Experience with surgical metastasectomy in osteosarcoma

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Lung metastases often represent the only site of relapse after curative treatment of osteosarcoma, or an isolated distant deposit at the time of initial diagnosis. Under such circumstances, complete removal of lung metastases can result in permanent cure of the patient. Mechanisms that determine the specific pathway of metastatic spread in the various tumours are largely unknown, but we know from clinical experience and autopsy data that a restricted metastatic pattern is typical of sarcomas, where the lung may represent the first filter of hematogenous spread, later followed by systemic dissemination. Despite the unequivocal efficacy of chemotherapy, lung metastases are still the main reason of failure in 40-50% of osteosarcomas [1,2] and metastasectomy can rescue as many as 50% of them [3]. Salvage surgery is indicated whenever complete resection is technically feasible, and the goal is permanent cure.

Selection and staging

The eligibility criteria for curative resection of lung metastases are the following: primary tumour previously cured or curable, no evidence of extrapulmonary metastases, complete resectability of all pulmonary lesions, planned resection volume tolerable by the patient. Patients presenting with synchronous metastases at the time of initial diagnosis, as well as patients with concurrent local relapse and lung metastases after the primary treatment, may still be eligible for metastasectomy provided that the primary tumour or local relapse are amenable to curative management. The issue of synchronous metastases is of particular importance in osteosarcoma where lung exploration may rule out false positive lesions, avoid unnecessary amputation in case of disseminated disease, and possibly improve the chances of permanent eradication of disease. The most appropriate timing for surgery, as well as the need of primary chemotherapy, have to be decided for each individual case by a team of specialists including medical oncologist, thoracic surgeon and radiotherapist.

In case of proven or suspicious lung metastases, clinical staging should provide the most accurate information on several aspects concerning the nature, dimension and and site of each individual lesion, likelihood of a lung primary, involvement of hilar or mediastinal lymphnodes, and total required volume of lung resection. Spiral CT scanning has improved the diagnostic yield of radiological staging, both in terms of minimum size of parenchymal nodules (less than 3 mm) and significant hilar or mediastinal adenopathies. However, with higher sensitivity, the chances of false positive lesions have increased as well.

The data from the International Registry of Lung Metastases showed an overall accuracy in the radiological assessment of the number of lung metasteses of 47%, with 34% of cases showing more metastases at the time of surgery and 19% showing less lesions than those detected by CT [4]. However, in the subset of patients who had bilateral surgical exploration, the number of radiological metastases was underestimated in 46%. In patients with multiple pulmonary lesions, a liver ultrasound, bone scan and brain CT should be part of preoperative staging, as well as a CT or MRI of primary tumour site to exclude local recurrence, or assess its resectability. The role of PET scan or targeted monoclonal antibodies is still under experimental evaluation. Although the specificity of

PET scan appears to be high, the minimum size of detectable pulmonary lesion may represent a critical factor.

Surgical Technique

The aim of lung metastasectomy is not cytoreduction or debulking but complete removal of detectable disease. This fundamental principle applies to any type of salvage surgery with curative intent, and is critical in pulmonary metastases where preoperative staging is grossly inaccurate. In order to achieve a macroscopically complete resection the surgeon must be able to palpate the lung, to detect any radiologically occult lesions and remove all of them. In osteosarcoma it is better to explore both lungs even in the case of single or unilateral metastases because the risk of occult contralateral metastases is high (30-50%) [5,6]. Most surgeons prefer a median sternotomy, others a bilateral thoracotomy (simultaneous or staged). Mid-sternal split causes little functional damage and postoperative pain, with early mobilisation of the patient, limited morbidity and mortality. Such a limited damage of thoracic muscles, nerves and parietal pleura reduces pleural adhesions and facilitates future reoperation, if needed. Nonetheless, in patients presenting with numerous or centrally located lesions involving both lungs, or mediastinal adenopathies, a sequential lateral approach may facilitate resection and prevent acute lung injury.

A limited (sublobar) resection is generally adequate, to preserve as much lung as possible in view of future resections. Cutting out a uniform layer of 5-10 mm of normal lung tissue around the nodule (precision resection, with diathermy or laser) may adapt better to the shape and location of metastatic deposits than wedge resection with mechanical staplers. A anatomical resection (segmentectomy or lobectomy) may be necessary in the rare event of nodal metastases.

We do not advocate the use of video-assisted thoracoscopy because this approach precludes thorough palpation of the lungs and proper staging. As demonstrated by McCormack, in patients who underwent thoracoscopy followed by immediate thoracotomy, open surgical exploration allowed resection of additional metastases in 56% of the cases [7].

Long Term Results

The overall experience of pulmonary metastasectomy indicates that permanent cure can be achieved in 30 to 50% of cases. Recently, the International Registry of Lung Metastases has provided long term results from 821 cases of lung metastasectomy for osteosarcoma. Among these patients, 734 (89%) underwent complete surgical resection [4]. The long term results are illustrated in **Table 1.** In summary, the actuarial survival after complete metastasectomy was 33% at 5 years, 27% at 10 years (median 40 months); the corresponding values for incomplete resection were 5% at 5 years and no survivors at 10 years (median 12 months). Among complete resections, the 5-year survival was better for patients with a long disease free interval (DFI of 36+ months) and for solitary lesions.

After the first metastasectomy, a recurrence of the disease was documented in 67% of patients, with pure intrathoracic relapse accounting for 74% of all events (365/491). A total of 304 patients (41%) underwent a second metastasectomy, and their long term survival was 35% at 5 years and 29% at 10 years.

Prognostic Factors

In retrospective studies, radicality, disease free interval and number of metastases are the most consistent prognostic factors, although their statistical significance may depend on the number of patients. As a matter of fact, the achievement of a macroscopically complete resection appears to be the most important independent prognostic factor. In the analysis of the Registry, disease free interval, number of metastases, and tumour type were highly significant independent prognostic variables at univariate as well as multivariate analysis.

A simplified system of prognostic grouping was defined on the basis of completeness of resection, and the two independent risk factors: disease free interval <36 months, multiple metastases. **Figure 1** shows the actuarial survival of the four prognostic groups. The difference among the curves was highly significant (logrank chi-square = 70.8; 3df). Median survival was not reached for group I, 35 months for group II, 23 months for group III and 12 months for group IV.

Conclusion

Although the efficacy of lung metastasectomy has never been confirmed by controlled clinical trials, it relies on a large cumulative evidence of long term survival (in comparison with unresected cases). Such experience indicates that systematic bilateral pulmonary resection, combined with neoadjuvant chemotherapy, has contributed to improve the final cure rate of osteosarcoma. Favourable results have been invariably linked to careful preoperative and intraoperative assessment of the extent of disease, complete resection with safe surgical margins, preservation of as much functional parenchyma as possible. In addition, intensive follow-up has been adopted, to rescue some of the patients with limited intrathoracic relapse.

The classification system proposed by the International Registry combines essential indicators of tumour biology (DFI), anatomical extent (number) and radicality of treatment into a simplified system which reliably predicts long term survival.

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Table 1 - The International Registry of Lung Metastases: long term survival after complete resection

		N.	5-year %	10-year %	median (months)
Overall		734	33	27	40
DFI	0 (synchronous)	102	38	31	23
	12-35 months	546	30	28	27
	36+ months	68	51	43	61
Number	1	252	46	43	43
	2-3	201	31	24	28
	4+	281	23	21	23
	10+	98	23	19	22

Figure 1 - Survival of the four prognostic groups: resectable, no risk factors (DFI ³ 36 months and single metastasis); resectable, 1 risk factor (DFI < 36 months or multiple metastases); resectable, 2 risk factors (DFI < 36 months and multiple metastases) and unresectable.