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In transit metastases in children, adolescents and young adults with localized rhabdomyosarcoma of the distal extremities: Analysis of the EpSSG RMS 2005 study

C.E.J. Terwisscha van Scheltinga [a, *], M.H.W.A. Wijnen [a], H. Martelli [b], F. Guerin [b], T. Rogers [c], R.J. Craigie [d], G. Guillén Burrieza [e], P. Dall'Igna [f], F. De Corti [g], N. Smeulders [h], R.R. van Rijn [i], R.Dávila Fajardo [a, j], H.C. Mandeville [k], I. Zanetti [l], B. Coppadoro [l], V. Minard-Colin [m], M. Jenney [n], G. Bisogno [l], M.M. van Noesel [a, o], A.F.W. van der Steeg [a], J.H.M. Merks [a]

[a] *Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands*
[b] *University Paris-Saclay, Assistance Publique Hôpitaux de Paris, Department of Pediatric Surgery, Le Kremlin Bicêtre, France*
[c] *Department of Paediatric Surgery, University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, UK*
[d] *Department of Pediatric Surgery, Royal Manchester Children's Hospital, Manchester, UK*
[e] *Department of Pediatric Surgery, Hospital Universitari Infantil Vall d'Hebron, Barcelona, Spain*
[f] *Pediatric Surgery, Department of Emergencies and Organ Transplantation, University of Bari, Bari, Italy*
[g] *Pediatric Surgery, Women and Children's Health Department, University Hospital of Padua, Padua, Italy*
[h] *Department of Pediatric Urology, Great Ormond Street Hospital, London, UK*
[i] *Department of Radiology and Nuclear Medicine, Amsterdam UMC, University Amsterdam, Amsterdam, the Netherlands*
[j] *Department of Radiation Oncology, University Medical Center Utrecht, Utrecht, the Netherlands*
[k] *Children and Young People's Unit, Royal Marsden Hospital, Sutton, Surrey, UK*
[l] *Department of Pediatric Haematology and Oncology, University Hospital of Padua, Padua, Italy*
[m] *Department of Pediatric and Adolescent Oncology, Gustave Roussy, Villejuif, France*
[n] *Department of Pediatric Oncology, University Hospital of Wales, Cardiff, UK*
[o] *Division of Imaging & Cancer, University Medical Center Utrecht, Utrecht, the Netherlands*

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ABSTRACT

In-transit metastases (ITM) are defined as metastatic lymph nodes or deposits occurring between the primary tumor and proximal draining lymph node basin. In extremity rhabdomyosarcoma (RMS), they have rarely been reported. This study evaluates the frequency, staging and survival of patients with ITM in distal extremity RMS.

Methods: Patients with extremity RMS distal to the elbow or knee, enrolled in the EpSSG RMS 2005 trial between 2005 and 2016 were eligible for this study.

Results: One hundred and nine distal extremity RMS patients, with a median age of 6.2 years (range 0 −21 years) were included. Thirty seven of 109 (34%) had lymph node metastases at diagnosis, 19 of them (51%) had ITM, especially in lower extremity RMS. ^{18}F-FDG-PET/CT detected involved lymph nodes in 47% of patients. In patients not undergoing ^{18}F-FDG-PET/CT lymph node involvement was detected in 22%. The 5-yr EFS of patients with ITM vs proximal lymph nodes vs combined proximal and ITM was 88.9% vs 21.4% vs 20%, respectively ($p = 0.01$) and 5-yr OS was 100% vs 25.2% vs 15%, respectively ($p = 0.003$).

Conclusion: Our study showed that in-transit metastases constituted more than 50% of all lymph node metastases in distal extremity RMS. ^{18}F-FDG-PET/CT improved nodal staging by detecting more regional and in-transit metastases. Popliteal and epitrochlear nodes should be considered as true (distal) regional nodes, instead of in-transit metastases. Biopsy of these nodes is recommended especially in distal extremity RMS of the lower limb. Patients with proximal (axillary or inguinal) lymph node involvement have a worse prognosis.

* Corresponding author. Pediatric surgery, Princess Máxima Center for Pediatric oncology, Heidelberglaan 25, 3584 CS, Utrecht, the Netherlands.
E-mail address: c.e.j.terwisschavanscheltinga@prinsesmaximacentrum.nl (C.E.J. Terwisscha van Scheltinga).

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1. Introduction

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children and accounts for approximately 3–5% of all childhood tumors [1].

RMS of the extremities has a higher propensity to metastasize to lymph nodes than RMS at other sites. Previous studies have shown regional lymph node involvement in 24–50% of patients [2](3) [4], with most cases occurring in the inguinal/femoral and axillary nodal basins. However, nodal involvement can also be observed in less commonly reported nodal regions such as the popliteal fossa or the epitrochlear nodes, as can tumor deposits in the draining lymphatic vessels (Fig. 1). For this paper the lymph nodes or deposits between the primary tumor and the proximal lymph nodes of the inguinal/femoral or axillary region are referred to as in-transit lymph nodes similar to previous publications on in-transit metastases (ITM) in RMS [5–8].

The aim of this study was to determine the staging procedures used, occurrence and survival of patients with ITM in extremity RMS distal to the elbow or knee enrolled in the prospective European pediatric Soft tissue sarcoma Study Group (EpSSG) RMS 2005 study.

2. Patients and methods

2.1. Patient selection

All patients with a localized non-metastatic RMS arising from the extremity either distal to the knee or the elbow who were enrolled in the prospective EpSSG RMS 2005 study between October 2005 and December 2016 were eligible for this study.

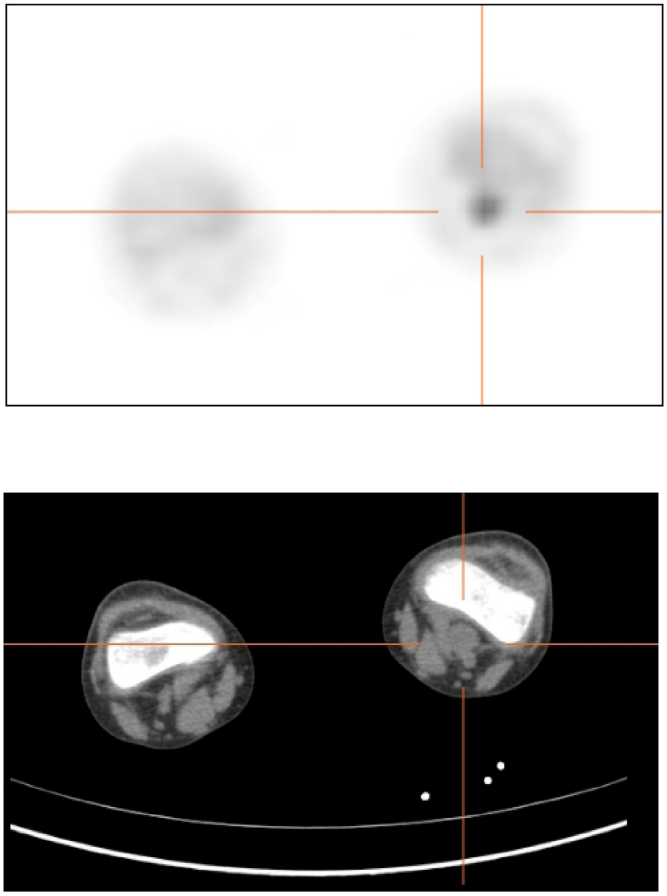

Fig. 1. Pathological lymph node of the popliteal region visible on PET- and CT-scan confirmed by lymph node biopsy.

2.2. Diagnosis

The EpSSG RMS 2005 protocol recommended to assess primary tumor and regional lymph nodes by clinical evaluation, ultrasound, CT-scan, MRI scan of the tumor site and regional lymph nodes and (if available) ^{18}F-FDG-PET/CT. The protocol recommended that suspicious nodes at diagnosis including; enlarged nodes (>1 cm short axis), round-shaped nodes, those without a fatty hilum, or a heterogeneous appearance on imaging, should be sampled by excision or core-needle biopsy. In addition, sampling of normal appearing axillary or groin nodes at diagnosis was recommended and could be performed by sentinel node biopsy or random node picking. There were no recommendations in the protocol as to whether histological confirmation for in-transit nodes was required. Determination of lymph node and ITM involvement wat made on data available in the RMS 2005 database.

2.3. Treatment

Systemic treatment consisted of 9 courses of ifosfamide, vincristin and actinomycin-D (IVA). In addition, many patients received one or more investigational drugs [9]. Local treatment was achieved by surgery, radiotherapy, or both. The aim of surgery was limb-sparing complete resection while maintaining acceptable limb function.

External beam radiotherapy of 41.4 Gy (in 23 fractions) or 50.4 Gy (in 28 fractions) were given to the primary tumor depending on histology (embryonal vs alveolar), IRS stage (I vs II/III), quality of response and second surgery. Radiotherapy to the involved lymph node sites was only performed in cases of clinical or pathologically confirmed involvement of lymph nodes. A radiation dose of 41.4 Gy (23 fractions) was delivered if nodes were not enlarged after initial therapy. An additional boost of 9 Gy (5 fractions) was delivered for residual lymphadenopathy on imaging [10]. Radical lymph node dissections were not recommended except when nodal radiotherapy was contraindicated, for instance in young children <3 years old.

2.4. Definitions

Distal extremity tumors, were defined as tumors distal to the knee or elbow. Proximal lymph nodes were defined as lymph nodes in the axilla or inguinal-femoral regions. ITM were defined as pathological lymph nodes located between the primary tumor and the axilla or inguinal-femoral regions, or the presence of metastatic deposits in the lymphatic vessels between the primary tumor and the axilla or inguinal-femoral regions. Lymph node involvement proximal to the regional lymph nodes was defined as distant metastasis. Both ITM and proximal lymph node metastases were staged as N1.

Patients were staged as N1 if they had a lymph node biopsy showing metastases or if the nodes were suspicious on imaging and no biopsy was performed.

2.5. Anatomy of the lymph nodes/vessels

2.5.1. Upper extremity

The lymphatic vessels accompanying the basilic vein converge to enter the epitrochlear lymph nodes [2,3] that are found medial to the vein and proximal to the medial humeral epicondyle. Lymphatic vessels draining these nodes terminate in the lateral axillary lymph nodes (4–6 nodes).

The lymphatic vessels accompanying the cephalic vein generally cross the proximal part of the arm and shoulder to enter the apical axillary lymph nodes (4–6 nodes), although in some exceptions they enter instead into the more superficial deltopectoral lymph nodes (3–4 nodes).

The deep lymphatic vessels of the upper limb follow the major deep veins (i.e. radial, ulnar and brachial veins), terminating in the humeral axillary lymph nodes (4–6 nodes). Some additional lymph nodes may be found along the ascending path of the deep vessels [11] (Fig. 2).

2.5.2. Lower extremity

The lymphatic vessels of the lower limb can be divided in two major groups: the superficial and the deep lymphatic vessels. The superficial vessels are subdivided into medial, that travel with the greater saphenous vein up to the superficial inguinal nodes, and lateral vessels that ascend on the lateral or anterior lower leg and drain first into the popliteal nodes and subsequently into the inguinal nodes. The popliteal nodes are imbedded in the fatty tissue in the popliteal fossa and are usually between 5 and 7 in number.

The inguinal nodes are found in the femoral triangle and are about 20 in number.

The deep lymphatic vessels accompany the arteries of the lower leg and drain first into the popliteal lymph nodes and subsequently into the inguinal nodes [12] (Fig. 3).

2.5.3. Endpoints and statistics

Data from the prospective EpSSG RMS 2005 study were retrospectively evaluated.

Statistical calculations were performed using SAS statistical package (release 9.4, SAS Institute Inc., Cary, North Carolina). The primary endpoints were 5-year event-free survival (EFS) and 5-year overall survival (OS). Event-free survival (EFS) was defined as the time from diagnosis to first failure (relapse, disease progression, second malignancy or death). Overall survival (OS) was defined as the time from diagnosis to latest follow up or death from any cause. The survival curves were estimated using Kaplan-Meier method.

All participating centers were required to obtain written approval from their local authorities and ethical committees, as well as written informed consent from patients or their parents or legal guardians.

3. Results

3.1. Patients

We included 198 patients with newly diagnosed localized (non-metastatic) extremity RMS. One hundred and nine of 198 patients had a tumor distal from the elbow or knee, 55/109 of the upper extremities and 54/109 of the lower extremity (Fig. 4).

Patient and tumor characteristics are summarized in Table 1. Median age of patients was 6.2 years (range 0–21 years). The majority of patients had tumors >5 cm, alveolar histology and IRS stage III tumors.

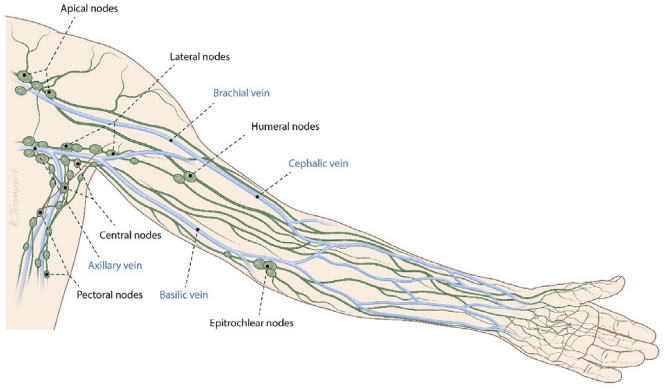

Fig. 2. Lymph node stations of the arm. Regional nodes of the distal arm are the distal epitrochlear and/or the proximal axillary nodes depending on site and infiltration of the primary tumor.

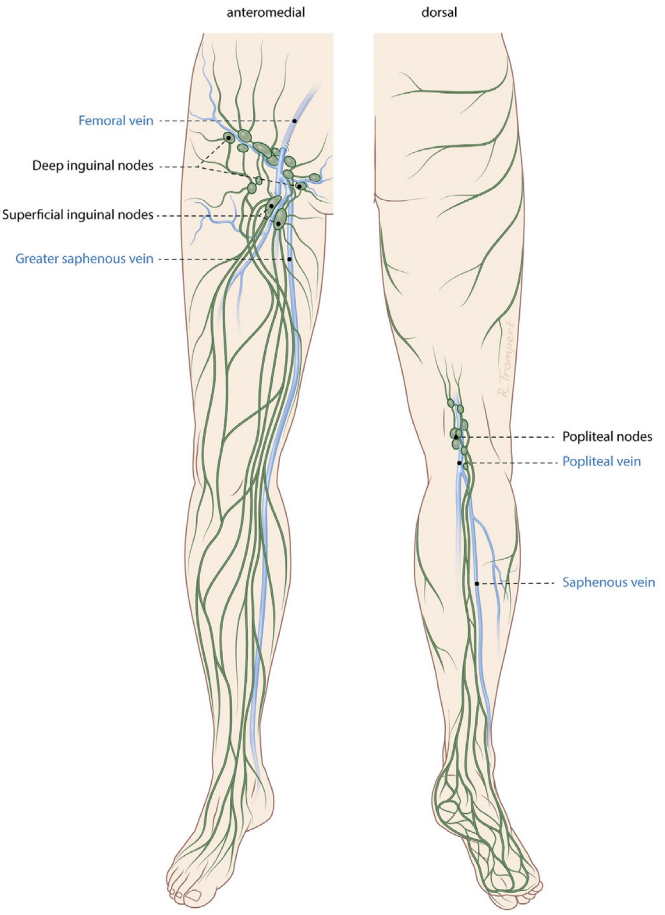

Fig. 3. Lymph node stations of the leg. Regional nodes of the distal leg are the distal popliteal nodes and/or the proximal inguinal nodes depending on site and infiltration of the primary tumor.

3.2. Diagnostic approach and results of lymph node involvement

Radiological evaluation of the lymph nodes was performed at diagnosis, using MRI, CT and/or ultrasound. An additional ^{18}F-FDG-PET/CT was performed in 51/109 patients. The use of ^{18}F-FDG-PET/CT was not dependent on age, size of tumor, histology, tumor site or IRS stage, but was country dependent. Use of ^{18}F-FDG-PET/CT increased during the course of the study.

Lymph node involvement was present in 34% (37/109) of patients.

In those that had ^{18}F-FDG-PET/CT, suspicious lymph nodes were detected in 24/51 (47%), with 14/24 (58%) of these patients having ITM (solitary or in combination with proximal nodes). In those patients not undergoing ^{18}F-FDG-PET/CT, suspicious lymph nodes were detected in 13/58 (22%) ($p = 0.007$), with in-transit metastases in 5/13 (38%) ($p = 0.31$).

Of all patients with N1 disease, 19/37 (51%) patients had ITM, 10/19 (53%) in combination with proximal metastases. When nodal metastases were present, lower extremity sites had more ITM than

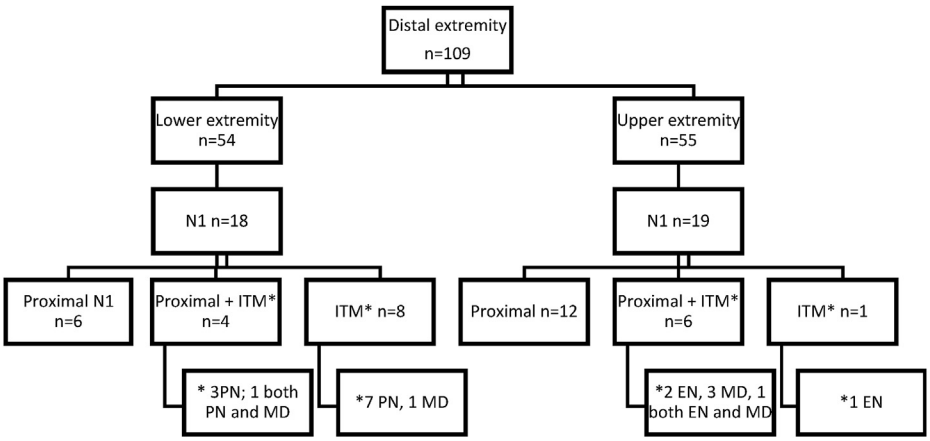

Fig. 4. Flow diagram showing pattern of lymph node metastases in extremity RMS. Distal extremity: primary tumor distal from knee or elbow; RMS: rhabdomyosarcoma; N1: lymph node metastases; ITM: in-transit metastases; PN: popliteal node; EN: epitrochlear node; MD: metastatic deposit in lymphatic vessel.

Table 1
Patient and tumor characteristics.

	N	Events	5-yr EFS (95%CI)	p-value	Deaths	5-yr OS (95%CI)	p-value
All patients	109	49	57.1 (47.1–65.8)	–	37	65.6 (55.2–74.2)	–
Gender							
Female	55	25	56.1 (42.0–68.0)	0.9739	19	65.8 (51.1–76.9)	0.8960
Male	54	24	58.3 (43.8–70.3)		18	65.2 (49.3–77.2)	
Age at diagnosis							
<10 years	74	34	56.3 (44.1–66.7)	0.9693	24	68.1 (55.5–77.8)	0.4641
≥10 years	35	15	58.9 (40.5–73.3)		13	60.2 (40.1–75.4)	
Histology							
Favourable hist.	18	3	83.3 (56.8–94.3)	**0.0259**	2	88.5 (61.4–97.0)	0.0670
Unfavourable hist.	91	46	51.9 (41.0–61.7)		35	61.7 (50.3–71.3)	
Fusion status (if performed)*							
Negative	18	6	77.4 (50.3–90.9)	0.1923	3	88.5 (61.4–97.0)	0.1061
Positive	79	40	49.9 (38.3–60.4)		31	59.7 (47.2–70.1)	
Loco-regional N involvement at diagnosis							
N0	72	27	66.4 (54.2–76.1)	**0.0219**	17	79.0 (67.0–87.1)	**0.0006**
N1	37	22	37.6 (21.7–53.3)		20	39.5 (22.7–55.9)	
N1 patients - Site of N							
In transit	9	1	88.9 (43.3–98.4)	**0.0126**	0	100.0	**0.0025**
Popliteal	7	1			0		
Epitrochlear	1	0			0		
Other	1	0			0		
Proximal	18	13	21.4 (5.5–44.1)		12	25.2 (7.8–47.4)	
Inguinal	6	4			3		
Axilla	12	9			9		
Both	10	8	20.0 (3.1–47.5)		8	15.0 (1.0–45.7)	
Inguinal/popl.	4	3			3		
Axilla/Epitroch.	6	5			5		
Site							
Lower extremities	54	22	64.0 (49.4–75.3)	0.3108	15	75.0 (60.0–85.0)	0.1457
Upper extremities	55	27	50.5 (36.6–62.8)		22	56.6 (41.7–69.1)	
Tumour size							
≤5 cm	46	19	62.8 (47.2–75.0)	0.4525	13	73.4 (56.8–84.5)	0.3903
>5 cm	63	30	53.0 (39.8–64.6)		24	60.4 (46.5–71.8)	
T-invasiveness							
T1	83	33	63.4 (52.0–72.8)	**0.0193**	25	71.1 (59.3–80.0)	**0.0321**
T2	26	16	35.9 (17.8–54.5)		12	46.4 (24.2–65.9)	
IRS Group							
IRS I	7	3	71.4 (25.8–92.0)	0.1080	3	85.7 (33.4–97.9)	0.1178
IRS II	12	2	83.3 (48.2–95.6)		1	90.9 (50.8–98.7)	
IRS III	90	44	52.3 (41.3–62.2)		33	60.2 (48.4–70.1)	

upper extremity sites: 12/18 (67%) vs 7/19 (38%) ($p = 0.07$) (Fig. 2).

In upper extremity, 18/19 (95%) of the N1 patients presented with proximal axillary metastases. In the lower extremity 10/18 (56%) of N1 patients present with proximal inguinal-femoral metastases. In the lower extremity more patients present with ITM in the nodes compared to metastatic deposits in the lymphatic vessels. (11 vs 2 (1 pt combined with popliteal nodes)) than in the upper extremity (4 vs 4 (1 combined with epitrochlear node)) (Fig. 2).

Histological confirmation of at least one lymph node station was obtained in 28/37 (76%) N1 patients. In patients with solitary ITM 8/9 (89%) of the nodes were biopsied.

In all patients with distal extremity RMS surgical staging of lymph nodes at diagnosis was performed in 65/109 (60%) patients and 28/65 (43%) patients had histologically proven nodal disease. Patients were staged as N1 on imaging only in 9/37 patients (3/9 based on conventional imaging alone and 6/9 in patients also staged with ^{18}F-FDG-PET/CT). In 13 of 65 (20%) biopsied patients (7 patients with ^{18}F-FDG-PET/CT) a biopsy changed the nodal status from 'suspected positive' to 'negative' or reversed.

3.3. Treatment

Primary resection was performed in 21/109 (19%) patients and delayed primary excision in 74/109 (68%) patients after induction chemotherapy. Thirteen patients did not undergo resection, and in three patients data were missing. An R0 (radical resection) was performed in 67 patients, an R1 (microscopic irradicale) resection in 23 patients and an R2 (macroscopic irradicale) in 3 patients. In 2 patients no tumor was found in the specimen after delayed primary excision.

Eighty patients received radiotherapy, 46/80 (58%) to the primary tumor, 31/80 (39%) to the primary tumor and the lymph nodes, and 3/80 (4%) to the lymph nodes alone.

RT was applied to the proximal nodes in 20 patients, to ITM in 5 patients and to both in 8 patients. In 1 patient the site of RT was unknown. Table 2 shows the field of radiotherapy in relation to the nodal relapse site. Reasons for no RT were young age in 9 patients, center decision in 6, not indicated in 11 and progressive disease in 3.

3.4. Treatment outcome

3.4.1. Relapse

Forty-nine out of 109 patients developed a relapse (45%); local 7, regional (inguinal/axillary nodes + ITM) 7, regional in combination with other relapse sites 7, metastatic 21, local in combination with metastatic 2, progressive disease 4, and second malignancy 1 (high grade glioma). Six of 14 nodal relapse patients developed a nodal relapse in the RT field, and 1/14 in the margins of the RT field.

Only one out of 9 patients with solitary ITM at diagnosis relapsed; all are still alive with a follow up of 82 months. Those with proximal (inguinal/axillary) lymph node metastases at diagnosis relapsed in 13/18 (72%), 12 of these 13 patients died. Patients with combined proximal and in-transit nodes at diagnosis relapsed in 80% (8/10); all 8 of these patients died.

Of the N0 patients 7/72 (10%) had a nodal relapse.

3.4.2. Survival

The median follow-up was 6.3 years (range 2–12,5). Sixty of 109 (55%) patients are in first complete remission and 9/109 (8%) are in remission after relapse. One patient is alive with disease and 37/109 (34%) died. Two patients were lost to follow up.

5-year EFS and OS of all 109 patients was 57.1% (47.1–65.8 95% CI) and 65.6% (55.2–74.2 95%CI) (Table 1). Survival was significantly better for patients without nodal disease compared to patients with nodal disease (EFS 66.4% vs 37.6% ($p = 0.02$) and OS 79% vs 39.5% ($p = 0.0006$)). Patients with solitary ITM had a significantly better outcome compared to proximal or combined ITM and proximal metastases (EFS 88.9% vs 21.4% and 20.0% respectively ($p = 0.01$) and OS 100% vs 25.2% and 15.0% respectively ($p = 0.003$)) (Fig. 5). In order to be able to compare survival of both these sub-groups with patients with proximal tumor locations (above knee and elbow) presenting with proximal (inguinal/axillary) lymph node involvement, we report here the 5-year EFS and OS in N1M0 patients with a proximal extremity tumor location, being 48.9% (24.6–69.4 95% CI) and 57.1% (30.4–76.9 95%CI)) respectively.

4. Discussion

Our study showed that ITM constituted more than 50% of all lymph node metastases in distal extremity RMS. In patients where ^{18}F-FDG-PET/CT was performed, more regional and ITM were detected. The database and not the source radiology reports were interrogated, so it was not possible to conclude whether ^{18}F-FDG-PET/CT was more sensitive than conventional imaging at identifying regional lymph nodes and ITM. It was not possible to determine from the available data whether in-transit lymph node sites were included in conventional imaging. However, previous published data from Federico et al. has demonstrated that ^{18}F-FDG-PET/CT to be more accurate for staging of RMS patients [13].

In RMS, only a limited number of studies document ITM at diagnosis and in-transit lymph node disease relapse. A study by Nishida et al. reported 7% in-transit metastatic spread in a cohort of 44 pediatric and adult patients with RMS from different tumor sites [7]. La et al. found a 4% rate of in-transit nodal involvement in 116 pediatric patients with distal extremity RMS [8]. We report a higher number of ITM, which we attribute to the increased use of ^{18}F-FDG-PET/CT. Despite these improvements in imaging, biopsy of the nodes remains important as it will change nodal status in 16% of those patients who have undergone ^{18}F-FDG-PET/CT staging [2].

In transit metastases in melanoma patients are well described. They present as deposits of tumor cells in dermal or subdermal lymphatics [14]. In extremity RMS, ITM typically present as pathological popliteal or epitrochlear lymph nodes, or as deposits within lymphatics that course with the blood vessels. This might be due to the mesenchymal origin of RMS, mostly with its origin deeper in the extremity. This suggests that, especially in the lower leg, drainage is mainly through the popliteal nodes up to the inguinal nodes. This drainage pattern can be endorsed by our data showing there is a high number of involved popliteal nodes. In epitrochlear nodes this is less clear. Epitrochlear nodes accompanying the basilic vene (Fig. 2), are more superficial nodes and might not always be involved in distal extremity tumors situated deeper in the muscles or on the radial side. If the tumor invades the dermis,

Table 2
Radiotherapy on the lymph nodes in relation to nodal relapse. ITM: in transit metastases (popliteal and epitrochlear nodes + metastatic deposits); RT: radiotherapy.

Site of nodes at diagnosis	RT field	Nodal relapse within RT field	Nodal relapse outside RT field
Proximal nodes (axilla and inguinal) n = 20	Proximal nodes (20)	3	2
ITM (epitrochlear and popliteal nodes and metastatic deposits) n = 7	ITM (7)	0	0
Proximal nodes + ITM n = 7	Only proximal nodes (3)	0	2
	Proximal + ITM (4)	1	0

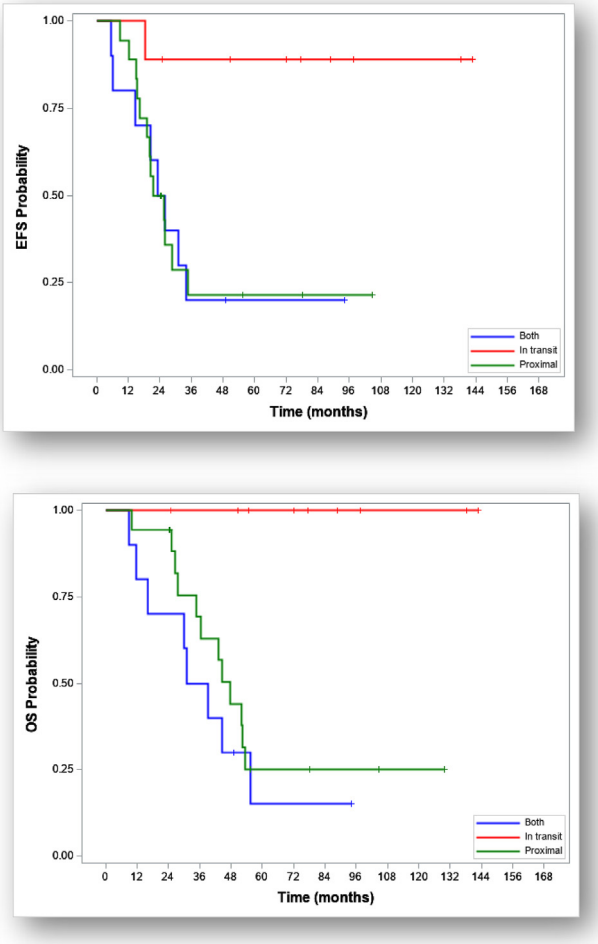

Fig. 5. Event free and Overall Survival in N1 patients with proximal nodes, in transit nodes and proximal combined with in transit nodes.

tumor cells can spread directly to the proximal inguinal or axillary nodes through the superficial lymphatic draining system [15].

Patients with distal extremity RMS presenting with involved proximal lymph nodes have a poor prognosis, comparable to patients presenting with metastatic (M1) disease [16,17]. Patients with only popliteal or epitrochlear nodal involvement do much better. We showed that many RMS of the distal extremity pass through the distal popliteal and epitrochlear nodes (first echelon nodes) before ascending to the inguinal and axillary nodes (second echelon nodes). It is unclear if in solitary inguinal/axillary nodal involvement, the in-transit nodes were evaluated and if the inguinal/axillary nodes can be considered as true first echelon nodes or actually are second echelon nodes. Considering the anatomy and poor outcome (comparable to M1 patients) in distal extremity RMS patients with proximal lymph node (second echelon) involvement, perhaps these inguinal or axillary nodes may be considered as distant metastatic (M1) disease. This theory is strengthened by the better survival of patients with tumor locations above the knee and elbow where the first echelon nodes must be the inguinal and axillary nodes.

Agreement on definition and staging of ITM and regional nodes is of utmost importance in the treatment of RMS, because involvement of lymph nodes beyond the first regional lymph node station basin are considered distant metastases. We suggest that popliteal nodes and epitrochlear nodes should be considered as true regional nodal stations and not as in-transit metastases, as stated in earlier publications [6–8]. The term in-transit metastases must only be assigned to the metastatic deposits in the lymphatic vessels.

The current EpSSG guidelines do not offer guidance on when biopsy of in-transit nodes is required. Biopsy of distal regional nodes can be surgically challenging. Sentinel node biopsy is feasible in extremity RMS and identifies which nodes to sample [15]. In the absence of a sentinel node biopsy, node sampling should be performed, unless clearly pathological. Especially in lower extremity tumors, we recommend biopsy of distal regional nodes combined with biopsy of the inguinal nodes even when they are clinically normal, because of the high number of positive popliteal nodes (67% in N1 patients). In upper extremity RMS, we advise at least node sampling of the axillary nodes because 95% of the N1 patients present with regional axillary metastases and only a small number (21%) with metastatic epitrochlear nodes. Metastatic deposits in the lymphatic vessels should be biopsied when clinically apparent.

There are some limitations to the study presented here, particularly the small number of patients from which only limited conclusions can be drawn. In addition, guidelines concerning imaging and surgical staging approach were not uniformly translated into practice across all 134 treatment centers, which is inherent to an international multicenter study in a rare disease, covering an inclusion period of 11 years. Finally, there was limited radiology data available in the EpSSG RMS 2005 database describing the characteristics of the suspicious nodes.

5. Conclusion

Lymph node and in-transit metastases are of clinical importance in distal extremity RMS and should be staged properly. Conventional imaging of the whole extremity and ^{18}F-FDG-PET/CT are recommended [18]. In the distal extremity, popliteal/epitrochlear nodes should be considered as true regional (first echelon) nodes, where inguinal/axillary nodes might be considered as metastatic second echelon nodes, depending on the exact localization of the primary tumor. Histological confirmation of suspected nodes should be performed. If nodes are clinically and radiologically negative, sentinel node biopsy is indicated when available, otherwise random node sampling should be performed, with particular consideration for biopsy of the popliteal nodes in lower extremity RMS. In upper extremity, at least a biopsy of the axillary nodes should be performed.

CRediT authorship contribution statement

C.E.J. Terwisscha van Scheltinga: Conceptualization, Data curation, Formal analysis, Conception and design, collection and assembly of data, and data analysis and interpretation. Writing - original draft, Article writing and final approval of article. **M.H.W.A. Wijnen:** Writing – original draft, Article writing and final approval of article. **H. Martelli:** Writing – original draft, Article writing and final approval of article. **F. Guerin:** Writing – original draft, Article writing and final approval of article. **T. Rogers:** Writing – original draft, Article writing and final approval of article. **R.J. Craigie:** Writing – original draft, Article writing and final approval of article. **G. Guillén Burrieza:** Writing – original draft, Article writing and final approval of article. **P. Dall'Igna:** Writing – original draft, Article writing and final approval of article. **F. De Corti:** Writing – original draft, Article writing and final approval of article. **N. Smeulders:** Writing – original draft, Article writing and final approval of article. **R.R. van Rijn:** Writing – original draft, Article writing and final approval of article. **R.Dávila Fajardo:** Writing –

original draft, Article writing and final approval of article. **H.C. Mandeville:** Writing – original draft, Article writing and final approval of article. **I. Zanetti:** Data curation, Formal analysis, Data analysis and interpretation, Writing – original draft, Article writing and final approval of article. **B. Coppadoro:** Data curation, Formal analysis, Data Formal analysis, and interpretation. Writing - original draft, Article writing and final approval of article. **V. Minard-Colin:** Writing – original draft, Article writing and final approval of article. **M. Jenney:** Writing – original draft, Article writing and final approval of article. **G. Bisogno:** Writing – original draft, Article writing and final approval of article. **M.M. van Noesel:** Writing – original draft, Article writing and final approval of article. **A.F.W. van der Steeg:** Writing – original draft, Article writing and final approval of article. **J.H.M. Merks:** Conceptualization, Data curation, Formal analysis, Conception and design and data analysis and interpretation. Writing - original draft, Article writing and final approval of article.

Declaration of competing interest

None.

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