

Contemporary Surgical Treatment of Advanced-Stage Melanoma

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Hypothesis: The clinical treatment of patients with stage IV melanoma according to criteria of the American Joint Committee on Cancer (AJCC) is controversial because the 5-year survival rate is approximately 5%. Specific clinicopathologic factors are predictive of survival following curative surgery.

Design: Cohort analysis of 1574 successive patients undergoing surgical resection of metastatic melanoma for a 29-year period. Patients received follow-up on a routine basis with serial examinations and radiographic studies. The median follow-up time was 19 months (range, 1-382 months).

Setting: Tertiary cancer center.

Patients: Surgical resection was performed in 1574 patients. The decision to perform surgery was individualized for each patient.

Intervention: The technique of surgical resection was based on the site of metastasis.

Main Outcome Measure: Computer-assisted database with statistical analyses using log-rank tests and Cox regression models.

Results: Of the 4426 patients with AJCC stage IV melanoma, 1574 (35%) underwent surgical resection;

970 (62%) were men, with a median age of 50 years. Of the primary melanomas, 46% arose on the trunk, and 56% were Clark level IV or V with a median thickness of 2.2 mm. We found 697 patients (44%) to have AJCC stage III melanoma (lymph node) prior to the development of stage IV metastases. The most common site for resection was the lung (42%), followed by the skin or lymph node (19%) and the alimentary tract (16%). Of our patients, 877 (56%) had melanoma at a single site. The 5-year survival rate was significantly ($P < .001$) better for patients with a solitary melanoma (mean $\pm$ SD, 29% $\pm$ 2%) than those with 4 or more metastases ($n = 147$; mean $\pm$ SD, 11% $\pm$ 3%). Skin and lymph node metastases had the most favorable survival rate (median, 35.1 months). Multivariate analyses identified an earlier primary tumor stage (I vs II) ($P < .001$), an absence of intervening stage III metastases ($P = .02$), solitary metastasis ($P < .001$), and a long (> 36 months) disease-free interval from AJCC stage I or II to stage IV ($P = .005$) as predictive of survival.

Conclusions: Our results demonstrate the benefit of surgical resection for advanced-stage melanoma. Patients with limited sites and numbers of metastases should be considered for curative resection regardless of the location of the disease.

Arch Surg. 2004;139:961-967

ONCE AN UNCOMMON malignancy, cutaneous melanoma is rapidly becoming a major health concern in the United States. It is estimated that 55 100 Americans will develop melanoma in 2004 and that 7910 will ultimately die.¹ Melanoma is the fifth most common cancer in men and the sixth most common in women, representing 4.5% of all cancer cases in the United States. Although most cases of cutaneous melanoma are cured by excision of the primary tumor, about 30% of patients will develop metastases. The treatment of advanced-stage melanoma is controversial.

During the last 30 years, chemotherapy, immunotherapy, and biologics have had no effect on overall survival. The results from many studies raise the question of whether surgery should be incorporated into the care of patients with advanced-stage disease.²⁻⁵

Surgery is not a new treatment modality for metastatic melanoma, but it has evolved during the last 150 years as the biology and natural history of the disease have been better understood. In 1857, Norris⁶ first described the concept of wide excision of the primary melanoma to prevent melanoma recurrence. In 1892, Snow⁷ advocated elective removal of the regional lymph nodes at the time of excising the primary

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Table 1. Clinicopathologic Features of 1574 Patients Undergoing Resection for Advanced-Stage Melanoma

Factor	No. (%)
Sex	
M	970 (62)
F	604 (38)
Age, y	
≤50	746 (47)
>50	828 (53)
Primary site	
Trunk	555 (35)
Extremity	400 (25)
Head and neck	263 (16)
Unknown	356 (23)
Clark level	
I/II	102 (6)
III	308 (20)
IV	453 (29)
V	78 (5)
Unknown	633 (40)
Breslow thickness, mm	
<1	228 (14)
1-2	301 (19)
>2-4	242 (15)
>4	118 (7)
Unknown	685 (44)
No. of metastases	
1	876 (56)
2-3	551 (35)
≥4	147 (9)
First site of metastasis (single site)	
Lung	364 (42)
Skin/subcutaneous/lymph node	162 (18)
Brain	119 (14)
Gastrointestinal	66 (7)
Adrenal	10 (1)
Bone	34 (4)
Other	121 (14)

melanoma and raised the debate about elective lymph node dissection, a controversy that persists more than 100 years later. In 1907, Handley⁸ demonstrated anatomic pathways of the lymphatic vessels from the primary tumor with local permeation of tumor cells along these pathways. On the basis of relatively few patients, Handley advocated wide excision for each case of melanoma. The first case of surgery for melanoma metastases to the lymph nodes was reported in 1851.⁹ The development of surgery for metastatic melanoma has evolved with increased operative experience at specialized centers. Advancements in surgical technique, anesthesia, and intensive care unit treatment have made the morbidity and mortality rates for extensive surgical resection acceptable. Whereas surgery for palliative purposes has relatively clear indications, resection for potentially curative intent is less well defined.^{10,11} The rationale for this study is to evaluate the outcome of patients with advanced-stage melanoma treated during the past 29 years at our institute in whom surgical resection was considered part of the curative intent.

METHODS

In the last 29 years, more than 4426 patients have come to our institute for treatment for stage IV melanoma according to cri-

teria of the American Joint Committee on Cancer (AJCC).¹² During that time, 1574 patients (35%) underwent surgical resection with curative intent. Our computer-assisted database was used to identify patient sex, age, primary melanoma site, and histologic features along with details of subsequent sites of metastasis and methods of treatment.

During the last 3 decades, the staging methods for patients considered for surgical resection have evolved from chest x-ray and radionuclide imaging (bone and gallium scans) to ultrafast computed tomographic (CT) scans, magnetic resonance imaging (MRI), and whole-body positron emission tomography (PET).¹³⁻¹⁶ The imaging modalities used for our patients were directed by the individual surgeon and varied according to the patient's disease state and symptoms. Patients underwent surgical resection with curative intent ($n=1574$) with a variety of operative techniques. Patients with skin or subcutaneous metastases limited to nonlocal and regional sites underwent resection of the lesions using wide surgical margins. Resection of distant lymph node metastases was performed according to the individual lymph node basin (axilla, inguinal/iliac, or cervical) being dissected.^{17,18} Patients with lung metastases typically underwent posterolateral thoracotomy, median sternotomy, or thoracoscopic-assisted resection; many had the hilar and mediastinal lymph nodes resected with removal of the lung parenchyma.¹⁹ Gastrointestinal, adrenal, and liver metastases were removed using open laparotomy techniques.²⁰⁻²² In each case, resection of all visible disease was the surgeon's goal. Follow-up ranged from 1 to 382 months, with a median of 19 months. Survival curves were constructed using Kaplan-Meier estimates.²³ Differences in survival distributions were tested with the log-rank method.²⁴ Differences in frequency distributions and proportions were evaluated using χ^2 analysis or the Fisher exact test. $P<.05$ was considered significant. Survival time was determined from the diagnosis of stage IV melanoma until death or the last follow-up visit.

RESULTS

Of the 4426 patients with AJCC stage IV melanoma, 1574 (35%) underwent curative resection. The decision to perform surgical resection in these cases was based on the individual surgeons. Most procedures were performed by only a few physicians, and the faculty has remained relatively stable in our institute during the last 29 years. Most (62%) of the patients were men, with a median age of 50 years (**Table 1**). Most patients undergoing resection of metastatic melanoma had primary tumors on the trunk, and most of these were Clark level IV or V with a median thickness of 2.2 mm. We found that 697 patients (44%) had stage III (regional lymph node) metastases prior to developing stage IV disease. The median time to develop stage IV melanoma was 13.5 months for patients with regional lymph node metastases (stage III) and 44 months for patients progressing from stage I or II to stage IV. Most (56%) of the patients had a single site or organ with metastatic disease; 9% had 4 or more metastases. The most common first site of metastatic disease was the lung (42%), followed by the skin and subcutaneous sites (18%) and the brain (14%). Less common first sites included the gastrointestinal tract, adrenal glands, bone, and other sites (eg, spleen, breast, or ovaries). The 5-year survival rate of the 1574 patients who underwent surgical resection (mean $\pm$ SD, 23% $\pm$ 2%) was significantly

Table 2. Comparison of Risk Factors for 1574 Surgically Treated and 2852 Nonsurgically Treated Patients With Stage IV Melanoma

Factor	Surgically Treated, No. (%)	Nonsurgically Treated, No. (%)	P Value
Sex			
M	970 (22)	1862 (42)	.02
F	604 (14)	990 (22)	
Age, y			
≤50	746 (17)	1226 (28)	.005
>50	828 (18)	1626 (37)	
Primary site*			
Trunk	555 (16)	1063 (30)	.48
Extremity	400 (11)	767 (22)	
Head and neck	263 (8)	439 (13)	
Primary stage*			
I	102 (2)	167 (3)	.02
II	839 (19)	1643 (37)	
Unknown	633 (14)	1042 (24)	
Prior stage III lymph node metastases*			
Yes	697 (17)	1529 (38)	.001
No	637 (17)	1091 (27)	
Disease-free interval (stage I/II to IV), mo*			
≤36	833 (21)	1862 (47)	.001
>36	497 (13)	744 (19)	
No. of metastases			
1	876 (20)	1563 (35)	.31
2-3	551 (12)	337 (8)	
≥4	146 (3)	952 (22)	
First site of metastasis†			
Low risk	649 (15)	931 (21)	.001
High risk	227 (5)	632 (14)	
Multiple	698 (16)	1289 (29)	

*Information is not complete in all groups.

†Low-risk sites include skin/subcutaneous/distant lymph nodes, lung, and gastrointestinal tract. High-risk sites include adrenal, brain, and liver. Patients who had more than 1 organ with metastases were categorized as having multiple sites.

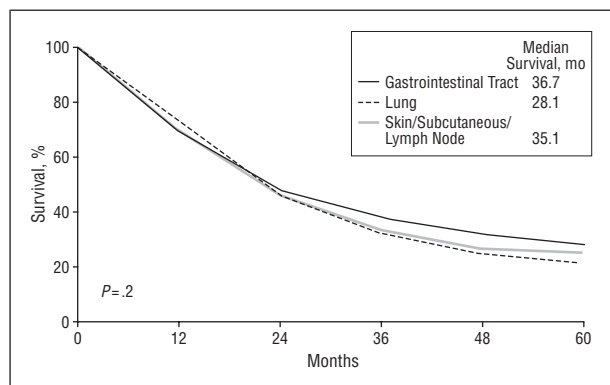


Figure 1. Five-year survival estimates for patients with gastrointestinal tract, lung, and skin/subcutaneous/lymph node metastases. Although median survival is slightly higher for patients with skin or subcutaneous sites (alone) than for lymph node, gastrointestinal tract, or lung sites, the 5-year estimates demonstrate no significant differences ($P=.29$) in survival rate.

($P<.001$) better than for the 2852 patients treated with nonsurgical approaches (mean $\pm$ SD, $6\% \pm 5\%$) (**Table 2**).

Most patients had resection of metastases to the distant skin, subcutaneous tissue, lymph nodes, gastrointes-

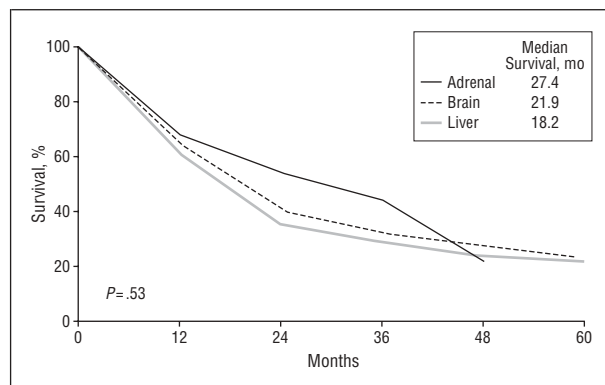


Figure 2. Five-year survival estimates for patients with adrenal, brain, and liver metastases. Five-year survival estimates demonstrate no significant difference ($P=.53$) in survival rates for these 3 patient groups.

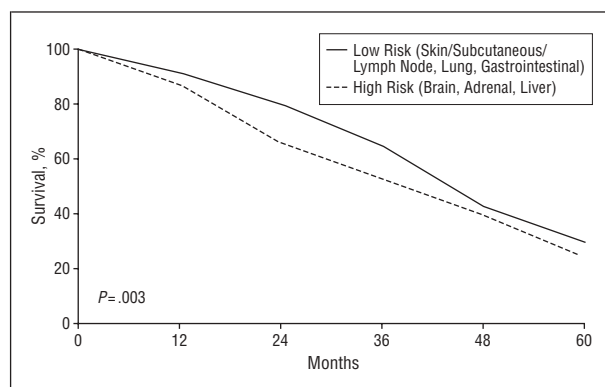


Figure 3. Five-year survival estimates for the combined favorable (skin/subcutaneous/lymph node, lung, and gastrointestinal) and unfavorable (brain, adrenal, and liver) sites. Mean $\pm$ SD 5-year survival rates were $30\% \pm 4\%$ for favorable sites and $24\% \pm 6\%$ for unfavorable sites. The survival rate was significantly ($P=.004$) better for the favorable sites of metastases.

tinal tract, and lungs. Patients with skin and subcutaneous metastases had the most favorable outcome, with a median survival rate of 48 months. We combined the survival data of patients with skin and subcutaneous metastases with those generated for patients with lymph node metastases because it is often difficult to clinically differentiate the 2 scenarios. When combined, the mean $\pm$ SD 5-year survival rate for these 260 patients was $25\% \pm 6\%$ (**Figure 1**). The mean $\pm$ SD 5-year survival rates of patients with gastrointestinal and lung metastases were similar: $28\% \pm 8\%$ and $21\% \pm 4\%$, respectively.

In general, patients with metastases to the adrenal gland, brain, and liver are not considered candidates for surgery because many of them have multiple sites of metastasis. However, long-term survival is achievable in these patients (**Figure 2**). The median survival rate was 27.4 months for patients with adrenal metastases, 21.9 months for those with brain metastases, and 18.2 months for patients with liver metastases. The mean $\pm$ SD 5-year survival rates for these 3 sites were 0% ($22\% \pm 18\%$ for 4 years), $23\% \pm 5\%$, and $22\% \pm 9\%$, respectively.

On the basis of statistical analysis, we were able to categorize the patients according to favorable and unfavorable outcome sites (**Figure 3**). Patients with favorable sites had significantly ($P=.004$) better survival rates than those with unfavorable sites. Patients who under-

Table 3. Univariate and Multivariate Analyses of Factors Predicting Overall Survival of 1574 Patients Undergoing Surgical Resection of Metastatic Melanoma*

Factor	Univariate	Multivariate
Age, ≤50 y	.09	.06
Sex	.01	.51
Primary site	.007	NA
Primary stage (I vs II)	.004	.002
Prior lymph node metastases	<.001	.001
1 vs > 1 metastasis	<.001	.66
Disease-free interval (stage I/II to IV)	.005	.005
First site of metastasis†	<.001	.03
Low risk		
High risk		

Abbreviation: NA, not applicable.

*Data are presented as *P* values.

†Low-risk sites include skin/subcutaneous/distant lymph nodes and lung. High-risk sites include adrenal, brain, and liver. Patients with multiple sites (organs) with metastases were included in the category of number of metastases.

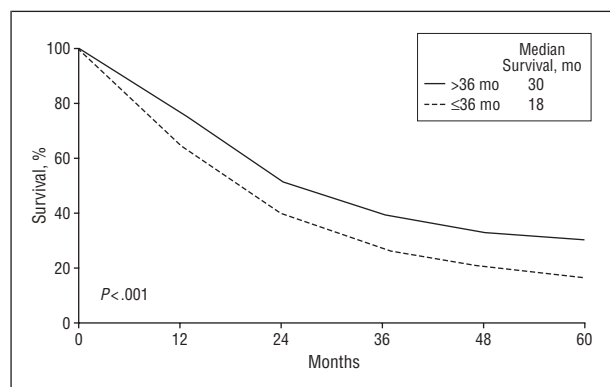


Figure 4. Overall survival of patients based on disease-free interval. Patients with a disease-free interval greater than 36 months demonstrated a significantly ($P<.001$) better survival rate.

went surgery primarily were men older than 50 years, had early-stage primary melanoma, and had short disease-free intervals from primary to metastatic disease. Most patients had a solitary metastasis and disease in a favorable site.

We performed univariate and multivariate analyses to determine the interactions of risk factors for metastatic disease and overall survival. Patients with early-stage primary melanoma (AJCC stage I), no intervening regional lymph node metastases, a long disease-free interval, and a low-risk site of metastasis achieved statistical significance ($P<.05$) in the multivariate analysis. The first site of metastasis interacted closely with the number of metastases (ie, patients with low-risk sites tended to have fewer metastases than those with high-risk sites). When the first site of metastasis is removed from the stepwise analysis, the number of metastases becomes statistically significant ($P=.001$) in the analysis (**Table 3**).

COMMENT

When melanoma has spread to a distant site, the median survival rate is only 7 to 8 months, and the 5-year

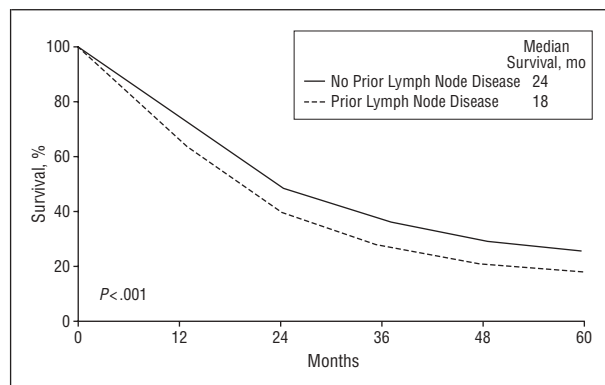


Figure 5. Overall survival of patients based on prior lymph node disease. The 5-year survival rate was significantly ($P<.001$) better for patients with no prior lymph node disease.

survival rate is about 5%.^{10,11} This grim prognosis, which has remained relatively unchanged for 30 years, reflects the continued inadequacy of systemic therapy for metastatic melanoma. The response to conventional chemotherapy is rarely complete, and 5-year survival rates are generally less than 5%.^{2,3} The results of biologic therapy with interleukin 2 are also disappointing; survival prolonged by either a complete or partial response is uncommon (20%).^{4,5} The toxicity associated with this therapy can be considerable. Complete responses to combination biochemotherapy are higher (20%-30%),²⁵ but the long-term durability is questionable.

In general, prognosis depends on the initial site of metastasis.^{26,27} Median and 5-year survival rates decrease progressively for surgically resected sites of the skin and subcutaneous tissue, distant lymph nodes, gastrointestinal tract, lung, bone, liver, and brain (Figures 1 and 2).²⁸⁻³² Median survival rates range from 48 to 18 months. The number of organ and tissue sites containing metastasis is also an important prognostic factor; the median survival rate is 29 months for patients with metastasis to 1 site, 16 months for those with metastasis to 2 or 3 sites, and only 14 months for those with metastasis to 4 or more sites. The disease-free interval before distant metastasis and the stage of the disease preceding distant metastasis also have prognostic significance.²⁹ The 5-year survival rate is 17% if the disease-free interval is less than 36 months and 30% if it is greater than 36 months (**Figure 4**). In addition, the median survival rate for patients who progress from regional to distant metastasis is 18 months, whereas it is 24 months for patients without prior lymph node metastases (**Figure 5**).

Although surgical excision is the treatment of choice for melanoma confined to the primary site and regional nodes, it is infrequently the initial intervention in patients with 1 or more distant metastases. This reflects the prevailing assumption that distant metastases are beyond the reach of local therapy. It is true that most patients who die of metastatic melanoma have multiple tumor-involved organ sites, but 86% of patients initially have only 1 metastatic organ site.^{29,30} This site is most commonly the lung, followed by the skin, lymph nodes, brain, liver, and gastrointestinal tract.

Although surgical resection is technically possible in most patients who have only 1 or 2 metastatic organ

sites, the surgeon's role is usually limited to occasional complete resection of a solitary visceral metastasis or for palliative resection for symptomatic metastases causing bowel obstruction or a bleeding brain lesion, resulting in neurologic symptoms. Many of these patients become the sole responsibility of the medical oncologist and are treated primarily with chemotherapy or biochemotherapy. However, the last few decades have brought numerous reports of long-term survival following resection of multiple distant metastases.^{10,17,31,32} In the absence of more active biologic and chemotherapeutic agents for the systemic treatment of metastatic melanoma, surgery should be reconsidered in the treatment paradigm.

In essence, the cancer cell either produces or induces the surrounding tissue to manufacture specific and nonspecific immunosuppressive factors that turn off the host's antitumor immune response.³³⁻³⁷ Complete surgical resection removes the tumor microenvironment. By mechanical reduction of the immunosuppressive factors of the tumor, surgery can restore immune function to a level that controls the progression of residual occult metastases and ensures a durable clinical response.^{38,39} Recent studies have shown a strong prognostic correlation with the development of an endogenous immune response to a melanoma-associated tumor antigen after the resection of melanoma metastatic to distant sites.⁴⁰ These findings suggest that the patient's immune response is an important determinant of long-term survival.^{41,42-44} The presence of a favorable immune response may explain why the 5-year survival rate following resection of multiple metastases is 15% to 20% even though a vast majority of these patients would be expected to have residual occult metastases and die of their disease.⁴⁵

Surgery for advanced melanoma is most effective when the disease is limited to a few sites and a small number of metastases. Surgical excision of isolated metastatic melanoma lesions can provide effective and quick palliation and, in some instances, survival rates exceeding 5 or 10 years.⁴⁶⁻⁴⁸ The favorable outcome resulting from surgical resection of distant metastases in selected patients has been shown at multiple major centers.⁴³⁻⁴⁶

Accepted for publication May 21, 2004.

This study was supported by grants CA 12582 and CA 29605 from the National Institutes of Health, Bethesda, Md; the California Cancer Research Fund, Sacramento, Calif; and the Saban Family Foundation and George Hoag Foundation, Los Angeles, Calif.

This paper was presented at the 75th Annual Meeting of the Pacific Coast Surgical Association; February 17, 2004; Maui, Hawaii; and is published after peer review and revision. The discussions that follow this article are based on the originally submitted manuscript and not the revised manuscript.

Dr Wanek was the validating statistician for this study.

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DISCUSSION

Jan H. Wong, MD, Honolulu, Hawaii: The management of patients with nonregional metastatic melanoma remains highly problematic. It is apparent that novel approaches to advanced melanoma are needed. The John Wayne Cancer Institute group has hypothesized that measurable tumor burden is immunosuppressive and that cytoreductive surgery of metastatic disease may augment host antitumor responses. They have been at the forefront of advocating cytoreductive surgery of metastatic disease in the multidisciplinary management of metastatic melanoma.

Dr Essner and his colleagues at the John Wayne Cancer Institute report on a remarkable experience with melanoma over a 3-decade period. During that 31-year period, over 11 000 patients have been seen at the institute, and 4426 patients either developed and/or were referred with stage IV disease. Of these 4426 patients, a notable number, 1574 (35%) underwent surgical resection of their metastatic disease. I want to reiterate that of particular interest is that 14% of these patients had primary tumors less than 1 mm in thickness, a lesion widely considered to be low risk and a finding consistent with a recent report from Duke University indicating that some thin melanomas indeed have a poor prognosis.

This report again supports, as is evident in almost all solid-tumor models in which retrospective experiences have examined the value of metastasectomy, that there is an approximately

20% long-term survival and evidence of a decrease in the slope of the survival curve at approximately 24 to 36 months, suggesting the possibility that some of these individuals may indeed be cured by this management approach to metastatic disease.

However, the unfortunate reality is, despite these most impressive results, only a small minority of all patients who ultimately develop stage IV disease have any durable survival with any current modalities of therapy including surgical resection. Having noted that fact, however, it behooves us to be cognizant that windows of opportunity may exist for some patients with metastatic melanoma and that substantive benefit is achieved by rendering individuals disease-free by surgical resection. Their report helps us better select and understand those individuals who most likely benefit from this approach.

I have a number of questions. The observation that individuals with fewer metastatic lesions with prolonged disease-free survival, with low risk (ie, skin or lymph node metastasis), have improved survival at least for me is somewhat intuitive. However, the observation that early primary tumors and the presence of intervening regional lymph node metastasis improves survival is far less intuitive to me. In fact, the most powerful predictor of survival in your multivariate analysis is the absence of stage III disease. Would you like to speculate on biologic rationale for these observations? Although you have stratified patients into high-risk and low-risk resection sites, were these metastatic sites all in single-organ sites? Have you performed multiorgan metastatic resections such as lung and adrenal, or brain and lung, or lung and skin, and if so, are these outcomes different than for those with 2 or 3 or 4 or more single-organ sites? In other words, is the outcome for a single lesion in the lung and liver perhaps the same as the outcome for 2 lesions in the lung?

Clearly, from your data, fewer metastases are better than multiple metastases. Is there a reasonable cost-effective algorithm that the authors would recommend that would help us identify those individuals most likely to benefit from a surgical intervention and exclude the majority of individuals with marginal benefit from this approach? Should all apparent disease-free individuals be subjected to routine imaging studies in an effort to identify isolated or limited disease? Has PET scan substantively influenced your approach to these individuals? Given your report, should only node-negative individuals with disease-free survival exceeding 36 months be routinely screened for recurrent disease?

If we presume that the surgical quality control has been constant during the 3-decade report, and this is not unreasonable, since the John Wayne Cancer Institute has been under the leadership of Dr Donald Morton throughout this period, why are the outcomes significantly improved during the last decade when compared with the initial decades of experience? Does this represent a disease that is evolving biologically, a referral bias, an evolving selection bias, or are there other explanations for this observation?

Were there any surgical morbidities and mortalities, and if so, would you elaborate on that for us? Finally, this report undoubtedly represents the largest experience with surgical resection and stage IV melanoma. Unfortunately it has to be classified as level III evidence and would be felt by many as insufficient to define standard treatments. The John Wayne Cancer Institute and Dr Morton are now performing a prospective randomized trial to evaluate the value of surgical resection of stage IV disease, and we look forward to the completion and results of that trial. I want to congratulate you for this outstanding presentation and for the John Wayne Cancer Institute's leadership in this vexing problem.

Stanley P. L. Leong, MD, San Francisco, Calif: I have 1 question, and that is how do you diagnose stage IV disease in this group of patients being followed with stage I/II or stage III disease? In other words, what routine tests do you do, or do you initiate the workup based on symptoms?

James E. Goodnight, Jr, MD, PhD, Sacramento, Calif: Dr Essner and the group from John Wayne do indeed have an extraordinary experience. Dr Wong has very nicely covered the questions. Within this context of patients that actually do enjoy prolonged survival from resection of metastatic melanoma, there is an even more select group that go on for years and years and years, resection after resection after resection, and show extraordinary favorable biology. Have you found any common denominator or marker for these people that enjoy years and years and years of survival in this unusual biology?

Dr Essner: Dr Wong and other discussants, thank you very much for your comments. They certainly do bring about a lot of questions. Sometimes our presentations raise more questions than they actually answer. The reality is that our study is a retrospective analysis done over a 29-year time period, and even though the leadership at our institute has remained the same, we as surgeons change our styles over the years of experience. Certainly it is difficult to quantitate exactly what has happened through the 3 decades of our study. There is a possibility that the disease biology has changed with earlier removal of lymph node metastases by sentinel lymphadenectomy. We are identifying early manifestations of distant metastases (ie, a lymph node metastasis may be only a favorable form of AJCC stage IV disease, and the short disease-free interval for patients going from stage III to IV is just a reflection of the biology of concurrent metastases). Nevertheless, it is unclear at this point really what a sentinel node metastasis reflects. So the absence of stage III disease in our patients is just the reflection of a favorable tumor biology, and those patients that progress from stage I or II to IV having longer disease-free intervals are similarly another reflection of favorable tumor biology.

In regard to Dr Wong's question about the significance of multiple sites vs total number of metastases, it's apparent from our data that no matter what the sites are, the survival is essentially the same. Over and over again, we get a 20% 5-year survival from almost every site of solitary metastasis that gets resected. So there is value in removing gross tumor when it is limited. Patients with disease in multiple organ sites have a worse prognosis than those with a similar number of tumors in 1 organ. The biologic significance of this finding is not known.

We do not have set algorithms for preoperatively evaluating these patients. We do use whole-body PET scanning. We have run into the same problem that Dr Leong mentioned in that PET is sensitive but not very specific. In patients that we consider for surgery, we usually do conventional CT scans and then follow with PET scan to ensure that we have identified all sites. If we do find an abnormality on PET that is not confirmed on CT scan, we will usually wait several months. The additional scans probably help us to better select patients for surgery by waiting longer to ensure that the tumor biology is favorable. Many of our patients are in adjuvant therapy trials, so we often have no control over the imaging scans that they get preoperatively. Many of our patients will show up with CTs, MRIs, bone scans, PET scans, etc, when often times the reality is that the additional scans do not add much to treatment.

We did not measure surgical quality control in this study. We did have a few perioperative deaths, and certainly any time that you do extensive operative procedures you must accept the morbidities. The morbidity has diminished over time with improved anesthesia technique, better ICU (intensive care unit) care, and certainly improvements in our surgical procedures and surgeon experience.

Dr Leong asked about how the metastases are identified. As previously mentioned, many of these patients show up with a multitude of scans. Our patients with early-stage disease are followed with a chest x-ray alone. The CT scans do not appear to add significantly to our ability to identify treatable metastases.

Dr Goodnight did mention the characteristics of good survivors. How do we pick them out? What kinds of things have we looked at immunologically? Yes, we have found some parameters in our laboratory that suggest favorable immunologic profiles do exist, which may be useful for stratifying patients for surgery or not. We also have data to suggest that removing the tumor allows the immunological profile to improve, so these are a number of different parameters that may be useful to prospectively identify patients for surgery. Overall our data suggest that long disease-free intervals, lack of stage III metastasis, and lower primary stage are factors that should be used to select patients for resection of metastatic melanoma. Patients with limited numbers and sites of metastases should be considered for resection.