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Original Article

AMORE treatment as salvage treatment in children and young adults with relapsed head-neck rhabdomyosarcoma

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ABSTRACT

Background and purpose: Survival after relapse of head and neck rhabdomyosarcoma (HNRMS) after prior external beam radiotherapy (EBRT) is poor, since options for adequate local treatment are often lacking. In this study we describe our experience with salvage AMORE in patients with relapsed HNRMS after prior EBRT.

Materials and methods: Patients with relapsed HNRMS after prior EBRT in which salvage AMORE treatment was considered feasible were analysed; this includes patients with parameningeal, head and neck non-parameningeal and orbital localization. AMORE treatment consisted of Ablative surgery, MOuld technique brachytherapy and surgical REconstruction.

Results: In total 18 patients received salvage AMORE treatment; nine patients had relapsed parameningeal (PM) RMS, two patients had relapsed head and neck non-parameningeal RMS (HN-nonPM) and seven patients had relapsed orbital RMS. Local control rate was 67% and 5-year overall survival was 54% (95% confidence interval: 31–78%); 3/9 patients with PM RMS, 0/2 patients with HN-nonPM RMS and 6/7 patients with orbital RMS were alive after a median follow-up of 8.6 years. One patient with PM RMS survived more than 5 years after which he died from a secondary cancer. Six patients developed a local relapse (of which one patient also developed a distant metastasis) and two patients developed distant metastases.

Conclusions: Salvage AMORE treatment is a feasible and effective local therapy approach even after prior EBRT. Since salvage AMORE treatment is sometimes the only curative option in patient with relapsed HNRMS, we encourage physicians to consider salvage AMORE treatment for patients with relapsed HNRMS after prior EBRT.

Rhabdomyosarcoma (RMS) is the most common soft-tissue sarcoma in childhood and approximately 40% of the RMS cases arise in the head and neck region [1]. This tumour site can be further divided into the parameningeal, head and neck non-parameningeal and orbital region.

The treatment of childhood rhabdomyosarcoma consists of a combination of chemotherapy with additional surgery and/or radiotherapy. Local therapy, i.e. surgery and/or radiotherapy, is essential to achieve local control. However, in patients with head-neck rhabdomyosarcoma (HNRMS) a microscopically radical resection is often impossible, advocating the use of external beam radiotherapy (EBRT) in the majority of the cases.

In the '90s an innovative new treatment protocol was developed in the Emma Children's Hospital-Academic Medical Centre (EKZ-AMC) called AMORE. This acronym stands for Ablative surgery, MOuld technique with afterloading brachytherapy and surgical REconstruction. The advantage of brachytherapy above EBRT is the more conformal dose delivery to the tumour bed with rapid dose fall-off beyond the target volume, thereby sparing more of the healthy surrounding tissue. In the EKZ-AMC, patients with

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HNRMS are treated according to the AMORE treatment if feasible. Otherwise patients receive EBRT (either photon- or protontherapy). AMORE treatment as first-line local therapy has shown to result in similar survival and less adverse events (AEs) compared to local therapy according to international standard (i.e. EBRT) [2–5].

Despite the continuous efforts of several international study groups to improve survival, still up to 1/3 of all patients with localized RMS at diagnosis experience a relapse [6–8]. In a study of Dantonello *et al.* the relapse rate was 29% for parameningeal localization, 34% for head and neck non-parameningeal localization and 28% for orbital localization in patients with RMS in complete remission at the end of treatment [6]. In general, outcome after relapsed RMS is poor and survival is strongly depending on previous received treatment [9–11]. Chisholm *et al.* analysed the survival of patients with localized RMS who relapsed after complete local control and found prior radiotherapy treatment together with metastatic relapse to be most strongly associated with poor outcome [11]. Survival, specifically in patients with relapsed HNRMS who previously received EBRT, is extremely poor because options to achieve local control are lacking. However, in specific cases AMORE can be used as salvage treatment. In this current study we report on the results of our experience with AMORE as salvage treatment in patients with relapsed HNRMS after prior EBRT. We specifically report on survival probabilities and the severity and frequency of late sequelae.

Materials and methods

Patients

Eligible patients were patients with relapsed HNRMS, after previous chemotherapy and EBRT (as initial treatment or relapse treatment), with salvage AMORE treatment between January 1993 and December 2014. Patients with second or third relapse were also eligible. This study included patients from our own centre ($n = 7$) and patients referred to us specifically for salvage AMORE treatment ($n = 11$).

Diagnostic work-up and treatment

Patients included in this analysis were staged and treated at first diagnosis according to consecutive European RMS treatment guidelines; SIOP MMT (International Society of Paediatric Oncology Malignant Mesenchymal Tumour; SIOP-MMT-89 and SIOP-MMT-95), CWS (German Cooperative Soft Tissue Sarcoma; CWS-96), or E*p*SSG (European *paediatric* Soft tissue sarcoma Study Group; E*p*SSG-RMS-2005). The outlines of these trials have been described previously [8,12–14]. Patients were staged according to TNM criteria [15] and the Intergroup Rhabdomyosarcoma Group post-surgical staging system (IRSG-staging) [16].

In general, the majority of patients underwent an incisional biopsy after which patients received chemotherapy. Treatment with multidrug chemotherapy was carried out according to protocol, followed by local therapy. If a microscopic radical resection was not possible, patients received standard EBRT (or AMORE treatment if feasible). Patients with parameningeal tumours received EBRT on initial tumour volume. Patients with tumours located in the head and neck non-parameningeal and orbital area received EBRT on the residual volume.

AMORE procedure

The technical feasibility of a salvage AMORE procedure was assessed in the multidisciplinary tumour board. Participating specialties in these multidisciplinary meetings were: paediatric oncologists, radiation oncologists, head and neck radiologists, head and neck surgeons, reconstructive surgeons, orbital surgeons and in specific cases also neurosurgeons. Salvage AMORE treatment was considered feasible based on the possibility to perform a macroscopic tumour resection and the possibility to adequately position the mould after resection taking into account the morbidity of the procedure [17]. AMORE as first line treatment in naïve patients includes conservative, minimal-mutilating surgery as the goal of AMORE treatment is to effectively treat the primary tumour with maximal sparing of the organs at risk. However, when considering AMORE for previously irradiated patients with relapsed local disease (so called AMORE salvage treatment) more mutilating surgery was accepted, as there were no other alternative local treatment options.

Details of the AMORE treatment can be found in previous manuscripts [2,4,18,19]. In brief, local therapy by AMORE treatment is targeted at the residual tumour volume. The aim is to perform a macroscopic radical resection of the residual tumour mass. During the same operative procedure a mould with polyethylene catheters is made and placed in the surgical bed to deliver brachytherapy. Possible microscopic remnants in the tumour bed were irradiated, using iridium-192. Radiotherapy dose (40–50 Gy) is planned up to 5 mm from the mould surface. Until 2001, continuous low-dose-rate (LDR) brachytherapy was given and from 2002 pulsed-dose-rate (PDR) brachytherapy was used. One week after the first operation and after completion of brachytherapy, a second surgical procedure is performed to remove the mould and catheters after which the surgical defect is reconstructed by using a free vascularized or pedicled flap.

Follow-up and statistical analysis

Local control rate was defined as the time between AMORE treatment and date of local event. Progression free survival was defined as the time between AMORE treatment and date of any disease progression. Overall survival was defined as the time between AMORE treatment and date of last follow-up or patient death. Outcomes for living patients were censored at the time of their last reported contact. Cut off point of this analysis was March 31, 2017. For a part of this population, AEs were systematically assessed in a multidisciplinary outpatient clinic, of which results were reported previously [3]. When these data were not available, often for patients referred from abroad, we asked treating physicians to fill out a predefined AEs form graded according to the Common Terminology Criteria for Adverse Events (CTCAEv4.0, available at http://evs.nci.nih.gov/ftp1/CTCAE/About.html), based on the form used in the multidisciplinary follow-up clinic at the EKZ/AMC (Supplementary table S1, online only) [3].

R Studio version 1.1.453 was used for the survival analysis. Local control rate, progression free survival and overall survival was calculated using the Kaplan–Meier method.[20] Because of the small number of patients, results are presented in a descriptive manner.

Results

Between January 1993 and December 2014, 18 patients (11 boys, 7 girls) with relapsed HNRMS after prior EBRT received a salvage AMORE procedure in the EKZ/AMC. The median age at initial diagnosis was 5.7 years (range: 1.1–23.0 years). Median age at time of salvage procedure was 9.3 years (range: 3.0–26.1 years).

Initial tumour localizations were: parameningeal ($n = 9$), head and neck non-parameningeal ($n = 2$) or orbital ($n = 7$) localizations. Two patients had an orbital RMS initially, but at relapse the orbital tumour extended into the parameningeal area. These two were

Table 1
Initial tumour characteristics of included patients.

Patient	Age[a] (yrs)	Sex	Histology	Initial localization	Initial treatment	Relapse site	Indication AMORE
Parameningeal							
1	3.0	M	Embryonal	Mastoid	MMT-89[b]/EBRT (50 Gy)	Mastoid	1st LR
2	4.4	M	Embryonal	Nasal cavity	RMS2005/EBRT (45 Gy)	Nasal cavity, ext. to nasopharynx	1st LR
3	4.5	F	Embryonal	Nasopharynx	Surgery/MMT95/EBRT (45 Gy)	Nasopharynx, ext. beyond soft palate	2nd LR[c]
4	5.4	F	Embryonal	Musculus pterygoideus	RMS2005/EBRT (50.4 Gy)	Parapharyngeal	1st LR
5	5.9	F	Embryonal	Parapharyngeal	MMT95/EBRT (54 Gy)	Parapharyngeal	1st LR
6	7.1	M	Embryonal	Sphenoidal sinus	RMS2005/EBRT (54 Gy)	Fossa pterygopalatine ext. intracranially[d]	1st LR
7	7.3	M	Embryonal	Nasal cavity	CWS96/EBRT (48.6 Gy)	Nasal cavity	1st LR
8	7.7	F	Embryonal	Pterygoid fossa	MMT95/EBRT (50 Gy)	Pterygoid fossa + pulmonary metastasis	1st LR
9	23.0	F	Embryonal	Masticator space	RMS2005/EBRT (55.8 Gy)	Sphenoid, ext. to orbita and m. temporalis	1st LR
Non parameningeal							
10	1.7	F	Alveolar	Cheek + distant metastasis	RMS-MET-2008/EBRT (51.2 Gy)	Cheek	1st LR
11	12.3	M	Embryonal	Parotid gland	CWS96/Surgery	Parotid gland	2nd LR[e]
Orbit							
12	1.1	M	Alveolar	Orbit	Surgery/MMT95/EBRT (45 Gy)	Orbit	1st LR
13	3.6	M	Embryonal	Orbit	MMT95/EBRT (45 Gy)	Orbit	1st LR
14	3.9	F	Embryonal	Orbit	RMS2005/AMORE	Orbit	2nd LR[f]
15	4.9	M	Embryonal	Orbit	MMT95/EBRT (45 Gy)	Orbit	1st LR
16	7.2	M	Embryonal	Orbit	RMS2005/EBRT (45 Gy)	Orbit ext. parameningeal	1st LR
17	11.2	M	Embryonal	Orbit	MMT89/surgery	Orbit	3rd LR[g]
18	11.5	M	Embryonal	Orbit	RMS2005/EBRT (50 Gy)	Orbit, ext. parameningeal	1st LR

Abbreviations: CWS95, German Cooperative Soft Tissue Sarcoma 95 study; EBRT, external beam radiotherapy; ext., extending; F, female; L, left; LR, local relapse; M, male; MMT, SIOP malignant mesenchymal tumour protocol (SIOP-MMT-89, SIOP-MMT-95); R, right; RMS2005, European *paediatric* Soft tissue sarcoma Study Group rhabdomyosarcoma 2005 study (EpSSG-RMS-2005); RMS-MET-2008, EpSSG RMS metastatic 2008 study; yrs, years.

[a] Age at time of diagnosis.
[b] Including myeloablative chemotherapy and autologous stem cell rescue.
[c] Treatment of 1st relapse consisted of macroscopic surgery and chemotherapy.
[d] Intracranial extension was no longer visible pre-operative, therefore AMORE procedure was conducted.
[e] Treatment of 1st relapse consisted of chemotherapy and EBRT 54.0 Gy.
[f] Treatment of 1st relapse consisted of chemotherapy and EBRT 50.4 Gy.
[g] Treatment of 1st relapse consisted of chemotherapy and AMORE, 2nd relapse; chemotherapy and EBRT 55.8 Gy.

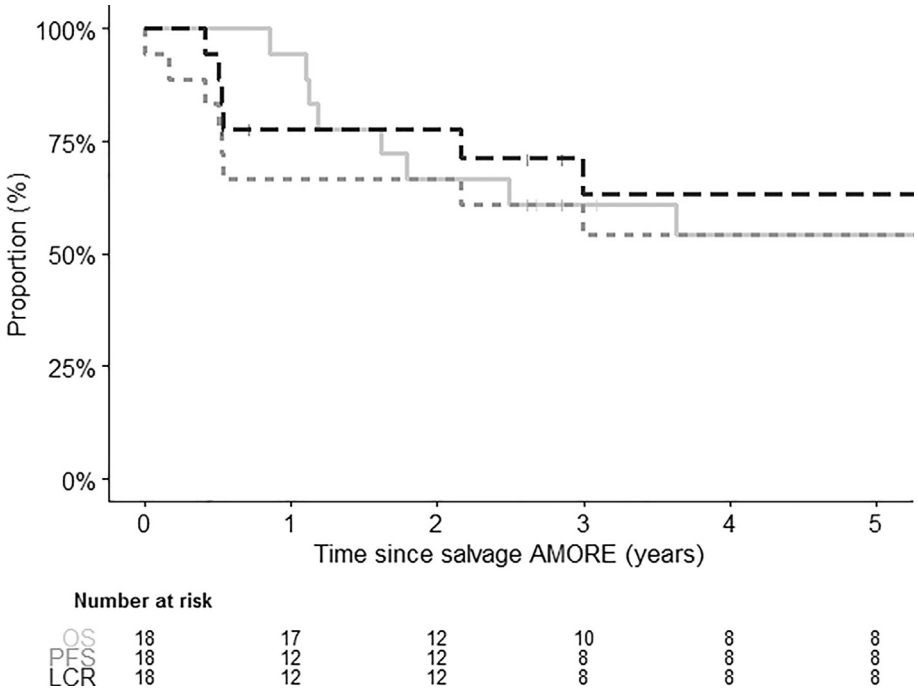

Fig. 1. Kaplan–Meier curves showing Local control rate (LCR in grey), Progression free survival (PFR in yellow) and overall survival (OS in blue) for patients who received a salvage AMORE procedure for relapsed HNRMS after prior EBRT. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Details of salvage treatment and relapse.

Patient	Age[a] (yrs)	Salvage treatment	Surgery	Brachytherapy		Reconstruction	Outcome		Event
				Dose (Gy)	Dose rate	Donor site	Status	FU (yrs)	
Parameningeal									
1	4.2	AMORE	Resection partial mastoid, partial os petrosus and cochlea	50	LDR/61	RA	NED	23.8	SPT[b]
2	6.9	CT/AMORE	Denker procedure[c], resection fossa pterygopalatine, partial resection hard palate, partial resection pterygopalatine bone[d]	40	PDR/1.25	GA	Died	1.1	2nd LR
3	7.9	CT/AMORE	Denker procedure[c], resection lacrimal bone	40	LDR/60	RA	Died	1.2	3rd LR/DM
4	8.3	CT/AMORE	Resection of all stylohyoid muscles, selective neck dissection (I, IIA)	39	PDR/1.5	GR	NED	8.5	–
5	10.7	CT/AMORE	Partial resection soft palate, oropharynx mucosa and tongue base + selective neck dissection (level 2A)	42	PDR/1.5	RA	Died	2.5	2nd LR
6	9.6	CT/AMORE	Resection of fossa pterygopalatine, partial resection skullbase, resection pterygoid muscles	40	PDR/1.25	TF	NED	8.6	–
7	10.0	CT/S/AMORE[e]	Total ethmoidectomy plus conga resection partial vomer resection, partial resection maxillary sinus	45	PDR/1.25	GA	Died	6.4	SPT[f]
8	9.9	CT/M/AMORE	Resection fossa pterygopalatine including muscles, partial resection mastication muscles partial parotidectomy, selective neck dissection (I, II, III)	40	LDR/140	LD[#]	Died	0.9	DM
9	26.1	CT/AMORE	Fronto-temporal craniotomy, partial orbitotectomy and partial resection skull base	45	PDR/1.25	TF	Died	1.8	2nd LR
Non-parameningeal									
10	3.0	CT/AMORE	Partial maxillectomy, partial nose amputation, resection soft tissue cheek, partial lateral nose dissection, lymph node biopsy (level II)[g]	45	PDR/1.25	LD	Died	1.1	DM
11	16.9	CT/AMORE	Parotidectomy, including cranial nerves 7 and 11 (involved in tumour)	40	PDR/1.2	RA	Died	3.6	3rd LR
Orbit									
12	3.6	CT/AMORE	Orbital exenteration	40	PDR/1.25	GA	NED	11.3	–
13	12.2	CT/AMORE	Orbital exenteration	40	PDR/1.25	GA	NED	6.3	–
14	7.9	CT/AMORE	Orbital exenteration	40	PDR/1.25	GA	NED	2.7	–
15	5.9	CT/AMORE	Orbital exenteration	40	PDR/1.25	GA	NED	11.2	–
16	8.9	CT/AMORE	Orbital exenteration + partial resection of bony orbita	40	PDR/1.25	GR	NED	3.1	–
17	14.2	CT/AMORE	Orbital exenteration	40	LDR/70	TF	NED	21.7	-
18	12.9	CT/S[h]/AMORE	Orbital exenteration, partial resection of bony orbita and skull base + dura resection.	40	PDR/1.25	RA	Died	1.6	2nd LR

Abbreviations: CT, 2nd or 3rd line chemotherapy; DM, distant metastasis; FU, follow-up since relapse in years; GA, tunnelled galea flap; GR, gracilis free muscle flap; LD[#], latissimus dorsi pedicled flap; LD, latissimus dorsi free muscle flap; LDR, low continuous dose rate (in cGy/hour); LR, local relapse; M, metastasectomy pulmonary nodule; NED, no evidence of disease; PDR, pulse dose rate (in Gy/pulse); RA, rectus abdominis free muscle flap; S, surgery; SPT, second primary tumour; TF, temporalis transposition flap; yrs, years.

[a] Age at time of salvage AMORE treatment.
[b] Patient developed a medulloblastoma.
[c] Adjusted Denker procedure: lateral rhinotomy with Denker incision.
[d] Lateral and posterior wall of maxillary sinus was tumour positive and only received 50% of radiation dose, therefore additional brachytherapy threads were placed during reconstruction and additional radiotherapy was given.
[e] Residual disease after surgery and chemotherapy therefore AMORE treatment.
[f] Patient died of second primary tumour; glioblastoma.
[g] Lymph nodes were tumour negative, however salivary gland contained tumour and was not radically resected; subsequent adequate radiotherapy was not possible.
[h] Surgical resection was abandoned based on frozen section biopsies showing the tumour extended in the margins of dural resection.

allocated to the orbital group, based on their initial localization (Table 1). The median follow-up time since diagnosis of relapse was 8.6 years (interquartile range: 4.7–16.5 years) for patients alive; local control rate was 67% (12/18 patients) and the 5-year overall survival of the total group was 54% (Fig. 1).

Parameningeal (n = 9)

All patients with parameningeal tumours had localized embryonal RMS at initial diagnosis. Eight out of nine patients had a local relapse and one patient had a local relapse combined with a solitary pulmonary metastasis. This patient was first treated with

chemotherapy and underwent a metastasectomy after which an AMORE salvage procedure was performed. Details of salvage treatment are provided in Table 2.

Three out of the nine patients were alive after a follow-up ranging from 8.5 to 23.8 years. In 5/9 (55.6%) patients local control was achieved; three patients developed a local relapse and one developed a local relapse and a distant metastasis. Two patients developed a secondary malignancy; patient 1 developed a medulloblastoma within the initial EBRT field, 8.2 years after AMORE treatment and patient 7 developed a glioblastoma 5 years after AMORE treatment and died after surgery (exact location of the glioblastoma was unknown).

Non-parameningeal (n = 2)

Two patients had a head and neck non-parameningeal located relapse; patient 10 had a non-parameningeal alveolar RMS, with pulmonary metastases and bilateral lymphadenopathy at initial diagnosis and patient 11 had localized non-parameningeal embryonal RMS. Both patients developed a local relapse for which they received a salvage AMORE procedure.

At preoperative radiologic imaging patient 10 showed potential lymph node involvement/solitary salivary gland metastasis. Therefore, in addition to the resection of the primary tumour during the first AMORE procedure, a lymph node biopsy was performed. The salvage treatment was well tolerated however pathology results showed a not radically resected salivary gland metastasis. Additional EBRT after salvage AMORE was considered necessary, however not feasible because of potential toxicity. She received maintenance chemotherapy; however she developed a distant metastasis without locoregional relapse and died a year after AMORE treatment. Patient 11 received second line chemotherapy and salvage AMORE treatment for his second relapse. The salvage treatment was well tolerated; however he developed a third local relapse 3 years after the AMORE procedure and died subsequently.

Orbital (n = 7)

Seven patients had orbital RMS; one tumour was of alveolar histology, six were embryonal. All seven patients developed a local relapse for which they received salvage AMORE; in two patients the relapsed tumour showed parameningeal extension at relapse. Resection of the tumour included orbital exenteration for all patients; one of these patients also underwent a craniotomy with excision of part of the involved dura (Table 2).

Six out of the seven patients were alive after a follow-up ranging from 2.7 to 21.7 years. One patient developed a local relapse, six months after salvage AMORE treatment and died a year after salvage treatment.

Adverse events

The surviving patients with parameningeal tumours all developed more than 5 AEs as result of local treatment. All patients developed (grade 2 or 3) musculoskeletal deformities and growth hormone deficiency for which they received growth hormone replacement. Patient 6 developed a grade 3 optic nerve disorder. Other reported AEs were grade 1 or 2 and included dysarthria, trismus, telangiectasia, dermatitis, cataract, skin/fat atrophy, scarring, induration/fibrosis or hearing loss.

The surviving patients with orbital tumours all had grade 4 musculoskeletal deformity due to the orbital exenteration (i.e. musculoskeletal deformity grade 4). Furthermore, they developed grade 1 or 2 AEs, including scarring, induration/fibrosis, hearing loss, telangiectasia, pigmentation, epistaxis, alopecia, skin/fat atrophy and dry eyes. Patient 13 developed growth hormone deficiency and received growth hormone replacement. Patient 17 developed secondary generalized seizures 13 years after salvage AMORE treatment, possibly caused by radiation necrosis in his frontal lobe (treated with anticonvulsant medication in the past for <1 year, no medication needed afterwards).

Discussion

The outcome for patients with locally relapsed HNRMS is determined by the feasibility of local treatment. Curative options are often lacking in patients who have previously received EBRT. Consequently, the survival rates for children with relapsed HNRMS after receiving EBRT are poor; ranging from 0% to 18% [9–11]. Microscopic radical resection of the tumour is often not possible without serious mutilating cosmetic and functional consequences. Furthermore, in the majority of patients, re-irradiation is considered not feasible, since the total radiation dose would exceed the tolerable dose for healthy tissue.

We show that in specific cases a salvage AMORE treatment is feasible, consisting of a macroscopic radical resection, directly followed by brachytherapy to treat potential microscopic remnants, allowing a precise conformal dose distribution with rapid fall-off, thereby sparing the surrounding healthy often previously irradiated tissue. In these patients salvage AMORE treatment enables re-irradiation in patients with relapsed HNRMS.

In this study we show that salvage AMORE treatment can lead to long-term survival. Nine of 18 treated patients are alive and 1 patient survived >5 years after which he died from a secondary cancer.

We previously (in 2004) reported on salvage AMORE treatment; this was a smaller series (9 patients in total) that also contained two patients groups (6 of the 9 patients) which were excluded from the current analysis [18]. The first of those two groups consisted of patients with residual disease after initial EBRT for which they underwent salvage AMORE treatment. However, a North-American analysis showed that patients with residual masses at the end of therapy had comparable prognosis as to patients showing complete tumour response at end of therapy [21]. Therefore patients with residual disease after EBRT are no longer eligible for salvage AMORE treatment. The second group consisted of patients which were not treated with EBRT previously. According to SIOP-MMT and EpSSG guidelines, specific more favourable subgroups (based on tumour site) did not receive radiotherapy in case of complete response. In case of relapse, AMORE treatment would not be the only remaining curative options for these patients, since EBRT would still be possible in these patients; therefore, we excluded this group from the current analysis.

A comparison of survival rates with other cohorts is not possible since we only report outcomes for patients that were actually treated with salvage AMORE; we do not have accurate follow-up of all patients in whom salvage AMORE was considered. Nevertheless, salvage AMORE treatment is often one of the few remaining local treatment modalities available in patients previously treated with EBRT and therefore the outcome data of this cohort are relevant for the future management of patients with relapsed head and neck RMS after prior EBRT.

In this cohort, overall survival for patients with orbital relapse was high. One could argue that salvage surgery by an orbital exenteration might have been adequate therapy for these patients; however surgical resection in 5/7 patients was microscopically incomplete (as anticipated in the AMORE approach), therefore we believe that the subsequent brachytherapy was essential.

The feasibility of AMORE was systematically discussed in a multidisciplinary setting, using predefined in- and exclusion criteria. When considering newly diagnosed patients for AMORE, potential

severe mutilation is a contra-indication for AMORE, unless more AEs are expected when using EBRT. In case of patients with relapsed disease after EBRT, when often no other local treatment is available, the AMORE working group accepts more mutilating and higher risk surgery.

Re-irradiation with adequate dose in case of relapse after prior EBRT is generally considered impossible. Patients in this cohort were all re-irradiated with brachytherapy nevertheless, the salvage AMORE treatment was well tolerated. We believe that the reconstruction with well-vascularized muscle tissue flaps plays a pivotal role in this [22]; acute complications were rarely seen and only one patient developed a major wound infection.

However, successful salvage procedures did cause important (late) sequelae. An orbital exenteration was conducted in all 7 patients with orbital tumours and one patient developed radiation necrosis.

Two patients developed a secondary malignancy; patient 1 developed a medulloblastoma which was located in the fields of prior EBRT, patient 7 developed a glioblastoma of which the exact location was unknown since primary treatment and follow-up for this patient was done in a different hospital abroad. The three surviving parameningeal patients all experienced many AEs; however, these patients received EBRT, brachytherapy and (mutilating) surgery making it difficult to determine the causative factor.

Conclusion

Salvage AMORE treatment is a feasible and can be an effective local therapy approach for a specific group (after careful consideration by a multidisciplinary head-neck oncology team) of patients with relapsed HNRMS after prior EBRT. Local therapy by AMORE procedure is often one of the few remaining curative options in patients with relapsed HNRMS after prior EBRT treatment and we would like to encourage physicians to consider AMORE treatment as salvage treatment for relapsed HNRMS patients.

Conflict of interests

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.10.036.

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