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OPTIMIZING RHABDOMYOSARCOMA TREATMENT

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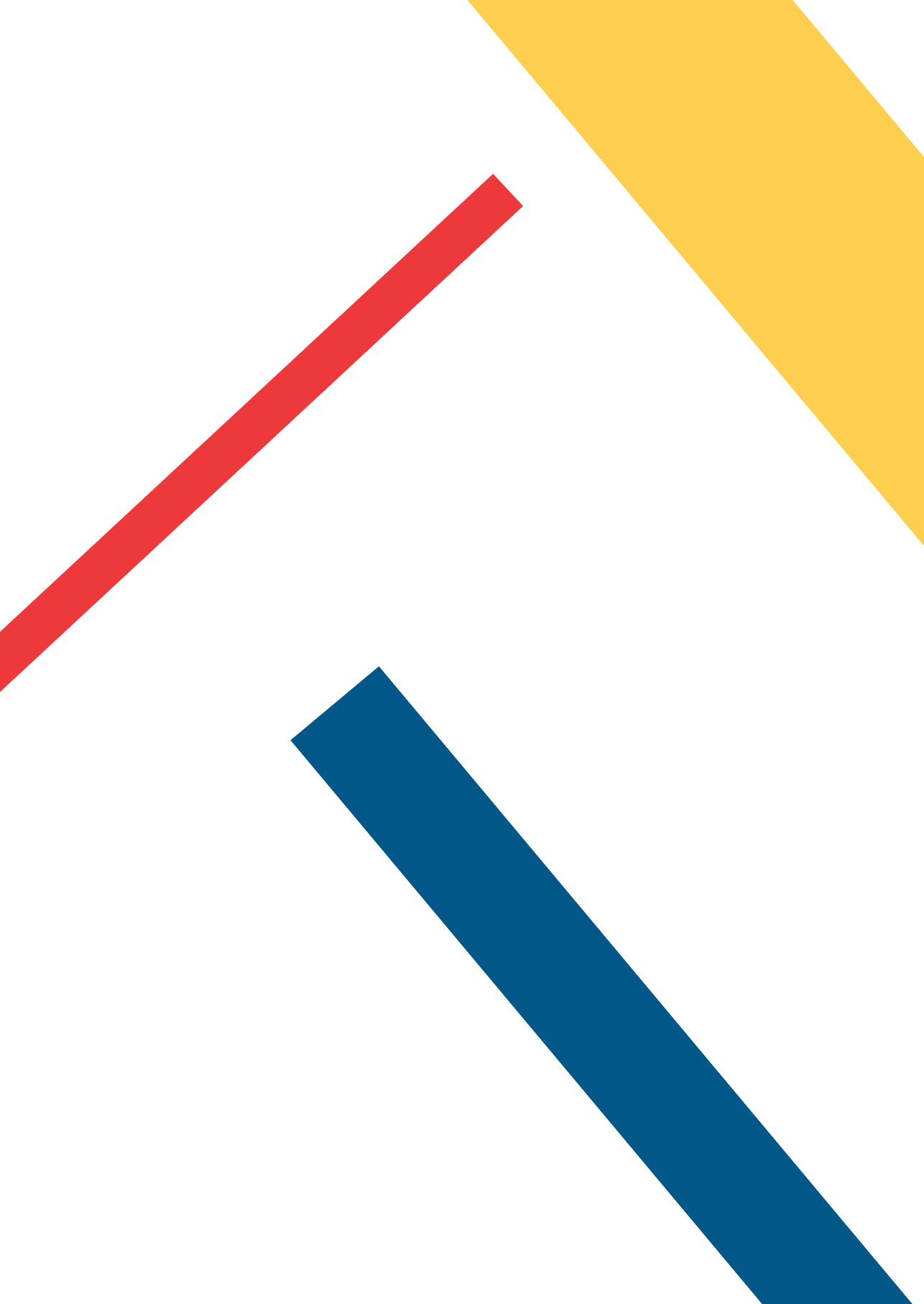

CHAPTER 1

INTRODUCTION, AIM AND OUTLINE OF THIS THESIS

RHABDOMYOSARCOMA

Around 600 children are diagnosed with cancer in the Netherlands each year.(1) Improvements in treatment techniques have led to a significant increase in survival over the last decades, however childhood cancer is still the leading cause of death in children aged 1-15 years.(2, 3) The most frequently diagnosed cancers in children are acute lymphoblastic leukemia and brain and central nervous system (CNS) tumors. Rhabdomyosarcoma (RMS), the focus of this thesis, is the most common soft tissue sarcoma in childhood and accounts for approximately 4% of all pediatric malignancies.(2) In the Netherlands around 20 patients are diagnosed with rhabdomyosarcoma annually. RMS generally affects young children with a median age at diagnosis of 5 years, although it also occurs later in life.

Rhabdomyosarcoma can occur anywhere in the body; around 40% of RMS cases are located in the head and neck region, 30% in the genitourinary region, 15% in the extremities and 15% in other regions.(4, 5) The assumption is that RMS arises from primitive mesenchymal cells destined to develop into striated muscle cells.(6) However, recent research showed that RMS could also arise from non-myogenic cells, which might explain the occurrence at sites lacking skeletal muscles.(7)

Risk stratification and survival

In the Netherlands, patients with RMS are included in international trials coordinated by the European *paediatric* Soft tissue sarcoma Study Group (E*p*SSG). These trials are aimed to improve survival, while at the same time minimizing toxicity of treatment.

Survival for newly diagnosed patients with RMS depends on several factors, patients with localized disease have a 5-year overall survival of around 75%, whereas this is 10-50% for patients with metastatic disease.(8-11) However, the chance of survival not only depends on the extent of the disease, but on other prognostic factors as well. These factors are used to stratify subsequent treatment to the risk of relapse. First we will focus on the risk factors associated with survival in patients with localized RMS.

Historically, RMS is divided into two main histological subtypes; embryonal (ERMS) and alveolar (ARMS). Patients with ARMS have a significantly impaired prognosis compared to patients with ERMS.(12) More recently it was discovered that a substantial proportion (70-80%) of patients with ARMS carry a PAX3-FKHR or PAX7-FKHR gene fusion.(13, 14) These patients are so called fusion-positive. Recent studies showed that fusion status is a strong prognostic factor for outcome in patients with RMS.(15, 16) Patients with fusion-positive ARMS have a dismal prognosis, whereas patients with fusion-negative ARMS have a comparable prognosis as patients with ERMS.(14) Future RMS studies will incorporate a more advanced risk stratification in which fusion status plays a pivotal role in sub classifying RMS.

The chance of survival for patients with localized disease also depends on post-surgical stage (defined by the Intergroup Rhabdomyosarcoma Study [IRS] Grouping system).(17) Patients with completely resected tumor at initial diagnosis (IRS group I) have a better prognosis than patients with microscopic residual (IRS group II), incompletely resected tumors or patients that underwent a biopsy at initial diagnosis (IRS group III). Furthermore, survival depends on the tumor site. Patients with a tumor located at an orbital site, head and neck non-parameningeal site and genitourinary non-bladder/prostate site have a favorable prognosis compared to patients with a tumor located at other sites. RMS can also spread to lymph nodes. At diagnosis, around 20% of the patients have locoregional nodal involvement which is associated with impaired prognosis.(4) Finally, treatment is tailored based on tumor size and age at diagnosis.

Smaller tumor size (less than 5 cm) and lower age at diagnosis (below 10 years) are factors associated with a favorable prognosis. The above mentioned risk factors are all incorporated in the risk stratification of the previous E*p*SSG study (see table 1), entitled E*p*SSG-RMS 2005. (18, 19)

Table 1. E*p*SSG-RMS 2005 risk stratification

Risk Group	Subgroups	Pathology	Post-surgical Stage (IRS Group)	Site	Node stage	Size & Age
Low Risk	**A**	Favorable	I	Any	N0	Favorable
Standard risk	**B**	Favorable	I	Any	N0	Unfavorable
	C	Favorable	II, III	Favorable	N0	Any
	D	Favorable	II, III	Unfavorable	N0	Favorable
High Risk	**E**	Favorable	II, III	Unfavorable	N0	Unfavorable
	F	Favorable	II, III	Any	N1	Any
	G	Unfavorable	I, II, III	Any	N0	Any
Very High risk	**H**	Unfavorable	II, III	Any	N1	Any

As previously indicated, the prognosis for patients with metastatic disease is inferior compared to patients with localized disease. About 16% of the newly diagnosed patients with RMS have metastasized disease at diagnosis, with the lungs and bones being the most frequently affected metastatic sites.(4) The following risk factors are associated with an impaired survival in patients with metastatic disease; age at diagnosis (younger than 1 or 10 years or older), tumor site (extremities or other sites), bone or bone marrow involvement and number of metastatic sites (3 or more metastatic sites).(9, 10) Adding up the number of risk factors results in an 'Oberlin score'; a previous study showed a 3-year event free survival for patients with no Oberlin risk factor of around 50%, whereas this was 5% for patients with four risk factors.(9)

The differences in prognosis and the complexity of the risk stratification illustrates the importance of accurate staging; based on the risk stratification, patients with metastatic disease receive more intensified chemotherapy, maintenance chemotherapy and surgery and/or radiotherapy to the metastatic sites.

Clinical work-up and treatment

The clinical manifestation of RMS is diverse and is strongly depending on the tumor localization. In general, the diagnostic workup consists of initial ultrasonography followed by magnetic resonance imaging of the primary site. At diagnosis patients usually undergo an incisional biopsy after which the diagnosis is confirmed by histopathology. Further staging is done by imaging. A chest CT is used to assess the presence of pulmonary metastases. Fluorine-18- fluorodeoxyglucose (FDG) position emission tomography (PET)-computed tomography (CT) and bilateral bone marrow aspirates are used to identify distant metastasis. Patients with parameningeal located tumors also undergo a lumbar puncture to assess the presence of tumor cells in the cerebrospinal fluid.

Treatment

Treatment is stratified according to the risk factors mentioned above; the treatment for RMS usually consists of chemotherapy, surgery and/or radiotherapy. At diagnosis, the majority of patients undergo an incisional biopsy (IRS-Group III patients) after which patients start with induction chemotherapy. Chemotherapy in European protocols consists of a standard combination of ifosfamide, vincristine and dactinomycin, often complemented with other agents in randomized trials.(8, 11)

The previous EpSSG-RMS 2005 study for patients with localized disease consisted of an observational part and two randomized controlled trials for high risk patients. Chemotherapy approach was based on risk grouping. Low risk patients received a combination of vincristine and actinomycin D and standard risk patients received IVA chemotherapy.

High risk patients were eligible for the first randomized trial. In this trial participating patients were randomized between 9 courses of standard chemotherapy consisting of ifosfamide, vincristine and actinomycin D (IVA), and IVA with doxorubicin (IVADo). This study showed that adding doxorubicin to standard chemotherapy regimen did not improve outcome in patients with high-risk metastatic RMS.(11) According to the E*p*SSG-RMS 2005 study, very high risk patients and patients with metastatic disease received IVADo chemotherapy.

In the second randomized trial, high risk patients in clinical complete remission were eligible for a second randomization between end of therapy (standard) and 6 courses (4 weeks each) of metronomic maintenance therapy with vinorelbine and cyclophosphamide. This study showed an improvement in overall survival for patients that received six months of maintenance chemotherapy compared to standard end of therapy arm.

(20) Very high risk patients (patients with alveolar histology and positive regional lymph node) and patients with metastatic disease at diagnosis all received maintenance therapy with vinorelbine and cyclophosphamide (6 months for very high risk patients, 12 months for patients with metastatic disease).

Local therapy is fundamental in the treatment for RMS and consist of surgery and/or radiotherapy. In the E*p*SSG-RMS 2005 study the decision on local therapy was depending on the anticipated consequences of the therapy of choice; in general, surgery was performed if it was considered conservative surgery (without important long-term functional/cosmetic consequences), if not, radiotherapy was the treatment of choice. Historically, in European study protocols more patients in favorable subgroups did not receive radiotherapy in comparison to other collaborative groups. In the E*p*SSG-RMS 2005 study, radiotherapy was given based on histology, chemotherapy response and secondary resection. If recommended, radiotherapy for patients with localized disease was given starting at week 13. Patients with metastatic disease received radiotherapy starting at week 19. Radiation doses ranged between 36 and 50.4 Gy depending on histology, resection margins and tumor response. Patients with metastatic disease received radiotherapy to the local tumor and to all metastatic sites if feasible.

Part 1 Imaging in rhabdomyosarcoma

In current European treatment protocols, the role of imaging at diagnosis, during treatment, at the end of treatment and during follow-up is clearly stated. However, the clinical value of radiologic and functional imaging and the guidelines for decision-making based on the imaging is ambiguous at best. A proper evaluation of the value of specific imaging techniques and measurements in RMS was required before the start of the next E*p*SSG-RMS study.

Objective and outline of part 1

Part 1 of this thesis describes our effort to assess the value of specific imaging techniques performed at time of diagnosis, during treatment and during follow-up in patients with rhabdomyosarcoma.

Imaging at diagnosis

The lungs are the most frequently involved metastatic site and historically a chest radiograph was performed to assess the presence of possible pulmonary metastases. Since 2005, with the introduction of the current E*p*SSG-RMS 2005 protocol, chest radiographs were replaced by chest CT's because of their much higher sensitivity. However the introduction of a new diagnostic technique with higher resolution also introduced new dilemmas since smaller nodules also became detectable and the differentiation between

small metastatic and benign nodules can be very difficult. Differentiation is important since the 3-year overall survival (OS) for patients with localized disease is nowadays around 75%, compared to 10-55% for patients with metastatic disease.(8-11) Since a biopsy is often not possible, the decision to treat patients as localized or metastatic is therefore based on the assessment of radiologists. In the E*p*SSG-RMS 2005 protocol patients with 4 or less pulmonary nodules smaller than 5 mm or 1 nodule ranging from 5 to less than 10 mm were considered to have indeterminate pulmonary lesions. It was assumed that these nodules were either incidental benign lesions or micro-metastases which in the past were not visible because of the use of chest radiographs with inherent lower resolution. Since all patients are considered to have undetectable micro-metastases at diagnosis, patients with indeterminate lesions and no other metastases were treated according to localized disease protocols. However, this policy was solely based on theoretical assumptions. If this assumption was wrong, patients with indeterminate pulmonary nodules were undertreated in the E*p*SSG- RMS 2005 study. The objective of **chapter 2** was to evaluate if the presence of indeterminate pulmonary nodules at diagnosis affected survival in patients with (otherwise) localized rhabdomyosarcoma.

As previously stated, accurate staging for potential metastases is of utmost importance, since the presence of metastases requires an intensification of treatment and implies impaired prognosis. Over the years FDG/PET-CT gradually replaced the use of ^{99}m-Technetium skeletal scintigraphy for the staging of bone metastases in pediatric RMS. In several other malignancies FDG/PET-CT has proven to have important value in the staging at diagnosis and FDG/PET-CT is therefore incorporated in the treatment protocols for several other malignancies.(21) In pediatric RMS, FDG/PET-CT could potentially identify bone, lung and lymph node metastases. However, the accuracy of FDG/PET-CT in RMS has not been established. The aim of **chapter 3** was to evaluate the diagnostic accuracy of FDG/PET-CT for the detection of bone, lung and lymph node metastases in RMS. Therefore, we performed a systematic literature analysis.

Imaging during treatment

The vast majority of newly diagnosed patients undergo an incisional biopsy at diagnosis after which neo-adjuvant chemotherapy is started. Early radiologic response is measured after three courses of chemotherapy and continuation of chemotherapy and decisions on local therapy are depending on this response assessment. In the E*p*SSG-RMS 2005 study, patients with less than 1/3 tumor volume reduction were switched to second line chemotherapy treatment, based on the assumption that radiologic response was prognostic for survival. However, the prognostic value of early radiologic response on survival is unclear.

Two North-American studies (Burke et al. and Rosenberg et al.) on two large cohorts including consecutive patients revealed no significant difference in survival between patients with complete response (complete disappearance of tumor), partial response (≥50% decrease in tumor area) and no response (< 50% decrease in tumor area).(22, 23) However, previous European data suggested a different conclusion; Dantonello et al. analyzed the prognostic value of early radiologic response on survival on the data of 5 consecutive Cooperative Weichteilsarkom Studiengruppe (CWS) trials (1980-2005) and found early radiologic response to be an important prognostic factor for survival. (24) The same conclusion was drawn by Ferrari et al. in a retrospective single center study.(25) These contradictory results underline the need for proper evaluation of the prognostic value of early radiologic response in a large European cohort. If indeed radiologic response appears not to be prognostic for outcome, patients with a poor response are currently withheld effective gold standard chemotherapy within E*p*SSG protocols. Furthermore, if radiologic response is not prognostic for survival, we currently lack an early surrogate marker for outcome.

In **chapter 4** and **chapter 5** we evaluated if early radiologic response is prognostic for survival. In **chapter 4** we evaluated this in a cohort of consecutive patients uniformly treated and included in the International Society for Pediatric Oncology (SIOP)-Malignant Mesenchymal Tumour 95 (MMT-95) study.

In **chapter 5** we used a systematic approach to review existing literature on the value of early radiologic response in pediatric rhabdomyosarcoma, a formal quality assessment was performed for all included studies and the outcomes of these studies were compared.

Imaging during follow-up

Although overall survival for patients with localized RMS has improved to around 80% over the last decades, still up to one third of the patients experience a relapse.(8, 11) The vast majority (2/3) of these relapses are local relapses. For this reason, patients with RMS are subject to intensive radiologic tumor surveillance after completion of therapy. Today, this follow-up includes a clinical examination together with an MRI (or CT scan) of the primary tumor site and a chest X-ray, performed every three months in the first year. In the second and third year these investigations are performed every four months and the interval is extended to once a year in the fourth and fifth year after end-of-treatment.

McHugh and Roebuck previously questioned the value of surveillance by pointing out that radiologic imaging is only useful if it detects tumor recurrence with acceptable specificity and sensitivity before the appearance of clinical signs and if the earlier detection of tumor recurrence is associated with an improved overall survival.(26)

However, no evidence is available for either position. On the contrary, a single center study by Lin et al. assessed the clinical value of off-therapy surveillance imaging in RMS

and found no significant difference in survival between patients with relapsed RMS detected by routine imaging compared to patients with a relapse detected by clinical symptoms.(27)

Routine follow-up imaging could give reassurance to parents and caregivers about the health condition of the patient, but it could also cause additional anxiety and distress.(28) In a substantial proportion of patients (generally patient 8 years or younger) the use of general anesthesia is required to acquire good quality MR imaging with inherent patient risks.(29) Furthermore, there is growing concern that the repetitive use of general anesthetics causes neurotoxic changes on the developing brain, although available evidence is contradicting.(30-33) These potential adverse factors together with a questionable survival benefit of routine follow-up imaging emphasizes the need for an evaluation of the value of routine imaging after treatment for RMS.

The aim of **chapter 6** was to assess the clinical value of surveillance imaging.

The diagnosis of a child with cancer is a dramatic event for the entire family, causing significant distress in patients and parents.(34-36) Most parents adjust well to this period of great uncertainty, however a considerable proportion of parents report clinical distress, anxiety and posttraumatic stress symptoms not only during the period of treatment, but also after completion of treatment.(37-40) The completion of treatment has a positive and a negative psychosocial impact on parents.(39) It is often a celebrated landmark,(28) and parents report feelings of relief and joy, but it can also cause significant distress.(41-43) In this period patients and parents try to reintegrate in everyday life. However, although treatment has finished, treatment related adverse events might become evident and parents begin to realize that there is a potential risk of relapse causing additional distress and anxiety.(28) During this period, the scheduled follow-up imaging could give reassurance to parents about the health-condition of their child, but it could also elicit additional distress.

We anticipated that the result of chapter 6 would lead to a change in follow-up, however we believed it was necessary to assess the feelings and thoughts of parents on the examinations after completion of therapy to integrate their preferences and needs in future guidelines.

Chapter 7 describes a qualitative study in which we assessed the views and experience of parents of children treated for RMS or Ewing sarcoma on the follow-up examinations after completion of therapy.

Part 2: Local therapy in rhabdomyosarcoma

Part 2 of this thesis focuses on local therapy in patients with head-neck rhabdomyosarcoma (HNRMS). Local therapy for patients with RMS, i.e. surgery and/or radiotherapy, is essential to achieve local control. In the head and neck area, a microscopically radical

resection is often impossible; therefore patients with HNRMS are usually treated with external beam radiotherapy. However, applying radiotherapy in young children with head-neck RMS could affect the growth and function of many organs and tissues. For this reason, since the '90s an innovative treatment approach was used in the Emma Children's Hospital-Amsterdam UMC (EKZ-AUMC) called AMORE. This acronym stands for Ablative surgery, MOld technique with afterloading brachytherapy and surgical REconstruction. Theoretically, applying brachytherapy instead of external beam radiotherapy results in a more conformal dose delivery to the tumor bed with rapid dose fall-off beyond the target volume, and thus sparing more of the healthy surrounding tissue. In the EKZ-AUMC, naïve patients with HNRMS were treated according to the AMORE protocol, if considered feasible. Otherwise patients received external beam radiotherapy (either photon- or proton therapy), which is considered the international standard. AMORE treatment as first-line local therapy has shown to result in similar survival and less adverse events compared to local therapy with external beam radiotherapy.(44-47)

Objective and outline of part 2

The decision on local therapy approach in head-neck area is generally based on minimizing potential adverse events while optimizing treatment efficacy. Nevertheless, patients treated for HNRMS suffer from serious adverse events, mainly caused by local therapy (i.e. radiotherapy). Radiotherapy in young children could affect the growth and function of many organs and tissues. Patients with RMS are generally young (median age 5 years), therefore many HNRMS experience facial disfigurements.(45, 48-50) Besides musculoskeletal disfigurements, other adverse events such as growth hormone deficiency, alopecia, hearing loss and cataract are also frequently reported in HNRMS survivors. Although we know that survivors of HNRMS frequently suffer from these adverse events, the impact on their psychosocial well-being is unclear.

Previous studies showed that the health related quality of life (HRQoL) in survivors of childhood cancer is generally comparable to healthy peers, nevertheless there are some subgroups at risk for impaired psychological distress, neurocognitive dysfunction and impaired HRQoL.(51-54) Early identification of subgroups at risk to develop psychosocial difficulties is necessary to adequately monitor their psychosocial well-being and develop interventions to improve it, if necessary. Evaluating the psychosocial functioning of head-neck RMS survivors is important because they frequently encounter adverse events, with musculoskeletal disfigurements being the most frequent one. Previous studies indicated that social interactions are strongly affected by facial appearances, potentially affecting psychosocial well-being of head-neck RMS survivors.(55)

In **chapter 8**, we evaluated the psychosocial well-being of HNRMS survivors treated in three large pediatric oncology centers. Psychosocial well-being was systematically assessed by using HRQoL questionnaires and more disease specific questionnaires.

Whereas the decision on local therapy approach in primary head-neck RMS is based on minimizing adverse events, the situation in patients with relapsed HNRMS is different. As previously stated, up to 1/3 of all patients with localized RMS at diagnosis experience a relapse.(8, 56, 57) In general, survival after relapsed RMS is poor and is strongly depending on previously received therapy.(58-60) Patients with relapsed HNRMS who previously received external beam radiotherapy have an extremely poor prognosis, since local therapy options are often lacking. In specific cases, the AMORE approach can be used as salvage treatment.

In **chapter 9**, we report on our experience with salvage AMORE treatment in patients with relapsed HNRMS after prior external beam radiotherapy.

Summary and discussion

The main results and the general discussion and future directions are described in **chapter 10**. Finally, **chapter 11** provides a Dutch summary of this thesis.

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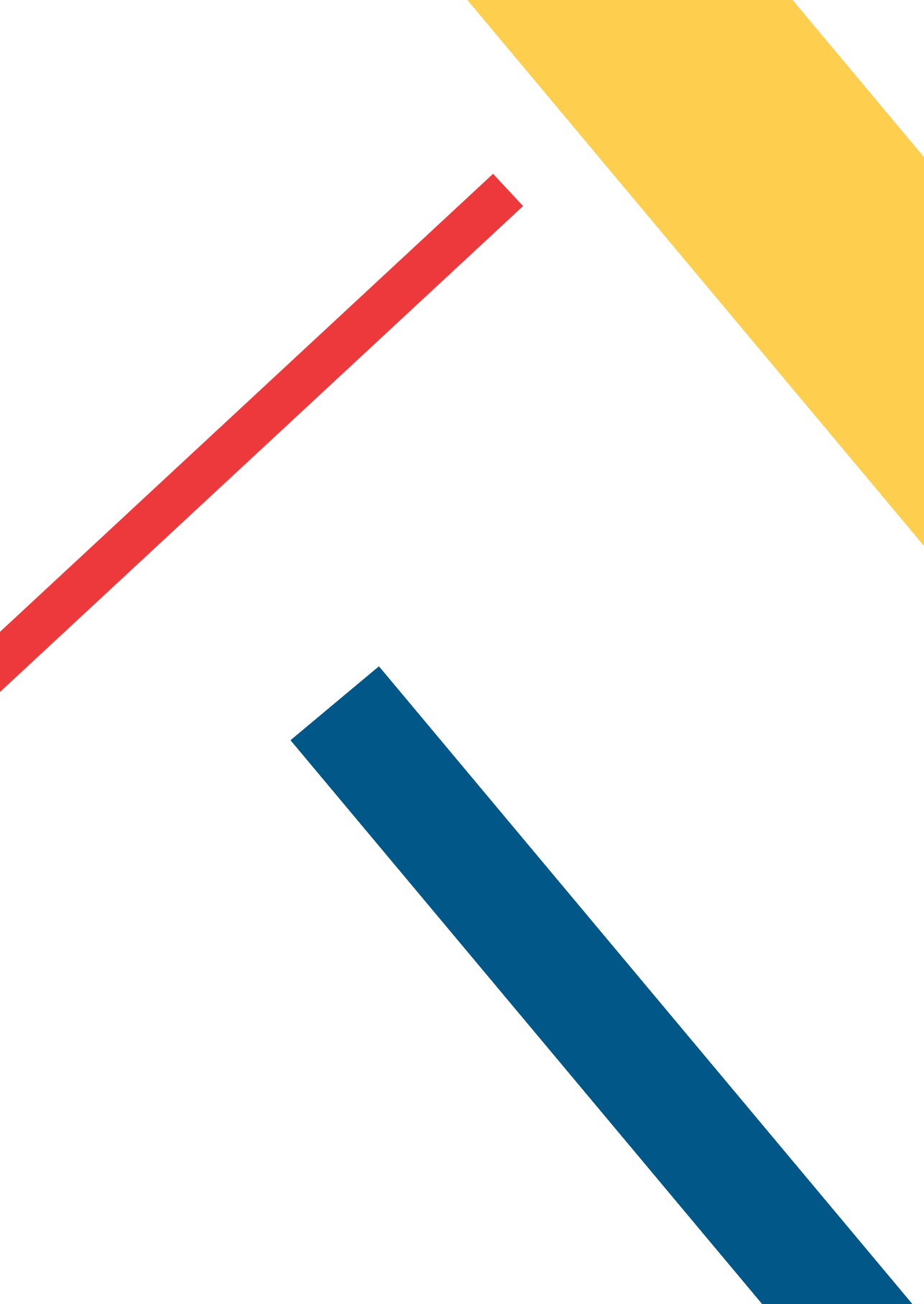
PART ONE



CHAPTER 2

INDETERMINATE PULMONARY NODULES AT DIAGNOSIS IN RHABDOMYOSARCOMA: ARE THEY CLINICALLY SIGNIFICANT? A REPORT FROM THE EUROPEAN PEDIATRIC SOFT TISSUE SARCOMA STUDY GROUP

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ABSTRACT

Purpose

To evaluate the clinical significance of indeterminate pulmonary nodules at diagnosis (defined as ≤ 4 pulmonary nodules <5 mm or 1 nodule measuring ≥ 5 and < 10 mm) in patients with pediatric rhabdomyosarcoma (RMS).

Patients and methods

We selected patients with supposed nonmetastatic RMS treated in large pediatric oncology centers in the United Kingdom, France, Italy, and the Netherlands, who were enrolled in the European *paediatric* Soft Tissue Sarcoma Study Group (EpSSG) RMS 2005 study. Patients included in the current study received a diagnosis between September 2005 and December 2013, and had chest computed tomography scans available for review that were done at time of diagnosis. Local radiologists were asked to review the chest computed tomography scans for the presence of pulmonary nodules and to record their findings on a standardized case report form. In the EpSSG RMS 2005 Study, patients with indeterminate pulmonary nodules were treated identically to patients without pulmonary nodules, enabling us to compare event-free survival and overall survival between groups by log-rank test.

Results

In total, 316 patients were included; 67 patients (21.2%) had indeterminate pulmonary nodules on imaging and 249 patients (78.8%) had no pulmonary nodules evident at diagnosis. Median follow-up for survivors (n = 258) was 75.1 months; respective 5-year event-free survival and overall survival rates (95% CI) were 77.0% (64.8% to 85.5%) and 82.0% (69.7% to 89.6%) for patients with indeterminate nodules and 73.2% (67.1% to 78.3%) and 80.8% (75.1% to 85.3%) for patients without nodules at diagnosis (P = .68 and .76, respectively).

Conclusion

Our study demonstrated that indeterminate pulmonary nodules at diagnosis do not affect outcome in patients with otherwise localized RMS. There is no need to biopsy or upstage patients with RMS who have indeterminate pulmonary nodules at diagnosis.

INTRODUCTION

Over the past decades, the 5-year overall survival (OS) for patients with nonmetastatic rhabdomyosarcoma (RMS) has improved to approximately 80%.[1-3] Nevertheless, survival for patients with metastatic disease remains poor, with 3-year OS ranging between 34% and 56%.[4,5] The lungs are the most frequently involved metastatic site and patients with only pulmonary metastases have a better prognosis than patients with metastases located outside the lungs.

Nevertheless, accurate staging of the lungs is important to select patients who require chest radiotherapy and additional chemotherapy. Staging for lung metastases is usually done by chest computed tomography (CT). Improved quality and increased spatial resolution chest CT scans have introduced new diagnostic dilemmas, because smaller nodules also became detectable.

Small subcentimeter pulmonary nodules are a frequent normal finding in healthy children; however, differentiation between small metastatic and benign nodules is difficult or even impossible in children with extrathoracic malignancies.[6-12] Because of the size of these small nodules, percutaneous needle biopsy is usually not feasible and the decision to treat patients according to nonmetastatic or metastatic guidelines is based, therefore, on the characteristics and number of nodules seen on chest CT imaging. Among other parameters, radiologists use nodule size, margins, the presence of calcification, and the total number of nodules to estimate the likelihood that the nodules represent metastases. However, none of these characteristics adequately distinguishes malignant from benign lesions.[7,9,10]

In the European *paediatric* Soft Tissue Sarcoma Study Group (EpSSG) RMS 2005 protocol, patients with no more than four pulmonary nodules of less than 5 mm or one nodule measuring between 5 and less than 10 mm were considered to have indeterminate or equivocal lesions.

The assumption was made that some of these nodules were benign lesions and others were micrometastases, which, in the past, were not visible because of the use of chest radiographs. Because the impact of these micrometastases on survival was unclear, it was decided by the EpSSG protocol committee that patients classified as having indeterminate pulmonary lesions should be treated as those with localized disease.

If this assumption is wrong, survival may be impaired for this patient group and, consequently, these patients should be upstaged to a higher risk category with intensified treatment in future protocols. Therefore, the aim of this study was to assess the clinical significance of indeterminate pulmonary nodules at diagnosis in children with otherwise nonmetastatic RMS, by comparing event-free survival (EFS) and OS for patients with indeterminate pulmonary nodules to those without such lesions (i.e., lungs entirely clear on CT scans).

PATIENTS AND METHODS

Patients included in this analysis were those enrolled in the EpSSG RMS 2005 study (EudraCT no: 2005-000217-35) for nonmetastatic RMS and for whom the diagnosis was confirmed by central pathology review and whose chest CT scan at diagnosis was available for radiologic review.

Informed consent had been obtained from the patient or guardian or both, according to the research ethics requirements of the individual institutions. Included patients received a diagnosis between September 2005 and December 2013 to allow adequate follow-up. Patients in whom indeterminate pulmonary nodules had been biopsied were excluded.

For the current analysis, we invited local radiologists from larger pediatric oncology centers to review the chest CT scans at diagnosis for patients with localized disease diagnosed in their center (Fig 1). Eligible patients were recruited in 12 larger pediatric oncology centers in France (Institut Curie, Paris; and Centre Léon Bérard, Lyon), Italy (Istituto Nazionale Tumori Milano; and Padova University Hospital), the Netherlands (Beatrix Children's Hospital-University Medical Center Groningen; and Emma Children's Hospital-Academic Medical Center), and the United Kingdom (Birmingham's Children's Hospital; Bristol Royal Hospital for Children; Children's Hospital for Wales; Great Ormond Street Hospital for Children; Royal Manchester Children's Hospital; and Royal Marsden Hospital).

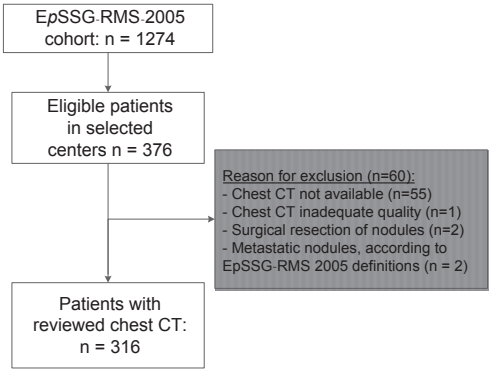


Fig 1. Flow diagram for the current analysis. CT, computed tomography; EpSSG, European *paediatric* Soft Tissue Sarcoma Study Group; RMS, rhabdomyosarcoma.

The outline of the randomized part of the EpSSG RMS 2005 study has been described previously.[3] Treatment was stratified according to risk group on the basis of pathology, postsurgical stage (IRS group), site, nodal involvement, size, and age (Data Supplement). In general, all patients received multidrug chemotherapy comprising ifosfamide

(except for low- risk patients), vincristine, and dactinomycin (IVA). High-risk patients were randomly assigned to either nine courses of standard IVA therapy or IVA with doxorubicin. The results of this randomization did not show a difference in survival between the treatment arms.[3] After nine courses of chemotherapy, high-risk patients in clinical complete remission were eligible for a second randomization between end of therapy (standard) and six courses (4 weeks each) of metronomic maintenance therapy with vinorelbine and cyclophosphamide. Patients at very high risk (i.e., with alveolar histology and positive regional lymph nodes) received IVA with doxorubicin, followed by standard maintenance therapy with vinorelbine and cyclophosphamide.[13]

Local primary therapy was determined by risk group, tumor site, age of patient, and response assessment. Delayed surgery, on the basis of resectability without mutilating consequences, was performed for residual tumor. If recommended, radiotherapy was given at week 13. Radiation doses ranged between 36 and 50.4 Gy, depending on histology, resection margins, and tumor response.

Central radiology review was not part of the EpSSG-RMS 2005 protocol; for the current analysis, all chest CT scans at diagnosis were reviewed by the local radiologist in the treating centers for the presence of indeterminate pulmonary nodules. Data were recorded using a standardized case report form to enhance uniformity among the radiologists. According to protocol, chest CT scans were performed with a minimum reconstruction slice width of 3 to 5 mm.

Scanning parameters and number and size of nodules were noted. Patients were classified as having no nodules, indeterminate pulmonary nodules, or misclassified as indeterminate lesions. Indeterminate pulmonary nodules, according to the EpSSG RMS 2005 protocol, were defined as no more than four nodules of less than 5 mm or one nodule measuring between 5 mm and less than 10 mm. Patients with pulmonary nodules fulfilling definitions of pulmonary metastases were categorized as having nodules misclassified as indeterminate lesions and excluded from the current analysis (n = 2).

Statistical analyses

Analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC). Data from the reviews of the chest CT scans were combined with treatment and outcome data from the EpSSG database. The distribution of patient characteristics between patients with indeterminate pulmonary nodules at diagnosis and patients without pulmonary nodules was compared using x^2 tests. OS was calculated from the date of diagnosis to death from any cause, and EFS was measured from the date of diagnosis to disease progression, relapse, a second malignancy, or death from any cause. Outcomes for living patients were censored at the time of their last reported contact. EFS and OS curves were obtained using the Kaplan-Meier method (data cutoff point was November 1, 2017).[14] A log-rank test

was used to compare the EFS and OS levels between the patients with indeterminate pulmonary nodules and patients without pulmonary nodules at diagnosis. Subgroup analyses were performed on the basis of histology, fusion status, age at diagnosis, and received therapy.[4,15,16] P less than .05 was considered statistically significant.

RESULTS

Patients

In total, 376 eligible patients were enrolled in the EpSSG RMS 2005 study for localized disease. The primary reason for exclusion was that the chest CT scan at diagnosis was not available for review (n = 55). Patients were also excluded because they had a surgical resection of pulmonary nodules (n = 2), radiologic review showed pulmonary nodules considered metastatic (n = 2), or the chest CT scan had a slice thickness greater than 5 mm, considered inappropriate to determine the presence of small pulmonary nodules (n = 1). Eventually, data from 316 patients were available for analysis (Fig 1). Clinical characteristics for the included patients were comparable to the total group of eligible patients. CT slice thickness was no greater than 3 mm in 214 of 316 of the included patients (67.7%) and the reconstruction width was no greater than 1.25 mm in 77 of 316 patients (24.4%). Median age at diagnosis was 5.4 (the range was 0 to 21.9) years, and the median follow-up time for survivors was 75.1 (interquartile range was 54.4 to 94.6) months.

The majority of patients (80.7%) had an Intergroup Rhabdomyosarcoma Study Group III (IRS group III) tumor at diagnosis (i.e., incompletely resected tumor/biopsy only) and specimens of 70.9% of the patients showed favorable histology. All patients received chemotherapy according to protocol. In total, 77 patients (24%) received maintenance chemotherapy. Most patients (77%) received local radiotherapy and 135 of 255 IRS group III patients (53%) underwent secondary surgery. Patients' and treatment characteristics are further described in Table 1 and in the Data Supplement. Compared with the total EpSSG RMS 2005 cohort, within this subgroup with reviewed chest CT scans, there were significantly more IRS group III and high-risk patients (P = .01; Data Supplement).

Nodule Characteristics

In total, 249 patients (78.8%) did not have pulmonary nodules at diagnosis; 67 of the 316 patients (21.2%) had at least one indeterminate pulmonary nodule. Patient and treatment characteristics were comparable for patients with indeterminate nodules and patients without nodules (Table 1). A total of 100 nodules were observed in 67 patients, 46 of whom (68.7%) had only one nodule. The size of the nodules ranged from 1 to 8 mm and in 37 of the 67 patients (55.2%), the largest nodule was 1 to 2 mm (Table 2).

Table 1. Patients and tumor characteristics at diagnosis based on presence of indeterminate pulmonary nodules

	No nodule (n=249)		Indeterminate pulmonary nodules (n=67)		
Characteristics	**n**	**%**	**n**	**%**	**p***
Age at diagnosis, years					0.30
<1	13	5	1	2	
1-9	173	70	45	67	
≥ 10	63	25	21	31	
Sex					0.45
Male	143	57	35	52	
Female	106	43	32	48	
Histology					0.17
Favorable †	172	69	52	78	
Unfavorable ‡	77	31	15	22	
Fusion status §					0.78
Fusion negative	149	77	37	79	
Fusion positive	45	23	10	21	
Tumor site					0.68
Orbit	23	9	11	16	
Parameningeal	65	26	18	27	
HN nonPM	22	9	6	9	
GU, nonbladder/prostate	39	16	10	15	
GU, bladder/prostate	32	13	5	8	
Extremity	30	12	8	12	
Other	38	15	9	13	
Risk group					0.87
Low risk	3	1	1	2	
Standard risk	84	34	25	37	
High risk	136	55	36	54	
Very high risk	26	10	5	7	
IRS Group ‖					0.77
Group I	18	7	6	9	
Group II	28	11	9	13	
Group III	203	82	52	78	
Tumor size, cm ¶					0.14
≤ 5	108	44	36	54	
> 5	139	56	31	46	
Nodal status #					0.80
N0	201	81	52	80	
N1	46	19	13	20	

Abbreviations; GU, genitourinary; HN non-PM, head-neck nonparameningeal.

* Based on chi-square test.

† All embryonal, spindle cell, botryoid rhabdomyosarcoma

‡ All alveolar rhabdomyosarcoma

§ Fusion status was not investigated in 75 patients (no pulmonary nodules, n = 55; indeterminate pulmonary nodules, n = 20).

‖ IRS group: Group I, primary complete resection (R0); Group II, microscopic residual (R1) or primary complete resection but N1; Group III, macroscopic residual (R2).

¶ Tumor size was unknown in two patients (no pulmonary nodules, n=2).

\# Nodal status was unknown in four patients (no pulmonary nodules, n=2; indeterminate pulmonary nodules, n=2)

Table 2. Characteristics of indeterminate pulmonary nodules in 67 patients

Characteristics	n	%
No. of nodules		
1	46	69
2	13	19
3	4	6
4	4	6
Nodule maximum diameter, mm		
1	13	19
2	24	36
3	15	22
4	10	15
5	3	4
7	1	2
8	1	2
Laterality		
Unilateral	57	85
Bilateral	10	15

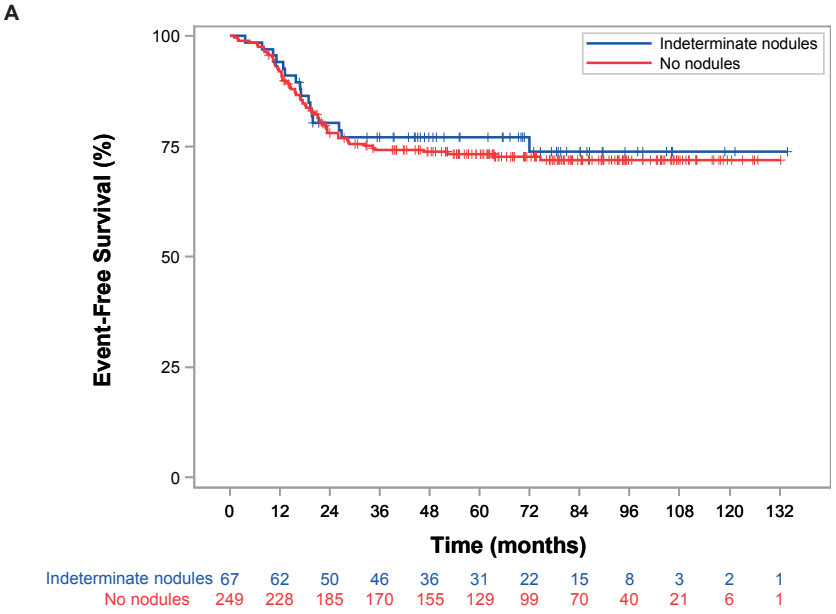
Table 3. EFS and OS, based on number and size of nodules at diagnosis.

Characteristics	No.	5-yr EFS (95% CI)	EFS p*	5-yr OS (95% CI)	OS p*
No. of nodules			.79		.93
0	249	73.2 (67.1 to 78.3)		80.8 (75.1 to 85.3)	
1	46	75.4 (60.0 to 85.6)		81.5 (66.4 to 90.3)	
> 1	21	80.2 (55.4 to 92.1)		81.8 (51.9 to 94.0)	
Size of largest nodule, mm			.74		.95
< 3 mm	37	75.3 (57.9 to 86.3)		82.7 (65.4 to 91.8)	
≥ 3 mm	30	79.2 (59.4 to 90.1)		80.7 (59.2 to 91.6)	

Abbreviations: EFS, event-free survival; OS, overall survival.
*Based on log-rank test.

Table 4. Type of event, based on presence of indeterminate pulmonary nodules

	No nodule (n=249)		Indeterminate pulmonary nodules (n=67)	
	No.	**%**	**No.**	**%**
Type of event				
Local recurrence	53	21	11	16
Metastatic recurrence	5	2	3	4
Local and metastatic recurrence	6	2	1	1
Second primary malignancy	3	1	1	1
Metastatic site				
Lung	4	2	2	3
Other	7	3	2	3



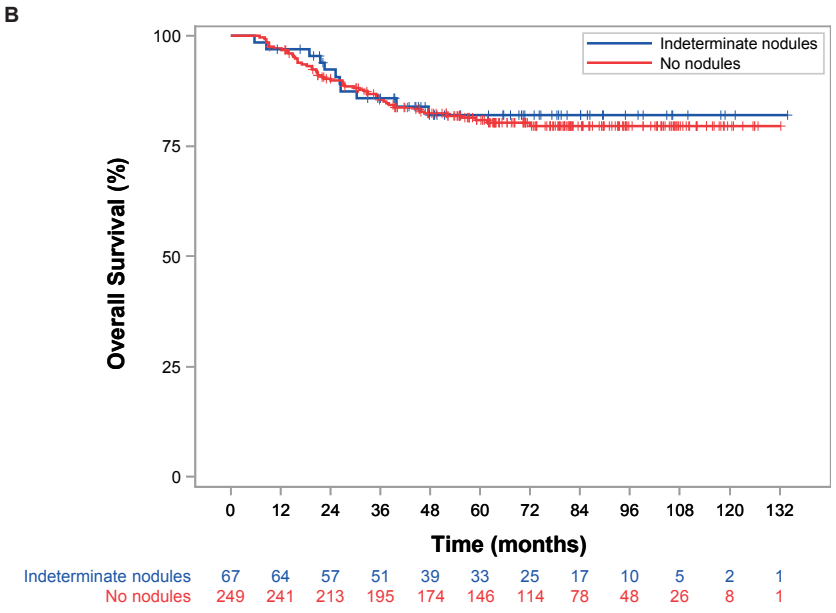


Fig 2. Kaplan-Meier survival curves showing (A) event-free survival and (B) overall survival for patients based on the presence of indeterminate pulmonary nodules at diagnosis.

Indeterminate Nodules and Impact on Survival

Five-year EFS was 77.0% (95% CI: 64.8% to 85.5%) for patients with indeterminate nodules and 73.2% (95% CI: 67.1% to 78.3%) for patients without nodules (P = .68). Five-year OS was 82.0% (95% CI: 69.7% to 89.6%) for patients with indeterminate pulmonary nodules and 80.8% (95% CI: 75.1% to 85.3%) for patients without nodules (P= .76). No significant differences in EFS and OS were found on the basis of the presence of indeterminate pulmonary nodules (Fig 2) or on the basis of the number and size of the largest nodule (Table 3). Subgroup analyses according to histology, fusion status, age at diagnosis, and received chemotherapy regimen (with or without doxorubicin or with or without maintenance chemotherapy) showed no significant differences in EFS and OS based on the presence of indeterminate nodules.

Eighty-three patients experienced at least one event; 67 patients (80.7%) had no pulmonary nodules at diagnosis and 16 patients (19.3%) had at least one indeterminate pulmonary nodule at diagnosis. First relapse was locoregional in 64 patients (77.1%), only metastatic in eight patients (9.6%), and combined locoregional and metastatic in seven patients (8.4%). Four patients developed a second malignancy (no tumor predisposition syndromes were reported for these patients). In the group of 67 patients with indeterminate pulmonary nodules, lung metastases developed in two (3.0%), compared with four of 249 patients (1.6%) in the group without nodules (P = .46; Table 4).

DISCUSSION

Small pulmonary nodules at time of diagnosis are a diagnostic challenge in children with RMS. The results of this study confirm that the presence of indeterminate pulmonary nodules is a frequently encountered diagnostic problem. More importantly, the results of this study demonstrate that the presence of indeterminate pulmonary nodules at diagnosis does not affect survival for patients treated according to E*p*SSG guidelines for localized disease.

The incidence of pulmonary nodules in our cohort was lower than reported in non-oncologic populations (up to 38%).[11,12] This difference might be explained by variability in CT slice reconstruction methods. In the E*p*SSG RMS 2005 study, a minimum reconstruction width of 3 to 5 mm was required, whereas this was no more than 1.25 mm in the other studies.11,12 Reconstruction width in chest CT scans of 214 of 316 patients (67.7%) in our cohort was not more than 3 mm, but only 77 (24.4%) had a reconstruction width of not more than 1.25 mm.

Thinner slice thickness may have resulted in the identification of a higher number of small nodules. Because of continuous technical improvement of CT units, the incidence of small lung nodules might artificially increase in the next studies. Based on the results

of the current analysis, one could argue that performing a fine-cut CT of the lungs in patients with RMS has no added value; however, the current E*p*SSG definition for pulmonary metastases also incorporates patients with five or more small nodules for which a fine-cut CT scan is required.

Although indeterminate pulmonary nodules are a frequent finding in (otherwise) healthy children, finding indeterminate pulmonary nodules in patients with newly diagnosed RMS is more complicated. Histopathologic examination is considered the gold standard for final characterization of these nodules; however, it generally requires surgical biopsy by thoracic surgery, with the chance of false-negative results on examination of biopsy specimens. This strategy was not considered acceptable by the protocol committee of the E*p*SSG. Therefore, the final decision to upstage patients with indeterminate pulmonary nodules, leading to intensification of standard chemotherapy, and surgery and/or radiotherapy for the pulmonary nodules, was generally based on the assessment of the chest CT scans by pediatric radiologists in collaboration with involved clinicians in tumor board meetings. Radiologists use several parameters to try to distinguish benign from malignant lung nodules; however, none of these parameters have proven to reliably differentiate these nodules.[9,10,17] Silva et al.[10] evaluated chest CT scans of 488 children with extrapulmonary malignancies. Of the 488 children, 111 (22.7%) had pulmonary nodules at diagnosis; 27 patients also underwent a biopsy and none of the CT characteristics assessed (e.g., number and size of nodules) reliably differentiated benign from malignant nodules. McCarville et al.[9] assessed the chest CT scans of 41 children with malignant solid tumors in whom pulmonary nodules were biopsied (81 nodules in total) and found that small pulmonary nodules (i.e., less than 5 mm) were as likely to be malignant as larger nodules.

Because of this limitation, radiologists and pediatric oncologists of the E*p*SSG established an arbitrary CT definition of stage IV lung disease, based on number and size of nodules, to be used as a non-inclusion criterion in the E*p*SSG RMS 2005 study. Patients with other small pulmonary nodules (≤ four nodules < 5 mm or one nodule measuring ≥ 5 mm and < 10 mm) were classified as "indeterminate nodules" and were treated according to localized disease protocol.

The results of the current analysis justify the use of this definition. They illustrate that the presence of these very small indeterminate pulmonary nodules does not affect survival, implying that there is no need to intensify treatment (i.e. chest radiotherapy, longer period of maintenance therapy, or other treatment intensification) for these patients in future protocols. Previous studies of patients with lung-only metastatic RMS indicated that survival was affected by histology, age at diagnosis, and the intensity of therapy.[4,15,16] We found no evidence that these factors influenced our finding that indeterminate pulmonary nodules do not affect survival in RMS, although numbers are limited.

The clinical significance of small pulmonary nodules has previously been assessed in other pediatric malignancies; however, the definition of small pulmonary nodules and the results were inconsistent. Absalon et al.[17] included 210 newly diagnosed patients with bone or soft tissue sarcoma and found pulmonary nodules (diameter ≤ 2 cm) in 66 patients (median size of nodules was 5 mm; range, 1 to 20 mm). The size of pulmonary nodules was not significantly associated with outcome; however, the number and distribution of nodules was. The same conclusion was drawn by Cipriano et al.[18] in a retrospective, single-center analysis of 126 patients with high-grade bone or soft tissue sarcoma in which survival was significantly decreased in patients with multiple nodules not larger than 5 mm and patients with multiple bilateral nodules. Both studies included patients with several histologic diagnoses in whom treatment also differed based on the diagnostic assessments.

In contrast, patients included in our analysis all had RMS and were uniformly and prospectively treated according to one study protocol. Both patient groups (i.e., with and without indeterminate pulmonary nodules) were stratified as having localized disease, allowing us to compare survival between both groups. Although the E*p*SSG RMS 2005 protocol clearly stated that patients with indeterminate pulmonary nodules should be treated as having localized disease, a small subset of patients underwent a surgical biopsy at diagnosis. We excluded those patients from our analysis; inclusion would have introduced bias because only tumor-negative biopsy specimens (n = 2) would have been included in the E*p*SSG RMS 2005 study for localized disease.

A standardized radiology reporting template was not used in the E*p*SSG RMS 2005 study and the definition of indeterminate pulmonary nodules was an arbitrary cutoff, we therefore expected an underestimation of reported incidence of indeterminate pulmonary nodules in the radiology reports. This was confirmed by the difference in incidence between initial reports and the reviewed imaging (incidence was more than 10% higher in reviewed imaging).

The strength of this study is that chest CT scans were reviewed by local pediatric radiologists using a standardized case-report form. Furthermore, this analysis is based on a large cohort of consecutive patients treated according to the same treatment protocol with adequate follow- up. Limitations were that we only included large centers participating in the E*p*SSG-RMS 2005 study, and 55 of 376 potential patients were excluded because the chest CT scan at diagnosis was not available for review. The current cohort (n = 316) contained relatively more high-risk patients and patients with higher IRS groups. The participating centers are often international referral centers, which might explain the higher incidence of high-risk patients. Another limitation is that we did not use central review, because previous studies demonstrated substantial interobserver variability in the detection of pulmonary nodules, more specifically in the detection of smaller nod-

ules.[12,19,20] A central review of chest CT images could have led to more consistent assessments and reporting. However, this was not possible for organizational reasons; review of chest CT scans by local radiologists was in compliance with the informed consent of the E*p*SSG-RMS 2005 study, whereas central review would have caused regulatory issues. We tried to limit the bias by using a standardized case-report form; nevertheless, this did not exclude interobserver variability.

Another limitation is that we did not assess the CT pattern changes during chemotherapy nor the histology of residual nodules removed after chemotherapy. Nodules that decrease in size or disappear more likely, intuitively, represent micrometastases, whereas unchanged nodules more likely represent benign lesions.

To conclude, in this study, we demonstrated that the presence of indeterminate pulmonary nodules, as defined in the E*p*SSG-RMS 2005 protocol, in patients with newly diagnosed RMS treated for localized disease does not affect survival, implying that patients with indeterminate pulmonary nodules were adequately treated according to the nonmetastatic disease protocol in the E*p*SSG-RMS 2005 study. Importantly, this study indicates that patients with indeterminate pulmonary nodules do not require chest radiotherapy, therewith limiting potential toxicity for these patients.[21]

For future studies, we emphasize the importance of standardized imaging-reporting templates to improve consistency of reporting. The new International Society of Pediatric Oncology- Quality and Excellence in Radiotherapy and Imaging for Children and Adolescents with Cancer across Europe initiative could contribute to this.[22]

SUPPORT

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APPENDIX: SUPPLEMENTARY MATERIAL

Table S1: E*p*SSG-RMS 2005 risk stratification
Table S2: Treatment characteristics
Table S3. Comparison of characteristics between included patients and total included patients in E*p*SSG-RMS 2005 cohort diagnosed before 31 December 2013 (n=1759).

Table S1: E*p*SSG-RMS 2005 risk stratification

Risk Group	Subgroups	Pathology	Post-surgical Stage (IRS Group)	Site	Node stage	Size & Age
Low Risk	**A**	Favorable	I	Any	N0	Favorable
Standard risk	**B**	Favorable	I	Any	N0	Unfavorable
	C	Favorable	II, III	Favorable	N0	Any
	D	Favorable	II, III	Unfavorable	N0	Favorable
High Risk	**E**	Favorable	II, III	Unfavorable	N0	Unfavorable
	F	Favorable	II, III	Any	N1	Any
	G	Unfavorable	I, II, III	Any	N0	Any
Very High risk	**H**	Unfavorable	II, III	Any	N1	Any

Pathology:
Favorable = all embryonal, spindle cell, botryoid RMS
Unfavorable = all alveolar RMS

Post-surgical stage (IRS Group):
Group I = primary complete resection (R0)
Group II = microscopic residual (R1) or primary complete resection but N1
Group III = macroscopic residual (R2)

Site:
Favorable = orbit, GU non bladder prostate and head & neck non parameningeal
Unfavorable = parameningeal, extremities, GU bladder-prostate and other site

Node stage:
N0 = no clinical or pathological node involvement
N1 = clinical or pathological nodal involvement

Size & Age:
Favorable = Tumor size <5cm and Age <10 years
Unfavorable = all others (i.e. Size >5 cm or Age ≥10 years)

Table S2. Treatment characteristics

	n	%
Chemotherapy received		
VA	4	1
VA + IVA	40	13
IVA	138	44
IVA + maintenance*	24	8
IVADo	54	17
IVADo + maintenance*	53	17
Other regimen	3	1
Radiotherapy given		
Yes	244	77
No	72	23
Secondary surgery #		
Yes	135	53
No	120	47

* Maintenance chemotherapy comprised vinorelbine/cyclophosphamide

\# Only for IRS III patients

Abbreviations: VA, vincristine, dactinomycin; IVA, ifosfamide, vincristine and dactinomycin; IVADo, ifosfamide, vincristine, dactinomycin, doxorubicin

Table S3. Comparison of characteristics between included patients and total included patients in E*p*SSG-RMS 2005 cohort diagnosed before 31 December 2013 (n=1759).

	Chest CT reviewed (n=316)		Not reviewed patients (n=1443)		
Characteristics	**No.**	**%**	**No.**	**%**	**P #**
Age at diagnosis, years					0.28
<1	14	4	99	7	
1-9	218	69	969	67	
≥ 10	84	27	375	26	
Sex					0.10
Male	178	56	885	61	
Female	138	44	558	39	
Histology [a]					0.08
Favorable	224	71	1090	75	
Unfavorable	92	29	351	25	

Table S3. Comparison of characteristics between included patients and total included patients in E*p*SSG-RMS 2005 cohort diagnosed before 31 December 2013 (n=1759). (continued)

	Chest CT reviewed (n=316)		Not reviewed patients (n=1443)		
Characteristics	**No.**	**%**	**No.**	**%**	**P #**
Tumor site					0.62
Orbit	34	11	152	11	
Parameningeal	83	26	334	23	
HN non PM	28	9	138	10	
GU, nonbladder/prostate	49	16	290	20	
GU, bladder/prostate	37	12	167	12	
Extremity	38	12	159	11	
Other	47	15	203	14	
Risk group [b]					0.01*
Low risk	4	1	73	5	
Standard risk	109	35	540	37	
High risk	172	54	711	49	
Very high risk	31	10	116	8	
IRS Group [c]					0.01*
Group I	24	8	190	13	
Group II	37	12	194	13	
Group III	255	81	1059	73	
Tumor size, cm [d]					0.42
≤ 5	144	46	686	48	
> 5	170	54	732	52	
Nodal status [e]					0.39
N0	253	81	1176	83	
N1	59	19	239	17	

p-value based on chi-square test. * *p*-value <0.05.

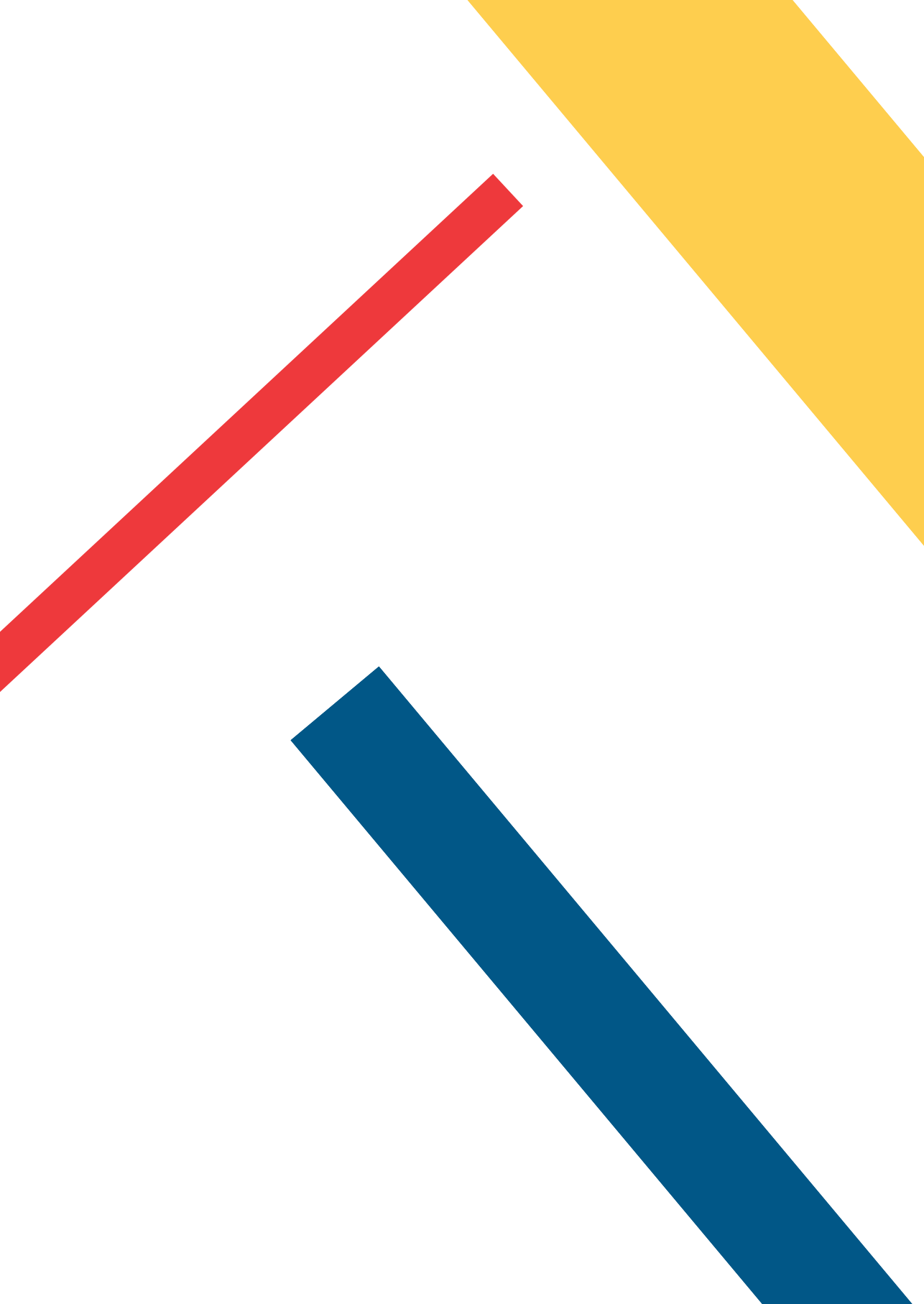
Abbreviations; HN non PM, head-neck nonparameningeal; GU, genitourinary; N0, no clinical or pathological node involvement; N1, clinical or pathological nodal involvement.

a Favorable histology are all embryonal, spindle cells, botryoid RMS, unfavorable are all alveolar RMS.

b Three patients were not allocated in a risk category: two patients had pleomorphic RMS, 1 patient had pleural effusion at diagnosis. These patients were not included in current analysis.

c IRS group: Group I, primary complete resection (R0); Group II, microscopic residual (R1) or primary complete resection but N1; Group III, macroscopic residual (R2).

d In 27 patients tumor size was unknown (n=2; included in current analysis, n=25 not included in current analysis). e Nodal status was unknown in 32 patients (n=4; included in current analysis, n=28; not included in current analysis).



CHAPTER 3

FLUORINE-18-FLUORODEOXYGLUCOSE (FDG) POSITRON EMISSION TOMOGRAPHY (PET) COMPUTED TOMOGRAPHY (CT) FOR THE DETECTION OF BONE, LUNG AND LYMPH NODE METASTASES IN RHABDOMYOSARCOMA

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Manuscript in preparation

This is a draft and pre-peer review version of a Cochrane Review. Upon completion and approval, the final version is expected to be published in the Cochrane Database of Systematic Reviews (www.cochranelibrary.com).

ABSTRACT

Background

Rhabdomyosarcoma (RMS) is the most common pediatric soft-tissue sarcoma. It arises from mesenchymal cells and can emerge throughout the whole body. For patients with newly diagnosed RMS, prognosis depends on multiple factors associated with survival such as histology, tumor site and extent of the disease. Patients with metastatic disease at diagnosis have impaired prognosis compared to patients with localized disease. Therefore, appropriate staging at diagnosis plays an important role in choosing the right treatment regimen for the individual patients.

Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) is a functional molecular imaging technique that uses the increased glycolysis of cancer cells to visualize both structural information and metabolic activity. ^{18}F-FDG-PET combined with computed tomography (CT) could help to accurately stage the extent of disease in patients with newly diagnosed RMS.

Objectives

To determine the diagnostic accuracy of ^{18}F-FDG-PET/CT imaging for the detection of bone, lung and lymph node metastases in rhabdomyosarcoma patients at first diagnosis.

Search methods

We searched MEDLINE in PubMed (from 01-01-1966 to 26-11-2018) and EMBASE in Ovid (from 1980 to 26-11- 2018) for potentially relevant studies. We also checked the reference lists of relevant studies and review articles, scanned conference proceedings and contacted the authors of the included studies and other experts in the field of RMS for information about any ongoing or unpublished studies.

Selection criteria

We included cross-sectional studies including patients with newly diagnosed proven RMS, either prospective or retrospective, if they reported the diagnostic accuracy of ^{18}F-FDG-PET/CT in diagnosing lymph node involvement or bone metastases or lung metastases or a combination of these metastases in patients with histologically proven RMS. For the reference standard, studies needed to compare the results of the ^{18}F-FDG-PET/CT imaging with those of histology or with the evaluation by a multidisciplinary tumor board.

Data collection and analysis

Two review authors independently identified studies meeting the inclusion criteria and performed study selection, data extraction, and methodological quality assessment ac-

cording to QUADAS-2. We analyzed data of the three outcomes (nodal involvement, and lung and bone metastases) separately. We used data from the 2×2 tables (consisting of true positives, false positives, true negatives and false negatives) to calculate sensitivity and specificity in each study. We planned to use random-effects bivariate meta-analysis to obtain summary estimates of accuracy.

Main results

In total, two studies met the inclusion criteria. Study quality was considered low in one study, because no clear definition of positivity for ^{18}F-FDG-PET/CT was reported, and not all patients underwent adequate conventional imaging. The diagnostic accuracy of ^{18}F-FDG-PET/CT was reported in both studies, including 36 patients in total. Sensitivity and specificity of ^{18}F-FDG- PET/CT for the detection of bone metastases was 100% in both studies (95%-confidence interval [CI] for sensitivity ranged from 29-100%, for specificity it ranged from 66-100%). The reported sensitivity of ^{18}F-FDG-PET/CT for the detection of lung metastases was 50% (95%-CI: 1-99%); for one study sensitivity could not be estimated. Reported specificity ranged from 96% to 100% (95%-CI ranged from 72-100%) across studies. The reported sensitivity for the detection of nodal involvement was 100% (95%-CI ranged from 40-100%); the reported specificity in the separate studies ranged from 89% to 100% (95%-CI ranged from 52-100%). A formal meta- analysis was not considered relevant because of the large heterogeneity between studies and the scarcity of data.

Authors' conclusions

The diagnostic accuracy of ^{18}F-FDG-PET/CT for the detection of bone, lung and lymph node metastases was only reported in two studies, including only 36 patients with newly diagnosed RMS in total. There is currently insufficient evidence to reliably determine the diagnostic accuracy of ^{18}F-FDG-PET/CT in the detection of distant metastases, which implies that ^{18}F-FDG-PET/CT could not replace all other staging investigations (local ultrasound and MR imaging of primary site and chest CT for example) as a single diagnostic test for metastases. However, although data are scarce, ^{18}F-FDG-PET/CT appeared to be 100% sensitive and specific to detect bone metastases. Larger series evaluating the diagnostic accuracy of ^{18}F-FDG-PET/CT for the detection of metastases in patients with RMS are necessary.

PLAIN LANGUAGE SUMMARY

The accuracy of ^{18}F-FDG-PET/CT for the detection of metastatic rhabdomyosarcoma in newly diagnosed patients.

Why is accurate staging of rhabdomyosarcoma important?

Rhabdomyosarcoma (RMS) accounts for 3-5% of all childhood malignancies. The treatment for patients consists of multidrug chemotherapy and surgery and/or radiotherapy. This treatment for newly diagnosed patients depends on the extent of the malignancy. Survival for patients with localized disease is around 75%, whereas this is 30% in patients with the disease spread to different part(s) of the body (i.e. metastatic disease). Accurate staging (i.e. metastatic or not) of the extent of the disease is of utmost importance because not recognizing patients with metastatic disease would lead to undertreatment, whereas incorrectly identifying lesions as being metastatic would lead to overtreatment. ^{18}F-FDG-PET/CT could be helpful to visualize the extent of the disease in patients with newly diagnosed RMS. However, the accuracy (ability to discriminate RMS metastases from other lesions) of ^{18}F-FDG-PET/CT is currently unknown.

What was the aim of this review?

The aim of this review was to find out how accurate ^{18}F-FDG-PET/CT is for the detection of bone and lung metastases and lymph node involvement in patients with newly diagnosed RMS.

What was studied in this review?

We searched scientific literature databases for studies comparing the results of ^{18}F-FDG-PET/CT to histologic examinations or multidisciplinary tumor board results. The advantage of using ^{18}F-FDG-PET/CT compared to standard staging investigations would be the use of ^{18}F-FDG-PET/CT as single diagnostic test to detect metastases, thus reducing patient burden and lowering radiation exposure.

Main results

In total, we identified 2 studies, including 36 patients with RMS. Because of the low number of patients in the included studies and the differences in quality between the included studies, we were not able to calculate average values of sensitivity and specificity, and our results should be considered with caution.

The sensitivity and specificity of ^{18}F-FDG-PET/CT for the detection of bone metastases was 100% in both studies. The sensitivity for the detection of lung metastases was 50% in one study, and could not be estimated in the other study; specificity ranged from 96% to 100%. In both studies, the sensitivity for the detection of lymph node involvement was 100%, and specificity ranged from 89% to 100%.

How reliable are the results of the studies in this review?

In the included studies, histopathological confirmation was considered the optimal reference standard, however this was not done in all patients. In these cases where no histopathological confirmation was done, the judgement from a multidisciplinary tumor board was considered as reference standard. In one of the included studies all study participants underwent the same diagnostic procedures, whereas in the other study this was not the case for all participants. This study did not clearly define what was considered a positive test result for ^{18}F-FDG-PET/CT imaging. This might have biased the results.

What are the implications of this review?

The total number of studies and participants was too low to draw firm conclusions. Large studies evaluating the accuracy of ^{18}F-FDG-PET/CT in patients with RMS are needed.

How up to date is this review?

The review authors searched for and used studies published from 1966 to 26 November 2018.

BACKGROUND

Target condition being diagnosed

Rhabdomyosarcoma (RMS) is the most common pediatric soft-tissue sarcoma and constitutes about 3% to 5% of all malignancies in childhood (Miller 1995; Ward 2014). The annual incidence in children varies between four per million and seven per million depending on the age group. In the USA, about 340 new cases are diagnosed in children each year (Ward 2014). RMS is a tumor of mesenchymal cell origin and can arise throughout the whole body. About 40% of RMS arises in the head and neck area, 25% to 30% in the genitourinary region, 15% in the extremities and 15% to 20% in other regions (e.g. trunk) (McDowell 2003; Weiss 2013). Prognosis for patients with localized disease is based on several factors including histology, tumor site and size, post- surgical stage (Intergroup Rhabdomyosarcoma Studies (IRS) grouping), nodal status, distant metastasis and patient's age. In children, two main histological subtypes have been identified, being embryonal (ERMS) and alveolar (ARMS). The prognosis of patients with ARMS is significantly worse compared to patients with ERMS (Meza 2006). Orbital site, head and neck non- parameningeal and genitourinary non-bladder/prostate sites have favorable prognosis compared to other sites. Younger patients (aged less than 10 years) and patients with small tumors (less than 5 cm) do better than older patients or patients with large tumors. Patients with completely resected tumors do better than

patients with residual disease. In about 21% of RMS patients lymph nodes are involved (Weiss 2013), negatively influencing prognosis. Distant metastases are identified in about 16% of newly diagnosed RMS patients (including 6% lung metastases, 5% bone metastases). Prognosis for patients with metastatic RMS compares unfavorably to patients with localized disease and prognostic factors for patients with metastatic tumors include age, primary tumor site (patients with extremity and other sites have dismal prognosis), presence of bone or bone marrow metastases, and number of metastatic sites (Oberlin 2008). Based on these risk factors, RMS patients are subdivided into risk groups (Arndt 2009; Arndt 2013; Meza 2006; Pappo 2007; Raney 2001; Raney 2011). In current treatment protocols, intensity of chemotherapy and application of radiotherapy to the primary site, involved nodes and metastatic sites is tailored based on these risk categories (E*p*SSG RMS 2005 (Bisogno 2018), COG ARST0531 (NCT00354835)). With current multimodal treatment protocols, five-year overall survival for RMS patients is about 65% (Gatta 2014; Ward 2014).

However, survival for patients with or without metastasis is dramatically different. Patients with local disease at diagnoses have a five-year overall survival around 70% whereas this is below 30% in metastatic RMS patients (Crist 2001; Oberlin 2008). Patients with lung metastases have a better outcome than patients with bone or bone marrow metastases. Moreover, patients with more than two metastatic sites have a more dismal outcome compared to only one site (Oberlin 2008). To apply most optimal treatment in terms of survival but also in term of late effects, risk group stratification for individual patients at diagnosis is extremely important.

Index test(s)

Fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) is a functional molecular imaging technique that uses the increased glycolysis of cancer cells to visualize both structural information and metabolic activity. By combining ^{18}F-FDG-PET with computed tomography (CT), the exact anatomical location and structural information of the lesion can be acquired (Gambhir 2002). In several cancer types, such as lung cancer and lymphoma, FDG- PET/CT has proven to be of important value in accurately staging at diagnosis (Gallamini 2014). ^{18}F-FDG-PET/CT is being evaluated for clinical use in patients with sarcoma (Quak 2011). Several studies on children with sarcoma report the additional value of using ^{18}F-FDG-PET/CT in initial staging compared to conventional imaging (Eugene 2012; Federico 2013; Kumar 2010; Ricard 2011; Tateishi 2007). Unfortunately, FDG uptake is not unique to cancers cells. In addition, an ^{18}F-FDG-PET scan visualizes physiological FDG uptake in tissues such as the brain, brown adipose tissue and the thymus, and tissues with inflammation and infection, causing increased glucose metabolism (Quak 2011).

Clinical pathway

Depending on the localization of the tumor, patients present with a range of clinical symptoms. Patients with head and neck tumors can present with asymptomatic masses, proptosis, epistaxis, cranial nerve palsies or chronic otitis media whereas patients with a tumor located in the bladder/prostate region could present with hematuria, urinary retention, abdominal mass and constipation. The diagnosis of RMS is confirmed by histology obtained by biopsy. The standard workup of newly diagnosed RMS patients includes a magnetic resonance image (MRI) of the primary tumor and several conventional imaging modalities to determine the extensiveness of the disease.

- To exclude bone and bone marrow involvement, investigation involves a whole body ^{99m}Tc bone scintigraphy and bilateral bone marrow aspirates and trephine biopsies.
- Lung metastases are identified with chest CT scan.
- To identify suspected lymph nodes, the MRI of the primary tumor site is performed and if indicated an ultrasound of the regional lymph nodes is made.
- In patients with a parameningeal tumor, a lumbar puncture is indicated.

As the majority of newly diagnosed RMS patients is under the age of six years (Yang 2014), this means that general anesthesia is indicated to obtain the results of different staging tests, including MRI and bone marrow punctures and trephines. It is common practice that findings are discussed at a multidisciplinary tumor board meeting. Based on histology (ARMS/ERMS), tumor site and size, post-surgical stage, nodal status, presence of distant metastasis and age, patients are assigned to a risk group and treatment decisions are made accordingly.

Patients diagnosed with metastatic disease will receive a more intense chemotherapeutic regimen compared to patients with local disease. Evidence of regional lymph node involvement defined as those appropriate to the primary tumor site are not classified as patients with metastatic tumors. However, when nodal involvement beyond the regional lymph nodes has been identified the patient should be treated according to a protocol for metastatic disease. An example of regional lymph node involvement is the involvement of inguinal nodes in a patient with a tumor located in the leg. In this case, iliac or peri-aortic lymph nodes are classified as distant metastases.

Alternative test(s)

One disadvantage of ^{18}F-FDG-PET/CT, especially in children, is the radiation exposure when multiple follow-up scans are indicated. This radiation burden can be reduced when PET/MRI is being used instead (Partovi 2014). The value of PET/MRI for diagnosis, staging follow-up and therapy assessment for different pediatric malignancies needs to be further evaluated and is not in the scope of this review. Another alternative could be the

use of whole body MRI including diffusion-weighted imaging, this technique has shown to be a potential alternative for ^{18}F-FDG- PET/CT in pediatric lymphoma (Littooij 2014).

Rationale

One of the aims of the current treatment protocols is to identify patients with a good prognosis so that they are not overtreated, and to make sure that patients with a poorer prognosis receive a more aggressive treatment regimen to obtain the best overall survival with the lowest late effects of treatment. The main risk stratification systems used at the moment to allocate treatment include site, size of the primary tumor, IRS post-surgical stage, age at diagnosis, nodal status and presence of distant metastases (Crist 2001; NCT00354835; NCT00379457; Oberlin 2008; Sultan 2010).

One of the disadvantages of the current workup at diagnosis is that many different imaging modalities are being used and often anesthesia is needed. Another disadvantage of the currently employed imaging modalities is that metastases could be located outside the field of view of the imaging technique used.

^{18}F-FDG-PET/CT is increasingly used in the diagnostic and staging process of sarcoma, including RMS. ^{18}F-FDG-PET/CT may have sufficient sensitivity and specificity to identify bone and bone marrow metastases, lung metastases and lymph node involvement. This might lead to adequate stratification of patients with RMS, and subsequently to application of adequate treatment intensity, duration and modalities, with the advantage of using the ^{18}F-FDG-PET/CT as a single diagnostic test for detection of metastases.
The objective of this Cochrane review was to systematically assess all diagnostic accuracy data on the use of ^{18}F-FDG-PET/CT in the diagnostic and staging process of patients with RMS at first diagnosis to detect metastases, in order to assess the efficacy of this method in the diagnostic workup.

Objectives

To determine the diagnostic accuracy of ^{18}F-FDG-PET/CT imaging for detecting lymph node involvement and bone and lung metastases in rhabdomyosarcoma patients at first diagnosis.

METHODS

Criteria for considering studies for this review

Types of studies

Prospective or retrospective cross-sectional studies that report the diagnostic accuracy of ^{18}F-FDG-PET/CT in diagnosing bone metastases, lung metastases or lymph node in-

volvement or a combination of these metastases in patients with confirmed RMS were eligible for inclusion. Studies needed to compare the results of the ^{18}F-FDG-PET/CT imaging with the tests described as reference standards (as described below). Figure 1 shows the general criteria used for considering studies for this review. Studies needed to report sufficient data to construct (part of) a 2×2 table, so the absolute number of true positives, false positives, true negatives, false negatives, or a combination of these had

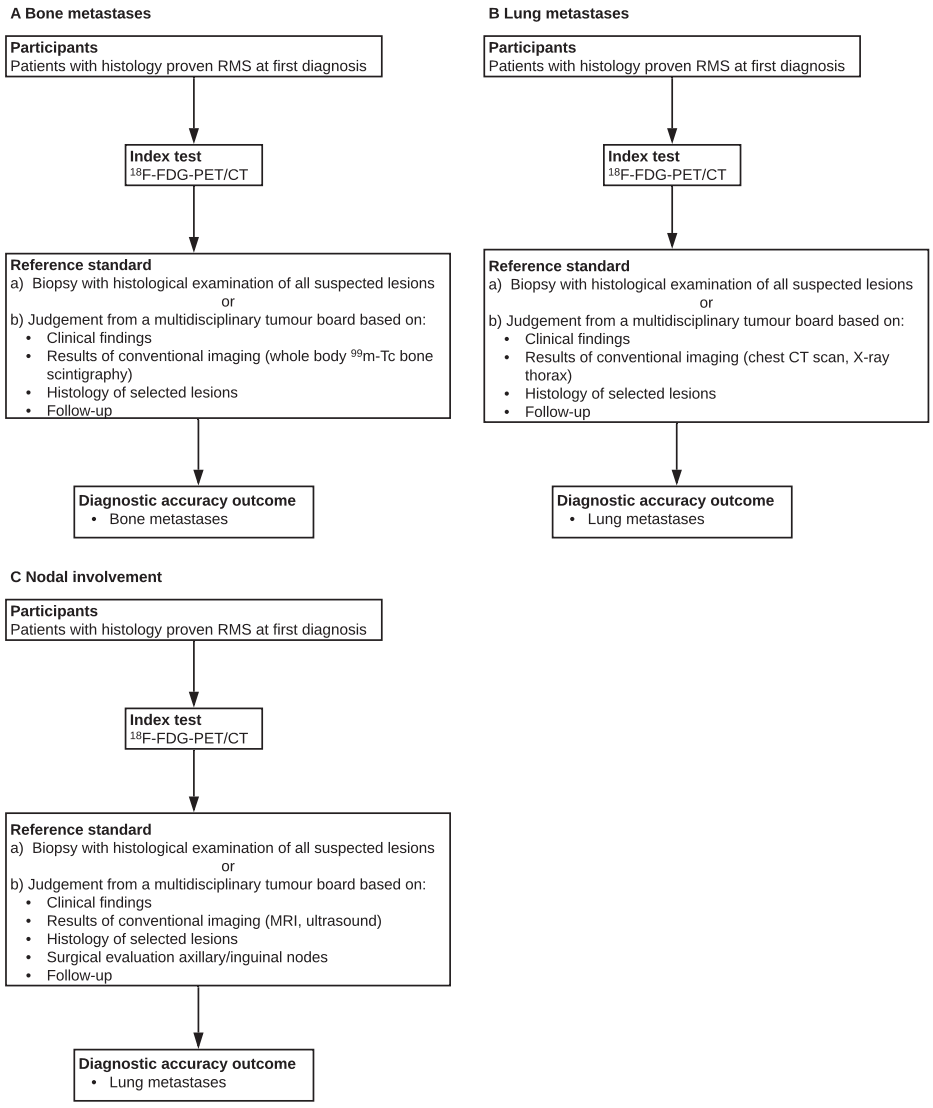

Figure 1. Criteria used to define eligible studies for this review. ^{18}F-FDG-PET/CT: fluorine-18-fluorodeoxyglucose - positron emission tomography/computed tomography; CT: computed tomography; MRI: magnetic resonance imaging; RMS: rhabdomyosarcoma.

to be available from the data in the primary studies or to be obtained from authors to reassess sensitivity and specificity. We excluded review articles, editorials or letters and case reports.

Participants

Patients with histologically confirmed RMS of any stage at first diagnosis. We included studies with patients who were not eligible for this review (such as patients with recurrence of RMS or other sarcoma types) if data for only the eligible participants were available.

Index tests

^{18}F-FDG-PET/CT scans.

Target conditions

Newly diagnosed RMS with:

- bone metastases;
- lung metastases;
- nodal involvement;
- any combination of the above.

Reference standards

The most optimal reference standard for suspected distant metastases and lymph node involvement in RMS patients would be confirmation by histopathology obtained by biopsy. For both ethical and practical reasons, this cannot be done for every suspected lesion.

When biopsy results were not available, the results of the ^{18}F-FDG-PET/CT should be compared with the judgement from a multidisciplinary tumor board, where experts have the knowledge of a patient's clinical findings, results from conventional imaging and histological data. Clinical follow-up and imaging follow-up could also be used to support the final diagnosis of nodal involvement, and bone and lung metastases (see Figure 1). In general, after nine weeks of chemotherapy, tumor response was evaluated with imaging including an X-ray of the thorax.

- Bone and bone marrow involvement

A whole body ^{99m}Tc bone scintigraphy and bilateral bone marrow aspirates and trephine biopsies is performed to identify bone metastases and bone marrow involvement. When possible, in case of doubt a biopsy is performed.

- Lung metastases

Lung metastases are detected by chest CT scan of diagnostic quality. In most patients, an X-ray of the thorax was also performed. Pulmonary metastatic disease was defined as one or more pulmonary nodules of 10 mm or more of diameter or two or more well-defined nodules of 5 mm to 10 mm diameter, in the absence of another medical explanation. In case of doubt or 5 or more small (less than 5 mm) nodules, a multidisciplinary tumor board decides whether a biopsy was indicated to confirm the diagnosis.

- Nodal involvement

The presence of loco-regional nodal involvement was evaluated using MRI and ultrasound. In case of doubt, a biopsy was performed. In addition to such conventional imaging modalities, for upper and lower limb tumors, it was highly recommended to have surgical evaluation of axillary (for upper limb tumors) or inguinal (for lower limb tumors) nodes, even if nodes were clinically or radiological normal.

Search methods for identification of studies

Cochrane Childhood Cancer ran the searches in MEDLINE and EMBASE; all other searches were run by the review authors. We did not impose language restrictions. Searches will be updated every two years.

Electronic searches

We searched two electronic databases: MEDLINE in PubMed (from 1966 to 26-11-2018) and EMBASE in Ovid (from 1980 to 26-11-2018). Appendix 1 and Appendix 2 show the search strategies for the different electronic databases (using a combination of controlled vocabulary and text words).

Searching other resources

We located information about studies not indexed in MEDLINE and EMBASE, either published or unpublished, by hand searching the reference lists of relevant articles and review articles. The review authors also contacted the authors of the included studies and other experts in the field of RMS for information about any ongoing or unpublished studies. The review authors also scanned conference proceedings electronically if available and otherwise by handsearching; we searched the International Society for Paediatric Oncology (SIOP), the American Society of Pediatric Hematology/Oncology (ASPHO), the Connective Tissue Oncology Society (CTOS), the American Society of Clinical oncology (ASCO) and the European Musculo-Skeletal Oncology Society (EMSOS) (2014 till 2018). In EMBASE, we used the search fields conference publication (cg) and conference information (cf) in combination with Emtree terms and text words as mentioned in Appendix 2.

Data collection and analysis

Selection of studies

After employing the search strategy described previously, two review authors independently identified studies meeting the inclusion criteria. We obtained in full text any study that seemed to meet the inclusion criteria on the grounds of title, abstract or both. Two review authors independently undertook full-text article screening. Study selection was done by using the data management platform Covidence.

Only full-text studies that fulfilled all predefined criteria for considering studies for this review were eligible for inclusion. We clearly stated reasons for exclusion of any study considered for the review. Disagreements during both initial selection and definite selection were resolved by consensus. If this was impossible, we achieved final resolution using a third-party arbitrator. We included a flow chart of the selection of studies in the review.

Data extraction and management

Two review authors independently performed data extraction using a predefined data extraction form. We extracted data on the following items:

- Article author, year of publication (or presentation), journal (or conference);
- Study population: age at diagnosis, sex, histology (ARMS/ ERMS), fusion status (PAX3/7-FOXO1), primary tumor site, IRS group (I, II, III), nodal status, metastasis status (bone, lung, other), number of participants (including number eligible for the study, number enrolled in the study, number receiving the index test and reference standard, number for whom results are reported in the 2×2 table, reasons for withdrawal);
- Index test: ^{18}F-FDG-PET/CT scan including the system and protocol used and the definition of an ^{18}F-FDG-PET/CT positive lesion. Interpretation blinded to reference standards;
- Conventional imaging modalities used (MRI, CT, or both of the primary site, chest CT-scan, chest X-ray, radionucleotide bone scan, craniospinal MRI, ultrasound abdomen, CT and or MRI abdomen);
- Reference standard: description of the reference standard used. Verification of findings by: biopsy of suspected lesions or judgement by an interdisciplinary tumor board (based on combination of clinical findings, results from conventional imaging, additional biopsy and follow-up;
- Study design: basic design of the study (prospective cohort or historical cohort with data collection based on medical records or case-control study), time span between index test and reference test, treatment between index test and reference test;

- Data for the 2×2 table: true positive, false positive, true negative and false negative rates or, if not available, relevant parameters (sensitivity, specificity or predictive values) to reconstruct the 2×2 table.

We piloted the data extraction form using two studies. There was a high concordance between the review authors, therefore we concluded that the form could be used for all studies.

When data were missing in a published report, we attempted to contact the authors for the missing information. In case of disagreement, we re-examined the abstracts and articles and undertook discussion until we achieved consensus. If not possible, we achieved final resolution using a third-party arbitrator.

Assessment of methodological quality

Two review authors independently assessed each included study for methodological quality. For this, we adapted a four-domain tool from QUADAS-2 (Whiting 2011). We adapted this tool to our review; it comprised the following domains;

- Participant selection;
- Index test;
- Reference standard;
- Flow of participants through the study and timing of both the index text and reference standard (flow and timing).

For each domain, we classified the risk of bias and concerns about the applicability of study findings as low, high or unclear. See Table 1 (see additional tables).

For example, in domain 'Participant selection', we evaluated whether a consecutive or random enrolment of participants had taken place. Some studies may have performed ^{18}F-FDG-PET/CT solely in participants with unclear results obtained with standard tests, which could be a potential bias. We resolved discrepancies between review authors by consensus. If this was not possible, we sought final resolution using a third-party arbitrator.

We presented the methodological quality in the text, a graph and tables.

Statistical analysis and data synthesis

We performed a participant-based analysis of the data. We analyzed data of the three separate outcomes (lung and bone metastases and nodal involvement) separately. We used the data from the 2×2 tables (consisting of true positives, false positives, true negatives and false negatives) to calculate sensitivity and specificity for each study and each test. We generated a paired forest plot showing estimates of sensitivity and specificity together with 95% confidence intervals. Such a forest plot provides a visual impression

of the precision by which sensitivity and specificity have been measured in each study as well as an indication of the amount of variability in these parameters across studies.

Investigations of heterogeneity

When assessing study results, we considered methodological and clinical sources of heterogeneity as well as variation in the criteria used to define a positive test result. Anticipated sources of heterogeneity include ^{18}F-FDG-PET/CT protocol (e.g. FDG dose), participant population (e.g. percentage of alveolar histology) and reference standard (biopsy confirmed or not).

Sensitivity analyses

We did not perform sensitivity analyses since we did not perform formal meta-analyses.

Assessment of reporting bias

We undertook no formal assessment of reporting bias. However, we highlighted the possibility of reporting bias and interpreted the results of any analysis cautiously.

Results

Results of the search

The electronic search was performed on the 26th of November 2018. The electronic database searches identified a total of 2094 records. After removal of duplicates, 1936 records were screened on title and abstract (see Figure 2). We excluded 1876 references after screening of titles and abstracts for the following reasons: studies were review articles, editorials or letters, or case reports, studies on animals, studies not performed in patients with newly diagnosed rhabdomyosarcoma. We evaluated 60 studies in full-text of which 2 studies fulfilled the inclusion criteria. We excluded 50 studies after assessing the full-text study for reasons described in Characteristics of excluded studies table. For 8 studies we needed additional information to determine whether they could be included in this review. The reasons are described in Characteristics of studies awaiting classification table.

Included studies

The characteristics of the included studies are summarized in the Characteristics of included studies table and in table 2 (see additional tables). Both included studies were single center retrospective cohort studies. One study performed in France (Eugene 2012) included patients with histologically proven RMS, with a median age at diagnosis of 8.7 years. In total 23 patients were included. Patients underwent an MRI of the primary tumor, chest CT and ^{99m}Tc bone scintigraphy and an ^{18}F-FDG-PET/CT as staging investiga-

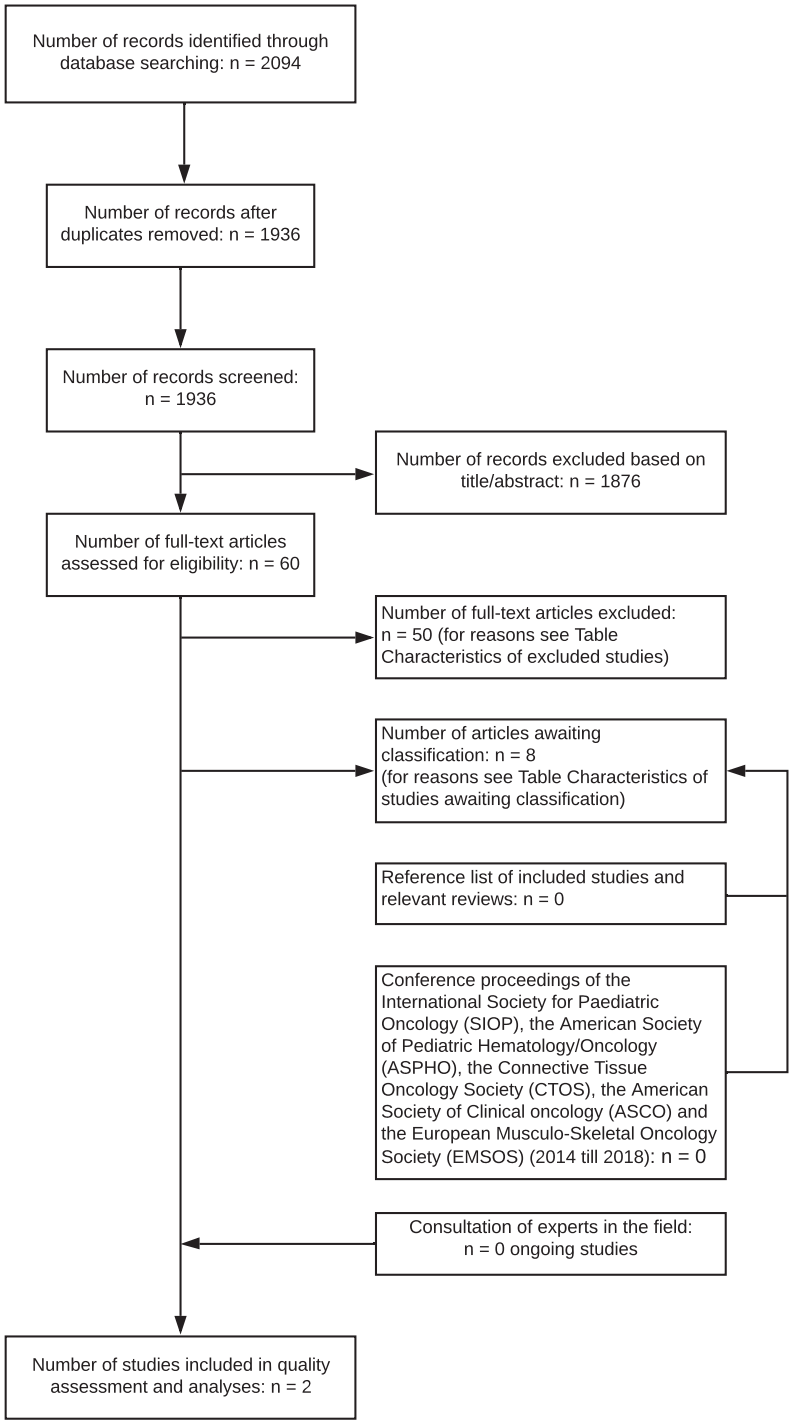

Figure 2. Flow diagram

tions. All images retrieved by conventional imaging modalities were reviewed by two reviewers blinded for results of ^{18}F-FDG- PET/CT. All ^{18}F-FDG-PET/CT images were reviewed by two experienced readers blinded for results of conventional imaging modalities.

The other study (Ricard 2011) was also performed in France and included patients with histologically proven RMS, with a median age at diagnosis of 9.6 years. In total 13 patients were included. The included patients underwent an MRI of the primary tumor, chest CT and 99mTc bone scintigraphy, except for one patients in whom only a chest CT and abdominal ultrasound were performed. All images retrieved by conventional imaging modalities were reviewed by two nuclear physicians and a radiologist blinded for results of ^{18}F-FDG-PET/CT. All ^{18}F-FDG-PET/CT images were analyzed by two nuclear medicine physicians blinded for results of conventional imaging modalities.

In both studies (Eugene 2012; Ricard 2011), histology was used as reference standard if available, and in case histologic confirmation was not obtained, the results of the multidisciplinary tumor board served as reference standard.

All included participants underwent an ^{18}F-FDG-PET/CT at initial diagnosis. The interval between conventional imaging and ^{18}F-FDG-PET/CT was less than 15 days in the study of Ricard 2011. The time interval between conventional imaging and ^{18}F-FDG-PET/CT was not reported in the study of Eugene 2012. The administered dose of ^{18}F-FDG varied from 3-7 MBq/kg, and images were acquired 60-80 minutes after intravenous injection of ^{18}F-FDG. Ricard 2011 described that the ^{18}F-FDG-PET/CT was from head to upper thigh; a whole body CT (head to toes) was only performed in case the primary tumor was located in the extremities. In the study of Eugene 2012 it was described that whole body ^{18}F-FDG-PET/CT was performed, however the field of view was not further specified. The study of Ricard 2011 did not present a definition of a positive ^{18}F-FDG-PET/CT lesion. Eugene 2012 defined a positive ^{18}F-FDG-PET/CT lesion as abnormal ^{18}F-FDG uptake greater than that of surrounding (adjacent) tissue without a known physiologic explanation. The interpretation of ^{18}F-FDG-PET/CT imaging was done by two experienced observers in both studies (Eugene 2012; Ricard 2011).

Excluded studies

We excluded 50 studies (see Characteristics of excluded studies table) for the following reasons: 22 studies used a wrong study design, 8 studies were not diagnostic studies, 7 studies were review articles, 6 studies did not or only included one patient with RMS, 5 studies were conference proceedings of which the full study was also evaluated for inclusion, 1 study was a duplicate publication (in French, primary publication in English excluded because of wrong study design), 1 study included patients that were also included in another publication.

Methodological quality of included studies

The quality assessments of the included studies can be found in the Characteristics of included studies table. Figure 3 and Figure 4 give an overview of the quality assessment according to the adapted QUADAS-2 tool.

In summary, the selection of patients in both studies introduced a low risk of selection bias, and the included patients and settings were judged applicable to the review question.

Eugene 2012 reported a clear definition and cut-off of a positive lesion on FDG PET/CT whereas this was not reported in the study of Ricard 2011. This might have introduced bias and resulted in applicability concerns and problems regarding reproducibility.

Reference standard in both studies was comparable, however in the study of Ricard 2011 1 of 13 patients did not undergo all staging imaging tests and therefore risk of bias was considered high for the reference standard domain, which also raised applicability concerns. Risk of bias regarding flow and timing was considered low for Ricard 2011, whereas in the study of Eugene 2012 the time between index test and reference test was not reported and potential bias was therefore scored as 'unclear'.

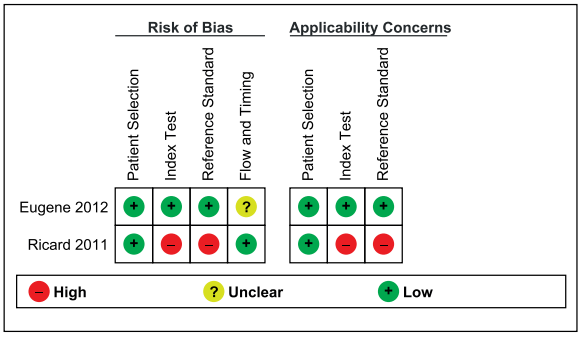

Figure 3 Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study.

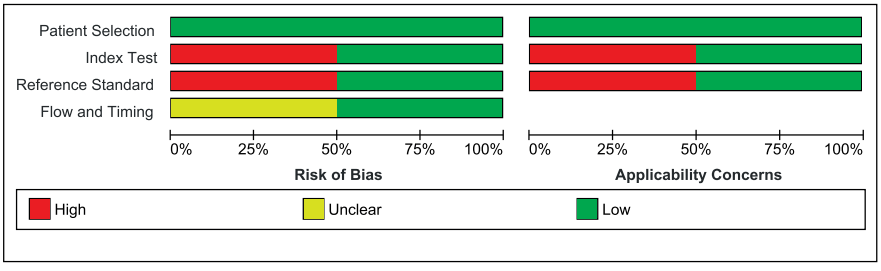

Figure 4. Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies.

Findings

Because of the scarcity of data and heterogeneity between the included studies, a formal meta- analysis of diagnostic accuracy was not considered relevant. We were able to estimate the sensitivity and specificity of ^{18}F-FDG-PET/CT using data from all included study participants (n=36 in total) and for all our pre-defined accuracy outcomes, except sensitivity for lung metastases that was not estimable in Eugene 2012 since no patients had lung metastases; see Figure 5.

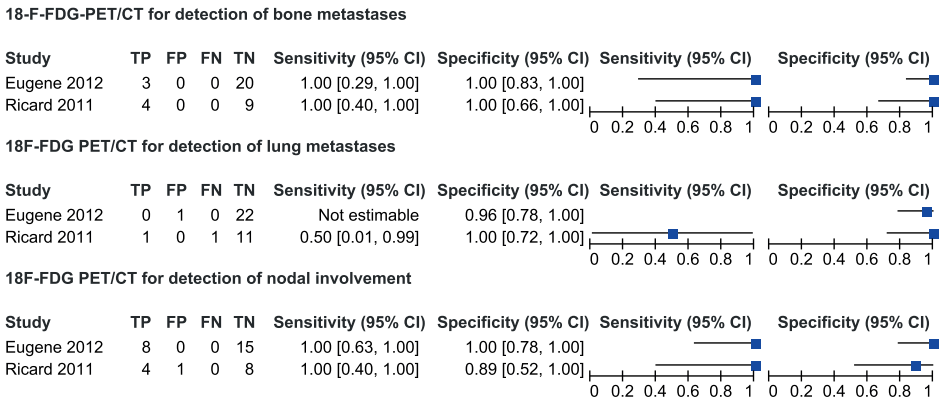

Figure 5. Forest plot for the accuracy of ^{18}F-FDG-PET/CT for detection of bone metastases, lung metastases, and nodal involvement.

Bone metastases

The diagnostic accuracy of ^{18}F-FDG-PET/CT for the detection of bone metastases was reported in both studies (Eugene 2012, Ricard 2011). In total, 7 out of 36 participants were considered to have bone metastases at presentation. The reported sensitivity and specificity was 100% (95%- CI for sensitivity was 29-100% in Eugene 2012 and 40-100% in Ricard 2011, 95%-CI for specificity was 83-100% for Eugene 2012 and 66-100% for Ricard 2011) in both studies.

Lung metastases

The diagnostic accuracy of ^{18}F-FDG-PET/CT for the detection of lung metastases was reported in both studies (Eugene 2012, Ricard 2011). In total, 2 out of 36 patients were considered to have lung metastases at presentation. Patients included in Eugene 2012 did not have lung metastases, therefore sensitivity could not be estimated. Sensitivity for the detection of lung metastases was 50% (95%-CI: 1-99%) in Ricard 2011. Reported specificity was 96% (95%-CI was 78-100%) in Eugene 2012 and 100% (95%-CI: 72-100%) in Ricard 2011.

Nodal involvement

The diagnostic accuracy of ^{18}F-FDG-PET/CT for the detection of nodal involvement was reported in both studies (Eugene 2012, Ricard 2011). In total, 12 out of 36 patients were diagnosed with nodal involvement at presentation. The reported sensitivity in both studies was 100% (95%-CI was 63% to 100% in Eugene 2012, and 40% to 100% in Ricard 2011). The reported specificity was 100% (95%-CI: 78-100%) in Eugene 2012, and 89% (95%-CI: 52-100%) for Ricard 2011.

Discussion

Summary of main results

In this Cochrane DTA review we assessed the diagnostic accuracy of ^{18}F-FDG-PET/CT for the detection of bone metastases and lung metastases and lymph node involvement in RMS at first diagnosis. Only two small studies fulfilled all our inclusion criteria, which impeded formal meta-analysis of accuracy outcomes. Across these two studies we report the sensitivity and specificity of ^{18}F-FDG-PET/CT:

- The sensitivity and specificity of ^{18}F-FDG-PET/CT for the detection of bone metastases, determined in 36 patients included in 2 studies, was 100% (Figure 5; Summary of findings table).
- The sensitivity of ^{18}F-FDG-PET/CT for the detection of lung metastases, determined in 13 patients was 50% (one study). Specificity in the two included studies ranged from 96% to 100% (Figure 5; Summary of findings table).
- The sensitivity of ^{18}F-FDG-PET/CT for the detection of lymph node involvement, determined in 36 patients included in two studies was 100%. Specificity in the included studies ranged from 89% to 100% (Figure 5; Summary of findings table)

Strengths and weaknesses of the review

The results of this review provide a clear overview of the current available evidence regarding the accuracy of ^{18}F-FDG-PET/CT for the detection of bone and lung metastases and lymph node involvement in newly diagnosed RMS. Two review authors independently identified studies and extracted the data, according to the protocol of this review (Breunis 2016).

Reference standard

The most optimal reference standard for suspected distant metastases and lymph node involvement in patients with RMS is histopathologic confirmation by biopsy. However, this cannot be done for every suspected lesion. Therefore, we also included studies in which, when biopsy results were not available, the results of ^{18}F-FDG-PET/CT were compared with the judgement from multidisciplinary tumor boards, together with clinical

follow-up and imaging follow-up. For this review we considered this as the reference standard because this reflects clinical practice.

We excluded several studies reporting on the diagnostic accuracy of ^{18}F-FDG-PET/CT in patients with RMS, because they just compared results of ^{18}F-FDG-PET/CT with conventional imaging, which was not in the scope of this review. This resulted in a very limited number of included studies.

Scarcity of the available evidence

The most important limitation of this review was the lack of available data. We identified only 2 studies, encompassing 36 participants, which impeded performing any meta-analysis. Therefore, the results of this review should be interpreted with great caution.

All included studies were retrospective single center studies, including a maximum of 23 participants per study. Due to these small numbers and because the number of participants with metastatic disease was even lower, one ^{18}F-FDG-PET/CT scan more or less scored as false negative would have had a large impact on sensitivity. The lowest sensitivity estimate for ^{18}F-FDG-PET/CT was reported by Ricard 2011 for the detection of lung metastases, but this was only based on one patient identified as true positive and one patient identified as false negative. The inclusion of a small number of participants might also explain the differences in participant characteristics between participants included in the study of Ricard 2011 (13 patients included) and larger series on RMS, such as Weiss 2013 (n=1687). The majority of patients in the study of Ricard 2011 (77%) had alveolar RMS whereas this was 35% in Weiss 2013.

The included studies reported a surprisingly high percentage of patients with bone metastases (7/36 patients [19%]), whereas this was 5% in Weiss 2013, suggesting potential selection bias in the studies we included.

In this review we performed a participant-based analysis of the accuracy of ^{18}F-FDG-PET/CT for the detection of lymph node involvement and bone and lung metastases, because one positive metastatic lesion is enough to classify patients as having metastatic disease. However, reported sensitivity using participant-based data is probably higher than expected for a lesion-based analysis. Moreover, accurate classification of all metastatic lesions is necessary to apply adequate local therapy regimens.

Eligibility of studies awaiting classification

We were not able to assess the eligibility for inclusion in this review of 13 studies. We tried to contact the study authors to obtain additional information, but were unsuccessful. The impact of this issue on the outcomes of this review is unclear, however it is uncertain whether these studies would have fulfilled the inclusion criteria for this review.

Applicability of findings to the review question

The findings of this review show the paucity of evidence regarding the diagnostic accuracy of ^{18}F-FDG-PET/CT for the detection of bone and lung metastases and lymph node involvement in newly diagnosed RMS. Findings of this review are applicable to patients with newly diagnosed RMS only. Based on the available evidence we could not reliably determine the accuracy of ^{18}F-FDG-PET/CT in the detection of bone and lung metastases and lymph node involvement in RMS.

Authors conclusions

Implications for practice

Based on the available evidence from two included studies we conclude that there is insufficient evidence to reliably determine the diagnostic accuracy of ^{18}F-FDG-PET/CT in the detection of bone and lung metastases and lymph node involvement in newly diagnosed patients with RMS. For clinical practice this implies that ^{18}F-FDG-PET/CT could not replace all other staging investigations as a single diagnostic test for metastases at the moment.

Although we could not determine the diagnostic accuracy of ^{18}F-FDG-PET/CT in RMS, ^{18}F-FDG- PET/CT is extensively used in staging investigations for newly diagnosed patients with RMS. In current treatment protocols ^{18}F-FDG-PET/CT has replaced ^{99m}Tc bone scintigraphy for the detection of bone metastases. The results on the accuracy of ^{18}F-FDG-PET/CT to detect bone metastases are promising, since the included studies in this review reported a 100% sensitivity and 89 to 100% specificity of ^{18}F-FDG-PET/CT to detect bone metastases, however larger prospective studies on the accuracy of ^{18}F-FDG-PET/CT are needed to confirm these findings. Implications for research

Larger series evaluating the diagnostic accuracy of ^{18}F-FDG-PET/CT for the detection of bone and lung metastases and lymph node involvement in patients with newly diagnosed RMS are necessary. Such studies might prove challenging to undertake, or even unethical, because RMS mainly affects young children, and because ^{18}F-FDG-PET/CT is already established in the initial workup of patients with RMS in state-of-the-art study protocols (for example, NCT00379457). A prospective study comparing the diagnostic accuracy of ^{18}F-FDG-PET/CT to whole body ^{99m}Tc bone scintigraphy is not expected, because this would lead to additional radiation exposure.

Besides the use of ^{18}F-FDG-PET/CT for the detection of lymph node involvement and bone and lung metastases, we expect that future studies will also focus on the use of PET/MRI techniques because of limited radiation doses (Partovi 2014). This technique is relatively new and needs to be evaluated in pediatric malignancies. Furthermore, future studies should evaluate the addition of diffusion-weighted imaging to whole body MRI as a potential alternative to ^{18}F-FDG- PET for the staging of paediatric RMS, as was previously shown in pediatric lymphoma (Littooij 2014).

Summary of findings for the main comparison

Objective: Diagnostic accuracy of ^{18}F-FDG-PET/CT for the detection of bone and lung metastases and lymph node involvement in newly diagnosed rhabdomyosarcoma.

Patients/population:	**Patients with histology proven RMS at first diagnosis**
Index test:	^{18}F-FDG-PET/CT
Reference standard:	Biopsy with histological examination of all suspected lesions or if not available judgement from a multidisciplinary tumor board based on: Clinical findings, results of conventional imaging (i.e. whole body ^{99m}-Tc skeleton scintigraphy, chest CT scan, X-ray thorax, MRI, ultrasound), histology of selected lesions, follow-up
Studies	Prospective or retrospective cross-sectional studies, 2 in total (number of participants enrolled: 36)

Subgroup	**Sensitivity**	**Specificity**	**Number of patients with event/ Total number of participants**
Bone metastases	100%	100%	7/36
Lung metastases	50%¥	Range: 96%-100%	2/36
Nodal involvement	100%	Range: 89%-100%	12/36

¥ Sensitivity of lung metastases only reported in the study of Ricard 2011. In the study of Eugene 2012 none of the patients had lung metastases.

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Differences between study protocol and review

- We intended to perform formal meta-analysis with meta-regression and sensitivity analyses, but the studies were too heterogeneous and data was limited so we considered this not useful.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies

Eugene 2012

Study characteristics	
Patient sampling	Inclusion period: 2003-2010 Patient population: All children treated for histologically proven RMS at University Hospital of Nantes Consecutive or random sample: Consecutive patients who underwent a whole-body ^{18}F-FDGPET/CT before therapy initiation
Patient characteristics and setting	Retrospective cohort study In total 23 patients were included Diagnostic work up: Conventional imaging (Chest radiograph, CT or MRI of primary site, bone scan), and bone marrow biopsy Median age at diagnosis: 8.7 years, range: 9 months to 21.6 years Sex distribution: 16 males (70%), 7 females (30%) Histology: ARMS: n=9 (39%), ERMS: n=13 (57%), Botryoid RMS: n=1 (4%) Primary tumor site: orbit, n=5 (22%); parameningeal, n=5 (22%); head/neck nonparameningeal, n=2 (9%); genito-urinary bladder prostate, n=4 (17%); limbs, n=5 (22%); other, n=1 (4%); unknown, n=1 (4%)
Index tests	Whole-body ^{18}F-FDG-PET/CT images were acquired using a Discovery LS PET/CT imaging system (GE Medical systems) or mCT Biograph imaging system (Siemens) Intravenous injection of 5-7 MBq/kg of ^{18}F-FDG Or Intravenous injection 3 MBq/kg ^{18}F-FDG 60-80 minutes before imaging Children fasted for at least 4 hour before ^{18}F-FDG injection and blood glucose level controlled before injection. Images evaluated in consensus by two experienced readers Positive test result: Abnormal uptake greater than that of surrounding background not explained by normal organ uptake
Target condition and reference standard(s)	Target condition: Newly diagnosed histologically proven RMS Reference standard: The results of conventional imaging modalities and ^{18}F-FDG-PET/CT were finally verified by an interdisciplinary tumor board. All staging examinations, histopathology of biopsies and resected specimens, and clinical data including the serial follow-up examinations were used
Flow and timing	All patients receive the same reference standard Time between index test and reference standard not described No treatment between index test and reference standard
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test (^{18}F-FDG-PET/CT)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Did the study provide a clear definition of what was considered to be a positive test result?	Yes		
Were uninterpretable/ intermediate test results reported?	Unclear		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Was the delay between the performance of the ^{18}F-FDGPET/CT and the reference standard less than 2 weeks?	Unclear		
		Unclear	

Ricard 2011

Study characteristics	
Patient sampling	Inclusion period: September 2004-March 2009 Patient population: Patients aged 1-20 years at diagnosis of histologically proven RMS Consecutive or random sample: Consecutive patients who underwent staging with conventional imaging and ^{18}F-FDG-PET/CT before systemic therapy.
Patient characteristics and setting	Retrospective cohort study In total 13 patients included Diagnostic work-up: Conventional imaging (MRI for the primary tumor, chest CT, bone scan) Median age at diagnosis: 9.6 years, range: 1.8-19.1 years Sex distribution: 12 males (92%), 1 female (8%) Histology: ARMS: n=10 (77%), ERMS: n=3 (23%) Tumor site: Parameningeal, n=2 (15%); head/neck nonparameningeal, n=4 (31%); genito- urinary, n=3 (23%); limbs, n=4 (31%)
Index tests	^{18}F-FDG-PET/CT images were acquired on a Philips Gemini PET/CT system after intravenous injection of 5MBq/kg of FDG. Images were acquired approximately 60minutes after tracer injection Head-to upper thigh CT scan, only whole-body if RMS located in the extremity Analyzed by 2 nuclear medicine physicians blinded to results of CI. SUVmax was measured in positive primary lesions. Positive test result: Not specified
Target condition and reference standard(s)	Target condition: Newly diagnosed histologically proven RMS Reference standard: When CI and ^{18}F-FDG-PET/CT produced discordant results, patient's histologic data and final clinical evaluation of the multidisciplinary tumor board were considered as the reference standard
Flow and timing	One patient only underwent chest CT and abdominal ultrasound, but was included in the 2x2 table Time between index test and reference standard: <15 days No treatment between index test and reference standard
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test (^{18}F-FDG-PET/CT)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
Did the study provide a clear definition of what was considered to be a positive test result?	No		
Were uninterpretable/ intermediate test results reported?	Unclear		
		High	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	No		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		High	**High**
DOMAIN 4: Flow and Timing			
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Was the delay between the performance of the 18F- FDGPET/CT and the reference standard less than 2 weeks?	Yes		
		Low	

Characteristics of excluded studies

Study	Reason for exclusion
Andersen 2015	No patients with rhabdomyosarcoma
Arush 2007	Wrong study design: PET CT performed at time of relapse
Baek 2015	Study was not primary diagnostic
Bar-Sever 2007	Wrong study design: Compared FDG-PET-CT to FDG-PET
Baum 2010	Study was not primary diagnostic
Becher 2015	No original research: review
Bentancourt 2016	Wrong study design; no comparison described
Brisse 2009	No original research: review
Ceyssens 2011	No original research: review
Charest 2009	Wrong study design; only focused on diagnostic accuracy of primary tumor
Daldrup-Link 2001	Wrong study design; no FDG-PET/CT performed
Dong 2017	Wrong study design; compared FDG-PET to conventional imaging
Elkholy 2017	Wrong study design; compared FDG-PET to conventional imaging
Eugene 2010a	Duplicate publication of Eugene 2012; primary study included
Federico 2012	Conference proceeding; full report evaluated
Federico 2013	Wrong study design; one study investigator compared results between CI and FDG-PET
Fuglo 2012	Wrong study design; compared FDG-PET to conventional imaging No separate results for patients with RMS
Gambhir 2016	Study was not primary diagnostic
Gupta 2015	Wrong study design: Compared FDG-PET-CT to FDG/PET
Hagi 2018	No patients with rhabdomyosarcoma
Iagaru 2006	Wrong study design: Compared FDG-PET to CT
Iagaru 2006a	Wrong study design; compared FDG-PET to conventional imaging No separate results for patients with RMS
Kleis 2009	Wrong study design; compared FDG-PET to conventional imaging No separate results for patients with RMS
Klem 2007	Wrong study design; no FDG-PET-CT performed
Kumar 2008	Wrong study design; compared FDG-PET to conventional imaging No separate results for patients with RMS
Locantore 2013	Wrong study design; compared FDG-PET to conventional imaging
Ma 2015	Conference proceeding, full report Dong 2015
Macpherson 2018	Wrong study design; compared FDG-PET to conventional imaging
Massardo 2012	Only included 1 patient with rhabdomyosarcoma at time of diagnosis
McCarville 2005	No original research: review
McCarville 2011	Conference proceeding, full report included Federico 2013
Mody 2010	Only included 1 patient with rhabdomyosarcoma
Murphy 2008	No original research: review
Piperkova 2009	Wrong study design: Compared accuracy of PET and CT separately
Reichert 2004	No patients with rhabdomyosarcoma
Ricard 2010	Conference proceeding, full report included Ricard 2011
Sciuto 2014	Study was not primary diagnostic

Characteristics of excluded studies (continued)

Study	Reason for exclusion
Sheikhbahaei 2015	No original research: review
Shin 2008	No patients with rhabdomyosarcoma
Singhal 2014	Wrong study design; reference standard was bilateral bone marrow biopsy only
Sorschag 2011	Study was not primary diagnostic
Tabachhi 2016	No original research: review
Tateishi 2007	Partly same population as Tateishi 2009
Tateishi 2009	Wrong study design; compared FDG-PET to conventional imaging Unclear how many patients with RMS underwent FDG-PET/CT at staging
Terwisscha 2015	Study was not primary diagnostic
Turpin 2016	Study was not primary diagnostic
Volker 2007	Wrong study design; no FDG-PET/CT performed
Wagner 2017	Study was not primary diagnostic
Zapata 2015	Conference proceeding, full report evaluated
Zapata 2018	Wrong study design; reference standard was bilateral bone marrow biopsy only

Characteristics of studies awaiting classification

De Ferrater 2013

Study characteristics	
Patient sampling	Inclusion period: June 2006-December 2012 Patient population: Pediatric patients with head-neck malignancies excluding lymphoma Consecutive or random sample: Consecutive patients who received a ^{18}F-FDG-PET/CT at diagnosis, during therapy or at end of therapy
Patient characteristics and setting	Retrospective cohort study In total 31 patients were included: - Rhabdomyosarcoma n=9 - Bone sarcoma n=8 - Nasopharyngeal carcinoma n=5 - Other histology n=8 Diagnostic work-up: Conventional imaging (CT, MRI, ultrasound, bone scan) 161 scans were performed; 21 during staging, 42 during therapy and 98 at end of treatment Number of patients with rhabdomyosarcoma and ^{18}F-FDG-PET/CT at diagnosis was not reported
Index tests	^{18}F-FDG-PET/CT; information on tracer not reported, imaging protocol not reported Information on interpreter and positive lesions of ^{18}F-FDG-PET/CT not provided
Target condition and reference standard(s)	Target condition: Pediatric patients with head-neck malignancies excluding lymphoma Reference standard: histopathology and/or clinical follow-up, not further specified.
Flow and timing	Time between index test and reference standard not described Treatment between index test and reference standard not described
Comparative	18F-FDG-PET/CT had higher sensitivity and specificity compared to conventional imaging in staging at initial diagnosis, not further specified for RMS only
Notes	This study has not been reported in full-text upon: July 2019 No separate results for patients with RMS available. Unclear if this study used histology or multidisciplinary tumor board as reference standard. We could not get in contact with study authors via: mariaboronat@gmail.com

Mazurek 2011

Study characteristics	
Patient sampling	Inclusion period: not described Patient population: Children with various types of sarcomas 22 patients were included Consecutive or random sample: unclear
Patient characteristics and setting	Cohort study not reported whether study was prospective or retrospective In total 22 patients included; Diagnostic work-up: not reported 22 patients underwent ^{18}F-FDG-PET/CT for staging at diagnosis
Index tests	^{18}F-FDG-PET/CT; images were acquired using a 16-row PET-scanner, using 0,21 mCi/kg ^{18}F-FDG Images acquired 60 minutes after tracer injection. Area of interest not reported Information on interpreter and positive lesions not reported
Target condition and reference standard(s)	Target condition: children with various types of sarcomas ^{18}F-FDG-PET/CT findings were compared with other imaging studies and with histopathology if available
Flow and timing	Time between index test and reference standard not described Treatment between index test and reference standard not described
Comparative	Sensitivity or specificity not described. No results reported for RMS separately.
Notes	This study has not been reported in full-text upon: July 2019 No separate results for patients with RMS available. Unclear if this study used histology or multidisciplinary tumor board as reference standard. Contact information of the study authors not available

Nguyen 2011

Study characteristics	
Patient sampling	Inclusion period: 2003-2010 Patient population: Patients with various types of sarcoma 48 patients were included Consecutive or random sample: consecutive
Patient characteristics and setting	Retrospective cohort study 48 patients were included: - Rhabdomyosarcoma, n=14 Diagnostic work-up; all included patients underwent an ^{18}F-FDG-PET/CT and ^{99}Tc-Bone scintigraphy, other diagnostic work-up not reported 48 patients underwent ^{18}F-FDG-PET/CT
Index tests	^{18}F-FDG-PET/CT; information on tracer not reported, imaging protocol not reported Information on interpreter and positive lesions of ^{18}F-FDG-PET/CT not provided
Target condition and reference standard(s)	Target condition: patients with various types of sarcoma, ^{18}F-FDG-PET/CT findings were compared with ^{99}Tc-Bone scintigraphy, no gold standard described
Flow and timing	Time between index test and reference standard; within 3 months Treatment between index test and reference standard not described
Comparative	No results reported for RMS separately.
Notes	This study has not been reported in full-text upon: July 2019 No separate results for patients with RMS available. Unclear if this study used histology or multidisciplinary tumor board as reference standard. Contact information of the study authors; Not available.

Oguz 2013

Study characteristics	
Patient sampling	Inclusion period: 1991-2013 Patient population: Pediatric patients with solid tumors outside CNS with ^{18}F-FDG-PET/CT at diagnosis 73 patients were included Consecutive or random sample: Consecutive
Patient characteristics and setting	Retrospective cohort study 73 patients were included: - Soft tissue sarcoma n=8 58 patients underwent ^{18}F-FDG-PET/CT for staging at initial diagnosis
Index tests	^{18}F-FDG-PET/CT information on tracer not reported, imaging protocol not reported Information on interpreter and positive lesions of ^{18}F-FDG-PET/CT not provided
Target condition and reference standard(s)	Target condition: patients with solid tumors outside CNS Reference standard not reported
Flow and timing	Time between index test and reference standard; not reported Treatment between index test and reference standard not described
Comparative	No results reported for RMS separately.
Notes	This study has not been reported in full-text upon: July 2019 No separate results for patients with RMS available. Unclear how many RMS patients are included, if any. Unclear if this study used histology or multidisciplinary tumor board as reference standard. Contact information of the study authors; Not available.

Riad 2010

Study characteristics	
Patient sampling	Inclusion period: Not reported Patient population: Pediatric patients with histologically proven head & neck cancer Consecutive or random sample: Consecutive
Patient characteristics and setting	Retrospective cohort study 36 patients were included: - Rhabdomyosarcoma n=9 9 patients underwent ^{18}F-FDG-PET/CT for staging at initial diagnosis, unclear if these patients had RMS
Index tests	^{18}F-FDG-PET/CT information on tracer not reported, imaging protocol not reported ^{18}F-FDG-PET/CT images were reviewed by 3 nuclear medicine specialists Information on positive lesions of ^{18}F-FDG-PET/CT not provided
Target condition and reference standard(s)	Target condition: patients with histologically proven head & neck cancer Reference standard: not reported
Flow and timing	Time between index test and reference standard; not reported Treatment between index test and reference standard not described
Comparative	No results reported for RMS separately.
Notes	This study has not been reported in full-text upon: July 2019 No separate results for patients with RMS available. Unclear how many RMS patients underwent ^{18}F-FDG-PET/CT at diagnosis, if any. Unclear if this study used histology or multidisciplinary tumor board as reference standard. Contact information of the study authors; Not available.

Sourabh 2010

Study characteristics	
Patient sampling	Inclusion period: August 2007-May 2010 Patient population: Patients with bone and soft tissue sarcoma Consecutive or random sample: Consecutive
Patient characteristics and setting	Retrospective cohort study 47 patients with bone and soft tissue sarcoma were included: Histological subtype not specified 14 patients underwent a ^{18}F-FDG-PET/CT for staging at initial diagnosis
Index tests	^{18}F-FDG-PET/CT information on tracer not reported, imaging protocol not reported ^{18}F-FDG-PET/CT images were reviewed by 3 nuclear medicine specialists Information on positive lesions of ^{18}F-FDG-PET/CT not provided
Target condition and reference standard(s)	Target condition: patients with histologically proven head & neck cancer Reference standard: not reported
Flow and timing	Time between index test and reference standard; not reported Treatment between index test and reference standard not described
Comparative	No results reported for RMS separately.
Notes	This study has not been reported in full-text upon: July 2019 No separate results for patients with RMS available. Unclear how many RMS patients underwent ^{18}F-FDG-PET/CT at diagnosis, if any. Unclear if this study used histology or multidisciplinary tumor board as reference standard. Contact information of the study authors; Not available.

Tuncel 2015

Study characteristics	
Patient sampling	Inclusion period: December 2011-March 2015 Patient population: Pediatric patients with soft tissue sarcoma 23 patients were included Consecutive or random sample: consecutive
Patient characteristics and setting	Cohort study, not reported whether retrospective or prospective 23 patients were included: - Rhabdomyosarcoma, n=17 Diagnostic work-up: not reported 9 patients underwent a ^{18}F-FDG-PET/CT for staging
Index tests	^{18}F-FDG-PET/CT; information on tracer not reported, imaging protocol not reported Information on interpreter and positive lesions of ^{18}F-FDG-PET/CT not provided
Target condition and reference standard(s)	Target condition: pediatric patients with soft tissue sarcoma Reference standard: not reported
Flow and timing	Time between index test and reference standard; not reported Treatment between index test and reference standard not described
Comparative	No separate data for ^{18}F-FDG-PET/CT at initial diagnosis in RMS reported
Notes	This study has not been reported in full-text upon: July 2019 No separate results for patients with RMS available. Unclear how many RMS patients underwent ^{18}F-FDG-PET/CT at diagnosis. Unclear if this study used histology or multidisciplinary tumor board as reference standard. Contact information of the study authors; Not available.

Walter 2012

Study characteristics	
Patient sampling	Inclusion period: January 2005-February 2005 Patient population: Pediatric patients with sarcoma 29 patients were included Consecutive or random sample: consecutive
Patient characteristics and setting	Retrospective cohort study, assessing the diagnostic accuracy of ^{99m}-Tc-bone scintigraphy, ^{18}F-FDG-PET/CT and the combination for the assessment of bone involvement 29 patients were included: - Rhabdomyosarcoma, n=4 Diagnostic work-up: ^{99m}-Tc-bone scintigraphy, ^{18}F-FDG-PET/CT 10 patients underwent ^{18}F-FDG-PET/CT for staging
Index tests	^{18}F-FDG-PET/CT was acquired using, 0.15 mCi/kg of ^{18}F-FDG. Images were acquired 60 minutes after tracer injection Area of interest: whole body ^{18}F-FDG-PET/CT images were reviewed by one nuclear medicine specialist and one pediatric radiologist Positive lesions: Readers graded it as benign, likely benign, equivocal, likely malignant or malignant
Target condition and reference standard(s)	Target condition: Pediatric patients with sarcoma Reference standard: defined by the follow-up results including clinical, imaging results, and/or biopsy, discussed in multidisciplinary discussion.
Flow and timing	Time between index test and reference standard: median 4 days ± 7 days Treatment between index test and reference standard: not reported
Comparative	No separate data for ^{18}F-FDG-PET/CT at initial diagnosis in RMS reported
Notes	No separate results for patients with RMS available. Unclear how many RMS patients underwent ^{18}F-FDG-PET/CT at diagnosis. Unclear if this study used histology or multidisciplinary tumor board as reference standard. We could not get in contact with the study authors, via nfederman@mednet.ucla.edu

ADDITIONAL TABLES

Table 1. Items of the adapted QUADAS-2 tool and risk of bias and level of concerns about applicability

Domain 1: participant selection	
Was a consecutive or random sample of participants enrolled?	'Yes' if a consecutive or random sample of participants was enrolled 'No' if enrolled participants did not form a consecutive or random series 'Unclear' if the study did not describe the method of participant's enrolment
Was a case-control design avoided?	'Yes' if the study did not use a case-control design 'No' if the study used a case-control design 'Unclear' if the study did not report enough information to ascertain whether a case-control design was used
Did the study describe exclusion criteria and were inappropriate exclusions avoided?	Yes' if the characteristics of the participants were well described and inappropriate exclusions were avoided 'No' if participants were included that meet the exclusion criteria or inappropriate exclusions were not avoided 'Unclear' if the source or characteristics of participants was not adequately described
Could the selection of participants have introduced bias?	**Low risk** if 'yes' to all signaling questions **High risk** if 'no' to any of the signaling questions **Unclear risk** if there was insufficient information to judge the risk of bias
Is there concern that the included participants and setting do not match the review question?	A judgement of **low**, **high**, **unclear** concerns about applicability will be based on the question if the exclusion criteria were well described and appropriate and how closely the sample matches the target population of interest **Low concern** if answer was 'yes' on the third signaling question and study population matched the target population **High concern** if answer was 'no' on the third signaling question and the study populations did not match the target population **Unclear concern** if there was insufficient information to judge
Domain 2: index test (^{18}F-FDG-PET/CT)	
Were the results of the ^{18}F-FDG-PET/CT interpreted without knowledge of the results of the reference standard?	'Yes' if the report stated that the person undertaking the index test did not know the results of the reference test 'No' if the report stated that the same person performed both tests or that the results of the reference tests were known to the person undertaking the index tests 'Unclear' if insufficient information was provided
If an SUV or lesion size threshold was used, was it pre-specified?	'Yes' if pre-specified 'No' if not pre-specified or the authors selected the optimal cut-off value based on the results of the study 'Unclear' if there was a range of cut-off values and there was doubt which cut-off was used or if no cut-off value was mentioned in the report
Did the study provide a clear definition of what was considered to be a positive test result?	'Yes' if the definition of a positive result was clearly stated (e.g. SUV) 'No' if no definition of what was considered a positive result was stated or the definition of a positive result varied between the participants 'Unclear' if not enough information was given to make a judgement
Were uninterpretable/ intermediate test results reported?	'Yes' if it was clear that all information on uninterpretable and intermediate results was reported 'No' if uninterpretable results occurred but were not reported in detail 'Uncertain' if it was not clear whether all test results were reported
Could the conduct or interpretation of the ^{18}F- FDG-PET/CT have introduced bias?	**Low risk** if 'yes' to all signaling questions **High risk** if 'no' to any of the signaling questions **Unclear risk** if there was insufficient information to judge the risk of bias
Are there concerns that the ^{18}F-FDG-PET/CT its conduct, or interpretation differs from the review question?	**Low concern** if 'yes' to all signaling questions **High concern** if the definition of a positive test result was not clear formulated or if more than 1 signaling question was answered by 'no' **Unclear concern** if there was insufficient data to judge

Domain 3: reference standard	
Is the reference standard likely to correctly identify distant metastasis?	'Yes' if the correct conventional imaging modality was used (e.g. CT thorax for lung metastases, whole body ^{99m}-Tc skeleton scintigraphy for bone metastases and MRI/ultrasound for nodal involvement) in combination with histological confirmation or confirmation by a tumor board opinion 'No' if the conventional imaging modality was not supported by histological confirmation or confirmation by a tumor board opinion. 'Unclear' if it was not reported what reference standard was used exactly
Were the results of the reference standard interpreted with blinding of the results of the ^{18}F-FDG-PET/CT?	'Yes' if the report stated that the person who was interpreting the reference test results did not know the results of the ^{18}F-FDG-PET/CT 'No' if the report stated that the ^{18}F-FDG-PET/CT results were known to the person who was interpreting the reference tests results 'Unclear' if it was not reported whether blinding of the tests results took place
Could the reference standard, its conduct or its interpretation have introduced bias?	**Low risk** if 'yes' to all signaling questions **High risk** if 'no' to any of the signaling questions **Unclear risk** if there was insufficient information to judge the risk of bias
Is there concern that the target condition as defined by the reference standard do not match the review question?	**Low concern** for identification of the primary tumor as the reference standard defined, this will always be confirmed by histopathology. For lymph node involvement and distant metastases, histological confirmation will not always be available **High concern** when the study did not report how false negative and false positive results were obtained
Domain 4: flow and timing	
Did all participants receive the same reference standard?	'Yes' if the same reference test was used in all included participants regardless of the index tests results 'No' if different reference tests were used to verify the disease status, depending on the results of the index test 'Unclear' if there was insufficient information whether different reference standards were used
Were all participants included in the analysis?	'Yes' if there were no participants excluded from the analysis, or if exclusions were adequately described 'No' if there were participants excluded from the analysis and there was no explanation given 'Unclear' if there was insufficient information whether all participants were included in the analysis
Was the delay between the performance of the ^{18}F-FDG-PET/CT and the reference standard less than 2 weeks?	'Yes' if the period between ^{18}F-FDG-PET/CT and the reference standard was less than 2 weeks and no treatment was started 'No' if the period between ^{18}F-FDG-PET/CT and the reference standard was more than 2 weeks or treatment was already started 'Unclear' if there was insufficient information about the time period between tests
Could the participant flow have introduced bias?	**Low risk** if 'yes' to all signaling questions **High risk** if 'no' to any of the signaling questions **Unclear risk** if there was insufficient information to judge the risk of bias

^{18}F-FDG-PET/CT: fluorine-18-fluorodeoxyglucose - positron emission tomography/computed tomography; CT: computed tomography; MRI: magnetic resonance imaging; SUV: standardized uptake value.

Table 2 Summary of patient characteristics

	Eugene 2012 (n=23)	Ricard 2011 (n=13)
Median age at diagnosis	8.7	9.6
(years)	range: 0.8-21.6	range: 1.8-19.1
Sex		
Male	16 (70%)	12 (92%)
Female	7 (30%)	1 (8%)
Histology		
Embryonal	13 (57%)	3 (23%)
Alveolar	9 (39%)	10 (77%)
Spindle cell	-	-
Botryoid RMS	1 (4%)	-
Mixed histology	-	-
RMS NOS	-	-
Primary tumor site		
Orbit	5 (22%)	-
Head-neck non parameningeal	2 (9%)	4 (31%)
Parameningeal	5 (22%)	2 (15%)
GU-bladder/prostate	4 (17%)	3 (23%)
GU-non bladder/prostate	-	-
Extremity	5 (22%)	4 (31%)
Other	1 (4%)	-
Primary site unknown	1 (4%)	-
Post-surgical staging *	Not reported	
IRS I		4 (31%)
IRS II		1 (8%)
IRS III		2 (15%)
IRS IV		6 (46%)

* IRS I = primary complete resection (R0); IRS II = microscopic residual (R1) or primary complete resection but N1; IRS III = macroscopic residual (R2); IRS IV = Distant metastatic disease present at onset

APPENDICES

Appendix 1. Search strategy for MEDLINE/PubMed

1. For **rhabdomyosarcoma**, we used the following MeSH headings and text words: rhabdomyosarcom* OR rhabdomyosarcoma OR rhabdomyosarcomas OR embryonal rhabdomyosarcom* OR embryonal rhabdomyosarcoma OR embryonal rhabdomyosarcomas OR rhabdomyosarcomas, embryonal OR alveolar rhabdomyosarcom* OR alveolar rhabdomyosarcoma OR alveolar rhabdomyosarcomas OR rhabdomyosarcomas, alveolar OR myosarcom* OR myosarcoma OR myosarcomas OR soft tissue sarcom* OR soft tissue sarcoma[tiab] OR soft tissue sarcomas[tiab] OR botryoid sarcoma[tiab]
2. For **^{18}-F-FDG-PET/CT scan**, we used the following MeSH headings and text words: Positron Emission Tomography[mh] OR Positron Emission Tomography[tiab] OR Positron Emission Tomograph* OR PET Scan OR PET Scans OR PET Scan* OR PET OR SPECT OR SPECT-CT OR tomography, emission-computed, single- photon[mh] OR Single Photon Emission Computed Tomography[tiab] OR Single photon emission computerized tomography[tiab] OR Single photon emission computerised tomography[tiab] OR Single Photon Emission Computed Radionuclide Tomography[tiab] OR Single Photon Emission CT Scan[tiab] OR Single Photon Emission CAT scan[tiab] OR Single Photon Emission Computer Assisted Tomography[tiab] OR Single Photon Emission Computed Radionuclide Tomograph* OR Single Photon Emission CT Scan*OR Single Photon Emission CAT scan* OR Single Photon Emission Computer Assisted Tomograph* OR Single Photon Emission Computed Tomograph* OR Single photon emission computerized tomograph* OR Single photon emission computerised tomograph* OR 18F-FDG- PET-CT OR 18 F-FDG-PET OR 18-fluorodeoxy* OR 18fluorodeoxy* OR fdgpet OR fdg pet OR 18f fdg* OR fluorodeoxyglucose f18
   Final search (1 AND 2) NOT (case reports OR case report)
   * = zero or more characters

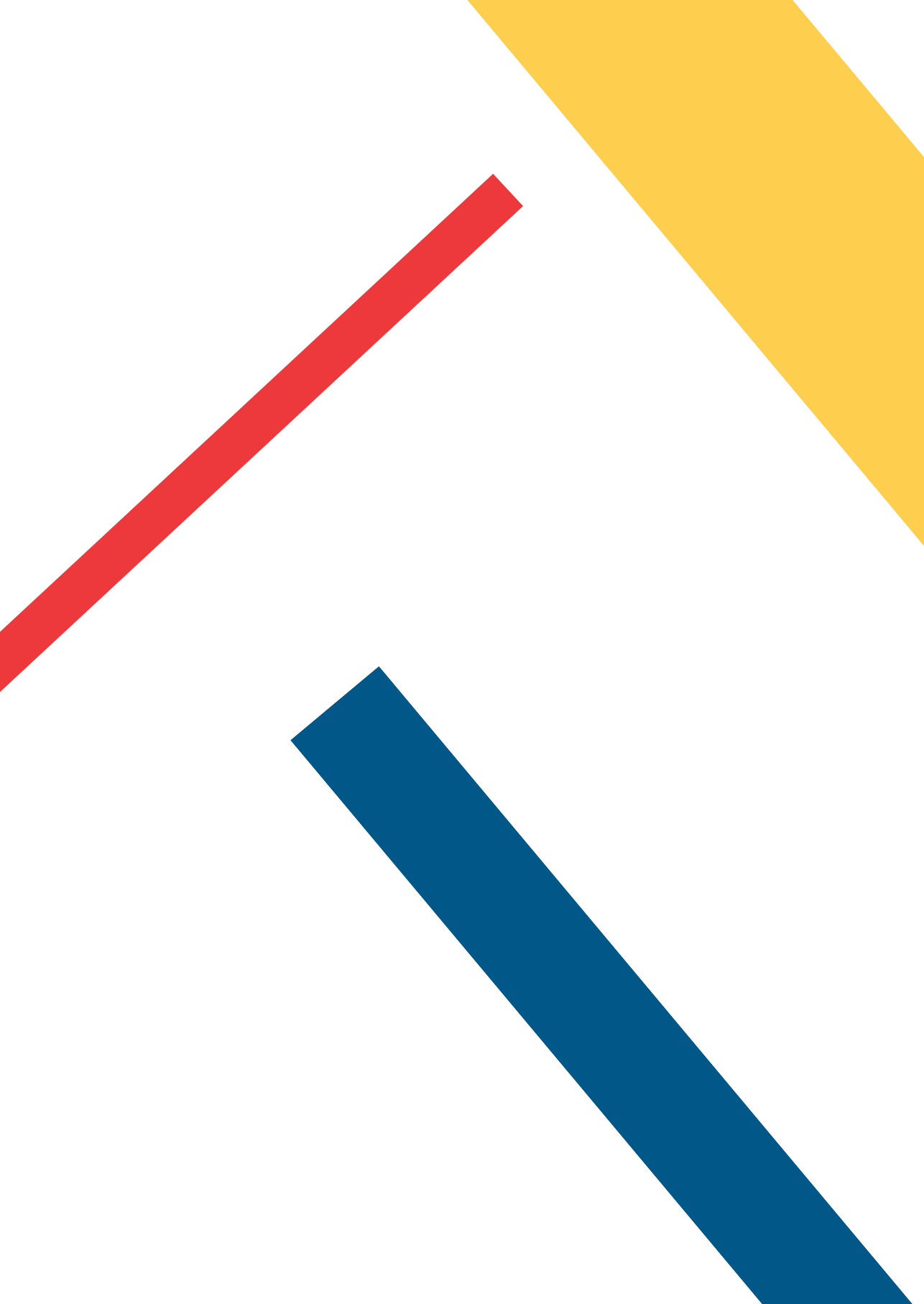
Appendix 2. Search strategy for EMBASE (Ovid)

1. For **rhabdomyosarcoma**, we used the following Emtree terms and text words:
   1. Rhabdomyosarcoma/ or embryonal rhabdomyosarcoma/
   2. Soft Tissue Sarcoma/ or myosarcoma/
   3. (myosarcom$ or myosarcoma or myosarcomas or soft tissue sarcom$ or soft tissue sarcoma or soft tissue sarcomas).mp.
   4. (rhabdomyosarcom$ or rhabdomyosarcoma or rhabdomyosarcomas).mp.
   5. (embryonal rhabdomyosarcom$ or embryonal rhabdomyosarcoma or embryonal rhabdomyosarcomas or embryo rhabdomyosarcoma).mp.

6. (alveolar rhabdomyosarcom$ or alveolar rhabdomyosarcoma or alveolar rhabdomyosarcomas or alveolus-like rhabdomyosarcoma).mp.
7. botryoid sarcoma.mp. 8. or/1-7

2. For **^{18}F-FDG-PET/CT scan**, we used the following Emtree terms and text words:
   1. exp positron emission tomography/ or exp fluorodeoxyglucose f18/
   2. (positron emission tomography or positron emission tomograph$).mp.
   3. (PET scan or PET scans or PET scan$ or PET).mp.
   4. (SPECT or SPECT-CT or 18F-FDG-PET-CT).mp.
   5. exp single photon emission computer tomography/
   6. (single photon emission computed tomography or single photon emission computed tomograph$ or single photon emission computerized tomography or single photon emission computerised tomography).mp.
   7. (Single photon emission computerized tomograph$ or Single photon emission computerised tomograph$).mp.
   8. (single photon emission computed radionuclide tomography or single photon emission computed radionuclide tomograph$).mp.
   9. (Single Photon Emission CT Scan or Single Photon Emission CT Scan$).mp.
   10. (Single Photon Emission CAT scan or Single Photon Emission CAT scan$).mp.
   11. (Single Photon Emission Computer Assisted Tomography or Single Photon Emission Computer Assisted Tomograph$).mp.
   12. (18 F-FDG-PET or 18-fluorodeoxy$ or 18fluorodeoxy$ or fdg pet or fdgpet or 18f fdg or 18ffdg or fluorodeoxyglucose f18).mp.
   13. or/1-12

Final search was (1 AND 2) NOT (case reports OR case report)
mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name; /= Emtree term; $=zero or more characters



CHAPTER 4

PROGNOSTIC RELEVANCE OF EARLY RADIOLOGIC RESPONSE TO INDUCTION CHEMOTHERAPY IN PEDIATRIC RHABDOMYOSARCOMA A REPORT FROM THE INTERNATIONAL SOCIETY OF PEDIATRIC ONCOLOGY MMT-95 STUDY

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ABSTRACT

Background

Early response to induction chemotherapy is used in current European guidelines to evaluate the efficacy of chemotherapy and subsequently to adapt treatment in pediatric patients with rhabdomyosarcoma (RMS). However, existing literature on the prognostic value of early radiologic response on survival is contradictory; here the prognostic value is analyzed with data from the International Society of Pediatric Oncology (SIOP) Malignant Mesenchymal Tumor 95 (MMT-95) study.

Methods

This study examined 432 Intergroup Rhabdomyosarcoma Study Grouping III (macroscopic residue) patients enrolled in the SIOP MMT-95 study with a response assessment after 3 courses of chemotherapy (a 2-dimensional assessment). Patients with progressive disease (PD) after 3 courses of chemotherapy were excluded (n=7). Failure-free survival (FFS) and overall survival (OS), calculated with the Kaplan-Meier method, were compared for 3 groups (complete response [CR]/partial response [PR], objective response [OR], and no response [NR]). The prognostic impact of early response was assessed through the calculation of Cox proportional hazards.

Results

After 3 courses of chemotherapy, 85.2% of the patients had CR/PR, 8.6% had OR, and 6.3% had NR. For all patients, the 5-year FFS and OS rates were 60% (95% confidence interval [CI], 56%- 65%) and 74% (95% CI, 70%-78%), respectively. However, a Cox proportional hazards regression analysis revealed no significant difference in FFS or OS between the response groups. The adjusted hazard ratios for an OR and NR were 1.09 (95% CI, 0.63-1.88) and 0.81 (95% CI, 0.39-1.67), respectively, for FFS and 0.91 (95% CI, 0.47-1.76) and 1.27 (95% CI, 0.61-2.64), respectively, for OS.

Conclusion

No evidence was found for the idea that early radiologic response to chemotherapy is prognostic for survival for patients with RMS. Treatment adaptation based on early response (except for patients with PD) should, therefore, no longer be incorporated into future studies.

INTRODUCTION

Early response to induction chemotherapy is used as a prognostic factor for several pediatric malignancies, such as Ewing sarcoma, neuroblastoma, and acute lymphoblastic leukemia.[1-3] Under the assumption that early response is also prognostic for outcomes in children with localized rhabdomyosarcoma (RMS), the European Pediatric Soft Tissue Sarcoma Study Group RMS-2005 protocol (recruitment closed in December 2016) required a tumor volume reduction of at least one-third for the continuation of treatment with first-line chemotherapy.[4] Patients with a lesser response were switched to second-line chemotherapy.

However, the prognostic value of early radiologic response was questioned by Burke et al.[5] In an analysis of the Intergroup Rhabdomyosarcoma Study IV (IRS-IV) cohort (1991-1997) based on radiologic response at week 8, no evidence of a difference in failure-free survival (FFS) was found. Rosenberg et al.[6] came to the same conclusion on the basis of an analysis of the data of the Children's Oncology Group (COG) D9803 cohort (1999-2005), in which the radiologic response was assessed at week 12.

Dantonello et al.[7] analyzed the prognostic value of early radiologic response for survival with data for 529 patients with embryonal RMS treated in 5 consecutive German Cooperative Soft Tissue Sarcoma (CWS) trials (1980-2005), and they found no response (NR) to induction chemotherapy to be associated with a poor outcome. However, the latter study, in contrast to the 2 North American studies, included patients with progressive disease (PD) at the first response evaluation.

Because of the ambiguity in the literature and the fact that radiologic response is still used to adapt treatment for pediatric patients in European study protocols, we aimed to evaluate its prognostic value for survival in a cohort of consecutive patients uniformly treated and included in the International Society of Pediatric Oncology (SIOP) Malignant Mesenchymal Tumor 95 (MMT-95) study cohort.

MATERIALS AND METHODS

Patients included in this retrospective analysis were treated in the SIOP MMT-95 trial. This trial, performed in 13 countries between July 1995 and June 2003, comprised 2 parts: a randomized trial for patients with high-risk localized RMS who were 6 months to 18 years old and a registration study standardizing treatment for all other RMS patients who were less than 18 years old. Informed consent was obtained from all parents or patients, or both, according to the research ethics requirements of the individual institution. The outline of the study protocol and the results of the randomized part have been described previously[8;] patients with high-risk nonmetastatic RMS were eligible

for randomization to treatment with either vincristine, ifosfamide, and dactinomycin (IVA) or a 6-drug therapy with IVA plus carboplatin, epirubicin, and etoposide. Standard and high-risk patients in the registration study with an incompletely resected tumor or biopsy only (Intergroup Rhabdomyosarcoma Study Group III [IRSG-III] tumor) received IVA chemotherapy except for patients with nodal involvement or patients younger than 3 years with a parameningeal tumor; these patients were systematically allocated to the 6- drug therapy. All patients received 3 courses of chemotherapy, after which the tumor response was assessed at week 8. The decision on local therapy, by surgery and/or radiotherapy, was based on the response to chemotherapy and the resectability of the residual tumor (delayed surgery). Radiotherapy was delivered after week 17 to patients with an incomplete response after chemotherapy with or without surgery, except for patients aged 3 years or older with parameningeal disease and patients with less than partial response (PR) after 3 courses of 6- drug chemotherapy, who received radiotherapy at week 9, regardless of the response. The recommended dose was 45 Gy, and the target volume was based on the residual tumor volume plus the standard margin except for parameningeal tumors, for which the initial tumor volume was targeted.

The response was assessed with radiologic imaging techniques comparable to those used at diagnosis (computed tomography and/or magnetic resonance imaging) by radiologists at local sites. The tumor response was grouped according to the World Health Organization criteria, which are based on 2-dimensional measurements.[9] A complete response (CR) was defined in the protocol as the complete disappearance of the tumor on radiologic imaging, and PR was defined as a ≥50% decrease in the tumor area and no new lesions. Objective response (OR) was defined as a decrease of 25% to 50%. NR was defined as a <25% decrease and a<25% increase in the tumor area. PD was defined as a ≥25% increase in the tumor area. Because the MMT-95 protocol distinguishes between patients with less or more than PR to determine the necessity of treatment alteration, patients with CR or PR were grouped in a sufficient response (SR) group.

Patients with less than PR (ie, OR, NR, or PD) after 3 courses of IVA were switched to 6-drug chemotherapy, and those with less than PR after 3 courses of 6-drug therapy were further treated off protocol.

Patients were included in this analysis if the diagnosis was confirmed by a central pathology review, the tumor was classified as IRSG-III, and a response assessment was performed after 3 courses of chemotherapy. Patients with PD at the time of the response evaluation were excluded because early tumor progression on therapy is known to be associated with a poor outcome.[10]

Overall survival (OS) was defined as the time from the start of treatment to death from any cause, and FFS was defined as the time from the start of treatment to disease progression, a second malignancy, or death. Outcomes for living patients were censored at the time of their last reported contact.

Statistical Analysis

Data from patients included in the randomized study were combined with data from those who were only registered and received standard treatment because the randomized part of the SIOP MMT-95 study revealed no difference in survival between treatment arms.[8] The 5-year FFS and OS were obtained with Kaplan-Meier estimators.[11] A log-rank test was used to compare the FFS and OS levels between the 3 groups. In addition, the prognostic value of early radiologic response for FFS and OS was further assessed with univariate and multivariate Cox proportional hazards regression analyses. After checking the proportional hazards assumption, we investigated the following variables as potential confounders: histology, size, site, nodal status, age at diagnosis, radiotherapy, and delayed surgery. These variables were chosen on the basis of earlier studies identifying these factors as prognostic for survival for pediatric patients with localized RMS.[12-14] The potential confounders were added one by one to the model. Variables were incorporated into the model if the regression coefficient of the principal determinant, radiologic response, changed more than 10% after the addition of the variable to the model. P values lower than .05 were considered statistically significant.

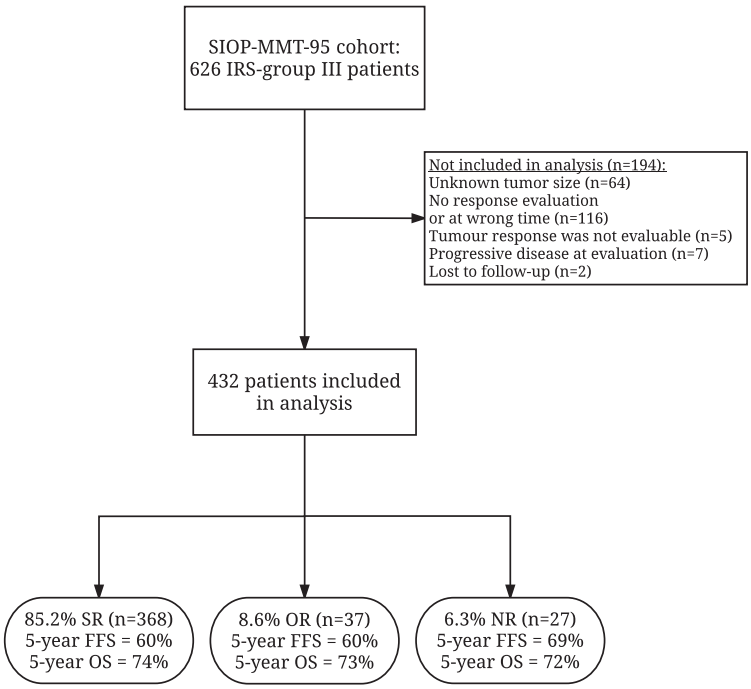

Figure 1. Flow diagram for the current analysis. FFS indicates failure-free survival; IRSG, Intergroup Rhabdomyosarcoma Study Group; MMT-95, Malignant Mesenchymal Tumor 95; NR, no response; OR, objective response; OS, overall survival; SIOP, International Society of Pediatric Oncology; SR, sufficient response.

RESULTS

Patient Population

The MMT-95 cohort contained 626 IRS-III patients, 432 of whom were included in this analysis. The reasons for exclusion are listed in Figure 1. The cohort contained 7 patients with PD at the first response assessment, and they were excluded (2 of the 7 patients died within 5 years). The median age at diagnosis was 5.0 years (range, 0.3-17.8 years), and the median follow-up time for survivors was 99 months (range, 3-198 months). Induction chemotherapy comprised IVA for 232 of the 432 patients (53.7%) and 6-drug chemotherapy for 193 of the 432 patients (44.7%). Patients' characteristics are further described in Table 1 and Supporting Table 1.

Table 1. Patients characteristics (n=432)

	Patients	
Characteristic	**No.**	**%**
Sex		
Male	248	57
Female	184	43
Age		
<10 y	345	80
≥10 y	87	20
Tumor site		
Orbit	59	14
Head and neck	43	10
Parameningeal GU	134	31
bladder/prostate GU	66	15
nonbladder/prostate	26	6
Limbs	47	11
Other	57	13
Histology		
Embryonal	288	67
Alveolar	144	33
Tumor size		
≤5 cm	217	50
>5 cm	215	50
T status		
T1	152	35
T2	272	63
Unknown	8	2
N status		
N0	347	80
N1	71	16
Unknown	14	3

Abbreviations: GU, genitourinary; N0, no evidence of lymph node involvement; N1, evidence for lymph node involvement; T1, tumor confined to organ or tissue of origin; T2, tumor not confined to organ or tissue of origin.

Response Assessment and Treatment Continuation

After 3 courses of chemotherapy, 368 of the 432 patients (85.2%) had SR (CR, 11.1%; PR, 74.1%), 37 of 432 (8.6%) had OR, and 27 of 432 (6.3%) had NR. Of the 64 patients with less than PR, 40 initially received IVA, and 24 initially received 6-drug chemotherapy. Six patients continued treatment with IVA, 57 patients were further treated with 6-drug chemotherapy, and 1 continued treatment according to the preferences of the local institution.

Early Response and Effect on Survival

For all patients, the estimated 5-year FFS and OS rates were 60% (95% confidence interval [CI], 56%-65%) and 74% (95% CI, 70%-78%), respectively. There was no evidence of differences in FFS or OS for randomized and nonrandomized patients (*P* for FFS =.4 and *P* for OS =.9 [log-rank test]). No significant differences were observed in FFS or OS according to early response (Fig. 2A,B). For patients with embryonal histology, the 5-year

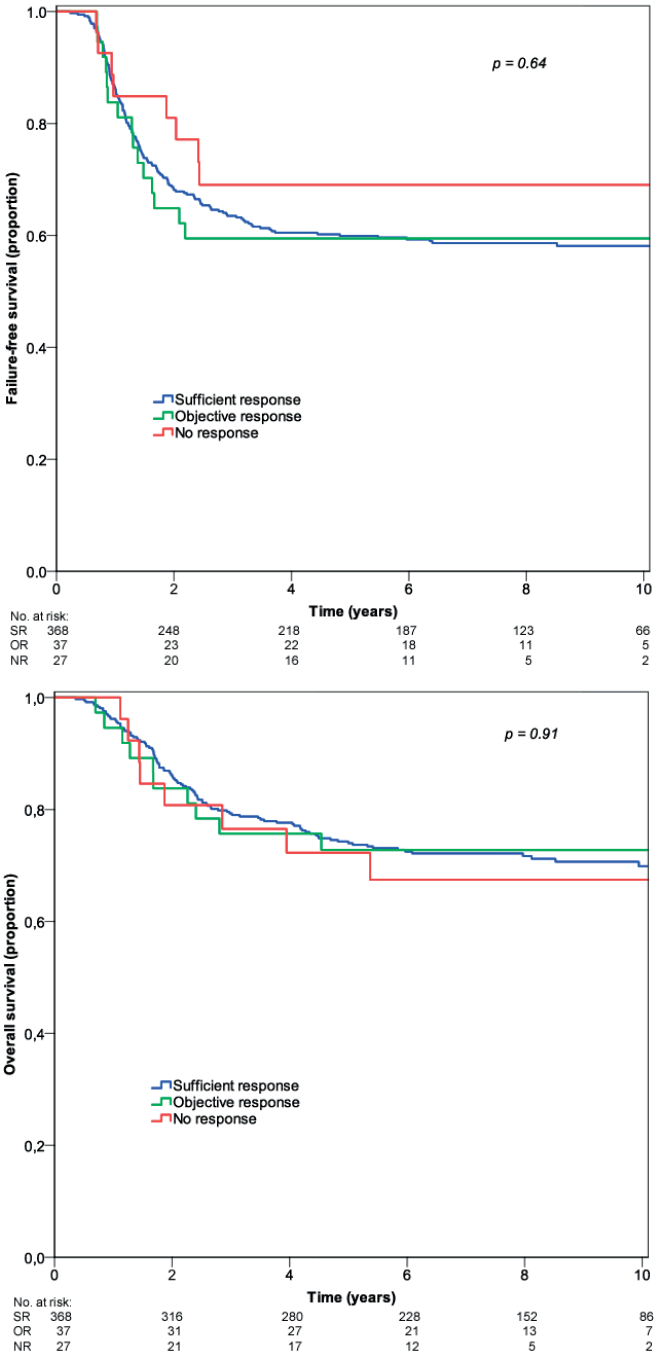

Figure 2. (A) Failure-free survival and (B) overall survival based on an early radiologic response for 432 patients included in SIOP MMT-95. MMT-95 indicates Malignant Mesenchymal Tumor 95; NR, no response; OR, objective response; SIOP, International Society of Pediatric Oncology; SR, sufficient response.

Table 2. Comparison of 5-year FFS and 5-year OS for clinical characteristics based on radiologic response.

	Sufficient response			Objective response			No response			Log-rank test	
	n	5-year FFS, % (95% CI)	5-year OS, % (95% CI)	n	5-year FFS, % (95% CI)	5-year OS, % (95% CI)	n	5-year FFS, % (95% CI)	5-year OS, % (95% CI)	*P* for FFS	*P* for OS
All patients	368	60 (55-65)	74 (69-79)	37	60 (44-75)	73 (58-87)	27	69 (51-87)	72 (55-90)	.6	.9
Age											
<10 y	296	62 (44-80)	75 (71-80)	30	60 (43-77)	70 (53-86)	19	73 (53-93)	73 (53-93)	.6	.9
≥10 y	72	51 (40-63)	68 (57-79)	7	57 (20-94)	86 (60-100)	8	58 (22-95)	69 (32-100)	.9	.5
Tumor site											
Favorable [a]	115	58 (49-67)	82 (75-89)	9	56 (23-88)	89 (68-100)	4	100	100	.3	.6
Unfavorable	253	61 (55-67)	70 (64-76)	28	61 (43-79)	68 (50-85)	23	64 (44-84)	68 (48-87)	.9	.9
Histology											
Embryonal	243	62 (56-68)	76 (71-82)	28	71 (55-88)	86 (73-99)	17	74 (52-96)	79 (47-95)	.4	.5
Alveolar	125	57 (48-65)	69 (61-77)	9	22 (0-49)	33 (10-57)	10	60 (30-90)	60 (30-90)	.1	.07
Tumor size											
≤5cm	192	65 (57-71)	84 (79-89)	13	69 (44-94)	92 (78-100)	12	100	100	.07	.2
>5cm	176	55 (47-62)	63 (55-70)	24	54 (34-74)	62 (42-79)	15	41 (15-68)	48 (21-75)	.8	.4
T status [b]											
T1	131	62 (54-70)	82 (75-88)	12	58 (30-86)	83 (62-100)	9	56 (23-88)	56 (23-88)	.9	.1
T2	230	59 (52-65)	69 (63-75)	25	60 (41-79)	68 (49-86)	17	75 (56-94)	81 (62-100)	.4	.8
N status [c]											
N0	294	60 (55-66)	77 (73-82)	31	61 (44-78)	77 (63-92)	22	71 (51-91)	75 (56-94)	.6	.9
N1	61	63 (49-74)	63 (51-75)	5	40 (0-83)	40 (0-83)	5	60 (17-100)	60 (17-100)	.5	.5
Radiotherapy received											
Yes	231	67 (61-73)	73 (67-78)	25	60 (41-79)	68 (49-86)	19	61 (38-84)	65 (42-88)	.7	.6
No	137	49 (40-57)	76 (69-83)	12	58 (30-86)	83 (62-100)	8	88 (65-100)	88 (65-100)	.1	.5
Post-chemotherapy surgery											
Yes	154	64 (56-71)	72 (65-79)	23	61 (41-81)	78 (61-95)	19	66 (44-88)	66 (43-88)	.9	.6
No	214	57 (51-64)	76 (70-81)	14	57 (31-83)	64 (39-89)	8	75 (45-100)	88 (65-100)	.6	.8

Abbreviations: CI, confidence interval; FFS, failure-free survival; N0, no evidence of lymph node involvement; N1, evidence for lymph node involvement; OS, overall survival; T1, tumor confined to the organ or tissue of origin; T2, tumor not confined to the organ or tissue of origin.

a 'Favorable' is defined as tumors located in the orbit, non-parameningeal head/neck and genito-urinary tract (nonbladder/prostate). b For 8 patients T-status was unknown. c For 14 patients N-status was unknown.

Table 3. Summary of local treatment for survivors (307 of 432 patients).

	Total		Sufficient response		Objective response		No response	
	No	%	No.	%	No.	%	No.	%
All patients	307	100	261	85.0	27	8.8	19	6.2
No local treatment	56	18.2	55	21.1	1	3.7	0	
Local treatment								
Radiotherapy only	114	37.1	100	38.3	8	29.6	6	31.6
Surgery only	60	19.5	44	16.9	9	33.3	7	36.8
Radiotherapy and surgery	77	25.1	62	23.8	9	33.3	6	31.6

FFS rate was 62% (95% CI, 56%-68%) for SR (n=243), 71% (95% CI, 55%-88%) for OR (n=28), and 74% (95% CI, 52%-96%) for NR (n=17). Among patients with alveolar RMS, the 5-year FFS rate was 57% (95% CI, 48%-65%) for SR (n=125), 22% (95% CI, 0%-49%) for OR (n=9), and 60% (95% CI, 30%-90%) for NR (n=10). No significant differences in FFS were observed on the basis of early response in embryonal patients (P=.4 [log-rank test]) or alveolar patients (P=.1 [log-rank test]; Table 2).

A Cox proportional hazards regression analysis did not show early radiologic response as a significant prognostic factor for survival. Unadjusted hazard ratios for OR and NR were 1.01 (95% CI, 0.59-1.71) and 0.71 (95% CI, 0.35-1.45), respectively, for FFS and 0.97 (95% CI, 0.51-1.85) and 1.17 (95% CI, 0.57-2.39), respectively, for OS. Adjusted for histology, tumor size, tumor site, nodal involvement, age, radiotherapy, and post-chemotherapy surgery, the hazard ratios for OR and NR were 1.09 (95% CI, 0.63-1.88) and 0.81 (95% CI, 0.39-1.67), respectively, for FFS and 0.91 (95% CI, 0.47-1.76) and 1.27 (95% CI, 0.61-2.64), respectively, for OS.

Burden of Therapy

The burden of local therapy for the primary tumor in patients who survived is summarized in Table 3. Among the 307 survivors, 137 (44.6%) underwent secondary surgery to obtain local control; 126 patients (92%) had conservative surgery (without important long-term functional/cosmetic consequences), 2 patients (1.6%) had major surgery without functional/cosmetic consequences, and 2 patients (1.6%) had mutilating surgery (both patients had an SR after induction chemotherapy). Further information on surgical margins, radiotherapy fields, and dosages is provided in Supporting Figure 1 and Supporting Tables 3 and 4.

DISCUSSION

The vast majority of IRSG-III RMS patients (>85%) included in the SIOP MMT-95 study showed a very good response (at least PR) to induction chemotherapy; however, in this study, we found no evidence that early radiologic response, in terms of tumor size reduction, was prognostic for survival.

These findings are consistent with 2 consecutive COG studies in which no significant difference in 5-year FFS was observed based on early response.[5,6] In the first analysis by Burke et al[5] of a cohort of 444 consecutive patients with localized RMS who were enrolled in the IRS-IV trial, the 5-year FFS rate was 75% for patients with CR, 71% for patients with PR, and 78% for patients with NR. No significant difference in FFS was observed between the groups (*P*=.57). In a similar analysis performed with data (n=338) from the COG D9803 study[6,] the 5-year FFS rate was 74% for patients with CR, 75% for patients with PR, and 64% for patients with NR; again, no significant difference in FFS was observed between the response groups (*P*=.49).

What could be the reason that early radiologic response did not prove to be prognostic for survival in both COG studies and our study? First, the measurement of the radiologic response is subject to important interobserver and intra-observer variability, as demonstrated in previous studies.[15,16] The interobserver variability could (potentially) lead to different treatment decisions in more than 10% of patients, as observed in a retrospective study by Schoot et al.[17] Second, although some tumor masses do not show radiologic response, there might be other changes in response to therapy, such as the maturation of rhabdomyoblasts. Several small studies have suggested that patients with persistent mature rhabdomyoblasts at the end of therapy do not have an impaired prognosis.[18,19] Furthermore, the radiologic response may not reflect actual tumor necrosis.[20,21]

In contrast to our study, Dantonello et al[7] found early response to induction chemotherapy to be an important prognostic factor for survival in an analysis of data from 529 patients with embryonal RMS treated in 5 consecutive CWS trials (1980-2005). In their study, the authors compared the outcomes of patients with PR and patients with NR; the latter group also included patients with PD. The risk ratio of NR to PR was 2.0 (95% CI, 1.3-3.2). The same conclusion was drawn by Ferrari et al[22] in a retrospective single-center analysis of 108 RMS patients in which a multivariate analysis indicated tumor response to be a significant prognostic factor for survival.

Comparing the results of our study with those of the COG studies and the studies of Dantonello et al[7] and Ferrari et al[22] is difficult because the study populations, initial treatments, measurements of response, definitions of response, and treatments after response assessment all differed. However, in contrast to our study and both COG studies, patients with PD at the time of response assessment were included in the studies of Ferrari et al and Dantonello et al. A study by Minn et al.[10] showed that the prognosis for

patients with PD was poor, and including these patients in the group of patients with a poor response (<33% tumor response) might explain the inferior outcomes for this group. Ferrari et al and Dantonello et al included patients treated over a period of more than 20 years; as a result, the included patients were treated differently, and also cruder imaging methods were used to assess the response to induction chemotherapy. In the study by Ferrari et al, the radiologic response was measured as a continuous variable in contrast to our study and the other mentioned studies, in which the response was assessed categorically. Although measuring tumor response as a continuous variable increases the statistical power, these continuous measurements are not applicable in clinical practice.

In the SIOP MMT-95 study, the radiologic response was measured by the local radiologists, and this possibly confounded our results; a central review of radiologic imaging could lead to more consistent measurements and hence treatment decisions. Moreover, the MMT-95 protocol contained treatment modifications based on the response measurement, and this potentially influenced our results. Although the MMT-95 randomized trial showed no difference in effectiveness between the IVA and 6-drug arms, it might be that the intensified 6-drug chemotherapy was more effective than standard IVA in the patients with less than PR (n=64); however, 29 of 64 patients were not switched to a different treatment regimen.

Besides the modifications to chemotherapy, decisions regarding local treatment were also partly based on the response to chemotherapy[8] Specifically, more patients in favorable subgroups in SIOP MMT studies did not receive radiotherapy in comparison with studies by other collaborative groups, and this treatment strategy potentially confounded our analysis because certain patients, on the basis of the tumor site and the tumor response, did not receive radiotherapy.[23] Nevertheless, we found no significant difference in survival based on the response after we had divided the SR subgroup into patients with CR (patients with CR and a tumor located at specific sites did not receive radiotherapy) and patients with PR (Supporting Table 2).

We realize that historically the reason to switch chemotherapy in patients with less than PR was based not solely on the assumption that response is prognostic for survival but also on the assumption that further reduction in tumor volume might reduce the extent of subsequent local therapy. However, we did not find differences in the number of patients with mutilating surgery or in the radiotherapy dose and targeted area based on the response. The therapeutic decisions concerning radiotherapy fields and dosages (i.e. radiotherapy on the residual tumor vs the initial volume) depended not on the response to chemotherapy but rather on the tumor site; however, a larger residual tumor resulted in a larger radiotherapy field (Supporting Figure 1 and Supporting Table 3).

In conclusion, on the basis of this study and the COG studies, we propose that future phase 3 trials should include a switch in chemotherapy only for patients with PD at early

response assessment. All other patients should continue firstline chemotherapy. We are uncertain whether our findings also apply to phase 2 trials, in which patients generally have relapsed or refractory disease and patterns of tumor response might not be comparable with the response seen in previously chemotherapy-naive patients. Nevertheless, all phase 3 trials conducted by SIOPMMT or COG, adding a promising chemotherapeutic agent to standard backbone therapy yielded no improvement in survival in comparison with standard therapy.[8,12,24,25]

Therefore, we advocate that future phase 3 trials focus on the efficacy of functional imaging techniques, such as diffusion-weighted magnetic resonance imaging and fludeoxyglucose positron emission tomography, to determine early response, although preliminary results are conflicting.[20,26-29] Furthermore, for consistency and standardization of response measurements and subsequent treatment decisions, we emphasize the importance of the use of standardized imaging protocols and central radiology review as part of future trials.

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Conflict of interest

Julia C. Chisholm reports personal fees from F. Hoffman–La Roche outside the submitted work.

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Table S1. Patient characteristics total cohort, divided based on early radiologic response.

	Total	CR	PR	OR	NR
All patients	432	48 (11.1%)	320 (74.1%)	37 (8.6%)	27 (6.3%)
Sex					
Male	248 (57.4%)	30 (62.5%)	183 (57.2%)	23 (62.2%)	12 (44.4%)
Female	184 (42.6%)	18 (37.5%)	137 (42.8%)	14 (37.8%)	15 (55.6%)
Age (years)					
<3	172 (39.8%)	12 (25.0%)	135 (42.2%)	15 (40.5%)	10 (37.0)
3-10	173 (40.0%)	26 (54.2%)	123 (38.4%)	15 (40.5%)	9 (33.3%)
>10	87 (20.1%)	10 (20.8%)	62 (19.4%)	7 (18.9%)	8 (29.6%)
Tumor site					
Orbit	59 (13.7%)	10 (20.8%)	43 (13.4%)	4 (10.8%)	2 (7.4%)
Head & neck	39 (10.0%)	9 (18.8%)	30 (9.4%)	3 (8.1%)	1 (3.7%)
Parameningeal	134 (31.0%)	11 (22.9%)	95 (29.7%)	14 (37.8%)	14 (51.9%)
GU-BP	66 (15.3%)	3 (6.3%)	55 (17.2%)	6 (16.2%)	2 (7.4%)
GU non-BP	26 (6.0%)	6 (12.5%)	17 (5.3%)	2 (5.4%)	1 (3.7%)
Limbs	47 (10.9%)	4 (8.3%)	36 (11.3%)	3 (8.1%)	4 (14.8%)
Other	56 (13.2%)	5 (10.4%)	44 (13.8%)	5 (13.5%)	3 (11.1%)
Randomized					
Yes	211 (48.8%)	17 (35.4%)	158 (49.4%)	21 (56.8%)	15 (55.6%)
No	221 (51.2%)	31 (64.6%)	162 (50.6%)	16 (43.2%)	12 (44.4%)
Chemotherapy					
IVA	232 (53.7%)	32 (66.7%)	160 (50.0%)	23 (62.2%)	17 (63.0%)
6-drug chemotherapy	193 (44.7%)	16 (33.3%)	153 (47.8%)	14 (37.8%)	10 (37.0%)
Other	7 (1.6%)	0	7 (2.2%)	0	0
T status					
T1	152 (35.2%)	24 (50.0%)	107 (33.4%)	12 (32.4%)	9 (33.3%)
T2	272 (63.0%)	21 (43.8%)	209 (65.3%)	25 (67.6%)	17 (63.0%)
Unknown	8 (1.9%)	3 (6.3%)	4 (1.3%)	0	1 (3.7%)
N status					
N0	347 (80.3%)	40 (83.3%)	254 (79.4%)	31 (83.8%)	22 (81.5%)
N1	71 (16.4%)	7 (14.6%)	54 (16.9%)	5 (13.5%)	5 (18.5%)
Unknown	14 (3.2%)	1 (2.1%)	12 (3.8%)	1 (2.7%)	0
Tumor size:					
≤5 cm	217 (50.2%)	37 (77.1%)	155 (48.4%)	13 (35.1%)	12 (44.4%)
>5 cm	215 (49.8%)	11 (22.9%)	165 (51.6%)	24 (64.9%)	15 (55.6%)
Pathology:					
Embryonal	288 (66.7%)	26 (54.2%)	217 (67.8%)	28 (75.7%)	17 (63.0%)
Alveolar	144 (33.3%)	22 (45.8%)	103 (32.2%)	9 (24.3%)	10 (37.0%)
Radiotherapy					
Yes	275 (63.7%)	17 (35.4%)	214 (66.9%)	25 (67.6%)	19 (70.4%)

Table S1. (continued)

	Total	CR	PR	OR	NR
No	157 (36.3%)	31 (64.6%)	106 (33.1%)	12 (32.4%)	8 (29.6%)
Late surgery					
Yes	196 (45.4%)	0	154 (48.1%)	23 (62.2%)	19 (70.4%)
No	236 (54.6%)	48 (100%)	166 (51.9%)	14 (37.8%)	8 (29.6%)

Abbreviations: CR, complete response; GU, genitourinary; IVA, ifosfamide, vincristine and dactinomycin; N0, no evidence for lymph node involvement; N1, evidence for lymph node involvement; OR, objective response; PR, partial response; T1, tumor confined to organ or tissue of origin; T2, T2 tumor not confined to organ or tissue of origin.

Table S2. Table showing targeted area for radiotherapy.

	SR	OR	NR
Initial tumor + margins	99 (42.9%)	14 (56.0%)	10 (52.6%)
Residual tumor + margins	48 (20.8%)	5 (20.0%)	1 (1.9%)
Initial tumor + boost	34 (14.7%)	3 (12.0%)	3 (7.5%)
Unknown target volume	50 (21.6%)	3 (12.0%)	5 (26.3%)
Total patients received RT	231	25	19

Data on radiotherapy fields available for 217/275 (78.9%) patients that received radiotherapy.
Abbreviations: SR, sufficient response; OR, objective response; NR, no response; RT, radiotherapy.

APPENDIX; SUPPLEMENTARY MATERIAL

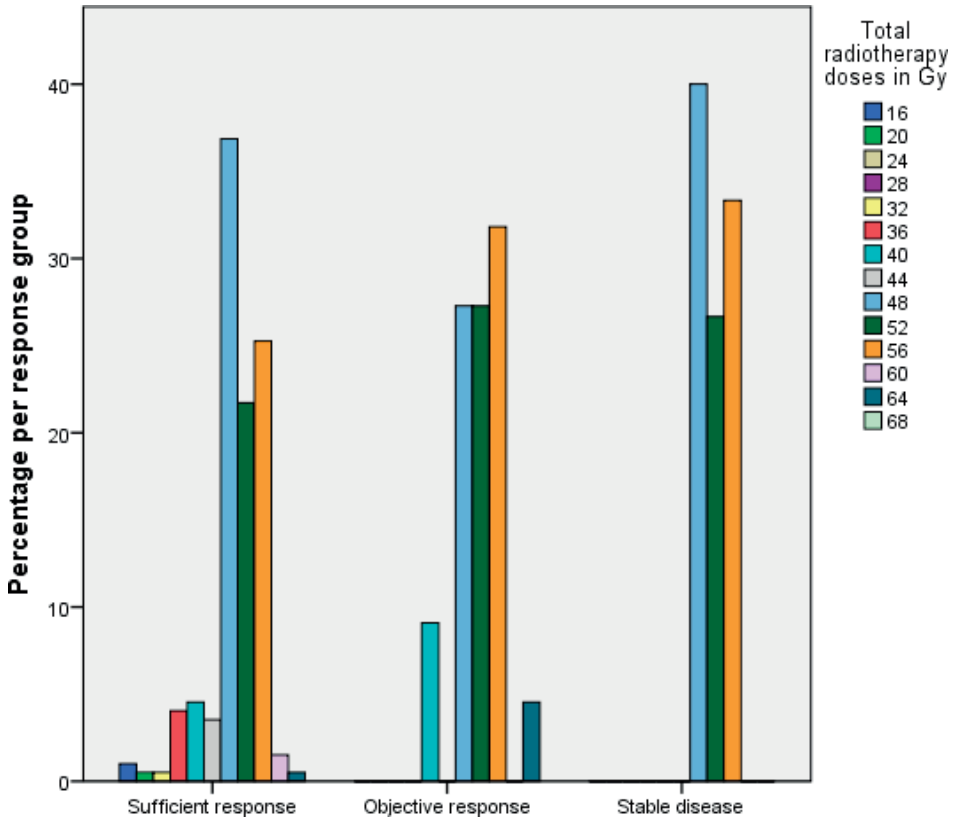
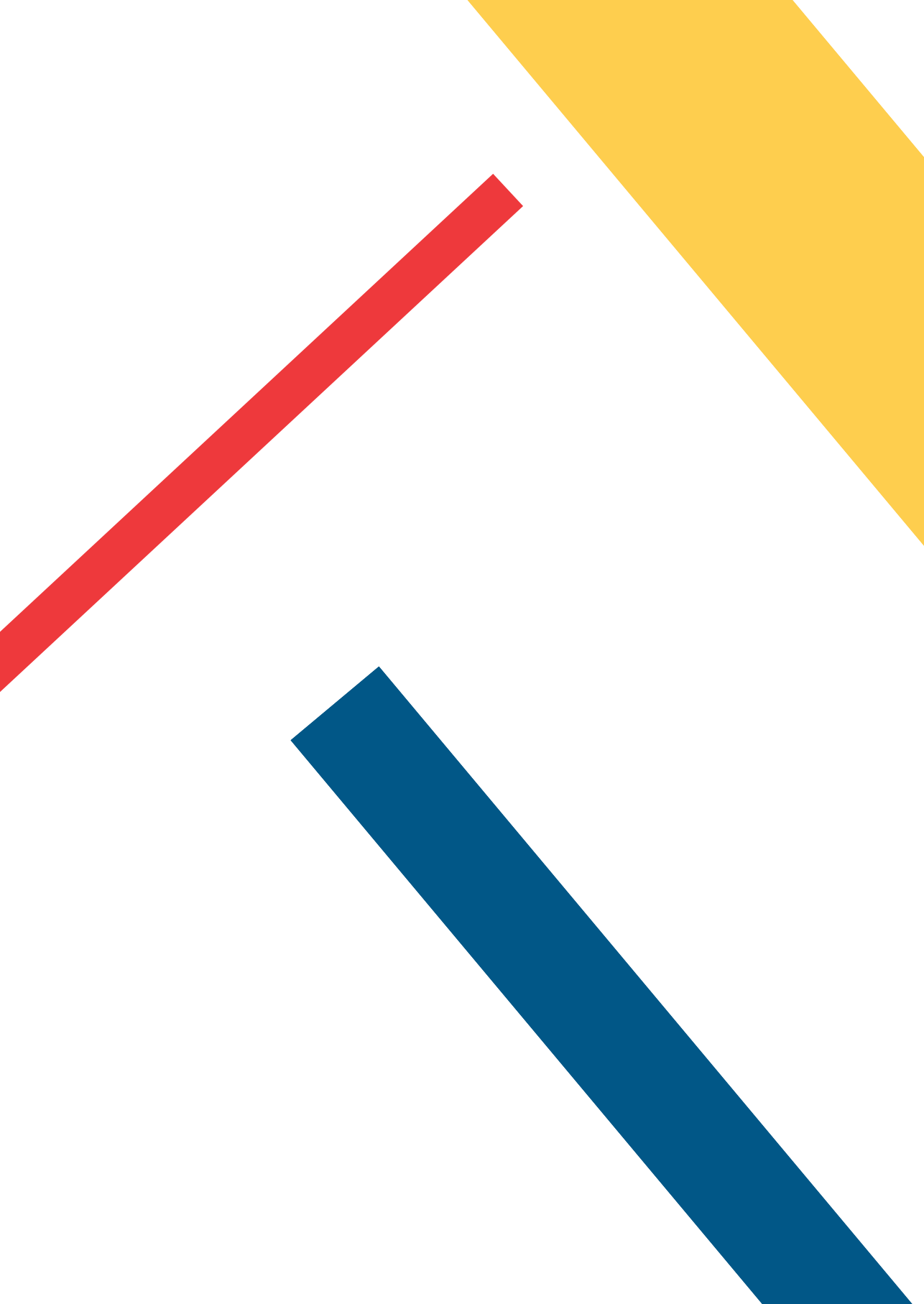


Figure S1. showing information on radiotherapy dose, grouped by response category.
Data on radiotherapy dosages available for 235/275 (85.5%) patients that received radiotherapy.



CHAPTER 5

THE PROGNOSTIC VALUE OF EARLY RADIOLOGICAL RESPONSE TO CHEMOTHERAPY IN PEDIATRIC RHABDOMYOSARCOMA; A SYSTEMATIC REVIEW

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Manuscript in preparation

ABSTRACT

This systematic review provides an overview of existing evidence on the prognostic value of early radiological response measurement in pediatric rhabdomyosarcoma (RMS) for event/failure-free (EFS/FFS) and overall survival (OS). We searched MEDLINE and EMBASE to 28 November 2018. Inclusion criteria: (1) study population of pediatric patients with IRSG stage III histologically proven RMS, (2) radiological response assessment by MRI or CT done after 2-4 courses of chemotherapy and (3) the prognostic value of early radiological response for EFS/FFS and/or OS after at least three years was assessed. Risk of bias was assessed using the Quality in Prognosis Studies (QUIPS) instrument. Six studies were included, describing 2010 patients. Due to heterogeneity a meta-analysis was not performed. Four of the six studies found no evidence that radiologic response is prognostic for survival, whereas two studies reported a significant difference in survival based on response. These studies included patients with progressive disease at early response measurement, whereas these patients were excluded from analysis in the other four studies, potentially explaining the differences in outcomes between studies.

Based on the available literature we conclude that in children with RMS, there is insufficient evidence that, except for patients with progressive disease, the degree of early radiological response is prognostic for survival. Early radiological response could therefore not be used as surrogate marker for survival. This implies that, at present, early markers for survival in pediatric RMS are lacking, we there advocate that there is an urgent need for new early response markers. PROSPERO (2017: CRD42017036060)

INTRODUCTION

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in childhood and accounts for about 3-5% of all pediatric malignancies.(1, 2) RMS can present at any site, most commonly in the head and neck region, the genitourinary tract, and limbs. The treatment for pediatric patients with RMS is based on a multimodality approach; at diagnosis the majority of patients undergo an incisional biopsy, after which induction (multidrug) chemotherapy is given, supplemented with surgery and/or radiotherapy followed by adjuvant chemotherapy. With this multimodality approach, overall survival (OS) for patients with localized disease has improved to around 75% nowadays, which, with an event-free survival (EFS) of 60%, remains unsatisfactory.(3, 4)

Development and evaluation of new treatment strategies are needed to improve survival in pediatric patients with RMS. However, results of clinical trials, with EFS and OS as primary outcomes, often take 7-10 years.(5) Identification of early biomarkers that may serve as surrogate endpoints is therefore crucial. First of all, early surrogate markers for survival facilitate a faster selection of promising new agents in phase I/II trials, therewith accelerating transition of promising new agents into phase III trials. At the same time, agents with less promising results can be excluded early, enabling an earlier introduction and evaluation of other agents. Secondly, early surrogate markers could also identify patients at high risk for relapse. If we are capable of identifying patients at high risk for relapse at an early phase, treatment could be intensified or innovative systemic and local treatment strategies could be introduced to improve outcome.(6)

In European treatment protocols of the European *paediatric* Soft tissue sarcoma Study Group (E*p*SSG) and the German Cooperative Soft Tissue Sarcoma (CWS), early radiological response, e.g. volume response, is measured after 2-3 courses of chemotherapy and subsequent treatment is adjusted based on response. This implies that in patients with insufficient response (tumor volume reduction < 33%), the chemotherapy regimen is changed to a second line chemotherapy. In contrast, patients treated according to North- American Children's Oncology Group (COG) protocols were only switched to second line chemotherapy in case of progression of disease under therapy.(4, 7) This contrast merely reflects a historical difference, instead of being based on available evidence. For the development of future treatment protocols, it is necessary to evaluate current evidence to determine the value of early radiological response measurement. Therefore, the goal of this systematic literature review was to assess the evidence of the prognostic value of radiological response to induction chemotherapy for survival in patients with localized RMS.

METHODS

The protocol was registered on PROSPERO (2017: CRD42017036060) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used as guidance for reporting.(8, 9)

Search strategy and study selection

We searched the database of MEDLINE and EMBASE from inception to 28 November 2018, without restrictions on language or publication status. The electronic search strategy was developed and executed by a medical librarian. Search terms for rhabdomyosarcoma, tumor response and prognostic value were combined (see appendix A for complete search strategy). Reference lists of included articles were checked for additional studies. Inclusion and exclusion criteria were defined a priori. The following inclusion criteria were defined: (1) the study population consisted of pediatric patients with IRSG stage III (10) histologically proven RMS, (2) radiological response assessment was done after 2-4 courses of induction chemotherapy and (3) the prognostic value of early radiological response for survival was assessed with outcomes being event-free survival and/or overall survival after at least 3 years. Cohort studies, either in isolation or as part of randomized controlled trials and controlled clinical trials, were eligible for inclusion. Review articles, editorials or letters and case reports were excluded, but references of these papers were checked for relevant studies. All studies identified in the literature search were screened for titles and abstracts, followed by full-text screening of selected articles, by two reviewers (BV and RvE) independently. Discrepancies between reviewers were resolved by consensus or consultation of a third reviewer (JHMM). Studies were screened and evaluated using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia).

Data extraction and quality assessment

Two reviewers independently extracted data using a predefined form (appendix B). For all included studies we extracted data on: patient characteristics (inclusion criteria, baseline characteristics), early radiological response (method of measurement and definition of response, timing of measurement), outcomes (definition and outcomes based on response assessment), study design, follow-up duration, reported association between radiological response, survival (both unadjusted and adjusted association) and any confounding factors used in the analyses.

The quality of the included studies was critically appraised independently by two reviewers (RvE and BV; the study of Vaarwerk et al. was appraised by RvE and RAS). Discrepancies between reviewers were resolved by consensus or consultation of a third reviewer (JHMM). Risk of bias was assessed using the Quality in Prognosis Studies (QUIPS)

instrument, designed to assess risk of bias for prognostic factor studies.(11) The QUIPS instrument consists of six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and reporting.

Data synthesis

The extracted data were presented descriptively in tables summarizing details on study design, in- and exclusion criteria, treatment, definition and timing of radiological response, outcomes and results. Due to differences in response measurement and definition of response, differences in treatment based on response and differences in outcome measures the included studies in this review were not considered suitable for meta-analysis.

RESULTS

The search identified a total of 2810 records. After removal of duplicates, 2284 records were screened on title and abstract. We evaluated 61 full-text reports; seven studies were excluded because they all described the same cohort. We decided to only include the most recent report (Dantonello et al.).(12) Further reasons for exclusion are shown in figure 1.

Baseline characteristics

In total, six studies were included in this review (table 1), describing a total of 2010 patients of which 40% were female and with a predominance of the embryonal RMS subtype (77%).(12-17) Two studies only included patients with embryonal rhabdomyosarcoma.

Five studies were prospective multicenter cohort studies and one was a retrospective single center cohort, none of the studies were primarily designed to address early radiological response evaluation, but data was collected to allow for retrospective assessment as part of the studies. The period of enrolment ranged from 6-25 years. Study sample sizes ranged from 62 to 529 patients with IRS stage III RMS. Characteristics of patients included in the separate studies are reported in table S1. Induction chemotherapy differed per study protocol; in general, it comprised a combination of alkylators (cyclophosphamide or ifosfamide), vincristine and dactinomycin, often complemented with other agents.

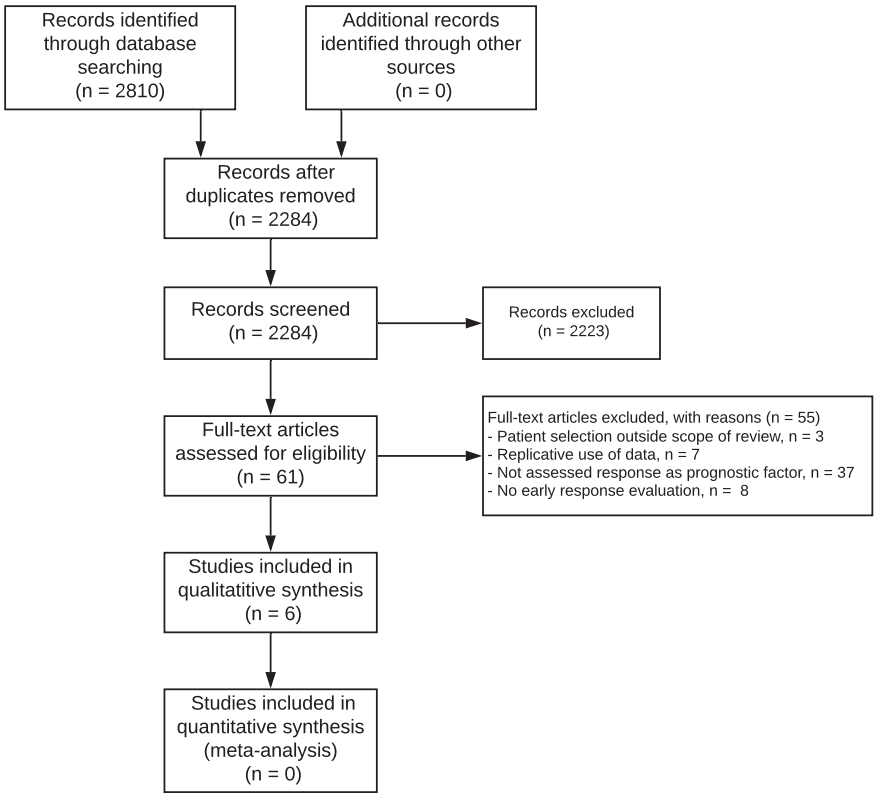

Figure 1. Flowchart

Risk of bias

Table 2 present the results of the QUIPS risk of bias assessment. In summary, all studies were found to have methodological limitations. *Study participation and attrition* was generally good. In Ermoian et al. only patients with orbital embryonal rhabdomyosarcoma were included, the risk of participation bias was considered moderate.(18) In Burke et al.(13), Dantonello et al.(12), Rosenberg et al.(17) and Vaarwerk et al.(19) only baseline characteristics were presented of the included patients, characteristics of excluded patients were not available in the report; therefore the risk of bias was considered moderate. Ferrari et al. described a total cohort of 205 patients, data on response assessment were available for 108/205 patients.(15) Patients and treatment characteristics of this subset of patients were not specified separately. Therefore, risk for study attrition bias was considered high for this study.

Response assessments were based on reports from local radiologists; none of the studies performed central review of the radiological response, potentially contributing to bias on the *prognostic factor measurement* domain. However, most of the included

Table 1. Summary of the studies included in this systematic review.

Study (year)	Country	Study design	Enrolment period	No. of patients included	Reason for excluding patients from response assessment analysis
Burke et al. (2007)	Multinational	Multicenter prospective cohort study	1991-1997	444	Off therapy before completion of induction therapy/no response assessment (n=49) Other histology than ERMS or ARMS (n=41) Start date of RT could not be determined (n=14)
Dantonello et al. (2015)	Multinational	Multicenter prospective cohort study; 5 consecutive trials	1980-2005	529	In total n=229 excluded: - No documented response measurement at correct evaluation point - Relevant tumor part removed at primary surgery - Surgery/radiotherapy prior to evaluation of response
Ermoian et al. (2017)	USA	Multicenter prospective cohort study	2004-2010	53	- PD before week 12 evaluation (n=2) - Insufficient or missing week 12 evaluation (n=7)
Ferrari et al. (2010)	Italy	Single center retrospective cohort study	1982-2008	205 (108 with response assessment)	In total n=216 excluded: - Metastatic disease - missing information on initial tumor size - Radiological diameter and volume not assessed
Rosenberg et al. (2014)	Multinational	Multicenter prospective cohort study	1999-2005	338	Other histology than ERMS or ARMS (n=90) Not IRS group III (n=139) No response measurement documented (n=20) PD at response assessment (n=6)
Vaarwerk et al. (2017)	Multinational	Multicenter prospective cohort study	1995-2003	432	In total n=194 excluded: - Unknown tumor size (n=64) - No response evaluation or at wrong time (n=116) - Tumor response was not evaluable (n=5) - Progressive disease at response assessment (n=7) - Lost to follow-up (n=2)

Abbreviations: ARMS, alveolar rhabdomyosarcoma; ERMS, embryonal rhabdomyosarcoma; IRS, Intergroup Rhabdomyosarcoma Group post-surgical staging; PD, progressive disease; RT, radiotherapy.

¥ based on unclear p value

according to RECIST criteria.(21)

* according to WHO criteria.(20)

Table 2. Quality assessement, based on QUIPS (11) instrument; assessing the prognostic value of early radiologic response to chemotherapy in pediatric rhabdomyosarcoma.

Study (year)	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis reporting
Burke et al (2007)	Low	Moderate	Low	Low	Moderate	High
Dantonello et al (2015)	Low	Moderate	Moderate	Low	High	Moderate
Ermoian et al (2018)	Moderate	Low	Moderate	Low	Low	Low
Ferrari et al (2010)	Moderate	High	Low	Moderate	High	High
Rosenberg et al (2014)	Low	Moderate	Low	Low	Moderate	Moderate
Vaarwerk et al (2017)	Low	Moderate	Moderate	Low	Moderate	Low

studies were part of multicenter international studies with concomitant guidelines on response assessment, therefore we judged the risk of bias low to moderate. In line with this assumption, we considered the *outcome measurement* bias low, as we expect this to be imbedded in the multicenter study protocols, although (lost to) follow-up data were mostly not specified. Common limitations were concentrated on the *study confounding domain* as can be expected in observational studies; in three studies (Dantonello et al.(12), Ferrari et al.(15), Vaarwerk et al.(19)) subsequent therapy was based on the response assessment; one study (Ferrari et al.(15)) was a single institution cohort, which included patients diagnosed over a period of 26 years; one study (Dantonello et al.(12)) merged patients with progressive disease and patients with objective response.

Findings

The results of the included studies are summarized in table 3. Different response criteria were used to assess radiological response; three studies used two-dimensional measurements according to WHO criteria (20), three studies used volumetric measurements. Ferrari et al.(15) used both one-dimensional measurements (according to RECIST criteria(21)) and volumetric measurements. Details on study design and early response methodology are summarized in tables 1 and 3.

In general, the vast majority of included patients showed early radiological response to first line chemotherapy, with complete response at early evaluation ranging from 11-31% between the included studies.

Table 3. Summary of study methods and outcomes of included studies.

Study (year)	Response evaluation criteria	Timing response evaluation (after n courses of chemotherapy)	Response parameters	Treatment switch based on response	Outcomes
Burke et al. (2007)	Two- dimensional*	Week 8 (3 courses)	CR: complete resolution PR: decrease of 50% or more in sum of the product of maximum perpendicular diameters NR: decrease of <50% or increase of <25% in product of maximum perpendicular diameters PD: increase of 25% or more in product of maximum perpendicular diameters	No	5-yr FFS: CR 75%, PR 71%, NR 78%, *p*=0.57
Dantonello et al. (2015)	Volumetric measurement	Week 8-11 (3 courses)	PR: ≥33% volume reduction NR: <33% volume reduction; • OR: 0-33% volume reduction • SPD: no reduction or new lesions	Patients with NR switched in chemotherapy	5-yr EFS: PAR; 68.1% ±4, NR; 59.2% ±13 p=0.03 5-yr OS: PAR; 76.4% ±4, NR; 62.6% ±13 p=0.004 Risk ratio: PAR+OR=1, SPD=4.8(2.8-8.2) Risk ratio: PAR=1, NR =2(1.3-3.2)
Ermoian et al. 2017	Volumetric measurement, not further specified	Week 12 (4 courses)	CR: complete resolution PR: decrease of 64% or more in volume SD: decrease of less than 64% or increase of less than 40% in volume PD: increase of 40% in volume	No	5-yr FFS: CR 100, PR/SD 84 (71-96, p=0.11) 5-yr OS: CR 100, PR/SD 97 (91-100, p=0.52)
Ferrari et al. (2010)	- One dimensional# - Volumetric measurement	Week 9 (3 courses)	Continuous variable, quantified as relative percentage reduction in tumor size (both volume and diameter).	Based on response, not further described	Tumor response significant predictor of survival (Wald test P<0.001 for both diameter and volume). V measure was 0.300 for diameter, 0.323 for volume.

Table 3. Summary of study methods and outcomes of included studies. (continued)

Study (year)	Response evaluation criteria	Timing response evaluation (after n courses of chemotherapy)	Response parameters	Treatment switch based on response	Outcomes
Rosenberg et al. (2014)	Two- dimensional*	Week 12 (4 courses)	CR: complete resolution PR: decrease of 50% or more in product of maximum perpendicular diameters NR: decrease of <50% or increase of <25% in product of maximum perpendicular diameters PD: increase of 25% or more in product of maximum perpendicular diameters	No	5-yr FFS: CR 74% (64-82%), PR 76% (63-83%), NR 64% (47-82%) *p*=0.49
Vaarwerk et al. 2017	Two- dimensional according to WHO criteria	Week 8 (3 courses)	CR: complete resolution PR: decrease of 50% or more in product of maximum perpendicular diameters SR: CR or PR OR: decrease of 25 - 50% NR: decrease of <25% or increase of <25% in product of maximum perpendicular diameters PD: increase of 25% or more in product of maximum perpendicular diameters	- Patients with less than SR switched in chemotherapy - Favorable subgroups with CR did not receive RT	5-yr FFS: SR: 60% (55-65%), OR: 60 (44-75%), NR: 69% (51-87%), *p*=0.6 5-yr OS: SR: 74% (69-79%), OR: 73% (58-87%), NR: 72% (55-90%), *p*=0.9 Adjusted hazard ratios for response:$ FFS; SR: 1, OR: 1.09 (95% CI, 0.63-1.88), NR: 0.81 (95% CI, 0.39-1.67) OS: SR: 1, OR: 0.91 (95% CI, 0.47-1.76), NR: 1.27 (95% CI, 0.61-2.64)

Abbreviations: CR, complete response; EFS, event-free survival; FFS, failure-free survival; HR, hazard ratio; IRS, Intergroup Rhabdomyosarcoma Group post-surgical staging; NR, non-response; OR, objective response; OS, overall survival; PR, partial response; RMS, rhabdomyosarcoma; RT, radiotherapy; SPD, stable/progressive disease; yr, years.

¥ statistical test not specified

according to RECIST criteria.(21)

* according to WHO criteria.(20)

$ Adjusted for histology, tumor size, tumor site, nodal involvement, age, radiotherapy, and postchemotherapy surgery

Prognostic value of early radiological response assessment

The results on the prognostic value of early radiological response differed between the studies. Results are summarized, including response parameters in table 3.

Burke et al. reported the results on 444 patients with RMS (irrespective of histologic subtype or site) included in the Intergroup Rhabdomyosarcoma Study IV. (13) They compared failure- free survival between patients with complete (CR), partial (PR) and no response (NR). Patients with progressive disease at early response assessments were excluded. Five-year FFS based on response was 75% for patients with CR, 71% for patients with PR and 78% for patients with NR, respectively. Survival distribution based on response was compared by log- rank test, showing a *p*-value of 0.57.

Dantonello et al. evaluated the prognostic value of early radiological response in 529 patients with embryonal RMS (irrespective of site) treated in 5 consecutive German Cooperative Soft Tissue Sarcoma (CWS) trials.(22) Event-free survival (EFS) and overall survival (OS) were compared based on early radiological response, with log-rank testing. Five-year EFS for patients with partial response (PR) was 68.1% (±4%) and 59.2% (±13%) for patients with no response (NR), p=0.03. Five-year OS was 76.4% (±4%) for patients with PR and 62.6% (±13%) for patients with NR, p=0.004. The authors also analyzed early radiological response in a multivariate analysis, analyzing response, treatment period, tumor site, age, tumor size and T-status. The risk ratio for death for patients with stable/progressive disease (SPD) was 4.8 (95% CI: 2.8-8.2) compared to patients with PR/objective response and early response had the highest risk ratio for death for all analyzed factors. The risk ratio for death for patients with NR was 2 (95% CI: 1.3-2.2) compared to patients with PR.

Ermoian et al. analyzed 53 patients with orbital embryonal RMS included in COG ARST0331 and compared FFS and OS between patients based on response.(18) Five-year FFS was 100% for patients with CR and 84% (95% CI: 71-96%) for patients with PR or stable disease; *p*-value of log-rank test 0.11. Five-year OS was 100% for patients with CR and 97% (95% CI: 91- 100%), *p*-value; 0.52.

Ferrari et al. analyzed the predictive value of early radiological response in 108 patients with RMS (irrespective of histology or site). Patients with progressive disease were included in the analysis. The predictive value of radiological response was evaluated in a multivariable model, evaluating sex and age, type of surgery, radiotherapy, histologic subtype and nodal status. They found, irrespective of the method of measurement (either diameter or volume), radiological response to be a significant predictor of survival. The predictive accuracy of two multivariable models (with one model containing radiological response as decrease in maximum diameter and the other model containing radiological response as volumetric reduction) was compared and no significant differences in predictive accuracy were found between the two models.(23)

Rosenberg et al. analyzed patients with RMS (irrespective of histologic subtype or site) included in Children's Oncology Group (COG) study D9803.(17) In this analysis, 338 patients with RMS were included, patients with progressive disease were excluded. Five-year FFS based on response was 74% (95% confidence interval [CI]: 64-82%) for patients with CR, 75% (95%-CI: 63-83%) for patients with PR and 64% (95%-CI: 47-82%) for patients with NR; *p*- value of log-rank test 0.49.

Vaarwerk et al. evaluated the prognostic value of radiological response in 432 patients with RMS (irrespective of histology or site) included in the International Society of Pediatric Oncology (SIOP) Malignant Mesenchymal Tumor 95 (MMT-95) study. FFS and OS was compared between three groups; sufficient response (CR/PR), objective response (OR) and no response (NR). Patients with progressive disease (n = 7) were excluded from the analysis. Five-year FFS was 60% (95% CI: 55-65%) for patients with CR/PR, 60% (95%-CI: 44-75%) for patients with OR and 69% (95% CI: 51-87%) for patients with NR, *p*-value log rank test: 0.6. Five-year OS was 74% (95% CI: 69-79%) for patients with CR/PR, 73% (95% CI: 58-87%) for patients with OR and 72% (95% CI: 55-90%) for patients with NR, *p*-value 0.9). The prognostic value of radiological response was further evaluated in a Cox regression analysis; adjusting for histology, tumor size, tumor site, nodal involvement, age, radiotherapy and late surgery. The adjusted hazard ratios for OR and NR were 1.09 (95% CI: 0.63-1.88) and 0.81 (95% CI: 0.39-1.67) for FFS and 0.91 (95% CI 0.47-1.76) and 1.27 (95% CI: 0.61-2.64) for OS.

DISCUSSION

This systematic review provides an overview of the available literature on the prognostic value of early radiological response assessment in pediatric patients with localized rhabdomyosarcoma.

Summary of findings

The six included studies in this systematic review clearly illustrate the ambiguous results in the existing literature on the prognostic value of early radiological response assessment in pediatric patients with localized RMS. Two of the six included studies concluded that early radiological response is a prognostic factor in pediatric RMS, whereas the four other studies did not find a significant difference in survival based on early radiological response. Included studies showed important methodological limitations. The studies of Dantonello et al.(12) and Ferrari et al.(15) that concluded that radiologic response is an important prognostic factor for survival, were both considered to have a high risk of bias on at least one domain. The studies of Ermoian et al.(18), Rosenberg et al.(17) and Vaarwerk et al.(13) were considered of higher quality; these studies did not find early

radiological response to be prognostic for survival. The study of Burke et al. was also considered to be at high risk of bias on the statistical analysis reporting; this study found no evidence that early radiological response is prognostic for survival.(13)

The discrepancies in results might further be explained by differences between the studies; the studies of Dantonello et al. and Ferrari et al. included patients with progressive disease at early response evaluation. Early disease progression was previously indicated to be associated with poor outcome.(24) Including patients with progressive disease may have affected outcome in the studies of Dantonello et al. and Ferrari et al., resulting in an association between radiologic response and survival. This was partly illustrated in the study by Dantonello et al; patients with overt disease progression showed a 5-year OS of 17% (±30%), compared to 47% (±23%) for patients with unchanged tumor (p=0.03).(12)

The European studies included in this review (Dantonello et al.(12), Ferrari et al.(15) and Vaarwerk et al.(19)) incorporated a switch in chemotherapy based on response assessment. Furthermore, in the studies of Dantonello et al.(12) and Vaarwerk et al.(19) specific patients in favorable subgroups with complete response to induction chemotherapy did not receive radiotherapy as first line therapy. This approach is based on the assumption that a subgroup of these patients do not require radiotherapy, whereas patients with a relapse could be salvaged with radiotherapy in case of relapse.(25)

Strengths and weaknesses

We conducted a systematic evaluation without restriction on language and publication status of the currently available evidence on the prognostic value of early radiological response in pediatric RMS. The key limitation of this study is that the data is reported descriptively, since performing a meta-analysis was considered inappropriate due to large heterogeneity between included studies. This heterogeneity was caused by different methods of response measurement (one-dimensional, two-dimensional and three-dimensional), different statistical methods and differences in treatment consequences based on response assessment outcome. Response measurement in all included studies was done by local radiologists, yet previous studies showed that radiological response measurement is subject to important interobserver variability irrespective of the method of response measurement.(26, 27) Furthermore, three of the included studies used radiological response to guide treatment decisions after response measurement. Therefore, patients with less response to induction chemotherapy received different therapy compared to patients with better response. These decisions potentially biased the results of the included studies.

CONCLUSION

The results of this study illustrate the ambiguous results in current literature on the prognostic value of early radiological response in RMS. Therefore, based on the results of the included studies, the differences in methods, and the quality of the included studies, we conclude that current literature shows insufficient evidence of a difference in survival between children with RMS in complete response versus any or no response at early radiological response measurement. For this reason, we believe that future protocols should no longer contain a treatment adaptation based on early radiological response. In contrast, patients with early progression of disease under therapy have an impaired prognosis, as was indicated in previous studies, and these patients should be switched to second line chemotherapy.(12, 24)

As a result, we conclude that we currently lack an early surrogate marker for survival in pediatric RMS, making survival the only reliable endpoint in clinical trials; it therefore often takes 7-10 years to answer few randomized study questions, hampering efficient progress of the field. Therefore, we strongly believe that future research should focus on identifying early response markers. A potential marker could be functional imaging, either FDG-PET- response or diffusion weighted MRI-response, although results on FDG-PET are conflicting, and good quality studies on the use of diffusion weighted MRI are currently lacking.(28-33) Future research could also focus on potential biological markers, that might predict outcomes for patients with RMS, but could also be an early indicator for relapse.(34)

As for radiologic measurements in general, either radiological or functional, it is important that in future prospective RMS studies standardized imaging acquisition and central imaging collection and/or review becomes standard; this will lead to large and robust imaging datasets. Automated assessment of large datasets in combination with radiomics could lead to a whole new way of assessing and interpreting imaging, where inter-observer variability is a non-issue and response measurement can be defined with minimal local acquisition protocols , therewith potentially improving the reproducibility of response measurements.(35-39)

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SUPPLEMENTAL MATERIAL

Table S1. Patient Characteristics

	Burke et al. 2007	Dantonello et al. 2015	Ermoian et al. 2018	Ferrari et al. 2009	Rosenberg et al. 2014	Vaarwerk et al. 2017	Total
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Total number of patients	444	529	62	205	338	432	2010
Sex							
Female	189 (43)	NS	24 (39)	72 (35)	127 (38)	184 (43)	596 (40)
Male	255 (57)	NS	38 (61)	133 (65)	211 (62)	248 (57)	885 (60)
Age, years							
≤10	327 (74)	450 (85)	***	103 (50)	249* (74)	345* (80)	1474 (76)
>10, ≤14	71 (16)	79 (15)		40 (20)	89* (26)	87* (20)	366 (19)
>14	49 (11)			62 (30)			111 (6)
Tumor site							
Extremity	40 (9)	16 (3)		24 (12)	49 (15)	47 (11)	176 (9)
GU-nonbladder/ prostate	32 (7)	28 (5)		51 (25)	43** (13)	26 (6)	180 (9)
GU-bladder/prostate	58 (13)	91 (17)		13 (6)		66 (15)	228 (11)
PM	178 (40)	194 (37)		50 (24)	155 (46)	134 (31)	711 (35)
HN-nPM	20 (4)	31 (6)		34 (17)	7 (2)	43 (10)	135 (7)
Orbit	47 (11)	72 (14)	62 (100)	NS	12 (4)	59 (14)	252 (13)
Pelvis/trunk	NS	NS		33 (16)	42 (12)	NS	75 (4)
Other	69 (15)	97 (18)			30 (9)	57 (13)	253 (13)
Histological subtype							
Alveolar	103 (23)			61 (30)	132 (39)	144 (33)	440 (22)
Embryonal	323 (71)	529 (100)	62 (100)	136 (66)	206 (61)	288 (67)	1544 (77)
NOS	18 (4)			8 (4)			26 (1)
Tumor size, cm							
≤ 5	187 (42)	212 (40)	60 (97)	78 (38)	139 (41)	217 (50)	893 (44)
> 5	255 (58)	263 (50)	1 (2)	127 (62)	199 (59)	215 (50)	1060 (53)
Unknown	54 (10)						57 (3)
T status							
T1	140 (32)	146 (28)		66 (32)	152 (45)	152 (35)	656 (34)
T2	302 (69)	370 (70)		139 (68)	185 (55)	272 (63)	1268 (65)
Unknown	2	13 (2)				8 (2)	23 (1)
N status							
N0	332 (79)	437 (83)		158 (77)	274 (81)	347 (80)	1548 (80)
N1	86 (21)	62 (12)		47 (23)	64 (19)	71 (16)	330 (17)
Unknown	26	30 (6)				14 (3)	70 (4)

Abbreviations: GU, genitourinary; HN-nPM, head and neck non parameningeal; N0, no evidence of lymph node involvement; N1, evidence for lymph node involvement; NOS, not otherwise specified; PM, parameningeal; T1, tumor confined to the organ or tissue of origin; T2, tumor not confined to the organ or tissue of origin.

* Definition in Rosenberg et al. 2014 and Vaarwerk et al. 2017, Age < 10 and Age ≥10

** Genitourinary not further specified

*** Cut of at 6 years

APPENDIX A

The following MESH terms and text words were used for Medline:

1. (((exp Rhabdomyosarcoma/ or (rhabdomyosarcoma$ or rhabdomyoblastoma$ or rhabdosarcoma$).ti,ab,kw.) and (Antineoplastic Combined Chemotherapy Protocols/ or Neoadjuvant Therapy/ or Induction Chemotherapy/ or exp Antineoplastic Agents/ or ((induction adj therap*) or chemotherap* or neoadjuvant or ifosfamide or Cyclophosphamide or vincristine or etoposide or dactinomycin or carboplatin or Doxorubicin or Cisplatin).ti,ab,kw,rn.)) or exp Rhabdomyosarcoma/dt) and (Validat$.mp. or Predict$.ti. or Rule$.mp. or (Predict$ and (Outcome$ or Risk$ or Model$)).tw. or ((History or Variable$ or Criteria or Scor$ or Characteristic$ or Finding$ or Factor$) and (Predict$ or Model$ or Decision$ or Identif$ or Prognos$)).tw. or (Decision$.tw. and ((Model$ or Clinical$).tw. or logistic models/)) or (Prognostic and (History or Variable$ or Criteria or Scor$ or Characteristic$ or Finding$ or Factor$ or Model$)).tw. or ("Stratification" or "Discrimination" or "Discriminate" or "c-statistic" or "c statistic" or "Area under the curve" or "AUC" or "Calibration" or "Indices" or "Algorithm" or "Multivariable" or failure-free survival or survival.ti,ab.).tw. or exp Survival/)
2. (exp Rhabdomyosarcoma/ or (rhabdomyosarcoma$ or rhabdomyoblastoma$ or rhabdosarcoma$).ti,ab,kw.) and ((tumo?r$ adj2 (reduction or respons)) or (decreased adj3 (tumo?r$ or size or volume or area))).ti,ab,kw.
3. 1 or 2
4. animals/ not humans/
5. (case reports or review).pt.
6. 4 or 5
7. 3 not 6

The following Emtree terms and text words were used for Embase:

1. (((rhabdomyosarcoma/ or (rhabdomyosarcoma$ or rhabdomyoblastoma$ or rhabdosarcoma$).ti,ab,kw.) and (combination chemotherapy/ or induction chemotherapy/ or exp antineoplastic agent/ or ((induction adj therap*) or chemotherap* or neoadjuvant or ifosfamide or Cyclophosphamide or vincristine or etoposide or dactinomycin or carboplatin or Doxorubicin or Cisplatin).ti,ab,kw,rn.)) or exp exp rhabdomyosarcoma/dt) and (Validat$.tw. or Predict$.ti. or Rule$.tw. or (Predict$ and (Outcome$ or Risk$ or Model$)).tw. or ((History or variable$ or Criteria or Scor$ or Characteristic$ or Finding$ or Factor$) and (Predict$ or Model$ or Decision$ or Identif$ or Prognos$)).tw. or (Decision$.tw. and ((Model$ or Clinical$).tw. or statistical model/)) or (Prognostic and (History or Variable$ or Criteria or Scor$ or Characteristic$ or Finding$ or Factor$ or Model$)).ti,ab,kw. or ("Stratification" or "Discrimination" or "Discriminate" or "c-statistic" or "c statistic" or "Area under the curve" or "AUC" or "Calibration" or "Indices" or "Algorithm" or "Multivariable" or ailure-free survival or survival).tw. or exp survival/)
2. (exp rhabdomyosarcoma/ or (rhabdomyosarcoma$ or rhabdomyoblastoma$ or rhabdosarcoma$).ti,ab,kw.) and ((tumo?r$ adj2 (reduction or respons)) or (decreased adj3 (tumo?r$ or size or volume or area))).ti,ab,kw.
3. 1 or 2
4. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
5. "review"/
6. case report/
7. 4 or 5 or 6
8. 3 not 7
9. limit 8 to (conference abstract or conference paper or conference proceeding or "conference review")
10. 8 not 9

APPENDIX B

Review Title: Radiological response to induction chemotherapy
Date..... Reviewer: .....
Study Title .....

First author	
Year of publication	
Country of publication	
Publication type	Journal / Abstract / other (specify)

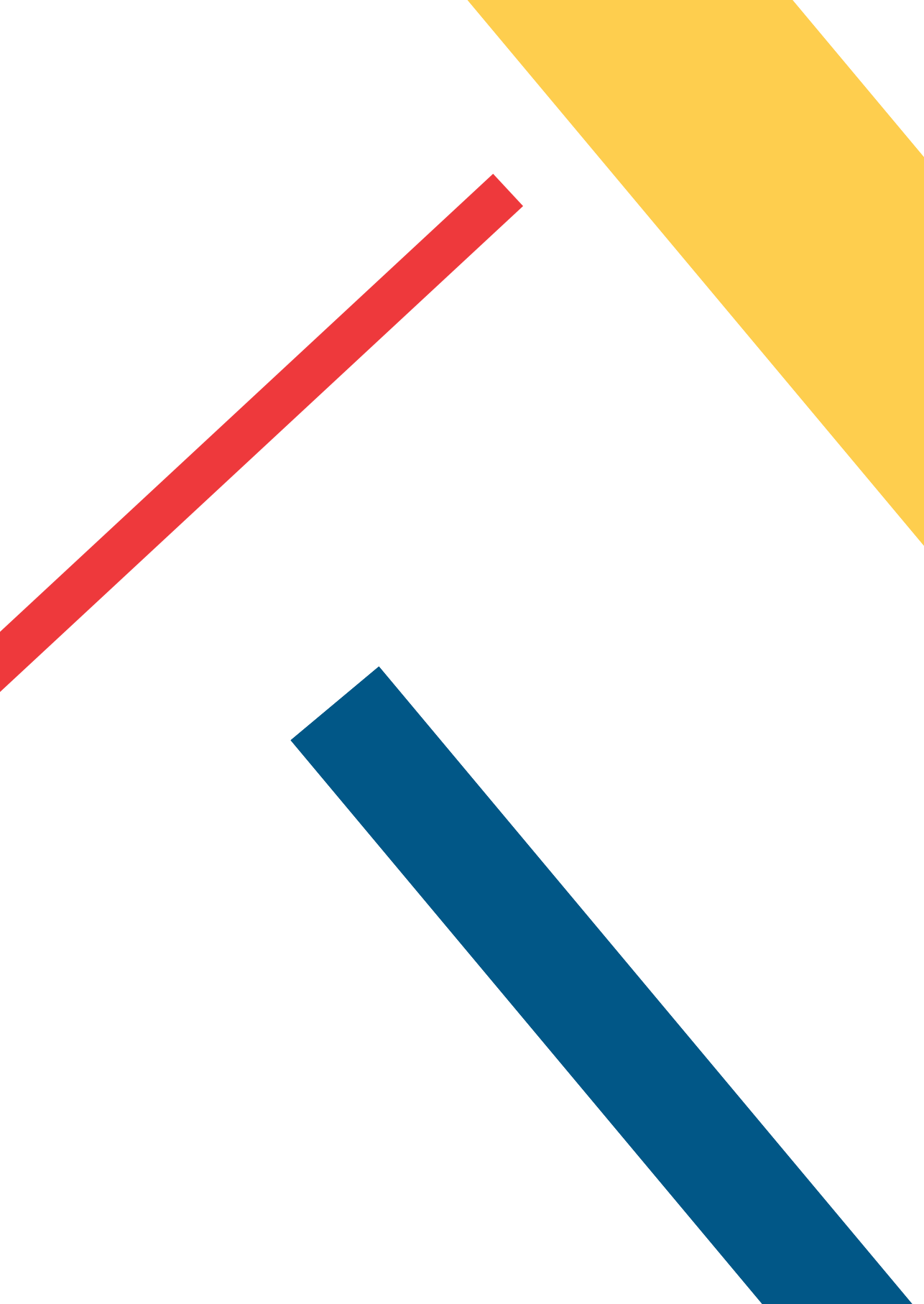
Study characteristics	
Methods	**Description as stated in paper**
Aim of study	
Study design	Eg RCT, historically controlled trial
Study period	•
Setting	source eg multicenter, university teaching hospitals:

Inclusion criteria	
Exclusion criteria	
Informed consent obtained	☐ Yes ☐ No ☐ Unclear
Total no. of subjects	
Missing data & reasons	
Participants	• Age at diagnosis: Median…….Mean…… range…… • Sex • Histology • Primary site • Tumor size • T-status: • Nodal status
Definition of early response	
Timing of response assessment	
Post-induction treatment	
Statistical analysis	
Outcome(s)	Primary outcome

Definition, measure & classification	**Secondary outcomes:**
Confounding factors/ effect modifiers accounted for	
Results (specify, e.g. OS, EFS, OR, RR,)	
Authors' reported limitations of study's methods/results	

Results for the review

	Good response	**Partial response**	**Stable disease**
Event free survival			
*Reasons for loss/exclusion: **Other**			
Contact with primary investigators	• **Clarify methods** • **Clarify results**		
Notes			



CHAPTER 6

IS SURVEILLANCE IMAGING IN PEDIATRIC PATIENTS TREATED FOR LOCALIZED RHABDOMYOSARCOMA USEFUL? THE EUROPEAN EXPERIENCE

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** Contributed equally to this work*

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Cancer, in press

ABSTRACT

Background

After completion of therapy patients with localized rhabdomyosarcoma (RMS) are subjected to intensive radiologic tumor surveillance. However the clinical benefit of this surveillance is unclear. We retrospectively analyzed the value of off-therapy surveillance, by comparing survival between patients in whom relapse was detected by routine imaging (imaging group) and patients in whom relapse was first suspected by symptoms (symptoms group).

Methods

We included patients with relapsed RMS, after completion of therapy for localized RMS, treated in large pediatric oncology hospitals in France, United Kingdom, Italy and the Netherlands who were enrolled in either SIOP-MMT-95 (1995-2004), STSC-RMS96 (1996-2004) or E^{p}SSG-RMS 2005 (2005-2013) studies. Survival time after relapse was compared by log-rank test between patients in the imaging group and patients in the symptoms group.

Results

In total, 199 patients with relapsed RMS were included of which 78 patients (39.2%) in the imaging group and 121 patients (60.8%) in the symptoms group. Median follow-up time after relapse was 7.4 years (IQR: 3.9-11.5) for survivors (n=86); 3-year post-relapse survival [95% CI] was 50% [38-61%] for the imaging group and 46% [37-55%] in the symptoms group (p=0.7).

Conclusion

Although systematic routine imaging is standard of care after RMS therapy, the majority of relapses were detected as a result of clinical symptoms. We found no survival advantage for patients with relapse detected before the emergence of clinical symptoms. These results show that the value of off-therapy surveillance is controversial, particularly since repeated imaging may also entail potential harm.

INTRODUCTION

Pediatric patients treated for rhabdomyosarcoma (RMS) are subject to intensive surveillance after therapy, since up to one third of patients with localized disease at initial diagnosis experience tumor relapse.(1-3) The majority of these relapses are loco-regional and the lungs are the most affected metastatic site. Three year survival after relapse is around 37%, and is associated with several factors such as histology, initial tumor site, pattern of relapse (local or metastatic) and prior radiotherapy.(4-8)

The recommended surveillance after treatment, according to the European *paediatric* Soft tissue sarcoma Study Group (E^{P}SSG) RMS 2005 protocol, includes a clinical examination together with a MRI or CT scan of the primary tumor site and a chest X-ray, performed every three months in the first year and every four months in the second and third year after treatment. The recommended surveillance is once a year in the fourth and fifth year after treatment.

However, no evidence is available that current surveillance recommendations leads to earlier detection of relapse and therewith to improved survival in patients with relapsed RMS.(9-11) Furthermore, repetitive imaging is associated with substantial costs, could add additional radiation exposure and often requires anesthesia.(12, 13) Furthermore, frequent hospital visits could potentially cause psychological distress to patients and parents.(14-16)

The questionable survival benefit of current surveillance strategies and potential adverse factors associated with surveillance emphasize the need for an assessment of the value of surveillance imaging. In this international multicenter retrospective study we aimed to evaluate the value of surveillance imaging by determining the method of detection of relapse and its impact on survival in a cohort of patients treated according to consecutive European pediatric protocols.

PATIENTS AND METHODS

Included patients were treated in the International Society of Pediatric Oncology (SIOP) Malignant Mesenchymal Tumour 95 (MMT-95) study, the Italian pediatric Soft Tissue Sarcoma Committee (STSC) RMS-96 study or the E^{P}SSG-RMS 2005 study.(1, 3) All studies were approved by the appropriate national review boards. Patients or guardians, or both gave informed consent to participate in the individual studies according to the research ethics requirements of the individual institutions.

Eligible patients, identified from the databases of the individual studies, suffered from relapsed RMS 0-5 years after having achieved complete remission at end of therapy (or

stable residual mass > 6 months after end of therapy); all had localized RMS at initial diagnosis, were diagnosed between 1995 and December 2013 and were aged 0-18 years at time of initial diagnosis.

Treatment at initial diagnosis was according to the risk stratification of the reference protocol at time of diagnosis. Treatment generally consisted of a combination of chemotherapy with surgery and/or radiotherapy, as described previously.(1, 3, 5, 17, 18) Local therapy approach differed per protocol. If possible delayed surgery was performed in case of residual tumor. Patients received radiotherapy according to protocol, with specific favorable subgroups not receiving radiotherapy (based on site, response to chemotherapy, secondary surgery and risk group).

Treatment after relapse was dependent on initial therapy; chemotherapy regimens were left to the discretion of the treating physician or were part of phase 2 trials. Local therapy (surgery and/or radiotherapy) was applied if feasible; in general radiotherapy was administered to patients who did not receive radiotherapy during initial treatment.

Tumor surveillance after end-of-treatment was done according to the applicable treatment protocol. In general, surveillance imaging comprised of imaging of the primary site by ultrasound, CT or MRI repeated every 3-4 months in the first three years after end-of- treatment. Frequency of follow-up was once or twice a year in the fourth and fifth year after end-of-treatment (see table S1, supplementary material).

Data was collected from patients who had been treated in 21 larger pediatric oncology centers in France, Italy, the United Kingdom and the Netherlands. Data was collected from patient charts and radiology reports by one dedicated physician nationwide or by experienced pediatric oncologists, depending on the participating country, and recorded using a standardized case report form (CRF). The following information was collected: clinical characteristics at initial diagnosis, therapy for initial tumor, type of relapse, information on the method of relapse detection, and the presence of clinical symptoms at time of relapse detection, total number of imaging studies, and follow-up technique used to detect disease relapse. Furthermore we collected data on treatment after relapse and outcome after relapse. Type of relapse was classified as loco-regional (defined as relapse at local site, loco-regional nodal, or both), metastatic or loco-regional and metastatic.

The method of relapse detection was grouped as: 'routine imaging with/without clinical symptoms', (shortened to 'routine imaging') and 'imaging initiated because of clinical symptoms' (shortened to 'clinical symptoms'). This distinction was made based on patient charts and radiology reports.

Statistical analysis

Analyses were performed using SPSS (Version 24.0.0.1) and R (Version 3.4.3). The distribution of variables at diagnosis and relapse, and treatment characteristics between

patients detected by routine imaging and patients detected by clinical symptoms were compared using X^2 tests.

Overall survival (OS) was calculated from time of diagnosis of relapse to death from any cause. Outcomes for living patients were censored at the time of their last reported contact (data cut-off point: December 31st, 2017). OS curves were obtained by the Kaplan-Meier method.(19) A log-rank test was used to compare OS levels between routine imaging patients and clinical symptoms patients. P values lower than 0.05 were considered statistically significant. The following predefined subgroups were evaluated to determine whether specific patients might benefit from surveillance; histology, tumor site, tumor size, nodal status at presentation, IRS grouping, risk group, prior radiotherapy and treatment protocol. No statistical tests were performed for these groups because of the large number of groups and subsequently small numbers of patients per group. Patients with a pulmonary relapse were specifically described, since chest radiographs are also routinely performed during surveillance after end-of-treatment.

RESULTS

Patient population

In total, 202 patients with relapsed rhabdomyosarcoma were diagnosed in the participating centers of which 199 were included in the current analyses. Three patients were excluded; due to missing date of relapse (n=1), missing method of relapse detection (n=1), lost to follow-up (n=1). Information on characteristics at initial diagnosis are described in Table 1.

Median time from initial diagnosis to relapse was 18.5 months (IQR: 13.5-25.2 months) for the total cohort. Relapse was loco-regional in 153 patients (76.9%), 26 patients (13.1%) had a metastatic relapse and 20 patients (10.1%) had a combined loco-regional and metastatic relapse.

Relapse detection

In 121 patients (60.8%) relapse was detected by clinical symptoms, in 22 patients (11.0%) relapse was detected by routine imaging with clinical symptoms present at the time of routine imaging, and in 56 patients (28.1%) relapse was detected by routine imaging without clinical symptoms. Median time from end of treatment to relapse was 8.0 months (IQR: 5.3-13.9 months) for patients detected by routine imaging (± clinical symptoms) and 12.0 months (5.6-19.2 months) for patients detected by clinical symptoms (p= 0.003) (Figure 1). The latest relapse detected by routine imaging occurred 2.5 years after end-of-treatment. Previously identified factors associated with outcome after relapse did not differ significantly between the two groups based on method of relapse

Table 1. Characteristics of patients included in this analysis

	Patients (n=199)
	No. (%)
Age at initial diagnosis	
<10 years	150 (75.4)
10+ years	49 (24.6)
Sex	
Male	121 (60.8)
Female	78 (39.2)
Primary site	
Orbit	34 (17.1)
Head & neck	18 (9.0)
Parameningeal	47 (23.6)
GU bladder-prostate	19 (9.5)
GU non bladder-prostate	17 (8.5)
Limbs	26 (13.1)
Other	38 (19.1)
Histology [a]	
Favorable	138 (69.3)
Unfavorable	61 (30.7)
Tumor size	
≤5 cm	90 (45.2)
>5 cm	98 (49.2)
Unknown	11 (5.5)
Nodal status	
N0	162 (81.4)
N1	34 (17.1)
Unknown	3 (1.5)
T status	
T1	90 (45.2)
T2	64 (32.2)
Unknown	45 (22.6)
IRS Group [b]	
I	14 (7.0)
II	24 (12.1)
III	161 (80.9)
Protocol	
SIOP-MMT95	76 (38.2)
STSC-RMS96	22 (11.1)
EpSSG-RMS 2005	101 (50.8)

Abbreviations: E*p*SSG-RMS 2005, European *paediatric* Soft tissue sarcoma Study Group-Rhabdomyosarcoma 2005 study; GU, genito-urinary; IRS, Intergroup Rhabdomyosarcoma Study Group post-surgical stage; SIOP-MMT95, International Society of Paediatric Oncology Malignant Mesenchymal Tumor-95 study; STSC-RMS96, Italian paediatric Soft Tissue Sarcoma Committee Rhabdomyosarcoma-96 study.
a Favorable histology are all embryonal, spindle cells, botryoid RMS; unfavorable are all alveolar RMS, including RMS NOS (n=2). b IRS group: Group I, primary complete resection (R0); Group II, microscopic residual (R1) or primary complete resection but N1; Group III, macroscopic residual (R2).

detection. However, a significant difference was observed between the two groups based on the treatment protocol (p=0.02, Table 2).

The most frequently reported symptoms were a palpable mass (n=80) and pain (n=80). Furthermore patients presented with mass effect leading to obstruction (n=20), dysuria/hematuria (n=6), neurological symptoms (n=5) or 'other symptoms' (n=30).

Total number of follow-up exams for the total cohort consisted of 405 MRIs, 206 ultrasounds and 45 CTs of the primary site, and 601 chest X-rays and 47 chest CTs. MRI of the primary site was the most frequent modality detecting the relapse in the routine imaging group (n=56).

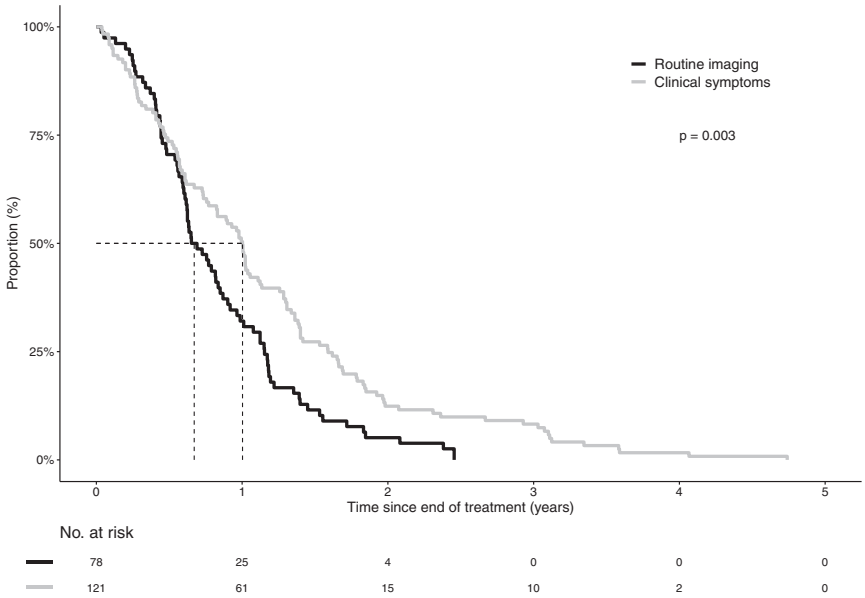

Figure 1. Relapse free survival from end of initial treatment to relapse based on method of relapse detection. p-value based on log-rank test.

Survival after relapse

Three-year OS after relapse for the total group was 48% (95% confidence interval [CI]: 40-55%); 3-year OS for routine imaging patients was 50% (95%-CI: 38-61%) and 46 % (95%-CI: 37-55%) for clinical symptoms patients (p=0.7) (Figure 2). Among patients who had not received prior radiotherapy, the 3-year OS for routine imaging patients was 72% (95%-CI: 55-90%) and 63% (95%-CI: 50-76%) for clinical symptoms patients (p=0.7). The relationship between patient and treatment characteristics, and 3-year OS for both groups is shown in Table 3.

Table 2. Distribution of characteristics associated with survival based on mode of relapse detection.

	Routine imaging (n=78)	Clinical symptoms (n=121)	p-value [d]
	No. (%)	No. (%)	
Histology [a]			0.36
Favorable	57 (73)	81 (67)	
Unfavorable	21 (27)	40 (33)	
Tumor size			0.19
≤5 cm	31 (40)	59 (49)	
>5 cm	43 (55)	55 (45)	
Unknown	4 (5)	7 (6)	
Primary site			0.16
Orbit	9 (12)	25 (21)	
Head & neck	6 (8)	12 (10)	
Parameningeal	19 (24)	28 (23)	
GU bladder-prostate	9 (12)	10 (8)	
GU non bladder-prostate	11 (14)	6 (5)	
Limbs	12 (15)	14 (12)	
Other	12 (15)	26 (21)	
IRS group [b]			0.54
I	4 (5)	10 (8)	
II	8 (10)	16 (13)	
III	66 (85)	95 (79)	
Nodal status			0.94
N0	63 (81)	99 (82)	
N1	13 (17)	21 (17)	
Nx	2 (3)	1 (1)	
Type of recurrence			0.74
Local	59 (76)	94 (78)	
Metastatic with/without local	19 (24)	27 (22)	
Prior radiotherapy			0.17
No	26 (33)	52 (43)	
Yes	52 (67)	69 (57)	
Time to relapse [c]			0.57
<1.5 years	44 (56)	60 (50)	
≥1.5 years	38 (44)	61 (50)	
Treatment protocol			**0.02**
SIOP-MMT 95	24 (31)	52 (43)	
STSC-RMS 96	5 (6)	17 (14)	
EpSSG-RMS 2005	49 (63)	53 (43)	

Abbreviations: E*p*SSG-RMS 2005, European *paediatric* Soft tissue sarcoma Study Group-Rhabdomyosarcoma 2005 study; GU, genito-urinary; IRS, Intergroup Rhabdomyosarcoma Study Group post-surgical stage; SIOP-MMT95, International Society of Paediatric Oncology Malignant Mesenchymal Tumor-95 study; STSC-RMS96, Italian paediatric Soft Tissue Sarcoma Committee Rhabdomyosarcoma-96 study.

a Favorable histology are all embryonal, spindle cells, botryoid RMS; unfavorable are all alveolar RMS, including RMS NOS (n=2).

b IRS group: Group I, primary complete resection (R0); Group II, microscopic residual (R1) or primary complete resection but N1; Group III, macroscopic residual (R2).

c Time to relapse in years after initial diagnosis

d Based on X^2 test

In total, 18 patients had pulmonary metastatic relapse (7 patients had only pulmonary metastases, 6 patients also had loco-regional relapse and 5 patients had a relapse at multiple metastatic sites); in 11/18 patients relapse was detected by routine imaging, in 7/18 patients by clinical symptoms (symptoms were related to the loco-regional or extrapulmonary metastatic relapse). Median OS for patients with pulmonary relapse was 11.8 months (95%-CI: 2.1-21.6 months). All patients with only a pulmonary relapse (n=7, all detected by routine imaging) died; median post-relapse survival for these 7 patients was 12.4 months (95%-CI: 0 – 29.2 months).

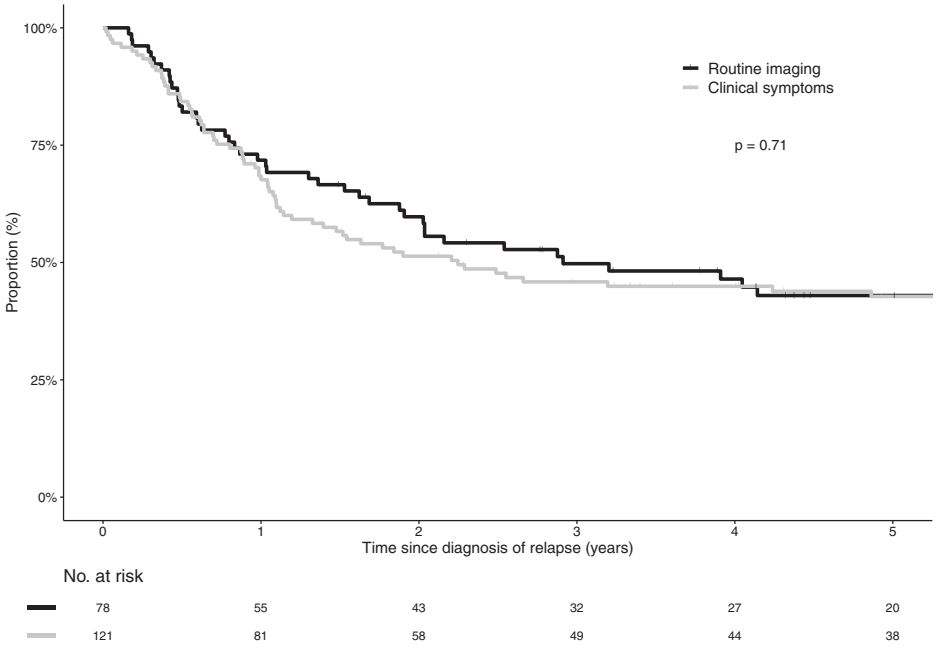

Figure 2. Overall survival after relapse (including 95%-confidence interval) based on method of relapse detection. p-value based on log-rank test

DISCUSSION

Surveillance imaging after completion of therapy for pediatric RMS is recommended in current treatment protocols. The assumption is that surveillance imaging leads to earlier detection of tumor relapse and subsequently to improved prognosis after relapse. So far, no evidence is available for this assumption.(9, 20) This study shows that the majority of patients with relapsed RMS experience clinical symptoms at time of relapse (71.8%). We found no evidence that the detection of a relapse before clinical symptoms emerge, results in improved survival after relapse. As might be expected, the time to first relapse

Table 3. Survival analyses based on initial characteristics and prior treatment.

	Routine imaging		Clinical symptoms	
	No.	**3-yr OS %, (95%-CI)**	**No.**	**3-yr OS %, (95%-CI)**
All patients	78	50 (38 to 61%)	121	46 (37 to 55%)
Histology [a]				
Favorable	57	55 (42 to 68%)	81	51 (40 to 62%)
Unfavorable	21	35 (14 to 57%)	40	35 (19 to 50%)
Primary site				
Orbit	9	100	25	88 (75 to 100%)
Head & neck	6	83 (54 to 100%)	12	67 (40 to 93%)
Parameningeal	19	21 (3 to 40%)	28	13 (0 to 26%)
GU bladder-prostate	9	56 (23 to 88%)	10	20 (0 to 45%)
GU non bladder-prostate	11	73 (46 to 99%)	6	80 (45 to 100%)
Limbs	12	25 (1 to 50%)	14	52 (23 to 81%)
Other	12	40 (7 to 73%)	26	27 (10 to 44%)
Tumor size				
≤5 cm	31	80 (65 to 94%)	59	65 (53 to 77%)
>5 cm	43	30 (16 to 44%)	55	28 (16 to 40%)
Nodal status				
N0	63	58 (45 to 70%)	99	54 (44 to 64%)
N1	13	23 (0 to 46%)	21	11 (0 to 26%)
IRS group [b]				
I	4	75 (33 to 100%)	10	80 (55 to 100%)
II	8	38 (4 to 71%)	16	69 (46 to 92%)
III	66	50 (38 to 62%)	95	38 (28 to 48%)
Prior radiotherapy				
No	26	72 (55 to 90%)	52	63 (50 to 76%)
Yes	52	39 (25 to 52%)	69	32 (21 to 44%)
Risk group [c]				
Low risk	0		4	100
Standard risk	29	90 (78 to 100%)	42	69 (54 to 83%)
High risk	43	27 (13 to 41%)	62	35 (23 to 47%)
Very high risk	6	17 (0 to 47%)	13	8 (0 to 15%)
Treatment protocol				
SIOP-MMT 95	24	46 (26 to 66%)	52	60 (47 to 74%)
ICG-RMS 96	5	40 (0 to 83%)	17	47 (23 to 71%)
E*p*SSG-RMS 2005	49	53 (39 to 68%)	53	31 (18 to 44%)

Abbreviations: E*p*SSG-RMS 2005, European *paediatric* Soft tissue sarcoma Study Group-Rhabdomyosarcoma 2005 study; GU, genito-urinary; IRS, Intergroup Rhabdomyosarcoma Study Group post-surgical stage; SIOP-MMT95, International Society of Paediatric Oncology Malignant Mesenchymal Tumor-95 study; STSC-RMS96, Italian paediatric Soft Tissue Sarcoma Committee Rhabdomyosarcoma-96 study.

a Favorable histology are all embryonal, spindle cells, botryoid RMS; unfavorable are all alveolar RMS, including RMS NOS (n=2).

b IRS group: Group I, primary complete resection (R0); Group II, microscopic residual (R1) or primary complete resection but N1; Group III, macroscopic residual (R2).

c Based on E*p*SSG-RMS-2005 risk group stratification, see Table S2

was significantly shorter for the routine imaging group compared to the clinical symptoms group. As the interval between surveillance imaging was gradually extended in the years after therapy, it was less likely that patients were detected by routine imaging after the first 3 years of follow-up. Nevertheless, also in the first two years after end-of-therapy, in the majority of patients (106/180) relapse was detected because of clinical symptoms.

Our findings are consistent with a single center study of Lin et al. (n=43), where authors compared survival for relapsed RMS patients in whom events were detected by clinical symptoms to survival for patients in whom events were detected by routine imaging. Three- year OS was 20% (n=15) for relapsed patients detected by routine imaging and 11% (n=28) for relapsed patients detected by clinical symptoms (p=0.38).(9) However, Lin et al. included a heterogeneous group of patients, including patients with metastatic disease at initial diagnosis and patients that relapsed during treatment.

Recent studies assessing the value of routine imaging in other soft-tissue and bone sarcoma have shown contradictory results, which illustrates the necessity for tumor specific studies assessing the value of surveillance imaging, since its value is dependent on tumor specific factors (e.g. tumor biology and chance of survival after relapse).(21-23)

The current study is limited by its retrospective design. We tried to limit this bias by using a standardized CRF. Furthermore, data was collected by one dedicated physician nationwide or by experienced pediatric oncologists to limit the number of data collectors and ensure required expertise. A further limitation is that we only included patients treated in larger pediatric oncology centers. this might have biased our results| However patient and tumor characteristics were comparable to a previously described large cohort of patients with relapsed RMS by Chisholm et al.(4) Because of its retrospective design, and the uncertainty that clinical symptoms that were present at time of routine imaging would have led to additional imaging, we decided to combine this group (routine imaging with symptoms) with the group of patients detected by routine imaging without symptoms. Furthermore, the included patients were treated according to different protocols over almost two decades; treatment approaches have changed over time and higher resolution imaging techniques have become available. This might be the reason why more patients were detected by routine imaging in the subgroup treated according to the E*p*SSG-RMS 2005 protocol; yet still the majority of patients (51.5%) were detected by clinical symptoms and 64.4% of the patients had clinical symptoms at time of relapse detection (n=65).

Although we included almost 200 patients with relapsed RMS, the number of patients did not allow us to evaluate the value of surveillance imaging in specific subgroups (e.g. patients less likely to present with clinical symptoms because of tumor localization). We cannot be certain that specific patients might benefit from early detection of relapse;

the time span before clinical symptoms become apparent could be longer for tumor relapses at specific sites.

Based on the number of patients that did not experience a tumor relapse after achieving complete remission in the E*p*SSG-RMS 2005 study (79.6%), the number of patients without clinical symptoms at time of relapse (28.1%), and the follow-up recommendations (12 scans of the primary site and 12 chest X-rays in the first 5 years after therapy), we estimated that 178 scans of the primary site and 178 chest X-rays were needed to detect one patient with a relapse without clinical symptoms.

Since RMS generally occurs in young patients, a substantial proportion of patients requires general anesthesia (often below age of 8 years; 58.3% in the current analysis) to generate good quality imaging. Besides the short term risk associated with general anesthesia,(24) there is an ongoing debate about the consequences of the use of general anesthesia in the developing brain.(25-27) Worrisome as well is that there is increasing evidence of gadolinium deposition in parts of the brain after repeated administration of gadolinium-contrast agents, although the clinical significance of these findings remains unclear.(28, 29) In addition, follow-up imaging also implies repetitive radiation exposure, mainly caused by chest radiographs, since local imaging is usually done by MRI. (12, 13) Furthermore, the repetitive surveillance imaging causes stress and anxiety for patients and parents.(14-16) Based on our analyses it appears that the risk of these potential side effects could be reduced by reducing the number of radiological examinations.

McHugh and Roebuck previously questioned the value of surveillance imaging and stated that randomized controlled trials are needed to determine whether earlier detection of relapse by routine imaging results in improved survival.(20) The feasibility of including pediatric patients in a trial randomizing between radiologic follow-up and only clinical follow-up is questionable, and the question is whether we need a randomized trial to modify surveillance recommendations.

Whereas the treatment for newly diagnosed patients with RMS is based on extensive risk stratification models, the follow-up recommendations after end-of-treatment are identical for all patients.(30) Potentially, patients with a high chance of successful salvage treatment might benefit more from frequent radiologic imaging than patients with a small chance of cure after relapse; a nomogram previously developed by Chisholm et al. might help to select those patients potentially benefitting from frequent surveillance. (4) We strongly feel we should try to achieve international consensus on surveillance recommendations in patients treated for RMS.

To conclude, based on the results of this study there is no evidence that current surveillance regimens after therapy for patients treated for localized RMS lead to improved survival after relapse. There is a need for risk-adapted follow-up strategies to improve

the efficiency of follow- up after RMS treatment, but the needs and preferences of patients and parents should also be taken into account.

Funding

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Table S1. Follow-up recommendations after end-of-therapy according to SIOP-MMT 95 study, STSC-RMS 96 and E*p*SSG-RMS 2005 study.

SIOP-MMT 95	**1st year**	**2nd year**	**3rd year**	**4th and 5th year**
Clinical examination	Every 2 months	Every 2 months	Every 3 months	Every 6 months
Local imaging by ultrasound/CT/MRI	Every 3-4 months	Every 3-4 months	Every 3-4 months	Every 6 months
Chest radiograph	Every 3-4 months	Every 3-4 months	Every 3-4 months	On indication

STSC-RMS 96	**1st year**	**2nd year**	**3rd year**	**4th and 5th year**
Clinical examination	Every 2 months	Every 2 months	Every 4 months	Every 6 months
Local imaging by ultrasound/CT/MRI	Every 4 months	Every 4 months	Every 6 months	Yearly
Chest radiograph	Every 4 months	Every 4 months	Every 4 months	Every 6 months

E*p*SSG-RMS 2005	**1st year**	**2nd year**	**3rd year**	**4th and 5th year**
Clinical examination	Every 3 months	Every 4 months	Every 4 months	Yearly
Local imaging by ultrasound/CT/MRI	Every 3 months	Every 4 months	Every 4 months	Yearly
Chest radiograph	Every 3 months	Every 4 months	Every 4 months	Yearly

Table S2. E*p*SSG-RMS-2005 risk stratification

Risk Group	Subgroups	Pathology	Post-surgical Stage (IRS Group)	Site	Node stage	Size & Age
Low Risk	**A**	Favorable	I	Any	N0	Favorable
Standard risk	**B**	Favorable	I	Any	N0	Unfavorable
	C	Favorable	II, III	Favorable	N0	Any
	D	Favorable	II, III	Unfavorable	N0	Favorable
High Risk	**E**	Favorable	II, III	Unfavorable	N0	Unfavorable
	F	Favorable	II, III	Any	N1	Any
	G	Unfavorable	I, II, III	Any	N0	Any
Very High risk	**H**	Unfavorable	I, II, III	Any	N1	Any

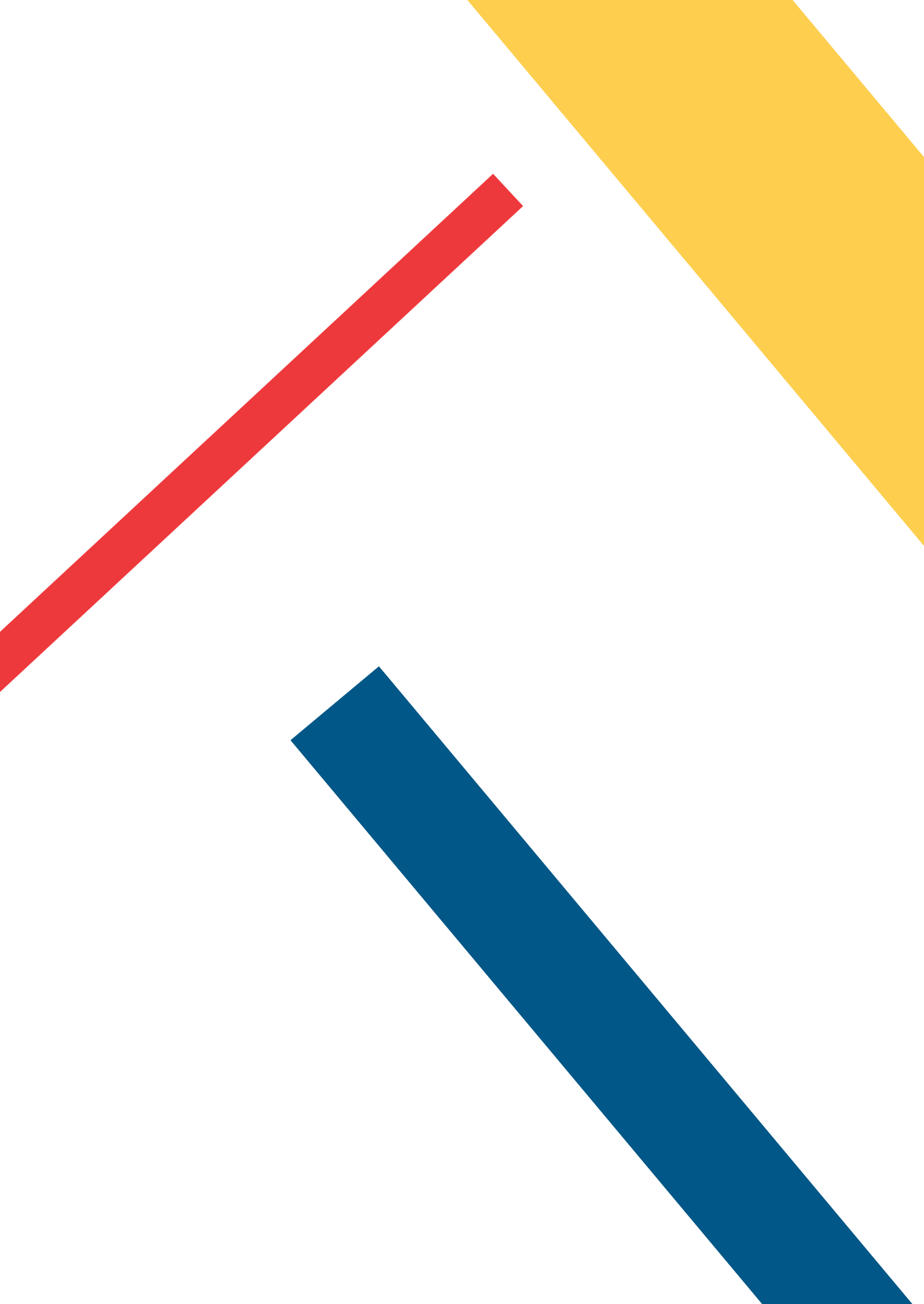
Pathology:
Favorable = all embryonal, spindle cells, botryoid RMS
Unfavorable = all alveolar RMS

Post-surgical stage (IRS Group):
Group I = primary complete resection (R0)
Group II = microscopic residual (R1) or primary complete resection but N1
Group III = macroscopic residual (R2)

Site:
Favorable = orbit, GU non bladder prostate and head & neck non parameningeal
Unfavorable = parameningeal, extremities, GU bladder-prostate and other site

Node stage:
N0 = no clinical or pathological node involvement
N1 = clinical or pathological nodal involvement

Size & Age:
Favorable = Tumor size <5cm and Age <10 years
Unfavorable = all others (i.e. Size >5 cm or Age ≥10 years)



CHAPTER 7

GETTING CONTROL DURING FOLLOW-UP VISITS: THE VIEWS AND EXPERIENCES OF PARENTS ON TUMOR SURVEILLANCE AFTER THEIR CHILDREN HAVE COMPLETED THERAPY FOR RHABDOMYOSARCOMA OR EWING SARCOMA

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ABSTRACT

Purpose

Patients treated for rhabdomyosarcoma (RMS) or Ewing sarcoma (ES) are subject to extensive follow-up after completion of therapy. The aim of this follow-up is to monitor treatment side effects and to detect relapse in an early phase to improve prognosis after relapse. Little is known about parental emotional experiences during this period. We assessed the views and experiences of parents of children treated for RMS or ES on the follow-up examinations after completion of therapy.

Methods

We conducted two focus group meetings and four semi-structured telephone interviews with parents of children treated for RMS or ES in Dutch pediatric oncology centers. Parents of children 0–5 years after end-of-therapy were invited via letters (response rate 31%) and via social media channels of "Dutch Childhood Association for Children and Parents" (VOKK). An inductive thematic approach was used to analyze the data.

Results

In total, 12 parents (fathers, n = 3; mothers, n = 9) of 12 patients treated for RMS (n = 6) or ES (n = 6) participated. Median age at diagnosis for their children was 7.9 years and median time after end-of-treatment was 37 months. Four major themes were identified: content of follow-up, distress and anxiety, search for reassurance and hope, and interaction with others. Parents of children treated for RMS or ES report experiencing significant distress after completion of treatment. They report that their distress was decreased by adequate communication about content, timing, and reasoning behind follow-up.

Conclusion

Physicians should pay attention to the needs of individual parents to reduce distress in the period after completion of therapy.

INTRODUCTION

Over the last decades, the overall survival for pediatric rhabdomyosarcoma (RMS) and pediatric Ewing sarcoma (ES) has increased to around 64% for RMS and 72% for ES.[1] Nevertheless, still many patients experience a tumor relapse after end-of-treatment.[2,3] Over 50% of the relapses in RMS and ES occur within 2 years from initial diagnosis and survival after relapse in RMS and ES is generally poor.[4-6]

After completion of treatment, patients treated for RMS or ES are subject to extensive follow- up. The goal of this follow-up is to detect a tumor relapse before clinical symptoms occur and to monitor treatment side effects, although the clinical value of follow-up after childhood cancer is assessed and debated in several studies[7-9], the views of parents on the content of the follow-up has received no attention. The end-of-therapy entails a major transition in care[10]; it is often a celebrated milestone, but end-of-therapy could also be a period of significant distress and fear of cancer recurrence for parents, especially in the first year.[11-14] Furthermore, parents could also fear long-term sequelae of the treatment and these sequelae could impact the quality of life of patients and parents.[15-17] Besides the fear for long-term sequelae, parents could also experience uncertainty, disease-related fear, and loneliness.[18] Although, in general, elevated levels of distress return to normal over time, the scheduled follow-up examinations could result in additional distress.[19] On the other hand, the routine imaging could give reassurance to parents about the health condition of their child and no follow-up imaging could result in additional distress. Although the coming-off treatment period has been described previously, relatively little is known about fear of recurrence in parents of children treated for RMS and ES.

The results of the studies on the clinical value of follow-up examinations after childhood cancer could result in a change of follow-up recommendations in future study protocols with potential decrease in screening intensity and/or duration. The question arises what do parents need to be in control during the period after completion of therapy. To address this question, we aimed to assess the views and experiences of parents of children treated for RMS or ES on the period after completion of therapy. We asked parents to reflect on their physical and psychological reactions during the follow-up period, what helped them to keep control during this period, and how they reacted to the follow-up examinations. We focused on RMS and ES, since the risk of recurrence in both entities is comparable, survival after recurrence is poor, and the follow-up recommendations for both tumor subtypes are also comparable (see Table 1).

Table 1. Follow-up recommendations for patients treated for Rhabdomyosarcoma (RMS) or Ewing sarcoma (ES).

	1st year	2nd year	3rd year	4th year	5th year
Rhabdomyosarcoma *					
Clinical examination	Every 3 months	Every 4 months	Every 4 months	Yearly	Yearly
Imaging primary tumor site	Every 3 months	Every 4 months	Every 4 months	Yearly	Yearly
Lung imaging	Every 3 months	Every 4 months	Every 4 months	Yearly	Yearly
Ewing sarcoma #					
Clinical examination	Every 2 months	Every 2 months	Every 3 months	Every 6 months	Yearly
Imaging primary tumor site	Every 4 months	Every 4 months	Every 6 months	Every 6 months	Yearly
Lung imaging	Every 2 months	Every 2 months	Every 3 months	Every 6 months	Yearly

* Follow-up recommendations according to the European *paediatric* Soft tissue sarcoma Study Group-RMS-2005 protocol for localized disease. # Follow-up recommendations according to the EWING 2008 protocol.

METHODS

Study design

To assess the views of parents on the follow-up examinations after completion of therapy, we conducted a qualitative analysis with focus group (FG) meetings and semi-structured telephone interviews. We chose to use FG meetings to obtain a broad overview of the views and experiences of the group of parents on the follow-up after completion of treatment. A FG can provide more detailed information about an experience compared to a questionnaire and generates more disclosures or discussion compared to individual interviews. This study was conducted in the Academic Medical Centre (AMC) Amsterdam between January 2017 and December 2017. We invited parents of patients treated for RMS and ES in their follow-up period (0–5 years after completion of therapy) and in persistent remission of their disease to participate in the FG meetings. We recruited parents of children treated at the AMC and, to include a more diverse group of parents, we also recruited parents from other regions via the Dutch Childhood Cancer Parent Organization (VOKK). Parents were eligible if their child was 0– 18 years at time of diagnosis of RMS or ES.

The FG meetings were held at the AMC and at the office of the VOKK. Semi-structured telephone interviews were conducted with parents who were not able or who were not willing to participate in the FG meetings but were willing to share their experiences.

In total, 26 parents of children treated in the AMC were invited by letter, with a reminder after 2 weeks; 11 parents responded and finally, 8 parents participated in this study (response rate 31%). Furthermore, we invited parents via the newsletter and social media channels (such as Facebook) of the VOKK, resulting in 4 additional participants. The institutional review board of the AMC decided that the Medical Research Involving Human Subjects Act (WMO) did not apply for this study.

Data collection

The FG meetings were moderated by two researchers (B.V. and M.A.G.) and lasted 1.5–2 h; both were unacquainted with participating parents. A topic guide was developed for the FG meetings based on a review of the literature on adult patients and input from pediatric oncologists (Table 2). The topic guide was designed to determine the views of parents on the period after completion of therapy, to determine physical and psychological functioning experienced by parents in relation to the follow-up visits, and to assess whether follow-up imaging influenced their functioning in everyday life. Furthermore, it was evaluated if questions were open and in line with the research question. The focus group discussions were audio recorded (with the permission of the participants). The semistructured interviews were conducted by one researcher (B.V.). The same topic list was used for these interviews and the interviews were audio recorded.

Table 2. Topic list used in the FG meetings and in the semi-structured interviews.

Opening questions
- Could you introduce yourself, your family situation and elaborate on your child's illness?
- What does the follow-up of your child look like at the moment, in terms of frequency and content of the follow-up?
Key questions
- How did you experience the moment directly after end-of-treatment?
- How do you experience the moments of follow-up appointments?
- How do you experience the follow-up imaging?
- Do you experience specific emotions and/or stress?
- What helped you to control your emotions around a follow-up visit?
- What is the influence of the following factors on emotions/stress;
- Upcoming follow-up appointments?
- Health status of child?
- Partner or other family members?
- What is the influence on your daily life functioning?
Final question
- Do you have specific recommendations for future follow-up

Data analysis

The FG meetings and interviews were audio recorded and transcribed verbatim. These data were analyzed by using an inductive thematic approach, suitable to report a range of experiences[20]; three authors (B.V., P.F.L., M.A.G.) were involved in the analysis.

Data analysis was performed by using MAXQDA software (version 12.2.1.) First, the researchers independently read, reread, and subsequently open-coded the transcripts of the FG meeting by highlighting and categorizing keywords. Thematic analysis was used to identify recurring topics and these general codes were discussed in team meetings and grouped into themes. No formal interrater reliability assessment was done.

In addition, the semi-structured interviews were read and coded by one author (B.V.). All themes were reviewed and, if necessary, adapted, after coding of a new interview. This process continued until data saturation was reached. No new themes emerged following the semi- structured interviews.

RESULTS

In total, 12 parents (9 mothers, 3 fathers) of 12 patients treated for RMS (n = 6) or ES (n = 6) participated in this study. In both FG meetings, four different parents participated and the other four parents participated in semi-structured interviews. The median age at diagnosis for the children of participating parents was 7.9 years (range 0.5–15.5 years) and the median time since end-of-treatment was 37 months (range 5 to 52 months).

Four major themes were identified, discussed in detail below. The themes covered the content of follow-up, distress and anxiety in the period after completion of therapy, search for reassurance and hope, and interaction with others in the period after completion of therapy. Table 3 describes the major themes and corresponding examples of statements of the participants.

Content of follow-up

The follow-up for the children of participating parents was depending on the type of treatment, type, and localization of the tumor, but also on the suggested follow-up regimens of the different hospitals. Most parents describe the moment directly after end-of-treatment as a very difficult period. Although the treatment was finished, they did not feel relieved. A mother described this period as 'it felt like I had to swim, but I didn't know how to do it' (diagnosis: RMS, time since end-of-treatment: 26 months).

For all children, the follow-up consisted of regular imaging, with extension of the interval over time. One parent described the follow-up moments as 'tough but necessary' (mother, ES, 50 months), and parents with younger children expressed that the necessity of general anesthesia during follow-up made them extra nervous.

How parents experienced the different parts and content of follow-up was related to previous experiences during treatment and follow-up and potential adverse effects experienced by the child. For example, a mother of a child treated for ES reported the follow-up visits to the orthopedic surgeon as most stressful, because in multiple occasions, the visit to the orthopedic surgeon led to additional surgery. For other parents receiving the results of the MRI was most stressful, because the initial diagnosis was also confirmed on MRI results.

Table 3. Themes emerging from focus groups and semi-structured interviews.

Themes	Characteristics*	Examples
Content of the follow- up	Mother, RMS, 26 months	*'The period directly after end-of-therapy felt like I had to swim, but I didn't know how to do it'*
	Mother, ES, 50 months	*'The follow-up period is tough but necessary ´*
	Mother, ES, 52 months	*'We always felt relieved after the MRI, since our son always gets very upset by the anesthesia'*
	Mother, ES, 51 months	*'Besides the follow-up imaging and the appointment with the pediatric oncologist, we also have appointments with the orthopedic surgeon, urologist and rehabilitation physician.'*
	Mother, ES, 38 months	*'I am surprised that the follow-up is different between hospitals'*
	Mother, ES, 52 months	*'If the protocol prescribes the end of follow-up, than it is okay for me'*
Distress/anxiety over time	Mother, RMS, 35 months	*'The first year, I was getting nervous a month before the follow-up'*
	Mother, ES, 50 months	*'You just want the five years to get over'*
	Father, RMS, 29 months	*'On the day of the imaging I'm always more agitated'*
	Mother, RMS, 12 months	*'You get more confident over the years'*
	Father, ES, 50 months	*'Especially the first few times I was really anxious'*
	Mother, ES, 51 months	*'It would be nice if the different specialists would also discuss their individual advice with each other'*
	Mother, ES, 52 months	*'I know that the outpatient clinic from our oncologist is open on Monday and Friday, so we always arrange the imaging on Friday to have the results on Monday.'*
Search for reassurance and hope	Mother, RMS, 47 months	*One mother on the value of the MRI: 'it feels reassuring to know that everything looks good on the inside'*
	Father, ES, 50 months	*'It is unbelievable how strong our boy was, which also made us feel strong and proud'*
	Father, RMS, 5 months	*'You do get the information one way or another, because during follow-up you also receive unsolicited information from parents sitting next to you'*
	Mother, RMS, 12 months	*'Our oncologist tells us that the risk of recurrence is small after the first year, but what is small? I can't find stories of children surviving this tumor on the internet, so where are these survivors?'*
Interactions with others	Mother, RMS, 35 months	*'I notice that I want to protect my child in everything and I need to be aware not to do this too much'*
	Mother, RMS, 26 months	*'On the day of a follow-up visit our other children are really nervous, so when we get the results we call them immediately which make them really happy'.*
	Mother, ES, 50 months	*'My husband always says "it not useful to worry about something that is not there and may never be there". This really helps me as well'.*
	Mother, RMS, 47 months	*'Before, when I heard a mother talking about her child having the flu, I thought, let's swap our situation … now I'm able to react with compassion again'.*

* Characteristics includes sex of parent, diagnosis of child, and time since end-of-treatment. ES, Ewing sarcoma; RMS, rhabdomyosarcoma.

Most parents were aware of the content of the follow-up prescribed in the treatment protocol, which was also explained by their pediatric oncologist. In general, parents understood that the extension of the interval between the imaging was possible because of the decreasing chance of relapse over time. To the question whether parents would accept it if in the future no imaging would be performed, one mother replied; 'the follow-up is according to a protocol and is explained by the oncologist and because of the explanations I felt confident that this is okay; however, the moment approaches that the follow-up imaging might no longer be done and that feels very difficult' (ES, 52 months). Another mother said 'oh I don't know, I hope that moment doesn't come soon' (ES, 15 months).

Distress and anxiety over time

The most reported theme in this study was distress and anxiety after end-of-therapy; almost all parents reported experiencing distress during the follow-up period and this was influenced by several factors. Most parents reported experiences of distress in the years after end-of-therapy, increasing in the days (for one mother even a month) prior to follow-up imaging; some parents experienced physical complaints, others were agitated prior to follow-up. Several parents described feeling extremely tired after having received the positive results of the follow-up visit.

Although most parents described the follow-up as stressful, some reported experiencing it as pleasant to be back in the hospital. One mother described it as 'feeling like coming home' (RMS, 47 months), whereas another mother preferred to stay home waiting for a call from her partner (ES, 52 months).

The distress was influenced by the time passed since end-of-therapy; although most parents felt relieved when the imaging did not show signs of tumor recurrence, this feeling did not endure for a long time in the first year of follow-up. Over the years, the distress decreased and the extension of the interval between follow-up decreased the feeling of distress for a longer period of time.

Distress was further influenced by treatment-related adverse events, such as fatigue and physical rehabilitation of the child. Several parents described that they could have never imagined it would take years for their child to fully rehabilitate after end-of-treatment. Distress during the follow-up period further accumulated by inadequate communication between different medical specialists. For example, one mother told that her daughter (ES, 51 months) had regular follow-up visits with a rehabilitation physician and with an orthopedic surgeon; however, both physicians gave contrary advice without consulting each other which caused distress and uncertainty for the child.

Communication regarding the results of follow-up examinations also influenced distress. All parents made arrangements with their oncologist regarding the communication of the results; this structure helped them to reduce distress around the follow-up, as

illustrated by one mother; 'I know that the outpatient clinic from our oncologist is open on Monday and Friday, so we always arrange the imaging on Friday to have the results on Monday.' (mother, ES, 52 months).

Increasing age of the children also influenced distress; some parents noticed that their children were aware or were becoming aware of their history of cancer. These children were also nervous before follow-up imaging or very vigilant about their own health. Some children were examining their body for potential signs of relapse regularly.

Participating parents also reported positive consequences of the disease such as developing a different attitude towards life. One mother described that 'it does have positive sides; our family, my husband and I, became much closer' (ES, 51 months). Another mother said 'because of what has happened, I'm nowadays more aware of the simple things in life; I could sit at a table and just enjoy being there' (RMS, 12 months).

Reassurance and hope

To cope with the distress around the follow-up examinations, many parents were looking for reassurance and hope and had their own strategies of coping. Most parents reported to find reassurance in the positive results of the follow-up imaging. Parents described it as 'reassuring to know that everything looks good on the inside,' although they were aware that an MRI was not predictive for the upcoming period.

Previous experiences determined the reassurance. One mother reported that, although she was anxious for the results of the MRI, she did not worry about the result of the chest X-ray since her child (ES, 38 months) did not have lung metastases at diagnosis.

Parents felt reassured by (improvements in) the health condition of their child and also by their strength, attributing positive characteristics to the child. One father said 'it is unbelievable how strong our boy was, which also made us feel strong and proud' (ES, 50 months).

Furthermore, hope of parents was influenced by information received during the follow-up period, but also information received during treatment. Some parents were actively looking for 'all' available information; others were trying to protect themselves by not looking for additional information, although they did receive information passively. A participating father explained 'you do get information one way or another, because during follow-up you also receive unsolicited information from parents sitting next to you' (RMS, 5 months). Parents specifically mentioned survival chances; almost all parents were aware of survival chances; nevertheless, they reported to find it difficult to understand the meaning of risks. One mother described her feelings about risks of relapse as follows: 'Our oncologist tells us that the risk of relapse is small after the first year, but what is small? I can't find stories of children surviving this tumor on the internet, so where are these survivors?' (RMS, 12 months).

Interaction with others

The period after end-of-treatment influenced the interaction with partners, especially around the follow-up visits. Some parents discussed their feelings with their partners, whereas others did not discuss their feelings at all, which sometimes led to tension in their relationship/marriage. Mothers often indicated that fathers were more sensible or less emotional with respect to the follow-up visits. The follow-up visits also influenced other children in the family. One mother stated that 'On the day of a follow-up visit our other children are really nervous, so when we get the results we call them immediately which made them really happy' (RMS, 26 months).

Parents described that they had the feeling that their friends and relatives did not understand their situation; their friends and relatives generally thought that parents should feel relieved since the treatment was finished, whereas parents had the feeling they were still in the middle of the whole process. This feeling also faded out, as one mother described 'Before, when I heard a mother talking about her child having the flu, I thought, let's swap our situation … now I'm able to react with compassion again' (RMS, 47 months).

DISCUSSION

This qualitative study describes the views and experiences of parents of children treated for RMS or ES on the follow-up examinations after completion of therapy. We asked parents to reflect on their physical and psychological reactions during the follow-up period, what helped them to keep control during this period, and how they reacted to the follow-up examinations. The results centered around four major themes; the content of follow-up, distress and anxiety in the period after completion of therapy, search for reassurance and hope, and interaction with others in the period after completion of therapy. This study helped us in our understanding what parents need to feel in control during the period after completion of treatment.

This period is difficult for parents; it entails a major transition in pediatric oncology care and can cause significant distress.[10-14] Whereas social support is generally high at time of diagnosis, support tends to decline over time.[21] Although the treatment has finished, the threat of a potential relapse becomes apparent in parents.[19,22] During this period, parents and child try to reintegrate in everyday life, while children might still suffer from adverse effects caused by the treatment. Distress and anxiety caused by fear of cancer recurrence play a significant role during the follow-up period, which is traditionally described as *The Damocles Syndrome*.[23] Fear of cancer recurrence can significantly impact the quality of life of cancer survivors, which was shown in other cancer types.[24]

Because of the qualitative nature of this study, we were able to obtain a detailed description of the period after completion of therapy. Most participating parents felt reassured by the scheduled follow-up examinations; nevertheless, these examinations also evoked additional distress and anxiety, which was reported previously.[19]

However, the experienced distress and anxiety were not only caused by fear of cancer recurrence, but also by treatment-related adverse effects, which are common in patients treated for RMS or ES.[25] These adverse events depend on the tumor localizations, received treatment, and on patient characteristics. Therefore, parents indicated that specific parts of follow-up visits, for example, visits to the orthopedic surgeon, were more important than other parts.

Throughout the follow-up period, parents were continuously looking for reassurance and hope. Reassurance was found in the radiologic examinations and was further enhanced by getting control over specific situations, for example, by making strict arrangements around the follow- up examinations. These strategies can be considered cognitive control coping strategies to get a hold on the situation, which is for the most part uncontrollable.[26] This study shows again the importance of coping strategies throughout the cancer trajectory. Many studies have shown that psychological functioning of both children and parents is affected by how families cope with the illness.[27,28] It is important that health care providers are sensitive to the control strategies used by parents and take this into account during the follow-up process. Health care providers could play a significant role in promoting normal family life by providing clear information on the condition of the child and enhancing family coping strategies.[29] Participating parents felt reassured by the knowledge that the risk of relapse decreased over time and with that also the frequency of follow-up; however, some parents experienced more distress by knowing the risk of relapse specifically. Health care providers need to think of which information at which time point is given to individual parents.[30,31]

Finally, the period after completion of therapy affected the interaction with partners, other children, and their social life. Although parents reported, on the one hand, to enjoy life more, they also reported feelings of loneliness. As previously suggested by Kearney et al., parents need to receive early and ongoing assessment of their mental health needs with access to appropriate interventions to optimize parents well-being but also family functioning.[32]

Limitations

A limitation of this study is that the response to the invitation letters was only 31% and most of the participating parents were mothers. Underrepresentation of fathers in studies on the impact of the off-therapy period after childhood cancer treatment was previously reported and the results of this study indicate that there might be differences in views and coping styles between fathers and mothers.[13] Furthermore, we only

included Dutch parents making it difficult to determine whether our results are generalizable to families with other backgrounds. A further limitation is that we included patients treated for RMS or ES. We are uncertain whether the views of parents on the follow-up examinations after end-of-therapy are comparable since specific patients may experience specific adverse effects. Nevertheless, major themes identified in this study are comparable to those identified in a review focused on the psychosocial impact of childhood cancer treatment including studies from different countries and patients with different tumor types.[13] Therefore, we believe that the views of parents of children treated in other countries and with different tumor types might be comparable.

Furthermore, although the qualitative design of the current study enabled the collection of detailed data, it is difficult to assess whether the participating parents were representative for the total group of parents. We tried to limit selection bias by inviting parents via letters and via the VOKK website and social media channels. We conducted semi-structured interviews with parents not able or not willing to participate in FG meetings; however, the number of interviews was small (n = 4).

Clinical implications

Our findings are of utmost importance for clinical practices to be acted upon by health care providers. We would advise physicians to pay attention to the individual needs of parents to reduce the distress in the off-therapy period and to focus on parental coping strategies. Future studies and education should focus on communication strategies to discuss follow-up care with parents, to assist parents in the follow-up period[33] Furthermore, continuing attention should be paid to the mental health needs of parents also after completion of therapy.

In light of the recent and ongoing studies regarding the clinical value of follow-up imaging after end-of-therapy, future follow-up recommendations should be adapted and more tailored on tumor characteristics, but they should also take parental preferences into account.[8,34,35]

Conflict of interest

This work has been supported by the KIKA foundation (Children Cancer-free), but this foundation had no role in study design or interpretation of the data.

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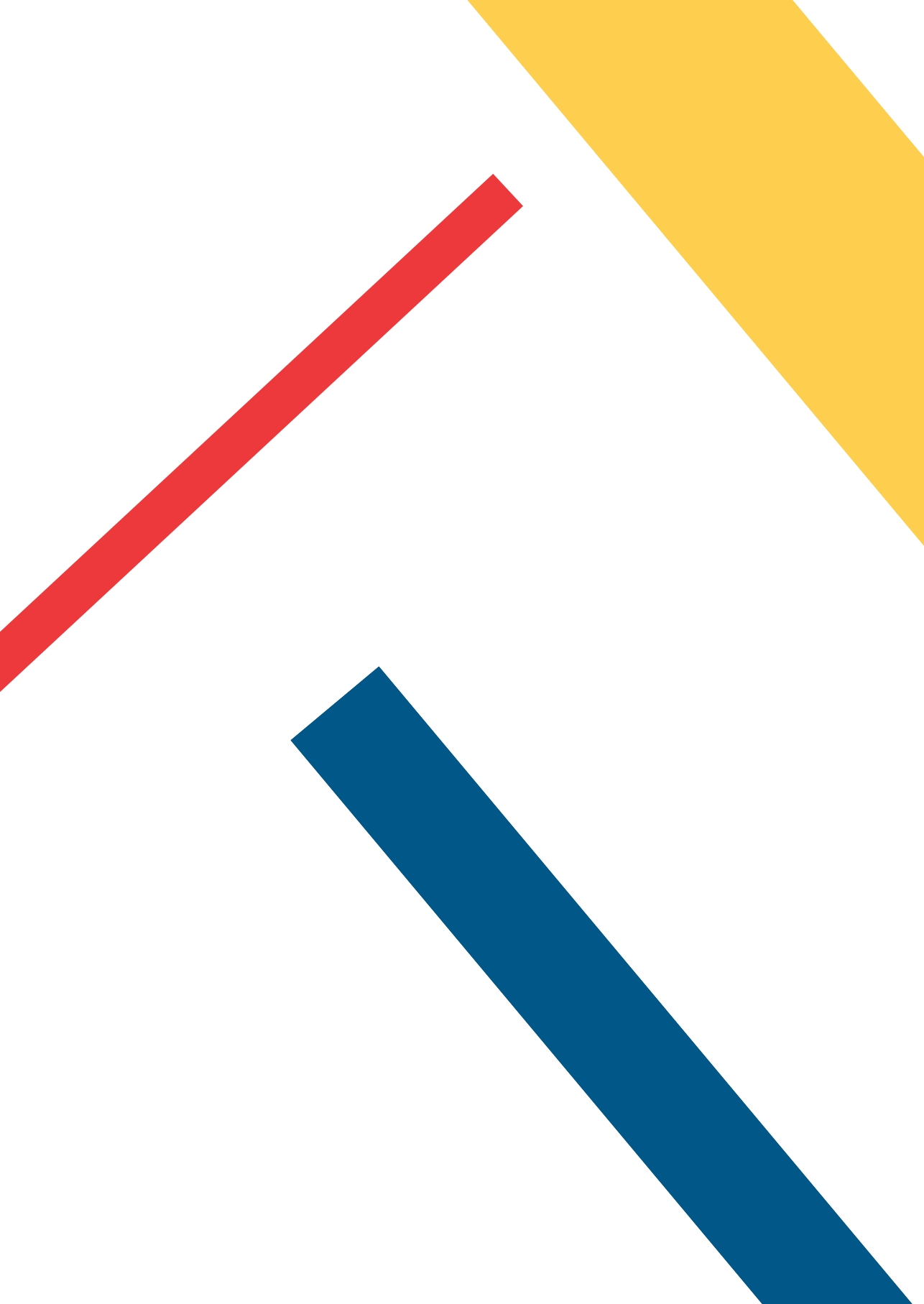
PART TWO



CHAPTER 8

PSYCHOSOCIAL WELL-BEING OF LONG-TERM SURVIVORS OF PEDIATRIC HEAD–NECK RHABDOMYOSARCOMA

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ABSTRACT

Background

Head and neck rhabdomyosarcoma (HNRMS) survivors are at risk to develop adverse events (AEs). The impact of these AEs on psychosocial well-being is unclear. We aimed to assess psychosocial well-being of HNRMS survivors and examine whether psychosocial outcomes were associated with burden of therapy.

Procedure

Sixty-five HNRMS survivors (median follow-up: 11.5 years), treated in the Netherlands and the United Kingdom between 1990 and 2010 and alive ≥2 years after treatment visited the outpatient multidisciplinary follow-up clinic once, in which AEs were scored based on a predefined list according to the Common Terminology Criteria for Adverse Events. Survivors were asked to complete questionnaires on health-related quality of life (HRQoL; PedsQL and YQOLFD), self-perception (KIDSCREEN), and satisfaction with appearances (SWA). HRQoL and self-perception scores were compared with reference values, and the correlation between physician assessed AEs and psychosocial well-being was assessed.

Results

HNRMS survivors showed significantly lower scores on PedsQL school/work domain ($P \leq 0.01$, $P = 0.02$, respectively), YQOL-FD domains negative self-image and positive consequences ($P \leq 0.01$, $P = 0.04$, respectively) compared with norm data; scores on negative consequences domain were significantly higher ($P = 0.03$). Over 50% of survivors negatively rated their appearances on three or more items. Burden of AEs was not associated with generic HRQoL and self-perception scores, but was associated with disease-specific QoL (YQOL-FD).

Conclusion

In general, HRQoL in HNRMS survivors was comparable to reference groups; however, survivors did report disease-specific consequences. We therefore recommend including specific questionnaires related to difficulties with facial appearance in a systematic monitoring program to determine the necessity for tailored care.

INTRODUCTION

Pediatric rhabdomyosarcoma (RMS) accounts for 3% to 5% of all pediatric malignancies, and 40% of the cases arise in the head and neck area (HNRMS).[1] Overall survival for patients with localized RMS has increased to around 80% nowadays,[2,3] and the treatment for HNRMS usually consists of chemotherapy followed by local therapy. Microscopically free surgical margins are often difficult to achieve in the head and neck area; therefore, external beam radiotherapy is often the therapy of choice.

RMS generally occurs in young children, and radiotherapy at young age leads to abnormal growth and function of musculoskeletal tissues; therefore, many HNRMS survivors suffer from facial disfigurements (incidence rate, 35–77%).[4-6] Furthermore, other adverse events, such as growth hormone deficiency and cataract, are frequently reported.[4-7] The impact of these adverse events on psychosocial well-being is unclear. Multiple studies showed that, in general, health-related quality of life (HRQoL) in survivors of childhood cancer is comparable with normative values of healthy individuals; however, specific subgroups are at risk for impaired psychosocial wellbeing.[8-11] Identifying these subgroups at risk is important to develop adequate interventions to improve psychosocial well-being. Kinahan et al showed that in childhood cancer survivors, facial disfigurement negatively affected general health, mental health, and emotional wellbeing.[12] Previous studies also showed that HRQoL in children with facial deformities, such as cleft lip patients, is impaired.[13,14]

Therefore, psychosocial well-being of HNRMS survivors needs proper attention. Schoot et al previously showed that HRQoL among HNRMS survivors was comparable with normative values.[6] However, this study only described rather general HRQoL measurements. A more comprehensive understanding of the psychosocial well-being of HNRMS survivors is lacking. In this study, psychosocial well-being was assessed by measuring HRQoL, self-perception, and satisfaction with appearances, in HNRMS survivors treated in three large pediatric oncology centers (Great Ormond Street Hospital [GOSH], London, The Royal Marsden Hospital [RMH], Sutton and Emma Children's Hospital-Academic Medical Centre [EKZ-AMC], Amsterdam). Furthermore, we examined whether physician-assessed adverse events were associated with psychosocial well-being.

METHODS

HNRMS survivors

All patients (aged 0–18 years) treated for HNRMS in GOSH, RMH, or EKZ-AMC, between 1990 and 2010 and alive ≥2 years after end of therapy were invited to the outpatient multidisciplinary clinic (n = 113).

In this cross-sectional study, all survivors were evaluated once at the outpatient multidisciplinary clinics to evaluate the occurrence of adverse events.6 Survivors ≥ 8 years of age were asked to complete questionnaires regarding their psychosocial well-being. Written informed consent was obtained from all survivors (>12 years) and their guardians treated in GOSH/RMH. For Amsterdam, the local institutional review board decided that the Act on Medical Research Involving Human Subjects did not apply, because data were collected during a regular follow-up clinic.

Rhabdomyosarcoma treatment

Treatment details for this cohort have been described previously6; in general, all patients received multidrug chemotherapy and decisions on local therapy were made after two or three courses of chemotherapy. If local therapy was indicated, the patients from the United Kingdom (UK) received external beam radiotherapy and the EKZ-AMC patients received AMORE (Ablative surgery, MOld technique after loading brachytherapy, and surgical REconstruction) treatment if feasible and otherwise external beam radiotherapy.[6,7,15-17] AMORE treatment was considered feasible if a macroscopic radical resection and adequate mold placement seemed possible.

Instruments

HNRMS survivors were asked to complete *the Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales*, self-perception domain of the *KIDSCREEN, Youth Quality of Life Instrument—Facial Differences Module (YQOL-FD)*, and the *Satisfaction with appearances (SWA)* questionnaire. The questionnaires are described in detail below. All HNRMS survivors were asked to complete respective questionnaires, unless explicit age groups are specified below.

PedsQL

This questionnaire consists of 23 items assessing HRQoL on four subscales: physical functioning, emotional functioning, social functioning, and school/work functioning.18 Each item states a problem, for example "I have trouble keeping up with school/work" or "I have trouble sleeping." Each item was scored on a five-point Likert scale. Total score (all subscales) and psychosocial health (emotional, social, and school/work) were calculated by summing up scores of the corresponding subscales. Scores ranged 0 to 100, with higher scores indicating better HRQoL. We used weighted reference data, adjusted for sex, for Dutch (NL) survivors and for survivors < 18 years from the United Kingdom.[19-21] We used NL ≥18 years sex-adjusted reference data for UK survivors ≥18 years because no UK reference data were available for adults. We considered this legitimate because reference data for UK and Dutch children aged 11 to 18 years were comparable, and we assumed that reference data in ≥18 years old would also be comparable. Cronbach's alphas for both NL and UK survivors were moderate to good (α: 0.73–0.96).

KIDSCREEN

The KIDSCREEN self-perception domain consists of five items, for example, "have you been happy with the way you are?" Each item was scored on a five-point Likert scale. Raw domain scores were transformed into T-values, with a mean of 50 and standard deviation of 10 in the reference population. Higher scores indicate better HRQoL. We used age- and sex-adjusted country-specific reference values.[22] Cronbach's alphas for both NL and UK survivors were moderate to good (α: 0.77–0.88).

YQOL-FD

The YQOL-FD questionnaire, completed by survivors aged 11 to 18 years, consisted of 30 items assessing quality of life across five domains: stigma, negative self-image, positive consequences, negative consequences, and coping. The instrument is focused on the impact of living with a facial difference, and each item addresses a specific concern, for example, "people stare at me because of how my face looks." Domain scores ranged from 0 to 100. Higher scores on the domains coping and positive consequences indicate higher quality of life. Higher scores on the domains negative consequences, negative self-image, and stigma indicate lower quality of life. No reference data were available for the YQOL-FD; one study reported data for 307 patients with congenital or acquired facial deformities, in which patients were grouped as mild, moderate, or marked based on self-rated facial deformities.[23] The scores obtained from patients with mild facial deformities (n = 250) served as norm data for the functioning of HNRMS survivors. Cronbach's alphas for negative self-image, positive consequences, negative- consequences, and stigma domain were moderate to good (α: 0.66–0.96). Cronbach's alpha for the coping domain was 0.03 for NL survivors, and we decided to exclude this domain from further analyses.

SWA

The SWA, developed by the Psychology Special Interest Group of the Craniofacial Society of Great Britain and Ireland, consists of 18 items (score range, 0–10), with higher scores indicating higher satisfaction with appearance. Each item assesses patients' satisfaction with a specific aspect of the way they look and function in society, for example, "How do you feel about the way you look?" We considered item scores less than 6 as negative. Two items, wearing a hearing aid and braces, were not used in the present study, because the number of survivors with hearing aids or braces was limited. A total mean score was calculated; missing data were imputed by mean scores on the individual item (max two items were imputed). So far, no reference data were published for the SWA. Cronbach's alphas for both NL and UK survivors were good (α: 0.85–0.91).

CTC AE

Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAEv4.0, available at http://evs.nci.nih.gov/ftp1/CTCAE/About.html). We used a selection of predefined adverse events as reported previously.[6] For each survivor, we assessed the total number of adverse events, any grade 3/4 adverse event, and total burden of adverse events by using a burden score adapted from Geenen et al.[24]

Statistical analyses

Data were analyzed with SPSS version 23.0. Differences between participants and non-participants with respect to sex, tumor site and side, histology, treatment protocol, and radiotherapy were analyzed by Fisher exact tests, and difference in age at diagnosis was assessed by the Mann–Whitney test.

One-sample t tests were conducted to analyze whether HNRMS survivors' scores on PedsQL, KIDSCREEN, and YQOL-FD differed from reference values.

The SWA was analyzed descriptively. Mean, standard deviation, and the proportion of negative scores were calculated for each individual item and for the mean item score.

If appropriate, effect sizes were calculated by dividing differences in mean scores between the HNRMS survivors and reference values by the standard deviation of the reference group. Effect sizes of 0.2 were considered small, 0.5 medium, and 0.8 large.[25] Pearson product–moment correlation coefficients were calculated to investigate whether adverse events (defined with CTC AE) were associated with psychosocial outcomes. We considered correlation coefficients of 0.1 as small, 0.3 as medium, and 0.5 as large.[25]

RESULTS

Survivors

In total, 80 survivors attended the follow-up clinic; 65 individuals (81.3%) also completed the questionnaires (Figure 1). The 15 nonparticipating survivors did not differ significantly from participating survivors with respect to demographic and medical variables (Supporting Information Table S1). Median age at time of questionnaire completion was 19.6 years (range, 8.6–35.7 years) for NL survivors and 16.0 years (range, 8.5–27.9 years) for UK survivors. Survivors' characteristics are further described in Table 1.

Health-related quality of life (PedsQL)

In general, subdomain-specific HRQoL of HNRMS survivors did not differ significantly from weighted reference values, except for the school/work domain (Table 2). HRQoL in the school/work domain was significantly lower in both NL and UK survivors compared with the weighted reference for all ages. This was also seen in the NL survivors ≥18 years

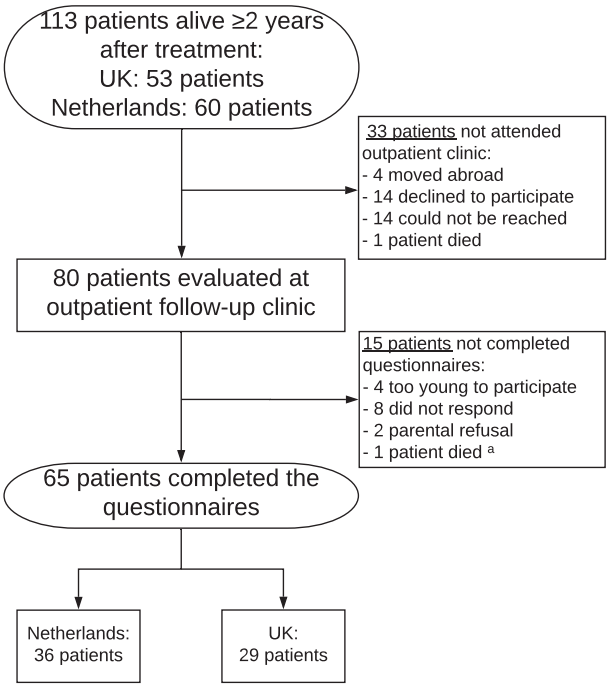

Figure 1. Flow diagram: long-term survivors of HNRMS.
a Patient developed recurrence after follow-up evaluation and did not fill out questionnaire.

and in the group of UK survivors 8 to 17 years, but not in other substrata. Effect sizes were moderate to large (d = 0.58 to d = 0.88). UK survivors also showed significantly lower HRQoL in the psychosocial health domain compared with the weighted reference, with moderate effect size (d = 0.55).

Self-perception (KIDSCREEN)

Self-perception of HNRMS survivors did not differ from the weighted reference values (Supporting Information Table S2).

YQOL-FD

HNRMS survivors scored significantly lower on negative self-image and positive consequences compared with patients with mild facial deformities described by Patrick et al.23 HNRMS survivors scored significantly higher on negative consequences (Table 3). Effect sizes ranged from moderate on positive consequences (d = 0.53), to large (d = 0.91) on negative self-image.

Table 1. Characteristics (n=65) of HNRMS survivors.

		Netherlands N=36	United Kingdom N=29
Age at diagnosis (years)	Median (range)	6.4 (0.5-13.4)	5.1 (1.0-11.9)
Attained age (years)	Median (range)	19.6 (8.6-35.7)	16.0 (8.5-27.9)
Follow-up (years)	Median (IQR)	11.5 (8.5-18.0)	10.9 (6.0-18.5)
Sex, *n* (%)	Male	20 (55.6%)	22 (75.9%)
	Female	16 (44.4%)	7 (24.1%)
Histology, *n* (%)	ERMS	32 (88.9%)	21 (72.4%)
	ARMS	4 (11.1%)	4 (13.8%)
	RMS NOS		4 (13.8%)
Primary site, *n* (%)	PM	15 (41.7%)	15 (51.7%)
	ORB	13 (36.1 %)	9 (31.0%)
	ORB&PM	2 (5.6%)	2 (6.9%)
	HNNPM	6 (16.7%)	3 (10.3%)
Side	Left Right	18 (50.0%)	10 (34.5%)
	Midline	13 (36.1%)	17 (58.6%)
		5 (13.9%)	2 (6.9%)
Treatment protocol	MMT 89	11 (30.6%)	9 (31.0%)
	MMT 95	19 (52.8%)	13 (44.8%)
	MMT 98	0	1 (3.4%)
	RMS 2005	4 (11.1%)	6 (20.7%)
	Other	2 (5.6%)	0
Initial local Tx	No RT	2 (5.6%)	2 (6.9%)
	AMORE	22 (61.1%)	0
	EBRT	12 (33.3%)	27 (93.1%)
Number of RT Tx	0	2 (5.6%)	2 (6.9%)
	1	27 (75.0%)	27 (93.1%)
	2	5 (13.9%)	0
	3	2 (5.6%)	0

Abbreviations: AMORE, Ablative surgery MOld brachytherapy and REconstruction; ARMS, alveolar rhabdomyosarcoma; EBRT, external beam radiotherapy; ERMS, embryonal rhabdomyosarcoma; HNNPM, Head and neck non-parameningeal; IQR, interquartile range; MMT, consecutive study of International Society of Paediatric Oncology Malignant Mesenchymal Tumour group; ORB&PM, orbital with parameningeal extension; ORB, orbital; PM, parameningeal; RMS 2005, European paediatric Soft Tissue Sarcoma group RMS 2005 protocol; RMS NOS, Rhabdomyosarcoma not otherwise specified; RT, radiotherapy; Tx, treatment.

Satisfaction with appearances

Over 50% of NL and UK survivors negatively rated their appearances on three or more items. Over one-third of survivors in the NL and the UK scored negative on the items "noticeable to others" and/or "get on with others" (Table 4). Furthermore, over one-third of the UK survivors scored negative on the items "good looking," "overall appearance," and "teeth," whereas one- third of the NL survivors scored negative on the item "face."

Table 2. HRQOL (PedsQL) of HNRMS survivors.

	Netherlands			NL reference	NL cohort vs reference		United Kingdom			UK reference	UK cohort vs reference	
	n	Mean	SD	Mean[a]	Effect size	p[b]	N	Mean	SD	Mean	Effect size	p[b]
8-17 years	**16**						**17**					
Total score		80.3	13.5	82.15	-0.21	0.60		73.1	21.9	82.65	-0.73	0.09
Physical		88.3	13.7	85.39	0.31	0.41		76.2	28.8	[c] 86.08	-0.70	0.18
Emotional		70.3	17.8	76.78	-0.46	0.17		74.5	22.4	78.10	-0.20	0.52
Social		87.4	14.0	87.65	-0.02	0.95		77.4	20.4	[c] 86.85	-0.56	0.07
School/work		70.6	19.4	76.87	-0.49	0.22		62.4	23.7	[c] 77.29	**-0.88**	**0.02**
Psychosocial health		76.1	15.4	80.42	-0.42	0.27		71.4	20.0	80.32	-0.64	0.08
18+ years	**20**						**11**					
Total score		82.3	12.1	84.81	-0.20	0.36		82.5	13.5	85.73[d]	-0.25	0.45
Physical		86.6	17.3	88.28	-0.11	0.66		88.6	12.7	89.49[d]	-0.06	0.83
Emotional		79.5	15.0	78.69	0.05	0.81		71.8	18.6	80.18[d]	-0.48	0.17
Social		88.0	13.4	87.6	0.03	0.90		87.3	11.5	88.09[d]	-0.06	0.82
School/work		72.5	15.0	82.57	**-0.58**	**0.007**		78.9	19.3	82.87[d]	-0.26	0.55
Psychosocial health		80.0	11.2	82.95	-0.22	0.25		78.9	15.2	83.71[d]	-0.35	0.32
All ages	**36**						**28**					
Total score		81.4	12.6	83.63	-0.20	0.30		76.8	19.4	83.86	-0.54	0.06
Physical		87.3	15.6	86.86	0.04	0.86		81.1	12.7	87.42[c]	-0.45	0.18
Emotional		75.4	16.7	77.70	-0.14	0.42		73.4	18.6	78.92	-0.31	0.17
Social		87.7	13.5	87.48	0.02	0.91		81.3	11.5	87.34[c]	-0.37	0.08
School/work		71.7	16.9	80.27	**-0.58**	**0.004**		68.1	19.3	79.48[c]	**-0.70**	**0.02**
Psychosocial health		78.2	13.2	81.83	-0.29	0.11		74.3	15.2	81.97	**-0.55**	**0.04**

Paediatric Quality of Life Inventory (PedsQL) scale scores range 0-100, with higher scores indicating better health-related quality of life (HRQoL).

a Country specific weighted reference scores, adjusted for sex and age

b Based on one-sample *t*-test

c Not adjusted for sex because there was no sex effect in reference group.

d No country specific reference scores available, NL norm used for UK patients ≥18 years, adjusted for age and sex distribution

Association between adverse events and psychosocial well-being

Adverse events were previously described by Schoot et al.[6] In summary, over half of NL and UK survivors experienced any grade 3/4 adverse event and more than five adverse events of any grade. This was also reflected in high burden scores (Supporting Information Figures S1 and S2). Most common adverse events were musculoskeletal deformities of the face in NL and UK survivors, followed by fibrosis and scarring.

Table 3. Quality of life Facial Differences (YQOL-FD) of HNRMS survivors.

	HNRMS				Mild facial deformities*		Survivors vs mild facial differences	
	n #	Mean	SD	95% CI	Mean	SD	p¥	Effect size
Negative self-image								
NL	12	17.1	15.8	7.1-27.1				
UK	11	12.0	17.4	0.3-23.6				
Total	23	14.6	16.4	7.5-21.7	37.3	25.7	**<0.001**	**-0.91**
Positive consequences								
NL	12	55.2	25.7	38.8-71.5				
UK	11	38.5	33.1	16.3-60.7				
Total	23	47.2	30.0	34.2-60.2	60.7	24.9	**0.042**	**-0.53**
Negative consequences								
NL	12	42.7	27.1	25.4-59.9				
UK	11	23.5	31.4	2.3-44.6				
Total	23	33.5	30.2	20.4-46.6	18.4	20.1	**0.026**	**0.72**
Stigma								
NL	12	20.6	22.8	6.1-35.1				
UK	11	19.1	29.5	0.0-38.9				
Total	23	19.9	25.6	8.8-31.0	27.3	23.5	0.179	-0.31

YQOL-FD scale scores range 0-100, with higher scores on domain negative consequences, negative self-image and stigma indicate lower quality of life, whereas higher scores on domain positive consequences indicate higher quality of life.

¥ p-value based on one-sample *t*-test

Only patients 11-17 years.

* Values obtained from patient group reported in Patrick et al. (17) with self-rated mild facial deformities.

There were small negative correlations for CTC AE scores with HRQoL and self-perception (mainly not statistically significant). CTC AE scores (reflected in burden score and any grade 3/4 event) and YQOL-FD domains (except for positive consequences domain) showed medium to large, positive correlations (Table 5). Only small, negative (not significant) correlations between SWA scores and CTC AE scores were observed.

DISCUSSION

In this cross-sectional study, we assessed psychosocial well-being specifically in a cohort of HNRMS survivors. These survivors were evaluated by a standardized protocol at a multidisciplinary outpatient clinic with a median follow-up of >10 years. This study, therefore, provides important insights into the psychosocial well-being of long-term HNRMS survivors and its association with adverse events.

Table 4. Satisfaction with appearance (SWA) of HNRMS survivors.

	Netherlands				United Kingdom			
	n	Mean	SD	Negative*	n	Mean	SD	Negative*
Mean score (16-items)	35	7.44	1.35	14%	29	7.48	1.61	24%
How do you feel about the way you look?								
How you face looks?	36	6.81	2.39	33%	29	7.34	2.50	28%
The whole of you appearance?	36	7.44	1.75	14%	29	7.41	2.38	35%
Side view/Profile?	36	6.94	2.39	22%	28	7.14	2.55	29%
How good-looking do you think you are?	36	6.75	2.35	25%	29	6.17	2.45	45%
How do you feel about these parts of your face?								
Nose	36	7.69	2.32	14%	29	8.00	2.17	17%
Lips	36	7.97	2.01	11%	29	8.10	2.32	10%
Chin	36	7.61	2.62	17%	29	8.17	1.97	14%
Teeth	36	7.03	2.24	22%	29	6.21	2.88	41%
Cheeks	36	7.83	1.89	14%	29	7.69	2.47	24%
Hair	36	8.17	2.01	11%	29	8.83	1.65	3%
Ears	36	8.50	1.52	8%	28	8.04	2.65	18%
Eyes	35	7.74	2.31	19%	29	7.97	2.57	24%
How happy are you with your speech?	36	7.72	2.24	17%	29	7.41	2.68	21%
How happy are you with your hearing?	36	8.22	2.21	14%	29	8.14	2.17	10%
Overall how noticeable do you feel your face is to other people?	36	5.94	2.96	44%	25	6.56	3.42	36%
Does the way you look make a difference to how you get on with other people?	36	6.81	2.03	36%	25	6.48	2.87	52%

SWA scale scores range 0-10.

*scores of ≤5 were considered negative

In general, HRQoL and self-perception in HNRMS survivors was comparable to reference groups despite the high prevalence of (musculoskeletal) adverse events. However, survivors did report disease specific consequences, which emphasize the need for systematic monitoring of psychosocial well-being.

Other studies in childhood cancer survivors (mainly tumors other than HNRMS) also found HRQoL to be comparable to reference values except for specific subgroups such as central nervous system tumor survivors, bone tumor survivors, and survivors who had cranial radiotherapy.[8-11,26,27]

In our cohort, HNRMS survivors showed impaired scores on school/work functioning, which was not shown in previous studies in other groups of childhood cancer survivors, except for survivors of central nervous system tumors.[28-31] We speculated that this finding may be related to specific adverse events experienced by these HNRMS survivors. Over 40% of the survivors had hearing loss, and many survivors suffered from eye conditions potentially causing difficulties to keep up at school/work. However, these conditions

Table 5. Correlations of physician assessed adverse effects (CTC AE outcome measures) with psychosocial outcomes

	≥5 AEs		Any Grade 3/4		Burden score[a]	
	r[b]	p	r[b]	p	r[b]	p
FD-Negative self-image#	0.073	0.740	**0.553**	**0.006**	**0.531**	**0.009**
FD-Positive consequences#	-0.302	0.162	0.403	0.057	0.300	0.165
FD-Negative consequences#	0.007	0.973	**0.463**	**0.026**	**0.434**	**0.038**
FD-Stigma#	0.066	0.764	**0.476**	**0.022**	**0.465**	**0.025**
SWA (mean score)	-0.127	0.318	-0.223	0.076	-0.231	0.066
PedsQL total	-0.155	0.222	-0.156	0.218	**-0.270**	**0.031**
PedsQL Physical	-0.227	0.071	-0.182	0.151	**-0.277**	**0.027**
PedsQL emotional	-0.034	0.792	-0.009	0.941	-0.193	0.126
PedsQL social	-0.209	0.098	-0.179	0.157	**-0.284**	**0.023**
PedsQL school/work	-0.015	0.906	-0.147	0.254	-0.149	0.247
PedsQL psychosocial	-0.090	0.482	-0.122	0.337	-0.233	0.064
Kidscreen self-perception	0.060	0.646	0.016	0.903	0.083	0.520

In bold P value < 0.05.

[a] burden score adapted from Geenen et al., combining number and severity of AE.[24]

[b] Pearson correlation coefficient

YQOL-FD domains only for patients 11-17 years

Abbreviations: AE, adverse effects; CTC, Common Terminology Criteria; FD, subscale of Youth Quality of Life Instrument–Facial Differences Module; HRQOL, health-related quality of life; PedsQL, Pediatric Quality of Life Inventory; SWA, satisfaction with appearance.

were not significantly correlated with school/work domain scores. The scores on school/work functioning could also be impaired because of radiotherapy treatment. Almost all included patients received radiotherapy (61/65 patients) and radiotherapy fields potentially involved parts of the brain. Although this effect might be less in patients treated according to the AMORE principle, this could not be assessed because data on radiotherapy fields were not available.

The survivors also reported difficulties in more disease-specific domains. Musculoskeletal deformities were noticed in 63% of the patients and over one-third of all survivors considered their facial deformities very noticeable to other people and felt that their facial deformities negatively affected the way they get on with others. This was also reflected in the impact of facial differences on quality of life; HNRMS survivors experienced more negative consequences and fewer positive consequences due to their facial deformities, compared with a group of patients with mild facial deformities. Although the number of patients with musculoskeletal deformity was comparable between patients from the United Kingdom and the Netherlands, this did not reflect the severity of adverse events in both cohorts. Schoot et al previously showed that the severity of facial asymmetry (by clinical assessment) was larger in the UK survivors, compared with NL survivors.[32] Nega-

tive self-image, negative consequences, and stigma appeared to be associated with the severity of adverse events and the positive consequences appeared not to be associated with severity of adverse events. This result is in line with the study of Patrick et al, who found no relationship between severity of facial deformities and experienced positive consequences, whereas patients with more severe deformities reported significantly higher scores on negative consequences, negative self-image, and stigma.[23]

We observed important discrepancies in strength of correlation between the psychosocial outcomes and physician-assessed adverse events. Burden of adverse events showed only weak correlations with generic HRQoL and self-perception, whereas burden scores showed moderate/large correlation with experienced negative self-image, negative consequences, and stigma, underlining the necessity to use disease-appropriate instruments to monitor psychosocial well-being in HNRMS survivors.

There are several limitations to this study. First, we have used disease-related questionnaires (YQOL-FD and SWA) based on the high incidence of facial deformities in this group of HNRMS survivors which were not previously used in childhood cancer survivors. Its applicability as well as our findings should therefore be confirmed in future studies. As for the YQOL-FD questionnaire, we have excluded the coping domain from our analyses because of low Cronbach's alpha. We recommend paying special attention to its reliability in future studies.

Second, this study included survivors treated over a period of 20 years in which treatment protocols have changed significantly and local treatment for patients in this cohort were different between countries. In a previous study, we showed that the local treatment strategy in the EKZ-AMC (i.e., AMORE treatment if feasible) resulted in fewer adverse events compared with standard external beam radiotherapy.[6] Because country-specific reference values were often not comparable or not available, we considered a comparison of psychosocial well-being between patients treated in EKZ-AMC with patients treated in the United Kingdom inappropriate.

Finally, although we have included survivors treated over a long period, total numbers of survivors in our analyses were limited, further complicated by the different age groups and related age-specific questionnaires. Nevertheless, we believe that this study offers important insights as this is the first study assessing psychosocial well-being in HNRMS survivors in depth. In this study, we did not pay special attention to bullying. However, social interactions are strongly affected by facial appearances[33] and previous studies have shown that children (other than HNRMS survivors) with craniofacial conditions are at higher risk of being bullied compared with healthy peers.[34]

Based on the reported incidences and severity of adverse events in these long-term HNRMS survivors and reported dissatisfaction with appearances and HRQoL, we believe that monitoring of psychosocial well-being of HNRMS survivors should play an important part in standard aftercare. Merely administering generic HRQoL questionnaires is

not enough to adequately measure whether long-term HNRMS survivors encounter problems in everyday life, which was also shown in adult head and neck cancer survivors.[35,36] We therefore recommend including disease-appropriate questionnaires in a systematic monitoring program, followed by tailored interventions such as psychosocial care or reconstructive surgery.

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Conflict of interest

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SUPPLEMENTARY TABLES

Table S1. Self-perception (KIDSCREEN) of HNRMS survivors

	Netherlands							United Kingdom						
	HNRMS			Reference[a]		HNRMS vs reference		HNRMS			Reference[a]		HNRMS vs. reference	
	n	Mean	SD	Mean	SD	Effect size	p-Value[b]	n	Mean	SD	Mean	SD	Effect size	p-Value[b]
8-17 years	16	50.00	9.29	51.26	8.83	-0.14	0.60	15	55.00	11.53	49.93	8.66	0.59	0.11
18+ years	19	49.30	7.95	50.70	8.73	-0.16	0.61	12	47.18	12.31	47.85	8.69	0.08	0.85
All ages	35	49.62	8.47	50.96	8.97	-0.15	0.36	27	51.52	12.31	49.01	9.14	-0.27	0.30

Kidscreen scale: mean = 50, SD = 10.
a Country specific weighted norm, adjusted for sex and age
b based on one-sample *t*-test.

Table S2. Prevalence of adverse events (any grade) in cohort of HNRMS survivors from the Netherlands and the United Kingdom.

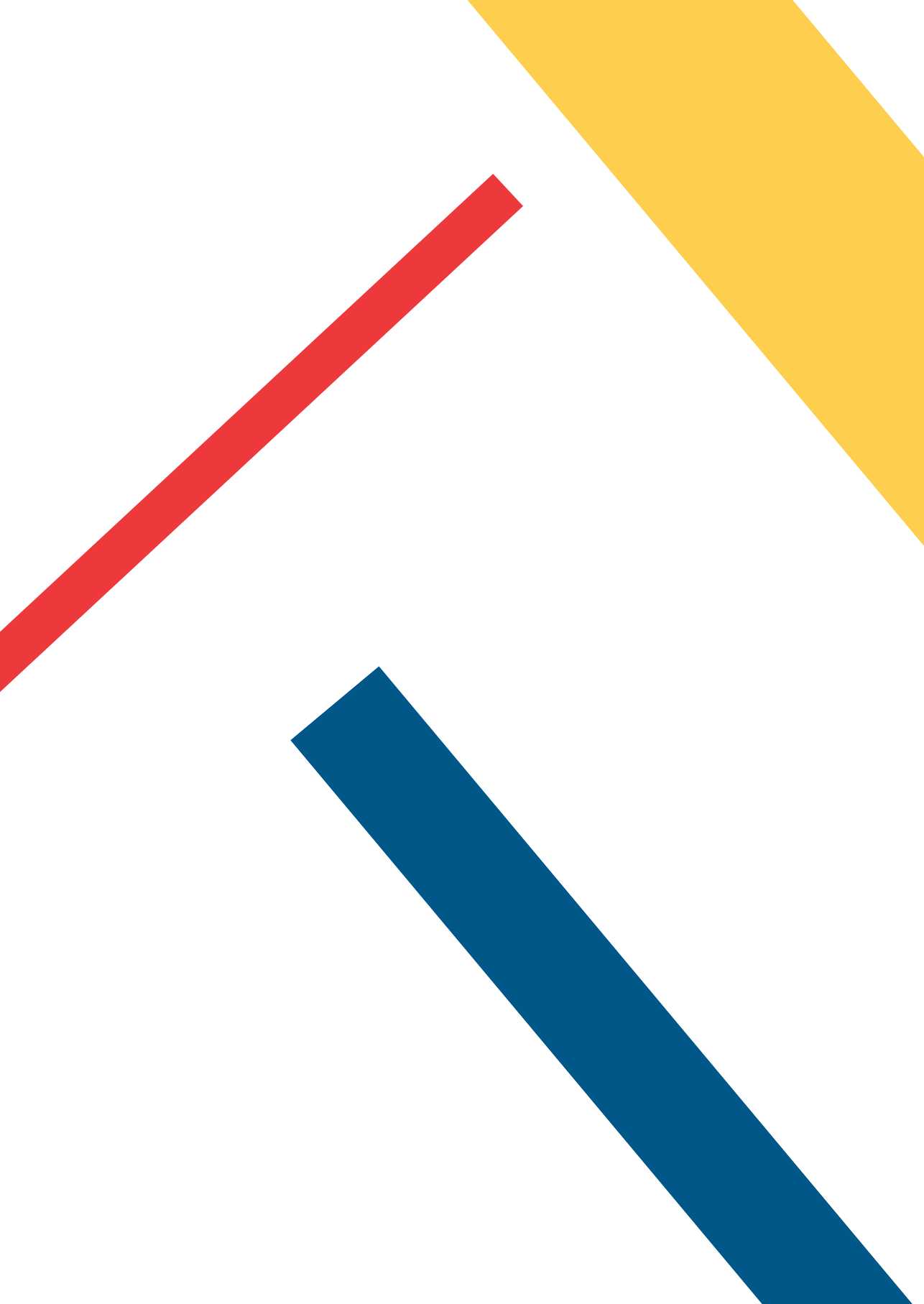
Most common adverse events	Netherlands (n=36)	United Kingdom (n=29)
Musculoskeletal deformity [a]	23 (64%)	18 (62%)
Hearing loss [b]	15 (44%)	12 (48%)
Fibrosis	19 (53%)	15 (52%)
Scar	22 (61%)	12 (41%)
Dry eye	9 (25%)	16 (55%)
Enophthalmos	12 (33%)	12 (41%)
Skin and/or fat atrophy [c]	12 (33%)	12 (41%)
Alopecia	9 (25%)	12 (41%)
Cataract	6 (17%)	11 (38%)
Eyelid deformity [d]	11 (31%)	7 (24%)
Growth hormone deficiency	2 (6%)	14 (48%)
Epistaxis	7 (19%)	10 (35%)
Pigmentation [e]	8 (22%)	6 (21%)
Telangiectasia	9 (25%)	5 (17%)
Infection [f]	4 (11%)	9 (31%)
Rhinolalia aperta	3 (8%)	8 (28%)
Dysarthria	4 (11%)	9 (31%)
Keratitis	6 (17%)	5 (17%)

a Musculoskeletal deformity of the faces comprises: deformity, hypoplasia and asymmetry.
b Audiometry data missing for 6/65 survivors (NL survivors n=2, UK survivors n=4)
c Skin and/or fat atrophy comprises: fat atrophy, skin atrophy
d Eyelid deformity comprises: ectropion, entropion, eyelid retraction and ptosis.
e Pigmentation comprises: hypopigmentation, hyperpigmentation.
f Infection comprises: 'gastro-intestinal infection' and 'respiratory infection'

Table S3. Summary of adverse events (graded according to Common Terminology for Adverse Events) in HNRMS survivors from the Netherlands and the United Kingdom.

	Netherlands (n=36)		United Kingdom (n=29)	
	n	**%**	**n**	**%**
≥5 Adverse events	25	69.4%	26	89.7%
Any grade 3/4	20	55.6%	22	75.9%
Burden score [a]				
None	1	2.8%	0	0
Low	7	19.4%	4	13.8%
Medium	15	41.7%	14	48.3%
High	13	36.1%	7	24.1%
Severe	0	0	4	13.8%

a Burden score adapted from Geenen et al.[24]



CHAPTER 9

AMORE TREATMENT AS SALVAGE TREATMENT IN CHILDREN AND YOUNG ADULTS WITH RELAPSED HEAD-NECK RHABDOMYOSARCOMA

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ABSTRACT

Background and purpose

Survival after relapse of head and neck rhabdomyosarcoma (HNRMS) after prior external beam radiotherapy (EBRT) is poor, since options for adequate local treatment are often lacking. In this study we describe our experience with salvage AMORE in patients with relapsed HNRMS after prior EBRT.

Materials and methods

Patients with relapsed HNRMS after prior EBRT in which salvage AMORE treatment was considered feasible were analyzed; this includes patients with parameningeal, head and neck non-parameningeal and orbital localization. AMORE treatment consisted of Ablative surgery, MOld technique brachytherapy and surgical REconstruction.

Results

In total 18 patients received salvage AMORE treatment; nine patients had relapsed parameningeal (PM) RMS, two patients had relapsed head and neck non-parameningeal RMS (HN-nonPM) and seven patients had relapsed orbital RMS. Local control rate was 67% and 5- year overall survival was 54% (95% confidence interval: 31–78%); 3/9 patients with PM RMS, 0/2 patients with HN-nonPM RMS and 6/7 patients with orbital RMS were alive after a median follow-up of 8.6 years. One patient with PM RMS survived more than 5 years after which he died from a secondary cancer. Six patients developed a local relapse (of which one patient also developed a distant metastasis) and two patients developed distant metastases.

Conclusions

Salvage AMORE treatment is a feasible and effective local therapy approach even after prior EBRT. Since salvage AMORE treatment is sometimes the only curative option in patient with relapsed HNRMS, we encourage physicians to consider salvage AMORE treatment for patients with relapsed HNRMS after prior EBRT.

INTRODUCTION

Rhabdomyosarcoma (RMS) is the most common soft-tissue sarcoma in childhood and approximately 40% of the RMS cases arise in the head and neck region.[1] This tumor site can be further divided into the parameningeal, head and neck non- parameningeal and orbital region. The treatment of childhood rhabdomyosarcoma consists of a combination of chemotherapy with additional surgery and/or radiotherapy. Local therapy, i.e. surgery and/or radiotherapy, is essential to achieve local control. However, in patients with head-neck rhabdomyosarcoma (HNRMS) a microscopically radical resection is often impossible, advocating the use of external beam radiotherapy (EBRT) in the majority of the cases.

In the '90s an innovative new treatment protocol was developed in the Emma Children's Hospital-Academic Medical Centre (EKZ-AMC) called AMORE. This acronym stands for Ablative surgery, MOld technique with afterloading brachytherapy and surgical REconstruction. The advantage of brachytherapy above EBRT is the more conformal dose delivery to the tumor bed with rapid dose fall-off beyond the target volume, thereby sparing more of the healthy surrounding tissue. In the EKZ-AMC, patients with HNRMS are treated according to the AMORE treatment if feasible. Otherwise patients receive EBRT (either photon- or protontherapy). AMORE treatment as first-line local therapy has shown to result in similar survival and less adverse events (AEs) compared to local therapy according to international standard (i.e. EBRT)[2-5]

Despite the continuous efforts of several international study groups to improve survival, still up to 1/3 of all patients with localized RMS at diagnosis experience a relapse.[6-8] In a study of Dantonello et al. the relapse rate was 29% for parameningeal localization, 34% for head and neck non-parameningeal localization and 28% for orbital localization in patients with RMS in complete remission at the end of treatment.[6] In general, outcome after relapsed RMS is poor and survival is strongly depending on previous received treatment.[9-11] Chisholm et al. analyzed the survival of patients with localized RMS who relapsed after complete local control and found prior radiotherapy treatment together with metastatic relapse to be most strongly associated with poor outcome.[11] Survival, specifically in patients with relapsed HNRMS who previously received EBRT, is extremely poor because options to achieve local control are lacking. However, in specific cases AMORE can be used as salvage treatment. In this current study we report on the results of our experience with AMORE as salvage treatment in patients with relapsed HNRMS after prior EBRT. We specifically report on survival probabilities and the severity and frequency of late sequelae.

MATERIALS AND METHODS

Patients

Eligible patients were patients with relapsed HNRMS, after previous chemotherapy and EBRT (as initial treatment or relapse treatment), with salvage AMORE treatment between January 1993 and December 2014. Patients with second or third relapse were also eligible. This study included patients from our own center (n = 7) and patients referred to us specifically for salvage AMORE treatment (n = 11).

Diagnostic work-up and treatment

Patients included in this analysis were staged and treated at first diagnosis according to consecutive European RMS treatment guidelines; SIOP MMT (International Society of Paediatric Oncology Malignant Mesenchymal Tumour; SIOP-MMT-89 and SIOP-MMT-95), CWS (German Cooperative Soft Tissue Sarcoma; CWS-96), or E*p*SSG (European paediatric Soft tissue sarcoma Study Group; E*p*SSG-RMS 2005). The outlines of these trials have been described previously.[8,12-14] Patients were staged according to TNM criteria[15] and the Intergroup Rhabdomyosarcoma Group post-surgical staging system (IRSG-staging).[16]

In general, the majority of patients underwent an incisional biopsy after which patients received chemotherapy. Treatment with multidrug chemotherapy was carried out according to protocol, followed by local therapy. If a microscopic radical resection was not possible, patients received standard EBRT (or AMORE treatment if feasible). Patients with parameningeal tumors received EBRT on initial tumor volume. Patients with tumors located in the head and neck non- parameningeal and orbital area received EBRT on the residual volume.

AMORE procedure

The technical feasibility of a salvage AMORE procedure was assessed in the multidisciplinary tumor board. Participating specialties in these multidisciplinary meetings were: pediatric oncologists, radiation oncologists, head and neck radiologists, head and neck surgeons, reconstructive surgeons, orbital surgeons and in specific cases also neurosurgeons. Salvage AMORE treatment was considered feasible based on the possibility to perform a macroscopic tumor resection and the possibility to adequately position the mold after resection taking into account the morbidity of the procedure.[17] AMORE as first line treatment in naïve patients includes conservative, minimal-mutilating surgery as the goal of AMORE treatment is to effectively treat the primary tumor with maximal sparing of the organs at risk. However, when considering AMORE for previously irradiated patients with relapsed local disease (so called AMORE salvage treatment) more mutilating surgery was accepted, as there were no other alternative local treatment options.

Details of the AMORE treatment can be found in previous manuscripts.2,4,18,19 In brief, local therapy by AMORE treatment is targeted at the residual tumor volume. The aim is to perform a macroscopic radical resection of the residual tumor mass. During the same operative procedure a mold with polyethylene catheters is made and placed in the surgical bed to deliver brachytherapy. Possible microscopic remnants in the tumor bed were irradiated, using iridium-192. Radiotherapy dose (40–50 Gy) is planned up to 5 mm from the mold surface. Until 2001, continuous low-dose-rate (LDR) brachytherapy was given and from 2002 pulsed-dose-rate (PDR) brachytherapy was used. One week after the first operation and after completion of brachytherapy, a second surgical procedure is performed to remove the mold and catheters after which the surgical defect is reconstructed by using a free vascularized or pedicled flap.

Follow-up and statistical analysis

Local control rate was defined as the time between AMORE treatment and date of local event. Progression free survival was defined as the time between AMORE treatment and date of any disease progression. Overall survival was defined as the time between AMORE treatment and date of last follow-up or patient death. Outcomes for living patients were censored at the time of their last reported contact. Cut off point of this analysis was March 31, 2017. For a part of this population, AEs were systematically assessed in a multidisciplinary outpatient clinic, of which results were reported previously.[3] When these data were not available, often for patients referred from abroad, we asked treating physicians to fill out a predefined AEs form graded according to the Common Terminology Criteria for Adverse Events (CTCAEv4.0, available at http://evs.nci.nih.gov/ftp1/CTCAE/About.html), based on the form used in the multidisciplinary follow-up clinic at the EKZ/AMC (Supplementary table S1).[3]

R Studio version 1.1.453 was used for the survival analysis. Local control rate, progression free survival and overall survival was calculated using the Kaplan–Meier method.[20] Because of the small number of patients, results are presented in a descriptive manner.

RESULTS

Between January 1993 and December 2014, 18 patients (11 boys, 7 girls) with relapsed HNRMS after prior EBRT received a salvage AMORE procedure in the EKZ/AMC. The median age at initial diagnosis was 5.7 years (range: 1.1–23.0 years). Median age at time of salvage procedure was 9.3 years (range: 3.0–26.1 years).

Initial tumor localizations were: parameningeal (n = 9), head and neck non-parameningeal (n=2) or orbital (n = 7) localizations. Two patients had an orbital RMS initially, but at relapse the orbital tumor extended into the parameningeal area. These two were

allocated to the orbital group, based on their initial localization (Table 1). The median follow-up time since diagnosis of relapse was 8.6 years (interquartile range: 4.7–16.5 years) for patients alive; local control rate was 67% (12/18 patients) and the 5-year overall survival of the total group was 54% (Fig. 1).

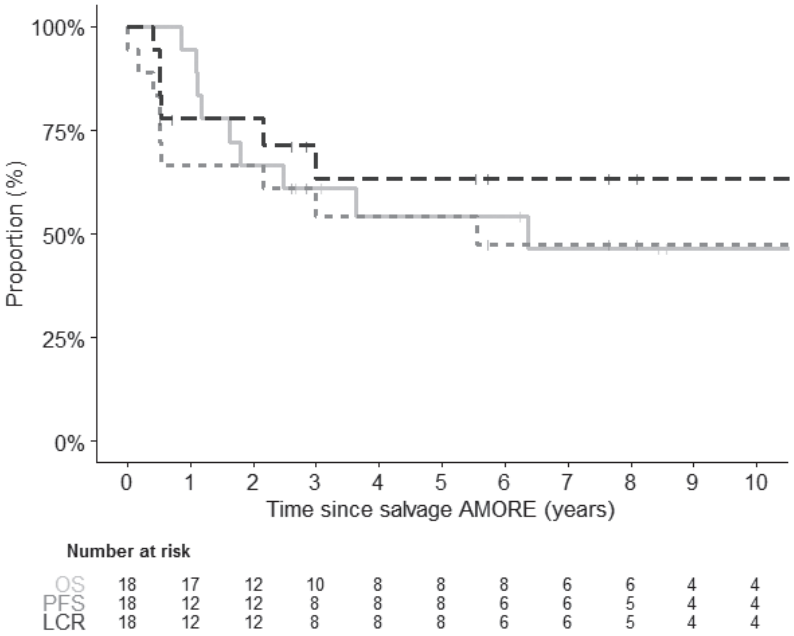

Figure 1. Kaplan–Meier curves showing Local control rate (LCR in grey), Progression free survival (PFR in yellow) and overall survival (OS in blue) for patients who received a salvage AMORE procedure for relapsed HNRMS after prior EBRT.

Parameningeal (n = 9)

All patients with parameningeal tumors had localized embryonal RMS at initial diagnosis. Eight out of nine patients had a local relapse and one patient had a local relapse combined with a solitary pulmonary metastasis. This patient was first treated with chemotherapy and underwent a metastasectomy after which an AMORE salvage procedure was performed. Details of salvage treatment are provided in Table 2.

Three out of the nine patients were alive after a follow-up ranging from 8.5 to 23.8 years. In 5/9 (55.6%) patients local control was achieved; three patients developed a local relapse and one developed a local relapse and a distant metastasis. Two patients developed a secondary malignancy; patient 1 developed a medulloblastoma within the initial EBRT field, 8.2 years after AMORE treatment and patient 7 developed a glioblastoma 5 years after AMORE treatment and died after surgery (exact location of the glioblastoma was unknown).

Table 1. Initial tumor characteristics of included patients

Patient	Age[a] (yrs)	Sex	Histology	Initial localization	Initial treatment	Relapse site	Indication AMORE
Parameningeal							
1	3.0	M	Embryonal	Mastoid	MMT-89 [b] / EBRT (50 Gy)	Mastoid	1st LR
2	4.4	M	Embryonal	Nasal cavity	RMS2005/ EBRT (45 Gy)	Nasal cavity, ext. to nasopharynx	1st LR
3	4.5	F	Embryonal	Nasopharynx	Surgery/MMT95/ EBRT (45 Gy)	Nasopharynx, ext. beyond soft palate	2nd LR [c]
4	5.4	F	Embryonal	Musculus pterygoideus	RMS2005/EBRT (50.4 Gy)	Parapharyngeal	1st LR
5	5.9	F	Embryonal	Parapharyngeal	MMT95/EBRT (54 Gy)	Parapharyngeal	1st LR
6	7.1	M	Embryonal	Sphenoidal sinus	RMS2005/EBRT (54 Gy)	Fossa pterygopalatine ext. intracranially [d]	1st LR
7	7.3	M	Embryonal	Nasal cavity	CWS96/EBRT (48.6Gy)	Nasal cavity	1st LR
8	7.7	F	Embryonal	Pterygoid fossa	MMT95/EBRT (50 Gy)	Pterygoid fossa + pulmonary metastasis	1st LR
9	23.0	F	Embryonal	Masticator space	RMS2005/EBRT (55.8 Gy)	Sphenoid, ext. to orbita and m. temporalis	1st LR
Non parameningeal							
10	1.7	F	Alveolar	Cheek + distant metastasis	RMS-MET-2008/EBRT (51.2Gy)	Cheek	1st LR
11	12.3	M	Embryonal	Parotid gland	CWS96/Surgery	Parotid gland	2nd LR [e]
Orbit							
12	1.1	M	Alveolar	Orbit	Surgery/MMT95/ EBRT (45 Gy)	Orbit	1st LR
13	3.6	M	Embryonal	Orbit	MMT95/EBRT (45 Gy)	Orbit	1st LR
14	3.9	F	Embryonal	Orbit	RMS2005/AMORE	Orbit	2nd LR [f]
15	4.9	M	Embryonal	Orbit	MMT95/EBRT (45 Gy)	Orbit	1st LR
16	7.2	M	Embryonal	Orbit	RMS2005/EBRT (45 Gy)	Orbit ext. parameningeal	1st LR
17	11.2	M	Embryonal	Orbit	MMT89/surgery	Orbit	3rd LR [g]
18	11.5	M	Embryonal	Orbit	RMS2005/EBRT (50 Gy)	Orbit, ext. parameningeal	1st LR

Abbreviations: CWS95, German Cooperative Soft Tissue Sarcoma 95 study; EBRT, external beam radiotherapy; ext., extending; F, female; L, left; LR, local relapse; M, male; MMT, SIOP malignant mesenchymal tumour protocol (SIOP-MMT-89, SIOP-MMT-95); R, right; RMS2005, European *paediatric* Soft tissue sarcoma Study Group rhabdomyosarcoma 2005 study (E*p*SSG-RMS 2005); RMS-MET-2008, E*p*SSG RMS metastatic 2008 study; yrs, years.

a Age at time of diagnosis

b Including myeloablative chemotherapy and autologous stem cell rescue.

c Treatment of 1st relapse consisted of macroscopic surgery and chemotherapy

d Intracranial extension was no longer visible pre-operative, therefore AMORE procedure was conducted

e Treatment of 1st relapse consisted of chemotherapy and EBRT 54.0 Gy.

f Treatment of 1st relapse consisted of chemotherapy and EBRT 50.4 Gy

g Treatment of 1st relapse consisted of chemotherapy and AMORE, 2nd relapse; chemotherapy and EBRT 55.8 Gy.

Table 2. Details of salvage treatment and relapse.

Patient	Age[a] (yrs)	Salvage treatment	Surgery	Brachytherapy		Reconstruction	Outcome		Event
				Dose (Gy)	Dose rate	Donor site	Status	FU (yrs)	
Parameningeal									
1	4.2	AMORE	Resection partial mastoid, partial os petrosus and cochlea	50	LDR/61	RA	NED	23.8	SPT[b]
2	6.9	CT / AMORE	Denker procedure[c], resection fossa pterygopalatine, partial resection hard palate, partial resection pterygopalatine bone[d]	40	PDR/1.25	GA	Died	1.1	2nd LR
3	7.9	CT / AMORE	Denker procedure[c], resection lacrimal bone	40	LDR/60	RA	Died	1.2	3rd LR/ DM
4	8.3	CT / AMORE	Resection of all stylohyoid muscles, selective neck dissection (I, IIA)	39	PDR/1.5	GR	NED	8.5	-
5	10.7	CT / AMORE	Partial resection soft palate, oropharynx mucosa and tongue base + selective neck dissection (level 2A)	42	PDR/1.5	RA	Died	2.5	2nd LR
6	9.6	CT / AMORE	Resection of fossa pterygopalatine, partial resection skullbase, resection pterygoid muscles	40	PDR/1.25	TF	NED	8.6	-
7	10.0	CT / S / AMORE[e]	Total ethmoidectomy plus conga resection partial vomer resection, partial resection maxillary sinus.	45	PDR/1.25	GA	Died	6.4	SPT[f]
8	9.9	CT / M / AMORE	Resection fossa pterygopalatine including muscles, partial resection mastication muscles partial parotidectomy, selective neck dissection (I, II, III)	40	LDR/140	LD[#]	Died	0.9	DM
9	26.1	CT / AMORE	Fronto-temporal craniotomy, partial orbitotectomy and partial resection skull base	45	PDR/1.25	TF	Died	1.8	2nd LR
Non-parameningeal									
10	3.0	CT / AMORE	Partial maxillectomy, partial nose amputation, resection soft tissue cheek, partial lateral nose dissection, lymph node biopsy (level II)[g]	45	PDR/1.25	LD	Died	1.1	DM

Table 2. Details of salvage treatment and relapse. (continued)

Patient	Agea (yrs)	Salvage treatment	Surgery	Brachytherapy		Reconstruction	Outcome		Event
				Dose (Gy)	Dose rate	Donor site	Status	FU (yrs)	
11	16.9	CT / AMORE	Parotidectomy, including cranial nerves 7 and 11 (involved in tumor)	40	PDR/1.2	RA	Died	3.6	3rd LR
Orbit									
12	3.6	CT / AMORE	Orbital exenteration	40	PDR/1.25	GA	NED	11.3	-
13	12.2	CT / AMORE	Orbital exenteration	40	PDR/1.25	GA	NED	6.3	-
14	7.9	CT / AMORE	Orbital exenteration	40	PDR/1.25	GA	NED	2.7	-
15	5.9	CT / AMORE	Orbital exenteration	40	PDR/1.25	GA	NED	11.2	-
16	8.9	CT / AMORE	Orbital exenteration + partial resection of bony orbita	40	PDR/1.25	GR	NED	3.1	-
17	14.2	CT / AMORE	Orbital exenteration	40	LDR/70	TF	NED	21.7	-
18	12.9	CT /S h/ AMORE	Orbital exenteration, partial resection of bony orbita and skull base + dura resection.	40	PDR/1.25	RA	Died	1.6	2nd LR

Abbreviations: CT, 2nd or 3rd line chemotherapy; DM, distant metastasis; FU, follow-up since relapse in years; GA, tunneled galea flap; GR, gracilis free muscle flap; LD#, latissimus dorsi pedicled flap; LD, latissimus dorsi free muscle flap; LDR, low continuous dose rate (in cGy/hour); LR, local relapse; M, metastectomy pulmonary nodule; NED, no evidence of disease; PDR, pulse dose rate (in Gy/pulse); RA, rectus abdominis free muscle flap; S, surgery; SPT, second primary tumor; TF, temporalis transposition flap; yrs, years.

a Age at time of salvage AMORE treatment

b Patient developed a medulloblastoma.

c Adjusted Denker procedure: lateral rhinotomy with Denker incision.

d Lateral and posterior wall of maxillary sinus was tumor positive and only received 50% of radiation dose, therefore additional brachytherapy threads were placed during reconstruction and additional radiotherapy was given.

e Residual disease after surgery and chemotherapy therefore AMORE treatment.

f Patient died of second primary tumor; glioblastoma.

g Lymph nodes were tumor negative, however salivary gland contained tumor and was not radically resected; subsequent adequate radiotherapy was not possible.

h Surgical resection was abandoned based on frozen section biopsies showing the tumor extended in the margins of dural resection.

Non-parameningeal (n = 2)

Two patients had a head and neck non-parameningeal located relapse; patient 10 had a non- parameningeal alveolar RMS, with pulmonary metastases and bilateral lymphadenopathy at initial diagnosis and patient 11 had localized non-parameningeal embryonal RMS. Both patients developed a local relapse for which they received a salvage AMORE procedure.

At preoperative radiologic imaging patient 10 showed potential lymph node involvement/solitary salivary gland metastasis. Therefore, in addition to the resection of the primary tumor during the first AMORE procedure, a lymph node biopsy was performed. The salvage treatment was well tolerated however pathology results showed a not radically resected salivary gland metastasis. Additional EBRT after salvage AMORE was considered necessary, however not feasible because of potential toxicity. She received maintenance chemotherapy; however she developed a distant metastasis without locoregional relapse and died a year after AMORE treatment. Patient 11 received second line chemotherapy and salvage AMORE treatment for his second relapse. The salvage treatment was well tolerated; however he developed a third local relapse 3 years after the AMORE procedure and died subsequently.

Orbital (n = 7)

Seven patients had orbital RMS; one tumor was of alveolar histology, six were embryonal. All seven patients developed a local relapse for which they received salvage AMORE; in two patients the relapsed tumor showed parameningeal extension at relapse. Resection of the tumor included orbital exenteration for all patients; one of these patients also underwent a craniotomy with excision of part of the involved dura (Table 2).

Six out of the seven patients were alive after a follow-up ranging from 2.7 to 21.7 years. One patient developed a local relapse, six months after salvage AMORE treatment and died a year after salvage treatment.

Adverse events

The surviving patients with parameningeal tumors all developed more than 5 AEs as result of local treatment. All patients developed (grade 2 or 3) musculoskeletal deformities and growth hormone deficiency for which they received growth hormone replacement. Patient 6 developed a grade 3 optic nerve disorder. Other reported AEs were grade 1 or 2 and included dysarthria, trismus, telangiectasia, dermatitis, cataract, skin/fat atrophy, scarring, induration/fibrosis or hearing loss.

The surviving patients with orbital tumors all had grade 4 musculoskeletal deformity due to the orbital exenteration (i.e. musculoskeletal deformity grade 4). Furthermore, they developed grade 1 or 2 AEs, including scarring, induration/fibrosis, hearing loss, telangiectasia, pigmentation, epistaxis, alopecia, skin/fat atrophy and dry eyes. Patient

13 developed growth hormone deficiency and received growth hormone replacement. Patient 17 developed secondary generalized seizures 13 years after salvage AMORE treatment, possibly caused by radiation necrosis in his frontal lobe (treated with anti-convulsant medication in the past for <1 year, no medication needed afterwards).

DISCUSSION

The outcome for patients with locally relapsed HNRMS is determined by the feasibility of local treatment. Curative options are often lacking in patients who have previously received EBRT. Consequently, the survival rates for children with relapsed HNRMS after receiving EBRT are poor; ranging from 0% to 18%.[9-11] Microscopic radical resection of the tumor is often not possible without serious mutilating cosmetic and functional consequences. Furthermore, in the majority of patients, re-irradiation is considered not feasible, since the total radiation dose would exceed the tolerable dose for healthy tissue.

We show that in specific cases a salvage AMORE treatment is feasible, consisting of a macroscopic radical resection, directly followed by brachytherapy to treat potential microscopic remnants, allowing a precise conformal dose distribution with rapid fall-off, thereby sparing the surrounding healthy often previously irradiated tissue. In these patients salvage AMORE treatment enables re-irradiation in patients with relapsed HNRMS. In this study we show that salvage AMORE treatment can lead to long-term survival. Nine of 18 treated patients are alive and 1 patient survived >5 years after which he died from a secondary cancer.

We previously (in 2004) reported on salvage AMORE treatment; this was a smaller series (9 patients in total) that also contained two patients groups (6 of the 9 patients) which were excluded from the current analysis.[18] The first of those two groups consisted of patients with residual disease after initial EBRT for which they underwent salvage AMORE treatment.

However, a North-American analysis showed that patients with residual masses at the end of therapy had comparable prognosis as to patients showing complete tumor response at end of therapy.[21] Therefore patients with residual disease after EBRT are no longer eligible for salvage AMORE treatment. The second group consisted of patients which were not treated with EBRT previously. According to SIOP-MMT and EpSSG guidelines, specific more favorable subgroups (based on tumor site) did not receive radiotherapy in case of complete response. In case of relapse, AMORE treatment would not be the only remaining curative options for these patients, since EBRT would still be possible in these patients; therefore, we excluded this group from the current analysis.

A comparison of survival rates with other cohorts is not possible since we only report outcomes for patients that were actually treated with salvage AMORE; we do not have accurate follow-up of all patients in whom salvage AMORE was considered. Nevertheless, salvage AMORE treatment is often one of the few remaining local treatment modalities available in patients previously treated with EBRT and therefore the outcome data of this cohort are relevant for the future management of patients with relapsed head and neck RMS after prior EBRT.

In this cohort, overall survival for patients with orbital relapse was high. One could argue that salvage surgery by an orbital exenteration might have been adequate therapy for these patients; however surgical resection in 5/7 patients was microscopically incomplete (as anticipated in the AMORE approach), therefore we believe that the subsequent brachytherapy was essential.

The feasibility of AMORE was systematically discussed in a multidisciplinary setting, using predefined in- and exclusion criteria. When considering newly diagnosed patients for AMORE, potential severe mutilation is a contra-indication for AMORE, unless more AEs are expected when using EBRT. In case of patients with relapsed disease after EBRT, when often no other local treatment is available, the AMORE working group accepts more mutilating and higher risk surgery.

Re-irradiation with adequate dose in case of relapse after prior EBRT is generally considered impossible. Patients in this cohort were all re-irradiated with brachytherapy nevertheless, the salvage AMORE treatment was well tolerated. We believe that the reconstruction with well- vascularized muscle tissue flaps plays a pivotal role in this[22]; acute complications were rarely seen and only one patient developed a major wound infection.

However, successful salvage procedures did cause important (late) sequelae. An orbital exenteration was conducted in all 7 patients with orbital tumors and one patient developed radiation necrosis. Two patients developed a secondary malignancy; patient 1 developed a medulloblastoma which was located in the fields of prior EBRT, patient 7 developed a glioblastoma of which the exact location was unknown since primary treatment and follow-up for this patient was done in a different hospital abroad. The three surviving parameningeal patients all experienced many AEs; however, these patients received EBRT, brachytherapy and (mutilating) surgery making it difficult to determine the causative factor.

Conclusion

Salvage AMORE treatment is a feasible and can be an effective local therapy approach for a specific group (after careful consideration by a multidisciplinary head-neck oncology team) of patients with relapsed HNRMS after prior EBRT. Local therapy by AMORE procedure is often one of the few remaining curative options in patients with relapsed

HNRMS after prior EBRT treatment and we would like to encourage physicians to consider AMORE treatment as salvage treatment for relapsed HNRMS patients.

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SUPPLEMENTARY MATERIAL

Table S1. Predefined list of adverse events, graded according to the Common Terminology Criteria for adverse events version 4.0.

Was patient examined by an ophthalmologist? Yes/ No

Please fill out this form for OD and OS separately

OD

EYE			Grade			
Adverse event	**unknown**	**0**	**1**	**2**	**3**	**4**
Optic nerve disorder		-	Asymptomatic	Limiting vision of the effected eye (20/40 or better)	-Limiting vision of the affected eye (20/40- 20/200)	Blindness (20/200 or worse)
Retinopathy		-	Asymptomatic	-Symptomatic -Moderate decrease in visual acuity (20/40 or better) -Limiting instrumental ADL**	-Marked decrease in visual acuity (20/40-20/200) -Disabling -Limiting self care ADL**	Blindness (20/200 or worse)
Keratitis (corneal inflammation, ulceration)		-	-	-Symptomatic -Medical intervention indicated -Limiting instrumental ADL**	-Limiting self care ADL** -Decline in vision 20/40- 20/200	Perforation or blindness (20/200 or worse)
Ectropion*		-	-Asymptomatic	-Symptomatic -Non-operative intervention indicated -Limiting instrumental ADL**	-Limiting self care ADL** -Operative intervention indicated	-
Entropion*		-	-Asymptomatic	-Symptomatic -Non-operative intervention indicated -Limiting instrumental ADL**	-Limiting self care ADL** -Operative intervention indicated	-
Lid retraction†		-	-Asymptomatic	-Symptomatic -Non-operative intervention indicated -Limiting instrumental ADL**	-Limiting self care ADL** -Operative intervention indicated	-
Ptosis†		-	-Asymptomatic	-Symptomatic -Non-operative intervention indicated -Limiting instrumental ADL**	-Limiting self care ADL** -Operative intervention indicated	-

Cataract	-	Asymptomatic	-Symptomatic: moderate decrease visual acuity (20/40 or better)	-Marked decrease visual acuity (20/40-20/200) -Operative intervention indicated	-Blindness (20/200 or worse) in affected eye
Enophthalmos*	-	Asymptomatic	-Symptomatic -Limiting instrumental ADL**	-Limiting self care ADL** -Disabling	-
Exophtalmos†	-	Asymptomatic	-Symptomatic -Limiting instrumental ADL**	-Limiting self care ADL** -Disabling	-
Dry eye	-	-Asymptomatic -Mild symptoms relieved by lubricants	-Symptomatic -Multiple agents indicated -Limiting instrumental ADL**	-Decrease in visual acuity (<20/40) -Limiting self care ADL**	-

**Activities of Daily Living (ADL): Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money etc. Self care ADL refer to bathing, (un)dressing, feeding self, using the toilet, taking medications and not bedridden.

OS

EYE			**Grade**		
Adverse event	**unknown**	**0** **1**	**2**	**3**	**4**
Optic nerve disorder		- Asymptomatic	Limiting vision of the effected eye (20/40 or better)	-Limiting vision of the affected eye (20/40- 20/200)	Blindness (20/200 or worse)
Retinopathy		- Asymptomatic	-Symptomatic -Moderate decrease in visual acuity (20/40 or better) -Limiting instrumental ADL**	-Marked decrease in visual acuity (20/40-20/200) -Disabling -Limiting self care ADL**	Blindness (20/200 or worse)
Keratitis (corneal inflammation, ulceration)		- -	-Symptomatic -Medical intervention indicated -Limiting instrumental ADL**	-Limiting self care ADL** -Decline in vision 20/40- 20/200	Perforation or blindness (20/200 or worse)
Ectropion*		- -Asymptomatic	-Symptomatic -Non-operative intervention indicated -Limiting instrumental ADL**	-Limiting self care ADL** -Operative intervention indicated	-
Entropion*		- -Asymptomatic	-Symptomatic -Non-operative intervention indicated -Limiting instrumental ADL**	-Limiting self care ADL** -Operative intervention indicated	-

Lid retraction†	-	-Asymptomatic	-Symptomatic -Non-operative intervention indicated -Limiting instrumental ADL**	-Limiting self care ADL** -Operative intervention indicated	-
Ptosis†	-	-Asymptomatic	-Symptomatic -Non-operative intervention indicated -Limiting instrumental ADL**	-Limiting self care ADL** -Operative intervention indicated	-
Cataract	-	Asymptomatic	-Symptomatic: moderate decrease visual acuity (20/40 or better)	-Marked decrease visual acuity (20/40-20/200) -Operative intervention indicated	-Blindness (20/200 or worse) in affected eye
Enophthalmos*	-	Asymptomatic	-Symptomatic -Limiting instrumental ADL**	-Limiting self care ADL** -Disabling	-
Exophthalmos†	-	Asymptomatic	-Symptomatic -Limiting instrumental ADL**	-Limiting self care ADL** -Disabling	-
Dry eye	-	-Asymptomatic -Mild symptoms relieved by lubricants	-Symptomatic -Multiple agents indicated -Limiting instrumental ADL**	-Decrease in visual acuity (<20/40) -Limiting self care ADL**	-

Dermatology			**Grade**			
Adverse event	**unknown**	**0**	**1**	**2**	**3**	**4**
Alopecia		-	-Hair loss up to 50% of normal for that individual, only visible on close inspection -No wig etc required	-Hair loss of >50% normal for that individual, readily apparent -Wig required for camouflage -Associated with psychological impact	-	-
Atrophy skin		-	-Covering <10% BSA -Associated with telangiectasias or changes in skin color	-Covering 10-30% BSA -Associated with striae or adnexal structure loss	-Covering >30% BSA -Associated with ulceration	-

Dermatitis, associated with radiotherapy	-	-Faint erythema -Dry desquamation	-Moderate erythema -Moist desquamation confined to skin folds -Moderate edema	-Moist desquamation other than skin folds -Bleeding induced by minor trauma	-Skin necrosis or ulceration of full thickness dermis -Spontaneous bleeding
Dry Skin	-	Covering <10% BSA and no associated erythema or pruritus	-Covering 10-30% BSA and associated with erythema or pruritus -Limiting instrumental ADL**	-Covering >30% BSA -Painful blisters -Limiting self care ADL**	-
Fat atrophy	-	Covering <10% BSA and asymptomatic	-Covering 10-30% BSA and associated with erythema or tenderness -Limiting instrumental ADL**	-Covering >30%BSA -Associated with erythema or tenderness -Limiting self care ADL**	-
Induration/ Fibrosis	-	-Mild induration; able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	-Moderate impairment of function -Able to slide, but unable to pinch the skin -Limiting instrumental ADL**	-Limiting self care ADL** -Unable to slide or pinch the skin -Limiting joint or orifice movement	-Generalized; associated with signs or symptoms of impaired breathing or feeding

Infections					**Grade**	
Adverse event	**unknown**	**0**	**1**	**2**	**3**	**4**
Infection: gastro- intestinal (within last month)		-	Mild	Moderate	Severe	Life-threatening/ disabling
Infection: respiratory (within last month)		-	Mild	Moderate	Severe	Life-threatening/ disabling

Was patient examined by an ENT-specialist? Yes/No

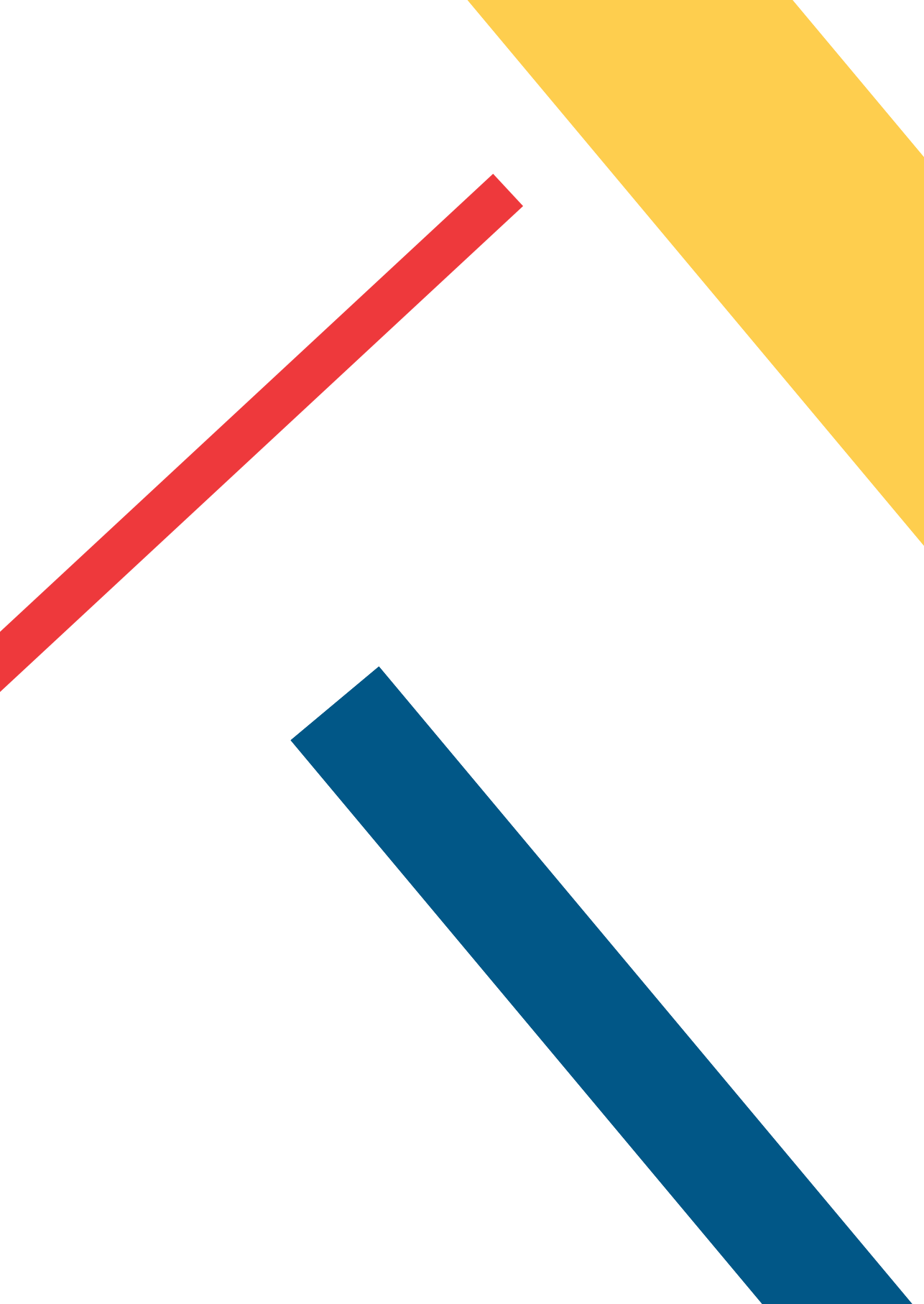
ENT		Grade			
Adverse event	**unknown 0**	**1**	**2**	**3**	**4**
Trismus	-	Decreased range of motion (ROM)	Decreased ROM, requiring small bites, soft foods or purees	Decreased ROM, inability to adequately aliment or hydrate orally	-
Dysarthria/ voice alteration	-	-Mild slurred speech -Mild or intermittent change from normal voice	-Moderate impairment of articulation or slurred speech -Moderate or persistent change from normal voice; still understandable	-Severe impairment of articulation or slurred speech -Severe voice changes including predominantly whispered speech -May require frequent repetition or face-to-face contact for understandability -May require assistive technology	-
Rhinolalia aperta (nasal aspirate sound)†	-	Mild change of speech, no effect on audibility	Moderate change of speech, influences audibility	Barely understandable, verbal communication limited	-
Epistaxis (within last month)	-	- Mild symptoms	-Moderate symptoms -Medical intervention indicated (e.g. nasal packing, cauterization, topical vasoconstrictors)	-Transfusion, radiologic, endoscopic, or operative intervention indicated	-Life-threatening consequences -Urgent intervention indicated
Hearing* (subjective)	-	-	Hearing loss	Hearing loss requiring intervention	Profound bilateral hearing loss (>90dB)
Hearing loss uni- or bilateral?			Unilateral	Bilateral	
Musculoskeletal deformity	-	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be covered	-Significant deformity, hypoplasia or asymmetry, not covered -Disabling	Orbital exenteration
Please describe deformity:					
Scar†	-	Asymptomatic, cosmetic and functionally unimportant	- Symptomatic, - Functionally uncomfortable	-Loss of function -Impairment of ADL	Life-threatening

Was patient examined by an endocrinologist? Yes/No

Endocrine		Grade			
Adverse event	**unknown**	**0**	**1**	**2**	**3**	**4**
ACTH deficiency*		-	Asymptomatic	-Symptomatic -Intervention indicated	-Symptoms interfering with ADL -Hospitalization	Life-threatening consequences (i.e. severe hypotension)
ADH secretion abnormality* (i.e. SIADH, low ADH)		-	Asymptomatic	-Symptomatic -Intervention indicated	Interfering with ADL	Life-threatening consequences
Adrenal insufficiency		-	Asymptomatic	Intervention indicated	Hospitalization	-Life-threatening -Urgent intervention indicated
Cushingoid appearance		-	-Mild symptoms -Intervention not indicated	-Moderate symptoms -Medical intervention indicated	-Severe symptoms -Medical intervention or hospitalization indicated	-
Feminization (acquired)		-	-Mild symptoms -Intervention not indicated	-Moderate symptoms -Medical intervention indicated	-	Present
Gonadotropin* secretion abnormal		-	Asymptomatic	Intervention indicated	-Interfering with ADL -Osteopenia -Fracture -Infertility	-
Growth hormone secretion abnormality		-	Asymptomatic	-Symptomatic -Medical intervention indicated -Limiting instrumental ADL**	-	-

Neurologic		Grade				
Adverse event	**unknown**	**0**	**1**	**2**	**3**	**4**
Thrombo-embolic event Specify:		-	Venous thrombosis (e.g. superficial)	-Venous thrombosis (e.g. uncomplicated deep vein) -Medical intervention indicated	-Thrombosis (e.g. uncomplicated pulmonary embolism [venous], non-embolic cardiac mural [arterial]) -Medical intervention	-Life-threatening (e.g. pulmonary embolism, CVA, art. Insufficiency) -Hemodynamic or neurologic instability -Urgent medical intervention

Neurological deficit	- Asymptomatic	-Moderate symptoms	-Severe symptoms	-Life-threatening
cranial nerves;		-Limiting instrumental ADL	-Limiting self care ADL	consequences
Specify:			-Assistive device indicated	-Urgent intervention
				indicated
Please specify cause of neurological deficit	**Iatrogenic**		**Tumor**	



CHAPTER 10

SUMMARY AND GENERAL DISCUSSION

SUMMARY AND GENERAL DISCUSSION

Around 20 patients are diagnosed with RMS in the Netherlands annually.(1) This limited number of patients illustrates the necessity of cooperation in international research groups to improve survival for patients with RMS, while at the same time limiting the burden of therapy.(2) Despite the existence of these large international research groups randomized trials in RMS still last 7-10 years.

Patients with RMS are stratified according to comprehensive risk stratification with differences in treatment and prognosis based on risk groups. In Europe, the majority of patients are treated according to study protocols initiated by the European *paediatric* Soft tissue sarcoma Study Group (E*p*SSG). With the final evaluation of the E*p*SSG-RMS 2005 study and the design of the new E*p*SSG Frontline and Relapse rhabdomyosarcoma study (E*p*SSG FaR-RMS study) several important clinical questions emerged.

Part 1: Imaging in rhabdomyosarcoma

The aim of **part 1** of this thesis was to address questions around the value of imaging techniques and measurements performed at time of diagnosis, during treatment and during follow-up in patients with RMS (Chapter 2, 3, 4, 5, 6, and 7). The aim was to assess these questions before the start of the new FaR-RMS study.

Imaging at primary diagnosis

Although the overall survival for patients with localized rhabdomyosarcoma has increased over the last decades to around 80%, the survival for patients with metastatic disease at diagnosis is considerably worse with survival rates of 10-50%.(3-6) Accurate staging is important to intensify treatment for patients with poorer prognosis, while limiting treatment for patients with better prognosis.

With the start of the E*p*SSG-RMS 2005 study a chest CT became mandatory to diagnose potential lung metastases. The introduction of a higher resolution imaging technique introduced new diagnostic dilemmas, since small pulmonary nodules now became visible. These small nodules, per protocol called indeterminate pulmonary nodules, are often too small to biopsy, making a histopathological classification of these nodules generally impossible. These small pulmonary nodules are a frequent finding in healthy children, with an incidence up to 38% (7, 8), however finding indeterminate pulmonary nodules during the staging of RMS poses a diagnostic dilemma. The decision to consider these nodules as pulmonary metastases would imply an intensification of chemotherapy (adding doxorubicin to standard chemotherapy), adding a year of maintenance chemotherapy and administering chest radiotherapy. In the E*p*SSG-RMS 2005 study, patients

with indeterminate pulmonary nodules at diagnosis were treated according to localized disease protocol since the assumption was made that some of these nodules were incidental benign lesions and others were micro-metastases which in the past were not visible because of the use of chest radiographs.

In **chapter 2** we assessed whether the presence of these indeterminate pulmonary nodules at diagnosis affects survival in patients with rhabdomyosarcoma. In this international multicenter study, we included patients enrolled in the E*p*SSG-RMS 2005 study for localized RMS. The chest CTs at diagnosis were reviewed for the presence of pulmonary nodules by local radiologists. In total, we included 316 patients of which 67 patients (21.2%) had at least one indeterminate pulmonary nodule. Five-year event-free survival (EFS) for patients with indeterminate nodules was 77.0 (95% confidence interval [CI]: 64.8-85.5%) and 73.2% (95% CI: 67.1-78.3%) for patients without nodules. Five-year overall survival (OS) for patients with indeterminate nodules was 82.0% (95% CI: 69.7-89.6%) and 80.8% (95% CI: 75.1-85.3%) for patients without nodules. We found no significant difference in survival between patients with indeterminate pulmonary nodules and patients without pulmonary nodules at diagnosis. This implies that patients with indeterminate pulmonary nodules were sufficiently treated with chemotherapy regimens for localized disease, and that there is no need to administer chest radiotherapy in these patients. The results of this study demonstrated that indeterminate pulmonary nodules are a frequent finding in newly diagnosed patients with RMS; more importantly the study justified the definition and treatment of patients with indeterminate pulmonary nodules according to localized disease protocols. The strength of this study is that chest CTs at diagnosis were reviewed by local radiologists according to a standardized case-report form. However, this study also demonstrated the need for standard radiology reporting, since we observed a large difference (>10%) in reported incidence of indeterminate pulmonary nodules between the initial chest CT reports and the chest CT reports generated during the review for this study.

In **chapter 3** we evaluated the diagnostic accuracy of ^{18}F-FDG PET/CT for the detection of distant metastases in RMS. Although ^{18}F-FDG PET/CT is an established diagnostic examination for the staging of other tumor types such as lung cancer and lymphoma(9), the value of ^{18}F-FDG PET/CT for the staging of rhabdomyosarcoma is less clear. We performed a Cochrane Diagnostic Test Accuracy review, in which we included two studies (Eugene et al. 2012, Ricard et al. 2011) with a total of 36 patients.(10, 11) Based on the included studies we concluded that there is currently insufficient evidence to reliable determine the accuracy of ^{18}F-FDG PET/CT for the detection of lymph node involvement and distant metastases in patients with RMS. The paucity of available evidence surprised us, since multiple studies have evaluated the role of ^{18}F-FDG PET/CT for the staging of

RMS. However, these studies generally compared results of PET/CT with conventional imaging without defining a gold standard. Sensitivity and specificity could therefore not reliably be determined. More surprising is that ^{18}F-FDG PET/CT imaging is currently an established imaging modality for the detection of potential distant metastases, therewith replacing ^{99m}-Tc bone scintigraphy for the detection of bone metastases. Although the scarce evidence might suggest that ^{18}F-FDG PET/CT imaging has a higher sensitivity and specificity for the detection of bone metastases, its actual accuracy could not be determined. The upcoming E*p*SSG FaR-RMS study has incorporated ^{18}F-FDG PET/CT imaging for the detection of potential distant metastases. The data will be collected prospectively and analyzed to better determine the value of ^{18}F-FDG PET/CT imaging in the staging of RMS.

Imaging during treatment

Patients with RMS generally undergo an incisional biopsy at diagnosis, after which patients receive neo-adjuvant chemotherapy. Chemotherapy for patients with localized disease, treated according to European study protocols, consists of a standard combination of ifosfamide, vincristine and dactinomycin, complemented with other agents in different trials.(5, 6) Historically, RMS trials in Europe encompass an early radiologic response measurement (usually after 3 courses of chemotherapy) to evaluate efficacy of chemotherapy.

There are multiple ways to measure response (according to WHO-criteria(12), volumetric measurement or according to RECIST criteria(13)), yet none of these methods have shown to be superior in the measurement of response in RMS.(14, 15) Furthermore, a study by Schoot et al. showed that, irrespective of the method of measurement, the measurement of radiologic response is subject to important interobserver variability, potentially leading to different treatment decision in over 10% of the patients with RMS. (15) The prognostic value of early radiologic response remains debated amongst different cooperative study groups; in North American Children's Oncology Group (COG) protocols first line chemotherapy is continued irrespective of response unless patients show progressive disease at response assessment, whereas the E*p*SSG-RMS 2005 prescribed a treatment switch to second line chemotherapy for patients showing less than one-third tumor volume reduction at early response assessment.(14, 16-18)

In **chapter 4** we evaluated the European approach by assessing the prognostic value of early radiologic response on survival in a cohort of consecutive patients uniformly treated and included in the International Society of Pediatric Oncology (SIOP) Malignant Mesenchymal Tumor 95 (MMT-95) study cohort. In total, we included 432 patients with an incompletely resected tumor or biopsy only at diagnosis, and a response evaluation

after three courses of chemotherapy. We found that the majority of patients (85.2%) showed at least partial response (≥ 50% decrease in tumor area) to induction chemotherapy, however we found no evidence that early radiologic response was prognostic for survival. Five-year failure free survival (FFS) was 60% (95% CI: 55-65%) for patients with sufficient response, 60% (95%-CI: 44-75%) for patients with objective response and 69% (95%-CI: 51-87%) for patients with no response to induction chemotherapy.

Because of the ambiguity in existing literature and the fact that early radiologic response is still used in current European RMS treatment guidelines to adapt treatment in case of insufficient response we conducted a systematic review (**chapter 5**), assessing the quality of the available evidence for the prognostic value of early radiologic response in RMS. We included 6 studies, describing a total of 2010 patients. Unfortunately, due to heterogeneity in response measurement, response grouping and treatment adaptation based on response, we considered a meta-analysis inadequate. Two of the six studies (Ferrari et al.; Dantonello et al.) found early radiologic response to be associated with survival, four studies (Burke et al.; Ermoian et al; Rosenberg et al.; Vaarwerk et al.) reported no correlation between early response and survival.(14, 16-20) These differences in outcomes were possibly explained by the fact that both Ferrari et al. and Dantonello et al. included patients which showed progression of disease at early response evaluation, whereas this subset was excluded from the analyses in the other studies. Unfortunately, these studies did not perform a separate analysis excluding patients with progressive disease.

Based on the results of **chapter 4** & **chapter 5** we concluded that there is insufficient evidence that early radiologic response is prognostic for survival in patients with localized RMS. Future RMS studies should no longer contain a treatment adaptation based on early response, except for patients with progressive disease at early response measurement.

Imaging during follow-up

Since almost one-third of all patients diagnosed with localized RMS experience a tumor relapse, (5, 6, 21) patients are subject to intensive radiologic tumor surveillance after completion of therapy. The assumption is that detecting a tumor relapse in an (presymptomatic) early phase would be associated with improved survival, however no evidence is available for this assumption.

The confirmation that surveillance imaging revealed no signs of relapse could give reassurance to patients and parents, however the prospect of upcoming surveillance imaging could also cause additional distress and anxiety for patients and parents. This distress and anxiety could be intensified by the necessity of general anesthesia to acquire good quality images, in a substantial proportion of patients. Besides the short term risk as-

sociated with general anesthesia, such as respiratory depression and desaturation,(22) the consequences of the repetitive use of general anesthetics on the developing brain remains debated.(23-25) Additionally, there is increasing evidence of gadolinium depositions in parts of the brain after repeated administration of gadolinium-contrast agents, although the clinical significance of these findings are yet unclear.(26)

Because of the lacking evidence for the benefit of surveillance imaging and the associated risks, we retrospectively evaluated the value of radiologic tumor surveillance (**chapter 6**), by comparing survival of patients in whom relapse was detected by routine imaging to patients in whom relapse was first suspected by symptoms. In a European cohort of 199 patients with relapsed RMS we found that the majority of patients with relapse (n=121, 60.8%) were detected because of clinical symptoms leading to additional imaging. Three-year post relapse survival for patients with a relapse detected by routine imaging was 50% (95%-CI: 38-61%), this was 46% (95%-CI: 37-55%) for patients with a relapse detected because of symptoms. We found no evidence that survival after relapse was affected by the method of relapse detection (p=.7). We estimated that 178 MR's and 178 chest X-rays were needed to detect one relapse in before clinical symptoms become apparent.

We anticipate that the outcomes of **chapter 6** would result in a modification of current follow- up guidelines. However, changing current follow-up strategies could also impact the experienced distress and anxiety in patients and parents. We believed an assessment of the views and experiences of parents on existing follow-up practice was necessary to better understand the emotional experiences of parents following completion of therapy, and this assessment was also necessary to successfully implement such a profound change in follow-up practice (**chapter 7**). The views and experiences of parents during the follow-up was evaluated in a qualitative study for which we invited parents of children who were treated for RMS or Ewing sarcoma in Dutch pediatric oncology centers and were 0-5 years after completion of therapy. We conducted 2 focus group meetings and 4 semi-structured telephone interviews; in total 12 parents of 12 patients participated. The views and experiences of parents were focused around four major themes: content of the follow-up, distress/anxiety in the follow-up period (influenced by several factors), search for reassurance and hope, and the functioning of parents in the period after end-of-treatment. The results illustrate the difficult period that parents encounter after finalizing treatment; although treatment has finished, parents experience significant distress caused by the fear of recurrence, but also because of potential adverse effects caused by treatment. Most participating parents indicated that they felt reassured by the scheduled follow-up examinations, however these examinations also evoked additional distress and anxiety. Participating parents were well aware of the

recommended frequency and content of follow-up in the treatment protocol. Finally, parents explicitly expressed the importance of communication in the follow-up period.

Implications for clinical practice based on part 1

The outcomes of the different studies in part 1 of this thesis will be implemented in the radiology guidelines for the upcoming FaR-RMS trial.

First of all, **chapter 2** illustrates that the presence of indeterminate pulmonary nodules at diagnosis do not affect outcome in patients with otherwise localized RMS. These findings are important, since the study illustrates that there is no need to upstage these patients in future treatment protocols and there is no need for intensified chemotherapy, one year of maintenance chemotherapy and additional surgery and/or chest radiotherapy. Patients with indeterminate pulmonary nodules will be treated according to localized diseased protocols in future studies.

Chapter 3 clearly shows the paucity of data on the accuracy of ^{18}F-FDG-PET/CT, yet ^{18}F-FDG- PET/CT widely applied to detect potential distant metastases in RMS. Clinicians should be aware of the scarce data. CT scanning of the lungs should remain the gold standard for the detection of potential lung metastases, whereas potential lymph node metastases detected by ^{18}F-FDG- PET/CT should always be evaluated histologically. In the upcoming EpSSG Frontline and Relapse RMS (FaR-RMS) trial, ^{18}F-FDG-PET/CT will be standard practice for the staging of potential bone metastases, therewith replacing whole body ^{99m}-Tc bone scintigraphy. However, determining the accuracy of ^{18}F-FDG-PET/CT for the detection of bone metastases will almost be impossible, since no ^{99m}-Tc bone scintigraphy Far-RMS will be done and histopathological confirmation of all suspected lesions will be impossible.

Based on the results of **Chapter 4** and **Chapter 5** of this thesis, we advise that in future RMS guidelines only patients with progressive disease at early response assessment should be switched to second line chemotherapy. It is important that the limited clinical value of radiologic response is explained to parents, especially in patients where the tumor is (almost) unchanged in size after three courses of chemotherapy.

Finally, based on the result of **chapter 6** a new follow-up strategy for patients treated for localized RMS should be developed, taking into account the risk of relapse over time based on risk group and the associated prognosis. We believe that based on the results of chapter 6, the duration of follow-up imaging could be decreased, and it is important that the rationale behind a new follow-up strategy should be clearly explained to patients and parents.

Part 2: Local therapy in rhabdomyosarcoma

The aim of part 2 of this thesis was focused on local therapy in patients with head-neck RMS (**Chapter 8** & **9**). Around 40% of all RMS cases occur in the head-neck area.(27) All patients with RMS receive chemotherapy, however local therapy, i.e. surgery and/or radiotherapy, is essential to achieve local control. For tumors situated in the head-neck area this generally implies radiotherapy, since a microscopically radical resection is often impossible and a macroscopic resection without additional radiotherapy is inadequate. Therefore, the majority of the patients with RMS in the head-neck area receive external beam radiotherapy, which is considered the international standard.

The AMORE protocol, developed in the Emma Children's Hospital-Amsterdam UMC (EKZ-AUMC) in the '90s, is an innovative protocol combining macroscopic surgery with brachytherapy. The theoretical advantage of brachytherapy compared to external beam radiotherapy is the more conformal dose delivery to the tumor bed with rapid dose fall-off beyond the target volume, thereby sparing more of the healthy surrounding tissue.

AMORE treatment as first-line local therapy has shown to result in similar survival and less adverse events compared to local therapy with external beam radiotherapy.(28-31) Nevertheless, patients treated for head-neck RMS, either according to the AMORE protocol or with external beam radiotherapy, frequently suffer from adverse events such as musculoskeletal disfigurements, speech problems, growth hormone deficiency, alopecia, hearing loss and cataract.(29, 32-35)

Psychosocial well-being of survivors of head-neck rhabdomyosarcoma

In **chapter 8** we evaluated the psychosocial well-being of survivors of head-neck RMS. In total, 65 survivors of head-neck RMS treated in the Netherlands and the United Kingdom participated in this study. Survivors completed questionnaires regarding their health-related quality of life, self-perception and satisfaction with appearances. In general, health-related quality of life in these survivors was comparable to reference groups; however, they did report difficulties on potentially more disease related domains. Head-neck RMS survivors reported lower scores on the school/work functioning compared to sex-adjusted reference data and also reported more disease related consequences, potentially caused by their facial deformities. Furthermore, in this study strength of correlations between psychosocial outcomes and burden scores (which combines the number and severity of adverse events) were stronger for specific questionnaires focused on facial differences. This illustrates the need for specific follow-up in patients treated for head-neck RMS by using questionnaires focusing on difficulties encountered by these patients, which was also shown in adult survivors of head-neck cancer.(36, 37)

Feasibility of AMORE as salvage treatment

Despite the effort of different cooperative study groups to improve survival for patients with RMS, still up to one third of all patients with localized RMS at diagnosis experience a relapse. The relapse rate and survival after relapse is strongly depending on previously received therapy.(38-40) Whereas local treatment options are available for patients with a relapse who did not receive radiotherapy, the situation is different for patients experiencing a relapse after prior external beam radiotherapy. Re-irradiation with external beam radiotherapy is generally considered impossible due to unacceptable toxicity, and therefore local treatment options in relapsed head-neck RMS after prior external beam radiotherapy are generally lacking; however, in specific cases of head-neck RMS the AMORE approach can be used as salvage treatment. The previously mentioned theoretical advantage of brachytherapy over external beam radiotherapy still holds, yet in this salvage setting more mutilating surgery and additional adverse events caused by a second episode of radiotherapy, in this case brachytherapy, is accepted to achieve long term survival.

In **chapter 9** we reported on the results of our local experience (>20 years) with AMORE as salvage treatment in patients with relapsed head-neck RMS after prior radiotherapy. In this period 18 patients underwent a salvage AMORE procedure. With AMORE treatment local control was achieved in 67% of the patients and 5-year overall survival was 54%. In this study we showed that AMORE treatment is feasible in specific cases and with this treatment we were able to achieve long term survival for a considerable proportion of selected patients with relapsed head-neck RMS after prior external beam radiotherapy. Importantly, salvage AMORE was only applied after careful discussion within a multidisciplinary team. Since only a selection of the discussed patients did actually receive a salvage treatment, a direct comparison with other cohorts was considered impossible. The results of this study on AMORE treatment in relapsed head-neck RMS patients show that re-irradiation with an adequate (curative) dose in patients with relapsed RMS is possible. Although the re-irradiation was well-tolerated (potentially because of reconstruction with a well-vascularized muscle tissue flap), surviving patients all experienced important sequelae.

Implications for clinical practice based on part 2

The results of **chapter 8** illustrate the necessity of systematic monitoring of the psychosocial well-being of these survivors. However, administering generic health-related quality of life questionnaires is not enough to adequately measure potential problems encountered by survivors of head-neck RMS. We recommend including disease-appropriate questionnaires in a systematic monitoring program. This monitoring program should also pay special attention to bullying, since patients treated for head-neck

RMS frequently suffer from musculoskeletal deformities(29) and social interactions are strongly affected by facial appearances.(41) This systematic assessment of patient reported outcomes (PROs) should play an integral part in the follow-up of long term survivors of head-neck RMS. Previous studies illustrated the value of using PROs to systematically evaluate psychosocial functioning of patients.(42, 43) These questionnaires could be integrated in the online KLIK platform, enabling patients and physician to measure psychosocial functioning before consultation.(44, 45) This systematic measurement should be followed by tailored interventions, where available. These interventions could range from psychosocial care to reconstructive interventions.

The results of **chapter 9** illustrates that a salvage AMORE procedure, including re-irradiation of previous irradiated site, is a feasible and effective local therapy approach in selected patients with relapsed head-neck RMS after prior external beam radiotherapy. Therefore, we encourage physicians to consider AMORE treatment for patients with relapse head-neck RMS after prior external beam radiotherapy.

General recommendations and future perspectives

The results of this thesis illustrate the necessity of multidisciplinary and international collaboration in the diagnosis, treatment and follow-up of RMS. However, the results also illustrate the current gaps in our knowledge of this disease. Furthermore this thesis also elicit study questions that may be transposed to other pediatric malignancies.

Based on the results of **part 1** of this thesis we believe that standardized imaging reporting templates are minimal requirements to improve consistency of reporting and increase the potency of data mining in future radiology studies. Ideally, future pediatric RMS trials should contain central radiology review, to enhance reporting consistency to adequately assess the clinical value of specific radiologic measurements. The initiated QUARTET project (Quality and Excellence in Radiotherapy and Imaging for Children and Adolescents with Cancer across Europe in Clinical Trials) could contribute to this by enabling prospective collection of radiology imaging.(46)

As mentioned in **chapter 2**, pulmonary metastases in the E*p*SSG-RMS 2005 protocol were defined as; one or more nodules ≥10 mm, two or more nodules 5-10 mm or 5 or more nodules <5mm. This definition was based on an arbitrary cut-off and in other pediatric malignancies different definitions for pulmonary metastases are used. For patients with Wilms' tumors, pulmonary nodules ≥3 mm are considered to be pulmonary metastases.(47) For patients with Ewing sarcoma, a solitary nodule of 5 mm -10 mm or multiple nodules of 3-5 mm are considered questionable evidence of metastases and in these patients biopsy is recommended; patients with larger nodules are considered to have pulmonary metastases.(48) For patients with osteosarcoma 3 or more lesions

≥5 mm were considered pulmonary metastases.(49) The question arises if it is justified that these definitions for pulmonary metastases are different between different types of malignancies, or whether these definitions should be aligned. For Wilms' tumor the significance of chest CT only lung nodules was previously assessed.(50, 51) However, we believe that an evaluation of the currently used definition for pulmonary metastases in patients with Ewing sarcoma and osteosarcoma is necessary.

As stated above, the results of **chapter 3** shows that there is currently insufficient evidence to determine the accuracy of ^{18}F-FDG-PET/CT for the detection of distant metastases in pediatric RMS. We believe that a prospective analysis of the accuracy of ^{18}F-FDG-PET/CT, comparing results of ^{18}F-FDG-PET/CT to a gold standard is necessary. Although the E*p*SSG FaR-RMS study will prospectively collect the data of ^{18}F-FDG-PET/CT performed at diagnosis, it is difficult to determine its accuracy since a whole body ^{99m}-Tc bone scintigraphy will no longer be performed and histopathological confirmation of all potential distant metastases will not be required.

Therefore, a gold standard to evaluate the accuracy of ^{18}F-FDG-PET/CT is lacking, making an evaluation of its accuracy for the detection of bone metastases impossible. However, determining the accuracy for the detection of lymph node involvement and lung metastases is possible. For future treatment protocols it is important that the accuracy of newly introduced (and promising) imaging techniques, such as ^{18}F-FDG-PET/MRI, is determined, before introducing these techniques as standard practice.

It is disappointing that the results of this thesis show that tumor response (two dimensional, three dimensional or according to RECIST) is not prognostic for survival and could therefore not serve as surrogate endpoint in RMS trials. This clearly shows that we currently lack an early prognostic marker for survival and underlines the need for future studies to focus on other potential surrogate markers.

First, future studies should focus on functional imaging techniques such as diffusion-weighted magnetic resonance imaging (DW-MRI) and ^{18}F-FDG-PET/CT evaluation tumor response by determination of the tumor cell density and metabolic activity before and after induction chemotherapy. The question is if the cell density and the metabolic activity, as determined by DW-MRI or ^{18}F-FDG-PET/CT, are prognostic for survival and whether this measurements might serve as surrogate endpoint in RMS trials.(10, 52-55) An earlier study by Casey et al. reported that ^{18}F-FDG-PET/CT response, measured in 107 patients with RMS (irrespective of stage), was predictive for survival.(53) However, a different study by Harrison et al. did not found ^{18}F-FDG- PET/CT response to be predictive for survival in an analysis of two cohorts of a total of 121 patients with RMS.(54) These conflicting results in relatively small cohorts illustrates the necessity of a larger

prospective study; the E*p*SSG FaR-RMS trial will prospectively assess the value of the ^{18}F-FDG-PET/CT response.

The evidence for the value of DW-MRI in the measurement of response in pediatric RMS is even more limited.(56) DW-MRI measures the motion of water molecules within a voxel, which implies that lower diffusion coefficient are measured in tissue with higher cellularity (such as tumor tissue).(57) Theoretically, DW-MRI has the potential to determine tumor response in RMS by measuring the apparent diffusion coefficient (ADC) before and after induction chemotherapy.(55) Although DW-MRI is frequently used as additional imaging information for diagnostic purposes, its value as early prognostic marker in pediatric RMS is unclear. In the limited available literature on the value of DW-MRI in RMS, the methods used to determine ADC values vary widely.(56) Since the value of DW-MRI in pediatric RMS is unclear, we are currently designing a future study evaluating the value of DW-MRI retrospectively within the EpSSG radiology network, established in the study of chapter 2. In addition, a prospective study aimed to evaluate the value of DW-MRI in RMS is proposed as add-on study to the FaR-RMS. The QUARTET platform enables the collection and central review of the imaging.

Concomitantly, future research should focus on identifying new biomarkers, for instance minimal residual disease [MRD] markers, with the potential to measure response to therapy.(58) As example, in acute lymphoblastic leukemia MRD markers have been proven to be a strong biomarker currently used to stratify patients.(59, 60) Identifying MRD markers in RMS could potentially also results in an early identification of patients at high risk of relapse.(61)

Finally, although we did not found evidence that radiologic response is prognostic for survival, this lack of evidence could partly be caused by important interobserver variation in the measurement of response.(15) This interobserver variation could be limited by using computer aided diagnosis systems, such as semi-automated response measurements. Future studies should focus on the possibility to use computer aided diagnosis systems to classify response to therapy more accurately.(62) It might appear that more accurate measurements, including other parameters than volume response only, are prognostic for survival and could therefore serve as surrogate endpoint in future studies. This technique could be especially helpful in patients with metastatic disease, in which response measurement is often a time-consuming process for radiologists and the clinical value is generally unknown. In addition, the possibilities of machine learning also offers opportunities to evaluate existing stratification. Furthermore, it could also help better identify patients at high risk of relapse at time of diagnosis to ensure early therapy intensification. Machine learning could lead to a whole new look on imaging and could offer a better understanding of differences in outcome in patients with RMS and should be exploited in future studies.(63)

In regard to surveillance imaging after end-of-treatment, a randomized controlled trial evaluating the clinical value of off-therapy surveillance by imaging should be done. The proposed study would randomize patients between existing follow-up schedules and follow-up based on risk of relapse and chance of survival after relapse. Importantly, such a study should assess parental anxiety and distress, and fear of recurrence as important outcome measures.

Potentially, MRD markers could serve as early markers for relapse in future studies.

The results of **part 2** of this thesis on local therapy approaches in patients with head-neck RMS illustrate the impact of treatment and the limitations in our treatment options. The results illustrate the necessity of specific follow-up for survivors of head-neck RMS, however, the best approach for long term follow-up of these survivors is unclear.

Future studies should focus on determining which questionnaires are most valuable in the follow-up of survivors of head-neck RMS. Furthermore, the possibilities for tailored interventions should be examined, but should also be reported. We believe that patients with head-neck RMS should have a specialized long-term follow-up in a multidisciplinary outpatient clinic. Ideally future studies should compare survival outcome, experienced adverse events and psychosocial outcomes between different large centers with different local treatment approaches for patients with head-neck RMS (i.e. photon radiotherapy, proton radiotherapy and AMORE technique).

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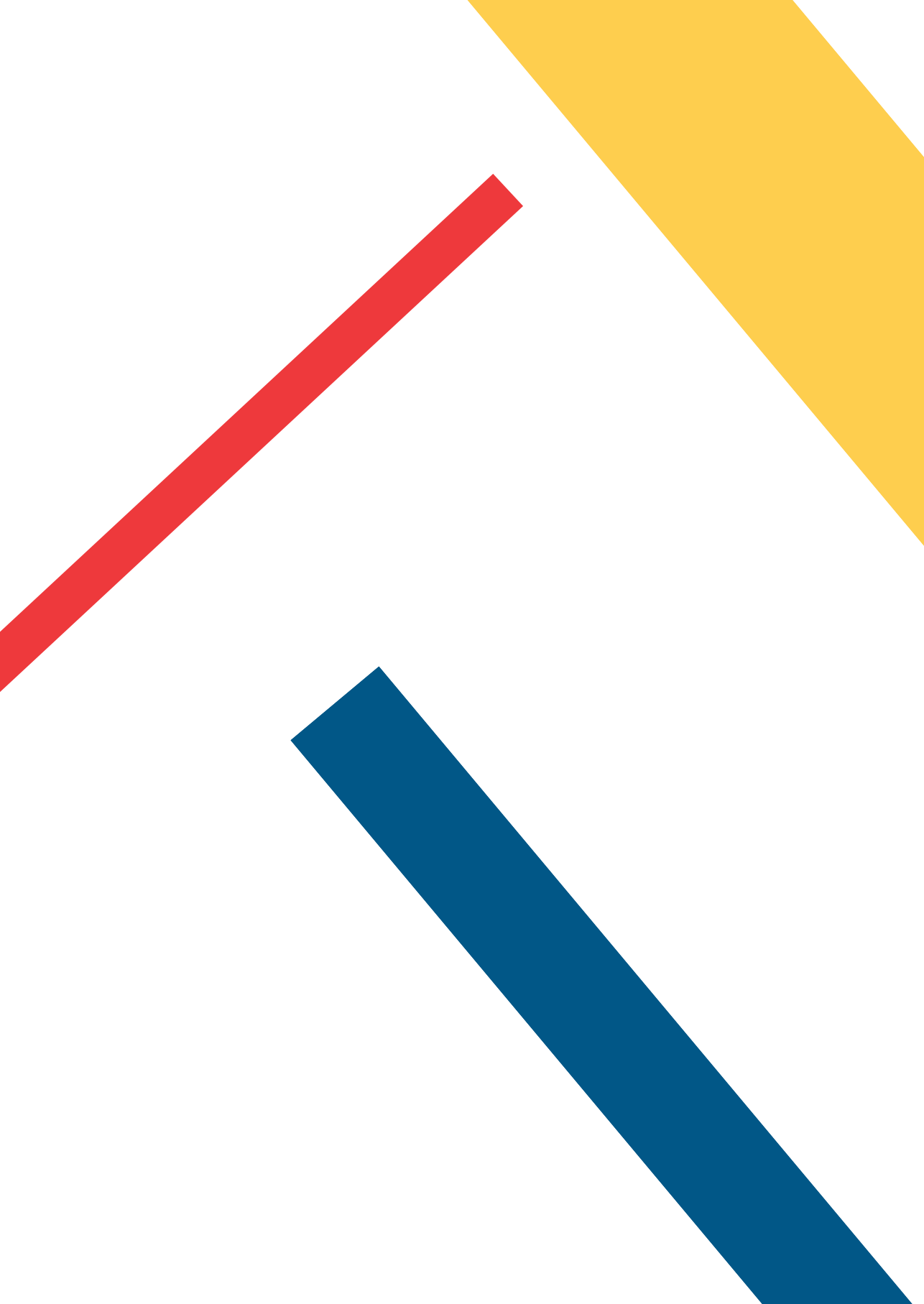


CHAPTER 11

NEDERLANDSE SAMENVATTING (DUTCH SUMMARY)

Rhabdomyosarcoom (RMS) is een weke delen tumor en in Nederland wordt bij ongeveer 20 kinderen per jaar deze diagnose gesteld. Hiermee is RMS de meest voorkomende weke delen tumor op de kinderleeftijd.

Op welke manier een RMS zich manifesteert is afhankelijk van de plek waar de tumor zit. Aangezien RMS zich in het gehele lichaam bevinden kan de presentatie erg divers zijn. De behandeling van kinderen met een RMS is ook afhankelijk van de plek van tumor, en wordt daarnaast bepaald door het subtype RMS, de grootte van de tumor, de leeftijd van het kind en ook of er eventuele metastasen (uitzaaiingen) zijn. Al deze factoren worden meegenomen om te bepalen tot welke risicogroep een nieuwe patiënt met RMS behoort om de uiteindelijke behandeling te bepalen. Dit wordt stadiëring genoemd. De prognose voor kinderen met een RMS waarbij geen sprake is van metastasen is ongeveer 75%, echter is de overleving van kinderen met metastasen bij diagnose slechts 10-50%. Om deze prognose te verbeteren is het belangrijk om onderzoek te doen.

Echter, gezien het relatieve kleine aantal patiënten met RMS en de vele factoren die samenhangen met de overleving is internationaal onderzoek onontbeerlijk. Dit heeft tot doel de prognose van patiënten met een RMS te vergroten en tegelijkertijd de schadelijke effecten van de behandeling (toxiciteit) te verminderen. In Europa worden de meeste kinderen met een RMS behandeld volgens (onderzoeks)protocollen van de European *paediatric* Soft tissue sarcoma Study Group (EpSSG). De E*p*SSG-RMS 2005 studie is inmiddels afgerond en de nieuwe studie, genaamd de Frontline and Relapse (FaR) RMS studie, zal in 2019 van start gaan. Echter voor de start van deze studie waren er een aantal belangrijke vragen omtrent de waarde van beeldvormende (radiologische) onderzoeken die beantwoord dienden te worden.

Dit proefschrift bestaat uit twee delen. Het eerste gedeelte beschrijft de waarde van verschillende radiologische onderzoeken bij de diagnose, tijdens de behandeling en gedurende de follow-up na einde behandeling van een RMS. Het tweede gedeelte gaat over de lokale behandeling van kinderen met een RMS, waarbij het specifiek gaat over de lokale behandeling van kinderen met een RMS in het hoofd-hals gebied.

Deel 1: Beeldvorming bij rhabdomyosarcomen

Beeldvorming bij diagnose

De belangrijkste prognostische factor voor overleving bij kinderen met een RMS is de aan- of afwezigheid van metastasen bij diagnose. Derhalve is het zeer belangrijk dat de stadiëring van nieuwe patiënten accuraat is, zodat patiënten met gemetastaseerde ziekten een intensievere behandeling kunnen krijgen.

Ongeveer 16% van de patiënten met RMS heeft gemetastaseerde ziekte bij diagnose; metastases zitten het vaakst in de longen (in ±6% van alle patiënten) en daarnaast komen bot metastases (in ±5% van alle patiënten) veelvuldig voor.

Sinds de start van de E*p*SSG-RMS 2005 studie wordt er ten tijde van de diagnose bij elke patiënt met een RMS een CT (computertomografie) scan van de thorax (borstkas) gemaakt om te kijken of er sprake is van longmetastases. Voorheen gebeurde dit middels een conventionele thorax foto (röntgen foto). CT heeft als voordeel ten opzichte van een conventionele foto dat het een hogere resolutie heeft. Echter zorgt de introductie van een beeldvormende techniek met hogere resolutie ook voor nieuwe diagnostische dilemma's; kleine long afwijkingen zijn namelijk ook zichtbaar op een CT scan terwijl deze op een conventionele thorax foto niet zichtbaar zijn. Deze kleine afwijkingen zijn veelal te klein om te kunnen biopteren en daarom moet er op basis van de beeldvorming bepaald worden of deze afwijkingen beschouwd worden als bewijs voor metastasen of dat ze goedaardig zijn en bijvoorbeeld het gevolg zijn van een infectie.

Volgens het E*p*SSG-RMS 2005 protocol worden patiënten met kleine long afwijkingen (minder dan 5 afwijkingen, kleiner dan 5 mm) behandeld volgens het schema voor niet gemetastaseerd RMS. In **hoofdstuk 2** hebben we onderzocht of deze patiënten met kleine long afwijkingen een adequate behandeling hebben gehad. In een internationaal multicenter onderzoek hebben we van 316 patiënten de CT thorax bij diagnose laten herbeoordelen door een kinderradioloog met de vraag of er kleine long afwijkingen aanwezig waren. In 67 patiënten (21.2%) was er sprake van kleine long afwijkingen, echter vonden we geen aanwijzingen dat de overleving van deze patiënten slechter was dan de overleving van patiënten zonder deze afwijkingen bij diagnose.

Dit betekent dat deze patiënten adequaat behandeld zijn en dat er geen reden is om de behandeling voor patiënten met kleine long afwijkingen aan te passen voor toekomstige behandel protocollen. Daarnaast vonden we dat er bij de herbeoordeling van de CT thorax middels een gestandaardiseerd formulier meer dan 10% vaker patiënten werden gevonden waar sprake bleek van kleine aspecifieke longafwijkingen.

Naast een CT thorax worden bij patiënten met RMS nog andere beeldvormende onderzoeken verricht om mogelijke metastasen op te sporen. Met behulp van echografie en/of MRI wordt gekeken of er tumor uitbreiding is naar lymfeklieren en daarnaast wordt er een botscan gemaakt om te kijken of er sprake is van bot metastasen. Tegenwoordig wordt er ook frequent een FDG-PET/CT gemaakt, dit is een beeldvormende techniek waarbij gebruikt wordt gemaakt van een radioactief gelabelde marker. Middels deze techniek kan de metabole activiteit worden gemeten, waarbij tumor cellen vaker een hogere metabole activiteit hebben. Het nadeel echter is dat de tracers die gebruikt worden alleen iets zeggen over de metabole activiteit van cellen in het algemeen en dat deze niet specifiek voor tumor cellen zijn. In **hoofdstuk 3** hebben we middels een

gestructureerd literatuuronderzoek (een systematische Cochrane review) onderzocht hoe nauwkeurig FDG-PET/CT is voor het detecteren van betrokken lymfeklieren en bot en long metastasen vergeleken met de standaard radiologische onderzoeken. Hierin hebben we geconcludeerd dat er op dit moment onvoldoende bewijs beschikbaar is om de nauwkeurigheid van FDG-PET/CT te bepalen. Het gebrek aan bewijs was opvallend, aangezien FDG-PET/CT in huidige protocollen de botscan vervangen heeft als eerste keus onderzoek voor het opsporen van botmetastasen.

Beeldvorming tijdens de behandeling

Patiënten die worden gediagnosticeerd met een RMS krijgen bij diagnose vaak een biopt. Aan de hand van het biopt en radiologische onderzoeken wordt het subtype en eventuele uitzaaiingen bepaald, waarna chemotherapie (meestal 3 kuren) wordt gegeven. Vervolgens wordt er lokale therapie toegepast (chirurgie en/of radiotherapie), waarna wederom chemotherapie wordt gegeven.

In Europese behandelprotocollen wordt er na 3 kuren chemotherapie een MRI (of CT) gemaakt om de response op therapie te bepalen. Indien de tumor onvoldoende in grootte is afgenomen (minder dan 1/3 afname in het volume van de tumor zoals bepaald op de beeldvorming) dan wordt de chemotherapie (eerste keus) omgezet naar tweede keus chemotherapie op basis van de gedachte dat tumor afname op chemotherapie voorspellend is voor overleving. Dit beleid is in Europese protocollen verschillend van Noord-Amerikaanse protocollen waarin er alleen bij een toename van de tumor geswitcht wordt naar de tweede keus chemotherapie.

In **hoofdstuk 4** hebben we onderzocht of de afname in tumor volume voorspellend is voor de overleving van patiënten met niet-gemetastaseerd RMS in een groep patiënten behandeld volgens het International Society of Pediatric Oncology (SIOP) Malignant Mesenchymal Tumor 95 (MMT-95) protocol. In deze groep van 432 patiënten vonden we dat de overgrote meerderheid (85.2%) voldoende tumor afname liet zien op inductie chemotherapie. Echter vonden we geen verschil in overleving tussen patiënten op basis van de afname in tumor volume. Deze resultaten kwamen overeen met de resultaten van twee Noord-Amerikaanse studies, maar waren tegenstrijdig aan een analyse van de Duitse Cooperative Soft Tissue Sarcoma (CWS) groep.

Vanwege deze tegenstrijdige resultaten hebben we besloten om op een systematische wijze de bestaande onderzoeken naar de prognostische waarde van radiologische response op overleving te verrichten (**hoofdstuk 5**). In totaal hebben we zes studies geïncludeerd, met in totaal 2010 patiënten. Vanwege de verschillen in definitie en methode van response bepaling waren we helaas niet in staat om een meta-analyse te verrichten. Van de zes geïncludeerde studies werd er in twee een verschil in overleving gevonden op basis van vroege afname van tumor grootte. In vier studies werden er geen aanwijzingen gevonden dat radiologische response voorspellend was voor over-

leving. Opvallend was dat de twee studies die een verschil vonden, patiënten hadden geïncludeerd met een toename van tumor grootte tijdens de eerste response meting, terwijl deze patiënten in de andere vier studies waren uitgesloten van analyse.

Op basis van de resultaten van de verschillende studies hebben wij geconcludeerd dat er op dit moment onvoldoende bewijs is dat vroege radiologische response voorspellend is voor overleving, behoudens voor patiënten met progressieve ziekte bij response meting. Radiologische response kan daarom niet gebruikt worden als vroege voorspeller voor overleving.

Beeldvorming tijdens follow-up

Ondanks dat de overleving van patiënten met niet-gemetastaseerd RMS de laatste decennia is toegenomen krijgt ongeveer 1/3 van de patiënten een tumor recidief. Vanwege dit hoge aantal recidieven staan patiënten behandeld voor een RMS onder intensieve controle na einde behandeling. Deze controle bestaat onder andere uit frequente radiologische scans om mogelijke recidieven vroeg op te sporen. Er is nooit aangetoond dat de frequente scans recidieven eerder opspoort en daarmee zou leiden tot een hogere kans op overleving bij een recidief, terwijl het potentieel wel een belasting is voor patienten en ouders. Daarnaast zijn patiënten met een RMS vaak jong (mediane leeftijd bij diagnose is 6 jaar), waardoor bij een groot deel van de patiënten algehele anesthesie noodzakelijk is om goede kwaliteit scans te kunnen maken. Het is onduidelijk wat de mogelijke gevolgen zijn van het herhaaldelijk toepassen van algehele anesthesie (alsmede herhaaldelijk toedienen van contrastmiddelen) op een ontwikkelend brein.

Om deze redenen vonden we het noodzakelijk om in **hoofdstuk 6** de klinische waarde van radiologische follow-up te onderzoeken. In een retrospectieve studie hebben we gekeken naar hoe recidieven bij patiënten met een RMS worden ontdekt en hoeveel patiënten met een recidief RMS overleven. We hebben hierbij twee groepen onderscheiden; patiënten met een recidief ontdekt op routine beeldvorming en patiënten met een recidief ontdekt op beeldvorming verricht vanwege klinische symptomen. In een internationale retrospectieve multicenter studie hebben we 199 patiënten met een recidief geïncludeerd. Hierbij vonden we dat de meerderheid van de recidieven ontdekt werden vanwege klinische symptomen, ondanks de frequente follow-up scans. Daarnaast vonden we geen verschil in overleving tussen patiënten met een recidief ontdekt op routine beeldvorming en patiënten met een recidief ontdekt vanwege klinische symptomen.

Bij het begin van dit onderzoek verwachtten we dat de resultaten van hoofdstuk 6 mogelijk aanleiding zouden kunnen zijn tot een verandering in de follow-up na einde behandeling van RMS. Echter om een dergelijke ingrijpende verandering door te voeren vonden we het noodzakelijk om ook onderzoek te doen naar de gedachten en ervaringen van ouders omtrent de huidige follow-up na einde behandeling. In **hoofdstuk 7** hebben

we een kwalitatief onderzoek verricht, waarbij we aan de hand van groepsgesprekken (focusgroepen) en semigestructureerde interviews onderzoek hebben gedaan naar de gedachten en ervaringen rondom de follow-up onderzoeken. Hierbij hebben we ouders van kinderen behandeld voor

RMS of Ewing sarcoom gevraagd om deel te nemen aan dit onderzoek. In deze studie hebben we thema's geïdentificeerd die invloed hebben op hoe ouders zich voelen na het einde van de behandeling en de invloed die de follow-up onderzoeken hierop hebben. De resultaten laten zien dat de periode na einde behandeling een periode van transitie is die veel stress bij ouders kan veroorzaken. De meeste ouders gaven aan dat ze gerustgesteld worden door de follow-up beeldvorming, echter veroorzaakt het doen van de beeldvorming ook stress en angst. Om deze stress en angst beter te controleren maken de meeste ouders strikte afspraken met hun arts over de follow-up en hoe de uitslagen gecommuniceerd worden. De deelnemende ouders benadrukten specifiek het belang van communicatie tijdens de follow-up periode. Uitleg over de waarde van follow-up, maar ook uitleggen waarom follow-up uiteindelijk stopt is essentieel en geeft ouders bevestiging over de situatie van hun kind en is derhalve essentieel in de follow-up periode.

Deel 2: Lokale behandeling van rhabdomyosarcomen.

Naast de systemische behandeling (behandeling door middel van chemotherapie) is een essentieel onderdeel van de behandeling van RMS de lokale behandeling. Lokale behandeling bij RMS bestaat uit chirurgie en/of radiotherapie (bestraling). Voor tumoren in het hoofd-hals gebied is een complete chirurgische resectie (een resectie van de tumor met een marge met gezond weefsel) vaak niet mogelijk doordat tumoren zich vaak in de buurt van vitale structuren bevinden of omdat een resectie onacceptabele mutilerende gevolgen zou kunnen hebben. Daarom is bij tumoren in het hoofd-hals gebied uitwendige radiotherapie vaak de therapie van keuze. Nadeel van radiotherapie is dat ook gezond weefsel bestraald wordt en dit kan leiden tot verschillende late effecten, zoals bijvoorbeeld uitgroeiproblemen in het gelaat. Deze uitgroeiproblemen kunnen leiden tot asymmetrie. Het doel van **deel 2** van dit proefschrift was het onderzoeken van de uitkomsten van behandeling bij kinderen met een RMS in het hoofd- hals gebied.

In 1990 is er in het Emma Kinderziekenhuis/Amsterdam UMC een nieuw behandel protocol ontwikkeld, gericht op de behandeling van patiënten met een hoofd-hals RMS, het AMORE protocol. AMORE is een acroniem en staat voor Ablatieve chirurgie, MOulage techniek brachytherapie en REconstructie. Hierbij wordt een macroscopische resectie van de tumor verricht, waarna er met behulp van inwendige radiotherapie (brachytherapie) de randen met mogelijk microscopische rest worden bestraald. Het voordeel van deze techniek is dat de straling zeer gericht kan worden gegeven, waardoor minder

gezond weefsel wordt bestraald. Eerdere onderzoeken hebben laten zien dat AMORE behandeling een effectieve behandelmethode is, waarbij de overleving van patiënten vergelijkbaar is met patiënten die behandeld zijn met uitwendige radiotherapie (is de internationale standaard).

Psychosociaal functioneren van kinderen behandeld voor een RMS in het hoofd-hals gebied.

Uit eerder onderzoek weten we dat patiënten behandeld volgens het AMORE protocol minder late effecten ervaren dan patiënten behandeld met uitwendige radiotherapie. Desalniettemin ervaren patiënten, behandeld voor een hoofd-hals RMS, veelvuldig late effecten veroorzaakt door de lokale behandeling zoals uitgroeiproblemen van het gelaat, problemen met spraak, groei hormoon deficiëntie en gehoorverlies. Er is echter weinig onderzoek gedaan naar de gevolgen van deze late effecten op het psychosociaal functioneren van kinderen.

In **hoofdstuk 8** hebben we met behulp van vragenlijsten gekeken naar de gevolgen van de behandeling van een RMS in het hoofd-hals gebied op het psychosociaal functioneren van deze kinderen 2 of meer jaar na de behandeling. In totaal hebben 65 patiënten, behandeld voor een hoofd-hals RMS in Engeland en Nederland tussen 1990 en 2010, aan deze studie deelgenomen. Het bleek dat de kwaliteit van leven van overlevers van een hoofd-hals RMS over het algemeen vergelijkbaar is met hun leeftijdgenoten, echter zijn er ook belangrijke verschillen. De overlevers rapporteerden bijvoorbeeld meer problemen op school of op werk. Een belangrijke uitkomst was ook dat veelgebruikte kwaliteit van leven vragenlijsten matig samenhingen met door artsen gerapporteerde late effecten van behandeling, terwijl specifiekere vragenlijsten dit beter deden. De resultaten van deze studie laten zien dat het meten van kwaliteit van leven van patiënten behandeld voor een hoofd-hals RMS belangrijk is. Belangrijk is echter wel dat er specifieke vragenlijsten worden gebruikt om dit meten.

AMORE behandeling voor patiënten met een recidief RMS

Zoals eerder beschreven krijgt ongeveer 1/3 van de patiënten met een niet-gemetastaseerd RMS een tumor recidief. De overleving van patiënten met een recidief RMS is matig en dit wordt voornamelijk veroorzaakt doordat er weinig therapie opties zijn bij patiënten met een recidief RMS. Zeker in het geval van patiënten met een recidief RMS in het hoofd-hals gebied na eerdere uitwendige bestraling zijn er weinig mogelijkheden meer over om lokale controle te bereiken. In specifieke gevallen is een behandeling volgens het AMORE protocol mogelijk.

In **hoofdstuk 9** hebben we de resultaten van AMORE behandeling bij patiënten met een recidief RMS na eerdere uitwendige radiotherapie gerapporteerd. In een periode van 20 jaar hebben 18 patiënten met een recidief RMS in het hoofd-hals gebied een

AMORE behandeling ondergaan na eerdere uitwendige radiotherapie. De resultaten van de studie laten zien dat deze procedure een veilige en effectieve lokale therapie is, waarbij 50% van de behandelde patiënten nog in leven is. Het is belangrijk om hierbij te vermelden dat de groep patiënten die deze behandeling ondergingen allereerst uitgebreid in een multidisciplinaire bespreking met chirurgen, radiotherapeuten, radiologen en (kinder)oncologen besproken waren en de risico's en de consequenties van een dergelijke ingreep zorgvuldig waren afgewogen. Gezien deze strenge voorselectie hebben we geoordeeld dat een vergelijk met andere cohort studies niet geïndiceerd was.

Conclusie

Samenvattend hebben de resultaten van de verschillende studies in dit proefschrift belangrijke gevolgen voor de toekomstige behandelprotocollen voor rhabdomyosarcoom.

In het algemeen concluderen wij, op basis van de resultaten van **deel 1** van dit proefschrift, dat gestandaardiseerde rapportage van beeldvormende onderzoeken noodzakelijk is om de betrouwbaarheid van deze metingen te vergroten. De betrouwbaarheid kan verder worden vergroot door radiologische onderzoeken centraal te laten herbeoordelen door ervaren radiologen in toekomstige RMS studies.

De resultaten van **hoofdstuk 2** laten zien dat patiënten met kleine longafwijkingen behandeld kunnen worden volgens het behandel protocol voor patiënten met niet uitgezaaid RMS. Dit betekent dat deze patiënten geen extra chemotherapie en radiotherapie van de borstholte nodig hebben.

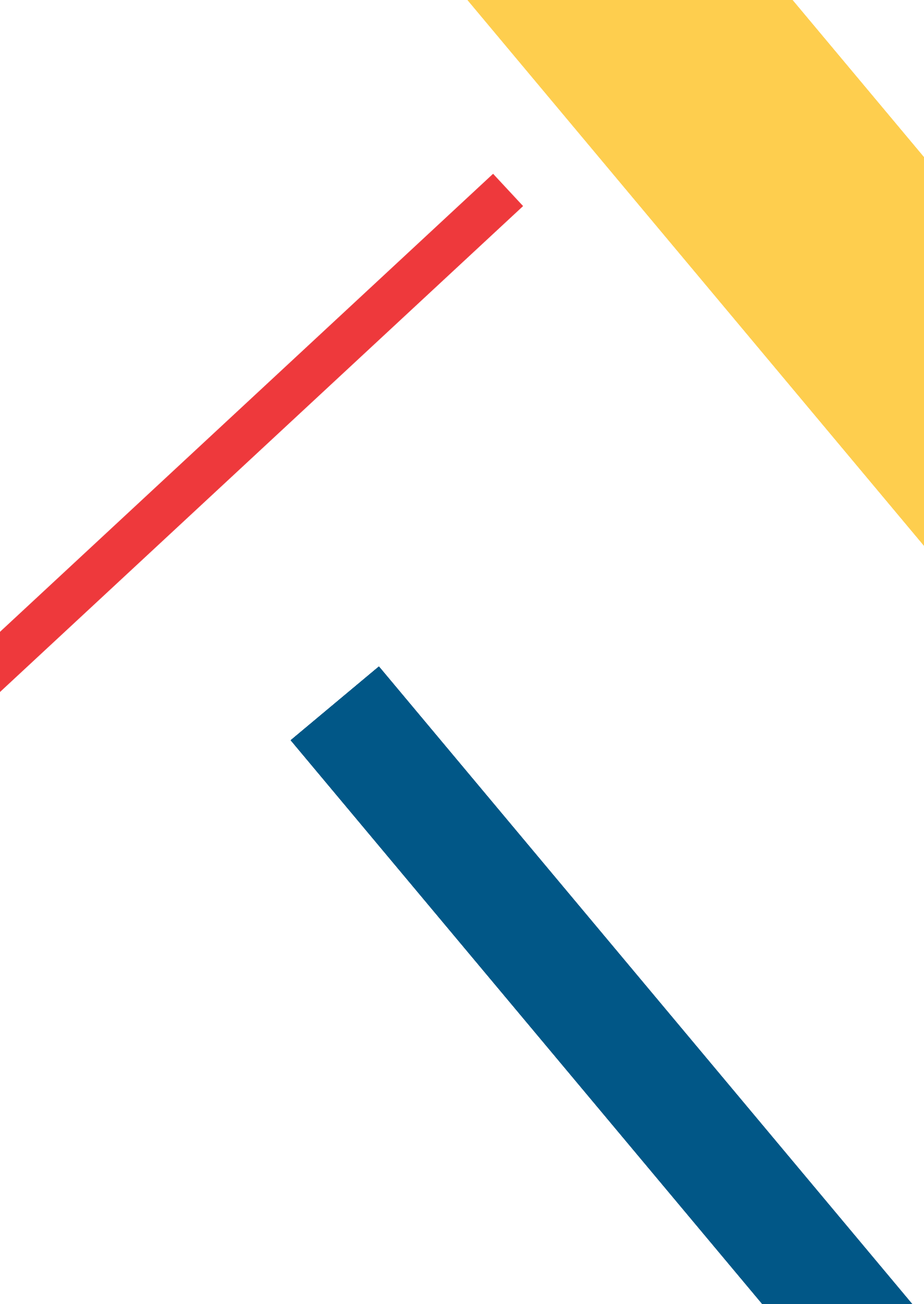
Hoofdstuk 3 laat zien dat er op dit moment onvoldoende bewijs is om de nauwkeurigheid van FDG-PET/CT voor de detectie van betrokken lymfeklieren en mogelijke afstandsmetastases te bepalen. Hierdoor is er op dit moment onvoldoende bewijs dat FDG-PET/CT andere beeldvormende onderzoeken kan vervangen tijdens de stadiering van RMS. Tijdens de behandeling van een RMS is het belangrijk om de effectiviteit van de behandeling in een vroeg stadium te kunnen vast stellen. Dit zorgt er voor dat er in individuele patiënten in een vroeg stadium therapie aanpassingen kunnen worden gedaan als de behandeling niet lijkt aan te slaan. Daarnaast is het ook belangrijk voor onderzoek. Op dit moment kost het 7-10 jaar om een studie naar een nieuw medicijn voor RMS te verrichten. Dit komt omdat overleving op dit moment als uitkomstmaat gebruikt wordt. De resultaten van **hoofdstuk 4** en **5** laten zien dat er onvoldoende bewijs is dat vroege radiologische response voorspellend is voor overleving. Hierdoor is vroege radiologische response op dit moment niet bruikbaar als uitkomstmaat voor de effectiviteit van de behandeling. Dit betekent dat we onderzoek moeten doen naar andere uitkomstmaten waarmee we in een vroege fase van behandeling de effectiviteit van de behandeling kunnen bepalen.

Aangezien duidelijk is geworden dat een recidief RMS niet sneller wordt opgespoord met frequente radiologische scans zal er op basis van de resultaten van **hoofdstuk 6** en **7** een nieuwe follow-up richtlijn moeten worden opgesteld binnen de EpSSG. Indien toekomstige follow-up gewijzigd wordt dan is het wel essentieel om nauwkeurig te monitoren wat het effect van minder beeldvorming op ouders is. Daarnaast zal er onderzoek moeten worden verricht naar andere technieken, zoals bijvoorbeeld bloed testen die mogelijk in een vroeg stadium een recidief tumor kunnen opsporen. Ook in deze gevallen zal moeten worden aangetoond dat vroege detectie van een recidief ook resulteert in een betere overleving na het recidief.

In **deel 2** van dit proefschrift hebben we de behandeling en de gevolgen van de behandeling van patiënten met een RMS in het hoofd-hals gebied besproken.

Op basis van de resultaten van **hoofdstuk 8** hebben we geconcludeerd dat in de follow-up van overlevers van een hoofd-hals RMS aandacht voor het psychosociale functioneren van deze patiënten belangrijk is. Hiervoor zullen specifieke vragenlijsten moeten worden gebruikt om eventuele problemen vroeg op te sporen. Indien nodig zal aanvullende hulpverlening aangeboden moeten worden.

Aan de hand van de resultaten van **hoofdstuk 9** moedigen we artsen aan om een AMORE behandeling te overwegen in het geval van een recidief RMS na eerdere uitwendige bestraling, aangezien dit (indien mogelijk) vaak één van de weinige resterende behandelopties is.



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begin zijn we bezig geweest met de Cochrane review en ik ben er trots op dat we deze bijna hebben afgerond. **Roelof,** ik vind het waanzinnig leuk dat we aan het eind van mijn promotietijd nog een project samen konden doen, dank voor je hulp bij het schrijven van de systematische review. Zonder jouw hulp was deze niet in dit proefschrift gekomen en ik ben nu al een beetje jaloers op de inhoud van jouw proefschrift.

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PHD PORTFOLIO

Name PhD student:	Bas Vaarwerk
PhD period:	April 2015- November 2019
Promotor:	Prof. dr. H.N. Caron
Promotor:	Prof. dr. R.R. van Rijn
Co-promotor:	Prof. dr. M.A. Grootenhuis
Co-promotor:	Dr. J.H.M. Merks

PhD training

	Year	Workload (Hours/ECTS)
Courses		
BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2015	0.6
Scientific Writing in English	2015	1.5
Oral presentation in English	2016	0.8
Project Management	2016	0.6
Clinical Data Management	2016	0.3
Practical Biostatistics	2015	1.1
Clinical Epidemiology: Systematic reviews	2015	0.7
Clinical Epidemiology: Randomized Clinical Trials	2017	0.6
Clinical Epidemiology: Evaluation of Medical Tests	2016	0.9
Qualitative health research	2016	1.9
Advanced biostatistics	2018	2.1
Oral presentations		
European *paediatric* Soft tissue sarcoma Study Group Winter meeting Amsterdam 2015	2015	0.5
European *paediatric* Soft tissue sarcoma Study Group Winter meeting Lyon 2017	2017	0.5
49th Congress of the International Society of Paediatric Oncology, Washington, United States	2017	1.4
54th Congress of the European Society of Paediatric Radiology (ESPR), Berlin, Germany	2018	1.4
50th Congress of the International Society of Paediatric Oncology, Kyoto, Japan	2018	1.4
7th International Tübingen Symposium on Pediatric Solid Tumors	2018	1.0
European *paediatric* Soft tissue sarcoma Study Group Winter meeting Utrecht 2018	2018	0.5
Poster presentations		
49th Congress of the International Society of Paediatric Oncology, Washington, United States	2017	0.1

50th Congress of the International Society of Paediatric Oncology, Kyoto, Japan	2018	0.3
23rd Meeting of the Connective Tissue Oncology	2018	0.3
Society, Rome, Italy		
Symposia and meetings		
European *paediatric* Soft tissue sarcoma Study Group Winter meeting, Brussel, Belgium	2016	0.6
Amsterdam Kindersymposium, Amsterdam	2016-2018	1.0
Princess Máxima Center research symposium	2018	0.6
Other		
Organizing committee Amsterdam Kindersymposium, Amsterdam, The Netherlands	2017 & 2018	4.0
Biweekly meeting of the multidisciplinary working group on pediatric head-neck oncology	2015-2018	1.5
Weekly meetings childhood tumors working group	2015-2018	3.0
Organizing committee workshops on intercultural communication in international research collaborations.	2018	1.0
Parameters of Esteem		
Grants		
KiKa pilot project number 270 'Optimizing rhabdomyosarcoma treatment; assessing the role of radiologic imaging in pediatric rhabdomyosarcoma'.	2016	
Awards and Prizes		
Young investigators award International Society of Pediatric Oncology (SIOP) | "Does early detection with off-therapy surveillance imaging improve survival in pediatric rhabdomyosarcoma patients? The European experience"	2017	
Young investigators award European Society of Pediatric Radiology (ESPR) | "Does surveillance imaging lead to earliest detection of relapse and thus to improved survival in paediatric patients with RMS? The European experience"	2018	

CURRICULUM VITAE

Bas Vaarwerk was born in Winterswijk on March 31st, 1989. He grew up in Winterswijk, a village in the eastern parts of the Netherlands, together with his parents, and two sisters. In 2007, he graduated from secondary school at Scholengemeenschap de Driemark in Winterswijk. Afterwards, he moved to Amsterdam where he started medical school at the Vrije Universiteit Amsterdam in 2008.

During this period he developed a special interest in pediatrics. His enthusiasm for research was evoked during his research internship at the department of pediatric infectious diseases and immunology at the Wilhelmina Kinderziekenhuis under supervision of prof. dr. Debby Bogaert and dr. Wouter de Steenhuijsen Piters focused on the composition of the microbiome of the upper respiratory tract.

After his graduation in 2015 he immediately started his PhD focused on pediatric rhabdomyosarcoma under supervision of prof. dr. Rick van Rijn, prof. dr. Huib Caron, dr. Hans Merks and prof. dr. Martha Grootenhuis. During this period he conducted several international studies on radiologic measurements in the diagnosis, treatment and follow-up of RMS. Furthermore, his thesis also focused on local treatment in patients with rhabdomyosarcoma in the head-neck area. The work described in this thesis was presented and discussed on multiple international congresses. For his study on the value of off-therapy surveillance Bas was awarded with a Young Investigator award from the International Society of Paediatric Oncology (SIOP) and the European Society of Paediatric Radiology (ESPR).

Since December 2018 Bas started working as pediatric resident in Noordwest Ziekenhuisgroep Alkmaar. Bas lives in Amsterdam, together with his girlfriend Geerte and their cat.