Role of pulmonary metastasectomy in osteosarcoma and soft tissue sarcoma

Rachel F Dear[1] and Martin HN Tattersall[2]
1. Sydney Cancer Centre, Royal Prince Alfred Hospital, New South Wales.
2. University of Sydney, New South Wales.
Email: rachel.dear@sydney.edu.au

Abstract

There are no randomised control trials to guide the management of patients with potentially resectable lung metastases from osteosarcoma and soft tissue sarcoma, however evidence from retrospective cohort series supports that all patients should be considered for pulmonary metastasectomy. Pulmonary metastasectomy can improve overall survival and some patients may even be cured. Careful patient selection is important. The most important favourable prognostic factor after pulmonary metastasectomy, in both osteosarcoma and soft tissue sarcoma, is the ability to achieve complete resection of metastatic disease. Incomplete resection carries a shorter survival than complete resection of lung metastases in almost all series. The outcome is poorer if the primary tumour is not controlled or, if there is a local recurrence that is not controllable. Patients with metastatic disease outside the lung are generally excluded from pulmonary metastasectomy. The number of lung metastases is not a contraindication to metastasectomy, nor a poor prognostic factor if it is assessed the metastases can be resected. It is not uncommon to perform sequential metastasectomies for bilateral disease. Even when features associated with a poor prognosis are present (for example high grade tumours), pulmonary metastasectomy may improve the survival of these patients because their survival without it is less than one year. Recurrence of lung metastases after pulmonary metastasectomy should be treated with repeat pulmonary metastasectomy if complete resection can be achieved. The addition of peri-operative chemotherapy is widely used, but its effectiveness remains an area of controversy and is a priority for future research.

Epidemiology

Patients with metastatic sarcoma were rarely considered for pulmonary metastasectomy (PM) prior to the 1970s, were treated palliatively and most died within one year of the development of metastatic disease. Variability in individual survival reflected the different histological types and biological behavior of the histological subtypes of soft tissue sarcoma (STS).

The lungs are the most common site of metastatic disease in sarcoma. Pulmonary metastases develop in 20% to 38% of all STS patients.[1-3] Even today, 30% of patients with osteosarcoma develop disease recurrence even after optimal surgery and chemotherapy, and more than 80% of these relapses are in the lungs.[4, 5] Long-term survival after recurrence is reported to be less than 20 to 30%.[4, 6-9] Most patients who die of metastatic sarcoma will have pulmonary metastases.

Pulmonary metastasectomy

PM is a surgical procedure to resect metastases from the lung. The surgical approach is similar whatever the primary tumour site of origin. Currently, PM may be considered in a number of primary cancers, including colorectal cancer, germ cell tumours, melanoma and renal cell cancer, as well as osteosarcoma and STS.

Surgical exploration of the chest may be performed by thoracotomy or thoracoscopy. The surgical approaches and procedures to resect metastases include segmentectomy, wedge resection, lobectomy and rarely pneumonectomy. Most pulmonary metastases can be removed by wedge resection. Bilateral synchronous metastases are usually treated with staged (sequential) procedures.

Advances in anaesthesia, surgical techniques and peri operative care have resulted in low peri-operative mortality and morbidity. Thoracoscopic resection has reduced peri operative complications and in-hospital stay. Mortality rates in recent series are less than one per cent and operative complications less than 10%. Potential complications include haemorrhage, infection, prolonged thoracostomy tube drainage, chest wall pain and reduced lung function.

Metastases to lung are most commonly blood borne. The growth rate of micrometastases is conventionally thought to be continuous at least until metastases are detected.[10] However, clinical observation is not always consistent with this model and some patients followed closely without recurrence for several years suddenly present with large volume metastatic disease. The continuous growth model does not explain these events.

Alternative models of metastastic growth have been proposed. Demicheli et al propose that micrometastases present in the pre-clinical phase, grow at different rates depending on tumour and/or host factors.[11] Micrometastases can escape dormancy by at least two different mechanisms: a) the loss of an angiogenesis inhibitor; or b) the transformation of a subpopulation of tumour cells to an angiogenic phenotype.

The continuous growth model predicts that metastatic cancer will rarely be curable by surgical removal. Long-term survival after resection of the primary tumour can be explained by the absence of metastases or by the slow growth of microscopic metastases. In contrast, the tumour dormancy model predicts elimination of metastatic disease is possible by a complete response following systemic treatments or removal of tumour cells with an angiogenic phenotype. A complete response is essential for long-term survival and this most commonly may be achieved by metastasectomy in selected cases.

An alternative hypothesis is that adjuvant chemotherapy eliminates rapidly dividing tumour cells in micrometastases, but slow growing or dormant micrometastatic disease can remain. These transiently dormant or slow growing cells are the source of isolated pulmonary or hepatic metastases, which become apparent after completion of adjuvant chemotherapy. Surgical removal can potentially eliminate all disease.

Another rationale for metastasectomy is that untreated metastases may give rise to other metastases - tertiary spread.[12,13] Metastasectomy may prevent further dissemination of disease to other metastatic sites.

Retrospective single institution cohort studies have reported that PM has significantly improved the life expectancy of patients with metastatic osteosarcoma and STS, with five year overall survival rates of 25 to 40%. Some of these patients are 'cured'. In STS, five year overall survival of 18% to 44% is reported after PM.[2, 14-18] The variability in survival is most likely due to patient selection and the different duration of follow-up in reported series.

A number of studies in osteosarcoma have retrospectively analysed outcomes in all patients presenting with disease recurrence, both limited to the lung and outside the lung. Overall survival is improved in those who achieve a complete surgical resection. In almost all patients surgery was for lung metastasectomy rather than resection of other sites of metastatic disease. Five year overall survival reports range from 39% to 50% for those with complete surgical resection compared to 0% who did not have surgery.[19, 20] In the former study, the median survival period for patients achieving a second surgical remission was 2.2 years (range, five days to 18.4 years), compared with 0.6 years for other patients (range, two days to 3.7 years).

There are a number of problems with the existing evidence that supports PM. Retrospective studies are subject to selection bias. In many reports it is unclear if the survival figures relate to overall survival (any death after PM) or crude survival (death related to sarcoma after PM). Disease free survival data are rarely presented. The absence of randomised control trials makes the survival effects of PM difficult to assess.

Prognostic factors for overall survival

The prognostic factors statistically significantly associated with survival vary across the reported series of PM. Below is a summary of the existing evidence about the effect of the most commonly assessed prognostic factors.

Two studies have reported a better outcome for patients younger than 40 years compared to older than 40 years at diagnosis.[16, 21] One study reported females have a better outcome than males, but in the majority of studies where it has been examined there is no significant gender difference.[14, 22-29]

Two studies have found a longer survival for a trunk primary, [22, 23] and one study has found a better prognosis for a limb primary.[21] Primary tumour histological type has been reported to influence survival after PM. Malignant fibrous histiocytoma was reported to have a better outcome than other types.[15] In other studies malignant fibrous histiocytoma has been reported to have a worse outcome.[17,30] Synovial sarcoma has been reported to have a worse outcome.[17,25] High tumour grade is reported to be a poor prognostic feature.[16,25, 26, 31] Others have found no association.[14, 21, 27-29, 32]

Disease free interval (DFI) (time from treatment of primary tumour until evidence of lung metastasis) is considered one of the most important prognostic factors and is thought to be a surrogate marker for disease biology. Although not confirmed in all reports,[15,21,25,26,28,29,33] a longer disease free interval is associated with a long overall survival after PM. Most studies report improved survival for a DFI longer than 12 months.[3,22-24, 27, 34] Others have found a statistically significant advantage for a DFI of more than 18 months,[30] more than 2.5 years,[16] and more than 25 months.[14]

Apart from one report showing a longer survival for unilateral disease,[15] the majority of studies show no difference in survival for unilateral metastases compared to bilateral metastases. Many studies report that the number of metastases, either on pre-operative imaging and/or on surgical pathology, has no bearing on prognosis.[16,21-23,28,29,32,33] In contrast, other studies report a shorter survival after PM for a greater number of metastases. The cut-off varies from two or more,[30] three or more,[35] four or more,[15] or five or more.[24] The maximum diameter of metastases on pre-operative imaging and/or surgical pathology has been examined as a prognostic factor in a limited number of studies.[17, 30] In both cases a diameter greater than two centimetres was found to carry a worse prognosis. Studies report that there is no difference in life expectancy in patients treated by unilateral thoracotomy (or thoracoscopy) and a bilateral (staged) procedure.[2, 16, 25, 26, 29]

Almost all studies report that complete resection of metastatic disease (histologically clear margins) is critical for long-term survival after PM. For example, Billingsley reported that the median survival time among patients with completely resected disease is 20 months, compared with 10 months for patients who have incompletely resected disease.[3] It seems that patients with an incomplete resection have a prognosis similar to patients who do not have a PM. Two small studies did not report a statistically significant effect on survival for complete resection.[21, 25]

In osteosarcoma most studies addressing prognostic factors for survival concentrate on children and adolescents, whereas adult patients constitute only a small proportion.[5] Complete resection of metastatic disease has consistently been shown to be an independent prognostic factor for survival.[20, 36-39] Patients with residual microscopic compromised surgical margins, or measurable disease, are unlikely to be cured. As for STS, a longer DFI is also associated with a longer survival after PM.[36, 40, 41] In most reports a DFI of less than 12 months carries a worse prognosis,[5, 42, 43] but others have found a cut-off of 24 months to be important.[7] In contrast to STS, the number of lung metastases appears to be an important prognostic factor for survival in osteosarcoma. Some reports show solitary lesions have a better prognosis.[19, 20, 42, 44] In other reports less than three to four nodules is favourable compared to more than four.[5, 7, 36] Only a few studies report the number of lung metastases is not a prognostic factor for overall survival.[43, 45]

Age, sex and metastases in one or both lungs have not been shown to be important prognostic factors. In 247 patients with lung metastases (47 of which had a PM) there was no survival difference for patients greater than or equal to 40 years, compared to those less than 40 years.[5] In one report of paediatric patients, males had a better overall survival than females.[8]

Patient selection

All patients with metastatic osteosarcoma and STS should be evaluated for the possibility of PM.[3, 14, 25, 29, 46-49]

Careful patient selection is important. The most important favourable prognostic factor after PM in both osteosarcoma and STS is the ability to achieve complete resection of metastatic disease. Incomplete resection carries a poorer prognosis in almost all series. Patients being considered for PM should have a good performance status and be a medical candidate for anaesthesia and lung resection. The primary tumour site should be controlled or, if there is a local recurrence, it should be controllable. Patients with metastatic disease outside the lung are generally excluded from PM. In general a high number of metastases is not a contraindication if it is felt they can be resected. It is not uncommon to perform sequential metastasectomies for bilateral disease. Even when features associated with a poor prognosis are present (for example high grade tumours) these patients are most likely to live longer with PM because their life expectancy without PM is less than two years.

Data collected by the International Registry of Lung Metastases, established in 1991 to assess the long-term results of PM, highlight important prognostic factors.[50] Of 5206 cases of PM from departments of thoracic surgery in Europe, the United States and Canada, the primary tumour was epithelial in 2260 cases, sarcoma in 2173, germ cell in 363 and melanoma in 328. The actuarial survival after complete resection was 36% at five years (median 35 months) and for incomplete resection was 13% at five years (median 15 months). Among complete resections, the five year survival was 33% for patients with a DFI of less than 12 months and 45% for a DFI of greater than 36 months; 43% for solitary metastases and 27% for four or more metastases. Multivariate analysis demonstrated a better prognosis for patients with germ cell tumors, DFI of greater than 36 months and solitary metastases. These three factors were used to develop a useful prognostic grouping applicable to sarcoma, as well as melanoma, epithelial and germ cell tumours:

- Group I resectable, no risk factors (DFI greater than or equal to 36 months, solitary metastasis), median survival 61 months
- Group II resectable, 1 risk factor (DFI less than 36 months or multiple metastases), median survival 34 months
- Group III resectable 2 risk factors (DFI less than 36 months and multiple metastases, median survival 24 months and
- Group IV unresectable, median survival 14 months.

Peri operative chemotherapy

Peri operative chemotherapy in conjunction with metastasectomy may destroy micrometastatic disease. It may be given pre or post thoracotomy or both. Peri operative chemotherapy (particularly given pre-operatively) may be particularly advantageous for patients with a DFI of less than one year and other unfavourable prognostic factors. If recurrence occurs more than one year after treatment for the primary sarcoma, consideration of PM alone without chemotherapy is reasonable. Alternatively, PM followed by adjuvant chemotherapy may be considered. Peri operative chemotherapy does not lead to increased morbidity or mortality after thoracotomy.[21]

Existing evidence does not support the routine use of peri operative chemotherapy. This might be a problem of selection bias in the retrospective case studies because chemotherapy tends to be used in patients where the relapse pattern suggests aggressive tumour behaviour.

There is conflicting evidence about the benefit of peri operative chemotherapy in STS. Pastorino reported a longer three-year survival (from 27% to 60%) when peri operative chemotherapy was included with surgical treatment of lung metastases.[51] It is possible that this benefit was due to patient selection. On the other hand, Lanza showed no survival benefit for 26 patients who had peri operative chemotherapy followed by PM.[52]

Some studies have shown children have better survival when peri operative chemotherapy is given with PM.[44,53] Kempf-Bielack demonstrated chemotherapy use correlated with a favourable event-free survival compared to those who did not have chemotherapy.[19] However, most studies do not demonstrate a survival benefit with the addition of chemotherapy to PM in osteosarcoma. In 125 patients made surgically disease free by PM, chemotherapy did not increase post-relapse free survival, although there was a suggestion of a positive role in patients with three or more pulmonary nodules.[7] One other study confirms this finding.[4]

Cost effectiveness

Porter compared the cost effectiveness of four treatment strategies for pulmonary metastases in STS: 1) PM; 2) chemotherapy (doxorubicin and ifosfamide); 3) PM and chemotherapy; and 4) no treatment.[48] In 1999, the mean cost of PM was US$20,339 per patient and the mean cost of six cycles of chemotherapy was US$99,033. Compared with no treatment and assuming a 12 month survival advantage with chemotherapy, the incremental cost effectiveness ratio was US$14,357 per life-year gained for PM, US$104,210 per life-year gained for chemotherapy, and US$51,159 per life-year gained for PM and chemotherapy. Compared with PM, the incremental cost effectiveness ratio of PM and systemic chemotherapy was US$108,036 per life-year gained. The authors concluded that PM was the more cost effective management strategy, even with favourable assumptions regarding the benefit of chemotherapy.

Repeat pulmonary metastasectomies

Sixty nine per cent of patients having PM for STS will develop recurrent lung metastases following complete resection.[2] Repeat thoracotomies are considered for subsequent pulmonary recurrence if all the disease can be resected. Most series report a favourable prognosis for repeat resection, with five year survival after the second operation up to 36%,[54] and a median survival of approximately 25 months.[55] Complete resection is the most important prognostic factor.[54-57]

Similar survival outcomes after a second PM have been reported in osteosarcoma. In 94 patients having a second PM, three and five year event-free survival probabilities were 33% and 32%, respectively.[58]

In an unselected cohort series of 249 patients with second osteosarcoma recurrences of any site, five year actuarial overall and event-free survival rates were 16% and 9% respectively.[6] As for first osteosarcoma recurrences, longer DFI and solitary lesions at recurrence correlated with better outcomes.[19] Among the 119 patients who achieved a second surgical remission, the five year actuarial overall survival rate was 32%.[6] Even after subsequent recurrences, the five year survival estimate for patients who again achieved surgical remissions was approximately 25%. As reported by others, there was almost no long-term survival without surgical clearance, re-enforcing the importance of surgery in the curative therapy of recurrent osteosarcoma.[9]

Research priorities

Health related quality of life is an important consideration after any medical intervention, particularly when the intervention is performed in the setting of advanced cancer and where the evidence of survival benefit is uncertain. Health related quality of life has not been measured prospectively in patients undergoing PM for metastatic sarcoma. During 2010, a new study will commence, titled “A prospective longitudinal cohort study describing quality of life in patients undergoing pulmonary metastasectomy for metastatic sarcoma”, supported by the Australian Sarcoma Study Group and Psycho-oncology Cooperative Group. This study will collect clinical and quality of life data in patients undergoing PM for lung-only metastatic sarcoma from around Australia and New Zealand.

The optimal treatment strategy using surgery and chemotherapy in relapsed sarcoma is unknown due to the absence of prospective trials. A European Organisation for Research and Treatment of Cancer randomised trial of PM and peri operative chemotherapy was closed due to poor accrual in the mid-1990s. More recently there has been renewed interest in this unresolved question. One of the most important aspects of the Australian Sarcoma Study Group and Psycho-oncology Cooperative Group study is that it will provide information about the frequency, nature and timing of systemic therapy used in combination with PM. It is envisaged that these data will inform a multi-site randomised trial of PM and/or systemic therapy. The challenges of such a study include the rarity of sarcoma and the heterogeneity of sarcoma pathology and biology. With international collaboration these difficulties can be overcome and provide worthwhile data to improve the outcomes of sarcoma patients with lung-only metastases.

Conclusion

All patients with osteosarcoma or STS and potentially resectable lung metastases should be evaluated for PM. PM is a procedure with low operative mortality and morbidity which may improve survival, and even cure some patients. Patients with a lung recurrence after PM should also be assessed for PM if complete resection can be achieved. The role of peri operative chemotherapy is uncertain and is a priority for future research to improve the outcome for these patients.

References

1. Potter DA, Kinsella T, Glatstein E. High-grade soft tissue sarcomas of the extremities. Cancer. 1986;58(1):190-205.
2. Gadd MA, Casper ES, Woodruff JM, McCormack PM, Brennan MF. Development and treatment of pulmonary metastases in adult patients with extremity soft tissue sarcoma. Ann Surg. 1993 Dec;218(6):705-12.
3. Billingsley KG, Burt ME, Jara E, Ginsberg RJ, Woodruff JM, Leung DH, et al. Pulmonary metastases from soft tissue sarcoma: analysis of patterns of diseases and postmetastasis survival. Ann Surg. 1999 May;229(5):602-10; discussion 10-2.
4. Chou AJ, Merola PR, Wexler LH, Gorlick RG, Vyas YM, Healey JH, et al. Treatment of osteosarcoma at first recurrence after contemporary therapy: the Memorial Sloan-Kettering Cancer Center experience. Cancer. 2005 Nov 15;104(10):2214-21.
5. Aljubran AH, Griffin A, Pintilie M, Blackstein M. Osteosarcoma in adolescents and adults: survival analysis with and without lung metastases. Ann Oncol. 2009 Jun;20(6):1136-41.
6. Bielack SS, Kempf-Bielack B, Branscheid D, Carrle D, Friedel G, Helmke K, et al. Second and subsequent recurrences of osteosarcoma: presentation, treatment, and outcomes of 249 consecutive cooperative osteosarcoma study group patients. J Clin Oncol. 2009 Feb 1;27(4):557-65.
7. Ferrari S, Briccoli A, Mercuri M, Bertoni F, Picci P, Tienghi A, et al. Postrelapse survival in osteosarcoma of the extremities: prognostic factors for long-term survival. J Clin Oncol. 2003 Feb 15;21(4):710-5.
8. Meyer WH, Schell MJ, Kumar AP, Rao BN, Green AA, Champion J, et al. Thoracotomy for pulmonary metastatic osteosarcoma. An analysis of prognostic indicators of survival. Cancer. 1987 Jan 15;59(2):374-9.
9. Bacci G, Briccoli A, Longhi A, Ferrari S, Mercuri M, Faggioli F, et al. Treatment and outcome of recurrent osteosarcoma: experience at Rizzoli in 235 patients initially treated with neoadjuvant chemotherapy. Acta Oncol. 2005;44(7):748-55.
10. Bathe OF, Kaklamanos IG, Moffat FL, Boggs J, Franceschi D, Livingstone AS. Metastasectomy as a cytoreductive strategy for treatment of isolated pulmonary and hepatic metastases from breast

cancer. Surgical Oncology. 1999 Jul;8(1):35-42.
11. Demicheli R. Tumour dormancy: findings and hypotheses from clinical research on breast cancer. Seminars in Cancer Biology. 2001 Aug;11(4):297-306.
12. Viadana E, Bross ID, Pickren JW. An autopsy study of some routes of dissemination of cancer of the breast. British Journal of Cancer. 1973 Apr;27(4):336-40.
13. Bross ID, Viadana E, Pickren J. Do generalized metastases occur directly from the primary? Journal of Chronic Diseases. 1975 Mar;28(3):149-59.
14. Smith R, Pak Y, Kraybill W, Kane Iii JM. Factors associated with actual long-term survival following soft tissue sarcoma pulmonary metastasectomy. European Journal of Surgical Oncology (EJSO). 2008;In Press, Corrected Proof.
15. Casson AG, Putnam JB, Natarajan G, Johnston DA, Mountain C, McMurtrey M, et al. Five-year survival after pulmonary metastasectomy for adult soft tissue sarcoma. Cancer. 1992 Feb 1;69(3):662-8.
16. van Geel AN, Pastorino U, Jauch KW, Judson IR, van Coevorden F, Buesa JM, et al. Surgical treatment of lung metastases: The European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group study of 255 patients. Cancer. 1996 Feb 15;77(4):675-82.
17. Kimura H, Suzuki M, Ando S, Iida T, Iwata T, Tatesaki S, et al. [Pulmonary metastasectomy for osteosarcomas and soft tissue sarcomas]. Gan To Kagaku Ryoho. 2004 Sep;31(9):1319-23.
18. Suzuki M, Iwata T, Ando S, Iida T, Nakajima T, Ishii T, et al. Predictors of long-term survival with pulmonary metastasectomy for osteosarcomas and soft tissue sarcomas. Journal of Cardiovascular Surgery. 2006 Oct;47(5):603-8.
19. Kempf-Bielack B, Bielack SS, Jurgens H, Branscheid D, Berdel WE, Exner GU, et al. Osteosarcoma relapse after combined modality therapy: an analysis of unselected patients in the Cooperative Osteosarcoma Study Group (COSS). J Clin Oncol. 2005 Jan 20;23(3):559-68.
20. Saeter G, Hoie J, Stenwig AE, Johansson AK, Hannisdal E, Solheim OP. Systemic relapse of patients with osteogenic sarcoma. Prognostic factors for long term survival. Cancer. 1995 Mar 1;75(5):1084-93.
21. Robinson MH, Sheppard M, Moskovic E, Fischer C. Lung metastasectomy in patients with soft tissue sarcoma. Br J Radiol. 1994 Feb;67(794):129-35.
22. Jablons D, Steinberg SM, Roth J, Pittaluga S, Rosenberg SA, Pass HI. Metastasectomy for soft tissue sarcoma. Further evidence for efficacy and prognostic indicators. J Thorac Cardiovasc Surg. 1989 May;97(5):695-705.
23. Creagan ET, Fleming TR, Edmonson JH, Pairolero PC. Pulmonary resection for metastatic nonosteogenic sarcoma. Cancer. 1979 Nov;44(5):1908-12.
24. 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 Mar 15;55(6):1361-6.
25. Ueda T, Uchida A, Kodama K, Doi O, Nakahara K, Fujii Y, et al. Aggressive pulmonary metastasectomy for soft tissue sarcomas. Cancer. 1993 Sep 15;72(6):1919-25.
26. van Geel AN, Hoekstra HJ, van Coevorden F, Meyer S, Bruggink ED, Blankensteijn JD. Repeated resection of recurrent pulmonary metastatic soft tissue sarcoma. Eur J Surg Oncol. 1994 Aug;20(4):436-40.
27. Kawai A, Fukuma H, Beppu Y, Yokoyama R, Tsuchiya R, Kondo H, et al. Pulmonary resection for metastatic soft tissue sarcomas. Clin Orthop Relat Res. 1995 Jan(310):188-93.
28. Pfannschmidt J, Klode J, Muley T, Dienemann H, Hoffmann H. Pulmonary metastasectomy in patients with soft tissue sarcomas: experiences in 50 patients. Thorac Cardiovasc Surg. 2006 Oct;54(7):489-92.
29. Rehders A, Hosch SB, Scheunemann P, Stoecklein NH, Knoefel WT, Peiper M. Benefit of surgical treatment of lung metastasis in soft tissue sarcoma. Arch Surg. 2007 Jan;142(1):70-5;discussion 6.
30. Choong PF, Pritchard DJ, Rock MG, Sim FH, Frassica FJ. Survival after pulmonary metastasectomy in soft tissue sarcoma: Prognostic factors in 214 patients. Acta Orthopaedica Scandinavica. 1995;66(6):561-8.
31. Putnam JB, Jr., Roth JA, Wesley MN, Johnston MR, Rosenberg SA. Analysis of prognostic factors in patients undergoing resection of pulmonary metastases from soft tissue sarcomas. J Thorac Cardiovasc Surg. 1984 Feb;87(2):260-8.
32. Verazin GT, Warneke JA, Driscoll DL, Karakousis C, Petrelli NJ, Takita H. Resection of lung metastases from soft-tissue sarcomas. A multivariate analysis. Arch Surg1992 Dec;127(12):1407-11.
33. Flye MW, Woltering G, Rosenberg SA. Aggressive pulmonary resection for metastatic osteogenic and soft tissue sarcomas. Ann Thorac Surg. 1984 Feb;37(2):123-7.
34. Pastorino U, Valente M, Gasparini M, Azzarelli A, Santoro A, Tavecchio L, et al. Median sternotomy and multiple lung resections for metastatic sarcomas. Eur J Cardiothorac Surg. 1990;4(9):477-81.
35. Temeck BK, Wexler LH, Steinberg SM, McClure LL, Horowitz M, Pass HI. Metastasectomy for sarcomatous pediatric histologies: results and prognostic factors. Annals of Thoracic Surgery. 1995 Jun;59(6):1385-9; discussion 90.
36. Putnam JB, Jr., Roth JA, Wesley MN, Johnston MR, Rosenberg SA. Survival following aggressive resection of pulmonary metastases from osteogenic sarcoma: analysis of prognostic factors. Ann Thorac Surg. 1983 Nov;36(5):516-23.
37. Tabone MD, Kalifa C, Rodary C, Raquin M, Valteau-Couanet D, Lemerle J. Osteosarcoma recurrences in pediatric patients previously treated with intensive chemotherapy. J Clin Oncol. 1994 December 1, 1994;12(12):2614-20.
38. Duffaud F, Digue L, Mercier C, Dales JP, Baciuchka-Palmaro M, Volot F, et al. Recurrences following primary osteosarcoma in adolescents and adults previously treated with chemotherapy. European Journal of Cancer. 2003;39(14):2050-7.
39. 39. Pfannschmidt J, Klode J, Muley T, Hoffmann H, Dienemann H. Pulmonary resection for metastatic osteosarcomas: a retrospective analysis of 21 patients. Thorac Cardiovasc Surg. 2006 Mar;54(2):120-3.
40. 40. Goorin AM, Delorey MJ, Lack EE, Gelber RD, Price K, Cassady JR, et al. Prognostic significance of complete surgical resection of pulmonary metastases in patients with osteogenic sarcoma: analysis of 32 patients. J Clin Oncol. 1984 May;2(5):425-31.
41. Briccoli A, Ferrari S, Picci P, Mercuri M, Bacci G, Guernelli N. [Surgical treatment of pulmonary metastases of osteosarcoma. Apropos of 206 operated cases]. Ann Chir. 1999;53(3):207-14.
42. Pastorino U, Valente M, Gasparini M, Azzarelli A, Santoro A, Tavecchio L, et al. Lung resection as salvage treatment for metastatic osteosarcoma. Tumori. 1988 Apr 30;74(2):201-6.
43. Harting MT, Blakely ML, Jaffe N, Cox CS, Jr., Hayes-Jordan A, Benjamin RS, et al. Long-term survival after aggressive resection of pulmonary metastases among children and adolescents with osteosarcoma. J Pediatr Surg. 2006 Jan;41(1):194-9.
44. Baldeyrou P, Lemoine G, Zucker JM, Schweisguth O. Pulmonary metastases in children: the place of surgery. A study of 134 patients. J Pediatr Surg. 1984 Apr;19(2):121-5.
45. Carter SR, Grimer RJ, Sneath RS, Matthews HR. Results of thoracotomy in osteogenic sarcoma with pulmonary metastases. Thorax. 1991 Oct;46(10):727-31.
46. Takita H, Edgerton F, Karakousis C, Douglass HO, Jr., Vincent RG, Beckley S. Surgical management of metastases to the lung. Surg Gynecol Obstet. 1981 Feb;152(2):191-4.
47. Abecasis N, Cortez F, Bettencourt A, Costa CS, Orvalho F, de Almeida JM. Surgical treatment of lung metastases: prognostic factors for long-term survival. J Surg Oncol. 1999 Dec;72(4):193-8.
48. Porter GA, Cantor SB, Walsh GL, Rusch VW, Leung DH, DeJesus AY, et al. Cost-effectiveness of pulmonary resection and systemic chemotherapy in the management of metastatic soft tissue sarcoma: a combined analysis from the University of Texas M. D. Anderson and Memorial Sloan-Kettering Cancer Centers. J Thorac Cardiovasc Surg. 2004 May;127(5):1366-72.
49. Abdalla EK, Pisters PW. Metastasectomy for limited metastases from soft tissue sarcoma. Curr Treat Options Oncol. 2002 Dec;3(6):497-505.
50. Pastorino U, Buyse M, Friedel G, Ginsberg RJ, Girard P, Goldstraw P, et al. The International Registry of Lung Metastases, Writing Committee: Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. J Thorac Cardiovasc Surg. 1997 Jan;113(1):37-49.
51. Pastorino U, Valente M, Santoro A, Gasparini M, Azzarelli A, Casali P, et al. Results of salvage surgery for metastatic sarcomas. Ann Oncol. 1990 Jul;1(4):269-73.
52. Lanza LA, Putnam JB, Jr., Benjamin RS, Roth JA. Response to chemotherapy does not predict survival after resection of sarcomatous pulmonary metastases. Ann Thorac Surg. 1991 Feb;51(2):219-24.
53. Rosen G, Huvos AG, Mosende C, Beattie EJ, Jr., Exelby PR, Capparos B, et al. Chemotherapy and thoractomy for metastatic osteogenic sarcoma. A model for adjuvant chemotherapy and the rationale for the timing of thoracic surgery. Cancer. 1978 Mar;41(3):841-9.
54. Weiser MR, Downey RJ, Leung DHY, Brennan MF. Repeat resection of pulmonary metastases in patients with soft-tissue sarcoma. Journal of the American College of Surgeons. 2000;191(2):184-90.
55. Pogrebniak HW, Roth JA, Steinberg SM, Rosenberg SA, Pass HI. Reoperative pulmonary resection in patients with metastatic soft tissue sarcoma. Ann Thorac Surg. 1991 Aug;52(2):197-203.
56. Casson AG, Putnam JB, Natarajan G, Johnston DA, Mountain C, McMurtrey M, et al. Efficacy of pulmonary metastasectomy for recurrent soft tissue sarcoma. J Surg Oncol. 1991 May;47(1):1-4.
57. Rizzoni WE, Pass HI, Wesley MN, Rosenberg SA, Roth JA. Resection of recurrent pulmonary metastases in patients with soft-tissue sarcomas. Arch Surg. 1986 Nov;121(11):1248-52.
58. Briccoli A, Rocca M, Salone M, Bacci G, Ferrari S, Balladelli A, et al. Resection of recurrent pulmonary metastases in patients with osteosarcoma. Cancer. 2005 Oct 15;104(8):1721-5.