Optimizing rhabdomyosarcoma treatment

Assessing the role of imaging and local treatment in pediatric rhabdomyosarcoma

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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. 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. 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. 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. The assumption is that RMS arises from primitive mesenchymal cells destined to develop into striated muscle cells. However, recent research showed that RMS could also arise from non-myoogenic cells, which might explain the occurrence at sites lacking skeletal muscles.

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 (EpSSG). 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. 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. More recently it was discovered that a substantial proportion (70-80%) of patients with ARMS carry a PAX3-FKHR or PAX7-FKHR gene fusion. These patients are so called fusion-positive. Recent studies showed that fusion status is a strong prognostic factor for outcome in patients with RMS. Patients with fusion-positive ARMS have a dismal prognosis, whereas patients with fusion-negative ARMS have a comparable prognosis as patients with ERMS. 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). 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. 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 EpSSG study (see table 1), entitled EpSSG-RMS 2005.

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<th>Subgroups</th>
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<th>Post-surgical Stage (IRS Group)</th>
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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. 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). 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.
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 actinomycin, 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 EpSSG-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 EpSSG-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 EpSSG-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 EpSSG-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 EpSSG-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 EpSSG-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 EpSSG-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 99m-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 EpSSG-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 EpSSG 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, naive 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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