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Original Research

Non-parameningeal head and neck rhabdomyosarcoma in children, adolescents, and young adults: Experience of the European paediatric Soft tissue sarcoma Study Group (EpSSG) – RMS2005 study

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Abstract ***Backgroundlobjectives:*** The primary aim of this study was to analyse and evaluate the impact of different local treatments on the pattern of relapse in children with primary head and neck non-parameningeal (HNnPM) rhabdomyosarcoma (RMS), treated in the European paediatric Soft tissue sarcoma Study Group (EpSSG) RMS2005 study. The secondary aim was to assess whether current risk stratification is valid for this specific site.
Designlmethods: This study includes all patients with localised HNnPM RMS enrolled in the RMS2005 study between 2005 and 2016. Treatment comprised chemotherapy adapted to risk group, with local surgery and/or radiation therapy. The main outcome measures were event-free survival (EFS) and overall survival (OS).
Results: A total of 165 patients were identified; the median age was 6.4 years (range, 0.1–25). The most common tumour sites were cheek/chin (22%) and nasal ala/nasolabial fold (20%). Histology was unfavourable for 40%, and regional nodal involvement present in 26%. Local therapy included surgery (58%) and/or radiotherapy (72%) to primary tumour and/or regional lymph nodes. After a median follow-up of 66 months (range, 6–158), 42 patients experienced an event, and 17 are still alive. Tumour events were frequent in oral primary (36%), parotid site (26%), cheek/chin (24%), and nasal ala/nasolabial fold (24%) and included locoregional failure in 84% of cases. The 5-year EFS and OS were 75% (95% confidence interval [CI]: 67.3–81.2) and 84.9% (95% CI: 77.5–89.7), respectively. Favourable histology was associated with a better EFS (82.3% versus 64.6%; $p = 0.02$) and nodal spread with a worse OS (88.6% versus 76.1%; $p = 0.04$). Different sublocations within the HNnPM primary did not have significant impact on outcome.
Conclusion: Locoregional relapse/progression is the main tumour failure event in this site. Despite frequent unfavourable risk factors, HNnPM RMS remains a favourable location in the context of a risk-adapted strategy.

1. Introduction

Rhabdomyosarcoma (RMS), an aggressive malignant tumour arising from primitive mesenchymal cells, is one of the most common non–central nervous system paediatric solid tumours and accounts for 4–5% of cancers in patients aged younger than 18 years [1–3]. The most common location is the head and neck area (40% of cases) [4], classically divided in orbital, parameningeal (PM), and non-parameningeal (HNnPM) sites [5–7]. The results from several large studies have shown that HNnPM represents less than 10% of all localised RMS and is considered a favourable site with an overall survival (OS) of >70% [5,8,9]. Although HNnPM is considered a favourable site, patients with alveolar histology and/or nodal involvement at this site appear to have a less favourable outcome with increased risk of local or regional lymph node relapse [5,10,11]. The European paediatric Soft tissue sarcoma Study Group (EpSSG) developed a therapeutic protocol adapted for clinical risk factors in young patients with localised RMS (RMS2005-study) [1,2].

The purpose of this study was to analyse and evaluate the impact of different local treatments on the pattern of relapse in children, adolescents, and young adults with HNnPM RMS primary, treated in the EpSSG RMS2005 study. The secondary aim was to confirm the validity of the current risk stratification for this disease site.

2. Material and methods

The EpSSG RMS2005 study was an investigator-initiated prospective clinical trial conducted at 108 hospitals in 14 Countries (Argentina, Belgium, Brazil, Czech Republic, France, Ireland, Israel, Italy, Norway, Slovakia, Slovenia, Spain, The Netherlands, and the United Kingdom). The trial enrolled patients (aged 0–25 years) with localised RMS from October 2005 to December 2016 (EudraCT, number 2005-000217-35)

[1,2]. Ethical approval was obtained prospectively in participating countries. Signed informed consent was obtained from each patient/parents according to national and institutional guidelines.

Histological diagnosis was made by the local pathologist and reviewed by the EpSSG national and international Pathology Panel. Classification by histology was based on definitive histology. Alveolar subtype was mainly based on histology, as assessment of fusion status (defined as testing for PAX3/7 and FOXO1 gene rearrangements) was not mandatory. Fusion status was investigated by fluorescence in situ hybridisation (FISH) and/or reverse transcription-polymerase chain reaction (RT-PCR). Each tumour was classified according to the site of origin [12]. 'Non-parameningeal head and neck' tumours (HNnPM) arise in neck, parotid region, oropharynx, cheek, masseter muscle, scalp, oral cavity, and larynx [5]. Orbital and PM primaries (nasopharynx, nasal cavity, paranasal sinuses, temporal bone, pterygopalatine fossa, and infratemporal fossa) were excluded.

2.1. Risk group and staging

Patients included in the RMS2005 protocol were stratified into four risk groups: low risk (LR), standard risk (SR), high risk (HR), and very high risk (VHR), based on the following risk factors: histological subtype, post-surgical stage, tumour site and size, nodal involvement, and patient age (Table 1) [1]. LR consisted only of Group A (favourable histology, Intergroup Rhabdomyosarcoma Studies [IRS] I, any site, N0, and favourable size and age); SR consisted of Group B (favourable pathology, IRS I, any site, N0, and unfavourable size and age), Group C (favourable pathology, IRS II-III, favourable site, N0, and any size and age), and Group D (favourable pathology, IRS II-III, unfavourable site, N0, and favourable size and age); HR consisted of Group E (favourable pathology, IRS II-III, unfavourable site, N0, and unfavourable size and age), Group F (favourable pathology, IRS II-III, any site, N1, and any size and age), and Group G (unfavourable pathology, IRS I-II-III, any site, N0, and any size and age); and VHR only consisted of Group H (unfavourable pathology, IRS II-III, any site, N1, and any size and age; Table 1).

2.2. Treatment

Treatment was administered according to specific recommendations for each risk group (Table 1). After the diagnosis of RMS was confirmed, usually by biopsy, all patients received chemotherapy followed by delayed primary excision (DPE) with surgical removal of the primary tumour and/or radiotherapy (RT) according to their risk groups. HR patients were randomised to neoadjuvant chemotherapy with ifosfamide–vincristine–D-actinomycin (IVA) or IVA + doxorubicin (IVADo) for the initial four courses followed by five courses of IVA. Patients in complete remission (CR) after induction therapy were offered randomisation between 6 months of maintenance therapy with low-dose vinorelbine/cyclophosphamide (VNL/Cy) versus stop treatment [1,2]. VHR

Table 1
Risk grouping stratification and therapy in EpSSG RMS 2005 study.

Risk group	Subgroups	Pathology	Post-surgical stage (IRS group)	Site	Node stage	Size and age	Chemotherapy	Delayed surgery	Radiation therapy
Low risk	**A**	Favourable	I	Any	N0	Favourable	8 × VA	Not necessary	No
Standard risk	***B***	Favourable	I	Any	N0	Unfavourable	4 × IVA + 5 × VA	Not necessary	No
	C	Favourable	II, III	Favourable	N0	Any	9 IVA **or** 5 × IVA + 4 × VA if radiotherapy	Yes, if not mutilating	Optional
	D	Favourable	II, III	Unfavourable	N0	Favourable	9 IVA	Yes, if not mutilating	Yes
High risk	***E***	Favourable	II, III	Unfavourable	N0	Unfavourable	9 × IVA vs 4 IVADo + 5	Yes	Yes
	F	Favourable	II, III	Any	N1	Any	IVA ± 6 × maintenance		
	G	Unfavourable	I, II, III	Any	N0	Any			
Very high risk	***H***	Unfavourable	II, III	Any	N1	Any	4 IVA Do + 5 IVA + 6 × maintenance	Yes	Yes

Pathology (histology): *Favourable* = all embryonal, spindle cells, botryoid RMS. *Unfavourable* = all alveolar RMS (including the solid-alveolar variant).
Post-surgical stage (according to the IRS grouping, see appendix A.2): *Group I* = primary complete resection (R0); *Group II* = microscopic residual (R1) or primary complete resection but N1; *Group III* = macroscopic residual (R2).
Site: *Favourable* = orbit, GU non-bladder prostate (i.e. paratesticular and vagina/uterus) and non-PM Head & neck. *Unfavourable* = all other sites (parameningeal, extremities, GU bladder prostate and 'other site').
Node stage (According to the TNM classification, see appendix A1 and A.5): *N0* = no clinical or pathological node involvement. *N1* = clinical or pathological nodal involvement.
Size and age: *Favourable* = Tumour size (maximum dimension) ≤5 cm and age <10 years. *Unfavourable* = all others (i.e. size >5 cm *or* age ≥10 years).
Chemotherapy: VA= vincristine-dactinomycin; IVA= ifosfamide-vincristine-dactinomycin; IVADo = IVA-Doxorubin.

Table 2
Patient and tumour characteristics according to risk group for HNnPM RMS.

Patient and tumour characteristics	Low risk (LR)	Standard risk (SR)	High risk (HR)	Very high risk (VHR)	Total
Number of patients	3	78	58	26	**165**
Gender					
Male	1	46	30	11	**88**
Female	2	32	28	15	**77**
Age at diagnosis (median, ranges)	1.5 (1.5–8.5)	6.7 (0.1–24.9)	6.3 (0.2–19.9)	7.0 (0.9–16.0)	**6.4 (0.1–24.9)**
≤1 year	_	7	7	1	**15**
1–9 years	3	48	32	16	**99**
10–17 years	_	21	17	9	**47**
≥18 years	_	2	2	_	**4**
Primary sites					
Cheek/chin	_	24	9	4	**37**
Hypopharynx	_	_	1	_	**1**
Larynx/trachea	_	4	2	_	**6**
Nasal ala/nasolabial fold	_	2	24	7	**33**
Neck	_	6	5	6	**17**
Oral cavity	2	13	6	1	**22**
Oropharynx	_	9	5	1	**15**
Parotid	_	10	2	3	**15**
Scalp (including ear primary)	1	10	4	4	**19**
Histology					
ARMS	_	_	40	25	**65**
Non-ARMS	3	75	17	_	**95**
NOS	_	3	1	1	**5**
Fusion status (N = 125)					
Positive	_	_	31	17	**48**
Negative	2	48	21	6	**77**
Not analysed	1	30	6	3	**40**
Invasiveness					
T1	3	57	36	14	**110**
T2	_	17	21	12	**50**
Tx	_	4	1	_	**5**
Primary tumour size					
≤5 cm	3	64	47	15	**129**
>5 cm	_	12	11	11	**34**
Not evaluable	_	2	_	_	**2**
Nodal involvement					
N0	3	78	41	_	**122**
N1	_	_	17	26	**43**
IRS group					
I	3	1	1	_	**5**
II	_	23	8	_	**31**
III	_	54	49	26	**129**

T1 confined in the tissue of origin, T2 extension outside of the tissue/organ of origin.

patients received IVADo/IVA and 6 months of VNL/Cy [13].

Primary resection and/or immediate primary re-excision were recommended only when microscopic complete tumour resection without mutilation was feasible. Groups A and B received no further local therapy after initial surgery. Subgroup C could have DPE after four courses of chemotherapy without any RT (if CR and favourable age/size risk factors) and adjuvant chemotherapy or adjuvant RT and reduced chemotherapy. Patients in Groups D to H were recommended to receive DPE after four courses of chemotherapy if macroscopic resection was deemed feasible without mutilation. The surgical resection system from the *Union Internationale Contre le Cancer* was used to define the quality of the DPE: R0 resection was defined by a microscopically complete resection, R1 was defined by a microscopically incomplete resection, and R2 was defined by a macroscopically incomplete resection [14].

RT was planned after four courses of chemotherapy, with doses varying from 41.4 to 50.4 Gy according to

histology, chemotherapy response, and surgical margins. A boost of 5.4 Gy to the residual tumour was recommended for large tumours with poor response to chemotherapy (Supplemental Table I). RT (41.4 Gy) to the regional nodes was performed in cases of initial clinical, radiological, and/or pathological regional node involvement. In addition, a boost of 9 Gy was recommended when the lymph nodes were enlarged at the onset of RT. Exceptions were made in very young patients (aged <3 years), for whom RT could be avoided.

2.3. Assessment of tumour response and treatment decisions

In patients with macroscopic disease after initial surgery (IRS III), response to treatment was assessed after three courses of chemotherapy [15]. Complete response (CR) and partial response continued allocated treatment, whereas stable disease and progressive disease (PD) were considered for second-line treatment with either anthracycline-based regimen or phase II treatment.

2.4. Statistical methods

The principal end-points for the analyses were 5-year event-free survival (EFS) and OS, calculated using the Kaplan–Meier method. EFS was defined as the time from diagnosis to disease progression, relapse, secondary malignant tumour, death due to any cause, or latest follow-up (FU) for patients who never experienced an event. OS was defined as the time from diagnosis to death due to any cause or latest FU for patients alive. The log-rank test was used to compare survival rates between different subgroups of patients in the univariate analysis, considering patient age and gender and tumour characteristics (histology, site, size, invasiveness, sublocations, lymph node involvement, and IRS group). Statistical significance was defined as $p < 0.05$. A multivariate analysis of different patient characteristics and risk factors was performed using Cox's proportional hazards model. All statistical analyses were performed using the SAS statistical package.

3. Results

A total of 165 patients with localised HNnPM RMS were prospectively enrolled in the EpSSG RMS2005 study, representing 9.5% of all patients in the protocol. The HNnPM patients belonged to all risk groups except E and F because the HNnPM site is favourable (Table 1). Clinical characteristics are summarised in Table 2. The median age at diagnosis was 6.4 years (1 week to 25 years). Only 9% were less than 1 year and 31% older than 10 years. There was a slight excess of males (M/F: 88/77). Overall, 2% were LR, 47% SR, 35% HR, and 16% VHR. The most common tumour sites were cheek/chin (22%) and nasal ala/nasolabial fold (20%; Fig. 1). The risk grouping differed between sublocations; tumours in cheek/chin were frequently SR (65%), whereas tumours in the nasal/nasolabial area mostly were HR or VHR (94%). The tumours were mainly small (<5 cm; 78%) and confined to the organ/tissue of origin (T1; 67%).

Histology was favourable in 95 (58%) and unfavourable in 70 (42%). A total of 125 tumours were assessed for PAX-FOXO gene fusions; 77 were fusion negative (31 FISH, 31 RT-PCR, and 15 FISH and RT-PCR), whereas a gene fusion was detected in 48 of 70 (69%) tumours with unfavourable histology (19 FISH,

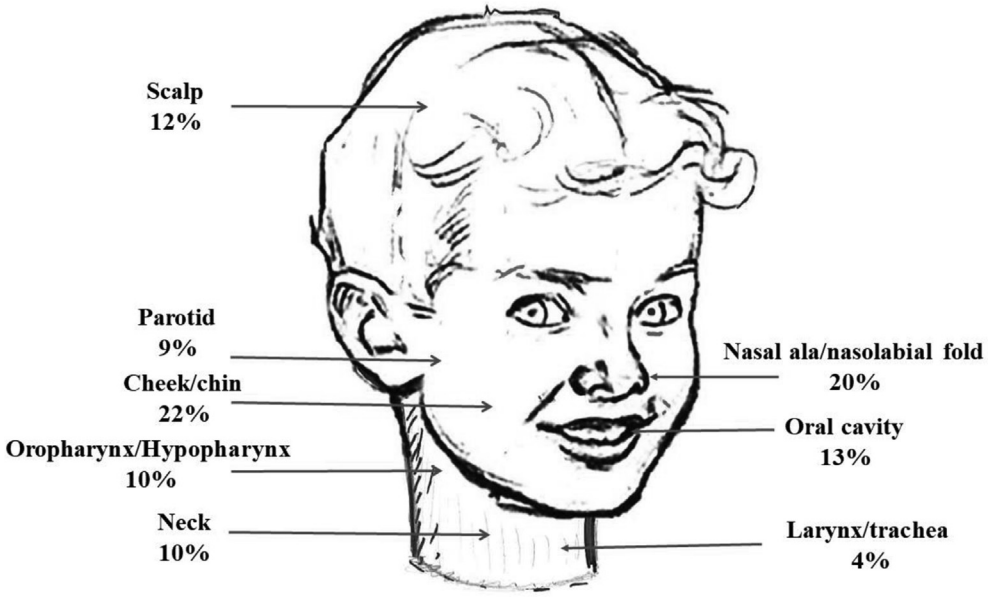


Fig. 1. Sites' distribution in patients with HNnPM RMS.

Table 3
Patient distribution by event (N = 42) according to initial risk group.

Type of events	Low risk n = 1	Standard risk n = 15	High risk n = 18	Very high risk n = 8	Total % n = 42	Status at the end of follow-up Number of alive patients
Local relapse (LR)	_	12	4	1	17	10
Local progressive disease (PD)	_	1	4	1	6	2
Regional lymph node relapse (NR)	_	_	4	_	4	3
LR/PD + Metastases (MTS)	_	1	2	_	3	0
LR + NR + MTS	_	_	_	1	1	0
Isolated MTS	_	_	3	3	6	2
PD + N	_	_	_	1	1	0
Second tumour	1	1	_	_	2[a]	0
Fatal infection	_	_	_	1	1	0
Sudden death[b]	_	_	1	_	1	0
Percentage of event within each risk group	33%	19%	31%	31%	25%	

[a] One medulloblastoma, one undifferentiated sarcoma
[b] One sudden death (cardiovascular cause) in complete remission off therapy after 2 months from the end of therapy.

24 RT-PCR, and 5 FISH and RT/PCR). No gene fusion was present in the 63 of 95 patients with favourable histology for whom fusion status was assessed. Unfavourable histology was frequent in nasal ala/nasolabial fold (29/33 cases, 88%), neck (9/17 cases; 53%), scalp (7/19 cases; 37%), and check/chin sublocations (12/37 cases; 32%).

Among the 129 IRS III group patients (78%), 88 had surgical biopsy, 14 had a tru-cut biopsy, and 26 had a partial surgical resection of primary tumour (missing data: one case). Regional lymph node involvement (N1) was present in 43 patients (26%) in all groups (17 HR and 26 VHR), mostly when primary site was nasal ala/nasolabial fold (9/33 cases, 27%), neck area (8/17, 47%), or scalp (5/19 cases, 26%). Lymph node involvement was associated with unfavourable histology in 26 of 43 patients (61%).

3.1. Local treatment delivered

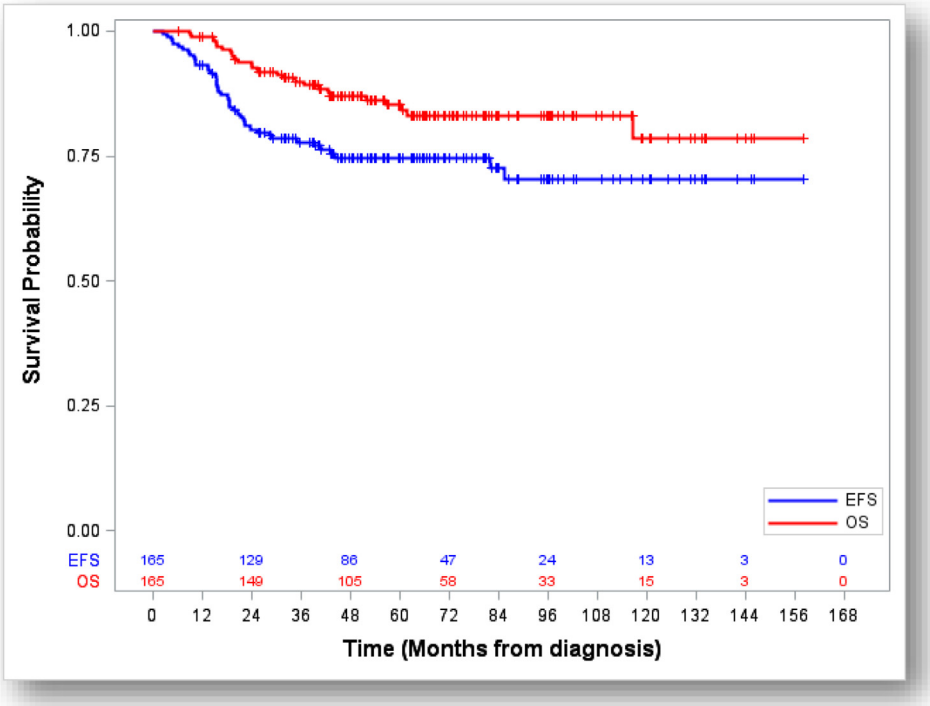
Among the three patients in the LR group, one received additional RT because of the initial diagnosis of alveolar subtype, modified after pathology review.

Among the 78 SR (subgroup B: 1 and subgroup C: 77), eight patients received no further local therapy, 23 had DPE (no residual tumour/R0: 21 cases; R1 margins: two cases) without adjuvant RT, 26 received radical RT (median dose of 50.4 Gy; range, 36.0–60.0) as the sole local therapy, and 18 received DPE (no residual tumour/R0: 11 cases; R1: five cases; R2 two cases) and RT (45.0 Gy; range, 36.0–65.4).

Within the 58 patients in the HR group, five had no local therapy (early progression: three cases; physician decision: two cases [IRS I and tongue primary; CR after three cycles and young age, one case each]), four had only DPE (early progression: one case; young age: three cases), 29 received radical RT (50.4 Gy; range, 36.0–55.8) as the sole local therapy, and 19 had DPE with RT (50.4 Gy, range, 36.0–56.0). Delayed surgery showed no residual tumour/R0 in 19 cases and R1 margins in four cases. Among the 17 patients with nodal involvement in this group, 16 received RT to the primary tumour and affected lymph nodes, whereas one did not receive RT due to early PD after initial chemotherapy. In addition, four had cervical nodal exploration (unilateral lymph node adenectomy: two cases; and node sampling: two cases).

Among the 26 patients classified as VHR, 22 received RT; 14 received exclusive RT to the primary tumour and nodal area (median dosage 47.6 Gy; range, 41.4–60.0), whereas eight received DPE and adjuvant RT (to primary and nodal areas: six cases; primary tumour: two cases; median dosage, 50.4 Gy; range, 41.4–55.8). Two patients received no local therapy due to early PD and CR after three cycles with parental refusal of RT (1 case each). Finally, two patients had exclusive DPE for physicians' preference. Additional delayed lymph node sampling (four cases) or unilateral lymph node dissection (one case) was performed. Surgical results showed no residual tumour/R0 in eight cases and R1 margins in two cases.

In summary, RT was omitted in 26 R0 patients and three R1 patients. The details on RT treatment are available for 161 of 165 patients. Overall, 115 patients (72%) received RT; photon therapy (63%), proton therapy (20%), electrons ± photon therapy (10%), brachytherapy (5%), and Cobalt 60 therapy (2%). The median dose for external RT was 50.4 Gy (range, 36.0–65.4), and the median dose for brachytherapy was 42.5 Gy (range, 36.0–55.8). Overall, local ± nodal surgery was performed, at diagnosis or after neoadjuvant chemotherapy, for 96 of 164 patients (data missing: one case); all 36 IRS I-II and 60/128 IRS III.



	N patients	Failed	5-yr Survival (95%CI)
Event Free Survival	165	42	74.7 (67.1-80.8)
Overall Survival	165	25	85.2 (78.3-90.1)

Fig. 2. Event-free and overall survivals of the population with HNnPM RMS.

3.2. Outcome

After a median FU of 65.6 months (range, 6.2–158.2), 42 patients experienced an event (38 tumour related and four others; Table 3). Tumour events included locoregional failure in 32 of 38 cases (84%), including six nodal relapses. The 38 tumour-related events were frequent in patients with primary tumour in oral cavity (8/22, 36%), parotid site (4/15, 26%), cheek/chin (9/37, 24%), and nasal ala/nasolabial fold (8/33, 24%). Among the 38 patients with a tumour-related event, there were 14 SR (three DPE, four DPE/RT, two RT, and five with no local therapy), 17 HR (five DPE, four DPE/RT, six RT, one no local therapy, and one no information about local therapy), and seven VHR (zero DPE, one DPE/RT, five RT, and one no local therapy). Overall, 21 of these patients died despite further treatment (36 chemotherapy [missing data: 2], 14 received RT and surgery, four only received RT, and six only received surgery, but the data are incomplete. The surgery was mutilating in four patients). In addition, four patients died from other causes (Table 3). Among the 28 patients with isolated locoregional failure (local ± cervical nodal progression/relapse), 15 survived after second-line therapies, whereas only two of the ten patients with distant metastases survived. Among the 165 patients with HNnPM RMS, two developed a second malignancy (one medulloblastoma and one undifferentiated sarcoma), and one of these patients are among the four who died from other causes. At the last FU, 124 patients are alive in the first CR, 14 in the second CR, and two are alive with disease.

Among 43 patients with lymph node involvement at diagnosis (17 HR and 26 VHR), 11 experienced a tumour-related event: five had local failure at primary site, including two with regional nodal relapse; six have distant metastases relapses ± locoregional failure. Among them, only two, with isolated distant metastases, survived.

Among the 17 patients (10%) who received neither DPE nor RT, ten experienced an event (five local relapses, four PD, and one PD + N). Among the 12 patients who achieved local control without surgery nor RT, six were salvaged after additional treatment.

The 5-year EFS and OS of the entire population are 75% (95% confidence interval [CI]: 67.3–81.2) and 84.6% (95% CI: 77.5–89.7), respectively (Fig. 2). Outcome is similar for patients according to risk groups (Supplemental Figs. 1–2).

Univariate analysis for EFS shows a significant impact only of histology with an EFS of 83.4% (95% CI: 73.4–89.8) for favourable versus 64.6% (95% CI: 51.9–74.8) for unfavourable histology ($p = 0.02$; Supplemental Table II). Univariate analysis for OS shows a significant impact only of lymph node involvement with an OS of 88.6% (95% CI: 80.6–93.4) for N0 versus 76.1% (95% CI: 60.0–86.4) for N1 (Supplemental Table II). Multivariate analyses for EFS (model including histology or fusion status, IRS group, and risk group) and OS (model including histology, tumour size, T-invasiveness, lymph node involvement, risk group, and IRS group) show no significant impact for any of the studied variables.

4. Discussion

This large study of patients with HNnPM RMS after risk-adapted treatment according to the EpSSG RMS2005 stratification shows outcomes remained excellent (EFS 75.0% and OS 84.6%) and compare favourably to the outcome from similar studies performed by other cooperative groups, such as SIOP-MMT group (International Society of Paediatric Oncology—Malignant Mesenchymal Tumour, 5-year EFS 48.9% [95% CI: 40.6–57.2] and OS 74.7% [95% CI: 67.4–81.9]) [5], STSC (Italian Soft Tissue Sarcoma Committee, 10-year progression-free survival 65.1% [95% CI: 52.3–75.3] and OS 74.2% [95%CI: 61.8–83.1]) [11], CWS (*Cooperative Weichteilsarcoma Study,* 5-year EFS 61.7% [95% CI: ±16] and 5-year OS 80.8 [95% CI: ±12]) [16], and IRSG (Intergroup Rhabdomyosarcoma study 5-year failure-free survival 76% [95% CI: 69–83] and OS 83% [95% CI: 77–89]) [8]. These results confirm that HNnPM primary is a favourable site, despite the frequent association with certain unfavourable features such as regional lymph node involvement at diagnosis (26%) or alveolar histotype (41%). Notably, tumours in the head and neck region tend to be frequently small (<5 cm, in 79% of all cases) possibly noticed earlier because of visibility and proximity to important anatomical structures. In this location, the main diagnostic difficulties are to distinguish RMS from all other differential diagnoses, such as malformations, benign lesions, or pseudotumours [17]. This might lead to earlier diagnosis and prompt start of treatment and thereby may improve the final outcome [18]. Within the HNnPM site, there is a variety of subsites with different presentations. The midline locations (e.g. ala nasa/nasolabial fold) appear to be more aggressive than the peripheral locations (e.g. cheek/chin) with frequent unfavourable histology and/or lymph node involvement, leading to the categorisation of these subsites frequently in higher risk groups. Despite these differences, the outcome was not significantly affected by location within HNnPM, probably because of the role of more intensive treatment delivered to higher risk groups. This stratification used in RMS2005 was built on the prognostic factors developed over time in previous international protocols that ensure risk-adapted treatment, and the outcome from this study with comparable outcome between different risk groups confirms the importance of this stratification [4,19–21]. The importance of cervical regional tumour spread stresses the need for a strict nodal work-up at diagnosis. In this study, regional lymph node involvement was clinically assessed by imaging (ultrasound/computed tomography scan or magnetic resonance imaging), and when necessary, confirmed by cytoaspiration, biopsy, or surgical resection. The role of positron-emission tomography scan, sentinel node biopsy, or systematic cervical lymph node dissection is not yet defined in HNnPM RMS but should be considered in high-risk patients with unfavourable histology subtype (26 nodal spread among 70 alveolar histology, 37.2%) and/or some sublocations (primary in neck, nasal ala/nasolabial fold, or scalp) [22].

Overall, the RMS2005 study showed no significant difference in outcome between IVA and IVADo for patients with localised RMS treated in the HR group [2]. Therefore, the conclusion was that doxorubicin should be omitted from first-line chemotherapy for HR patients with localised RMS sparing them from acute toxic effects and late morbidity. On the other hand, maintenance therapy after induction therapy improved the outcome compared with patients, given no more treatment after the induction therapy with 5-year OS 86.3% versus 73.5% ($p = 0.011$), respectively [1].

The best local treatment in these relatively young patients must be decided during multidisciplinary discussion [23]. The risk of long-term effects after significant surgery and RT to the head and neck area are frequent [7]. They must be considered and well balanced according to the patients' age, the site of primary, the initial tumour extension, and the presence of nodal tumour spread [9], whilst optimising the chance of cure. The overall philosophy is to avoid large initial resection at diagnosis and to recommend delayed radical local surgery after tumour size reduction. As HNnPM RMS is often located close to important anatomical structures in the head and neck region, primary surgery with clear margins is sometimes challenging at diagnosis. As a consequence, in this cohort of 165 patients, there were only 34 tumours initially classified as grossly resected (five IRS I and 29 IRS II) because large mutilating surgery is discouraged.

The difference between EFS 74.7% (95% CI: 67.1–80.8) and OS 85.2% (95% CI: 78.3–90.1) indicates a possible salvage gap in this population of patients,

especially in the absence of initial aggressive local therapy during the first line of therapy or if the tumour failure is restricted to locoregional area [19]. To increase local tumour control and try to reduce long-term effects, some teams have developed the AMORE technique consisting of a large Ablative surgery, at diagnosis or after local relapse in HNnPM RMS, supplemented with MOuld brachytherapy and surgical REconstruction [24,25].

This study confirms the importance of risk stratification for adapting treatment in HNnPM RMS. In addition, to better stratify patients, recent biological data have made it possible to distinguish among the non-alveolar forms of RMS, some more pejorative prognostic subtypes, in particular, those with a MyoD1 mutation, which nowadays may be considered as a high-risk tumour [26,27]. This study highlights the frequency of poor risk factors at diagnosis and the importance of adequate local therapy in the treatment of RMS frequently challenging in the head and neck area. This focus is continued in the future EpSSG protocol for RMS (FaR-RMS: An overarching study for children and adults with Frontline and Relapsed RhabdoMyoSarcoma; EudraCT Number: 2018-000515-24) in which there is a special emphasis on the optimisation of local treatment by investigating optimal delivery of RT, for example, dose escalation and timing of its delivery.

Authors' contributions

H.G. contributed to investigation and writing the original article. G.B. contributed to conceptualisation, funding acquisition, project administration, investigation, and reviewing and editing the article. A.K., J.C.C., J.H.M.M., M.J. contributed to conceptualisation, investigation, and reviewing and editing the article. M.G. contributed to conceptualisation and reviewing and editing the article. F.K., K.M, J.S., L.S., H.M., V.M.-C., and N.C. reviewed and edited the article. S.G. contributed to investigation and reviewing and editing the article. A.F. contributed to conceptualisation, funding acquisition, investigation, and reviewing and editing the article. M.J. contributed to conceptualisation, investigation, and reviewing and editing the article. I.Z. contributed to data curation, formal analysis, validation, visualisation, and reviewing and editing the article. G.L.D.S. contributed to conceptualisation, data curation, formal analysis, validation, visualisation, and reviewing and editing the article. D.O. contributed to investigation and writing the original article.

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.04.007.

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