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A 20-Year Experience of Hepatic Resection for Melanoma: Is There an Expanding Role?

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Abstract

Background—Melanoma liver metastasis is most often fatal with a 4–6 month median overall survival (OS). Over the past 20 years surgical techniques have improved in parallel with more effective systemic therapies. We reviewed our institutional experience of hepatic melanoma metastases.

Study Design—OS and disease specific survival (DSS) were calculated from hepatic metastasis diagnosis. Potential prognostic factors including primary tumor type, depth, medical treatment response, location and surgical approach were evaluated.

Results—Among 1,078 patients with melanoma liver metastases treated at our institution since 1991, 58 (5.4%) were received surgical therapy (resection+/-ablation). Median and 5-year OS were 8 months and 6.6 %, respectively, for 1,016 non-surgical patients versus 24.8 months and 30%, respectively, for surgical patients ($p < 0.001$). Median OS was similar among patients undergoing ablation (with or without resection) relative to those undergoing surgery alone. On multivariate analysis of surgical patients, completeness of surgical therapy (HR 3.4, 95% CI 1.4–8.1, $p = 0.007$) and stabilization of melanoma on therapy prior to surgery (HR 0.38, 95% CI 0.19–0.78, $p = 0.008$) predicted OS.

Conclusions—In this largest single-institution experience, patients selected for surgical therapy experienced markedly improved survival relative to those receiving only medical therapy. Patients whose disease stabilized on medical therapy enjoyed particularly favorable results, regardless of the number or size of their metastases. The advent of more effective systemic therapy in melanoma may substantially increase the fraction of patients who are eligible for surgical intervention, and this combination of treatment modalities should be considered whenever it is feasible in the context of a multidisciplinary team.

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Keywords

Melanoma; hepatectomy; ablation

Introduction

The therapeutic options for patients with Stage IV metastatic melanoma have evolved in the last decade with the introduction of novel, effective therapies.^{1,2} This is particularly relevant since previous systemic therapy has been associated with low response rates and minimal survival benefit.³ Recently, a human monoclonal antibody to CTLA-4 demonstrated a significant survival benefit in patients with metastatic melanoma in a prospective randomized trial, opening the door to novel effective immunotherapeutic agents.²

There has been considerable debate about the role of surgery in metastatic melanoma particularly with limited systemic options. Resection of distant metastatic disease has been shown in several studies to have favorable outcomes but these studies have been criticized because selection criteria are not well defined in a heterogeneous group of patients.^{4–11} Many patients however with metastatic melanoma succumb to liver failure from liver metastases. Some groups have therefore demonstrated that hepatectomy may improve survival in patients with limited hepatic disease.^{12–15} In the time when essentially no progress was being made in systemic melanoma therapy, improvements in liver surgery were substantial. These included advances in intraoperative and perioperative care that were accompanied by falling morbidity and mortality.¹⁶ Finally, several generations of ablation technologies have been developed making it possible to completely treat metastases in patients who would not have been candidates in the past. Because the majority of studies have included few patients with limited follow-up the optimal surgical approach has not been well defined. Furthermore little is known about the selection of patients for surgery in the era of modern systemic therapy. We therefore evaluated our patients with liver metastases from a large melanoma database over two decades to determine whether selection criteria have changed with the use of more effective systemic agents and whether this has impacted survival.

Methods

The prospectively maintained John Wayne Cancer Institute melanoma database was queried for patients with hepatic melanoma metastases between the years of 1991 and 2010. Identified patients were evaluated for demographic (age, gender), pathologic (primary tumor characteristics, metastatic sites) and clinical (treatment type, response to therapy, recurrence and survival) characteristics. Patients were selected for surgical therapy based upon the judgment of their surgeon. Generally our center uses the pace of progression as indicated by disease-free interval or tumor volume doubling time and patient co-morbidities as relative selection factors for surgery. Those who were treated with surgical or ablative therapy for their hepatic disease were also examined for the number of lesions treated, response to prior therapy for hepatic disease, types of resection, and reasons for resection. In each case the

decision to perform a surgical intervention was made by the patient's attending surgeon on clinical grounds for either therapeutic or palliative reasons. Ablation was typically used for patients that were considered unresectable, those with bilobar disease and/or poor operative candidates. The ablation technology evolved over twenty years from cryosurgery and ethanol ablation to radiofrequency ablation and more recently microwave ablation. Response to prior systemic therapy was defined by RECIST criteria on pre- and post-therapy imaging.

Written informed consent was provided by each patient to receive the recommended therapy. This retrospective evaluation of the data was performed in a de-identified manner, and was independently determined to be exempt from Institutional Review Board review.

Overall survival (OS) and disease-specific survival (DSS) were calculated from diagnosis of hepatic metastases. Comparisons of group characteristics were performed using chi-square with log-transformation of data as appropriate or Fisher's exact test. Survival rates were estimated with the Kaplan-Meier method and compared using the logrank test. Cox proportional hazard models were constructed to determine the impact of variables on outcome. A p-value of <0.05 was considered significant.

Results

Between 1991 and 2010, 1,078 patients with melanoma metastatic to the liver have been treated at our institution among over 7500 patients with melanoma. Among those, 58 (5.4%) were considered candidates for surgical therapy (resection+/-ablation). Surgical and non-surgical patients were similar in demographic, pathologic and clinical characteristics with trends toward slightly thinner tumors and longer disease-free intervals for surgical patients. (Table 1) A large majority of tumors in both the surgical and non-surgical groups were of cutaneous origin; 16% of surgical patients had ocular primaries as did 11% of non-surgical patients (p=0.27). There was also a male predominance in both groups, which is typical for our advanced melanoma population. The extent of disease, both intra- and extra-hepatic cannot be accurately determined retrospectively for this large cohort. In the surgical group a mean of 1.8 and median of 1 lesion was present in liver. Among the patients who had ablation as a component of their treatment, the rationale for its use was clear in 15 and included extent of disease (n=10 (67%)), technical reasons (n=3 (20%)), and patient comorbidities (n=2, (13%)). As a result of selection factors for surgical treatment, this is very likely to be less than the number of lesions in the non-surgical group.

Among the surgical patients, 40 underwent resection only, 10 underwent ablation only and 8 had both ablation and resection. These three groups were similar in age and gender distribution. (Table 2) There was one death within 30 days (1.7%). The surgical intent for all but 4 patients was curative with palliative procedures primarily being performed to control bleeding (n=2) or compressive symptoms (n=2). The majority of patients were able to have all evident disease addressed at the time of surgery either by resection or by a combination of resection and ablation. This included 88% of surgical patients overall and 87.5% of patients undergoing resection alone. Four patients underwent palliative procedures for bleeding or compressive symptoms, and three of four were successfully palliated. Twenty-seven patients (47%) underwent anatomic resections, 19 (33%) underwent wedge

resections, and in 12 the resection type is unknown. In 19% of cases, extrahepatic disease was resected at the time of hepatic resection. Sites of extrahepatic disease included spleen (n=3), omentum (n=1), colon (n=1), small bowel (n=2), stomach (n=1), renal (n=2), adrenal (n=2) and portal/celiac lymph nodes (n=3).

Both overall and disease-specific survival were markedly better in the surgical group relative to the non-surgical patients. Among the non-surgical patients, median OS and 5-year rate of OS were 8 months and 6.6 %, respectively. In the surgical group these were 24.8 months and 30%, respectively ($p<0.001$) (Figure 1). Examining the surgical group, outcomes were not significantly different among the resection, ablation and resection/ablation groups, with the resection/ablation group having slightly higher and the ablation alone group having slightly lower OS and DSS ($p=0.16$, Figure 2.) Rates of 5-year OS were 28.6% and 33.3%, for the resection-only or ablation +/- resection groups, respectively ($p=0.726$).

Univariate survival analyses in the surgical group demonstrated incomplete resection was associated with much worse outcomes, with no survivors beyond 3 years (Figure 3, $p<0.001$). Outcomes of patients who underwent concomitant resection of extrahepatic metastases were not significantly worse than those with liver-only disease (Figure 4, $p=0.14$). Patients who underwent systemic therapy with stabilization of disease prior to surgery had favorable survival relative to those who did not (OS and DSS $p=0.01$, Figure 5).

On multivariable analysis in the surgical group, overall survival was found to be independently related to the completeness of surgical treatment (HR 3.4, 95%CI 1.4–8.1, $p=0.007$) and to stabilization of disease on prior systemic therapy (HR 0.38, 95%CI 0.19–0.78, $p=0.008$). For disease-specific survival, only completeness of surgical therapy was significant (HR 5.1, 95%CI 2.0–12.9, $p=0.0007$).

Discussion

Metastatic melanoma has carried an extremely poor prognosis throughout the history of the disease. Visceral metastases constitute the most advanced stage of melanoma (Stage IV, M1c) and are associated with one-year survival of 25% in cooperative group clinical trials and 5-year survival of under 10% in population-based measures.^{3,17} Hepatic metastases have traditionally been associated with even worse outcomes with reported median survivals of 2–7 months.¹³ Responses to earlier generations of systemic therapy were infrequent and generally short-lived.¹⁸

In that context, surgical resection provides an attractive option for therapy.^{5–11} Surgery leads to rapid and complete resolution of all evident disease and numerous series have now demonstrated long-term survival in patients who have undergone metastasectomy at various anatomic sites, even in the absence of effective systemic treatment. Prior series of hepatic resection for melanoma were generally quite small in number and required combination of data from multiple centers for analysis.^{12–15,19} A report from the John Wayne Cancer Institute and the Sydney Melanoma Unit found that among 1750 patients with liver disease, only 34 underwent surgery and only 24 (1.4%) had complete resection.¹² Similarly, at four

major referral centers, only 40 patients were found to have undergone hepatic resection for melanoma over a 12 year period.¹³ The current series suggests the frequency of resection may have increased marginally since 5.4% of patients with liver metastases treated at our institution underwent surgery since 1991. While this increase could be due to changes in referral patterns, it may also be related to improvements in radiographic staging and early detection of metastatic disease. Indeed, in an analysis of patients with Stage IV melanoma recurrence occurring during follow up of the Multicenter Selective Lymphadenectomy Trial, over half of the patients underwent surgical therapy as part of their Stage IV treatment.¹¹ Despite this apparent increase in the proportion of surgically treated patients, median survival and 5-year survival were very similar in this series to those reported in much earlier series.¹²

Hepatic resection has also become safer in recent years, most likely due to improved intraoperative management and techniques. A study by Jarnagin et al, examining perioperative outcomes of over 1,800 patients between 1991 and 2001 showed a decline in operative blood loss and length of hospital stay.¹⁶ Importantly, operative mortality over that period of time declined by more than half to under 2% despite the frequent use of major hepatic resection in that series.

Unfortunately, resection is not possible in the vast majority of patients with metastatic melanoma due to the extensive nature of metastases in most cases. The current series suggests there are hopeful signs that more patients can be treated successfully by surgical techniques than in the past. In addition to early detection, discussed above, two factors that may play a role are the use of ablation techniques and the availability of systemic agents with improved efficacy.

In this series, nearly a third of patients underwent ablation as a component of their surgical therapy. This was most often due to the extent of disease identified at surgery (10 cases, 56%, data not shown) or to patient comorbidities precluding major hepatectomy. Current ablation techniques, which provide the ability to address unresectable disease, result in more uniform tumor killing than in the past and make complete tumor treatment possible more often.²⁰ In contrast to earlier series of hepatic resection for other types of metastases, the current series did not demonstrate significantly inferior outcomes for patients undergoing a combination of resection and ablation. It appears that the expansion of eligibility for surgical therapy has not been accompanied by a decline in long-term survival if all disease can be addressed by one modality or another.

This series also identifies disease response or stabilization during prior systemic therapy as a major predictor of favorable outcomes. This is similar to the finding of the multi-institutional series reported by Pawlik et al that prior systemic chemotherapy was associated with improved survival.¹³ While this is likely to be due in part to improved selection of patients with favorable disease biology, it may also be related to a beneficial combination of control of unseen microscopic disease by systemic therapy and eradication of macroscopic disease by surgery. In this study, a large variety of systemic and regional therapies were applied to the population. These include chemotherapy, biochemotherapy, checkpoint blockade (e.g. anti-CTLA-4 antibodies) and clinical trials. This large variety of therapies

precludes any meaningful comparison of non-surgical treatments or the impact of any particular therapy on post-surgical outcomes. The use of arterial infusion of chemotherapy has not, in our experience yielded promising results, but isolated hepatic perfusion is an interesting recent technique that may provide benefit. The role of that therapy relative to surgery is yet to be determined.

The modern era of melanoma medical treatment may increase the fraction of patients who can benefit from this combination of modalities. New drug therapies targeting aberrant molecular pathways in melanoma have yielded very high response rates among patients whose tumors have specific mutations.¹ Unfortunately responses to these drugs appear to be temporary in almost all cases, but surgical consolidation in cases of mixed or partial responses may be beneficial and is worthy of additional study. In addition, several new immune-based therapies targeting immune checkpoints (e.g. CTLA-4, PD-1)^{2, 21} or using oncolytic viruses²² have demonstrated durable clinical responses and/or improved outcomes. These therapies often result in incomplete responses or stable disease. The current series suggests that patients who experience such stability might enjoy particularly favorable long-term survival with surgical consolidation of their therapy. Another interesting question, which we are not able to address in this analysis, is the role of adjuvant therapy. The most effective systemic therapies in our study were likely clinical trial agents, which were not available in the adjuvant setting then. Increased availability of these effective agents makes the prospect of adjuvant clinical trials after Stage IV metastasectomy more likely.

This may be true not only for patients with liver-only metastases, but also for patients with limited extrahepatic disease. In cutaneous melanoma, there is concomitant extrahepatic disease in most cases. Our data suggest that if this disease can also be removed, patients may enjoy a similar likelihood of long term survival. Retrospective reviews, such as this one, are subject to several limitations. The precise criteria for treatment selection cannot be fully known, nor can the fraction of non-surgical patients who might have actually been candidates for surgery. Our center is also recognized as a proponent of surgical treatment of metastases, which may have altered patterns of referral. It is also very difficult to capture all of the potentially pertinent variables retrospectively.

No existing study can provide level 1 evidence to support the use of liver-directed, surgical therapy in hepatic melanoma metastases or selection factors for such treatment. It is important to note that these patients were heavily selected, given that the vast majority of patients did not undergo surgical therapy. Selection factors include the pace and extent of disease in order to identify patients who are most likely to enjoy prolonged survival after treatment. Our series, however, provides the largest institutional data set regarding prognostic factors among patients who undergo such treatment. We would recommend consideration of surgical therapy only when all disease can be addressed, as patients with disease remaining after resection and/or ablation had uniformly poor outcomes. In light of this, initial laparoscopic evaluation to rule out miliary disease seems appropriate. In addition, the biology or pace of the metastatic disease appears paramount. Tumors with slow growth rates, either through natural biology or after treatment with systemic therapy, are more likely to experience prolonged survival after surgery and may be optimal candidates for this approach.

Overall, it appears patients who can undergo complete surgical treatment of hepatic metastases of melanoma should consider that option. The advent of improved surgical techniques, improved perioperative care, improved imaging and dramatically improved systemic therapy suggest that resection should be considered more often from this point forward and that investigation of the therapeutic role of resection in the context of modern medical therapy is warranted.

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Figure 1. Kaplan-Meier survival curves for patients undergoing surgical (resection, ablation or resection and ablation) therapy and those receiving only systemic medical therapy.

Figure 2. Kaplan-Meier survival curves for patients undergoing resection, ablation or resection and ablation.

Figure 3.

Kaplan-Meier survival curves for patients undergoing complete surgical therapy (i.e. all evident lesions addressed by complete resection or ablation versus patients in whom some lesions could not be either resected or ablated).

Figure 4.

Kaplan-Meier survival curves for patients undergoing surgical therapy of hepatic melanoma metastases with or without concomitant resection of extrahepatic metastatic disease.

Figure 5. Kaplan-Meier survival curves for patients undergoing surgical therapy who had stabilization of disease (complete response, partial response or stable disease by RECIST) during systemic medical therapy prior to surgery.

Table 1

Demographic/Pathologic Characteristics: Entire Population

Characteristic	Resection (n=58)	Non-resection (n=1,020)	P Value
Age at liver metastasis, y (range)	54.1 (25–78)	55.1 (1–100)	0.60
Sex (male:female)	36:22 (62:38%)	670:350 (65:35%)	0.57
Breslow (mean)	2.23	2.72	0.12
Clark I	0	11 (1.3%)	0.20
II	5 (8.6%)	41 (4.7%)	
III	5 (8.6%)	140 (16.2%)	
IV	14 (24.1%)	344 (39.8%)	
V	4 (6.9%)	62 (7.2%)	
Unknown/ N/A	30 (51.7%)	267 (30.9%)	
Ulceration			0.56
Yes	9 (15.5%)	127 (14.7%)	
No	17 (29.3%)	308 (35.6%)	
Unknown/missing	32 (55.2%)	430 (49.7%)	
Primary site			0.37
Eye (ocular)	9 (16%)	88 (11%)	
Extremity	14 (24%)	236 (29%)	
Trunk	15 (26%)	313 (39%)	
Head/neck	11 (19%)	173 (21%)	
Missing	9 (16%)	3 (0.4%)	
Prior stage III			0.36
Yes	25 (43.1%)	426 (49.3%)	
No	33 (56.9%)	439 (50.8%)	
Diagnosis to hepatic metastasis interval, mo	73.1	63.6	0.10

Table 2**Surgical Patients**

Characteristic	Resection	Resection+ ablation	Ablation	All surgical
n	40	8	10	58
Age at surgery, y, mean	54.4	51.3	55.3	54.1
Sex (male:female)	26:14	4:4	6:4	36 : 22
30-d mortality, n (%)	1 (2.5)	0	0	1 (1.7)
Surgical intent				
Cure	36	8	9	52
Palliation	4	0	0	4
Complete treatment				
Yes	35	6	10	51
No	5	2	0	7
Extrahepatic disease resected, n (%)	8 (20)	3 (37.5)	0	11 (19)
Disease stabilized on prior therapy, n (%)				
Yes	14 (35)	3 (37.5)	3 (30)	20 (34)
No	22 (55)	5 (62.5)	6 (60)	33 (57)
Unknown	4 (10)	0	1 (10)	5 (9)