

Long-Term Survival After Complete Resection of Melanoma Metastatic to the Adrenal Gland

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Background: Survival of patients with American Joint Committee on Cancer stage IV melanoma is generally poor, although there are occasional long-term survivors who have undergone surgical resection of a limited number of metastases. In the study, we examined the outcome of patients with adrenal gland metastases.

Methods: Eighty-three patients with adrenal metastases were identified from our computerized melanoma database of 8250 patients. Univariate and multivariate analyses for overall survival differences were performed by using proportional hazards modeling.

Results: Median survival for the 83 patients was 9.3 months (1–67 months). Of the 27 patients who underwent surgical exploration, 18 (66%) were rendered clinically free of disease by adrenalectomy alone (12 cases) or by adrenalectomy and resection of additional disease (6 cases). Nine patients underwent palliative adrenal resection. Median survival was 25.7 months after complete resection compared with 9.2 months after palliative resection ($P = .02$).

Conclusions: Patients with adrenal metastases from melanoma, either isolated or with a limited number of additional metastases, may benefit from surgical resection if all visible disease can be removed. Patients with unresectable extra-adrenal disease achieve no survival benefit from adrenalectomy.

Key Words: Melanoma—Adrenal—Metastases—Surgery.

The prognosis of patients with American Joint Committee on Cancer stage IV melanoma is generally poor. Most patients with metastatic melanoma are treated with chemotherapy; only a select group is eligible for surgical palliation of symptoms or potentially curative resection. Although retrospective evidence indicates improved survival of selected patients undergoing complete surgical resection of metastatic melanoma to isolated sites in the lung, gastrointestinal tract, and, occasionally, brain,^{1–12} there are limited data on the role of surgery in patients with melanoma that has spread to the adrenal gland.¹³ Recent studies have shown encouraging results for resection of clinically isolated adrenal metastases, but these are mostly from primary

lung, kidney, and colorectal carcinomas.^{14–16} Although about half of cases in an autopsy series devoted to patients with advanced melanoma were found to harbor adrenal metastases,¹⁷ the premortem diagnosis of adrenal gland metastases from melanoma remains rare.¹³ However, computed tomography and magnetic resonance imaging have allowed detection of adrenal metastases before symptoms appear. Usually other organs are involved simultaneously, and nonoperative management is the preferred strategy. Occasionally, patients have no other metastatic disease, and in this scenario, treatment planning is more difficult. In this report, we document the experience at the John Wayne Cancer Institute (JWCI) in the treatment of patients with melanoma metastatic to the adrenal gland and attempt to identify those patients who have prolonged survival after adrenalectomy.

MATERIALS AND METHODS

Eighty-three patients with melanoma metastatic to the adrenal gland were identified from our computerized

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data base of 8250 melanoma patients treated by the medical staff of JWCI between 1971 and 1997. Records were analyzed for patient and tumor characteristics, disease progression, and surgical treatment. In general, patients were staged before adrenalectomy, with computed tomographic scans of the chest, abdomen, and pelvis, and brain magnetic resonance imaging. Some patients, in more recent years, were staged with fluorodeoxyglucose positron emission tomographic scanning. This retrospective review was unable to delineate the exact selection criteria used in the decision for operation; but, for the most part, patients with limited disease deemed resectable were offered adrenalectomy. Survival in months was calculated from the time of diagnosis of adrenal metastases to death or last follow-up. Median follow-up for the group was 9.2 months (range, 1–67 months).

Factors examined for survival differences were age at diagnosis of adrenal metastases, gender, thickness of the primary lesion, disease-free interval (DFI) before adrenal metastases (analyzed as a continuous variable and as a categorical variable using 18 months as a break point), first site of distant disease, presence of concurrent extra-adrenal stage IV disease, and treatment received for adrenal metastases (curative surgery, palliative surgery, or no surgery). Survival curves were estimated by using the Kaplan-Meier method.¹⁸ Univariate and multivariate survival analysis was performed by using proportional hazards modeling. Proportions of prognostic factors and demographic variables between groups were compared by using χ^2 statistic or Fisher exact test. Statistical significance was determined by using an α -level of 0.05 and two-sided *t*-tests.

RESULTS

Patient Demographics and Tumor Characteristics

Of 83 patients with a radiological or intraoperative diagnosis of adrenal metastases, 56 (67%) were treated nonoperatively, and 27 (33%) underwent surgical exploration. Age, gender, site, and thickness of primary melanoma, previous regional (American Joint Committee on Cancer stage III) disease, and DFI before stage IV disease were similar in the nonoperative and operative groups (Table 1). A similar proportion of patients in the two groups was treated with chemotherapy or immunotherapy before diagnosis of adrenal metastases. The adrenal gland was the first site of distant metastases in 10 (37%) operative patients but only 3 (5%) nonoperative patients. Synchronous extra-adrenal metastases were found in 12 (44%) patients in the surgical group, compared with 50 (89%) patients treated nonoperatively.

Surgical Treatment

Potentially curative surgery was defined as resection of all visible metastatic disease. Of the 27 operative patients, 18 (67%) underwent potentially curative surgery; i.e., 12 patients had adrenalectomy alone (Table 2), 6 patients had additional resections at the same operation, and 2 of these patients remain clinically free of disease after each had resections of their recurrences (Table 3). Adrenal metastases were asymptomatic and diagnosed by routine imaging studies in 12 of 18 (67%) patients undergoing curative surgery. The remaining 6 patients (33%) presented with pain or adrenal hemorrhage, prompting radiological evaluation.

TABLE 1. Characteristics of patient population

	Operative group (n = 27)	Nonoperative group (n = 56)	P value
Age at diagnosis of adrenal metastases years (mean \pm SE)	49 \pm 2.7	52 \pm 1.9	.33
Gender, %			
Male	78	70	.44
Female	22	30	
Site of primary melanoma, %			
Extremity	30	18	.33
Nonextremity	44	61	
Unknown	26	21	
Breslow thickness, mm			
Median	1.6	1.8	.23
Range	0.8–3.5	0.1–11.0	
Disease-free interval before stage IV, mo			
Median	10	4	.53
Mean	25	19	
Range	1–223	1–162	
Systemic treatment before adrenal disease, %	52	41	.35
Stage III before stage IV disease, %	52	45	.90
Synchronous metastases, %	44	89	.001
Adrenal as initial stage IV site, %	37	5	.001

TABLE 2. Outcome of patients treated with potentially curative adrenalectomy alone

Patient	Recurrence site after adrenalectomy	Disease-free survival (mo)	Overall survival (mo)	Status
1	Spinal cord	24.0	51.7	EXP
2	Subcutis	12.0	38.2	EXP
3	Brain	8.7	36.4	EXP
4	Axilla	3.0	31.3	EXP
5	Lung	10.0	25.7	EXP
6	Brain	5.2	23.1	EXP
7	Liver Adrenal	10.3	17.4	EXP
8	Subcutis	3.0	15.8	EXP
9	Neck Retroperitoneum	5.0	9.8	EXP
10	Subcutis	6.6	6.7	AWD
11	Brain	6.1	6.1	EXP
12	Adrenal bed	2.0	4.4	EXP

EXP, expired; AWD, alive with disease.

Palliative surgery was performed for control of symptoms of pain or bleeding, leaving patients with gross extra-adrenal disease. Nine patients underwent palliative surgery (Table 4). One of these patients had bilateral adrenal disease and required adrenalectomy for a large metastasis causing pain; 6 months later, an adrenalectomy was performed on the contralateral side for a lesion, which remained stable, rendering the patient clinically free of disease. The indications for palliative surgery were pain, adrenal hemorrhage, or upper gastrointestinal bleeding secondary to jejunal metastases (Table 4).

The abdominal approach to adrenalectomy was used most frequently ($n = 21$), followed by a flank approach ($n = 4$) and a transthoracic approach in two patients whereby the adrenalectomy was performed through a diaphragmatic incision after resection of ipsilateral lung metastases. Major complications occurred in three patients (11%). Two patients required reoperation within 30 days for proximal small bowel obstruction secondary to metastases; in one patient the adrenalectomy was performed transthoracically, and in the other patient adrenalectomy was completed by a standard abdominal

approach. The third major complication also occurred in a patient whose procedure was performed transthoracically; this patient developed a persistent pleural effusion requiring tube thoracostomy. Minor complications occurred in two patients (7%), one with a wound seroma and one with prolonged ileus. There were no perioperative deaths.

Survival Analysis

Median overall survival was 9.3 months (range, 1–67 months) for the entire group. The median survival was 18.6 months (range, 1–67 months) for operative patients and 7.7 months (range, 1–61 months) for nonoperative patients (Fig. 1). In the operative group, the median survival was 25.7 months for patients undergoing potentially curative surgery and 9.2 months for those undergoing palliative surgery (Fig. 2). Of the 18 patients undergoing potentially curative surgery, 10 (56%) survived for 2 or more years. The median disease-free survival of these 18 patients was 12 months (Fig. 3); median disease-free survival of those 12 patients undergoing adrenalectomy alone was 10 months and was 29

TABLE 3. Outcome of patients treated by resection of adrenal and synchronous extra-adrenal metastases

Patient	Additional resection(s) for metastases at adrenalectomy	Site of recurrence	Disease-free survival (mo)	Overall survival (mo)	Current status
13	Splenectomy Small bowel resection	Neck	17	37	Alive, NED
14	Lung lobectomy	Small bowel	20	30	Alive, NED
15	Omentectomy	Subcutis	24	25	AWD
16	Subcutaneous metastasectomy	Adrenal	29	67	EXP
17	Retroperitoneal lymphadenectomy	Sacrum	24	24	EXP
18	Large/small bowel resection Axillary lymphadenectomy	Kidney	7	8	EXP

NED, no evidence of disease; AWD, alive with disease; EXP, expired.

TABLE 4. Procedure, indications, and survival in palliative surgical group

Patient	Additional resection(s) for metastases at adrenalectomy	Indication	Site(s) of other metastases	Overall survival (mo)	Current status
19	—	Flank pain	Contralateral adrenal	24.8	Alive, NED
20	—	Adrenal hemorrhage	Lung	19.8	EXP
21	—	Flank pain	Subcutis	10.9	EXP
22	Iliac node dissection	Flank pain	Contralateral adrenal	9.3	EXP
23	—	Flank pain	Subcutis	9.2	EXP
24	Colectomy, small bowel resection, nephrectomy	GI bleed/obstruction	Subcutis	8.1	EXP
25	Splenectomy	Flank pain	Liver	5.7	EXP
		Fever	Brain		
			Lung		
26	Small bowel resection	GI bleed	Lung	5.4	EXP
27	Lung lobectomy	Flank pain	Small bowel	4.3	EXP
			Brain		

NED, no evidence of disease; EXP, expired.

months for those 6 patients who also had extra-adrenal metastases resected.

By univariate analysis, host features of age and gender were not significant factors for any survival differences among the patients (Table 5). Primary tumor thickness, site of initial stage IV disease, DFI before adrenal disease, a previous diagnosis of stage III disease, and presence of extra-adrenal disease were also not predictive of survival. Only those patients who underwent complete surgical resection of metastases had a better survival by

both univariate and multivariate analysis. It is noteworthy that the patients who had incomplete surgical resection did no better than the patients who were treated nonoperatively.

DISCUSSION

The experience at JWCI confirms that patients with metastatic melanoma involving distant visceral sites typically have a poor prognosis.^{3,5,7} However, surgical re-

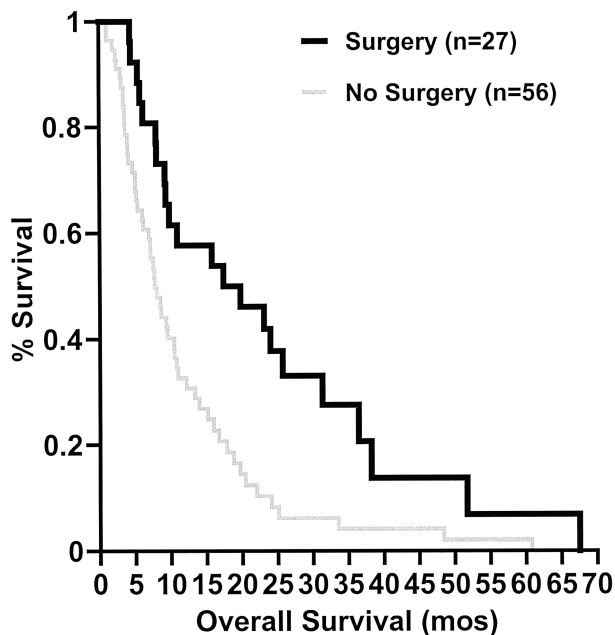


FIG. 1. Survival rates of patients with melanoma and adrenal metastases treated either by operative or by nonoperative methods. The median survival of the operative group was significantly better ($P = .001$) than the nonoperative group.

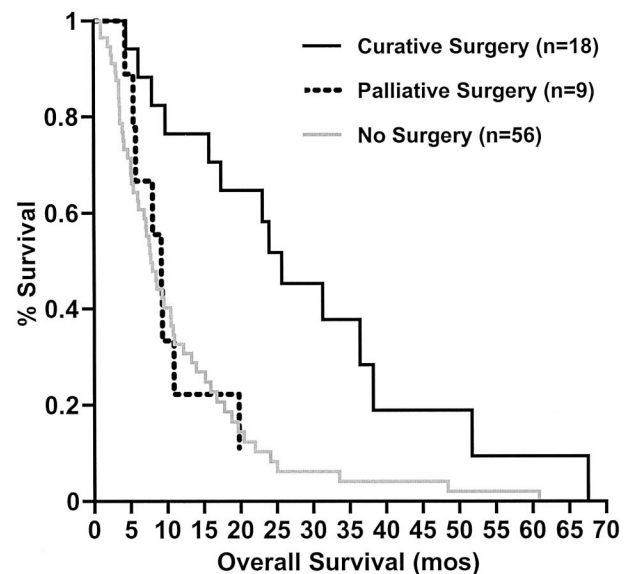


FIG. 2. Survival rates of patients with melanoma undergoing potentially curative resection vs. palliative resection vs. no surgery. Median survival of patients completely resected for attempted cure was significantly better ($P = .02$) than the other two groups. The survival of the surgically palliated patients was no different compared with the patients treated nonoperatively.

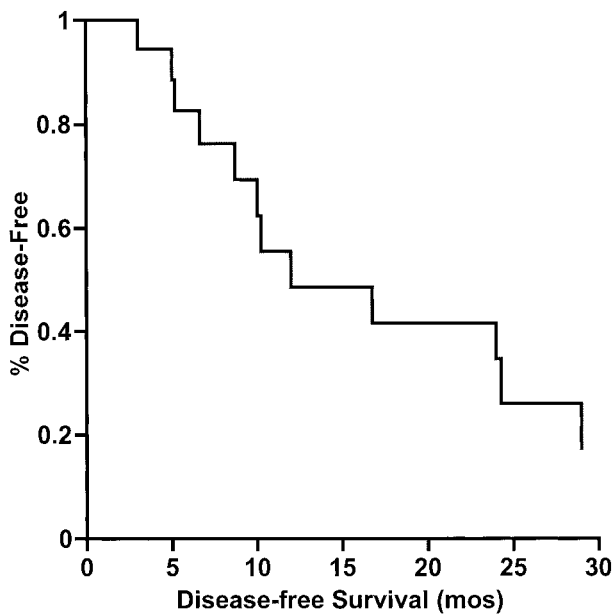


FIG. 3. Disease-free survival in the 18 patients who underwent potentially curative resection. Median survival was 12 months for this group.

section can improve the outcome of occasional patients with isolated metastatic disease. In this series, only approximately 1 of every 5 patients with adrenal metastases could be rendered free of disease after adrenalectomy alone or in combination with an additional metastasectomy. Most patients were treated nonoperatively, largely because of widespread disease, or because adrenal involvement occurred late in the natural history of the disease. In the selected patients who were offered surgery, those who underwent a potentially curative resection had a longer median survival than those who had a

palliative procedure. It is interesting that the survival of patients who required concomitant resection of extra-adrenal disease to achieve complete resection was also better than that of patients who had multiple sites of metastases that were treated nonoperatively.

Results of two large series that investigated the role of surgery for adrenal metastases from a wide spectrum of primary tumors suggested that complete resection offers a survival benefit.^{14,15} There were conspicuously few patients with melanoma in these series; but, in general, adrenalectomy for metastases was safe and provided excellent palliation of symptoms related to the adrenal metastases. Another recent study compare survival after adrenalectomy with survival after resection of metastases at other organ sites; it was found that patients with adrenal metastases from a variety of primary tumors treated with adrenalectomy have a projected 5-year survival of 13%, which compared less favorably with patients who had lung and liver resections for colorectal metastases.¹⁶ In a study by Branum et al.,¹³ the only series devoted entirely to resection for melanoma metastatic to the adrenal gland, the mean survival of eight patients undergoing complete resection of all known disease was 59 months. The DFI of these eight patients selected for curative resection was 45 ± 17 months, compared with our mean DFI of 25 months, which may be partly responsible for the difference in survival between studies. However, the survival of patients with melanoma compiled from other published series of adrenalectomy for metastatic disease from a variety of neoplasms is presented in Table 6; it is evident that, because of such limited numbers from the other series, no meaningful conclusions can be made regarding survival data in those series.

It is uncertain whether surgical resection altered the natural history of the disease, or if the survival would have been prolonged because the particular tumor in selected patients was biologically less aggressive. In small case series, adrenalectomy for isolated adrenal metastases from lung carcinoma, compared with radiotherapy or chemotherapy, has been demonstrated to improve survival.^{19,20} A small group of patients who had isolated symptomatic adrenal metastases from lung carcinoma treated with radiotherapy had a median survival of 6 months.²¹ There are no similar studies of radiotherapy as primary treatment of adrenal metastases from melanoma. Controversy will continue regarding the benefit of adrenal metastasectomy for melanoma because of the impact that heterogeneity of tumor biology and host factors have in the study of an uncommon disease entity, which, when taken together, would make a larger study

TABLE 5. Univariate and multivariate survival analysis of patients with adrenal metastases

Factor	P value	
	Univariate analysis	Multivariate analysis
Surgical treatment		
Curative vs. no surgery	.001	.001
Curative vs. palliative surgery	.021	.018
Palliative vs. no surgery	NS	NS
Synchronous metastases at adrenal diagnosis	.06	.07
Initial stage IV site: adrenal vs. other	.09	—
Gender	.09	—
Breslow thickness	.21	—
Age	.80	—
DFI before adrenal diagnosis	.96	—
Previous stage III diagnosis	.96	—

NS, not significant; DFI, disease-free interval.

TABLE 6. Series of adrenalectomy for adrenal metastases from melanoma or other neoplasms

Author	Total No. undergoing adrenalectomy	No. with melanoma	No. with melanoma completely resected	Survival with melanoma after complete resection (mo)
Lo et al.	52	3	3	NR
Kim et al.	37	1	1	NR
Wade et al.	47	3	3	12 (mean)
Branum et al.	10	10	8	59 (mean)
Current series	27	27	18	26 (median)

NR, not reported.

comparing different treatments virtually impossible to conduct, and difficult to justify.

We examined multiple prognostic factors in our analysis of survival and identified that complete resection was associated with improved outcome for the entire group. These results concur with other series that demonstrate an improved survival in patients undergoing complete resection of metastatic melanoma in the lung, gastrointestinal tract, skin and subcutaneous tissue, distant nodes, and even brain.¹⁻¹² Although not directly comparable with other studies, the median survival of 9.3 months for the total group is similar to that of patients with melanoma metastatic to the subcutis,^{2,4} lung,^{1,9,11,22,23} and gastrointestinal tract.^{8,10}

With the poor prognosis associated with stage IV melanoma, and no great impact from standard chemotherapy or radiotherapy, we will continue to investigate the role of adjuvant immunotherapy in the treatment of patients with stage IV disease. Our earlier reports from phase II studies support a therapeutic effect from CancerVax, a polyvalent melanoma cell vaccine developed at JWCI, in patients with stage IV disease.²⁴⁻²⁶ However, any evidence of survival benefit from CancerVax must be confirmed with a phase III trial. We have started enrolling patients in a multicenter trial in which patients who have undergone complete resection of distant melanoma metastases are randomized to treatment with CancerVax or placebo, after stratification by site of distant metastases and number of resected lesions. It is our hope that for these patients who have resectable disease, treatment with immunotherapy will further improve their survival.

In our series, adrenalectomy was performed by using conventional open surgical techniques. None of our operations was performed laparoscopically. The laparoscopic approach is safe for resecting benign adrenal tumors, and is associated with shorter hospital stays and less postoperative pain compared with conventional approaches.^{27,28} The role of laparoscopic adrenalectomy for malignant disease has not yet been defined, but there are

a few reports of adrenalectomy for primary adrenocortical carcinoma and metastatic disease from lung, cervical, and kidney carcinoma.²⁸⁻³¹ However, the need for additional organ resection for synchronous abdominal metastases may not allow a minimally invasive approach. The patient with a small adrenal metastasis from melanoma may be an ideal candidate for laparoscopic adrenalectomy if the tumor can be completely resected. On the other hand, laparoscopic resection may be inappropriate, as melanoma metastases tend to be friable and, therefore, may be difficult to prevent tumor rupture. Obviously, much investigation is required in the realm of laparoscopic resection for malignancy.

In our series, morbidity was low after adrenalectomy, and there was no perioperative mortality. One patient survived more than 5 years after complete resection of all gross disease. Resection of adrenal metastases from melanoma compares favorably with resection for solitary metastases in other organs. In the carefully selected patient with no major coexistent morbidity who has isolated melanoma metastatic to the adrenal gland or with limited extra-adrenal sites of disease, complete resection may be associated with a survival benefit.

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