Published in final edited form as:
J Pediatr Surg. 2012 June ; 47(6): 1250–1254. doi:10.1016/j.jpedsurg.2012.03.033.

Patients with osteosarcoma with a single pulmonary nodule on computed tomography: a single-institution experience☆

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Abstract

Background/Purpose—The purpose of this study is to determine if patients with osteosarcoma (OS) with metachronous metastatic pulmonary disease presenting with a single pulmonary nodule (SPN) on computed tomography (CT) were found to have other lesions at the time of thoracotomy.

Methods—Data were collected retrospectively on consecutive patients with OS treated at our institution from 1982 to 2007. Patients with no evidence of disease at the end of initial therapy who subsequently relapsed in the lung were identified.

Results—In our study, 16 (8%) of 198 patients with OS with metachronous metastatic pulmonary disease presented with a SPN on CT scan. In all patients, only 1 metastatic nodule for OS was found at the time of thoracotomy. The median time between diagnosis and first lung relapse was 23.8 months (range, 4–80 months). Eleven patients (68.7%) subsequently had a second lung relapse, but only 3 patients had involvement of the ipsilateral lung (mean time interval between first and second pulmonary relapses of 17 months; range, 2–44 months). Five-year overall survival from diagnosis was 56.2%. Seven patients (43.8%) died of disease progression.

Conclusions—In our experience, patients with OS with metachronous metastatic pulmonary disease presenting with a SPN on CT were not found to have additional malignant lesions at the time of thoracotomy. Consideration should be given in this group of selected patients to use a minimally invasive approach to nodule removal with image-guided localization, if needed, rather than open thoracotomy because ipsilateral metastases are not likely to be found.

Keywords

Osteosarcoma; Lung nodule; Thoracotomy; Computed tomography

☆Supported in part by Cancer Center Support grants CA21765 and CA23099 from the National Cancer Institute and by the American Lebanese Syrian Associated Charities.

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Osteosarcoma (OS) is the most common malignant bone tumor arising in children and adolescents and has an annual incidence of approximately 400 cases in children younger than 20 years [1]. The combination of chemotherapy, local surgical control, and aggressive pulmonary metastasectomies in patients with metastatic disease has improved long-term survival of patients with OS. Fifteen to 20% of patients will have radiographically detectable pulmonary metastases at diagnosis (synchronous metastatic pulmonary disease). Among patients with nonmetastatic disease at diagnosis, 20% to 25% will relapse, usually in the lungs (metachronous metastatic pulmonary disease). Depending on the time of metastasis detection (early on therapy vs late off therapy), 20% to 45% of patients can be salvaged by resection of the pulmonary lesions, even if multiple operative procedures are required [2]. Complete resection of all disease is required for cure in patients with OS, even in patients with pulmonary metatastatic disease [3]. Because computed tomographic (CT) scans of the chest have been shown to underestimate the number of metastatic pulmonary nodules found at surgery [4], open thoracotomy, not thoracoscopy, is recommended for patients with metachronous pulmonary metastases (single or multiple) to permit thorough palpation of the pulmonary parenchyma and identification of all subcentimeric (<3 mm) nodules. We conducted this retrospective study to test our observation that patients with OS having a metachronous single pulmonary nodule (SPN) detected on CT 2 months or longer after completion of therapy do not appear to have additional lesions at the time of thoracotomy and may be able to avoid open thoracotomy. Open thoracotomy can result in substantial pleural and pulmonary scarring, which can complicate subsequent thoracotomies that are often needed in these patients. With improvement in minimally invasive surgery, most single pulmonary lesions depending on the nodule location can be completely resected by thoracoscopy, with or without preoperative image-guided localization. To verify this observation, we reviewed our experience treating patients with OS who presented with a metachronous SPN on CT.

1. Material and methods

A search of the solid tumor database of all patients with OS treated at St Jude Children's Research Hospital between 1982 and 2007 found 16 patients who had a SPN on follow-up CT imaging and then underwent thoracotomy (Figure). One pediatric radiologist (MBM) reviewed the CT imaging and confirmed the presence of a SPN. From 1982 to 1987, CTs were performed on a GE 8800 axial scanner (GE Medical Systems, Milwaukee, WI); from 1987 to 1992, on a Siemens DRH axial scanner (Siemens, Erlangen, Germany); from 1991 to 1992, on a Siemens Plus-S single-detector helical scanner; from 1992 to 2000, on a Siemens Plus-4 4-detector helical scanner; from 2000 to 2007, on a GELightspeed Ultra 8-detector helical scanner; and in 2007, on a GE VCT 64-detector helical scanner. Computed tomographic examinations performed after 1993 were available for review in our picture archive and communication system. All other CTs were reviewed as hard-copy film. Data regarding patient demographics, treatment, lung relapses, surgical findings at relapse, and survival status were collected. Surgical findings were analyzed qualitatively. Chemotherapy and surgical management of the primary tumor varied over the study period. All patients were treated on institutional protocols (OST-77, OS-86, OS-91, and OS-99) with chemotherapeutic agents that included cyclophosphamide, cisplatin, doxorubicin, methotrexate, carboplatin, and ifosfamide [5–7]. Patients were monitored at regular intervals to detect pulmonary metastases with CT scan. Between 1982 and 1999, follow-up evaluation after completion of therapy consisted of plain radiography of the chest every 6 to 8 weeks and CT of the chest every 4 months for the first 2 years. After this point, patients were evaluated by clinical assessment and plain radiography of the chest unless symptoms suggested tumor recurrence. After 1999, patients were monitored by plain radiography or CT of the chest every 2 to 3 months for the first year. Subsequently, patients underwent radiography or CT of the chest every 3 to 6 months for at least 4 years after completion of

therapy. After 2006, patients were monitored with CT chest and not chest radiographs. All patients with isolated pulmonary metastases had surgical resection via open thoracotomy. This retrospective review was approved by our institutional review board.

2. Results

Patient distribution and characteristics are shown in the Figure and Table 1. One hundred thirty-three patients with OS developed metachronous pulmonary nodules. Eighteen (13.5%) of these patients had nonmalignant pulmonary nodules confirmed on pathology after excision. Among them, 2 patients had a benign SPN, and 16 had multiple benign nodules. Among the identified 115 cases with OS and metachronous metastatic lung disease, 16 (13.9%) presented with a SPN. Therefore, among 133 patients with OS, 18 presented with a SPN during follow-up; 16 (88.8%) of the nodules were malignant, and 2 (11.2%) were benign. For the study group of 16 patients having a SPN that was found to be malignant, median age at diagnosis of primary OS was 11.5 years (range, 3–23 years). There were 9 male patients (56%). At diagnosis, 15 patients had localized OS without radiographic evidence of pulmonary metastasis, and 1 patient had metastatic lung disease that cleared after neoadjuvant chemotherapy. Primary tumor location was distal femur (n = 9), proximal tibia (n = 5), proximal humerus (n = 1), and iliac bone (n = 1).

The median time to first lung relapse was 23.8 months (range, 4–80); 3 (18.8%) of these 16 patients developed a SPN within the first year of diagnosis. Single pulmonary nodule location was left upper lobe (n = 6), right lower lobe (n = 5), left lower lobe (n = 3), right upper lobe (n = 1), and right middle lobe (n = 1). All patients underwent thoracotomy, and the entire lung was manually explored; no additional lesions were found either manually or by pathologic identification in the specimen. Pulmonary wedge resection was performed in 14 patients, and lobectomy, in 2 patients. A second lung relapse was observed in 11 (68.7%) of the 16 patients with involvement of the ipsilateral lung in 3 patients (median time interval between first and second pulmonary relapse was 17 months; range, 2–44 years) and contralateral lung in 8 patients (median time interval between first and second pulmonary relapses was 16 months; range, 1–43 months). The surgical approach for the second relapse was via open thoracotomy in all cases. Details of nodule location, surgical approach, and time interval between relapses are summarized in Table 2. Nine patients (56%) are alive without evidence of disease at follow-up of 2 to 27 years (median time, 12.4 years). Seven patients died of disease progression.

3. Discussion

Osteosarcoma accounts for approximately 5% of childhood cancers. At diagnosis, 20% of patients will have radiographically detectable metastases, with the lung being the most common site [1]. Factors that predict a better outcome in patients with pulmonary metastatic disease include fewer pulmonary nodules, unilateral pulmonary metastases, and longer intervals between primary tumor resection and metastases [2]. Hawkins and Arndt [3] also identified that solitary pulmonary nodules at recurrence, more than 24 months between the initial diagnosis and first disease recurrence, and achievement of a second complete response were positive factors for improving survival rates. Five-year overall survival is 65% to 75% for patients without lung metastases; in contrast, only 10% to 30% of patients with detectable metastatic OS at diagnosis will become long-term disease-free survivors [8,9]. The ability to achieve a complete resection of recurrent disease is the most important prognostic factor at first relapse, with a 5-year survival rate of 20% to 45% after complete resection of metastatic pulmonary disease. Treatment for patients with OS with pulmonary metastases remains a significant challenge at present [10–14], and the efficacy of systemic chemotherapy is variable using regimens based on combinations of ifosfamide, etoposide,

cyclophosphamide, gemcitabine, and docetaxel [15–18]. The ability to detect pulmonary nodules has increased by the use of refined helical CT that permits thinner axial sections and with picture archive communications systems that provide magnification and window/level to improve lesion conspicuity and characterization [19–21].

Our results suggest that patients with OS who present with a SPN on CT 2 months or longer after completion of therapy (metachronous metastasis) could be possibly spared an open thoracotomy; because this procedure is associated with pulmonary and pleural scarring that can complicate subsequent thoracotomies, this is a potentially important observation. This patient population frequently required multiple thoracotomies, and two-thirds of our patients had a second pulmonary relapse with a significant portion being ipsilateral.

Repeated thoracotomy with resection of pulmonary tissue can lead to a significant decrease in pulmonary function, thereby increasing the risk of postoperative respiratory complications. Although several adult studies document increased postoperative morbidity in patients with diminished pulmonary function, there is little information in the pediatric population. Tobias et al [22] reviewed the postoperative courses of 19 patients who underwent thoracotomy who preoperatively had diminished pulmonary function. They concluded that aggressive surgical treatment of metastatic pulmonary disease is indicated even in this group of patients, although aggressive perioperative management is suggested. Preoperative teaching, incentive spirometry, early ambulation, and effective pain management are recommended. Further prospective studies in pediatric patients who need repeated lung resections focusing on the perioperative and postoperative management are needed to optimize their care. Our observation for patients with OS with a SPN that is amenable to thoracoscopy may help to decrease the number of thoracotomies in this selected group of patients.

Video-assisted thoracoscopic surgery (VATS) has gained widespread acceptance as a method of resecting pulmonary metastases in pediatric patients with cancer. Advantages of the thoracoscopic approach include shortened hospital stay, decreased postoperative pain, improved cosmetic results, shorter convalescence, faster return to normal activity, and reduced pulmonary adhesions [23,24]. This is particularly important for patients with OS who are at risk to experience multiple metachronous pulmonary metastases and may need repeated thoracic surgeries. The better visualization of the pleura and the pulmonary surface owing to the magnification by the optic system permits the identification of nodules on the pleural surface [25]. The major disadvantage of VATS is that the surgeon cannot palpate the lung parenchyma, so that identification of deeper lesions is difficult. A few localization techniques have been described such as CT-guided hook-wire localization with or without injection of methylene blue, radioisotope marking under CT guidance using a handheld gamma probe during VATS for localizing pulmonary lesions, and intrathoracoscopic ultrasound [26]. Waldhausen et al [27] reported 3 pediatric cases using CT-guided needle localization, methylene blue staining, and VATS. Partrick et al [25] confirmed this technique as excellent for approaching pulmonary nodules less than 1 cm in size or those greater than 0.5 cm deep to the pleural surface in a group of 11 children. In 2008, Gow et al [28] published the use of thoracoscopic ultrasound for localization of pulmonary nodules in 7 children and concluded that this is a real-time imaging tool that helps isolate small pulmonary lesions that may otherwise be difficult to see intraoperatively. These techniques may be helpful to facilitate thoracoscopic resection of deeper seated SPNs, but they do not overcome the missed detection of additional subcentimeric nodules. Treatment for the patients with OS with pulmonary metastases remains a significant challenge. Repeated resections of pulmonary recurrences can lead to extended disease control and possible cure for some patients. In our experience, patients who presented with single metachronous pulmonary lesions on CT did not have other malignant nodules at the time of thoracotomy.

This finding may help to reduce the number of thoracotomies performed on this select group of patients. Our study is limited by the small number of patients, and prospective clinical trials are needed to confirm this retrospective observation.

Acknowledgments

The authors thank Valerie McPherson, CCRP, for data management.

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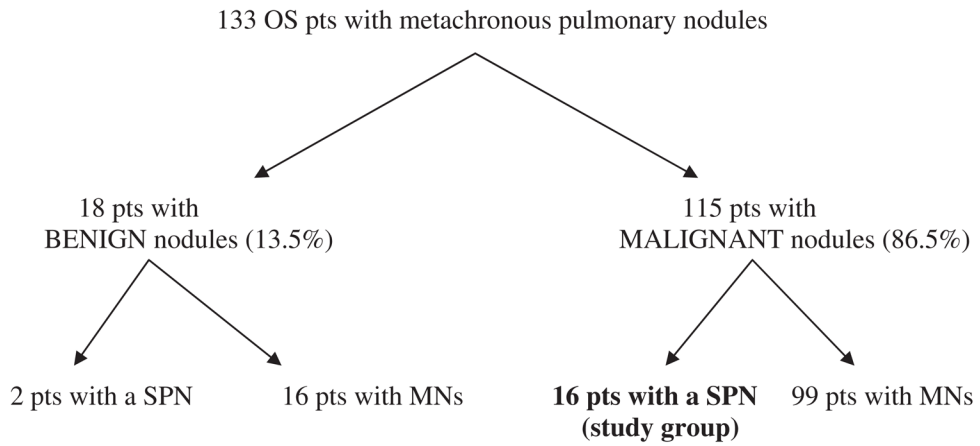

Figure. Patient's distribution
pts: patients, SPN: single pulmonary nodule, MNs: multiple nodules

Table 1

Patient characteristics, treatment protocol, and outcome

Patient	Sex	Age at diagnosis (y)	Treatment protocol	Outcome (time from diagnosis)
1	Female	23	OS 86	DOD 3 y
2	Female	3	OST 77	NED 28 y
3	Male	16	OST 77	DOD 2.1 y
4	Male	13	OST 77	DOD 2.1 y
5	Male	4	OST 77	DOD 4.1 y
6	Male	12	OST 77	DOD 9 y
7	Female	17	OS 99	NED 11 y
8	Male	12	OS 99	NED 10 y
9	Male	16	OS 91	NED 12 y
10	Female	10	OS 86	DOD 4 y
11	Male	9	OST 77	DOD 1.6 y
12	Male	16	OST 77	NED 30 y
13	Male	11	OST 77	NED 26 y
14	Female	10	OS 91	NED 13 y
15	Female	6	OS 91	NED 14 y
16	Female	7	OS 99	NED 5 y

Abbreviations: DOD, died of disease; NED, no evidence of disease.

Table 2

Location of pulmonary nodules, pathology, surgical approach, and time interval to relapse

Patient	First relapse (months between diagnosis and first relapse)/pathology	Surgical approach	Second relapse (months between first and second relapse)
1	LUL (16)/malignant SPN	Thoracotomy, wedge resection	LLL (5)
2	LUL (6)/malignant SPN	Thoracotomy, wedge resection	RLL (2)
3	LUL (20)/malignant SPN	Thoracotomy, wedge resection	Left pleural massive involvement (2)
4	RUL (13)/malignant SPN	Thoracotomy, wedge resection	LUL (1)
5	LUL (18)/malignant SPN	Thoracotomy, lobectomy	RLL (15)
6	ML (28)/malignant SPN	Thoracotomy, wedge resection	Left diaphragm massive involvement (12)
7	RLL (21)/malignant SPN	Thoracotomy, wedge resection	LUL (36)
8	RLL (22)/malignant SPN	Thoracotomy, wedge resection	RML (44)
9	LLL (12)/malignant SPN	Thoracotomy, wedge resection	RML (43)
10	RLL (17)/malignant SPN	Thoracotomy, wedge resection	LLL (11)
11	LLL (4)/malignant SPN	Thoracotomy, wedge resection	RLL, RUL, ML (9)
12	LUL (15)/malignant SPN	Thoracotomy, wedge resection	No second lung relapse
13	LLL (80)/malignant SPN	Thoracotomy, wedge resection	No second lung relapse
14	RLL (27)/malignant SPN	Thoracotomy, wedge resection	No second lung relapse
15	LUL (50)/malignant SPN	Thoracotomy, wedge resection	No second lung relapse
16	RLL (38)/malignant SPN	Thoracotomy, lobectomy	No second lung relapse

Abbreviations: RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe.