
# Hepatic Ultrasonography Compared with Computed Tomography and Magnetic Resonance Imaging at Diagnosis of Metastatic Uveal Melanoma

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**ABSTRACT**

PURPOSE: To evaluate the consistency of hepatic ultrasonography (US) with staging computed tomography (CT) and magnetic resonance imaging (MRI), to analyze why US was inconsistent with CT/MRI, and to compare CT/MRI.

DESIGN: Reliability analysis.

METHODS: Two hundred fifteen patients whose primary uveal melanoma was managed in the Helsinki University Hospital and who were diagnosed with hepatic metastases by US within 60 days of staging CT/MRI from January 1999 to December 2016, were included. Patients attended a real-life follow-up schedule including hepatic US, liver function tests (LFT), and a confirmatory CT/MRI. We evaluated the consistency of US with staging CT/MRI regarding the presence and number of metastases.

RESULTS: The enrolled patients underwent 215 US, 167 CT, and 69 MRI examinations, and 67% of them had biopsy-confirmed metastases. Screening was regular for 98% of the patients, and 66% were asymptomatic. US was fully consistent with CT/MRI in detecting metastases in 113 (53%) patients, in 63 (29%) CT/MRI showed more metastases, and in 16 (7%) less metastases than US. CT/MRI was inconsistent with US in 23 (11%) patients. The sensitivity of US in detecting metastases was 96% (95% confidence interval, 92-98). US failed to suggest metastases in 10 patients. LFT were abnormal in six of them, and a newly-detected hepatic lesion was present by US in four.

CONCLUSIONS: Hepatic US is a sensitive screening modality in detecting metastases in patients with primary uveal melanoma, if combined with LFT and in case of any new detected lesion, a confirmatory MRI.

# Hepatic Ultrasonography Compared with Computed Tomography and Magnetic Resonance Imaging at Diagnosis of Metastatic Uveal Melanoma

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**Short title:** Screening Imaging with US and CT/MRI

**Supplemental Material available at AJO.com**

- Supplemental Text for Methods
- Supplemental Table 1
- Supplemental Table 2
- Supplemental Table 3
- Supplemental Figure 1

## INTRODUCTION

Even 25 years after treatment, metastatic disease is the leading cause of death for patients with primary uveal melanoma (UM).[1] At the time of diagnosis of the primary UM, only less than 3% of patients have hepatic metastases and they more frequently have benign abnormalities or a synchronous primary cancer.[2,3] However, more than half of the patients develop metastases[1] and in 90% of them the liver is the first site of metastases.[4] The median overall survival of patients with metastatic UM is 13 months.[5] Patients whose metastases are resected may survive longer, but resection requires early detection of metastases.[5,6]

Currently each center has its own preferred modality and frequency of imaging for screening of metastases from UM. The frequency varies depending on participation in ongoing trials and perceived risk of dissemination indicated by tumor stage, genetic profile, and histology. High risk patients are often surveilled 4- to 6-monthly,[6-10] based in part on estimated tumor doubling times of metastases.[11] In some centers, hepatic ultrasonography (US) is performed every 6 to 12 months for 10 to 15 years, followed by staging computed tomography (CT) and magnetic resonance imaging (MRI) if a suspicious new lesion is visualized.[12-15] In other centers, surveillance using MRI with contrast agent for the liver and CT for the chest, abdomen and pelvis is frequent,[16] US being rejected because of its possible limitations in obese patients,[9] insurance incentives, and fear of malpractice claims in the absence of preferred practice guidelines.[17]

It is crucial that the chosen surveillance modality will detect at least one metastatic focus if any exist and thus informs need for confirmatory imaging and biopsy. Because of a paucity of comparative clinical data on choice and frequency of screening imaging to detect metastases from UM, some national guidelines,[13,18-22] but no international agreement has been reached. Therefore, we make use of our population-based real-life data to evaluate screening hepatic US compared with staging CT and MRI performed within 60 days and additionally, we obtained information on differences between CT and MRI.

## METHODS

**Aims of Study:** Our primary aim was to evaluate, at the time of diagnosis of metastatic UM, the agreement between hepatic US and staging CT/MRI, performed within 60 days. Our secondary aim was to analyze the reasons why US in some patients was interpreted inconsistently compared with CT/MRI, and the differences between CT and MRI.

**Study Design:** Eligible to our retrospective cohort study were patients who had been treated for primary UM in the Ocular Oncology Service, Department of Ophthalmology, Helsinki University Hospital, Finland, a national referral center, who were diagnosed with hepatic metastases in the absence of another active cancer from January 1999 to December 2016, and who underwent CT, MRI, or both within 60 days of upper abdominal US. The first imaging was performed on a prescheduled screening visit in 194 (90%) of patients or based on symptoms or an unrelated medical condition. The study was approved by the Institutional Review Board and the National Institute for Health and Welfare. Informed consent for participation in this research was not required by Finnish law because the study was entirely based on past records and almost all patients in our study already had died.

**Data Collection:** We obtained patient charts from all hospitals that had participated in management of metastatic UM. Because the Finnish law permits destroying of most

patient records 12 years after death, data were partial for 21 patients. Of 338 consecutive patients with newly diagnosed metastatic UM (Figure 1), we excluded 58 patients who did not undergo CT or MRI, 10 patients who did not have an US, 21 patients who underwent CT/MRI more than 60 days from the US, 26 patients who did not have liver metastases at the time of diagnosis of dissemination, and three patients with a concurrent active second cancer (metastatic renal cell carcinoma, metastatic thyroid carcinoma, and progressive breast cancer, all biopsy-proven). Finally, two patients were diagnosed with metastases at autopsy, and two had all US or MRI documentation already destroyed after death.

We recorded the gender, age, date of diagnosis of the primary UM and metastases, American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) stage for the primary UM and its metastases,[23-25] participation in regular review to detect metastases early,[13] symptoms from metastases, the largest diameter of the largest metastasis (LDLM), liver function tests (LFTs), sites of metastases, the number of hepatic metastases (multiple if >10),[26] the Eastern Cooperative Oncology Group (ECOG) performance status (also known as the WHO performance score) at the time of treatment decision,[27] the stage predicting the median OS by using the Helsinki University Hospital Working Formulation (WF),[28,29] and the date and registered cause of death. The screening was generally annual, and from 2014 semiannual for TNM stage III, and included US and LFTs, followed by staging MRI or CT by decision of the managing hospital when metastases were suspected. Follow-up ended on December 31, 2018, and the median follow-up time was 44 months (range, 2-285).

Hepatic US and CT/MRI were performed by general radiologists in the health-care unit nearest to the patient's place of residence. We categorized suspected and definite hepatic metastases as hypo- or hyperechoic, target-like (nodular areas with a hypoechoic rim and a hyperechoic center), or mixed according to the original reports, noted the number of lesions, and recorded the diameter of the largest lesion. We first compared the consistency of diagnosis of metastases between US and CT/MRI. If one examination had been interpreted as metastases and the other not, an experienced radiologist (EP) reviewed the CT/MRI images. Secondly, we compared the reported number of lesions reported as metastases between US and CT/MRI.

We categorized patients in four groups according to the consistency of findings in US with those in CT/MRI. Group 1: US fully consistent with CT/MRI; Group 2: US consistent with CT/ MRI but the latter showed more metastases; Group 3: US consistent with CT/ MRI but the latter showed less metastases; Group 4: US inconsistent with CT/MRI. Patients with inconsistent findings, i.e. Group 4, were further analyzed.

**Verification of Metastases:** We adapted definitions of the Collaborative Ocular Melanoma Study (COMS) to ascertain whether metastatic UM was present[1,30] and obtained specimens for review as required (Supplemental Text; Supplemental Material available at AJO.com). By this review, one patient did not have lesions consistent with metastases and was excluded. Metastases were later biopsy-confirmed in 67% of patients.

**Statistical Analysis:** Statistical analysis was performed with Stata (version 15, Stata Corp., College Station, TX). Level of significance was set at 0.05. All *P*-values are two-tailed. We report median with range and interquartile range (IQR) for continuous variables. We used nonparametric test for trend to compare continuous variables between ordered groups. The sensitivity of US for detecting hepatic metastases was calculated.

Recurrence-free interval (RFI) was defined as the time from the diagnosis of the primary UM to diagnosis of metastases and overall survival (OS) as the time from the diagnosis of metastases to death. We estimated OS using Kaplan-Meier product-limit method and report the median OS with 95% confidence interval (CI).

## RESULTS

**Basic Characteristics:** Of 215 enrolled patients, 49% were female (Table 1). Their median age at diagnosis of metastases was 68 (range, 23-94) years. Of the primary tumors, 10% were small (T1), 39% medium-sized (T2), 41% (T3) large, and 10% very large (T4), and 41% extended to the ciliary body or extrasclerally (Supplemental Table 1; Supplemental Material available at AJO.com). Screening was regular for 210 patients (98%) and 142 (66%) were asymptomatic when metastases were diagnosed.

**Diagnosis of Metastases:** The median RFI was 30 months (range, 0-265; IQR, 13-61; the metastases of ten patients were diagnosed before confirmation of the primary tumor; Supplemental Figure 1; Supplemental Material available at AJO.com). Only liver metastases were detected in 155 (72%) patients with 215 US, 167 CT and 69 MRI examinations (Table 1 and Figure 2). The median LDLM of the liver metastases was 26 mm (range, 6-130) as measured with US.

At least one LFT was elevated in 55 (30%) of 183 patients with available data, including AST in 79%, ALT in 67%, AP in 60%, and LD in 89% of them (Supplemental Table 2; Supplemental Material available at AJO.com). The likelihood of at least one LFT being abnormal increased with increasing LDLM (M1a vs. M1b vs. M1c; $P$=.028, nonparametric test for trend). This was also true of AP, LD, and AST ($P$<.001, $P$<.001, and $P$=.007, respectively) but not of ALT, analyzed individually.

The first imaging modality was US, except for CT in 18 patients (8%) and MRI in two patients, prompted by symptoms in 16 (80%) and an unrelated medical condition in 4 (20%). The median interval was 17 days (range, 0-56; IQR, 8-27) from the first to the second imaging modality that was US, CT, and MRI for 19, 141, and 55 patients, respectively (one patient underwent CT twice and two patients MRI twice, with consistent findings).

The ECOG performance status was 0-2 for 85%, and 3-4, often regarded as unsuitable for active treatment, for 14%. Of 213 patients with known WF stage, 56%, 23%, and 21% fell in IVa, IVb, and IVc, respectively. Of the 215 patients, 12 were alive with metastases at the time of analysis. The audited primary cause of death was metastatic UM for all others. The median OS from diagnosis of metastases was 12 months (range, 0-166).

**Sensitivity of ultrasonography:** US was diagnostic of metastases in 205 of the 215 patients (95%; 95% CI 92-98). The metastases were hypoechoic in 67% of patients with a specified type, hyperechoic in 3%, target-like in 6%, and of mixed type in 16%, respectively. LFTs and US did not reveal biopsy-positive hepatic metastases in 4 patients (2%). The sensitivity of US calculated against CT/MRI for findings that were suspected of metastases was 96% (95% CI 92-98); 215 US scans were true-positive and 10 were false-negative.

**Consistency of US with CT/MRI:** Of the 215 patients, 113 (53%) were categorized to Group 1 (US fully consistent with CT and MRI), 63 (29%) to Group 2 (US consistent with

CT/MRI but the latter showed more metastases), 16 (7%) to Group 3 (US consistent with CT/MRI but the latter showed less metastases), and 23 (11%) to Group 4 (US inconsistent with CT/MRI; Figure 1 and 3). MRI detected more metastases than US in 54% of scans and less in 3%, and CT detected more metastases in 31% and less in 16% of scans (Figure 4).

In the inconsistent Group 4 (Figure 3), a gadolinium ethoxybenzyl dimeglumine injection, a liver-specific contrast agent, was used in one MRI and a non-specific gadolinium chelate in seven of the eight scans (Supplemental Table 3; Supplemental Material available at AJO.com). US was positive but a CT negative in nine patients because of misinterpretation of CT in two, a small size of metastasis (≤10 mm) in two, only non-contrast agent scans in one because of contraindications, and without apparent reason in four patients. US was negative in ten patients of whom seven eventually had biopsy-confirmed metastases. A subsequent CT was performed in three, MRI in six, and both scans in one patient. In six of them, at least one abnormal LFT prompted the further CT/MRI. In the remaining four patients, a CT was scheduled because of a new suspected pancreatic pseudocyst, new anechoic hepatic cysts with no comments on shadowing, a new presumed hemangioma and cyst, and as part of initial work-up of the primary UM in one patient each.

**CT vs MRI:** Both CT and MRI were ordered for 8 patients (7%) in Group 1, 9 (14%) in Group 2, none in Group 3, and 1 (4%) in Group 4. In these 18 patients MRI detected more metastases than CT in six, CT more than MRI in one, both detected multiple (>10) metastases in nine, and two had an equal number of metastases.

## DISCUSSION

Our population-based comparative study on the consistency of hepatic US with staging CT/MRI, performed within 60 days of each other, shows that US can efficiently be used to screen metastases in patients with primary UM and suggests that MRI is superior to CT, in a real-life setting. Upper abdominal US detected metastases in 95% of the patients and agreed with a staging CT/MRI on their presence in 89% of patients, showing in 72% of patients at least the same number of lesions than CT/MRI. MRI detected more metastases than CT in six of 18 patients.

Limitations of our study include its retrospective nature, varying imaging protocols reflecting the geographically long distances that make the screening only in tertiary-centers unfeasible, and lack of knowledge on the genetic profile of the metastases that might show in their imaging characteristics in low and high-risk patients. The maximum interval of 60 days between the scans somewhat biases the comparison of modalities because the median doubling time of untreated metastases is 63 days.[11] This, however, is three times longer than the median interval of 17 days (IQR, 8-27) between scans in our series. Our study mostly compares the three imaging methods in one direction: 91% of US scans preceded CT/MRI. Thus, our results and conclusions cannot be applied to the reverse scenario: the results would not have been the same both because of the higher resolution of CT/MRI and because the up to 56 day interval between screening and staging will somewhat favor the later examination as the metastases will grow.

In our series, the sensitivity of US was 96% matching a previous estimate of 96%.[9] A combination of US and LFTs did not reveal hepatic metastases in four patients (2%), also comparable to earlier publications (4%).[13] However, three of these patients had a new lesion in US that led to a CT/MRI scan, highlighting that in case of any newly detected

lesion it should be considered a metastasis until proven otherwise,[31] although benign liver lesions, cysts and hepatic steatosis are common at baseline.[2] In agreement with previous publications,[13,32,33] despite obesity-related challenges and dependence on the skill of the operator,[32] hepatic US confirmed its utility as a surveillance tool in our practice.

The higher soft tissue differentiation of CT as compared to US may explain those 51 scans in which the staging CT showed more metastases than US, and the higher resolving power the 26 scans in which CT showed less metastases than US. The finding that in three patients CT showed multiple metastases while US detected none, only a cyst (one earlier and one newly detected) in two patients and hepatic steatosis in one patient, likely results from the lower resolving power of US, but we cannot exclude the possibility that particular characteristics of the metastases in these patients might have contributed by making them isoechoic. The minimum diameter of the detectable lesions in US has been suggested to be 5 mm,[33] in CT 10 mm,[34] and in MRI 1 mm.[8] It ranged from 6 mm in US to 4 mm in CT, and 2 mm in MRI in our series.

MRI outperformed US and, notably, CT in detecting metastases, justifying a review[16] that suggested that MRI should replace CT as the standard modality in liver imaging in context of UM. MRI with contrast agent is the most specific imaging modality, and at least as sensitive as CT (reported sensitivity 67-100% and specificity 80-99%).[8,12,35,36] In the inconsistent Group 4, one patient with equivocal findings had a lesion with a short T1 and long T2 pattern, a finding reported in 27% of patients with UM, a short T1 and short T2 pattern being the most common (Figure 3 and Supplemental Table 3; Supplemental Material available at AJO.com).[16,37] Previous studies have reported that when one metastasis is seen in CT, 90% have multiple lesions in the liver.[34] MRI is a more sensitive method to detect liver metastases than even FDG-PET-CT[12,36] because the normal mottled hepatic uptake of FDG obscures small FDG-avid lesions, owing to a poor target-to-background ratio.[16]

CT and MRI are relatively more expensive and somewhat less accessible than US. Although a global cost comparison is not applicable because of differences in insurances and reimbursements, a rough estimate can be obtained from the Helsinki University Hospital prices for a self-paying patient: a hepatic US costs 93 € (105 $), CT with contrast 250 € (280 $), MRI with gadolinium 350 € (390 $) and with a liver-specific contrast agent 550 € (615 $), and FDG-PET-CT 1500 € (1675 $). A limitation of CT is also ionizing radiation, but it benefits patients in whom MRI is contraindicated.[2,34] These considerations together with our results support continued use of US for screening and using MRI for confirmation and staging of metastases.

Surveillance practices differ geographically: many centers in Europe advocate US whereas many centers in North America have policies that support use of CT over US.[12,13,16,38] MRI is preferred by some center on both continents. LFTs are widely accepted in the surveillance protocols, although they may become abnormal only when hepatic metastases are advanced.[7,34] However, LFTs have been reported to rise within normal limits already six months prior to metastases detectable by US.[39]

In conclusion, our real-life observations support surveillance with US followed by a confirmatory staging MRI, to be performed also when any new lesion is detected in the US scan or US is normal but LFTs are increased. A chest radiograph is not included in our surveillance protocol because metastases to the lung are exceptional at the time when

hepatic US already shows dissemination.[7,15] We see the need for a study comparing US and MRI head-to-head as a screening tool for patients with primary UM, including a cost-benefit comparison, to establish a universally accepted screening strategy.

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**FIGURE CAPTIONS**

**FIGURE 1**. Study flowchart.
CT = computed tomography; MRI = magnetic resonance imaging; US = hepatic ultrasonography.

**FIGURE 2.** Study groups with the number of scans, A, and biopsy-confirmed uveal melanoma metastases, B, indicated.
CT= computed tomography; MRI= magnetic resonance imaging; US= hepatic ultrasonography.

**FIGURE 3.** Flow chart that shows patients in Group 4 according to the lack of consistency of imaging.
CT = computed tomography; MRI = magnetic resonance imaging; US = hepatic ultrasonography.

**FIGURE 4.** Number of reported metastases in hepatic ultrasonography compared to computed tomography, A, to magnetic resonance imaging, B, and computed tomography compared to magnetic resonance imaging, C.
CT = computed tomography; MRI = magnetic resonance imaging; US = hepatic ultrasonography.

**TABLE 1. Patient characteristics.**

| Variable | All patients N=215 | Group 1 N=113 | Group 2 N=63 | Group 3 N=16 | Group 4 N=23 |
|---|---|---|---|---|---|
| Gender, No. (%) | | | | | |
| Female | 105 (49) | 52 (46) | 33 (52) | 7 (44) | 13 (57) |
| Male | 110 (51) | 61 (54) | 30 (48) | 9 (56) | 10 (43) |
| Age, median (range, IQR), y | | | | | |
| Primary tumor | 64 (19-92, 54-73) | 66 (21-92, 53-72) | 62 (28-85, 55-75) | 60 (51-85, 55-73) | 63 (19-90, 57-73) |
| Metastatic disease | 68 (23-94, 59-77) | 70 (23-93, 57-76) | 68 (34-87, 59-78) | 63 (54-94, 60-76) | 65 (24-91, 59-76) |
| Death | 69 (24-95, 60-78) | 70 (24-94, 59-77) | 70 (34-87, 61-79) | 65 (58-95, 61-77) | 66 (24-93, 60-76) |
| Primary tumor extent, No. (%) | | | | | |
| Limited to choroid | 127 (59) | 67 (59) | 38 (60) | 8 (50) | 14 (61) |
| With ciliary body involvement | 84 (39) | 43 (38) | 25 (40) | 8 (50) | 8 (35) |
| Extraocular extension | 4 (2) | 3 (3) | 0 (0) | 0 (0) | 1 (4) |
| Regularity of screening, No. (%) | | | | | |
| None | 2 (1) | 2 (2) | 0 (0) | 0 (0) | 0 (0) |
| Irregular | 3 (1) | 1 (1) | 0 (0) | 0 (0) | 2 (9) |
| Regular | 210 (98) | 110 (97) | 63 (100) | 16 (100) | 21 (91) |
| Symptoms, No. (%) | | | | | |
| No | 142 (66) | 69 (61) | 46 (73) | 14 (88) | 13 (57) |
| Yes | 70 (33) | 43 (38) | 15 (24) | 2 (13) | 10 (43) |
| Unknown | 3 (1) | 1 (1) | 2 (3) | 0 (0) | 0 (0) |
| Median recurrence-free interval, years (range, IQR); No. (%) | 2.5 (0-22.1, 1.1-5.1) | 2.1 (0-16.2, 1.0-4.9) | 3.0 (0-22.1, 1.7-6.2) | 3.1 (1.0-12.0, 2.6-5.0) | 1.6 (0-10.1, 0.7-4.0) |
| <2.0 years | 88 (41) | 52 (46) | 22 (35) | 2 (13) | 12 (52) |
| 2.0-3.5 years | 46 (21) | 25 (22) | 12 (19) | 7 (44) | 2 (9) |
| >3.5 years | 81 (38) | 36 (32) | 29 (46) | 7 (44) | 9 (39) |

**TABLE 1. Patient characteristics** (continued).

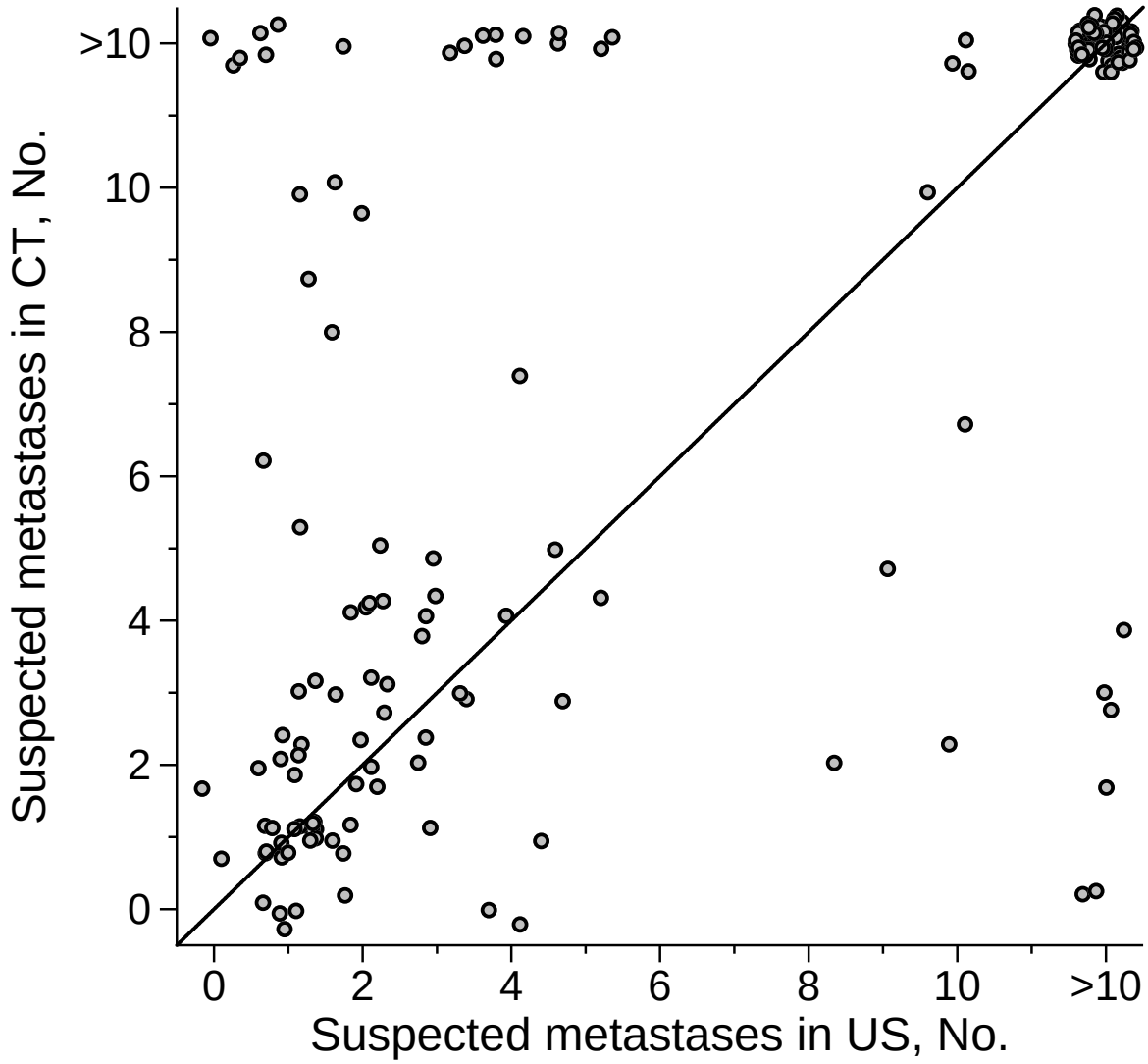
| | | | | | |
|---|---|---|---|---|---|
| Median largest diameter of the largest hepatic metastasis, mm (range, IQR); No. | | | | | |
| In US | 26 (6-130, 15-47); 169 | 30 (6-130, 17-54); 86 | 26 (8-130, 13-40); 58 | 34 (10-60, 10-47); 15 | 15 (6-37, 10-17); 10 |
| In CT | 30 (4-270, 17-53); 76 | 29 (7-270, 17-50); 40 | 30 (10-120, 16-55); 23 | 36 (4-80, 20-47); 10 | 20 (17-100, 17-100); 3 |
| In MRI | 20 (2-160, 10-40); 55 | 17 (2-90, 7-40); 22 | 30 (10-160, 20-42); 26 | 8 (N/A); 1 | 9 (5-20, 7-12); 6 |
| AJCC TNM category, No. (%) | | | | | |
| ≤30 mm (M1a) | 97 (45) | 48 (42) | 30 (48) | 5 (31) | 14 (61) |
| 31-80 mm (M1b) | 73 (34) | 36 (32) | 22 (35) | 10 (63) | 5 (22) |
| >80 mm (M1c) | 36 (17) | 21 (19) | 11 (17) | 1 (6) | 3 (13) |
| Unknown | 9 (4) | 8 (7) | 0 (0) | 0 (0) | 1 (4) |
| ECOG performance, No. (%) | | | | | |
| 0-1 | 162 (75) | 81 (72) | 55 (87) | 14 (88) | 12 (52) |
| 2 | 22 (10) | 14 (12) | 4 (6) | 0 (0) | 4 (17) |
| 3-4 | 30 (14) | 17 (15) | 4 (6) | 2 (13) | 7 (30) |
| Unknown | 1 (0) | 1 (1) | 0 (0) | 0 (0) | 0 (0) |

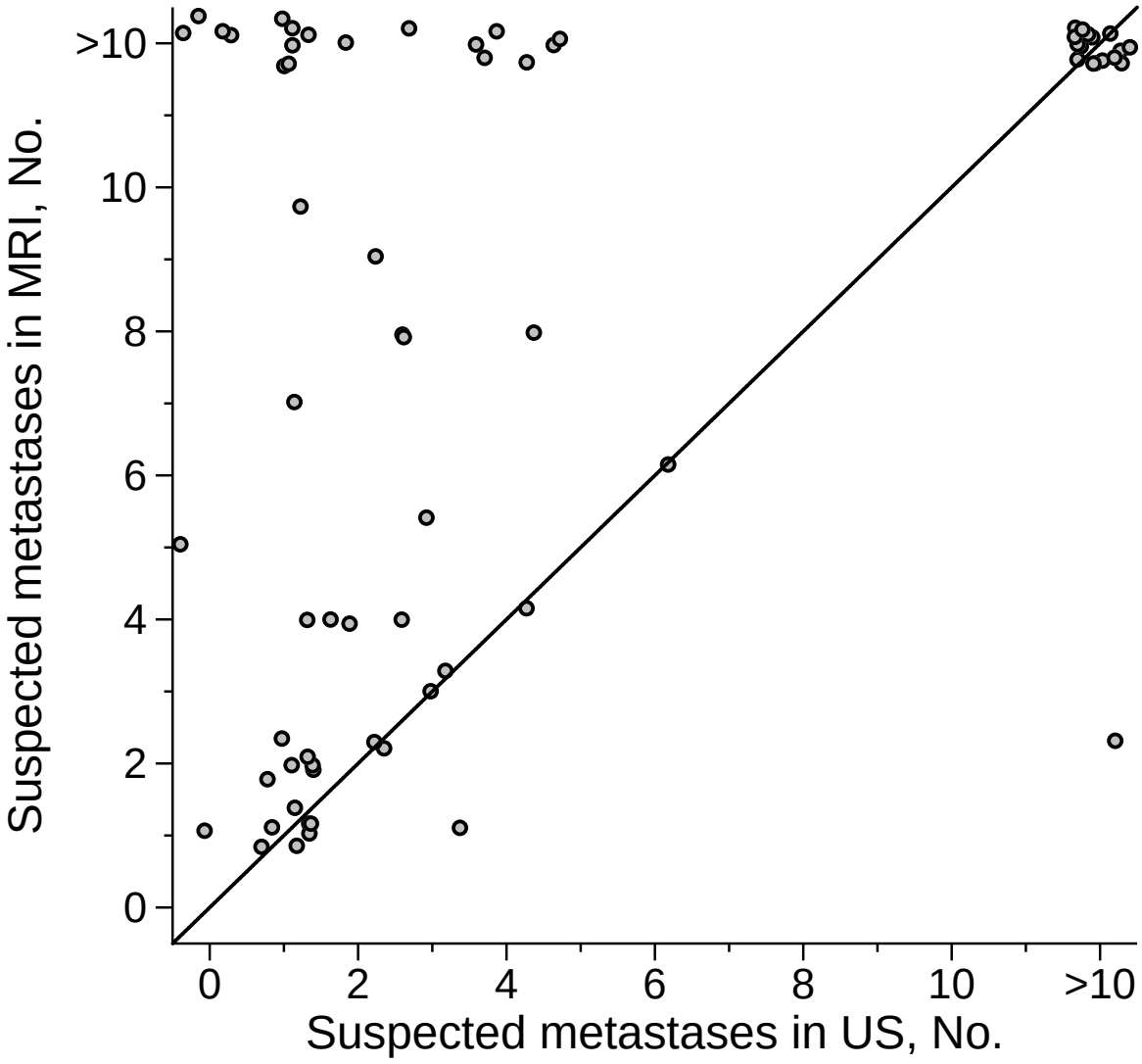
**TABLE 1. Patient characteristics** (continued).

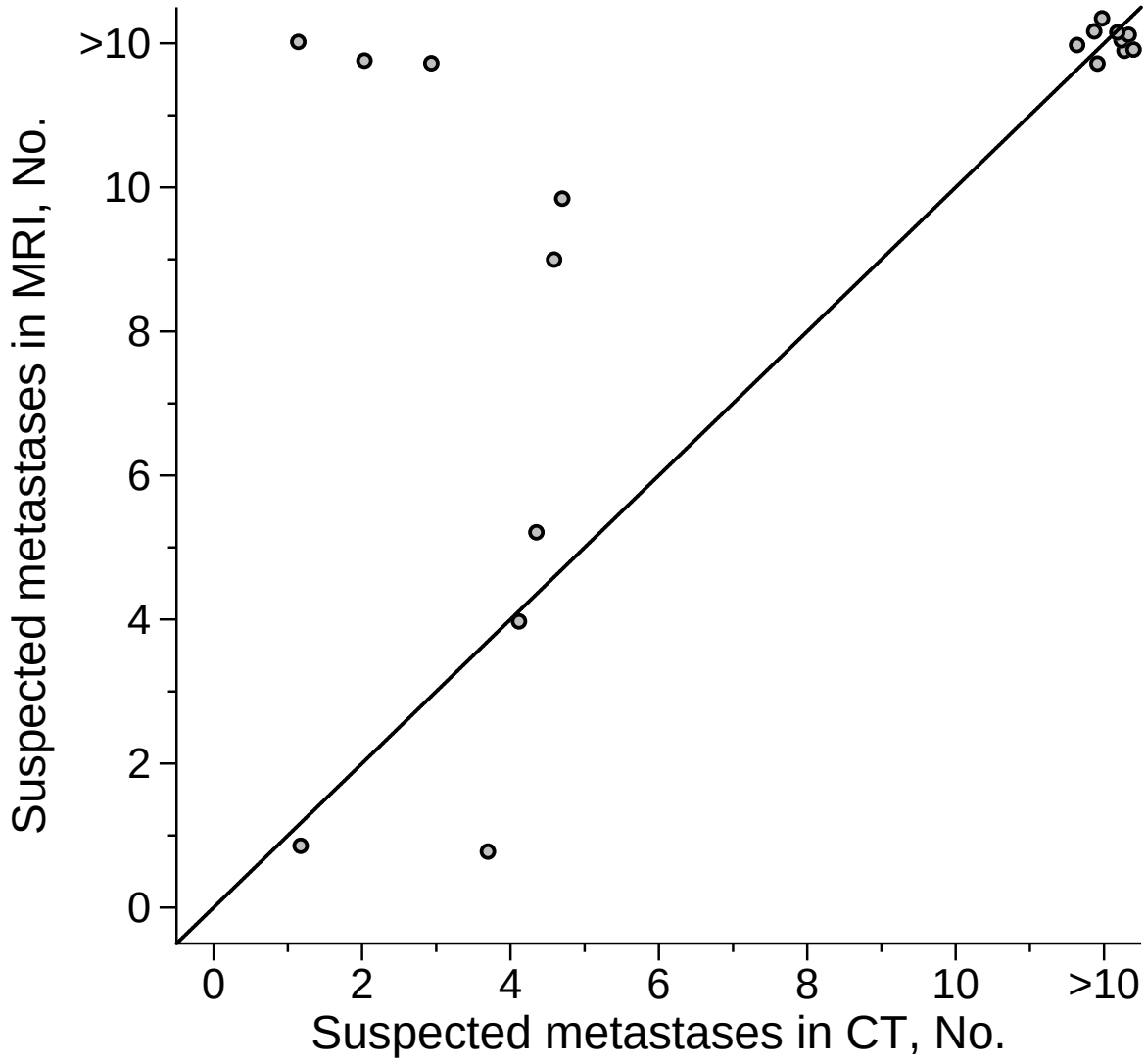
| | | | | | |
|---|---|---|---|---|---|
| Location of metastases at the time of diagnosis, No. (%) | | | | | |
| Liver only | 155 (72) | 81 (72) | 47 (75) | 11 (69) | 16 (70) |
| Liver and other sites | 60 (28) | 32 (28) | 16 (25) | 5 (31) | 7 (30) |
| Lungs | 36 | 20 | 8 | 3 | 5 |
| Bone | 25 | 11 | 9 | 2 | 3 |
| Lymph nodes | 14 | 9 | 3 | 1 | 1 |
| Subcutaneous | 9 | 7 | 2 | 0 | 0 |
| Kidney | 6 | 3 | 0 | 0 | 3 |
| Spleen | 3 | 1 | 1 | 0 | 1 |
| Gastrointestinal tract | 3 | 2 | 0 | 1 | 0 |
| Adrenal gland | 3 | 2 | 0 | 1 | 0 |
| Brain | 2 | 1 | 1 | 0 | 0 |
| Other[a] | 5 | 4 | 1 | 0 | 0 |
| 1st imaging modality, No. (%) | | | | | |
| US | 195 (91) | 98 (87) | 61 (97) | 15 (94) | 21 (91) |
| CT | 18 (8) | 14 (12) | 1 (2) | 1 (6) | 2 (9) |
| MRI | 2 (1) | 1 (1) | 1 (2) | 0 (0) | 0 (0) |
| Median interval between the 1st and 2nd imaging modality, days (range, IQR) | 17 (0-56, 8-27) | 16 (0-56, 7-27) | 21 (0-50, 12-27) | 11 (0-54, 8-18) | 21 (0-53, 8-31) |
| Status at the end of follow-up, No. (%) | | | | | |
| Alive with metastases | 12 (6) | 8 (7) | 2 (3) | 0 (0) | 2 (9) |
| Dead of metastases | 203 (94) | 105 (93) | 61 (97) | 16 (100) | 21 (91) |

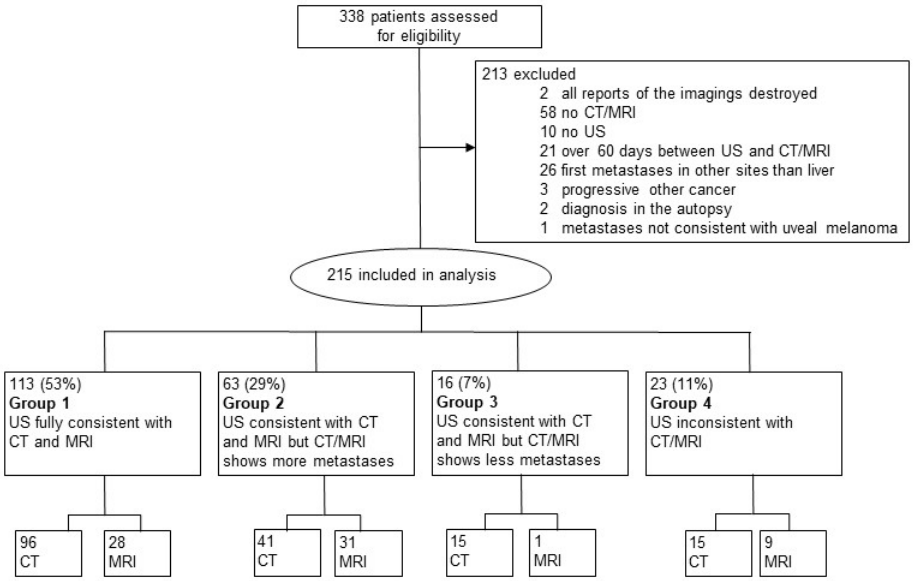
AJCC = American Joint Committee on Cancer; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; MRI = magnetic resonance imaging; N/A = not applicable; TNM = tumor, node, metastasis; US = hepatic ultrasonography.

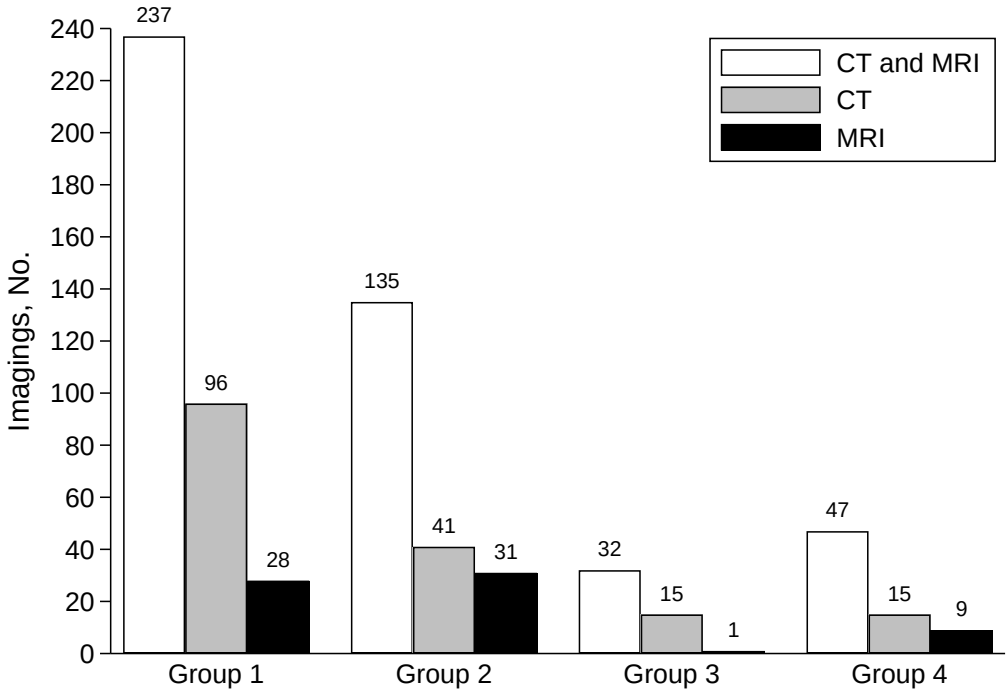
[a] pancreas, ovary, breast, chest wall, muscle; one each.

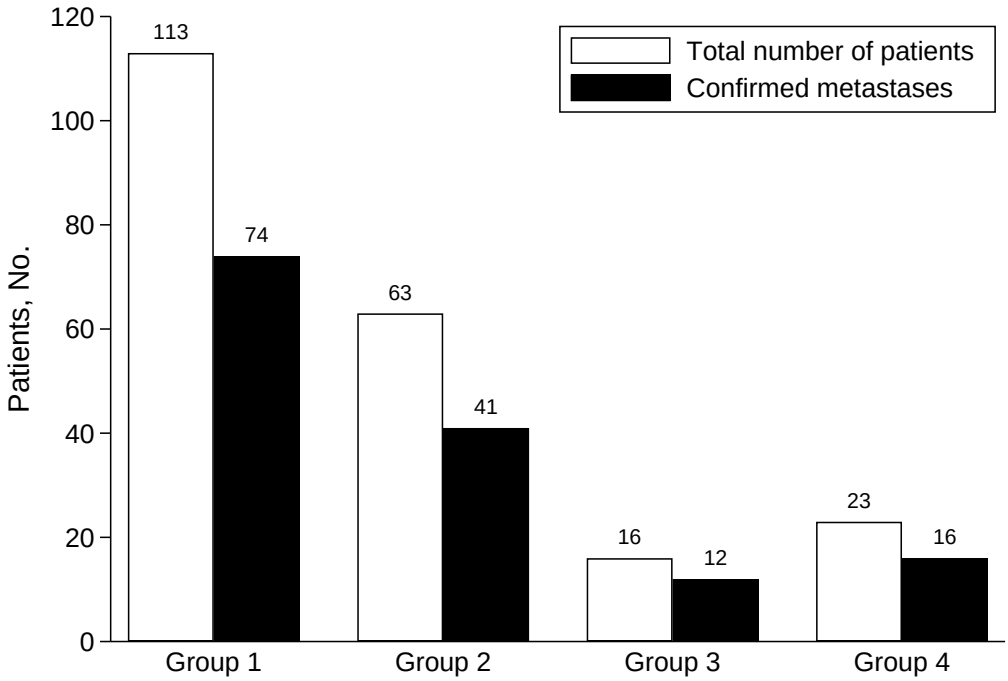

Suspected metastases in CT, No.
>10
10
8
6
4
2
0
0
2
4
6
8
10
>10
Suspected metastases in US, No.


Suspected metastases in MRI, No.
>10
10
8
6
4
2
0
0
2
4
6
8
10
>10
Suspected metastases in US, No.


Suspected metastases in MRI, No.
>10
10
8
6
4
2
0
0
2
4
6
8
10
>10
Suspected metastases in CT, No.


338 patients assessed for eligibility
213 excluded
2 all reports of the imagings destroyed
58 no CT/MRI
10 no US
21 over 60 days between US and CT/MRI
26 first metastases in other sites than liver
3 progressive other cancer
2 diagnosis in the autopsy
1 metastases not consistent with uveal melanoma
215 included in analysis
113 (53%)
Group 1
US fully consistent with CT and MRI
63 (29%)
Group 2
US consistent with CT and MRI but CT/MRI shows more metastases
16 (7%)
Group 3
US consistent with CT and MRI but CT/MRI shows less metastases
23 (11%)
Group 4
US inconsistent with CT/MRI
96 CT
28 MRI
41 CT
31 MRI
15 CT
1 MRI
15 CT
9 MRI





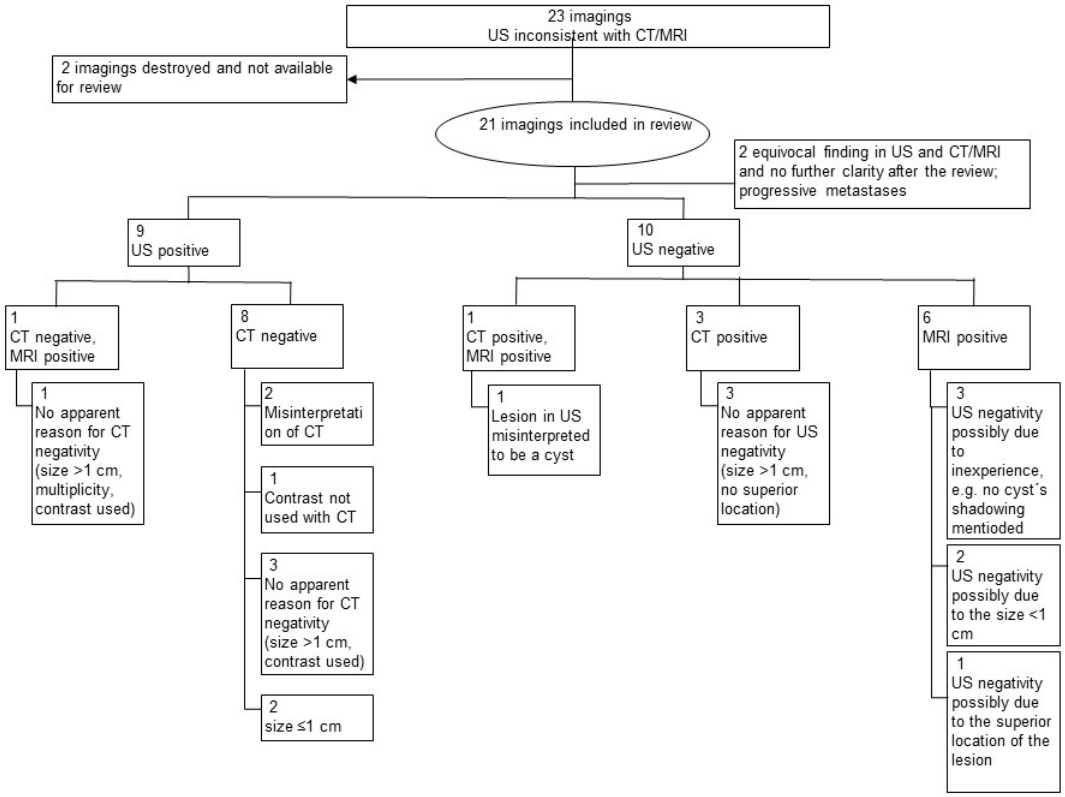

23 imagings
US inconsistent with CT/MRI
2 imagings destroyed and not available for review
21 imagings included in review
2 equivocal finding in US and CT/MRI and no further clarity after the review; progressive metastases
9
US positive
10
US negative
1
CT negative, MRI positive
8
CT negative
1
CT positive, MRI positive
3
CT positive
6
MRI positive
1
No apparent reason for CT negativity (size >1 cm, multiplicity, contrast used)
2
Misinterpretation of CT
1
Contrast not used with CT
3
No apparent reason for CT negativity (size >1 cm, contrast used)
2
size ≤1 cm
1
Lesion in US misinterpreted to be a cyst
3
No apparent reason for US negativity (size >1 cm, no superior location)
3
US negativity possibly due to inexperience, e.g. no cyst´s shadowing mentioded
2
US negativity possibly due to the size <1 cm
1
US negativity possibly due to the superior location of the lesion

**FIGURE CAPTION FOR THE SUPPLEMENTAL FIGURE 1**

**SUPPLEMENTAL FIGURE 1**. Cumulative frequency plot of recurrence-free interval.

**A Table of Contents Statement**

In this consecutive cohort of 215 patients with primary uveal melanoma, hepatic ultrasonography was diagnostic of metastases in 95% of patients. The findings also suggest that subsequent magnetic resonance imaging is a more sensitive staging modality than computed tomography in detecting hepatic metastases from uveal melanoma. Ultrasonography should be followed by magnetic resonance imaging in case of any new hepatic lesion.