Prospective study of surveillance testing for metastasis in 100 high-risk uveal melanoma patients

Étude prospective de suivi chez 100 patients atteints de mélanome uvéal à haut risque métastatique

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High risk of metastasis;
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Summary  Despite advances in the local treatment of UM, half of patients develop metastases typically to the liver with poor survival. Microscopic complete surgical resection (R0) of liver metastases improves survival in high selected patients. Early identification of high-risk patients might allow detection of asymptomatic metastases, and increase R0 liver surgery rate. From October 2006 to December 2009, we conducted a prospective study to detect early minimal lesions with 6-monthly liver function tests (LFTs) and liver MRI in 100 high-risk patients. High risk was defined by primary tumor clinical or genomic criteria: thickness > 8 mm or diameter > 15 mm, or extra-scleral extension, or monosomy 3 by FISH or aCGH. With a median follow-up of 49 months, the 5-year metastasis-free survival and overall survival were 47 and 33%, respectively. Of the 60 patients who became metastatic, 50 (83%) had exclusive liver metastasis.

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LFTs screening had no sufficient accuracy, but biannual MRI showed high predictive value to detect metastasis and select patients eligible for curative surgery: 25/50 underwent laparotomy and among them, 8/25 (32%) had a R0 surgery. Median survival after metastasis was 14 months, mean survival reached 40 months in the R0 resected population. Six-monthly liver MRI screening is recommended in patients with large tumors or genomic high risk in order to detect early patient candidates to complete resection of liver metastases.
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Résumé  Malgré un traitement local optimal du mélanome uveal, la moitié des patients vont développer des métastases le plus souvent hépatiques, de très mauvais pronostic. Seuls les patients bénéficiant d’une chirurgie microscopiquement complète d’une atteinte métastatique hépatique limitée ont une survie prolongée. La détection précoce de telles métastases chez les patients à haut risque de rechute et asymptomatiques permet d’espérer un meilleur taux de chirurgies complètes. D’octobre 2006 à décembre 2009, nous avons mené une étude prospective testant le bilan sanguin de la fonction hépatique et l’imagerie par IRM tous les 6 mois chez 100 patients à haut risque, défini sur des critères cliniques ou génomiques de la tumeur primitive : épaisseur > 8 mm ou diamètre > 15 mm, ou extension extralésionnelle, ou monosomie par FISH ou CGH. Avec un suivi médian de 49 mois, la survie sans métastase et la survie globale à 5 ans sont de 47 et 33 %, respectivement. Parmi les 60 patients qui ont développé des métastases, 50 (83 %) avaient une atteinte hépatique exclusive. Les tests sanguins de la fonction hépatique n’ont pas permis la détection des métastases au stade infraclinique ; en revanche l’IRM hépatique, avec une sensibilité et une valeur prédictive négative de 100 %, a permis de sélectionner les patients éligibles à une chirurgie curative : 25/50 ont bénéficié d’une laparotomie et parmi eux, 8/25 (32 %) d’une chirurgie R0. La survie médiane après diagnostic des métastases est de 14 mois pour l’ensemble des patients, la survie moyenne des 8 patients opérés R0 atteint 40 mois dans cette étude. Un suivi semestriel par IRM hépatique est donc recommandé chez les patients atteints de mélanome uveal à haut risque clinique ou génomique dans le but de détecter précocement les patients candidats à une chirurgie complète des métastases hépatiques.
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Introduction

Liver metastasis is the major challenge in uveal melanoma (UM). Up to 50% of patients develop metastases within a median time of 2.4 years: liver is the first site in 90% of patients, and the median survival with metastasis ranges from 3 to 12 months in the absence of effective treatments [1,2]. Very little is modified by the treatment: survival varies from 2–6 months with best supportive care, to 6–12 months with any systemic treatment and 10–24 months for liver procedures [3]. Microscopic complete resection of liver metastases is the best option, but remains feasible in less than 25% of resectable patients because of hepatic or extrahepatic extension of the disease [4]. However, some patients with metastatic disease do have long-term survival: 22% of 119 patients and 9% of 470 patients are alive 4 and 3 years after diagnosis of metastases in the series of the Memorial Sloan-Kettering Cancer Center [5] and institut Curie [6], respectively.

There is no consensus about the best imaging modalities or the optimal interval and duration of screening for metastases in newly diagnosed UM patients. Six-monthly liver ultrasound is recommended for all patients, without any significant demonstrated impact on survival or R0 liver resection rate in the large prospective published series: the metastatic rate ranges from 16 to 24% with follow-up modalities combining liver US, chest X-ray and serum liver function tests (LFTs) [7–9]. In a recent literature review, Augsburger et al. [10] found no evidence of a survival benefit for any regimen or frequency of surveillance for metastasis in UM patients. Magnetic resonance (MR) imaging has been shown to be the gold standard for early detection of liver metastases in different cancer types; its superiority has been demonstrated over ultrasound and computed tomography imaging mainly in colorectal cancer metastases [11]. MR imaging efficiency to detect liver metastases before the onset of symptoms was recently demonstrated in high-risk UM patients [12].

Beside clinical and pathological risk factors for metastasis, including large basal tumor diameter, ciliary body involvement, extra-ocular spread, epithelioid cell type, and high mitotic rate, genomic alterations of the tumor, affecting chromosomes 3, 6 and 8 mainly, have been identified by karyotype analysis, fluorescence in situ hybridization (FISH) and array comparative genomic hybridization (aCGH). Monosomy 3 has been the gold standard for metastatic prediction
in a series of 54 enucleated patients [13]. Genome-wide profiling in 86 primary tumors led to a genome-based classifier focusing on 8q gain associated with loss of 3 in 50% of cases leading to a 76% risk of metastasis [14]. Finally, monosomy 3 and gain of 8q by aCGH have been shown to be independent predictors for metastatic risk in multivariate analysis in 338 patients as recently published by Cassoux et al. [15]. FISH or multiplex ligation-dependent probe amplification (MLPA) may also be used to assess the prognostic value of chromosome 3 and 8 status, with a risk of failure and limitation by a partial view of genomic imbalances [16,17]. Molecular classification based on gene expression profiling of the primary tumor has been shown to be superior to monosomy 3 alone detected by aCGH or FISH [18]. Onken identified 2 subsets of UM called class 1 tumors-low risk of metastasis (1%), and class 2 tumors-high risk of metastasis (26%), using a PCR-based 15-gene assay comprising 12 discriminant genes which has been validated in a large prospective series of 609 tumor samples and is now available in US for routine clinical testing [19].

These recent advances in genetics and molecular biology underlying UM have improved the knowledge of prognostic factors, allowing for stratification of patients regarding their risk of metastasis, and leading to new strategies for surveillance and adjuvant clinical trials.

We conducted a prospective surveillance study for patients with high risk of metastasis combining clinical criteria and chromosome 3 status. The aim of our study was to facilitate the early identification of patients eligible for surgery to increase the complete surgical resection rate of liver metastases.

Materials and methods

Patients

Between October 2006 and December 2009, newly diagnosed high-risk patients were enrolled in this prospective unicentric study, institut Curie being a reference center for uveal melanoma care, and were planned to be screened according to the protocol until metastases were detected, and for a minimum of 3 years. High risk was defined by either clinical criteria (tumor thickness > 8 mm or largest tumor diameter (LTD) > 15 mm or extra-scleral extension), or monosomy 3. Other inclusion criteria were age > 18 years, absence of metastases, no contraindication to MRI, no social, medical or psychological condition preventing the protocol.

The clinical, pathological and genomic items were recorded in the French national database dedicated to UM (MACRO, Inferred 3.075). All events (local and distant relapses, secondary cancer, death from UM or any cause) were prospectively collected. Chromosome 3 loss was identified using aCGH or FISH in enucleated eyes as described in our previous work [14]. Patients underwent LFTs and liver MRI every 3 and 6 months, respectively; initial thoraco-abdominal CT scan was performed, and serum samples were collected every 6 months at the time of each clinical visit.

MR imaging protocol

MR imaging was performed on different 1.5T clinical systems. The liver MR imaging protocol and acquisition parameters are described in Wagner et al. [20]. All sequences covered the whole liver with a total examination time of approximately 30 minutes. Diffusion-weighted imaging was not systematically performed at the time of this study. An information document was sent to each patient’s radiologist and a MRI central review was organized at institut Curie. MRI was considered as normal in the absence of lesion or in case of any typically benign lesion. MRI was abnormal when lesions described as possible metastases following Wagner et al.’s criteria [20] were present. The onset of lesions non-typical of metastasis led to classify liver MRI as unreliable. Equivocal abnormalities were investigated by repeating liver MRI 3 months later. MRI suspicious abnormalities conducted the patient to a pathological diagnostic procedure. CT-guided percutaneous biopsy or surgical liver biopsy was performed for lesions not easily accessible via percutaneous route in non-R0 resectable patients. In R0 operated patients with a complete description of the liver disease, imaging findings were compared to surgical and pathological conclusions.

Liver MRI was planned on a six-monthly basis, unless highly suspicious lesions were identified and discussed during weekly multidisciplinary meetings. Decision of liver surgery in a curative intent was based on a limited number of lesions < 4, and the absence of detectable extensive capsular miliary disease [4]. Non-resectable patients were referred to medical oncologists, and enrolled in a clinical trial if possible.

Statistical analysis

The main objective of the study was to increase the R0 resection rate from 10 to 30% (α risk = 0.04 and β risk = 0.05) in high-risk uveal melanoma patients eligible for liver metastasis surgery. High risk was defined by an estimated 5-year metastasis-free survival rate not exceeding 50%, due to either clinical criteria (tumor thickness > 8 mm or LTD > 15 mm or extra-scleral extension), or monosomy 3. These criteria were settled given the retrospective series of 2241 patients from our institution: 42% of patients had a primary tumor with LTD > 15 mm and/or thickness > 8 mm; monosomy 3 was detected in 54% of enucleated eyes by FISH. These features were associated with a shorter metastasis-free interval and a poor survival [21].

Primary endpoint was the R0 resection rate by liver surgery. Secondary endpoints were overall survival, metastasis-free survival, sensitivity, specificity and predictive values of LFTs and MRI. R0 surgery was defined as the microscopically complete resection of metastases. The metastasis-free survival (MFS) was defined as the time elapsed between the date of diagnosis of the primary tumor and the date of first metastasis. Overall survival (OS) was defined as the time elapsed between the diagnosis of the primary UM and the death of any cause. Descriptive statistics were provided for patients’ demographics, baseline characteristics, laboratory parameters, and imaging findings. Survival probabilities were calculated by the Kaplan–Meier method and compared using the log-rank test. Differences were considered to be significant when the log-rank P-value was < 0.05. In order to identify variables associated with R0 resection and MFS, we performed a Cox regression analysis of prognostic factors.
The study was approved by institutional ethics committee and review board, and followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants.

**Results**

During the study period, 102 patients were enrolled, but 2 did not meet eligibility criteria (one was 14-years-old, one had synchronous metastases). Finally, 100 patients were suitable for the study. Demographic data and tumor characteristics are summarized in **Table 1** and matched to the institut Curie registered cohort of 4219 consecutive UM patients at the time of analysis, excluding the 100 high-risk patients of the present study. Not surprisingly, the primary tumor LTD and thickness were larger in high-risk patients (18 and 11.7 mm, respectively versus 13.5 and 5.2 mm), and were more frequently associated with retinal detachment; 90% of high-risk patients underwent enucleation, but only 11.8% of the unselected patients in our institution. The majority of high-risk enucleated patients had mixed (54.5%) or epithelioid (22.2%) UM histotype and monosomy 3 was detected in 52 of 86 (61%) untreated primary tumors, either by aCGH (n = 48) and/or FISH (n = 46). Six cases with partial loss of chromosome 3 were excluded. Genomic analysis was not informative in 4 cases of large tumors for technical issues. Additional abnormalities were detected by aCGH on chromosomes 6, 8 and 16: monosomy 3 and any type of gain of chromosome 8 were associated in 24 patients (29%).

The median follow-up was 49 months (range, 45–54 months) in the 100 patients.

Three patients underwent enucleation for local relapse. Surveillance imaging detected metastases in 60/100 patients (60%); metastases were limited to the liver in 50 patients (83%), or involved liver and extra-hepatic sites in 6 (10%); metastases were only located outside the liver in 4 patients (7%) involving lung in 2, pancreas in 1, and skin in 1 patient. At the time of detection, all patients but 2 were asymptomatic (98%): one had palpable cutaneous metastasis, one had symptoms of liver dysfunction (fatigue, anorexia and weight loss). Following discussion at our multidisciplinary board, the first treatment for the metastatic disease consisted in surgery in 28 (47%), systemic treatment in 26 (43%) and best supportive care in 6 patients (10%). Laparotomy was performed in 25 patients considered to be operable and to have potentially complete resectable liver disease. The number of lesions described by the surgeon was 1 in 2 patients (8%), 1 to 4 in 7 patients (28%), 4 to 8 in 5 patients (20%), > 8 in 11 patients (44%). The metastases involved the 2 hepatic lobes in 18 patients, and ailiary was assessed peroperatively in 21 patients (84%). The resection was microscopically complete (RO) in 8/25 (32%) operated patients, corresponding to 8/50 (16%) patients with metastases confined to the liver.

During the screening period, 3 patients developed a second primary cancer: thyroid and pancreatic adenocarcinoma, clear cell renal carcinoma.

**Survival**

In this cohort of 100 high-risk patients, the 5-year OS rate was 47% (95%CI; 36—61.5) with a median OS of 59 months; the 5-year MFS was 33% (95%CI; 23.3—48.1), with a median MFS of 35 months (**Fig. 1**).

In univariate analysis, male gender, fusiform histotype and normal chromosome 3 were statistically significant favorable prognostic factors for MFS (**Fig. 2**); moreover, patients with a tumor genomic profile by aCGH combining monosomy 3 and any gain of chromosome 8 were of very poor prognosis with a 3-year MFS of 12% (95%CI; 5—36) and a median MFS of 13 months whereas normal 3 and monosomy 3 patients reached 3-year MFS of 78% (95%CI; 63—97) and 24%

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**Table 1** Patients’ characteristics: unselected cohort of 4219 uveal melanoma (UM) consecutive patients referred to institut Curie and registered in the database at the time of analysis; high-risk population of 100 patients enrolled in the study.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Curie UM (n = 4219)</th>
<th>High-risk UM (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>61 [4—96]</td>
<td>59 [32—83]</td>
</tr>
<tr>
<td>Sex ratio (male/female)</td>
<td>2046 / 2173</td>
<td>47 / 53</td>
</tr>
<tr>
<td>Median tumor diameter</td>
<td>13.5 mm [1—35]</td>
<td>18 mm [10.9—26]</td>
</tr>
<tr>
<td>Tumoral thickness (mm)</td>
<td>5.2 mm [0.5—18.2]</td>
<td>11.7 mm [2.7—17]</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>1296 / 4161 (31%)</td>
<td>75 / 97 (77%)</td>
</tr>
<tr>
<td>Primary tumor treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>3721 (88.2%)</td>
<td>10 (10%)</td>
</tr>
<tr>
<td>Proton beam therapy</td>
<td>3140</td>
<td>10</td>
</tr>
<tr>
<td>I 125 plaque</td>
<td>573</td>
<td>—</td>
</tr>
<tr>
<td>External radiotherapy</td>
<td>8</td>
<td>—</td>
</tr>
<tr>
<td>Enucleation</td>
<td>498 (11.8%)</td>
<td>90 (90%)</td>
</tr>
<tr>
<td>Histological cell type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelioid</td>
<td>138 (28.6%)</td>
<td>20 (22.2%)</td>
</tr>
<tr>
<td>Fusiform</td>
<td>183 (37.8%)</td>
<td>21 (23.3%)</td>
</tr>
<tr>
<td>Mixed</td>
<td>152 (31.5%)</td>
<td>49 (54.5%)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (2.1%) NA = 14</td>
<td>—</td>
</tr>
<tr>
<td>Monosomy 3 (aCGH±FISH)</td>
<td>169 / 299 (56%)</td>
<td>52 / 86 (61%)</td>
</tr>
</tbody>
</table>
Figure 1. Overall survival (a) and metastasis-free survival (b) in 100 high-risk patients using the Kaplan–Meier method.

(95%CI; 14–42); with a median MFS of 62 and 19 months, respectively.

By the close of the study, 43 patients were dead (metastatic disease 41, second cancer, 1 myocardial infarction 1), 15 patients were alive with metastasis. Two patients were alive after diagnosis of second primary cancer. Thirty-four patients were free of disease at the time of the analysis. The median overall survival after diagnosis of metastasis was 14 months (range, 11–18) for all 60 patients. In the R0 resected subgroup of 8 patients, 3 are free of disease 30+ to 41+ months, and 4 are alive 38+ to 101+ months after liver surgery. The mean survival was 40 months (range, 8–101 months) in these highly selected patients.

Figure 2. Kaplan–Meier curves: actuarial rates of metastasis-free survival according to presence (solid line) or absence (dashed line) of monosomy 3 by FISH or aCGH in primary tumors of 100 high-risk patients. Statistical significance determined by the log-rank test is shown.

Biological and imaging screening
Of the 100 enrolled patients, 92 patients underwent at least the first set of MRI and LFTs, and 14 did not meet the 3-year planned screening program (main reasons: long travel time or comorbidities, claustrophobia or MRI refusal). The final analysis was performed in 78 patients, corresponding to 39 metastatic and 39 non-metastatic patients at the end of the study period.

Serum LFTs consisted of total bilirubin, transaminases (ALT/AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH) every 3 months for 3 years. LFTs results were considered abnormal if at least one parameter was >2 fold the upper limit of normal (ULN) before the first detection of metastases (by MRI or otherwise). Eighty-five patients had a complete biological follow-up dataset; the median number of LFTs per patient was 8 (range, 1–12). Sensitivity and specificity for LFTs were 49% (95%CI; 38–60) and 54% (95%CI; 43–65), respectively, with positive predictive value (PPV) and negative predictive value (NPV) of 51% both (Table 2).

The median number of MRI per patient was 4 (range, 1–6). The median time to the first abnormal MRI was 30...
months. Sensitivity and negative predictive value of MRI were 100%, whereas specificity and positive predictive value reached 80% (95%CI; 71–88) and 83%, respectively (Table 3).

During the study period, the number of abnormal or unreliable liver MRI ranges from 15.4 to 29.8%, (Fig. 3) leading to pathological confirmation of liver metastases in 39/47 patients. The planned MRI schedule included liver imaging every 6 months from inclusion to 36 months. The median observed time to each MRI achievement was 5, 11, 17, 23, 29 and 36 months. Suspicion of subcapsular miliary lesions by MRI in 8 patients was confirmed by surgery in all 8 patients. The presence of miliary was detected only by surgery in 4 patients, in the absence of miliary disease at the time of preoperative MRI. Numbers were too small for statistical analysis.

| Table 2 | Liver Function Tests according to MRI detection of liver metastasis. |
|---------|-------------------------|-------------------|
|         | Normal liver MRI | Abnormal or unreliable liver MRI | Total number of patients |
| Normal LFTs | 21 | 20 | 41 |
| Abnormal LFTs ≥ parameter > 2ULN | 18 | 19 | 37 |
| Total number of patients | 39 | 39 | 78 |

Sensitivity: 49%; PPV: 19/37 (51%); specificity: 54%; NPV: 21/41 (51%).

| Table 3 | Liver metastases proven by biopsy or surgery according to their MRI detection. |
|---------|-------------------------|-------------------|
|         | Absence of liver metastases | Proven liver metastases | Total number of patients |
| Normal MRI or benign lesion | 31 | 0 | 31 |
| Abnormal or unreliable MRI | 8 | 39 | 47 |
| Total number of patients | 39 | 39 | 78 |

Sensitivity: 100%; PPV: 39/47 (83%); specificity: 80%; NPV: 31/31 (100%).

Discussion

Large basal tumor diameter and monosomy 3 have been shown to be associated with a poor survival after treatment of primary uveal melanoma. In the adjuvant randomized phase III study conducted at institut Curie in the eighties in 348 high-risk patients defined by thickness > 5 mm and/or LTD > 10 mm, the 5-year OS was 70% with no difference between dacarbazine and control arm [22]. Large tumors (LTD > 15 mm) patients who had not received chemotherapy showed a 5-year OS rate of 57% with a 6-month US liver follow-up (Piperno-Neumann, personal communication). Monosomy 3 correlated strongly with metastatic death in the series of Prescher and Scholes, data indicating a reduction in the 5-year survival to 30% [13,23]. More recently, the 5-year MFS was < 40% in patients with loss of chromosome 3 alone and < 20% in patients with monosomy 3 and 8q gain [15]. The present study in 100 patients with large tumors or monosomy 3 showed a 5-year OS rate of 47% and a 5-year MFS of 33%, in line with reported poor prognosis rates in this group of patients.

Six-monthly MR imaging detected the metastases before the onset of symptoms in 98% of the 100 patients, avoiding any comparison between symptomatic versus asymptomatic patients in terms of baseline prognostic factors or survival. The diagnosis of metastasis at a substantial less advanced and asymptomatic substage may increase early identification of patients suitable for potentially curative surgery, reduce tumor-related morbidity and identify eligible patients for innovative treatments in clinical trials. In the 50 patients with metastases confined to the liver, 25 were considered resectable following preoperative staging and underwent laparotomy in the intent of R0 liver surgery. Liver surgery consisted in R0 resection in 8 (32%) operated patients, corresponding to 16% of liver-restricted metastatic patients. In our study, the rate of patients who achieved curative surgery is in the same range that the 17/52 operated patients (32%) corresponding to 17/97 (16%) potentially
resectable patients reported by Gomez et al. [24]. Mean survival with metastasis in these highly selected patients reached 40 months consistent with previous reports: in the Curie’s retrospective series of 252 operated patients, the median survival of 76 R0 (30%) resected patients was 27 months whereas patients with incomplete resection had a median survival of 14 months [4]; the survival rates were 27 and 8 months in 17 R0 and 137 non-resected patients in the prospective Liverpool study [24].

Serum LFTs screening showed a low sensitivity (49%) and a poor PPV (51%) as previously published; the lack of specificity of LFTs elevations in hepatic dysfunction is well known, and combination with chest X-rays and liver ultrasonography did not improve the detection rate in large screening studies [7—9].

Other serum markers have been tested as potential tools for surveillance in UM (i.e. vascular endothelial growth factor, S-100 protein, insulin-like growth factor 1, osteopontin), but no study has demonstrated their utility in a large prospective cohort [25]. Madic et al. [26] developed a molecular tool to detect circulating tumor-derived DNA (ctDNA) in the plasma from UM patients as a biomarker of tumor burden and treatment monitoring, based on a highly sensitive PCR-derived method due to the presence of specific GNAQ and GNA11 mutations in 85% UM. In 26 metastatic UM patients with detectable mutations, ctDNA was detected in 84% and correlated with the presence of liver miliary, metastatic volume estimated by MRI and survival [27]. Ongoing studies will try:

• to assess the clinical usefulness of ctDNA levels as a surrogate marker for clinical decision in metastatic patients;
• to detect micrometastatic disease at early stage, and select high-risk patients for clinical trials in the adjuvant setting.

Different imaging modalities have been assessed in UM surveillance. In the context of selecting UM patients for R0 liver surgery of metastases, MRI appears the most sensitive available imaging tool for extent of metastasis detection, and this may possibly argue for earlier detection of metastasis [25]. Efficiency of liver MRI has been demonstrated by the Liverpool group for UM screening [12]. The authors included patients if their risk of metastatic death at 5 years exceeded 50%, using their prognostication tool combining clinical stage, histological grade and chromosome 3 status. The median follow-up was only 28 months, and the median overall survival of 34 months was shorter than the median OS of 59 months in our study. This could be explained by a shorter time to detection of metastasis of 18 months versus 30 months in our study, related to genomics. While 87/90 (97%) of the English patients displayed tumors with loss of chromosome 3, with no information regarding the chromosome 8 status, in our study 25 patients had tumors with monosomy 3 (29%), and 24 had tumors with monosomy 3 and 8 gain (28%), corresponding to median MFS of 19 and 13 months, respectively.

We looked at the therapeutic implications in terms of R0 surgery rate and survival, and tried to correlate MRI findings to surgical and pathological conclusions. In this high-risk population, 60% of the patients became metastatic after a median time of 30 months. The planned MRI screening program was feasible, and the compliance to the planned schedule was good. In our study, sensitivity of preoperative MRI reached 100%, and specificity remained high (80%) with only a few false positive cases. MRI detection of UM liver metastases requires trained radiologists in this rare tumor, since metastases are frequently smaller than 5 mm and preferentially located in the subcapsular area. The addition of diffusion-weighted imaging did not increase MR sensitivities for liver metastasis detection in UM as recently published [20].

Several authors compared F-fluorodeoxyglucose (FDG) PET/CT with CT or MRI in UM, even though 41% of UM may be FDG avid compared to 100% of cutaneous melanomas [28—30]; all these studies suggest MRI is the best method to detect UM metastases today, consistent with perioperative surgical staging, and stress the caveats of CT (lack of sensitivity and specificity, radiation exposure) or PET/CT (lack of detection of small lesions and high false-positive rate). Liver ultrasound is non-invasive, non-expensive and widely used in Europe, but may not be the imaging modality of choice in the United States where 30% of adults are obese; furthermore, its high sensitivity is very dependent from the operator [25]. Preoperative staging with liver MRI seems the best imaging option to detect metastases and select properly patient candidates for R0 surgery, and the best way to offer them a prolonged survival after metastasis.

The main strengths of this study are: the number of 100 high-risk patients prospectively enrolled in a short period of time of 3 years; the long follow-up of 49 months; the correlation between imaging and surgical and pathological findings.

The main weaknesses are: the absence of comparison to a similar subgroup in which no surveillance testing was performed; unfortunately, we and others did not identify such a study in the peer-reviewed literature [10]; the absence of cost-effectiveness study; however this economic aspect was enhanced by selecting high-risk patients; systematic MRI screening in 159 UM patients led to detect metastases in 9% of patients after a mean follow-up of 5.7 years [31].

According to recent NICE recommendations [32], prognostication and surveillance have to be led by a multidisciplinary team with the expertise in this rare cancer. In France, the Melachonat network (INCa grant for rare tumors) gathers expert centers for UM treatment with the aim to facilitate access to recommended medical care for the French patients. Metastatic risk prediction is based on clinical, pathological and genetic features determined by aCGH. Since 2009, fine needle aspiration biopsies (FNAB) have been routinely performed by opthalmologists on smaller tumors before treatment by proton beam radiotherapy or iodine 125 brachytherapy. Intraoperative FNAB is safe as reported by several authors, and provides successful genetic testing with no increase in ocular morbidity or metastatic risk [33]. Only patients with very small tumors < 5 mm or declining the biopsy procedure cannot benefit from this genomic prognostication. All patients should be offered an holistic information to discuss their risk, the surveillance options and the emotional impact of screening. Six-monthly oncolgical follow-up and liver MRI should be proposed to high-risk patients for 5 years. In the other hand, genomic low risk patients could be reassured and managed with 6-monthly liver US for the 5 first years, then annually. The adjuvant randomized phase III trial FOTEAJD in running
in 302 clinical and genomic high-risk patients (LTD > 15 mm with retinal detachment or LTD > 18 mm or monosomy 3 with or without 8 gain); in this study, all patients benefit from an intensive surveillance program, half of them receive 6 cycles of fotemustine after the local treatment of the primary tumor (EudraCT: 2008-005691-27).

**Conclusion**

In this prospective study of 100 high-risk UM patients, LFTs screening showed no sufficient accuracy in the detection of liver metastases. Biannual MR imaging confirmed a high predictive value but requires trained radiologists to detect small lesions. The observation of a miliary diffusion of metastases may be highly suggested by MRI, but peroperative confirmation is needed before decision of major liver surgery. Half of the patients underwent surgery after early detection of metastases, leading to a R0 liver resection rate of 32% in the liver operated patients. With a median follow-up of 49 months, the 5-year MFS and the 5-year OS were 33 and 47%, respectively in this high-risk population. Median survival after metastasis was 14 months, mean survival reached 40 months in the R0 resected 8 patients. Six-monthly liver MRI screening is recommended in patients with large tumors or genomic high risk in order to detect early patients candidate to complete resection of liver metastases.

**Disclosure of interest**

The authors declare that they have no conflict of interest concerning this article.

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