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RESEARCH ARTICLE

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

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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 (Paris-method), 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

Abbreviations: AMC, Academic Medical Center; AMORE, ablative surgery, mold brachytherapy, and reconstructive surgery; DSM, dense surface modeling; FSD, face signature difference; GOSH, Great Ormond Street Hospital for Children; HNRMS, head and neck rhabdomyosarcoma; IGR, Institute Gustave Roussy; IMRT, intensity-modulated radiotherapy technique; NPM, nonparameningeal; PC, principal components; PC1, first principal component; PM, parameningeal; PMC, Princess Máxima Center in Utrecht; PT, proton therapy; RT, photon therapy; UFHPTI, University of Florida Health Proton Therapy Institute; VMAT, volumetric modulated arc therapy.

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deformation and investigates the differences in facial deformation between treatment modalities.

Methods: Across four European and North American institutions, HNRMS survivors treated between 1990 and 2017, more than 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: A total of 173 HNRMS survivors were included, survivors showed significantly reduced facial growth ($p < .001$) compared to healthy controls. Partitioned by tumor site, there was reduced facial growth in survivors with nonparameningeal primaries ($p = .002$), and parameningeal primaries ($p \leq .001$), but not for orbital primaries ($p = .080$) All patients were significantly more asymmetric than healthy controls, independent of treatment modality ($p \leq .001$). There was significantly more facial deformation in orbital patients when comparing RT to AMORE ($p = .046$). In survivors with a parameningeal tumor, there was significantly less facial deformation in PT when compared to RT ($p = .009$) and Paris-method ($p = .007$).

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

KEYWORDS
facial asymmetry, facial deformation, late effects, protontherapy, rhabdomyosarcoma, surgery

1 | INTRODUCTION

With modern therapy, most children treated for head and neck rhabdomyosarcoma (HNRMS) have a favorable prognosis, with a 5-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 5 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 (PM) 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.[6,5,14] 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.[15,16] The 3D images can capture the soft tissue of the face with sub-millimeter

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accurate surface geometry, which is accompanied by detailed texture information.[16,17] 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 analyze 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.[17–20] In a previous study using DSM, we observed a significantly higher degree of facial asymmetry in survivors of HNRMS compared to controls.[21] 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.

2 | 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, UK; IGR in Paris, France; and University of Florida Health Proton Therapy Institute (UFHPTI) in Jacksonville, USA. 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 and 2017, who were a minimum of 2 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 bloodwork and 3D photography.

2.1 | 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 (E*p*SSG) 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 mold placement was considered feasible by a multidisciplinary 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 three different head and neck surgeons (at GOSH, PMC, and 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, that is, after three cycles of induction chemotherapy. Patients were grouped based on tumor site, defined according to international RMS treatment protocols, that is, orbital, nonparameningeal (NPM), and PM.

2.2 | 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.

3 | 3D STEREOPHOTOGRAMMETRY CAPTURE AND ANALYSIS

3D facial images were taken either with a Vectra handheld camera (www.canfieldsci.com) or the 3dMD 3-pod camera (www.3dMD.com). Both cameras perform with reliable precision, and geometric accuracy does not differ between them.[22] The captured images consist of approximately 30,000 3D surface points per image. A single user (MLF Hol) manually annotated all images with a sparse set of 24 anatomically reliable landmarks; all landmark positions were confirmed by a second researcher (M Suttie) 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.

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Using the localized DSM models, we computed heatmaps (facial signatures) for each patient to show surface displacement relative to 35 age–sex–ethnicity-matched controls. These heatmaps 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 corresponding points. 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. Further technical details and method descriptions are provided elsewhere.[18,20]

Additionally, we computed individual facial asymmetry by comparing the original image with its reflected form. As with previous DSM asymmetry analyses.[17,23,24] 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-matched 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.

3.1 | Statistical methods

As 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 .25–.50, moderate for .50–.75, strong for .75–.9, and very strong for .9–1.0). All *p*-values were set at a statistical significance level of .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.

4 | RESULTS

4.1 | 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 as 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, 19.3, and 16.8 for RT, AMORE, and Paris method, respectively (all $p < .05$). Follow-up time was shorter for survivors who received PT and Paris method, with a mean of 7.8 and 8.8, and 12.4 and 12.6 years for RT and AMORE, respectively (all $p < .05$). 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.

4.2 | 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 to 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 an NPM site ($p = .002$) (mean −0.273, 95% CI [−0.667 to 0.119]) and a PM site ($p \leq .001$) (mean −0.671, 95% CI [−1.127 to 0.214]), but not in survivors with an orbital site of the tumor ($p = .080$) (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 ($p = .108$) or NPM patients ($p = .074$).

In survivors with a PM tumor, there was potentially less impact on facial growth with PT in comparison to AMORE ($p = .008$), RT ($p = .008$), and Paris method ($p = .007$); 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 ($p = .894$), RT and Paris method ($p = .284$), or AMORE and Paris method ($p = .224$).

4.3 | 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 ($p \leq .001$).

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TABLE 1 Baseline characteristics.

	RT (*N* = 58)	AMORE (*N* = 49)	Proton therapy (*N* = 34)	Paris (*N* = 32)
Mean age at 3D photo in years (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 years	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 years (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; NPM, nonparameningeal; PM, parameningeal; RT, external beam photon radiotherapy.

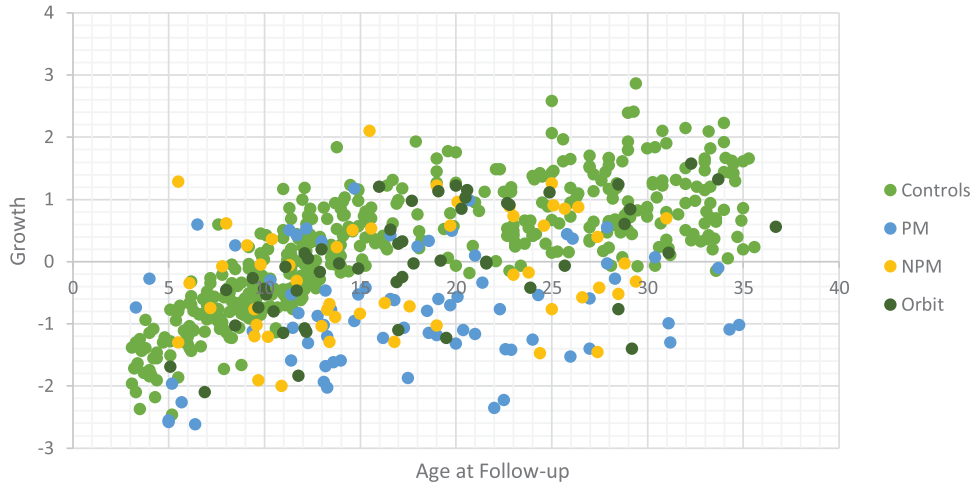

FIGURE 1 Growth of healthy controls and rhabdomyosarcoma survivors partitioned by different tumor sites (i.e., PM, NPM, orbit). The figure shows that both controls and survivors show growth of the face up until about 12 years[5,10–14] of age, after which they reach full growth (above horizontal zero-line). There is a normal variation in both controls and patients. The survivors with NPM or PM tumor show reduced growth; however, the survivors of a tumor located in the orbit show similar growth to the healthy controls. NPM, nonparameningeal; PM, parameningeal.

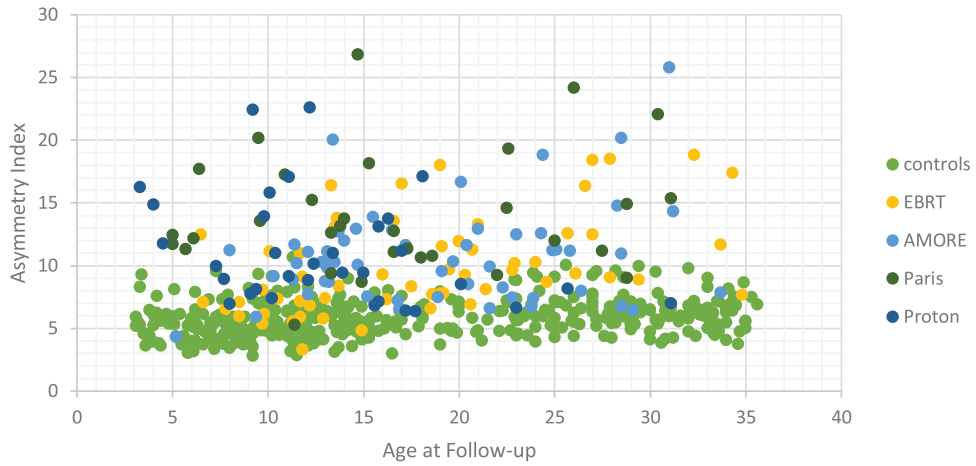

FIGURE 2 Normalized asymmetry score for all survivors and healthy controls, partitioned by treatment modality. Regardless of age at scan, healthy controls have mild asymmetry (varying from near zero to about 10 asymmetry index). Survivors treated with RT who are under the age of 15 show similar asymmetry to the healthy controls. However, patients treated with AMORE, Paris method, or proton treatment show a broad spectrum of asymmetric facial development. AMORE, ablative surgery, Moulage brachytherapy, and reconstructive surgery; RT, external beam photon radiotherapy.

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Survivors with an orbital tumor were significantly less asymmetric than survivors with a PM tumor ($p = .001$) and an NPM tumor ($p = .005$). There was no significant difference in asymmetry between survivors with NPM and PM sites ($p = .970$).

There was no significant difference in asymmetry between treatment with AMORE and RT in survivors with an orbital tumor ($p = .631$) or NPM tumor ($p = .075$). Survivors with a PM tumor were significantly more asymmetric when treated with Paris method compared to all other modalities: RT ($p = .003$), AMORE ($p = .012$), and PT ($p = .03$). There was no significant difference in asymmetry in survivors with an NPM tumor treated with RT versus AMORE ($p = .648$), RT versus PT ($p = .064$), AMORE versus PT ($p = .128$) or PT versus Paris method ($p = .288$).

4.4 | Facial signature analysis

Mean facial signatures for each treatment modality are shown in Figure 3 (including means and ranges). In the earless model, there is significantly more facial deformation in orbital patients when comparing RT to AMORE ($p = .046$). There is no significant difference between patients with 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 ($p = .009$) and also compared to Paris method ($p = .007$). There was no difference in survivors with a PM tumor between RT and Paris method ($p = .282$).

4.5 | 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 [$r = .213$ ($p < .001$)]. 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.

5 | 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 PM and NPM tumors. For patients with 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.[8,25] In previous studies, facial asymmetry and hypoplasia are widely reported in up to 77% of HNRMS survivors.[5,6,23,26] 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.[23] However, facial asymmetry may not be the best measurement in these patients, as 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, as 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.

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 subsite, 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 pretreatment 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 multidisciplinary team for each patient, weighing all

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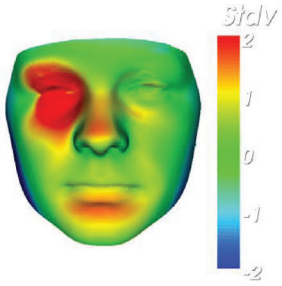
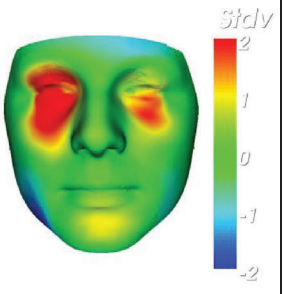
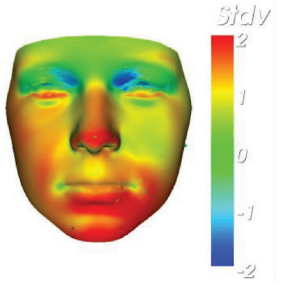
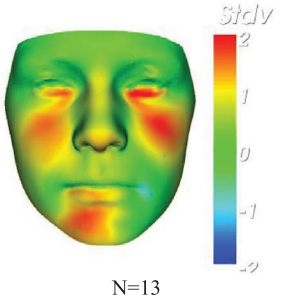
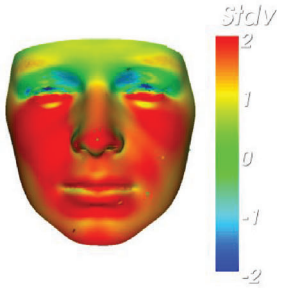
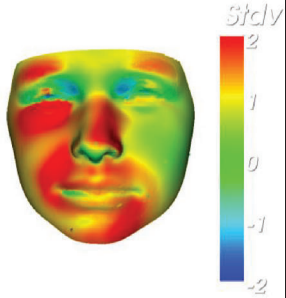
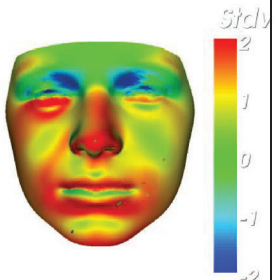
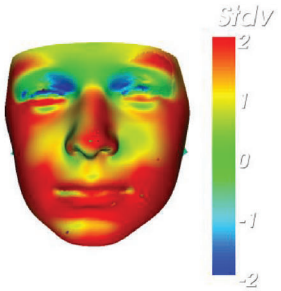
	RT	AMORE	PROTON	PARIS
ORBIT	 N= 15	 N= 16	*No mean – not large enough group*	*No mean – not large enough group*
MEAN SW (range)	193.67 (126.8 – 330.4) *p=0.04639 EBRT vs. AMORE*	146.18 ((87.2 – 311.7)		
Non Parameningeal	 N=13	 N=13	*No mean – not large enough group*	*No mean – not large enough group*
MEAN SW (range)	211.68 (84.0 – 346.7) *p=0.660 EBRT vs. AMORE*	226.79 (97.0 – 368.9)		
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 Heatmaps of mean faces. For each treatment modality, a mean face is made partitioned by tumor site. The orbital tumor group and nonparameningeal tumor group only has images for RT and AMORE treatment, as there are not enough survivors included to make a mean face for the proton and Paris method groups. The heatmaps are depicted using color, 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. *Significant difference: RT versus PT: $p = .00998$; **significant difference: PT versus Paris; $p = .007592$. AMORE, ablative surgery, Moulage brachytherapy, and reconstructive surgery; RT, external beam photon radiotherapy; SW, signature weight.

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.[27]

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,

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computed tomography (CT)-planned 3D conformal techniques were used, and in recent years, more developed RT 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, as no meaningful statistical analysis of the IMRT/VMAT group could be performed due to small numbers ($n = 9$). However, as IMRT/VMAT allows 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 multinational, trans-Atlantic 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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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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