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A novel local treatment strategy for advanced stage head and neck rhabdomyosarcomas in children: results of the AMORE protocol

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Abstract

The AMORE protocol is a local treatment regimen for head and neck rhabdomyosarcomas (HNRMS), consisting of Ablative surgery, Moulage technique brachytherapy and surgical Reconstruction. The aim of AMORE is to intensify local treatment for children with HNRMS and to avoid external beam radiation therapy (EBRT) and its long-term sequelae. All children with primary irresectable, non-orbital HNRMS in whom EBRT was indicated, were evaluated for the feasibility of AMORE. In 20 children, AMORE was performed (15 with parameningeal disease and five with non-parameningeal disease). Complete remission was achieved in all 20 patients. Local complications were limited. 5 patients experienced a local relapse and 1 patient developed distant metastases. Estimated 5-year OS and EFS were 67.5 and 64.1% for the entire group, and 64.2 and 60.0% for the parameningeal subgroup. We conclude that the AMORE protocol is a feasible strategy, with a good local control rate. Long-term sequelae of EBRT might be avoided although, to date, the follow-up is too short for definitive conclusions regarding these sequelae.

Keywords: Head and neck neoplasms; Rhabdomyosarcoma; Combined modality therapy; Surgery; Brachytherapy; Reconstructive surgical procedures

1. Introduction

In general, survival for paediatric rhabdomyosarcoma (RMS) patients has improved dramatically in the past decades using combined modality treatment strategies [1–3]. The outcome mainly depends on tumour stage, size, site, histology and age. In current treatment protocols, all five prognostic factors are used in the allocation to treatment regimens to provide a risk-based treatment. Some 40% of RMS are located in the head and neck region [3,4]. Within the head and neck region, a division into three sites can be made: parameningeal (±50%), non-parameningeal (±25%) and orbital (±25%), each representing a distinct prognostic category [5]. Despite the general increase in survival, patients with parameningeal and locally advanced non-parameningeal RMS still pose a dilemma to the paediatric oncologist. Achieving long-term complete remission or cure with chemotherapy alone is unlikely for this patient category and relapse rates are unacceptably high [6,7]. Local therapy in these cases is pivotal. Complete surgical excision achieving oncological safe margins is usually impossible given the size of tumours, the difficult accessibility and the close relationship of the tumour to vital structures or the unacceptable cosmetic and functional consequences of a radical resection. The role of primary surgery is therefore limited [6]. The 'standard of care' in most protocols consists of multidrug chemotherapy and external beam radiotherapy (EBRT).

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Substantial remission rates of up to 90% have been reported and (early) radiation therapy is considered one of the most important reasons for an improved survival rate [8]. In spite of these remission rates, a considerable morbidity is attributable to EBRT. An adequate dose (45–50 Gy) has to be delivered to the tumour with a 2—3 cm margin, leading to serious late sequelae, particularly among children whose growing tissues and organs in the head and neck region are susceptible to radiation damage [9–11]. Moreover, 20–30% of the patients relapse, mostly local relapse [6,12,13]. Survival rates after relapse are dismal [13]. Improvement of local control strategies therefore remains an important issue. An innovative multidisciplinary local treatment strategy, termed the AMORE protocol, was designed in our centre. This strategy consists of consecutive Ablative surgery, Moulage technique afterloading brachytherapy and surgical Reconstruction. Initial results have been reported on the feasibility and morbidity of the protocol [14]. This report focuses on the local control rate and sequelae of the AMORE protocol applied in advanced stage and non-orbital, non-metastatic head and neck (HN)RMS, mainly at the parameningeal sites.

2. Patients and methods

2.1. Eligibility criteria

Patients were enrolled from January 1993 until May 2002. Two categories of patients were considered for inclusion. Firstly, at our institution there is a consistent policy to evaluate the feasibility of the AMORE protocol in children with advanced stage (irresectable) non-orbital HNRMS, for whom local treatment is indicated in addition to multidrug chemotherapy according to the guidelines of the International Society of Paediatric Oncology (SIOP) Malignant Mesenchymal Tumors (MMT) group. These patients form our consecutive single centre series. Secondly, patients referred from other institutions, specifically for the AMORE protocol, were also evaluated. In all patients with primary non-orbital HNRMS, the possibility of macroscopical complete resection of the residual tumour mass was assessed on clinical and radiological examinations. Patients from both groups who could not meet this criterium, mainly due to intracranial extension of the tumour, were excluded from this study.

2.2. Diagnostic work-up

Diagnostic work-up was performed according to the SIOP MMT diagnostic guidelines. Diagnosis of RMS was based on fine needle or open surgical biopsies which were revised and classified according to the SIOP pathology guidelines [15]. Staging was performed according to pretreatment tumour-node-metastasis (TNM) classification [16]. Tumour extent was based on computed tomography (CT) and/or magnetic resonance imaging (MRI) dimensions, nodal status was based on clinical grounds, radiographic studies and/or histopathology. Work-up for distant metastasis included chest radiography, skeletal scintigraphy, cerebrospinal fluid (CSF) analysis and bone marrow aspirate. Parameningeal sites were defined in accordance to the SIOP MMT guidelines, i.e. the nasal cavity, nasopharynx, paranasal sinuses, middle ear/mastoid and pterygoid fossa. The remaining head and neck sites (parotid region, buccal region and oral cavity) were considered non-parameningeal. In patients with parameningeal tumours, the risk for meningeal involvement was estimated, classifying patients having cranial nerve palsy, erosion of the skull base or intracranial growth as 'high-risk' and patients with malignant cells in the CSF aspirate as having proven central nervous system (CNS) involvement.

2.3. AMORE strategy

The AMORE strategy is aimed at the residual tumour volume and consists of ablative surgery, intracavitary brachytherapy with a moulage technique and surgical reconstruction in two surgical sessions [14]. Total treatment is scheduled in 1 week. During ablative surgery, the residual tumour mass (Fig. 1) is removed without leaving macroscopical remnants and, if feasible, with sparing of vital structures around the tumour bed. In

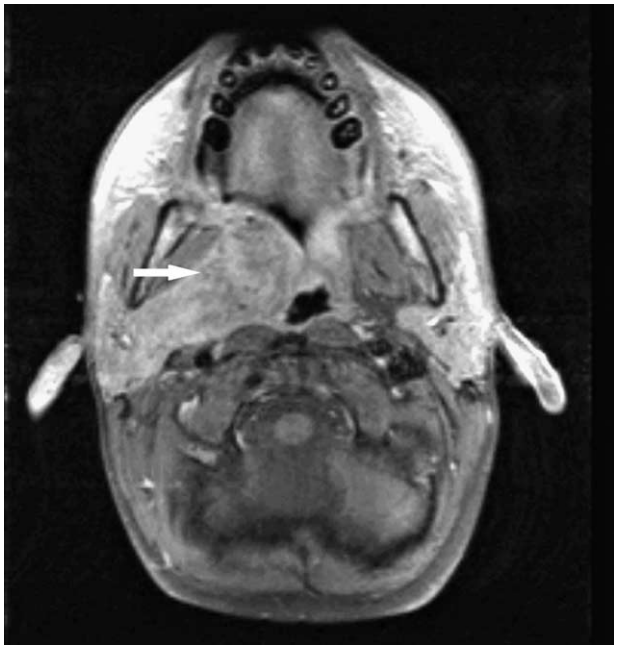


Fig. 1. Spin echo T1-weighted magnetic resonance (MR) image after intravenous (i.v.) contrast enhancement. The arrow indicates the residual tumour mass in the right pterygoid fossa.

the same surgical session, the wound bed is obliterated using a thermoplastic gutta percha moulage in which flexible polyethylene catheters are embedded. The moulage exactly fits the surgical cavity ensuring a maximal coverage of the wound bed. The clinical target volume is set 5 mm from the surface of the moulage. Dosimetry is performed by identifying the catheters (loaded with radiopaque dummies) using plain radiographs and CT scans postoperatively and subsequent computer-aided calculation of the dose distribution (Fig. 2). After calculation of the desired dose and dose rate, radiation commences on the second or third postoperative day. The patient is transferred to an isolated room and the catheters are loaded with Iridium-192 line sources. The determined dose is administered over a 3–4 day period, depending on the dose and dose rate. In the second surgical session, the moulage is taken out and after debridement and rinsing of the wound bed, the defect is reconstructed using a free vascularised or a regional pedicled muscle or musculocutaneous flap. The AMORE strategy is scheduled when local treatment is indicated according to the SIOP guidelines. For patients with non-parameningeal RMS, this is generally in week 18. For patients >3 years of age having parameningeal disease, standard EBRT in week 9 is withheld and replaced by brachytherapy as an integral part of the AMORE protocol. In general, no further chemotherapy is given, unless the treating physician decides otherwise. Care is taken to perform the protocol in a non-neutropenic stage to avoid slow or hampered wound healing. All patients received perioperative antibiotic treatment.

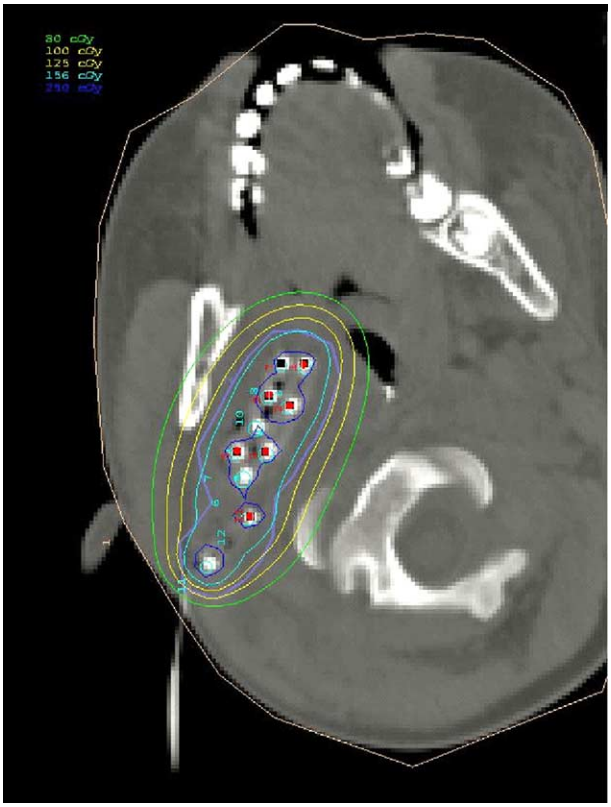


Fig. 2. Computed tomography (CT) scan image at brachytherapy treatment planning. The residual tumour mass is removed and the gutta percha moulage is *in situ*. The moulage is loaded with dummies and the dose distribution is calculated. Reference isodose lines (cGy/h) around the moulage are depicted in colour: green line 80 cGy/h, outer yellow line 100 cGy/h, inner yellow line 125 cGy/h, light blue line 156 cGy/h, dark blue lines 250 cGy/h.

2.4. Statistics

Event-free survival (EFS) and overall survival (OS) were calculated using Kaplan–Meier statistics. EFS is defined from diagnosis (first tumour-positive biopsy) to progressive disease, recurrent disease or toxic death. OS is defined from diagnosis until death from any cause. Patients who did not experience the events of interest were censored at the time of their last follow-up. The cut-off point of the analysis is 1 November 2002.

3. Results

From January 1993 until May 2002, 29 children with non-orbital HNRMS were treated in our centre and represent our consecutive single centre series. In 7 patients with non-parameningeal HNRMS, chemotherapy was instituted according to the SIOP MMT protocol after initial surgery (biopsy and/or surgical excision). Complete remission was achieved in all 7 patients and therefore additional local treatment was not indicated. One parameningeal case had stage IV disease. In the remaining 21 patients, additional local treatment was indicated. In 5 parameningeal cases, the AMORE protocol could not be performed because complete macroscopical tumour ablation was not feasible, mainly due to intracranial extension of the residual tumour mass. Hence, a total of 16 patients with primary irresectable non-orbital RMS were included in this study. Therefore, the AMORE protocol proved to be feasible in 16 out of 21 patients (76%) of our single centre patients needing additional local treatment. 5 additional patients were referred to our centre specifically for the AMORE protocol as the primary local treatment. 4 of them were included and 1 was considered not feasible. The results of all 20 patients treated according to the AMORE protocol are reported.

Patient characteristics of the 20 patients are depicted in Table 1. The male-to-female ratio was 1.2:1. The median age at diagnosis of RMS was 4.6 years (range 0.5–12.4 years) and the median age at the time of AMORE treatment was 5.1 years (range 1.2–12.9 years). In most cases, the disease was locally advanced (Table 1). 5 patients (25%) initially had involved regional lymph nodes and 1

Table 1
Patient characteristics

Patient	Gender	Age (years)[a]	Site	TNM stage	SIOP stage	Histology	Follow-up[b]	Status	Event
			Parameningeal						
1	F	6.2	Pterygoid fossa	T2bN0M1	IV	embryonal	10.3	NED	
2	M	7.6	Pterygoid fossa	T2bN0M0	II	embryonal	*3.8*	D	LR
3	M	5.5	Pterygoid fossa	T2bN0M0	II	embryonal	*0.7*	D	DM
4	M	4.3	Nasopharynx	T2bN1M0	III	embryonal	*1.1*	D	LR
5	F	2.9	Pterygoid fossa	T2bN0M0	II	embryonal	*1.8*	D	LR
6	M	9.2	Pterygoid fossa	T2bN0M0	II	embryonal	7.5	NED	SP
7	M	2.9	Pterygoid fossa	T2bN1M0	III	embryonal	7.4	NED	
8	M	5.4	Pterygoid fossa	T2aN0M0	II	embryonal	6.6	NED	
9	F	1.7	Paranasal sinus	T2aN0M0	II	embryonal	6.0	NED	
10	F	11.0	Pterygoid fossa	T2bN0M0	II	embryonal	2.9	AWD	LR
11	M	2.2	Nasopharynx	T2aN0M0	II	embryonal	2.3	NED	
12	F	2.6	Maxillary sinus	T2bN0M0	II	embryonal	1.7	NED	
13	M	2.3	Nose/nasopharynx	T2bN0M0	II	embryonal	1.4	NED	
14	F	12.9	Temporal fossa	T2bN0M0	II	alveolar	1.1	NED	
15	F	4.8	Infratemporal fossa	T2bN0M0	II	embryonal	1.1	NED	
			Non-parameningeal						
16	M	3.8	Parotid region	T2bN1M0	III	embryonal	10.1	NED	
17	M	7.4	Buccal region	T1bN1M0	III	pleomorphic	*2.0*	D	LR
18	F	5.6	Buccal region	T2bN0M0	II	embryonal	9.2	NED	
19	F	1.2	Oral cavity	T2aN1M0	III	alveolar	8.7	NED	
20	M	6.3	Parotid region	T2aNxM0	II	embryonal	1.9	NED	

NED, no evidence of disease; D, deceased; AWD, alive with disease; LR, local recurrence; DM, distant metastases; SP, second primary tumour; M, male; F, female; SIOP, International Society of Paediatric Oncology; AMORE, see Methods for description.
[a] At time of the AMORE protocol.
[b] Years after diagnosis.

patient had a single pulmonary metastasis at diagnosis which disappeared after chemotherapy. In 15 patients, the RMS had a parameningeal localisation, 5 were non-parameningeal. 4 patients where at high-risk for meningeal seeding: skull base erosion was found in 2 patients, intracranial extension in 1 and facial nerve palsy in 1 patient. None of the patients had tumour cells in the CSF. In 2 of the non-parameningeal cases located at the parotid region, a facial nerve palsy was noted. Bone erosion at sites other than the skull base was found in 12 patients. This mainly involved the mandible, walls of the nasal cavity and paranasal sinuses, zygoma, pterygoid process and orbit.

Systemic treatment consisted of the SIOP protocol for malignant mesenchymal tumours MMT 89 ($n=10$) and MMT 95 ($n=8$). In 2 cases, the German Cooperativen Weichteil-Sarkom-Studie (CWS) 91 and Pediatric Oncology Group (POG) D9803 protocols were applied, respectively. A total of 7–8 courses of conventional multiagent chemotherapy was given prior to the AMORE protocol. 5 of the 15 parameningeal cases received 1–2 additional chemotherapeutic courses after completing the AMORE treatment.

In all 20 patients, complete macroscopic resection of the residual tumour could be achieved. Additional bone resection was performed in 9 cases, including dental elements in 5 patients. Treatment data are depicted in Table 2. Supraomohyoidal or modified radical neck dissection was performed in 12 cases as a part of the approach to the tumour. Surgical nerve lesions occurred in 5 patients. The facial nerve was affected in 4 cases (Table 2). Complete wound bed coverage by the moulage and adequate catheter positioning for brachytherapy was achieved in 19 patients. In 1 patient, an additional moulage had to be implanted due to an inadequate dose at one of the margins. The median brachytherapy dose and dose rate were 42.5 Gy (40–50 Gy) and 68 cGy/h (49–117 cGy/h), respectively. Surgical reconstruction consisted of free tissue transfer in 12 and a pedicled flap in 5 patients (Table 2). Reconstruction was not necessary in three cases. In two of them, the tumour was located in the nasal cavity/nasopharynx and in 1 patient uneventful primary closure of the parotid region was likely. Histopathological analysis of the resected specimen revealed vital tumour in 14 and no vital tumour cells in 6 cases.

In general, morbidity was low and recovery was quick, reflected by a median duration of hospital admission of 17 days (range 11–35 days). No mucositis or skin reactions were observed. Short-term complications were noted in 4 patients. 3 patients suffered from a wound infection needing intravenous (i.v.) antibiotic treatment. Ischaemia of the muscle transplant with subsequent removal occurred in 1 patient. There was no morbidity at the donor site of the graft. Long-term sequelae of varying severity were noted in 10 patients (Table 2).

The median follow-up time after AMORE treatment of the surviving patients is 5.6 years (range 0.6–9.8

Table 2
Treatment data

Patient	Surgery		Brachytherapy		Reconstruction	Vital tumour (±)	Long-term sequelae	
	Bone resection (±)	Lymph node resection (±)	Dose (Gy)	Dose rate (cGy/h)			Surgical	Other
1	+	+	40	90	LD	+	Partial VII palsy	Malocclusion, atrophy muscle flap
2	+	+	50	55	LD	+		
3	–	+	50	70	STCM	+		
4	–	+	50	60	LD	+		
5	–	+	50	49	STCM	+		
6	–	+	50	80	STCM	+	Lesion n IX	Rhinolalia aperta
7	–	+	45	117	LD	–	VII palsy	articulation disorders, recurrent external otitis
8	–	+	50	60	LDP	+		
9	+	–	45	50	–	+		Epiphora
10	–	–	40	80	LD	+		Malocclusion, conductive hearing loss
11	+	–	40	100	RA	–		Epiphora, dental problems
12	+	–	40	66	RA	+		
13	+	–	40	100	–	+		
14	–	–	40	75	GRF	–		
15	+	–	40	80	RA	+		Trismus
16	–	+	46	80	–	–		Dental/occlusional problems
17	–	+	40	50	LD	+		
18	+	+	40	60	LD	–	VII palsy	Malocclusion
19	+	+	45	54	LD	+	Flap ischaemia lesion n XI, infraorbital nerve	Craniofacial asymmetry, velopharyngeal insufficiency, swallowing disorders
20	–	–	40	60	GRM	–	VII palsy	(pre-existent partial VII palsy)

LD, latissimus dorsi-free muscle flap; LDP, latissimus dorsi pedicled muscle flap; STCM transposition sternocleidomastoid muscle; RA, rectus abdominis-free muscle flap; GRF, galea rotation flap; GRM, gracilis-free muscle flap.

years). 6 patients have relapsed, 5 local and 1 distant. Two out of five local relapses occurred within the radiation field. The other three local relapses were situated beyond the radiation field. Salvage treatment consisted of second-line chemotherapy and local treatment, if feasible. 5 patients died of disease. One of the non-recurrent patients developed a second primary malignancy, a muco-epidermoid carcinoma of the contralateral parotid gland. For the whole population of 20 HNRMS patients, the 5 year EFS is 64.1% (standard error (S.E.) 0.12), with an overall survival of 67.5% (S.E. 0.12). For the parameningeal cases, the 5-year EFS is 60.0% (S.E. 0.14), with an OS of 64.2% (S.E. 0.15) (Fig. 3).

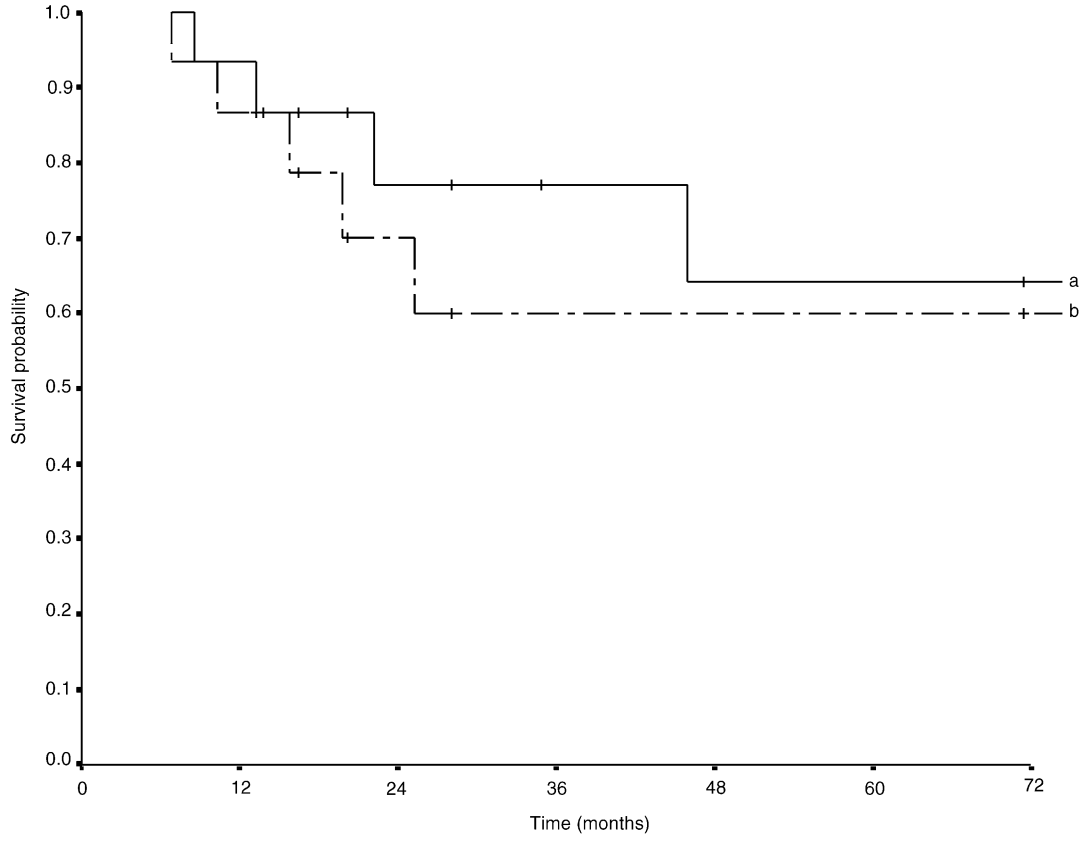
4. Discussion

4.1. Current practice

In the head and neck region, the ability to achieve a primary complete resection at diagnosis (Clinical Group I by IRS nomenclature) is estimated to be 0.5–7% at parameningeal sites and 10% at non-parameningeal sites [6,13]. Half of the non-parameningeal and up to 94% of the parameningeal RMS cases present in clinical group III [5,13]. Multidrug chemotherapy is the mainstay of current strategies, providing tumour shrinkage and control of (micro)metastases. New drug combinations and intensified regimens are reported to be increasingly beneficial [17]. Definitive local treatment, however, remains of vital importance. Although new (cranial-based) surgical techniques in the head and neck region can allow for an increased possibility of secondary resection of residual masses, the 'standard of care' in most protocols consists of EBRT [7,18]. However, differences exist in the timing, treatment volume, total dose and fractionation schemes [6,19]. Brachytherapy is not routinely applied, although several studies report favourable results and limited sequelae in the treatment of soft-tissue sarcomas [20,21].

4.2. The AMORE protocol

The aim of the ablative surgery is to perform conservative surgery, minimising morbidity at the site of surgery, at the expense of possible microscopical remnants at the margins. Thus, the tumour is converted, in the worst-case scenario, to microscopic residual disease which makes it suitable for brachytherapy. Starting brachytherapy directly after surgery ensures minimal tumour-cell proliferation and maximal oxygenation of



Patients in Follow-up	15	14	9	7	6	6	5
Cumulative Deaths (a)	0	1	3	3	4	4	4
Cumulative Events (b)	0	2	4	5	5	5	5

Fig. 3. Kaplan–Meier survival analysis plots for patients with parameningeal rhabdomyosarcoma ($n = 15$). Both overall survival (OS) (a) and event-free survival (EFS) (b) are shown. Numbers of patients at risk, cumulative events and cumulative deaths are given at 12-monthly intervals.

tumour cells, thereby presumably increasing radiosensitivity. The advantages of brachytherapy over EBRT include a reduction in the treatment time and a focused dose delivery to the tumour bed and rapid fall-off of the dose beyond the treatment volume. Sparing of the surrounding tissues and skin reduces morbidity, allowing organ preservation and bone growth, and improves the functional and cosmetic outcome [20]. However, this small dose depth makes the technique suitable for microscopic residual disease only. The physical properties of the moulage carry some advantages. Firstly, collapse of the wound is avoided, resulting in adequate exposition of the margins. Secondly, the moulage allows for equal isodose curves. Doses of 40–50 Gy were given without impaired wound healing, wound dehiscence or skin reaction. The tissue reaction to gutta percha was limited. Disadvantages of low-dose rate (LDR) brachytherapy are the treatment is in isolation and the practical problems of nursing and visiting. Current improvements of the technique are the development of three-dimensional treatment planning and pulse-dose rate (PDR) schemes.

Surgical reconstruction of the wound bed serves the following purposes: primary wound healing, decreased wound tension (and subsequent compromised circulation), protection of vital structures, prevention of communications between the upper aero-digestive tract and intracranial space, obliteration of dead spaces and restoration of function and contour. The transfer of non-irradiated, well-vascularised tissue to the irradiated wound bed increases oxygenation, improves wound healing and introduces polymorphonuclear leucocytes, enhancing antibacterial activity [22,23]. The latter can explain the limited wound complications encountered. All flaps except one survived. In 1 case, considerable atrophy occurred, needing secondary surgical intervention. A disadvantage of tissue transfer into the former tumour area could be that problems may be encoutered in interpreting future radiological studies with respect to the assessment of recurrent disease. A routine 'baseline scan' is therefore made 6 weeks after the AMORE protocol.

4.3. Outcome in head and neck rhabdomyosarcoma

Outcome of patients with HNRMS is either reported in several single institution studies or as a part of large

multicentre trials. Differences in staging, definition of endpoints and distribution of location and stages within groups make comparisons difficult. In general, specific head and neck studies report an overall survival (OS) of 55–83% [24]. In the parameningeal subsite, an OS of 39–74% has been reported [6,13]. The IRS III study reports a 3-year failure-free survival (FFS) of 70% for both non-parameningeal and parameningeal HNRMS, all stages included, and a FFS of 53% for patients with gross residual tumour (clinical group III) after initial surgery [1,17]. The latest IRS study (IRS IV) reports a 72% 3-year FFS for parameningeal HNRMS and 90% for the patients with primary irresectable non-parameningeal head and neck tumours [17]. Pooled analysis of the IRS studies II through IV shows an estimated 5-year FFS of 67% for patients with parameningeal sarcoma [13]. In European studies, the EFS is lower, but OS is comparable. The SIOP MMT 84 study reports 5-year EFS rates of 35% for non-parameningeal and 42% for parameningeal HNRMS. The overall survival is 77 and 58%, respectively [2]. Relapse rates of 20–30% are reported in children with non-orbital HNRMS, parameningeal disease representing the topend of the relapses reported [6,13]. In general, 95% of the relapses occur within 3 years, with a median time to relapse of 1.1 year (range, 1 week–9 years) [25]. In cases of relapse, local recurrences are involved in 55–85% in non-orbital HNRMS, and the CNS is involved in 30–40% of the recurrent parameningeal cases [5,6,13,24]. Survival after relapse is extremely poor, reported between 0 and 35% [6,24]. Pooled data of IRS II–IV show a 25% long-term survival rate in cases of pure local relapse after parameningeal RMS [13].

The outcome of patients in this study has to be interpreted considering the site, size and stage of the disease. Except for 1 patient, all patients were staged as T2. All were IRS group III, intermediate risk category. In 15 cases, the tumour measured 5 cm or more in the largest diameter at diagnosis. 15 patients had parameningeal RMS. The most common subsite (Table 1), was the pterygoid fossa, that is associated with an unfavourable outcome [13]. However, most patients had a low probability for meningeal involvement. The number of patients is limited, but the 60% EFS compares well with the results reported in the literature. However, a comparison of our series, consisting of a selected group of patients, with other studies has to be done with caution. As might be expected, most failures occurred at parameningeal sites (Table 1). The relapse was local in 5 cases and distant (CNS) in 1. The site of local relapse was skull base ($n=3$), mastoid tip ($n=1$) and maxillary sinus ($n=1$). In 3 of the 5 patients, there was extensive bone erosion at diagnosis. Bone erosion is estimated to be associated with a higher risk of local failure [26]. Whether the dose depth provided with brachytherapy can adequately cover erosion of bony boundaries remains a topic of discussion. However, no meningeal failure has been observed. Histopathological analysis revealed no vital tumour cells in 6 cases. All 6 cases are currently without evidence of disease. Analysis of resection specimens can be difficult and may not always be accurate. Two studies report a 40–50% incidence of relapse in patients who underwent second-look surgery and had negative reports of histopathological analysis [27,28]. Analysis of the neck dissection did not reveal positive nodes in any of the patients. This finding is consistent with the general opinion of a low-risk of nodal failure [29]. Prophylactic neck dissection is not recommended by the SIOP protocol, but the node dissections performed in the 12 patients of this study was performed as a part of the approach of the tumour and/or exposure of the vessels for the anastomoses of the free flap.

4.4. Sequelae

Although the AMORE protocol aims at performing minimally mutilating surgery, in certain cases major nerves had to be sacrificed. This resulted in the important surgical sequela of partial facial nerve palsy in 2 out of 15 parameningeal and 2 out of 5 non-parameningeal cases. Acute toxicity related to brachytherapy was limited. The three wound infections could be treated with antibiotics alone. EBRT is often considered to be the major contributor in the development of late sequelae after treatment for HNRMS. Radiotherapeutic strategies to improve local control and reduce sequelae include three dimensional treatment planning and alterations in dose and fractionation [12,19,30]. In our group, important sequelae of EBRT, like severe fibrosis, xerostomia and radionecrosis, did not occur. Only 1 patient in this series developed a severe trismus. One of the most disturbing consequences of EBRT is the considerable craniofacial asymmetry. To date, 19 out of 20 patients have no clinical signs of craniofacial asymmetry. This sequela was experienced in only 1 patient, probably due to resection of an important part of the hard palate and maxilla. Currently, quantification of craniofacial growth is assessed using CT-derived measurements. Other consequences were malocclusion, articulation and swallowing disorders, but in all patients oral feeding and normal speech development was possible. Nasolacrimal duct disorders could be treated effectively by the ophthalmologist. Reconstructive surgery was needed in 2 patients for restoring the palatal defect and cosmetic appearance due to atrophy of the muscle flap, respectively. To date, the late sequelae were acceptable and could be managed adequately in most patients. However, as the length of the follow-up time in a substantial amount of the patients is insufficient, definitive conclusions regarding late effects cannot be made at this time.

5. Summary and conclusions

After a median follow-up duration of 5.6 years, a 5-year EFS of 64% has been reached in 20 patients with advanced HNRMS and of 60% in the parameningeal cases by application of the AMORE protocol. The procedure proved to be feasible for 76% of the patients with advanced stage non-orbital HNRMS in our single-centre series. To date, the long-term sequelae of EBRT were avoided in most patients. We believe the AMORE protocol should be considered as an alternative local treatment in HNRMS.

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