



Kala Pohl. *Budding Romance*. Acrylic on canvas, 16" × 20".

*Experience with resection
of pulmonary metastases
from malignant melanoma
supports a rationale for
close subsequent follow-up.*

Survival After Surgical Resection of Isolated Pulmonary Metastases From Malignant Melanoma

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Background: *The overall prognosis for patients with metastatic malignant melanoma remains poor. However, careful staging and identification of patients with limited metastatic disease offers the opportunity for surgical salvage and improved survival for selected patients.*

Methods: *We reviewed the experience over the last 17 years at our institute with isolated pulmonary metastasectomy in 86 patients with advanced malignant melanoma.*

Results: *Our data demonstrate an overall median time to relapse of approximately 8.4 months and a median survival of 35 months. The 5-year survival rate is estimated at 33%, and 16% remain continuously free of disease after a median follow-up of 35 months. Resection of properly staged and evaluated patients with limited pulmonary metastases appears to convey a significant survival benefit. Patients with a single metastasis fare best.*

Conclusions: *These encouraging results offer a rationale for the careful follow-up of resected patients. One third of all relapses will be limited and additional surgery contributes to their overall survival.*

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Abbreviations used in this paper: CT = computed tomography.

Introduction

Stage IV metastatic malignant melanoma is an unremitting disease with a 5-year survival rate of approximately 5% to 10%. Therefore, survival is usually referenced in months rather than years.¹ Response rates from systemic therapy are only 10% to 15%, most of which are partial, are of modest duration, and convey a significant survival benefit to only a few.² Pulmonary metastases are frequent, usually asymptomatic, multiple, and detected only by imaging. On occasion, patients pre-

sent with a solitary lung nodule as their only site of metastatic disease.³ Resection is performed in select cases, particularly when there is no evidence of metastasis elsewhere, when a complete resection is possible, and when the patient's general condition is good. A 1993 review described reported survivals after complete resection of pulmonary metastasis.⁴ The number of patients in these series ranged from 8 to 98. Five-year survival rates varied from 0% to 25%, with median survivals ranging from 7 to 20 months. A follow-up review of selected series in 2004 reported median survivals of 10 to 20 months with 5-year survival rates of 5% to 25%.⁵

The prognostic factors influencing the extent of clinical benefit of resection of isolated pulmonary metastases remain uncertain. The extent of complete resection, interval from diagnosis, and number of pulmonary metastases have each been shown to predict survival in some studies.^{3,6,7} This report describes the experience with pulmonary metastasectomy at our institute and with the patients evaluated and followed subsequent to resection performed elsewhere.

Materials and Methods

We utilized our center's Cutaneous Program database, hospital records, and Tumor Registry information to identify patients with metastatic malignant melanoma who had undergone pulmonary resection of histologically confirmed melanoma in the years between 1988 and 2005. Approval to conduct this review was obtained from the Institutional Review Board. We excluded patients who had procedures performed for diagnostic purposes only. The patients' age, sex, date of diagnosis, site of primary disease, initial stage of disease at presentation, and information regarding their clinical course were noted. Clinical assessment, staging studies, adjuvant therapies, and prior recurrences were identified. The revised American Joint Committee on Cancer (AJCC) staging system⁸ for melanoma was used to identify extent of disease at presentation and relapse. The surgical procedure, histopathologic analysis of resected tissue, and number and size of the pulmonary lesions removed were tabulated. Postresection therapies as well as relapse and survival dates were recorded. For patients who underwent resection at our institution, the surgical approach, type of resection, length of stay, and morbidity were determined.

Data Analysis

The Kaplan-Meier method⁹ was used to estimate survival and relapse-free survival over time. Time to relapse was defined as the interval from the date of first metas-

tectomy to the date of recurrence. Survival time data were calculated from the date of resection to date of last follow-up or death. The log rank test¹⁰ was used to compare groups with respect to survival. All *P* values are two-sided.

Results

We reviewed 86 cases of individuals with stage IV melanoma who were seen, evaluated, and followed at our institute. The majority of cases were accrued within the last 6 years. Patients' ages ranged from 16 to 81 years of age. Among them, were 64 men and 22 women. Ten patients had an unknown primary site of melanoma. The median time to pulmonary resection from identification of the primary lesion was 36 months. Table 1 depicts patient demographics according to whether the

Table 1. — Patient Demographics

	Resected at Our Center	Resected Elsewhere
Number of Patients	52	34
Age Median (yrs)	56	59
Age Range (yrs)	16–80	25–81
Sex		
M	45	19
F	7	15
Primary Site		
Unknown	2	8
Mucosal	2	0
Ocular	1	0
Skin (depth unknown)	2	7
T Stage		
in situ	1	0
T1	10	2
T2	6	7
T3	8	8
T4	20	2
Breslow Depth		
Median	3.9 mm	2.1 mm
Range	0.4–20 mm	0.75–4.14 mm
Nodal Assessment at Diagnosis		
cN0	26	29
pN0	13	5
pN1	7	0
pN2	6	0
Metastases at Diagnosis		
M1a	0	2
M1b	1	6
M1c	1	0
Prior Resections for Recurrence		
Nodal	9	2
Subcutaneous/Soft Tissue	4	1
Brain	3	0
Nodal and Brain	1	0
Concomitant Resections		
Soft Tissue	3	0
Nodal	2	0
Hepatic	1	0
Spleen	1	0

Table 2. — Current Patient Status

	Our Center	Elsewhere	Total	Range (mos)	Median (mos)
Dead	25	23	48	3–152	24
Alive with recurrence	8	2	10	10–139	16
Alive NED after subsequent surgery for additional recurrence	7	6	13	9–82	67
Chemotherapy	0	1	1	28	
Alive without recurrence	12	2	14	<1–84	35

NED = no evidence of disease

pulmonary resection was performed at our center or elsewhere. Patients resected at our center were predominately men, and they presented with deeper primary cutaneous lesions (median Breslow depth 3.9 mm in contrast to 2.1 mm), had more advanced T-stage disease, and were more likely to have undergone histopathologic nodal assessment at initial diagnosis. Two individuals had been resected elsewhere, while 20 individuals resected at our center presented with T4 lesions. Pathologic nodal assessments had been performed at our institute in 26 patients and elsewhere in 5 patients. Those resected at our institution had undergone considerably more prior resections with curative intent for an earlier recurrence (17 vs 3), and 7 patients underwent concomitant resections to render them disease-free. Physical examinations, computed tomography (CT) scanning, and magnetic resonance imaging (MRI) of the brain were used to exclude extrapulmonary foci of unresectable disease prior to surgical resection.

The surgical resections performed at our institution were well tolerated with minimal complications. The median length of hospital stay was 3 days. Thirty-five wedge resections were performed, with 22 utilizing video-assisted thoracoscopy.

Thoracoscopy was chosen selectively as the surgical approach to resection in cases where the high-resolution helical chest CT scan, which was employed with all patients at our institute, showed 3 or fewer small, easily respectable peripheral lesions. Ten segmental resections and 9 lobectomies were done, all utilizing an open thoracotomy approach. No pneu-

monectomies or partial resections were performed. Operative complications were minimal. A return to the operating room for control of postoperative bleeding in 1 patient was the most serious complication encountered. There was no operative mortality.

Most patients underwent resection of an isolated pulmonary nodule, though 2 lesions were removed from 13 patients, 3 pulmonary nodules were resected in 2 patients, and 4 nodules were removed in 1 patient. Four required contralateral thoracic surgical procedures. The largest tumor removed was 6 cm, but the majority were 1 to 3 cm in size. At our institute, positron-emission tomography (PET) scanning in 27 patients identified hypermetabolic metastatic lesions, and preresection biopsy was rarely done. All resected lesions were histopathologically confirmed; there were no false-positive PET scans.

Postsurgical adjuvant treatments were administered to 28 patients. These treatments included multiple vaccines, granulocyte-macrophage colony-stimulating factor (GM-CSF), chemotherapy, and interferon. Canvaxin¹¹ was the most commonly used vaccine.

The current status of all patients is described in Table 2. Of the 86 patients in this review, 48 died (median survival time = 24 months), 10 are alive with recurrent disease, and 13 are currently free of disease after one or more subsequent resections. One patient is in complete remission after high-dose interleukin, and 14 patients remain continuously relapse-free at a median follow-up of 35 months.

Overall, the median time to recurrence approximates 8.4 months with a median survival of 35 months (Fig 1). The estimated 5-year survival rate is 33%. Despite a preponderance of poor prognostic factors in patients treated at our institution, there were no statistically significant differences in time to progression or survival between patients resected at our institute or elsewhere (Figs 2 and 3). Similarly, differences in age, sex, Breslow depth, T stage, clinical stage, and prior recurrences failed to demonstrate a statistically significant impact on survival. The time interval from diagnosis to pulmonary resection did not affect survival. Only the number of pulmonary metastases (1 vs 2–4) made a statistically significant difference in survival. Patients with a solitary lesion had a median survival of 41 months com-

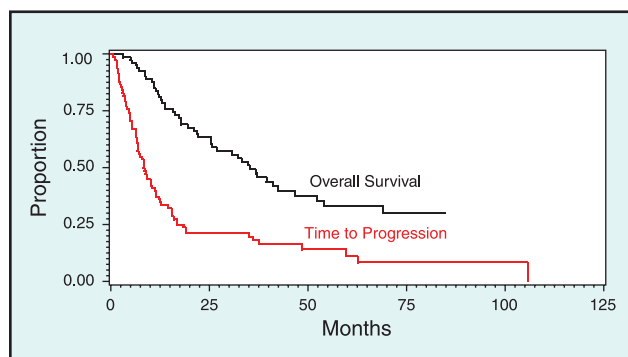


Fig 1. — Time to progression and overall survival of all patients.

pared to 25 months for those with more than 1 lesion ($P = .05$) (Fig 4).

One patient died without available information on relapse. The pattern of relapse by AJCC staging criteria is shown in Table 3. Visceral rather than pulmonary recurrences predominated. Among 71 recurrences, 40 (55%) were visceral; 13 of these were apparently isolated and were amenable to brain, bowel, bone, liver, and spleen resection procedures. Nineteen patients recurred in the lung, and 6 single lesions were subsequently resected. Of the 25 patients who underwent a subsequent resection, 13 are alive with no evidence of disease. The impact of additional salvage surgery on survival is depicted in Fig 5. Patients with limited recur-

Table 3. — Initial Site of Recurrence After Pulmonary Resection

Category of Recurrence	Total Number	Subsequently Resected
Unknown	1	N/A
M1a Soft Tissue	12	6
M1b Pulmonary	19	6
M1c Visceral	40	13

rences who underwent resection showed a gain in survival (median not yet reached vs 20 months, $P < .0001$) compared to patients with systemic relapse treated with chemotherapy and/or immunotherapy. One of the latter is without evidence of disease.

Discussion

Advances in diagnostic techniques and surgical management have improved the accuracy of diagnosis, assessment of disease extent, and dramatically reduced surgical morbidity. Overall, these factors have resulted in longer survival for patients with limited pulmonary involvement by metastatic malignant melanoma. Helical CT of the lung accurately detects small lesions, and metabolic activity can be confirmed with PET scanning. These diagnostic techniques, together with a history of melanoma, frequently obviate the need for presurgical biopsy; benign lesions or another malignancy are rarely found. These findings contrast markedly to the findings of older series where misdiagnosis,¹² incomplete resections,¹³ long hospital stays,¹⁴ and substantial surgical morbidity were common, resulting in a lower proportion of patients achieving temporary freedom from disease and also a short median survivorship overall. These difficulties have gradually abated in recent years, although a review by Wong and Coit⁵ in 2004 still demonstrated a median disease-free interval of about 6 months and a median survival of 2 years. Our data suggest a modest improvement over these results, ex-

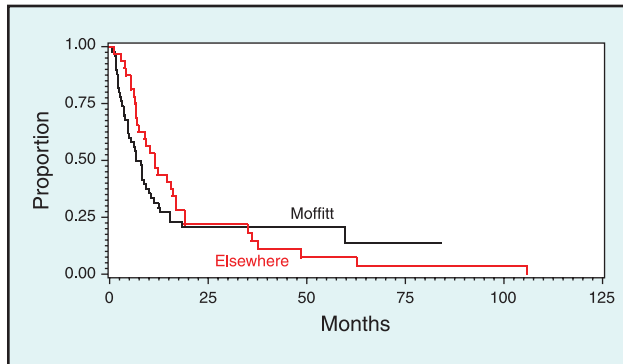


Fig 2. — The effect of site of surgery on time to progression — surgery at Moffitt vs elsewhere (P Value = 0.55).

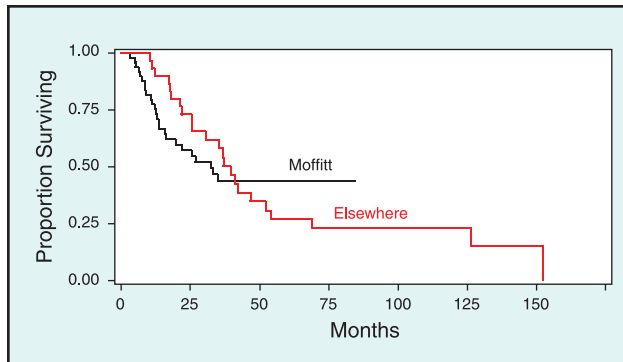


Fig 3. — The effect of site of surgery on survival — resection at Moffitt vs elsewhere (P Value = 0.82).

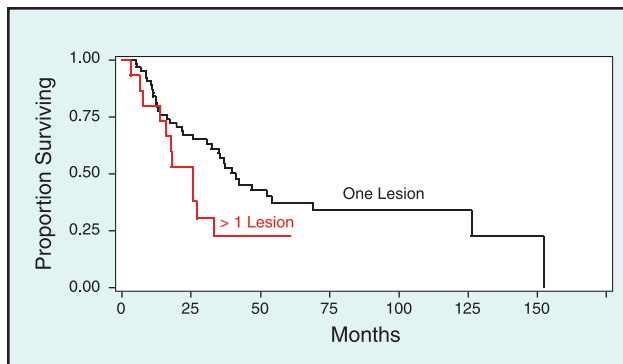


Fig 4. — The influence of number of lesions completely resected on overall survival (P Value = 0.48).

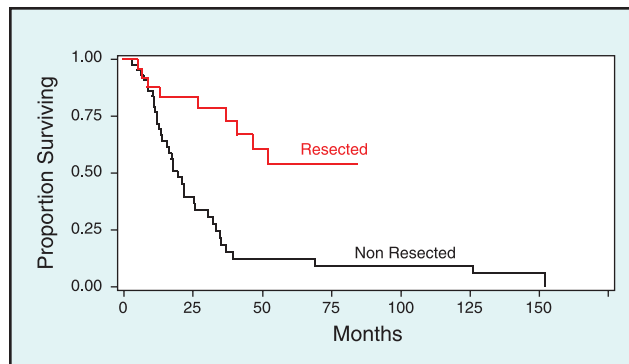


Fig 5. — The influence of subsequent surgery after relapse on overall survival (P Value = 0.0001).

tending median survival to approximately 3 years. Our data in part suggest a possible value of regular periodic imaging after resection of pulmonary metastases; one third of patients with relapse presented with another isolated manifestation of metastatic disease, which was resected. Our general practice of periodic physical examinations and radiographic scans at 2- to 3-month intervals for 2 years and 4- to 6-month intervals thereafter may have facilitated the identification of patients with limited recurrences more frequently than in other reports. Reresection clearly contributes to overall survival, given the limitations of current systemic treatment.

Determining when to intervene has been problematic to some who fear that early surgical intervention will lead to a needless procedure in patients who are destined to have rapid proliferation at multiple sites. Accordingly, they recommend a period of observation or treatment to assess patients for stability and the lack of new lesions. Our management policy is to proceed with resection without delay when metastatic disease is identified accurately. If localized concomitant non-pulmonary disease is encountered, it is resected as well. This policy does not appear to have resulted in many fruitless operations as judged by our median time to relapse and survival data. Six of 12 patients who relapsed within 3 months were deemed appropriate for subsequent surgical salvage.

The use of thoracoscopy as the surgical approach to resection of pulmonary metastases became controversial with the publication of a small series of 18 patients published by McCormack et al¹⁵ in 1996. In this study, metastatic nodules found on CT scanning were resected by thoracoscopy; then, at the same anesthetic, an open thoracotomy was subsequently performed to search for additional nodules. In 10 of 18 patients (56%), additional metastatic nodules were found at thoracotomy not shown on the preoperative chest CT scan. The primary weakness in the study is that in 16 of the 18 patients, preoperative imaging was performed on old-generation CT scanners rather than ultrafast, high-resolution helical scanners. Subsequent larger series, reviewed by Lin and Landreneau,¹⁶ that selectively used thoracoscopy for resection of pulmonary metastases with imaging based on more sensitive high-resolution scanners have provided results comparable to open thoracotomy but with far less morbidity. We therefore used thoracoscopy as the surgical approach in selected patients. Only 2 of the 6 patients who relapsed with a second lung lesion had undergone a thorascopic procedure; both relapsed at 8 months, and both remain alive at 64 and 82 months. These results appear to vindicate the use of this technique.

Many investigators have sought to define prognostic factors that better predict the relative benefit from surgical intervention. Factors considered include age, sex, depth of primary lesion, prior metastatic spread,

time from diagnosis to pulmonary metastasis, and the number of pulmonary metastases. Unfortunately, many of these factors have not been subject to confirmation of validity largely due to the heterogeneity of the population under study and the overall small number of patients in any particular series. This same limitation applies to this review. The largest cooperative study,⁶ conducted by the International Registry on lung resection, attempted to define prognostic variables with a database of 292 individuals. Two of the most commonly suspected factors emerged as significant: the influence of multiple lesions and time from diagnosis to resection. Combining these factors produced three cohorts of survivorship: those with a single pulmonary metastasis presenting 3 or more years after a primary did best, while patients presenting with either a single lesion less than 3 years later or multiple lesions fared less well, and those with both factors did even worse. Five-year survival rates for these three cohorts were 29%, 20%, and 7%, respectively. Our data did not confirm the prognostic value of time from diagnosis to recurrence. Survival time was influenced only by the number of metastases. Several differences in patient demographics may account for these findings. In the registry data, the median time from diagnosis to complete pulmonary resection was 54 months compared to 36 months in our data. Staging, both clinical and pathologic, was more limited in that series; a greater proportion presented with multiple lesions and fewer underwent salvage surgery.

No current standard effective systemic therapy exists for resected stage IV disease. Some of our patients participated in investigations of adjuvant approaches with vaccines or cytokines. The greatest number of patients were managed on the Canvaxin trial. Unfortunately, this large randomized prospective trial of a vaccine did not improve survival.¹⁷ Other trials of adjuvant therapy are underway. These studies of resected metastatic malignant melanoma demonstrate the potential influence of still ill-defined prognostic factors on outcome and call attention to the need for careful stratification in such trials.

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