AMORE (Ablative surgery, MOulage technique brachytherapy and REconstruction) for childhood head and neck rhabdomyosarcoma
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The AMORE protocol in pediatric head and neck rhabdomyosarcoma: a descriptive analysis of failure patterns

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Abstract

*Background.* The AMORE protocol is a local treatment for non-orbital pediatric head and neck rhabdomyosarcoma (HNRMS). The objectives of this study were: (1) to assess the adequacy of the concept, and (2) to identify factors associated with relapse.

*Methods.* A retrospective multidisciplinary review of 24 children primarily treated according to the AMORE protocol was performed.

*Results.* Seven patients relapsed locally: six within- and one outside the residual tumor area. Five of the six patients relapsing in the residual area had either gross total or debulking (incomplete) surgery or sub-optimal position of the mould for brachytherapy, or both. In the 15 non-recurrent cases, four patients had either incomplete surgery or sub-optimal mould position. Both surgical and brachytherapeutic factors appear to be associated with relapse.

*Conclusions.* AMORE is an adequate concept. 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.
6.1 Introduction

Rhabdomyosarcoma (RMS) is the most common pediatric soft-tissue sarcoma and constitutes 3-4% of all malignancies in childhood. Most children are younger than 10 years of age at diagnosis. Some 35% of RMS is localized in the head and neck region. The application of multimodality treatment protocols has improved the outcome dramatically in the past decades. Prognosis in head and neck (HN) RMS is mainly determined by the ability to achieve local control. Controversy still exists as to the appropriate local management. Surgery respecting healthy margins is often not feasible in the head and neck region without severe functional or cosmetic consequences. External beam radiation treatment (EBRT) is applied routinely in parameningeal RMS, but is known for its long term sequelae, especially when applied in young children. The introduction of new techniques has improved beam shaping and reduced the dose to healthy tissues. Nevertheless, it is still advocated to irradiate the pre-treatment tumor volume plus a 2 cm margin. To our knowledge, studies reporting diminished sequelae in patients treated with these new techniques are still lacking.

In 1993 we introduced a local treatment strategy (AMORE) for pediatric HNRMS. AMORE is the acronym for Ablative surgery, Moulage technique brachytherapy and surgical Reconstruction. In contrast to EBRT, the AMORE approach is directed to the residual tumor area after multi-agent chemotherapy. The aim of AMORE was to optimize local treatment and to avoid EBRT and its long-term sequelae. Results of this treatment in a cohort of 20 children have been reported recently and show a 64% event free survival and 67.5% overall survival at five years, respectively.

In this study we describe a retrospective analysis of all 24 HNRMS children primarily treated according to the AMORE protocol at non-orbital sites. The objectives of the study were: (1) to assess the adequacy of the AMORE concept in targeting the residual tumor, and (2) to identify factors associated with relapse after AMORE treatment.

6.2 Patients and Methods

6.2.1 The AMORE protocol

Details of the AMORE protocol have been described previously. In brief, AMORE treatment covers the residual tumor area (post-chemotherapy volume). The aim is to perform macroscopic complete resection of the residual tumor mass. The wound bed, containing possible microscopic disease is subsequently irradiated, using Iridium wires embedded in rubber (Gutta Percha) moulds. The therapeutic dose (40-50 Gy) is calculated up to 5 mm from the surface of the mould. In most patients low dose-rate (LDR) brachytherapy was given. More recently, the pulsed
dose-rate (PDR) technique has been introduced. After irradiation, the wound bed is reconstructed using a pedicled or free vascularized muscle transplant. The procedure is scheduled when local treatment is indicated according to the subsequent guidelines of the International Society of Pediatric Oncology (SIOP) for the treatment of Malignant Mesenchymal Tumors (MMT).

6.2.2 Eligible patients and data analysis
The initial study population consisted of all children who were treated according to the AMORE protocol between January 1993 and December 2002. This analysis of failure patterns covers all children who received primary local treatment for non-orbital HNRMS. AMORE salvage cases were excluded. Charts, histopathology, imaging studies and brachytherapy treatment planning were reviewed by a panel consisting of a head and neck surgeon, brachytherapist, head and neck radiologist, pathologist and two pediatric oncologists. The following features were analyzed in relation to clinical outcome: histology, age at diagnosis, primary tumor site, tumor size, tumor extent, erosion of bony boundaries, skull base erosion, metastases, chemotherapeutic treatment (agents and number of courses), response to chemotherapy, size of the residual lesion, pre-operative evaluation of surgical risk factors, completeness of tumor resection, histopathologic analysis of the resected specimen, position of the mould for brachytherapy and dose and dose rate of brachytherapy.

In patients with local recurrent disease, the sites of recurrence were described as being within the residual (post-chemotherapy) area or initial (pre-chemotherapy) tumor area. The cut-off date for this analysis was 1 September 2003. Statistical evaluation could not be performed due to the small number of patients and wide variety of factors analyzed. We present the data of our analysis in a descriptive manner.

6.2.3 Definitions
Tumor site. Non-orbital HNRMS are divided in parameningeal and non-parameningeal sites. Parameningeal sites are defined as those adjacent to the meninges: nasal cavity, paranasal sinuses, nasopharynx, middle ear/mastoid, parapharyngeal space, infratemporal fossa and pterygopalatine fossa. The remaining sites are considered non-parameningeal: oral cavity, oropharynx, face, cheek, parotid region and soft tissues of the neck.

Tumor size and extent. The gross tumor volume is given as the maximum antero-posterior (AP), left-right (LR) and cranio-caudal (CC) diameters in cm. Intracranial extension is defined as radiological extension of the tumor mass above the level of the skull base. Tumor staging is performed according to the SIOP-MMT guidelines, based on the pre treatment Tumor-Node-Metastasis (TNM) system.
Response to chemotherapy. Response to initial multidrug chemotherapy was defined, according to the SIOP MMT 95 protocol, as clinical complete response, partial remission, objective response, no response or progressive disease. Clinical complete response (CCR) is defined as disappearance of signs of tumor based upon both clinical and imaging evidence or unchanged partial remission lasting for at least six months after completion of treatment. Partial remission (PR) is defined as a ≥ 50% decrease in tumor area on the MRI/CT scan. Objective response (OR) is a > 25% but < 50% decrease in tumor area. No response (NR) is defined as either no increase or an increase of < 25% in tumor area, or, no decrease or a decrease of < 25%. Progressive disease (PD) is an increase ≥ 25%.

Surgical risk factors. A pre-operative assessment of factors impeding macroscopically complete tumor resection was made on imaging studies (CT and/or MRI). Complete macroscopic resection of the residual (post-chemotherapy) tumor mass was considered not feasible when one or more of the following five criteria were present: (1) extension into one or more foramina at the skull base (e.g. foramen ovale); (2) intracranial extension; (3) invasion of the nasopharynx; (4) encasement of the carotid artery (> 270 degrees); (5) extensive involvement of the orbit, requiring orbital exenteration.

Tumor resection. The completeness of resection performed during AMORE was graded as follows: (1) radical surgery (the tumor was removed with a 1-2 cm margin of uninvolved tissue or a fascial plane), (2) macroscopically radical surgery (the tumor mass was resected without safe margins; possible residual disease was microscopic at most), (3) gross total resection (the tumor mass was resected by a debulking procedure, i.e. intralesional surgery, but without leaving macroscopical tumor remnants), (4) debulking (leaving macroscopical tumor remnants), (5) explorative surgery (the area of residual disease as shown by imaging was reached and explored, but only fibrous tissue was encountered), (6) compartment resection (complete remission was achieved with initial treatment; the anatomical compartment in which the original tumor was located was removed completely). Gross total and debulking surgery were considered as 'incomplete' surgery.

Dose distribution. Brachytherapy dose distribution was determined by reviewing the CT scans and plain X-rays for brachytherapy planning. The position of the mould was determined and the panel assessed whether the residual tumor area was covered adequately at all borders. If not, the mould position was graded 'sub-optimal'. The therapeutic dose was defined 5 mm from the surface of the mould (i.e. an envelope of 0.5 cm around the mould).
6.3 Results

From 1993 –2003, 39 children were treated according to the AMORE protocol, 33 for HNRMS and six for other soft-tissue sarcomas. In 24 out of the 33 RMS cases, the AMORE protocol was instituted as primary local treatment. In the remaining nine patients AMORE was given as salvage treatment. The 24 primary cases are the subject of this analysis. Two patients were excluded because insufficient imaging data were available. Hence, a total of 22 patients were included for the analysis of failure patterns. Sixteen of these patients had parameningeal and six non-parameningeal HNRMS. Patient characteristics are summarized in Table 1. The median age at diagnosis was 4.8 years (range 0.5-12.4 years). Only two patients were > 10 years of age. Histopathologic subtypes were embryonal in 20 patients and alveolar in two. One patient had lung metastases at diagnosis and five had positive neck nodes. Initial treatment consisted of biopsy and multidrug chemotherapy in all cases. One patient was treated according to the pediatric oncology group (POG) D98Ü3 regimen. All other patients were treated according to the SIOP protocol for malignant mesenchymal tumors (MMT): MMT 89 in 10- and MMT 95 in 11 cases. AMORE was scheduled after a median of 8 courses (range 3-13 courses). Response to chemotherapy was PR in 16 and CCR in three cases. OR, NR and PD were seen in one case each (Table 1). Seven patients received 1-5 chemotherapy courses after completion of AMORE. Fourteen patients remained disease free with a median follow-up duration of five years (range 1.1-11.1 years). The two cases excluded because of insufficient imaging data, are disease free with a follow-up of 2.5 and 2.8 years respectively. Eight patients relapsed 0.7-2.2 years after diagnosis. One patient developed brain metastases. Seven patients relapsed locally: six with initial parameningeal disease and one with non-parameningeal RMS (Table 1). In one patient the relapse occurred within the initial tumor area but outside the residual tumor area. In the remaining six recurrences, the relapse was located in the residual (post-chemotherapy) tumor area.

6.3.1 Patterns of relapse and associated risk factors

Surgery

In six cases resection was incomplete (Table 1), all at parameningeal sites. Gross total resection was achieved in five patients and debulking surgery in one. Four out of six cases with incomplete surgery relapsed. In 13 cases, macroscopically complete resection (n=10), radical resection (n=1) or exploration (n=2) were performed (Table 1). Three out of these 13 patients relapsed. The three patients with compartment resection are without evidence of disease. Pre-operative risk factors for incomplete macroscopic surgery were infiltration of the nasopharynx and intracranial extension of the residual tumor mass. Involvement of the pterygopalatine fossa was found to impede macroscopic radical surgery during the operation in two patients. Radiological extension of the residual tumor into the foramen ovale and presumed destruction
of the medial orbital wall were not visible preoperatively and did not influence the completeness of macroscopic surgery (Table 1). Encasement of the carotid artery did not occur.

**Brachytherapy**

Retrospectively, in four out of six cases relapsing in the residual area, a sub-optimal position of the implanted mould was noted (Table 1). In the non-recurrent group, two out of 15 positions were retrospectively judged as sub-optimal. Considering all seven cases with inadequate mould position, six were at parameningeal sites. In these six cases dose distribution was insufficient at the pterygoid fossa \( (n=3) \), skull base \( (n=2) \) and nasopharynx \( (n=1) \).

**The combination of surgery and brachytherapy**

When the combination of surgery and brachytherapy (BT) is considered, one patient in the recurrent group had complete surgery and adequate BT. The other 5 patients relapsing in the residual tumor area had either incomplete surgery and adequate mould position \( (n=1) \) or complete surgery and sub-optimal mould position \( (n=2) \) or both incomplete surgery and sub-optimal mould position \( (n=2) \). In the 15 non-recurrent cases, 11 patients had complete surgery and adequate BT. Two patients had incomplete surgery and adequate mould position and another two had complete surgery and sub-optimal mould position.

**6.3.2 Factors without influence on outcome**

Histopathologic analysis was not predictive with respect to recurrent disease. In nine out of the 22 post-chemotherapy surgical specimens, histopathological and immunohistochemical investigations failed to identify tumor cells. Two out of these nine patients relapsed. The remaining 13 specimens contained recognizable tumor cells with varying patterns of chemotherapy-induced changes. These changes varied from hardly any change, to an inhomogeneous shrinkage of the tumor, characterized by a background of fibrosis with scattered areas of vital tumor varying in size, to a diffuse spread of solitary lying tumor cells. In most of the specimens, resection was considered irradical as tumor cells were found near or into the borders of the specimen (Table 1). Of these 13 patients, 5 relapsed. Also, the kind of chemotherapy and the dose of individual agents (both prior to AMORE and cumulative) and the response to chemotherapy did not influence outcome.

The small amount of patients precluded an analysis of the prognostic significance of the classical risk factors age, histology and distant metastasis (Table 1). No major differences were found between the recurrent and non-recurrent group with respect to the factors parameningeal subsite, tumor size, nodal status, size of the residual lesion, timing of the AMORE procedure and dose and dose rate of brachytherapy.
6.4 Discussion

AMORE has shown to be an effective local treatment regimen with local control and overall survival rates similar to earlier publications on HNRMS treated with chemoradiation. In this study we found that the recurrences mainly developed within the residual tumor area. The patterns found in this study suggest a relation between local relapse and incomplete surgery and sub-optimal position of the mould for brachytherapy.

The AMORE protocol was designed to intensify local treatment and to diminish late radiation sequelae like growth disturbances of the craniofacial skeleton. AMORE aims to achieve local control of residual tumor after pre-operative chemotherapy. We feel that the reduction of the area receiving local treatment is justified, as only one out of seven recurrent cases originated outside the residual tumor area. This is supported by the findings of Chen and co-workers, who did not find important differences in the number of recurrences between "traditional" and shrinking...
Failure analysis of the AMORE protocol

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nasopharynx; d, dubious; PR, partial response; PD, progressive disease; CR, complete response; OR, objective response; NR, no response; PDR, pulsed dose rate; res area, residual (post-chemotherapy) tumor area; init area, pre-treatment tumor area; DM, distant metastases; 2nd prim, second primary malignancy

field technique radiotherapy in a small cohort of parameningeal RMS cases. Moreover, even when radiotherapy is applied to the initial tumor volume (using traditional or three-dimensional conformal techniques), recurrences occur mostly in or at the edge of the treatment field. These relapse patterns suggest that in HNRMS intrinsic radiosensitivity is an important factor as well. The brachytherapy part of AMORE is effective. In seven patients microscopic residual tumor after surgical resection was controlled by brachytherapy. Taken together, we feel that the AMORE strategy is a valuable local treatment strategy for HNRMS.

Out of the seven patients with a local recurrence, six relapsed within the area targeted by AMORE. In only one of these six patients, surgery was graded as macroscopically radical, brachytherapy was adequate and no tumor cells were found in the specimen (patient 6). Two patients (patient 3 and 5) had both incomplete surgery and sub-optimal mould position. The latter was partly related to the access provided by surgery. High-quality imaging, performed
directly prior to AMORE, might be able to identify surgical risk factors like intracranial extension and invasion of the nasopharynx more adequately, leading to exclusion from AMORE treatment and application of conventional treatment of patients in whom those factors are present. Two patients (patients 1 and 2) had complete surgery and sub-optimal mould position. Due to the size of the relapse it was not easy to relate the relapse to the exact site of inadequate brachytherapy. However, the finding of a high relapse rate in the group of patients with a sub-optimal mould position stresses the need for meticulous verification of the mould position. Intra-operative imaging after placement of the mould might optimize mould positioning. In case of malposition, adjustments can be made directly. When it is not possible to achieve an adequate mould position, adjuvant EBRT could be added after brachytherapy, or given instead of brachytherapy. In one relapsing patient (patient 7), gross total surgery was followed by adequate brachytherapy. However, this combination was successful in two cases (patient 17 and 20). Therefore, brachytherapy might be able to control microscopic residual disease after gross total resection. Careful consideration of the pterygopalatine fossa and its boundaries is warranted. Based on our experience, we might conclude that this parameningeal subsite seems not suitable for the AMORE procedure anymore. Although the outcome remains poor in case of EBRT, the risk of postsurgical complications and functional deficits can be avoided. Two other studies defined the pterygopalatine and infratemporal fossa as separate poor prognostic subsites within the parameningeal site. Extension of the residual tumor mass into the foramen ovale is found to be no reason for exclusion in our series. Besides the extent of surgery and the mould position, no other evaluable factors were related to outcome in this study. A striking finding was that the recurrence rate of patients with tumor negative specimens was not different from that of patients with tumor positive specimens. Godzinski and co-workers already reported that tumor negative biopsies in patients in complete remission were not predictive with respect to recurrent disease. These findings illustrate the necessity of local treatment, even in the case of complete response after chemotherapy. Multicenter trials and single institution studies in larger populations of HNRMS patients mention age, size, stage, nodal status, bone erosion, histology and subsite in parameningeal disease as prognostic factors. Not all of these factors are, however, found to be consistently related to outcome. The present series, however, consists of selected cases and therefore a comparison with other studies should be made with caution. This study was conducted to assess the adequacy of the AMORE concept and to identify risk factors for relapse associated with the AMORE protocol. Due to the limited number of cases we have not performed statistical analysis. Definitive conclusions, therefore, cannot be made at this time and an extension of our series is necessary. Nevertheless, we were able to detect some trends, which may be of value for setting up further guidelines for the treatment of HNRMS.
In summary, our experience with the AMORE protocol as local treatment for HNRMS shows that treatment of the residual post-chemotherapy tumor mass can safely be performed, provided macroscopically radical tumor resection can be achieved. We feel that more rigid pre-operative imaging to evaluate the feasibility of macroscopically radical surgery and meticulous verification of the brachytherapy mould position might achieve a reduction in the number of local recurrences. AMORE requires a complex multidisciplinary team effort and therefore this technique should be practiced in highly specialized centers only.
References


