Paediatric Head and Neck Rhabdomyosarcoma

Marinka L.F. Hol

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The cover of this thesis was painted by Aya Smeele, drawing inspiration from numerous patient photographs shared with explicit permission. Nevertheless, the completed artwork portrays a fictional patient.

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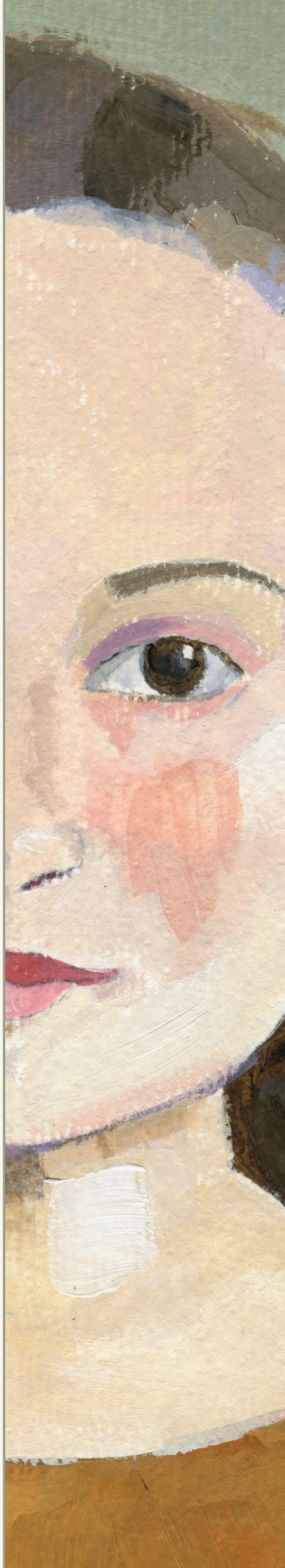

RHABDOMYOSARCOMA

Epidemiology

Rhabdomyosarcoma is an aggressive malignant tumour and, although rare, is the most common soft tissue sarcoma in children. Rhabdomyosarcomas account for 4-5% of all malignancies in patients under the age of 18 years (1). Currently, across Europe, 400 new patients are diagnosed yearly, corresponding to an annual incidence of four per million people aged 0-19 years (2). Rhabdomyosarcoma typically occurs in young children with a median age of diagnosis of five years and 72-81% of patients diagnosed before the age of 10 years (3). The incidence of rhabdomyosarcoma is slightly higher in boys, by a 1.4 ratio (4). Rhabdomyosarcomas can arise anywhere in the body. However, they most often occur in the head and neck area, the genitourinary tract, and the extremities. Approximately 40% of rhabdomyosarcomas occur in the head and neck area, which is further subdivided into three sites, namely, the orbit, parameningeal site, and non-parameningeal site (1,4,5).

Clinical presentation

As rhabdomyosarcomas may occur nearly anywhere in the body, symptoms mostly depend on tumour location. In general, tumours are painless, and often, the initial symptoms manifest similarly to those of more common and relatively innocent diseases. For example, symptoms in the head and neck area can mimic upper respiratory tract infections and allergies. Consequently, a suspected infection is reported as the initial diagnosis in up to 50% of patients. As a result, the average time from the start of clinical symptoms until the initial diagnosis of rhabdomyosarcoma ranges from 2-4 months. Ultimately, the relatively long duration of clinical symptoms and/or an increase in severity should alert the treating physician to the possibility of a malignancy. In cohorts describing head and neck rhabdomyosarcoma patients, clinical symptoms largely depend on anatomical localization. Symptoms such as facial swelling, trismus, hoarseness, dysphagia, pain, nasal obstruction, nasal discharge, recurrent epistaxis, otitis media with hearing loss, otalgia, otorrhea, epiphora, vision loss, and proptosis are reported. Skull base extension may cause neurological symptoms such as nerve deficits (predominantly in the cranial nerves, i.e., the facial nerve, trigeminal nerve, and abducens nerve). In general, rhabdomyosarcoma is locally aggressive and typically manifests as a mass or presents signs caused by the bulk effect of the growing mass on the surrounding structures.

Regional lymph node involvement is relatively limited in rhabdomyosarcoma and presents in only approximately 17% of patients. Furthermore, it is even rarer in the head and neck site, presenting in approximately nine percent of patients (1,6). In embryonal rhabdomyosarcoma, nodal involvement is more frequent compared

to alveolar rhabdomyosarcoma in the head and neck area as opposed to other sites such as the extremities (7). In embryonal head and neck rhabdomyosarcoma patients regional lymph node involvement varies between the different sites, with only 0.6% of patients with orbital tumours presenting with regional lymph node involvement as opposed to 17% in non-parameningeal head and neck patients and 19%in patients with a tumour in a parameningeal site (7). Radiologically or clinically evident distant metastatic disease is present in around 20% of children at diagnosis (8). In the case of metastatic disease, symptoms may be related to the organs involved, most often the lungs, bone, and bone marrow (8).

Etiology

The etiology of rhabdomyosarcoma is still unclear. Most commonly, the myogenic progenitor cell is included in the etiological explanation as rhabdomyosarcomas have a myogenic phenotype (9). Tumour cells show morphologically various degrees of skeletal muscle differentiation, ranging from immature round cells to fully differentiated muscle fibres and all intermediate rhabdomyoblast stages. Tumourgenesis is believed to arise from interrupted normal skeletal muscle development. Rhabdomyosarcoma mainly occurs as a sporadic disease. Only in five percent of patients rhabdomyosarcoma is associated with tumour predisposing germ line aberrations such as Li-Fraumeni-, Noonan-, Beckwith Wiedemann-, Costello-, and DICER1 syndrome, and neurofibromatosis type 1 (8,9). Apart from prenatal exposure to ionizing radiation, exposure to alkylating agents, and parental recreational drug use, an association with environmental factors is lacking for rhabdomyosarcoma (8,10).

Histopathology

Rhabdomyosarcoma is a paediatric small blue round cell tumour. Other tumours in the “small blue round cell” group include lymphoma, small cell osteosarcoma, chondrosarcoma, Ewing sarcoma, and neuroblastoma. Immunohistochemistry is used to establish the final diagnosis. Rhabdomyosarcoma is positive for myogenin, demin, sarcomeric actin, and myoglobin and often negative for CD99, CD45, CK, S100, NSE, and NKX2.2. Depending on the degree of differentiation, tumour cells vary from primitive round cells to multinucleated muscle fibres with longitudinal and transverse structures. Consequently, it is postulated that RMS derives from primitive mesenchyme cells, exhibiting a profound tendency for myogenesis. Myogenic tumours are classified into four categories by the WHO: (i) embryonal; (ii) alveolar; (iii) pleomorphic and (iv) sclerosing/spindle cell (11). Embryonal and alveolar subtypes are the most common subtypes accounting for 70% and 20% of cases respectively. When looking at gene expression PAX3/7-FOXO1 fusion-positive and fusion-negative tumours are classified as they determine prognosis. The majority, around 80%, of alveolar rhabdomyosarcomas tend to be fusion positive whereas embryonal rhabdomyosarcoma is fusion negative. PAX3/7-FOXO1 fusion-positive

tumours have a higher propensity for metastases and consequently a negative impact on survival (12). Typically, rhabdomyosarcomas of the embryonal subtype occur in younger patients. MYOD1 fusion proteins can also occur in embryonal tumours in general predicting poor prognosis. Alveolar rhabdomyosarcomas typically exhibit rhabdomyoblasts in interseptal nests and small round blue cells. Histochemically, there is diffuse strong staining for myogenin and staining with desmin and MyoD1. Alveolar rhabdomyosarcoma mostly affects older children with a median age at diagnosis of 15 years. Spindle cell rhabdomyosarcoma, or sclerosing rhabdomyosarcoma, accounts for the remaining five percent of tumours and affects children of all ages. Spindle cell rhabdomyosarcoma is driven by fusion genes in young children (VGLL2, NCOA2) and consequently has a good prognosis in general. Spindle cell rhabdomyosarcoma in older children is commonly caused by mutations in MYOD1 and has a poorer prognosis. Spindle cell rhabdomyosarcoma occurring intraosseous, particularly in the craniofacial bones is found to be defined by the EWSR1/FUS-TFCP2 or MEIS1-NCOA2 fusion and is associated with poor prognosis owing to the regional and distant spread (13).

Risk stratification

Following the histologic and molecular diagnosis of rhabdomyosarcoma, staging is important to allow for proper risk stratification and resulting risk-stratified treatment. Even though both the Childhood Oncology Group (COG) protocols and the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG) protocols use the same prognostic factors there are differences in weighting these factors into the different risk stratifications. The following factors are taken into account: tumour site, tumour size, PAX-FOXO-1 fusion status, patient age, nodal involvement, metastatic disease, and Intergroup Rhabdomyosarcoma Studies (IRS) Post-Surgical Group staging (see the overview included in Table 1) (14,15). Intergroup Rhabdomyosarcoma Studies Post-Surgical Group staging identifies four groups, as shown in Table 1, based on whether a tumour is removed: Group I, where the tumour can completely be removed with surgery. Group II, in which the tumour was removed but there is microscopic residual disease, or there are positive regional lymph nodes. Group III, in which the tumour cannot be removed with surgery and there is gross residual disease. and finally, Group IV for patients in whom there are distant metastases.

In the European studies favourable head and neck rhabdomyosarcomas are localized tumours within the orbit or the non-parameningeal site, tumours smaller than five centimetres, and those with negative fusion status in patients <10 years of age. Consequently, parameningeal site, size over five centimetres, positive PAX-FOXO1 fusion status, age >10 years, and regional or metastatic disease spread are adverse prognostic factors. Regional lymph node status, local spread, bone marrow involvement, and distant metastases are assessed with FDG-PET/CT or PET/MRI. In case of suspected lymph node involvement, this should be histologically confirmed (16).

Table 1. Intergroup Rhabdomyosarcoma Study Clinical Group Classification System

Group	Definition
IRS group 1	Localized disease, completely resected
IRS group 2	Total gross resection with evidence of regional spread
A	Microscopic residual disease, regional lymph nodes not involved
B	Involved regional lymph nodes completely resected with no microscopic residual disease
C	Involved regional nodes and regional disease grossly resected with microscopic residual disease in most distal node
IRS group 3	Biopsy only or incomplete resection with gross residual disease
IRS group 4	Distant metastatic disease present at onset (excluding regional nodes and adjacent organ infiltration)

* Adapted from Crane et al. (15).

In the EpSSG protocols patients are stratified into four different risk groups using the aforementioned criteria as shown in Table 2. In Europe, these are referred to as low risk, standard risk, high risk, and very high risk. It is important to note that these risk stratifications changed for the Far-RMS study with the inclusion of fusion status as a prognostic marker. It is important to note that patients presented in this dissertation are all treated according to the previous EpSSG studies and consequently treated accorded to previous risk stratification protocols, not including fusion state.

Table 2. Risk stratification in the European FaR-RMS study

Risk Group	Subgroup	Fusion Status	IRS Group	Site	Node Stage	Size or Age
Low Risk	A	Negative	I	Any	N0	Both Favourable
Standard Risk	B	Negative	I	Any	N0	One or both Unfavourable
	C	Negative	II, III	Favourable	N0	Any
High Risk	D	Negative	II, III	Unfavourable	N0	Any
	E	Negative	II, III	Any	N1	Any
	F	Positive	I, II, III	Any	N0	Any
Very High Risk	G	Positive	II, III	Any	N1	Any
	H	Any	IV	Any	Any	Any

Fusion status. When fusion gene status is unavailable histopathology will be used. Non-alveolar disease should be defined as fusion gene negative and alveolar disease should be defined as fusion gene positive. **Site.** Favourable sites: GU including bladder-prostate, head & neck non-parameningeal, orbit and biliary primaries. Unfavourable: all other sites. **Node stage.** N0 = 0 positive lymph nodes, N1= ≥ 1 positive lymph nodes **Age.** Favourable is defined as age over 1 and under 10 years at diagnosis **Size**. Favourable primary tumour is ≤ 5 cm in longest diameter, patients that are assessed as not evaluable, will be included in > 5 cm group). **IRS Group**. See Table 1.
*Adapted from Study protocol FaR-RMS (NCT04625907).

In the North American protocols, patients are stratified according to the Childhood Oncology Group protocols. The risk stratification used in those protocols is presented in Table 3 and Table 4. The risk stratification in Table 4 also categorises patients into low, intermediate, and high-risk groups.

Table 3. Updated COG pre-treatment stage definition

Stage	Site	Size	N	M
1	Orbit head, and neck (excluding parameningeal) GU-non-bladder/non-prostate	any	N0 or N1 or Nx	M0
2	Parameningeal Bladder/prostate Extremity Other (incl trunk, retroperitoneum)	5cm in longest diameter	N0 or Nx	M0
3	Parameningeal Bladder/prostate Extremity Other (incl trunk, retroperitoneum)	5cm in longest diameter	N1	M0
		>5cm in longest diameter	N0 or N1 or Nx	M0
4	All	any	N0, N or Nx	M1

Regional Nodes: N0: regional nodes not clinically involved, N1: regional nodes clinically involved as defined as 1cm measured in short axis on CT or MRI, Nx: clinical status of regional nodes unknown (especially sites that preclude lymph node evaluation). Metastases: M0; no distant metastases, M1 distant metastases present. Note; the presence of positive cytology in pleural fluid, abdominal fluid, or CSF are considered evidence of metastases.
*Adapted from Crane et al. (15).

Table 4. Risk stratification and treatment in the COG studies

Risk group	Stage	Clinical group	Age	Fusion status
Low	1	I, II, III (orbit only)	Any	*FOXO1*-
	2	I, II		
Intermediate	1	III (non-orbit)	Any	*FOXO1*-
	1, 2, 3	I, II, III	Any	*FOXO1*+
	2, 3	III	Any	*FOXO1*-
	3	I, II	Any	*FOXO1*-
	4	IV	<10 years	*FOXO1*-
High	4	IV	≥10 years	*FOXO1*-
			Any	*FOXO1*+

Stage as presented in Table 3, Clinical Group as presented in Table 1.
*Adapted from Crane et al. (15).

Treatment

Treatment for rhabdomyosarcoma is multimodal, including chemotherapy combined with radiotherapy, surgery, or both. Local treatment alone is rarely curative due to micro metastasis, and early studies adding systemic treatment to local treatment improved survival from 10-30% to over 70% (9). With rhabdomyosarcoma being a rare disease, most children are treated within clinical trials. There are two distinct treatment regimens with many similarities but some distinct differences. The North American treatments have been defined by the Children's Oncology Group ("COG") (previously the Intergroup Rhabdomyosarcoma Study Group (IRS)) The European treatment regimens are led by the European paediatric Soft tissue sarcoma Study Group (EpSSG). Currently, both groups use slightly different risk stratification as well as differ in treatment, hampering easy comparison (9). There is consensus on the backbone of treatment of rhabdomyosarcoma consisting of multidrug chemotherapy and local treatment, however, there are some important differences. In terms of the chemotherapy approaches, the main difference between EpSSG and COG treatment regimens is the use of Cyclophosphamide in North America as opposed to Ifosfamide in Europe as an alkylating agent (17). Both agents are equally effective in tumour treatment but have different adverse effect profiles. Ifosfamide may lead to long-term tubulopathy resulting in Fanconi syndrome, and it may induce neurotoxicity Meanwhile, Cyclophosphamide might cause leukopenia and male infertility (18,19). Both treatment regimens use Ifosfamide and Vincristine. Both Europe and North America aim for the highest survival rates while maintaining quality of life and reducing late adverse effects. More conformal radiation techniques are used in Europe and North America to mitigate late adverse effects. Localization in the head and neck area very rarely allows for complete initial resection at diagnosis without causing major morbidity. The European treatment regimens utilize primary surgical resection more often, albeit in specific scenarios. Systemic multi-agent chemotherapy treatment is given to achieve local control and reduce the risk of distant metastasis. After 3-4 cycles of neoadjuvant multi-agent chemotherapy, local treatment is applied; surgery and/or radiotherapy. To plan for local therapy an MRI is performed after three cycles of chemotherapy. The possibility of delayed primary resection is henceforth contemplated. When a tumour is resectable with the preservation of organ function, an initial complete resection may be performed. However, in the head and neck area, complete resection is rarely possible with organ preservation. Consequently, the majority of patients are treated with radiotherapy. Excision after chemotherapy does generally not obliviate the need for radiotherapy, although it may allow for a lower dosage of radiotherapy (1,5). The only patients in whom radiotherapy might be omitted are those with localized, low-risk, fusion-negative tumours in whom a complete resection with margins (R0) is possible.

LOCAL TREATMENT OPTIONS FOR HEAD AND NECK RHABDOMYOSARCOMA

As previously described, local treatment in addition to systemic treatment is necessary to cure rhabdomyosarcoma. Local control depends on ionizing radiation, surgical resection, or a combination of both.

Radiotherapy

Ionizing radiation is called 'ionizing' as it forms ions and deposits energy in cells and tissues it passes through (20). The energy deposited causes cell death through two different pathways. The first is direct, as radiation causes changes in the DNA (single-strand breakage), which subsequently results in cell death. The second is indirect, as free radicals resulting from radiation cause DNA damage (double-strand breakage), also leading to cell death. Ionizing radiation does not kill cells right away. However, cells start to die after a couple of days to weeks, and continue to die weeks to months after the end of treatment (20,21).

The downside of radiation therapy is that it affects all cells the radiation passes through and consequently damages both healthy and cancer cells. Therefore, radiotherapy delivery techniques aim to administer high doses to the tumour and limit radiation to the adjacent organs, making treatment more conformal. In general, there are two main delivery techniques for ionizing radiotherapy. The most used technique is called External Beam Radiotherapy ("EBRT"), which is delivered from outside the body by aiming a beam of ionizing radiation at the tumour. External beam radiotherapy can use photons (XRT), protons (PT), or particles. Brachytherapy, or internal radiation therapy, is administered from inside the body by placing radioactive sources in the tumour area with catheters or seeds. Both photons and protons are used for EBRT in rhabdomyosarcoma. From a physics standpoint, photons and protons differ in that photons are essentially electromagnetic bundles of energy and are weightless, whereas protons are positively charged subatomic particles. The advantage of protons is the pronounced peak of ionizing radiation (also known as the Bragg peak), resulting in often a more favourable dose distribution (21). For example, the integral radiation dose is potentially reduced by 3.5 times when using proton therapy compared to conventional radiation in orbital rhabdomyosarcoma (19). This consequently limits radiation dose to important surrounding structures. An example of two treatment plans is shown in Figure 1.

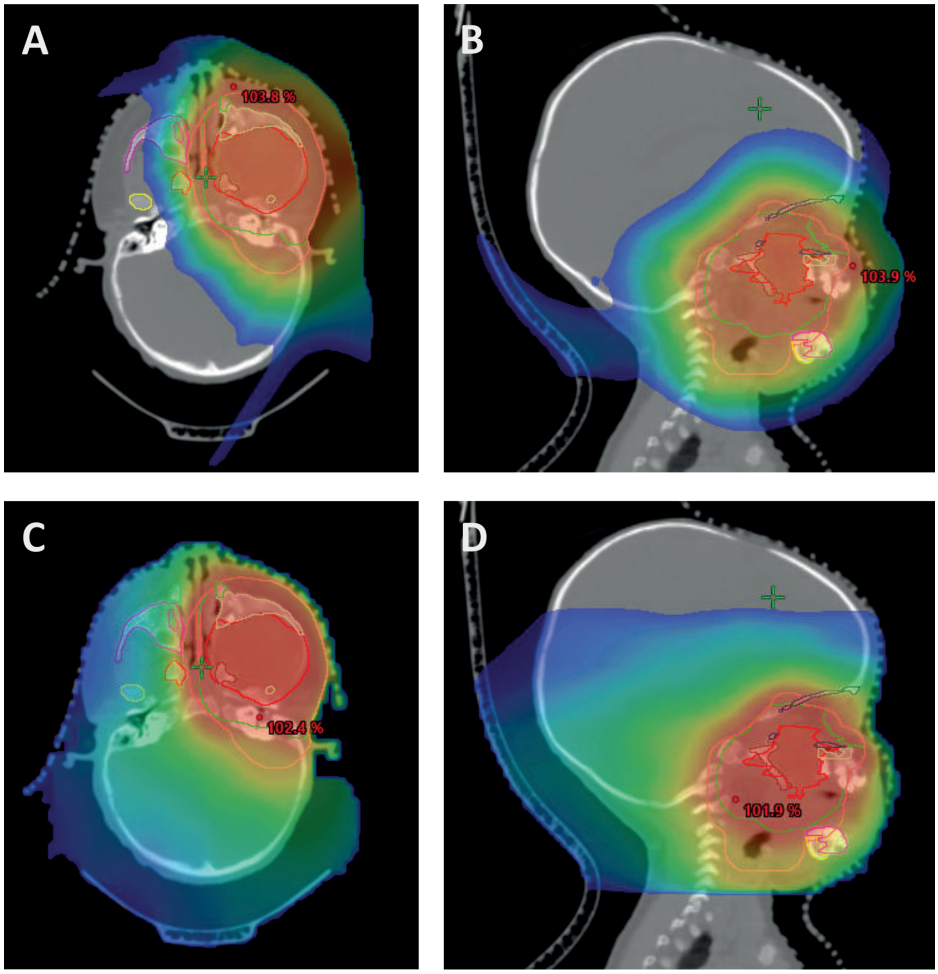

Figure 1. Dose distribution comparison between a photon and proton treatment plan for a patient with a rhabdomyosarcoma in the right mandible.

A and B show the dose distribution for a proton radiotherapy plan using Pencil Beam Scanning. C and D show the dose distribution for a photon radiation plan using volumetric arc.
* Adapted from the work of dr. Davies et al. as presented in 2023 at the 55th annual conference of the International Society for Paediatric Oncology (SIOP) 2023 (61).

In addition to the use of protons, advanced EBRT techniques, such as Intensity-Modulated Radiotherapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT), as well as Magnetic Resonance image-Guided Radiotherapy (MRgRT) or pencil beam scanning Intensity-Modulated Proton Therapy (IMPT), can provide a dose reduction to the surrounding normal structures while still respecting the target volume (4,22).

Brachytherapy in head and neck rhabdomyosarcoma is mainly used through the 'AMORE' technique. AMORE is an acronym for Ablative surgery, MOuld brachytherapy, and REconstructive surgery. AMORE was initially developed in the early 1990s in the Netherlands to limit radiation to healthy surrounding tissue (23,24). With AMORE treatment, the tumour is surgically removed on day-one aiming for a macroscopic radical resection, potentially leaving microscopic residual disease (R1 resection). Within the same procedure, a mould containing polyethylene brachytherapy catheters is implanted. Using the mould, or sometimes interstitial brachytherapy wires radiation is administered for about three days using afterloading brachytherapy with Irridium. This radiation was first administered using low-dose-rate brachytherapy regimens and later with pulsed-dose-rate brachytherapy (23). In the days following completion of brachytherapy, a second procedure in which the mould is removed and reconstructive surgery is performed. Figure 2 below shows images of the initial surgery, the mould with brachytherapy catheters, and the procedure on day seven, encompassing the removal of the mould and reconstruction. In Figure 3 a dose comparison between AMORE and XRT is shown for an orbital rhabdomyosarcoma patient. Chapter 6 of this dissertation further describes the surgical methods used in AMORE.

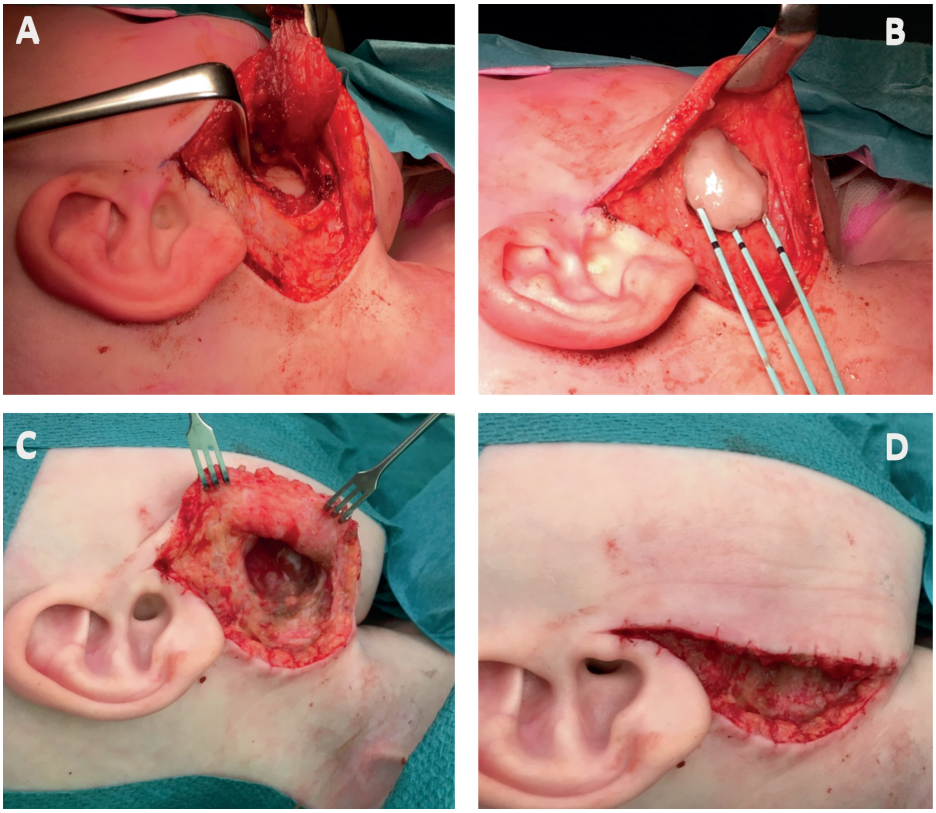

Figure 2. Patient treated with AMORE – Ablative surgery, MOuld afterloading brachytherapy and REconstructive surgery.

A patient presenting with a tumour in a non-parameningeal site, in the right superficial parotid region extending to the mandible. The first image (A) shows the ablative surgery with the tumour before it's taken out, on the second image (B) the mould for brachytherapy is shown, image C shows the tumour bed after removal of the mould and the last image (D) shows the situation at the end of treatment.

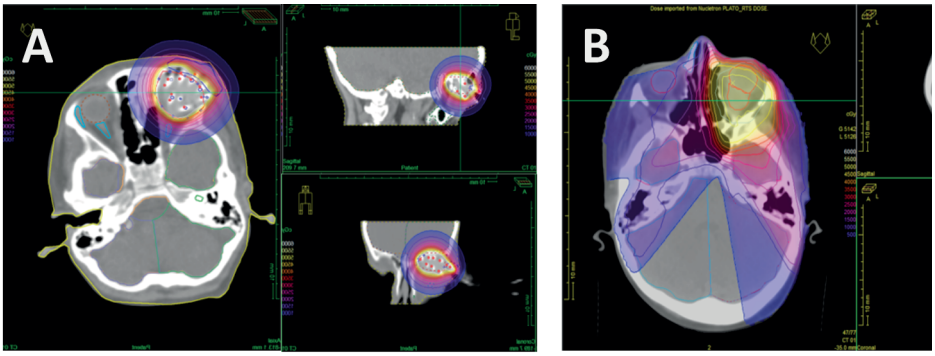

Figure 3. Dose comparison between AMORE and EBRT with photons for an orbital rhabdomyosarcoma patient.

The first image (A) shows the treatment plan for a patient with a rhabdomyosarcoma in the left orbit. The second image (B) shows the dose distribution of a patient with a rhabdomyosarcoma of the left orbit treated with external beam radiotherapy (photons).

Surgery

For most head and neck rhabdomyosarcomas, it is not possible to perform a complete resection with margins while maintaining form and function. Consequently, complete surgical resection is usually not recommended. In selected cases, complete resection is possible without damage to surrounding functional tissue and precludes the need for radiation therapy. However, radiotherapy is still necessary in most cases (excluding low-risk cases) (1,5,25), especially for the parameningeal site (26). Generally, it is recommended to avoid extensive, invasive primary surgery. When surgery is considered feasible, delaying the surgical procedure until there is a reduction in tumour size is advised. There are few studies showcasing surgery for head and neck rhabdomyosarcoma. One retrospective study demonstrated increased survival for patients with both a non-parameningeal and parameningeal tumour when surgery was added to treatment with chemotherapy and radiation (27). In that particular study in which they looked at 97 patients, surgery was as expected more commonly used to treat patients with non-parameningeal head and neck rhabdomyosarcoma. Furthermore, it was found that patients who had surgery had a significantly higher five-year survival rate overall and reduced risk of mortality after accounting for tumour site and TNM stage 4 (27).

The Parisian head and neck team has established surgery for specifically selected head and neck cases in which survival used to be poor, in an attempt to improve survival, by adding major surgery for tumours in the pterygopalatine fossa and infratemporal fossa (28). Two examples of these surgeries are shown in Figure 4. In addition to extensive surgery, the patient receives postoperative radiation using photons or protons. with henceforth this treatment will be referred to as the

"Paris-method", a the combination of an in-set-up R0 resection and postoperative radiation. Surgery as part of the AMORE procedure was discussed in the previous paragraph.

In conclusion, there are currently four main local treatment options for paediatric head and neck rhabdomyosarcoma: (i) EBRT using photons (XRT); (ii) EBRT using protons (PT); (iii) surgery combined with brachytherapy (i.e. AMORE) and (iv) extensive surgery combined with either XRT or PT EBRT (i.e. the Paris-method).

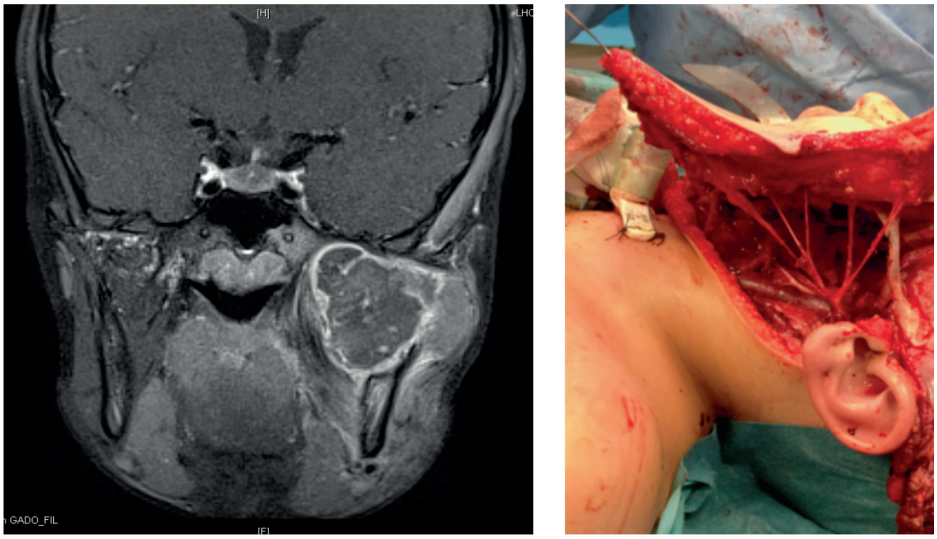

Figure 4. Patient treated with the 'Paris method' in which extensive surgery is combined with radiotherapy aiming to improve survival for infratemporal fossa patients.

An extended infratemporal fossa tumour including the masticator space and parotid space. The surgery used a lateral tempora-facial-cervical approach including a hemimandibulectomy, parotidectomy, masseter resection, pterygoid bone flap, dissection of the V3 and V2 up to the Gasserain ganglion, resection of the greater sphenoid wing and cavernous sinus resection whilst preserving the facial nerve.
*Images courtesy of doctor Frederic Kolb, Institut Gustave Roussy, Paris, France.

Survival

For the entire group of rhabdomyosarcoma patients, the 5-year overall survival in paediatric rhabdomyosarcoma exceeds 70%. Survival rates depend largely on the risk group, with overall three-year survival rates in the metastatic patient groups being less than 48% but low-risk rhabdomyosarcoma patients showing excellent survival rates of over 90% (1,29). The most recent European collaborative study, the EpSSG RMS 2005 study, showed an 80% five-year overall survival rate for children with non-metastatic disease (1). The high survival outcomes are partially explained

by 42 % of the population consisting of low-risk and standard-risk patients who have long-term survival rates of over 90%. Looking specifically at head and neck tumour patients, the overall survival for head and neck non-parameningeal tumours was 85%, and the five-year event-free survival was 75% (5). These results are comparable to the survivals reported by the Intergroup Rhabdomyosarcoma Group and the Cooperative Weichteil sarcoma Study (5). In patients with parameningeal disease, ten-year event-free survival is reported at around 63% and overall survival at around 66%. For patients with parameningeal disease, several risk factors have been identified: age under three or over ten, risk factors for meningeal involvement (intracranial extension, cranial nerve palsy, cranial base bony erosion), unfavourable site, and large tumour size. These predictive factors could be used to reclassify patients into altered risk groups with ten-year overall survival ranging between 51% and 81% (26).

It is important to note that in this sub-analysis of the European historical studies, patients who did not receive radiotherapy at initial treatment showed worse survival with a ten-year overall survival of around 41%, whereas patients who did receive radiotherapy showed 69% ten-year overall survival. In patients with orbital rhabdomyosarcoma, survival is excellent, with five-year event-free survival of over 97%, even with a de-escalated radiation dose (19). It is important to note that at subset analyses within the RMS 2005 study, patients with orbital (lymph node-negative) embryonal rhabdomyosarcoma with initial microscopically complete resection showed excellent survival with five-year event-free survival of 91% and overall survival of nearly 97%. However, these cases are rare. In the entire cohort of the RMS2005 trial, of the 165 patients who underwent surgery, only 34 tumours were grossly resected (1).

LATE ADVERSE EFFECTS FOLLOWING TREATMENT

With both systemic as well as local treatment given to young children, who are amidst growth and development, most survivors suffer from late adverse effects. For cancer survivors, late adverse effects are commonly recorded using the Common Terminology Criteria for Adverse Events (“CTCAE”). Within the CTCAE, late adverse effects are classified based on severity ranging from 0 (non-existent) to 4, the latter representing life-threatening effects. Late adverse effects are very common yet varied in the paediatric head and neck rhabdomyosarcoma survivor group. The most common adverse effects for head and neck rhabdomyosarcoma survivors are musculoskeletal deformities, orbital sequelae, hearing impairment, dental problems, and speech impairment (30–34). In our study, further described in Chapter 1, 82% of the included survivors experienced at least one grade 2 CTCAE

late effect, and 61% of patients suffered from at least one grade 3 or higher adverse effect. In that study, survivors had a median of eight adverse late effects.

Facial deformation is one of the most prevalent late adverse effects in paediatric head and neck rhabdomyosarcoma survivors (30–33,35). Facial deformation can be a very debilitating late adverse effect, and up to now, treatment options in terms of reconstructions for these children are rather limited. These facial deformations can be reduced midfacial growth or severe asymmetries and underdevelopment of specific parts of a patient's face. An example of facial deformation, represented as a 3D image of paediatric rhabdomyosarcoma survivors, is shown in Figure 5.

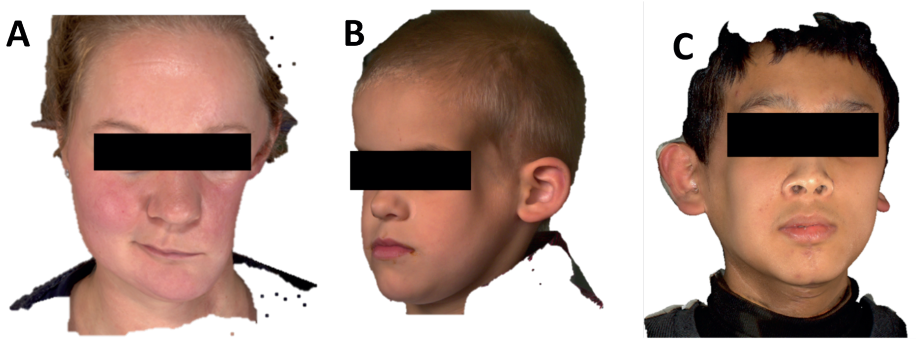

Figure 1. 3D images of rhabdomyosarcoma survivors post-treatment with very distinctive facial deformation.

A, shows a 28 year old woman, 24 years post treatment, she was treated according to the AMORE protocol for a rhabdomyosarcoma in left the infratemporal fossa. B, shows a boy 6 years post treatment with proton therapy for an infratemporal fossa rhabdomyosarcoma on the left when he was 5 years old. C, shows a 10 year old boy treated with the Paris method (surgery and radiotherapy for an infratemporal fossa rhabdomyosarcoma on the right, he is now 5 years post treatment and was treated when he was 5 years old.

In addition to physician-reported late adverse effects, it is important to note the effect of treatment and late adverse effects on the quality of life and general well-being of childhood cancer survivors. Most studies document impaired physical function, usually reported by physicians; however, these data do not reflect the patients' experience and burden (36). Lately, more emphasis is put on patient-reported outcome measures and quality of life assessments, which explore the experience of the patients rather than the health care professional. It is known that cancer survivors in general experience reduced quality of life, however in head and neck sarcoma survivors this seems to differ, some studies show reduced quality of life whereas others show no difference in quality of life compared to healthy controls (37,38). There are several PROMs specifically designed for cancer survivors as well as for head and neck cancer patients; however, there are not many validated

paediatric scales and there are very few disease-specific, site-specific questionnaires evaluating functional late adverse effects and the consequences on quality of life (39,40).

PENTEC – Pediatric normal tissue effects in the clinic

With survival rates for cancer vastly improving, more emphasis is put on debilitating late adverse effects. The Quantitative Analysis of Normal Tissue Effect in the Clinic ("QUANTEC") aims to identify radiation dose constraints for healthy tissues. In children, due to the vulnerability of the developing tissues, the extent of the late adverse effects is quite different from those in adults. Adding to the growing challenge of analysing such dose-effect studies in children is the interplay between the child's developmental stage, therapeutic interventions, limited patient numbers, and the use of multimodal treatments. Paediatric Normal Tissue Effects in the Clinic, also referred to as "PENTEC", was developed as a volunteer research collaboration of over 150 medical professionals, physicists, mathematicians, and epidemiologists aiming to establish risk guidelines to inform radiotherapy planning (41). PENTEC has conducted several studies on salivary and dental complications, cardiac disease, endocrine complications, pulmonary effects, and neurocognitive effects. However, no data exists on facial development (35,41,42).

CRANIOFACIAL ONTOGENESIS

With musculoskeletal deformations being the most common late adverse effect, a deeper understanding of the development of facial deformation and potential treatment options is important. Understanding the development of facial deformation requires knowledge of healthy, normal growth. Postnatal ontogeny of the human craniofacial structures is a complex process in which two distinct features are characterized, namely growth and development (43). With growth, an increase in size is indicated, whilst development describes a change in shape. A thorough knowledge of normal growth and development is relevant to managing congenital disease and understanding the development of craniofacial abnormalities. Furthermore, when healthy development is fully understood the impact of local forces such as radiation or surgery in a developing head and neck area can be better understood and potentially diminished. Growth and development of the craniofacial complex is considered a multifactorial process in which functional, developmental, genetic, and evolutionary traits can be identified (44). Many studies have focused on the ontogenesis of the human skull, describing a morphological growth interaction between the skull, skull base, and the brain. The skull matures in a superior-inferior gradient, which may have knock-on effects on the face (45). The cranial base is considered a platform for facial growth. It is thought that the brain drives the growth of the skull and skull base, but also other facial aspects,

such as the nasal cavity and oral cavity, which contribute to the development and shape of the facial structures. Muscle forces, masticator systems, and volumes of soft tissue also influence size and shape. For the cranial interactions, the cranial base is influenced by other components like speech and posture (46). Moreover, biological and genetic variations influence growth and development (47). Hormones, predominantly, growth hormone and testosterone, affect the cranial base.

The cranial base (also named the basicranium) is one of the most complex structures of the human skeleton (48). The cranial base is composed of basioccipital, sphenoid, ethmoid, frontal, and temporal bones (Figure 6). The cranial base is divided into the posterior and the anterior cranial base. The anterior cranial base embryologically originates from the neural crest, as do the other facial bones, and the posterior cranial base is formed by the paraxial mesoderm (48). The anterior cranial base has a direct connection with the upper middle face and integrates with the upper middle face into a growth complex named the ethmo-maxillary complex. The mandible articulates with the posterior cranial base.

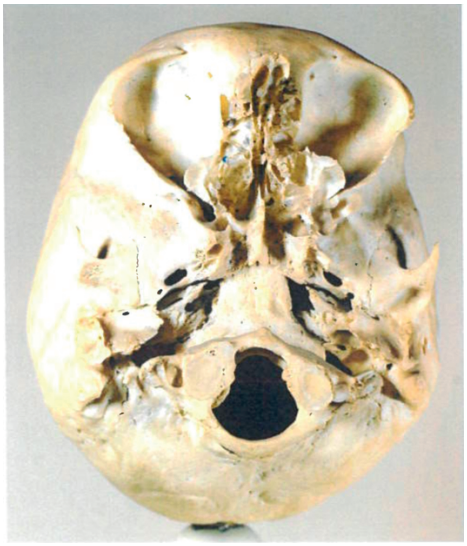

Figure 6. Cranial base of an adult (interestingly with an attached atlas).

*Courtesy of the Bleulandinum Museum of the Medical University of Utrecht.

For healthy growth and separation equilibrium of the cranial sutures, a delicate balance between cell proliferation, differentiation, migration, and apoptosis to regulate osteogenic fronts at the sutural interface is needed (46,49). The cranial base is formed through endochondral ossification, in which a cartilage plate is formed and then replaced by bones, which are connected by cartilaginous structures (long bone

growth plates). The cranial synchondrosis is present in the midline of the cranial base, essentially two growth plates sharing one resting zone in which chondrocyte precursors direct formation and organization (48). In contrast, most craniofacial bones are formed through intramembranous ossification through mesenchymal condensation (45,46,48). As previously mentioned, the cranial base is considered a key structure in craniofacial growth. It is widely accepted that the growth of the cranial base is significantly influenced and driven by brain growth (45,46,48). The brain drives cranial base growth through mere force and the hormonal component in which developmental genes are expressed from the dura mater to the bones. Enlow and Hans hypothesized different levels of maturation in what they characterized as different craniofacial levels: the neurobasocranial complex, the ethmo-maxillary complex, and the mandibular complex (50). They suggested a superior-inferior gradient of maturation, with different components achieving morphological adulthood size and shape at different times, with the more cranial components maturing before the inferior parts (45,50). Current studies support Enlow and Hans's theory in that the basicranium reaches adult size and shape earlier than the maxillary and mandibular parts of the face. Some earlier studies have hypothesized different developmental and growth stages for the ethmo-maxillary complex and the mandible; however, differences in maturity could not be shown in 3D studies (45), with both the midface and lower facial units reaching maturity at around 16 years of age. The ethmo-maxillary complex mainly shows vertical growth and a forward and upward rotation, resulting in later maturation of the upper facial region, whereas the mandible shows elongation of the ramus and a rotation of the corpus, effectively increasing the angulation of the mandible, resulting in a more pronounced chin area. The mandible is known to undergo the greatest change in size and shape in the first year of life, with increasing ramus height and corpus length and width (51). Following the first year of life, there are no such growth spurts, with consistent growth throughout time (51). In early childhood, the craniofacial structures undergo rapid growth and development to accommodate the development of all soft tissues. Typically, there is no sexual dimorphism in the cranial shape trajectories in the first four years of age; sexual differences in cranial growth mostly become pronounced during puberty following hypermorphosis in males. In the first four years of age, the variance in craniofacial form is mostly related to size changes and only mildly related to shape changes. In the first 12 months, initial rapid growth is seen, potentially driven by an increase in nasal, orbital, and intracranial volumes, resulting in upper cranial growth (47). The nasal septum seems to be key in nasofacial skeletal development and is established by at least seven years of age (52). So, following Enlow and Hans's theory, the maturation of the skull follows a gradient, starting with maturation in the midline cranial base (up to eight years of age) and continuing to the lateral cranial floor and neurocranial outline (12 years of age) and lastly, the face, which reaches maturity at around 15 years of age (45). Size shows a superior-inferior growth gradient. Facial bones and the difference

in size and shape of facial bones between different ages is demonstrated in skulls presented in Figure 7.

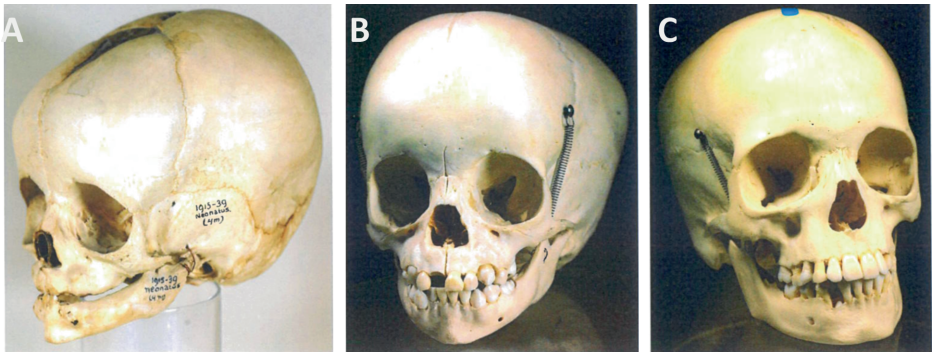

Figure 7. Craniofacial development illustrated in different skulls.

Image (A) shows the skull of an estimated four-month-old, image (B) shows the skull of a seven-year-old child and image (C) the skull of an adult.
* Courtesy of the Bleulandinum Museum of the Medical University of Utrecht.

LATE ADVERSE EFFECTS FOLLOWING LOCAL TREATMENT FOR HEAD AND NECK RHABDOMYOSARCOMA

When radiotherapy and surgery are administered in young children, it is often hard to predict the amount of facial deformation following local treatment. Most surgeons are hesitant to perform reconstructive surgery when both soft tissue and bony tissue have been exposed to radiotherapy. Consequently, with limited reconstructive options, preventing facial deformation is extremely important without compromising the dose of the tumour. As previously mentioned, strides are being made to limit the dose to developing tissue, radiotherapy is being made more conformal, and studies are run to investigate the possibility of treatment de-escalation. To limit facial deformation, the amount of radiation delivered to at-risk organs, in this case, the facial bones should be limited. There are no known dose limits for most facial bones, and the effect of radiation on growing facial bones is largely unknown. As previously described, there are currently four different local treatment strategies for head and neck rhabdomyosarcoma. In terms of survival, these treatment methods are all similar; however, they may differ in terms of late adverse effects as they all have different dose distributions, and some local treatment options add surgery to the treatment, potentially adding adverse effects to the effects of radiotherapy. The difference in terms of late adverse effects between all four different treatment options is largely unknown. A previous study from our group comparing AMORE and XRT-based treatment showed an increased risk of developing CTCAE grade three and four late adverse effects and more than

five adverse effects when patients were treated with XRT compared to AMORE (32). Furthermore, studies on facial deformation showed increased facial asymmetry in patients treated with XRT compared to AMORE (31,32). Some theoretical studies have compared dose distributions for head and neck sarcoma between PT and XRT, favouring PT for having inherently better dose distributions that spare at-risk organs (53). However, no studies are comparing the late adverse effects in head and neck rhabdomyosarcoma between XRT and PT nor are there studies investigating the effect of radiation on craniofacial bone growth. Furthermore, no studies compare all four treatment modalities, nor are there dose-effect studies for specific facial bones. These studies aimed to compare the differences in late adverse effects between the different treatment modalities. Additionally, these studies aimed to find dose thresholds for craniofacial bones. The outcomes of these studies will further optimize treatment planning and consequently reduce late adverse effects and diminish facial deformation.

Set up of study collaboration network and the study population

Given the rarity of paediatric head and neck rhabdomyosarcoma, collaboration among major treatment centres was necessary to include sufficient patient numbers for all four treatment modalities. A study collaboration started between four large tertiary treatment centres for paediatric oncology, namely:

- Academic Medical Center (AMC) in Amsterdam, which later transferred its paediatric oncology care to the Prinses Maxima Center for Pediatric Oncology (PMC).
- Great Ormond Street Hospital, London, United Kingdom (GOSH).
- Institute Gustave Roussy, Paris, France (IGR).
- University of Florida Health Proton Therapy Institute, Jacksonville, USA (UFPTI).

At the AMC, our preferred local treatment is resection of the tumour followed by brachytherapy and reconstruction (i.e AMORE). With the collaboration of these four centres, we have been able to include all treatment options and a large number of patients. For this research project, follow-up clinics were established at all four participating centres to systematically assess late adverse effects. Paediatric head and neck rhabdomyosarcoma survivors who were at least two years post-treatment, with localized disease and no secondary malignancies or relapse, were invited to visit the multidisciplinary structured follow-up clinics.

When survivors visited the outpatient clinic, they were systematically investigated by a multi-disciplinary outpatient physician team. Survivors were seen by a paediatric or medical oncologist, radiation oncologist, head and neck surgeon, plastic surgeon, ophthalmologist, and a dentist. Survivors attended these late adverse effect clinics and underwent well-structured and systematic check-ups based on a pre-set

list of relevant CTCAE criteria, which were filled out by all individual physicians. Furthermore, survivors had a 3D photograph taken, functional impairments were measured, a dental X-ray was taken, speech tests were recorded, and a blood draw was performed. Information on patient and tumour characteristics at the time of diagnosis and treatment parameters were collected. When available, the raw dosimetry radiotherapy data were collected. All specialist teams were formed from local physicians. To ensure uniform reporting and data collection, one researcher attended all clinics and had a consultation with all included survivors. The set-up of the study is illustrated in the graphic in Figure 8.

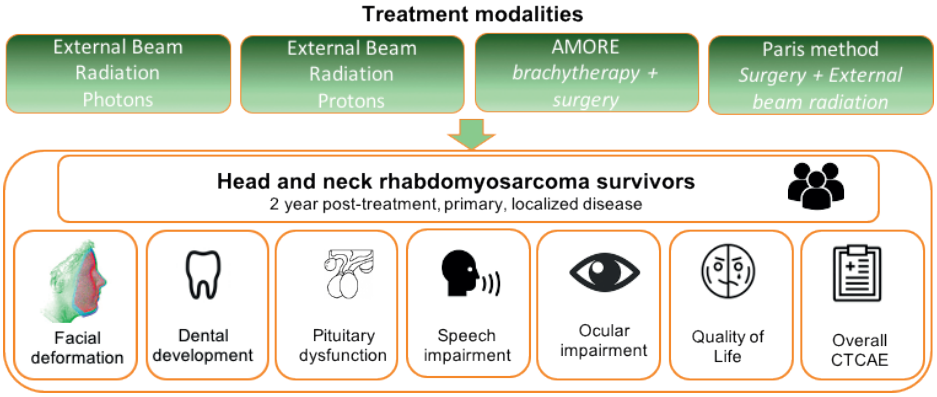

Figure 8. Set-up of multi-centre late adverse effect study including four treatment modalities

AMORE: Ablative surgery, MOld technique with afterloading brachytherapy, REconstruction.

OBJECTIVES AND OUTLINE OF THIS DISSERTATION

The general objective of this dissertation is to investigate real-life clinical information on late adverse effects in paediatric head and neck rhabdomyosarcoma survivors and to describe potential differences in adverse effects between treatment regimens. Local treatment options were investigated and radiation dose-effect relations for facial bones will be explored.

Part I of this dissertation shows a general introduction on pediatric head and neck rhabdomyosarcoma and the different local treatment options. Furthermore, bone development is described for facial bones.

Part II of this dissertation examines different late adverse effects in patients with head and neck rhabdomyosarcoma. In **Chapter 1**, the overall long-term sequelae in survivors of HNRMS are investigated, with an exploration of differences between treatment modalities. In **Chapter 2**, 3D stereophotogrammetry is utilized to

investigate facial deformation, analysing the difference between treatment modalities. **Chapter 3** shifts focus to patient-reported outcomes, including appearance, psychosocial well-being, and facial function.

In **Part III**, the emphasis turns to radiation therapy and dose constraints for facial bones. **Chapter 4** explores orbital bone morphology following proton beam radiotherapy. **Chapter 5** contains an exploration of facial deformation (using 3D-stereophotogrammetry as earlier described in Chapter 2) and actual radiotherapy dose, suggesting dose constraints for facial bones. **Chapter 6** encompasses the University of Florida study examining the potential for limiting dose in orbital rhabdomyosarcoma patients.

Part IV of this dissertation centres on surgery, highlighting the AMORE treatment developed in the Netherlands. **Chapter 7** details the surgical development of AMORE, its technique, and assessing treatment as it is. **Chapter 8** describes AMORE as a salvage treatment for patients with relapsed head and neck rhabdomyosarcoma. **Chapter 9** assesses surgeons' predictive abilities for facial deformation function post-surgery.

Part V concludes with an impact on clinical practice statement, general discussion and outlines possibilities for further research as well as suggests possible improvements to the care of patients with head and neck rhabdomyosarcoma.

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PART II

1

Long term adverse events following treatment for head and neck rhabdomyosarcoma in children, results of an international multi-center cross-sectional cohort study

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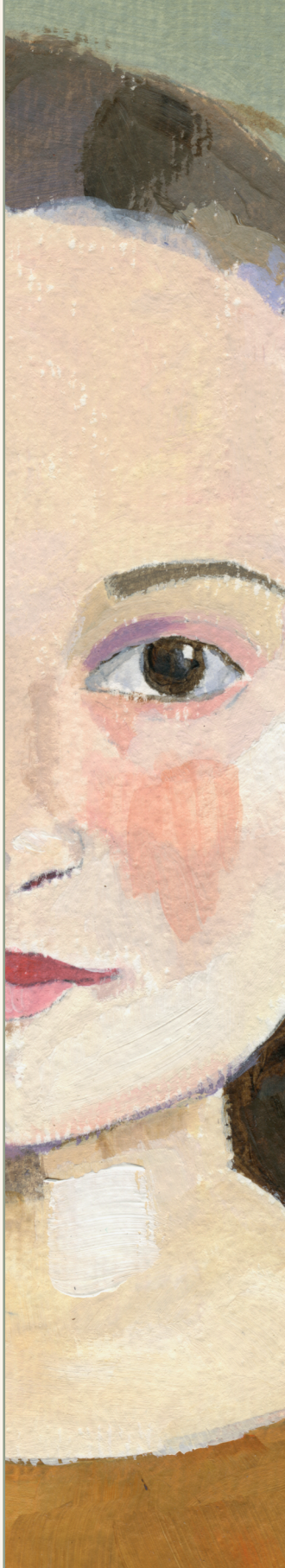

ABSTRACT

Purpose

Local therapy for head and neck rhabdomyosarcoma (HNRMS) typically includes radiation therapy and occasionally surgery. Adverse events (AEs) of local treatment are common among survivors. Efforts are being made to limit these AEs by utilizing highly conformal radiation planning and new treatments strategies. Theoretical differences drive the selection of local therapy but the clinical benefit for survivors is still under debate. The primary purpose of the current study was to describe the prevalence and severity of AEs in a large HNRMS survivor cohort. In addition, we compared AEs between four local treatment strategies: definitive external beam radiotherapy with photons; definitive external beam radiation with protons; microscopically radical surgery combined with external irradiation; macroscopic radical surgery combined with brachytherapy.

Patients and methods

We conducted an international, multicenter cross-sectional cohort study. Survivors with ≥2 years follow-up after treatment for a primary pediatric HNRMS were eligible. A multidisciplinary team systematically assessed a predefined list of AEs according to the Common Terminology Criteria for Adverse Events system in these survivors.

Results

Ninety-eight survivors, with median follow-up of 9 years, were included. Survivors had a median of 8 different AEs and 60% experienced at least one grade ≥3 AE. Musculoskeletal deformity, cataract, hearing impairment, speech abnormalities and eyelid malfunction were the most common AEs. Tumor size ≥5cm was an independent risk factor for a grade ≥3 AE. When looking at our results descriptively, we noticed differences in grades and types of AEs between different local treatment strategies, but these were not statistically significant.

Conclusions

AEs are highly prevalent and diverse in HNRMS survivors. The data from this study can be used to optimize follow-up care. The grades and types of AEs might differ between local treatment strategies, but further studies are needed to fully characterize the therapeutic ratio and inform clinical decisions in the future.

INTRODUCTION

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in pediatric patients, constituting 3-5% of all malignancies in childhood, and often arises in the head and neck (HN). Patients are young at diagnosis, with a median age of 5 years. In the past decades, survival has improved by introducing the combination of systemic chemotherapy and local treatment typically consisting of radiotherapy with or without surgery. With long-term survival exceeding 70% [1], the chronic adverse events (AEs) have become more apparent.

Currently, there are different local treatment strategies for HNRMS. Historically the standard of care was definitive 2D external beam radiotherapy using photons (XRT). XRT plans have become more conformal, initially with the application of 3D-conformal radiotherapy and more recently with rotational intensity modulated radiotherapy (IMRT). At Institute Gustave Roussy (IGR) in Paris, a new method was developed, combining microscopically radical resection with external radiotherapy used for parameningeal tumors (Paris-method[2]). AMORE (Ablative surgery, MOuld technique brachytherapy, and REconstructive surgery), developed in Amsterdam, aims to spare healthy tissue by using brachytherapy, harnessing the rapid dose fall off beyond the target volume of this technique [3,4]. However, both the Paris-method and AMORE involve surgery, potentially contributing to additional late AEs. Over the past decade, to reduce the collateral dose of external radiation, definitive proton therapy (PBT) has been adopted for pediatric HNRMS. Due to the physical characteristics of protons, with no significant radiation exposure beyond the end of the Bragg peak, often improved sparing of surrounding tissue can be achieved. The first PBT outcomes in orbital and parameningeal site HNRMS have suggested a reduction in late AEs [5–8]. All four local treatment techniques produce similar survival rates but, due to the inherent different dose distributions and surgical techniques used, the burden and nature of late AEs may vary. Until now, only a few small studies performed a systematic assessment of late AEs in HNRMS patients [5,6,9,10] and no comparison was made between all different local treatment strategies. The purpose of this paper was to both describe the prevalence and severity of late AEs in a large cohort of HNRMS survivors, as well as compare late AEs between the four local treatment strategies.

MATERIALS AND METHODS

Survivors

To include all four local treatment approaches, collaborative multidisciplinary outpatient clinics were established at the University of Florida Health Proton Therapy Institute, Jacksonville, United States; IGR, France; Great Ormond Street

Hospital, London, United Kingdom; and Amsterdam University Medical Centers, Amsterdam, the Netherlands. The latter transferred its pediatric oncology care to the Princess Máxima Center, Utrecht, the Netherlands in 2018. This study was approved by all ethical committees of the participating centers and relevant national review boards. Oral or written consent was obtained based on national and local standards. All survivors of pediatric (0-18 years) HNRMS, treated between 1993 – 2017, with a minimum of two years follow-up after the end of treatment were invited to participate. Survivors who relapsed or had a secondary malignant neoplasm were excluded. Eligible survivors were invited to a multidisciplinary outpatient clinic during which they underwent a systematic clinical assessment by a pediatric oncologist, head and neck surgeon, plastic surgeon, ophthalmologist, radiation oncologist, and a dentist. One author (MH) attended all clinics to ensure consistency of AE scoring in the different clinics. A predefined list of AEs was evaluated and graded according to the Common Terminology Criteria for Adverse Events (CTCAE v. 4.0) (supplementary data table 1). The selection of AEs was based on results from previous studies [10] as well as experts' experience. Patients were staged and treated according to the SIOP-MMT[1,11] (International Society of Paediatric Oncology-Malignant Mesenchymal Tumour group), E*p*SSG[12–14] (European paediatric Soft tissue sarcoma Study Group), COG[15–17] (Children's Oncology Group) and CWS[18] (Cooperative Weichteilsarkom-Studiengruppe) protocols. Treatment consisted of induction chemotherapy followed by one of the described local treatment strategies.

Surgical eligibility

The allocation of local treatment strategy was based on patient and tumor characteristics as well as availability and local expertise. Hence, a comparison between different treatment groups is very likely affected by bias. In order to facilitate comparison of AEs between the different local treatment groups, we only performed a comparison between patients that would have been eligible for all four local treatment strategies. The deciding factor to qualify for the AMORE or Paris-method is the feasibility of performing macroscopic or microscopic radical surgery, respectively. We only compared survivors in whom a radical resection after the initial induction chemotherapy would have been considered feasible: 'surgery-eligible group'. Feasibility was evaluated based on pre-defined criteria, similar to those used in clinical practice: perineural spread, intracranial extension (ICE), and encasement of the carotid artery were considered absolute contraindications for surgery. Tumor extension into the orbital apex was considered a relative contraindication, since resection would necessitate exenteration of the orbit.

Statistical analyses

Differences between baseline characteristics and treatment groups were analyzed using Fisher's exact test or Kruskal Wallis test, depending on the type of variable. We calculated the sum of AEs grades for every survivor, referred to as the 'cumulative

grade score' (example: 1 grade 3 AE and 2 grade 2 AEs gives a cumulative grade score of 7). We calculated a burden score adapted from Geenen et al [19], taking into account both the number and grade of AEs (low: >1 grade 1 AE; medium: ≥1 grade 2 and/or 1 grade 3 AE; high: ≥2 grade 3 AEs or 1 grade 4 AE and at most 1 grade 3 AE; severe: ≥2 grade 3 AEs and ≥1 grade 4 AE, or ≥2 grade 4 AEs). A binary logistic regression analysis for: any AE grade ≥2, any AE grade ≥3, patients with a high or severe burden of AEs, and diversity of number of AEs (dichotomized into more or less different AEs compared to the cohorts' median) was performed. We included the following variables in the univariable analyses: local treatment modality, tumor site, histology, period of treatment (dichotomized into prior to 2005 or 2005 onwards based on the availability of protons and start of the RMS2005 trial), age at diagnosis, follow-up period, attained age and tumor size. The different age and time variables were tested both as continuous and categorical variables. Owing to small sample sizes per subgroup, those analyses were exploratory. Predictors with $p \leq 0.05$ in the univariable analysis were included in the multivariable model. Treatment modality was brought into a multivariable model. Data were analyzed using IBM SPSS statistics version 25.0.

RESULTS

Survivors

Ninety-eight survivors were included with a median age at clinic visit of 16 years (range 5 – 35) and a median follow-up time of 9 years (range 2 - 27). Baseline characteristics are shown in Table 1. Eight survivors were considered not 'surgery-eligible' based on ICE (n=6), carotid artery encasement (n=1) or combination of both (n=1) (n=4 XRT, n=4 PBT) and consequently excluded for group comparisons. PBT-treated survivors had a statistically significantly younger attained age, shorter follow-up period and were treated more frequently following 2005 compared to XRT - and AMORE - treated survivors.

Table 1: Baseline characteristics of the survivors evaluated at the multidisciplinary outpatient clinic.

		All ◊		All / surgery eligible †		XRT / surgery eligible		PBT / surgery eligible		AMORE		Paris-method	
		N = 98		N = 90 / 98		N = 33 / 37		N = 26 / 30		N = 19		N = 12	
Age at diagnosis	**Median, range**	5	0.04 – 15	6	0.5 – 15	5	0.5 – 15	5	1 - 12	6	1 - 13	6	2 - 15
>10Y	**N, %**	14	14	14	16	3	9	3	12	5	26	3	25
Attained age	**Median, range**	16	4 – 35	16	4 – 35	19	6 - 35	11*	4 - 22	20	5 - 34	13	5 - 27
>18y	**N, %**	38	39	37	41	21	64	1	4	12	63	3	25
Follow-up period	**Median, range**	9	2 – 27	9	2 - 27	13	3 - 27	6*	2 - 14	12	2 - 27	6	2 - 12
>5y	**N, %**	77	79	70	78	31	94	15	58	15	79	9	75
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Gender	**Male**	54	55	50	56	21	64	12	46	12	63	7	58
Site[a]	**Orbit**	21	21	21	23	7	21	8	31	6	32		
	PM	66	67	58	64	23	70	14	58	9	47	12	100
	NPM	11	11	11	12	3	9	4	15	4	21		
Histology[b]	**Favorable**	79	81	73	82	25	76	23	89	15	79	10	83
	Unfavorable	18	18	16	18	8	24	3	12	4	21	1	8
Tumor size	**>5cm**	35	36	29	32	7	21	8	31	4	21	10	83
	<5cm	60	62	58	64	25	76	18	69	15	68	2	17
	missing	3	3	3	3	1	3			2	11		
Metastasis	**N1**	8	8	7	8	1	3	3	12	0		3	25
	M1	8	8	7	8	1	3	1	4	1	5	4	33
Protocol	**MMT-89**	4	4	4	4	3	9	0		1	5	0	
	MMT-95	24	25	21	23	14	42	0		7	37	0	

		n	%	n	%	n	%	n	%	n	%	n	%
	CWS-91	1	1	1	1	0		0		1	5	0	
	CWS-09	1	1	1	1	1	3	0		0		0	
	RMS-2005	48	49	43	48	13	39	15	58	6	32	9	75
	BERNIE	1	1	1	1	0		0		0		1	8
	IRS-IV	1	1	1	1	1	3	0		0		0	
	ARST0331	8	8	8	9	0		8	31	0		0	
	ARST0531	1	1	1	1	0		1	4	0		0	
	missing	*9*	*9*	*9*	*10*	*1*	*3*	*2*	*8*	*4*	*21*	*2*	*17*
Period of treatment	**1993-2004**	25	26	24	27	16	49	0		8	42		
	2005-2017	73	75	66	73	17	52	26*	100	11	58	12	100
Prescribed RT dose GyRBE[c]	**36**	1	1	1	1			1	4				
	41.4	16	16	16	18	1	3			11[d]	58	4	33
	45	19	19	17	19	7	21	5	19	5	26		
	50.4	40	41	37	41	17	52	16	62	3[e]	16	1	8
	54-55.8	12	12	10	11	6	18	2	8			2	17
	missing	*10*	*10*	*9*	*10*	*2*	*6*	*2*	*8*			*5*	*42*

[◊]all: all included survivors
[ł]all / surgery eligible: subset of all the included survivors who would have been eligible for all four local treatment strategies
XRT: external beam radiotherapy with use of photons; PBT: external beam radiotherapy with protons; AMORE: Ablative surgery, MOld brachytherapy and REconstruction; Paris-method: R0 resection followed by external beam radiotherapy (XRT or PBT).
*statistically significant difference between groups:
Attained age: PBT-treated surgery eligible survivors are statistically significantly younger compared to both XRT-treated surgery eligible (p .000) and AMORE-treated survivors (p .000) (Mann-Whitney U test)

Table 1: *Continued*

Follow-up period: PBT-treated surgery eligible survivors have a statistically significantly shorter follow-up period compared to both XRT-treated surgery eligible (p .000) and AMORE-treated survivors (p .002) (Mann-Whitney U test)
Period of treatment: PBT-treated surgery eligible survivors were statistically significant more often treated in period 2005-2017 versus 1990-2005 compared to both XRT-treated surgery eligible (p .000) and AMORE-treated (p .000) survivors (Fisher exact test)
[a]orbit: orbital tumors; PM: parameningeal site tumors; NPM: head and neck non parameningeal tumors
[b]favorable histology includes: embryonal type. Unfavorable includes: alveolar (N = 14), undifferentiated (N = 1) and NOS (N = 3)
[c]total prescribed dose, including boost dose
[d]for the AMORE treated survivors, brachytherapy dose 40GyRBE instead of 41.4
[e]for the AMORE treated survivors, brachytherapy dose 50GyRBE instead of 50.4
Y: years;; MMT: Malignant Mesenchymal Tumour group protocols of the International Society of Paediatric Oncology (SIOP); CWS: consecutive Cooperative Weichteilsarkom group protocols; RMS 2005: European paediatric Soft tissue sarcoma Study Group (EpSSG) RMS2005 protocol; ARST: ARST protocols of the Children's Oncology Group
Tumor size >5cm: at time of diagnosis, on first available imaging
N1: regional (cervical) lymph nodes positive at diagnosis
M1: distant metastasis positive at diagnosis

Adverse events

All but one survivor experienced at least one AE, 82% of survivors experienced at least one grade ≥ 2 AE, 61% experienced at least one grade ≥3 AE (table 2). Survivors had a median of 8 (range 0 - 28) different AEs with a median cumulative grade score of 11 (range 0 - 51). Twenty-four (25%) survivors had a high burden of AEs. Three survivors had a severe burden of AEs (Supplemental data 3). Figure 1 shows the distribution of the number of different AEs and the highest grade AE per survivor, organized by site, this same graph is presented partitioned for treatment modality in supplemental figure 1. The 20 most prevalent AEs grade ≥2 are shown in Table 3, an overview of all observed AEs is presented in Supplemental Table S2. The distribution of AEs (any grade) per treatment modality is presented in figure 2.

Table 2. Proportion of patients with a grade 0, 1, 2, 3 or 4 as highest grade for any adverse event. By treatment strategy

	All		**All / surgery eligible**		**XRT / surgery eligible**		**PBT / surgery eligible**		**AMORE**		**Paris-method**	
	N= 98		**N=90**		**N=33**		**N=26**		**N=19**		**N=12**	
	N	***%***	***N***	***%***	***N***	***%***	***N***	***%***	***N***	***%***	***N***	***%***
Grade 0	1	***1***	1	***1***	0	***0***	0	***0***	1	***5***	0	***0***
Grade 1	17	***17***	17	***19***	7	***21***	8	***31***	2	***11***	0	***0***
Grade 2	21	***21***	20	***22***	7	***21***	4	***15***	7	***37***	2	***17***
Grade 3	52	***53***	47	***52***	16	***49***	12	***46***	9	***47***	10	***83***
Grade 4	97	***7***	5	***6***	3	***9***	2	***8***	0	***0***	0	***0***

'all'; all survivors fulfilling the inclusion criteria for this study
'all / surgery eligible'; subset of all the included survivors who would have been eligible for all four local treatment modalities
XRT: external beam radiotherapy with use of photons; PBT: external beam radiotherapy with protons; AMORE: Ablative surgery, MOld brachytherapy and REconstruction; Paris-method: R0 resection followed by external beam radiotherapy.

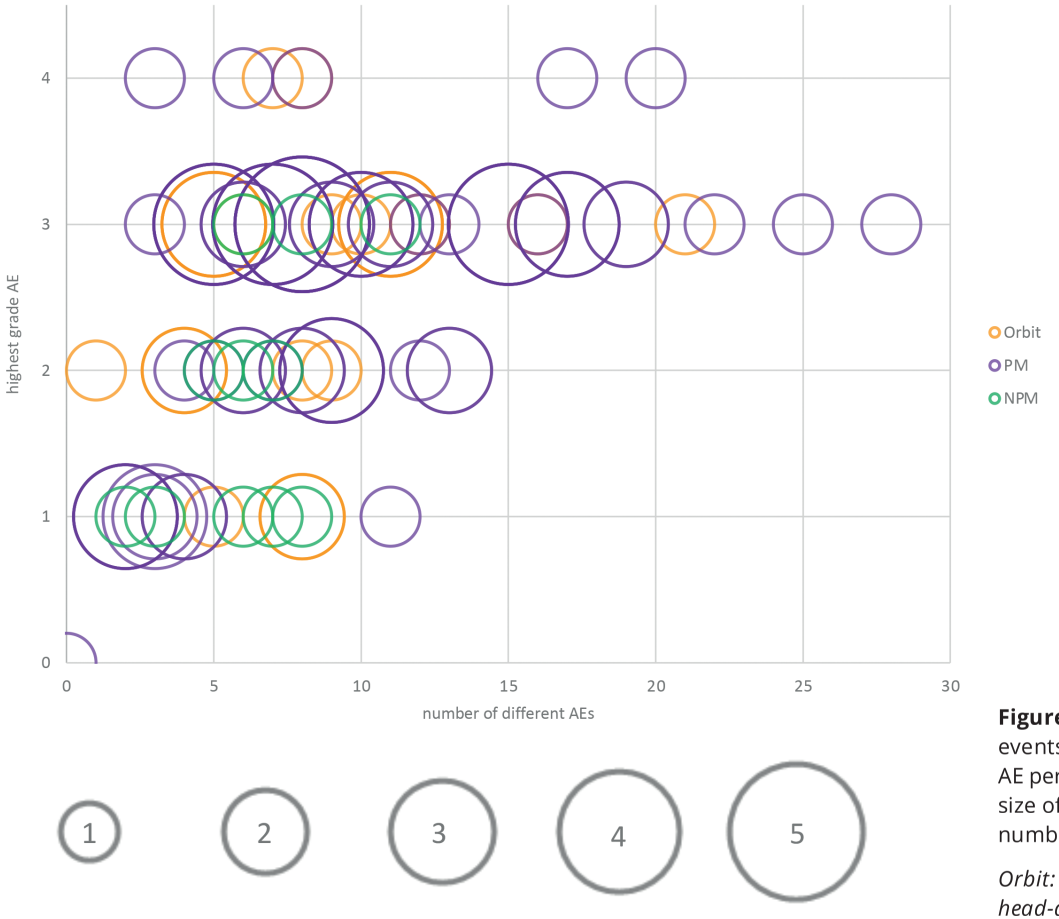

Figure 1. Total number of different adverse events (AE) plotted against the highest grade AE per survivor. Organized by tumor site. The size of the circles represent the contributing numbers of survivors.

Orbit: orbital site; PM: Parameningeal; NPM: head-and-neck non parameningeal (NPM).

Table 3. Percentage of occurrence of the 20 most prevalent grade ≥2 adverse events (AE). Shown in order of prevalence.

	Grade ≥2											
	All N = 98		all / surgery eligible N = 90		XRT / surgery eligible N = 33		PBT / surgery eligible N = 26		AMORE N = 19		Paris-method N = 12	
	n (N)	%	n (N)	%	n (N)	%	n (N)	%	n (N)	%	n (N)	%
Facial deformation	45 (98)	44	40 (90)	44	14 (33)	42	9 (26)	35	5 (19)	26	12 (12)	100
Cataract	29 (94)	31	27 (84)	32	12 (31)	39	8 (24)	33	4 (17)	24	3 (12)	25
Hearing	20 (90)	22	18 (84)	22	5 (30)	17	2 (25)	8	5 (18)	28	6 (11)	55
Speech abnormality	18 (90)	20	16 (83)	19	6 (30)	20	4 (26)	15	0 (16)*	0	6 (11)	55
Eyelid malposition	17 (84)	20	16 (76)	21	3 (29)	10	5 (23)	22	6 (19)	32	2 (8)*	40
GHD	17 (91)	19	12 (84)	14	7 (29)	24	4 (25)	16	0 (18)	0	1 (12)	8
Scar	15 (94)	16	15 (86)	18	4 (32)	13	1 (26)	4	6 (17)	35	4 (11)	36
Dry eye	15 (96)	16	12 (88)	14	5 (33)	15	4 (25)	16	1 (19)	5	2 (12)	17
Epiphora	11 (80)*	14	10 (72)*	14	2 (28)*	7	3 (23)	13	4 (19)	21	1 (2)*	50
Sinus disorder	12 (91)	13	12 (84)	14	8 (30)	27	3 (26)	12	0 (17)	0	1 (11)	9
Xerostomia	11 (89)	12	9 (82)	11	6 (29)	21	1 (26)	4	1 (16)*	6	1 (11)	9
Ear inflammation	11 (91)	12	11 (84)	13	4 (30)	13	2 (26)	8	1 (17)	6	4 (11)	36
Fat/skin atrophy	11 (98)	12	11 (90)	12	2 (33)	6	3 (26)	14	3 (18)	17	3 (13)	23
Dermal changes	10 (99)	10	10 (91)	11	2 (33)	6	3 (26)	12	3 (19)	16	2 (13)	15
Globe displacement	7 (83)*	8	7 (75)*	9	2 (29)	7	2 (23)	9	2 (19)	11	1 (4)*	25
Induration/fibrosis	8 (97)	8	6 (89)	7	1 (33)	3	1 (26)	4	3 (18)	17	1 (12)	8
Trismus	5 (82)*	6	5 (76)*	7	3 (26)*	12	1 (25)	4	1 (16)*	6	0 (9)*	0
Epistaxis	5 (91)	6	5 (84)	6	1 (30)	3	3 (26)	12	0 (17)	0	1 (11)	9
Strabismus	4 (82)*	5	4 (74)*	6	2 (29)	7	1 (23)	4	1 (19)	5	0 (10)*	0
Alopecia	1 (97)	1	1 (89)	1	0 (33)	0	1 (26)	4	0 (18)	0	0 (12)	0

n (N): number of survivors with the AE per total number of survivors for whom the AE is registered.
*data on specific AE missing for ≥10% of survivors
Colors indicate a range of prevalence: green: 0-10%; blue; 11-20%; orange: 21-30%; red: 31-40%; purple >40%

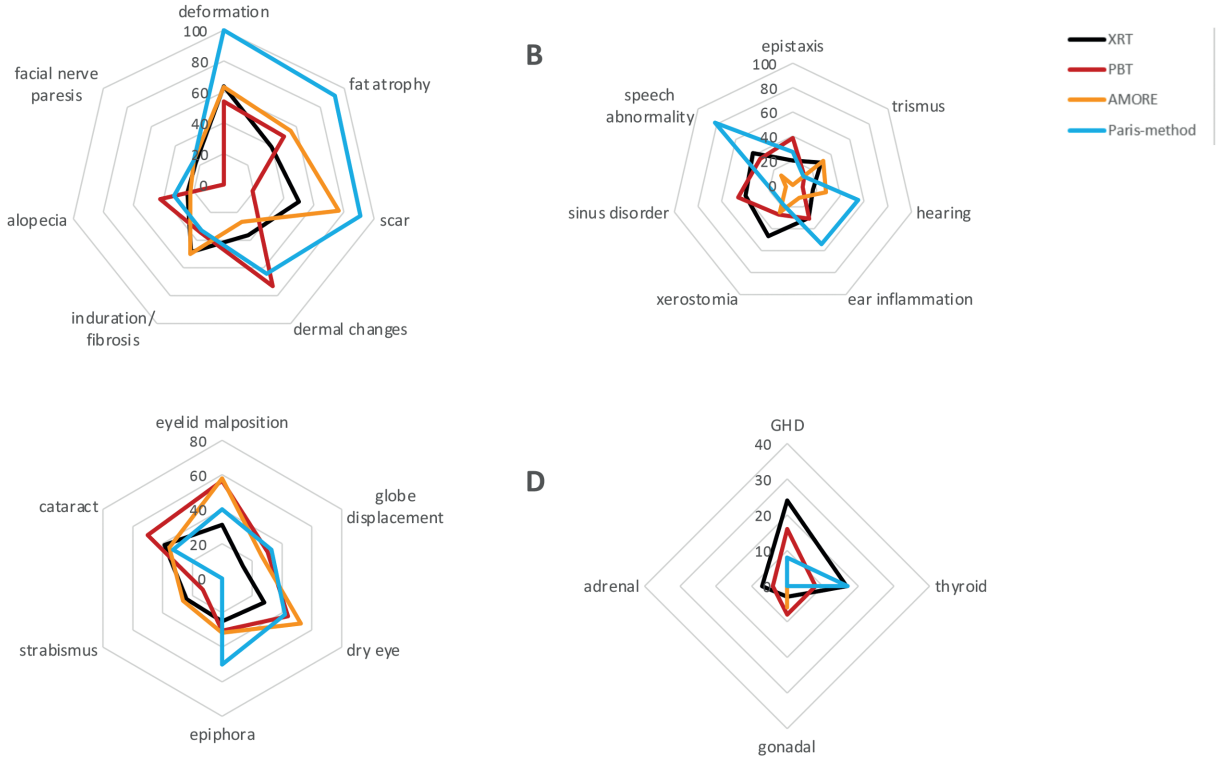

Figure 2. Percentage of survivors with adverse events (AEs) of any grade. Adverse events clustered per domain of AEs: AEs leading to a visible facial difference (axis 0 -100%) (A); AEs leading to functional impairments (axis 0 – 100%) (B); AEs leading to ocular impairment (axis 0 - 80%) (C); endocrinopathies, both central and peripheral (axis 0 - 40%) (D). Displayed by treatment type.

GHD: growth hormone deficiency

Facial deformation
AEs representing visible changes in the facial skin, soft tissue or bones were most prevalent and occurred in 91 (93%) survivors. Severe facial deformity (grade ≥3) was observed in 31% of the survivors and 16% of survivors had some form of facial reconstructive surgery for esthetic reasons prior to the clinic visit.

Nerve function
Thirty-two survivors had cranial nerve palsy of any or more cranial nerves. The cranial nerves most often affected were the trigeminal nerve (n=19), facial nerve (n=14), vestibulocochlear nerve (n=10), glossopharyngeal nerve (n=6) and hypoglossal nerve (n=4). In 22 of 32 survivors, the cause of nerve palsy was retrieved from patient files; in 18 (82%) nerve damage was iatrogenic, in 4 (19%) survivors the cranial nerve damages was most likely caused by invasion of the tumor. Nine survivors had facial sensory nerve dysfunction, for which the etiology was unknown. Seven of the 9 received surgery as part of the local treatment.

Ear
Recurrent external ear infection and subjective hearing loss was reported in 29% and 22% respectively.

Eye
Seven survivors (7%) were blind in one eye; due to enucleation (N=2), optic nerve damage (N=2), combined cataract and optic neuropathy (N=2), retinopathy (N=1). Forty (42%) survivors had dry eyes, in 9 (21%) corneal scarring was seen. Lid retraction and ptosis were the most observed eyelid deformities.

Endocrinopathy
Growth hormone deficiency (GHD) was the most prevalent endocrinopathy, present in 17 of the 91 (20%) survivors for whom grading on endocrine function was available. Six out of 96 (6%) survivors had a short stature (i.e. height ≤-2SD). Of these, 2 (33%) also had a clinical diagnosis of GHD.

Multivariable analysis of associated risk factors
Based on univariable logistic regression (Table S3), tumor site, tumor size and follow-up time were included in the multivariable regression model (table 4). Survivors with tumor size >5cm showed a significantly higher odds for developing a grade ≥3 AE compared to survivors with size <5cm tumor. Follow-up period of 10-15 years showed a significantly higher odds for developing a high-severe burden of AEs, compared to shorter follow-up time.

We also investigated a model incorporating treatment modality (Table S4). Paris-method was not included because of collinearity with tumor site (all PM site). In

this model, treatment modality remained a non-significant risk factor for all the tested outcomes, with OR 1.0 (95% CI 0.2 – 4.2) for PBT and OR 0.7 (0.2 – 2.6) for AMORE compared to XRT to develop a grade ≥3 AE. Figure 2 shows the different types of AEs, by domain, per treatment strategy. Although based on low numbers per group, and only descriptively, this figure does suggest some differences per treatment strategy. Scars might be more prevalent in the treatment strategies that involve surgery (AMORE and Paris-method). Xerostomia and sinus disorders seem to occur more prevalently in XRT and PBT treated survivors. None of the AMORE treated survivors developed GHD.

Table 4. Multivariate logistic regression model with covariates: tumor site, tumor size and follow-up period

	OR (95% CI)			
	≥grade 2 AE	**≥grade 3 AE**	**High/severe burden**	**>8 AEs**
Site				
NPM	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Orbit	4.8 (0.7 – 33.4)	5.6 (1.0 – 33.1)	2.9 (0.3 – 33.3)	4.9 (0.5– 51.5)
PM	2.0 (0.4 – 10.2)	2.3 (0.5 – 11.0)	2.2 (0.2 – 21.3)	5.9 (0.7 – 52.7)
Size				
<5cm	1 [ref]	1 [ref]	1 [ref]	1 [ref]
>5cm	4.2 (1.0 – 18.2)	**3.7 (1.3 – 10.7)**	2.3 (0.8 – 6.8)	1.9 (0.7 – 5.2)
Follow-up period				
2-5y	1 [ref]	1 [ref]	1 [ref]	1 [ref]
5-10y	1.6 (0.4 – 6.3)	2.7 (0.8 – 9.4)	3.4 (0.6 – 18.3)	2.1 (0.6 – 7.5)
10-15y	9.3 (0.9 – 91.3)	3.0 (0.8 – 12.3)	**5.8 (1.0 – 33.6)**	3.1 (0.8 – 12.7)
>15y	3.2 (0.6 – 15.9)	1.9 (0.5 – 7.0)	3.9 (0.7 – 23.1)	2.4 (0.6 – 9.5)

Comparison of the odds of occurrence of a grade ≥2, grade ≥3, a high or severe burden or >8 different AEs. OR; odds ratio, CI; confidence interval, AE; adverse event, PM; parameningeal, NPM: head-and-neck non-parameningeal, orbit; orbital, Y; years, Tumor size; size of the tumor at diagnosis on the first available imaging. Statistically significant (p value < 0.05) different odds are shown in **bold**.

DISCUSSION

We presented results on a unique and large cohort of HNRMS survivors, with long follow-up time, treated according to four different local treatment strategies in whom the presence of AEs was systematically assessed at multidisciplinary follow up clinics. The results of this study show late AEs in HNRMS survivors are highly

prevalent and diverse, with 82% of survivors experiencing at least a grade ≥2 AE and 61% at least a grade ≥3 AE. Facial deformation, cataract, hearing impairment, speech abnormalities and eyelid malfunction were the most common grade ≥2 AEs and each occurred in over 20% of survivors. This underlines the need for systematic and specialized follow-up care for HNRMS survivors, independent of local treatment strategy.

In general, AEs observed in this study are comparable to those reported in literature [5,6,9,20–25]. However, comparisons with other studies are complicated by differences in data collection and study design, different selection or grading of AEs, differences in follow-up duration or by the selection of very specific subgroups. Childs et al [6] performed a retrospective analysis in 10 survivors of PM RMS treated with PBT and reported ocular AEs and hearing loss in 3/10 and 5/10 survivors respectively; these impairments were all present before the initiation of radiotherapy. Visual dysfunction (30%) and subjective hearing loss (35%) were also amongst the most prevalent AEs in our cohort. Doyen et al [5] prospectively assessed toxicity data on 46 PM RMS survivors at a median follow-up of 34 months following PBT. The authors only observed grade 2 or 3 AEs in 26% and 4% of survivors respectively. Most observed AEs in their study were dry eyes, hyperpigmentation, alopecia and sinusitis. The authors did not evaluate facial deformities, which was the most prevalent AE in our cohort. The difference in prevalence of AEs might very well be due to the shorter follow-up time compared to our study. Our study had a median follow-up time of 9 years (range 2-27), which is long in comparison to other studies. Therefore, we likely have seen more numerous and more severe late AEs, since most AEs develop over time and some, like facial deformation, become more apparent after puberty. Lockney et all [9] evaluated 30 patients treated with IMRT for HNRMS and found facial disfigurement, growth hormone deficiency and cataract (any grade) to be the most common late AEs with 77, 37 and 34 percent of survivors respectively affected. These percentages are comparable to our cohort with 67% facial deformation, cataract in 40% and growth hormone deficiency in 20%.

Schoot et al. reported on a partially overlapping cohort, in a similar cross-sectional analysis inviting survivors to a systematic follow-up clinic [10]. They compared HNRMS survivors treated at 2 different centers according to 2 different national standards: London, with an XRT-based treatment and Amsterdam with an AMORE-based treatment (if feasible, otherwise XRT was used). Despite the partial overlap, we have undertaken the current study because of the addition of 2 other local treatment strategies (PBT and Paris-method). Besides that, to further understand the association between treatment strategy and prevalence and severity of AEs, we only included survivors who had received one round of local treatment (i.e., no relapse and/or secondary malignancies). In the current study, there is a lower prevalence of AEs in both the XRT treated (surgery eligible) and AMORE treated group

compared to that reported by Schoot et al. In the previous report, 20% of survivors in the AMORE-based treatment group received AMORE as a salvage treatment. Also, intended to minimize an allocation bias, Schoot et al. based treatment-group allocation on treatment center rather than treatment modality. This resulted in the fact that part of the survivors in the AMORE-based treatment group were treated with XRT. In the current study, we only included XRT-treated survivors who were surgery-eligible into the comparison between treatment strategies. The hereby excluded XRT-treated not-surgery-eligible survivors all had grade 3 and/or 4 AEs. In the Schoot et al. study, PM-site was an independent risk factor for the occurrence of ≥5 different AEs. In the present study, PM-site showed a higher odds for any or more grade ≥2 AE, grade ≥3 AE and >8 different AEs compared to NPM sites. However, this failed to show statistical significance in the multivariable analysis. Tumor size >5cm at diagnosis was an independent risk factor for the occurrence of any or more grade ≥2 and grade ≥3 AEs in the current cohort. This is likely explained by the simple fact that with a larger tumor the radiation target volume and therefore the quantity and dosage to organs at risk are larger.

With improvement in overall survival for HNRMS survivors, more emphasis is put towards AEs prevention. The XRT techniques are being improved and new strategies, like AMORE and PBT have been implemented. The dosimetric benefit of PBT in comparison to XRT has already been shown in papers analyzing physical dose differences and in the first clinical comparison studies[26-28], but further studies with longer follow-up are necessary to show the true clinical benefit on late AEs. Furthermore, since XRT techniques also improved over time, the late AEs described in historic cohorts might not reflect the toxicity following modern XRT treatment. However, treatment era (prior to or after 2005) was not a statistically significant risk factor on univariable analysis. In the current study we have tried to assess differences in the occurrence of AEs between different treatment strategies. Direct comparison proved to be difficult due to small numbers of survivors per treatment strategy and the heterogeneity between survivors in terms of patient and tumor characteristics. Our results suggest potential differences in grades and types of AEs between different local treatment strategies, but more data are necessary to reveal statistically valid differences.

Further complicating comparative analyses, baseline characteristics between the treatment groups differed in attained age, follow-up duration and treatment era. This is not surprising given the relative novelty of the use of PBT in pediatric HNRMS treatment. These baseline differences might influence our results by underestimating late AEs in the PBT-treated survivors. For example, facial deformation might only become apparent with the growth of unaffected tissues during puberty, leading to visible—but delayed-- asymmetry and hypoplasia [29]. Chemotherapeutic protocols differed slightly between the treatment groups. The prescribed alkylating agent in

COG protocols is cyclophosphamide whereas the European protocols use ifosfamide. Both agents are equally effective in RMS patients and have known toxicity patterns[15]. No differences in long-term HN AEs are expected from these different chemotherapy regimens[30]. All four treatment strategies for HNRMS were included in this study. We aimed to eliminate allocation bias of treatment strategy by using the surgery eligibility criteria. However, in reality the choice to perform AMORE is more refined, a case is discussed in a multi-disciplinary team that discusses the advantages and potential disadvantages of AMORE and decides based on experience and subtle differences. In this study we only used absolute contraindications for AMORE treatment to exclude survivors for comparison, potentially still selecting a less favorable cohort of patients than patients who actually received AMORE treatment. The Paris-method[2] is uniquely indicated for pterygopalatine fossa or infratemporal fossa sites and the vast majority of survivors treated according to the Paris-method had a tumor size >5cm at diagnosis. Both site and size are known risk factors for worse survival. The aim of the Paris-method is to improve survival in this specific patient-group. This might lead to different choices regarding acceptability of late toxicity. The CTCAE is the standard approach to clinical AE reporting in oncology research. However, it is known to have low levels of absolute-agreement of grading in symptomatic patients. Atkinson et al [31] reported agreement ranging from 15-43%. In this study, AEs were scored by locally selected multidisciplinary teams at the four different centers. To ensure uniformity, the lead author (MH) attended all the clinics and explained how different AE scores were interpreted for this study in order to improve agreement.

Conclusion

Late AEs are highly prevalent and diverse in pediatric HNRMS survivors, where 80% of survivors suffer from grade ≥2 AEs. Our results suggest differences in grades and types of AEs between different local treatment strategies, but we were unable to identify statistically valid differences. To better understand and compare the influence of local treatment on the development of AEs, future studies could be directed at radiation dose reduction to specific organs. This could help to advance individualized treatment choices based on AE risk analysis in a process of shared decision making. The data from this study may also be used to optimize follow-up care and guide post treatment clinic visits. The occurrence and prevalence of AEs should help inform parents and patients of difficulties anticipated in later life.

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SUPPLEMENTAL DATA

Table S1. Proportion of patients with a low, medium, high and severe burden of adverse events. By treatment type

	All		**All / surgery eligible**		**XRT / surgery eligible**		**PBT / surgery eligible**		**AMORE**		**Paris-method**	
	N= 98		**N=90**		**N=33**		**N=26**		**N=19**		**N=12**	
	N	***%***	***N***	***%***	***N***	***%***	***N***	***%***	***N***	***%***	***N***	***%***
Low	18	***18***	18	***20***	7	***21***	8	***31***	3	***16***	0	
Medium	54	***55***	49	***54***	15	***46***	13	***50***	13	***68***	8	***67***
High	23	***24***	22	***22***	10	***30***	3	***12***	3	***16***	4	***33***
Severe	3	***3***	3	***3***	1	***3***	2	***8***	0		0	

'all'; all survivors fulfilling the inclusion criteria for this study
'all / surgery eligible'; subset of all the included survivors who would have been eligible for all four local treatment modalities
XRT: external beam radiotherapy with use of photons; PBT: external beam radiotherapy with protons; AMORE: Ablative surgery, MOld brachytherapy and REconstruction; Paris-method; R0 resection followed by external beam radiotherapy.

Table S2. All evaluated adverse events (AE) of any grade. In order of prevalence

	any grade AE											
	all		all / surgery eligible		XRT / surgery eligible		PBT / surgery eligible		AMORE		Paris-method	
	n (N)	%	n (N)	%	n (N)	%	n (N)	%	n (N)	%	n (N)	%
facial deformation	65 (98)	66	59 (90)	66	21 (33)	64	14 (26)	54	12 (19)	63	12 (12)	100
fat/skin atrophy	61 (97)	63	57 (89)	64	19 (33)	58	15 (26)	58	12 (18)	67	11 (12)	92
dermal changes	47 (98)	48	43 (90)	48	12 (33)	37	19 (26)	73	7 (19)	27	5 (12)	42
scar	45 (94)	48	44 (86)	51	16 (32)	50	5 (26)	19	13 (17)	77	10 (11)	91
induration/fibrosis	42 (97)	43	38 (89)	43	16 (33)	49	9 (26)	35	9 (18)	50	4 (12)	33
eyelid malposition	36 (83)	43	35 (75)*	47	9 (29)	31	13 (23)	57	11 (19)	58	2 (4)*	50
dry eye	40 (96)	42	35 (88)	40	9 (32)	28	11 (25)	44	10 (19)	53	5 (12)	42
speech abnormality	37 (90)	41	32 (83)	39	12 (30)	40	9 (26)	35	2 (16)*	13	9 (11)	82
cataract	37 (92)	40	34 (84)	41	12 (31)	39	12 (24)	50	6 (17)	35	4 (12)	33
sinus disorder	29 (91)	32	23 (84)	32	12 (30)	40	12 (26)	46	1 (17)	6	2 (11)	18
xerostomia	28 (89)	32	26 (82)	32	13 (29)	45	7 (26)	27	4 (16)*	25	2 (11)	18
alopecia	30 (97)	31	27 (89)	30	8 (33)	24	11 (26)	42	4 (18)	22	4 (12)	33
ear inflammation	26 (91)	29	25 (84)	30	9 (30)	30	8 (26)	31	2 (17)	12	6 (11)	55
epiphora	22 (80)*	28	21 (72)*	30	7 (28)*	25	7 (23)	30	6 (19)	32	1 (2)*	50
globe displacement	19 (82)*	23	17 (74)*	23	4 (29)	14	7 (23)	39	5 (19)	26	1 (4)*	25
trismus	19 (82)*	23	16 (76)*	21	7 (26)*	27	3 (25)	12	5 (16)*	32	1 (9)*	11
hearing	20 (90)	22	18 (84)	21	5 (30)	17	2 (25)	8	5 (17)	28	6 (11)	55
epistaxis	20 (91)	22	19 (84)	23	6 (30)	20	10 (26)	39	0 (17)	0	3 (11)	27
strabismus	15 (81)*	20	15 (73)*	20	7 (29)	24	3 (23)	13	5 (19)	26	0 (2)*	0

Table S2. *Continued.*

	any grade AE											
	all		all / surgery eligible		XRT / surgery eligible		PBT / surgery eligible		AMORE		Paris-method	
	n (N)	%	n (N)	%	n (N)	%	n (N)	%	n (N)	%	n (N)	%
GHD	17 (91)	19	12 (84)	14	7 (29)	24	4 (25)	16	0 (18)	0	1 (12)	8
facial nerve palsy	14 (75)*	19	12 (67)*	18	7 (30)	23	0 (14)*		4 (16)*	25	2 (8)*	25
taste alteration	14 (89)	16	13 (82)	16	5 (30)	17	5 (25)	20	2 (16)*	13	1 (11)	9
conjunctivitis	12 (78)*	15	10 (71)*	14	2 (28)*	7	7 (23)	31	0 (18)		1 (2)*	50
photofobia	11 (78)*	14	10 (71)*	14	4 (28)*	14	5 (23)	22	0 (18)		1 (2)*	50
thyroid dysfunction	13 (92)	14	9 (85)	11	5 (30)	17	2 (25)	8	0 (18)		2 (12)	17
keratitis	10 (79)*	13	8 (72)*	11	2 (28)*	7	3 (22)*	14	1 (18)	6	2 (4)*	50
osteonecrosis jaw	9 (98)	9	8 (90)	9	5 (33)	15	1 (26)	4	0 (19)		2 (12)	17
opticopathy	7 (78)*	9	5 (71)*	7	2 (29)*	7	3 (23)	13	0 (18)		0 (2)*	
Flashers/floaters	6 (77)*	8	6 (70)*	9	4 (28)	14	2 (22)	9	0 (18)		0 (2)*	
gonadal dysfunction	7 (94)	7	4 (86)	5	1 (31)	3	2 (25)	8	1 (18)	6	0 (12)	0
resp. infection	6 (90)	7	4 (83)	5	1 (30)	3	0 (26)		1 (16)*	6	2 (11)	18
short stature	6 (96)	6	5 (88)	6	1 (32)	3	1 (25)	4	2 (19)	11	1 (12)	8
retinopathy	5 (89)	6	5 (84)	6	1 (30)	3	3 (25)	12	1 (18)	6	0 (11)	
adrenal dysfunction	5 (95)	6	43 (86)	5	2 (31)	6	1 (25)	4	0 (18)		0 (12)	0
soft tissue necrosis	5 (97)	5	5 (89)	6	4 (33)	12	1 (26)	4	0 (19)		0 (11)	
GI infection	4 (91)	4	2 (84)	2	0 (30)		2 (26)	8	0 (17)		0 (11)	
early puberty	4 (91)	4	1 (85)	1	1 (30)	3	0 (25)		0 (18)		0 (12)	
papiledema	1 (77)*	1	1 (70)*	1	1 (28)*	4	0 (22)*		0 (18)		0 (2)*	

Table S2. *Continued.*

	any grade AE											
	all		all / surgery eligible		XRT / surgery eligible		PBT / surgery eligible		AMORE		Paris-method	
	n (N)	%	n (N)	%	n (N)	%	n (N)	%	n (N)	%	n (N)	%
uveitis	1 (72)*	1	1 (67)*	2	0 (27)*		1 (22)*	5	0 (17)		0 (2)*	
glaucoma	0 (78)*	0										
scleral disorder	0 (76)*	0										
vitreous hemorrhage	0 (75)*	0										
retinal detachment	0 (90)	0										

XRT: external beam radiotherapy with use of photons; PT: external beam radiotherapy with protons; AMORE: Ablative surgery, MOuld brachytherapy and REconstruction; Paris-method: R0 resection followed by external beam radiotherapy
GHD; growth hormone deficiency
Resp. infection: respiratory tract infection
GI infection: gastro-intestinal tract infection
*data on specific AE missing for ≥10% of survivors

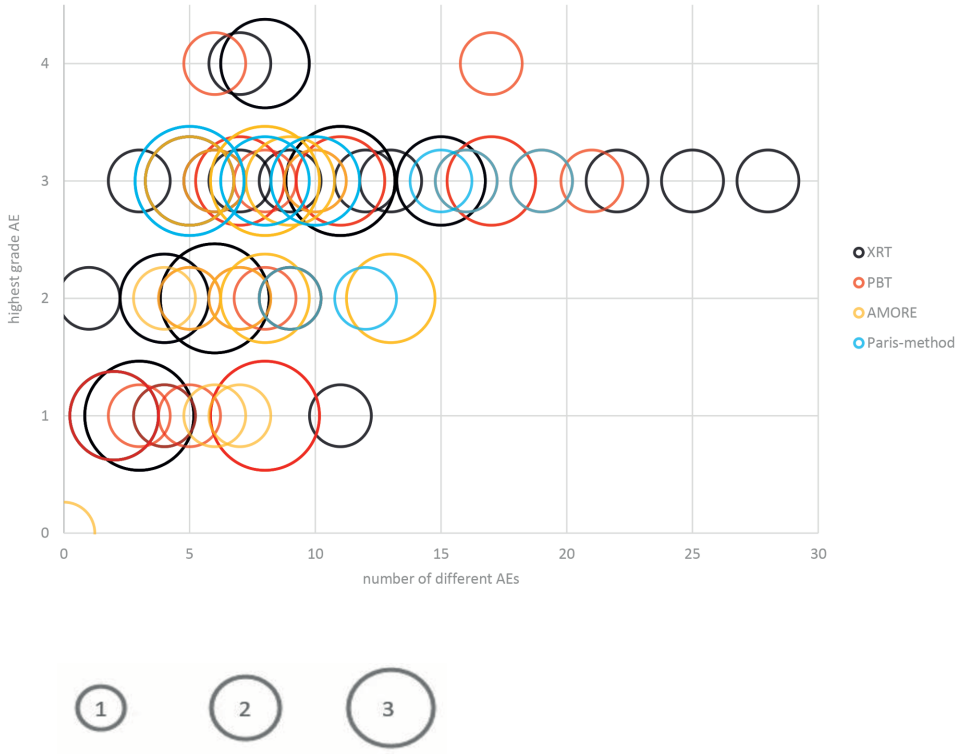

Figure S1. Total number of different adverse events (AE) plotted against the highest grade AE per survivor.

Organized by treatment strategy. The size of the circles represent the contributing numbers of survivors.
XRT: external beam radiotherapy with photons; PBT; external beam radiotherapy with protons; AMORE: Ablative surgery, MOld brachytherapy and REconstruction; Paris-method: R0 resection followed by external beam radiotherapy to the margins. Only surgery eligible survivors are included.

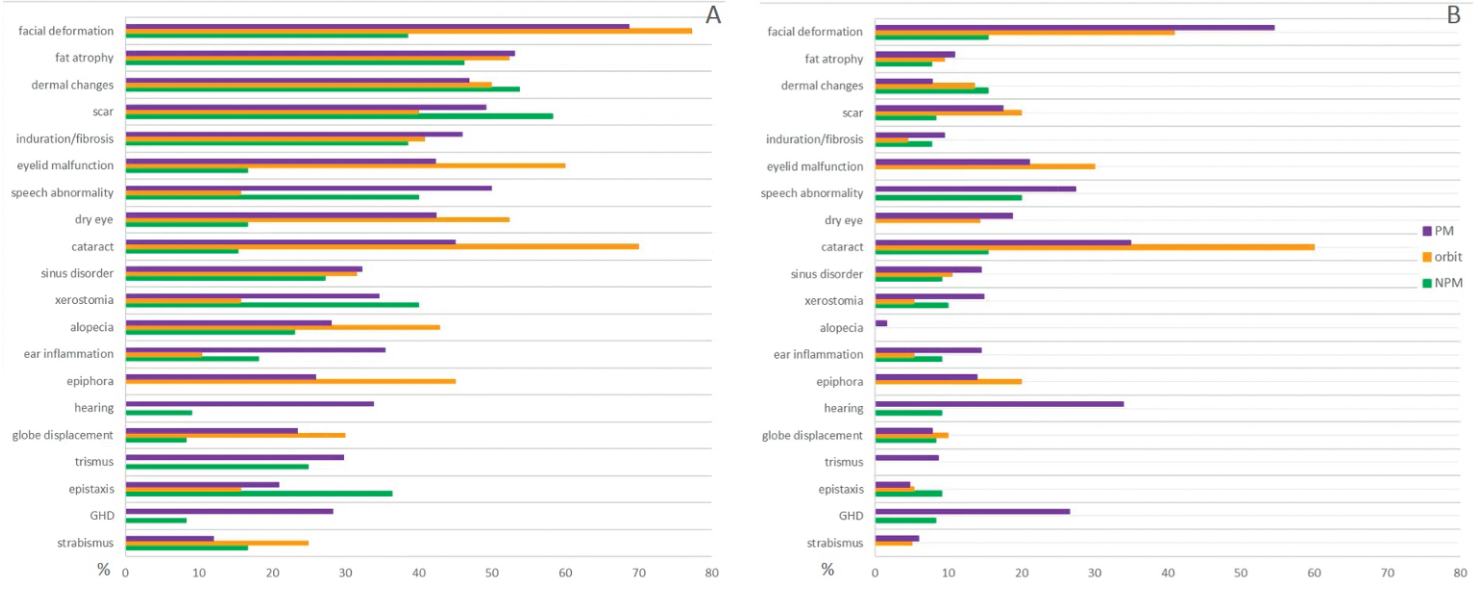

Figure S2a. Percentage of occurrence of the 20 most prevalent AEs of any grade (A) and grade ≥2 (B), organized by tumor site.

PM; parameningeal, NPM: head-and-neck non-parameningeal, orbit; orbital.
* In case of missing data on a specific AE, the presented percentages are based on the number of survivors with data available. A more detailed description of the AEs can be found in supplement 2.

Table S3. Univariate analyses comparing the odds of experiencing a grade ≥2, grade ≥3, a high or severe burden of adverse events (AEs) or >8 different AEs for different potential risk factors

	OR (95% CI)			
	≥grade 2 AE	**≥grade 3 AE**	**High/severe burden**	**>8 AEs**
Age at diagnosis				
0-5y	1 [ref]	1 [ref]	1 [ref]	1 [ref]
5-10y	0·7 (0·2 – 2·3)	0·4 (0·2 – 1·1)	1·8 (0·7 – 4·6)	1·1 (0·5 – 2·8)
>10y	0·3 (0·07 – 1·1)	0·4 (0·1 – 1·4)	1·0 (0·2 – 4·1)	0·8 (0·2 – 2·9)
Attained age				
4,5 - 12y	1 [ref]	1 [ref]	1 [ref]	1 [ref]
12- 18y	2·1 (0·5 – 8·0)	1·6 (0·6 – 4·8)	2·1 (0·6 – 7·1)	2·6 (0·9 – 7·8)
>18y	1·5 (0·4 – 4·7)	0·8 (0·3 – 2·2)	2·1 (0·7 – 6·9)	2·0 (0·7 – 5·7)
Follow-up period				
2-5y	1 [ref]	1 [ref]	1 [ref]	1 [ref]
5-10y	2·3 (0·7 – 8·3)	**3·2 (1·0 – 10·0)**	4·0 (0·8 – 20·3)	2·5 (0·8– 8·5)
10-15y	4·8 (0·9 – 26·4)	2·7 (0·8 – 9·3)	**5·8 (1·1 – 32·1)**	3·5 (0·9 – 13·2)
>15y	3·2 (0·7 – 14·5)	1·6 (0·5 – 5·3)	3·6 (0·6 – 20·2)	2·2 (0·6 – 8·3)
Tumor site				
NPM	1 [ref]	1 [ref]	1 [ref]	1 [ref]
orbit	5·0 (0·9 – 27·5)	**5·3 (1·1 – 26·6)**	3·1 (0·3 – 30·8)	5·0 (0·5 – 47·3)
PM	**4·7 (1·2 – 18·3)**	**4·7 (1·1 – 19·3)**	4·3 (0·5 – 36·3)	**9·4 (1·1 – 77·8)**
Histology*				
Favorable	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Unfavorable	0·8 (0·2 – 2·6)	0·6 (0·2 – 1·7)	0·3 (0·1 – 1·3)	1·5 (0·6 – 4·3)
Tumor size				
<5cm	1 [ref]	1 [ref]	1 [ref]	1 [ref]
>5cm	3·2 (0·9 – 12·2)	**2·9 (1·2 – 7·5)**	2·1 (0·9 – 5·4)	2·2 (0·9 – 5·2)
Treatment modality**				
XRT	1 [ref]	1 [ref]	1 [ref]	1 [ref]
PBT	0·6 (0·2– 2·0)	0·9 (0·3 – 2·4)	0·5 (0·1 – 1·6)	1·0 (0·3 – 2·8)
AMORE	1·4 (0·3 – 6·4)	0·7 (0·2 – 2·1)	0·4 (0·1 – 1·6)	0·5 (0·2 – 1·9)
Paris-method	>>>	3·7 (0·7 – 19·5)	1·0 (0·2 – 4·1)	2·5 (0·6 – 8·2)
Period of treatment				
1993-2005	1 [ref]	1 [ref]	1 [ref]	1 [ref]

Table S3. *Continued.*

	OR (95% CI)			
	≥grade 2 AE	**≥grade 3 AE**	**High/severe burden**	**>8 AEs**
2005-2017	0·5 (0·1 – 1·9)	1·2 (0·5 – 3·1)	1·2 (0·4 – 3·4)	0·9 (0·3 – 2·2)

*favourable histology includes embryonal rhabdomyosarcoma. Unfavourable histology includes: alveolar rhabdomyosarcoma, undifferentiated and NOD
**only surgery eligible patients included in analysis with comparison of treatment groups
Univariate binary logistic regression. Statistically significant difference in OR in bold.
OR: odds ratio; CI: confidence interval
Y: years, PM: parameningeal; NPM: head-and-neck non-parameningeal; orbit: orbital, Tumour size: size of the tumour at diagnosis on the first available imaging
XRT: external beam radiotherapy with photons; PBT; external beam radiotherapy with protons; AMORE: Ablative surgery, MOld brachytherapy and REconstruction; Paris-method: R0 resection followed by external beam radiotherapy

Table S4. Multivariate logistic regression model comparison the odds of occurrence of a grade ≥2, grade ≥3, a high or severe burden or >8 different AEs.
With covariates tumor site, tumor size, follow-up period (based on univariate logistic regression) and treatment modality brought into the model.

			OR (95% CI)	
	≥grade 2 AE	**≥grade 3 AE**	**High/severe burden**	**>8 AEs**
Modality *				
XRT	1 [ref]	1 [ref]	1 [ref]	1 [ref]
PBT	1·7 (0·3 – 8·8)	1·0 (0·2 – 4·2)	0·7 (0·1 – 4·2)	1·7 (0·4 – 7·6)
AMORE	2·4 (0·3 – 17·1)	0·7 (0·2 – 2·6)	0·5 (0·1 – 2·1)	0·8 (0·2 – 3·2)
Site				
NPM	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Orbit	4·8 (0·6 – 35·9)	**7·0 (1·1 – 44·5)**	3·0 (0·3 – 36·2)	3·6 (0·3 – 37·7)
PM	1·5 (0·3 – 8·4)	1·6 (0·3 – 8·1)	1·8 (0·2 – 18·3)	5·3 (0·6 – 48·2)
Tumor size				
<5cm	1 [ref]	1 [ref]	1 [ref]	1 [ref]
>5cm	2·5 (0·5 – 12·5)	**5·1 (1·3 – 19·3)**	2·7 (0·7 – 10·8)	1·0 (0·3 – 3·4)
Follow-up period				
2-5y	1 [ref]	1 [ref]	1 [ref]	1 [ref]
5-10y	1·5 (0·3 – 7·2)	2·1 (0·5 – 9·2)	4·4 (0·5 – 43·4)	3·2 (0·6 – 15·8)
10-15y	**15·6 (1·2 – 195·8)**	**5·3 (0·9 – 32·0)**	8·6 (0·7 – 109·4)	3·7 (0·6 – 25·2)
>15y	5·7 (0·8 – 40·8)	2·5 (0·5 – 13·7)	5·8 (0·5 – 74·2)	3·8 (0·6 – 25·5)

*only surgery-eligible survivors included. Paris-method not included because of collinearity with site (all PM site), total N = 78 included in the model
OR: odds ratio; CI: confidence interval
Y: years, PM: parameningeal; NPM: head-and-neck non-parameningeal; orbit: orbital,
Tumor size: size of the tumor at diagnosis on the first available imaging
XRT: external beam radiotherapy with photons; PBT; external beam radiotherapy with protons; AMORE: Ablative surgery, MOld brachytherapy and REconstruction; Paris-method: R0 resection followed by external beam radiotherapy
Statistically significant (p value < 0.05) different odds are shown in **bold**

SUPPLEMENTAL DATA 2

Description of categories of adverse events (AEs):
A selection of predefined AEs was graded according to the Common Terminology Criteria for Adverse
Events (CTCAEv4.0, available at http://evs.nci.nih.gov/ftp1/CTCAE/About.html).
Our group has previously tested all potential AEs of local treatment in the head and neck area in a pilot study in 14 HNRMS survivors. All essential items not listed in CTCAEv4.0 were then added and graded in analogy of the CTCAE system.
Since part of the specifically graded AEs describe a similar clinical problem, we have grouped these AEs into categories for the analyses:

"Dermal changes" consists of the CTCAE categories dry skin, dermal changes due to lymfedema, radiation dermatitis
"Eyelid malfunction" consists of: ectropion, entropion, lid retraction, ptosis or trichiasis
"Speech abnormality" consists of: rhinolalia or dysarthria
"Globe displacement" consists of: enophtalmus or exophtalmus
"Strabismus" consists of: esotropia, exotropia, hypertropia, hypotropia, vertical displacement or horizontal displacement of the eye
"adrenal" consist of: ACTH deficiency, cushingoid appearance or adrenal deficiency
"gonadal" consist of: gonadotrofin deficiency or late puberty

SUPPLEMENTAL DATA 3

Description of patient cases with a severe burden of AEs (N = 3)

Case 1:
Girl, diagnosed at age 6y with a parameningeal tumor with extension to the orbit, localized disease, with a favorable histology. She was treated with 50.4GyRBE protons. At the time of the clinic visit she was 10y after treatment. Her most important AEs consisted of visible facial differences and ocular problems. She had a grade 3 facial deformity and fat atrophy, induration and fibrosis of the skin. She was blind in one eye because of cataract, besides that she had grade 3 dry eyes, watering eyes and eyelid displacement consisting of lidretraction and trichiasis. She had corneal damage with a grade 3 keratitis. She had a photofobia which limited her daily activities (grade 3).

Case 2:
Boy, diagnosed at age 3y with a parameningeal tumor >5cm with extension to the orbit, localized disease, with favorable histology. He was treated with 45Gy XRT. At the time of the clinic visit he was 17y after treatment. He had a growth hormone deficiency requiring growth hormone suppletion. He was blind because of a grade 4 opticopathy and grade 4 cataract. He had a grade 3 keratitis. He had had squint surgery performed in the past.

Case 3:
Girl, diagnosed at age 0.8y with a parameningeal tumor >5cm arising from the mandible to the temporal fossa, localized disease with favorable histology. She was treated with 50.4GyRBE protons. At the time of the clinic visit she was 8 years after treatment. She presented with visible facial differences including a grade 3 facial deformity, fat- and skin atrophy. Besides that, she had a mild trismus, subjective hearing loss and mild rhinolalia. She was blind in one eye because of grade 4 opticopathy and cataract. She had a grade 2 photofobia.

2

Facial deformation following treatment for pediatric head and neck rhabdomyosarcoma; the difference between treatment modalities. Results of a trans-Atlantic, multi-center cross-sectional cohort study

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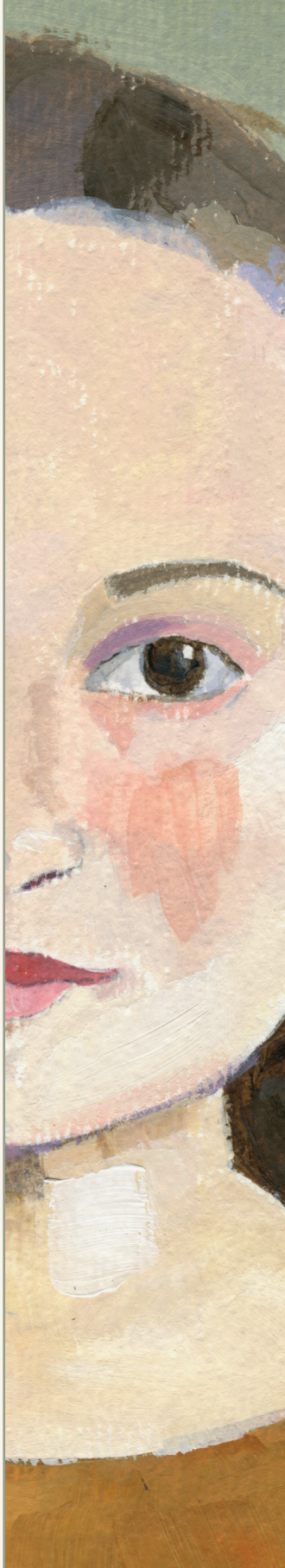


ABSTRACT

Background

The four different local therapy strategies used for head and neck rhabdomyosarcoma (HNRMS) include proton therapy (PT), photon therapy (RT), surgery with radiotherapy, and surgery with brachytherapy (AMORE). Local control and survival is comparable; however, the impact of these different treatments on facial deformation is still poorly understood. This study aims to quantify facial deformation and investigates the differences in facial deformation between treatment modalities.

Methods

Across four European and North-American institutions, HNRMS survivors treated between 1990-2017, >2 years post-treatment, had a 3D-photograph taken. Using dense surface modeling, we computed facial signatures for each survivor to show facial deformation relative to 35 age-sex-ethnicity matched controls. Additionally, we computed individual facial asymmetry.

Findings

173 HNRMS survivors were included, survivors showed significantly reduced facial growth ($p<0.001$) compared to healthy controls. Partitioned by tumor site, there was reduced facial growth in survivors with non-parameningeal primaries ($p=0.002$), parameningeal primaries ($p=<0.001$), but not for orbital primaries ($p=0.080$) All patients were significantly more asymmetric than healthy controls, independent of treatment modality ($p=<0.001$). There was significantly more facial deformation in orbital patients when comparing RT to AMORE ($p=0.046$). In survivors with a parameningeal-site, there is significantly less facial deformation in PT when compared to RT ($p=0.009$) and Paris-method ($p=0.007$).

Interpretation

When selecting optimal therapy, musculoskeletal facial outcomes are an expected differences between treatment options. These anticipated differences are currently based on clinicians' bias, expertise, and experience. This data supplements clinician judgement with an objective analysis highlighting the impact of patient age and tumor site between existing treatment options.

INTRODUCTION

With modern therapy, most children treated for head and neck rhabdomyosarcoma (HNRMS) have a favorable prognosis with a five-year survival rate of up to 70-95% depending on risk group (1–4). Long term adverse effects of treatment may be life-altering in survivors. Facial deformation is a frequently occurring late adverse effect, which has a recognized negative impact on quality of life (5–8). As we continue to improve the trajectory of disease control, treatments that reduce the potential negative impact on quality of life without jeopardizing survival become a clinical priority.

Currently, treatment for HNRMS consists of systemic chemotherapy and local treatment. The latter usually involves some form of radiotherapy and/or surgery (9). With a mean age at diagnosis of five years, patients are typically young at the time of local control interventions, which may result in extensive adverse effects on musculoskeletal development in the head and neck area. There are currently four different local treatment options for HNRMS. The international standard for HNRMS treatment has traditionally been definitive external beam radiotherapy with photons (RT). Because of the high risk of substantial late adverse effects, attempts have been made to explore other local therapy modalities to reduce side effects. In the 1990s, a new treatment was developed in the Netherlands, combining surgery with brachytherapy (ablative surgery, mold brachytherapy, and reconstructive surgery (AMORE)) (10). AMORE limits the radiation dose to healthy tissues because of a rapid dose fall-off, however, it also introduces potentially harmful surgery. In a previous report by our group, we showed AMORE caused fewer late adverse effects than RT (6). Another advancement aiming to reduce treatment burden was the development of definitive external beam proton therapy (PT). PT capitalizes on the unique physical properties of heavy particles to maintain high tumor doses while reducing normal tissue exposure to ionizing radiation with a rapid dose fall-off, hypothetically mitigating late adverse effects (11,12). At Institute Gustave Roussy, Paris (IGR), surgery is combined with lower dose adjuvant RT or PT to a limited target defined by the surgical resection, referred to as Paris-method (13). While PT and RT can be used in all HNRMS, the Paris-method is used in a selected high-risk population with parameningeal tumors and AMORE is used in a selected cohort of patients. In most clinics, the choice of local control depends on the availability of treatment modalities, regional practice, and clinical experience.Current literature suggests that all four treatment options achieve similar survival rates; however, differences in rate and characterization of late adverse effects remain unclear.

In survivors of paediatric HNRMS, the prevalence of facial deformity approaches 90% in recent reports (6,14,15). However, these studies use only patient- or physician-reported facial assessments and fail to assess facial deformation objectively. The

development of 3D stereophotogrammetry, also called 3D photography, has made it possible to produce accurate, life-like, 3D images of the human face (16,17). The 3D images can capture the soft tissue of the face with sub-millimetre accurate surface geometry, which is accompanied by detailed texture information (17, 19). The advent of 3D photography has made it possible to produce objective and reliable representations of the face, enabling quantification of facial abnormalities, growth, and dysmorphism. Dense surface modeling (DSM) is a statistical method used to analyse 3D images enabling comparisons between patients and healthy controls, providing an objective and quantifiable assessment of facial deformation. DSMs have been used extensively to analyze 3D facial characteristics associated with neurodevelopmental and facially-affected genetic conditions (19–22). In a previous study using DSM, we observed a significantly higher degree of facial asymmetry in survivors of HNRMS compared to controls (23). However, there are no studies comparing variation of facial deformation among HNRMS local treatment options.

Accurately assessing facial deformation following radiation and surgery could advance decision-making and personalize treatment choices for each child based on tumor and patient characteristics. Therefore, this study aims to quantify facial deformation in HNRMS survivors using a new objective measurement method and investigate the differences in facial deformation among the four contemporary treatment approaches.

MATERIALS AND METHODS

To include all four treatment modalities and enroll a sufficient number of HNRMS survivors, we established a collaboration between the Academic Medical Center (AMC) in Amsterdam, which later transferred its pediatric oncologic care to the Princess Máxima Center in Utrecht, the Netherlands (PMC); Great Ormond Street Hospital for Children (GOSH), University College London Hospital and The Royal Marsden Hospital in London, United Kingdom; IGR in Paris, France; and University of Florida Health Proton Therapy Institute (UFHPTI) in Jacksonville, United States. This study was approved by the local ethical committees of all participating centers and relevant national review boards. Written or oral consent was obtained based on local and national standards. For study purposes, late adverse events clinics for HNRMS survivors were held at AMC/PMC, GOSH, IGR and UFHPTI. All children with primary HNRMS treated between 1990-2017 who were a minimum of two years post-treatment were invited to participate in this study. Survivors were physically examined and assessed using the Common Terminology Criteria for Adverse Effects (CTCAE version 4.0) by multiple clinicians who also acquired blood work and 3D photography.

Survivors

All survivors were treated following consecutive International Society for Pediatric Oncology (SIOP)-Malignant Mesenchymal Tumour group (MMT), European paediatric Soft tissue sarcoma Study Group (EpSSG)RMS 2005 or Children's Oncology Group (COG) guidelines. For local treatment, RT, PT, AMORE or Paris-method was used. At the AMC, patients were eligible for AMORE when a macroscopic resection followed by brachytherapy mould placement was considered feasible by a multi-disciplinary team. If not feasible, patients received definitive RT or PT. At GOSH, local treatment was delivered according to the international standard: definitive RT, or in later years, PT. At UFHPTI, all patients underwent PT. At IGR, if deemed possible, the local treatment consisted of the Paris-method; otherwise, patients received definitive PT or RT. For group comparisons with AMORE or Paris-method, patients who received RT or PT but would not have been eligible for surgery were excluded to eliminate treatment selection bias. Surgical eligibility was assesed by 3 different head and neck surgeons in 3 of the participating centers (GOSH, PMC, IGR) based on radiological imaging and resulted in the exclusion of patients in the RT and PT group with intracranial extension, carotid artery encasement and peri-neural spread at the time of assessment of local therapy approach, i.e. after three cycles of induction chemotherapy. Patients were grouped based on tumor site, defined according to international RMS treatment protocols, i.e., orbital, non-parameningeal (NPM), and parameningeal (PM).

Healthy controls

All survivor 3D images were compared to healthy individuals of the same sex, age, and ethnicity. Healthy individuals were recruited as volunteers when attending clinics with siblings at UCL Great Ormond Street Institute of Child Health or the AMC in Amsterdam. Healthy controls were also recruited at schools in the Netherlands. Controls had no known syndrome, craniofacial surgery, or substantial trauma in their history or received treatment for cancer in their past. The database of healthy individuals available to be used as controls in this study consisted of 588 3D images.

3D stereophotogrammetry capture and analysis

3D facial images were taken either with a Vectra handheld camera (www.canfield.com) or the 3dMD 3-pod camera (www.3dMD.com). Both cameras perform with reliable precision, and geometric accuracy does not differ between them (24). The captured images consist of approximately 30,000 3D surface points per image. A single user (MH) manually annotated all images with a sparse set of 24 anatomically reliable landmarks; all landmark positions were confirmed by a second researcher (MS) and corrected where necessary. DSM construction requires these landmarks for surface alignment and warping to create a dense correspondence of points across all surfaces; a principal component analysis (PCA) was then applied to represent the variation of this point correspondence. An individual 3D surface was

resynthesized as a weighted linear sum of principal components (PCs) that account for 99% of the shape variation. We computed DSMs for five different representative models: the full face, the zygomatic area, the lower midface, the full face excluding orbits, and the nose.

Using the localized DSM models, we computed heat maps (facial signatures) for each patient to show surface displacement relative to 35 age-sex-ethnicity matched controls. These heat maps represent localized shape differences for an individual compared to an age-sex-ethnicity matched mean, to quantify the severity and location of facial deformities. To determine a metric for the severity of dysmorphism, we utilize the facial signature weight (FSW) as the Euclidean distance between the vectors representing the normalized differences across all densely corresponded points. Further technical details and method descriptions are provided elsewhere (20,22).

For a pair of faces, we defined a metric face signature difference (FSD) as the Euclidean distance between the vectors indexed by the densely corresponded vertices of the DSM and the representative face signatures. Thus, FSD is based on tens of thousands of 3D surface points. FSD is a measure of the difference in morphology between two individuals after each has been normalized with respect to suitable sets of age and sex-matched controls.

Additionally, we computed individual facial asymmetry by comparing the original image with its reflected form. As with previous DSM asymmetry analyses (19,25–27) we generated reflected facial surfaces for each patient, swapping left and right landmarks before generating new DSM models containing both original and reflected surfaces. For asymmetry analysis, patients were matched to 35-age-sex-ethnicity healthy controls, where asymmetry was corrected for age. We calculated a simple measure of asymmetry (asymmetry index) for each patient as a generalized Euclidean distance between the PC vectors representing each face and its reflected form.

Statistical methods

Since the data were not normally distributed, we used Mann-Whitney tests to compare treatment groups in the four different models. For subgroup analysis, post-hoc Bonferroni testing was performed. For correlation models, Spearman's rank correlation coefficient was used (weak correlation if 0.25-05, moderate for 05-0.75, strong for 0.75-0.9, and very strong for 0.9-1.0). All p-values were set at a statistical significance level of 0.05. All analyses were conducted using SPSS version 26.0 (SPSS Inc). There was no group comparison made when a group contained less than 12 survivors, therefore in survivors with an orbital and NPM site, only RT and AMORE were compared. For the PM site, all treatment types were evaluated. In this

analysis, we used age at treatment and age at follow-up as a univariate variable. Age at treatment was calculated as the date of ending local treatment, and age at follow-up as the date of outpatient clinic visits.

RESULTS

Survivors

In total 173 patients were included, divided into treatment groups; RT (n=58), AMORE (n=49), PT (n=34), and the Paris-method (n=32). Baseline characteristics are shown in Table 1. For group comparisons, six patients were excluded since they would not have been eligible for macroscopic surgery due to carotid encasement and perineural spread. The main difference between treatment groups was the age at follow-up and consequently follow-up time. For PT, the age at follow-up was significantly younger with a mean age of 13.4 years compared to 18.1 years, 19.3 and 16.8 for RT, AMORE, and Paris-method respectively (all $p<0.05$). Follow-up time was shorter for survivors who received PT and Paris-method, with a mean of 7.8 years and 8.8 years, and 12.4 and 12.6 years for RT and AMORE, respectively (all $p< 0.05$). Survivors treated with the Paris-method were older at the time of treatment, with a mean treatment age of 8.1 years of age compared to 5.5, 6.6 and 5.7 years for RT, AMORE and PT, respectively.

Table 1. Baseline characteristics

	RT (N=58)	AMORE (N=49)	Proton therapy (N=34)	Paris (N=32)
Mean Age at 3D photo yrs (Range)	18.1 (6.5 – 32,3)	18.9 (5.2 – 31.7)	13.4 (3.3 – 28.1)	16.8 (5.0 – 31.1)
Mean Treatment Age (Range) in yrs	5.7 (0.8 – 15.7)	6.3 (0.2 – 14.6)	5.6 (0.5 – 16.4)	7.9 (2.1 – 17.4)
Mean Follow-up time in yrs (Range)	12.4 (2.1 – 23.7)	12.6 (2.8 – 24.8)	7.8 (2.0 – 22.9)	8.8 (2.7 – 21.7)
Sex (% Female)	37.3%	46.9%	50%	52.9%
Location				
PM n (%)	30 (52%)	20 (41%)	16 (47%)	22 (69%)
NPM n (%)	13 (22%)	13 (27%)	9 (26%)	8 (25%)
Orbit n (%)	15 (26%)	16 (33%)	9 (26%)	2 (6%)

Abbreviations: AMORE; Ablative Surgery, Moulage Brachytherapy and Reconstructive Surgery, RT; External Beam Photon Radiotherapy, NPM; Non-parameningeal, PM; Parameningeal, yrs; years.

Growth

The first principal component (PC1) is representative of facial growth. Facial growth is depicted in Figure 1 using the entire face (earless model), where PC1 is representative of overall size variation, shown partitioned for treatment location. Compared to age-sex-ethnicity-matched healthy controls, patients overall show significantly reduced facial growth (p<0.001), with a PC1 mean of -0.404 (95% CI [-0.54—0.27] for survivors and a mean of 0.503 (95% CI [0.382 – 0.624] for healthy controls. However, when partitioning by tumor site, there was significantly less facial growth in patients with both a NPM site (p=0.002) (mean -0.273 [95% CI -0,667-0,119]) and a PM site (p=<0.001) (mean -0.671, 95% CI [-1.127—0.214]), but not in survivors with an orbital site of the tumor (p=0.080) (mean 1.672, 95% CI [1.328-1.996]).

Due to insufficient patient numbers, PT and Paris-method were not compared in NPM and orbital patients. When comparing AMORE and RT there was no statistically significant difference in facial growth in orbital patients (p=0.108) or NPM patients (p=0.074).

In survivors with a PM tumor, there was potentially less impact on facial growth with PT in comparison to AMORE (p=0.008), RT (p=0.008), and Paris-method (p=0.007); however, in terms of baseline characteristics, survivors treated with PT had a shorter follow-up period and were significantly younger at their return clinic visit, with a median age of 13.4 years (3.3 – 31.1 years. In the PM-group, this was 70% (n=11). Therefore, when follow-up age for patients receiving PT was taken into account, group size decreased to below the threshold for a meaningful comparison. There is no significant difference in survivors with a PM tumor between RT and AMORE (p=0.894), RT and Paris-method (p=0.284), or AMORE and Paris-method (p=0.224).

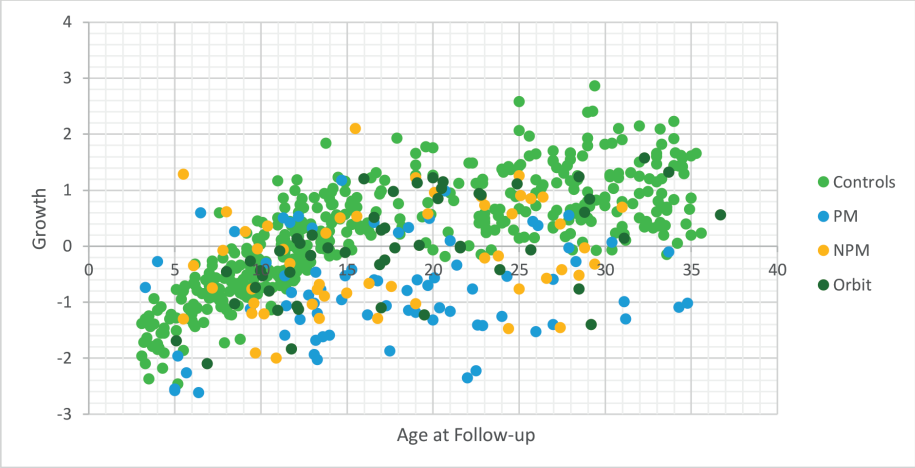


Figure 1. Growth for all survivors and healthy controls split out for tumor site.

Growth of healthy controls and rhabdomyosarcoma survivors with different tumor sites (i.e., Parameningeal (PM), Non-parameningeal (NPM), Orbit). The figure shows that both controls and survivors show growth of the face up until about 12 (10-15) years of age, after which they reach full growth (above horizontal zero-line). There is a normal variation in both controls and patients. The survivors with a NPM or PM tumor show reduced growth, however, the survivors of a tumor located in the orbit show similar growth to the healthy controls. Abbreviations:, NPM; Non-parameningeal, PM; Parameningeal.

Normalized Asymmetry Score

The facial asymmetry index is depicted in Figure 2. All patients were significantly more asymmetric than the healthy controls, no matter the treatment modality (p=<0.001).

Survivors with an orbital tumor were significantly less asymmetric than survivors with a PM tumor (p=0.001) and a NPM tumor (p=0.005). There was no significant difference in asymmetry between survivors with a NPM and PM site (p= 0.970).

There was no significant difference in asymmetry between treatment with AMORE and RT in survivors with an orbital tumor (p=0.631) or NPM tumor (p=0.075). Survivors with a PM tumor were significantly more asymmetric when treated with Paris-method compared to all other modalities: RT (p=0.003), AMORE (p=0.012) and PT (p=0.03). There was no significant difference in asymmetry in survivors with a NPM tumor treated with RT vs AMORE (p=0.648), RT vs PT (p=0.064), AMORE vs PT (p=0.128) or PT vs Paris-method (p=0.288).

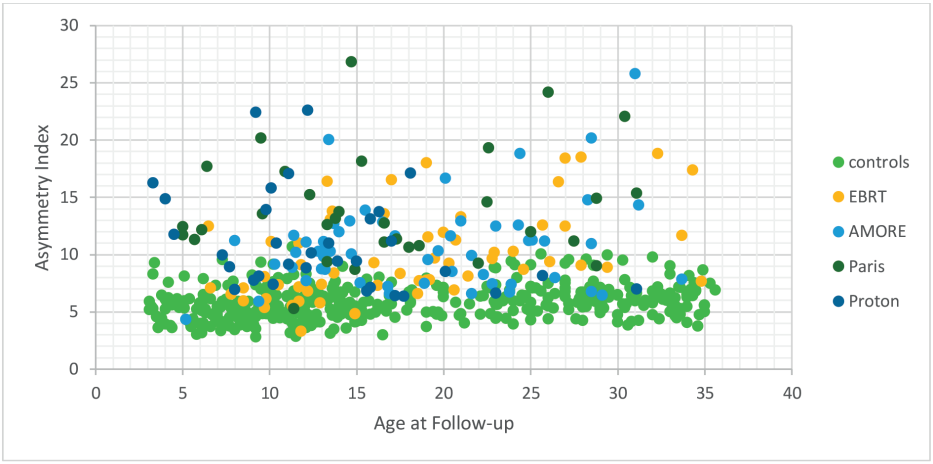


Figure 2. Normalized asymmetry score for all survivors and healthy controls, split out for treatment modality.

The asymmetry index for both healthy controls and survivors treated with different treatment modalities is shown in this figure. Regardless of age at scan, healthy controls have mild asymmetry (varying from near zero to about 10 asymmetry index). Survivors treated with RT who are still before the age of 15 show similar asymmetry to the healthy controls. However, patients treated with AMORE, Paris-method or proton treatment show a broad spectrum of asymmetric facial development.
Abbreviations: AMORE; Ablative Surgery, Moulage Brachytherapy and Reconstructive Surgery, RT; External Beam Photon Radiotherapy.

Facial Signature Analysis

Mean facial signatures for each treatment modality are shown in figure 3 (incl. means and ranges). In the earless model, there is significantly more facial deformation in orbital patients when comparing RT to AMORE ($p=0.046$). There is no significant difference between patients with a NPM tumor location between RT and AMORE. In survivors with a PM site, there is significantly less facial deformation in PT when compared to RT ($p=0.009$) and also compared to Paris-method ($p=0.007$). There was no difference in survivors with a PM-tumor between RT and Paris-method ($p=0.282$).

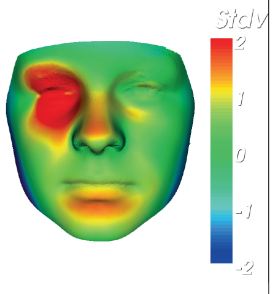
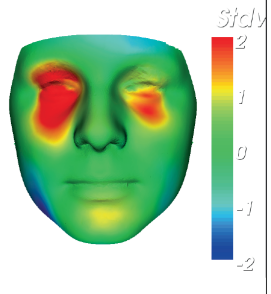
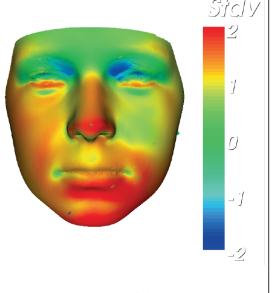
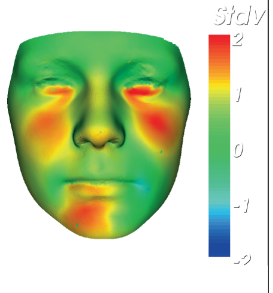
Age effect

Facial growth increased as patients aged until it plateaued when survivors achieved adult facial maturity at 10-15 years old (Figure 1). Beyond that point, increased follow-up duration does not result in additional facial deformation [$r = 0.213$ ($p<0.001$)]. In patients with a PM location AMORE, PT and RT result in similar trendlines resulting in less facial deformation in older patients. However, the Paris-method results in more facial deformation in older patients compared to young patients treated with the Paris-method.

DISCUSSION

The data from our cross-sectional cohort study suggest that all HNRMS survivors show significantly reduced facial growth along with more facial deformation and asymmetry in comparison to their healthy counterparts. Survivors with an orbital tumor have more favorable facial growth and symmetry compared to survivors with a PM and NPM tumor. For patients with a NPM and orbital tumor location, only AMORE and RT could be compared. In survivors with an orbital tumor, AMORE caused less facial deformation than RT. These data suggest that in patients with an orbital tumor where facial deformation is the only expected difference AMORE is favorable over RT. In patients with a PM site PT is favorable over RT and the Paris-method. All treatment options except the Paris-method showed a similar trend of decreased facial deformation with increasing age at the time of treatment. The uncoupling of age-effect for the Paris-method patients may be explained by the extent of surgery needed for microscopic tumor resection and subsequent necessary reconstruction (13).

The data from this study align with the rationale and pursuit of modern techniques intended to diminish late adverse events. The potential dosimetric advantage favoring PT over RT for HNRMS has previously been evaluated in a dosimetric comparison study, although the clinical relevancy of the dosimetric differences is still subject of discussion (13). Poor facial cosmesis and facial abnormalities negatively affect mental health and emotional well-being, resulting in impaired quality of life (8,28). In previous studies, facial asymmetry and hypoplasia are widely reported in up to 77% of HNRMS survivors (5,6,25,29). All these studies use patient- or physician-reported outcome measurements and are therefore inherently subjective. In a pilot study only including patients treated with either AMORE or RT, we used 3D facial analysis to quantify facial asymmetry, showing all survivors experienced more facial asymmetry than their healthy counterparts (25). However, facial asymmetry may not be the best measurement in these patients since the contralateral face can also be affected by impaired growth and development caused by radiation and/or surgery. Paradoxically, the more conformal treatment options could actually lead to more asymmetry by sparing the healthy side of the face. Therefore, we mainly used facial difference scores in this current study partitioned for specific areas of the face. In our study, we have not considered the effect of chemotherapy since all facial deformations observed are asymmetric or localized, and chemotherapy is expected to result in symmetric, general effects. All children were treated according to the same contemporary systemic treatment protocols, and therefore differences in musculoskeletal deformation can reasonably be attributed to variation in local treatment techniques.

	RT	AMORE	PROTON	PARIS
Orbit	 N= 15	 N= 16	*No mean – not large enough group*	*No mean – not large enough group*
MEAN SW(range)	193.67 (126.8 – 330.4) *p=0.04639 EBRT vs. AMORE*	146.18 ((87.2 – 311.7)		
Non Parameningeal	 N=13	 N=13	*No mean – not large enough group*	*No mean – not large enough group*
MEAN	211.68 (84.0 – 346.7	226.79 (97.0 – 368.9)		

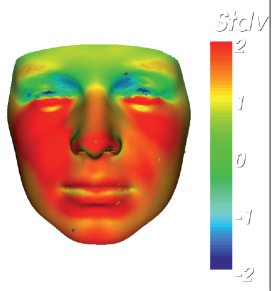
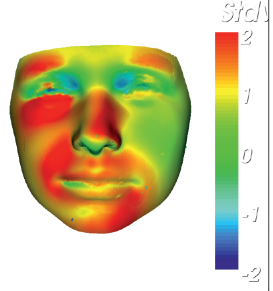
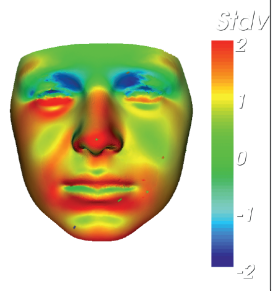
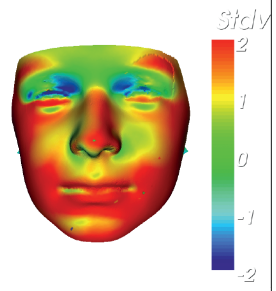
SW(range)	*p=0.660 EBRT vs. AMORE*			
Parameningeal	 N=30	 N=20	 N=16	 N=22
MEAN SW (range)	255.22 (127.8 – 482.1) *	229.42 (101.3 – 393.8)	189.66 (90.5 – 349.7) */**	269.51 (100.8 – 485.1) **

Figure 3. Heat maps of mean faces.

For each treatment modality, a mean face is made split out for tumor site. The orbital tumor group and non-parameningeal tumor group only has images for RT and AMORE treatment since there are not enough survivors included to make a mean face for the proton and Paris-method groups. The heat maps are depicted using colour, green represents mean growth (patient group is same as healthy controls), red represents underdevelopment of the facial area whereas blue represents more growth compared to the healthy individuals.
*indicates significant difference: RT vs PT: p=0.00998,
** indicates significant difference: PT vs. Paris; 0.007592.
Abbreviations: AMORE; Ablative Surgery, Moulage Brachytherapy and Reconstructive Surgery, RT; External Beam Photon Radiotherapy. SW; signature weight.

It is important to acknowledge the limitations of this study. As previously stated, although the total number of patients (n = 173) was noteworthy for a rare disease, when broken down by modality and disease sub-site, valid statistical comparisons were limited in some groups and analysis was performed using univariate analysis. Furthermore, differences in patient age at treatment and follow-up length between the groups could have introduced bias as facial deformation is a dynamic, age-dependent process. Also, this is a cross-sectional cohort study with a randomized study obviously not being possible. Future studies might be strengthened by acquiring images of each patient pre-treatment and at multiple time points during follow-up. Adding that data to this model, including the enrichment with new prospectively collected patient cohorts treated with contemporary local treatment modalities, would make it more adaptable and applicable to more subgroups. Also, in this current study, we have excluded patients from the PT and RT groups who would not be eligible for AMORE or Paris-method treatment using standardized broad criteria of intracranial growth and peri-neural spread. However, the decision to perform the advanced surgery used in AMORE and Paris-method patients is normally made by a multi-disciplinary team for each patient weighing all the treatment effects. Therefore, there might be residual selection bias influencing our findings in an unpredictable manner. With AMORE and Paris-method only being available in the Netherlands and France, even though they accept international referrals, these local treatment options might be less applicable in some institutions.

Ultimately, the Paris-method has been developed for patients with tumors in the pterygoid-palatine fossa or infratemporal fossa aiming to improve survival rates through extensive tumor resections, yet whether there is an actual benefit in survival remains to be confirmed (30).

In relation to RT, it should be recognized that treatment techniques evolved substantially between 1990 and 2017. At the outset, large parallel opposed lateral fields or simple two- or three-field techniques were often used with 2D planning. These may have treated substantial volumes of adjacent normal tissue and contained appreciable dose heterogeneity across the musculoskeletal structures. Subsequently, CT planned 3D conformal techniques were used, and, in recent years, more developed photon therapy techniques (intensity modulated radiotherapy technique (IMRT), and lately, volumetric modulated arc therapy (VMAT)) became available, which allowed greater conformality. In this study, all RT patients are reported as one cohort, regardless of the precise technique used. Only 30% of the PM patients were treated using new techniques (IMRT/VMAT). Analyzing the PM group as a whole was a conscious choice since no meaningful statistical analysis of the IMRT/VMAT group could be performed due to small numbers (n=9). However, since IMRT/VMAT allow a better sparing of normal tissues, including the bony structures, in comparison to 2D/3D techniques, it is conceivable that the results

shown for this patient category in terms of growth, normalized asymmetry score and facial signature analysis do not fully represent the IMRT/VMAT cohort. Finally, while we implemented a system that objectively measures facial deformation, the ultimate burden on quality of life is subjective and may differ between individuals. Therefore, future studies should consider correlating facial deformation scores with patient-reported quality of life and perceived body image outcome data. Ultimately, a decision model not only based on musculoskeletal development but including all adverse effects such as endocrine dysfunction, orbital dysfunction, speech problems, dental maldevelopment and quality of life would facilitate optimal local treatment selection for each patient.

Despite these limitations, this multi-national, transatlantic study is noteworthy in that it is the first to gather a large cohort of HNRMS survivors treated with four different primary local treatment strategies for HNRMS. It underpins a decision model applicable when facial deformation is the expected outcome difference between treatment modalities. As such, it provides a solid framework for future advancement into the differential impact of local control on musculoskeletal deformation in children with HNRMS, an endpoint too often overlooked in calculations of therapeutic ratio.

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3

Patient-reported outcomes in childhood head and neck rhabdomyosarcoma survivors and their relation to physician-graded adverse events - A multicenter study using the FACE-Q Craniofacial module

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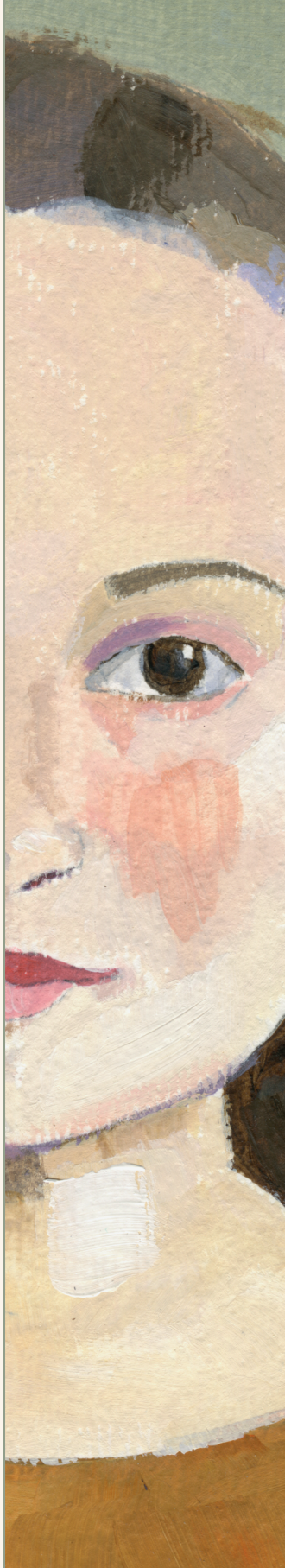

ABSTRACT

Introduction
Adverse events (AE) of treatment are prevalent and diverse in head and neck rhabdomyosarcoma (HNRMS) survivors. These AEs are often reported by physicians, however patients' perceptions of specific AE is not well known. In this study we explore patient reported outcomes on appearance, health related quality of life (HRQOL) and facial function in HNRMS survivors. Secondly, we assess the relation between physician grading of AE and patient reporting.

Materials and methods
Survivors of pediatric HNRMS, diagnosed between 1993-2017, with ≥2 years follow-up after treatment were invited to an outpatient clinic as part of a multicenter cross-sectional cohort study. At the outpatient clinics, survivors aged ≥8 years filled out the FACE-Q craniofacial module; a patient reported outcome instrument measuring issues specific to patients with facial differences. AE were systematically assessed by a multidisciplinary team based on the Common Terminology Criteria of Adverse Events system.

Results
Seventy-seven (77) survivors with a median age of 16y (range 8 – 43) and median follow-up of 10 years (range 2 – 42) completed the questionnaire and were screened for AEs. Patient reported outcomes varied widely between survivors. Many survivors reported negative consequences: 82% on appearance items, 81% on HRQOL items and 38% on facial function items. There was a weak correlation between physician scored AEs and the majority of patient reported outcomes specific for those AEs.

Conclusions
Physician graded AEs are not sufficient to provide tailored care for HNMRS survivors. We advise systematic attention to patient reported outcome measures.

INTRODUCTION

Rhabdomyosarcoma (RMS) accounts for around 4% of all childhood cancers and originates in the head and neck (HN) area in 40% of patients (1). Survival has increased significantly since the use of multimodality therapy including local treatment with radiotherapy and in some cases added surgery. However, radiotherapy and surgery also damage healthy tissues. This results in a wide range of adverse events (AEs) in survivors, including visible facial differences, ocular impairments, hearing impairment, speech abnormalities and endocrinopathies (2–7). With more patients becoming long-term survivors, these AEs are an important topic. In oncology research, the Common Terminology Criteria of Adverse Events (CTCAE)(8) is a clinical grading system used to report AEs(9). However, the relation between the grade of AEs and the patients' perception of those AEs is not consistent in adult studies(10–12) and not well described for children and adolescents. A better understanding of the patients' perception could improve the quality of care for survivors.

Our group(13) has previously reported on the psychosocial wellbeing of a partially overlapping cohort of 65 childhood HNRMS survivors. It was concluded that HRQOL was comparable to general population norm data on most domains. But, survivors reported disease specific issues such as negative self-image and satisfaction with appearance. To further specify these issues, specific patient-reported outcome (PRO) instruments can be used. It was previously shown that the majority of the available PROs for children and youth with craniofacial conditions contain few appearance and facial function items and lack content validity(14). To fill this need, the FACE-Q Craniofacial module was developed(15). This questionnaire is composed of a comprehensive set of independently functioning scales and is applicable to a wide range of conditions associated with facial differences, including childhood cancer. The scales measure issues on 3 domains: appearance, HRQOL and facial function.

The aim of the present study was to explore specific PROs on appearance, HRQOL and facial function within a cohort of pediatric HNRMS survivors, using relevant scales from the FACE-Q Craniofacial module. We explored differences between survivors in terms of gender, age at diagnosis, attained age, follow-up period, tumor site and side. Secondarily, we assessed relationships between physicians' grading of AEs and specific PROs.

METHODS

Setting

Survivors were recruited at 4 international centers: Great Ormond Street Hospital, London, United Kingdom; University of Florida Health Proton Therapy Institute, Florida, United States; Institut Gustave Roussy, Paris, France; Emma Childrens' Hospital, Amsterdam, The Netherlands which transferred its oncologic care to the Princess Máxima Center for pediatric oncology, Utrecht, The Netherlands in 2018. Survivors of pediatric (0-18 years) HNRMS, diagnosed between 1993 and 2017 who were ≥2 years after completion of treatment were eligible. All survivors had been treated with multidrug chemotherapy and local treatment(1,16,17). Four local treatment strategies were available during the period studied: definitive external beam radiation with photons (XRT); definitive external beam radiation with protons (PT); microscopically radical surgery combined with XRT or PT (the Paris-method); macroscopic radical surgery combined with brachytherapy (AMORE)(18). Data on AEs were collected during standardized multidisciplinary outpatient clinics held between January 2017 and December 2019. Survivors aged ≥8 years were also invited to complete the FACE-Q Craniofacial scales. Oral or written informed consent was obtained based on national and local standards.

Patient reported outcomes

We used 11 of the FACE-Q Craniofacial module(15) scales, each containing 7-12 items, answered on a 1 – 4 Likert scale. This PRO instrument assesses concepts from 3 different domains: appearance (of face, nose, teeth, lips, and jaw), HRQOL (psychological, social, and school function and speech distress) and facial function (speech function and eating & drinking). The appearance scales ask how much the respondent like their current appearance. The HRQOL and facial function scales ask respondents how often or much a set of statements applied to them in the previous week. Participants completed only relevant scales (e.g., jaws, for participants aged ≥12y; school, for participants aged ≤18 y and attending school). The eating & drinking scale was only used as an item checklist(19). For all other scales, the sum score of items was available as a Rasch transformed score(20) from 0-100. Lower scores reflect worse outcome. Internal consistency of scales was good(21), with Cronbach's alpha between 0.83 and 0.97 in our cohort. If missing data comprised <50% of the scale's items, the mean of the completed items for a scale was used, otherwise a score was excluded for that survivor.

AE assessment

A pre-defined list of AEs were graded according to CTCAE 4.0(8). We assessed musculoskeletal deformity, short stature (<-2SD), speech abnormalities, oral malfunction (trismus, xerostomia, taste alterations), hearing impairment, ocular impairment, facial nerve paresis. AEs were dichotomized into </≥ grade 2 to reflect

the absence/presence of a clinically relevant problem (i.e., being symptomatic, requiring alterations in activities of daily living, and/or the need for an intervention or medication) (Supplemental data B).

Statistical analysis

Data were analyzed with SPSS version 26.0. To explore PRO scores, mean and standard deviations (±SD) were calculated for the scales, for the whole cohort and for subgroups. Subgroups were based on: gender, age at diagnosis, attained age, follow-up period, tumor site and side. Differences between subgroups were tested with one-way ANOVA and/or independent sample t-test. Differences between appearance scale scores within survivors were tested with dependent t-test. Effect sizes (Cohen *d*) were calculated and considered as: 0.2 small, 0.5 medium and ≥0.8 large(22). Correlations between scale scores were calculated with Pearson correlation coefficient (r) and considered as: 0.1 weak, 0.3 medium and ≥0.5 strong(22).

To get more detailed insight, item level analyses were explored. We calculated the percentage of survivors that reported negatively for the appearance scales (i.e. "not at all", "a little bit"), HRQOL scales (i.e., "never", "sometimes") and speech distress, speech function and eating and drinking scales (i.e., "always", "often").

To assess the relation between grading of AEs and PRO scores, we compared the mean scale scores of the survivors with a clinically relevant AE to that of survivors without a clinically relevant AE, using independent sample t-test and Cohen's *d*. For the psychological and social scales, the relation with every AE was assessed. In addition, appropriate scales were examined per AE. The relation of the number of different AEs with the psychological and social scale scores was examined with Spearman rho test.

RESULTS

Survivors

Ninety-five (95) survivors aged ≥8 years attended the clinics. Seventy-seven (81%) completed the questionnaire. The 18 non-participants were significantly more often treated with the Paris-method and had more PM site tumors compared to the participants (table A1). Table 1 presents the survivor characteristics. For 76 of the 77 participants (99%), CTCAE grading was available. Sixty-three (82%) had ≥1 AEs, 29 (38%) ≥2 AEs, with a maximum of 5 AEs in 2 (3%) survivors (figure A1).

Table 1. Characteristics of the participants (total N= 77)

Gender, male N (%)	43 (56)
Age at diagnosis, y *Median (min - max)*	6 (0 – 16)
Age at clinic, y *Median (min - max)*	16 (8 – 43)
Follow-up duration, y *Median (min - max)*	10 (2 – 42)
Site, N (%)	
PM	45 (58)
NPM	12 (16)
orbit	20 (26)
Country of residence, N (%)	
United Kingdom	31 (40)
United States	6 (8)
France	8 (10)
The Netherlands	32 (42)
Local treatment received, N (%)	
XRT	32 (42)
Protons	22 (29)
AMORE	18 (23)
Paris-method	5 (6)

Y: years PM: parameningeal; NPM: head and neck non-parameningeal XRT: external beam radiotherapy with photons, AMORE: Ablative surgery MOuld placement and Reconstruction.

Exploring patient reported outcomes:

The face, psychological, school and social scales are presented in table 2. Table A2 shows the scales concerning specific aspects of the face (nose, teeth, lips, jaw) and the speech distress and speech function scales. The prevalence of negative reporting at item level is presented in table 3.

Appearance
The distribution of scores on the face scale varied widely: range 7 - 100. The mean face score was significantly higher for survivors aged 8-12y compared to survivors aged 1318y (*d* 0.6). The mean score on the lips scale was significantly higher for survivors aged 812y compared to older survivors (1317y *d* 0.7; ≥18y *d* 0.8). Mean lips and jaw scores were significantly higher for orbit site compared to PM site (*d* ≥0.9).

Within survivors, scores on appearance of the lips, nose and jaw were significantly higher compared to their face score (*d* 0.9, 0.8, 0.5 respectively).

Sixty-three (82%) survivors reported negatively on ≥1 of the appearance-scales items. Every item of the face, jaw and teeth scales was reported on negatively by >20% of survivors. Sixty percent of survivors reported negatively on the item '...how both sides of your face match'.

HRQOL
The mean psychological scale score was significantly higher for survivors aged 8-12y compared to older survivors (1318y *d* 0.7; ≥18y *d* 1.0). Survivors with >10y follow-up had lower mean psychological score compared to those with shorter follow-up (25y *d* -0.4; 610y *d* -0.8). Sixty-two (81%) survivors reported negatively on ≥1 of the HRQOL-scales items. Nearly half (47%) of all survivors reported negatively on the item 'I feel good about how I look'.

Facial function
Twenty-nine (38%) survivors reported negatively on ≥1 of the speech function items. Over 13% of survivors reported they need to try hard to speak well and/or they have trouble reading out loud. Twenty-eight (36%) survivors reported negatively on ≥1 of the eating and drinking items. Strong correlations (r ≥0.5) across the domains were seen for the: face and psychological scale; face and social scale; and speech function and speech distress scale (Table A3).

Relation between AEs and PROs
Both the highest and the lowest scores on the face scale were reported by the survivors with a grade 0 or 1 deformity (figure 1). No differences were seen between survivors with or without a musculoskeletal deformity grade ≥2 on any of the tested scales (table 4).

Large (*d* ≥0.8) differences in some PRO scale scores between survivors with and without a clinically relevant AE were seen for: speech abnormality, oral malfunction and facial nerve paresis (table 4), with lower scores for the survivors with the AE present. The number of different AEs was non-significantly, weakly associated with the mean psychological and social scores (r 0.106 and -0.129 respectively) (figure S2).

Tabel 2. Mean scale scoresa on appearance of the face, psychological function, school function and social function

		Domain							
		Appearance		**HRQOL**					
		Face (N = 77)		**Psychological (N = 76)**		**School[b] (N = 41)**		**Social (N= 76)**	
All	**N (%)**	**mean**	**SD**	**mean**	**SD**	**mean**	**SD**	**mean**	**SD**
	77	54.0	16.1	64.9	17.8	69.2	17.1	70.1	16.3
		min	**max**	**min**	**max**	**min**	**max**	**min**	**max**
		7	100	15	100	42	100	32	100
	N (%)	**mean**	**SD**	**mean**	**SD**	**mean**	**SD**	**mean**	**SD**
Gender									
Male	43 (56)	52.7	16.8	63.6	18.9	67.1	19.2	69.3	16.1
Female	34 (44)	56.3	15.2	66.4	16.4	71.8	14.5	71.0	16.9
Age at diagnosis *(median, range)*	*6 (0 – 16)*								
0 - 5y	43 (56)	55.5	14.4	66.7	15.3	70.4	17.5	69.8	14.9
6 – 10y	21 (27)	53.1	14.7	63.5	19.0	68.5	16.0	71.7	18.7
> 10y	12 (16)	51.8	24.3	61.5	24.3	65.4	20.6	69.0	18.4
Attained age *(median, range)*	*16 (8 – 43)*								
8 - 12y	21 (27)	**59.5**[c]	16.6	**75.2**[d]	16.0	70.9	16.2	72.6	17.1
13 - 18y	23 (30)	49.2	15.9	61.7	20.3	67.7	18.3	66.5	19.7
> 18y	33 (43)	54.6	15.3	60.8	14.5	-	-	70.8	13.2
Follow-up duration *(median, range)*	*10 (2 – 42)*								
2 - 5y	19 (25)	52.4	22.1	67.1	22.9	70.7	16.1	70.1	17.9
6 - 10y	21 (27)	58.9	14.9	71.9	16.9	68.6	18.7	71.1	20.6

Tabel 2. *Continued.*

		Domain							
		Appearance		**HRQOL**					
		Face (N = 77)		**Psychological (N = 76)**		**School[b] (N = 41)**		**Social (N= 76)**	
All	**N (%)**	**mean**	**SD**	**mean**	**SD**	**mean**	**SD**	**mean**	**SD**
	77	54.0	16.1	64.9	17.8	69.2	17.1	70.1	16.3
		min	**max**	**min**	**max**	**min**	**max**	**min**	**max**
		7	100	15	100	42	100	32	100
	N (%)	**mean**	**SD**	**mean**	**SD**	**mean**	**SD**	**mean**	**SD**
> 10y	37 (48)	52.7	12.8	**59.8**[e]	13.9	67.3	17.3	69.4	12.8
Site[f]									
PM	46 (60)	52.4	15.0	63.8	17.6	69.5	17.8	70.0	16.0
NPM	12 (16)	58.7	19.9	65.0	13.1	62.2	11.8	68.3	17.6
orbit	19 (25)	56.4	16.3	67.6	21.1	71.8	18.0	71.3	17.0
Side									
Lateral	63 (82)	53.8	17.2	65.3	19.0	69.2	17.1	69.8	16.7
Midline	12 (16)	56.7	10.3	62.5	12.0	69.7	19.1	71.1	16.0

[a]Mean Rasch transformed scores on scale 0-100; higher scores reflecting better outcome
[b]only fulfilled by survivors aged <18years and attending school
In **bold**; statistically significant difference between groups:
[c]Survivors aged 8-12y scored significantly higher compared to survivors aged 13-18y (*d* 0.63, p = 0.041)
[d]Survivors aged 7-12y scored significant higher compared to survivors aged 13-18y (*d* 0.74, p= 0.021) and survivors aged ≥18y (*d* 0.95, p = 0.001)
[e]Survivors with a follow-up duration >10y scored significantly lower compared to survivors with follow-up duration 6-10y (*d* -0.81, p = 0.005)
[f] 'PM': parameningeal site, 'NPM': head and neck non parameningeal site, 'orbit': orbital site

Table 3. Percentage of survivors reporting negatively on the scale items of (A) appearance, i.e. "not at all" or "a little bit" (B) psychological, social and school, i.e. "never" or "sometimes" (C) speech distress, speech function and eating & drinking i.e., "always" or "often". Items negatively reported by ≥20% of survivors in bold. Items negatively reported by ≥50% of survivors with*.

A

How much do you like…	Face	Nose	Teeth	Lips	Jaw
…Both sides match	**60***	12	-	-	**-**
…Photos	**58***	13	-	15	**23**
…Laugh	**49**	-	**-**	**24**	**-**
…Up close	**48**	-	**55***	15	**-**
…Smile	**42**	16	**48**	**20**	**26**
…From the side	**38**	**25**	**39**	**-**	**30**
…Shape	**34**	16	**-**	15	**24**
…Look your best	**26**	-	-	-	-
…When ready to go out	**21**	-	-	-	-
…In the mirror	-	17	**-**	15	**26**
…Size	-	13	**31**	13	**24**
…Closed	-	-	-	16	**21**
…Top and bottom meet	-	-	**61***	-	-
…Showing when you smile	-	-	**51***	-	-
…Straight	-	13	**44**	-	-
…Close together	-	-	**39**	-	-
…Full	-	-	**-**	15	-
…Length	-	13	**-**	-	-
…Middle part	-	16	**-**	-	-
…Bottom	-	10	**-**	-	-
…Tip	-	10	**-**	-	-

B

Psychological	%	Social	%	School	%
Feel good	**47**	Same as others	**30**	Make friend	**31**
Feel great about self	**33**	Make friends	**30**	Join activities	**24**
Feel confident	**30**	People look	**29**	Happy	**22**
Happy with life	**26**	Confident out	**28**	Listen to me	**20**
Like self	**24**	Fit in	**24**	Safe	18
Believe in self	**24**	Like being with others	16	Seeing friends	13

B

Psychological	%	Social	%	School	%
Proud of self	**22**	People listen	13	Nice to me	11
Feel happy	**22**	Treat me the same	11	Teachers	11
Feel okay about self	**21**	Fun with friends	5	Feel accepted	11
Enjoy life	16	Friends accept	5	Liked	9

C

Speech distress	%	Speech function	%	Eating & drinking	%
Not understood	**29**	Slowly	18	Slowly	**22**
Repeat	**26**	Reading out loud	16	Trouble biting	18
Worry	16	Try hard	13	Hard to chew	18
Nervous	12	Concentrate	13	Gets stuck*[a]	18
Avoid	7	Repeat	12	Avoid certain foods	14
Frustrated	7	Avoid words	10	Trouble straw	12
Embarrassed	4	Trouble saying words	10	Falls out of my mouth	11
Teased	5	On the phone	9	Small bites	9
Avoid going out	4	Family	9	Up my nose*[b]	3
New friends	4	Sentences	8		
		New people	8		
		Friends	7		

Note: - : item not applicable in scale
* Note: [a,b] Items only available in the Dutch and French version of FACE-Q Kids (at the time of our study).
[a] N=39; [b] N=31.

Table 4. Meana and standard deviation of the PRO scale scores for survivors without and with (N = X / N = X) a physician graded AE grade ≥2.

	AE grade <2		AE grade ≥2			
Scale	**Mean**	**SD**	**Mean**	**SD**	***D*** [b]	**P** [c]
	Musculoskeletal deformity (N = 44 / 32)					
Psychological	67.0	18.8	62.2	16.5	-0.3	0.32
Social	71.9	17.7	67.8	14.5	-0.2	0.41
School	70.0	15.9	68.1[d]	19.4	-0.1	0.99
Face	57.1	19.1	51.0	10.2	-0.4	0.08
Nose	69.6	22.5	66.6	16.5	-0.1	0.57
Teeth	53.0	21.0	50.8	17.5	-0.1	0.67
Lips	76.0	23.4	67.2	19.7	-0.4	0.11
Jaw	65.7	24.1	59.6[e]	21.9	-0.3	0.21
	Short stature (N = 70 / 6)					
Psychological	65.0	18.4	62.4	9.2	-0.1	0.76
Social	69.9	16.4	70.9	19.2	0.1	0.91
	Speech abnormality (N = 57 / 11)					
Psychological	65.4	18.3	64.2	12.3	-0.1	0.83
Social	71.1	16.9	64.3	11.0	-0.3	0.20
School	71.2	17.0	58.7[d]	7.7	**-0.8**	0.09
Speech distress	77.3	17.1	65.9	15.5	-0.7	0.04*
Speech function	78.7	17.3	55.6	16.3	**-1.3**	0.00*
	Oral malfunction (N = 60 / 8)					
Psychological	65.5	17.3	62.9	19.4	-0.1	0.69
Social	70.3	15.3	67.4	21.4	-0.2	0.63
Speech distress	75.9	17.6	72.6	15.3	-0.2	0.62
Speech function	75.4	19.5	72.3	15.5	-0.2	0.66
Teeth	51.0	17.8	56.3	19.3	0.3	0.44
Lips	72.4	22.2	65.4	23.0	-0.3	0.41
Jaw	63.5	22.5	44.0[e]	15.8	**-0.9**	0.03*
	Hearing impairment (N = 59 / 13)					
Psychological	65.9	17.7	56.7	18.0	-0.5	0.26
Social	70.5	16.3	68.8	14.6	-0.1	0.73
School	70.4	16.8	67.7[d]	17.9	-0.2	0.71
Speech distress	76.1	17.1	72.8	17.8	-0.2	0.53
Speech function	76.2	18.6	70.2	20.5	-0.3	0.30
	Ocular impairment (N = 30 / 36)					
Psychological	66.8	17.0	65.3	17.8	-0.1	0.99

Table 4. *Continued.*

	AE grade <2		AE grade ≥2			
Scale	**Mean**	**SD**	**Mean**	**SD**	***D*** [b]	**P** [c]
	Musculoskeletal deformity (N = 44 / 32)					
Social	71.3	15.2	70.0	18.2	-0.1	0.66
School	69.6	17.2	72.4[d]	19.2	0.2	0.69
	Facial nerve paresis (N = 64 / 6)					
Psychological	66.0	17.7	58.5	23.9	-0.4	0.34
Social	70.2	16.5	72.8	14.5	0.2	0.71
Face	56.0	16.3	42.2	18.0	**-0.8**	0.05*
Lips	73.9	22.0	59.5	25.3	-0.6	0.14
Speech function	73.7	19.4	83.2	15.9	0.5	0.25

[a] Mean Rasch transformed scores on scale 0-100; higher scores reflecting better outcome
[b] Effect sizes, large (≥0.8) effect sizes are presented in bold
[c] Statistical significance of the difference in means, difference at the p ≤ 0.05 level shown with an asterix
[d] School scale only filled out by children aged ≤18 and attending school: musculoskeletal deformity N = 16, speech abnormality N = 6, hearing impairment N = 7, ocular problem N = 21 in the category with an AE grade ≥2. Results for short stature are not presented because of very small number of survivors with the AE present (N = 2).
[e] Jaw scale only filled out by participants aged ≥12y: musculoskeletal deformity N = 27, oral malfunction N = 7 in the category with an AE grade ≥2.

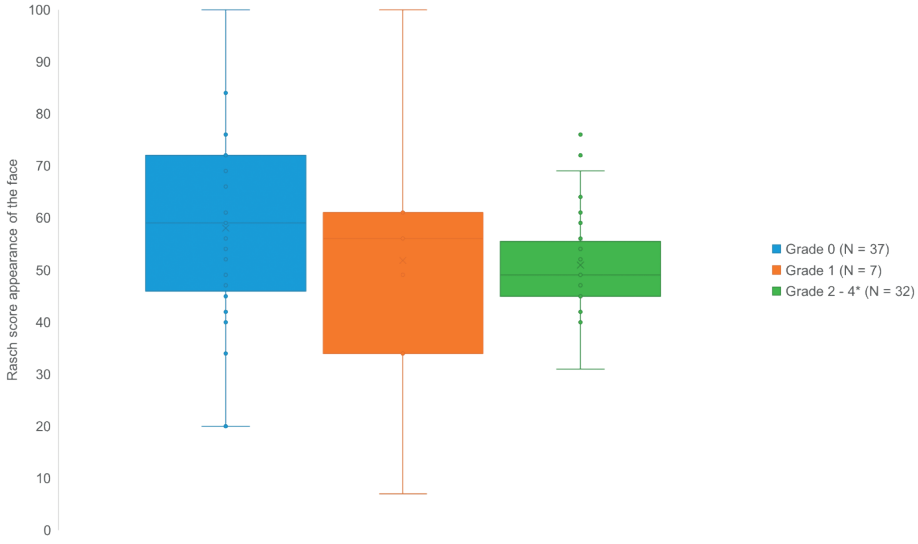

Figure 1. Face scale score per grade of musculoskeletal deformity (0 – 4).

*grade 2 N = 9, grade 3 N = 21, grade 4 N = 2.

DISCUSSION

The PROs for appearance, HRQOL and facial function varied widely in this cohort of HNRMS survivors. Survivors reported negatively in up to 83% of items concerning appearance, 82% of HRQOL items and 38% of facial function items. PRO scores across the 3 domains were associated with each other. The correlation between the presence of a clinically relevant AE as graded by physicians and PROs was weak for the majority of the tested PROs, and strong in only a few.

Our group published previously on a partially overlapping cohort(13), and showed HNRMS survivors experienced negative disease specific issues. In the current study, we further specified these issues by using a questionnaire designed to measure facial appearance and function in addition to HRQOL. The FACE-Q Craniofacial module is the first PRO instrument designed to measure respondents' appreciation of their appearance rather than appearance distress. We found a weak correlation between specific AEs and most of the PROs related to those AEs. We only saw lower scores on some appearance, HRQOL and facial function scales for survivors with a speech abnormality, oral malfunction and facial nerve paresis compared to the survivors without these problems. Similarly, the correlation between CTCAE grading and associated PROs in adult cancer patient literature was weak to moderate in multiple studies(12). These findings have also led to the development of a patient language version of the CTCAE (CTCAE-PRO)(23), to complement the CTCAE and incorporate patient reporting of symptoms more systematically into research and decision making. The described weak correlation between physician reporting and PROs fits with theories arguing factors other than the presence of a chronic condition affect the consequences of a condition on an individuals' psychosocial wellbeing(24–27). Overall, HRQOL is lower in groups of people with a visible facial difference compared to groups without such a difference, but large individual variations exist(28–31). These variations may be attributable to multiple psychological and social factors (i.e., personality, coping strategies, social support)(26,32–34) which need to be studied into more detail in the future. In our study, survivors with younger age (8-12y) and shorter follow-up time (<10y) scored significantly higher on appearance and HRQOL than older survivors and longer follow-up time. A similar report was noted for a large cohort of patients with cleft lip/palate, assessed with partly overlapping scales from the CLEFT-Q(19). This age and time effect might be explained by the importance of appearance during different developmental stages(27). In addition, in HNRMS survivors, facial deformity may aggravate over time with the growth of the facial bones. Within our cohort we did not see differences in reporting for the tested subgroups based on gender, age at diagnosis, tumor site and side. Studies on HRQOL in childhood cancer survivors have previously described more negative scoring on emotional health for females compared to males (35,36), and on worry and social function for patients with older age at diagnosis compared to younger

age at diagnosis(36). This difference might be explained by the specific (instead of generic) HRQOL items included in the current study.

Strengths and limitations

We present an international, cohort of HNRMS survivors, with long follow-up. Our results on specific aspects of appearance, HRQOL and facial function give a detailed description of the issues HNRMS survivors' experience. An important limitation of the study is inherent to the population under investigation: patient numbers are small and cohorts heterogeneous. Therefore, the results are mainly exploratory and the analyses have limited power.To date normative values were not available for the FACE-Q Craniofacial module, which impairs interpretation of our results in reference to the general population. Ideally, our data would be compared to a general population control group or a childhood cancer survivor group in whom cancer treatment has not affected the head and neck area. The larger portion of our currently described cohort was used for a validation study which is in preparation for publication(37) and reference values are expected to follow from this. Important to take into account are the differences in patient and treatment characteristics between the participants and non-participants. The non-participants were more often treated with the Paris-method and had PM site tumors. The combination of these factors was unsurprising since the Paris-method is developed for PM site tumors. This method includes extensive surgical tumor resection and thereby introduces a risk of significant facial deformation. Because of this, a proportion of the objectively more severely affected children have not been included in the current study. However, only a minority of all international HNRMS patients are treated according to this method.

Clinical implications

Many survivors reported negatively on appearance, HRQOL and facial function items. Relying on the physician graded AEs is not enough to provide tailored care to the survivors because of the weak correlation between AEs and the majority of PRO scores. We recommend health care professionals to pay attention to issues on all 3 domains in every HNRMS survivor. The FACE-Q Craniofacial module can be used for this goal. Training to help physicians use PROs in clinical care and how to discuss these with their patients is recommended in order to incorporate the patients' perspective next to objective measures of AEs(38). The systematic use of questionnaires can be facilitated by the use of electronic portals such as the Dutch "Kwaliteit van Leven In Kaart" (KLIK) PROM portal(39). In this portal, patients are asked to complete online PROs at home before a consultation. Scores are then converted into an individual electronic profile and discussed during the consultation. The use of PROs in clinical practice has been shown beneficial as it resulted in increased discussion of patient outcomes, enhanced patient-clinician communication, higher patient satisfaction, better HRQOL, and improved treatment outcomes(40,41). Furthermore, children

should be provided if possible with psychosocial interventions to empower them in coping with the consequences of their disease(42).

CONCLUSION

PRO scores for appearance, HRQOL and facial function varied widely between HNRMS survivors, though many survivors reported negative consequences in all three domains. The presence of clinically relevant AEs as graded by physicians was weakly correlated with the majority of disease specific PRO scores. We therefore advise a systematic assessment of potential concerns from the patient perspective, such as by use of the FACE-Q Craniofacial module, in the care for every individual HNRMS survivor.

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SUPPLEMENTAL DATA A

Table A1. Characteristics for participants and non-participants

	Participants N = 77	**Non-participants N = 18**	**p**
Gender, N (%)			0.794
Male	43 (56)	11 (61)	
Female	34 (44)	7 (39)	
Age at diagnosis			
Median (range)	*6 (0 – 16)*	6 (1 – 15)	0.562
0 - 5y	43 (56)	10 (56)	
6 - 10y	21 (27)	5 (28)	
> 10y	12 (16)	3 (17)	
Attained age			
Median (range)	*16 (8 – 43)*	14 (8 – 34)	0.372
7 - 12y	21 (27)	7 (39)	
13 - 18y	23 (30)	4 (22)	
≥ 18y	33 (43)	7 (39)	
Follow-up duration			
Median (range)	*10 (2 – 42)*	8 (4 – 29)	0.575
2 - 5y	19 (25)	3 (17)	
6 - 10y	21 (27)	8 (44)	
> 10y	37 (48)	7 (39)	
Local treatment, N (%)			**0.004**
XRT	32 (42)	5 (28)	
protons	22 (29)	5 (28)	
AMORE	18 (23)	1 (6)	
Paris-method	5 (6)	7 (39)[a]	
Site, N (%)			**0.040**
PM	45 (58)	16 (89)[b]	
NPM	12 (16)	0	
orbit	20 (26)	2 (11)	
Side, N (%)			0.114
Lateral	63 (82)	18 (100)	
Midline	12 (16)	0	
Adverse Events grade ≥2			
Musculoskeletal deformity	42%	73%	
Speech abnormality	16%	20%	

Table A1. *Continued.*

	Participants N = 77	Non-participants N = 18	p
Oral malfunction	11%	30%	
Hearing impairment	18%	11%	
Ocular problems	55%	50%	
Facial palsy	9%	29%	
Short stature	16%	30%	

'y': years
'PM': parameningeal site, 'NPM': head and neck non parameningeal site, 'orbit': orbital site
XRT: external beam radiotherapy with photons
AMORE: Ablative surgery MOulage brachytherapy and REconstruction
[a] statistically significant differences according to Fisher exact: more Paris-method in the non-responders compared to the responders group (p = 0.001)
[b] statistically significant differences according to Fisher exact: more PM site in non-responders compared to the responders group (p = 0.02)

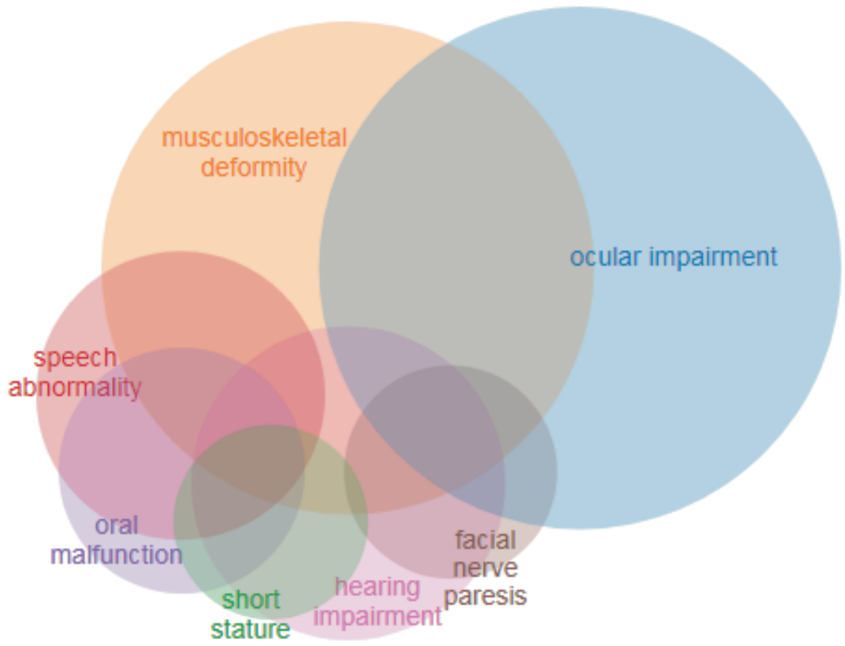

Figure A1: Venn diagram showing the overlap between the different adverse events within survivors.

Venn constructed via: https://www.meta-chart.com/venn.

Table A2. Mean scale scores a on appearance of the face, psychological function, school function and social function. Exploring differences within the cohort, based on patient and tumor characteristics.

	Domain	**Appearance**								**HRQOL**		**function**	
	Scale	**Nose**		**Teeth**		**Lips**		**Jaw**[b]		**Speech distress**		**Speech function**	
All	**N (%)**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
	77	68.2	20.0	52.2	19.4	72.1	22.1	62.8	22.9	75.7	17.4	75.2	19.0
		Min	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
		0	100	9	100	23	100	22	100	42	100	31	100
	N (%)	**Mean**[a]	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Gender													
Male	43 (56)	65.0	20.5	51.9	20.8	70.6	22.9	63.1	23.7	79.4	17.3	78.6	19.2
Female	34 (44)	72.3	18.9	52.5	17.7	73.9	21.2	62.4	22.2	71.0	16.6	71.0	18.1
Age at diagnosis *(median, range)*	*6 (0 – 16)*												
0 - 5y	43 (56)	69.8	20.5	51.0	17.6	73.7	21.1	56.5	20.8	76.3	17.6	77.1	18.0
6 - 10y	21 (27)	62.2	19.9	49.6	18.0	70.1	23.6	66.8	27.3	74.1	16.9	74.5	19.0
> 10y	12 (16)	70.0	19.6	61.3	26.9	70.7	24.9	19.3	5.6	75.1	19.3	67.8	21.7
Attained age *(median, range)*	*16 (8 – 43)*												
8 - 12y	21 (27)	70.1	24.0	53.0	16.7	**83.7**[d]	20.7	59.6	4.5	71.0	16.9	73.1	20.2
13 - 18y	23 (30)	66.4	18.4	49.0	20.9	69.0	22.7	63.6	22.8	77.0	16.8	71.7	16.5
> 18y	33 (43)	68.2	18.8	53.8	20.4	67.2	20.4	62.7	24.7	77.8	18.1	79.0	19.7
Follow-up duration *(median, range)*	*10 (2 – 42)*												
2 - 5y	19 (25)	65.4	25.1	52.8	17.8	75.4	27.3	67.1	21.2	75.6	15.2	68.6	18.9

Table A2. *Continued.*

	Domain	**Appearance**								**HRQOL**		**function**	
	Scale	**Nose**		**Teeth**		**Lips**		**Jaw[b]**		**Speech distress**		**Speech function**	
All	**N (%)**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
	77	68.2	20.0	52.2	19.4	72.1	22.1	62.8	22.9	75.7	17.4	75.2	19.0
		Min	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
		0	100	9	100	23	100	22	100	42	100	31	100
	N (%)	**Mean[a]**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
6 - 10y	21 (27)	72.0	18.0	52.1	24.8	77.6	20.9	67.7	25.8	71.0	19.8	73.1	20.1
> 10y	37 (48)	67.5	18.4	51.9	17.2	67.3	19.3	60.0	22.4	78.4	16.9	79.8	17.6
Site[c]													
PM	46 (60)	67.8	19.2	48.4	17.6	66.3	21.7	55.7	19.8	76.7	18.3	74.0	20.6
NPM	12 (16)	68.2	17.8	60.3	20.0	74.6	20.5	63.4	27.0	72.9	16.4	70.3	16.0
orbit	19 (26)	69.1	24.0	56.3	21.7	**85.1[e]**	18.8	**79.8[f]**	18.9	74.9	16.6	81.3	15.5
Side													
Lateral	63 (82)	68.6	21.1	52.2	19.9	72.4	21.9	63.7	22.4	75.1	17.8	74.2	19.2
Midline	12 (16)	68.7	14.0	54.1	17.3	74.0	23.3	57.8	28.6	76.2	16.1	76.2	16.8

[a]Mean Rasch transformed scores on scale 0-100; higher scores reflecting better outcome
[b]only fulfilled by survivors aged ≥12 years
[c]PM: parameningeal site; NPM: head and neck non parameningeal site; orbit: orbital site
[d]survivors aged 8-12y scored statistically significantly higher on the lips scale compared to the older age groups: compared to 1317y *d* 0.7, p=0.033; compared to ≥18y *d* 0.8, p=0.006
[e]survivors with orbit site scored significantly higher on the lips scale compared to PM site (*d* 0.9, p=0.002)
[f]survivors with orbit site scored significantly higher on the jaws scale compared to PM site (*d* 1.2, p=0.000)

Table A3. Correlations between the scale scores across the 3 domains of the FACE-Q

			Face	Nose	Lips	Teeth	Jaw	Psychologic	School	Social	Speech distress
Domains	Appearance	Face	X								
		Nose	**0,56****	X							
		Lips	**0,61****	**0,60****	X						
		Teeth	0,34*	0,36**	0,44**	X					
		Jaw	0,43**	0,31*	0,47**	0,40*	X				
	HRQOL	Psychologic	**0,69****	**0,51****	**0,62****	0,19	0,34*	X			
		School	0,46*	0,41**	**0,50****	0,07	0,34	**0,66****	X		
		Social	**0,55****	0,28*	0,41**	0,19	0,29*	**0,68****	**0,88****	X	
		Speech distress	0,08	-0,06	0,004	0,10	0,23	0,15	0,31*	0,24*	X
	Function	Speech function	0,20	0,004	0,11	-0,01	0,22	0,22	0,41*	0,31*	**0,75****

Pearson correlation coefficients of large (≥0.5) size are presented in bold.
*p <0.05, ** p<0.001

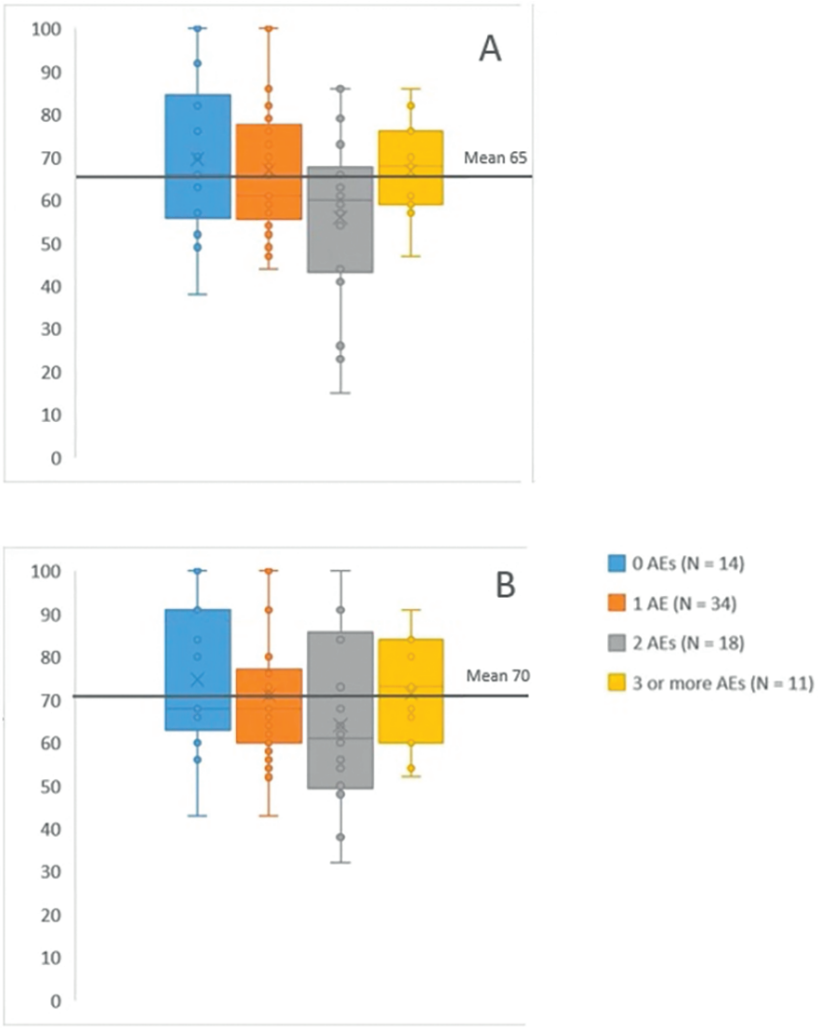

Figure A2. Number of different adverse events (AEs) versus the scores on the PRO scales (A) psychological functioning (B) and social functioning. Horizontal line corresponds to the cohort mean score on the PRO scales.

SUPPLEMENTAL DATA B

Definition of Adverse Events, selection of Common Terminology Criteria for adverse events version 4.0. Conditions are classified as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening or disabling (grade 4) (grade 5 (fatal) not included in the current study).

1. Musculoskeletal deformity

	Grade				
Adverse event	**0**	**1**	**2**	**3**	**4**
Musculoskeletal deformity	-	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be covered	-Significant deformity, hypoplasia or asymmetry, not covered -Disabling	Orbital exenteration

2. Speech abnormality

	Grade				
Adverse event	**0**	**1**	**2**	**3**	**4**
Rhinolalia aperta (nasal aspirate sound)†	-	Mild change of speech, no effect on audibility	Moderate change of speech, influences audibility	Barely understandable, verbal communication limited	-
Dysarthria/ voice alteration	-	-Mild slurred speech -Mild or intermittent change from normal voice	-Moderate impairment of articulation or slurred speech -Moderate or persistent change from normal voice; still understandable	-Severe impairment of articulation or slurred speech -Severe voice changes including predominantly whispered speech -May require frequent repetition or face-to-face contact for understandability -May require assistive technology	-

1.

3. Oral malfunction

	Grade				
Adverse event	**0**	**1**	**2**	**3**	**4**
Taste alteration* (Dysgeusia)	-	Altered taste	-Changed diet -Noxious, unpleasant -Loss of taste	-	-
Trismus	-	Decreased range of motion (ROM)	Decreased ROM, requiring small bites, soft foods or purees	Decreased ROM, inability to adequately aliment or hydrate orally	-
Xerostomia (dry mouth)	-	Symptomatic (e.g. dry or thick saliva) without significant dietary alterations	-Moderate symptoms -Oral intake alterations	-Inability to adequately aliment orally -TPN/tube feeding indicated	-

4. Hearing impairment

		Grade			
Adverse event	**0**	**1**	**2**	**3**	**4**
Hearing* (subjective)	-	-	Hearing loss	Hearing loss requiring intervention	Profound bilateral hearing loss (>90dB)

*Not available in CTCAEv4.0, description as defined in CTCAEv3.0

5. Ocular problem

	Grade				
Adverse event	**0**	**1**	**2**	**3**	**4**
Eyelid function disorder	-	-Asymptomatic	-Symptomatic -Non-operative intervention indicated -Limiting instrumental ADL**	-Limiting self care ADL** -Operative intervention indicated	-
Diplopia*	-	Intermittently symptomatic, intervention not indicated	Symptomatic and interfering with function but not interfering with ADL	-Symptomatic and interfering with ADL -Surgical intervention indicated	Disabling
Enophtalmus*	-	Asymptomatic	-Symptomatic -Limiting instrumental ADL**	-Limiting self care ADL** -Disabling	-
Exophtalmus†	-	Asymptomatic	-Symptomatic -Limiting instrumental ADL**	-Limiting self care ADL** -Disabling	-
Strabismus	-	Asymptomatic	-Symptomatic -Limiting instrumental ADL**	-Limiting self care ADL** -Disabling	-
Dry eye	-	-Asymptomatic -Mild symptoms relieved by lubricants	-Symptomatic -Multiple agents indicated -Limiting instrumental ADL**	-Decrease in visual acuity (<20/40) -Limiting self care ADL**	-
Watering eyes	-	Symptomatic	Intervention indicated	Operative intervention indicated	-
Blurred vision	-	Symptomatic	Limiting instrumental ADL**	Limiting self care ADL**	-
Cataract	-	Asymptomatic	-Symptomatic: moderate decrease visual acuity (20/40 or better)	-Marked decrease visual acuity (20/40-20/200) -Operative intervention indicated	-Blindness (20/200 or worse) in affected eye
Conjunctivitis	-	-Asymptomatic -Intervention not indicated	-Symptomatic -Limiting instrumental ADL** - Topical intervention indicated	Limiting self-care ADL**	-

5. Ocular problem *Continued*

	Grade				
Adverse event	0	1	2	3	4
Flashing lights/ floaters	-	Symptomatic	Limiting instrumental ADL**	Limiting self-care ADL**	
Glaucoma	-	-Elevated intraocular pressure with single topical agent -No visual field deficit	-Early visual field deficit -Multiple agents indicated (oral/topical) -Limiting instrumental ADL**	-Marked visual field deficits -Operative intervention indicated -Limiting self-care ADL**	-Blindness (20/200 or worse)
Keratitis (corneal inflammation, ulceration)	-	-	-Symptomatic -Medical intervention indicated -Limiting instrumental ADL**	-Limiting self-care ADL** -Decline in vision 20/40-20/200	Perforation or blindness (20/200 or worse)
Optic nerve disorder	-	Asymptomatic	Limiting vision of the effected eye (20/40 or better)	-Limiting vision of the affected eye (20/40-20/200)	Blindness (20/200 or worse)
Papilledema	-	-Asymptomatic -No visual field defects	-Symptomatic decline in vision -Visual field defect present sparing the central 20 degrees	-Marked visual field defect (20/40-20/200)	Blindness (20/200 or worse)
Photophobia	-	Symptomatic	Limiting instrumental ADL**	Limiting self-care ADL**	-
Retinal detachment	-	Asymptomatic	Exudative and visual acuity (20/40 or better)	-Rhegmatogenous or exudative detachment -Operative intervention indicated -Decline in vision (20/40-20/200)	Blindness (20/200 or worse)
Retinal vascular disorder	-	-	Topical medication indicated	-Intravitreal medication -Operative intervention indicated	-

PART III

4

Dose-effect analysis of early changes in orbital bone morphology after radiation therapy for rhabdomyosarcoma

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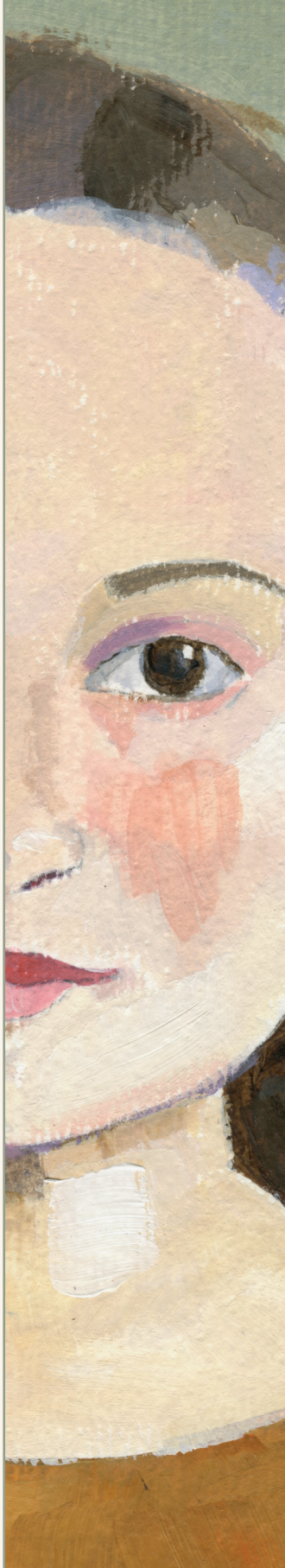

ABSTRACT

Purpose

In survivors of orbital embryonal rhabdomyosarcoma (ERMS), late effects include facial deformation and asymmetry. We sought to quantify orbital asymmetry in ERMS survivors and characterize the dose effect of radiation to the orbital bones.

Methods and Materials

We evaluated the most recent follow-up magnetic resonance imaging therapy between 2007 and 2018. For all patients, the orbital socket volumes were calculated and (MRI) in 17 children (21 years old) with stage 1 group III orbital ERMS treated with proton compared with the contralateral, unirradiated orbital socket. Patient age, orbital tumor quadrant, and the radiation dose delivered to the major orbital bones (maxillary, frontal, and zygomatic bones) were recorded and correlated with the orbital socket volume difference.

Results

The mean age at diagnosis was 5.4 years old (range, 1.1-9.7 years). All patients received a prescription dose of 45 GyRBE. The mean time interval between radiation and MRI was 2.9 years (range, 0.8-3.2years).The mean age at most recent MRI was 8.4 years (range, 2.3-12.9 years). In 16 of 17 patients, the volume of the ipsilateral orbit was significantly smaller than the contralateral orbit on follow-up MRI ($P < .001$). In one patient with nonviable tumor in situ, the irradiated orbit was larger. The volume difference increased with follow-up time and did not correlate with age at treatment or age at MRI. A dose >40 GyRBE to all bones of the orbital rim was associated with a significant decrease in orbital volume ($P <.05$), but an isolated dose of >40 GyRBE to either the frontal, maxillary, or zygomatic bone was not.

Conclusions

Despite the dosimetric precision of proton therapy, orbital asymmetry will develop after >40 GyRBE to multiple bones of the orbital rim. These data may be used to guide treatment planning and counsel patients on expected cosmesis.

INTRODUCTION

With long-term survival in pediatric embryonal rhabdomyosarcoma (ERMS) patients exceeding 90%, the impact of adverse late effects from radiation therapy have become more apparent. In patients with orbital tumors, these late effects include poor cosmesis associated with facial deformation, orbital hypoplasia, and facial asymmetry (1-5), which can compromise quality of life and mental well-being. Given the limited reconstructive options for patients treated in the head and neck area, proactively avoiding such late effects is important. Incremental progress is being made in radiotherapy to de-intensify treatment and consequently mitigate late adverse effects. De-intensifying treatment may be accomplished by lowering prescription radiation doses, reducing the size of target volumes, and limiting unnecessary dose outside of the target volume via more conformal technology such as proton therapy (6). Early data from our institution suggest that dose de-intensification using proton therapy maintains excellent disease control and improves aspects of acute and late toxicities (7).

Nevertheless, orbital bone hypoplasia from radiation therapy remains an evident concern, and the modern dose-effect models necessary to guide improvements in treatment planning do not yet exist. The purpose of this paper was to assess the early trajectory of orbital volume (OV) changes in patients treated with radiation for orbital ERMS and to characterize the dose-effect to the bones responsible for periorbital cosmesis.

MATERIAL AND METHODS

All consecutive patients enrolled in our institutional review board-approved prospective study (IRB# 2006-153) who were treated with proton therapy for Children's Oncology Group (COG) stage 1, group III orbital ERMS were eligible for this sub-study (IRB # 2017-01138). Only patients for whom a follow-up MRI was available at least 6 months after radiation treatment were included. Patients who received prior radiation treatment to the head and neck area were excluded.

Patient age, orbital tumor quadrant, and the radiation dose independently delivered to the bones forming the orbital rim (the maxillary bone, frontal bone, and zygomatic bone) were recorded. All dose effects were calculated for the maximum 0.1-cm3 dose delivered to the orbital rim bones. To calculate OV, the MRI was loaded as a DICOM image into MimVista (Mim Software Corporation, Cleveland, Ohio), which allows scaled digital measurements. The measurement of the orbit was consistently recorded on the axial slice demonstrating the maximum lens size. The anterior-posterior orbital depth was defined as the distance from the most anterior part of

the lens to the deepest part of the bony orbit. The width of the orbit was defined as the maximum transverse distance between the most anterior part of the zygomatic bone and the most posterior part of the nasal bone. To calculate OV, the orbit was considered cone-shaped. OV hypoplasia was then calculated by subtracting the OV of the irradiated side from the OV of the untreated side. The OV change was considered clinically relevant when the volume differential exceeded 1 cm3. All dimensions were measured twice and the average was recorded if small discrepancies were found.

OV characteristics were compared between the irradiated orbit and the unirradiated (control) orbit using a student t-test or Mann-Whitney U test. We evaluated the correlation between orbital rim bones and OV differential using a univariate, rather than multivariate, analysis due to the limited sample size.

RESULTS

Patient, tumor, and treatment characteristics

A total of 30 children with COG stage 1, group III orbital ERMS were treated with proton therapy at our institution between 2006 and 2018. Of these, 17 children met the study inclusion criteria. The mean age at diagnosis was 5.4 years old (range, 1.1-9.7). Fifty-nine percent of the patient population was male. Seven tumors were located in the superior orbit, 6 in the medial orbit, 2 at the inferior orbit, and 2 in the lateral orbit. Patients were treated according to our institution's pediatric treatment guidelines for rhabdomyosarcoma. The gross tumor volume (GTV) was defined by the gross disease at the time of radiation, following induction chemotherapy. The clinical target volume (CTV) was defined by the GTV + 5 mm, with further modification as necessary to encompass all surfaces originally in contact with the tumor and all soft tissue originally infiltrated by disease. The standard prescription dose was 45 GyRBE, delivered via two sequential phases. The initial planning target volume (PTV1), defined as the CTV + 3 mm, received 36 GyRBE followed by a 9-GyRBE boost to the PTV2, defined as the GTV + 3 mm. The primary goal when developing the radiation plan was to ensure that the entire CTV was encompassed by >99% of the nominal dose and that the entire PTV was covered by 95% of the nominal dose. Plans were optimized to minimize the dose to the retina, lacrimal gland, pituitary, hypothalamus, and brain tissue without compromising target coverage. All patients in this series were treated with double-scattered proton plans using 2 to 3 beams per phase. Each field was treated once daily. The distal and proximal beam margins in millimeters were calculated through the empirically derived institutional formula of (2.5% x field range) + 1.5 mm. The aperture margin was 4 to 7 mm from the lateral PTV edge. The typical beam smearing margin was 5 mm.

MRI review and orbital volume

The mean interval between the end of radiation and the first follow-up MRI was 2.9 years (range, 0.8–3.2 years). The mean age at MRI was 8.4 years (range, 2.3–12.9 years). The mean OV on the irradiated side was 11 cm3 (range, 5.3–17.3 cm3). The mean OV on the contralateral (non-irradiated) side was 12.9 cm3 (range, 7.4–17.9 cm3). The mean OV differential was 1.9 cm3 (range, 1.0–4.9 cm3). In 16 of 17 (94%) patients, the irradiated orbit was significantly smaller on the irradiated side ($p<0.005$). More than 1 cm3 of OV differential was observed in 75% of the patients. In one patient with a large tumor in situ, the irradiated orbit was larger than the non-irradiated side. This patient was excluded from the hypoplasia risk factor and dose-effect analyses.

The OV differential did not correlate with age at treatment (R=-0.2; p=0.8). It moderately correlated with the amount of follow-up time (R=0.49; P=0.02), with a more notable volume differential observed in patients with >4 years of follow-up (p=0.017). The OV differential did not correlate with age at the time of the follow-up scan (R=0.01). Follow-up time, age at diagnosis, and age at follow-up in relation to OV differential for all 16 patients is shown in Figure 1.

Patients with a tumor located in the medial orbit demonstrated a non-significant trend toward greater volume differential compared to patients with a tumor located in the superior, lateral, or inferior orbit (p=0.2). Patients with a tumor located in the lateral orbit seemed to have the least OV differential.

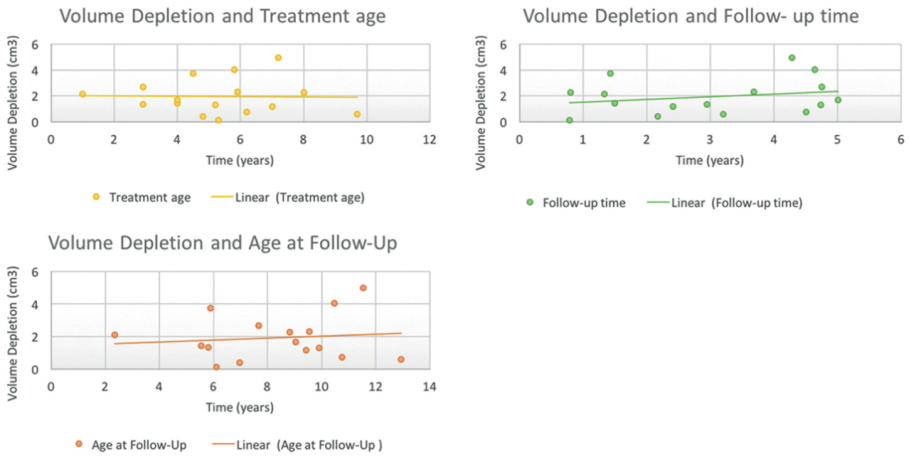

Figure 1. Volume differential between irradiated and nonirradiated orbits (cm3) correlated to age at follow-up, follow-up time, and treatment age.

The OV differential did not correlate with age at treatment (R Ze0.2; P Z .8). It moderately correlated with the amount of follow-up time (R Z 0.49; P Z .02). The OV differential did not correlate with age at the time of the follow-up scan (R Z 0.01).

Dose-effect

The mean maximum doses received by the maxillary, frontal, and zygomatic bones were 41 GyRBE (range, 27–45 GyRBE), 41.9 GyRBE (range, 22–45 GyRBE), and 40.8 GyRBE (range, 31–45 GyRBE), respectively. The composite orbital rim received a mean maximum dose of 41.25 GyRBE. A maximum 0.1 cm^3 dose >40 GyRBE to all orbital rim bones resulted in a significant differential in OV (p = 0.018). However, an isolated dose of >40 GyRBE to the frontal, maxillary, or zygomatic bones did not correlate with a differential in OV (R=0.32, R=0.22, and R=0.15, respectively). A graphic depiction showing the dose to each of the individual bones and the orbital rim in relation to the OV differential is shown in Figure 2.

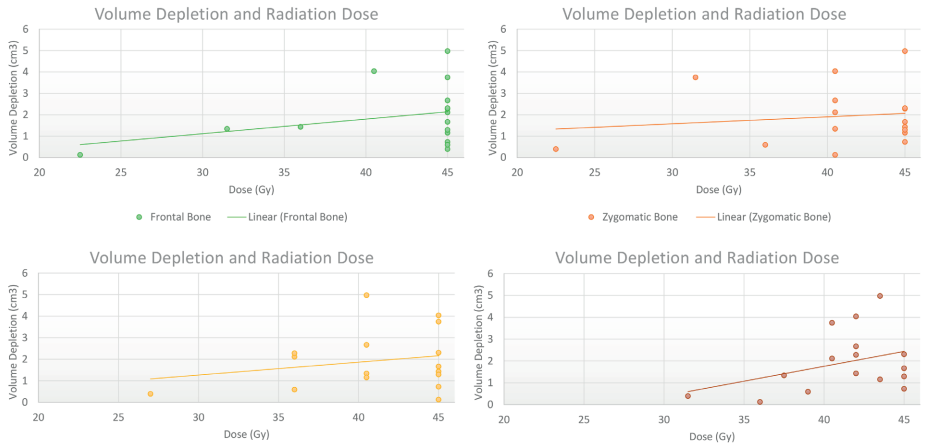

Figure 2. Volume differential between irradiated and nonirradiated orbits (cm3) in relation to radiation dose to the orbital rim bones.

The radiation dose delivered to each patients' frontal bone, zygomatic bone, and maxillary bone is depicted as well as the radiation dose to the orbital rim bones. A maximum 0.1 cm3 dose >40 GyRBE to all orbital rim bones resulted in a significant differential in OV (P Z .018). However, an isolated dose of >40 GyRBE to the frontal, maxillary, or zygomatic bones did not correlate with a differential in OV (R Z 0.32, R Z 0.22, and R Z 0.15, respectively).

DISCUSSION

Our findings on OV differential suggest that, despite the dosimetric precision of proton therapy and the radiation de-intensification in modern protocols, orbital asymmetry will still develop in many survivors of ERMS, with a mean OV difference of nearly 2 cm3 observed even in early follow-up. Our findings also suggest that limiting the maximum dose to the combined orbital rim bones may reduce OV asymmetry. To minimize the impact of radiation, regardless of treatment modality, it may be worthwhile to delineate the orbital rim during treatment planning and

limit the volume receiving >40 GyRBE. Beyond this, efforts to reduce CTV and PTV margins in orbital ERMS patients may be necessary to achieve further improvements in cosmetic outcomes.

Children with facial abnormalities show impaired quality of life (8, 9). Poor facial cosmesis also negatively affects mental health and emotional well-being (10). Soft-tissue sarcoma survivors are one of the most at-risk groups of cancer survivors for reduced quality of life (11), and facial asymmetry and hypoplasia are widely reported in head and neck rhabdomyosarcoma survivors (4, 12, 13). Previous studies have focused mainly on facial asymmetry as described by physicians. For example, Lockney et al. estimated that 77% of survivors of head and neck rhabdomyosarcoma suffer from subjective facial abnormalities as judged by their medical team (4). The Intergroup Rhabdomyosarcoma Study focused on orbital rhabdomyosarcoma survivors. In this study, orbital hypoplasia was reported in 48 of 82 patients (14). A study using questionnaires for physicians showed orbital hypoplasia reported in 29% of surviving patients, with a mean follow up of 8 years, in the pooled analysis of European studies (5). A potential limitation in these studies is the use of questionnaires and recognized biases of physician-reported outcome measurements. These studies lack objective, longitudinal auxology data such as orbital measurements. Another way of analyzing facial asymmetry is through 3-dimensional stereophotogrammetry. Investigators using this technique found that survivors of head and neck rhabdomyosarcoma exhibited significantly more facial asymmetry compared to their healthy counterparts (2). Unfortunately, 3-dimensional stereophotogrammetry is limited to facial surface anatomy and therefore may obscure bone deformation. In none of these prior studies was orbital volume calculated on scans making comparisons with our data challenging. We found that there is some OV differential in all survivors, with more than a 1 cm3 differential in 75% percent of the patients. When considering 1 cm3 as a clinically relevant loss of volume, our estimated rates resemble the previously reported outcomes on facial asymmetry and orbital hypoplasia.

There are no studies specifically correlating OV asymmetry with radiation dose and the clinical consequences of impaired orbital bone growth. However, much data exist on OV differential following orbital blow-out fractures, which show that a small change in OV, as little as 1 cm3, can result in enophthalmos of 0.8 mm (15). Investigators analyzing significant alterations in facial cosmesis found that enophthalmos exceeding 2 mm resulted in an abnormal appearance. An example of a radiation patient in our series with reduced OV and the corresponding setback of the eye is shown in Figure 3. The question remains, however, if growth trajectory following radiation is analogous to trauma.

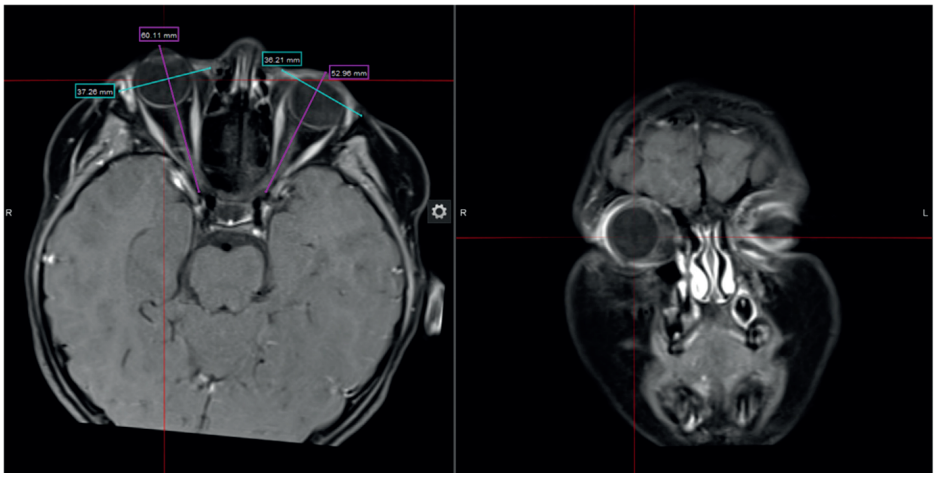

Figure 3. Reduced orbital volume resulting in enophthalmos in an 8-year-old patient who was treated at 5.3 years of age for a tumor in the medial superior quadrant.

Reduction of the orbital volume was measured on the axial slice showing maximum lens size. Width was measured as the most anterior part of the zygomatic bone to the posterior part of the nasal bone. Anterior-posterior depth was measured as the highest part of the lens and the deepest part of bony orbit. To calculate orbital volume, the orbit was considered a cone: $\frac{1}{3}\pi * R^2 * h$.

Defining empiric dose constraints for bones in the developing head and neck area is challenging due to the many factors influencing bony growth such as pubertal status, attained age, nutrition status, chemotherapy regimen, and differences in bone growth (16). Previous work has suggested delineating the entire orbit as a separate organ at risk to limit the dose as much as possible; yet, no thresholds for bones are offered (16). Our data reinforce this concept correlating dose and volume: an isolated high dose to one of the orbital rim bones poses less risk than a radiation dose over 40 GyRBE to the entire orbital rim.

This study has important limitations. Although it is the first study to objectively track orbital bone data in the post-radiation therapy setting, the small sample size and limited follow-up time prohibits definitive conclusions. In our study, the mean follow-up was about 2 years and the mean age at MRI about 9 years of age; therefore, most survivors have not yet gone through their growth spurt and more growth of the orbit is expected through the age of 15 years (17). It would be useful to follow this patient group through puberty and validate the findings against an external cohort. We also cannot draw definitive conclusions by comparing proton data to photon data as very little photon data exist, and what does exist relates to an era of different (larger) treatment volumes. Nevertheless, our data offer a useful starting point for radiation treatment planning with 40 GyRBE as the maximum

orbit dose. It also reminds us that, despite advances in treatment protocols and technology, there is room to improve upon cosmetic outcomes.

CONCLUSION

Despite the dosimetric precision of proton therapy and radiation de-intensification in modern protocols, orbital asymmetry will develop in survivors with ERMS who receive >40 GyRBE to multiple bones of the orbital rim. These data may be used to guide treatment planning and to counsel patients on expected cosmesis.

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5

Dose-effect analysis of facial bone morphology following radiation therapy for head and neck rhabdomyosarcoma

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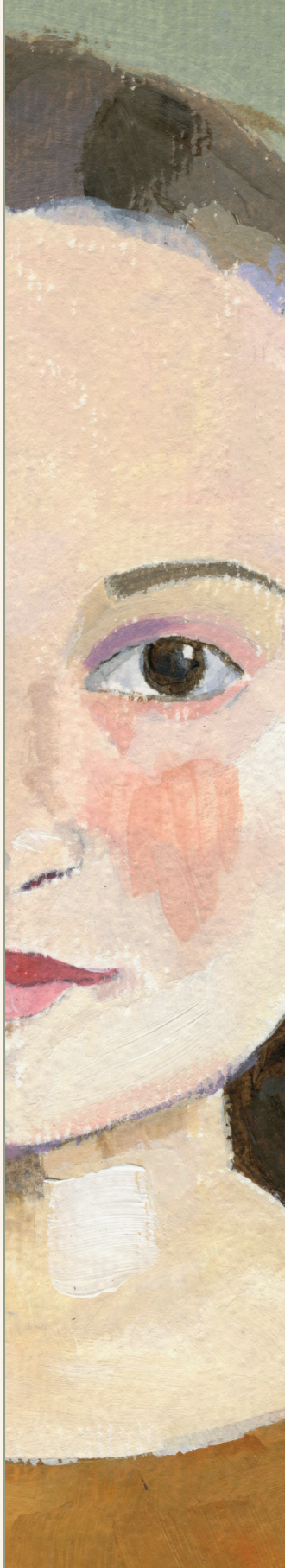

ABSTRACT

Introduction

With the long-term survival of paediatric rhabdomyosarcoma patients improving, the impact of late adverse effects becomes more important. These late effects in head-neck-rhabdomyosarcoma survivors include poor cosmesis associated with facial deformation. This study aims to correlate facial deformation with radiation dose and propose new dose-effect models.

Materials and Methods

We evaluated 3D facial images of children treated with radiotherapy enrolled in our multi-center cross-sectional study with a primary head-neck-rhabdomyosarcoma. Facial deformation was calculated from 3D image analysis at follow-up and compared to a healthy control population (n=537). The radiation dose delivered to all individual facial bones and sutures was extracted from original radiotherapy plans. Dose-effect probability curves were constructed by converting the dose to its equivalent 2Gy/fraction EQD2 using binary logistic regression.

Results

Thirty-four survivors with a median follow-up of 9.2 years were included. Survivors with facial deformation all received significantly higher mean doses to the corresponding bony structures ($p<.001$). The ethmo-maxillary complex shows increased susceptibility for facial deformation at 28GyEQD2 and a 50% probability of growth deformation at 51GyEQD2. The mandibular complex shows increased growth deformation probability at 26GyEQD2 and a 50% probability at 41GyEQD2. The threshold for increased risk of bone deformation for individual facial bones varied from 26 GyEQD2 to 43 GyEQD2 and a 50% probability for deformation varied from 44 GyEQD2 to 55 GyEQD2.

Conclusion

Dose thresholds for specific facial bones impacting cosmesis in survivors of paediatric sarcoma are shown. These data are essential to improve treatment planning thereby limiting the debilitating late adverse effect of facial deformation.

INTRODUCTION

Forty percent of rhabdomyosarcomas (RMS) occur in the head and neck (HN) area at a median age of 6 years, where the vast majority of children needs radiotherapy (1,2). With overall survival increasing over the past few decades, the care of long-term survivors takes a more prominent role. In survivors of HNRMS, these late adverse effects include facial deformation, asymmetry, and orbital hypoplasia, which can compromise self-image and quality of life (3–6). Proactively avoiding these late adverse effects is vital since reconstructive options are limited in the irradiated HN area.

Achieving high survival rates in this population requires a combination of chemotherapy and local treatment. There are currently four different local treatment modalities for HNRMS; External beam radiotherapy with the use of photons (RT), external beam radiotherapy with protons (PT), macroscopic resection combined with brachytherapy (AMORE), and radical resection combined with either PT or RT (henceforth "Paris-method") (7,8). Organs at risk and their threshold doses are used during radiation planning to protect tissue that is vulnerable to radiation (9). These organs include the eye, optic nerve, pituitary gland, parotid gland, and lacrimal gland (10). However, there are no validated dose parameters for the facial bones to guide treatment. Growth and development of the craniofacial complex is considered a multifactorial process in which functional, developmental, genetic and evolutionary traits can be identified (11). The cranial base is considered a platform for facial growth (12). The cranial base is composed of basioccipital, sphenoid, ethmoid, frontal bones and temporal bones . The cranial base is divided into the posterior and the anterior cranial base. The anterior cranial base has a direct connection with the upper middle face and integrates with the upper middle face into a growth complex, named the ethmo-maxillary complex. The mandible articulates with the posterior cranial base.

In previous studies, we showed that all survivors of HNRMS demonstrated reduced facial growth compared to healthy sex-age-ethnicity matched controls (13). Also, survivors showed more asymmetry in comparison to the healthy population (13). Even with modern techniques, healthy tissue is compromised, and the resulting facial deformation remains as a persistent debilitating treatment effect. If incorporated into the treatment plan, an accurate dose-effect model for individual bones and for the ethmo-maxillary complex and mandible of the face might limit facial growth reduction and deformation. This study aims to characterize the radiation dose effect on bones, facial bone complexes and sutures responsible for facial growth and shape.

MATERIALS AND METHODS

Patient selection

As a collaborative project, we established a research agreement between the Academic Medical Center (AMC), Amsterdam, the Netherlands [which later transferred its pediatric oncologic care to the Princess Máxima Center for paediatric oncology in Utrecht in the Netherlands (PMC)], Gustave Roussy Cancer Campus (IGR), France, Great Ormond Street Hospital for Children (GOSH), United Kingdom, and University of Florida Health Proton Therapy Institute (UFHPTI), United States. The local ethical committees of all participating centers and relevant national review boards approved this study. Written or oral consent was obtained in accordance with local and national standards. Late adverse events clinics for HNRMS survivors were held for study purposes at AMC/PMC, GOSH, IGR, and UFHPTI. All children with primary HNRMS treated between 1990-2017 who survived a minimum of two years post-treatment were invited to participate in this study at the multidisciplinary outpatient clinic. Relapsed patients and patients with secondary malignancies were excluded. Survivors were physically examined and assessed using the Common Terminology Criteria for Adverse Effects (CTCAE version 4.0) by multiple clinicians who also acquired blood work and 3D facial photography. Only patients with both adequate diagnostic imaging, radiotherapy treatment plans, and 3D photographs available were selected for this study. When available, the diagnostic imaging and radiotherapy treatment plans were collected. As described above, there are four local treatment options for head and neck rhabdomyosarcoma. For this study, survivors treated with Paris-method were excluded since the introduction of radical resection made it impossible to isolate dose-effect relationships from the cosmetic impact of radical surgery. Also, patients treated with AMORE who underwent a bone resection as part of their treatment, as well as patients with substantial bony invasion (regardless of treatment modality) were excluded. All survivors were treated according to the consecutive International Society for Pediatric Oncology (SIOP) -Malignant Mesenchymal Tumour group (MMT), European *paediatric* Soft tissue sarcoma Study Group (E*p*SSG) RMS 2005 or Children's Oncology Group (COG) protocols.

Facial deformity analysis

Facial deformation was quantified from 3D facial images using *dense surface models* (DSM), a statistical shape analysis method previously utilized to quantify facially affected genetic conditions, fetal alcohol spectrum disorder, and childhood cancer (14–17). DSM provides principal component analysis (PCA) based method in which principal components (PCs) account for shape variation across the model. The 3D surface geometry of each face can be reconstructed as a weighted linear sum of the PCs. Facial signatures were computed for each HNRMS survivor to quantify normalized surface displacement relative to a mean of 35 age-sex-ethnicity matched

controls. Separate DSMs were constructed containing the aforementioned healthy controls and the thirty four HNRMS survivors for three facial regions representing the lower face, midface, and nasal region. Facial analysis using DSMs uses similar approaches described in our previous studies (13,15,16), and more technical detail is available from work undertaken by Hammond and colleagues (18,19).

Radiotherapy data

Facial bones and sutures were delineated on the radiation treatment plan imaging by one researcher (MH) and checked by a head and neck radiologist with over 40 years' experience (NF). Delineation of facial bones and sutures as organs at risk was consistent with a head and neck anatomy app (20). Dose to facial bones and sutures was exported from treatment data. During the study period, patients were treated with either RT, PT, or brachytherapy as part of the AMORE protocol. Brachytherapy in the AMORE protocol was first delivered using continuous Low-Dose Rate (LDR) until 2001, after which it was delivered as a Pulsed-Dose Rate (21). To aid assessments between treatment modalities, all radiotherapy physical doses were recalculated as biologic equivalent doses in 2 Gy per fraction (EQD2). The relative effective dose reflective of biological potency of protons was represented by q_{let} as 1.1 relative to photons (RT and BT) . The alpha-beta ratio indication of the cell repair capacity in the Linear Quadratic model for facial bones was assumed to be 2 Gy, in the range as applied by van Dijk et al (22,23). The half time for DNA repair was assumed to be 1.5 hours (21). As an outcome variable, the EQD2 for the mean dose was used.

Statistical methods

Laterality was recorded for all facial bone delineation. Correlation matrices for bones and facial deformation were assessed using Spearman's rho ranking. Binary logistic regression models were made for all bones and sutures corresponding to a facial area. ROC curves will be used to assess model fit. An area under the ROC curve of >0.7 was considered a good model fit. For significant dose-toxicity models with a good model fit, dose cut-off values for increased risk (increasing risk and probability of >0.5) of facial deformation were identified.

RESULTS

For thirty-four survivors, both 3D planning CT scans and 3D stereophotography were available. Patient characteristics are shown in **table 1**. In general, survivors with facial deformation received a higher dose for the relevant bones and sutures, as shown in **Supplementary data table 1.1 – 1.3**. Overall, Spearman's rho correlation coefficients between the doses to facial bones and sutures and the associated facial deformation model were moderate to strong, ranging from 0.46 - 0.69 (**Supplementary data table 2.1-2.3**).

Table 1. Baseline of the 34 survivors included for whom radiotherapy and a 3D photo were available

		N = 34	
Age at diagnosis	Median, range	4.8	0.5 – 13.3
Attained age	Median, range	19.1	4.3 – 33.3
Follow-up period	Median, range	9.2	3.2 – 27.0
Gender			
Male	N %	22	64%
Site			
NPM	N %	7	21%
Orbit	N %	10	29%
PM	N %	17	50%
Local treatment modality			
RT	N %	11	33%
PT	N %	10	29%
AMORE	N %	13	38%

*AMORE: Ablative surgery MOuld placement and REconstructive surgery. Brachytherapy consisted of consisting of low-dose rate (LDR) (N = 3) and pulsed dose rate (PDR) (N = 10) RT: external beam radiotherapy with photons, PT definitive external beam radiotherapy with proton beam radiation, NPM; non-parameningeal, PM; parameningeal tumor location.

Dose-response associations

Univariable logistic regression models were created for facial deformation depending on the Dmean GyEQD2 to the associated bone and suture. From this regression coefficient, a dose-probability curve was constructed. All statistically significant models were assessed with ROCs for model fit and showed good model fit (all >0.74 (95% CI all over 0.703-1.000).

Dose effect models were made for the two main parts of the face, the ethmo-maxillary complex and the mandible. The ethmo-maxillary complex shows increased susceptibility for facial deformation when the cranial base was irradiated at 28GyEQD2 and a 50% probability of growth deformation at 51GyEQD2. The mandibular complex was more susceptible to deformation, already showing increased probability at 26GyEQD2 to the mandible and a 50% probability at 41GyEQD2. Data shown in figure 1.

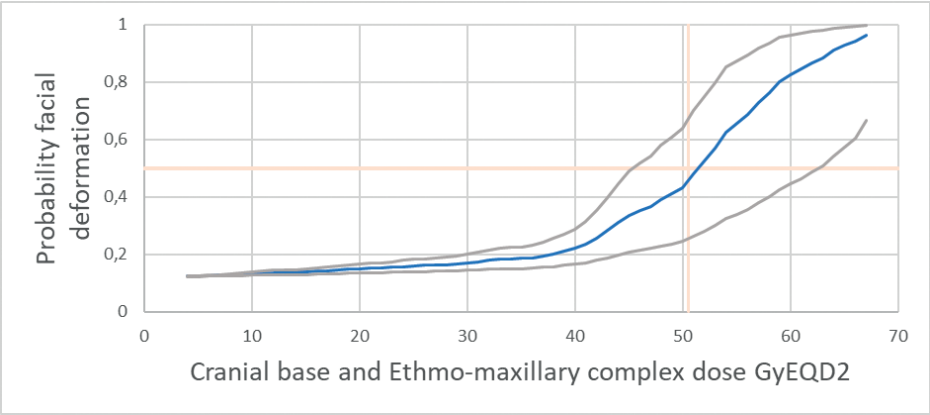

Figure 1A. Dose-effect models for the facial deformation of the ethmo-maxillary complex and the mandibular complex.

Represents the dose to the cranial base and mandibular complex and the probability of facial deformation. The grey lines represent the 95% confidence intervals and blue represents the actual dose-effect curve. The 50% probability is depicted using the peach line.

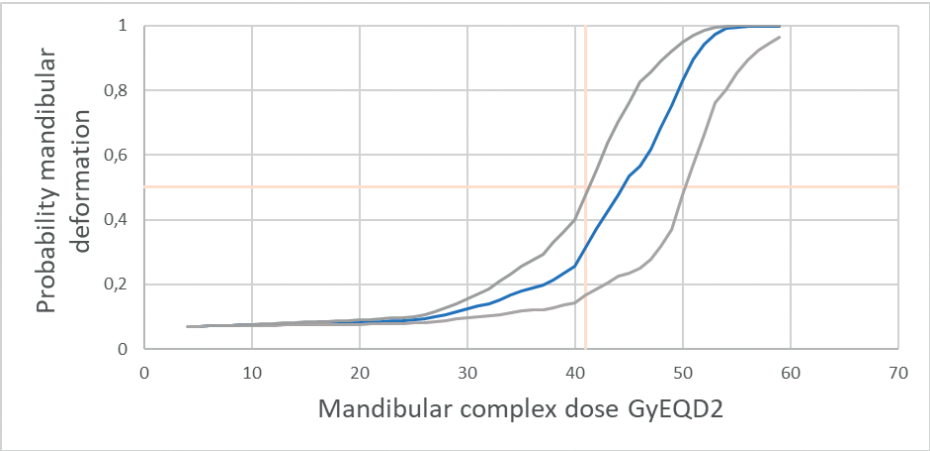

Figure 1B. Dose-effect models for the facial deformation of the ethmo-maxillary complex and the mandibular complex.

Represents the dose to the mandibular complex and the probability of facial deformation of the mandibular area. The grey lines represent the 95% confidence intervals and blue represents the actual dose-effect curve. The 50% probability is depicted using the peach line.

Dose-effect relations for the midface were assessed for the maxilla, zygoma, pterygoid plates, spheno-zygomatic suture, zygomatic-maxillary suture, and zygomatic-temporal suture. The dose-effect models, with confidence intervals, are shown in **Supplemental figure 1a-e**. The dose-effect model for the zygomatic-temporal suture was not significant and therefore is not included for further

analysis. A maxillary dose over 40GyEQD2 started to result in increased midface deformation, and a dose over 51 GyEQD2 resulted in a probability of 50% for midfacial deformation. The zygoma showed increased facial deformation starting from a dose of 28 GyEQD2 and a 50% probability at 44 GyEQD2. Pterygoid plates dose of 37 GyEQD2 showed an increased risk of midfacial deformation, and a dose over 50 GyEQD2 resulted in a 50% probability for midfacial deformation. Midface deformation began at 26 GyEQD2 to the spheno-zygomatic suture and reached a 50% probability at 48 GyEQD2. Facial deformation began at 19 GyEQD2 to the zygomatic-maxillary suture, and a 50% risk of midfacial deformation was observed at 44 GyEQD2.

Dose-effect models for nasal deformation were created for the nasal septum, nasal bone, and vomer (**Supplementary figure 2a-2c)**. The nasal septum started showing a higher probability for nasal deformation when radiated over 37 GyEQD2 and a 50% probability at 55 GyEQD2. The nasal bone started to show an increased likelihood of nasal deformation at 28 GyEQD2 and a probability of 50 % at 47 GyEQD2. A dose over 39 GyEQD2 to the vomer resulted in an increased probability of facial deformation, and a 50% probability for nasal deformation was found at a dose of 51 GyEQD2.

Dose-effect models for deformation of the mandibular area were constructed for the mandibular body and the mandibular condyle (**Supplementary figure 3a-3b)**. A radiation dose over 43 GyEQD2 to the mandibular body resulted in an increased risk for mandibular deformation, and a dose over 55 GyEQD2 resulted in a 50% probability. For the condyle, a dose over 27 GyEQD2 resulted in mandibular deformation whilst a 50% probability for mandibular deformation started at a dose of 47 GyEQD2.

DISCUSSION

Our previous paper highlighted facial deformation as a common problem in HNRMS survivors (13). The current study advances on those findings, analyzing the dose to specific parts of the face in relation to its impact on growth deformation. Our findings suggest that limiting the mean dose to specific bones in the facial area might mitigate the rate and severity of facial deformation. For the first time, we provide clinicians with facial bone dose-effect data in children to guide treatment planning, applicable across all treatment modalities.

Children and adolescents with facial deformation and impaired cosmesis are impacted in domains of mental health and quality of life (4,5). Survivors of pediatric head and neck tumors show high rates of facial deformation and facial asymmetry (3,4,6). Unfortunately, reconstructive options in the irradiated head and neck area

are limited due to the quality of bone and soft tissue, and consequently, we need to minimize the risk at the time of treatment. However, only a few studies specifically look at facial deformation following irradiation (6), and these provide no threshold doses, only qualitative descriptions. In our previous work, we looked at orbital volume changes on MRI. We suggested that when all bones of the orbital rim receive a dose of >40GyRBE, orbital asymmetry will develop (24). Our analysis implicates that delineating the orbital rim may benefit treatment planning to minimize orbital hypoplasia. In the current study, we did not examine orbital volume development as we used 3D stereophogrammetry which does not provide information on orbital volume. In our current study dose thresholds of 28GyEQD2 for the ethmo-maxillary complex and 26GyEQD2 for the mandible were found. The similar dose constraints are largely explained by the maturation of the craniofacial levels. Enlow & Hans hypothesized different levels of maturation in what they characterized as different craniofacial levels; the neuro-basocranial complex, the ethmoid-maxillary complex and the mandibular complex (25). Current studies support Enlow's theory in that the basicranium reaches adult size and shape earlier than the maxillary and mandibular parts of the face explaining the higher threshold doses for the sphenoid in comparison to the ethmoid-maxillary and mandibular complex doses found in this study. Some earlier studies have hypothesized different developmental and growth stages for the ethmoid-maxillary complex and the mandible, however, recently difference in maturity could not be shown in 3D studies (12), with both the midface and lower facial units reaching maturity at around 16 years of age. The mandible is known to undergo the greatest change in size and shape in the first year of life, with increasing ramus height, increasing corpus length and increase in width (26). Following the first year of life no incline or decrease is shown in growth with consistent growth throughout time (26,27).In this study we explore specific dose constraints for all the facial bones but dose constraints for an entire facial complex might be more clinically relevant. Also, the range of different doses found for the individual facial bones might largely be explained by the relatively small sample size and heterogeneity in age at treatment, follow-up time and attained age.

Defining dose constraints for bones in the developing head and neck area is challenging due to the many factors influencing bone growth, such as growth centers in facial bones, pubertal status, attained age, chemotherapy regimen, and differences in bone growth (6). Concurrent chemotherapy is believed to exacerbate normal tissue reactions, although there is limited available data characterizing facial bone growth. The role of chemotherapy in this process is not known, but the asymmetry and localization of problems in the radiated area suggest effect of irradiation independent of the potential influence of concurrent chemotherapy.

Even though this is the first study to propose objective dose-effect models for facial growth, it is important to note the limitations of our approach. Although thirty-

four HNRMS survivors participated, it is still a rather small sample size. Owing to the small sample size, we were not able to do a multivariate analysis or correct for treatment age, attained age, or sex. One could imagine that potentially younger age at treatment would result in larger facial deformation or greater impact of a lower dose. The median attained age at the time of study inclusion was 19.1 years, ranging broadly from 4.3 -33.3 years. Consequently, this means part of our analyzed population was not yet past their growth spurt, potentially underestimating effects. It would be most interesting to follow this survivor cohort until all reach adulthood and repeat the study to validate these results. Lastly, three different local treatment strategies were included, namely RT, PT, and AMORE. We did recalculate all doses into EQD2 and corrected for different qualities of radiation. However, it might be worthwhile to repeat a similar study only using one type of local therapy. There are 13 survivors who were treated with AMORE, and as part of the AMORE treatment, a macroscopic resection of the tumor is performed. None of the 13 survivors had bone resections or large muscles removed, but one could imagine that surgery also plays a role in the effect of facial deformation. In this study, we have not corrected for the potential effect of this local surgery. When analyses were performed excluding all AMORE patients, threshold doses remained the same, but statistical power was lost for many models. We did not include survivors treated with the Paris method because, as mentioned, for this treatment extensive microscopic radical resections are performed, removing bones and muscle segments (8). We excluded these patients because the effect of surgery and radiation could not be disentangled. Lastly, we did not make use of dose-volume histograms. Potentially taking treated volumes into account might make a difference in threshold dose, especially for the larger facial bones (for example, the frontal bone). Regardless of the limitations, the data in this study provide an uniquely useful starting point for future studies, and for treatment planning today. Delineation of facial bones or potentially only facial bone complexes (the ethmo-maxillary complex and the mandible) and sutures adds clarity to treatment planning, and limiting radiation doses to the proposed thresholds might limit facial growth retardation as well as facial deformation. Future studies should be aimed at adding data to these dose-effect models making them more robust and incorporating more multifactorial data (treatment age, follow-up time). Also, it would be worthwhile to explore whether it is possible to develop treatment plans that incorporate the threshold doses presented in this study.

CONCLUSION

The data from our study suggest dose thresholds for bones and sutures in the facial area that impact the risk and severity of facial deformation. These dose thresholds should be validated in external cohorts and ultimately implemented in treatment planning to limit facial deformation.

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SUPPLEMENTAL DATA

Supplemental Figure 1. dose-effect models for the midface deformation for specific bones and sutures in the midfacial area (excluding nose).
The grey lines represent the 95% confidence intervals and blue represent the actual dose-effect curve. The 50% probability is depicted using the peach line.

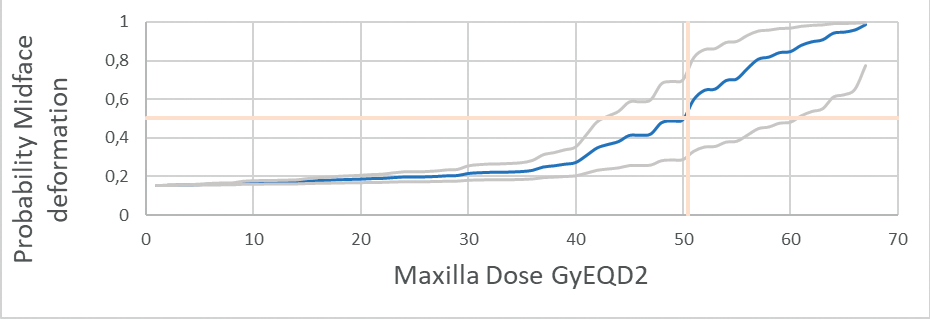

Figure 1A. Dose-effect model maxilla and midfacial deformation

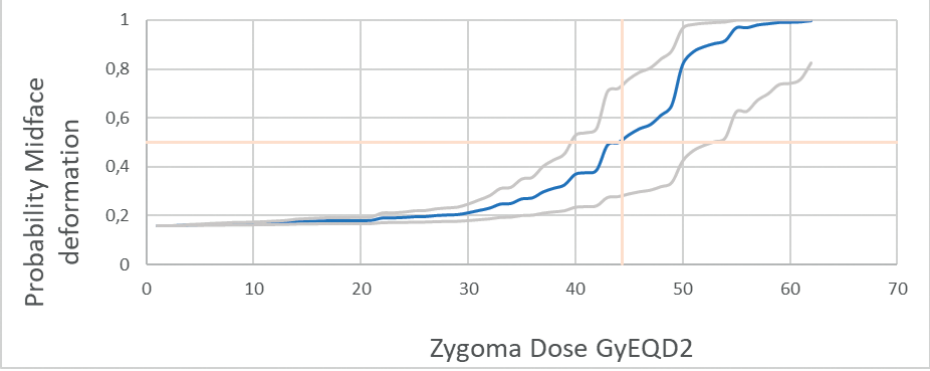

Figure 1B. Dose-effect model zygoma and midfacial deformation

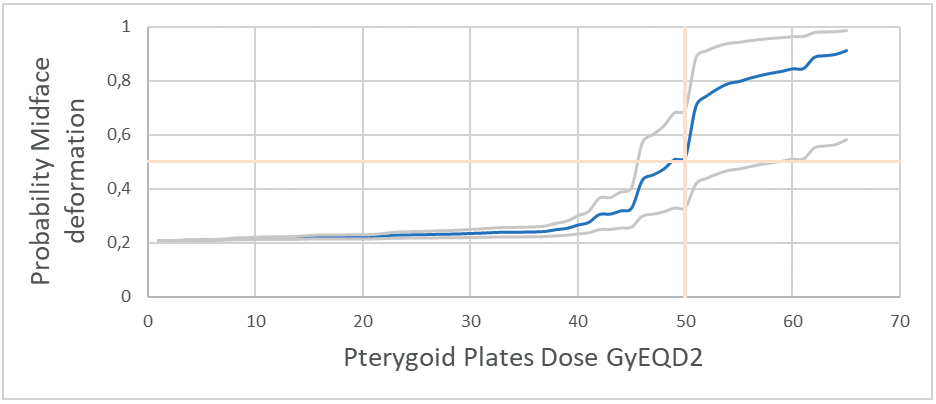

Figure 1C. Dose-effect model pterygoid plates and midfacial deformation

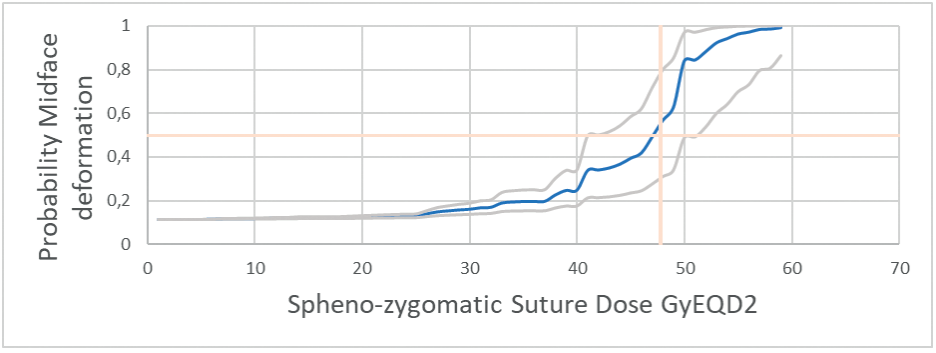

Figure 1D. Dose-effect model spheno-zygomatic suture and midfacial deformation

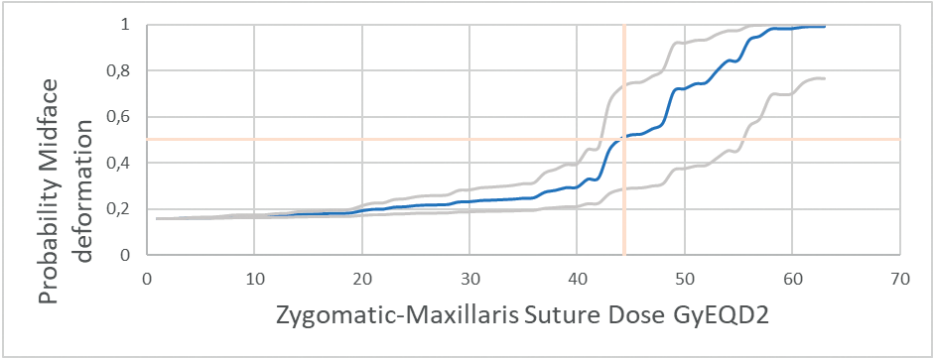

Figure 1E. Dose-effect model zygomatic-maxillaris suture and midfacial deformation

Figure 2. dose-effect models for nasal deformation
The grey lines represent the 95% confidence intervals and blue represent the actual dose-effect curve. The 50% probability is depicted using the peach line.

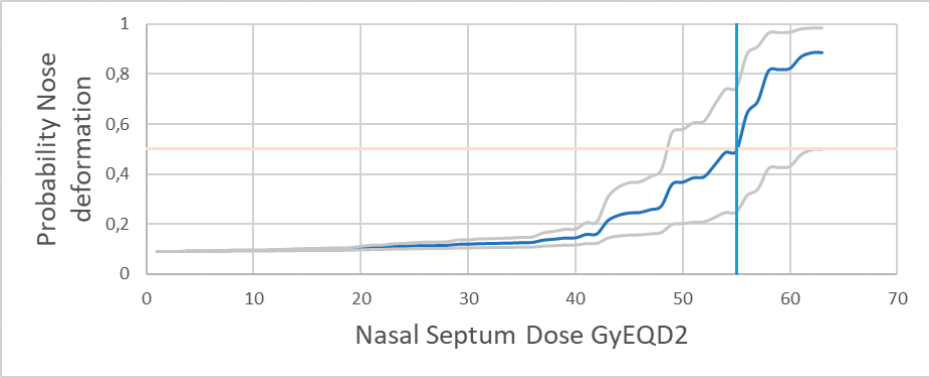

Figure 2A. Dose-effect model nasal septum and nasal deformation

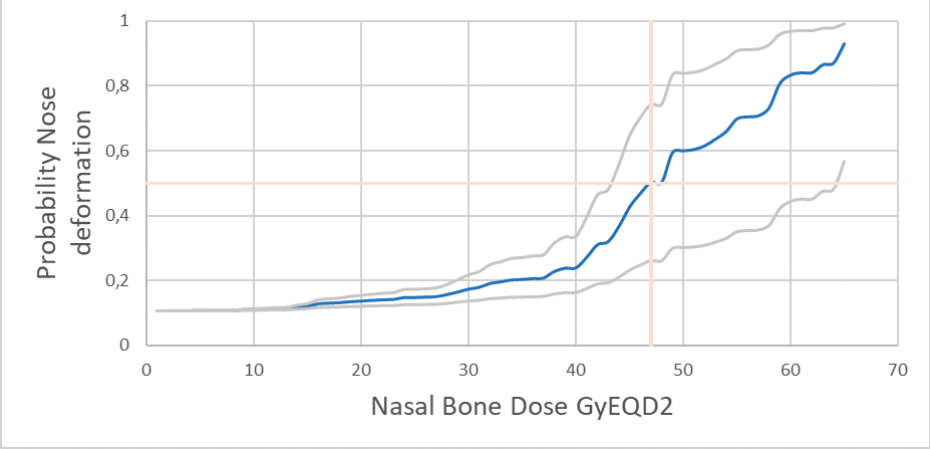

Figure 2B. Dose-effect model nasal bone and nasal deformation

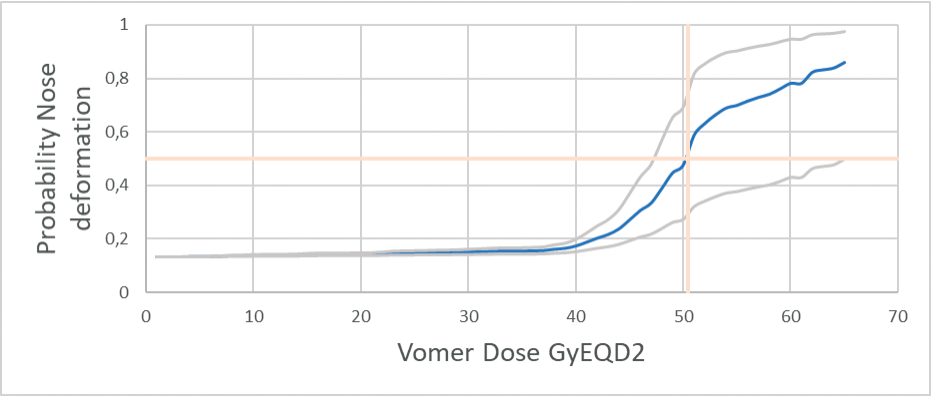

Figure 2C. Dose-effect model vomer and nasal deformation

Supplemental Figure 3. dose-effect models for mandibular deformation the mandibular and condyle.
The grey lines represent the 95% confidence intervals and blue represent the actual dose-effect curve. The 50% probability is depicted using the peach line.

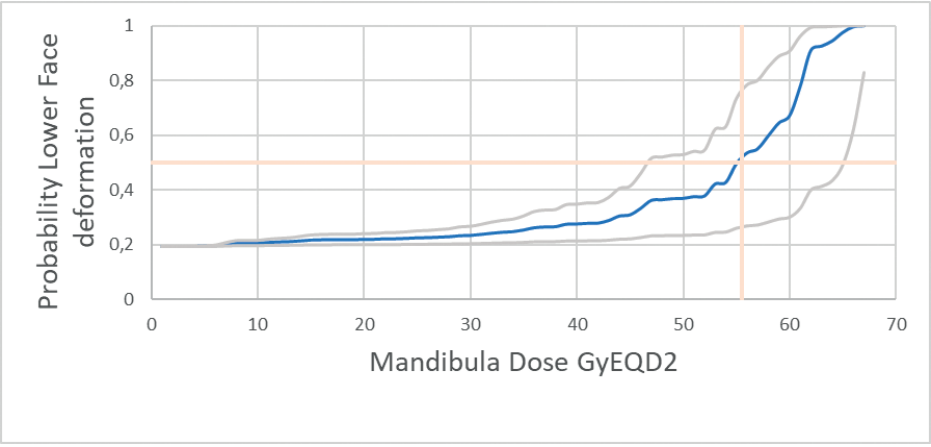

Figure 3A. Dose-effect model mandible and mandibular deformation

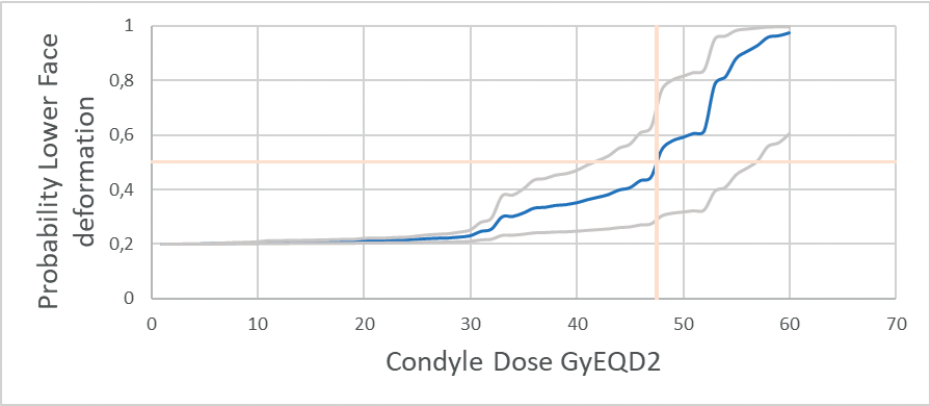

Figure 3B. Dose-effect model condyle and mandibular deformation

Supplementary Table 1.1. Midface Deformation mean Radiation dose in GyEQD2 for survivors with and without midfacial deformation specified for specific bones and sutures in the area

	No Midface Deformation		**Midface deformation**		
	Mean dose (GyEQD2)	Range	Mean Dose (GyEQD2)	Range	Difference t-test
Maxilla	7.3	0.0 - 36.6	16.5	0.0 - 39.3	<0.001
Zygoma	3.4	0.0 - 30.5	21.7	0.0 - 56.5	<0.001
Pterygoid Plates	7.4	0.0 - 54.4	25.2	0.0 - 54.7	<0.001
Spheno-zygomatic Suture	7.2	0.0 - 32.3	21.6	0.0 - 45.9	<0.001
Zygomatic-Maxillary Suture	4.3	0.0 - 56.5	23.0	0.0 - 56.1	<0.001

Supplementary Table 1.2. Nasal Deformation mean radiation dose in GyEQD2 for survivors with and without nasal deformation specified for specific bones in the nasal area

	No Nasal Deformation		**Nasal Deformation**		
	Mean dose (GyEQD2)	Range	Mean Dose (GyEQD2)	Range	Diff sign
Nasal Septum	10.3	0.0 - 46.9	33.0	0.8 - 55.9	<0.001
Nasal Bone	8.9	0.0 -51.0	28.9	0.5 - 59.6	<0.001
Vomer	9.3	0.0 - 58.3	32.7	0.0 - 58.9	<0.001
Frontal Bone	3.1	0.0 - 20.6	16.9	0.0 - 45.9	<0.001
Ethmoid	7.6	0.0 - 38.8	24.7	0.0 - 46.8	<0.001

Supplementary Table 1.3. Lower midfacial deformation mean radiation dose in GyEQD2 for survivors with and without lower midfacial deformation specified for specific bones in the lower midface area

	No Lower Facial Deformation		**Lower Facial Deformation**		
	Mean dose (GyEQD2)	Range	Mean Dose (GyEQD2)	Range	Diff sign
Mandible	1.9	0.0 - 17.0	9.1	0.0 - 50.0	<0.001
Condyle	4.3	0.0 - 50.0	19.2	0.0 - 60.9	<0.001

* All tested.

Supplementary Table 2. Spearman Rho Correlation testing for different facial models and doses to facial bones and sutures.

Supplementary Data 2.1. Mandibular shape and specific bones in lower face

	Mandible Model
Condyle Mean EQD2	.466**
Mandible Mean EQD2	.513**
Maxilla Mean EQD2	.559**

** Correlation is significant at the 0.01 level (2-tailed).

Supplementary Data 2.2. Nose shape and overall facial shape and specific bones in nasal area

	Nose Model
Nasal Bone Mean EQD2	.564**
Nasal Septum Mean EQD2	.519**
Vomer Mean EQD2	.577**
Frontal Bone Mean EQD2	.690**
Ethmoid Bone Mean EQD2	.596**

** Correlation is significant at the 0.01 level (2-tailed).

Supplementary Data 2.3. Midface Deformation and specific bones in midfacial area

	Zygoma Model (Malar Model)
Zygoma Mean EQD2	.522**
Nasal Bone Mean EQD2	.457**
Nasal Septum Mean EQD2	.491**
Maxilla Mean EQD2	.523**
Spheno-zygomatic Suture Mean EQD2	.530**
Zygomatic-maxillaris Suture Mean EQD2	.526**
Zygomatic-temporal Suture Mean EQD2	.518**
Pterygoid Plates Mean EQD2	.603**

** Correlation is significant at the 0.01 level (2-tailed).

6

45 GyRBE for group III orbital embryonal rhabdomyosarcoma

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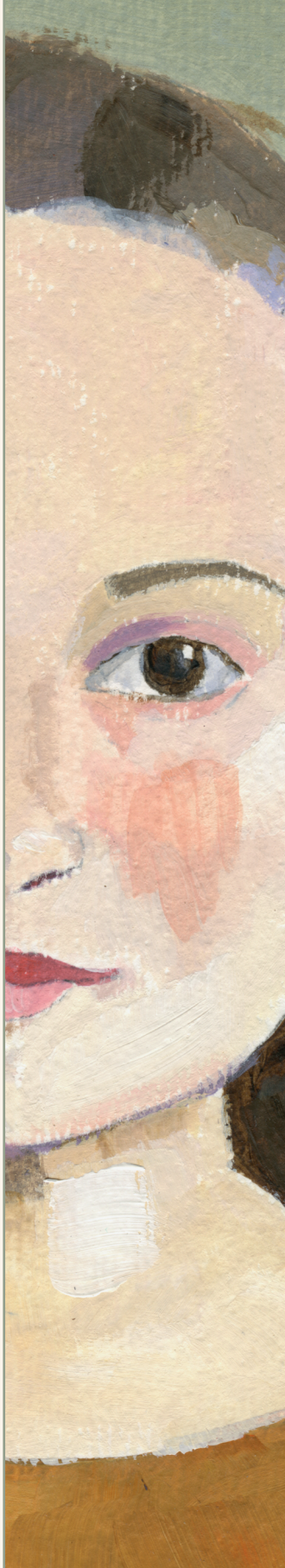

ABSTRACT

Purpose

Despite widespread concerns of radiotherapy toxicity in children with head and neck tumors, recent Children's Oncology Group (COG) findings suggest that the use of 45 Gy results in an unacceptably high rate of local recurrences in patients with low-risk orbital rhabdomyosarcoma. We therefore evaluated outcomes in our pediatric patients who received 45 GyRBE using proton therapy.

Methods & Materials

To assess disease control and toxicity, we reviewed the medical records of 30 children (≤21 years old) with COG stage 1, group III embryonal orbital rhabdomyosarcoma enrolled on a prospective outcome study and treated with proton therapy between 2007 and 2018.

Results

Median age at the time of radiation was 4.8 years old. Twenty-one and 9 patients received ifosfamide- and cyclophosphamide-based chemotherapy according to their respective cooperative group regimens. Median duration between the start of induction chemotherapy and radiation was 12 weeks. Two patients had a complete response to induction chemotherapy and 2 had stable disease. Twenty-six patients had a partial response to induction chemotherapy, with a median volume reduction of 66%. With a median follow-up of 4.0 years (range, 0.5-9.5 years), we observed 1 local failure 6 months following treatment in a patient who had a partial response to cyclophosphamide-based induction chemotherapy. The 5-year local control, progression-free survival, and overall survival rates were 97%, 97%, and 100%, respectively. Serious late toxicities included 18 patients with cataracts, 4 with exposure keratoconjunctivitis resulting in permanently reduced visual acuity, and 1 with chronic sinusitis.

Conclusion

45 GyRBE offers effective local control for most patients with group III orbital rhabdomyosarcoma. The delivery of proton therapy to the post-induction tumor volume plus a small margin can mitigate early- and intermediate-term toxicity, but side effects still occur and long-term data are needed to demonstrate the dosimetric advantage of proton therapy.

INTRODUCTION

Over the past two decades, the high cure rate for embryonal rhabdomyosarcoma of the orbit has prompted international efforts to de-intensify treatment. This effort has taken two broad forms in cooperative group studies via (a) reducing exposure to alkylating chemotherapy and (b) reducing exposure to ionizing radiation through lower prescription doses and smaller radiotherapy target volumes. A recent report from the Children's Oncology Group (COG) (1), however, asserts that children with group III embryonal orbital rhabdomyosarcoma who receive lower cumulative doses of cyclophosphamide (4.8 g/m2) and a lower radiation dose (45 Gy) to the tumor plus a 1-cm margin are at an increased risk of local failure compared to the historic Intergroup Rhabdomyosarcoma Study (IRS)-IV patients who received 26.4 g/m2 cyclophosphamide and 50.4 to 59.4 Gy to the tumor plus a 2-cm margin. Specifically, the 5-year local failure rate increased from 2% to 13%. Patients with tumors demonstrating a partial response to induction chemotherapy were shown to be at particular risk of failure—approaching 16%—following the de-intensified therapy regimen. These findings prompted many COG institutions to revert to a dose of 50.4 Gy for group III orbital rhabdomyosarcoma.

Beyond lowering prescription radiation doses and reducing target volumes, advanced technology can be used to further reduce patients' exposure to ionizing radiation. For example, proton therapy for orbital rhabdomyosarcoma reduces the integral radiation dose by 3.5 times compared to conventional radiation and is associated with significantly less radiation to developing facial bones, optic nerve, lens, lacrimal gland, temporal lobe, hypothalamus, and pituitary gland (4). Such dose reduction results in improved survivor quality of life (1), which is critical in a young population with a long-term survival rate exceeding 90%. Based on this rationale, proton therapy has been the standard of care at the University of Florida for over a decade. While all patients have been treated with 45 GyRBE and ≤1-cm target margin, some have received low-dose cyclophosphamide (per COG ARST0331) and others have received standard-dose ifosfamide (per EpSSG RMS2005). In light of the recent report from the COG, we examined our outcomes to determine patterns of failure and whether our institutional treatment guidelines should be revised to ensure an optimal balance between efficacy and toxicity.

MATERIALS AND METHODS

Between September 2006 and October 2018, 1,657 pediatric patients (age ≤ 21 years) were treated with proton therapy at University of Florida Proton Therapy Institute. Under an institutional review board-approved prospective study (IRB# 2006-153), 30 of these patients were identified with a group III embryonal rhabdomyosarcoma

of the orbit with a minimum 6 months of potential follow-up since proton therapy. No patients were lost to follow-up. Patients who had received prior radiation were excluded.

Patients were treated according to our institution's pediatric treatment guidelines for rhabdomyosarcoma. The gross tumor volume (GTV) was defined by the gross disease at the time of radiation, following induction chemotherapy (Figure 1). The clinical target volume (CTV) was defined by the GTV + 5 mm, with further modification as necessary to encompass all surfaces originally in contact with the tumor and all soft tissue originally infiltrated by disease. The standard prescription dose was 45 GyRBE, delivered via two sequential phases. The initial planning target volume (PTV1), defined as the CTV + 3 mm, received 36 GyRBE followed by a 9-GyRBE boost to the PTV2, defined as the GTV + 3 mm. The primary goal when developing the radiation plan was to ensure that the entire CTV was encompassed by >99% of the nominal dose and that the entire PTV was covered by 95% of the nominal dose. All patients in this series were treated with double-scattered proton plans using 2 to 3 beams per phase. Each field was treated daily. The distal and proximal beam margins in millimeters were calculated through the empirically derived institutional formula of (2.5% x field range) + 1.5 mm. The aperture margin was 4 to 7 mm from the lateral PTV edge. The typical beam smearing margin was 5 mm. As part of the prospective component of the study, acute and late treatment toxicity information was collected during weekly on-treatment and follow-up visits. To assess disease outcomes, we calculated crude rates of local control, disease-free survival, and overall survival.

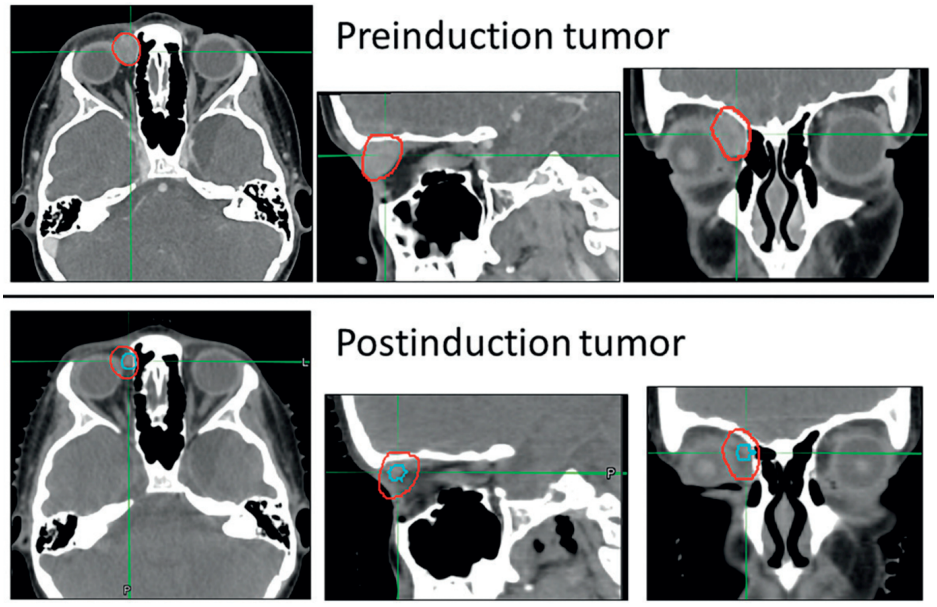

Figure 1. Imaging of the patient with group III embryonal rhabdomyosarcoma of the orbit who recurred.

The figure exhibits (A) the tumor at diagnosis; (B) the tumor following partial response to ARST0331 induction chemotherapy; (C) target volumes, with the gross tumor volume shown in red and the clinical target volume in yellow; (D) the local recurrence at 6 months following radiation within the 45 GyRBE isodose line. Dosimetry: green colorwash, 36 GyRBE; blue colorwash, 45 GyRBE.

RESULTS

Patient, Tumor, and Treatment Characteristics

All 30 patients had COG stage 1, group III embryonal rhabdomyosarcoma of the orbit. The median age at the time of radiation was 4.8 years old (range, 1-11.4 years). Nineteen patients were male; 29 were white and 1 was Asian. One patient had a known germline p53 mutation. The median maximum tumor size at diagnosis was 3.4 cm (range, 2.2-6.1 cm) and the median tumor volume at diagnosis was 8.5 ml (range, 2.4-45.9 ml). Overall, 21 and 9 patients received ifosfamide- and low-dose cyclophosphamide-based chemotherapy according to their respective contemporary European Paediatric Soft Tissue Sarcoma Study Group (EpSSG) and COG regimens. The median duration between the start of induction chemotherapy and radiation was 12 weeks (range, 6-20 weeks). The median maximum tumor size at the time of radiation was 2.3 cm (range, 0.1-4.0 cm) and the median tumor volume at the time of radiation was 2.6 ml (range, 0.4-13.4 ml). Two patients had a complete response to induction chemotherapy (>95% volume reduction) and 2 patients had

stable disease (<5% volume reduction). Twenty-six patients had a partial response to induction chemotherapy, with a median volume reduction of 66% (range, 38-91%).

All 30 patients received 45 GyRBE to the PTV2 according to our guidelines outlined above. In 2 patients, the PTV1 was treated to 30.6 GyRBE (rather than the standard 36 GyRBE). In 2 other patients, the full dose of 45 GyRBE was delivered to the PTV1 (i.e., there was no boost volume). All patients received 1.8 GyRBE per day, 5 days per week. Due to cyclotron maintenance, 4 patients were treated with a component of 6-MV photon radiation (median 2 days; range, 2-3 days). The median treatment duration was 36 calendar days (range, 33-40 days). For the whole cohort, the median mean dose to the ipsilateral lens was 43.5 GyRBE (range, 19.3-52.2 GyRBE). The median mean dose to the ipsilateral lacrimal gland was 43.3 GyRBE (range, 5.5-50.4 GyRBE). On average, 2.9% of patients' supratentorial brain received between 1-20 GyRBE. A full detail of dose exposure to normal tissue is outlined in Table 1.

Table 1. Doses to normal tissues in a cohort of 30 patients treated with proton therapy for orbital rhabdomyosarcoma

Structure	Median (GyRBE)	Range (GyRBE)
Ipsilateral retina (max. dose)	46.5	45.5-54.1
Contralateral retina (max. dose)	1.3	0-22.2
Ipsilateral lens (mean dose)	43.5	19.3-52.2
Contralateral lens (mean dose)	0.1	0-3.1
Ipsilateral optic nerve (max. dose)	45.5	0-52.4
Contralateral optic nerve (max. dose)	0.2	0-11.8
Ipsilateral lacrimal gland (mean dose)	43.3	5.5-50.4
Contralateral lacrimal gland (mean dose)	0	0-0.1
Hypothalamus (mean dose)	0	0-16.8
Pituitary (mean dose)	0.7	0-27.4
Percent of brain receiving 1-20 Gy	2.90%	0.3-34.4%
Percent of brain receiving >20 Gy	1.60%	0-10.8%

Disease control

With a median follow-up of 4.0 years (range, 0.5-9.5 years), we have observed 1 local failure, which occurred 6 months following treatment in a patient with a 3.4-cm tumor of the inferior orbital rectus who had a partial response to COG ARST0331 chemotherapy (see Figure 2). The recurrence was addressed with an orbital exenteration followed by COG ARST0921 chemotherapy. The patient is currently 22 months free of disease. We have observed no distant failures. The local control, disease-free survival, and overall survival rates in this group are 97%, 97%, and 100%. Two patients experienced post-treatment changes consistent with

pseudoprogression: one patient had a documented finding on magnetic resonance imaging (MRI) 2 months following radiation that showed a slight increase in tumor volume and contrast enhancement, which resolved without intervention on a repeat follow-up scan 4 months later. The patient is currently 1.8 years from treatment with continued regression. Another patient had a similar documented finding on MRI 6 months following treatment, likewise demonstrating a slight increase in tumor volume with contrast enhancement. A biopsy was performed, but the pathology specimen was inconsistent with viable tumor. The decision was made to continue with close surveillance and the tumor has remained stable for 22 months.

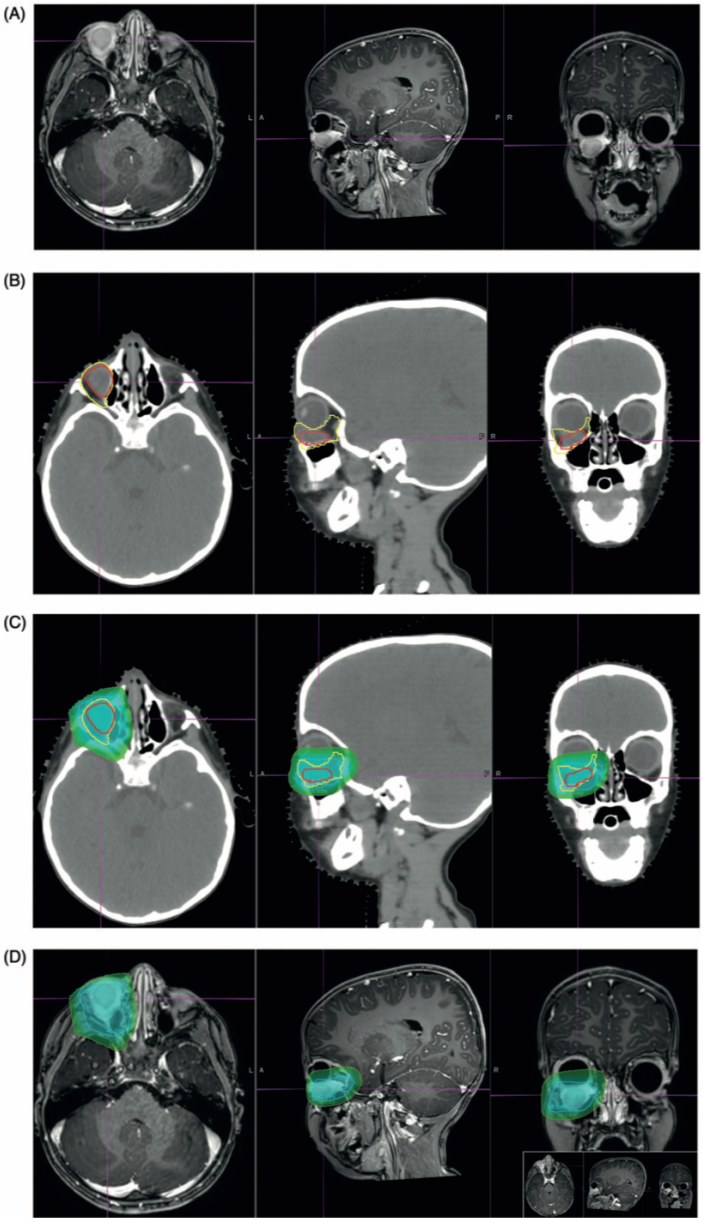

Figure 2. Imaging of the patient with group III embryonal rhabdomyosarcoma of the orbit who recurred.

Exhibiting (A) the tumor at diagnosis; (B) the tumor fol- lowing partial response to ARST0331 induction chemotherapy; (C) target volumes, with the gross tumor volume shown in red and the clinical target volume in yel- low; (D) the local recurrence at 6 months following radiation within the 45 GyRBE isodose line. Dosimetry: green colorwash, 36 GyRBE; blue colorwash, 45 GyRBE.

Toxicity

Non-hematologic acute toxicity consited of mild periorbital edema, erythema, epiphora, photosensitivity, and conjunctival erythema. Serious late toxicity included 18 patients with cataracts at a median of 29.6 months following treatment (range, 23.8-51.6 months), 15 of whom required surgery or laser treatment. Despite surgery, 2 of 15 cataract patients still have significantly reduced visual acuity. In addition, 4 patients developed severe exposure keratoconjunctivitis. As a result, each has had corneal scarring or posterior capsule opacification causing permanent reduction in visual acuity and 4 have had severe dry eye requiring a protective shell implant to maintain conjunctival vitality. Another patient in the series with a rhabdomyosarcoma of the superior rectus developed chronic sinusitis with rhinorrhea, possibly radiation-induced, and underwent tonsillectomy with adenoidectomy and a turbinate reduction with septoplasty. Other late toxicities observed in this cohort include 14 patients with chronic dry eye requiring artificial tears, 4 patients with recurrent epistaxis, and 3 patients with keratitis or conjunctivitis, now resolved (specifically exposure keratitis, papillary conjunctivitis, and conjunctival infection not otherwise specified). In 1 patient, dental imaging revealed shortened tooth roots. Two patients have elected surgery for cosmetic sequelae related to the tumor and treatment: One patient underwent a fat pad implant for facial asymmetry and one patient had surgery to correct eyelid ptosis and entropion. Interestingly, we have observed 1 case of combined growth hormone and gonadotrophin deficiency and 1 case of isolated growth hormone deficiency. The radiation dose to the hypothalamus and pituitary gland was <0.1 GyRBE in both patients.

DISCUSSION

Our prospective outcome data suggest that 45 GyRBE proton therapy to a small, post-induction target volume results in a 5-year local control rate of 97%. If validated in a larger patient cohort, this technique could represent a significant step in reducing radiation exposure in a young population at known risk of treatment toxicity. Our findings also suggest that the recent decline in local control observed in orbital rhabdomyosarcoma patients on COG ARST0331 may be more directly attributable to recent low-dose chemotherapy regimens than radiotherapy modifications.

The rationale for radiation de-intensification in orbital rhabdomyosarcoma is well-justified. Historic pooled data from the United States and Europe suggest that 51-82% of treated children develop cataracts, 29-59% develop orbital hypoplasia, and 54-70% experience reduced vision. As many as 11-14% may require enucleation for symptom relief (6). Other common sequelae include ptosis, dry eye, keratitis, corneal ulceration, and dental abnormalities (7). Efforts to reduce toxicity through

the use of intensity-modulated radiotherapy have been largely unsuccessful (8-10), likely owing to similar dosimetric profiles (8). Another explanation for persistent toxicity could be the practice of defining the target volume based on tumor extent at the time of diagno- sis. In patients with a good response to induction chemotherapy, this might result in targets unnecessarily encompassing parts of the lacrimal gland, tooth buds, and orbital bone. Our institutional guidelines instead use a post- induction chemotherapy volume, based on patterns of failure analysis from our institution [11] and elsewhere [12,13].

Theorizing that attenuated chemotherapy might lead to fewer hematologic, hepatotoxic, and fertility risks, while less radiation could reduce the damage to ocular and peri-ocular tissue, investigators of COG ARST0331 reduced the therapy for embryonal rhabdomyosarcoma by using a lower dose of cyclophosphamide and 45 Gy, as opposed to the 50.4-59.4 Gy used in IRS-IV. The radiotherapy target margin was also reduced from 2 cm to 1 cm. While it is too early to assess the impact of these treatment modifications on toxicity rates, the ARST0331 results were disappointing from a disease-control perspective: The 5-year local failure rate increased from 2% on IRS-IV to 13% on ARST0331 (1). COG physicians have thereby questioned the impetus for this increase in local failures and deemed the use of 45 Gy “insufficient”, particularly following an incomplete radio- graphic response to induction chemotherapy (14).

Under the close oversight of our prospective outcome protocol, our approach has been to continue the use of 45 Gy and, by applying proton therapy and even smaller target margins, aggressively push forward with radiation toxicity reduction. In contrast to the ARST0331 data, our results suggest that such an approach does not compromise the therapeutic ratio. An important distinction, however, is that our cohort can be further divided by chemotherapy: approximately one-third received COG-based chemotherapy and two-thirds received EpSSG-based chemotherapy. The single local recurrence we observed was in a patient who received low-dose cyclophosphamide, for a crude recurrence rate of 11% (1/9), similar to the 13% observed on ARST0331. Although anecdotal, this finding supports other recent data indicating that lower cumulative cyclophosphamide dose and dose-intensity results in excessive treatment failures among patients with low-risk rhabdomyosarcoma (11-13).

Our findings raise important questions: First, if we establish that a lower cumulative dose of cyclophosphamide is impermissible in the United States, is the next option a return to the higher-dose cyclophosphamide regimens of the past, a switch to the ifosfamide regimens used in Europe, or a replacement to alkylators altogether?. Leukopenia and male infertility is the dose-limiting toxicity of cyclophosphamide, whereas ifosfamide may cause neurotoxicity and long-term tubulopathy resulting

in Fanconi syndrome (14). COG ARST1431, a phase 3 study for intermediate-risk rhabdomyosarcoma, is currently on hold as the COG Soft Tissue Sarcoma committee deliberates the best course for North American trial patients. Second, despite the use of proton therapy, a dose of 45 Gy, and small target margins, we continue to observe ocular and peri-ocular toxicity in our patients and these occurrences will only increase with time. The next incremental advancements in low-risk orbital rhabdomyosarcoma may need to take the form of risk-adapted therapy, wherein good responders receive even lower doses of radiation and complete responders forgo radiotherapy entirely. Off study, this has been the practice in many European countries for decades, and radiation avoidance was an option for some complete responders on EpSSG RMS2005. Risk adaptation may be further refined by advanced imaging and molecular subtyping. Finally, radiotherapy continues to evolve. Given a mean lens dose threshold of 7 Gy is necessary to keep cataract risk under 25% (19), it is unsurprising that 18 of 30 patients in our series developed cataracts given a mean lens dose of 43.5 GyRBE across the series. To mitigate this toxicity, we developed a system to fix the gaze of older patients in a reproducible manner that can reduce lens exposure. All the patients in this series were treated with double-scattered proton therapy. We can now use next-generation pencil-beam scanning to further shape the radiation dose to the lacrimal gland, and dose-painting to treat the PTV1 at <1.8 GyRBE/fx. Advances in brachytherapy also allow for treatment that does not sacrifice the globe. This approach provides particularly conformal dosimetry in cases where the brachytherapy can completely replace the use of external-beam radiation [20,21].

Despite provocative findings, this study has important limitations that should be considered. For example, although patients were treated according to standardized chemother- apy roadmaps, alkylator dose modifications were sometimes necessary to mitigate systemic toxicity according to normal clinical routine. If these dose modifications were imple- mented following the completion of radiation in a child who was referred from an outside center, the actual delivered chemotherapy dose may have deviated from the standard regimen. Furthermore, in the COG ARST 0331 study only 7% of patients received proton therapy. If any radiobiologic dif- ferences in proton therapy affect embryonal rhabdomyosar- coma beyond the common 1.1 cobalt-Gy modification, a straight comparison of 45 GyRBE might be inaccurate. Finally, late effects may manifest beyond the 4-year median follow-up described in our cohort. It is therefore important that we continue to follow this group of survivors to accurately characterize any differences in proton therapy-induced late toxicity relative to that reported in photon series.

CONCLUSION AND FUTURE DIRECTION

Our data suggest that 45 GyRBE delivered to the postin- duction tumor volume with a small margin remains an effective radiotherapy approach for most patients with group III orbital embryonal rhabdomyosarcoma. While this approach seems to mitigate early- and intermediate-term toxicity, side effects still occur and long-term data are needed to conclu- sively demonstrate the dosimetric advantages of proton therapy. To this end, our orbital rhabdomyosacoma patients have been offered co-enrollment on an international study examining cosmetic and facial morphologic effects in long- term survivors; this protocol also enrolls comparative cohorts of brachytherapy and photon patients. When mature, the findings will provide invaluable information from various per- spectives. Finally, from a broader oncologic standpoint, we must urgently characterize the impact of reduced-dose cyclophosphamide on local control in this setting and among others with rhabdomyosarcoma.

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PART VI

7

The AMORE protocol as primary local treatment for nonorbital head-neck rhabdomyosarcoma in children: an update of the past 25 years

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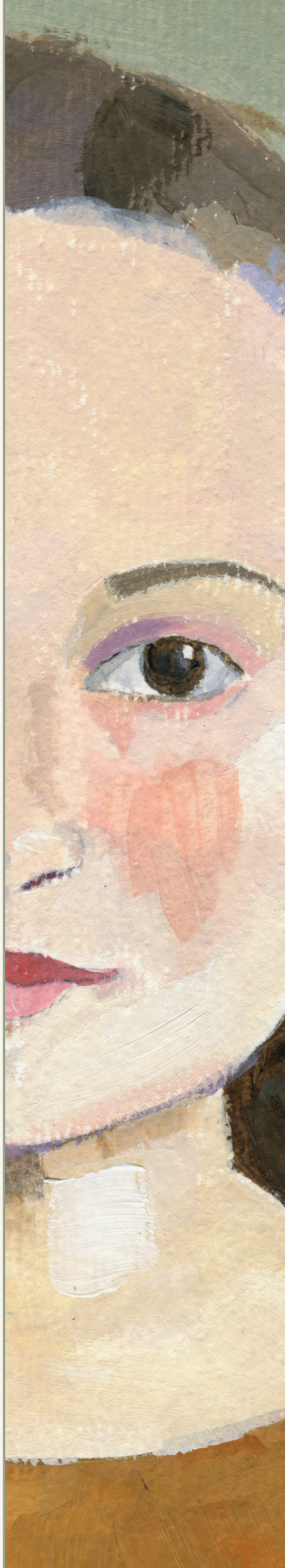

ABSTRACT

Objectives/Background

The AMORE protocol consists of ablative surgery, moulage brachytherapy, and reconstructive surgery and is used for the local treatment of head and neck rhabdomyosarcoma (HNRMS) in children. The benefit of AMORE over external beam radiotherapy lies in reducing adverse late effects. This paper aims to describe AMORE's surgical procedures and update on the survival of patients with primary nonorbital, non-metastatic HNRMS.

Materials and Methods

All children treated with AMORE for HNRMS between January 1, 1993, and December 31, 2017, were included in this study. We evaluated charts and surgical notes for all patients to assess and evaluate outcomes and surgical methods.

Results

Thirty-five patients received AMORE for primary nonorbital HNRMS. The median age at diagnosis was 4.8 years, and the median follow-up was 10.0 years. Twenty patients were included in the 1993-2002 cohort and 15 in the 2002-2017 cohort. Ten patients underwent a parotidectomy, nine had a paranasal sinus procedure, seven underwent a (partial) jaw bone resection, six had a muscle resection, two underwent a petrosectomy, and one patient with a nasopharyngeal tumor only underwent endoscopic debulking. In 19 patients, a selective (n=16) or modified radical (n=3) neck dissection was part of the surgery. The facial nerve was involved in four patients, of whom two had pre-existing facial nerve palsy. A reconstruction followed moulage removal in 74% of patients. Reconstruction was not performed in the remaining nine patients since there was no esthetical or functional need. The 10-year overall survival for the entire group was 73.7%.

Conclusion

When the AMORE protocol is feasible, it is a valuable technique with survival and event-free survival similar to other local treatment options. Our previous papers have proven the reduction of late adverse effects by using the AMORE protocol compared to conventional external beam radiotherapy; therefore, we feel the AMORE protocol should be considered more often in primary nonorbital HNRMS patients.

INTRODUCTION

Rhabdomyosarcoma (RMS) is the most common soft tissue tumor in children, with about 40% arising in the head and neck (HN) (1). RMS, in general, is very responsive to chemotherapy; consequently, most therapy schemes are multimodality-based and incorporate chemotherapy. Both local and systemic treatment are essential to yield high survival rates. Locoregional failure is the most common issue in relapsed patients (2). Radiotherapy, potentially combined with surgery, or in rare cases, surgery alone, is used as a therapeutic strategy. In patients with HNRMS, surgical options are often limited in view of obtaining acceptable surgical margins at the cost of causing morbidity in important structures and surrounding organs. An innovative local treatment technique was developed in the seitenin at the Emma Children's Hospital-Academic Medical Centre (EKZ-AMC) to overcome these limitations, consisting of Ablative surgery, MOulage technique brachytherapy, and surgical REconstruction (AMORE protocol). The tumor is macroscopically resected with close margins (R1-type resection). In the same procedure, catheters are placed in a moulage in the tumor bed. Thereafter, the wound is closed, and the catheters exit through the incision (Figure 1). After surgery and moulage placement, the patient undergoes a CT scan for brachytherapy planning. Brachytherapy is delivered to the surgical bed at a high local dose during the next 3 to 4 days to treat potential microscopic residual disease, thereby limiting radiation to adjacent healthy organs. In a second surgical procedure, the catheters are removed, and the wound is reconstructed, preferably with a pedicled flap or a free flap, to bring in well-oxygenated tissue to promote wound healing, protect vital structures, and restore a proper contour. Our previous papers (3-6) have extensively described the AMORE protocol. The possibility of performing a macroscopic surgical resection, the feasibility of moulage placement, and the reconstruction options, bearing in mind the cosmetic results, are hypothesized at the moment of local treatment selection. A multidisciplinary team considers the expected late adverse effects of all possible treatments and ultimately chooses a local treatment strategy, either AMORE or external beam radiotherapy (EBRT, using photons (XRT) or protons (PBT)). In previous publications by our group, we showed that AMORE is equally effective as conventional EBRT treatment in terms of survival rates and results in fewer adverse effects (7). Furthermore, the AMORE protocols can be successfully used as a local treatment approach for relapsed HNRMS (8). In 2003, we reported on the novel AMORE protocol with reference to its surgical aspects (3). Now, 20 years later, the current paper aims to provide an update on the surgical procedures used and patient survival.

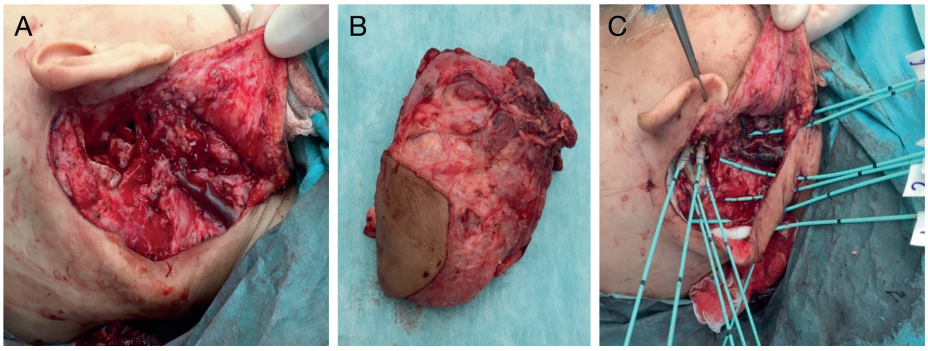

Figure 1. The AMORE procedure in a patient with rhabdomyosarcoma of the petrosus bone.

A shows the tumor bed after removal of the tumor. B is the resected tumor, and C demonstrates the tumor bed with the brachytherapy wires placed in the brachytherapy moulage.

METHODS

Patients

All patients treated with AMORE at the EKZ-AMC for a primary nonorbital RMS between January 1, 1993, and December 31, 2017, were included in this study. In 2018, all pediatric oncology care was centralized in the Netherlands and now occurs at the Princess Maxima Center for Pediatric Oncology (PMC). As this is an update on the AMORE protocol techniques, we have not only included recent patients but also included the former cohort as published in 2003, in which inclusion ran from January 1, 1993, until May 2002 (3). All patients with primary, nonorbital HNRMS treated according to the AMORE protocol at the EKZ-AMC were included. As the AMORE protocol is only practiced in the Netherlands, this cohort included two types of patients: patients diagnosed with HNRMS at the EKZ-AMC and patients referred from other institutions specifically for the AMORE protocol from across Europe.

Diagnostic workup and systemic treatment

All patients were treated according to the consecutive European RMS treatments: SIOP MMT (International Society of Pediatric Oncology: Malignant Mesenchymal Tumours; SIOP-MMT-89 and SIOP-MMT-95), CWS (German Cooperative Soft Tissue Sarcoma; CWS-96), or the EpSSG (European Paediatric Soft Tissue Sarcoma Study Group; EpSSG-RMS-2005). These trials have been thoroughly described elsewhere (9-11). In short, most patients had an incisional biopsy to confirm the diagnosis, after which they received multi-agent neoadjuvant chemotherapy according to their risk stratification. Disease staging was according to the TNM criteria and IRS risk grouping in all patients.

AMORE protocol

A multidisciplinary team (MDT) meeting discusses the feasibility of AMORE for each individual patient by reviewing pre-treatment imaging and post-third-cycle chemotherapy imaging, as well as clinical features such as nerve deficits, co-morbidity, and general well-being. The specialties present at these MDT meetings are pediatric oncology, radiology, radiation oncology, head and neck surgery, plastic surgery, orbital surgery, and, if necessary, neurosurgery. Firstly, the feasibility of each key part of the AMORE protocol (i.e., ablative surgery, brachytherapy, and reconstruction) is discussed during the meeting. Ablative surgery is considered feasible if a macroscopic complete resection can be performed. Carotid encasement, gross perineural spread, or intracranial extension are now considered contraindications for surgery in primary HNRMS patients; however, this was not the case for patients in the first cohort. Secondly, the feasibility of moulage placement and brachytherapy catheter placement is considered. Thirdly, the options for reconstructive surgery are taken into consideration. Lastly, the expected adverse events, including expected cosmesis following the performed surgical treatments, are weighed against expected adverse events following radiotherapy. Ultimately, the MDT selects the local strategy with the fewest expected adverse events.

If a patient is eligible for the AMORE protocol, both surgical procedures and brachytherapy are scheduled, ideally after the fourth cycle of chemotherapy. After resection of the tumor and moulage placement, a CT scan is performed to verify the correct placement of the moulage and catheters, and the scan is used to make a radiotherapy treatment plan. While in radioprotective isolation, the catheters are loaded with iridium-192 sources, and doses of 40-55 Gy are delivered (depending on the patient's risk group). Low dose rate (LDR) brachytherapy was used up until 2001, after which pulsed dose rate (PDR) brachytherapy became standard care. After completion of brachytherapy, the second surgical procedure consists of removing the moulage and catheters, debriding the wound bed, and, if needed, performing a reconstruction. Reconstructive surgery is done using either a pedicled flap or a free vascularized flap. The entire AMORE protocol is carried out within one week: ablative surgery on day 1, brachytherapy on days 3-5, and removal of the moulage and surgical reconstruction on day 7.

Follow-up and statistical analysis

Patient and treatment characteristics are prospectively collected in our hospital database. Missing information on surgical procedures was retrospectively collected from charts, including surgical operation notes. Surgical techniques and radiological findings were extracted and documented from the files. Because of the relatively small number of patients and heterogeneity of HNRMS, surgical procedures and reconstructive techniques are presented descriptively. Complications are recorded according to the Clavien-Dindo classification; only Grade 2 or higher complications

are reported since all children are prescribed anti-emetics and analgesics as standard post-operative care. Overall survival was defined as the time between the second AMORE protocol surgery and the date of the last follow-up, relapse, or death from any cause. The cut-off point of this analysis was September 31, 2023. Overall survival and event-free survival, as well as local control (event-free survival only counting local relapse as an event), were calculated using the Kaplan-Meier method (SPSS version 29.0, IBM).

RESULTS

Thirty-five newly diagnosed patients (15 girls, 20 boys) underwent AMORE for primary nonorbital HNRMS between January 1, 1993, and December 31, 2017. The median age at diagnosis was 4.8 years (range: 1.0-13.6), and the median follow-up time was 12.0 years (range: 0.5-25.0). Eighty-three percent of patients (n=29) had a tumor with embryonal histology, 14% (n=5) had alveolar rhabdomyosarcoma, and one patient had a pleomorphic rhabdomyosarcoma. Sixty-three percent of patients (n=22) had a parameningeal tumor, while 37% (n=13) had a tumor in a non-parameningeal site.

Ablative Surgery

Ten patients underwent a parotidectomy, of whom six had a total parotidectomy and four a partial parotidectomy with preservation of the facial nerve. In all six patients who underwent a total parotidectomy, a superselective neck dissection was part of the procedure. The temporal muscle was also resected in two of the superficial parotidectomy procedures. The facial nerve was involved in four out of six patients undergoing total parotidectomy, with one patient having pre-existing facial nerve palsy. Resection resulted in additional, partial facial nerve palsy in two patients. Nine patients underwent a paranasal sinus procedure, either a Caldwell-Luc, Denker, or lateral rhinotomy. Resection of either the nasal bone or ethmoid and sphenoid sinuses was carried out in three out of nine patients, and in one patient, the lateral rhinotomy was combined with a selective neck dissection. Six patients had a mandibulectomy (two marginal, four partial segmental), and a partial maxillectomy was performed in one patient. In all seven patients, a selective (n=5) or modified radical (n=2) neck dissection was conducted together with the jaw bone resection. In six patients, the tumor was removed by performing a soft tissue resection, while in four patients, a neck dissection was part of the procedure. Two patients underwent a petrosectomy; this was combined with a selective neck dissection in one patient. One patient with a nasopharyngeal tumor only underwent moulage placement as the tumor was no longer detectable after an incomplete excisional biopsy. A R1 resection was achieved in the remaining 34 patients. Complete macroscopic resection was not possible in one patient due to

intracranial extension. In 19 patients, a selective (n=16) or modified radical (n=3) neck dissection was part of the surgery, and tumor-positive nodes were found in only one patient (four positive nodes, no extra-capsular extension). Further information on surgical procedures, including neck dissection levels, can be found in Table 1.

Reconstructive Surgery

A reconstruction was performed in 26 out of the 35 (74%) patients following moulage removal. Reconstruction was performed in 10 patients with a latissimus dorsi flap (nine free flaps, one pedicled flap). Four rectus abdominal free flaps, three pedicled sternocleidomastoid muscle flaps, three gracilis free flaps, two galea flaps, one temporoparietal pedicled muscle flap, one bone repositioning, one cartilage repositioning, and one fibula-flap were used for the remaining reconstructions. Further details on the reconstructions used in specific cases can be found in Table 1.

Complications

Four (11%) patients suffered from post-operative wound infections (Grade 2 short-term), requiring antibiotics. One patient required surgical intervention under general anesthesia as a free flap became ischemic, requiring its removal and the placement of a new free flap (Grade 3b). No short-term morbidity of the donor site of the graft was reported in any of the patients.

Overall Survival and Event-Free survival

The 10-year overall survival for the entire group was 74%. Twenty-seven patients were alive after a median follow-up of 12 years. The 10-year event-free survival for the entire cohort was 62%. In total, 12 events occurred after a median follow-up time of 2.5 years. Ten patients had a relapse, of whom nine had a local relapse, and one had distant metastases. Three of the nine local relapses occurred within the radiation field. Two of the nine patients with relapsed disease were successfully treated with salvage treatment consisting of chemotherapy and, in one patient, radiotherapy. Two patients developed a secondary tumor; in one patient, this was a mucoepidermoid carcinoma of the contralateral parotid gland (patient 6). The other patient died of a secondary malignancy, a medulloblastoma.

DISCUSSION

Treatment for HNRMS consists of both systemic therapy with multidrug chemotherapy as well as local treatment. Local treatment almost always consists of radiotherapy and can be combined with surgery. Only in rare cases, for example, when an R0 resection is performed in non-parameningeal rhabdomyosarcoma, can radiotherapy be omitted. Giving multimodality treatment to very young children leads to a variety of late adverse effects, which for the head and neck area typically

consist of musculoskeletal deformation, ocular impairment, hearing loss, and dental developmental issues (7,12,13). The AMORE protocol was developed in an attempt to limit late adverse effects. It utilizes the properties of high conformality in brachytherapy with surgery aiming at an R1 resection. In this paper, we assess surgical procedures and provide an update on survival.

The surgical procedures performed as part of the AMORE protocol for primary, non-metastatic, and nonorbital rhabdomyosarcoma patients were explored. One can observe the evolution of patient selection in terms of primary tumor resection. Some of the earliest treated patients had intracranial extension and bone erosions and received comparatively major surgery. Patient selection has since adapted. Exclusion criteria for performing ablative surgery have been formulated in the past 10 years, such as intracranial extension, carotid encasement, and perineural spread. For example, patients in whom the facial nerve was sacrificed during surgery all come from the first decade of AMORE treatment. Evaluating the patients selected for AMORE, one can observe a shift towards non-parameningeal cases over the past 10 years. In this entire cohort, 19 patients underwent neck dissection, and only one patient had positive nodes confirmed in pathology. This outcome potentially indicates that elective neck dissections should not be performed as part of the AMORE protocol. However, when the alternative is potential irradiation of the neck, an elective neck dissection as part of the initial surgery might be worthwhile in terms of sparing late adverse effects. The use of sentinel node procedures might make the aforementioned dilemma redundant. There are two main things to note when evaluating reconstructive surgery. First, there were very few complications, with only one free flap failure. This is particularly reassuring as many surgeons are hesitant to operate in previously operated and irradiated fields, but with the radiotherapy being administered so shortly before the reconstructive surgery, it potentially does not damage the tissue to the full extent as the AMORE cases in whom no reconstructive surgery was performed did well after surgery.

Secondly, with the AMORE protocol's evolution, one can observe a general reduction in reconstructions being performed. This largely has to do with the fact that at the beginning of the AMORE protocol, pedicled or free flap transplants were performed not only to restore aesthetics but also in the belief that transporting fresh tissue to the radiated area would stimulate wound healing and tissue response. With reconstructive surgery shifting from a mandatory part of the AMORE procedure to being based on functional or aesthetic needs, we are potentially saving patients from surgery and donor site morbidity. In conclusion, the AMORE protocol has changed over the past 25 years; the main change is that AMORE's feasibility is now dependent on more stringent contraindications. Nowadays, intracranial extension, skull base erosion, perineural spread, and carotid encasement are contraindications. It is important to note that these contraindications are relative in that when the

AMORE protocol is utilized in relapsed patients who previously were treated with radiotherapy, more harmful side effects are acceptable compared to the side effects of re-irradiation. Furthermore, the risks of facial nerve damage, skin resection, and extensive bone resection are weighed against the expected harm of other local therapy techniques.

The 10-year overall survival for the entire cohort was 74%. This cohort consisted roughly of 1/3rds of patients with a non-parameningeal site and 2/3rds with a parameningeal tumor. In the overview papers of the RMS2005 patients, the 5-year event-free and overall survival for non-parameningeal rhabdomyosarcomas was 75% (10). Data from the European and North American cooperative groups has been pooled for patients with parameningeal tumors, resulting in a 10-year overall survival of 63% (14). Overall, these results are comparable; however, performing subgroup analysis in the presented cohort of patients treated with the AMORE protocol, for example, per tumor site, is not possible due to the relatively small patient numbers.

As explained in the introduction, AMORE was developed to spare healthy tissue from irradiation and consequently reduce late adverse effects. In previous studies, the sparing effect of AMORE compared to conventional EBRT in terms of late effects was shown for endocrine disorders, ocular problems, hearing loss, and musculoskeletal deformity (7,12,15). However, radiotherapy has also developed quickly with the development of highly conformal external beam techniques like IMRT/VMAT; therefore, these data might differ in current practice. The first planning comparison data on PT show sparing effects on healthy tissues in the head and neck area compared to photons (16,17). Therefore, PT also has the possibility of limiting late adverse effects when compared to conventional EBRT. We have recently finished a large multicenter study examining the late adverse effects in head and neck rhabdomyosarcoma survivors treated with one of the four local treatment options for HNRMS: AMORE, EBRT using photons (XRT), EBRT using protons (PBT), and the Paris method, which combines surgery with EBRT for patients with infratemporal and pterygopalatine fossa tumors (18). Our overall results show a wide variety and high prevalence of late adverse effects, with the most common late adverse effect being facial deformation (*REF to insert when accepted – minor revisions at cancer).* AMORE is considered less favorable in cases where mutilation caused by surgery is expected to outweigh the potential adverse effects of radiotherapy. All expected potential late adverse effects and expected consequences of surgery are discussed in the MDT meetings with all of the aforementioned specialties involved in the discussion. This discussion is currently aided by the results from our multicenter study guiding the late adverse effects that can be expected and the potential facial deformation for each patient group (based on tumor site and, when patient numbers allowed, patient age).

The AMORE protocol has some drawbacks that need to be taken into account. Surgeons and radiation oncologists have to gain experience with the technique, and a learning curve is expected. Also, the considerations and hypotheses taken into account at the MDT when deciding AMORE feasibility are sometimes subjective and rely on extensive clinical experience. Therefore, we feel that the AMORE protocol is not feasible if there is no dedicated, trained team in place for both the MDT and the procedure itself. Lastly, the AMORE protocol has stringent planning and requires the availability of the entire surgical and radiotherapy team, a dedicated head and neck radiologist, and a pediatric oncologist. Consequently, the AMORE protocol's organizational burden is greater than that of other treatment modalities. We feel the AMORE procedures should be limited to a few international centers to ensure ample cases. However, with sufficient training, ample surgical and radiotherapy knowledge, and a dedicated multidisciplinary team, the AMORE protocol had benefits over other local treatment options. It is important to note the limitations of this current paper. All data presented in this paper was retrieved retrospectively from charts and surgical reports; therefore, the extent and precision of surgery, especially node excision, was sometimes difficult to determine.

CONCLUSION

In this study, we described the patients treated with the AMORE protocols in detail and explored the evolution of the surgical techniques. The exclusion criteria for patients with primary HNRMS have become more stringent, excluding patients with intracranial extension, carotid encasement, and perineural spread. Reconstructive surgery showed very few complications even though the reconstructions were performed in just irradiated tissue. Survival rates yielded with the AMORE protocol were similar to those described in the European and North American studies. In cases where surgery is non-mutilating, AMORE might be considered more often.

Table 1. Details of AMORE protocol and follow-up.
Abbreviations: SND: Selective Neck Dissection; Parotidectomy; Total Parotidectomy; NPM, Non-Parameningeal; PM, Parameningeal; LR, Local Relapse; DM, Distant Metastasis; SP; Secondary Primary.

Patient	Age at diagnosis (years)	Gender	Histology	Site	Subsite	Primary Surgery	Nodes	Reconstruction	Follow-up (years)	Status
1	1.0	F	ERMS	Pterygoid fossa	PM	Parotidectomy, SND, partial mandibulectomy	Level 2b-3	Latissimus dorsi free flap	25.02	Alive
2	7.6	M	ERMS	Pterygoid fossa	PM	Parotidectomy, SND, partial mandibulectomy	Level 1b-2a	Latissimus dorsi free flap	3.80	Died - LR
3	5.5	M	ERMS	Pterygoid fossa	PM	Floor of mouth resection (partial)	Level 2a, 3	Sternocleidomastoid muscle flap	0.70	Died - DM
4	4.3	M	ERMS	Nasopharynx	PM	Lateral rhinotomy, SND	Level 2a, 3	Latissimus dorsi flap	1.10	Died - LR
5	2.9	F	ERMS	Pterygoid fossa	PM	Parotidectomy, SND	Level 1b-3	Sternocleidomastoid muscle flap	1.80	Died - LR
6	9.3	M	ERMS	Pterygoid fossa	PM	Parotidectomy, SND	Level 1b-3	Sternocleidomastoid muscle flap	10.00	Secondary Tumor
7	2.9	M	ERMS	Pterygoid fossa	PM	Superficial parotidectomy, SND	Level 1b-3	Latissimus dorsi free flap	10.40	Alive
8	5.4	M	ERMS	Pterygoid fossa	PM	Superficial parotidectomy, SND	Level 1b-2a	Pedicled latissimus dorsi flap	21.27	Alive
9	1.7	F	ERMS	Paranasal sinus	PM	Denker			20.85	Alive
10	11.0	F	ERMS	Pterygoid fossa	PM	Parotidectomy		Latissimus dorsi free flap	7.50	Relapse - LR

Table 1. *Continued.*

Patient	Age at diagnosis (years)	Gender	Histology	Site	Subsite	Primary Surgery	Nodes	Reconstruction	Follow-up (years)	Status
11	2.2	M	ERMS	Nasopharynx	PM	Lateral rhinotomy, partial sphenoid resection, ethmoid cell reduction		Rectus abdominis free flap	12.51	Alive
12	2.6	F	ERMS	Maxillary sinus	PM	Caldwell-Luc, ethmoidectomy (total)		Rectus abdominis free flap	16.39	Alive
13	2.3	M	ERMS	Nose/ nasopharynx	PM	Denker			16.14	Alive
14	12.9	F	ARMS	Temporal fossa	PM	Extensive muscle resection		Galea rotation flap	15.66	Alive
15	4.8	F	ERMS	Intrafemporal fossa	PM	Denker		Rectus abdominis free flap	2.50	Relapse - LR
16	3.8	M	ERMS	Parotid region	NPM	Parotidectomy (facial nerve intact), SND	Level 1b		24.93	Alive
17	7.4	M	Pleomorphic	Buccal region	NPM	Neck dissection, floor of mouth resection (partial)	Commando	Latissimus dorsi free flap	2.02	Died - LR
18	5.6	F	ERMS	Buccal region	NPM	Parotidectomy, SND, partial mandibulectomy	Level 2a-3	Latissimus dorsi free flap	23.65	Alive
19	1.2	F	ARMS	Oral cavity	PM	Partial maxillectomy (cheek flap), SND	Level 1b-3	Latissimus dorsi free flap	23.29	Alive

Table 1. *Continued.*

Patient	Age at diagnosis (years)	Gender	Histology	Site	Subsite	Primary Surgery	Nodes	Reconstruction	Follow-up (years)	Status
20	6.3	M	ERMS	Parotid region	PM	Parotidectomy		Gracilis free flap	16.34	Alive
21	7.8	F	ARMS	Nose/ nasopharynx	PM	Lateral rhinotomy, nasal bone resection		Cartilage repositioning	13.89	Alive
22	2.2		ARMS	Parotid region	NPM	Superficial parotidectomy, temporal muscle resection		Rectus abdominis free flap	9.33	Alive
23	11.2	M	ARMS	Nasopharynx/ sinus	PM	Lateral rhinotomy, ethmoid cell reduction, concha reduction		Bone graft	0.52	Relapse - LR
24	4.8	F	ERMS	Infratemporal fossa	PM	Caldwell-Luc		Pedicled temporoparietal muscle flap	1.78	Died - LR
25	9.0	M	ERMS	Buccal region	PM	SND + muscle resection	Level2		4.03	Died - SP
26	5.6	F	ERMS	Oral cavity	PM	Partial floor of mouth resection, SND	Level 2		3.67	Died - LR
27	13.6	F	ERMS	Buccal region	NPM	Marginal mandibular resection, neck dissection	Commando	Gracilis free flap	11.79	Alive

Table 1. *Continued.*

Patient	Age at diagnosis (years)	Gender	Histology	Site	Subsite	Primary Surgery	Nodes	Reconstruction	Follow-up (years)	Status
28	1.6	M	ERMS	Parapharyngeal	PM	Parotidectomy, SND	Level 2		11.30	Alive
29	10.4	F	ERMS	Temporal fossa	PM	Subtotal petrosectomy		Galea flap	10.76	Alive
30	3.7	M	ERMS	Buccal region	PM	Partial mandibulectomy	Level 2a	Fibula free flap	8.28	Alive
31	1.6	F	ERMS	Nose/ nasopharynx	PM	Superficial parotidectomy, temporal muscle resection		Gracilis free flap	13.22	Alive
32	3.7	M	ERMS	Buccal region	NPM	Neck dissection, marginal mandibulectomy (cheek flap)	Commando		1.85	Alive
33	3.5	M	ERMS	Nasopharynx	NPM	Inspection			1.89	Alive
34	5.4	M	ERMS	Buccal region	NPM	Floor of mouth resection (partial)			1.05	Alive
35	1.1	M	ERMS	Temporal fossa	PM	SND, petrosectomy, digastric muscle resection,	Level 2a, 3	Latissimus dorsi free flap	1.05	Alive

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8

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

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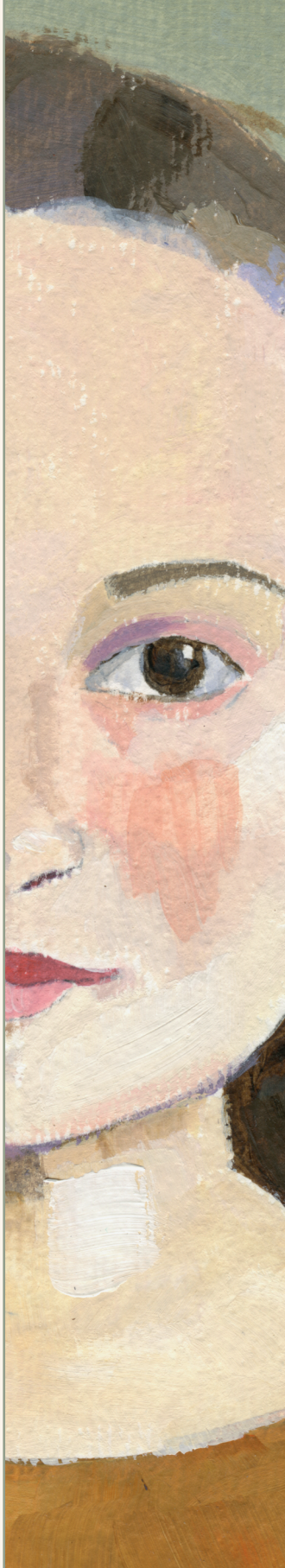

ABSTRACT

Purpose
Survival after relapse of rhabdomyosarcoma in the head and neck area (HNRMS) 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 external beam radiotherapy (EBRT).

Methods
Patients with relapsed HNRMS after prior EBRT in which salvage AMORE treatment was feasible were analysed. AMORE treatment consisted of Ablative surgery, MOulage technique brachytherapy and surgical REconstruction.

Results
In total 18 patients received salvage AMORE treatment; 9 patients had relapsed parameningeal RMS, 3 patients had relapsed head and neck non-parameningeal RMS and 7 patients had relapsed orbital RMS. Five-year overall survival was 54% and 9 of the 18 treated patients were alive after a median follow-up of 8.6 years. One patient survived >5 years after which he died from a secondary cancer. Six patients developed a local relapse, together with a distant metastasis in one and 2 patients developed a distant metastasis.

Conclusions
Salvage AMORE treatment is a safe 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 AMORE treatment for patients with relapsed HNRMS.

INTRODUCTION

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 parameningeal (PM), head and neck non-parameningeal and the orbital region.

The treatment of childhood rhabdomyosarcoma consists of a combination of chemotherapy, supplemented with 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 not possible, making external beam radiotherapy (EBRT) often the treatment of choice.

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 after loading brachytherapy and surgical REconstruction. The theoretical advantage of brachytherapy over EBRT is a conformal dose delivery to the tumour bed with rapid fall-off of the dose beyond the treatment volume sparing normal, healthy tissue. In the EKZ-AMC, patients with HNRMS are treated according to the AMORE treatment if feasible, otherwise patients receive EBRT (either proton or photon radiotherapy). 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 localisation, 34% for head and neck non-parameningeal localisation and 28% for orbital localisation 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 associated with 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 the options to achieve local control are simply 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.

PATIENTS AND METHODS

Patients

Eligible patients were relapsed HNRMS patients, 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. Included patients originated from our own centre or were referred to us for salvage AMORE treatment.

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 Pediatric Oncology Malignant Mesenchymal Tumour; SIOP-MMT-89 and SIOP-MMT-95), CWS (German Cooperative Soft Tissue Sarcoma; CWS-96), or the 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 undergo an incisional biopsy after which patients receive 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 >3 years with parameningeal tumours received EBRT on initial tumour volume with a margin of 2 cm. Patients with head and neck non-parameningeal tumours received EBRT on the residual volume.

AMORE procedure

The technical feasibility of a salvage AMORE procedure was discussed in a multidisciplinary meeting by discussing relevant clinical features and pre-operative imaging studies. Participating specialties in these multidisciplinary meetings were: paediatric oncologist, radiation oncologist, head and neck radiologist, head and neck surgeon, reconstructive surgeon, orbital surgeon and in specific cases also a neurosurgeon. AMORE treatment was considered feasible based on the possibility to perform a macroscopic tumour resection and adequate mould positioning after resection. AMORE as first line treatment in naïve patients includes conservative, non-mutilating surgery as the goal of AMORE treatment is to effectively treat the primary tumour with reduction of late adverse events. However, when considering AMORE for previously irradiated patients with relapsed disease, more mutilating surgery was accepted, as there was no alternative local treatment left.

Details of the AMORE treatment can be found in previous manuscripts. [2,4,17,18] 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. On the same day a mould is made to fit the wound bed and polyethylene catheters are drilled into the mould. Possible microscopic remnants in the wound bed are irradiated, using iridium-192 wires. Radiotherapy dose (40-50 Gy) is administered up to 5 mm from the mould. Until 2001, continuous low-dose rate brachytherapy was given and from 2002 pulsed dose rate brachytherapy was given. After completion of brachytherapy, a second surgical procedure is performed to remove the mould and catheters after which the surgical defect is reconstructed (if necessary) by using a free vascularized or pedicled flap.

Follow-up and statistical analysis

Overall survival was defined as the time between date of relapse and date of last follow-up or patient's death. Cut off point of this analysis was March 31, 2017. For a part of this population, adverse events were systematically assessed in a multidisciplinary outpatient clinic, of which results were reported previously. For other patients we asked treating physicians to fill out a predefined adverse events 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 outpatient clinic of the EKZ/AMC (supplementary table S1, online only). [3]

We used SPSS version 24.0 for the survival analysis. Overall survival was calculated using the Kaplan-Meier method.[19] Because of the small number of patients, results were 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 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).

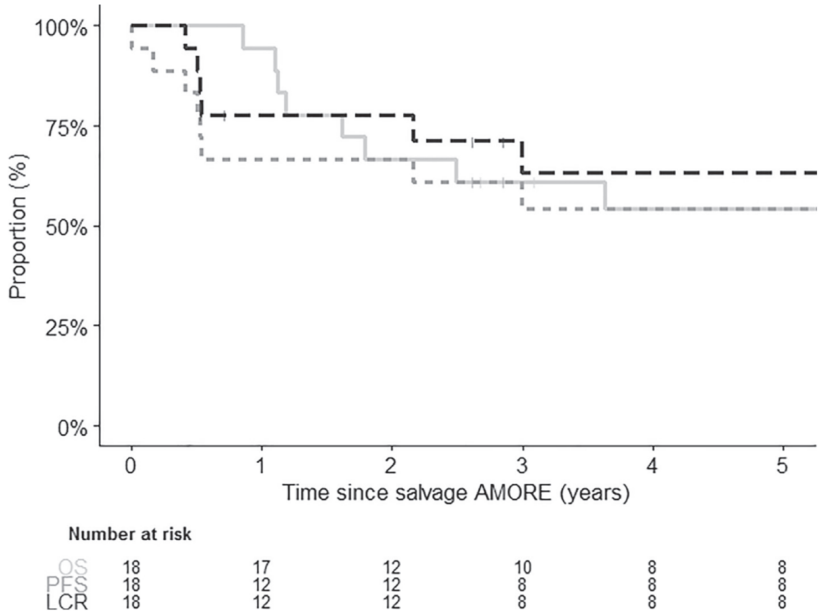

Figure 1. Kaplan Meier curves.

The figure shows 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.

Parameningeal

Histology was embryonal in all tumours with parameningeal localization (n=9). None of the parameningeal cases had metastatic disease at initial diagnosis. For eight of the nine patients the treatment of the initial tumour consisted of diagnostic incisional biopsy and induction chemotherapy followed by EBRT. One patient had a macroscopic complete resection at diagnosis followed by chemotherapy and EBRT. Applied radiotherapy dose on the initial tumour ranged between 45 and 55.8 Gy (table 1).

Eight of nine patients had a local relapse and one patient had both a local relapse and a solitary pulmonary metastasis. This patient was first treated with chemotherapy and underwent a metastatectomy after which an AMORE salvage procedure was performed. In one patient, the salvage AMORE treatment was applied directly after diagnosis of relapse and chemotherapy was withheld because of myeloablative chemotherapy followed by autologous stem cell transplant for the initial tumour. Six patients were first treated with chemotherapy after which an AMORE procedure was applied. In another patient (patient 7) the relapsed tumour was resected and

chemotherapy was started. After completion of chemotherapy, regrowth of a residual mass was detected and treated with AMORE (table 2).

All patients achieved complete remission after AMORE treatment. Three of the nine patients were alive after a follow-up ranging from 8.5 to 23.8 years. Five patients developed a relapse; three were local relapses, one developed a local relapse and a distant metastasis, another one developed a distant metastasis only. Two of the nine patients developed a secondary malignancy; patient 1 developed a medulloblastoma within the EBRT field, 8.2 years after AMORE treatment and patient 7 developed a glioblastoma 5 years after AMORE treatment (and died after surgery). Six of the nine patients died, 0.9 to 6.4 years after diagnosis of relapse for which salvage AMORE treatment was performed.

In all patients, the salvage treatment was well tolerated without short term complications, except for patients 8 who developed a major wound infection around the brachytherapy wires.

The three surviving patients all developed more than 5 adverse events. All three patients developed (grade 2 or 3) musculoskeletal deformities and they all developed growth hormone deficiency and 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.

Table 1: Initial tumor 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	pterygoid muscle	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 (48.6Gy)	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 orbit and m. temporalis	1st LR
Non parameningeal							
10	1.7	F	Alveolar	Cheek + distant metastasis	RMS-MET-2008/EBRT (51.2Gy)	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

Table 1: *Continued.*

Patient	Age [a] (yrs)	Sex	Histology	Initial localization	Initial treatment	Relapse site	Indication AMORE
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

[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.
Abbreviations: CWS95, German Cooperative Soft Tissue Sarcoma 95 study; EBRT, external beam radiotheray; 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 pediatric Soft tissue sarcoma Study Group rhabdomyosarcoma 2005 study (EpSSG-RMS-2005); RMS-MET-2008, EpSSG RMS metastatic 2008 study; yrs, years

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	-

Table 2. *Continued.*

Patient	Age[a] (yrs)	Salvage treatment	Surgery	Brachytherapy		Reconstruction	Outcome		Event
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	-

Table 2. *Continued.*

Patient	Age[a] (yrs)	Salvage treatment	Surgery	Brachytherapy		Reconstruction	Outcome		Event
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

[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.
Abbreviations: CT, 2nd or 3rd line chemotherapy; DM, distant metastasis; FU, follow-up since relapse in years; GA, tunneled 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, metastectomy 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.

Head and neck non-parameningeal

Two patients had a head and neck non-parameningeal located relapse; patient 10 had an alveolar RMS, with pulmonary metastases and bilateral lymphadenopathy at initial diagnosis. She was then treated with chemotherapy and EBRT (51.2 Gy) on the local tumour and metastatic sites. Patient 11 had an embryonal RMS initially treated with chemotherapy and surgery. His first local relapse was treated with chemotherapy followed by EBRT (54 Gy).

Both patients relapsed locally; i.e. first relapse in patient 10 and second relapse in patient 11. Patient 10 received second line chemotherapy and a salvage AMORE treatment (table 2). At preoperative radiologic imaging patient 10 showed potential lymph node involvement/salivary gland metastasis. Therefore a selective lymph node dissection was conducted in addition to the resection of the primary tumour in the first surgical procedure.

The salvage treatment was well tolerated, however after the procedure, pathology results showed microscopic remnants in the border of the resected specimen. Additional EBRT was considered necessary, however not possible because of potential toxicity. She received maintenance chemotherapy; however she died from distant metastasis a year after AMORE treatment. Patient 11 received second line chemotherapy and a 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

Seven patients had orbital RMS; one tumour was of alveolar histology, the other six were embryonal. All seven patients were treated with chemotherapy and EBRT; five for their initial tumour, and two for their first or second relapse. In patient 14 initial treatment consisted of chemotherapy and AMORE treatment and her first local relapse was treated with chemotherapy followed by EBRT. In patient 17 the initial tumour was treated with chemotherapy and local surgery, first local relapse was treated with chemotherapy and AMORE treatment and the second relapse was treated with chemotherapy and EBRT. EBRT dose for these seven patients ranged between 45 and 55.8 Gy. All seven patients developed a local relapse; in two patients the relapsed tumour showed parameningeal extension. Salvage treatment, for all seven, consisted of chemotherapy followed by a salvage AMORE treatment. Resection of the tumour included orbital exenteration; one of these patients also underwent a craniotomy with excision of part of the dura (table 2). In all patients the salvage treatment was well tolerated, without acute complications. Follow-up for patients alive ranged from 2.7 to 21.7 years. Patient 18 died of a local relapse, developed 6 months after AMORE procedure. Besides the orbital exenteration (graded as musculoskeletal deformity grade 4), surviving patients experienced

grade 1 or 2 AEs, including scarring, induration/fibrosis, hearing loss, telangiectasia, pigmentation, epistaxis, alopecia, skin/fat atrophy, dry eyes. Patient 13 developed growth hormone deficiency and received growth hormone replacement. Patient 17 developed radiation necrosis in his frontal lobe, 13 years after salvage AMORE treatment.

DISCUSSION

The outcome for patients with relapsed RMS is determined by the feasibility of local treatment. Curative options are often lacking in patients with relapsed rhabdomyosarcoma who have previously received EBRT. Consequently, the survival rates for children with relapsed HNRMS after receiving EBRT are poor; ranging from 0-18%.[9-11] Microscopic radical resection of the tumour is often not possible without serious 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.

However, in specific cases a salvage treatment according to the AMORE treatment is possible. The brachytherapy is added to treat the microscopic remnants, allowing a precise conformal dose distribution with rapid fall-off, thereby sparing the surrounding healthy tissue or previously irradiated tissue. In these patients the AMORE treatment enables re-irradiation in patients with relapsed HNRMS.

In this study we showed that a salvage AMORE treatment could lead to long-term survival, with 54% overall survival and median follow-up of 8.6 years. Nine of the 18 treated patients were alive and 1 patient survived >5 years after which he died from a secondary cancer.

We previously reported on salvage AMORE treatment, in which we also included patients with residual disease at the end of therapy for salvage AMORE.[17] Yet a North-American analysis showed that patients with residual masses at the end of therapy had comparable prognosis as patients showing complete tumour response at end of therapy.[20] Therefore patients with residual disease after EBRT are no longer eligible for an AMORE treatment. Patients who did receive AMORE treatment for residual disease after EBRT were excluded from the current analysis.

A comparison of survival rates with other cohorts is not possible since we only report outcomes for patients treated by AMORE instead of all patients in whom salvage AMORE was considered. Nevertheless, the AMORE treatment is often the only remaining local treatment modality available in patients previously treated

with EBRT and therefore the outcome data of this cohort is relevant in the future treatment of patients with relapsed head and neck RMS.

The feasibility of AMORE was systematically discussed in a multidisciplinary setting, using predefined in- and exclusion criteria as described in this manuscript. When considering newly diagnosed patients for AMORE, potential mutilation is a contra-indication for AMORE, unless more adverse events are expected when using EBRT. In case of relapse patients, when often no other local treatment is available, the AMORE working group tends to consider more mutilating and more risky surgery.

Re-irradiation in case of a relapse after prior EBRT is generally considered impossible. Patients in this cohort were all re-irradiated by brachytherapy; nevertheless the total AMORE treatment was well tolerated. Although the resection and reconstruction were conducted in a previously irradiated field, acute complications were rarely seen and only one patient developed a major wound infection. Nevertheless, successful salvage procedures did cause important (late) sequelae. An orbital exenteration was conducted in all patients with orbital tumours and one patient developed radiation necrosis in his frontal lobe. The 3 surviving parameningeal patients all experienced a high number of adverse events; however these patients also received prior EBRT making it difficult to determine the causative factor. Two patients developed a secondary malignancy; the medulloblastoma was located in the fields of prior EBRT and the exact location of the glioblastoma is unknown since primary treatment and follow-up for this patient was done in a different hospital. These cases indicate that salvage AMORE treatment is a complex procedure and in specific cases it could lead to long term survival.

CONCLUSION

Salvage AMORE treatment is a safe and effective local therapy approach for a specific group of patients with relapsed HNRMS. Local therapy by AMORE procedure is sometimes the only curative option in patients with relapsed HNRMS with prior EBRT treatment and we encourage physicians to consider AMORE treatment as salvage treatment for relapsed patients.

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9

Predicted future aesthetic and functional outcome following surgical treatment for pediatric head and neck sarcomas

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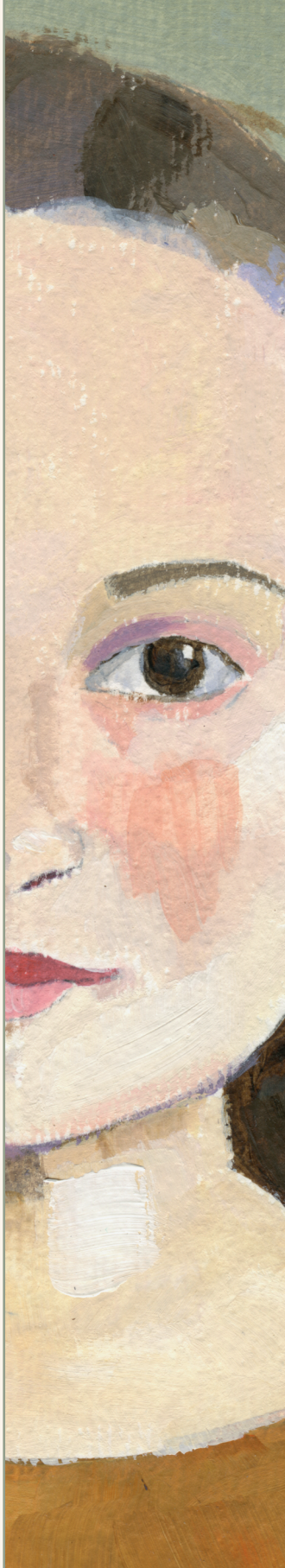

ABSTRACT

Objective

When choosing between different treatment options, functional and esthetic outcome following surgery is always taken into account and sometimes a key factor in multi-disciplinary discussions. However, especially in children who are growing and developing, predicting such outcomes can be tricky. The aim of this paper was to investigate if surgeons can predict functional and esthetic outcome in children undergoing surgery for head and neck sarcomas.

Study Design, Setting, and Methods

Nine patients were selected who were treated with surgery. Six peadiatric sarcoma surgeons were asked to predict facial and ethetical outcome according to the Common Terminology Criteria for late Adverse Events (CTCAE). These nine patients presented in the cases were evaluated in clinic at adult age and a 3D-photograph was taken. The predicted and actual outcomes were compared.

Results

Intra-rater reliability was high with an ICC of 0.872 for all observers combined. Musculo-skeletal deformation was scored with differences of CTCAE score up to 2 points (ranging 0-4). The correlation with the actual clinically scored CTCAE was low. For musculoskeletal deformations only 1 in 9 cases were scored correctly by 3 observers. Nerve damage was scored correctly by all observers in 8/9 cases. When comparing predicted facial outcome with the 3D stereophography, there was no correlation for the entire face or defined subunits (e.g. nose, mandible).

Conclusion

Paediatric surgeons involved in sarcoma surgery demonstrate difficulty in predicting the effect of surgery on potential facial deformation and scar development. The likelihood of nerve damage was shown to be more reliably predicted.

INTRODUCTION

Head and neck (HN) sarcoma (HNS) is treated with systemic therapy after which local therapy to the primary tumor is given. Local therapy may be radiotherapy, surgery, or a combination of both (1–5) . When choosing between these options, and during Multidisciplinary Team Meetings (MDT), expected late adverse effects are weighed against each other. Especially in a developing child's head and neck area, predicted facial deformations are of great essence when opting for a specific treatment. Also, functional deficits such as vision, endocrine disorders and swallowing should be considered. For radiotherapy planning, the radiation oncologist is asked to describe the planned treatment field and the expected adverse effects following radiation therapy. The surgeon is consulted to offer insight on the expected side- effects of surgery, after which the therapy considered least harmful is discussed with parents.

However, the question remains how well surgeons can predict the effects of surgery in a young child related to functional and esthetical outcomes in future adulthood. This is important as these considerations impact decision making as well as patient and parental interaction in the long-term. Within the field of pediatric HN oncologic surgery, the focus has characteristically been on short term outcomes such as 30-day morbidity and complications, but there is an ever-increasing recognition of the importance of late effects of multi-modality treatment (6–9). In this paper, we sought to assess predictions by pediatric oncologic head and neck surgeons as to the future functional and aesthetic impact of resection and reconstruction. These predictions would then be compared to the resulting aesthetic and functional outcome in patients with a known treatment history.

PATIENTS AND METHODS

Patients

Late adverse effect clinics were held in the Netherlands, United Kingdom, United States, and France. At these clinics, all patients who were treated for an HNS in the past 25 years were invited to come to the clinic and undergo analysis. Amongst other investigations, patients were seen by a plastic surgeon and a head and neck surgeon who scored patients for facial deformation, esthetical outcomes, and function according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Also, all patients had a 3D facial image taken using a stereophotogrammetric camera.

Rarely, patients were treated by a complete microscopically R0 resection when anatomic position made this possible. Surgery alone was only offered as a mono-modality treatment in the Netherlands, the United Kingdom, and France. One

clinical researcher (MH) selected 9 patients who were seen at the late adverse effect clinics. Patient selection was based on primary surgery undertaken under the age of 6 without adjuvant radiotherapy or chemoradiotherapy. Of all selected patients, a case description was made including anonymized patient and treatment details (age, staging of disease, clinical performance, performed ablative R0 resection, and reconstruction) and pre-surgery imaging, usually CT. One patient was presented twice with slightly different imaging slices and a readjusted case report to assess internal consistency. All patients included in this study had no previous history of illness or trauma to the HN area. 8 patients suffered from a embryonal rhabdomyosarcoma and one patient had a alveolar rhabdomyosarcoma. The surgeons were not aware of this and they were asked to assess ten cases.

Observers

Four observers were of senior-level, defined as over 20 years' experience in tertiary paediatric head and neck or reconstructive surgery as a lead surgeon. Two observers have vast experience with plastic and reconstructive surgery (JO, FK) (from now on 'plastic surgeons'), two observers have wide experience with head and neck surgery from an oncologic perspective (LS, RH) (from now on 'HN surgeons'). Two observers regularly participated in late adverse effect clinics (AH, CB) but had less than five years' experience in tertiary paediatric head and neck surgery (from now on 'Fellows'). All observers have experience with late adverse effects clinics for head and neck rhabdomyosarcoma survivors and the CTCAE scoring system. All cases were presented in one session, much like an official MDT, where all six surgeons were present and additional questions could be discussed.

Predicting aesthetic and functional outcomes

To predict facial deformation, items from the CTCAE were used since these are also applied in the actual late adverse effect clinics. The items chosen from the CTCAE lists were musculo-facial deformation, scar formation, and nerve damage. All items could be scored 0 to 4, as in the regular CTCAE, where a score of 0 is no abnormality, and a score of 4 represents maximal deformation, scar, or nerve damage. These standard CTCAE criteria were specified for each specific region of the face; overall face, zygomatic area, nose area, lower midface, and upper midface. All observers filled out the expected CTCAE criteria list independently (supplementary data 1) as if they were seeing the patient at 20 years old in the adverse effect clinic. Predicted CTCAE scores were compared to the clinical scored CTCAE at the follow-up clinics.

3D stereo photographs

All 3D stereo photographs were analyzed by Dense Surface Modelling (DSM) as described in previous papers (10–13). In short, each patient's face is compared to 50 healthy individuals of the same age, sex, and ethnicity resulting in a face shape model. This model can then represent the amount of facial deformation in a color

map exhibiting the amount of facial deformation. A normalized distance metric, 'signature weight', can be computed for comparing an individual, to the healthy population. These signature weights represent the severity of facial deformation. We used four models for the analysis of facial prediction: an overall face model, a malar model (corresponding to the zygomatic area), a nose model, and a lower-midface model.

Statistical methods

Inter- and intra- class correlations were calculated for expected facial deformation between the different observers, and for the different groups of observers, i.e., fellows, HN surgeons, plastic surgeons. Also, facial deformation was correlated to the actual facial deformation scored at the late adverse effect clinics as well as to the data from the 3D stereo photography. Statistical analysis was performed using SPSS 24.0.

RESULTS

Six observers individually rated expected aesthetic and functional outcomes in 10 presented cases of paediatric HNRMS. For all patients, CTCAE lists and 3D stereo-photographs were available.

Reliability

Intra-rater reliability was high with an ICC of 0.872 for all observers combined. There was no statistical difference in intra-rater reliability between the more experienced surgeons (Plastic surgeons and ENT surgeons) and the fellows (p=0.618). However, HN surgeons showed higher intra-rater reliability than plastic surgeons (p=0.0029). Inter-rater reliability was not high with an ICC of 0.684, 0.552, 0.516 for plastic surgeons, ENT surgeons, and fellows respectively. Musculo-skeletal deformation was scored with differences of CTCAE score up to 2 points, meaning some patients were rated a CTCAE 1 by one surgeon and a CTCAE 3 by another surgeon. For nerve function, this also differed up to 2 CTCEA points where patients either went from no expected dysfunction (CTCAE 0) to a CTCAE score of 2 representing substantial issues with nerve damage.

Correlation with clinically scored CTCAE

The correlation with the clinically scored CTCAE was low. For musculoskeletal deformations only 1 in 9 cases was scored correctly by 3 observers. Two observers scored 2 cases with the correct overall facial deformation and only 1 observer scored 3/9 cases with the correct musculoskeletal deformation. Differences in scoring were up to 3 CTCAE points, meaning the actual CTCAE score was 0 in the clinic whereas

a score of 3 was predicted. There were no cases where facial deformation was underestimated by the observers.

Scar outcome prediction varied greatly between the different observers, one observer scored all patients the same CTCAE as the actual scar outcome. However, four other observers only scored one case (11%) correct, and 1 observer scored four cases (44%) with the correct scar score. Scar outcome was both under- and overestimated.

Nerve damage was scored correctly by all observers in 8 cases; only 1 case scored differently were surgeons overestimated the nerve damage by 1 to 2 points CTCAE. No underestimation of nerve damage occurred.

Correlation to 3D stereophotographs

In figure 1 the overall predicted score and facial outgrowth are shown with 3D stereo photographs. Only 2 patients were predicted to have an overall score of musculo-skeletal deformation of 2, whereas as we can see, these patients do not differ much from the patients depicted in the row with patients scored as an overall musculoskeletal deformity of 3. In figure 2 the predicted musculo-skeletal CTCAE is compared to the facial deformation score. For the overall head and neck score patients with a median estimated score of 3 differ in signature weight within the same range as patients with a predicted score of 2. For patients with a nose score predicted of 2 or 3, there is no difference in actual outcome with patients who were estimated to have no facial deformation in their nasal area. For the mandible, there is no correlation between predicted facial outcome and actual facial deformation.

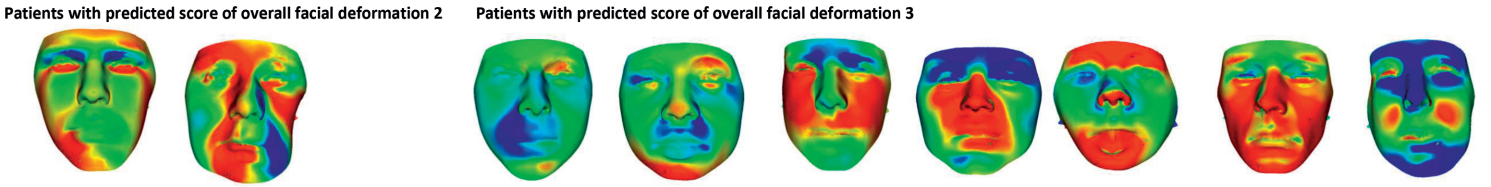

Figure 1. 3D photos of patients included in this study.

The two patients on the left were graded with a grade 2 deformation by observers and the other 7 with a grade 3 deformity. Blue means 2 standard deviation less development in comparison to the healthy population (age-sex-ethnicity matched). Whereas, red represents overgrowth –similarly 2 standard deviations to healthy population.

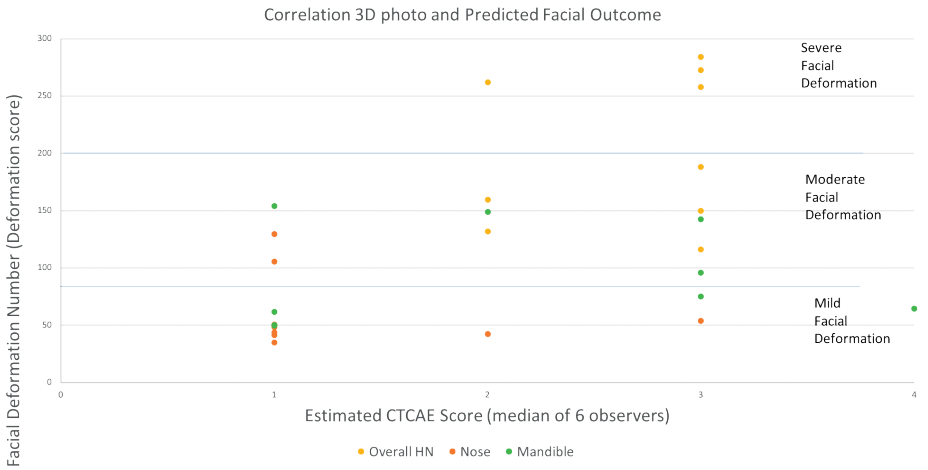

Figure 2. Correlation of 3D stereophotograph and estimated CTCAE score

DISCUSSION

The data from this current study show us, that however experienced surgeons are in the field of head and neck surgery, predicting actual patients outcomes remains difficult. Predicting musculoskeletal deformation at adult age for patients undergoing surgery when infants correlated poorly with actual clinical outcomes. Nerve damaged was scored reliable by all observers. When comparing predicted facial outcome with the 3D stereophography, there was no correlation for the entire face or defined subunits (e.g. nose, mandible).

Facial deformation is a typical late adverse effect of treatment for HNRMS in up to 79% of survivors (6,9,14). With modern treatment techniques more treatment options become available that may potentially spare healthy tissues (7).When choosing between different treatment options, the expected late adverse effects are among the main reasons to choose a specific treatment by experts. In the centers participating in this study, such decisions are made during an MDT meeting during which plastic surgeons and head and neck surgeons are usually consulted to comment on the expected morbidity following surgery. However, there is no literature describing how well we are actually capable of making such predictions in a developing, growing child.

When we take into account that surgery takes place in a growing and developing child, predicting the long term effect of bone and soft tissue resection and reconstruction is difficult. By contrast, nerve location shows anatomical consistency and as such, the direct effect of surgery to motor nerves and its associated musculature is more

straightforward. As shown in the present study, correlations with actual clinical ratings were poor for musculoskeletal outcome and scar formation. However, nerve damage was well predicted in almost all cases by all observers.

The intra-rater reliability was high, with a mean ICC of 0.872. However, inter-rater reliability was low with a median ICC of 0.552. There was no statistical difference between the inter-rater reliability of ENT, plastic surgeons, or fellows. We hypothesized there would be a difference in scoring depending on experience level, however we did not show this in this current study. CTCAE scores differed from no expected or expected mild symptom to a prediction of grade 3 (severe) adverse effects. Based on these statistics, we conclude that an MDT's advice can vary largely depending on the surgeon asked. The analysis of 3D pictures shows us there is no reliable estimation for facial deformation when comparing to the actual facial deformation in individual cases. Neither for the total for the face nor small parts of the face i.e., nose or mandible. These data show us that predicting how a child will grow and develop is extremely difficult, even in the expert' s eye, and therefore quite unreliable to use as a basis when choosing between treatment options.

It is important to realize the potential limitations of this current study. Predictions took place in a virtual form without the patient being physically present. However, this format is representative of a typical MDT meeting. Given the international composition of the surgical team and anonymized patient history, the chances of the surgeons recognizing the underlying cases would not be expected.

Facial deformation analysis in survivors of HNRMS by 3D stereophotogrammetry is an well established method (6). 3D predictions of facial deformation for each different treatment option would be a valuable tool when choosing treatment options. Currently, such 3D techniques are already used successfully for outcome prediction in reconstructive breast surgery (15). Also, 3D techniques are used in planning orthognathic surgery and cleft surgery, for which the reliability of predicting and analyzing treatments has been proved (16–19). Therefore, it would be our recommendation to further investigate the possibility of using 3D prediction of facial outcomes in children who are being evaluated for cancer treatment in the HN area. To build such a model, especially for HNRMS patients, more information on dose-effect relations for facial bones are needed as well as more patient data on growth and facial development. When such data becomes available a more robust model can be build in terms of predicting facial deformation.

CONCLUSION

Our experienced tertiary paediatric surgeons demonstrated considerable difficulty predicting the effect of surgery on potential facial deformation and scar development within this study. Cranial nerve dysfunction was predicted correctly. This study demonstrates the need for a reliable prediction tool for facial deformation and other late effects.

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SUPPLEMENTARY DATA 1

Questionnaire

Predicting Facial deformation following surgery

Name observer:

Case number:

Notes:

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.....

Proposed surgery:

.....
.....

Please score the effect you imagine the patient will have when reaching adulthood following the proposed surgery

The overall head and neck area, impression of the patient

Adverse event	0	1	2	3	4
Musculoskeletal deformity	None expected	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be covered	-Significant deformity, hypoplasia or asymmetry, not covered -Disabling	Orbital exenteration
Scar†	No expected concerns	Asymptomatic, cosmetic and functionally unimportant	- Symptomatic, - Functionally uncomfortable	-Loss of function -Impairment of ADL	Life-threatening
Neurological deficit cranial nerves; Specify:	-	Asymptomatic	-Moderate symptoms -Limiting instrumental ADL	-Severe symptoms -Limiting self care ADL -Assistive device indicated	-Life-threatening consequences -Urgent intervention indicated

The nose

Adverse event	0	1	2	3	4
Musculoskeletal deformity	None expected	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be covered	-Significant deformity, hypoplasia or asymmetry, not covered -Disabling	Amputation of >80% of nose
Scar†	No expected concerns	Asymptomatic, cosmetic and functionally unimportant	- Symptomatic, - Functionally uncomfortable	-Loss of function -Impairment of ADL	Life-threatening

The lower midface (jaws, not including the nose)

Adverse event	0	1	2	3	4
Musculoskeletal deformity	None expected	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be covered	-Significant deformity, hypoplasia or asymmetry, not covered -Disabling	Mandibulectomy/ maxillectomy
Scar†	No expected concerns	Asymptomatic, cosmetic and functionally unimportant	- Symptomatic, - Functionally uncomfortable	-Loss of function -Impairment of ADL	Life-threatening

The midface (zygomatic arch, not including the nose)

Adverse event	0	1	2	3	4
Musculoskeletal deformity	None expected	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be covered	-Significant deformity, hypoplasia or asymmetry, not covered -Disabling	Maxillectomy, large zygomatic arch resection
Scar†	No expected concerns	Asymptomatic, cosmetic and functionally unimportant	- Symptomatic, - Functionally uncomfortable	-Loss of function -Impairment of ADL	Life-threatening

The upper part of face (forehead, eye region)

Adverse event	0	1	2	3	4
Musculoskeletal deformity	None expected	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be covered	-Significant deformity, hypoplasia or asymmetry, not covered -Disabling	Orbital exenteration
Scar†	No expected concerns	Asymptomatic, cosmetic and functionally unimportant	- Symptomatic, - Functionally uncomfortable	-Loss of function -Impairment of ADL	Life-threatening

Comments/ issues not able to be captured in scoring list:

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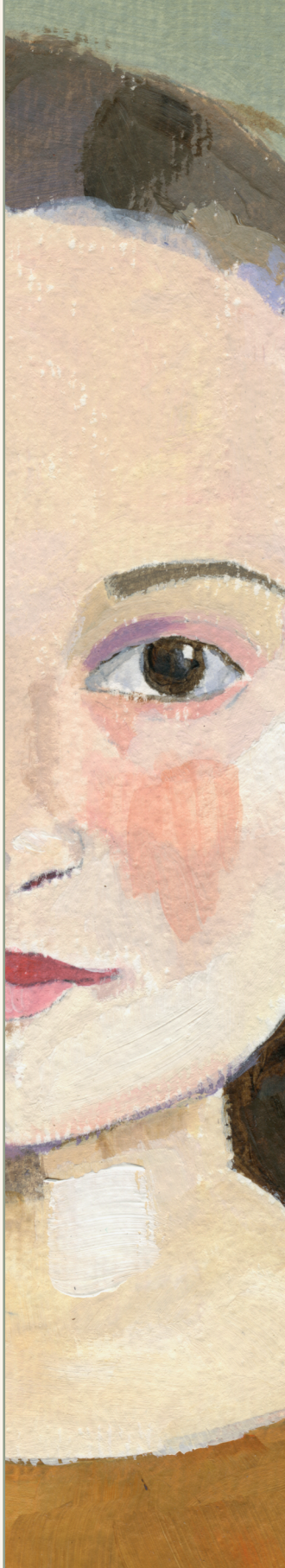
PART V

Impact on clinical practice



IMPACT ON CLINICAL PRACTICE

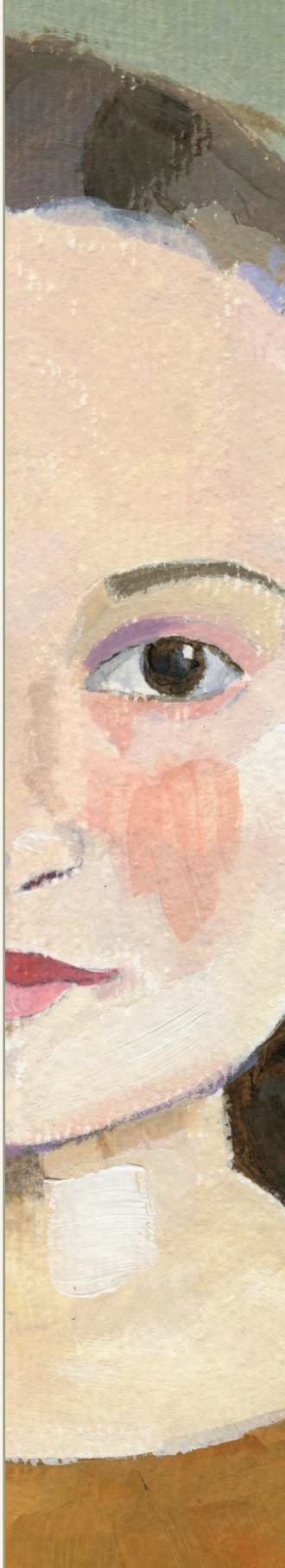
Potentially, the most relevant finding for clinical practice to improve treatment for head and neck rhabdomyosarcoma patients is the presented dose constraints. The facial dose-effect models presented highlight an important new finding, as it shows the need to delineate facial bones, or bone complexes, as organs at risk for treatment planning. Dose constraints are presented in **Chapters 4** and **5** and this dissertation's discussion (General Discussion – **Table 1**) of this dissertation. Using these dose constraints for facial bones and bone complexes during treatment planning may reduce the radiation dose, consequently limiting facial deformation.

The first part of this dissertation showed the prevalence and diversity of late adverse effects in paediatric head and neck rhabdomyosarcoma survivors seen in the uniform trans-Atlantic multi-centre study. This study shows the need for a standardised late adverse effects clinic, as 80 % of survivors suffered from grade two late adverse effects and 60 % from at least one grade three late toxicity (CTCAE criteria). The results underline the need for outpatient clinics to be multidisciplinary in their setup to deal with the variety and complexity of conditions that survivors present. The most common late adverse effects were musculoskeletal deformity, cataracts, hearing impairment, speech abnormalities and eyelid malfunction. There is a proven need for a robust, multidisciplinary late adverse effects clinic, which, based on these data, needs to include an ENT surgeon, an ophthalmologist or orbital surgeon, a surgeon performing reconstructions in the head and neck area (either a plastic surgeon or head and neck surgeon), a radiation oncologist, and a clinical oncologist). Currently, these data are used to better inform patients and parents on the expected late adverse effects following treatment. For treating physicians, these data are used to improve follow-up care as they point towards the most common expected late adverse effects. The discrepancy between patient-reported outcomes and physician-reported outcomes on facial function, appearance and quality of life is also shown, underlining the need to incorporate a patient-reported outcome measure in outpatient clinics. The difference in facial deformation between the different local treatment options is shown in the chapter on facial deformation. It showcases a decision model applicable when facial deformation is the main expected outcome difference between treatment modalities (**Figure 1** of the General Discussion), an endpoint often overlooked in calculations of therapeutic ratio. The data presented will be further used to build a decision model including all late adverse effects, providing a robust framework for future advancement in controlling musculoskeletal deformation in children with craniofacial rhabdomyosarcoma.

The last part of this dissertation focuses on surgery, specifically the AMORE protocol. For primary rhabdomyosarcoma in the head and neck area, AMORE shows similar survival rates compared to EBRT and can potentially limit late adverse

effects. AMORE proved to be feasible in relapsed patients who had already been irradiated and had very few other treatment options. AMORE should be considered in all relapsed head and neck rhabdomyosarcoma patients, as it is often the only therapeutic option providing a chance of survival. It is important to note that different choices are made for AMORE in salvage cases, as with it often being the last resort, more harmful surgery is accepted, aiming for survival rather than limiting late adverse effects.

General discussion



INTRODUCTION

This dissertation explored several aspects of paediatric head and neck rhabdomyosarcoma. **Part II** (**Chapters 1-3**) explored late adverse effects and investigated the differences between treatment modalities. The four local treatment options for head and neck rhabdomyosarcoma are further discussed in this dissertation's introduction and throughout the work. The local treatment options are external beam radiotherapy with photons (XRT); external beam radiotherapy with protons (PT); Ablative surgery, MOulage technique with afterloading brachytherapy and REconstructive surgery (AMORE); and aimed R0 resective surgery combined with either XRT or PT (the Paris method). The overall results of the trans-Atlantic multicenter study are shown in **Chapter 1**. **Chapter 2** further investigated facial deformation utilising 3D stereophotogrammetry. **Chapter 3** studied patient-reported outcomes for facial function and appearance. The first part of this dissertation paints a picture of the diversity and high prevalence of late adverse effects, facial deformation in particular, and patient-reported outcomes on facial function and the correlation with physician-reported outcomes. Local treatment must be improved for future patients to limit facial deformation and adverse effects. The dose to craniofacial bones must be reduced to spare these growing and developing tissues and limit facial deformation. Dose constraints must be known when attempting to limit the dose to craniofacial bones. **Part III** of this dissertation (**Chapters 4-6**) examined facial deformation in relation to radiation dose. In **Chapter 4**, the first analysis of orbital bone morphology changes was shown in relation to dose to the orbital bones and orbital rim bones. **Chapter 5** evaluated dose-effects relations for all facial bones. **Chapter 6** evaluated the possibility of limiting radiation dose for embryonal orbital rhabdomyosarcoma as limiting the dose, in general, would automatically reduce the dose to organs at risk. **Part IV** (**Chapters 7-9**) centres on a local treatment option for head and neck rhabdomyosarcoma – the AMORE treatment. **Chapter 7** describes AMORE for primary head and neck rhabdomyosarcoma and the surgical techniques. **Chapter 8** evaluates AMORE as a salvage treatment for patients with relapsed head and neck rhabdomyosarcoma. **Chapter 9** evaluates the ability of surgeons to predict both facial function and deformation.

Each aforementioned part of this dissertation will be examined in this general discussion, starting with the trans-Atlantic multicenter study on late adverse effects, followed by the dose-effect analysis, and finally, surgery for head and neck rhabdomyosarcoma.

TRANS-ATLANTIC MULTICENTER STUDY ON LATE ADVERSE EFFECTS FOLLOWING TREATMENT FOR HEAD AND NECK RHABDOMYOSARCOMA

Late adverse effects

In **Chapter 1**, a multidisciplinary group of physicians systematically evaluated the late adverse effects following local treatment for head-neck rhabdomyosarcoma using a preset list. This was done in four large paediatric oncology centers and included patients treated with all four different local treatment options: XRT, PT, AMORE, and the Paris method. Late adverse effects were highly prevalent and diverse; over 80% of survivors suffered from at least one grade 2 adverse effect, and over 60% of patients suffered from a grade 3 late adverse effect. Facial deformation, cataracts, hearing impairment and speech abnormalities were the most common grade 2 adverse effects. When looking at the four different local treatment options, there is a difference between the treatment modalities in adverse effects both in terms of grade and type; however, this was not statistically proven, possibly due to the relatively small patient numbers. Potential differences between treatment modalities were discerned to guide future patient care and aid in informed decision-making between the different local treatment options (**Supplemental Table 4** of **Chapter 1)**. In general, the adverse effects found in this study are comparable to those observed in other studies. However, making a direct comparison to other existing literature is complicated as the study design, methods of data collection, and selection of adverse effects differ. No other studies systematically and uniformly investigated late adverse effects in different hospitals for four different treatment modalities. Furthermore, differences in follow-up time and patient selection further contribute to the complexity of comparison between studies (1-5). It can be concluded that late adverse effects for head and neck rhabdomyosarcoma are highly prevalent and vary widely. Even though there is a difference between the late adverse effects of the different treatment modalities, this was not significantly proven.

Facial deformation, asymmetry and growth

Chapter 2, which also reports results from the multi-centre study, investigates facial deformation in more detail in a large group of head and neck rhabdomyosarcoma survivors (n=173) using an objective measurement method, 3D stereophotogrammetry. Reduced facial growth, facial deformation, and facial asymmetry were examined. All treatment modalities, except for the Paris method, caused more facial deformation in patients treated at a younger age. Patients were partitioned into different groups (based on age and tumour site) to discover patient groups more at risk and find the optimal treatment for each subgroup of patients.

Orbital site
Survivors with orbital tumours demonstrated better facial growth than those with parameningeal and non-parameningeal tumours. AMORE and XRT were compared as local treatment options, showing no significant difference in facial asymmetry. However, when looking at facial deformation (considering midfacial hypoplasia and growth deformation), AMORE caused significantly less deformation than XRT.

Non-parameningeal site
In survivors with a non-parameningeal head and neck rhabdomyosarcoma, only AMORE and XRT could be compared, as these were the only groups with sufficient patient numbers. There was no significant difference in facial asymmetry or deformation between the two treatment modalities. However, when partitioning for treatment age, an age-related treatment effect was seen, indicating a lower risk of deformation for very young patients treated with AMORE and a lower risk of facial deformation for patients over 6 years of age when treated with XRT.

Parameningeal site
Among survivors with a parameningeal rhabdomyosarcoma, PT was significantly favourable over XRT and the Paris method in terms of asymmetry and facial deformation. There was no statistically significant difference between PT and the AMORE method, nor did AMORE show statistically significant benefits compared to XRT and the Paris method in terms of facial deformation. There was no difference between survivors treated with the Paris method or XRT in relation to overall facial deformation. However, patients treated with PT showed less disruption in facial growth compared to the other three treatment modalities. Survivors treated with the Paris method showed significantly more facial asymmetry than those treated with all other methods.

The overall findings are visually presented in **Figure 1**, providing a graphical representation to guide shared decision-making, particularly in cases where facial deformation is the only expected difference in terms of late adverse effects.

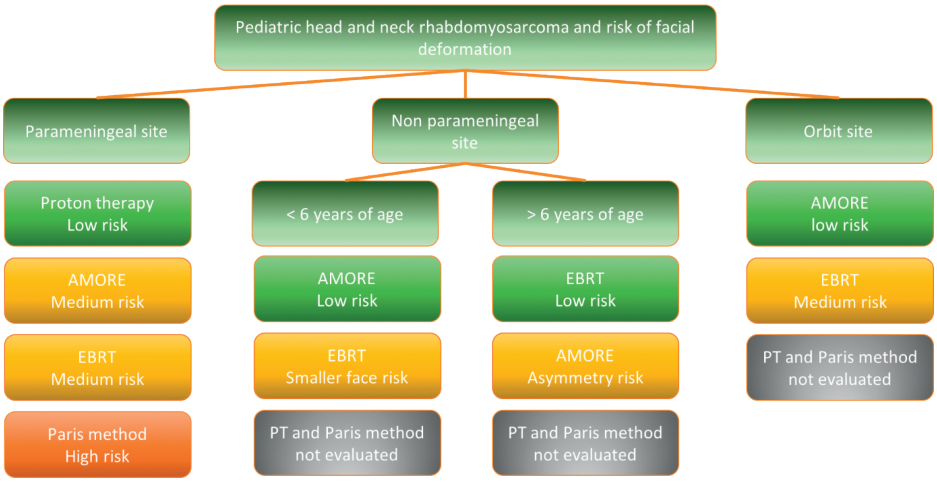


Figure 1. Paediatric head and neck rhabdomyosarcoma risk of facial deformation based on treatment modality.

AMORE: Ablative surgery, MOulage technique with afterloading brachytherapy, REconstructive surgery, EBRT: External Beam RadioTherapy (with photons), in this case, all sorts combined, conventional IMRT, VMAT). The Paris method consists of surgery and postoperative radiotherapy with photons or protons. PT: Proton therapy.

Patient-reported outcomes

Chapter 3 investigated patient-reported outcomes using the FACE-Q craniofacial module, as it is the only patient-reported outcome measurement designed specifically to record appreciation of appearance and facial function. Most survivors reported negatively concerning appearance, health-related quality of life, and facial function, although scores varied widely between survivors. Eighty-three per cent of survivors reported negatively on appearance scales, 82% reported negatively on health-related quality of life items and 38% reported negatively on facial function. Survivors with speech abnormalities, oral malfunction and facial nerve paresis scored significantly lower on appearance, health-related quality of life and facial function.

In previous studies of health-related quality of life in childhood cancer survivors, emotional health was scored worse by females in comparison to males (1,2). However, we did not observe this in our study, possibly due to using a more specific questionnaire. Younger survivors (between 8 and 12 years at the time of the questionnaire) who had a shorter follow-up time (<10 years) scored higher on the appearance and quality of life scales than older survivors with longer follow-ups. This finding is similar to the results observed in large cohorts of patients with cleft lips and palates scored on the CLEFT-Q scales (3). The observed age and follow-up time effect might be explained by the varying importance of appearance during

different life phases. Interestingly, clinically relevant late adverse effects, as scored by our physicians in **Chapter 1**, only weakly correlated with the majority of disease-specific patient-reported outcomes. This underlines the need to obtain survivors' perspectives during follow-up clinics and use patient-reported outcome measures. The fact that patient-reported outcomes and physician-reported outcomes do not always align has been described in previous studies, mostly in adults, and consequently, the CTCAE has recently developed a "patient language" version to complement the CTCAE scoring system (4,5).

DOSE EFFECT ANALYSIS

Orbital morphology

Chapter 4 quantified orbital asymmetry, characterising the dose effect on irradiated orbital bones. Orbital volume was measured by MRI, and the dose was calculated for the maxillary, frontal, and zygomatic bones, as well as the composite orbital rim. The main finding in this study was that limiting the maximum dose to the combined orbital rim bones may reduce orbital asymmetry. Consequently, regardless of treatment modality, it is advisable to delineate the orbital rim as an organ at risk and to reduce the dose to a maximum of 40 GyRBE. Interestingly, the composite orbital rim dose had more influence on orbital asymmetry than a high dose to one of the individual orbital socket bones. At the time of writing, no known studies examined orbital volume and dose effects. While some studies suggest that the entire orbit should be delineated as an organ at risk and the dose should be limited, they do not provide threshold doses for bony structures (6). There are some limitations to this study. The main drawback was the relatively small sample size of 17 children, with a relatively short follow-up period of a median of 2.9 years. This short follow-up may result in an underestimation of growth deformation, as most included survivors had not yet undergone their growth spurts, with a median age at MRI of 8.4 years (range 2.3-12.9 years). Nevertheless, using these proposed dose constraints may reduce facial asymmetry; consequently, it is advised to include the orbital bones as an organ at risk.

Facial bones and dose-effect analysis

Chapter 5 used the 3D stereophotogrammetry and facial deformation analyses from **Chapter 2** to identify dose thresholds for craniofacial bones. All individual facial bones and sutures were delineated on the original radiotherapy treatment planning scans. In general, survivors with considerable facial deformation received significantly higher doses to bony structures than those with less facial deformation. On examining the main facial complexes, the ethmoid-maxillary complex showed increased facial deformation when irradiated above 28 GyEQD2, and the mandibular complex showed increased growth deformation probability above a dose of 26

GyEQD2. Furthermore, we investigated dose thresholds for all individual facial bones and found varied dose thresholds ranging between 26 GyEQD2 and 43 GyEQD2, with the zygoma, nasal bone and sutures more susceptible than the maxilla, pterygoid and nasal septum potentially owing to the different maturing stages at treatment age. These findings suggest that limiting the mean dose to specific facial areas and even specific facial bones might mitigate or, at the very least, reduce the severity and prevalence of facial deformation. Defining dose constraints for bones in the developing head and neck area is difficult as many factors influence bone growth and development, such as attained age, chemotherapy, pubertal status, and general differences in bone maturation. Ideally, the dose thresholds found in this study should be further validated in large cohorts of patients. However, with no dose constraints currently available for facial bones, it would be advisable to use the presented dose constraints. Even though the presented constraints are validated in a relatively small cohort of patients, they can potentially limit facial deformation. The recommended dose thresholds based on the data in **Chapters 4** and **5** are presented in **Table 1**.

Table 1. Suggested dose constraints for facial bones and structures

Organ at risk	Dose threshold for increased risk of facial deformation	Dose threshold with a 50% probability of facial deformation
Ethmoid-maxillary complex	28 GyEQD2	51 GyEQD2
Mandibular complex	26 GyEQD2	41 GyEQD2
Maxilla	40 GyEQD2	51 GyEQD2
Zygoma	28 GyEQD2	44 GyEQD2
Pterygoid plates	37 GyEQD2	50 GyEQD2
Spheno-zygomatic suture	26 GyEQD2	48 GyEQD2
Zygomatic-maxillary suture	19 GyEQD2	44 GyEQD2
Nasal Septum	37 GyEQD2	55 GyEQD2
Nasal Bone	28 GyEQD2	47 GyEQD2
Vomer	39 GyEQD2	51 GyEQD2
Orbital rim	40 GyRBE	

* Orbital rim bone dose constraint results from Chapter 4 (7). The other dose constraints are all adapted from Chapter 5 (currently under review at Green Journal).

Limiting dose for group III embryonal orbital rhabdomyosarcoma

In **Chapter 6**, The University of Florida evaluated the use of 45 GyRBE for embryonal group III orbital rhabdomyosarcoma as there was concern about the (unacceptable) high local recurrence rates in patients treated with relatively low radiation dosages.

Thirty patients were treated with 45 GyRBE for embryonal group III orbital rhabdomyosarcoma, which proved an effective radiotherapy approach with a 5-year local control rate of 97%. This reduced dose showed a reduction in intermediate and short-term adverse effects and potentially mitigated long-term toxicity. It would be valuable to validate this treatment dose reduction in a larger cohort of patients as it would represent a significant step in reducing late adverse effects.

SURGERY FOR HEAD AND NECK RHABDOMYOSARCOMA

AMORE as the primary local treatment

Chapter 7 gives an update on AMORE over the past 25 years, outlining the technique, the decision-making process, overall survival, and event-free survival. The surgical interventions and reconstructive techniques used are described for each included patient. In total, 35 patients underwent AMORE treatment for a primary non-orbital head and neck rhabdomyosarcoma. AMORE feasibility is discussed in a multidisciplinary team meeting for each individual patient, considering pre-treatment imaging and imaging after three cycles of chemotherapy. Furthermore, clinical findings such as nerve deficits and other co-morbidities are taken into account. Overall, throughout these 25 years, the selection criteria for AMORE have become more stringent in primary head and neck patients, excluding patients with intracranial extension, carotid encasement, and perineural spread. A neck dissection was performed in 19 out of 35 patients, finding N1 disease in only one. In 26 out of 35 patients, reconstruction was performed using a pedicled or free flap as part of the reconstruction element of the AMORE treatment, showing no important complications. Both event-free and overall survival are similar to other local treatment options. As survivors treated with AMORE show reduced facial deformation compared to young patients treated with XRT for non-parameningeal tumours, as shown in **Chapter 2** and in **Figure 1** of this discussion, AMORE should be considered more often as a local treatment option in these patients.

AMORE as salvage treatment

Chapter 8 discusses AMORE as a salvage treatment option in a unique cohort of patients. AMORE, as a salvage treatment, is quite often the only remaining potentially curative option in cases of relapsed local disease. When AMORE was performed as salvage treatment (for the complete group of relapsed patients, including orbital and non-parameningeal sites and parameningeal cases), the 5-year overall survival was 54%. As discussed previously, each patient is discussed in a multidisciplinary team meeting to determine the feasibility of AMORE. In the case of salvage treatment, more extensive and consequently potentially more disfiguring or harming surgery is considered, as there are often no other treatment options. For example, in the described cohort, an orbital exenteration was deemed acceptable

in a patient with relapsed orbital rhabdomyosarcoma who had previously been radiated with external beam radiotherapy using photons. Additionally, as part of the AMORE treatment, some healthy tissue is re-irradiated. In general, re-irradiation was well tolerated by all patients; however, severe late adverse effects were seen in this patient group. Most patients had at least grade 2-3 musculoskeletal deformation, and all patients suffered from growth hormone deficiency and needed supplements. Furthermore, trismus, xerostomia and hearing loss were recorded as late adverse effects. One patient developed secondary generalised seizures 13 years post salvage treatment, potentially caused by radiation necrosis of the frontal lobe. Surgeons are often hesitant to perform surgery in a previously irradiated field. However, both the resection and reconstructive surgery demonstrated no major complications, such as free flap failures or wound healing issues. In conclusion, AMORE should be considered more often in patients with relapsed head and neck sarcoma as it has been proven to be a safe treatment option, potentially offering increased survival.

Predicting aesthetic and functional outcome

The initial title of this chapter was 'Does the surgeon know it all?' A significant aspect of deciding between treatment options and, potentially more importantly, deciding on the AMORE treatment is based on a) the debate on whether or not AMORE is feasible, b) what kind of late adverse effects may be expected, and c) the potential complications of surgery. In **Chapter 9**, six experienced sarcoma surgeons predicted facial and esthetical outcomes according to the CTCAE criteria for nine patients with head and neck rhabdomyosarcoma based on imaging and patient history. This study showed that predicting facial deformation and scar development following tumour resection surgery proved extremely difficult, even for extremely experienced surgeons in this field. Nevertheless, surgeons, possibly due to the anatomical consistency of nerves and the accuracy of tumours on imaging, predicted the likelihood of nerve sacrifice very reliably. This study also proves the need for a reliable prediction model for facial deformation, for which the backbone was presented in **Chapter 2** and a decision graph is presented in **Figure 1** of this chapter.

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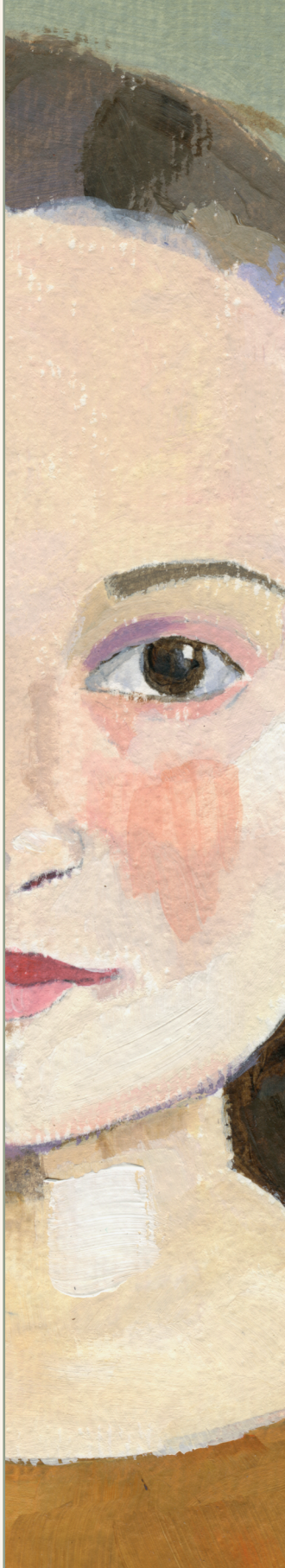
Future perspectives



FUTURE RESEARCH

Several plans and ideas for future research come to mind after gaining insights into head and neck rhabdomyosarcoma treatment and its late effects. Caring for these patients while collaborating with an incredible amount of dedicated, specialised, and extremely goal-driven physicians and physicists has been a great experience. However, the most impactful aspect has been the interaction with children, young adults and adult survivors at different outpatient clinics, talking to them and learning about their difficulties and the burden of their late adverse effects. Future research should focus on improving care and follow-up care for these patients and survivors. Ultimately, limiting facial deformation by deciding on the ideal local treatment modality and limiting the dose to facial bones is critical, and solutions for this are presented in this dissertation. To further improve these efforts, a general overview of plans and ideas is represented across four domains: late effects and, more specifically, facial deformation, and local treatment options divided into surgery and radiotherapy. These ideas for future research are shown in a mind map at the end of this chapter.

LATE ADVERSE EFFECT STUDIES

The trans-Atlantic multicentre study

The first part of this dissertation reported the extent and diversity of late adverse effects generally found in rhabdomyosarcoma survivors treated by one of the four local treatment modalities. Furthermore, it presented a detailed report on facial deformation, linking it to radiation dosage. Lastly, patient-reported outcomes in terms of appearance, health-related quality of life and facial function were reported. However, this multicentre study set out to collect data on more late adverse effects than those presented in this dissertation. **Figure 1** shows the graph of the multicentre study schematic and the included late adverse effects. As shown in this graph, we will report on the following additional late adverse effects: dental development, pituitary dysfunction, speech impairment, and ocular impairment. Furthermore, dose-effect models will be explored for each of these late adverse effects, as was done for facial deformation.

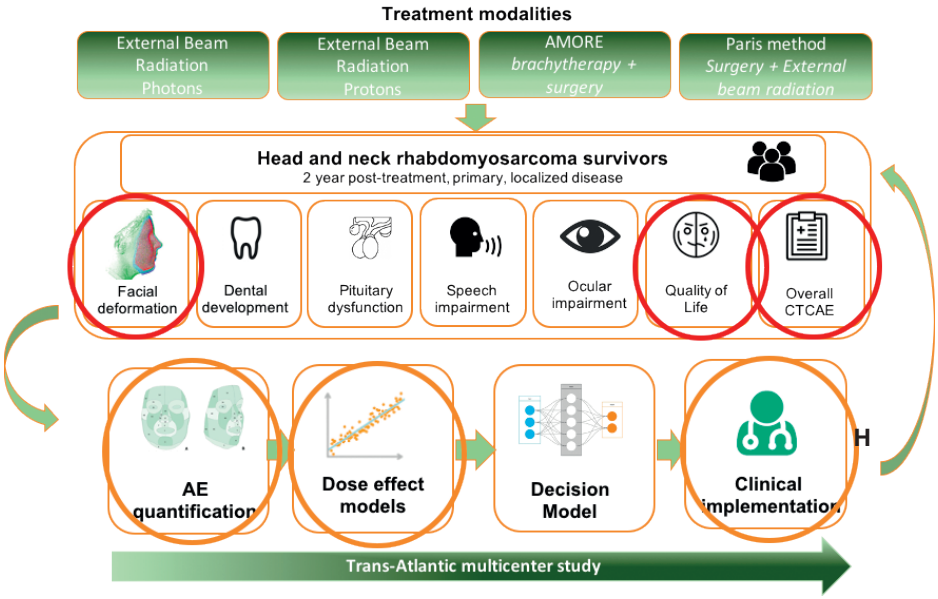


Figure 1. Schematic of the research project of the multicentre study.

Data inclusion has been finalised for all seven topics of this multicentre study. Red in Figure 1 indicates that the project is finalised, and this dissertation presents the data. Orange circles indicate that the project is finished for the late adverse effects circled in red above; further quantification and modelling will follow for the other late adverse effects. AMORE: Ablative surgery, MOld technique with after-loading brachytherapy, REconstructive surgery. AE: adverse effects. CTCAE: Common Terminology Criteria for Adverse Events
* Adapted from our KIKA grant application (grant number 297).

Decision model

Ultimately, the dose-effect models and the information on different late adverse effects in relation to treatment modality will be integrated into a decision model, providing physicians with improved guidance for treatment planning. This decision model, based not only on facial deformation but on all the included late adverse effects in this study – including endocrine dysfunction, ocular dysfunction, speech impairment, dental development and quality of life – ultimately aims to facilitate optimal local treatment selection for each individual patient. Ideally, the decision model should take all patient and tumour characteristics into account, enabling shared decision-making and improved information on expected late adverse effects for treating physicians, as well as for parents and patients.

As presented in the discussion chapter of this dissertation and the research throughout the work, the number of included patients is insufficient when patients are further subdivided into different subgroups. The data from this study will lay

a foundation to build a decision model. Adding more data to this decision model, including enriching new prospectively collected patient cohorts treated with different local treatment options, would enhance the model's adaptability and applicability. Currently, the decision for local treatment is made in a multidisciplinary team consultation where late adverse effects are often the only expected difference between treatment options. These expected late adverse effects are based on the experience of physicians and the techniques they have used before or those available to them. A model that presents the expected late adverse effects for all four available local treatment regimens for each individual patient would significantly aid in treatment decision-making. Moreover, such a model would enable physicians to better counsel patients and their parents on the expected late adverse effects.

Future late effect studies

This dissertation's late adverse effect studies have shown the prevalence and extent of late adverse effects following the treatment of paediatric head and neck rhabdomyosarcoma. These studies demonstrate the need for late adverse effect clinics and systematic patient follow-up. It is crucial to construct a solid research framework to collect data on late adverse effects, the latency of appearance, and the diversity of the development of adverse effects prospectively. When these data are combined with the treatment data, the information could be integrated into the previously proposed decision model to strengthen it and make it more robust. Since rhabdomyosarcoma is a rare disease, determining the least harmful treatment for each individual child with head and neck rhabdomyosarcoma based on patient and tumour characteristics requires collaboration.

Even though many centres currently have some form of late adverse effect clinic, a more uniform and structured follow-up clinic would not only provide survivors with the best care but also generate data that can be shared and pooled for further research endeavours. When such late adverse effect clinics take place, it is important to note that all late effects should be scored uniformly between the different centres. Furthermore, following these patients prospectively would give great insight into the delay of development and manner of development of late adverse effects. For example, gaining insight into how facial deformation develops could be achieved by obtaining 3D images of survivors every 2 years post-treatment until adulthood. This approach would generate valuable information on growth in general and on the development of facial deformation.

Some patients in the multicentre study had late adverse effects and complications that fell outside the scope of our research clinic. If new late adverse effects clinics were to start, it would be advisable to include free flap donor site morbidity, which might be extremely important in patients who underwent local treatment, including some form of surgery. Hearing loss was not included in the current research project.

However, we know that radiation to the head and neck area is an independent risk factor for the development of hearing loss. Furthermore, these survivors appear to develop a specific kind of conductive hearing loss, which might be a focus for further research (1,2).

The FACE-Q questionnaire was used in the study to evaluate patient-reported outcomes. In future studies, it is recommended to continue using this questionnaire as it is specific for head and neck patients, addressing not only emotional well-being but also taking into account facial function (3,4). Additionally, our current late adverse effect study used 3D stereophotogrammetry to quantify facial deformation. Ideally, facial deformation would be quantified not only based on the surface (e.g., a 3D image) but also on information on the underlying tissue such as muscle, fat and bone. For example, adding MRI or CT data to the dataset would provide information on actual bony and soft tissue development, allowing for a more precise understanding of affected structures.

A multi-national uniform late adverse effect clinic for head and neck sarcoma

A uniform late adverse effect clinic would fill an important gap in post-treatment care. A collaboration between large international treatment centres is needed to investigate further the development and extent of late adverse effects, identify at-risk patients, and further strengthen the model, which will aid shared decision-making for parents and physicians. A dedicated late adverse effect clinic would be needed in all participating centres for such a multicentre study. Practically, this would mean a uniform outpatient clinic run in all different treatment centres, prospectively seeing all patients treated for head and neck rhabdomyosarcoma. The key late adverse effects to focus on would be musculoskeletal deformation, adverse dental effects, late adverse ophthalmology effects, hearing impairment, hormonal deficiencies and general late adverse effects. Ideally, all patients would be seen post-treatment, at regular intervals, until adulthood. Patients with a very high risk profile may be seen on a yearly basis, where patients with very low risk may be followed less intensively.

Based on the late adverse effects presented throughout this dissertation, this would entail multidisciplinary outpatient clinics including, at the bare minimum, a radiation oncologist, paediatrician/medical oncologist, ENT-surgeon/head and neck surgeon, a surgeon performing reconstructive surgery in the head and neck area (either a plastic surgeon or head and neck surgeon), a dentist and an ophthalmologist. Patients should be seen bi-yearly by the entire team until adulthood; seeing patients only up to 18 years of age would be insufficient as many late adverse effects only present later in life. Therefore, we would see patients up to 30 years

of age systematically and after that when the patient wishes to visit the clinic or in case of ongoing medical issues.

In order to correlate late adverse effects to the radiotherapy dosage treatment plan and surgery data, all original treatment data needs to be available. As the study presented in **Chapter 5** showed, gathering these data is one of the main issues when studying late adverse effects. The radiotherapy data is currently prospectively collected for radiotherapy quality assurance (RTQA) for all randomised patients enrolled in the new FaR-RMS study. Currently, these data are being stored in QUARTET. Quartet is an acronym for Quality and Excellence in Radiotherapy and Imaging for Children and Adolescents with Cancer across Europe in Clinical Trials. QUARTET is a quality assurance tool for radiotherapy and aims to deliver high-quality radiotherapy for children treated in clinical trials. The FaR-RMS study uses the QUARTET database and prospective quality insurance for the patients randomised in the study but also allows for quality assurance and, more importantly for us, storage of treatment plans. Furthermore, follow-up imaging of all patients will be stored in the database, including imaging up to 5 years post-treatment. The surgery reports and data on pathology are also stored for the FaR-RMS study, enabling us to use all treatment data for this patient group. Using these treatment data and the prospectively collected late adverse effects would be of tremendous value in building a decision model for local treatment options.

In conclusion, this will mean setting up an international multidisciplinary head and neck late adverse effect clinic uniformly carried out in all participating treatment centres. Therefore, our efforts will go into setting up such an international study. For it to work, many facets need to be arranged: prospective, remote, data collection in a central database (potentially linked to the database currently used for the FaR-RMS study), contracts with all collaborative sites, and consequently, the (data) management of such a study and the accompanying budget and grant applications.

Concluding, such a multinational uniform late adverse effect clinic would aid in two important goals; first of all improve care for survivors of head and neck rhabdomyosarcoma and secondly put data into the described decision model and enrich it with further data ultimately providing a decision model based on all late adverse effects that incorporates all patient and tumour characteristics.

FACIAL DEFORMATION

Using imaging techniques such as MRI or CT to determine the underlying cause of facial deformation would be of added benefit. When fusing the MRI, CT, or both with the 3D stereophotogrammetry information, the underlying pathology – whether

bony or soft tissue developmental issues behind facial deformation- could be further identified. As discussed in the aforementioned outpatient clinic proposal, imaging of patients up to 5 years post-treatment is currently collected. It would also be of great value to have imaging of patients when reaching adulthood, or at the very minimum, post their growth spurt. Some studies look at facial asymmetry and the accompanying MRI imaging; however, these studies lack information on the eventual, clinically important facial deformation. Linking all the information, the treatment plans, the follow-up imaging, and the 3D stereophotogrammetry together would enable a clear understanding of the underlying pathophysiology of the facial deformation seen in this group of survivors.

For the decision model described in this dissertation, when the risk of facial deformation is calculated, a model that creates a morph of what the patient would look like following treatment would be of great interest to provide insight to physicians, parents and patients. While models are available to morph the effect of plastic surgery, creating a model that adequately morphs specific facial deformation in patients treated with surgery, radiotherapy, or a combination of both is not yet available. Many studies describe the growth of the human face; however, a clear overview of facial deformation development is not available. Conducting such a growth analysis and gaining a pathophysiologic understanding would benefit further studies into growth deformation.

It would be interesting to explore whether specific patients are more prone to facial growth and developmental issues. Specific genes have been identified in craniofacial developmental diseases (such as craniosynostosis), and some studies investigating craniofacial growth and development in mouse models have identified specific genes that drive cranial base development. It would be worthwhile to determine whether these genes play a role in the craniofacial abnormalities observed in patients treated with radiotherapy and surgery in the head and neck area. Similar to chemotherapy susceptibility, some patients may be more prone to developing facial deformation than others. Such genes have been identified in other late adverse effects, such as cardiomyopathy (5).

Much of this dissertation revolves around radiotherapy. One reason is that many of the late adverse effects found in our studies are attributed to radiotherapy. However, the exact extent and severity of surgery alone in the developing head and neck area have not been investigated in terms of growth. Therefore, it would be interesting for future studies to predict the amount of facial deformation resulting from the resection of (part of) a bone or muscle and its impact on facial development. As shown in **Chapter 9**, even experienced surgeons could not accurately predict the amount of facial deformation following surgery at a young age. Consequently, a prediction model or a model to demonstrate the effects of certain procedures would

be of great benefit. Furthermore, the effect of chemotherapy alone on facial bone growth has not been studied either. It is believed that chemotherapy exacerbates normal tissue reactions, and consequently, the dose constraints found in this study might be relatively low when applied to patients receiving only radiotherapy and no chemotherapy. All individual parts of multimodality treatment should be investigated separately, examining the contributing effects of each: chemotherapy, surgery and radiotherapy, to investigate the true effects of local treatment on facial development. This information could be gathered from other paediatric cancer survivor groups, for example, children receiving total body irradiation, survivors of central nervous system malignancies, and patients treated with chemotherapy alone.

These current studies focus on the quantification of facial deformation and facial asymmetry. However, the burden of facial deformity is rarely considered in research. **Chapter 3** showed that there is only a mild correlation between patient-rated late adverse effects and patient-reported outcomes in terms of clinical symptoms such as skin problems and other late effects. It would be interesting to report the correlation between objective facial deformation and the patient burden. Having such data would guide physicians in the future in terms of counselling patients, as well as when opting to offer late adverse effect clinics and consultations with head and neck surgeons and plastic surgeons to counsel patients on potential reconstructive surgery.

RADIOTHERAPY

SMILE

In 2021, the idea of a collaborative research group focusing on dentofacial sequelae in children following treatment with radiotherapy to the head and neck region resulted in the 'SMILE' project. SMILE is an acronym for 'Minimising long-terM Impact on dentition and faciaL asymmEtry in childhood cancer survivors.' This collaborative project consists of paediatric oncologists, clinical oncologists, radiation oncologists, surgeons, dentists, radiotherapy physicists and radiologists from many different centres and is embedded in the SIOPe radiotherapy working group. The first meeting was held in March 2023, where several joint research projects were discussed. **Chapters 4 and 5** of this dissertation propose dose-effect relations for facial bones and the orbital rim. As a result of these two studies, the suggestion is to delineate all the facial bones as standard practice and consequently reduce the dose to these specific structures in accordance with the presented dose thresholds. As a project from the SMILE working group, a digital survey with questions on clinical practice was distributed to participants (part of SIOPe) across Europe, Australia and New Zealand. There were 52 responses from 27 different countries. Only 29 out

of the 52 respondents routinely delineated facial structures. The most commonly delineated facial bones were the mandible, temporomandibular joint, orbit and maxilla. An 'as low as reasonably achievable' dose constraint was used for most contoured bones. Very few centres used specific dose constraints, such as for the mandible (60-72Gy) and the temporomandibular joint (50-60Gy). Despite it not being clinical practice for most centres, most participants agreed that delineating facial bones would be beneficial. Ninety-four per cent of participants said the largest barrier to clinical implementation was the lack of contouring evidence. Furthermore, 90% of the respondents said they would routinely contour dentofacial structures if a delineation atlas were available (6). The results of this survey drove several projects. First, work is underway on a delineation atlas for facial bones. Furthermore, efforts are being made to explore the success of auto-contouring for facial structures in children. Efforts are also ongoing within the SMILE working group to re-examine patients previously treated with both photon and proton plans to explore whether reducing or sparing the dentofacial structures, working with the presented dose constraints, is possible. In addition, we set out to develop a dictionary to uniformly report late adverse effects in the head and neck area. The setup of the aforementioned multicenter study will be in close collaboration with the SMILE working group.

Dose-effect models

Many studies aim to investigate threshold doses and dose-effect relations for paediatric patients. As described in the introduction, PENTEC gives advice on organising these studies and evaluating dose-effect relationships (7). The current study only considered the radiotherapy dose without taking the treated volume into account. Future studies should consider treatment volume, as this might make a difference for threshold doses, especially for the larger facial bones.

SURGERY

Primary tumour surgery

The role of delayed primary excision or surgical resection should be investigated further. A retrospective study investigating the charts of 97 patients with non-orbital rhabdomyosarcoma indicated the possibility for complete surgical resection in embryonal rhabdomyosarcoma cases, as it might allow for the omission of radiation therapy in such instances. However, only 11% of patients in the study who had surgery could avoid radiotherapy. Although this study only included a relatively small cohort of selected patients, complete surgical resection should be considered more extensively for all patients, as the previous study showed increased 5-year survival in children who underwent surgery (8). A study by the Parisian group, utilising surgery in patients with infratemporal fossa and pterygoid palatine fossa

tumours, showed improved 5-year event-free and overall survival in comparison to other datasets of alveolar rhabdomyosarcoma. However, the cost of improved survival for this cohort is adding extensive surgery to the radiotherapy treatment.

Fluorescence-guided surgery, which has demonstrated promising results in hepatobiliary cancers, could be used in solid paediatric tumours, including those in the head and neck area. Fluorescence-guided surgery could be further enhanced by developing targeted fluorescence tracers binding to tumour-specific receptors. However, few receptors have been identified for rhabdomyosarcoma. Receptors like B7-H3 and TEM1 show less promise, while CD56, IGF-1R and VEGF-A remain of interest for further research. Fluorescence-guided surgery could be used to explore the feasibility of more IRS Group 1 and Group 2a resections (R0/R1), which could help optimise the AMORE method presented in **Chapter 7**. That chapter illustrated the primary AMORE surgeries performed and the more stringent contra-indications adopted over the past 25 years. However, potential improvements in terms of the surgery itself have yet to be examined.

The possibility of international referral for head and neck rhabdomyosarcoma patients should be considered more often to enable each patient to receive the ideal local treatment modality, limiting late adverse effects, specifically craniofacial deformation. Alternatively, more centres should start performing AMORE treatment, although this should be limited to a few specialised centres. Several factors need to be taken into account when considering the implementation of AMORE. A learning curve is to be expected for both the radiation oncologist and surgeons when gaining experience with the AMORE technique. Furthermore, being able to decide on AMORE feasibility requires many, sometimes subjective, hypotheses and considerations that largely rely on extensive clinical experience. Moreover, AMORE treatment requires meticulous planning, given that the entire treatment should be performed within one week, requiring the entire team's availability. All equipment and hospital infrastructure should be in place before bringing AMORE treatment to a new centre.

Neck dissection

Neck dissections were performed as part of the AMORE treatment in 19 out of the 35 cases, and only one patient showed evidence of disease (pN1). There was no significant difference in event-free survival or overall survival between patients who underwent a neck dissection and those who did not. The Paris group has published a paper on their overall cohort of patients with infratemporal fossa and pterygopalatine fossa tumours. In that cohort of patients, 13 cervical lymph node dissections were performed, seven being elective and six showing evidence of N1 disease. None of the patients with elective neck dissections showed evidence of disease (pN0). Four of the six patients with an N1 neck had pathology confirmation

of pN1 disease. The 5-year overall survival and event-free survival in patients who underwent neck dissections was 92%, compared to 73% and 56%, respectively, for those without a neck dissection. Drawing definitive conclusions based on these relatively small cohort studies regarding the evidence and rationale for performing a neck dissection is difficult. However, one could argue that when the alternative is to irradiate the neck (electively), the burden of a neck dissection might be less than the burden of irradiating (half) a neck in a developing and growing child, especially when a child is receiving surgery anyway. It would be of interest to investigate how often a neck is irradiated electively and compare the treatment burden, including late effects, with cases in which an (elective) neck dissection was performed.

Sentinel Node

N1 disease is now better identified (9) with the improvement of [F-18]2-fluoro-2-deoxyglucose (FDG) positron emission tomography (PET)/CT, especially when combined with MRI (PET/MRI) for evaluating loco-regional lymph nodes. Pathology confirmation is needed when potential positive nodes are present on imaging. Furthermore, new advancements are being made with the development of different imaging techniques, such as using fibroblast activation protein inhibitor (FAPI) in combination with FDG-PET or, in the future, with FAPI-PET (10). Sentinel node procedures will be valuable in the decision to treat the neck electively in cases where there might be loco-regional spread. Developments are being made in sentinel node identification within oncologic surgery to guide risk stratification and treatment further. For example, sentinel node identification is used successfully in adult head and neck cancer. Sentinel node procedures are already standard care in breast, dermatologic, and gynaecological cancers. For rhabdomyosarcoma, lymph node sampling is advised in tumours located in the extremities but not yet for head and neck tumours. For rhabdomyosarcoma, indocyanine green (ICG) has shown promising results in a small sample of patients and needs further validation in a larger group, including head and neck rhabdomyosarcoma patients.

Reconstructive surgery

Facial deformation emerges as the most common and debilitating late adverse effect throughout this dissertation. For example, the Children's Oncology Group recommends yearly consultations with a head and neck surgeon (11). However, the impact and possibilities of such consultations are currently limited, as many surgeons are hesitant to perform reconstructive surgery in a previously irradiated, and in some cases previously operated, area as they fear worse wound healing, diminished bone formation and overall reduced tissue quality in general. This makes facial deformation even more serious as a late adverse effect, as very little can be offered to patients for improvement.

Together with the head and neck surgery group from E*p*SSG, we aim to collect all patients who have undergone reconstruction. Some patients who underwent reconstructive surgery for facial deformation following radiotherapy in the head and neck area were identified through the multidisciplinary late adverse effect clinic presented in this dissertation, but also from our own outpatient clinics and other late effect clinics. We aim to combine all these individual cases and present an update on methods applied for reconstruction and the success and complication rates. Whilst the data collected will be anecdotal and limited to descriptive analysis, it could give insight into the procedures performed and actual complication risks. The fear of operating in a radiated head and neck area might stem from a time when radiation was administered with large treatment fields and from an era in which supportive techniques (such as hyperbaric oxygen) were not available. This investigation will explore the use of larger (free flap) reconstructions, as well as minimally invasive surgery, such as lipofilling.

Lipofilling, a technique that is used relatively little in head and neck cancer survivors, has shown promising results. In our cohort of Dutch AMORE patients, we have attempted lipofilling in about ten survivors with considerable success. Lipofilling is also used frequently by the Paris group following treatment when patients reach adulthood. An example of a patient treated with lipofilling is shown in **Figure 2**. As lipofilling is a minimally invasive procedure carrying little risk, it could be offered more frequently to survivors. Depending on the results of our exploratory investigation, it might be valid to start performing more reconstructions in children with severe debilitating facial deformation. Various forms of reconstructions are offered to patients with facial deformation resulting from congenital facial abnormalities or trauma, and esthetically, if the effects of previous treatments on the tissue were deemed minimal, this might be offered more often to our survivor population. Another option in the future might be to use bioprinted materials to avoid performing large surgeries, including harvesting donor materials from the patient.

Figure 2. Female patient treated with three rounds of lipofilling following treatment for head and neck rhabdomyosarcoma of the right infratemporal fossa with surgery and radiotherapy at the age of 10 years of age.

In image A-D, the patient is 8 years post-treatment and has not had reconstructive surgery yet. In image E-G, the same patient is shown after three rounds of lipofilling. As presented, the contour of the defect is less visible. The midface and mandibular angle are more symmetrically filled.
* Images courtesy of Doctor Frederic Kolb.

CONCLUSION

This chapter presents many ideas for future research, split into four domains: late adverse effects, facial deformation, radiotherapy, and surgery. The main key for future research is that it should be done through collaborative networks. The results presented in this dissertation and their conclusions would not have been possible if we had not worked with four large paediatric hospitals. Future research should be within collaborative networks, potentially trans-Atlantic, as head and neck rhabdomyosarcoma is a rare disease, and large datasets of patients are needed to work on any ideas. An overview of the presented research ideas is presented as a mind map in **Figure 3** at the end of this chapter.

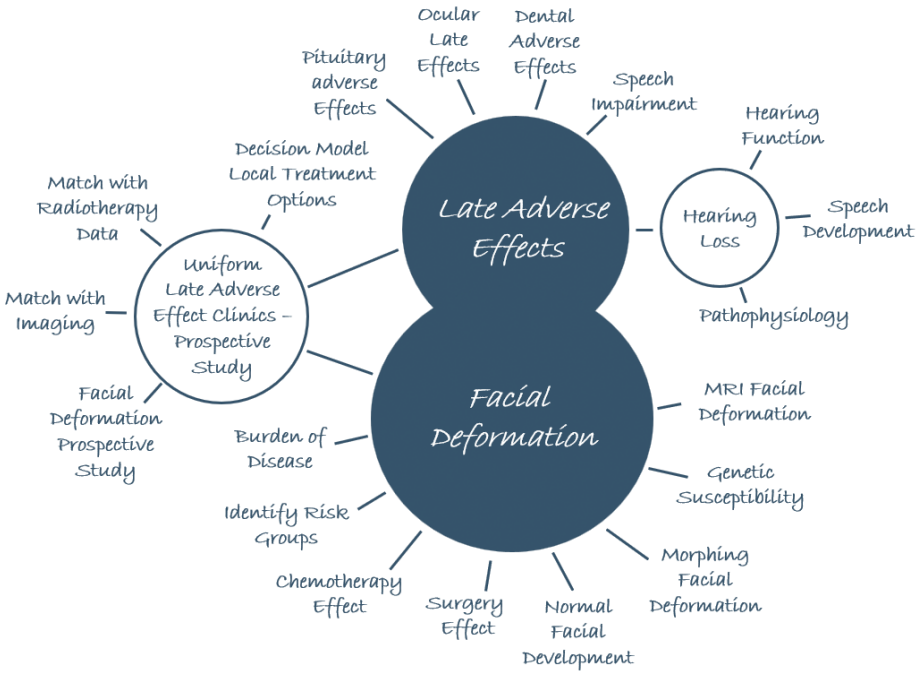


Figure 3A. Map of ideas for future studies.

Late adverse effects and facial deformation domain**.**

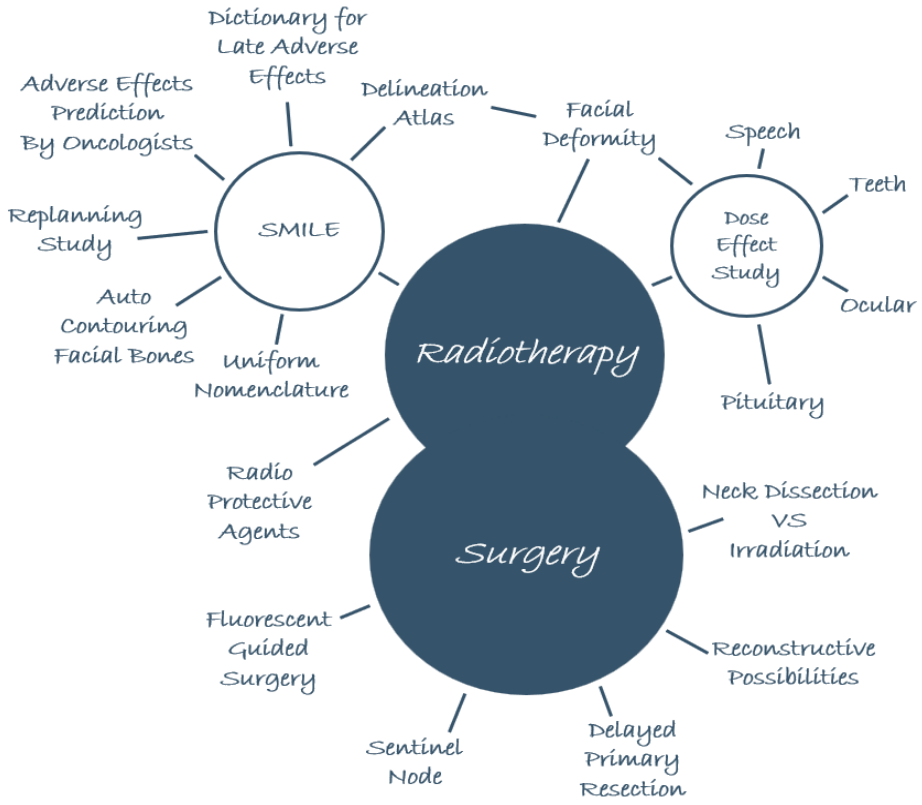


Figure 3B. Map of ideas for future studies.

Surgery and Radiotherapy domain.
SMILE: Minimising long-terM Impact on dentition and faciaL asymmEtry in childhood cancer survivors.

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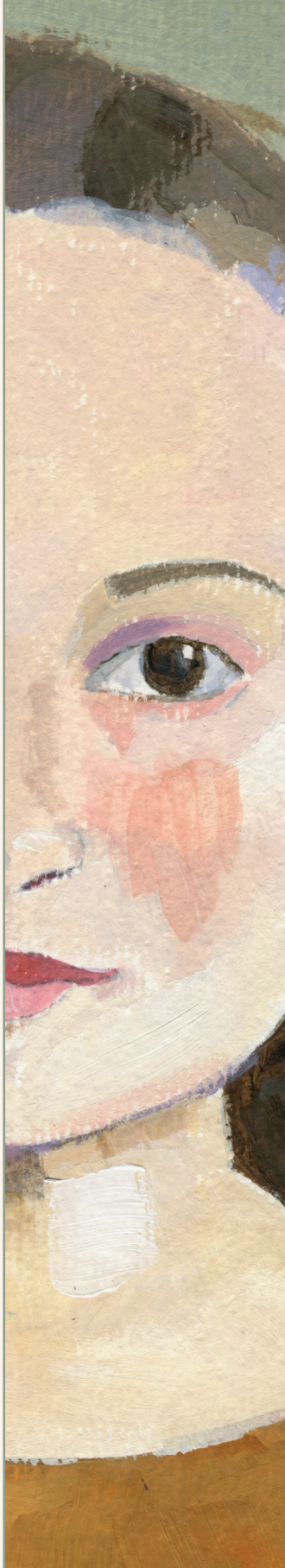
Summary in English



PAEDIATRIC HEAD AND NECK RHABDOMYOSARCOMA

The most common soft tissue sarcoma in children is rhabdomyosarcoma, constituting 3-5% of all paediatric malignancies, which arise in the head and neck area in about 40% of patients. Patients are typically young at diagnosis and need a combination of systemic and local treatment in order to yield high survival rates. As the overall survival for localised paediatric head and neck rhabdomyosarcoma has increased to up to 79-97%, more emphasis is needed on minimising potential late adverse events. Treating young patients with multimodality treatment consisting of chemotherapy, radiotherapy, and potentially surgery often results in late adverse effects in the surrounding organ systems. In past decades, efforts have been put into developing new local treatment options that limit doses to adjacent organs to limit late adverse effects. There are currently four different local treatment options for head and neck rhabdomyosarcoma: External Beam RadioTherapy utilising photons (XRT), External Beam RadioTherapy utilising protons (PBT), the combination of brachytherapy and surgery (AMORE – Ablative surgery, MOulage technique with afterloading brachytherapy, REconstructive surgery) and the combination of surgery with either XRT or PT (the Paris method, developed in Paris for patients with tumours in the infratemporal fossa or the pterygopalatine fossa). Three techniques yield the same survival rates (XRT, AMORE, PBT); however, the Paris method aims specifically to increase survival for the aforementioned patient groups. Due to the inherently different dose distributions between the radiotherapy techniques used (brachytherapy, PBT, XRT) and the addition of surgery in some techniques (AMORE and the Paris method), differences in late adverse effects are expected. The studies presented in this dissertation aimed to investigate the extent and variety of late adverse effects in survivors of paediatric head and neck rhabdomyosarcoma, explore the difference in late adverse effects between the four local treatment options, examine dose-effect relations for facial bones and further examine AMORE for head and neck rhabdomyosarcoma.

Chapter 1

The results of our trans-Atlantic multicentre study, which systematically investigated late adverse effects in paediatric head and neck rhabdomyosarcoma survivors in multidisciplinary outpatient clinics, show that late adverse effects are highly present and rather diverse. Eighty percent of all survivors suffered from at least one grade 2 late adverse effect. The most prevalent reported late adverse effects were facial deformation, ocular problems, hearing impairment and speech abnormalities. There was a difference in adverse effects between the different treatment options both in terms of grade and type; however, this was not statistically proven. The list of observed late adverse effects can be used to guide shared decision-making. Furthermore, this information can inform physicians, parents, and patients of expected late adverse effects.

Chapter 2
The data presented in **Chapter 2** also originates from the trans-Atlantic multicentre study. Facial deformation was objectively measured for 173 survivors, and comparisons between the four treatment modalities were made using 3D stereophotogrammetry. In general, facial deformation was worse in patients treated at a younger age. However, this did not apply to patients treated with the Paris method. Patients were partitioned per treatment site. All survivors with parameningeal and non-parameningeal tumours showed reduced facial growth; patients with a tumour in the orbit demonstrated normal facial growth. Treatment with AMORE and XRT was compared for orbital tumours, showing less facial deformation in patients treated with AMORE. AMORE and XRT were compared in survivors treated for a non-parameningeal tumour. Partitioning for treatment age showed a difference between AMORE and XRT, with a lower risk of deformation for patients treated with AMORE when they were young and a lower risk of facial deformation for patients over 6 years of age when treated with XRT. All four local treatment modalities were compared for survivors treated for a parameningeal tumour. PBT was significantly favourable over XRT and the Paris method in terms of facial deformation and growth. There was no statistical difference between AMORE and PT or XRT. Overall, facial deformation was the same for XRT and the Paris method; however, survivors treated with the Paris method showed significantly more facial asymmetry. The data from this study was used to present a decision tree for cases in which the only expected late adverse effect is facial deformation (**Figure 1**, General Discussion).

Chapter 3
This chapter reports on patient-reported outcome data collected during the trans-Atlantic multicentre study. The FACE-Q craniofacial module was used for this study, as it is the only measurement designed specifically to document appreciation of appearance and facial function. Scores varied highly among survivors; however, the majority reported negatively on appearance, health-related quality of life, and facial function. Over 80% of survivors reported negatively on appearance and health-related quality of life, and nearly 40% reported negatively on facial function. Survivors with speech abnormalities, oral malfunction and facial nerve paresis scored significantly lower in all three domains. Interestingly, clinically relevant late adverse effects reported by physicians in the study described in **Chapter 1** only correlated weakly with the majority of disease-specific patient-reported outcomes. The data from this study underline the need to obtain survivors' perspectives during follow-up clinics and use patient-reported outcome measures.

Chapter 4
This chapter describes changes in orbital bone morphology in relation to radiation dose to the orbital bones. Orbital asymmetry was measured by MRI and radiation

dose for the maxillary, frontal, and zygomatic bones, as well as the composite orbital rim bones. Orbital asymmetry resulting from orbital volume loss correlated with the composite dose to the orbital rim bones rather than one specific bone of the orbit.

This study has some limitations with a relatively small follow-up time and, consequently, potential underestimation of growth deformation, and was performed in a relatively small cohort of patients. However, with no other dose-effect models available for orbital bones in paediatric patients, capitalising on these results and using the suggested dose constraint of a maximum dose of 40 GyRBE to the composite orbital rim would potentially diminish orbital asymmetry in future patients.

Chapter 5
This chapter aimed to determine dose thresholds for craniofacial bones by identifying dose-effect models for facial deformation. We used the 3D stereophotographs taken at the trans-Atlantic multicentre study and combined them with the original treatment data. All facial bones were delineated on the original radiotherapy treatment plans, enabling extraction of doses to all the facial bones and sutures. These outcomes resulted in dose constraints of 26 GyEQD2 for the mandibular complex and 28 GyEQD2 for the ethmoid-maxillary complex. Furthermore, dose constraints for all the individual bones were characterised. We would advise using these dose constraints in future patients to limit facial deformation. An overview of the recommended dose thresholds based on the data presented throughout this dissertation is presented in **Table 1** in the General Discussion.

Chapter 6
This chapter reports on the results of a study by the University of Florida using 45 GyRBE for embryonal group III orbital rhabdomyosarcoma. Thirty patients were included and were treated with 45 GyRBE for embryonal group III orbital rhabdomyosarcoma. Treating patients with 'only' 45GyRBE seemed an effective approach, yielding a 5-year local control rate of 97%. The dose reduction lessened intermediate and short-term adverse effects and might also lessen long-term toxicity. Reducing doses in general would be a tremendous step towards limiting the dose to at-risk organs.

Chapter 7
This chapter showcases an update on AMORE over the past 25 years, focussing on surgeries performed and the decision-making process. Thirty-five patients underwent AMORE treatment for a primary non-orbital head and neck rhabdomyosarcoma. Overall, the selection criteria for AMORE have become stricter over the past 25 years in primary head and neck patients, excluding patients with intracranial extension, carotid encasement, and perineural spread. Reconstructive

surgery was performed in 26 out of 35 patients using a pedicled or free flap, resulting in no important complications. Both event-free and overall survival were similar to other local treatment options. With survivors treated with AMORE showing reduced facial deformation compared to young patients treated with XRT for non-parameningeal tumours, AMORE could be considered more often as a local treatment option in these patients.

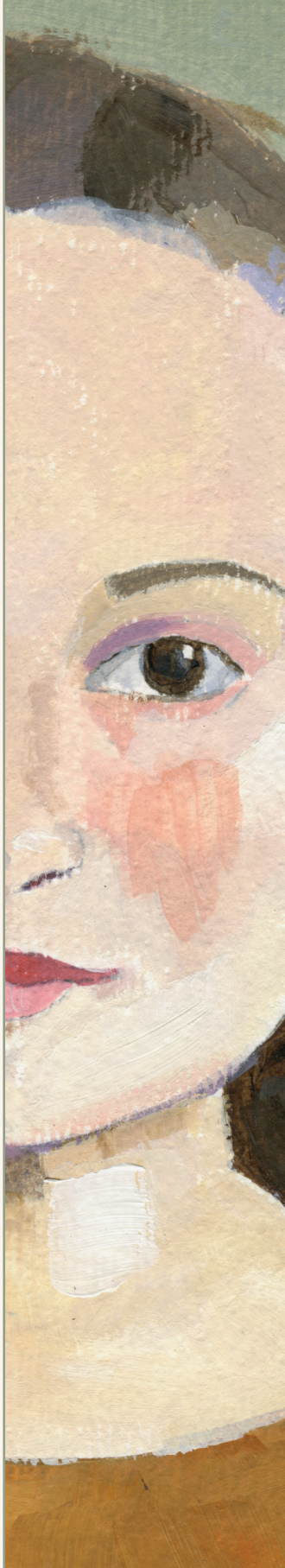
Chapter 8
This chapter explores AMORE in patients with relapsed rhabdomyosarcoma as a salvage option, as this is often the only remaining treatment option for patients who have already been irradiated.

As salvage treatment, AMORE yielded 5-year overall survival of 54% for the complete group of relapsed patients, including orbital and non-parameningeal sites as well as parameningeal cases. It is important to note that when AMORE is utilised as a salvage treatment, more rigorous surgery is considered, and the previously described exclusion criteria are less stringent as this is often the only curative option for the patient. Re-irradiation was well tolerated by all patients. However, due to the irradiation of some areas for the second time, as well as major surgery in some cases, severe late adverse effects were seen in this patient group. All patients needed suppletion for growth hormone deficiency, and most patients had at least grade 2-3 musculoskeletal deformation. Even though most surgeons are hesitant to perform surgery in a previously irradiated field, both the resection and reconstructive surgery demonstrated no major complications, such as free flap failures or wound healing issues. In conclusion, AMORE should be considered more often in patients with relapsed head and neck sarcoma as it has been proven to be a safe treatment option, potentially offering increased survival.

Chapter 9
This chapter investigated the ability of surgeons to predict nerve deficit, facial deformation, and scar formation. Six highly experienced surgeons predicted these late adverse effects for nine different children who had undergone surgery for head and neck tumours. Nerve sacrifice and nerve deficits were predicted very reliably. However, the effect of surgery on facial deformation was hard to predict. This study shows the need for a reliable prediction model for facial deformation. This dissertation presents the backbone for such a model, and a decision graph is presented in the discussion.

APPENDICES

Summary in Dutch



SUMMARY IN DUTCH

Hoofd hals rhabdomyosarcomen bij kinderen
De meest voorkomende wekedelentumor bij kinderen is een rhabdomyosarcoom; 3-5% van alle maligniteiten op kinderleeftijd betreft een rhabdomyosarcoom. Ongeveer 40% van deze tumoren ontstaat in het hoofd-halsgebied. Patiënten zijn doorgaans jong op het moment van de diagnose en moeten behandeld worden met een combinatie van chemotherapie en lokale behandeling van de tumor met radiotherapie of chirurgie. Door deze combinatie van behandelingen is de overleving, afhankelijk van de risicogroep, toegenomen tot 79-97%. Echter, een behandeling bestaande uit een combinatie van chemotherapie, radiotherapie en mogelijk een operatie veroorzaakt vaak late nadelige effecten in de omliggende weefsels. In de afgelopen decennia zijn er inspanningen geleverd om nieuwe lokale behandelingen te ontwikkelen. Deze lokale behandelingen hebben tot doel de bestralingsdosis op de omliggende organen te beperken en zo minder late effecten te veroorzaken.

Op dit moment zijn er vier verschillende lokale behandelingsopties beschikbaar voor rhabdomyosarcomen in het hoofd-halsgebied. Ten eerste is er externe radiotherapie met fotonen (XRT). Ten tweede bestaat er externe radiotherapie met protonen, ook wel protontherapie genoemd (PBT). Ten derde is in de jaren '90 is in Nederland een behandeling ontwikkeld waarbij chirurgie gecombineerd wordt met brachytherapie. Deze behandelmethode wordt ook wel verwezen met term AMORE (Ablatieve chirurgie, MOulage techniek brachytherapy en REconstructieve chirurgie). Ten vierde is in Parijs is een behandeling ontwikkeld voor kinderen met een tumor in de infratemporale of pterygopalatine fossa waarbij chirurgie met een vorm van externe radiotherapie gecombineerd wordt (Parijse-methode). Drie lokale behandeltechnieken resulteren in dezelfde overlevingspercentages (XRT, AMORE, PBT). De Parijse methode heeft specifiek tot doel de overleving van eerder genoemde patiëntengroepen te vergroten. Vanwege de verschillen in dosisverdelingen tussen de gebruikte radiotherapietechnieken (XRT, PBT en brachytherapie) en de toevoeging van chirurgie aan sommige behandelingen (AMORE en de Parijse methode), worden verschillen in late effecten verwacht.

De studies die in dit proefschrift worden gepresenteerd, hebben allereerst tot doel de omvang en verscheidenheid van late bijwerkingen te onderzoeken bij overlevenden van rhabdomyosarcomen in het hoofd-halsgebied. Een tweede doelstelling is het onderzoeken van de mogelijke verschillen in late bijwerkingen tussen de vier lokale behandelingsopties. Deze onderzoeksvragen staan centraal in het eerste deel van dit proefschrift. In het tweede deel van dit proefschrift kijken we naar radiotherapie en de dosis-effectrelaties voor botten in het aangezicht. In het derde deel van dit proefschrift staat de chirurgische behandeling van rhabdomyosarcomen in het hoofd-halsgebied centraal en in het bijzonder de behandeling met AMORE.

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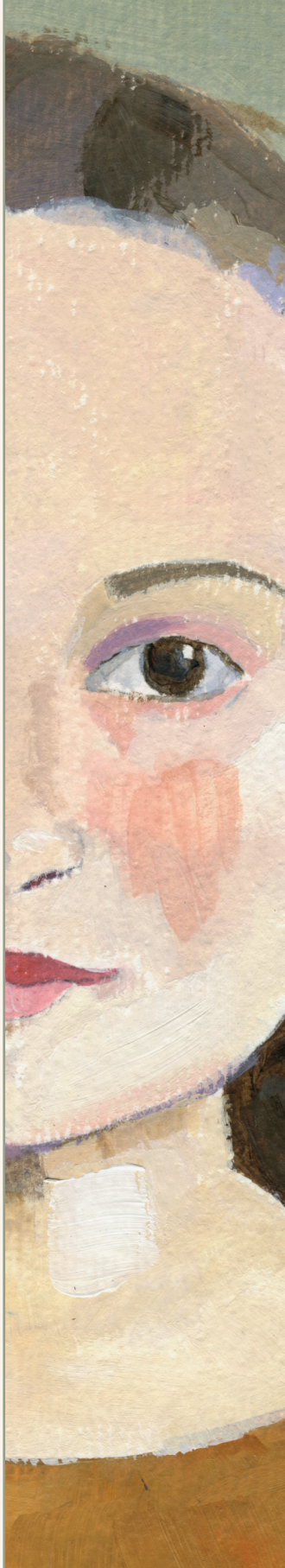

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45 GyRBE for group III orbital embryonal rhabdomyosarcoma

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Chapter 8.

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

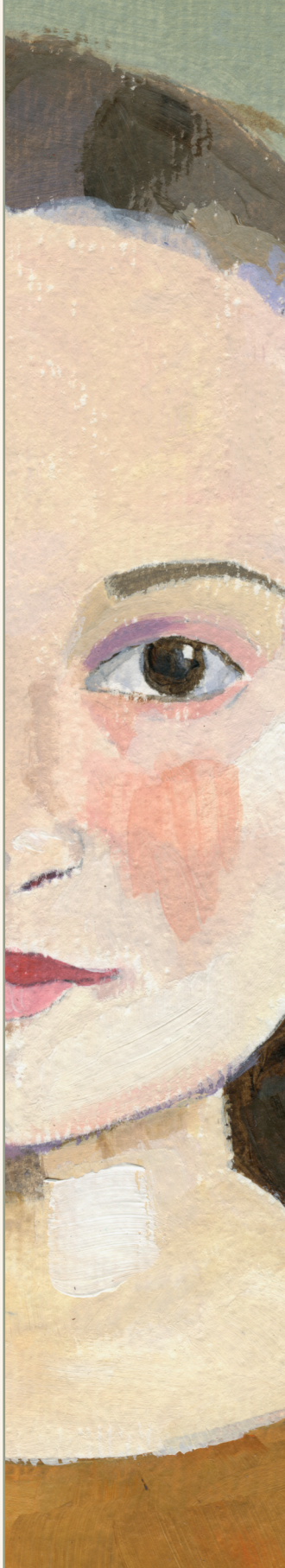
Bas Vaarwerk, concept and design, data aquisition, data analysis, interpretation of data, drafting
Marinka L.F. Hol, concept and design, data aquisition, interpretation of data, drafting
Reineke A. Schoot, concept and design, data aquisition, interpretation of data, revising
Willemijn B. Breunis, concept and design, interpretation of data, revising
Maartje M. de Win, concept and design, interpretation of data, revising
Bradley R. Pieters, concept and design, interpretation of data, revising
Henrike Westerveld, concept and design, interpretation of data, revising
Raquel Davila Fajardo, concept and design, interpretation of data, revising
Perooz Saeed, concept and design, interpretation of data, revising
Michiel W. van den Brekel, concept and design, interpretation of data, revising
Simon D. Strackee, concept and design, interpretation of data, revising
Ludi E. Smeele, concept and design, interpretation of data, revising
Johannes H.M. Merks, supervisor concept and design, interpretation of data, revising

Chapter 9.

Predicted future aesthetic and functional outcome following surgical treatment for pediatric head and neck sarcomas

Marinka Hol; concept and design, data interpretation, analysis, drafting,
Andrew Hall; data aquisition, data interpretation, revising
Micheal Suttie; concept and design, analysis, data interpretation, revising
Curtis Budden; data aquisition, data interpretation, revising
Colin Butler; data aquisition, data interpretation, revising
Richard J. Hewitt; concept and design, data aquisition, data interpretation, revising
Frederic Kolb; concept and design, data aquisition, data interpretation, revising
Juling Ong; concept and design, data aquisition, data interpretation, revising
Ludwig E. Smeele; supervisor, concept and design, data interpretation, data aquisition, revising

List of publications



LIST OF PUBLICATIONS

Facial asymmetry in head and neck rhabdomyosarcoma survivors
Schoot RA, **Hol MLF**, Merks JM, Suttie M, Slater O, Lennep M, Hopman S, Dunaway D, Syme-Grant J, Smeele LE, Zwinderman K, Caron H, Hammond P.
October 2017, Pediatric Blood and Cancer.

Three-Dimensional Imaging of the Face: A Comparison between Three Different Imaging Modalities
Verhulst AC, **Hol MLF**, Vreeken RD, Becking AG, Ulrich DJO, Maail TJJ.
May 2018, Aesthetic Surgery.

Medication use during prednancy and lactation in the dutch population
Waard de, Blomjous BS, **Hol MLF**, Sie S, Corpeleijn WE, Weissenbruch MM.
February 2019, Journal of Human Lactation

AMORE treatment as salvage treatment in children and young adults with relapsed head-neck rhabdomyosarcoma
Vaarwerk B, **Hol MLF**, Schoot A, Breunis W, Win M, Pieters B, Westerveld H, Fajardo R, Saeed P, Brekel van de M, Strackee S, Smeele LE, Merks JHM.
February 2019, Radiotherapy & Oncology

Psychosocial well-being of long-term survivors of pediatric head–neck rhabdomyosarcoma
Vaarwerk B, Schoot RA, Maurice-Stam H, Slater O, Hartley B, Saeed P, Gojdosova, Brekel, Balm, **Hol**, Jaarsveld, Kremer, Rockers, Mandeville, Pieters, Gaze, Davilla, Strackee, Dunaway, Smeele, Chisholm, Caron, Grootenhuis, Merks.
February 2019, Paediatric Blood and Cancer

App for head and neck anatomy
Hol MLF, Freling N, Veldhuis W.
August 2019, App Store

45 GyRBE for Group 3 Orbital Embryonal Rhabdomyosarcoma
Indelicato DJ, Rotonto RL, Mailhot Vega RB, Agarwal, S. Bradfield, Uezono H, **Hol MLF,** Bradley J.
October 2019, Acta Oncologica.

Dose-Effect Analysis of Early Changes in Orbital Bone Morphology Following Radiotherapy for Rhabdomyosarcoma
Hol MLF, Indelicato DJ, Rotondo RL, Mailhot Vega RB, Uezono H, Lockney N, Sandler E, Bradley JE.
January 2020, Practical Radiation Oncology,

An overview of radiological manifestations of acquired dental developmental disturbances in paediatric head and neck cancer survivors
Hoogeveen RC, **Hol MLF**, Pieters, BR, Balgobind B, Berkjout EWER, Schoot RA, Smeele LE, Merks JHM, Becking AG.
March 2020, Dentomaxillofacial Radiology

FACE-Q craniofacial module: Part 1 validation of CLEFT-Q scales for use in children and young adults with facial conditions
Klassen, Rae, Wond-Riff, Bulstrode, Denadai, Goldstein, **Hol**, Murray, Bracken, Courtemanche, O'Hare, Butler, Malic, Ganske, Phua, Marucci, Jonson, Swan, Breuning, Goodacre, Pusic, Cano
September 2021, Journal of plastic reconstructive and aesthetic surgery.

FACE-Q craniofacial module: Part 2 psychometric properties of newly developed scales for children and young adults with facial conditions
Klassen, Rae, Wong-Riff, Denadai, Murray, Bracken, Courtemache, Bulstrode, O'Hara, Butler, Goldstein, Tassi, **Hol**, Johnson, Ganske, Kolby, Benitez, Breuning, Malic, Allen, Pusic, Cano.
September 2021, Journal of Plastic reconstructive and Aesthetic Surgery

Psychometric validation of the FACE-Q Craniofacial module for facial nerve paralysis
Klassen, Rae, Gallo, Norris, Bogart, Johnson, van Leaken, Baltzer, Murray, **Hol**, Terese, Wong-Riff, Cano, Pusic.
January 2022, Facial plastic surgery aesthetic medicine

Patterns of Hearing Loss in Irradiated Survivors of Head and Neck Rhabdomyosarcoma
Diepstraten, Wiersma, Schoot, Knops, Zuur, Meijer, Daviala Fajardo, Pieters, Balgobind, Westerveld, Freling, van Tinteren, Smeele, Bel, van de Heuvel-Eibrink, Stokroos, Merks, Hoetink, **Hol**.
November 2022, Cancers

Patient reported outcomes in childhood head and neck rhabdomyosarcoma survivors and their relation to physician graded adverse events – a multicenter study using the FACE-Q Craniofacial module
Morfouace*, **Hol*** (shared first), Schoot, Slater, Indelicato, Kolb, Smeele, Merks, Rea, Maurice-Stam, Klassen, Grootenhuis.
February 2023, Cancer Medicine

Imaging in rhabdomyosarcoma: a patient journey
De Vries ISA, Ewijk R, Adriaansen, Bohte, Braat, Fajardo, Hiemcke-Jiwa, **Hol MLF**, ter Horst, de Keizer, Knops, Meister, Schoot, Smeele, Schltinga, Vaarwerk, Merks, van Rijn.
April 2023, Pediatric Radiology

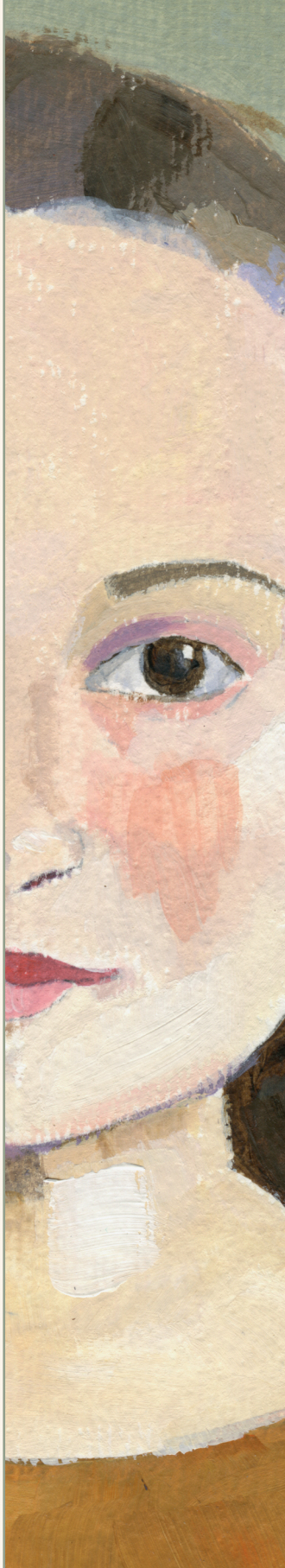
Facial deformation following treatment for pediatric head and neck rhabdomyosarcoma; the difference between treatment modalities. Results of a trans-Atlantic, multicenter cross-sectional cohort study
Hol, Indelicato, Slater, Kolb, Hewitt, Ong, Becking, Gains, Bradley, Sandler, Gaze, Pieters, Mandeville, Fajardo, Schoot, Merks, Hammond, Smeele, Suttie.
August 2023, Paediatric Blood and Cancer

Developments in the Surgical Approach to Staging and Resection of Rhabdomyosarcoma
Terwisscha van Scheltinga, Rogers, Smeulders, deCorti, Guerin, Craigie, Burrieza, Smeele, **Hol**, Rijn van, Fuchs, Seitz, Schmidt, Timmermann, Tunn, Chargari, Davila Fajardo, Slater, Gains, Merks.
Januari 2023, Cancers

The need for consensus on delineation and dose contraints of dentofacial structures in paediatric radiotherapy: outcomes of the A SIOP Europe survey
Davey, Pan, Bryce-Atkinson, Mandeville, Janssens, Kelly, **Hol**, Tang, Davies, SIOP Radiation Oncology Working Group, Aznar.
September 2023, Clinical and Translational Radiation Oncology

Book Chapter
Scott Brown - Otorhinolaryngology and Head and Neck Surgery, 9th Edition
Chapter 27 – Paediatric Head and Neck Tumours
Marinka Hol, Olga Slater

PhD portfolio



PHD PORTFOLIO

General Course	University	ECTS	Year
World of Science	Graduate school - AMC	1	2015
Statistiek, methodologie en SPSS	ACTA	3	2016
English Writing and Presenting	ACTA	4	2016
Project Managment	Graduate school - AMC	1	2017
E-science	Graduate school - AMC	2	2017
Mouse morphology, genetics and function	Graduate school - AMC	2	2018
Systematic Review	Graduate school - AMC	0.5	2017
Scientific Integrity	ACTA	2	2018

Specific Course	School - Location	ECTS	Year
Paediatric Radiation Oncology	ESTRO - Izmir	4	2015
Multidisciplinairy head and neck oncology	ESTRO - Florence	4	2016
Radiobiology	ESTRO - Dublin	4	2018

Presentations as first author	Conference	ECTS	Year
Invited talk: dentofacial late effects following paediatric cancer	Childhood Children Oncology Group – Radiotherapy Meeting	1	2023
2 Oral presentations: facial deformation following treatment for head and neck sarcoma and Reconstructive possibilities in the head and neck area following treatment for head and neck cancer in children	SMILE Meeting	1	2023
Invited talk: local treatment for paediatric head and neck sarcoma	Paediatric Radiation Oncology Society (PROS)	1	2022
Invited talk: late adverse effects following head and neck cancer in children	Childhood Children Oncology Group (CCLG)	1	2020
Poster presentation: A Dose-Effect Analysis of Early Changes in Orbital Bone Morphology Following Radiotherapy for Rhabdomyosarcoma'	American Society for Radiation Oncology (ASTRO)	0.5	2019
Oral Presentation: Radiological Manifestations of Acquired Dental Developmental Disturbances in Pediatric Head and Neck Rhabdomyosarcoma Survivors	American Association for Oral and Maxillofacial Surgery (AAOMS)	0.5	2019

Presentations as first author	Conference	ECTS	Year
Poster presentation: A Dose-Effect Analysis of Early Changes in Orbital Bone Morphology Following Radiotherapy for Rhabdomyosarcoma'	Paediatric Radiation Oncology Society (PROS)	0.5	2019
Oral presentation: Facial deformation following treatment for HNRMS; a difference between treatment modalities and dose-effect relations.	Paediatric Radiation Oncology Society (PROS)	0.5	2019
Oral presentation: Facial development in head and neck saromcoma survivors.	International Society of Paediatric Oncology (SIOP)	0.5	2018
Invited oral presentation: Development of the Surgical Young Investigators program	International Society of Paediatric Oncology (SIOP) Young Investigator Day	1.0	2018
2 Oral presentations; Facial deformation and dental developmental problems following paediatric head and neck sarcoma treatment.	European Association for Craniomaxillofacial Surgery (EACMFS)	1.0	2018
Invited oral presentation: Facial esthetics following brachytherapy.	European Radiation oncology Society (ESTRO)	1.0	2018
Oral presentation: The difference in growth and and developmental problems following the treatment of head and neck sarcoma in children: the difference between AMORE and EBRT.	Paediatric Radiation Oncology Society (PROS)	0.5	2017
Poster presentation: Analysis of the deformed human face.	European Association for cranio maxillofacial surgery (EACMFS)	0.5	2016
Oral presentation: A new method for the automatic analysis of 3D stereo photogrammetry.	Dutch Society for simulation in health care (DSSH)	0.5	2016

Committees	Role	ECTS	Year
SMILE working group	Steering committee member	2	2022-present
NVKNO – pediatrie kerngroep Dutch Society for ENT	Committee member paediatric working group	2	2022-present
NVWPO – Belgium-Netherlands Society for Paediatric ENT	Board member	1	2023–present

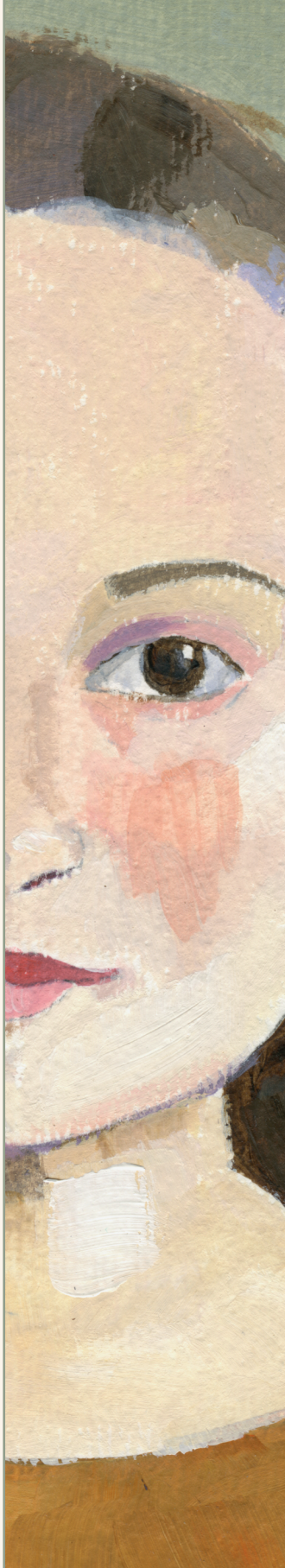
Committees	Role	ECTS	Year
Dutch Society for Simulation in Health Care	Board member (until 2022) Scientific committee member	3	2017–present
EpSSG Surgery Committee	Member	2	2018-present
SIOP Young Investigator Committee	Board Member Young-Investigator Network	2	2016-2017

Honors and Awards	Organisation	ECTS	Year
Posteraward. Title of poster 'A Dose-Effect Analysis of Early Changes in Orbital Bone Morphology Following Radiotherapy for Rhabdomyosarcoma'.	Paediatric Radiation Oncology Society	1	2019
University of Amsterdam 385 travel grant	UvA 385 Grant	1	2017
Research grant #297	KIKA (Dutch pediatric cancer foundation)	1	2017
Travel Grant	ESTRO	1	2016

Supervising	Organisation	ECTS	Year
Poyan Maghsoudi and Thomas Leung Bachelorthesis - dentistry 3rd year	Dental developmental problems in children treated for an head and neck sarcoma	1	2019
Lotte Hoogeveen; Research internship - Medical school 3rd year	Lipofilling as a reconstructive possibility in children treated for an head and neck sarcoma	1	2019
Nadine Hoonhout Masterthesis - Medical school 6th year	Radiobiology of facial bone growth	1	2018

Total ECTS		57.5	

Dankwoord



"What's the bravest thing you've ever said?" asked the boy.
"Help" said the horse.
"Asking for help isn't giving up," said the horse, "it's refusing to give up."'

The boy, The Mole, The Fox, and The Horse
Charlie Mackesy

First and foremost, I would like to thank all **patients and parents** who have been willing to participate in the research presented in this dissertation. It's been a humbling, joyful, impactful experience seeing and talking to each and every one of you. Thank you for coming to clinics on your weekends and free days! I will never forget all the personal stories, journeys, and incredible resilience in each of you. Your clinic visits improved care for future patients with head and neck rhabdomyosarcoma. I can't thank you enough.

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Geachte **Prof. Merks**, Beste Hans, je passie, grenzeloos enthousiasme en aandacht voor detail hebben mijn promotie tot een hoger detail getild. Fijn dat je in een overvolle agenda toch elke keer weer een plekje kan vinden. Dankjewel voor de vrijheid die je mij gaf om me te laten vliegen tijdens deze promotie. Ik kijk uit naar een toekomst met waardevolle, mooie projecten.

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Geachte **Prof. Bel**, Beste Arjen, dank voor je technische kennis binnen dit project, je kritische blik en al je hulp bij de nieuwe plannen en berekeningen en bedenken hoe we van oude data toch waardevolle invulling konden maken!

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Beste **Prof. Berge**, dank voor het beoordelen van dit werk en uw tijd. Naast deze wetenschappelijke bijdrage aan mijn carrière heeft u ook een bijdrage aan mijn chirurgische carrière geleverd want sinds de cursus in Nijmegen poets ik mijn tanden met mijn linker hand ;p. Beste **Prof. De Lange**, jaren geleden begon de reis van mijn PhD bij u op een prachtige, uitgebreide afdeling in Amsterdam. Dank voor de mogelijkheid om mijn onderzoeksproject vanuit u afdeling te mogen doen. Beste **Prof. Saeed**, Beste Peeroz, wat is het een feest geweest om met je samen te werken de afgelopen jaren, wat heb ik veel geleerd, het was even schrikken de eerste keer dat ik met je op OK stond en een orbita exenteratie mocht 'doen' – maar je hebt de liefde voor ons vak in me aangewakkerd en ik kijk uit naar meer – chirurgische – samenwerking in de toekomst. Beste **Prof Sonke** dank voor het zitting nemen in mijn promotiecommissie en dank voor het lezen en beoordelen van dit proefschrift.

Dear Dr. Slater, Dearest Olga, how wonderful that we started this project together all these years ago and that you are now an integral part of finishing this project with you taking a seat on this PhD examination committee. I could write a book about how thankful I am for all the effort and time you have been willing to pour into this project and me. One of the first things you told me was, 'Nothing good ever comes from comfort.' While that's been true for this project with endless ethical board meetings, Saturday clinics, and whatnot, it has also been a wonderful learning experience and extremely fun. I loved all the dinners, breakfasts, and lunches at Carluccio, the Ivy and every other place we have been to. Let's also not forget our workout sessions, champagne evenings, cold water swims, and train rides. You've become a dear friend, role model, and I can't thank you enough for everything. With thanking you, I also want to thank **Mike** and **Katarina** en **Klara** for all the sleepovers at your house, dinners, birthday parties, sushi, cinnamon socials, cups of tea, lovely talks and laughs. I hope many sleepovers, dinners, and bottles of champagne will follow shortly!

Dear Dr. Gaze, Dearest Mark, even though I am a little scared about the critical questions you undoubtedly will ask at this dissertation defense, thank you so much for being part of this moment. Thank you for your always critical and concise view of our papers, excellent comments, and ideas that add to our projects. Thank you for all the lovely evenings, dinners, drinks, talks, history walks with Robbert through London, hat shopping, wines, special dinners, and fun we have had over the years. I am so happy my son George's first visitor was you. Thank you for helping me build my career, your support, and introducing me to all committees, invited talks, and

the opportunities you create for me. I look forward to a future of conferences, visits, projects, and dinners!

Het **AMORE team**, Prof. Balm, Dr. Braunius, Prof. vd Brekel, Dr. Blank, Dr Davila-Fajardo, Dr. Dieleman, Dr. Pieters, Dr. Freling, Dr. Knops, Petra Kroon, Prof. Merks, Charlotte Ligthart-Beukhof, Dr. Paes, Prof. Saeed, Dr. Schoot, Inge Sieswerda, Dr. Strackee†, Dr Westerveld, Dr. Wiersma, jullie vriendschappelijke teamspirit om als groep de beste zorg voor deze complexe groep kinderen neer te zetten is inspirerend en hartverwarmend. Dank voor jullie kennis en dat ik deel mag zijn van deze fantastische groep. Ik kijk uit naar onze voortdurende samenwerking.

Dr. Freling, Lieve Nicole, door de jaren ben je een goede vriendin geworden. Wat begon als een les in anatomie in het hoofd hals gebied op de CT eindigde met een prachtige app. Het was een plezier om dit met je te mogen doen. Ik heb enorm veel geleerd van je en ben altijd onder de indruk geweest van je gedrevenheid en kennis van de hoofd hals anatomie. Daarnaast heb ik genoten van de gezellige bijeenkomsten samen, eindeloze koppen espresso, wijn, gezellige avonden samen met lieve Guy† en Robbert die al snel over Chinees en geschiedenis spraken. Ik hoop op nog veel gezellige avonden gevuld met muziek, wijn, boeken en gezellige gesprekken.

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Dear **members of the EpSSG**, thank you for your dedication to advancing the care and survival of children with soft-tissue sarcoma. This international collaborative group feels like family, combining fun at meetings and high-quality research. Regarding the surgical and radiotherapy working group, I thank you for your support in the studies we undertook. I look forward to working together on new projects in the future.

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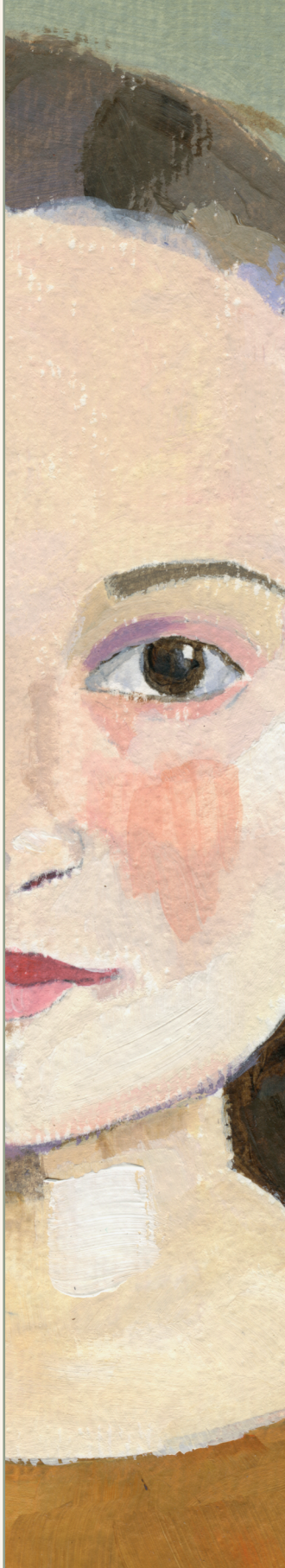
About the author



ABOUT THE AUTHOR

Marinka's journey in the medical field commenced with her graduation from the Vrije Universiteit in December 2014. During her time in medical school, she displayed a keen interest in research, collaborating with esteemed professors Smeele, Becking, Maal, and Merks. Together, they worked on a grant proposal focused on addressing facial deformations in children who had undergone treatment for head and neck rhabdomyosarcoma. This grant laid the foundation for her subsequent research endeavors and for the research presented in this dissertation.

Venturing beyond academia, Marinka spent a transformative period in Indonesia, contributing to the cleft surgery team at Hassan Sadikin Hospital in Bandung. This experience not only enriched her surgical acumen but also provided invaluable insights into challenging oncology cases and healthcare dynamics.

In 2016, Marinka commenced her research journey, delving into the intricate facets of late adverse effects following treatment for pediatric head and neck cancer. This pursuit took her across borders, where she collaborated with renowned institutions such as Great Ormond Street Hospital, the University of Florida, and the Institut Gustave Roussy, enriching her knowledge base and refining her methodologies. Having had the opportunity to spend time in these esteemed institutions has provided Marinka with invaluable insights into diverse perspectives on patient care, various treatment modalities, the latest treatment techniques, and has notably fortified her research abilities.

Transitioning into clinical practice, Marinka began her residency in otorhinolaryngology and head and neck surgery at the University of Utrecht in 2020, with a projected graduation in late 2024. With dedication she aspires to specialize in paediatric head and neck oncology, aiming to contribute meaningfully to this critical field.