European Journal of Surgical Oncology 45 (2019) 2431–2436

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

# Early detection of multiple bone and extra-skeletal metastases by body magnetic resonance imaging (BMRI) after treatment of Myxoid/Round-Cell Liposarcoma (MRCLS)

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ARTICLE INFO

*Article history:*
Received 17 March 2019
Received in revised form
28 July 2019
Accepted 12 August 2019
Available online 13 August 2019

*Keywords:*
Soft tissue sarcoma
Myxoid liposarcoma
Magnetic resonance imaging
Soft tissue metastasis
Bone metastasis
Surveillance

ABSTRACT

*Introduction:* Myxoid Round cell containing myxoid liposarcomas (MRCLS) have a high propensity to metastasize to soft tissue and bone. Whole Body Magnetic Resonance Imaging (BMRI) has been reported as a critical modality to early detect disease spreading in asymptomatic patients. The purpose of this study is to describe metastatic patterns and outcomes in patients through annual BMRI surveillance after diagnosis of MRCLS of the extremities and trunk.

*Materiel and patients:* This retrospective study included patients with histology confirmed MRCLS. Initial BMRI were done within 6 months following the first line treatment then once a year.

*Results:* Forty-five out of 51 consecutive MRCLS patients were included. At the last follow-up 10 patients (22.2%) had an extra-pulmonary soft-tissue or/and bone metastasis detected in a median delay of 22.7±16 months [0–49] from the diagnosis of the MRCLS. Nine patients were asymptomatic. Finally, 5-years metastatic free survival was 72±8%. All metastatic patients had multiple lesion within the year following the first lesion diagnosis.

*Conclusion:* Systematic BMRI in MRCLS patients following treatment frequently identify extra-pulmonary metastasis in asymptomatic patients within the first 5 years of follow-up. Despite a long survival can be expected after diagnosis, extra-skeletal metastasis was a signal of disseminated disease.



## Introduction

Myxoid liposarcoma is a malignant soft tissue tumor accounting for 15–20% of liposarcomas, which are the second most common soft tissue sarcoma (STS) in adults [1]. This liposarcoma sub-type typically arises between the 4th and 5th decade. Histologic analysis reveals a mixture of uniform round to oval-shaped non lipogenic cells and small signet ring lipoblasts in a prominent myxoid stroma. A subset of myxoid liposarcoma shows progression to hypercellular or round cell morphology [1]; any round cells component presence or more than 5% of round cells is associated with worse outcomes [1–4]. Diagnosis is currently completed by the FUS-DDIT3 gene fusion identification which is highly sensitive and specific for myxoid/round cell liposarcoma (MRCLS) and is absent in other morphological mimics [5].

The specific feature distinguishing MRCLS from other STS is its propensity to metastasized to other soft-tissue sites, such as extremity, retroperitoneum, chest wall, mediastinum, pleura and to bone, particularly spine [1,2,6–10]. Moreover, lung metastasis spreading is less common in MRCLS than in other soft-tissue sarcomas and is reported as the first metastatic event in only in 0–26%

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https://doi.org/10.1016/j.ejso.2019.08.014
0748-7983/

[2,7–9,11,12] of metastatic patients.

For these reasons, X-rays and computerized CT scan used in routine radiological surveillance for pulmonary metastasis occurrence in STS [13] is unsuitable for MRCLS. Moreover X-ray, bone scan [10,14,15], CT scan [7,12,15] and PET scan [11,12,14,16] fail in detecting soft-tissue and bone metastasis from primary MRCLS. On the other hand, magnetic resonance imaging (MRI) allow to detect marrow replacement due to metastatic seeding earlier than any adjacent bone detectable damage compared with other imaging tools [7,9,12,14,16,17] and a better detection for occult soft-tissue metastasis which often resembled cyst on T1-and T2-weighted and STIR images [9,12]. Whole Body MRI (BMRI) has subsequently been proposed for MRCLS staging and follow-up [7,9,12,15]. Gorelik et al. and Seo et al. [7,9] reported performances of BMRI for metastatic spreading detection at initial staging in 17 and 33 patients respectively, at a median follow-up of 17 and 55 months. Stevenson et al. [15] used BMRI at initial staging for superficial tumors detection in 28 patients, with the aim to identify a potential primary occult deep tumor, or a large primary tumor with a high metastatic risk and for suspicion or confirmed-relapse.

BMRI, including full spine, upper limbs, pelvis, and lower limbs down to the knees has been part of the initial work-up done after MRCLS diagnosis in our institutions and repeated every year during the follow-up period. The purpose of this retrospective study is to describe metastatic patterns and outcomes of patients followed by annual BMRI after diagnosis of MRCLS of the extremities and trunk.

## Patients and methods

Fifty-one consecutive patients with histological diagnosis of MRCLS of the extremities and trunk, treated in one of our 2 referral centers, who had at least a 12 months follow-up, were included from October 2006 and 2011 respectively. This study has been approved by the clinical research board of our University hospital. Six patients were excluded, wrong diagnosis (n = 1), lost to follow-up (n = 1), early death unrelated to the disease (n = 1) and lack of regular MRI for claustrophobia and unknown reasons (n = 3). Finally, 45 patients were available for clinical and imaging analysis (Fig. 1).

Demographic and tumor details are reported in Table 1.

Diagnosis and treatment strategy were discussed in Netsarc Multidisciplinary Tumor Boards (MTB of French Sarcoma Network). All MRCLS diagnosis were confirmed by a specialized pathologist (RRePS/Sarcoma French Pathologist Network), with 41 out 45 cases with the specific molecular *DDIT3* rearrangement confirmed.

According to FNCLCC classification [18], 21 tumors grade 1 (52.5%), 2 high grade (grade 3), and 14 intermediate grade 2 were identified. Twenty-four (55.5%) did not contain round cells component, 12 out of the 18 tumors containing round cells had a rate of round cells higher than 5% (26.8%) (Table 1).

Primary MRCLS were all located in the lower limb except for 2 located in the back. All tumors were deeply seated under the fascia. The mean tumor size was 11.8 cm (range 2–22 cm); 9 tumors were smaller than 10 cm and 36 were 10 cm wide or more in their largest diameter.

Primitive tumor resection was performed for all patients. According to the UICC classification, margins were clear (R0) in 33 cases and microscopically contaminated (R1) in 12 cases. Thirty-four patients (75.5%) received radiotherapy post-operatively except for one pre-operative irradiation. One patient received neo-adjuvant chemotherapy because of metastatic disease at diagnosis.

Patients follow-up included clinical and imaging surveillance (chest X-ray or chest CT and local MRI of the tumor resection site)

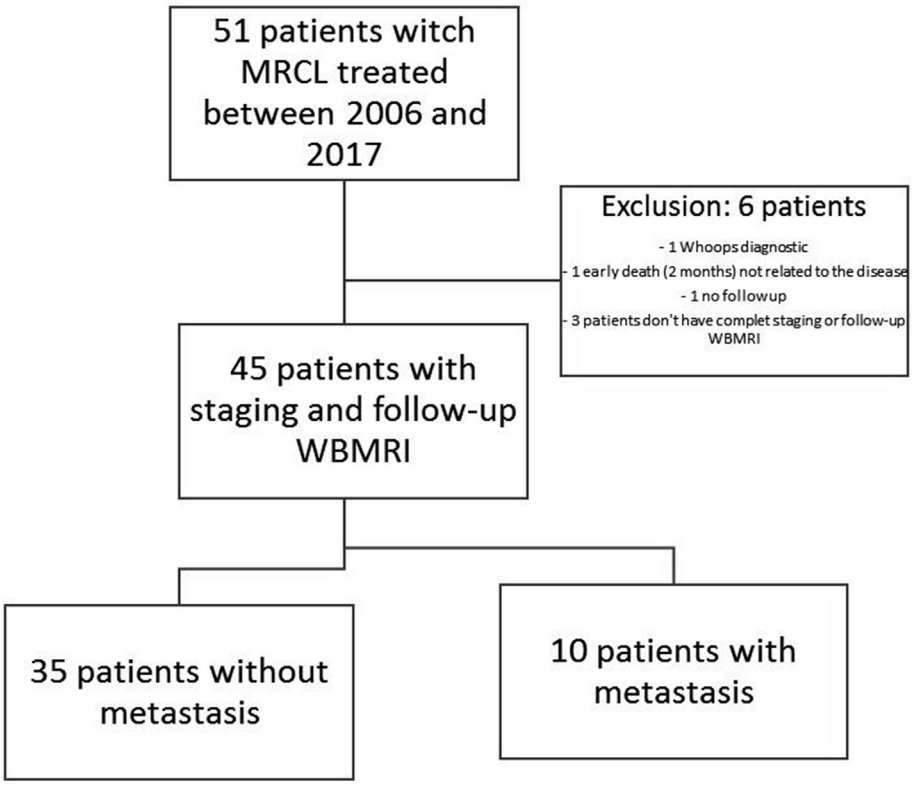


**Fig. 1.** Flow chart.

**Table 1**
Patients and tumors data. Round cell component: 0 = non round cell, 1 = less than 5% of round cells, 2 = 5% or more round cells. FNCLCC grading: 8 patients haven't been graded because of some pathologist considered FNCLCC grading inapplicable for MRCLS. First line treatment: RE = surgical resection/RT = radiotherapy/CT = chemotherapy.

| | | Total (n = 45) | Non metastactic patients (n = 35) | Metastatic Patient (n = 10/22.2%) |
|---|---|---|---|---|
| **Gender (male/female)** | | 33/12 | 27/8 | 6/4 |
| **Age at diagnosis** | | 46.6 | 46.3 [22–74] | 47.7 [22–66] |
| **FNCLCC grading (n = 37)** | Grade 1 | 21 | 17 | 4 |
| | Grade 2 | 14 | 10 | 4 |
| | Grade 3 | 2 | 2 | 0 |
| **Round cell component** | 0 | 25 (55.5%) | 20 (57 .1%) | 5 (50%) |
| | 1 | 8 (17.7%) | 7 (20%) | 1 (10%) |
| | 2 | 12 (26.8%) | 8 (22.9%) | 4 (40%) |
| **Size in mm.** | | 118 ± 49 | 113 [20–220] | 127.3 [80–220] |
| **First line treatment** | RE | 11 | 10 | 1 |
| | RE + RT | 24 | 21 | 3 |
| | RE + RT + CT | 10 | 4 | 6 |
| **Margins (according to UICC classification** | R0 | 34 (75.5%) | 28 | 6 |
| | R1 | 10 (22.2%) | 7 | 3 |
| | R2 | 1 | 0 | 1 |
| **Local recurrence** | | 2 (4.4%) | 1 | 1 |

every 6 months during the first 3 years after treatment initiation and then annually. An annual BMRI was also performed. In case of soft tissue or bone metastasis suspicion based on BMRI, targeted MRI, CT Scan, bone scan or FDG-PET imaging could be requested upon MTB radiologist recommandation. All but one patient (first BMRI 33 months after surgery) received staging BMRI for follow-up within 6 months following the primary tumor first-line treatment. Average and median follow-up were respectively 49 ±29 months and 43 (range15–133) months.

Up to 2015, BMRI were performed with a 1.5 T imager (Siemens Magnetom Avanto, Erlangen, Germany). From October 2015 a 1.5T system (Philips Healthcare Achieva, Amsterdam the Nederlands) a body coil with a 4-coil element was used to obtain the whole-body reformatted images. For the whole-body reformateted images, 4 stacks of contiguous images were obtained using T2 weighted STIR sagittal and coronal sequences and T1 weighted spin-echo sagittal sequences covering the body from the upper cervical spine to the knees. The total scan time extended from 30 to 40 min on both magnets.

*Statistical analysis*

Descriptive statistics were presented with mean ± SD or median for continuous variables and percentages for categorical variables. Survival analysis was carried out using Kaplan-Meier method with a 95% confidence interval. All statistical analyses were carried out using SPSS statistics (version 22).

## Results

At last follow-up 10 patients (22.2%) had a metastatic extra-pulmonary spreading of their primary tumor (Table 2). Two metastases were synchronous to the diagnosis of the primary tumor diagnosis (soft tissue synchronous metastasis), the delay from diagnosis of the primary tumor to metastasis recurrence for other patients was 22.7 ± 16 monts (range 2–49 montsh). No lung metastasis was detected during the follow-up. The 5-years metastasis free survival (MFS) was 0.72±0.08 (Fig. 2).

Metastatic status was established on pathologic specimen in 4

**Table 2**
Patients and tumors data for metastatic patietns. Round cell component: 0 = non round cell, 1 = less than 5% of round cells, 2 = 5% or more round cells. Met = metastasis. AWD = alive with disease/DOD = dead of disease.

| Patient | Time from initial diagnosis | FNCLCC grading | Round cell component | Number of met | Site of met | diagnosis | Met treatment | Evolution | Follow-up (from initial diagnosis) | Status at last follow-up |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 30 | grade 2 | 2 | >10 | Pelvis, femur, scapula, humerus, ribs, vertebra T7 T8 S3 (ST and Bone) | Pathological specimen | CT | Progression Free | 133 | AWD |
| 2 | 39 | NA | 2 | 1 | Spine Th10 (Bones) | Pathological specimen | Resection + RT | New met | 120 | AWD |
| 3 | 0 | grade 1 | 0 | 1 | Sub-cutaneous, (ST) | Pathological specimen | Resection + CT | New met | 114 | AWD |
| 6 | 6 | grade2 | 2 | 8 | Chest wall, sacrum, pelvis, femur (Bone) | Pathological specimen | RT + CH | Progression free | 55 | DOD |
| 10 | 13 | NA | 0 | 1 | Spine L4 (Bone) | MRI | thermal ablation | New met | 78 | AWD |
| 28 | 18 | grade 2 | 0 | >10 | Spine, pelvis, visceral, femur, thorax (ST and Bone) | MRI | CT | Progression | 24 | AWD |
| 29 | 2 | grade 1 | 1 (post RT) | 3 | Spine, pelvis (Bones) | MRI | CT | Progression | 14 | AWD |
| 31 | 0 | grade 1 | 0 | 2 | Knee, thigh (ST) | Pathological specimen | neo-adjuvant CT + resection + RT | New met | 15 | AWD |
| 33 | 49 | grade 2 | 2 (post CT neo-adj) | 2 | Paracardial (ST) | Pathological specimen | Resection + CT | New met | 86 | AWD |
| 35 | 25 | grade 1 | 0 | 5 | Spine, pelvis (bone) | MRI | CT | New met | 56 | AWD |

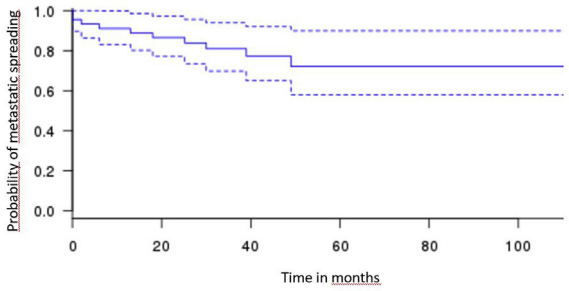


**Fig. 2.** Metastatic free survival after diagnosis of primary MRCLS. Kaplan-Meier curve of metastatic free survival and 95% confidence interval.

cases and on the presence of typical multiple and growing lesions on MRI in 6 patients. All except one patient (9/10) were asymptomatic at the time of metastasis diagnosis. One single metastatic site was detected in 3 patients (2 spine and 1 soft tissue localization), and multiple metastatic sites were identified for the 7 other patients. The first dissemination site was soft tissue for two patients, both diagnosed as synchronous metastatic dissemination (or multifocal primary tumor?). For the other 8 patients, first occult metastasis occurred in bone in a median delay from tumor diagnosis from 2 to 49 months (Table 2). At last follow-up, despite the initiation of oncologic treatment multiple dissemination occurred in all cases within 1 year following the first diagnosis of metastatic spreading.

Two (4.4%) patients had a local recurrence, 17 and 33 months after primary tumor treatment respectively. Both patients had surgical resection as first line treatment (low grade 1 primary tumor without round cell component). One of these 2 patients had metastatic spreading diagnosed 7 months after local recurrence.

Finally, at last follow-up, 2 patients had died, chemotherapy adverse effect 6 months after diagnosis (n = 1), unrelated reason 30 months after diagnosis (n = 1). Eight years disease specific survival was 0.94 ±0.06 (Fig. 3).

Tumor size (more or less than 10 cm), FNCLCC grading, or presence of round cell component were not identified as a metastatic spreading risk factor.

## Discussion

In the current study, high rate of extra-pulmonary metastasis was detected when using annual BMRI for patients' surveillance after treatment of MRCLS of the extremities and trunk. Ninety percent of them were clinically asymptomatic. Bone and/or soft tissue metastasis were identified in 10 out of 47 patients (19.6%); the 5-years MFS was 72% +/8%. These results are consistent with the 3 recent series of patients followed-up for extra-skeletal metastasis detection using BMRI [7,9,15]. Stevenson et et al. [15] reported a 5 years MFS of 71% (n = 28) with 7 (25%) metastatic patients. Seo et al. [9] detected extra-pulmonary metastasis in 4 (26%) patients (n = 15). Gorelik et al. [7] reported 9 (n = 27%) patients with distant metastasis at diagnostic or during follow-up (n = 33). Notably, the present study is the largest with BMRI for surveillance, and no patient was lost of follow-up. In addition, the strength of this series is the homogeneous patient population. Indeed, all diagnosis were reviewed by an expert pathologist within the French network NETSARC-RREPS, and 41 of the 45 patients (91%) had the MRCLS molecular signature.

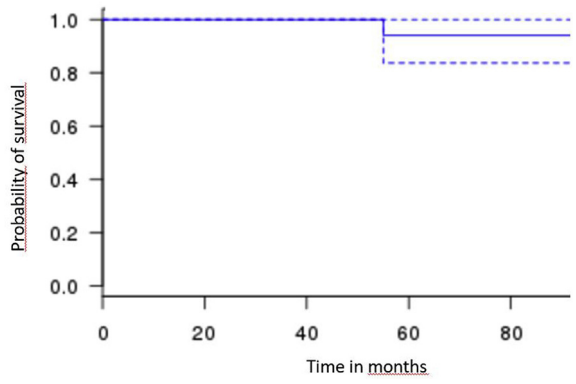


**Fig. 3.** Disease specific survival. Kaplan-Meier curve of disease specific survival spreading probability and 95% confidence interval.

Similar high rates of MRCLS extra-pulmonary spreading have been previously reported, ranging from 10.7 to 28% of the patients followed despite unusual or no BMRI imaging [3,4,8,10,12,14,19–21]. A highest percentage of extra-skeletal metastasis is reported by Haniball et al. (28%) in a large cohort of 160 patients, with a 10 years MFS of 60% [8]. To note, the incidence of patients with high grade primary tumor (>5% of cell round component) was 53%, compared with 26.8% in the present series and other recent series with BMRI (21 and 39%) [7,15]. In addition, follow-up was longer (86 months in average).

BMRI is considered as the most reliable tool to detect extra-pulmonary bone and soft-tissue MRCLS metastasis [7,9,11,14,15,22]. Detection sensibility reached 80 and 85% and detection specificity 97 and 99%, for soft-tissue and bone metastasis, respectively [9]. At the same time, all PET CT scans were negative. PET CT scan [11,12,14,16] and CT scan [7,12,15] have shown a limited diagnostic performance to detect MRCLS bone and soft tissue metastasis with a high false negative rate. X-Ray and bone scan [10,14,15] are not efficient either. In contrast to other STSs, BMRI must be considered for MRCLS staging and follow-up, as the standard and recommended method of imaging, faced with high detection failure reported with chest X-ray, CT or even PET-scan.

In the current study, BMRI detected extra-pulmonary bone, superficial and deep soft tissue, intra-abdominal and mediastinal metastasis. Bone sites were limited to axial skeleton, ribs, pelvis and proximal long bones. These results are consistent with previously reported sites of extra-pulmonary metastasis. Soft tissue metastasis are mainly reported in the retroperitoneum, abdominal and chest wall or intra-abdominal [1,2,6,8]. Bone dissemination affects mainly spine, pelvis and proximal long bones [7–9,17]. In our study, BMRI explored the body from the upper cervical spine to the knee, including femurs and humerus. To note, head and legs (under the knees) were not systematically explored, due to shortage of time and considering the incidence of extra-pulmonary metastasis sites reported in the literature. We recognize that distal metastases will not be detected with sub-total BMRI contributing to reduce the metastatic patient rate. However, only one of our patients had a below knee (calf) wide clinically detected metastasis associated with multiple bone and soft-tissue metastasis previously documented. Moreover, to the best of our knowledge in literature, distal metastases are rare, and never reported as first metastatic disease first event. Thus, limited BMRI, as carried out in the present study, looks appropriate to detect occult extra-pulmonary metastasis.

Only 1 out of 10 patients had clinical symptoms (S1 irritation) at the time of first diagnosis of extra-pulmonary metastasis. This ability for BMRI to detect infra-clinical secondary metastasis has also been reported in another study including systematic BMRI with 89% of asymptomatic patients [7]. To note clinical status not available in Seo [9]. Moreover, occult metastasis is frequently discovered when a MRI is performed for staging a metastatic lesion

in another site [9,15,17,23]. Despite BMRI ability to detect occult metastasis, our study is unable to assess the time gained with early detection of metastasis using BMRI rather than clinically or with conventional imaging.

Finally, the current study shows that systematic BMRI could detect first extra-skeletal metastasis within a median delay 21 months. However, Gorelik et al. [7] report a median from diagnosis of 10 months and the median occurrence of 16 months for Stevenson et al. [15] (to note, BMRI was only done for high risk or symptomatic patients) which are dramatically earlier than previously reported (30–54 months in average) [6,10,12,15,19,23]. None were detected after 48 months following primary diagnosis in the present study, and after 60 months for Gorelick et al. [7] but both studies had limited follow-up.

This early detection also probably explained the absence of pulmonary metastasis as the initial site of dissemination in our patients as previously reported [7,9], which differs from previous study without BMRI screening. Haniball et al. [8] reported 7 pulmonary metastasis cases alone and 7 cases of others pulmonary disseminations associated with extra-pulmonary sites in over 38 metastatic patients. Cheng et al. [6] reported 41% of pulmonary localization at the diagnosis of metastatic disease (including all types of liposarcoma). For Fiore et al. [2] 26% had only lung metastasis as a first event. When BMRI screening was done after pulmonary metastasis diagnosis, identified pulmonary site prior to bone metastasis occur in only 3 out of 40 patients with MRCLS metastasis to bone [10] and 1 out of 12 patients for Sheah et al. [12] Thus, pulmonary dissemination occurs at a later disease stage compared to other STS, and is not an appropriate target to detect early spreading of MRCLS metastasis.

Furthermore, an important information drawn from our study is the poor prognosis signification of a first extra-pulmonary metastasis diagnosis. Indeed, BMRI allowed to discover the presence of metastases mainly multiple except in 2 patients; these 2 patients with single metastases located in the spine were locally treated by spondylectomy and thermo-ablation respectively and multiple bone and soft-tissue metastasis occurred within 2 and 4 years later respectively. Propensity to develop metastasis to multiple sites has been documented. Unique extra-pulmonary metastatic spreading is rare, ranging from 14 to 33% [7,15,23] in literature. Only one team reported a high rate of unique metastasis [24]: 10 patients with a single metastasis at diagnosis out of 12. However, 6 of these patients developed further lesions, leading finally to a 25% rate of supposed single metastasis. To note, BMRI was not used to detect possible occult metastasis; as a consequence the single lesion rate was probably initialy overestimated.

Curative treatment including surgery or radiotherapy, is generally recommended for patients with a single metastasis [6,7,17,19]. Nevertheless, one might acknowledge the lack of information about long-term fate of these patients. Only 4 cases of long-term survival without disease after treatment of single or oligo bone or soft-tissue metastasis have been reported to our knowledge [17,19]. Two out of 33 patients with a spine secondary localization surgically resected are still alive without disease 84 and 400 months after primary diagnosis. Another 2 patients with abdominal and retroperitoneal metastasis, are considered disease free at 116 and 282 months of follow-up. Survival is reported from the diagnosis of the primary tumor. As a consequence, post-metastasectomy survival is unknown; moreover no MRI screening is mentioned, thus the long-term disease-free status is still questionable.

The occurrence of an extra-skeletal metastasis is generally considered as a poor survival prognosis factor in literature [22,23,25]. Spillane et al. reported a 11 times higher risk of death when a soft-tissue spreading is detected. Survival medians after metastatic diagnosis ranged from 8.5 to 21.9 months [2,8,10]. The 5 years overall survival after diagnosis of bone metastasis is 16% for Schwab et al. [10]. Surprisingly, in the present study only 1 patient died 49 months after metastatic dissemination diagnosis and 9 were alive with disease (mediane follow-up after metastatic diagnosis 51 months, 6–114 months). The high rate (93%) of 5-years over-all survival in the present study is consistent with previous results using BMRI for surveillance, achieving 5-years OS of 95% [15] and 5-years OS of 93.9% [24]. The later large series showed a high survival rate that could be explained by the majority of low grade tumors (only 7% tumors with more than 5% of round cells). The proportion of high risk tumors (round cells presence, tumors larger than 10 cm recognized as the 2 strongest risk factor for metastatic spreading and tumor-related death risk factors [1–4,8]) were similar in our series compared to other published series. This good survival rate raised the question of the benefic impact of an earlier treatment thanks to an earlier diagnostic of metastatic dissemination. Indeed, MRCLS is known to be highly radiosensible [26] and sensible to chemotherapy with more recent systemic treatment like trabectedin [27]. Further investigations are necessary to assess treatment protocols for metastatic MRCLS earlier diagnosed through BMRI surveillance to access to earlier treatment.

This study has some limitations. It is a retrospective study with a small number of patients. The lack of BMRI prospective standard protocol at the initial period could have induced a few inaccuracies; not only patients who received a BMRI at the staging phase where included, but also those who received imaging shortly after surgery. In fact, if all patients had received BMRI at the pre-operative period, only one could have had earlier bone metastasis diagnosis. Positive metastatic diagnosis was not histologically proven in all cases. Nevertheless, in the absence of biopsy (or resection) was not carried out, a second or third MRI performed from 3 to 6 months later and a significant increase in size and/or multifocal dissemination were considered to be a reliable sign of metastatic disease.

## Conclusion

The current study confirms that systematic BMRI (from the apex to the knee) for staging and follow-up of patients with MRCLS allows earlier identification of extra-pulmonary metastasis (bone, deep and superficial soft-tissue located) in many asymptomatic patients within the first 5 years follow-up. This is important information as it can improve patient selection for MRCLS treatment in clinical trials. Despite metastatic occurrence was the signal of disseminated disease in all cases in our experience, long survival can be expected after diagnosis.

## Disclosure of interest in the field of this work

None.

The authors thank Sophie Darnis PhD for medical editorial assistance with the manuscript.

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