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



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- BACKGROUND:** Melanoma liver metastasis is most often fatal, with a 4- to 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:** Overall and disease-specific survivals 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%) received surgical therapy (resection with or without ablation). Median and 5-year OS were 8 months and 6.6 %, respectively, for 1,016 nonsurgical patients vs 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 (hazard ratio [HR] 3.4, 95% CI 1.4 to 8.1,  $p = 0.007$ ) and stabilization of melanoma on therapy before surgery (HR 0.38, 95% CI 0.19 to 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. (J Am Coll Surg 2014;219:62–69. © 2014 by the American College of Surgeons)
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The therapeutic options for patients with stage IV metastatic melanoma have evolved in the last decade with the introduction of novel effective therapies.<sup>1,2</sup> This is

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particularly relevant because previous systemic therapy has been associated with low response rates and minimal survival benefit.<sup>3</sup> 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.<sup>2</sup>

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 were not well defined in a heterogeneous group of patients.<sup>4-11</sup> However, many patients 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.<sup>12-15</sup> In the time when essentially no progress was being made in systemic melanoma

**Abbreviations and Acronyms**

DSS = disease-specific survival

HR = hazard ratio

OS = overall survival

therapy, improvements in liver surgery were substantial. These included advances in intraoperative and perioperative care that were accompanied by falling morbidity and mortality rates.<sup>16</sup> 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 2 decades to determine whether selection criteria have changed with the use of more effective systemic agents and whether this has affected survival.

**METHODS**

The prospectively maintained John Wayne Cancer Institute melanoma database was queried for patients with hepatic melanoma metastases between 1991 and 2010. Identified patients were evaluated for demographic (age, sex), pathologic (primary tumor characteristics, metastatic sites), and clinical (treatment type, response to therapy, recurrence, and survival) characteristics. Patients were selected for surgical therapy based on 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 comorbidities 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 previous 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 whose disease was considered unresectable, those with bilobar disease, and/or poor operative candidates. The ablation technology evolved over 20 years, from cryosurgery and ethanol ablation to radiofrequency ablation and more recently, microwave ablation. Response to previous systemic therapy was defined by RECIST (Response Evaluation

Criteria In Solid Tumors) 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 deidentified 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 log-rank test. Cox proportional hazard models were constructed to determine the impact of variables on outcomes. A  $p$  value  $<0.05$  was considered significant.

**RESULTS**

Between 1991 and 2010, among more than 7,500 patients with melanoma, 1,078 patients with melanoma metastatic to the liver have been treated at our institution. Among these, 58 (5.4%) were considered candidates for surgical therapy (resection with or without ablation). Surgical and nonsurgical 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 nonsurgical groups were of cutaneous origin; 16% of surgical patients had ocular primaries as did 11% of nonsurgical 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 extrahepatic, cannot be accurately determined retrospectively for this large cohort. In the surgical group, a mean of 1.8 and median of 1 lesion were 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 nonsurgical group.

Among the surgical patients, 40 underwent resection only, 10 underwent ablation only, and 8 had both ablation and resection. These 3 groups were similar in age and sex distribution (Table 2). There was 1 death within 30 days (1.7%). The surgical intent for all but 4 patients was curative, with palliative procedures being performed primarily to control bleeding ( $n = 2$ ) or compressive symptoms ( $n = 2$ ). The majority of patients were able

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