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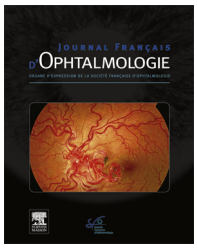

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Prospective study of surveillance testing for metastasis in 100 high-risk uveal melanoma patients

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

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Detection

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 accurary, 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.

MOTS CLÉS
Mélanome uvéal ;
Haut risque de métastase ;
Imagerie par résonance nucléaire ;
Métastases hépatiques ;
Détection

Résumé Malgré un traitement local optimal du mélanome uvéal, 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 extrasclérale, 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 uvéal à haut risque clinique ou génomique dans le but de détecter précocement les patients candidats à une chirurgie complète des métastases hépatiques.

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