

Hepatic Metastasis From Uveal Melanoma

Angiographic Pattern Predictive of Survival After Hepatic Arterial Chemoembolization

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Objective: To identify clinical features associated with survival after hepatic arterial chemoembolization (HACE) for uveal melanoma metastasis.

Methods: Retrospective case series including 11 men and 10 women with uveal melanoma metastasis.

Results: The hepatic angiographic pattern of metastasis was infiltrative in 12 patients (57%) and nodular in 9 patients (43%). The infiltrative pattern was associated with ciliary body involvement by the primary tumor (Fisher exact test, $P = .01$) and extrascleral tumor extension (Fisher exact test, $P = .01$). Mean survival after the first HACE treatment was 7.6 months overall, 3.7 months for the patients with the infiltrative pattern, and 12.7 months for those with the nodular pattern. This difference was highly

significant (Kaplan-Meier, $P < .001$). Chromosome 8p was found to be deleted in 4 patients with the infiltrative pattern and in no patients with the nodular pattern.

Conclusions: The hepatic metastasis pattern can be used to predict response to and survival after HACE. Loss of chromosome 8p may be a biomarker for the infiltrative metastasis pattern. Hepatic arterial chemoembolization may play an important role in the treatment of hepatic metastasis from uveal melanoma in patients with the nodular metastatic pattern. Regular screening for hepatic metastasis in patients with uveal melanoma may be beneficial in identifying those who would benefit from HACE.

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UVEAL MELANOMA IS THE most common primary intraocular neoplasm and leads to death due to metastatic disease in as many as half of the patients, with a median survival of 5 to 7 months after the detection of metastasis.¹ Despite improvements in the diagnosis and treatment of the primary tumor, there is no evidence of a concomitant decrease in metastasis or improvement in survival.² Recent work suggests that uveal melanomas often metastasize several years before diagnosis of the primary tumor,³ which would make preventing metastasis an unrealistic goal in the future. Therefore, improved survival will require earlier diagnosis and better treatments for metastatic disease. Indeed, it has been shown that patients with uveal melanoma in whom metastatic disease is diagnosed early by means of a screening examination and those who undergo prompt treatment of their metastatic disease have significantly longer survival than those who do not.⁴

A variety of treatments have been attempted for metastatic uveal melanoma.⁵ Patients with localized hepatic involvement may benefit from hepatic resection, but such patients are rare. Immunotherapy with interleukin 2 or interferon alfa has shown some activity in metastatic cutaneous melanoma but no significant activity in metastatic uveal melanoma.⁶ Systemic chemotherapy has been disappointing; the BOLD regimen (bleomycin sulfate, vincristine sulfate [Oncovin], lomustine, and dacarbazine) combined with interferon alfa is the only regimen to show objective tumor responses, and this has been in a small percentage of patients.⁷ For metastatic disease localized to the liver, intra-arterial infusion of fotemustine or carboplatin has shown disappointing results. On the other hand, hepatic arterial chemoembolization (HACE) with cisplatin, carmustine (1,3-bis[2-chloroethyl]-1-nitrosourea), mitomycin, and other agents has shown promising results, with response rates of up to 40%.⁷⁻¹⁰ We performed the present study to determine whether clinical factors could be

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identified that would predict which patients with metastatic uveal melanoma would benefit most from HACE.

METHODS

PATIENT SELECTION

This study was approved by the institutional review board of Washington University School of Medicine. A retrospective medical record review of sequential patients with liver-dominant metastases from uveal melanoma who were treated with HACE was performed from November 1, 2003, through July 31, 2007. All patients underwent prescreening with contrast-enhanced computed tomography (CT), positron emission tomography fused with CT, or both within 1 month of the initial treatment. Liver functions were evaluated before the procedure. Exclusion criteria for HACE included the presence of significant extrahepatic metastatic disease, severe liver dysfunction (defined as a serum bilirubin level of >3 mg/dL [to convert to micromoles per liter, multiply by 17.104] or hepatic encephalopathy), and main portal vein thrombosis. Informed consent was obtained from all patients before therapy. A minimum of 3 months of follow-up after at least 1 successful HACE session was required for study inclusion. Patients with incomplete medical records or a lack of follow-up were excluded. Results of genetic testing of tumor tissue were available in 9 patients to detect deletion of a metastasis modifier locus on chromosome 8p, and this was performed as previously described.¹¹

HEPATIC ARTERIAL CHEMOEMBOLIZATION

On the day of treatment the laboratory data, including a complete blood cell count, complete metabolic panel, and prothrombin time, were obtained. Standard preprocedural medications included ondansetron hydrochloride (8 mg), dexamethasone sodium phosphate (10 mg), and metronidazole hydrochloride (500 mg). Local anesthesia was obtained with buffered lidocaine hydrochloride, 1%, and sedation was achieved with intravenous midazolam hydrochloride and fentanyl citrate. After sterile preparation and draping, the common femoral artery was accessed with the use of the Seldinger technique. Superior mesenteric angiography was performed through the portal venous phase to evaluate for portal vein patency and flow direction and to detect variant arterial anatomic features. Celiac artery angiography was followed by selection of the right or left hepatic artery with a microcatheter. After confirmation of the appropriate position, HACE was performed with a mixture of cisplatin (50 mg), doxorubicin hydrochloride (50 mg), and mitomycin (10 mg) dissolved in sterile contrast material (ioversol [Optiray 350]; Mallinckrodt Medical, St Louis) and emulsified with ethiodized oil (Ethiodol, Savage Laboratories, Melville, New York). After infusion of the chemotherapeutic agents under fluoroscopic monitoring, embolization was performed with absorbable gelatin sponge slurry (Gelfoam; Pharmacia & Upjohn, Kalamazoo, Michigan) or 300- to 500- μ m polyvinyl alcohol particles mixed in contrast material. Embolization was continued until near-stasis of flow was achieved in the tumor-feeding branches. The decision to use polyvinyl alcohol particles was made by the primary operator (J.E.G. or D.B.B.) at the time of the procedure and was reserved for cases in which feeding arteries were severely pruned owing to prior treatment. The use of the particles did not limit further HACE. One- to 3-mL aliquots of lidocaine hydrochloride, 1%, were intermittently administered intra-arterially during infusion of the chemotherapeutic mixture. Up to 1 lobe was treated per HACE session. If necessary, the contralateral hepatic lobe was treated 4 to 6 weeks after the initial procedure.

After the procedure, patients received maintenance intravenous antiemetics (ondansetron hydrochloride, 8 mg, every 8 hours) and antibiotics (metronidazole hydrochloride, 500 mg, every 12 hours) until discharged from the hospital. Inpatient pain control was achieved with hydromorphone hydrochloride delivered through a patient-controlled anesthesia device. Patients were discharged from the hospital upon satisfactory oral intake and while receiving oral medications to control pain.

Follow-up cross-sectional imaging using contrast-enhanced CT or positron emission tomography fused with CT, was performed approximately 4 to 6 weeks after the treatment of all tumor-bearing branches to evaluate treatment response and to determine the need for additional HACE treatments. Additional HACE procedures were performed if there was residual hepatic disease or evidence of intrahepatic disease progression. Further therapy was withheld if patients developed portal vein thrombosis, liver failure, or extrahepatic disease progression or if the patient declined further treatment. Disease progression, response, and stability were defined according to the response evaluation criteria in solid tumors.¹² Complications were evaluated with the National Cancer Institute's Common Toxicity Criteria for Adverse Events, version 3.0, which is the accepted measurement tool for toxic effects in oncologic studies.¹³

The hepatic angiogram from each HACE procedure was reviewed after treatment by interventional radiologists (J.E.G. and/or D.B.B.) who were masked to information about recurrence, survival, and primary tumor characteristics. Two patterns of metastasis were defined. The nodular pattern was defined as discrete vascularized metastatic foci. The infiltrative pattern was characterized by diffuse vascular irregularity without discrete foci.

STATISTICAL ANALYSIS

Statistical significance was determined using the 2-tailed *t* test for continuous variables, Fisher exact test for categorical variables, and Kaplan-Meier life table analysis for time-dependent variables. We used commercially available software (MedCalc, version 9.5.1.0; MedCalc Software, Mariakerke, Belgium) for all calculations.

RESULTS

METASTASIS

On cross-sectional imaging, all of the patients had bilobar hepatic disease with more than 10 measurable tumors. On review of angiographic images, 2 distinct appearances of hepatic metastatic lesions were identified (**Figure 1**). The nodular pattern, characterized by discrete, well-defined tumor foci, was observed in 9 patients (43%), whereas a diffuse, infiltrative pattern was observed in 12 patients (57%). The appearance of the liver on CT was not predictive of the angiographic appearance.

The mean age at detection of hepatic metastasis was 61.6 years overall, 61.0 years for patients with the infiltrative pattern, and 62.4 years for those with the nodular pattern (*t* test, *P* = .78). The mean number of months from the treatment of the primary eye tumor to the detection of metastasis was 33.1 months overall, 34.6 months for patients with the infiltrative pattern, and 31.0 months for those with the nodular pattern (Kaplan-Meier, *P* = .79). Extrahepatic metastases were detected in 12 of 21 patients (57%) overall, 8 of the 12 patients (67%) with the

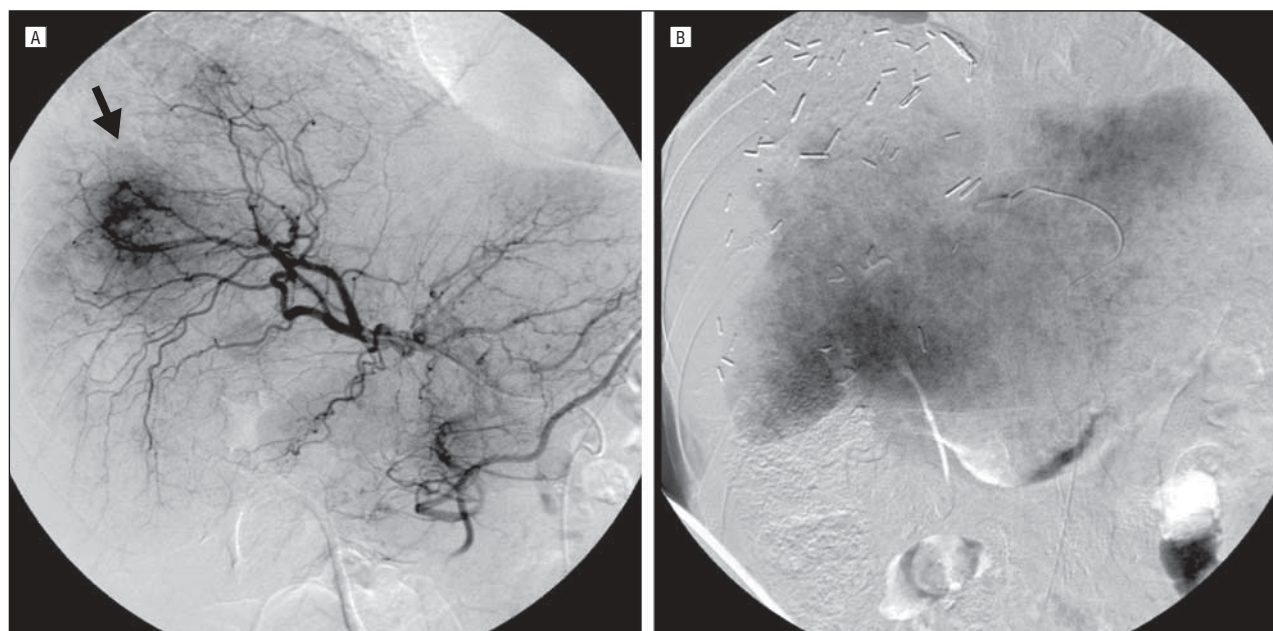


Figure 1. Hepatic angiograms demonstrating the nodular (A) and infiltrative (B) patterns of liver metastasis from uveal melanoma. Relatively discrete areas of contrast enhancement are detected with the nodular pattern (arrow points to 1 large metastasis), compared with the diffuse enhancement with the infiltrative pattern.

Table. Clinical Characteristics in 21 Patients With Uveal Melanoma Who Were Treated With HACE

Patient No./Sex	Metastasis Pattern	No. of HACE Treatments	Age at Ocular Treatment, y	Age at First HACE Treatment, y	Ocular Tumor Treatment	Pathological Ocular Tumor Findings	Extrahepatic Metastasis	Other Treatments for Metastasis
1/F	Infiltrative	2	68	70	Enucleation	Epithelioid	Skin, soft tissue	None
2/F	Infiltrative	2	74	74	Enucleation	Epithelioid	Lung	Chemotherapy
3/M	Infiltrative	1	64	64	Enucleation	Epithelioid	Lung	None
4/M	Infiltrative	2	61	63	Enucleation	Epithelioid	Bone	None
5/M	Infiltrative	2	61	64	Enucleation	Epithelioid	Soft tissue	None
6/M	Infiltrative	1	61	68	Enucleation	Mixed	Bone	None
7/F	Infiltrative	1	24	31	Enucleation	Spindle	None	None
8/F	Infiltrative	3	58	63	Transpupillary thermotherapy	NA	Lymph nodes	None
9/F	Infiltrative	1	61	64	Plaque radiotherapy	NA	None	None
10/M	Infiltrative	3	38	42	Plaque radiotherapy	NA	None	Partial hepatectomy
11/M	Infiltrative	2	60	61	Plaque radiotherapy	NA	None	None
12/M	Infiltrative	3	67	68	Plaque radiotherapy	NA	Bone	None
13/M	Nodular	3	42	54	Enucleation	Epithelioid	Soft tissue	None
14/M	Nodular	5	54	58	Enucleation	Mixed	None	None
15/M	Nodular	3	50	52	Enucleation	Mixed	None	None
16/M	Nodular	4	71	75	Plaque radiotherapy	NA	Lung	Chemotherapy
17/F	Nodular	5	50	51	Plaque radiotherapy	NA	Lymph nodes, lung, pancreas	Radiofrequency ablation
18/F	Nodular	2	65	66	Plaque radiotherapy	NA	None	None
19/F	Nodular	2	64	64	Plaque radiotherapy	NA	Skin, bone	None
20/F	Nodular	1	79	79	Enucleation	NA	None	None
21/F	Nodular	1	62	63	Plaque radiotherapy	NA	None	None

Abbreviations: HACE, hepatic arterial chemoembolization; NA, not available.

infiltrative metastasis pattern, and 4 of the 9 patients (44%) with the nodular pattern (Fisher exact test, $P = .39$).

PATIENT CHARACTERISTICS AND PRIMARY TUMOR FEATURES

Patient characteristics are summarized in the **Table**. Patients in the study included 11 men (7 with the infiltra-

tive pattern and 4 with the nodular pattern) and 10 women (5 with the infiltrative pattern and 5 with the nodular pattern) (Fisher exact test, $P > .99$). The mean age at eye tumor diagnosis was 58.8 years overall, 58.1 years for patients with the infiltrative pattern, and 59.7 years for those with the nodular pattern (t test, $P = .78$). Ciliary body involvement by the primary tumor was present in 8 of 9 patients with the infiltrative pattern and 2 of 9 patients

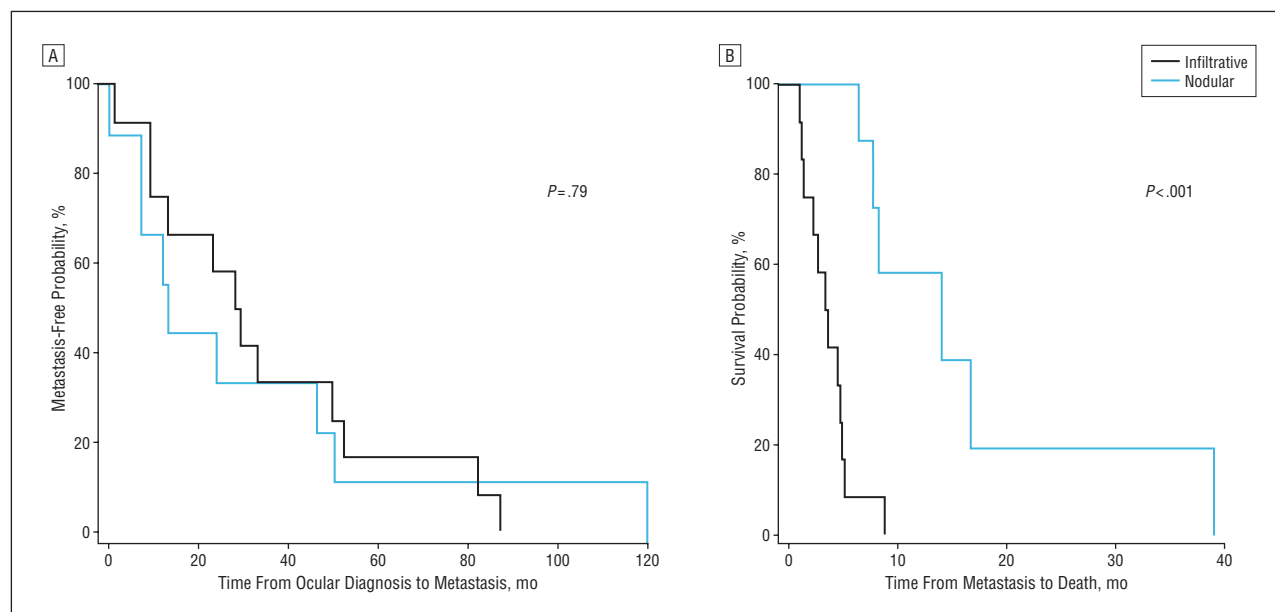


Figure 2. Kaplan-Meier survival plots. These demonstrate the relationship between angiographic pattern of liver metastasis and the time from the diagnosis of ocular tumor to liver metastasis (A) and the time from metastasis/hepatic arterial chemoembolization to death due to metastatic disease (B).

with the nodular pattern (Fisher exact test, $P = .01$) and was undetermined in the remaining 3. The largest mean basal dimension of the primary tumor was 17.0 mm overall, 18.5 mm for patients with the infiltrative pattern, and 15.5 mm for patients with the nodular pattern (t test, $P = .15$). The mean thickness of the primary tumor was 7.9 mm overall, 9.2 mm for patients with the infiltrative pattern, and 6.6 mm for patients with the nodular pattern (t test, $P = .09$). Treatment of the primary tumor was enucleation in 11 patients, plaque radiotherapy in 9, and transpupillary thermotherapy in 1. Pathological information was available for 10 of the 11 tumors treated by means of enucleation. The cell type was epithelioid in 5 cases with the infiltrative metastasis pattern and in 1 with the nodular pattern and was spindle/mixed cell type in 2 cases with the infiltrative pattern and 2 cases with the nodular pattern (Fisher exact test, $P = .6$). Extrascleral tumor extension was present in 4 of 7 cases with the infiltrative pattern and none of 4 cases with the nodular pattern (Fisher exact test, $P = .01$).

HEPATIC ARTERIAL CHEMOEMBOLIZATION

The mean age at the first HACE treatment was 61.6 years overall, 61.0 years for patients with the infiltrative pattern, and 62.4 years for those with the nodular pattern (t test, $P = .79$). The mean number of treatments was 2.3 overall (range, 1-5), 1.9 for patients with the infiltrative pattern, and 2.9 for those with the nodular pattern (t test, $P = .02$). The mean time from diagnosis of the ocular tumor to liver metastasis was 33.1 months overall, 34.6 months for patients with the infiltrative pattern, and 31.0 months for those with the nodular pattern (Kaplan-Meier, $P = .79$). The mean survival time after the first treatment was 7.6 months overall, 3.7 months for patients with the infiltrative pattern, and 12.7 months for those with the nodular pattern (Kaplan-Meier, $P < .001$) (**Figure 2**). Additional treatments undertaken for metastasis after

HACE therapy included chemotherapy (2 patients), partial hepatectomy (1 patient), and radiofrequency ablation (1 patient). In 9 patients, genetic testing of the primary tumor had been performed before treatment to analyze the status of chromosome 8p. A metastatic modifier locus that we previously described¹¹ was deleted in 4 patients with the infiltrative pattern and no patients with the nodular pattern (Fisher exact test, $P = .17$).

COMMENT

We have identified 2 patterns of hepatic metastasis from uveal melanoma defined by hepatic angiography: a nodular pattern in 43% of patients and an infiltrative or a diffuse pattern in 57% of patients. The angiographic pattern of liver metastasis was strongly predictive of survival after HACE. Patients with the nodular pattern exhibited a 1-year survival after HACE of 58% vs 0% for those with the infiltrative pattern, and the difference in overall survival was highly significant (Kaplan-Meier, $P < .001$). The angiographic pattern did not predict the time to metastasis after diagnosis of the ocular tumor. Future studies will be required to determine whether CT or other cross-sectional imaging can also be used for identifying these prognostically significant metastatic patterns.

This study also provided potentially important insights into the biological features of hepatic metastasis from uveal melanoma. With the exception of ciliary body involvement and extrascleral tumor extension, none of the well-established clinicopathological prognostic factors was associated with the pattern of hepatic metastasis, suggesting that the factors determining whether metastasis will occur may be different from those that determine the pattern of metastasis once tumor cells reach the liver. We recently identified a metastasis modifier locus on chromosome 8p, containing the metastasis suppressor gene *LZTS1*.¹¹ Deletion of

this locus is associated with more aggressive tumor cell behavior such as increased migratory and invasive capacity. Although 8p status was available in only 9 patients, there was an intriguing trend for 8p loss to occur in patients with the infiltrative metastasis pattern. It is interesting to speculate that this 8p deletion may be causally related to the infiltrative pattern by conveying an increased ability to migrate and invade hepatic tissue. Further studies are under way to determine whether this association can be verified in a larger number of patients. If this association can be substantiated, 8p status could potentially be used as a clinical test for predicting the response to HACE.

CONCLUSIONS

This study supports a potential role for HACE in the treatment of metastatic uveal melanoma confined to the liver, and it identifies a subset of cases with a nodular metastatic pattern that are most likely to benefit. These findings suggest that regular metastatic monitoring of patients with uveal melanoma after treatment of the primary tumor may be beneficial in detecting metastasis as early as possible. The prognostically significant liver metastasis patterns may be of benefit to clinicians in counseling patients regarding their likely response to HACE and their prognosis. Weaknesses of the study include the small study size and lack of randomization. However, the promising findings of the study indicate the need for a larger study to test these findings. If a larger study confirms the benefit of HACE, this would support the regular screening of patients with uveal melanoma for hepatic metastasis after treatment of the primary tumor.

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