AMORE (Ablative surgery, MOulage technique brachytherapy and REconstruction) for childhood head and neck rhabdomyosarcoma
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Chapter 7

General discussion
7.1 General principles of the AMORE concept

7.1.1 Treatment of the (post-chemotherapy) residual tumor area
The guidelines for treatment of (head and neck (HN)) rhabdomyosarcoma (RMS) prescribe large volume irradiation for all patients except those with radically resected T1-tumors of non-alveolar histology. In current treatment protocols, the portals of EBRT encompass the initial (pre-chemotherapy) tumor volume and a 2-cm margin, including the meninges in parameningeal disease (see Chapter 1, paragraph 1.7.3.3). AMORE, however, aims at the residual (post-chemotherapy) tumor area with a 0.5 cm margin. This raises the concern that AMORE treatment might not cover a sufficient volume. We feel that the AMORE concept, by targeting the residual area, can provide an adequate local control and prevention of meningeal spread, as only one of our local failures was situated beyond the residual area and no meningeal failures were encountered. This opinion is supported by the results of studies reporting low failure rates after treatment of the residual area with brachytherapy or shrinking field radiotherapy. The reason for the low failure rates beyond the residual tumor area might be high chemosensitivity and intensive chemotherapeutic treatment, effectively reducing the area at risk.

7.1.2 Assessment of residual disease
Two main groups of patients were considered for AMORE treatment. The first group consisted of initially irresectable (IRS group III and IV) HNRMS patients, requiring definitive local treatment after multidrug chemotherapy. The second group of patients had recurrent HNRMS (with or without prior EBRT) or a residual mass lesion after prior chemoradiation for parameningeal disease. In all patients, the planning for AMORE was based on a radiological rest mass. Radiological evaluation may, however, not be totally accurate in the prediction of presence of vital tumor tissue. Viable tumor cells may still be present despite complete radiographic resolution of the tumor, while a suspected residual tumor mass may be due to soft-tissue thickening and may contain only necrotic tumor cells or fibrous tissue. The role of PET scanning for this purpose is still not clear and histologic sampling is not entirely reliable. An alternative strategy for patients with an incomplete response after chemoradiation would be to ‘wait and scan’ and to commence treatment only in case of tumor progression. Nevertheless, recurrent disease is experienced in 75% of the patients displaying a radiological rest mass, and waiting for tumor progression decreases the likelihood for cure. Moreover, two studies show that resection of residual tumor after chemoradiation may favourably influence outcome. In view of the high recurrence rate and the absence of a reliable means for assessment of viable tumor, we feel that patients with a clearly discernable radiological rest mass should receive local treatment as this may improve their prognosis.
7.1.3 Timing of the procedure
AMORE was instituted after a median of 8 courses of conventional multidrug chemotherapy, with a wide range (3-13 courses). In general, AMORE was scheduled when maximal tumor regression was achieved. Logistic difficulties encountered in planning this multidisciplinary procedure were a cause for a delay and additional chemotherapy in some patients. This means that in the majority of the parameningeal cases, the interval between start of chemotherapy and radiation exceeded the 9 weeks recommended by the SIOP MMT 95 protocol. As outlined in Chapter 1 (paragraph 1.7.3.3), different opinions exist as to the optimal timing of initiation of EBRT and a delay up to 20 and 29 weeks did not adversely affect local control in two studies, respectively.10,11 Radiation in the ESSG 2004 study will be scheduled in week 12, after 4 courses of chemotherapy.

Our recommendations for future timing of AMORE treatment are outlined in Chapter 8. In summary, if surgery is feasible and non-mutilating, AMORE can be scheduled after three courses of chemotherapy. From a surgical point of view, a further reduction of the tumor will not be needed in these cases. A clearly discernable residual tumor can guide the surgeon, whereas the exact site and borders of a very small radiological rest mass may be difficult to define during surgery. When AMORE surgery is not feasible after three courses, chemotherapy is continued and feasibility is re-assessed after six courses. When surgery is still not possible, our management will depend on the response. If no further regression has been achieved, the patient should be scheduled for EBRT. If there is a clear continuing response in ‘doubtful’ cases, for example when there is a doubtful intracranial component, AMORE can be scheduled after nine courses.

7.2 Technical considerations

7.2.1 Surgery
Both initial and delayed radical resection are often not possible in the head and neck region, unless mutilating procedures are performed.9,12,13 The goals of surgery as the first part of the AMORE protocol are (1) to convert the tumor to microscopic residual by complete macroscopic resection (2) to perform minimally mutilating surgery, and (3) to provide access for brachytherapy and reconstruction.

An ‘a priori’ assessment of feasibility is made, based on imaging studies. In our single center series, 76% of the patients were included (see Chapter 3). Exclusion was based on intracranial extension or nasopharyngeal invasion of the residual tumor mass. However, the retrospective analysis of eligible patients revealed that complete macroscopic resection was not always possible without performing intraliesional surgery (Chapter 6). Resection was judged as gross total resection (complete debulking without leaving macroscopic tumor remnants) in five patients and debulking
surgery in one. In these cases, extension of the residual tumor into an area with limited access (nasopharynx, intracranial, pterygopalatine fossa, ethmoid sinus) was the reason for a debulking procedure. Parallel to a limited surgical access to the tumor area, mould placement can be jeopardized. The consequences of both incomplete surgery and mould position are discussed below (see paragraph 7.3.3). Also, mutilating surgery could not always be avoided. This could either be due to tumor invasion into important structures or secondary to the surgical approach to deeply seated (parameningeal) tumors (placing normal structures, like cranial nerves, dentition and bone at risk). Important surgical sequelae were facial nerve lesions, deafness and removal of dental elements and bone. It is difficult to compare surgical sequelae with the late morbidity that would have been encountered when these patients were treated with EBRT.

7.2.2 Brachytherapy

Brachytherapy (BT), the second part of the AMORE protocol, is a less standardized technique than EBRT. Radioisotopes, techniques and equipment vary among institutions. Expertise with pediatric BT exists only in a few centers. Therefore, BT is not routinely applied in the treatment of pediatric HNRMS, although this form of radiation treatment has some clear advantages. This is especially true for children who have an increased susceptibility for the late toxicity of EBRT. Conformal techniques and IMRT can overcome some of the limitations of standard EBRT. However, disadvantages of IMRT are the less predictable dose planning to the target volume (with the risk of 'hot-spots'), the increased area of exposure to low-dose radiation, the need for immobilization, and the prolonged treatment time.\[^{14}\] Brachytherapy can be considered as an extreme form of conformal radiation therapy.

By implanting low energy sources (0.37 MeV of Iridium\(^{192}\) vs 4-20 MeV of EBRT beam energy) into the tumor bed, a high focused dose can be delivered to the target area, while there is a rapid fall-off of the dose outside the implanted volume. Therefore, brachytherapy reduces the dose to healthy surrounding tissues. Consequently, acute toxicity and late sequelae can be reduced when compared to standard teletherapy.\[^{3,15}\] These characteristics make BT also suitable for re-treatment of recurrent disease in a previously irradiated field.\[^{2,16,17}\] In general, the biologic tumor effect of BT is equivalent to a higher dose of EBRT\[^4\] and the radiation dose can be administered in several days, while EBRT will take 4-6 weeks.

We used BT as the sole form of radiation treatment. The prescribed dose (40-50 Gy) and margin (0.5 cm) are in line with the recommendations of the American brachytherapy society.\[^{15}\] A disadvantage of the limited therapeutic dose-depth is that this technique is suitable for microscopic residual only. In our series, BT proved to be able to achieve local control in patients with microscopic residual disease. Some authors used an increased dose-depth (1-2 cm) and also treated patients with gross residual disease.\[^{1,2}\] Radiation started 2 days after surgery, ensuring no
tumor cell proliferation, maximal oxygenation and no trapping of tumor cells in healed scar tissue. BT starting within the first five days after surgery has been associated with significant wound complications in adult sarcoma patients\textsuperscript{18}, unless given in low doses as a boost to EBRT.\textsuperscript{19} Radiation in the early post-operative period is reported to impair fibroblast proliferation, which affects collagen formation and subsequent wound-breaking strength.\textsuperscript{20} Therefore, the American guidelines prescribe an interval of at least 5 days between surgery and BT to prevent wound complications.\textsuperscript{15} In AMORE, the risk of wound complications is probably reduced by the use of an uniradiated muscle flap for reconstruction of the defect (see paragraph 7.2.3). The advantage of continuous LDR BT (0.4-2Gy/h) is that virtually no acute toxicity is encountered. In our series tissue necrosis, skin reaction and mucositis, were not observed. The wide variation in dose rates in our group of patients (range 49-117 cGy/h) is caused by the ‘age’ and subsequent decay of the Iridium\textsuperscript{192} wire sources. Disadvantages of LDR are the radiation exposure hazard to caregivers and the need for isolated treatment. The disadvantage of dose planning using orthogonal films is that dose distribution around the sources cannot directly be visualised in relation to the target area. Treatment was well tolerated by all children and no sedation or general anesthesia were needed. Newer modalities include high-dose rate (HDR; > 12 Gy/h), intraoperative high-dose rate (IOHDR) and pulsed-dose rate (PDR).\textsuperscript{15} Promising results of fractionated (F)-HDR (3 Gy twice daily) are reported in a small and heterogeneous series of children with soft-tissue sarcoma.\textsuperscript{4,5} F-HDR reduces treatment time, immobilization and radiation exposure and can be given on an outpatient basis, but acute (skin and mucosal reactions) and late toxicity may increase.\textsuperscript{5} More recently, treatment at our institution is performed with a PDR stepping source technique (see Chapter 2). The advantages of our moulage technique over interstitial implants are the following: (1) ordinarily the soft tissue that remains after tumor resection will fall together to obliterate the surgical defect; the mould avoids collapse of the wound bed and maximizes the exposition of the target area, (2) extreme high radiation doses (hot-spots) are in the mould, while the dose over the target volume is rather homogeneous, (3) by embedding the catheters in a mould, displacement of the sources is avoided.

7.2.3 Surgical reconstruction
Reconstruction as the final part of the AMORE protocol is performed 1-2 days on conclusion of brachytherapy. Surgical reconstruction of irradiated areas has long been associated with a higher risk of failure. Nevertheless, it is common practice to reconstruct irradiated areas several weeks after termination of external beam radiation and success rates are high (~95%).\textsuperscript{21-24} Little is known about the optimal interval between radiation and reconstruction, but the advantage of our short time interval is that soft-tissue fibrosis is not present.
In most children with soft-tissue sarcoma, brachytherapy techniques are adapted from those used in adult sarcoma. Tumor resection and interstitial or intracavitary brachytherapy-catheter implants are scheduled in one surgical session. The catheters for brachytherapy are loaded ± 5 days after surgery to avoid wound complications. Our approach therefore is different, but wound complications are very limited. The advantage of AMORE planning is that the tissue used for reconstruction is not irradiated. Certainly, well vasularized tissue enhances wound healing and can prevent wound complications, like necrosis and infection of irradiated tissue. The uncompromised tissue used for reconstruction supposedly increases oxygenation and influx of leucocytes, macrophages and fibroblasts. It is important to schedule surgery in a non-neutropenic stage.

No significant donor site morbidity was experienced. Wound complications at the recipient site in our series were very limited. Three wound infections, one partial flap necrosis of a transpositional flap and only one free-flap failure occurred in 28 reconstructions (19 free flaps and 9 transpositional flaps). The free flap failure occurred in a patient who had a hypovolemic shock secondary to post-operative bleeding and this may well have contributed to the flap failure. Partial flap necrosis was experienced in a patient who received both (prior) EBRT and BT. In all other patients, the wounds healed uneventfully. In one patient, atrophy of the free flap resulted in a large visible defect due to partial mandibulectomy and zygomatic arch resection. Therefore, atrophy of the flap has to be kept in mind when soft-tissue fill is needed to restore contour, for example after bone resection. Alternatively, a bone flap can be used. Another important consideration is the interpretation of imaging studies in the follow-up of AMORE patients. The tissue used for reconstruction, positioned in the former tumor area, can be difficult to distinguish from recurrent disease. Our policy is to perform routine imaging after wound healing has completed. This study serves as a ‘baseline’ with which future studies can be compared.

7.3 Evaluation of results

7.3.1 Outcome in upfront local treatment

The outcome of primary treatment (OS 67.5% and EFS 64% for all HNRMS and OS 64% and EFS 60% for parameningeal disease) is within the range of results reported in the literature (Chapter 1, Table 6). However, a comparison of our series with other studies has to be done with caution for two reasons: (1) the eligibility for AMORE treatment is determined by the ability to achieve macroscopically complete tumor resection; a selection bias might be introduced due to exclusion of non-feasible cases (2) our group consists of both single center patients and patients referred from other institutions.

The feasibility for primary treatment was 76% of 21 patients in our single center series. The
question raises whether we have selected a favourable subset of patients. To answer this question, we have analyzed our total single center series. This analysis showed that the constitution of the AMORE group was not different from the ‘non-AMORE’ group with respect to the distribution of the established prognostic factors (age, site, size, TNM stage, high-risk parameningeal) (Chapter 3, Appendix 2). Exclusion was based on nasopharyngeal infiltration and/or intracranial extension of the residual tumor mass, impeding complete macroscopic surgery. However, with respect to the strict prognostic factors, the AMORE group is not a favourable subset of patients. Thus, the results achieved with AMORE as definitive local treatment in primary unresectable disease, are within the range reported in the various multicenter trials and single institution studies, but fail to demonstrate a superior outcome.

7.3.2 Outcome in salvage treatment
AMORE showed a high feasibility and promising local RMS control rates when applied as salvage treatment strategy (see Chapter 4). AMORE salvage was feasible in 9 out of 11 cases with locally recurrent HNRMS or incomplete response after chemoradiation for parameningeal disease. Salvage surgery for incomplete responders is often feasible and can be curative. Paulino and co-workers have reported a feasibility for surgical salvage in 8 out of 11 incomplete responders to chemoradiation in a cohort of 23 patients with parameningeal RMS.28 In their study, extensive surgical procedures have resulted in free margins and local control in 6 out of 8 patients.28 Surgery for recurrent parameningeal HNRMS is less successful and was not able to cure any of the patients in two studies.13,28 These papers, although consisting of small single center case series, illustrate that salvage surgery can be curative, but generally involves mutilating surgery. Moreover, in case of positive margins, a repeated course of EBRT cannot be given. The AMORE protocol is a possible solution by combining less mutilating surgery with brachytherapy, which also allows for re-irradiation. In our salvage group, AMORE proved to be a feasible procedure, with limited toxicity and promising local control rates. Therefore, AMORE should be added to the armamentarium of local salvage treatment strategies. We realize, however, that we have also included patients with recurrent disease without prior EBRT. These patients could still have been irradiated as a part of their salvage treatment.

7.3.3 Failures
Retrospective multidisciplinary analysis of failure patterns (Chapter 6) suggests a relation between local relapse and gross total or debulking surgery and sub-optimal position of the mould for brachytherapy. The local relapse rate of 29% (seven out of 24 patients), is within the range of relapse rates reported in the literature (see Chapter 1, paragraph 1.8).
In retrospection, surgery consisted of debulking procedures rather than macroscopically complete
resection around the tumor mass in 6 patients. In one of these patients, macroscopic residual disease remained at the site of surgery. Macroscopic residual tumor invariably leads to recurrent disease, as our method of BT is suitable for the treatment of microscopic residual disease only. When the combination of gross total resection (debulking, leaving only microscopic residual tumor) and BT is considered in relation to recurrent disease at the residual area, one case of gross total resection with adequate mould position led to recurrent disease, whereas in two patients adequate BT following gross total resection resulted in tumor control. Several studies applied BT after gross total resection of RMS and even for the treatment of gross residual disease and report good local control rates. \[^2,4,5,9\] Thus, BT can control microscopic residual disease and can also control the tumor bed remaining after complete debulking leaving only microscopic residual disease, provided an adequate BT dose distribution is delivered, covering all borders. The reasons for the inability to perform macroscopic radical surgery were invasion of the nasopharynx, intracranial extension, extension into the pterygopalatine fossa and ethmoid. Based on our experience, patients in whom the residual tumor mass shows nasopharyngeal infiltration or intracranial extension (above the level of the skull base) should be excluded from the AMORE procedure. When the pterygopalatine fossa and ethmoidal cells are involved, a decision should be made on a case-by-case basis. In the ethmoid, a complete macroscopic resection can never be achieved, while complete debulking may be possible.

It was difficult to assess whether recurrent disease in the cases with sub-optimal position of the mould for brachytherapy developed at the exact site that was inadequately covered. Nevertheless, the difference in number of recurrences in the group of patients with an adequate mould position suggests a true relation between inadequate mould position and local recurrence. Therefore, a routine verification of the position of the mould has to be performed timely (by intra-operative control) so that adjustments can be made. It was a concern whether BT could adequately cover bone erosions, mainly at the base of the skull in parameningeal disease. We experienced one CNS failure, but no failures at the meningeal side of the skull base. In the retrospective analysis, skull base erosion was not associated with a higher relapse rate.

With respect to histopathologic analysis, more patients with tumornegative surgical specimens were in the local control group (see Chapter 6, Table 1). However, also two 'tumornegative' patients relapsed, meaning that histopathological analysis is not entirely reliable in predicting the presence of vital tumor cells. The changes induced to tumor cells by multimodality treatment, like a higher cytoplasmatic component, less dense areas of tumor cells, fibrosis and cytodifferentiation, make recognition of vital tumor cells more difficult. \[^10\] Also, sampling errors can occur due to regression (leaving islands of vital tumor cells beyond the residual tumor mass) and processing of the specimen.

Trends as to the influence of initial tumor site, tumor size and extension at diagnosis, nodal
status and size of the post-chemotherapy tumor on outcome could not be detected in our series. There were three patients with a clinical complete remission in the local control group, but otherwise no clear differences in response to chemotherapy were observed (see Chapter 6, Table 1). Also, the kind of chemotherapy and the dose of the individual agents (both prior to AMORE and cumulative) did not influence outcome.

### 7.3.4 Late sequelae

For the assessment of late toxicity, we have focused on one of the most common and disturbing sequelae following EBRT, the radiation-induced suppression of craniofacial growth (see Chapter 5). Our clinical and quantitative study in 11 eligible patients showed that only two patients had a visible asymmetry of the craniofacial skeleton. In both patients, extensive bone resection was performed as part of their AMORE treatment. CT-quantification revealed mostly subclinical craniofacial growth suppression in another six patients. These results suggest a major benefit of the AMORE protocol. However, a longer follow-up is needed to reach final conclusions concerning skeletal facial growth, as most of the patients had not completed their pubertal growth spurt at the time of evaluation.

Other sequelae were recorded at outpatient visits, but were not systematically graded or quantified and chemotherapy-induced toxicity was not analyzed in this study. Typical surgical sequelae, like hypertrophic scar formation, soft-tissue defects and facial nerve palsy had consequences for cosmesis in a fair number of patients. Disorders of dental development and malocclusion were frequently encountered. Two patients developed a trismus and one of them was previously irradiated. No radiation dermatitis or pigmentation changes, soft-tissue fibrosis, xerostomia or osteoradionecrosis were observed. Three patients developed second primary tumors, which is a relatively high number for this small series. In two cases these second tumors could have been therapy-related, one originated in the AMORE field.

Thus, a number of sequelae associated with EBRT, such as craniofacial growth disorders can possibly be avoided. As for the other sequelae, a systematic comparison should be made with a matched group of irradiated patients.
General discussion

References


