Original Article

A Phase 2 Trial of Complete Resection for Stage IV Melanoma

Results of Southwest Oncology Group Clinical Trial S9430

Jeffrey A. Sosman[1]; James Moon[2]; Ralph J. Tuthill[3]; James A. Warneke[4]; John T. Vetto[5]; Bruce G. Redman[6]; P. Y. Liu[2]; Joseph M. Unger[2]; Lawrence E. Flaherty[7]; and Vernon K. Sondak[8]

BACKGROUND: On the basis of retrospective experience at individual centers, it appears that patients with stage IV melanoma who undergo complete resection have a favorable outcome compared with patients with disseminated stage IV disease. The Southwest Oncology Group (SWOG) performed a prospective trial in patients with metastatic melanoma who were enrolled before complete resection of their metastatic disease and provided prospective outcomes in the cooperative group setting. **METHODS:** Based on their physical examination and radiologic imaging studies, patients with a stage IV melanoma judged amenable to complete resection underwent surgery within 28 days of enrollment. All eligible patients were followed with scans (computed tomography or positron emission tomography) every 6 months until relapse and death. **RESULTS:** Seventy-seven patients were enrolled from 18 different centers. Of those, 5 patients were ineligible; 2 had stage III disease alone; and 3 had no melanoma in their surgical specimen. In addition, 8 eligible patients had incompletely resected tumor. Therefore, the primary analysis included 64 completely resected patients. Twenty patients (31%) had visceral disease. With a median follow-up of 5 years, the median relapse-free survival was 5 months (95% CI, 3-7 months) whereas median overall survival was 21 months (95% CI, 16-34 months). Overall survivals at 3 and 4 years were 36% and 31%, respectively. **CONCLUSIONS:** In a prospective multicenter setting, appropriately selected patients with stage IV melanoma achieved prolonged overall survival after complete surgical resection. Although median relapse-free survival was only 5 months, patients could still frequently undergo subsequent surgery for isolated recurrences. This patient population is appropriate for aggressive surgical therapy and for trials evaluating adjuvant therapy. ***Cancer*** **2011;117:4740–6.** © *2011 American Cancer Society.*

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Metastatic melanoma generally has a dismal prognosis, few good options for systemic therapy, and a median survival of 6 to 10 months.[1-4] However, when patients present with only a few metastatic sites, complete resection of stage IV disease has been associated with a much better prognosis than expected.[5-11] A favorable outcome has been reported in numerous series from single centers.[8-11] From these studies, we have learned that several factors appear to predict a better outcome after surgery for stage IV melanoma patients. These factors include nonvisceral sites of disease, fewer numbers of organs involved, and longer intervals from primary or regional disease to the development of metastatic disease.[8-17]

Although it is likely there are key biologic differences between patients who undergo resection of isolated metastases and those who have unresectable, disseminated, metastatic melanoma, these differences remain unknown. It is very possible that a favorable outcome may have more to do with the inherent biology of the disease than the actual surgical procedure, and it is also clear that patients undergoing complete surgical resection of all stage IV disease represent a highly selected population. Importantly, because the prognosis of patients undergoing complete surgical resection is incompletely understood, nonrandomized adjuvant therapy trials after complete resection are often interpreted as showing a

Corresponding author: Jeffrey A. Sosman, MD, Vanderbilt University School of Medicine, Division of Hematology/Oncology, 777 Preston Research Bldg, 2220 Pierce Ave, Nashville, TN 37232-7602; Fax: (615) 343-7602; jeff.sosman@vanderbilt.edu

[1]Vanderbilt University School of Medicine, Department of Medicine, Nashville, Tennessee; [2]Southwest Oncology Group Statistical Center, Seattle, Washington; [3]Cleveland Clinic Foundation, Department of Medicine, Cleveland, Ohio; [4]University of Arizona, Department of Surgery, Tucson, Arizona; [5]Oregon Health Sciences University, Department of Surgery, Portland, Oregon; [6]University of Michigan, Department of Medicine, Ann Arbor, Michigan; [7]Wayne State University/Karmanos Cancer Institute, Department of Medicine, Detroit, Michigan; [8]H. Lee Moffitt Cancer Center, Department of Cutaneous Oncology, Tampa, Florida

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favorable result for the adjuvant treatment that may more properly be attributed to the combination of patient selection and favorable outcome with surgery alone. Indeed, a nonrandomized experience with allogeneic tumor vaccination after complete resection of stage IV disease that showed much more favorable outcomes than expected led to the conduct of a large prospective randomized phase 3 trial.[18] In this trial, there was no beneficial impact of vaccine therapy, and the outcome of the control arm precisely reproduced that of the original nonrandomized trial and others like it.[19] In the Southwest Oncology Group (SWOG), we undertook a prospective multicenter clinical trial of complete resection for patients with stage IV melanoma.[20] We specifically designed this trial to enroll patients preoperatively, to capture the outcome of all patients, even those not able to undergo resection, and to assess how frequently resection was actually feasible. Also, there was an attempt to obtain tumor tissue from surgery on enrolled patients whenever feasible, although this was not required. The trial was thus designed to provide a more realistic prognosis for patients who were proceeding toward complete surgical resection and to not limit analysis to only those successfully resected, reevaluated after surgery, and confirmed free of disease, as is the case with most postoperative adjuvant therapy trials.

MATERIALS AND METHODS

Patient Eligibility

All patients were to have biopsy-proven stage IV melanoma with a SWOG performance status of 0 to 2. The surgical treatment was undertaken with the intent to resect all known disease. Patients had to be considered appropriate surgical candidates by the treating surgeon and must not have had systemic or radiation therapy within 14 days before enrollment. Within 42 days of registration before surgery, patients had to undergo a computed tomography (CT) of the chest, abdomen, and pelvis or a whole body positron emission tomography/computed tomography (PET/CT) scan, and brain CT or magnetic resonance imaging (MRI) scan. Patients with a history of other invasive cancers besides melanoma were required to have no evidence of malignancy within the past 5 years and to be considered disease-free from that cancer.

Treatment Plan

The goal of surgery was to obtain gross total removal of all known disease. Patients with a histologically positive margin without gross residual disease were still eligible, and they could undergo postsurgical radiation therapy at the discretion of the treating physician. Postoperatively, patients could receive whatever systemic or local therapy was deemed appropriate by the treating physicians, including participation in investigational adjuvant therapy trials.

Follow-Up

After surgery, patients were to be seen every 3 months for 1 year and then every 6 months thereafter until relapse. CT and/or PET scans appropriate to monitor for recurrence were to be performed every 6 months until relapse or death from other causes. All patients were followed every 6 months until death.

Statistical Considerations

The primary endpoint was overall survival (OS) for those patients with completely resected stage IV melanoma. OS was defined as the time from date of surgery to resect stage IV disease until death due to any cause. Relapse-free survival was also analyzed. Relapse-free survival was defined as the time from date of surgery to resect stage IV disease until relapse or death due to any cause. The sample size was primarily selected to obtain adequate tumor tissue from a significant proportion of patients to study the biologic features of these melanomas. However, as planned, the sample size was 100 fully evaluable patients, which would have been sufficient to estimate the 1-year survival probability to within 10% (95% confidence interval [CI]).[21] Survival estimates were derived from the Kaplan-Meier method.[22]

RESULTS

Patients Enrolled

The study was first activated in November, 1996, and closed officially to accrual in November, 2005. Planned accrual was 100 eligible patients. However, accrual slowed to less than 5 patients per year during the last 2 to 3 years, leading to termination after 77 patients were enrolled. Of these 77 patients, 5 were ineligible; 2 had only stage III disease (regional lymph nodes or satellite and/or in-transit disease), and 3 had no melanoma within the resected specimen. An additional 8 eligible patients did not have all gross disease completely resected (Table 1). Therefore, 64 fully eligible patients were included in the primary analysis, and 72 patients undergoing surgery for stage IV melanoma were included in a secondary analysis. As can be seen in Table 2, the demographics of the patients in the primary analysis were very typical of stage IV melanoma, with a median age of 53 years and more than two-thirds

Table 1. Patient Enrollment

Enrollment	No.
Patients enrolled	77
Ineligible	5
Local/regional disease only	2
Resected specimens contained no melanoma	3
Patients with stage IV disease	72
Stage IV disease not completely resected	8
Patients included in primary analysis	64

Table 2. Characteristics of Patients Undergoing Complete Resection (N=64)

Characteristics	No. (%)
Age	
Median	53
Range	23-80
Sex	
Male	44 (69)
Female	20 (31)
Race	
Caucasian	62 (97)
African American	1 (1.5)
Native American	1 (1.5)
Performance score	
0-1	64 (100)
Prior surgery	60 (94)
Prior systemic treatment	28 (44)
Prior adjuvant IFN	29 (45)
Disease-free interval, mo[a]	
Mean	36
Median	13.5
Range	0-316, interquartile range 0-48
Intervening regional disease[b]	
Yes	29 (45)
No	35 (55)
No. of organ systems involved	
1	50 (78)
2	14 (22)
Primary site	
Cutaneous	58 (91)
Ocular primary	1 (1.5)
Mucosal	1 (1.5)
Unknown	4 (6)

Abbreviation: IFN, interferon.
[a] From date resected free of disease to date of diagnosis with stage IV disease.
[b] Defined as appearance of regional lymph nodes or satellite/in-transit metastases after diagnosis of primary but before diagnosis of stage IV; for patients with unknown primary, diagnosis of regional lymph nodes or satellite/in-transit metastases before diagnosis of stage IV.

Table 3. Distant Metastatic Sites Completely Resected (N=64)

Disease Sites	No. (%) of Patients
Any visceral disease	20 (31)
Nonvisceral disease only	44 (69)
Skin/Soft tissue	34 (52)
Distant nodes	24 (37)
Lung	9 (14)
Brain/CNS	3 (5)
Liver	2 (3)
Other visceral disease	6 (9)

Abbreviation: CNS, central nervous system.
Fourteen (22%) patients had tumor resected from >1 site.

(69%) male. All 64 of the fully eligible patients had an excellent preoperative performance status ([PS] 0-1). In terms of prior therapy, 45% had received prior interferon-α (IFNα) in the adjuvant setting, and 44% had received prior systemic therapy in the metastatic setting. One patient had an ocular primary, 1 had a mucosal primary, 4 had unknown primaries, and the remainder had a known cutaneous primary site.

Stage IV Disease Sites

The sites of resected distant metastatic disease are given in Table 3. Many patients had more than 1 disease site, but the great majority of patients had involvement of only 1 organ system (Table 2). Skin and soft tissue sites were present in more than 50% of the cases. Distant lymph nodes were resected in 37% of the cases, lung in 14%, brain and/or central nervous system (CNS) in 5%, and liver in 3%. Preoperative serum lactate dehydrogenase (LDH) determination was not required and was rarely available as most patients were enrolled before its inclusion into the American Joint Commission on Cancer (AJCC) staging system for stage IV melanoma.[23] Hence, substaging according to the 2002 AJCC criteria for stage IV melanoma was not adequately captured and could not be incorporated into the study analysis.

Treatment Outcome

Sixty-four of 72 patients with presumed resectable metastatic melanoma were completely resected of all gross disease (89%; 95% CI, 75%-92%). The median follow-up among patients still alive was 5 years (range, 3-9 years). All but 6 of the 64 patients have had disease recurrence, with a median relapse-free survival (RFS) of approximately 5 months (95% CI, 3 to 7 months; Fig. 1). The estimated 4-year RFS was 13% (95% CI, 4%-21%). The 6-month, 1-, 2-, 3-, and 4-year RFS rates are shown in

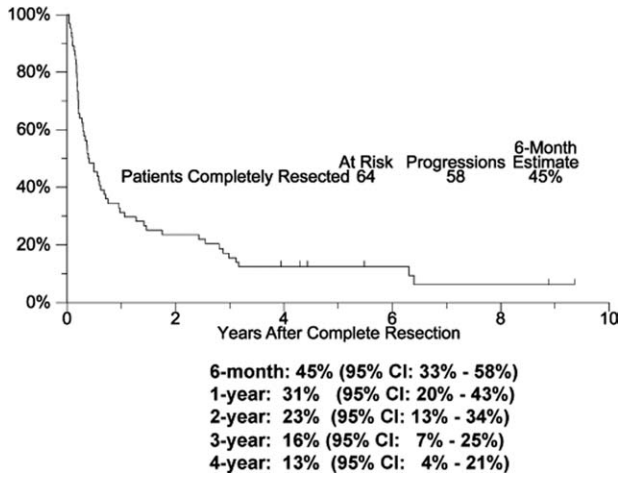

Figure 1. Kaplan-Meier estimates of relapse-free survival (RFS) for those patients who were completely resected of all disease are shown. RFS was defined as the time from the date of complete resection until the date of disease relapse or death due to any cause. Patients last known to be alive and without disease relapse were censored at the date of last contact and are marked on the curve with a tic representing the last follow-up time. RFS at specified time points with 95% confidence intervals are presented at the bottom of the figure.

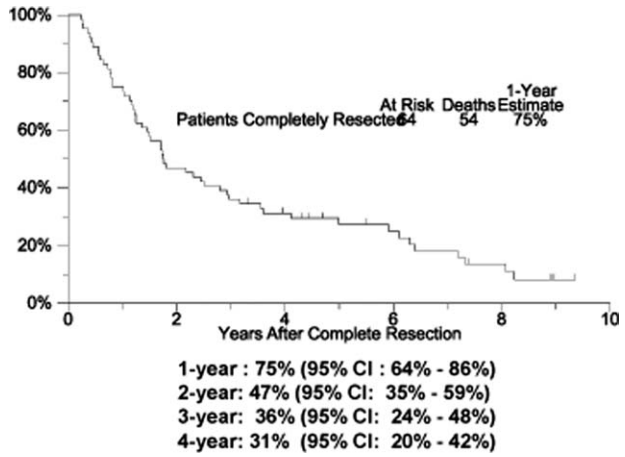

Figure 2. Kaplan-Meier estimates of overall survival (OS) for those patients who were completely resected of all disease are shown. OS was defined as the time from the date of complete resection until the date of death due to any cause. Patients last known to be alive were censored at the date of last contact and are marked on the curve with a tic representing the last follow-up time. OS at specified time points with 95% confidence intervals are presented at the bottom of the figure.

Figure 1 with their respective confidence intervals. Among the 58 patients who recurred after initial complete resection of their metastatic disease, postrecurrence treatment was further surgery in 21 (36%) patients. In an exploratory analysis to investigate whether resection of subsequent recurrence was associated with improved survival, a Cox regression model was fit with re-resection as a time-dependent covariate.[24] A significant relation with improved survival could not be detected ($P = .92$; hazard ratio [HR], 0.97; 95% CI, 0.53-1.76). OS was considerably longer than RFS (Fig. 2), with a median survival of 21 months (95% CI, 16-34 months) and an estimated 1-year survival of 75% (95% CI, 64%-86%). OS at 4 years was 31% (95% CI, 20%-42%). Among all stage IV patients enrolled (n = 72), including those who could not be completely resected, the median OS was also 21 months (95% CI, 15-29 months), and the estimated 1-year OS was 69% (95% CI, 59%-80%; Fig. 3). Eighteen patients survived more than 4 years. Fourteen of these patients had only skin, soft tissue, or lymph node disease, but 2 patients had lung metastases, 1 patient had lesions of the small bowel and pancreas, and 1 had gallbladder lesions resected. An exploratory analysis comparing patients with visceral disease versus those with only nonvisceral disease resected was unable to detect a statistically

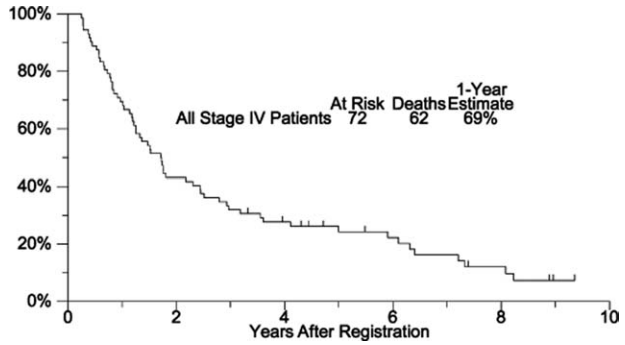

Figure 3. Kaplan-Meier estimates of overall survival (OS) for all patients with stage IV disease, including those who could not be completely resected of all disease, are shown. OS was defined as the time from the date of surgery until the date of death due to any cause. Patients last known to be alive were censored at the date of last contact and are marked on the curve with a tic representing the last follow-up time.

significant difference in OS or RFS between these 2 groups (Table 4 and Table 5). However, there was a trend ($P = .17$) favoring the nonvisceral melanoma patients in terms of OS. An exploratory post hoc analysis compared the 64 completely resected patients with the 8 patients who could not be completely resected. The completely resected patients had an estimated 1-year OS of 75% (95% CI, 64%-86%) versus a 1-year OS estimate of 25% (95% CI, 0%-55%) for those patients who could not be

Table 4. Prognostic Variables for Overall Survival in Completely Resected Patients (N=64)

Prognostic Variables	*P*	Hazard Ratio	95% CI
Visceral vs non-visceral	.17	1.50	0.84-2.68
Age	.37	0.99	0.97-1.01
Disease-free interval	.43	1.00	0.99-1.00
Intervening regional disease	.82	1.07	0.61-1.86
No. of organs involved	.84	1.07	0.56-2.04
Sex	.96	1.01	0.56-1.82
Prior systemic therapy	.99	1.01	0.59-1.73

Table 5. Prognostic Variables for Relapse-Free Survival in Completely Resected Patients (N=64)

Prognostic Variables	*P*	Hazard Ratio	95% CI
Visceral vs non-visceral	.55	1.19	0.68-2.09
Age	.59	0.99	0.98-1.02
Disease-free interval	.38	1.00	0.99-1.00
Intervening regional disease	.68	0.89	0.52-1.52
No. of organs involved	.90	1.04	0.55-1.97
Sex	.91	0.97	0.55-1.71
Prior systemic therapy	.50	1.19	0.71-2.02

completely resected. Only 19 patients received adjuvant therapy after their initial resection. This primarily included high-dose interferon[8] or radiation therapy,[7] but it also included interleukin-2 (IL-2), Canvaxin, or some combination of similar treatments. A time-dependent Cox model analysis was unable to show that adjuvant therapy after resection had any effect on survival ($P = .33$; HR, 0.74; 95% CI, 0.41-1.35). Finally, we also performed exploratory analyses examining the effect of disease-free interval (DFI) before presentation with distant metastases (continuous variable), the presence of intervening regional disease (between primary and metastatic presentation; yes or no), prior systemic therapy (yes or no), and finally number of organs involved (1 or 2; Table 2). As demonstrated in Tables 4 and 5, none of these factors were significant in univariate analyses, and, therefore, we did not look at a multivariate model.

DISCUSSION

It is now well accepted that patients with isolated resectable metastases from melanoma are candidates for complete resection, but the rate of complete resection and the disease-free and OS rates have largely been established in single center, retrospective reports.[5-11] This prospective trial was designed to provide a better understanding of the natural history of patients with stage IV melanoma who are considered candidates for resection of all of their disease. Typically, in most trials enrolling metastatic resected melanoma patients, the surgery has been completed, and patients were alive and free of disease for a few months before their participation. Patients on this trial were identified and enrolled before surgery. This trial represents the only prospective trial of these patients before surgery, and they were accrued from numerous centers.[18] This is a unique subset of stage IV melanoma that has not been well described previously, despite a large number of retrospective single center series and a few prospective (but mostly uncontrolled) trials of adjuvant therapy after successful resection.[5-11,18,19] Adjuvant therapy trials are likely to overestimate the survival rates for patients with resected stage IV melanoma, as patients who relapse rapidly after surgery or are recognized on postoperative imaging to have residual gross tumor are identified and excluded before study entry.

In our prospective trial, we were able to accrue 77 patients from 18 different institutions, with 7 institutions accruing 4 or more patients. Complete resection was feasible in a high percentage of patients (89%; 95% CI, 75%-92%) initially believed to be resectable. Eight patients were thought to be resectable, but at surgery, their operation either became only palliative, or there was no attempt at resection. Furthermore, in this series, 3 of 75 (4%) patients thought to have stage IV melanoma were found not to have melanoma at surgery. Alternative diagnoses at surgery were benign tumors, infection, and scarring. The overall RFS was generally short, with a median of 5 months and a 4-year disease-free survival estimate of only 13%. Some of the patients who recurred early would have been excluded from adjuvant therapy studies, artificially inflating the progression-free and OS outcomes for such trials compared with the true natural history of resected stage IV melanoma, making direct comparisons to our data inappropriate.

On the other hand, median OS was 21 months, and the 4-year OS estimate was 31%. OS for the 64 patients with resected stage IV melanoma on this study was much longer than for patients with unresected stage IV melanoma enrolled onto 42 phase 2 cooperative group clinical trials involving 2100 patients receiving systemic therapy (median OS, 21 months vs 6.2 months).[25] This recent large analysis of all phase 2 cooperative group trials for stage IV melanoma demonstrated a 1-year survival of

25.5%, whereas the median progression-free survival (PFS) was just 1.7 months, and 6-month PFS was 14.5%.[24] The corresponding values for patients with resected stage IV melanoma on our trial were far better: survival at 1 year was 75%, median RFS was 5 months, and 45% of patients were relapse-free at 6 months. Consideration should be given to modifying the AJCC melanoma staging system to reflect the better prognosis of this group than other stage IV subsets.[4-6,26]

In our trial, there was a large difference between median RFS and OS—a finding that has been seen in prospective adjuvant therapy trials as well.[19,27] This is likely due to the nature of these recurrences, which are frequently isolated and allow further surgery. In our trial, 36% of patients who recurred underwent re-resection, which would seem to be a much higher percentage than would be seen in unselected stage IV melanoma patients, although we were unable to demonstrate that patients undergoing re-resection had significantly improved OS compared with those that did not.

The study does have several weaknesses, including the relatively small number of patients enrolled during a 9-year period. The slow accrual was likely influenced by the requirement that enrollment occur before the actual surgery, whereas in the cooperative group setting, most clinical trial accrual is carried out after surgery. Another limitation is that we did not collect information on patients' serum LDH, a prognostic factor whose importance was recognized and was included in the AJCC staging system only well after the study was initiated.[23,26] The authors' experience is that it is unlikely many of these patients had elevated serum LDH levels given their limited metastases, but prospective data on this point are lacking.

Overall, our results are very much in line with single center experiences published to date, but with an apparently slightly worse outcome.[7-11] This is not surprising because of the selectivity of patient entry on previously reported studies and their retrospective nature. We believe this analysis provides a more realistic view of patients' outcome when operated on for stage IV disease with "curative intent". Even so, surgery for properly selected patients does provide a valuable option that can be associated with prolonged survival in the absence of any type of systemic therapy. Nonetheless, the high relapse rate and relatively short RFS time for most patients makes it imperative to continue to evaluate systemic interventions aimed at increasing RFS and OS after complete resection. The value of adjuvant therapy for resected stage IV melanoma patients can be adequately assessed only with well controlled randomized phase 3 trials.

It is also imperative that we continue to study the population of melanoma patients with "oligometastatic" disease to identify biologic determinants of improved outcome that are independent of the therapy used.[28-29] We have collected fresh frozen and formalin-fixed paraffin-embedded tumor tissue and blood from many of the patients enrolled on this trial in the hope of doing precisely that. This may provide us with information valuable to understanding mechanisms of tumor growth and metastases and may further improve selection of candidates for surgical versus nonsurgical or combined modality therapy in the future.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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