Annals of Surgical Oncology, **8**(8):658–662
Published by Lippincott Williams & Wilkins

Does Complete Resection of Melanoma Metastatic to Solid Intra-Abdominal Organs Improve Survival?

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Background: Patients with distant melanoma metastases have median survivals of 4 to 8 months. Previous studies have demonstrated improved survival after complete resection of pulmonary and hollow viscus gastrointestinal metastases. We hypothesized that patients with metastatic disease to intra-abdominal solid organs might also benefit from complete surgical resection.

Methods: A prospectively acquired database identified patients treated for melanoma metastatic to the liver, pancreas, spleen, adrenal glands, or a combination of these from 1971 to 2000. The primary intervention was complete or incomplete surgical resection of intra-abdominal solid-organ metastases, and the main outcome measure was postoperative overall survival (OS). Disease-free survival (DFS) was a secondary outcome measure.

Results: Sixty patients underwent adrenalectomy, hepatectomy, splenectomy, or pancreatectomy. Median OS was significantly improved after complete versus incomplete resections, but median OS after complete resection was not significantly different for single-site versus synchronous multisite metastases. The 5-year survival in the group after complete resection was 24%, whereas in the incomplete resection group, there were no 5-year survivors. Median DFS after complete resection was 15 months. Of note, the 2-year DFS after complete resection was 53% for synchronous multi-site metastases versus 26% for single-site metastases.

Conclusions: In highly selected patients with melanoma metastatic to intra-abdominal solid organs, aggressive attempts at complete surgical resection may improve OS. It is important that the number of metastatic sites does not seem to affect the OS after complete resection.

Key Words: Metastatic melanoma—Hepatic—Spleen—Adrenal gland—Surgical resection.

Development of distant metastases in melanoma patients portends a poor prognosis. The median survival of patients with American Joint Committee on Cancer (AJCC) stage IV melanoma is 4 to 8 months.[1–3] The majority of patients with distant melanoma metastases are treated with chemotherapy, radiotherapy, or both. Unfortunately, response rates to these modalities are low and seem to have little effect on survival.

A highly selected group of patients with distant melanoma metastases are candidates for either potentially curative (complete) or palliative (incomplete) resections of their disease. Multiple retrospective studies from our group and others have demonstrated a survival advantage for patients after complete resection of melanoma metastatic to the lung, hollow viscus gastrointestinal tract, soft tissues, or a combination of these.[1,4–15] However, the appropriateness of surgical management of intra-abdominal solid organ melanoma metastases remains controversial. Perhaps even more controversial is the resection of multiple organ-site disease.

Because of the dearth of effective systemic treatment for distant melanoma metastases, our group has taken an aggressive surgical approach in a highly selected subgroup of these patients with operable disease. We hypothesized that complete resection of intra-abdominal solid organ melanoma metastases improves survival. In this report, we describe the experience at the John Wayne

Received March 16, 2001; accepted June 4, 2001.

From the John Wayne Cancer Institute, Santa Monica, California.

Presented at the 54th Annual Meeting of the Society of Surgical Oncology, Washington, DC, March 15–18, 2001.

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Cancer Institute (JWCI) in the operative treatment of patients with melanoma metastatic to the intra-abdominal solid organs (liver, spleen, pancreas, and adrenals). Our experience with adrenal[16] and hepatic[17] metastases has been previously reported.

METHODS

The prospectively acquired database of >10,000 melanoma patients treated by the staff at the JWCI between 1971 and 2000 identified those patients with AJCC stage IV melanoma involving the liver, adrenal glands, spleen, or pancreas. A total of 838 patients were found with stage IV disease involving the organs of interest. Of these patients, only 60 underwent surgical exploration and attempts at resection of their disease. Patient records were abstracted for patient and tumor characteristics, extent of surgical treatment, surgical morbidity and mortality, and disease-free survival (DFS) and overall survival (OS). In most instances, patients were completely staged before operation by means of computed tomography scans of the chest, abdomen, and pelvis, computed tomography or magnetic resonance image of the brain, and bone scan. More recently, selected patients were staged by using fluorodeoxyglucose positron emission scanning.

Because this retrospective study included patients treated by multiple surgeons, there were no set strict patient selection criteria. Patients were selected for operative treatment by the managing surgeon's use of his judgment. In general, patients were approached with intent to perform R0 resections whenever possible, as deemed feasible by preoperative examinations. Multiple organ-site disease was usually resected at one operative setting, although a small number of patients required two separate operations to achieve a complete resection of multiple-site disease. Those patients who underwent palliative incomplete resections included those whose disease was found to be technically unresectable at operation as well as those patients who were approached with the intent of surgically palliating symptoms.

Factors examined for survival differences were age, sex, thickness and location of the primary lesion, disease-free interval (DFI; calculated from the time of operation for the primary lesion to the development of distant metastases) before diagnosis of stage IV disease, single- versus multiple-site metastases, and operative treatment received (complete vs. incomplete resection). Survival was calculated from the time of diagnosis of stage IV disease to death or last follow-up. Survival curves were generated by using the Kaplan-Meier method. Cox proportional hazards modeling was used for univariate and multivariate analysis. Proportions of prognostic factors and demographic variables between groups were compared by use of the χ^2 statistic or the Fisher's exact test. Statistical significance was set at a P value of .05.

RESULTS

Patient Demographics

Of the 838 patients diagnosed with stage IV disease involving the liver, adrenals, spleen, or pancreas, 778 (93%) were treated nonoperatively. The nonoperative group was heavily represented by patients with hepatic disease (n = 639), with adrenal (n = 66), splenic (n = 53), and pancreatic (n = 20) involvement less common. The 60 (7%) patients constituting the operative group included those who underwent adrenalectomy (n = 26), hepatectomy (n = 15), splenectomy (n = 11), or pancreatectomy (n = 8). The operative and nonoperative groups were similar in terms of age, sex, tumor characteristics, and DFI before stage IV disease (Table 1).

Surgical Treatment

Complete (curative intent) metastasectomy was defined as resection of all known disease. Of the 60 patients, 44 (73%) underwent complete resections. Of these patients, 30 patients had disease in multiple organ sites, and 14 had single organ involvement. Incomplete (palliative) resections were undertaken in 16 patients.

There was no operative mortality in this series. In the hepatic group, however, there were two deaths outside of the perioperative period. One of these was related to the operative procedure (multiple organ failure 2 months

TABLE 1. *Characteristics of patient population*

Variable	Operative group (n = 60)	Nonoperative group (n = 778)	*P* value
Age at diagnosis of stage IV disease, mean (range)	51 (27–78)	50 (1–100)	.82
Sex (%)			
Female	25	33	.24
Male	75	67	
Site of primary melanoma (%)			
Extremity	23	19	.55
Nonextremity	60	67	
Unknown	17	14	
Breslow thickness (mm)			
Median	1.5	1.9	.80
Range	0.3–11.9	0.1–15.0	
Disease-free interval before stage IV (mo)			
Median	23	17	.82
Mean	33	32	
Range	0–223	0–349	

TABLE 2. *Overall and 5-year survival of the patient groups*

	Operative			Nonoperative			Curative			Palliative		
Group	n	Median	5-y	n	Median	5-y	n	Median	5-y	n	Median	5-y
All patients	60	20.9	17%	778	9.6	7%	44	27.6	24%	16	8.4	0
Metastatic site												
Adrenal	26	20.0	9%	66	12.4	2%	18	28.2	13%	8	7.7	0
Liver	15	14.1	20%	639	9.0	6%	9	27.7	33%	6	10.4	0
Pancreas	8	23.8	37.5%	20	15.2	23%	6	24.4	50%	2	8.2	0
Spleen	11	27.6	0	53	14.3	15%	11	27.6	NA	0	NA	NA
Surgery type												
Single	30	27.6	23%	NA	NA	NA	30	27.6	NA	NA	NA	NA
Multiple	14	27.5	25%	NA	NA	NA	14	27.5	NA	NA	NA	NA
Palliative	16	8.4	0	NA	NA	NA	NA	NA	NA	NA	NA	NA
Surgery type												
Curative	44	27.6	24%	NA	NA	NA	NA	NA	NA	NA	NA	NA
Palliative	16	8.4	0	NA	NA	NA	NA	NA	NA	NA	NA	NA

NA, not available.

after a right hepatic lobectomy), but the other (cerebral vascular accident 3 months after a right hepatic lobectomy) probably was not. Complications occurred in four of the pancreatectomy patients (pancreatic fistula, small bowel obstruction secondary to an internal hernia, bile leak, and wound infection). Three complications occurred in the adrenalectomy group, including two bowel obstructions secondary to metastases and a pleural effusion requiring tube thoracostomy placement. There were no major complications in the splenectomy group.

Survival Analysis

For the 60 patients in operative group, the median survival was 20.9 months (range, 1–112 months) and the 5-year survival 17%. In the 778-patient nonoperative group, the median survival was 9.6 months (range, 0.2–214 months), whereas the 5-year survival was 7% (Table 2 and Fig. 1). Within the operative group, those who underwent complete (curative) resections had a median survival of 27.6 months (range, 1–112 months) and a 5-year survival of 24%. This survival was significantly better ($P = .0001$) than in the group who had incomplete (palliative) surgical resections in which the median survival was only 8.4 months (Fig. 2). It is interesting that those who had incomplete resections fared no better than the nonoperative group (Fig. 2). There were no 5-year survivors in the incomplete resection group. Median DFS after complete resection was 15 months (range, 1–47 months). Of note, the 2-year DFS after complete resection was 53% for synchronous multisite metastases versus 26% for single-site metastases.

When those patients who underwent complete resection were examined in terms of resection of single organ-site versus multiple organ-site metastases, notably there were no differences in terms of OS ($P = .742$). For the 30 patients who underwent complete resections involving only one site of disease, the median survival was 27.6 months, and the 5-year survival 23%. For the 14 patients undergoing complete resection of multiple organ site metastases, the median survival was 27.5 months, and the 5-year survival was 25%.

By univariate analysis, host features of age, sex, primary site, Breslow thickness, and DFI before stage IV diagnosis were not significant factors for survival differences among the complete and incomplete resection groups (Table 3). Only those patients undergoing complete surgical resection enjoyed improved survival by both univariate and multivariate analysis.

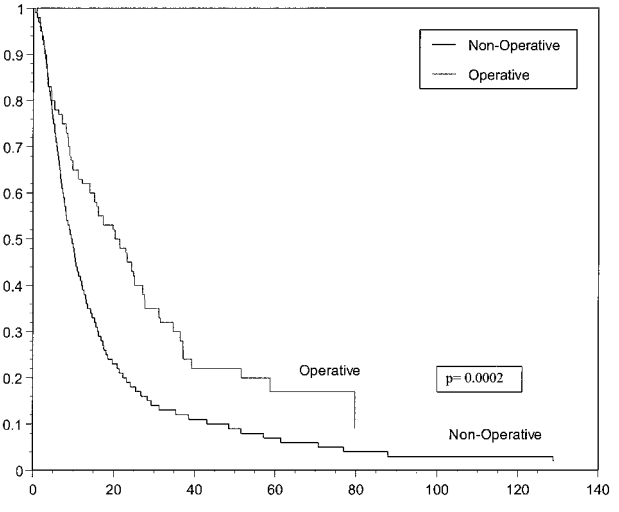

FIG. 1. Overall survival rates of patients with melanoma metastatic to intra-abdominal solid organs treated either by operative or nonoperative methods. The median survival of the operative group (20.9 months) was significantly better than that of the nonoperative group (9.6 months; $P = .0001$).

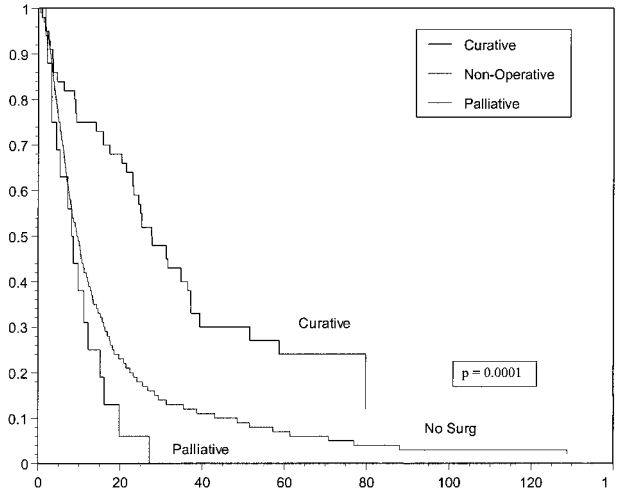

FIG. 2. Overall survival rates of patients with melanoma metastatic to intra-abdominal solid organs undergoing complete (curative intent) versus incomplete (palliative) surgical resections versus nonoperative management.

DISCUSSION

Distant metastases imply systemic disease. Because surgery is a local therapy, metastasectomy for systemic disease is controversial. Because response rates of metastatic melanoma to traditional single-agent and multiagent chemotherapy regimens and radiotherapy are low, many authorities have advocated complete (R0) resection to provide a surgical macroscopic complete response. In a highly selected group of patients with stage IV melanoma, extended survival can be afforded by this aggressive surgical approach.

Outcome analysis of patients treated at the JWCI confirms the overall poor prognosis of stage IV melanoma. The median survival is best in patients with skin or subcutaneous involvement, and survival progressively decreases as more vitally important visceral organs are involved.[8] Our group has previously demonstrated the survival advantage gained by complete resection of melanoma metastatic to the lung,[9,10,18] the hollow viscous gastrointestinal tract,[8] and the adrenal glands;[16] we have also demonstrated improved survival after resection of recurrent stage IV melanoma.[6] We also have recently reported the combined experience of the JWCI and the Sydney Melanoma Unit on hepatic resection for stage IV melanoma.[17] Consistent in each of our studies is the survival advantage of complete resection of melanoma metastases. However, it is also consistent that as a whole, those undergoing incomplete resections survive no longer than those managed nonoperatively. Therefore, we are proponents of aggressive complete surgical resection to render the patient free of macroscopic disease whenever possible. Incomplete resections should only be undertaken for true palliation of symptoms, such as obstruction, hemorrhage, or pain, with the understanding that there is no survival benefit to leaving disease behind. Other institutions have a similar experience in the operative management of patients with stage IV melanoma.[1,4,5,14,15] Median and 5-year survivals, respectively, of 19 to 25 months and 21% to 22% for lung, 15 to 49 months and 38% to 41% for gastrointestinal, and 13 to 24 months and 15% to 33% for combined organ site studies have been reported after complete resection of stage IV melanoma. The survival rates of this study are in line with those previously reported.

TABLE 3. *Univariate and multivariate analysis of patients with intra-abdominal melanoma metastases*

Factor	*P* value	
	Univariate analysis	Multivariate analysis
Surgical treatment		
Complete versus no resection	.0001	.0001
Complete versus incomplete resection	.0001	.0005
Incomplete versus no resection	.105	–
Sex	.39	–
Breslow thickness	.24	–
Age	.20	–
Disease-free interval before stage IV	.94	–

Our study is the first to demonstrate that improved survival may also be afforded by the complete resection of multiple organ-site metastases. Many of the previous studies,[1,4,5] including our own involving a different organ site,[10] have demonstrated that patients with single organ-site metastases have improved survival when compared with those with multiple organ-site metastases after complete resection. Although it is difficult to give firm recommendations on the basis of one retrospective study of a highly selected patient group, we believe that it is worthwhile to approach every patient as an individual and attempt to completely resect all disease, even if multiple organ sites are involved.

Early studies of the treatment of advanced stage melanoma with biochemotherapy have been encouraging, with reported response rates of 50% or higher.[19] However, the durability of the responses has been somewhat disappointing. In a selected subset of stage IV patients believed not to be surgical candidates for complete resection, we have used preoperative biochemotherapy in a neoadjuvant fashion; a number of these patients have undergone complete surgical resection of their remaining disease after responses to biochemotherapy. The appropriateness of the postoperative adjuvant use of biochemotherapy is unknown.

Although complete metastasectomy provides a clinically complete remission, these patients have a high likelihood of subclinical systemic metastases, and thus an effective adjuvant systemic treatment is desirable. We have reported the promising results of our phase II trials investigating the therapeutic efficacy of CancerVax (CancerVax Corporation, Carlsbad, CA), a polyvalent melanoma cell vaccine in patients with distant melanoma metastases.[20,21] An ongoing, multicenter phase III trial is investigating the possible therapeutic benefits of postoperative active immunization with CancerVax in those patients who have complete surgical resection of distant melanoma metastases. We have also proposed cytoreductive surgery as a form of immunotherapy in itself.[22] By greatly reducing the patient's tumor burden and the relative immunosuppression imposed on the host by the tumor, we hypothesize that the host's immune antitumor response is able to more effectively deal with the residual micrometastases.

Surgical resection of melanoma metastatic to intra-abdominal organs can be performed with acceptable morbidity and mortality. Complete surgical resection results in improved OS in a highly selected group of patients. Complete resection of multiple organ-site metastases can result in OS rates similar to those after complete resection of single-organ site disease. In lieu of effective systemic treatment, we recommend aggressive complete surgical resection of melanoma metastatic to the liver, spleen, pancreas, and adrenal glands.

Acknowledgments: Supported by grant CA 12582 from the National Cancer Institute and by funding from the Wrather Family Foundation, Los Angeles, CA.

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