AMORE (Ablative surgery, MOulage technique brachytherapy and REconstruction) for childhood head and neck rhabdomyosarcoma
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Implications for clinical practice and future research
8.1 Implications for clinical practice

Over 10 years of experience with the AMORE protocol and the retrospective analysis of our primary and salvage cases have resulted in a proposal for eligibility, surgical in- and exclusion criteria, timing of the procedure and brachytherapy monitoring for future patients.

8.1.1 Eligibility

The following patient groups with non-orbital HNRMS are eligible for AMORE treatment (fig. 1):

Primary local treatment

*Group A1:* patients with irresectable disease at diagnosis (IRS clinical group III), who receive initial chemotherapy and require definitive local treatment;

*Group A2:* patients with microscopic residual disease after initial resection (IRS clinical group II).

Salvage treatment

*Group A3:* patients with evident radiological residual disease after chemotherapy and EBRT, or patients who develop a local relapse.

AMORE is applied as definitive local treatment, meaning that no further local treatment will be given (fig. 2).

8.1.2 Surgical in- and exclusion criteria

In- and exclusion criteria for all eligible patients are summarized in Table 1.

Extension of the residual tumor mass into the pterygopalatine fossa, or one of the foramina at the skull base requires patient-by-patient evaluation.

Table 1. In- and exclusion criteria AMORE protocol

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>macroscopically complete resection can likely be achieved</em></td>
<td></td>
</tr>
<tr>
<td>distant metastases at the time of evaluation</td>
<td></td>
</tr>
<tr>
<td>macroscopically complete resection of the residual tumor mass requires mutilating surgery</td>
<td></td>
</tr>
<tr>
<td>the residual tumor displays: nasopharyngeal invasion; intracranial extension (beyond the foramina at the skull base); encasement of the carotid artery</td>
<td></td>
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</tbody>
</table>

*also if intrallesional surgery has to be performed
† for example hemimandibulectomy or orbital exenteration
Figure 1. General flow chart for the treatment of non-orbital head and neck rhabdomyosarcoma (non-metastatic disease). Patients eligible for AMORE treatment are indicated.

Group A1, A2 and A3, patients eligible for AMORE treatment:
CT, chemotherapy; EBRT, external beam radiation therapy; PRE, primary re-excision; CCR, clinical complete remission; IRS, Intergroup rhabdomyosarcoma study

1. Feasibility of radical resection is determined by the likelihood of respecting a 1-2 cm margin of uninvolved tissue or a fascial plane, without inducing severe mutilation or functional impairment.

2. Patients with parameningeal disease > 1 jr receive routine EBRT. In patients with non-parameningeal disease, local treatment depends on response to chemotherapy, but all patients receive EBRT. If CCR is achieved, patients receive 41.4 Gy. In case of no CCR at week 17, delayed surgery (if feasible) is followed by EBRT (36 Gy after radical resection; 50.4 Gy after irradical resection). If delayed surgery is not feasible, patients receive EBRT (50.4 Gy).

3. In non-parameningeal T1-tumors of non-alveolar histology, EBRT is withheld; all other patients receive 36 Gy.
8.1.3 Timing

Group A1
Treatment decisions are made at diagnosis, at first assessment (after the initial 3 cycles of chemotherapy (week 9)) and at second assessment (after 6 courses of chemotherapy (week 18)), based on high-quality imaging studies.
If the AMORE protocol is deemed feasible at diagnosis or at first assessment, planning should be performed soon after week 9. After recovery from AMORE, the patient resumes with the fourth cycle of chemotherapy to complete the treatment protocol to which he or she is allocated.
If the AMORE protocol is not feasible at first assessment, chemotherapy is continued up to the second assessment. If surgical resection is feasible after 6 courses of chemotherapy, AMORE is scheduled soon after week 18. After recovery from AMORE, the patient resumes with the seventh cycle of chemotherapy to complete the treatment protocol to which he or she is allocated. If feasibility is doubted in cases showing a continuing response, AMORE is delayed until week 27 (after 9 courses of chemotherapy). In non-feasible cases, showing little or no decrease in tumor volume, EBRT is scheduled instead of AMORE.

Group A2
AMORE is instituted prior to, or soon after start of the chemotherapeutic regimen.

Group A3
In patients with residual disease after initial chemotherapy and external beam radiation, AMORE is scheduled as soon as possible after the last course of chemotherapy. In patients with recurrent disease, AMORE is scheduled after 2-3 courses of second-line chemotherapy.

8.1.4 Brachytherapy monitoring
Brachytherapy monitoring consists of:
- intraoperative verification of the mould position, followed by adjustments, if necessary;
- EBRT in addition to or instead of brachytherapy when adequate mould position cannot be accomplished;
- EBRT in addition to brachytherapy if, in spite of careful case selection, macroscopic residual disease has remained after surgery.

8.2 Implications for future research
AMORE is a feasible technique that seems to be effective and, to date, has shown a limited effect on craniofacial skeletal growth. Its effectiveness as to outcome and late sequelae in relation to conventional treatment needs to be established with further research. This can either be done by means of a randomized controlled clinical trial (RCT) or a well designed case-control study. AMORE is to be performed in limited centers, by a collaborative group.

In a RCT, group II and group III HNRMS patients are randomized into two arms either to receive AMORE or conventional treatment. Inclusion and execution of the AMORE protocol will be performed according to our recent guidelines (see paragraph 8.1.2, Table 1). The ‘AMORE-arm’ is compared with the ‘conventional arm’ for outcome in terms of EFS and OS, and late toxicity. Patients excluded from AMORE treatment remain in the AMORE arm, based on intention to treat. Late toxicity is recorded during a systematic follow-up scheme. Toxicity grouping and grading are

To assess the benefit of AMORE regarding craniofacial skeletal growth, a case control study has to be performed, comparing quantification data in the AMORE group with those in a group of patients who have been treated with external beam radiation, matched for age at diagnosis, age at radiation, gender, tumor stage, tumor site, and follow-up duration.