Magnetic Resonance Screening Trial for Hepatic Metastasis in Patients with Locally Controlled Choroidal Melanoma

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Objective: The aim of the present study was to evaluate the value of magnetic resonance (MR) screening for detection of hepatic metastasis in patients with locally controlled choroidal melanoma.

Methods: MR examinations were performed after an initial diagnosis of choroidal melanoma in 159 patients (mean age 56 years; range, 10–86 years). The MR follow-up interval was 5.2 ± 1.7 years (range, 1.2–6.6 years). A total of 363 MR studies were reviewed by two radiologists for predominant signal intensity characteristics. Hepatic metastasis was verified by histological examination: tumor resection and CT-guided needle biopsy specimens and/or on the basis of an obvious progression in number and/or size of the lesions on the follow-up MR examination.

Results: The majority of patients underwent MR examinations from one to three times (n = 126, 79%). During a mean follow-up period of 5.7 years, a focal abnormality in the liver was found in 20 patients (13%). Of these, 15 patients (9%) were diagnosed as having hepatic metastasis. The number of the metastatic lesions with a short T1 and short T2 pattern were one (n = 1, 9%), two (n = 2, 18%), three (n = 1, 9%) and multiple (n = 7, 63%). The focal abnormalities of MR examinations in five other patients consisted of vascular artifacts (n = 3, 15%) and cysts with hemorrhage (n = 2, 10%).

Conclusions: The screening of MR examinations detected hepatic metastasis in 15 of 159 patients (9%) with locally controlled choroidal melanoma.

Key words: choroidal melanoma – metastasis – MRI – screening

INTRODUCTION

Choroidal melanoma most often metastasizes to the liver, followed by the lung, skin, and bone. Of these, hepatic metastasis from choroidal melanoma is predictive of a poor outcome, as its overall 10-year survival rate remains 70% (1). Thus, an adequate screening plan is desirable for patients with choroidal melanoma to enable early detection of hepatic metastasis in its early stage, when the patients have no symptoms and clinical laboratory tests results may still be within normal range.

Early detection of hepatic metastases by non-invasive imaging can have a critical impact on the treatment planning and survival (2–5). The imaging modalities used for assessment of hepatic metastases include ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) and [F-18] fluorodeoxyglucose (¹⁸FDG) positron emission tomography (PET). Kuan and colleagues (2) found that CT would be more sensitive for detection of metastatic melanoma than ultrasound in a comparative study of diagnostic performance. However, CT has limited specificity for detection of hepatic metastasis and is not sensitive enough to be used in screening for melanotic lesions in the early stage. Semelka and colleagues (3) suggested that contrast-enhanced dynamic MRI would be more sensitive for detecting focal hepatic metastasis than contrast-enhanced dynamic CT. Although MRI is a superior imaging technique for detection of hepatic metastasis compared with CT, the diagnostic accuracy of detecting hepatic metastasis using magnetic resonance (MR) screening has not been determined to our knowledge.

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MR features of melanotic lesions typically have shortened T1 and T2 relaxation times, and the presence of T1 shortening is closely correlated with the melanin content of the lesion (6,7). Shortened T1, which represents high signal intensity on T1-weighted images, is often observed in various histologic types of tumors (8). The causes of T1 shortening include the presence of fat, hemorrhage and high protein content other than melanin. However, these causes are considered extremely rare when we stratified by patients with hepatic metastasis of melanoma and short T1 pattern may be a characteristic finding in hepatic metastasis of melanoma.

The aim of the present study was to evaluate the value of MR screening for detection of hepatic metastasis in patients with locally controlled choroidal melanoma. We hypothesized that patients with choroidal melanoma might harbor occult melanotic metastases of the liver that require further treatment if MRI studies identified them.

PATIENTS AND METHODS

PATIENTS

A total of 159 patients with locally controlled choroidal melanoma that had undergone ocular and systemic examinations as well as MRI screening for hepatic metastasis in our institution were identified retrospectively between January 2000 and December 2005. All patients received enucleation and proved to have melanotic melanoma by histological examination. Additional treatment contained laser surgery (n = 40, 25%) and radiotherapy (n = 26, 16%).

A screening of MR examinations was performed annually after the initial presentation, and the follow-up time was 5.2 ± 1.7 years (mean ± SD; range, 1.2–6.6 years). The patient population included 63 females (40%) and 96 males (60%) who ranged in age from 10 to 86 years (mean age, 56 years). The number of MR examinations per patient is shown in Table 1. Clinical information was extracted from the patient files regarding patient age, gender, symptoms, treatment, associated conditions and final disease status. Informed consent was obtained from all patients.

IMAGING STUDIES

MR imaging was performed using 1.5-T units (Signa; General Electric Medical Systems, Milwaukee, WI and Visart; Toshiba Medical Systems, Tokyo, Japan). T1- and T2-weighted images were obtained in the transverse and coronal planes by using a body coil. T1-weighted gradient-echo images with fat saturation were obtained in coronal and axial planes by using a 24–30 cm field of view, 7–9 mm section thickness, 105–139/1–4 (repetition time ms/echo time ms, [TR/TE]), 224–256 × 256 matrix, two signals acquired. T2-weighted fast spin-echo acquisitions with fat saturation were performed in the axial plane by using a 24–35 cm field of view, 8–9 mm section thickness, 2050/120 (effective repetition time ms/effective echo time ms, [TR eff/TE eff]), 224–256 × 256 matrix, two signals acquired. T2-weighted single shot fast spin-echo acquisitions were performed in coronal plane by using a 24–30 cm field of view, 8–9 mm section thickness, 21700–23700/80, 224–256 × 256 matrix, one signal acquired. Intravenous administration of contrast material (gadopentate dimeglumine, 0.1 mmol/kg) was performed. Contrast-enhanced T1-weighted gradient-echo images with fat saturation were obtained in coronal and axial planes by using a 24–30 cm field of view, 7–9 mm section thickness, 105–139/1–4, 224–256 × 256 matrix, two signals acquired.

MR studies of each hepatic lesion were reviewed by two diagnostic radiologists by consensus. MR images were evaluated for predominant signal intensity characteristics (low, intermediate, high). Low signal intensity was defined as signal intensity that was less than that of normal liver parenchyma, intermediate signal intensity as similar to that of normal liver parenchyma and high signal intensity as greater than that of normal liver parenchyma.

MR findings of hepatic metastasis were classified into three groups: a short T1 and short T2 pattern, short T1 and long T2 pattern, and an indeterminate pattern. A short T1 and short T2 pattern was assigned when the lesion showed focal high signal intensity relative to adjacent normal liver parenchyma and focal low signal intensity relative to adjacent normal liver parenchyma on T2-weighted images.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>mean ± SD 56 ± 14 range 10–86</td>
</tr>
<tr>
<td>Gender</td>
<td>female 63 (40) male 96 (60)</td>
</tr>
<tr>
<td>Primary site</td>
<td>right eye 83 (52) left eye 76 (48)</td>
</tr>
<tr>
<td>No. of MR examinations per patient</td>
<td>1 60 (38) 2 29 (18) 3 37 (23) 4 31 (19) 5 2 (1)</td>
</tr>
<tr>
<td>Follow-up, years</td>
<td>mean ± SD 5.2 ± 1.7 range 1.2–6.6</td>
</tr>
</tbody>
</table>

SD, standard deviation; MR, magnetic resonance.
*The numbers in parentheses are percentages.
pattern was assigned when the lesion showed low signal intensity on fat-saturated T1-weighted images, high signal intensity on T2-weighted images, and heterogeneous enhancement on contrast-enhanced T1-weighted gradient-echo with fat saturation images. An indeterminate pattern was assigned when the MR findings did not conform to those of either of the other two patterns. In these lesions, follow-up MR examination was performed 6 months later and re-evaluated.

The assessment of hepatic metastasis was confirmed by histological examination: tumor resection \((n = 1)\) and CT-guided needle biopsy \((n = 1)\) and/or by an obvious progression in number and/or size of the lesions on the follow-up examinations \((n = 13)\). The surgical procedure or biopsy was performed within two weeks (mean 7 days) after the MR examination.

**Statistical Analysis**

Clinical variables, including age, follow-up duration and size of the lesion, were compared by means of the two-tailed Student’s \(t\) test with two-sample equal variance. Survival was calculated for one dependent endpoint. The primary endpoint was overall survival (OS) defined as the number of months between the date of the initial MR examination and the date the patient was known to be alive. Any death from any cause was considered a failure. Univariate analysis was performed by comparing Kaplan–Meier survival curves and carrying out log-rank tests. All analyses were conducted using software package SPSS 12.0J (SPSS, Chicago, IL). Differences and correlations at a \(P\) value of \(< 0.05\) were considered statistically significant.

**RESULTS**

Screening of MR examinations was performed in 159 patients with locally controlled choroidal melanoma, which yielded 363 MR studies for data analysis (Table 1). The majority of patients underwent MR examinations one to three times \((n = 126, 79%)\). During a mean follow-up of 5.7 years, focal abnormality in the liver was found in 20 patients \((13%)\).

Fifteen patients \((9%)\) were diagnosed with hepatic metastasis \(63.0 \pm 47.1\) months \((\text{mean} \pm \text{SD} ; \text{range, } 4.0–145.4\text{ months})\) after the initial treatment. Of these, one patient had a symptom of the right hypochondralgia. Laboratory test results were within normal range in all 15 patients. The hepatic metastasis measured \(15 \pm 4\) mm in diameter \((\text{range, } 11–23\text{ mm})\). In 11 of 15 patients \((73%)\), hepatic lesions exhibited the short T1 and short T2 pattern. The numbers of metastatic lesions were: one \((n = 1, 9%)\), two \((n = 2, 18%)\), three \((n = 1, 9%)\), and multiple \((n = 7, 63%)\). Of the eleven patients, three \((15%)\) had also extrahepatic metastases, including lung \((n = 2)\) and spine \((n = 1)\; \text{(Fig. 1)}, \text{which were precisely detected by chest radiograph and spinal MR imaging}. \text{In the other four of 15 patients (27%), hepatic metastasis was a solitary lesion and exhibited a short T1 and long T2 pattern.}\)

In five of 20 patients \((25%)\) with a non-metastatic abnormality in the liver on MR images, the lesion was solitary and was categorized as of indeterminate pattern. The size of focal abnormality was \(11 \pm 2\) mm \((\text{range, } 8–13\text{ mm})\), and was significantly smaller than those with hepatic metastasis \((p = 0.017)\). The initial follow-up MR examination was performed after 6 months in all five patients. In three of them, focal abnormality in the liver disappeared and was assumed to have been a vascular artifact. The signal characteristics in two patients changed and they were concluded to have been false positive MR findings produced by hepatic cysts. On the further follow-up MR images, no change was found in these two patients.

Fifteen patients with hepatic metastasis received transarterial embolization (TAE) using cisplatin \((n = 12, 80%)\), TAE + chemotherapy \((n = 2, 13%)\), and surgical resection + chemotherapy \((n = 1, 7%)\). Thirteen patients \((87%)\) died of their disease (DOD), one \((7%)\) was alive with disease (AWD) and one \((7%)\) had no evidence of disease (NED). Of the 144 patients without hepatic metastasis, 143 patients \((99%)\) had NED. However, the other patient \((1%)\) developed brain metastasis that was identified on brain MRI (Table 2). The 5-year overall survival rate of the patients with hepatic metastasis was 52% \((95%\text{ confidence interval, } 28–76%)\). This was significantly shorter than among the patients without hepatic metastasis \((100%, \ P < 0.001, \text{Fig. 2})\).

**DISCUSSION**

Early detection of hepatic metastasis has potentially significant implications for the management of patients with choroidal melanoma. Although it is generally accepted that MR imaging is superior as an imaging technique for detecting
Melanotic lesions typically cause T1 and T2 shortening, producing high signal intensity on T1-weighted images and low signal intensity on T2-weighted images. This may be attributable to a cytoprotective function as a paramagnetic intracellular scavenger of free metals. A majority of tumor lesions which exhibit a typical MR signal pattern have a high melanin content. However, this correlation depends on the anatomic location of the lesions. Demonstrating the MR signal characteristics of melanotic lesions enables us to detect early hepatic metastasis in screening settings. Other than a typical short T1 and short T2 pattern, metastatic lesions exhibit a short T1 and long T2 pattern or mixed pattern on MRI. In our study, such lesions were detected in four of the 15 patients (27%) and showed heterogeneous enhancement on contrast-enhanced MR images. When atypical MR signal characteristics exist for lesions with a short T1 and long T2 pattern, additional contrast-enhanced MR study is an effective screening method.

18FDG PET is being successfully used in patients with malignant melanoma. 18FDG PET may be a better method of detecting hepatic metastasis in patients with choroidal melanoma compared with conventional imaging. However, a few studies have shown no significant difference between 18FDG PET and MRI or CT with regard to detection of hepatic metastasis. 18FDG PET has limited spatial resolution for localization of areas of increased glucose metabolism. Gulec et al. found that the sensitivity, specificity, positive predictive value, negative predictive value and accuracy for detection of metastasis larger than 10 mm were 100, 75, 97, 97 and 100%, respectively, as opposed to smaller than 10 mm that were 13, 33, 17, 50 and 7%, respectively. In the present study, screening of MR examinations detected hepatic metastases that measured 15 ± 4 mm (mean ± SD; range 11–23 mm). Our results suggest that screening MRI can detect early hepatic metastasis precisely when stratified by lesion size around 10 mm, but that false negatives will increase regarding lesions less than 10 mm. Considering higher resolution and signal characteristics, MR is expected to be effective in detection of early hepatic metastases in patients with choroidal melanoma in screening settings.

In our study, the early identification of hepatic metastasis using screening of MR examinations was accomplished in 9% of the patients with locally controlled choroidal melanoma. However, there was a spectrum of disease ranging from a single lesion to multiple lesions that included extrahepatic metastasis. The majority of patients underwent MR examinations from one to three times, and four or more scans were performed in 20% of the patients. Although metastasis from choroidal melanoma usually becomes manifest within the first 5 years after diagnosis, it sometimes becomes manifest decades later. Predictive factors for shorter time to metastasis have been found to be older age over 60 years, male gender and tumor diameter greater than 10 mm, and late metastasis may be attributable to the

### Table 2. Patient characteristics with hepatic metastasis and without hepatic metastasis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hepatic metastasis (+)</th>
<th>Hepatic metastasis (−)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>15 (9)</td>
<td>144 (91)</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
<td>55 ± 11</td>
<td>56 ± 15</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>9 (6)</td>
<td>54 (34)</td>
</tr>
<tr>
<td>male</td>
<td>6 (3)</td>
<td>90 (57)</td>
</tr>
<tr>
<td>Follow-up, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
<td>4.7 ± 1.6</td>
<td>5.3 ± 1.7</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAE</td>
<td>12</td>
<td>N/A</td>
</tr>
<tr>
<td>TAE + chemotherapy</td>
<td>2</td>
<td>N/A</td>
</tr>
<tr>
<td>Surgery + chemotherapy</td>
<td>1</td>
<td>N/A</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOD</td>
<td>13 (8)</td>
<td>0</td>
</tr>
<tr>
<td>AWD</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>NED</td>
<td>1 (1)</td>
<td>143 (90)</td>
</tr>
</tbody>
</table>

SD, standard deviation; TAE, transarterial embolization; N/A, not available; DOD, dead of disease; AWD, alive with disease; NED, no evidence of disease. *The numbers in parentheses are percentages.

![Kaplan–Meier estimate of overall survival according to the presence of hepatic metastasis. Solid line: hepatic metastasis (−), dash line: hepatic metastasis (+). Patients without hepatic metastasis had a longer overall survival time than those with hepatic metastasis (P < 0.001).](https://academic.oup.com/jjco/article-abstract/37/4/282/969544)
long doubling time of melanoma cells (15). The MR screening schedule must be devised with factors associated with increased risk of hepatic metastasis in patients with choroidal melanoma.

Our study has several limitations that may have potentially affected the results. Although we discovered hepatic metastasis in 15 of 159 patients (9%), pathological verification of hepatic metastasis was performed in only two of 15 patients (13%). T1-shortening effects on T1-weighted images may be caused by extracellular methemoglobin, fat, and high content of protein besides melanin. Such lesions often contain malignant hepatic lesions: hepatocellular carcinoma, multiple myeloma, carcinoid, metastatic tumors from ovary, colon and pancreas (8). All 15 patients with hepatic metastasis in our study have received TAE, chemotherapy or surgery and followed-up after treatment. Another limitation of our study is that annual MR screening was performed in patients with locally controlled choroidal melanoma without clinical suspicion. Further validation study is needed to clarify the role of MR imaging in the detection of early hepatic metastasis in patients with locally controlled choroidal melanoma.

In conclusion, the results of our study indicate that screening annual MR examinations detects hepatic metastasis in patients with choroidal melanoma. The MR screening schedule has to be designed with risk factors and further validation study is needed to clarify the role of MR imaging studies in early detection of hepatic metastasis in patients with locally controlled choroidal melanoma.

Acknowledgments

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Conflict of interest statement

None declared.

References