Characterization of Computed Tomography Scan Abnormalities in Patients With Biopsy-Proven Hepatic Metastases From Uveal Melanoma

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Objectives: To describe the computed tomography (CT) features in patients with biopsy-proven hepatic metastases of uveal melanoma and correlate these findings with survival.

Methods: The medical records of patients with uveal melanoma evaluated at Memorial Sloan-Kettering Cancer Center from January 1998 to September 2009 were reviewed. Inclusion criteria were biopsy-proven liver metastasis and CT scan images available within 2 months of biopsy. Exclusion criteria were prior systemic or liver-directed therapy for uveal melanoma. Statistical analyses were carried out using the t test, \( \chi^2 \) test, and Kaplan-Meier log-rank analyses.

Results: Of 505 medical records reviewed, 76 were selected for study. Characteristic CT findings included multiple (68 patients [90%]), hypodense (100%), heterogeneous (100%), and enhancing (100%) hepatic lesions with a mean dominant lesion size of 46.8 cm\(^2\). Eighteen patients (24%) exhibited hepatomegaly. Predominant lesion size larger than 100 cm\(^2\), hepatomegaly, and ascites correlated with a lower survival rate (\( P = .008 \), \( P < .001 \), and \( P < .001 \), respectively). Radiographic evidence of extrahepatic metastases was present in 40 patients (53%). However, the presence of extrahepatic metastases did not affect survival. The results of at least 1 liver function test were abnormal in 46 of 67 patients (69%), and elevation of at least 1 serum transaminase and elevation of alkaline phosphatase were associated with larger lesions (\( P = .009 \) and \( P = .004 \), respectively) and hepatomegaly (\( P < .001 \) for both).

Conclusions: Radiographic evidence of predominant lesion size larger than 100 cm\(^2\), hepatomegaly, and ascites—but not radiographic evidence of extrahepatic metastases—correlate with a lower survival rate in patients with biopsy-proven hepatic metastases of uveal melanoma.

Arch Ophthalmol. 2011;129(12):1576-1582

Uveal melanoma is the most common primary intraocular malignant neoplasm in adults, with an annual incidence of 6 cases per million. The natural history of uveal melanoma is characterized by the frequent development of metastatic disease. It is thought that micrometastases often occur before diagnosis and local control of the primary tumor. Most commonly, metastases are initially identified in the liver, with a significant percentage of patients (>50% in some studies\(^{14} \)) developing liver metastases at any time from the diagnosis of the primary neoplasm to decades later. In patients who died of uveal melanoma, almost all had liver involvement.\(^7\)

Given the high rate of metastasis, ten decades after identification of the uveal melanoma, there has been significant interest in identifying tools for diagnosing metastatic disease in patients with uveal melanoma. Previous studies have shown that liver function tests (LFTs) are a poor surveillance tool. The Collaborative Ocular Melanoma Study (COMS) group reported that, although the specificity of LFTs in detecting hepatic metastases of uveal melanoma is 92.3%, sensitivity is exceedingly low at 14.7%.\(^8\)

On the basis of these findings, imaging might provide a better, more sensitive tool for diagnosing metastatic disease.\(^9\)\(^{13}\) Although imaging practices vary widely, oncology specialists have been turning increasingly to computed tomography (CT) scans. We recently reported on a retrospective study detailing the findings from CT scans done within 1 month of primary uveal melanoma diagnosis in 91 patients at Memorial Sloan-Kettering Cancer Center (MSKCC). Fifty of these 91 patients (55%) had 1 or more hepatic abnormality identified on CT scan. Of these, 6 patients exhibited lesions suspicious for metastatic melanoma, although metastatic disease was subsequently confirmed in only 3 patients.
The medical records of 505 patients with uveal melanoma referred to MSKCC between January 1998 and September 2009 were reviewed. The information noted included sex, date of birth, date of diagnosis of the primary uveal melanoma, therapy of the primary uveal melanoma, date of hepatic metastasis biopsy, and date of the CT.

Patients with biopsy-proven hepatic metastases and CT scans available within 2 months of biopsy were included in the study. Patients whose CT scans were performed at an outside institution were included if the images were available in our medical record. Patients who had received systemic or hepatic therapy for uveal melanoma were excluded. This retrospective study was conducted with approval by MSKCC’s institutional review board.

All scans were evaluated by a radiologist specializing in oncology. Scans performed at an outside institution were reviewed by one of us (C.B.W.). The type of CT scan performed (contrast vs noncontrast, triphasic vs nontriphasic) was recorded. Lesions were classified as solitary or multiple. Multiplicity was defined as the presence of at least 1 lesion in addition to the biopsied lesion that exhibited features characteristic of metastatic disease, including heterogeneity and/or growth over time. For scans showing multiple lesions, the maximal bidirectional dimensions of the largest lesions were determined. Lesions were subjectively categorized as hypodense or not hypodense. In scans conducted with intravenous contrast, a subjective assessment of heterogeneity and enhancement was performed. The presence or absence of hepatomegaly, ascites, vascular invasion, hemorrhage, and biliary dilatation was also recorded.

The CT scans were also evaluated for extrhepatic spread of disease. Features of lesions suggestive of metastatic disease included heterogeneity or growth over time. For lymph nodes, only those larger than 1 cm were included. For lesions that were difficult to classify as benign vs. malignant, careful comparisons were made with previous and subsequent imaging to detect marked growth consistent with malignancy.

Liver function tests, including aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin, were recorded for patients whenever available within 2 months of the CT. The reference ranges for these tests in our laboratory were 10 to 37 U/L, 5 to 37 U/L, 0 to 115 U/L, and 0 to 1 mg/dL, respectively. (To convert aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase to microkatal per liter, multiply by 0.0167; to convert bilirubin to micromoles per liter, multiply by 17.104.)

The 2-tailed t test and χ² analysis (1 df) were performed. Survival studies were conducted using Kaplan-Meier curves with log-rank analysis. For all statistical analyses, P < .05 was considered to be significant.

Methods

The 505 patients evaluated at MSKCC for uveal melanoma between January 1998 and September 2009, 139 patients (27.5%) had biopsy-proven liver metastases. This rate of metastatic disease in the overall patient population likely reflects the fact that MSKCC is a tertiary care center for cancer. A significant number of the 505 patients evaluated were suspected to have metastatic disease on the basis of clinical symptoms or radiography and had been referred to MSKCC for further evaluation and disease management. Seventy-six of the 139 patients had biopsy-proven liver metastases with CT scans available within 2 months of the biopsy and no prior systemic or liver-specific therapy for uveal melanoma (Figure 1). These 76 patients were included in our study.

Patient Selection

Of the 505 patients evaluated at MSKCC for uveal melanoma between January 1998 and September 2009, 139 patients (27.5%) had biopsy-proven liver metastases. This rate of metastatic disease in the overall patient population likely reflects the fact that MSKCC is a tertiary care center for cancer. A significant number of the 505 patients evaluated were suspected to have metastatic disease on the basis of clinical symptoms or radiography and had been referred to MSKCC for further evaluation and disease management. Seventy-six of the 139 patients had biopsy-proven liver metastases with CT scans available within 2 months of the biopsy and no prior systemic or liver-specific therapy for uveal melanoma (Figure 1). These 76 patients were included in our study.

Patient Characteristics

Of the 76 patients in this study, 36 were women and 40 were men. The mean age at diagnosis of the primary uveal melanoma was 58.1 years (range, 23-85 years). The mean time from diagnosis of that malignant neoplasm to the development of liver metastases was 5.5 years (range, 0-33.2 years).

Of the 76 patients, liver metastasis was identified in 1 patient before the uveal melanoma was diagnosed and liver metastasis was identified in 4 patients from CT scans conducted at the time of diagnosis of the primary uveal melanoma. Of the remaining 71 patients in whom metastatic disease was found after diagnosis of the primary uveal melanoma, 39 had previously received enucleation and 32 received only local therapies (radiation plaques, laser, and/or proton beam therapy).
At the time of this study, 7 patients were living and 69 had died. The mean time from diagnosis of the primary uveal melanoma to death was 6.2 years (range, 5 months to 34.5 years), and the mean time from diagnosis of metastatic disease to death was 10.1 months (range, 16 days to 4.4 years). The mean age at death was 64.5 years (range, 27-86 years).

**CT CHARACTERISTICS OF LIVER METASTASES**

The CT scans evaluated were performed a mean of 2.4 days before the biopsy (range, 47 days before to 58 days after). In all cases, a CT scan was conducted before the biopsy. However, in some cases, this scan was performed at an outside hospital, and the first available CT scan in our hospital system occurred shortly after the biopsy but within the specified period. Of the 76 scans, 6 were noncontrast (8%). Sixteen scans (21%) were triphasic. Fifty-four scans (71%) included imaging of the chest; 22 scans (29%) did not.

Eight patients (11%) had a solitary liver metastasis shown on CT scan, and 68 patients (90%) had multiple hepatic lesions (Figure 2A). Multiplicity was defined as the presence of at least 1 lesion in addition to the biopsied mass that exhibited features of metastatic disease, such as heterogeneity or growth. However, without biopsies of each of these lesions, it cannot be demonstrated conclusively that they represented metastatic disease. Of the 8 cases of solitary metastasis identified on CT scans, magnetic resonance imaging (MRI) performed in 2 patients at the time of the CT showed multiple lesions. The CT scan for another patient was limited by lack of contrast. The remaining 5 patients had no contemporaneous MRIs, although 4 had additional imaging, such as ultrasonography or positron emission tomography (PET) scans, that showed no other lesions suspicious for metastatic disease. Log-rank analysis of Kaplan-Meier survival curves revealed no significant difference in survival between patients with multiple lesions and those with solitary lesions shown on CT ($P = .96$, Figure 3). Even when patients with multiple lesions identified on MRI were excluded, there was no survival benefit ($P = .99$).

All lesions considered to be metastatic by the imaging tools were hypodense. All scans conducted with contrast exhibited heterogeneity and subjective features of enhancement (Figure 2A). The mean 2-dimensional area of the largest metastasis was 46.8 cm$^2$ (range, 0.7-245.2 cm$^2$). Kaplan-Meier analysis revealed better survival in patients whose dominant lesion was smaller than 100 cm$^2$ than in those whose dominant lesion was larger (median survival, 222 vs 53 days, $P = .008$ by the log-rank test, Figure 4). The hazard ratio for death was 0.31 for those whose dominant lesion was smaller than 100 cm$^2$ (95% confidence interval, 0.13-0.73).

Initial evaluation of 1 patient identified tumor encasement of vasculature; a later CT scan showed tumor invasion, resulting in a tumor thrombus extending up the inferior vena cava into the right atrium (Figure 2A-F). In another patient with an initial diagnosis of tumor encasement of the portal vasculature, ultrasonography later demonstrated tumor thrombus. Only 3 patients (4%) exhibited biliary dilatation at the time of diagnosis of the liver metastases, and all 3 of these individuals also exhibited compression of the portal or hepatic vessels.

Two CT scans (3%) showed hemoperitoneum; one of these scans was performed in the first patient described in the preceding paragraph. Another patient had coagulopathy presumed to be secondary to extensive involvement of the liver. The CT scan of 1 patient (1%) showed intratumoral bleeding at the time of initial diagnosis of the liver metastasis. This patient did not have coagulopathy on the basis of coagulation times and platelet count. None of these 3 patients with bleeding had undergone invasive procedures within 2 months of the bleeding, and none was receiving an anticoagulant. All these patients had much shorter survival than the mean survival from time of diagnosis of the liver metastases, but given the small number of cases, this was not statistically significant.

Eighteen patients (24%) exhibited hepatomegaly at the time of diagnosis of the liver metastases. Those without hepatomegaly demonstrated on CT scans at the time of diagnosis of liver metastases had significantly better survival compared with those with hepatomegaly, as determined by Kaplan-Meier analysis (median, 276.0 vs 43.5 days, $P < .001$ by log-rank analysis, Figure 5). The hazard ratio for death was 0.008 in patients without hepatomegaly (95% confidence interval, 0.002-0.024).

Eleven patients (15%) had ascites shown on imaging, and these patients fared worse than those without ascites (median survival, 57 vs 222 days, $P < .001$ by log-rank analysis, Figure 6). The hazard ratio for death was 0.008 for patients without ascites (95% confidence interval, 0.002-0.033).

**CT EVIDENCE OF EXTRAHEPATIC METASTASES**

Forty patients (53%) exhibited radiographic evidence of extrahepatic metastases at the time of diagnosis of the liver metastases, most commonly in the lungs (17 patients [31%]) and lymph nodes (21 [28%]). Of note, the calculation for percentage of patients with lung metastases is based only on those whose scans included chest imaging. Other sites with radiographic evidence of disease at the time of diagnosis of the liver metastasis included bone, peritoneum, subcutaneous tissues, retroperitoneum, adrenal glands, pancreas, soft tissues, pericardium, thyroid, spleen, and gallbladder (Table). Kaplan-Meier analysis indicated no significant difference in survival between patients with and those without radiographic evidence of extrahepatic metastases at the time of diagnosis of the liver metastasis ($P = .54$ by log-rank analysis, Figure 7).

**LIVER FUNCTION TESTS**

Liver function test results were available within 2 months of the CT scan for 67 patients (88%). Among those patients, 46 (69%) had an abnormality in at least 1 LFT. More specifically, 37 (55%) had elevation in concentrations of aspartate aminotransferase, alanine aminotransferase, or both; 29 (43%) had elevated alkaline phosphatase; and 22 (33%) had elevated bilirubin.

The size of the radiographically dominant lesion was significantly larger in patients with elevated transaminase concentrations than in patients without (mean [SD],...
59.8 [9.7] cm² and 27.1 [6.2] cm², respectively; \( P = .009 \) by unpaired \( t \) test), as well as in patients with elevated alkaline phosphatase than in those without (64.9 [11.6] cm² and 29.2 [5.2] cm², respectively; \( P = .004 \) by unpaired \( t \) test). There was no relationship between having an elevated bilirubin concentration and the size of the dominant lesion (\( P = .87 \) by unpaired \( t \) test).

Radiographic evidence of hepatomegaly was associated with an increased likelihood of elevated transaminase concentrations (\( P < .001 \) by \( \chi^2 \) analysis), as well as an increased likelihood of elevated alkaline phosphatase (\( P < .001 \) by \( \chi^2 \) analysis). There was no association between hepatomegaly and having an elevated bilirubin concentration (\( P = .13 \) by \( \chi^2 \) analysis).

**COMMENT**

Uveal melanoma frequently metastasizes to the liver, and the presence of hepatic metastases has been correlated...
with poor survival. The COMS recently reported that LFTs are a poor indicator of metastatic disease, with as few as 14.7% of patients with liver metastases exhibiting any abnormality in transaminase, alkaline phosphatase, or total bilirubin concentrations. Chest radiographs were similarly poor surveillance instruments, with a sensitivity of only 1.8%.

As such, clinicians are increasingly turning to more sophisticated imaging modalities for monitoring and/or diagnosing metastatic disease in patients with uveal melanoma. There are several reports in the literature on the ability of MRI or PET scans to identify metastatic lesions in patients with uveal melanoma, as well as in patients with known liver metastases. Overall, however, there is no universally accepted surveillance strategy, and there seems to be significant variability among clinicians in the type of imaging modality used (ultrasonography, CT, MRI, or PET scan), as well as the frequency of surveillance.

This review of the CT scans of 76 patients is a descriptive study characterizing some of the features identified on CT imaging of biopsy-proven liver metastases of uveal melanoma and correlating these to survival and LFT results. In keeping with the standard practice of radiologists to interpret studies with the clinical history in mind, the oncologic radiologists who interpreted these scans were aware that these patients had metastatic lesions in the liver. This knowledge might have led to a loosening of criteria to define metastatic lesions than might exist in a patient with no history of cancer or metastatic cancer. This again mirrors the reality of radiographic interpretations in patients with cancer. In the absence of biopsies of every lesion, it cannot be confirmed that all the extrahepatic lesions seen on imaging are metastatic disease. Moreover, in patients with radiographic evidence of multiple liver lesions, only 1 of the lesions had been biopsied and confirmed to be a metastasis. Similarly, some of the lesions thought to be benign on radiographic imaging may have been metastatic. As such, this study should be viewed as a description of radiologic features (and their correlates) rather than a description of the disease’s natural history and/or pattern of spread.
The vast majority (90%) of liver lesions in the 76 patients in our analysis appeared to be multiple on CT imaging. There was no significant difference in survival between patients with radiographic evidence of a single liver lesion vs those with radiographic evidence of multiple lesions. Moreover, of patients with a diagnosis of uveal melanoma metastasis to the liver with solitary lesions on CT scans, 2 had contemporaneous MRI results available, which revealed the presence of multiple lesions suspicious of being metastatic disease. These findings suggest that such patients infrequently demonstrate solitary lesions on CT scans, and, in those who do, multiple lesions may be identified when evaluated with other modalities, such as MRI. This also raises the question whether MRI may be a more sensitive tool for identifying metastatic lesions in patients with uveal melanoma. However, further studies are necessary to directly compare CT with MRI in identifying metastatic disease in this patient population. Of all the potential imaging modalities (CT, PET, MRI, and ultrasonography), CT scanning was chosen for screening purposes in this study because it is less expensive, faster, and readily available, and it enables imaging of the lungs in addition to the abdomen and pelvis. Both MRI and PET scans are more expensive, and, to date, there is no evidence indicating that they are superior to CT scans for identifying hepatic metastases in uveal melanoma. Moreover, our experience has indicated that PET scans are less sensitive in identifying small lesions in the liver. Although less expensive than the other imaging techniques, ultrasonography is highly operator dependent.

All lesions evaluated with contrast CT scans were hypodense and heterogeneous with enhancement. It is possible that other lesions with atypical features also represented metastatic disease and, thus, the rate of heterogeneity and/or enhancement is lower than that reported herein. We hoped to catch these atypical cases by reviewing all subsequent imaging, when available, to look for atypical lesions that enlarge over time. However, not all patients had subsequent imaging, and even those who had subsequent imaging did so at varying intervals.

As expected, patients whose CT scans exhibited larger lesions, hepatomegaly, or ascites experienced significantly worse survival. This may be clinically relevant for guiding patients with regard to prognosis and when making treatment decisions. Prospective studies are necessary to evaluate these findings. From a diagnostic standpoint, studies comparing imaging features in patients who underwent biopsy and were shown to have metastatic disease vs those whose biopsy results revealed benign disease would also be useful, as they might clarify which patients could be spared biopsies.

There were 2 cases of liver metastases invading into the vasculature, leading to radiographic evidence on CT or ultrasonography of tumor thrombi. In 1 case, the tumor thrombus extended up through the inferior vena cava into the right atrium. A proclivity for venothromboembolism is associated with malignant neoplasms in general; however, invasion of tumors into the vasculature to cause a tumor thrombus is rare and typically associated with renal cell carcinoma or hepatocellular carcinoma. These tumor thrombi are associated with clinical complications, including pulmonary embolism and acute obstruction of cardiac valves. To our knowledge, there is no report in the literature of tumor thrombi in uveal melanoma metastasis.

Metastases in uveal melanoma have classically been thought to occur in a “liver first” fashion. This study, however, indicates that 53% of patients have radiographic evidence of extrahepatic metastasis at the time of definitive diagnosis of liver metastasis by biopsy. A previous imaging study found that, in patients with liver metastases, 43% had radiographic evidence of extrahepatic lesions on CT scans.

In addition to the lungs and lymph nodes, these extrahepatic metastases appear to involve a range of additional sites, including the pericardium, soft tissues, thyroid, and peritoneum. Previous studies did not report the sites in detail, but our findings of a significant rate of ra-

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Table. Radiographic Evidence of Extrahepatic Disease at the Time of Diagnosis of Liver Metastasis

<table>
<thead>
<tr>
<th>Site</th>
<th>Frequency, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lungs</td>
<td>17/54 (31)</td>
</tr>
<tr>
<td>Lymph node</td>
<td>21/76 (28)</td>
</tr>
<tr>
<td>Adrenal glands</td>
<td>7/76 (9)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>4/54 (7)</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>5/76 (7)</td>
</tr>
<tr>
<td>Retroperitoneum</td>
<td>5/76 (7)</td>
</tr>
<tr>
<td>Subcutaneous tissue</td>
<td>5/76 (7)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3/76 (4)</td>
</tr>
<tr>
<td>Bone</td>
<td>3/76 (4)</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>2/76 (3)</td>
</tr>
<tr>
<td>Spleen</td>
<td>2/76 (3)</td>
</tr>
<tr>
<td>Mediastinum</td>
<td>1/54 (2)</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>1/76 (1)</td>
</tr>
</tbody>
</table>

*a Sites where radiographic evidence suggested the presence of metastatic disease at the time of biopsy diagnosis of the liver metastasis are noted, as well as the frequency for each site.
b Calculation of percentages for these sites was based on the number of patients with computed tomography scans including chest imaging rather than the total number of patients.

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Figure 7. Survival by extrahepatic metastases. A Kaplan-Meier survival curve compares survival of patients in whom a computed tomography scan exhibited radiographic evidence of extrahepatic metastases (red) vs those in whom there was no radiographic evidence of extrahepatic metastases (blue); (P=0.54 by log-rank analysis).
diographic evidence of extrhepatic involvement is consistent with prior reports. Of note, only 71% of these scans included chest imaging and, of these, 32% had radiographic evidence of lung metastases. Given the relatively high rate of lung lesions in patients at the time of diagnosis of liver metastases, it may be worthwhile to include chest imaging or consider full-body imaging when surveillance scans are conducted. Moreover, given the use and investigation of liver-directed therapies, such as hepatic infusion of chemotherapy and/or hepatic embolization, careful identification of these extrhepatic metastases may have important implications for treatment decisions.

It is possible that, with accurate imaging, radiographic evidence of extrhepatic metastasis is present at an earlier time in the disease than suspected. The rate of extrhepatic disease may be higher in our study given the possible referral bias of sicker patients to our tertiary center. Although this is a distinct possibility, if the high rate of extrhepatic lesions on imaging were merely a reflection of a sicker patient population referred to our center, one might expect there to be lower survival in patients with radiographic evidence of extrhepatic lesions than in those with no evidence of extrhepatic disease. However, there was no significant difference in survival for patients with and without extrhepatic metastasis, and there was no association between the presence of extrhepatic visceral metastases (excluding lymph node involvement) and survival.

Given the retrospective nature of the study, there is also significant variability in how metastatic disease was diagnosed (surveillance imaging vs imaging prompted by symptoms). In addition, there is likely to be a referral bias to our tertiary care center. The overall patient pool may have included those whose metastatic disease was more advanced or extensive at the time of diagnosis than the typical patient with an initial diagnosis of metastatic uveal melanoma. As such, the time from diagnosis to death, as well as radiographic evidence of larger lesions or extrhepatic disease, may be higher in our study than that found in all patients with uveal melanoma who develop biopsy-proven hepatic metastases.

Surveillance is unlikely to produce a significant survival benefit until an effective therapy for metastatic uveal melanoma is available. Indeed, in a recent study by Kim et al,10 patients diagnosed as having metastatic disease through surveillance showed no survival benefit compared with those diagnosed after symptom onset. A recent meta-analysis15 reported the absence of compelling evidence of survival benefit in any of the reported treatments for metastatic uveal melanoma. The lack of evidence stems largely from the fact that there have been no randomized phase 3 trials of any treatment vs no treatment. We are hopeful that the treatment arsenal will grow as better evidence accrues for these older therapies and as emerging therapies (including agents targeting the molecular signaling pathways implicated in uveal melanoma) reach clinical trials. If any of these treatments are effective, surveillance for metastatic disease will become increasingly important. Even in the absence of such advancements, however, it may be useful to clarify the radiographic features of metastatic uveal melanoma and their prognostic relevance.

Submitted for Publication: June 30, 2010; final revision received January 12, 2011; accepted January 17, 2011. Correspondence: David H. Abramson, MD, Department of Surgery, Memorial Sloan-Kettering Cancer Center, 70 E 66th St, New York, NY 10065 (abramsod@mskcc.org).

Financial Disclosure: None reported.

Funding/Support: This study was supported in part by The Fund for Ophthalmic Knowledge.

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