AMORE (Ablative surgery, MOulage technique brachytherapy and REconstruction) for childhood head and neck rhabdomyosarcoma
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The AMORE protocol as salvage treatment for non-orbital head and neck rhabdomyosarcoma in children


Eur J Surg Oncol, in press
Abstract

Aim. To investigate the feasibility and outcome of the AMORE protocol as salvage treatment in pediatric head and neck rhabdomyosarcoma (HNRMS).

Methods. The AMORE protocol is a local treatment regimen, consisting of Ablative surgery, Moulage technique brachytherapy and surgical Reconstruction, scheduled in 1 week. Patients with recurrent or residual non-orbital HNRMS were eligible for AMORE salvage treatment.

Results. The procedure was feasible in nine out of eleven eligible patients. Five patients were treated for recurrent or residual parameningeal RMS after prior chemoradiation. Local complete remission was achieved in all five patients and maintained in four. 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 one. 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 four patients (follow-up 5-10 years).

Conclusions. The AMORE protocol is a feasible salvage strategy for non-orbital HNRMS even after external beam radiotherapy. The local salvage rate in this series is promising.
4.1 Introduction

Rhabdomyosarcoma (RMS) is the most common soft-tissue sarcoma in childhood and is located in the head and neck region in 35-40% of the cases. The head and neck region is divided into three subsites based on prognosis: parameningeal and non-parameningeal sites and the orbit. Orbital RMS carries an excellent prognosis. In the treatment of primary non-orbital head and neck (HN) RMS, progress has been made by application of combined modality protocols.

Parameningeal HNRMS has the worst prognosis. The vast majority of patients present with locally advanced, non-metastatic disease and are considered unresectable (clinical group III according to the nomenclature of the Intergroup Rhabdomyosarcoma Studies (IRS)). The 'standard of care' in these patients generally consists of biopsy, multidrug chemotherapy and early external beam radiotherapy (EBRT). Local complete remission is achieved in ± 80% of the cases. Five-year event free survival rates vary between 50% and 70% in large trials. A considerable number (± 30%) of patients experiences recurrent disease. Mostly, local relapse is involved.

RMS at non-parameningeal sites has a more favorable outcome when compared to parameningeal disease. Differences in treatment strategies between study groups exist with respect to the application of EBRT in advanced stage disease. In IRS regimens, EBRT is used routinely, whereas the International Society of Pediatric Oncology (SIOP) guidelines for the treatment of malignant mesenchymal tumours (MMT) advocated omitting EBRT in patients with a complete response (CR) after chemotherapy with or without surgery. The consequence of a higher local relapse rate was accepted, because EBRT could still be applied in case salvage treatment was required. Only recently the SIOP MMT guidelines have been changed, applying EBRT at week 18 for all patients > 3 years of age with non-parameningeal HNRMS. The outcome in terms of 5-year overall survival of both IRS and SIOP regimens is comparable and is 70-80%. Recurrent disease, mostly local relapse, is experienced in 20-30% of the patients in IRS- and 50% in SIOP trials. Thus, some 30-40% of patients with HNRMS still experience disease progression or local recurrence.

The options for salvage treatment are limited. The outlook for these patients, therefore, is dismal and has not changed significantly over the past decades. The salvage rate for patients with parameningeal disease was only 15-30% in large trials. Recently, Raney and co-workers reported a 25% survival rate after pure local relapse in parameningeal HNRMS. For non-parameningeal HNRMS, the SIOP studies report a salvage rate of more than 50% for reasons mentioned above. The salvage rate in non-parameningeal disease in the IRS III-study, however, was 32%. Clearly, improvement in local salvage of non-orbital HNRMS is needed. A local treatment strategy, combining surgical resection with brachytherapy and reconstruction was designed at our institution. This technique is termed the AMORE protocol. The results of AMORE as first-line local treatment in pediatric HNRMS have been reported previously. In this paper, we report on the feasibility and results of salvage treatment in children with residual or relapsed non-orbital HNRMS.
4.2 Patients and methods

4.2.1 Eligibility criteria
Two patient groups were eligible for AMORE salvage treatment: patients with either recurrent or residual parameningeal HNRMS after first-line chemotherapy and external beam radiotherapy (EBRT), and patients with recurrent non-parameningeal disease after prior clinical complete response (CR). Technical feasibility of the AMORE protocol was determined by clinical examination and multidisciplinary evaluation of pre-operative imaging studies. Patients were included if macroscopically complete tumor resection could likely be achieved without inducing severe mutilation. Patients were excluded from the AMORE protocol when the tumor mass displayed either intracranial extension or invasion of the nasopharynx, as both features preclude macroscopically complete surgery. From July 1993 through January 2003, patients with a local or regional relapse of non-orbital HNRMS after CR and patients with a parameningeal HNRMS failing to achieve CR with chemotherapy and EBRT, were evaluated for treatment. Patients who had received AMORE treatment as first-line therapy were excluded.

4.2.2 Primary lesion: diagnostic work-up and treatment
Diagnostic work-up was performed according to the SIOP MMT diagnostic guidelines. Primary diagnosis of RMS was based on fine needle or open surgical biopsies, which were revised and classified according to the SIOP pathology guidelines. Staging was performed according to pre-treatment tumor-node-metastasis (TNM) classification. Tumor extent was based on computed tomography (CT) and/or magnetic resonance imaging (MRI) dimensions. Nodal status was based on clinical findings, radiographic studies and/or histopathology. Work-up for distant metastasis included chest radiography, skeletal scintigraphy, analysis of the cerebrospinal fluid (CSF) and bone marrow aspirate. Parameningeal sites were defined in accordance to the guidelines of SIOP MMT group, i.e. the nasal cavity, nasopharynx, paranasal sinuses, middle ear/ mastoid and pterygoid fossa. The remaining head and neck sites excluding the orbit, i.e. the oral cavity, oropharynx, face, cheek, parotid region and soft tissues of the neck, were considered non-parameningeal. In patients with parameningeal tumors, the risk for meningeal involvement was estimated. Patients with cranial nerve palsy, erosion of the skull base or intracranial growth were classified as ‘high-risk’.

Initial treatment was performed in accordance with the guidelines of the SIOP MMT group protocols MMT 89 and MMT 95, including standard EBRT to the initial tumour volume plus a 2 cm margin for patients > 3 years with parameningeal disease.
4.2.3 AMORE strategy

The AMORE strategy aims at the residual tumor volume and consists of ablative surgery, intracavitary brachytherapy with a MQulage technique and surgical REconstruction in two surgical sessions in 1 week. A description of the method is given in a recent publication. In brief, the residual tumor mass (fig. 1) is removed and a thermoplastic moulage is inserted in the wound bed. Flexible polyethylene catheters are embedded in the moulage. After computer-aided dosimetry (fig. 2), the catheters are loaded with Iridium-192 line sources and radiation starts on the second or third postoperative day. The determined dose is administered over a 3-4 day period, depending on dose and dose rate. In the second surgical session, the moulage is taken out and the defect is reconstructed using a free vascularized or pedicled muscle flap. In general, the AMORE strategy is scheduled after 2-4 courses of second line chemotherapy in case of local relapse. In patients failing to achieve CR, AMORE treatment is given after completion of the firstline treatment protocol.

4.2.4 Data processing

All surviving patients were followed at least 4 years after AMORE treatment. Clinical end points included local, regional or distant relapse. The cut-off point of the analysis was September 1st, 2003. Short-term complications as a consequence of treatment and late sequelae were registered. Chemotherapy-induced toxicity was left out of the analysis.

Figure 1
T1-weighted magnetic resonance (MR) image in the axial plane. The arrow indicates the residual tumor mass in the left pterygoid fossa after chemoradiation (patient 5).

Figure 2
Computed tomography (CT) scan image in the axial plane. The moulage has been introduced into the surgical cavity (patient 5). The sources have been identified and dose distribution is calculated. Reference isodose lines (cGy/h) are depicted in color. Each color corresponds with a different doserate, ranging from 200 cGy/h (inner green line) to 50 cGy/h (outer green line).
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Site</th>
<th>TNM stage</th>
<th>SIOP stage</th>
<th>Histology</th>
<th>Indication</th>
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<td>2nd LR</td>
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</table>

*a* age at the time of the AMORE protocol; **b** Tumor-Node-Metastasis stage at initial diagnosis; **c** including myeloablative chemotherapy and autologous stem cell rescue; **d** International Society of Pediatric Oncology; **e** AMORE, see Methods for description; **f** LR, local recurrence; **g** RES, residual disease; **h** RR, regional recurrence

4.3 Results

Between July 1993 and January 2003, 11 patients with non-orbital HNRMS were presented for salvage treatment at the Academic Medical Center. Two patients were found to be ineligible for the AMORE procedure due to intracranial extension of the tumor. A cohort of nine patients was included in this study, consisting of five parameningeal- and four for non-parameningeal cases (Table 1).

4.3.1 Parameningeal cases

All five parameningeal cases were initially staged T2b. One patient had regional lymph-node metastases. All patients were at high-risk for meningeal seeding due to skull base erosion. One patient had a facial nerve palsy at presentation. None of the patients had malignant cells in the CSF. The indication for AMORE treatment was local relapse in three patients and a residual mass lesion after completion of treatment in two patients, respectively (Table 1). All patients had received EBRT (42-56 Gy) as part of their first-line treatment. In the first recurrent patient, the protocol was performed directly after diagnosis of the local relapse. Second-line chemotherapy was withheld due to myeloablative chemotherapy at initial treatment. The second patient with recurrent disease was treated with surgery and 8 courses of second-line chemotherapy for a first local relapse resulting in CR. The AMORE strategy was applied in the treatment of the second recurrence after 6 courses of chemotherapy. The third recurrent patient had a simultaneous solitary pulmonary metastasis in addition to a local relapse. Two courses of second-line chemotherapy and metastasectomy were instituted prior to the AMORE protocol. The second patient with a residual mass were treated directly after completion of their SIOP regimen in week 27. Details concerning the three steps of the AMORE treatment are given in Table 2. Supraomohyoidal neck dissection was performed in two cases as a part of the approach to the tumor. Surgical
reconstruction consisted of a free muscle flap in four patients and a pedicled flap in one patient (due to poor condition of the recipient vessels).

In all five parameningeal cases local complete remission was achieved using the AMORE protocol (Table 2). A combined local and distant (CNS) recurrence occurred in one out of five patients (patient 2) after 6 months of follow-up. The range of follow-up for the surviving patients in local remission is 4.0-10.4 years (Table 2). Two of the three patients treated for recurrent parameningeal disease were salvaged locally by the AMORE protocol. The first (patient 1) is in permanent remission 10 years after treatment. The second patient (patient 3) was in local remission but developed distant metastases two months after treatment. Both patients with recurrent disease after AMORE died from their disease (Table 2). The two patients treated for a residual mass are currently without evidence of RMS, with a follow-up duration of 4.0 and 4.4 years respectively (Table 2). One patient (patient 1) developed a second primary malignancy, a medulloblastoma in the posterior cranial fossa (within the field of prior EBRT), 8.2 years after treatment.

Short-term sequelae as a consequence of surgery included nerve damage, resulting in a temporary facial nerve palsy and deafness resulting from labyrinthectomy (patient 1) and permanent infraorbital nerve palsy (patient 4). Four out of five muscle transplants survived. One wound infection was experienced, requiring surgical treatment, consisting of drainage and partial removal of the muscle transplant (patient 3). Long-term sequelae included growth retardation of statural height (patient 1 and 5), severe caries (patient 2), impatency of the lacrimal system (patient 4) and trismus due to fibrosis (patient 5).

### 4.3.2 Non-parameningeal cases

Four patients were treated for recurrent non-parameningeal HNRMS, three for a local relapse...
and one for a regional relapse. Staging of the lesion at first presentation is given in Table 1. In all four cases initial CR was accomplished after surgery (biopsy and/or surgical excision) and chemotherapy. CR was verified with second look surgery in three cases. According to the SIOP MMT guidelines none of these patients was irradiated (Table 2). Three patients relapsed at the primary site and the fourth relapse (patient 8) occurred at a regional site, i.e. the parotid gland after treatment of a buccal RMS with (radical) surgery and chemotherapy. At relapse, all patients were treated with second-line chemotherapy prior to the AMORE protocol. Details concerning the three steps of AMORE treatment are given in Table 2. Supraomohyoidal neck dissection was performed in three cases as a part of the approach to the tumor. Surgical reconstruction was not necessary in three cases.

Follow-up time after AMORE treatment was 5.2-9.8 years (Table 2). All four patients remain in remission at the site of recurrence. The fourth patient (patient 8) relapsed at the initial (buccal) site two months after the AMORE protocol. A permanent third CR was achieved with radical surgery and chemotherapy (follow-up 6.1 years). No short-term complications were noted. Long-term sequelae were mild swallowing disorders (patient 6) and disturbances in dental development of multiple elements (patient 6 and 7). The dental disturbances were found in all four quadrants, without a preference for the site of the treated lesion. One patient developed a second primary malignancy, a myofibrosarcoma originating within the treatment field, 7.8 years after AMORE treatment.

### Table 2. Treatment data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Surgery</th>
<th>Brachytherapy</th>
<th>Reconstruction</th>
<th>Follow-up (years)</th>
<th>Event</th>
<th>RMS status</th>
<th>Vital status</th>
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<tbody>
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<td>Dose rate (cGy/h)</td>
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<td>NED</td>
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<td>-</td>
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</table>

*additional resection of involved bony boundaries; b supraomohyoidal neck dissection as a part of the approach to the tumor and not for regional treatment purposes; c after AMORE treatment; cut off 1-9-03; RMS Rhabdomyosarcoma; AMORE, see methods for description; Gy, Gray; cGy/h, Centigray/hour; RA, rectus abdominis free muscle flap; LD*, latissimus dorsi pedicled flap; GR, gracilis free muscle flap; LD, latissimus dorsi free muscle flap; SMN, second malignant neoplasm; LR, local relapse; DM, distant metastases; CR, local complete remission; R, relapse; NED, no evidence of disease; DOD, dead of disease
4.4 Discussion

General guidelines for local salvage treatment of HNRMS include a combination of second-line chemotherapy and radiotherapy and/or surgery when possible. The SIOP MMT 95 protocol advocates a minimum of 6 courses of second-line chemotherapy. The drug choice depends on chemotherapy already received. Local treatment is undertaken after 2 courses of second-line chemotherapy. Difficulties in second-line chemotherapeutic treatment include the decreased efficacy and applicability of chemotherapeutic agents due to acquired drug resistance of tumor cells and toxicity as a consequence of intensive treatment of the primary tumor. Moreover, local treatment remains vitally important in mass lesions.

In local treatment two problems are encountered. Firstly, adequate re-irradiation with EBRT would exceed the radiation tolerance of normal tissues, especially in growing children, resulting in serious sequelae. Usually, a second course of EBRT is considered impossible. Secondly, radical salvage surgery for residual or recurrent HNRMS aiming for healthy margins is often not possible and will lead to cosmetic and functional consequences.

Thus, the options for salvage treatment with curative intent are very limited. In general, the prognosis is guarded, with a 0-30% long-term survival. A recent paper, however, reports a 60% 5-year survival in 8 patients feasible for salvage surgery out of 11 incomplete responders to chemoradiation. The AMORE approach, combining surgery and brachytherapy could overcome the problems of current practice. Surgery in the AMORE protocol is as conservative as possible, aiming at macroscopic complete resection. Subsequently, the role of brachytherapy is essential in controlling microscopic residual disease. The advantages of brachytherapy with its focal high dose and rapid fall-off beyond the target volume are well established. Brachytherapy has been used successfully in the primary treatment of soft-tissue sarcomas, with limited sequelae. Moreover, brachytherapy allows for re-irradiation without inducing irreversible damage to the surrounding structures. Experiences with brachytherapy in the treatment of recurrent RMS after prior EBRT have been reported in RMS at other sites than the head and neck. The moulage technique of the AMORE strategy has an additional value in avoiding collapse of the wound bed and optimal exposure of the area of residual disease. Fixation of the radioactive sources by the moulage is secure and more equal isodose curves are obtained (fig. 2). Surgical reconstruction of the tumor area serves the purposes of obliteration of dead spaces, protection of vital structures, prevention of communication between the upper aero-digestive tract and intracranial space and restoration of form and function. Moreover, uncompromised, well-vascularized tissue can improve wound healing of irradiated areas. The underlying mechanism might be the introduction of oxygen, polymorphonuclear leucocytes and the induction of angiogenesis.

Although our series is small, both the feasibility of the protocol and the local salvage rate observed
are promising. Survival of the tissue transfer and subsequent wound healing were good: five out of six muscle flaps survived in our series, although the majority of these patients received both prior EBRT and brachytherapy. In the parameningeal cases, there were no alternative treatment options. In the non-parameningeal cases, EBRT could still have been applied as a local treatment modality in addition to second-line chemotherapy. However, EBRT will generally lead to serious late sequelae. Recent advances in dosimetry, such as three-dimensional conformal radiation and intensity modulated radiation therapy (IMRT) could overcome some of the limitations of conventional EBRT. However, brachytherapy can deliver a more conformal dose to the tumor area than any form of teletherapy. In a recent study, we described that the AMORE protocol is feasible as first-line local treatment instead of EBRT. A disadvantage of the AMORE procedure is that experience with pediatric brachytherapy is available in a limited number of specialized centres.

In only one patient, a true failure of the AMORE protocol was observed. The relapse in this patient (patient 2) shows the tendency of parameningeal disease to spread towards the CNS. It is therefore essential that brachytherapy adequately cover skull base erosions. The second relapse (patient 8) suggests that, even in the case of radical resection, adjuvant radiotherapy is indicated. In general, surgical sequelae were limited, although it was not always possible to spare essential nerves or preserve organ function. Re-irradiation using brachytherapy was well tolerated. When acute radiation-induced toxicity is considered, no mucosal or skin reactions or tissue necrosis were encountered. Only one major wound infection was experienced. When the late sequelae are considered, nearly all serious sequelae attributable to local treatment developed in the group with prior EBRT. It is, therefore, difficult to distinguish the contribution of AMORE treatment and EBRT. Obviously, growth disorders of statural height can be contributed to EBRT involving the hypothalamic-pituitary axis. Growth retardation of the craniofacial skeleton is currently under investigation. Chemotherapeutic treatment also influences dental development, and contributes to dental sequelae. This can explain that the disturbances of dental development were found to be equally distributed instead of site-specific. A relatively high number of secondary malignancies were observed in this small series. It is difficult to assess the separate contribution of therapy or an underlying genetic predisposition to the pathogenesis. The myofibrosarcoma developed in the AMORE treatment field and the medulloblastoma was situated in the portals of prior EBRT. Both tumors could be radiation-induced.

4.5 Conclusion
The AMORE protocol is a feasible salvage treatment strategy in non-orbital HNRMS. This technique allows for local salvage treatment in already irradiated patients and can possibly avoid the long-term sequelae of EBRT in those who are not. In this small series a promising local

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control rate was achieved. We, therefore, believe the AMORE protocol should be considered as salvage treatment in HNRMS.

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