Hepatic Ultrasonography for Surveillance in Patients With Uveal Melanoma

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IMPORTANCE There is a lack of information regarding the role of systemic surveillance in patients with primary uveal melanoma.

OBJECTIVE To evaluate the utility of serial hepatic ultrasonography (USG) for detection of asymptomatic liver metastases in patients undergoing surveillance after primary treatment of uveal melanoma.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study reviewing data from patients with primary uveal melanoma treated between October 2003 and October 2012 at a multispecialty tertiary care center. Patients were managed using a standardized protocol. Initial staging was done with contrast-enhanced computed tomography of the chest, abdomen, and pelvis. This was followed by periodic surveillance with hepatic USG and liver function tests scheduled every 6 months for the first 5 years and annually thereafter. Abnormal surveillance hepatic USG findings were categorized as (1) cyst or hemangioma, (2) indeterminate lesion, (3) suspicious for metastasis, or (4) consistent with metastasis. If indicated, hepatic USG abnormalities were confirmed by additional imaging modalities (confirmatory scans) such as computed tomography or magnetic resonance imaging. Liver biopsy was performed only if the confirmatory scan was positive.

MAIN OUTCOMES AND MEASURES Sensitivity, specificity, and positive predictive value of hepatic USG for detecting asymptomatic liver metastases.

RESULTS In 263 patients (121 men, 142 women; mean [SD] age at diagnosis, 61.1 [13.9] years), a total of 1390 hepatic USGs were performed, with a mean of 5.3 per patient (range, 1-17 per patient). Overall, 86 hepatic USGs of 71 patients (27%) were reported as abnormal. Of the 13 lesions identified as a cyst/hemangioma and 17 as indeterminate, 1 was found to be metastatic in each group (8% and 6%, respectively). Of 36 patients with findings suspicious for metastasis, 23 (64%) had metastasis confirmed. All 5 patients (100%) with findings consistent with metastasis had biopsy-proven metastasis. The sensitivity, specificity, and positive predictive value of hepatic USG for findings that were indeterminate or suspicious for metastasis were 96% (95% CI, 80%-99%), 88% (95% CI, 83%-91%), and 45% (95% CI, 33%-59%), respectively. Specificity of the confirmatory scan was greater than that of hepatic USG (93% [95% CI, 89%-96%] vs 88% [95% CI, 83%-91%], respectively; P < .001). Only 4 of 30 patients (13%) with metastasis had abnormal findings on simultaneous liver function tests.

CONCLUSIONS AND RELEVANCE A stepwise surveillance protocol based on serial hepatic USGs followed by confirmatory scans offers high likelihood of detecting asymptomatic metastases in patients with primary uveal melanoma.
Metastasis occurs in 25% of patients with uveal melanoma by 5 years and remains the leading cause of death in patients regardless of enucleation or radiotherapy.1 Liver involvement is observed in up to 90% of cases with metastases.1,2 Other extrahepatic sites involved include the lungs (24%), bone (16%), and subcutaneous tissue.1,3,4 Very rarely, regional lymph nodes are involved, which is only observed with concomitant conjunctival invasion.5

It has been reported that 2% of patients have evidence of detectable metastasis at the time of initial presentation.6,7 However, micrometastasis, not visible by traditional imaging, could be present as early as 4 years prior to clinical diagnosis based on published tumor doubling times.8,9 Once the metastasis becomes clinically detectable, the mean survival is usually less than a year and depends on the site and extent of metastasis.1,4,10 With commercial availability of prognostic tests for uveal melanoma, it is important to incorporate systemic surveillance in patient care with or without use of adjuvant therapy.11,12

The Collaborative Ocular Melanoma Study (COMS) procedures for initial evaluation and subsequent surveillance included a general physical examination, chest radiography, liver function tests (LFTs), and an annual medical evaluation similar to that performed at the baseline visit.14 Even though the COMS report concluded that better tests were needed to identify earlier metastatic disease, it is unclear as to what constitutes an adequate surveillance strategy. There is lack of consensus regarding the type of tests, the frequency, and the duration for systemic surveillance, and some even question its clinical benefit.15 A survey revealed that European ophthalmologists used hepatic ultrasonography (USG) more commonly than North American physicians, who continue to use chest radiography and LFTs as included in the COMS guidelines.14,16 More recent survey of members of the International Society of Ocular Oncology reveals that the vast majority (85%) perform liver imaging (modality not specified) as part of systemic surveillance for metastases.17

Given that metastasis predominantly occurs in the liver with the highest risk of clinical manifestation in the first 5 years,1,2 the estimated 95% likelihood of detecting asymptomatic cases by biannual hepatic USG and LFTs,18 and low yields of chest radiography,14,18 we have been performing baseline contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis immediately prior to treatment of the primary tumor followed by periodic surveillance with hepatic USG and LFTs every 6 months. The Institutional Review Board at Cleveland Clinic approved this study. Informed consent was not required owing to the retrospective nature of the study.

Hepatic USG was performed using the Siemens Acuson HELX Evolution S2000 Ultrasound System or similar equipment. Curved (6- to 2-Hz) or phased (4-Hz) probes were used depending on the body habitus of the patient. Right upper quadrant USG images the liver, gallbladder, pancreas, biliary tree, and right kidney. The operators who performed the hepatic USG varied but interpretation was done by qualified radiologists. The LFT panel included alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, albumin, and bilirubin. Exclusion criteria were as follows: patients without follow-up as outlined earlier after initial diagnosis or treatment or patients with presence of metastatic disease at baseline.

Abnormal surveillance hepatic USG findings (excluding those present on baseline staging CT scans) were categorized as 1 of the following: (1) cyst or hemangioma; (2) indeterminate lesion; (3) suspicious for metastasis; or (4) consistent with metastasis (Figure 1). An abnormality on hepatic USG was recorded only once at initial detection unless it was observed at a different location on subsequent imaging. If necessary, based on discussion with the patient, hepatic USG abnormalities were confirmed by additional imaging modalities (confirmatory scans) such as CT or magnetic resonance imaging (MRI). The CT imaging included both oral and intravenous contrast. Images were obtained through the liver initially without intravenous contrast and then following contrast administration in the arterial and portal venous phases. The MRI for hepatic lesions included axial short tau inversion recovery, Dixon technique, time-of-flight imaging, 3-dimensional gradient-echo sequence (volumetric interpolated brain examination, without and with contrast), half-Fourier acquisition single-shot turbo spin-echo (including sagittal and coronal), diffusion-weighted imaging, and blade T2 imaging. If findings on the confirmatory scan (CT or MRI) were negative, the patient was periodically imaged by hepatic USG at his or her next scheduled follow-up visit. If findings on the confirmatory scan (CT or MRI) were positive, liver
biopsy was performed and the diagnosis of metastasis was confirmed. Once a patient was diagnosed as having metastasis, his or her date of last clinic visit or death was recorded.

All negative hepatic USG scans (indeterminate or suspicious for metastasis) were considered true-negative for metastasis if 2 subsequent hepatic USGs (at 6 and 12 months) showed unchanged appearance; they were considered false-negative if the biopsy was positive for metastasis. All positive hepatic USG scans were considered true-positive only if the biopsy was positive for metastasis.

Statistical analysis was performed by the Department of Quantitative Health Sciences at Cleveland Clinic Foundation using SAS version 9.2 statistical software (SAS Institute, Inc). Continuous variables were expressed as means (with standard deviations), whereas categorical factors were expressed as frequencies and percentages. Estimates of true- and false-positive scan rates were calculated at the patient level for 3 groups of hepatic USG findings (cyst or hemangioma; indeterminate and suspicious for metastasis; consistent with metastasis). Time from ophthalmic diagnosis to diagnosis of metastasis was recorded as recurrence-free survival (RFS), and time from ophthalmic diagnosis until death was recorded as overall survival (OS).

Results

Of the 380 total patients, 263 met the inclusion criteria. The male to female ratio was 0.8:1 (121 men [46%], 142 women [54%]). The mean (SD) age was 61.1 (13.9) years at the time of diagnosis. The mean (SD) follow-up duration was 39.5 (24.7) months (range, 6.0-125.3 months). Based on topography, more than 95% of the tumors were choroidal (206 [78%]), ciliochoroidal (36 [14%]), or iridociliary (9 [3%]). Right eye involvement was present in 148 cases (65%), whereas the left eye was affected in 115 patients (44%). Externacular extension was seen in only 7 patients (3%). The mean (SD) largest dimension of the tumor was 11.9 (4.3) mm (range, 2.4-30.0 mm) and the mean (SD) height was 4.8 (3.2) mm (range, 0.8-16.5 mm). Treatment modalities for primary tumor included brachytherapy in 179 cases (68%), enucleation in 54 (21%), and other methods in 30 (11%). Seven patients required a second treatment for locally recurrent disease (enucleation, 6; brachytherapy, 1).

A total of 1390 hepatic USGs were performed, with a mean of 5.3 per patient (median, 5; range, 1-17). Overall, 86 hepatic USGs of 71 patients (27%) were reported as abnormal (Table 1). Fifteen patients had 2 or more abnormal hepatic ultrasonographic scans during their entire follow-up (range, 0-4 abnormal scans).

Of the 13 initial lesions identified as a cyst or hemangioma, 1 (8%) was found to be metastatic at the next scheduled hepatic USG (6 months later). Follow-up studies of 17 patients with indeterminate lesions included repeated hepatic

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>No. (%)</th>
<th>Additional Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyst or hemangioma</td>
<td>13 (18)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Indeterminate lesion</td>
<td>17 (24)</td>
<td>0</td>
</tr>
<tr>
<td>Suspicious for metastasis</td>
<td>36 (51)</td>
<td>9 (13)</td>
</tr>
<tr>
<td>Consistent with metastasis</td>
<td>5 (7)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

* Fifteen patients had 2 or more abnormal hepatic ultrasonographic scans during their entire follow-up.
USG at the next scheduled visit (6 months later) for 12 patients indicating stability. Five patients underwent CT or MRI scan, and 1 of these 5 patients had biopsy-proven metastasis (Table 2).

Of 36 patients with lesions identified as suspicious for metastasis on hepatic USG, 35 underwent a confirmatory scan. This was followed by biopsy in 24, confirming the diagnosis of metastasis in 23 cases (64%) (Table 2).

All 5 patients categorized as having results consistent with metastasis on hepatic USG had metastasis proven by biopsy (Table 2).

Confirmatory scans (CT or MRI) were performed only in cases that were observed to have initial abnormal findings on hepatic USG other than cyst or hemangioma (Table 2). In 53 patients with hepatic USG findings that were indeterminate (17 patients) or suspicious for metastasis (36 patients), confirmatory scan findings were suspicious or consistent with metastasis in 24 cases (45%); in 23 of these 24 cases (96%), metastases were confirmed by liver biopsy. In all 5 cases reported as consistent with metastasis on hepatic USG, confirmatory scan results (CT or MRI) confirmed the findings and all these cases were proven to have metastasis by liver biopsy. The sensitivity, specificity, and positive predictive value of hepatic USG for findings that were indeterminate or suspicious for metastasis were 96% (95% CI, 80%-99%), 88% (95% CI, 83%-91%), and 45% (95% CI, 33%-59%), respectively (Table 3). Specificity of the confirmatory scan was statistically significant and greater than that for hepatic USG (93% vs 88%, respectively; McNemar test, \( P < .001 \)) (Table 3).

Of the 30 patients with biopsy-confirmed metastatic disease, 5-year RFS and OS were 3% and 23%, respectively. The median RFS was 23.2 months, and the median OS was 35.9 months (Figure 2). Overall, numerous lesions (>2) were observed in 24 cases, and 6 cases were oligometastatic (<2 lesions). Only 1 patient was symptomatic with nonspecific abdominal pain; the other 29 were asymptomatic. In 1 patient, metastatic disease to the breast was initially detected on routine screening mammography, and subsequent whole-body imaging confirmed hepatic involvement. Hepatic involvement was observed in all cases. Simultaneous pulmonary metastases were present in 3 patients (10%), and urinary bladder involvement was observed in 1 patient.

Only 4 of the 30 patients (13%) had abnormal simultaneous LFT results, whereas the results were normal in 26 patients (87%).

### Discussion

Our study describes the utility of hepatic USG for surveillance of metastasis in patients with primary uveal melanoma performed as part of standardized clinical care since 2003. Although there has been a great debate in the past decade about the benefit of surveillance studies,\textsuperscript{15,19} we had selected hepatic USG over CT and MRI because of ease of administration, absence of use of contrast material, and avoidance of radiation. Given the limitations of hepatic USG such as operator dependency, limited resolution, and depth penetration (in over-

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**Table 2. Follow-up Studies After Abnormal Findings on Initial Hepatic USG**

<table>
<thead>
<tr>
<th>Initial USG Abnormality</th>
<th>Subsequent Imaging, No.</th>
<th>Diagnosis After Confirmatory Scan, No.</th>
<th>Biopsy Performed, No.</th>
<th>Histopathologically Confirmed Metastasis, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyst or hemangioma\textsuperscript{a}</td>
<td>13</td>
<td>13</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>17</td>
<td>12</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Suspicious for metastasis\textsuperscript{b}</td>
<td>36</td>
<td>1</td>
<td>35</td>
<td>6</td>
</tr>
<tr>
<td>Consistent with metastasis</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

**Abbreviations:** NA, not applicable; USG, ultrasonography.

\textsuperscript{a} Repeated hepatic USG scan 6 months later.

\textsuperscript{b} Computed tomography or magnetic resonance imaging of the liver within 1 to 4 weeks.

\textsuperscript{c} One patient in this group was noted to have enlargement of the previously diagnosed cyst or hemangioma on repeated hepatic USG performed 6 months later, and liver biopsy confirmed metastasis.

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**Table 3. Sensitivity, Specificity, PPV, and NPV of Initial Hepatic USG for Diagnosing Metastasis**

<table>
<thead>
<tr>
<th>Abnormality on Initial USG</th>
<th>True-Positive, No.</th>
<th>% (95% CI)\textsuperscript{a}</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyst or hemangioma</td>
<td>13</td>
<td>NA</td>
<td>96 (80-99)</td>
<td>88 (83-91)</td>
<td>45 (33-59)</td>
</tr>
<tr>
<td>Indeterminate or suspicious for metastasis</td>
<td>24 of 53</td>
<td>83 (44-97)</td>
<td>100 (99-100)</td>
<td>100 (57-100)</td>
<td>99 (97-99)</td>
</tr>
<tr>
<td>Consistent with metastasis</td>
<td>5</td>
<td>83 (44-97)</td>
<td>100 (99-100)</td>
<td>100 (57-100)</td>
<td>99 (97-99)</td>
</tr>
</tbody>
</table>

**Abbreviations:** NA, not applicable; NPV, negative predictive value; PPV, positive predictive value; USG, ultrasonography.

\textsuperscript{a} The sensitivity, specificity, PPV, and NPV of the confirmatory scan for diagnosing metastasis in the indeterminate and suspicious for metastasis group were 96%, 93%, 60%, and 99%, respectively. These values did not differ for the other groups of lesions (cyst or hemangioma; consistent with metastasis). Specificity of the confirmatory scan was statistically significant and greater than that for hepatic USG (93% vs 88%, respectively; McNemar test, \( P < .001 \)).
weight individuals), when abnormal results were found on hepatic USG scans, the patients either had the hepatic USG scan repeated at the next scheduled visit (usually 6 months later) or underwent a confirmatory scan (CT or MRI) to confirm clinical suspicion prior to proceeding with an invasive procedure such as liver biopsy.

The operators who performed the hepatic USG varied but the interpretation was done by qualified radiologists. The value of this study in using routine hepatic USG performed and interpreted by a variety of operators and radiologists is advantageous in that the conclusions of this study could be applied in any institution within the United States without need for a special hepatic USG protocol. Cyst and hemangioma were the most common lesions observed on hepatic USG (13 patients among 71 with abnormal hepatic USG findings [18%]) (Table 1). Hepatic hemangioma, usually solitary, occurs in 1% to 2% of the population, whereas cysts, usually multiple, are also common (2.5% of the population). Among 30 biopsy-confirmed metastases, numerous lesions (>2) were observed in 24 cases, and 6 cases were oligometastatic (<2 lesions).

Assuming that all the patients who had hepatic USG findings negative for metastasis (indeterminate or suspicious for metastasis) were actually true-negatives (based on unchanged hepatic USG findings on follow-up), then USG would have a sensitivity and negative predictive value of 96% and 99%, respectively, for identifying asymptomatic metastatic disease. This is much higher compared with prior studies. This can be explained by our stepwise approach in our practice wherein confirmatory scans were performed as necessary. The positive predictive value of hepatic USG was 45%, which means about half of the hepatic USGs that were read as positive proved to be correct. The negative predictive value of 99% indicated a low chance of a false-negative test (ie, missing the diagnosis of metastasis), a desirable trait in the present clinical setting. The sensitivity of the hepatic USG and confirmatory scans was similar and high (96%) but the specificity was low for hepatic USG (88%) compared with confirmatory scans (93%) (McNemar test, \(P < .001\)), supporting our stepwise approach of using tests that require contrast (MRI and CT) or exposure to radiation (CT) with high specificity and high likelihood of not missing the metastases (negative predictive value of 99%) only in the prescreened at-risk population (Table 3). Such high detection rates (92%) of presymptomatic metastases have been reported with hepatic MRI performed every 6 months in high-risk individuals.

As cost comparisons may not be widely applicable, we did not attempt detailed cost analysis of the surveillance protocol. However, in an online resource with the Cleveland Clinic main campus zip code (44195) for a self-pay person, imaging study costs were quoted as $140, $825, and $925 for abdominal USG, CT, and MRI, respectively. Therefore, use of hepatic USG instead of CT or MRI for routine surveillance also provides a substantial cost advantage.

The positive and negative predictive values of a test are most helpful only when interpreted in the appropriate clinical context. Hicks et al reported low sensitivity (14%) of baseline hepatic USG performed in patients with large tumors (those undergoing enucleation) rather than abnormalities detected on sequential periodic hepatic USG. The prevalence of metastatic disease increases with increased duration since ophthalmic diagnosis. Therefore, any new hepatic lesion observed on hepatic USG that was not observed on a previous scan should raise the suspicion of metastasis unless proven otherwise and should always be investigated further. Similarly, change in appearance or size of a lesion previously diagnosed as a cyst/hemangioma or indeterminate should also be investigated further.

Similar to prior observations about lack of sensitivity and specificity of LFTs in the diagnosis of liver metastasis, simultaneous abnormalities in LFTs were observed in only 13% of patients at the time of metastasis, comparable with published studies. Abnormal LFTs did not trigger the cascade of workup for metastasis in any patient as the decision was driven by anatomical changes in the liver detected by imaging studies rather than nonspecific changes in LFT results.

Treatment of metastatic disease has failed to show a survival advantage compared with untreated patients in most...
studies. Similarly, early intervention (medical or surgical) by virtue of screening and diagnosing asymptomatic metastasis also has not been shown to improve longevity.\textsuperscript{15,23,27} The small survival advantage recorded from presymptomatic diagnosis is believed to result from lead-time and length-time biases. These facts argue against screening patients for metastatic disease.\textsuperscript{16,23}

The median OS of 35.9 months in our cohort is similar to that observed by Kim et al\textsuperscript{19} in the asymptomatic group (median survival, 40.6 months) who underwent surveillance testing by annual LFTs and confirmatory liver CT if LFT results were abnormal. Eskelin et al\textsuperscript{18} also did not observe any difference in the median RFS of patients whose metastases were diagnosed at screening or on the basis of symptoms (2.2 vs 2.0 years, respectively). Although the COMS reported a median survival of less than 6 months after diagnosis of metastasis, comparison cannot be performed with COMS data because the median RFS has not been published. Lead-time bias can account for a shorter median time from ophthalmic diagnosis to metastasis and a longer median time from diagnosis of metastasis to death with a similar median time from ophthalmic diagnosis to death when compared with data published by Kim et al\textsuperscript{19} (Figure 2). Furthermore, lack of control groups in the COMS (with regard to surveillance protocol) and in our study cohort restricts us from reaching any definite conclusions about survival advantage of our surveillance protocol.

From a patient’s perspective, however, such systemic surveillance provides them with a reassurance that is critical in dealing with a life-threatening diagnosis. As the benefits of such intervention may be questionable, it is important to understand whether any harm was done by false-positive tests that led to unnecessary invasive procedures given the high prevalence of cyst or hemangioma (18%) and indeterminate lesions (24%) noted on initial hepatic USG (Table 2). Our data suggest that with the stepwise approach reported herein, the high negative predictive value of both USG and the confirmatory scans (99%) limits unnecessary invasive testing as only 1 patient who underwent liver biopsy turned out to be negative for metastasis. In this patient, no new hepatic lesions have been observed on 3 subsequent hepatic USG scans performed at 6-month intervals, indicating absence of metastasis. However, negative biopsy results should be cautiously interpreted in view of technical difficulties that may yield false-negative results.

With availability of highly accurate prognostication tests\textsuperscript{11,12} for uveal melanoma and the trend toward adjuvant therapy,\textsuperscript{28,29} systemic staging for metastasis at baseline followed by periodic surveillance for metastasis will increasingly become an important component of the management strategy that may be tailored to a patient’s prognostic status and the adjuvant therapy that he or she might be receiving.\textsuperscript{29,31}

Conclusions

We recommend baseline staging at the initial ophthalmic diagnosis and a stepwise surveillance protocol based on serial hepatic USG scans followed by confirmatory scans, prior to liver biopsy, to be included in a comprehensive management strategy for patients with primary uveal melanoma. Although such a surveillance protocol offers a high likelihood of detecting asymptomatic metastasis, it may not provide survival advantage.

ARTICLE INFORMATION

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REFERENCES


Is Surveillance of Uveal Melanoma Just a Screen?

Jasmine H. Francis, MD

Despite the realization that half of patients with uveal melanoma will ultimately develop metastatic disease, questions remain regarding the utility of routine surveillance. In 2011, a literature review of 31 articles failed to demonstrate convincing evidence of a survival advantage from routine surveillance. However, these studies were conducted in the context of traditional chemotherapy regimens, none of which demonstrated adequate response rates for uveal melanoma. A phase 2 trial of selumetinib conducted between 2010 and 2013 yielded improved response rates and progression-free survival (despite no improvement in overall survival) compared with chemotherapy. These landmark findings shed some hope on the dismal landscape of metastatic uveal melanoma and have thus reignited the potential benefit of routine surveillance and early detection of disease.

For this reason, establishing the optimal surveillance method for uveal melanoma, should it prove to be meaningful, is an important proposition. Key characteristics of a screening regimen include adequate sensitivity and specificity as well as balancing the toxicity of the screening examination with the financial and emotional costs. Because 90% of metastases are first recognized in the liver, it is logical to focus on tests of the liver. Computed tomography is limited by its emission of radiation (especially if repeated every 6–12 months for many years) and the very high incidence of false-positive results. While magnetic resonance imaging (MRI) is perceived as being the most sensitive test, it is expensive and less accessible and also has many false-positive results. As Choudhary et al have pointed out in this issue of JAMA Ophthalmology, abdominal ultrasonography is an attractive screening modality. Historically, owing to its operator dependence and limitation by body habitus, abdominal ultrasonography was rarely used as a surveillance tool in the United States and has been more commonly adopted in Europe. Almost a decade ago, a study from Finland estimated that semiannual ultrasonography in concert with liver function tests could detect metastases in more than 95% of asymptomatic patients. At the time, the authors could not justify the expense of such a regimen in the face of poor response from the conventional chemotherapy used at the time. However, the promising results of targeted and immunotherapy treatments for metastatic disease may now justify an exploration of this proposed screening regimen.

The work of Choudhary et al is most intriguing because it addresses the model that was raised by the Finnish study a decade ago, in a US population that was historically believed to be less eligible for such a screening approach. The authors...