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Surgical Treatment of Pulmonary Metastases from Melanoma: Emerging Options

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1. Introduction

Malignant melanoma (MM) is rapidly becoming a major health problem in the USA and in Europe. It has been estimated that more than 55,000 Americans developed MM in 2004, and that about 8,000 ultimately died of it (1).

More than one third of patients operated for MM develop tumor recurrence; melanoma patients' annual risk of death in Stage IV of the American Joint Committee on Cancer (AJCC) has been estimated to be about 20% during the first 3 years (2). The site of relapse is a very important predictor of survival. Regional lymph node recurrences in fact, may be surgically resected and 5-year survival rate have been reported to be between 20% and 50% (3-4). Distant metastases (MTS), both in visceral and non-visceral sites, reported a 5-year survival of approximately 5% (5-7); for these patients surgery is not often feasible and systemic treatment (chemotherapy, immunotherapy, radiotherapy) is sometimes the curative option.

Lung is the second most common site for metastatic MM spread (8). The annual probability of developing lung MTS progressively increases from 10% at 5 years to 17% at 15 years after the resection of the primary tumor (9). Lung MTS are usually asymptomatic, sometimes multiple, occasionally detected with radiological imaging during patient follow-up.

Once lung MTS has developed, the possible surgical treatment remains controversial. Even if a clear clinical advantage in overall survival (OS) after resection of pulmonary MTS from osteogenic sarcoma, soft tissue sarcoma, non-seminomatous testicular neoplasms, colorectal and renal cell carcinoma has been demonstrated, 5-year survival rates in melanoma patients were lower, ranging between 5% and 31% (10-12). These ranges indicate how a preoperative patient selection is mandatory. In fact, only 10-35% of all metastatic melanoma patients are suitable for a complete surgical resection (13).

Systemic treatments including chemotherapy, radiotherapy, immunotherapy and more recently molecular target agents, demonstrated a partial clinical response only, with severe adverse effect and a dramatic impact on patient's quality of life (QOL), providing little, if any, attested survival benefit. Chemotherapy regimens may include: dacarbazine, cisplatin and carmusine, alone or in combination with a variety of immunotherapies, including cytokines, monoclonal antibodies and vaccination strategies with synthetic peptides, naked DNA, dendritic cells and recombinant viruses (14-17). Unfortunately, results are presently

discouraging: <20% of patients treated with such therapeutic options present with a partial response rate and very few are long-term survivors.
Due to these reasons, surgery remains the treatment of choice to improve OS in Stage IV melanoma patients; anyway, surgery cannot be offered to all of metastatic patients. The need for a correct patient preoperative clinical assessment, in order to avoid incomplete surgical resections, has been demonstrated by many studies.
The aim of this paper is to underline the prognostic factors which influence survival in melanoma patients with pulmonary metastases undergoing surgical resection. The first part regards the experience of the Thoracic Surgery Department of the University of Torino; lastly we discuss our results at the light of those of the most important series published in Literature.

2. Surgical treatment of pulmonary metastases: indications and results

2.1 *Oliaro-Filosso et al.* – University of Torino (2000-2008)

In 2010 our group, a dedicated high-volume thoracic surgical team with long time experience in the management of pulmonary metastases, published its experience on the surgical treatment of pulmonary metastases from MM (18). Twenty-six patients were operated between January 2000 and December 2008. Table 1 shows patients clinical characteristics.

Gender (male/female)	14/12
Mean age (years)	62 (range 28-79)
Localization of the lung MTS	
Left lung	8
Right lung	16
Bilateral	2
Number of pulmonary MTS	
1 node	14
2 nodes	5
>2 nodes	7
Median DFI (months)	36
Type of surgical resection	
Wedge/segmental resection	23
Lobectomy	3

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Table 1. University of Torino Department of Thoracic Surgery Stage IV melanoma metastatic to the lung: patients characteristics (number: 26).

Our patients' inclusion criteria were: 1) complete resection of the primary tumor; 2) no evidence of any other extrapulmonary MTSs; 3) resectable lung MTS; 4) predicted post-resection lung volumes compatible with the anticipated pulmonary resection.
In all cases lung MTSs were discovered with a routine chest X-ray during the follow-up program. The lesion/s was/were confirmed by a thoracic CT scan; since 2003, PET scan was available in our centre and routinely used.

Lung represented the first metastatic site in the majority of our patients (17; 65%); in 9 patients, lung MTS developed after metastatic spread in other viscera. A single pulmonary nodule was observed in 14 cases; 5 patients had 2 nodules and multiple nodules were observed in the remaining 7.
All patients received adjuvant or neoadjuvant systemic therapy (either chemotherapy or immunotherapy). The mean disease-free interval (DFI) was of 36 months.
Lung wedge resection was the commonest surgical procedure performed (23 cases) whereas lobectomy was necessary in 3 patients. A complete surgical resection was accomplished in all patients and it was confirmed by the histological examination. There was no postoperative mortality.
One, 3 and 5-year survival rates were 72%, 36% and 23% respectively.
The Cox regression analysis identified the female gender (p=0.05) as the only independent prognostic factor related to patients survival. This result can be attributed to the limited number of our patients and to their preoperative selection: these factors may explain why the number of pulmonary MTS and/or the DFI did not reach a statistical significance in our analysis (18).
A formal search in literature results in several small and out of date series, and many case reports regarding unusual clinical manifestations of pulmonary MTS from MM.
In order to analyze the results and to recognize possible prognostic factors we summarize the most interesting ones, comparing them to our data.

2.2 *Tafra et al.* - John Wayne cancer institute (1971 - 1993)

Tafra et al. (12) reviewed the John Wayne Cancer Institute's melanoma series: among 6129 patients treated from 1971 to 1993, 2167 had distant MTS and 984 presented with pulmonary nodules. Of these, only 106 (11%) were submitted to a surgical resection and received an overall of 117 procedures. All operations were performed through thoracotomy.
Wedge resection was performed in 71 cases (61%), lobectomy in 25 and pneumonectomy in 6. Fifteen patients received an extrapulmonary intrathoracic resection (not otherwise clarified).
More than half of patients (56/106) had a single pulmonary MTS; 23 had 2 or 3 nodules and 28 more than 3. In 41 patients (38.7%) an incomplete resection was performed.
Authors concluded that patients with complete resection survived longer than those with an incomplete one, even if this data did not reach statistical significance.
There was a trend towards a better survival in patients receiving a lobectomy when compared to those submitted to a wedge and for those with a single pulmonary lesion, but also these results were not statistically significant.

2.3 *Olilla et al.* - John Wayne cancer institute (1971 - 1994)

Olilla et al. (15) reconsidered the John Wayne Cancer Institute series of metastatic melanoma patients between 1971 and 1994 (129 cases) and pointed out the importance of the Tumor Doubling Time (TDT). TDT was calculated for each patient comparing successive chest radiographs in order to measure the changing diameters of each pulmonary nodule. When a patient presented with more than a nodule, TDT was calculated by measuring the fastest-growing one. Forty-five patients had at least two preoperative chest X-rays to compare, and only those were included in the study. Again, most of patients had a solitary nodule

(33,73%). A complete resection was accomplished in 38 cases (84.4%): wedge resection was the commonest surgical procedure (32, 71.1%), followed by lobectomy (11, 24.4%). The median TDT for these 45 patients was 66.9 days (range: 13.7-287.4 days). Sixty days was the TDT cut-off value decided by Authors.
A radical surgical resection (p=0.04) and a TDT≥60 days (p=0.01) were the two statistically positive prognostic factors. In particular, for patients with a TDT≥60 days, the median survival was 29.2 months with 20.7% 5-year survival rate.

2.4 *Leo et al.* - International registry of lung metastases (1945-1995)

Leo et al. (19) reconsidered 328 patients with pulmonary MTS from MM, previously collected by Pastorino *et al*., including them into the International Registry of Lung Metastases which gathered data from 18 mayor Thoracic Surgical centres from Europe, USA and North America (20).
Thoracotomic surgical approach was the commonest proposed in Leo's series (247 patients); sternotomy was performed in 74 and video-assisted thoracic surgery (VATS) in 7, only. Bilateral interventions were proposed in 74 patients. Wedge resection was the most common surgical procedure (230), followed by lobectomy (4) and pneumonectomy (14). An extrapulmonary resection (chest wall, pleura, diaphragm, liver, mediastinal structures) was required in 50 cases (15.2%). A complete surgical resection (R0) was accomplished in 282 patients (85.9%).
Patients receiving a R0 resection survived longer than others in whom an incomplete one (R1-2) was performed (22% 5-year and 16% 10-year survival rates for R0 patients; 0% 5-year survival for R1-2 ones, p<0.01). Considering R0 patients only, a DFI>36 months (30% 5-year, 22% 5-year, p<0.01) and a single lesion (25% 5-year and 22% 10-year, p=0.03) statistically influenced patients survival.
Leo proposed four prognostic groups of patients, according to his multivariate analysis results, which were: 1) R0 metastasectomy and no adverse factor (only 1 lesion *and* DFI>36 months); 2) R0 metastasectomy and 1 unfavourable factor (more than 1 pulmonary nodule *or* DFI<36 months); 3) R0 metastasectomy and 2 unvavourable factors; 4) R1-2 metastasectomy.
It was thus demonstrated that differences in survival among these groups were statistically highly significant: 29% 5-year survival rate and 26% 10 year for Group 1; 20% 5-year and 10% 10 year for Group 2; 7% 5-year and 0% 10 year for Group 3; no 5 year survivors in Group 4.
Leo concluded that a complete surgical resection and a DFI>36 months were the most important positive prognostic factors.

2.5 *Andrews et al.* - Lee Moffitt cancer center (1988-2005)

Andrews and Coll. (21) reported Lee Moffitt Cancer Center's experience of patients with pulmonary MTS from MM between 1988 and 2005. An overall of 86 cases (64 men) were enrolled in this study. Preoperative patient assessment included thoracic CT scan and brain magnetic resonance imaging (MRI) to confirm the number and location of pulmonary nodules seen at the chest radiograph, and also to exclude possible extrathoracic malignancies. PET scan was used in 27 patients. A complete resection was achieved in all cases. Wedge resection (35, 22 of which through VATS procedures) was the most frequent surgical procedure performed. Ten were the segmental resections and 9 the lobectomies, all of these performed with a thoracotomy.

The estimated 5-year survival rate was 33%.
While a long DFI did not statistically affect survival, only the number of pulmonary lesions (1 vs 2-4) was a statistical prognostic factor (41 months vs. 21, p=0.05).

2.6 *Neumann et al.* - Memorial Sloan-Kettering cancer center

Neumann and Coll. (22) studied 122 pulmonary MTS treated at the Memorial Sloan-Kettering Cancer Center (MSKCC). Of these, only 26 patients (21%) received a surgical resection while others were treated with systemic therapy (82) or did not receive any sort of treatment (14); a complete resection was accomplished in all operated patients (a wedge resection, most frequently). Metastasectomy was associated with improved survival (median 40 months vs 11 months in non-operated patients); in operated patients, Authors pointed out an estimated 29% 5-year survival rate.
At the Cox regression analysis, a solitary metastasis (HR 1.9, 95%CI 1.1-3.2, p<0.0005) and the absence of extrathoracic disease (HR 1.9, 95% CI 1.2-3.1, p=0.01) were strong positive predictors of long-term survival. The lung resection itself was an independent factor predictive of survival (HR 0.42, 95%CI 0.21-0.87, p=0.02).

2.7 *Petersen et al.* - Duke comprehensive cancer center (1970 – 2004)

Finally, *Petersen et al.* (23) retrospectively reviewed the experience with lung MTS from MM patients treated in the Duke Comprehensive Cancer Center between years 1970 and 2004. An overall of 1720 patients were recorded: those submitted to surgery were only 318 (18.5%) while others received a systemic treatment. Two hundred forty-nine (78%) of operated patients received a radical resection; those receiving an incomplete resection were more likely to have multiple pulmonary lesions. Patients receiving curative resections had 19 months median survival and 21% 5-year survival rate, compared to 11 months and 13% of those with an incomplete one (p<0.0001).
The univariate analysis highlighted that lymph nodes metastases (p=0.001), 2 or more pulmonary MTS (p<0.001), a short DFI (p<0.001) and the presence of extrathoracic MTS (p<0.001) were significant negative prognostic factors.
The number of pulmonary MTS (p=0.012), a short DFI (p<0.001) and the presence of extrathoracic MTS (p<0.001) were found to be independent predictors of survival at the multivariate analysis. Table 2 and 3 summarize the series results and their prognostic factors, respectively.

Author	*Year*	*#pts*	*Median survival (months)*	*5-year survival rate (%)*
Tafra	1995	63	25	-
Olilla	1998	38	26	-
Leo	2000	282	19	22 %
Andrews	2006	86	35	33 %
Neuman	2007	26	40	29 %
Petersen	2007	249	19	21 %
Oliaro-Filosso	2010	26	-	23 %

Table 2. Survival after complete resection of pulmonary MTS.

Author	*year*	*# pts*	*Prognostic factors*
Tafra	1995	63	n° MTS; no extrathoracic MTS; TDT
Olilla	1998	38	TDT
Leo	2000	282	n°MTS; DFI; complete resection
Andrews	2006	86	n° MTS
Neuman	2007	26	n° MTS; no extrathoracic MTS
Petersen	2007	249	complete resection; n° MTS; DFI; no extrathoracic MTS
Oliaro-Filosso	2010	26	female gender

Legenda: *TDT: Tumor Doubling Time; DFI: Disease Free Interval; MTS: metastases*

Table 3. Prognostic factors in the cited series.

3. Discussion and conclusions

One may observe, by means of a formal search in literature of surgical series of resected pulmonary MTS from MM, that only few papers have been published in a long interval of time; the most recent series were taken into consideration in order to obtain the most comparable results as possible.

Preoperative patient assessment in the oldest series (*Tafra*, *Olilla* and *Leo*) presented some limitations, especially due to the lack of new generation radiological imaging which are mandatory to avoid the risk of incomplete/non-radical resections. Percentages of reported non curative procedures were 38.7% (41/106) in Tafra, 15.6% (7/45) in Olilla and 14% (46/328) in Leo.

A preoperative patient assessment is fundamental: thoracic and abdominal CT scan, brain MRI and whole body PET scan should be proposed in all. In those patients with lung MTS and concomitant extrathoracic lesions, surgery is contraindicated: those patients should receive systemic therapy alone.

When prognostic factors are evaluated, the importance of the number of lung MTS has been emphasized by many Authors. In almost all series, a higher survival rate of patients with 1 lesion was observed. The role and the importance of the type of surgical procedure (wedge resection vs lobectomy) was not important; generally when the MTS is peripherally located, it can be easily removed with a wedge resection or a segmentectomy (Fig. 1). Instead, lobectomy is reserved to those deeply located lesions within the lung parenchyma, in which the risk of non-free resection margins of tumoral tissue may be high if a non-anatomic resection is performed. Also, the procedure used to perform the limited resection (thoracotomy or a VATS) did not influence the survival rate. With the development of mini-invasive thoracic procedures and of the technologies to it dedicated, the role of VATS (and of robotics in the next future) is rapidly growing. Patients operated in such manner face a limited surgical impact, less pain and may have a shorter postoperative course, which can also reduce the overall recovery health costs. Furthermore, if a limited pulmonary resection is performed, patients' postoperative respiratory function is conserved: this leads to a better tolerated adjuvant systemic therapy and the chance to propose a redo-surgery in case of possible tumor relapse, which unfortunately is not infrequent.

The importance of a strict follow-up is brought to evidence by the majority of Authors. The common follow-up should include a chest X-ray; thoracic CT scan should be performed

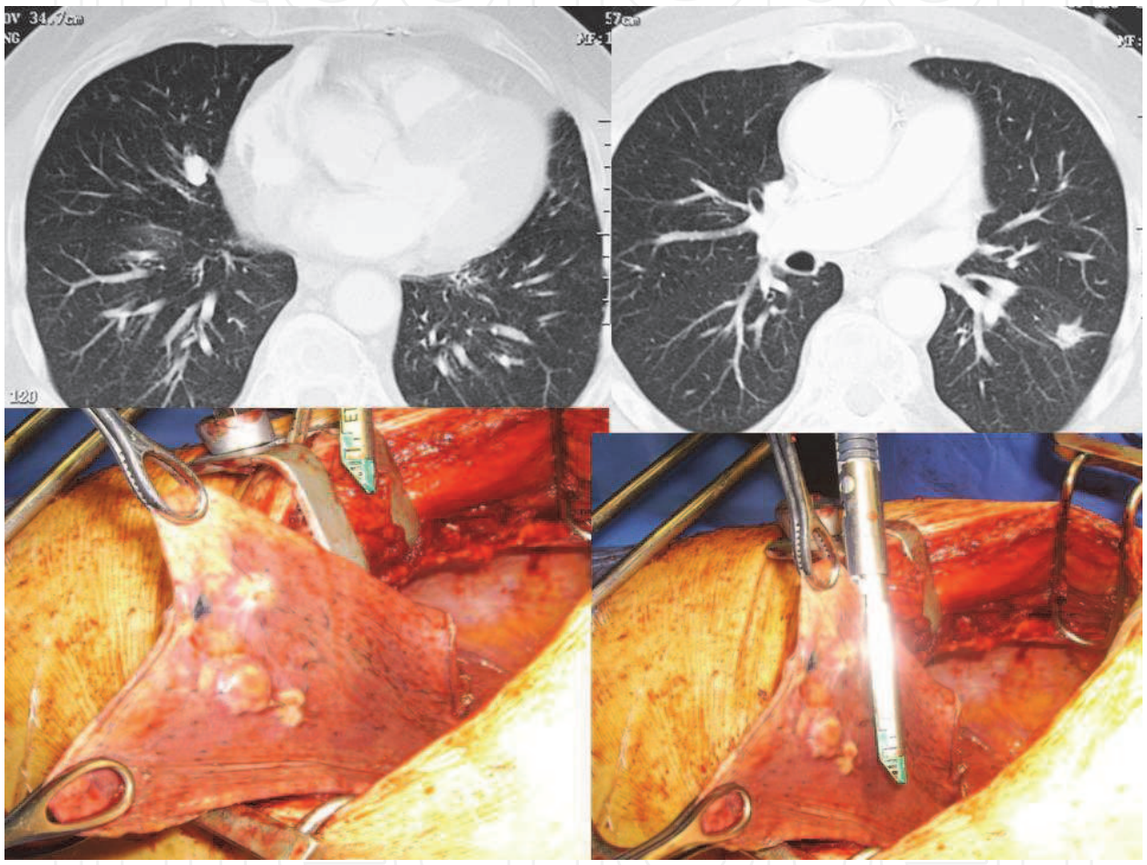


Fig. 1. Preoperative radiological and intraoperative images of resected pulmonary MTS from malignant melanoma.

whenever a nodule is detected. In case of its positivity at the PET scanning, surgery should be proposed immediately. We suggest to avoid repeated radiological controls of the nodule due to the high risk of possible tumor spreading.
Prognostic factors are almost the same: limited number of pulmonary MTS, a short DFI, absence of extrathoracic MTS, completeness of surgical resection (Table 3).
The role of the lymphadenectomy is not always put in evidence. We believe that lymph node sampling should be performed in all cases; many Author statistically demonstrated the significance of lymph node MTS as a prognostic factor: it's evident that patients with metastatic nodes have lower survival rate when compared to N0 patients. This data itself may suggest the role and importance of lymphadenectomy.
In conclusion, even if patients with pulmonary MTS from melanoma have a poor prognosis, those in whom a surgical resection can be proposed present a longer life expectancy than others treated with systemic therapy alone. In order to avoid incomplete surgical resections (in whom the survival is similar to chemotherapy) a selective preoperative patient assessment is mandatory. Surgical resection (wedge/segmentectomy) should be limited whenever possible and lymph nodal sampling should be routinely performed. Postoperative adjuvant therapy (chemotherapy, immunotherapy, radiotherapy) must always be proposed and a strict follow-up scheduled; in case of new pulmonary lesions developing, surgery should be planned, if feasible.

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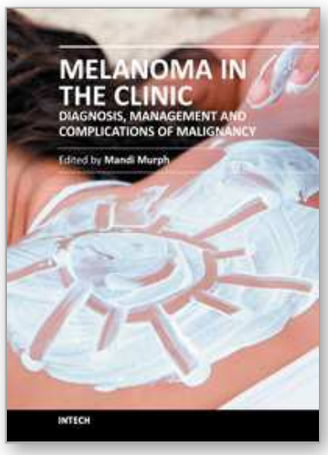
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Melanoma in the Clinic - Diagnosis, Management and Complications of Malignancy

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This book provides an excellent overview of how melanoma is treated in the clinic. Since oncologists and clinicians across the globe contributed to this book, each area also explores the unique burdens that geographical areas experience from melanoma subtypes and how these are treated in different settings. It also includes several chapters that illustrate novel methods for diagnosing melanoma in the clinic using new technologies, which are likely to significantly improve outcomes. Several chapters cover surgical techniques and other present very rare or challenging clinical cases of melanoma and how these were treated. The book is geared towards informing clinicians and even patients how melanoma arises, what tools are available and which decisions need to be made by patients and their families in order to treat this devastating disease.

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