Optimizing rhabdomyosarcoma treatment
Assessing the role of imaging and local treatment in pediatric rhabdomyosarcoma
Vaarwerk, B.

Link to publication

Creative Commons License (see https://creativecommons.org/use-remix/cc-licenses):
Other

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE is a service provided by the library of the University of Amsterdam (http://dare.uva.nl)
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 (EpSSG). With the final evaluation of the EpSSG-RMS 2005 study and the design of the new EpSSG Frontline and Relapse rhabdomyosarcoma study (EpSSG 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 EpSSG-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 EpSSG-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 EpSSG-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 reliably 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 EpSSG 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 EpSSG-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 (pre-symptomatic) 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-
associated 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 \(^{18}\text{F-FDG-PET/CT}\), yet \(^{18}\text{F-FDG-PET/CT}\) 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 \(^{18}\text{F-FDG-PET/CT}\) should always be evaluated histologically. In the upcoming EpSSG Frontline and Relapse RMS (FaR-RMS) trial, \(^{18}\text{F-FDG-PET/CT}\) will be standard practice for the staging of potential bone metastases, therewith replacing whole body \(^{99}\text{m-Tc bone scintigraphy}\). However, determining the accuracy of \(^{18}\text{F-FDG-PET/CT}\) for the detection of bone metastases will almost be impossible, since no \(^{99}\text{m-Tc bone scintigraphy}\) 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. 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. 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.

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.
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 and social interactions are strongly affected by facial appearances. 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 systematic evaluation of psychosocial functioning of patients. These questionnaires could be integrated in the online KLIK platform, enabling patients and physician to measure psychosocial functioning before consultation. 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 illustrate 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.

As mentioned in chapter 2, pulmonary metastases in the EpSSG-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. 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. 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 18F-FDG-PET/CT for the detection of distant
metastases in pediatric RMS. We believe that a prospective analysis of the accuracy of
18F-FDG-PET/CT, comparing results of 18F-FDG-PET/CT to a gold standard is necessary.
Although the EpSSG FaR-RMS study will prospectively collect the data of 18F-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 18F-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 ac-
curacy of newly introduced (and promising) imaging techniques, such as 18F-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 dimen-
sional, 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 18F-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 18F-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 18F-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 18F-FDG-PET/CT response to be predic-
tive 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 EpSSG FaR-RMS trial will prospectively assess the value of the \(^{18}\text{F}-\text{FDG-PET/CT}\) 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).
REFERENCES


31. Schoot RA, Saeed P, Freling NJ, Blank LE, Pieters BR, van der Grient JN, et al. Local Resection and Brachytherapy for Primary Orbital Rhab-


