AMORE PROTOCOL IN PEDIATRIC HEAD AND NECK RHABDOMYOSARCOMA: DESCRIPTIVE ANALYSIS OF FAILURE PATTERNS

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Abstract: Background. The AMORE protocol is a local treatment for patients with nonorbital 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. We performed a retrospective multidisciplinary review of 22 children primarily treated according to the AMORE protocol, excluding two children with inadequate imaging data.

Results. Seven patients had a local relapse, six within and one outside the residual tumor area. Five of the six patients with relapse in the residual area had gross total or debulking (incomplete) surgery, suboptimal position of the mold for brachytherapy, or both. In the 15 nonrecurrent cases, four patients had either incomplete surgery or suboptimal mold position. Both surgical and brachytherapeutic factors seem to be associated with relapse.

Conclusions. AMORE is an adequate concept. More rigid preoperative imaging and intraoperative verification of the brachytherapy mold position might lead to a reduction in the number of local failures. © 2005 Wiley Periodicals, Inc. Head Neck 27: 390–396, 2005

Keywords: head and neck neoplasms; rhabdomyosarcoma; combined modality therapy; surgery; brachytherapy

Rhabdomyosarcoma (RMS) is the most common pediatric soft-tissue sarcoma and constitutes 3% to 4% of all malignancies in childhood.1,2 Most children are younger than 10 years of age at diagnosis.3–6 Some 35% of RMS is localized in the head and neck region.4,5 The application of multimodality treatment protocols has improved the outcome dramatically in the past decades. Prognosis in head and neck RMS (HNRMS) is mainly determined by the ability to achieve local control.7–10 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 pretreatment 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 (BT), and surgical reconstruction. In contrast to EBRT, the AMORE approach is directed to the residual tumor area after multiagent 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 5 years, respectively. In this study, we describe a retrospective analysis of all 22 children with HNRMS 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.

PATIENTS AND METHODS

The AMORE Protocol. Details of the AMORE protocol have been described previously. In brief, AMORE treatment covers the residual tumor area (postchemotherapy 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-192 wires embedded in rubber (gutta percha) molds. The therapeutic dose (40–50 Gy) is calculated up to 5 mm from the surface of the mold. In most patients, low dose-rate BT was given. More recently, the pulsed dose-rate 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).

Eligible Patients and Data Analysis. At our institution, a consistent policy exists to evaluate the feasibility of the AMORE protocol as the definitive local treatment in all newly diagnosed patients with initially unresectable, nonorbital HNRMS (clinical group III, according to the nomenclature of the Intergroup Rhabdomyosarcoma Study Group). Feasibility for AMORE is determined by the ability to achieve macroscopically complete resection of the residual tumor mass after initial multidrug chemotherapy.

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 nonorbital HNRMS, both single-center cases and patients referred from other institutions. AMORE salvage cases were excluded. Charts, histopathologic findings, imaging studies, and BT 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: histologic findings, 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 mold for BT, and dose and dose rate of BT.

In patients with locally recurrent disease, the sites of recurrence were described as being within the residual (postchemotherapy) area or initial (prechemotherapy) tumor area. The cutoff date for this analysis was September 1, 2003. Statistical evaluation could not be performed because of the small number of patients and wide variety of factors analyzed. We present the data of our analysis in a descriptive manner.

Definitions.

Tumor Site. Nonorbital HNRMSs are categorized by parameningeal and nonparameningeal 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 nonparameningeal: 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 anteroposterior, left-right, and craniocaudal diameters in centimeters. Intracranial extension is defined as radiologic 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 pretreatment tumor node metastasis (TNM) system.17

Response to Chemotherapy. Response to initial multi-drug 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 is defined as disappearance of signs of tumor based on both clinical and imaging evidence or unchanged partial remission lasting for at least 6 months after completion of treatment. Partial remission is defined as a ≥50% decrease in tumor area on the MRI/CT scans. Objective response is a >25% but <50% decrease in tumor area. No response is defined as either no increase or an increase of < 25% in tumor area, or no decrease or a decrease of <25%. Progressive disease is an increase of ≥25%.

Surgical Risk Factors. A preoperative assessment of factors impeding macroscopically complete tumor resection was made on imaging studies (CT and/or MRI). Complete macroscopic resection of the residual (postchemotherapy) 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 (eg, 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- to 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 [ie, intralesional surgery] but without leaving macroscopic tumor remnants); (4) debulking (leaving macroscopic 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 anatomic compartment in which the original tumor was located was removed completely). Gross total and debulking surgery were considered as “incomplete” surgery.

Dose Distribution. BT dose distribution was determined by reviewing the CT scans and plain X-ray films for BT planning. The position of the mold was determined, and the panel assessed whether the residual tumor area was covered adequately at all borders. If not, the mold position was graded “suboptimal.” The therapeutic dose was defined 5 mm from the surface of the mold (ie, an envelope of 0.5 cm around the mold).

RESULTS

From 1993 to 2003, 39 children were treated according to the AMORE protocol, 33 for HNRMS and six for other soft-tissue sarcomas. In 24 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 22 primary cases with sufficient data are the subject of this analysis. Two patients were excluded because insufficient imaging data were available.

Sixteen of the 22 patients had parameningeal and six had nonparameningeal 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 patients. One patient had lung metastases at diagnosis, and five had positive neck nodes. Initial treatment consisted of biopsy and multi-drug chemotherapy in all cases. One patient was treated according to the pediatric oncology group D9803 regimen. All other patients were treated according to the SIOP protocol for MMT: MMT 89 in 10 cases and MMT 95 in 11 cases. AMORE was scheduled after a median of eight courses (range, 3–13). Response to chemotherapy was partial.
### Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age, y</th>
<th>Site</th>
<th>Size</th>
<th>Tumor extension*</th>
<th>Response to chemotherapy</th>
<th>Pre-AMORE</th>
<th>Surgical evaluation</th>
<th>Histopathologic analysis</th>
<th>Mold position</th>
<th>Dose, Gy/d</th>
<th>Dose rate, cGy/h</th>
<th>Site of recurrence</th>
<th>Follow-up, y</th>
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<td>+</td>
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<td>40/50</td>
<td>res area</td>
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<td>PD</td>
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<td>O</td>
<td>Macr rad</td>
<td>+</td>
<td>Suboptimal</td>
<td>50/55</td>
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<td>Debunking</td>
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<td>Suboptimal</td>
<td>50/60</td>
<td>res area</td>
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<td>Suboptimal</td>
<td>40/80</td>
<td>res area</td>
</tr>
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<td>40/PDR</td>
<td>res area</td>
<td>1.9</td>
</tr>
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<td>CR</td>
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<td>Compartment</td>
<td>–</td>
<td>Adequate</td>
<td>46/80</td>
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<td>T2aN1M0</td>
<td>CR</td>
<td>No visible tumor</td>
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<td>Adequate</td>
<td>40/60</td>
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<td>n n n n</td>
<td>T1aN0M0</td>
<td>CR</td>
<td>No visible tumor</td>
<td>Compartment</td>
<td>–</td>
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<td>40/75</td>
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<td>n n y y</td>
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<td>+</td>
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<td>FO</td>
<td>Explorative</td>
<td>–</td>
<td>Adequate</td>
<td>40/PDR</td>
<td>1.5</td>
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</table>

*At initial diagnosis.

**Abbreviations:** IC, intracranial extension; FO, foramen ovale; BE, bone erosion; SB, skull base erosion; BReg, buccal region; PReg, parotid region; n, no; PR, partial response; Macr rad, macroscopically radical resection; res area, residual (postchemotherapy) tumor area; ITF, infratemporal fossa; y, yes; PD, progressive disease; O, orbit; PPS, parapharyngeal space; d, dubious; NPH, nasopharynx; init area, pretreatment tumor area; PDR, pulsed dose rate; PPF, pterygopalatine fossa; N, neck; DM, distant metastasis; HP, hard palate; CR, complete response; TF, temporal fossa; OR, objective response; 2nd prim, second primary malignancy; PS, paranasal sinus; NC, nasal cavity; NR, no response.
remission in 16 and clinical complete response in three cases. Objective response, no response, and progressive disease were seen in one case each (Table 1). Seven patients received one to five chemotherapy courses after completion of AMORE.

Fourteen patients remained disease free, with a median follow-up duration of 5 years (range, 1–11 years). Eight patients had a relapse 0.7 to 2.2 years after diagnosis. One patient had brain metastases develop. Seven patients had a local relapse, six with initial parameningeal disease and one with nonparameningeal RMS (Table 1). In one patient, the relapse occurred within the initial tumor area but outside the residual tumor area; in the remaining six, the relapse was located in the residual (postchemotherapy) tumor area.

**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 of six patients with incomplete surgery had a relapse. In 13 cases macroscopically complete resection \( (n = 10) \), radical resection \( (n = 1) \), or exploration \( (n = 2) \) was performed (Table 1). Three of these 13 patients relapsed. The three patients with compartment resection are without evidence of disease. Preoperative 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.

Radiologic 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 of six cases with relapse in the residual area, a suboptimal position of the implanted mold was noted (Table 1). In the nonrecurrent group, two of 15 positions were retrospectively judged as suboptimal. Considering all seven cases with inadequate mold 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 \( (n = 1) \).

Combination of Surgery and Brachytherapy. When the combination of surgery and BT is considered, one patient in the recurrent group had complete surgery and adequate BT. The other five patients with relapse in the residual tumor area had incomplete surgery and adequate mold position \( (n = 1) \), complete surgery and suboptimal mold position \( (n = 2) \), or both incomplete surgery and suboptimal mold position \( (n = 2) \). In the 15 nonrecurrent cases, 11 patients had complete surgery and adequate BT. Two patients had incomplete surgery and adequate mold position, and another two had complete surgery and suboptimal mold position.

**Factors without Influence on Outcome.** Histopathologic analysis was not predictive with respect to recurrent disease. In nine of the 22 postchemotherapy surgical specimens, histopathologic and immunohistochemical investigations failed to identify tumor cells. Two of these nine patients had a relapse. 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, because tumor cells were found near or into the borders of the specimen (Table 1). Of these 13 patients, five had a relapse. Also, the kind of chemotherapy and the dose of individual agents (both before 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, histologic findings, and distant metastasis (Table 1). No major differences were found between the recurrent and nonrecurrent 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 BT.

**DISCUSSION**

AMORE has shown to be an effective local treatment regimen, with local control and overall survival rates similar to those in 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 suboptimal position of the mold for BT.

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 preoperative chemotherapy. We believe that the reduction of the area receiving local treatment is justified, because only one of seven recurrent cases originated outside the residual tumor area. This is supported by the findings of Chen et al,21 who did not find important differences in the number of recurrences between “traditional” and shrinking 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.8,13 These relapse patterns suggest that in HNRMS intrinsic radiosensitivity is an important factor as well. The BT part of AMORE is effective. In seven patients, microscopic residual tumor after surgical resection was controlled by BT. Taken together, we believe that the AMORE strategy is a valuable local treatment strategy for HNRMS.

Of the seven patients with a local recurrence, six had a relapse within the area targeted by AMORE. In only one of these six patients (patient 6), surgery was graded as macroscopically radical, BT was adequate, and no tumor cells were found in the specimen. Two patients (patients 3 and 5) had both incomplete surgery and suboptimal mold position. The latter was partly related to the access provided by surgery. High-quality imaging, performed directly before AMORE, might be able to identify surgical risk factors such as intracranial extension and invasion of the nasopharynx more adequately, leading to exclusion from AMORE treatment and application of conventional treatment of patients in whom these factors are present. Two patients (patients 1 and 2) had complete surgery and suboptimal mold position. Because of the size of the relapse, it was not easy to relate the relapse to the exact site of inadequate BT. However, the finding of a high relapse rate in the group of patients with a suboptimal mold position stresses the need for meticulous verification of the mold position. Intraoperative imaging after placement of the mold might optimize mold positioning. In case of malposition, adjustments can be made directly. When it is not possible to achieve an adequate mold position, adjuvant EBRT could be added after BT or given instead of BT. In one patient with relapse (patient 7), gross total surgery was followed by adequate BT. However, this combination was successful in two patients (patients 17 and 20). Therefore, BT might be able to control microscopic residual disease after gross total resection.

Careful consideration of the pterygopalatine fossa and its boundaries is warranted. On the basis of our experience, we might conclude that this parameningeal subsite does not seem suitable for the AMORE procedure anymore if adequate mold position cannot be accomplished. Although the outcome remains poor in the case of EBRT, the risk of postsurgical complications and functional deficits can be avoided.20 Two other studies defined the pterygopalatine and infratemporal fossa as separate poor prognostic subsites within the parameningeal site.9,20 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 mold 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 et al22 reported that tumor-negative biopsy specimens 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 with larger populations of patients with HNRMS mention age, size, stage, nodal status, bone erosion, histologic findings, and subsite in parameningeal disease as prognostic factors.9,10,19,21,23,24 Not all of these factors are, however, found to be consistently related to outcome.

This 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. Because of the limited number of cases, we have not performed statistical analysis. Definitive conclusions, therefore, cannot be made as of yet, 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 patients with HNRMS.

In summary, our experience with the AMORE protocol as local treatment for patients with HNRMS shows that treatment of the residual postchemotherapy tumor mass can safely be performed, provided macroscopically radical tumor resection can be achieved. Nasopharyngeal invasion and intracranial extension of the residual tumor mass will lead to exclusion from the AMORE protocol. We believe that more rigid preoperative imaging to evaluate the feasibility of macroscopically radical surgery and meticulous verification of the BT mold 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