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

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Craniofacial growth of children with head and neck rhabdomyosarcoma treated according to the AMORE protocol: a quantitative analysis


Submitted for publication
Abstract

**Background.** In the treatment of pediatric head and neck rhabdomyosarcoma (HNRMS), external beam radiation treatment (EBRT) is frequently applied. One of the most common and disturbing sequelae of EBRT is suppression of craniofacial growth, leading to clinically visible facial asymmetry in 59-97% of the irradiated children. The goal of this study was to quantify the growth of the craniofacial skeleton in children with HNRMS treated with AMORE (Ablative surgery, Moulage technique brachytherapy and surgical Reconstruction).

**Methods.** Children with a follow-up of > 3 years after AMORE were eligible for clinical and quantitative assessment of the craniofacial skeleton. Quantification was performed by two observers, using 14 paired (3D) CT-derived measurements. The left-right differences within each patient were assessed.

**Results.** Eleven patients were included. Two out of the 11 (18%) patients had visible craniofacial asymmetry as a consequence of bone surgery. The remaining nine patients (82%) had a symmetrical appearance of the craniofacial skeleton at clinical assessment. Three out of the nine patients had no CT asymmetry, whereas six had asymmetrical values. Only one of these six patients had severe CT asymmetry due to bone resection. The remaining five patients had 1-2 asymmetrical values. The majority of these values were secondary to mild growth suppression of the mandible at the side of the lesion.

**Conclusion.** The AMORE protocol results in a low incidence of clinical relevant growth disturbance of the craniofacial skeleton.
5.1 Introduction

The overall survival rate for children with rhabdomyosarcomas (RMS) has increased from 25 to over 70% in the past decades. This improvement in survival has been brought about by the application of multimodality treatment protocols and the use of multidrug chemotherapy. RMS is located in the head and neck region in 35-40% of the cases. In this region, especially at 'parameningeal' sites, treatment generally consists of surgery (or biopsy only), neoadjuvant chemotherapy and external beam radiotherapy (EBRT). As a consequence of the increasing number of surviving patients, late toxicity secondary to treatment has become an important issue. Some 77-100% of the children treated for head and neck (HN)RMS suffer from one or more late sequelae. The majority of these sequelae are attributed to EBRT.

One of the most common complications is the development of a disfiguring asymmetric facial appearance, caused by radiation-induced suppression of craniofacial growth. It has long been known that the growth of immature bone can be impaired by irradiation. Numerous studies report growth suppression of the craniofacial skeleton in patients treated with EBRT to the head and neck region compared to normal controls. Growth suppression of the facial skeleton can be caused by very small doses of radiation (4-30 Gy) and can extend beyond the target volume of radiation treatment. The extent and severity depend on radiation type and energy, fraction size, total dose, treatment portals, age at radiation and other treatment given.

Children with HNRMS are extremely susceptible for radiation-induced growth suppression of the craniofacial skeleton for several reasons: (1) the young age at the time of diagnosis, (2) the close proximity of structures in the head and neck region, (3) the large treatment volumes and (4) the high tumoricidal doses (50-60 Gy) given. An asymmetric craniofacial appearance is reported in as many as 59-97% of HNRMS patients treated with EBRT. Next to anatomic and physiologic deficits, this sequel often leads to major psychological problems. Surgery for reconstruction of these deformities is difficult and often includes extensive and repetitive procedures with a high complication rate. Efforts to prevent radiation-induced damage include: (1) reduction of radiation dose in selected cases, (2) hyperfractionation, (3) proton beam radiation, (4) improved dosimetry, e.g. shrinking field technique, three dimensional conformal radiation therapy, intensity modulation techniques and (5) preventive measures, like hyperbaric oxygen therapy and radiation response modifiers. To date, reports analyzing growth disorders after treatment according to new techniques are lacking.

Brachytherapy is not routinely applied in pediatric HNRMS patients. However, the limited dose to healthy tissues due to a rapid fall-off of the dose with distance from the sources, is a well established dosimetric advantage over EBRT. Preservation of bone growth and function have been reported after treatment of childhood sarcomas with brachytherapy.
In 1993, the AMORE procedure was developed, consisting of ablative surgery, moulage technique, brachytherapy, and surgical reconstruction. The aim of AMORE was to optimize local treatment and to avoid EBRT and its long-term sequelae. Results of this treatment in a cohort of 20 children have been reported recently and show a 64% event free survival and 67.5% overall survival at five years, respectively. The present study was conducted to quantify the growth of the craniofacial skeleton in HNRMS patients treated according to the AMORE protocol.

5.2 Patients and methods

5.2.1 Eligible patients and study design
All children with a follow-up of > 3 years after treatment according to the AMORE protocol for unilateral non-orbital HNRMS were eligible for inclusion. Technical details of the AMORE protocol have been reported previously. Patients who received prior EBRT were excluded. Craniofacial appearance was assessed both clinically and quantitatively. For the quantitative analysis, CT-derived measurements of the craniofacial skeleton were performed. The measurements at the side of the lesion and the corresponding contralateral side were compared within one patient. The measurements on the contralateral side were considered normal and were used as control-values. The study protocol was approved by the hospital's medical ethical board and written informed consent was obtained from patients, parents and/or guardians, as appropriate.

5.2.2 CT-data acquisition
Patient positioning was performed by one of the authors (JB) and was maintained using a head brace. Alignment was verified with the scout film. CT scans were obtained from a third generation, double helix CT imager (Twin RTS, Elscint, Haifa, Israel) and were performed according to a standard protocol: contiguous 1.3 mm slices from orbit to mandible, parallel to the orbitomeatal line, in bone window setting. Parameters were set as follows: 0.7 mm reconstruction index, pitch 1.0, 120 kV, 50 mAs.

The image data were transferred to a computer workstation (Omnipro, Elscint, Haifa, Israel). Multiplanar reconstruction software was used to adjust the axial scans, if necessary. Three dimensional (3D) reconstructions of the craniofacial skeleton and mandible were made separately by thresholding technique.

5.2.3 Quantification
Measurements were carried out on the computer workstation by two independent observers, blinded for treatment data, on both axial CT scans and 3D reconstructions. A series of fourteen measurements (13 linear and one angular) of each patient was obtained from both sides of the
Craniofacial growth after AMORE treatment

<table>
<thead>
<tr>
<th>Level</th>
<th>Measurement</th>
<th>CT study</th>
<th>Description</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orbit</td>
<td>1</td>
<td>Axial</td>
<td>Medial orbital-wall length</td>
<td>Distance between the lacrimal bone and the base of the optic strut&lt;sup&gt;39,40&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Axial</td>
<td>Lateral orbital-wall length</td>
<td>Distance between the most anterior tip of the lateral orbital wall and the base of the optic strut&lt;sup&gt;39,40&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Axial</td>
<td>Medial orbital-wall protrusion</td>
<td>Perpendicular distance between the anterior tips of the lateral orbital walls and the lacrimal bone&lt;sup&gt;39,40&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Axial</td>
<td>Lateral orbital-wall angle</td>
<td>Angle formed between a line joining the most anterior and posterior ends of the lateral orbital wall and the sagittal axis&lt;sup&gt;39,40&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>3D</td>
<td>Orbital height</td>
<td>Length of sagittal line from orbitale to the margin of the superior orbital rim&lt;sup&gt;42&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>3D</td>
<td>Orbital width</td>
<td>Length of transverse line from dacryon to the margin of the lateral orbital rim&lt;sup&gt;42&lt;/sup&gt;</td>
</tr>
<tr>
<td>Midface</td>
<td>7</td>
<td>Axial</td>
<td>Zygomatic-arch length</td>
<td>Distance between the anterolateral corner of the zygomatic bone and the insertion of the zygomatic arch into the squamous part of the temporal bone&lt;sup&gt;39,40&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>3D</td>
<td>Heigth of mandibular ramus</td>
<td>Distance fromo-nasal suture (nasion) to infraorbital foramen&lt;sup&gt;41&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>3D</td>
<td>Length of mandibular corpus</td>
<td>Distance anterior nasal spine to infraorbital foramen&lt;sup&gt;41&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>3D</td>
<td>Mandibular length</td>
<td>Distance caudal end posterior nasal spine to pterygoid hamulus</td>
</tr>
<tr>
<td>Mandible</td>
<td>11</td>
<td>3D</td>
<td>Heigth of mandibular ramus</td>
<td>Distance lowest point mandibular incisure to gonion</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>3D</td>
<td>Length of mandibular corpus</td>
<td>Distance gonion to pogonion</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>3D</td>
<td>Mandibular length</td>
<td>Distance most posterosuperior point condyl to pogonion</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>3D</td>
<td>Mandibular length</td>
<td>Distance between most lateral point condyl to mental foramen&lt;sup&gt;41&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>39, Waitzman et al., 1992; 40, Waitzman et al., 1992; 41, Lill et al., 1992; 42, Lo et al., 1996</sup>

CT, computer tomography; 3D, three dimensional

The craniofacial skeleton at three levels: orbit (measurement 1-6), midface (measurement 7-10) and mandible (measurement 11-14) (Table 1 and fig.1). Each measurement was repeated 3 times by each observer and then averaged. In case of extensive bone surgery, measurements involving the removed bony parts could not be performed. The majority of the measurements were chosen from earlier publications because of their proven reproducibility.<sup>39-42</sup>

Two axial CT-slices were studied for each patient. The first slice, at the level of the orbit, was the section parallel to orbitomeatal plane through the lens, optic nerve, rectus muscles, nasal bones and superior part of frontal process maxillary bone (fig.1a). The second slice, at the level of the midface, was the largest section through zygomatic arch and maxillary sinus (fig.1c).
Figure 1. Graphic representation of the 14 measurements used for quantification of the craniofacial skeleton (patient 5). Five measurements were performed on axial CT slices at the level of the orbit (fig. 1a, b) and midface (fig. 1c). Nine measurements were carried out on three dimensional reconstructions of the orbit and midface in anteroposterior view (fig. 1d), the midface in inferior view (fig. 1e) and the mandible in lateral (fig. 1f, g), oblique (fig. 1h) and anteroposterior view (fig. 1i). See Table 1 for description of the 14 measurements.
5.2.4 Data analysis

The Pearson correlation coefficient ($r$) was calculated for the measurements of the two observers. The Bland-Altman statistical method was used to assess the agreement of measurements between both observers. The 95% limits of agreement were set at two standard deviations (SD) above and below the mean. A one sample T-test was used to determine whether the mean difference between both observers significantly differed from zero. To determine the reproducibility of the measurements between both observers, the inter-observer coefficient of variation (CV%) was calculated (equation 1).

\[
CV\% = \frac{\sqrt{\frac{1}{n} \sum_{i=1}^{n} \sigma_i^2}}{\bar{X}} \times 100\% 
\]

(1)
\[ n = \text{the total number of observations}, \quad \sigma_i^2 = \text{the observer variance at point } i \quad \text{and} \quad \bar{X}_i = \text{the average of the two observer measurements at point } i. \]

The effect of treatment on the absolute difference in measurements between the observers was tested using a Mann-Whitney test. A p-value less than 0.05 was taken as the threshold for statistical significance.

The percentual difference (\%D) between the measurement at the side of the lesion and the corresponding contralateral (control) side was calculated (equation 2).

\[
\%D = \frac{\text{value treatment side} - \text{value control side}}{\text{value control side}} \times 100\% \tag{2}
\]

The percentual difference of all 14 measurements was calculated for each patient. In accordance with the method described by Guyuron and co-workers, a 10% threshold for asymmetry and subsequent grading into three classes was chosen. Percentual left-right differences > 10% were considered asymmetrical. Values of 10-20% were graded as mild (class 1), 20-30% moderate (class 2) and > 30% severe (class 3) asymmetry. Measurements that could not be performed due to bone resection were also graded as class 3 asymmetry. For each asymmetrical value, the correlation with the exact site of tumor surgery and brachytherapy was assessed.

5.3 Results

From January 1993 onwards, 33 HNRMS patients were treated according to the AMORE protocol. Seven patients have died, five received prior EBRT and one was lost to follow-up. Of the 20 evaluable patients, nine had an insufficient length of follow-up (< 3 years). The remaining 11 patients were included in this study. Characteristics of these 11 patients are summarized in Table 2. The median age at AMORE treatment was 5.4 years (range 1.2-9.2 years) and the median time between treatment and CT scanning was 5.9 years (range 3.1-10.9 years). It was not possible to perform five of the 14 planned measurements in two patients (patient 1 and 2) and three measurements in one patient (patient 7) due to partial mandibulectomy and zygomatic arch resection and hemimaxillectomy, respectively (Table 2). In the remaining eight patients, all 14 measurements were performed.

An excellent correlation was found between both observers \((r=0.99, p<0.001)\). There was no treatment-related effect on the absolute difference between the measurements of both observers \((p=0.569)\). The variability is illustrated by the Bland Altman plot (fig. 2). The mean difference between the observers was -0.053 mm and the 95% limits of agreement between measurements
Figure 2. Difference between observers at the untreated (■) and treated/at risk (○) side of the craniofacial skeleton, plotted against the mean distance measured. The solid horizontal line indicates the overall mean difference and the dotted horizontal lines the mean ± 2 SD.

*The linear measurements are given in mm, the angular measurement (measurement 4, in degrees) is also included in this figure.

Table 2. Characteristics of 11 HNRMS patients eligible for quantification of craniofacial growth

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (y)</th>
<th>G</th>
<th>Site</th>
<th>Side</th>
<th>Size (APxLRxCC)</th>
<th>Stage</th>
<th>BT dose (Gy)</th>
<th>Bone resection</th>
<th>Age at CT (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.2</td>
<td>F</td>
<td>Parameningeal</td>
<td>L</td>
<td>7x7x6</td>
<td>T2bN0M1</td>
<td>40</td>
<td>partial mandibulectomy; zygomatic arch</td>
<td>17.1</td>
</tr>
<tr>
<td>2</td>
<td>5.6</td>
<td>F</td>
<td>infratemporal fossa</td>
<td>R</td>
<td>5x5x6</td>
<td>T2bN0M0</td>
<td>40</td>
<td>partial mandibulectomy; zygomatic arch</td>
<td>15.2</td>
</tr>
<tr>
<td>3</td>
<td>5.4</td>
<td>M</td>
<td>infratemporal fossa</td>
<td>R</td>
<td>5x4x4</td>
<td>T2bN0M0</td>
<td>50</td>
<td>zygomatic arch</td>
<td>12.6</td>
</tr>
<tr>
<td>4</td>
<td>9.2</td>
<td>M</td>
<td>parapharyngeal</td>
<td>R</td>
<td>5.5x6.5x6.5</td>
<td>T2bN0M0</td>
<td>50</td>
<td>zygomatic arch</td>
<td>13.1</td>
</tr>
<tr>
<td>5</td>
<td>2.9</td>
<td>M</td>
<td>infratemporal fossa</td>
<td>L</td>
<td>not eval</td>
<td>T2bN1M0</td>
<td>45</td>
<td>zygomatic arch</td>
<td>6.0</td>
</tr>
</tbody>
</table>

| 6  | 1.7     | F | Non-parameningeal | R    | 2x2x3          | T2aN0M0 | 45           | hemimaxillectomy | 4.8           |
| 7  | 1.2     | F | hard palate | L    | 2x2x2          | T2aN1M0 | 45           | hemimaxillectomy | 10.3          |
| 8  | 3.8     | M | parotid region | L    | 5x5x3          | T2bN1M0 | 46           | zygomatic arch | 10.2          |
| 9  | 2.4     | F | oropharynx | L    | 4x6x3          | T2bN1M0 | 45           | zygomatic arch | 8.3           |
| 10 | 8.9     | M | nose/maxilla | R    | 1.5x1.5x1.5    | T2aN0M0 | 45           | zygomatic arch | 13.5          |
| 11 | 7.2     | M | neck | R    | not eval       | T1aN0M0 | 40           | partial mandibulectomy; zygomatic arch | 10.8          |

HNRMS, head and neck rhabdomyosarcoma; Age, age at time of AMORE treatment; G, gender; Size, size at initial presentation; APxLRxCC, maximum dimensions (in cm) of the tumor in anteroposterior, left-right and craniocaudal direction. Stage, TNM stage at initial diagnosis; BT, brachytherapy; Gy, Gray; CT, computer tomography; not eval, size of the tumor could not be evaluated because of surgery before referral.

Carried out by the two independent observers were -2.67 and 2.57 mm. The mean difference (-0.053 mm) did not significantly differ from zero (p=0.496). The inter-observer coefficient of variation was 2.1%. For the quantitative analysis of asymmetry, the measurements of both observers were pooled.
Two out of the 11 (18%) patients (patient 1 and 7) had visible craniofacial asymmetry as a consequence of bone surgery (fig. 3). The remaining nine patients (82%) had a symmetrical appearance of the craniofacial skeleton at clinical assessment. Out of these nine patients, six patients (patient 2, 3, 4, 8, 10 and 11) had CT asymmetry (Table 3). In the three remaining patients (patient 5, 6 and 9), no asymmetrical CT values were found.

In the two patients with clinical asymmetry (patient 1 and 7), CT-evaluation showed asymmetry at all three levels (orbit, midface and mandible) in both patients. The measurements that could not be performed were graded as class 3 (Table 3). The remaining CT measurements revealed four asymmetrical values in each patient (Table 3). Patient 7 had mild (class 1) asymmetry at all three levels, patient 1 had also moderate values (class 2) at two levels (orbit and midface).

Of the remaining nine patients without clinical asymmetry, three also had a symmetrical craniofacial skeleton at CT evaluation. One patient (patient 2) had non-quantifiable asymmetry in five measurements due to bone resection, which were consequently graded as class 3 (Table 3). The nine evaluable CT measurements in this patient were symmetrical. The skeletal asymmetry was well camouflaged by the overlying soft-tissues used in reconstructive surgery. In five patients, one or more CT measurements showed a >10% difference between the side of the treatment and the normal side. A total of seven asymmetrical CT-values were found in these five patients (Table 3). Three patients had only mild CT asymmetry, two patients in one out of 14 measurements (patient 3 and 8) and one patient in two measurements (patient 4). Two patients also had a single moderate asymmetrical value (patient 10 and 11). The mild asymmetrical
values involved the mandible (measurements 11 and 12) in four patients (Table 3). In all of these four patients, the brachytherapy mould was positioned close to the mandible. In three out of four patients (4, 8 and 11), the position of the mould exactly matched with the site of asymmetry, suggesting direct radiation-induced growth suppression (Table 3). The CT-values displaying moderate asymmetry involved measurement 3 (medial orbital wall protrusion) and were based on absolute left-right differences of 0.8 and a 1.8 mm, respectively (Table 3).
When class 3 asymmetry as a consequence of bone surgery is excluded, quantification revealed a total number of 15 mild to moderate asymmetrical CT values (Table 3). In 11 out of 15 asymmetrical values, asymmetry was caused by a smaller value of the measurement at the side of the lesion (Table 3). This indicates a true inhibition of bone growth at the side of the lesion, rather than an expression of 'normal' asymmetry. Four measurements had a larger value at the side of the lesion. One of these four involved the orbital height (measurement 5, patient 7). A larger value at the side of treatment, i.e. a larger distance between the superior and inferior orbital rim, can also indicate growth suppression. Two asymmetrical measurements with a larger value at the treated side concerned measurement 3, with small absolute differences of 1.1 mm (patient 1) and 1.8 mm (patient 11), respectively. These small differences can be caused by 'normal' asymmetry. The larger distance between anterior nasal spine and infra-orbital foramen (measurement 9) found at the side of the lesion in patient 1 cannot be explained. Only eight of the 15 asymmetrical values matched exactly with the site of surgery and mould position (Table 3). Therefore, the influence of AMORE treatment on craniofacial growth also extended beyond the site of treatment.

Other cosmetically important craniofacial sequelae included a soft-tissue defect (patient 1, 4, 5, 8 and 10), hypertrophic scar formation (patient 1, 2 and 4), (partial) facial nerve palsy (patient 1, 5, 8) and deviation of the cartilaginous and bony nasal pyramid (patient 6 and 7) (Table 3, fig. 3). Functional sequelae consisted of disorders of dental development (2, 6, 7, 8, 9), malocclusion (patient 1, 2, 8), disorders of articulation (rhinolalia aperta) (patient 4, 7 and 9) and epiphora (patient 6) (Table 3). No trismus, soft-tissue fibrosis and swallowing disorders were encountered.

5.4 Discussion

Local treatment for childhood HNRMS with EBRT has been reported to lead to craniofacial asymmetry in 59-97% of the patients. The use of AMORE instead of EBRT resulted in a very low incidence of clinically relevant craniofacial growth disturbances. Only two out of 11 patients (18%) had clinically detectable asymmetry of the craniofacial skeleton. In both patients, extensive bone resection was performed. The remaining nine patients had a symmetrical appearance at clinical assessment. Three out of these nine patients had no CT asymmetry, whereas in six patients asymmetrical CT values were found. In one of these six, skeletal asymmetry was secondary to bone resection. The remaining five patients had only a limited amount of asymmetrical values. Asymmetry was mainly mild and was caused by growth suppression at the side of the lesion.

Most of the studies reporting craniofacial growth disorders in HNRMS patients rely on clinical observation. Quantification allows for a precise definition of the site and extent of the growth
disorders and is mandatory to reach conclusions as to the possible benefit of alternative therapeutic strategies in avoiding radiation-induced growth suppression. In most quantitative studies, tracings of lateral cephalometric radiographs of irradiated patients are compared with normal values.\textsuperscript{13,17,19,43} This method allows for the assessment of general growth suppression, but left-right differences cannot be quantified. Craniofacial skeletal measurements based on (three-dimensional) CT scans proved to be consistent and precise.\textsuperscript{40,44,45} However, there are only few quantitative studies using CT-scanning.\textsuperscript{16,42,46}

In this study, the measurement at the side opposite to the tumor within one patient was used as normal value. Doing so, a perfectly matched control is ensured. However, a certain degree of asymmetry between both sides of the craniofacial skeleton is also encountered in the general population. Left-right differences may vary with region, but are in the range of 1-9\%, even in subjects with esthetically pleasing faces.\textsuperscript{47-51} A 10\% threshold for asymmetry was taken for all 14 measurements. Due to the small absolute value of measurement 3 (medial orbital wall length), limited absolute left-right differences have resulted in a large percentual differences, also in favor of the side of the lesion (Table 3). Therefore, the clinical relevance of the moderate asymmetrical values found in patient 10 and 11 is deemed unsignificant. In the patients displaying mild suppression of mandibular growth, a strong relation with the position of the brachytherapy mould was found. This finding suggests that mandibular growth is susceptible to small doses of radiation. Nwoku and Koch stated that growth in the condylar region of the mandible is influenced by low radiation doses, whereas Göz and co-workers did not find an increased susceptibility of the mandible to the influence of radiation.\textsuperscript{18-43} Nevertheless, based on our findings, a close relation of the mould to the mandible has to be avoided, if possible. Asymmetrical values were also found beyond the exact site of surgery and brachytherapy. This finding cannot be explained by radiation-induced growth suppression. A possible explanation is the influence of the AMORE procedure on the adjacent soft tissues, normally exerting a stimulus for bone growth.\textsuperscript{52}

The AMORE protocol did not succeed in the prevention of visible craniofacial growth disorders in two out of three patients with extensive bone surgery. Therefore, in patients in whom bone resection is considered necessary in the planning of the AMORE procedure, the effects on craniofacial growth should be weighed against the late effects of EBRT.

A drawback of this study is the small number of patients included. Also, the majority of the patients included have not yet completed their pubertal growth spurt. Two patients without asymmetrical growth (patient 5 and 6) were both young at the time of CT measurements and had a limited follow-up duration (3 years) after treatment. Growth disorders in these patients might become visible after a longer follow-up time. As for the functional consequences of the AMORE protocol, its value remains to be determined by comparing our group with a matched control group of patients irradiated according to new techniques.
In conclusion, severe (class 3) asymmetry was only experienced in patients after bone resection. Growth disorders in patients without bone resection were not visible on clinical observation. The results of quantification in these patients showed only limited growth disorders at the side of the lesion. We feel that the AMORE protocol reduces the risk of radiation-induced growth suppression of the craniofacial skeleton, especially in those patients in whom tissue (bone) sparing surgery is performed and mould position is not close to the mandible. The rapid fall-off of the brachytherapy dose beyond the target site reduces the radiation dose to growing bone and prevents soft-tissue fibrosis. Together with immediate surgical reconstruction using uncompromized muscular tissue, radiation-induced damage can be limited compared to EBRT.
References


