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Does metastasectomy improve survival in patients with Stage IV melanoma? A cancer registry analysis of outcomes

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Abstract

Introduction—Patients with Stage IV melanoma have limited therapeutic options with few long term survivors. Our goal was to study the impact of metastasectomy on survival in these patients.

Methods—Patients with Stage IV melanoma were identified from the Surveillance, Epidemiology and End Results (SEER) database (1988–2006). Those who had metastasectomy performed were compared with patients that did not.

Results—The median age of the study population (n= 4229) was 63 years and median survival was 7 months. Patients who underwent metastasectomy (33.6%) had an improved median and 5-year overall survival as compared to patients who did not; 12 months vs. 5 months and 16% vs. 7%, p <0.001). In patients with M1a disease (n= 1994), this improvement of survival following metastasectomy was enhanced; median survival of 14 months vs. 6 months and 5-year overall survival of 20% vs. 9% (p <0.001). Younger age and diagnosis from 2001–2006 were predictors of metastasectomy. Metastasectomy was an independent and significant predictor of survival for the entire cohort (HR 0.59, 95% CI 0.55– 0.63).

Conclusions—Metastasectomy in patients with Stage IV melanoma may improve long term survival. The true therapeutic benefit, if any, of metastasectomy needs to be determined by a randomized trial.

Keywords

Stage IV melanoma; metastasectomy; survival

Introduction

The dismal prognosis for Stage IV cutaneous melanoma has remained relatively unchanged over the past three decades, with a median survival of 7–8 months and a five year survival of 5–15%.^{1, 2} Due to improved awareness and access to screening, 80% of new cases of cutaneous melanoma are localized; however, 12% present with regional disease and 8% have distant disease at the time of initial diagnosis.³ Although the majority of patients with cutaneous melanoma will be cured by adequate surgical excision, about 30% will eventually go on to develop distant metastases, a phenomenon that can occur decades after the initial diagnosis.⁴ Heterogeneity in the disease process itself is seen within Stage IV melanoma, as

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reflected by the current American Joint Committee on Cancer (AJCC) TNM staging system for melanoma.⁵ Distant skin, subcutaneous, or nodal metastases (M1a) have a better prognosis than lung metastases (M1b), which in turn have a better prognosis than any visceral metastases (M1c). An elevated serum lactate dehydrogenase (LDH) level is also classified as M1c disease.

Although controversial because of the lack of efficacy, systemic therapy remains the mainstay of treatment. Dacarbazine and its active metabolite temozolomide are the most active single agents, with a clinical response in 15–20% of patients and a complete response in 3–5% of patients. However, the median duration of response is only 4–6 months.⁶ The only biologic agent approved by the US Food and Drug Administration (FDA) for patients with Stage IV melanoma is interleukin-2. This was on the basis of a phase II trial conducted by the National Cancer Institute showing objective responses in 20% of patients, with a complete response in 7%.⁷ However significant toxicity including potentially fatal pulmonary edema and shock were also seen with the high dose bolus approach used in this trial. A combination of chemotherapeutic agents (dacarbazine, cisplatin, vinblastine) with biological therapies (interleukin-2, interferon alfa) has also been tried by various investigators. This approach is known as biochemotherapy and randomized trials have not shown a significant difference in survival, even though a definite increase in toxicity was seen.^{8,9} The failure to develop ‘game-changing’ systemic therapy means there is a need to explore alternative treatment options to bend the survival curve.

Our group has long been a proponent of metastasectomy for patients with Stage IV melanoma. Metastasectomy is defined as resection of all radiographic and clinically evident sites of disease with histologically tumor-free margins (R0 resection). Although the majority of patients with Stage IV melanoma will ultimately succumb to their disease, 86% initially have only one metastatic site, which would theoretically be amenable to loco-regional therapy such as surgical resection.^{1, 4, 10} This site is most commonly the lung, followed by the skin, lymph nodes, brain, liver, and gastrointestinal tract. A new paradigm for the treatment of Stage IV melanoma involving surgery combined with immunotherapy was initially proposed by Morton et al.¹¹ The Malignant Melanoma Active Immunotherapy Trial, Stage IV (MMAIT IV) examined the value of Canvaxin plus Calmette-Guerin vaccine (BCG) versus BCG alone as adjuvant therapy for patients with completely resected stage IV melanoma.¹² Although the trial did not demonstrate a survival benefit for patients who received the Canvaxin vaccine, a strikingly high five year survival of 40% was seen in this patient population of Stage IV melanoma undergoing metastasectomy. Nevertheless, concerns about the applicability of the results of MMAIT IV outside the setting of a clinical trial remain. Other retrospective studies in the literature confirm improved survival in patients with Stage IV melanoma undergoing metastasectomy; however these reports are from specialized single institutions.^{4, 13, 14}

The purpose of this study was to use a cancer registry to study the use of metastasectomy in Stage IV melanoma patients in the general population of the United States. Our goal was to investigate the impact of metastasectomy on survival in Stage IV melanoma, explore trends over time, and to identify predictors of metastasectomy and survival in a ‘real-world’ scenario, as opposed to single institution series.

METHODS

SEER Database

The National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) tumor registry database was used for this study. SEER contains over 3 million cases from 18 geographic sites, covering approximately 26 percent of the United States population. The

database was designed to reflect the overall characteristics of the U.S. population and is regarded as a model population-based tumor registry. Quality control is an important component of the SEER program; the current standard for accuracy of the data in the registry is an error rate of less than 5%.¹⁵ SEER Program registries routinely collect data on patient demographics (age, sex, etc.), primary tumor characteristics (Breslow thickness, Clark level, ulceration, etc.), nodal staging (sentinel lymph node biopsy, number of positive nodes, etc.), surgery performed (primary site surgery and surgery for distant metastases), vital status and survival. Although information on radiation therapy is recorded, no information on chemotherapy is provided. Furthermore information on recurrence, disease free interval and number of actual metastases is not available. The November 2008 update was used for this study, providing information from 1973–2006.¹⁶ As a population-based study with no patient identifiers involved, our study was exempt from Institutional Research Board review.

Case Selection

The study period was from 1988–2006. The ICD-10 (International Statistical Classification of Diseases and Related Health Problems) histology codes 8720-8799 combined with the Site and Morphology code ‘melanoma of the skin’ was used to identify all patients with a diagnosis of cutaneous melanoma. Patients with Stage IV disease were identified and those with regional or localized disease were excluded. Patients with no histological confirmation of the diagnosis and cases identified from autopsy reports only were also excluded. Using the extent of disease codes in the SEER coding manual, patients were subdivided into M1a disease (cutaneous metastases) and Mbc disease (visceral metastases). Limitations in the coding schema meant we could not distinguish between lung metastases (M1b) and other visceral metastases (M1c), so we combined both groups into the Mbc category. Furthermore, information on LDH levels was available only from 2004+ so was not explored for the purposes of this study.

Statistical Analysis

Kaplan-Meier curves and log-rank tests were used to identify differences in overall survival, defined as duration of survival after diagnosis. Predictors for survival following surgical resection were identified by Cox regression analysis using proportional hazards modeling. Variables included in the model were age (continuous), sex, M1a vs. M1bc, time period of diagnosis and metastasectomy. Multivariate logistic regression analyses were used to identify predictors for metastasectomy. Variables included in the model were age (continuous), sex, M1a vs. M1bc and time period of diagnosis. Patients with incomplete data were excluded from regression analyses. All tests were two-tailed, significance levels were set at $p < 0.05$ and confidence intervals at 95%. Statistical analysis was performed using SPSS 16.0 statistical software (SPSS Inc., Chicago IL).

RESULTS

Demographics

Our study population consisted of 4229 patients diagnosed with Stage IV melanoma from 1988–2006. As outlined in Table 1 the median age was 63 years and the majority were male (67%). A total of 1422 patients (33.6%) underwent metastasectomy for either M1a or M1bc disease. Details of primary site surgery and regional nodal management are also presented.

Predictors of metastasectomy

Patients who underwent metastasectomy were likely to be younger and present in the latest time period of the study (2001–2006) than those undergoing no surgery. No differences

were seen between the two groups in distribution of metastases or sex (Table 2). On multivariate analysis, younger age at diagnosis and more recent time period of diagnosis were both predictors of metastasectomy (Table 3).

Improvement in overall survival with metastasectomy

For the entire cohort median survival was 7 months and overall survival at five years was 10% (Table 4). Patients who underwent metastasectomy showed an improvement in both median as well as overall survival at five years (Figure 1A). This improvement was seen for both M1a disease (Figure 1B) as well as M1bc disease (Figure 1C), with more than a doubling of median and overall survival in patients undergoing metastasectomy.

Predictors of survival

On multivariate analysis male sex, increasing age and M1bc disease all had an adverse impact on survival at five years. Diagnosis in the more recent time periods as well as metastasectomy (HR 0.59) had a beneficial impact on survival (Table 5).

DISCUSSION

In this study we investigate the use of metastasectomy for Stage IV melanoma in the general population of the United States. We show that 33.6% of patients with Stage IV melanoma underwent metastasectomy with an improvement in median survival from 5 months to 12 months and five year overall survival from 7% to 16%. This improvement in survival following metastasectomy was seen for both M1a as well as M1bc disease. Younger age and more recent time period of diagnosis were both predictors of metastasectomy. Multivariate analysis showed that metastasectomy had a beneficial effect on survival (HR 0.59). The results of this study show that even outside the controlled setting of a randomized clinical trial or specialized single institution reports, metastasectomy in patients with stage IV melanoma may confer a survival benefit.

Our results are comparable to those reported previously in the literature. Several institutions have published their experience with metastasectomy in Stage IV melanoma and show 5 year survivals that range from 14%–28%.^{4, 13, 14, 17–21} Similarly, in the largest published single institution report on the subject, a total of 35% of all patients seen with Stage IV melanoma underwent metastasectomy.⁴ The fact that almost a third of patients with Stage IV melanoma undergo metastasectomy suggests that many clinicians support the practice since it is unlikely that all of these surgeries are purely for palliation. The overall 5 year survival in our study is 16% which is on the lower end of the reported range and probably represents the ‘real-world’ scenario. We also confirm the validity of the current AJCC staging system for melanoma in that survival outcomes for M1a disease were significantly better than for M1bc disease, irrespective of whether metastasectomy was performed or not. This has been shown by others as well.^{1, 22–25}

Increasing age, male sex, and visceral metastases were identified as having an adverse impact on survival in patients with Stage IV melanoma. Skin, subcutaneous or distant nodal metastases and diagnosis in the later time periods of the study were beneficial. Others have also shown the impact of sex and site of metastases on survival,^{4, 22–25} as well as improvement in outcomes with a more recent date of diagnosis.²³ Although there was a statistically significant difference in median and five year overall survival between the time periods 1988–1995 and 2001–2006 in our study, this difference is unlikely to be clinically significant (median survival 6 months vs. 7 months and five year overall survival 9% vs. 11%, $p = 0.043$). Other reported prognostic factors for patients with Stage IV melanoma are number of metastatic sites^{4, 14, 22, 24, 25}, disease free interval^{4, 22}, stage prior to

metastases^{1, 4}, and serum LDH.^{19, 23} The importance of a complete surgical resection with negative margins (R0) is also highlighted by several groups.^{6, 19, 26}

Diagnosis in the later time periods of the study was predictive of metastasectomy, suggesting a greater willingness to consider this approach as part of the management plan. The percentage of patients undergoing metastasectomy increased from 30% in the time period 1988–1995 to 35% from 2001–2006. Younger age at diagnosis was also predictive of metastasectomy. This suggests a possible explanation for the results, in that younger patients are selectively chosen to undergo metastasectomy because of better functional status and hence have improved overall survival purely due to selection bias. Patients with poor functional status or medical comorbidity would likely not be offered metastasectomy even for resectable disease. In fact, burden of disease may have prognostic significance irrespective of resectability. Due to the limitations of data availability in the SEER registry we were unable to fully and accurately quantify the burden of disease in patients i.e. number of metastatic sites and number of metastases. Furthermore, other pertinent variables such as disease free interval, lymph node involvement prior to the development of metastases, relationship with serum LDH and completeness of surgical resection could not be studied for similar reasons. This represents the most significant limitation of this study and one we readily acknowledge. We also recognize that a causal relationship between metastasectomy and survival cannot be inferred from an observational study like this one and the possibility of selection bias to explain these results cannot be ruled out without performing a carefully controlled randomized trial.

Nevertheless, there remain several compelling arguments to re-position metastasectomy as a curative rather than a palliative option for patients with Stage IV melanoma. Improvements in imaging with better resolution computed tomography (CT) scans as well as the advent of positron emission tomography (PET) means staging is more precise and allows for a better assessment of resectability. Improvements in peri-operative care have led to a reduction in morbidity and mortality even for major surgery such as liver resections. As mentioned previously, the majority of metastases are initially confined to a single organ and amenable to resection and recurrence after initial metastasectomy does not rule out the performance of a second resection with good outcomes.²⁷ The failure of surgical therapy also does not preclude the use of systemic therapy with either chemotherapy or biologic agents. Finally, a putative benefit of metastasectomy is the mechanical reduction of the immunosuppressive tumor burden and improving the patient's immune function to the extent that progression of residual occult metastases is controlled.²⁶ As a reflection of this, current National Comprehensive Cancer Center (NCCN) guidelines for Stage IV melanoma recommend resection as a viable option for patients with limited metastatic disease.²⁸

This rationale has prompted our group to launch a multicenter phase III randomized trial of surgical resection with or without BCG versus best medical therapy as the initial treatment for patients with Stage IV melanoma (NCT01013623). Inclusion criteria are patients >18 years of age with AJCC Stage IV M1a, M1b or M1c disease and with less than 3 involved visceral organ sites and <6 individual lesions. All disease must be considered resectable by a surgical oncologist. We feel that it is only with a randomized trial can we truly answer the question of whether the improvement in survival seen with metastasectomy is causal or due to selection.

To conclude, metastasectomy in patients with Stage IV melanoma is being used frequently across the United States outside of specialized centers and may improve long term survival. In view of the lack of effective medical therapy, the role of surgery in this patient population needs to be re-examined and the impact of metastasectomy on survival confirmed by randomized trials.

Synopsis

We use a cancer registry to show that metastasectomy in patients with Stage IV melanoma may improve survival. There is a need for a randomized trial to determine whether a true causal relationship or selection bias is responsible.

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Metastatectomy vs. No Surgery **M1a Metastatectomy vs. No Surgery**

M1bc Metastatectomy vs. No Surgery **Figure 1.**

A Survival of patients undergoing metastasectomy compared with no surgery.

B Survival of patients with M1a disease undergoing metastasectomy compared with no surgery.

C Survival of patients with M1bc disease undergoing metastasectomy compared with no surgery.

Table 1

Demographic, tumor and treatment characteristics (n= 4339)

Characteristic	Number of Patients (%)
Mean Age $\pm$ SEM (years)	62 $\pm$ 0.1
Median age (years)	63
Male Sex	2823 (67%)
Metastatic disease	
M1a	1994 (47%)
M1bc	2235 (53%)
Metastasectomy	
Yes	1422 (33.6%)
No	2779 (65.7%)
Unknown	28 (0.7%)
Metastasectomy for M1a	
Yes	648 (32.5%)
No	1333 (66.9%)
Unknown	13 (0.6%)
Metastasectomy for M1bc	
Yes	774 (34.6%)
No	1446 (64.7%)
Unknown	15 (0.7%)
Surgery of primary site	
Yes	1268 (30%)
No	2873 (67.9%)
Unknown	88 (2.1%)
Regional nodal management	
SLNB	131 (3.1%)
RLND	251 (5.9%)
None	3632 (85.9%)
Unknown	215 (5.1%)

SEM: Standard error of the mean

SLNB: Sentinel lymph node biopsy

RLND: Regional lymph node dissection

M1a: Non-visceral metastases

M1bc: Lung and visceral metastases

Table 2

Comparison of groups undergoing metastasectomy and no surgery

Variables	Metastasectomy (n = 1422)	No surgery (n = 2779)	p-value
Mean age $\pm$ SEM (years)	59.9 $\pm$ 0.41	63.3 $\pm$ 0.31	<0.001
Male sex	966 (68%)	1836 (66%)	0.23
M1a	648 (46%)	1333 (48%)	0.14
M1bc	774 (54%)	1446 (52%)	
Time period 1988–1995	290 (20%)	669 (24%)	0.02
1996–2000	340 (24%)	653 (24%)	
2001–2006	792 (56%)	1457 (52%)	

SEM: Standard error of the mean

M1a: Non-visceral metastases

M1bc: Lung and visceral metastases

Table 3

Predictors of metastasectomy

N = 4201[†]	Odds Ratio	p-value	95% CI
Age (continuous)	0.987	<0.001	0.983–0.991
Time period of diagnosis			
1988–1995 [*]	1.0		
1996–2000	1.225	0.038	1.011–1.483
2001–2006	1.298	0.002	1.102–1.529

[†] Number entering regression

^{*} Referent

CI: Confidence Interval

Table 4

Improvement in median and overall survival at 5 years by metastasectomy

	Median survival (months)	Overall survival at 5 years	p-value
Entire cohort (n = 4229)	7 mos	10%	
No Surgery	5 mos	7 %	<0.001
Metastasectomy	12 mos	16%	
M1a only (n =1994)	8 mos	13%	<0.001
No Surgery	6 mos	9%	
Metastasectomy	14 mos	20%	
M1bc only (n = 2235)	6 mos	8%	<0.001
No Surgery	4 mos	5%	
Metastasectomy	10 mos	13%	

Table 5

Predictors of survival

N = 4201 [†]	Hazard Ratio	p-value	95% CI
Sex			
Female *	1.0		
Male	1.090	0.016	1.016–1.170
Age (continuous)	1.008	<0.001	1.006–1.010
Time period of diagnosis			
1988–1995 *	1.0		
1996–2000	0.907	0.039	0.826–0.995
2001–2006	0.888	0.004	0.818–0.964
Metastatic disease			
M1a *	1.0		
M1bc	1.329	<0.001	1.243–1.422
Metastasectomy			
No *	1.0		
Yes	0.589	<0.001	0.548–0.633

[†] Number entering regression

* Referent

CI: Confidence Interval