Original article

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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Highlights:

- Large prospective analysis of children with Head and Neck rhabdomyosarcoma
- Adapted strategy according to risk factors allows favourable outcome
- Unfavourable histology and cervical lymph node involvement is frequent in this site
- Loco-regional relapse/progression is the main tumour failure event

Abstract

Background/Objectives: The purpose is 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 is to assess whether current risk stratification is valid for this specific site.

Design/Methods: This study includes all patients with localized 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 (EFS) and overall survival (OS).

Results: A total of 165 patients were identified; median age 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 loco-regional failure in 84% of cases. The 5-year EFS and OS were 75% (95%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% vs. 64.6%, p=0.02) and nodal spread with a worse OS (88.6% vs. 76.1%, p=0.04). Different sub-locations within the HNnPM primary did not have significant impact on outcome.

Conclusion: Loco-regional 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.

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 younger than 18 years of age[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]. Results from several large studies have shown that HNnPM represents less than 10% of all localized RMS and is considered a favourable site with an overall survival (OS) above 70%[5, 8, 9]. Even though 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 is 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 is to confirm the validity of the current risk stratification for this disease site.

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 United Kingdom). The trial enrolled patients (0-25 years of age) with localized 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 FISH and/or RT-PCR. Each tumour was classified according to 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 parameningeal primaries (nasopharynx, nasal cavity, paranasal sinuses, temporal bone, pterygopalatine, fossa, infratemporal fossa) were excluded.

Risk group and staging

Patients included in the RMS2005-protocol were stratified into 4 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 I)[1]. LR consisted only of group A (favourable histology, IRS I, any site, N0, favourable size & age), SR consisted of group B (favourable pathology, IRS I, any site, N0, unfavourable size and age), C (favourable pathology, IRS II-III, favourable site, N0, any size & age) and D (favourable pathology, IRS II-III, unfavourable site, N0, favourable size & age), HR consisted of group E (favourable pathology, IRS II-III, unfavourable site, N0, unfavourable size & age), F (favourable pathology, IRS II-III, any site, N1, any size & age) and G (unfavourable pathology, IRS I-II-III, any site, N0, any size & age), whereas VHR only

consisted of group H (unfavourable pathology, IRS II-III, any site, N1, any size & age) (Table I).

Treatment

Treatment was administered according to specific recommendations for each risk group (Table I). 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 randomized to neoadjuvant chemotherapy with Ifosfamide-Vincristine-D-actinomycin (IVA) or (IVA + Doxorubicin (IVADo) for the initial 4 courses followed by 5 courses of IVA. Patients in complete remission (CR) after induction therapy were offered randomization between 6 months of maintenance therapy with low dose vinorelbine/cyclophosphamide (VNL/Cy) vs. stop treatment[1, 2]. VHR 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 4 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 4 courses of chemotherapy if macroscopic resection was deemed feasible without mutilation. The surgical resection system from the *Union Internationale Contre le Cancer* (UICC) 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 by a macroscopically incomplete resection[14].

Radiotherapy was planned after 4 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). Radiotherapy (41.4 Gy) to the regional nodes was performed in cases of initial clinical, radiological, and/or pathological regional node involvement. Additionally, 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 (<3 years old), for whom RT could be avoided.

Assessment of tumour response and treatment decisions

In patients with macroscopic disease after initial surgery (IRS III), response to treatment was assessed after 3 courses of chemotherapy[15]. Complete Response (CR) and Partial Response (PR) continued allocated treatment, whereas Stable Disease (SD) and Progressive Disease (PD) were considered for second line treatment with either anthracycline-based regimen or phase II treatment.

Statistical methods

The principal end-points for the analyses were 5 year event free (EFS) and overall survival (OS), calculated using the Kaplan-Meier method. EFS was defined as 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 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, sub-locations, 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.

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, since the HNnPM-site is favourable (Table I). Clinical characteristics are summarized in Table II. Median age at diagnosis was 6.4 years (1 week - 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%)(Figure 1). The risk grouping differed between sub-locations; 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 48/70 (69%) of the tumours with unfavourable histology (19 FISH, 24 RT-PCR and 5 FISH and RT/PCR). No gene fusion was present in the 63/95 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 sub-locations (12/37 cases; 32%).

Among the 129 IRS III group patients (78%), 88 had surgical biopsy, 14 a tru-cut biopsy, and 26 a partial surgical resection of primary tumour (missing data: 1 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%).

Local treatment delivered

Among the 3 patients in LR group, one received additional RT due to initial diagnosis of alveolar subtype, modified after pathology review.

Among the 78 SR (subgroup B: 1, subgroup C: 77), 8 patients received no further local therapy, 23 had DPE (no residual tumour/R0 21 cases; R1 margins 2 cases) without adjuvant RT, 26 received radical RT (median dose of 50.4 Gy; range, 36.0-60.0) as the sole local therapy, whereas 18 received DPE (no residual tumour/R0 11 cases; R1 5 cases; R2 2 cases) and RT (45.0 Gy; range, 36.0-65.4).

Within the 58 patients in the HR group, 5 had no local therapy [early progression 3 cases; physician decision 2 cases (IRS I and tongue primary; CR after 3 cycles and young age, 1 case each)], 4 had only DPE (early progression 1 case; young age 3 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 4 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, 4 had cervical nodal exploration (unilateral lymph node adenectomy 2 cases; and node sampling 2 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 8 received DPE and adjuvant RT (to primary and nodal areas 6 cases; primary tumour 2 cases; median dosage, 50.4 Gy; range, 41.4-55.8). Two received no local therapy due to early PD, and CR after 3 cycles with parental refusal of RT (1 case each). Finally, 2 patients had exclusive DPE for physicians' preference. Additional delayed lymph node sampling (4 cases) or unilateral lymph node dissection (1 case) was performed. Surgical results showed no residual tumour/R0 in 8 cases and R1 margins 2 cases.

In summary, RT was omitted in 26 R0-patients and 3 R1-patients. Details on radiotherapy treatment are available for 161 patients out of 165. Overall 115 patients (72%) received radiotherapy; photon-therapy (63%), proton-therapy (20%), electrons ± photon-therapy (10%), brachytherapy (5%) and Cobalt 60 therapy (2%). Median dose for external RT was 50.4 Gy (range, 36.0-65.4) and for brachytherapy 42.5 Gy (range, 36.0 – 55.8). Overall, local ± nodal surgery was performed, at diagnosis or after neoadjuvant chemotherapy, for 96 out of 164 patients (data missing: 1 case); all 36 IRS I-II and 60/128 IRS III.

Outcome

After a median FU of 65.6 months (range, 6.2 – 158.2), 42 patients experienced an event (38 tumour-related and 4 others) (Table III). Tumour events included loco-regional failure in 32/38 cases (84%) including 6 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 (3 DPE, 4 DPE/RT, 2 RT and 5 with no local therapy), 17 HR (5 DPE, 4 DPE/RT, 6 RT, 1 no local therapy and 1 no information about local therapy) and 7 VHR (0 DPE, 1 DPE/RT, 5 RT and 1 no local therapy). Overall, 21 of these patients died despite further treatment (36 chemotherapy (missing data: 2), 14 received RT and surgery, 4 only received RT and 6 only received surgery, but the data are incomplete. The surgery was mutilating in 4 patients). Additionally, 4 patients died from other causes (Table III). Among the 28 patients with isolated loco-regional failure (local ± cervical nodal progression/relapse), 15 survived after second line therapies, whereas only 2 out of the 10 patients with distant metastases survived. Among the 165 patients with HNnPM RMS 2 developed a second malignancy (1 medulloblastoma and 1 undifferentiated sarcoma) and one of these patients are among the 4 who died from other causes. At the last FU, 124 patients are alive in first CR, 14 in second CR and 2 are alive with disease.

Among 43 patients with lymph node involvement at diagnosis (17 HR and 26 VHR), 11 experienced a tumour-related event: 5 had local failure at primary site including 2 with regional nodal relapse; 6 have distant metastases relapses ± locoregional failure. Among them, only 2, with isolated distant metastases, survived.

Among the 17 patients (10%) who received neither DPE nor RT, 10 experienced an event (5 local relapses, 4 PD, 1 PD + N). Among the 12 patients who achieved local control without surgery nor RT, 6 were salvaged after additional treatment.

The 5-year EFS and OS of the entire population are 75% (95%IC: 67.3-81.2) and 84.6% (95%IC: 77.5-89.7), respectively (Figure 2). Outcome is similar for patients according to risk groups (supplemental Figures 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 vs. 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 vs. 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.

Discussion

This large study of patients with HNnPM RMS following 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, 5y-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*,5y-EFS 61.7% (95%CI, ±16) and 5y-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 due to 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 sub-sites 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 categorization of these sub-sites frequently in higher risk groups. Despite these differences, the outcome was not significantly affected by location within HNnPM, probably due to 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 ensures 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 and by imaging (US/CT-scan or MRI), and when necessary, confirmed by cyto-aspiration, biopsy or surgical resection. The role of PET-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 sub-locations (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 localized RMS treated in the HR group [2]. Therefore, the conclusion was that doxorubicin should be omitted from first line chemotherapy for HR-patients with localized RMS sparing them from acute toxic effects and late morbidity. On the other hand, maintenance therapy after induction therapy improved the outcome compared to

patients given no more treatment after the induction therapy with 5 y-OS 86.3% vs.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 radiotherapy 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. Since 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 (5 IRS I, 29 IRS II) since large mutilating surgery is discouraged.

The difference between 74.7% (95%IC, 67.1-80.8) and OS 85.2% (95% IC, 78.3-90.1) indicates a possible salvage gap in this population of patients, especially in the absence of initial aggressive local therapy during first line of therapy or if the tumour failure is restricted to loco-regional area[19]. To increase local tumour control and try to reduce long term effects, some teams have developed the AMORE technics 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 rhabdomyosarcoma (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, e.g. dose escalation and timing of its delivery.

Table and figures legends:

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

Table II: Patient and tumour characteristics according to risk group for HNnPM RMS

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

Figure 1. Sites' distribution in patients with HNnPM RMS

Figure 2. Event Free and Overall Survivals of the population with HNnPM RMS

Supplemental Table I: Radiation doses for the primary tumour according to histology and IRS-group for children age 3 years or older

Supplemental Table II. Univariate analysis regarding Event Free Survival (EFS) and Overall Survival (OS)

Supplemental Figure 1. Event Free Survival (EFS) by risk group of the population with HNnPM RMS

Supplemental Figure 2. Overall Survival (OS) by risk group of the population with HNnPM RMS

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Figures:

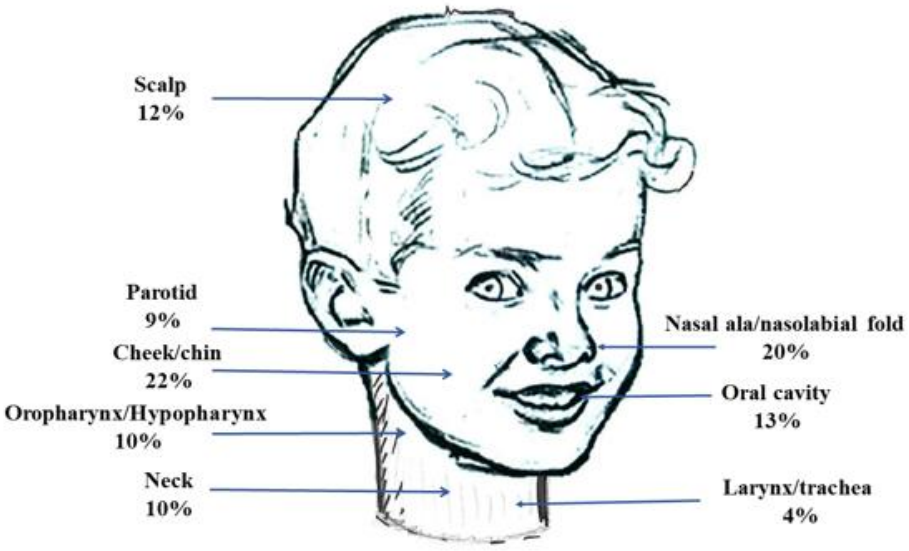
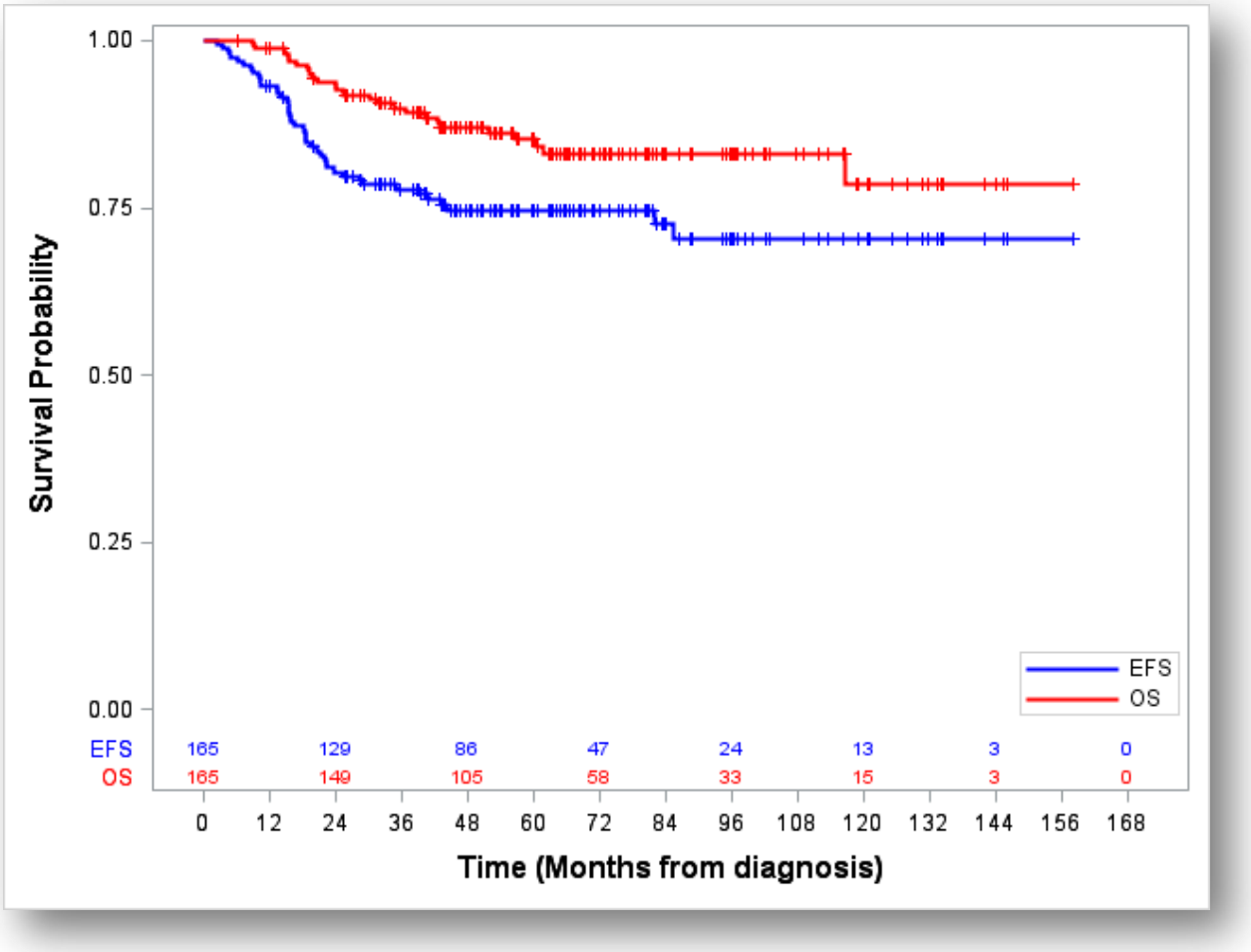


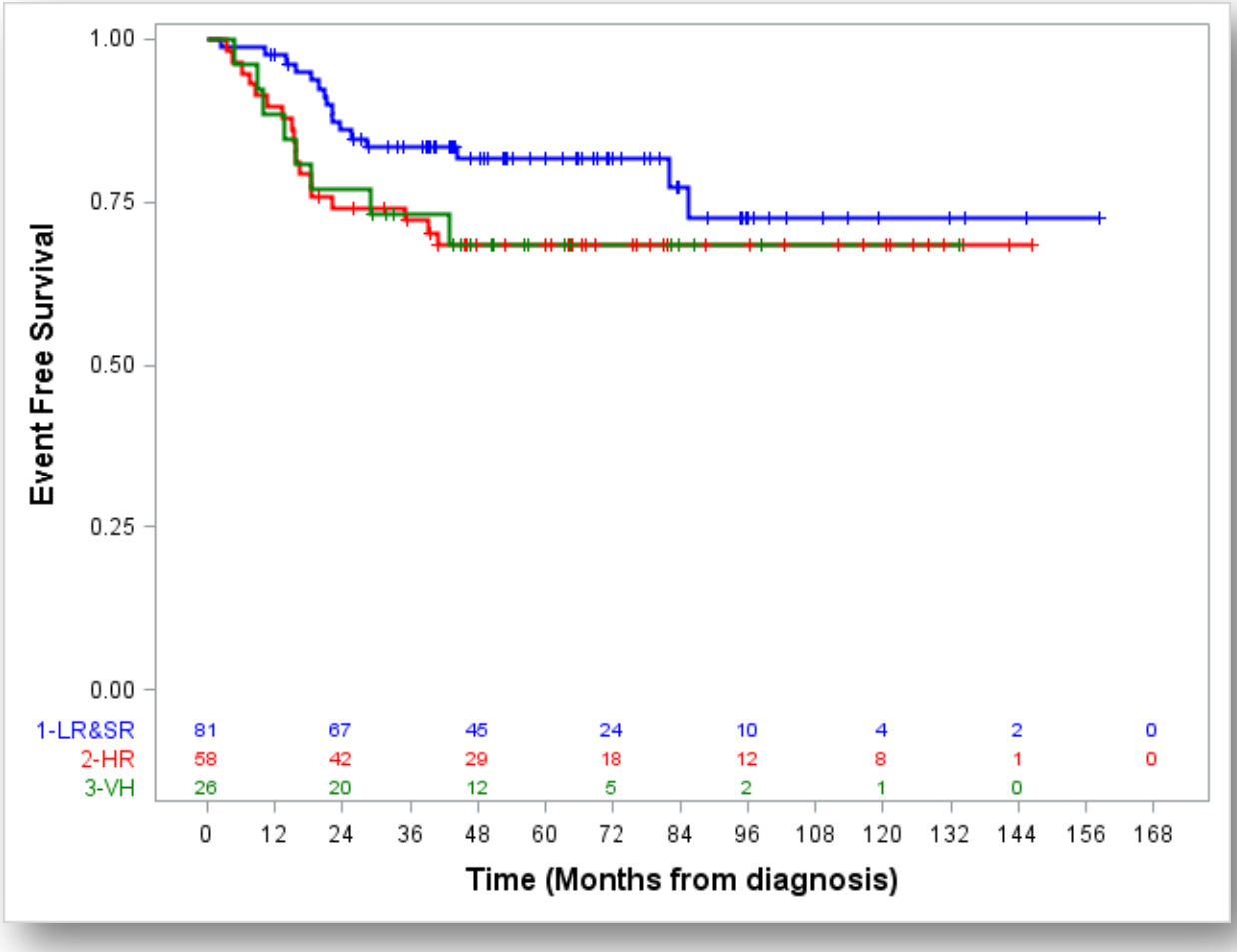
Figure 1. Sites' distribution in patients with HNnPM RMS

Figure 2. Event Free and Overall Survivals of the population with HNnPM RMS



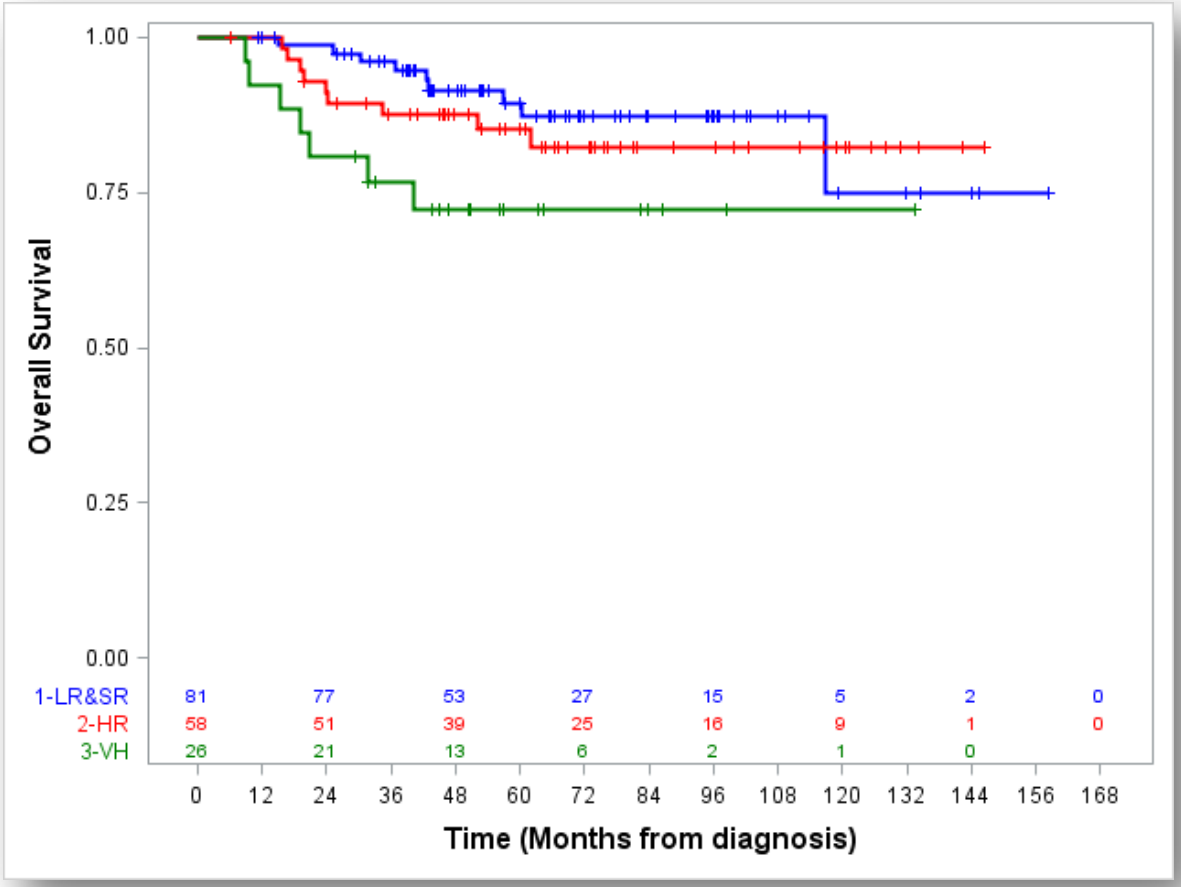
	N patients	Failed	5-yr Survival (95%CI)
Event Free Survival	165	42	74.7 (67.1-80.8)
Overall Survival	165	25	85.2 (78.3-90.1)

Supplemental Figure 1. Event Free Survival (EFS) by risk group of the population with HNnPM RMS treated according to EpSSG RMS2005



Risk Group	N patients	Failed	5 yr Survival (95% IC)	P
Low & Standard risk	81	16	81.6 (70.8-88.7)	0.2410
High risk	58	18	68.4 (54.6-78.8)	
Very High risk	26	8	68.5 (46.6-82.9)	

Supplemental Figure 2. Overall Survival (OS) by risk group of the population with HNnPM RMS treated according to EpSSG RMS2005



	N patients	Deaths	5-yr survival (95%CI)	P-value
Risk Group				
Low & Standard risk	81	9	89.5 (78.9-94.9)	0.0868
High risk	58	9	85.2 (72.4-92.3)	
Very High risk	26	7	72.2 (50.2-85.7)	

Tables:

Supplemental Table I: Radiation doses for the primary tumour according to histology and IRS-group for children age 3 years or older

IRS Group	Embryonal RMS	Alveolar RMS
I	No RT	41.4 Gy; 23 F
II a, b and c	41.4 Gy; 23 F	41.4 Gy; 23 F
III followed by:		
- secondary complete resection	36 Gy; 20 F (partial response) 41.4 Gy; 23 F (minor partial response, SD) Subgroup C: optional (no RT or 36 Gy)	41.4 Gy; 23 F
- second look surgery but incomplete secondary resection	50.4 Gy; 28 F	50.4 Gy; 28 F
- clinical complete remission, no second look surgery	41.4 Gy; 23 F	50.4 Gy; 28 F
- partial remission, minor PR, SD, progressive disease, no second surgery	50.4 Gy; 28 F (+ Boost of 5.4 Gy; 3 F)	50.4 Gy; 28 F (+ Boost of 5.4 Gy; 3 F)

RT: radiotherapy; F: fractions; Gy: Grays; PR: partial response; SD: Stable Disease.

Supplemental Table II. Univariate analysis regarding Event Free Survival (EFS) and Overall Survival (OS)

Characteristics		**Event Free survival**			**Overall survival**		
	N	Events	5-yr EFS (95%CI)	p-value	Deaths	5-yr OS (95%CI)	p-value
All patients	165	42	74.7 (67.1-80.8)	-	25	85.2 (78.3-90.1)	-
Risk Group							
Low & Standard risk	81	16	81.6 (70.8-88.7)	0.2410	9	89.5 (78.9-94.9)	0.0868
High risk	58	18	68.4 (54.6-78.8)		9	85.2 (72.4-92.3)	
Very High risk	26	8	68.5 (46.6-82.9)		7	72.2 (50.2-85.7)	
Age at diagnosis							
< 10 years	114	32	72.0 (62.5-79.4)	0.2651	19	83.4 (74.4-89.4)	0.4752
≥ 10 years	51	10	80.8 (66.0-89.6)		6	89.6 (76.7-95.5)	
Gender							
Male	88	23	75.1 (64.4-83.0)	0.9989	12	86.3 (76.6-92.2)	0.5004
Female	77	19	74.2 (62.5-82.8)		13	84.0 (72.7-90.9)	
T-invasiveness							
T1	110	29	74.5 (65.0-81.8)	0.8383	14	86.2 (77.2-91.8)	0.1584
T2	50	13	73.5 (58.7-83.7)		11	81.8 (67.8-90.1)	
Tumour size							
≤ 5 cm	129	31	76.5 (67.9-83.1)	0.7086	17	87.5 (79.6-92.4)	0.0715
> 5 cm	34	9	72.6 (53.8-84.7)		8	75.5 (56.8-87.0)	
Loco-regional N							
N0	122	30	76.0 (67.0-82.8)	0.5646	15	88.6 (80.6-93.4)	0.0388
N1	43	12	71.3 (54.9-82.6)		10	76.1 (60.0-86.4)	
IRS Group							
IRS I-II	36	7	82.4 (64.7-91.7)	0.2950	3	92.9 (73.9-98.2)	0.1642
IRS III	129	35	72.7 (63.8-79.7)		22	83.2 (75.0-88.8)	
Tumour primary site							

Characteristics		Event Free survival			Overall survival		
	N	Events	5-yr EFS (95%CI)	p-value	Deaths	5-yr OS (95%CI)	p-value
Cheek/Chin	37	10	71.5 (53.3-83.6)	0.5567	7	78.4 (59.5-89.2)	0.6372
Nasal Ala/Naso Labial Fold	33	8	75.5 (56.9-86.9)		4	90.6 (73.7-96.9)	
Ne ck	17	4	82.4 (54.7-93.9)		4	81.9 (53.8-93.8)	
Oral cavity	22	9	57.9 (34.3-75.6)		4	80.0 (54.9-92.0)	
Parotid	15	4	77.0 (43.2-92.2)		3	86.7 (56.4-96.5)	
Pharynx/Larynx/Trachea	22	5	75.7 (50.8-89.2)		2	90.9 (68.3-97.6)	
Scalp	19	2	88.5 (61.4-97.0)		1	92.9 (59.1-99.0)	
Histology							
Favourable histology	95	18	82.3 (72.6-88.8)	0.0236	11	89.0 (79.8-94.2)	0.1614
Unfavourable histology	70	24	64.6 (51.9-74.8)		14	80.0 (67.9-87.9)	
Fusion status							
Negative	77	15	82.5 (71. 7-89.4)	0.0958	9	87.7 (76.5-93.8)	0.3955
Positive	48	16	65.6 (50.0-77.4)		9	82.4 (67.6-90.8)	

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

Risk Group	Subgroups	Pathology	Post-surgical Stage (IRS Group)	Site	Node Stage	Size & Age	Chemotherapy	Delayed surgery	Radiation therapy
Low Risk	**A**	Favourable	I	Any	N0	Favourable	8 x VA	Not necessary	No
Standard Risk	***B***	Favourable	I	Any	N0	Unfavourable	4 x IVA + 5 x VA	Not necessary	No
	C	Favourable	II, III	Favourable	N0	Any	9 IVA **or** 5 x IVA + 4 x 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 x IVA vs 4 IVADo + 5 IVA ± 6 x maintenance	Yes	Yes
	F	Favourable	II, III	Any	N1	Any			
	G	Unfavourable	I, II, III	Any	N0	Any			
Very High Risk	***H***	Unfavourable	II, III	Any	N1	Any	4 IVA Do + 5 IVA + 6 x 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 & Age:**

Favourable= Tumour size (maximum dimension) ≤5cm ***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 II: Patient and tumour characteristics according to risk group for HNnPM RMS

	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**
NonARMS	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**
>5cm	-	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

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

Type of events	**Low risk**	**Standard risk**	**High risk**	**Very High risk**	**Total**	**Status at the end of follow up**
	n=1	n=15	n=18	n=8	n=42	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*	0
Fatal infection	-	-	-	1	1	0
Sudden death°	-	-	1	-	1	0
% of event within each risk group	33%	19%	31%	31%	25%	

*1 Medulloblastoma, 1 undifferentiated sarcoma; °1 Sudden death (cardiovascular cause) in complete remission off therapy after 2 months from end of therapy