AMORE (Ablative surgery, MOulage technique brachytherapy and REconstruction) for childhood head and neck rhabdomyosarcoma
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Summary
The AMORE protocol, consisting of Ablative surgery, Moulage technique brachytherapy and surgical Reconstruction, was developed in 1993 in the Emma Children’s Hospital/ Academic Medical Center Amsterdam for the local treatment of children with a rhabdomyosarcoma (RMS) in the head and neck region.

In Chapter 1, an overview of RMS in general is given, with an emphasis on head and neck (HN) RMS. RMS is a malignant embryonal tumor and is believed to originate from precursors of striated muscle cells. Most children are younger than 10 years of age at diagnosis (median age 6 years). RMS comprises 4-5% of all childhood malignancies. The tumor can emerge anywhere in the body, but 40% originates in the head and neck region. Various cooperative trials have identified prognostic factors and have developed treatment protocols incorporating multidrug chemotherapy, radiotherapy and surgery. With the application of so-called ‘risk-based’ multimodality treatment protocols, survival has increased from 25% in the 1970s to 70% at present. In spite of this general increase in survival, many dilemmas have persisted in the treatment of RMS.

The prognosis in children with HNRMS is mainly determined by the ability to achieve local control. Therefore, local treatment is of vital importance. Controversy exists as to the appropriate local treatment, both in primary local treatment and in local salvage of recurrent or refractory tumors. HNRMS is subdivided into three sites: orbit, parameningeal and non-parameningeal. Parameningeal sites are those sites at which the tumor is in close proximity to the meninges. The symptoms of non-orbital HNRMS are often insidious and non-specific. Therefore, tumors are often locally advanced at diagnosis. Surgical access to parameningeal sites can be difficult. Microscopic radical surgery in the head and neck region in children can have unacceptable functional and cosmetic consequences. Given the advanced stage at diagnosis, difficult surgical access and consequences of radical surgery, primary surgical treatment of pediatric HNRMS is therefore often considered not feasible. Delayed surgery can be considered after reduction of the tumor by chemotherapy, but carries the same disadvantages. Most children with HNRMS are treated with chemotherapy, followed by external beam radiation therapy (EBRT). The clinical target volume of EBRT covers the initial tumor area plus a 2 cm margin. Consequently, a substantial part of the head and neck region is exposed to high-dose ionizing radiation. Growing tissues are susceptible to radiation-induced damage. EBRT, applied in children with HNRMS can result in numerous late sequelae. One of the most frequent sequelae is radiation-induced growth suppression of the craniofacial skeleton, resulting in facial disfigurement.

The treatment options for patients with refractory or recurrent disease are very limited. Chemosensitivity is often reduced and a second course of EBRT exceeds the tolerance of normal tissues. Also, surgical treatment of recurrent disease is mutilating.

Tumor resection as a part of the AMORE protocol aims at macroscopically complete resection of the residual tumor, with sparing of the surrounding tissues, if possible. Subsequent brachytherapy...
is given (instead of EBRT) to control possible microscopic residual disease. The irradiated wound bed is reconstructed using a muscle transplant. The aims of AMORE are to intensify local treatment and to prevent the late sequelae of EBRT.

In this thesis, the methods of the AMORE protocol and the feasibility and results of AMORE applied for both primary and salvage treatment of children with non-orbital HNRMS are reported. Also, treatment-induced sequelae, with an emphasis on growth of the craniofacial skeleton, are reported. Finally, an attempt has been made to identify factors associated with the development of recurrent disease.

In Chapter 2, the methods of the AMORE protocol are described. The technical aspects of the three different parts (surgery, brachytherapy and reconstructive surgery) are explained.

In Chapter 3, feasibility and outcome of the AMORE protocol as primary treatment (after initial chemotherapy) for locally advanced HNRMS are described. All children with primary irresectable, non-orbital HNRMS in whom EBRT was indicated, were evaluated for the feasibility of AMORE. In 20 children, AMORE was performed (15 with parameningeal disease and 5 with non-parameningeal disease). Complete remission was achieved in all 20 patients. Local complications were limited. Five patients experienced a local relapse and 1 patient developed distant metastases. Estimated 5-year overall survival (OS) and event free survival (EFS) were 67.5 and 64.1% for the entire group, and 64.2 and 60.0% for the parameningeal subgroup. The conclusion of this study is that the AMORE protocol is a feasible strategy, with a good local control rate. Long-term sequelae of EBRT might be avoided although, to date, the follow-up is too short for definitive conclusions regarding these sequelae.

In Chapter 4, the feasibility and outcome of the AMORE protocol as salvage treatment are outlined. Patients with recurrent or residual non-orbital HNRMS were eligible for AMORE salvage treatment. The procedure was feasible in 9 out of 11 eligible patients. Five patients were treated for recurrent or residual parameningeal RMS after prior chemoradiation. Local complete remission was achieved in all 5 patients and maintained in 4. Three patients are without evidence of RMS with a follow-up duration of 4-10 years. Two patients developed a distant relapse, together with a local recurrence in 1. Both patients died of their disease. Four patients were included for recurrent non-parameningeal HNRMS. Long-term local control at the site of recurrence was obtained in all 4 patients (follow-up 5-10 years). The conclusion of this study is that the AMORE protocol is a feasible salvage strategy for non-orbital HNRMS, even after EBRT and that the local salvage rate in this series is promising.

In 59-97% of the children treated with EBRT in the head and neck region, clinically visible facial asymmetry will develop as a consequence of radiation-induced suppression of craniofacial skeletal growth. The goal of the study described in Chapter 5 was to quantify the growth of the craniofacial skeleton in children with HNRMS treated with AMORE. Children with a follow-up of > 3 years
after AMORE were eligible for clinical and quantitative assessment of the craniofacial skeleton. Quantification was performed by two observers, using 14 paired (3D) CT-derived measurements. The left-right differences within each patient were assessed. Eleven patients were included. Two out of the 11 (18%) patients had visible craniofacial asymmetry as a consequence of bone surgery. The remaining 9 patients (82%) had a symmetrical appearance of the craniofacial skeleton at clinical assessment. Three out of the 9 patients had no CT asymmetry, whereas 6 had asymmetrical values. Only 1 of these 6 patients had severe CT asymmetry due to bone resection. The remaining 5 patients had 1-2 asymmetrical values. The majority of these values were secondary to mild growth suppression of the mandible at the side of the lesion. The conclusion of this study is that the AMORE protocol results in a low incidence of clinical relevant growth disturbance of the craniofacial skeleton.

The objectives of the study, described in Chapter 6 were to assess the adequacy of the AMORE concept and to identify factors associated with relapse. A retrospective multidisciplinary review of 24 children primarily treated according to the AMORE protocol was performed. Seven patients relapsed locally: 6 within and 1 outside the residual tumor area. Five of the 6 patients relapsing in the residual area had either gross total or debulking surgery or sub-optimal position of the mould for brachytherapy, or both. In the 15 non-recurrent cases, 4 patients had either gross-total surgery or sub-optimal mould position. Both surgical and brachytherapeutic factors appear to be associated with relapse. The conclusion of this study is that AMORE is an adequate concept and that more rigid pre-operative imaging and intra-operative verification of the brachytherapy mould position might lead to a reduction in the number of local failures.

In Chapter 7, the AMORE concept, technique, outcome and sequelae are discussed. In Chapter 8, recommendations for future AMORE treatment with respect to patient selection, timing and brachytherapy monitoring are given, based on the data provided by the studies described in the previous chapters. Also, propositions for future research are given.