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Iterative treatment with surgery and radiofrequency ablation of uveal melanoma liver metastasis: Retrospective analysis of a series of very long-term survivors

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ABSTRACT

Background: After treatment of primary ocular uveal melanoma (UM), up to 50% of patients will develop metastases, mostly in the liver. Systemic treatments do not provide any overall survival benefit for these patients and surgery remains the most effective therapy for selected patients. Radiofrequency ablation (RFA) alone or in combination with surgery is frequently used to spare hepatic parenchyma. When patients relapse after treatment of their first metastases, and when the liver recurrence is limited, new local liver treatment is questionable.

Methods: A total of 14 patients with liver metastases from uveal melanoma (LMUM) were retrospectively evaluated. All patients had a complete first liver resection and a second treatment with RFA. Overall survival, recurrence-free interval after the first and the second treatment was evaluated.

Results: Treatment of hepatic recurrence was percutaneous RFA for ten patients and per-operative RFA for four patients associated with new metastasectomy. The median time to onset of LMUMs after ocular UM treatment was 50 months, and the median time to recurrence of hepatic metastasis after the first liver treatment was 20 months. The overall survival was 70% at five years and 35% at ten years. The recurrence-free interval was 50% and 56% at two years after the first and the second treatment, respectively.

Conclusion: Prolonged survival can be achieved by exclusive and iterative local treatment combining surgery and RFA in a small proportion of patients with a first recurrence of isolated LMUM.

Introduction

Uveal melanoma (UM) is the most common primary ocular malignancy among the adult Caucasian population. Despite successful treatment of the primary tumour, up to 50% of patients will develop metastases, mostly in the liver (90% of patients), with a metastatic median overall survival of 4–15 months [1,2]. Chemotherapy or targeted therapies do not provide any overall survival benefit for these patients [3,4]. Indeed, UM patients have dramatically lower response rates to immunotherapy than patients with cutaneous melanomas [5–8] and other local treatments such as intra-arterial chemotherapy, chemoembolization and radioembolization have not shown a significant therapeutic efficacy [9–13]. Intra-arterial chemosaturation with melphalan appears to be encouraging [14–16] but must be confirmed in a larger series of patients with a long follow-up. Taken together, surgery currently remains the most effective therapy for selected patients. In this setting, it has been shown that R0 (microscopically complete) resection could achieve median overall survivals reaching up to 27

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months compared with 11 months in patients with R1 or R2 resections [17–19]. Furthermore, it has been suggested that the use of radiofrequency ablation (RFA) alone or in combination with surgery could allow increasing the number of patients with negative margins. In our previous published series, we demonstrated that RFA ablation was as effective as surgery alone in that context [20]. When patients relapse after treatment of their first metastases, it is most often exclusively in the liver. In such situations, the management of limited recurrence remains poorly know and the relevance of a new local liver treatment is still a matter of ongoing debate. At our centre, repeated ablation of recurrent liver metastases of uveal melanoma (LMUM) has been attempted whenever technically feasible. .

Hence, the purpose of this monocentric retrospective study was to analyse the survival of patients who underwent percutaneous or per-operative RFA to treat hepatic recurrence following an initial R0 surgical treatment.

Methods

From January 2000 to December 2014, patients with LMUM who underwent hepatic resection with curative intent were identified from our prospectively maintained surgical database and retrospectively analysed. This retrospective study had IRB approval, and informed consent was waived.

R0 resected patients were first selected. According to our institutional practice, after R0 resection, patients underwent surveillance without chemotherapy. Patients were evaluated by liver MRI every four months during a period of three years and by thoraco-abdomino-pelvic CT scan once a year. When liver recurrence was suspected a new thoraco-abdomino-pelvic CT scan was performed to rule out any extra-hepatic involvement. Patients were then discussed in a multidisciplinary oncological meeting and were offered liver local treatment combining surgery and/or RFA whenever possible. The decision was made on a case-by-case analysis taking into account the number and size of the lesions, their location (proximity to major hepatic vessels and central bile ducts), the time to onset of recurrence, the general condition of the patient and its co-morbidities.

Data collection

The patient charts were retrospectively reviewed, and the following data were collected: age, sex, characteristics of primary UM and treatment, age at time of liver metastasis and time interval from the initial treatment of the primary uveal melanoma to metastasis. For the first metastatic liver event and for hepatic recurrence, the following were recorded: intrahepatic tumour number, location and size of metastases, presence of miliary disease (more than five lesions <5 mm located mainly in the area of the hepatic subcapsular region), type of surgical resection of the first metastases, type of treatment of recurrence of metastases with RFA, recurrence-free interval between the two procedures, treatment of metastatic recurrence after the second procedure, the date of last follow-up and date of death. The metastatic tumour size was defined as the largest diameter of the metastatic lesion. The liver resections were classified as metastasectomy, segmentectomy (1 or 2 segments) or major hepatectomy (3 segments or more).

Genomic analysis of LMUM and ocular UM

DNAs were obtained from snap-frozen samples according to standard procedures (proteinase K/RNAseA treatment and phenol/chloroform extraction using PLGL (Eppendorf, Hamburg, Germany), then qualified and quantified with a Nanodrop and a Qubit dsDNA BR Kit (Thermo Scientific, Wilmington USA). Up to 1 μg tumour and reference DNA were labelled and cohybridised to the NimbleGen or Agilent Microarrays. The slides were washed and scanned according to the manufacturers' instructions. Images were acquired, data extracted and produced files analysed on suitable devices and softwares (For Nimblegen: GenePix 4000B, V.6.6 Software, NimbleScan V.2.5, SignalMap V.1.9 (Roche NimbleGen Inc. Madison USA); For Agilent: SureScan, CytoScan V.2.7, CytoGenomics V.2.7 (Agilent Technologies, Santa Clara, USA). The quality of aCGH was assessed on Log2(R) standard deviation, smoothing signal and sex mismatch.

Then, patients were classified according to the status of chromosome 3 (disomy "D" or monosomy "M") and chromosome 8 (normal "nl", or with any type of gain "g"). Four risk classifications were defined as Low Risk: "D3/8 nl", Intermediate Risk: "D3/8g"and "M3/8 nl", High Risk: "M3/8g" based on the work of Cassoux et al. [21].

RFA procedure and liver MRI post-RFA ablation

The radiofrequency procedure and liver MRI post-RFA ablation were described previously [20]. Before RFA, a fine needle aspiration biopsy (22-gauge Chiba needle; Cook Medical, Bloomington, IN, USA) was obtained to confirm the malignant nature of the lesion. Expandable electrodes were then inserted under ultrasound guidance into the centre of the lesion for the per-operative procedure or under US or CT guidance for percutaneous procedure. The efficacy of RFA was evaluated by MRI two months after the procedure. Image subtraction at all dynamic acquisition phases (T1 with injection minus T1 without injection) were used to sensitize the detection of residual contrast enhancement [22]. The treatment was considered complete when no residual contrast enhancement was present in an ablation zone with a diameter larger than the initial lesion size.

Statistical analysis

Quantitative data are reported as median and ranges, and qualitative data were presented as numbers and proportions; missing data were not taken into account. The survival curves were constructed according to the Kaplan-Meier method. Overall survival was defined as the time from metastasis diagnosis to the occurrence of death from any cause. Two recurrence-free intervals were estimated. The first one was defined as the time from the treatment of metastasis to a first recurrence. The second one was defined as the time from radiofrequency ablation to a second recurrence (patients without post-RFA recurrence were censored at the date of last news.) All analyses were performed using R software (version 3.22; http://cran.r-project.org).

RESULTS

Among 97 patients operated with curative intent for LMUM between January 2000 and December 2014, 14 (14%) had two successive local treatments in the liver. The median follow-up of these 10 men and 4 women was 15.6 (4–19.5) years following the treatment of the primary ocular UM. The median age of onset of the primary UM was 52.5 (31-70) years. Clinical characteristics and treatment of the UM are presented in Table 1.

Characteristics and treatment of the first liver metastasis and metastatic recurrence

(Table 2) The median age of onset of LMUM was 59.5 years (range 42–72). None of the 9 patients treated with proton beam

Table 1
Patient (n = 14) demographic and clinical features.

Variable	
Median Age of onset metastases (years)	52.5 [31-70]
Sex ratio (male/female)	M 10/F 4
Primary Largest tumor diameter (median,mm)	16.2 mm [12–22]
Primary Tumor thickness (median, mm)	8.8 mm [3.2–14]
Treatment of primary	
Proton beam radiotherapy	9 (0.64)
Enucleation	5 (0.36)
Median Age of the first liver metastasis (years)	59.5[42 - 72]

showed ocular recurrence. The median time to onset of LMUMs after UM treatment was 50 months (range 8–155). The number of LMUMs was one in four patients, two metastases in three patients, three metastases in four patients and four metastases in three patients. The mean size of the metastases was 14.8 ± 12.7 mm. The lesions were unilobar in nine patients (64%) and bilobar in five patients (36%). All these patients underwent R0 resection of their lesions.

Before the recurrence of LMUM, no patients received systemic treatment after treatment of the first metastases. The median time to recurrence of hepatic metastasis was 20 months (range 2–123). Four patients (29%) recurred within one year and the remaining ten (71%) recurred after one year. Recurrences were single LMUMs in nine patients, two LMUMs in one patient, three LMUMs in two patients, and five LMUMs in two patients. The mean size of the all lesions was 9.4±6.7 mm. A total of 11 percutaneous RFA procedures and 6 per-operative RFA procedures were performed, the locations of which are shown in Fig. 1. The mean size of the lesions treated with RFA was 12.6±6.6 mm. All patients who had a single metastasis (nine patients) had percutaneous RFA as well as one patient who had two metastases. The remaining four patients had per-operative RFA associated with new metastasectomies. In these patients, the mean size of the surgically removed lesions was 4.7±3.4 mm. No complications related to surgery or radiofrequency ablation were recorded in these patients.

Follow-up after treatment with RFA

Eight patients died of new hepatic recurrences associated with pulmonary recurrence in five cases. In three patients, hepatic and pulmonary recurrences were isolated; in two patients, it was

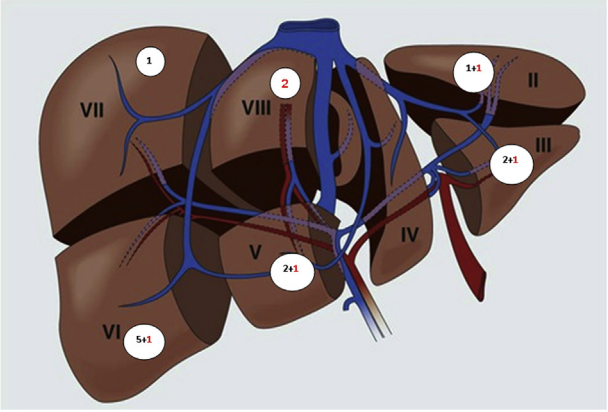

Figure 1. schematic representation according to Couinaud's classification of the localization of LMUM treated by RFA (11 per-cutaneous procedure in black, 6 surgical procedures in red).

associated with bone (one patient) and cerebral involvement (one patient). All but one of these patient received chemotherapy at diagnosis of recurrence after the second treatment with RFA. The six remaining patients were still alive at last follow-up, and four patients had received no systemic treatment. The other two patients experienced hepatic progression treated either by chemotherapy or by immunotherapy.

The overall survival after diagnosis of the first metastasis is presented in Fig. 2A. Survival at 5 years was 0.70 (range 0.49–1.0) and at 10 years was 0.35 (range 0.13–0.92). The overall survival after post-radiofrequency ablation is presented in Fig. 2B**.** Survival at 2 years was 0.68 (range 0.47–0.99) and at 4 years was 0.45 (range 0.23–0.90). The median follow-up after the diagnosis of the first liver metastasis was 7 (2.3–14) years. The median follow-up after the R0 resection was 3.9 (1–5.5) years.

Recurrence free survivals between the first surgical treatment of metastases and the date of onset of hepatic recurrence are provided in Fig. 3A. The recurrence free survivals were 0.64 (range 0.44–0.95) at 1 year, 0.5 (range 0.30–0.84) at 2 years, 0.36 (range 0.18–0.72) at 3 years, and 0.14 (range 0.04–0.52) at 4 years.

Recurrence free survivals between the RFA date and the date of occurrence of a post radiofrequency metastatic recurrence are provided in Fig. 3B. The recurrence was 0.71 (range 0.51–0.99) at 1

Table 2
Characteristics and treatments of the first LMUM and second LMUM.

	First LMUM	Second LMUM
Median time from treatment of primary tumor to LM (months [range])	50 [8-155]	NA
Median time from treatment of first LM to second LM (months [range])	NA	20 [2-123]
Size of LM treated by surgery (mean (mm), [range]	14.8 [1-50]	4.7 [1–12]
Size of LM treated with RFA (mean (mm), [range])	NA	12.6 [3–26]
Number of lesion		
1 lesion	6	9
1 < lesions < 4	5	3
≥4 lesions	3	2
Topography in the liver		
One lobe	9 (64%)	12 (86%)
Bilobar	5 (36%)	2 (14%)
If surgery:per-operative miliary disease[a]	0	0
Metastasectomy-segmentectomy	8/14	NA
Hepatectomy	6/14	NA
RFA alone	NA	10/14
RFA + metastasectomy	NA	4/14

[a] per-operative miliary: capsular liver disease only if patients had surgical treatment (14/14 patients for the first LM and 4/14 patients for the second LM); LM: liver metastasis.

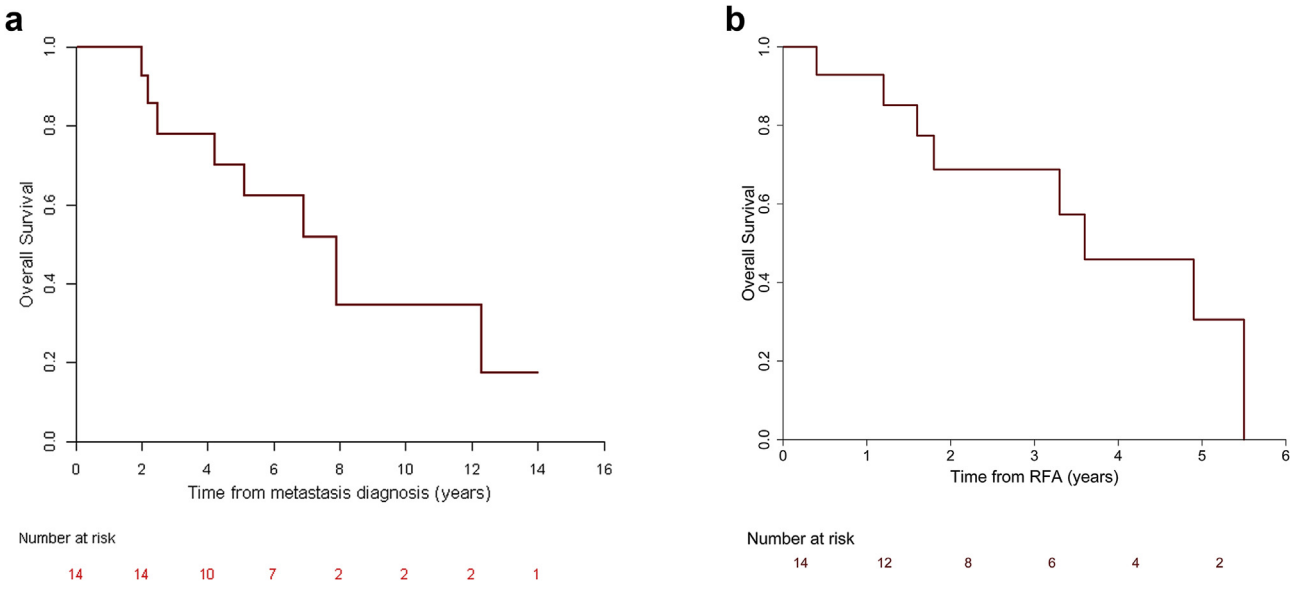

Fig. 2. Overall survival after the diagnosis of the first liver metastasis (Fig. 2A) and after radiofrequency ablation (Fig. 2B).

year, 0.56 (range 0.34–0.90) at 2 years, at 3 years 0.37 [0.18–0.78], and 0.19 (range 0.04–0.89) at 4 years.

Genomic analysis

The genomic data of liver metastases and UM are described in Table 3. Genomic analysis of liver metastasis was contributory in 13/14 patients (one technical failure). Ten patients were classified as high-risk in 5/13 (38%), intermediate-risk in 3/13 (23%) and low-risk in 2/13 (15%). Three unclassified patients (23%) presented a partial loss of 3p (2/13) and an isodisomy of 3p (1/13). Genomic analysis of the UM was available for 6/14 patients. Only chromosome 3 status was available for one patient (FISH analysis). The five remaining patients were classified as high-risk (3/5) and low risk (2/5). Among them four patients with all genome profiling had good concordance between chromosome abnormalities of primary UM and liver metastasis.

Discussion

This is a monocentric retrospective study of a small number of patients whose results should be interpreted with caution. Nevertheless, the results of this series show that radiofrequency ablation of second LMUMs recurrence after R0 resection of initial LMUMs was associated with a recurrence free interval of 56% at two years and overall survivals of 70% at five years and 35% at ten years. In this setting, the present study emphasizes the benefit of RFA treatment of recurrent LMUMs in selected patients.

In the two most recent series, the number of surgically treated patients for isolated LMUMs among all the metastatic patients varies between 32 and 34% [17,18]. Among these patients, R0 resection is performed in 30–36% of cases. The intraoperative discovery of a capsular miliary disease most often prevents R0 resection. After an R0 resection, in case of isolated liver recurrence, the question of a second local treatment is rarely asked and there is no established therapeutic strategy in this setting. We want thus to

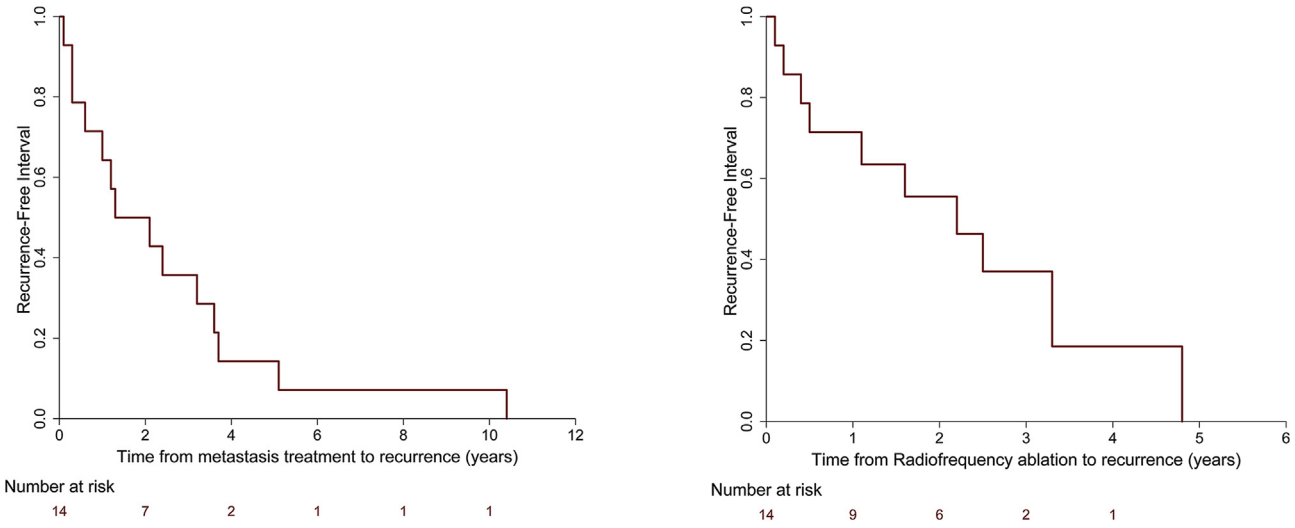

Fig. 3. Recurrence-free interval between surgical treatment and first liver recurrence (Fig. 3A) and between RFA treatment and second liver recurrence (Fig. 3B).

Table 3
genomic data and corresponding class of risk of primary UM ocular tumour and LMUM for the 14 patients (M = monosomy, D = disomy, g = gain, nl = normal, 3p- = partial loss of short arm of chromosome 3, *I3p = isodosomy of short arm of chromosome 3, 8q+ = gain of long arm of chromosome 8, HR = high risk, IR = intermediate risk, LR = low risk).

Patient number	UM Genomic			LMUM Genomic			Concordance
	Status	Class of risk	Technic	Status	Class of risk	Technic	
1	/	/	/	M3/8g	HR	Agilent	NA
2	D3	ND	FISH	M3/8g	HR	Agilent	No
3	/	/	/	M3/8g	HR	Agilent	NA
4	/	/	/	D3/8g	IR	Agilent	NA
5	/	/	/	D3/8g	IR	Agilent	NA
6	/	/	/	3p-/8g	HR ?	Agilent	NA
7	M3/8g	HR	Agilent	M3/8g	HR	Agilent	Yes
8	M3/8g	HR	Agilent	/	/	Agilent	NA
9	/	/	/	3p-/8q+	HR ?	Agilent	NA
10	/	/	/	I3p/8g*	HR ?	Agilent	NA
11	M3/8g	HR	Nimblegen	M3/8g	HR	Agilent	Yes
12	/	/	/	D3/8g	IR	Agilent	NA
13	D3/8 nl	LR	Nimbligen	D3/8 nl	LR	Agilent	Yes
14	D3/8 nl	LR	Agilent	D3/8 nl	LR	Agilent	Yes

emphasize that this series dealt with a very highly selected population, for several reasons. First, only a small proportion of patients initially operated on with R0 resection were included in this study (14%). Second, the onset of the first metastatic event after the treatment of the UM was late with a median delay of 50 months, a rather favourable prognostic factor according to our experience [17] and that of other authors [23]. Third, at the first metastatic event, patients had few metastases (fewer than four in 11/14 patients) without capsular miliary disease during surgical exploration. At recurrence, patients had even fewer metastases, since nine out of 14 patients had a single metastasis. For the four patients re-operated to perform RFA at recurrence, there were no cases of capsular miliary disease seen per-operatively. The recurrences were thus obviously oligo-metastatic, having an impact on the prognosis of these highly selected patients [23].

RFA is a well-established liver-sparing technique for the treatment of liver metastasis. We have previously shown that RFA alone or associated with surgical treatment gave the same survival results as that of surgical treatment alone for LMUM [20]. In the situation of second liver local treatment we favoured where possible the percutaneous RFA route (11/17 procedures). In addition to the usual size criteria, the percutaneous route is unfortunately not always possible given the position of metastases in the liver. We can see in Fig. 1 that among the 17 RFA procedures, nine were performed percutaneously on the anterior segments (segment VI, V and III) versus two in the posterior segments (II and VII). This result corresponds to the most easily accessible liver segments with imaging guidance. On the other hand, the six per-operative RFA procedures were carried out in all the hepatic segments (outside segment VII) because of the better accessibility of all the lesions linked to the liver mobilization carried out by the surgeon during the laparotomy.

The definition of a long-term survival in this metastatic disease is imprecise. Some authors consider that survival greater than 12 months makes patients long-term survivors [24]. Thus, the overall survival observed in this series is particularly long for patients with LMUM: 70% of patients alive at 5 years is an exceptional result, as is 35% of patients still alive at 10 years. Usually, patients are rarely alive at 5 years, with a median survival of 25–27 months [17,18]. Only our high-risk cohort [25] showed a median overall survival of 40 months in the R0 operated patients, already an unusually long period. Data published in the literature reporting long-term surviving metastatic surgical patients are rare [19,26]. The Hsueh series [26] focused on the analysis of 112 patients, 78 of whom had exclusive hepatic metastases. The 24 operated patients (21%) had a 5-year survival of 39% versus 0% for non-operated patients.

In this hyper-selected population, the median survival without recurrence between the initial surgical treatment and the first recurrence was 20 months, compared to the usual 8 months [17–20]. We did not know in advance the future of these patients after the second local treatment. Interestingly, in this population, when they had a second local treatment, the new recurrence-free interval was again 2 years, the same as the first recurrence-free interval (56% versus 50% at 2 years). Thus, we gave the patient a real second chance. In our centre, even if this attitude is not unanimously recognized, we propose systemic treatment only when the patient has a non-treatable liver disease by surgery and/or RFA. Thus, in anticipation, we always seek to favour metastasectomy to major hepatectomy during the first intervention to give priority to liver sparing in case of second local intervention.

Nevertheless, this observation implies that these are patients with slow spontaneous evolution of their disease without it being possible for us to predict this slowness of evolution on the basis of clinical or biological criteria. For UM, the metastasis risk factors are based on clinical characteristics and/or genomic analysis of the primary tumour. In the Cassoux study [21], patients were divided into three classes of metastatic risk. In multivariate Cox modelling analysis, high-risk profile (M3/8g) was more strongly associated with metastasis than were the other prognostic factors. Only a few studies [27–29] have compared the genomic profiles of the primary tumour and metastases. Our study showed that in the four cases where we could study concordance, the genomic profile was similar between the primary tumour and the metastasis. Nevertheless, once the patient's disease is metastatic, the prognostic value of the genomic profile is not established. Interestingly, in our series, 38% of patients had intermediate- or low-risk genomic profiles in metastases. However, the prognostic value of the genomic profile of LMUM should be studied on a largest series of patients.

The second recurrence was hepatic in all cases. According to our criteria, no patients have recurred at the level of RFA treated lesions. Five patients had a hepatic recurrence associated with extra-hepatic metastases, appearing logical in cases of long-term survival. Ten patients with second recurrence received systemic treatment, but 4 patients with isolated hepatic recurrence had not received any systemic treatment by the time of this writing; these four patients were alive without new recurrence, with survivals ranging from 12 months to 39 months.

Conclusion

Very long-term survival can be achieved by exclusive and

iterative local treatment combining surgery and RFA in a small proportion of patients with a first recurrence of isolated LMUM. Given the inefficiency of the currently available systemic treatments, we believe that this approach, which may appear aggressive, must be discussed more systematically during multidisciplinary oncological meetings at expert centres treating this pathology. Better knowledge of the biological factors explaining the evolution of this metastatic disease is nevertheless essential to improve the selection of patients who may benefit from this local therapeutic strategy.

Conflicts of interest statement

No authors have conflicts of interest to declare.

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