroqui Z, Murphy AJ, et al. Thoracoscopy or thoracotomy for the management of metastatic osteosarcoma: A pediatric surgical oncology research study. Presented at the American Pediatric Surgical Association; 2019.

[6] Bishop YMM, Feinberg SE, Holland PW. Discrete multivariate analysis. Cambridge MA: MIT Press; 1975.

[7] Briccoli A, Rocca M, Salone M, et al. High grade osteosarcoma of the extremities metastatic to the lung: long-term results in 323 patients treated combining surgery and chemotherapy, 1985-2005. Surg Oncol. 2010;19:193–9.

[8] Ferrari S, Briccoli A, Mercuri M, et al. Postrelapse survival in osteosarcoma of the extremities: prognostic factors for long-term survival. J Clin Oncol. 2003;21:710–5.

[9] Kempf-Bielack B, Bielack SS, Jurgens H, et al. Osteosarcoma relapse after combined modality therapy: an analysis of unselected patients in the Cooperative Osteosarcoma Study Group (COSS). J Clin Oncol. 2005;23:559–68.

[10] Salah S, Fayoumi S, Alibraheem A, et al. The influence of pulmonary metastasectomy on survival in osteosarcoma and soft-tissue sarcomas: a retrospective analysis of survival outcomes, hospitalizations and requirements of home oxygen therapy. Interact Cardiovasc Thorac Surg. 2013;17:296–302.

[11] Karplus G, McCarville MB, Smeltzer MP, et al. Should contralateral exploratory thoracotomy be advocated for children with osteosarcoma and early unilateral pulmonary metastases? J Pediatr Surg. 2009;44:665–71.

[12] Diemel KD, Klippe HJ, Branseheid D. Pulmonary metastasetomy for osteosarcoma: is it justified? Recent Results Cancer Res. 2009;179:183–208.

[13] Treasure T, Fiorentino F, Scarci M, et al. Pulmonary metastasectomy for sarcoma: a systematic review of reported outcomes in the context of Thames Cancer Registry data. BMJ Open. 2012;2.

[14] Kayton ML, Huvos AG, Casher J, et al. Computed tomographic scan of the chest underestimates the number of metastatic lesions in osteosarcoma. J Pediatr Surg. 2006;41:200–6 [discussion 200-206].

[15] Su WT, Chewning J, Abramson S, et al. Surgical management and outcome of osteosarcoma patients with unilateral pulmonary metastases. J Pediatr Surg. 2004;39: 418–23 [discussion 418-423].

[16] Fernandez-Pineda I, Daw NC, McCarville B, et al. Patients with osteosarcoma with a single pulmonary nodule on computed tomography: a single-institution experience. J Pediatr Surg. 2012;47:1250–4.

[17] Gow KW, Saad DF, Koontz C, et al. Minimally invasive thoracoscopic ultrasound for localization of pulmonary nodules in children. J Pediatr Surg. 2008;43:2315–22.

[18] Gossot D, Radu C, Girard P, et al. Resection of pulmonary metastases from sarcoma: can some patients benefit from a less invasive approach? Ann Thorac Surg. 2009;87: 238–43.

[19] Bhattasali O, Vo AT, Roth M, et al. Variability in the reported management of pulmonary metastases in osteosarcoma. Cancer Med. 2015;4:523–31.

[20] Participant Survey. MIB agents annual meeting Miami FL January 26 ; 2019.