

# Combined Soft and Hard Tissue Facial Lesions In Early Childhood Pioneering the Diagnosis of the Tumor Predisposition Syndrome Neurofibromatosis Type 1

REINHARD E. FRIEDRICH<sup>1\*</sup>, FELIX K. KOHLRUSCH<sup>1\*</sup>, CHRISTIAN HAGEL<sup>2</sup> and MANFRED GIESE<sup>3</sup>

<sup>1</sup>Department of Oral and Craniomaxillofacial Surgery, Eppendorf University Hospital, University of Hamburg, Hamburg, Germany;

<sup>2</sup>Institute of Neuropathology, Eppendorf University Hospital, University of Hamburg, Hamburg, Germany;

<sup>3</sup>Department of Oral and Craniomaxillofacial Surgery, Military Hospital, Hamburg, Germany

## Abstract

**Background/Aim:** Neurofibromatosis type 1 (NF1) is an autosomal dominant hereditary tumor predisposition syndrome. The haploinsufficiency of the cells of NF1 patients is also evident in skeletal development and maintenance. Bone deformities of the facial skull often occur early in life and are topographically associated with a certain nerve sheath tumor, the plexiform neurofibroma (PNF), which is considered a precursor to malignant degeneration. The aim of the study was to analyze skeletal changes in the jaw and teeth over a longer period to differentiate between tumor-associated, development-dependent, and adaptive processes.

**Case Report:** The male patient, who was 2 years and 9 months old at the time of the initial examination, had developed a right-sided facial PNF. The patient, who underwent multiple surgical procedures, was examined clinically and radiologically over a period of 12.5 years. The follow-up examination revealed both the progression of the deformity in the ramus and jaw angle area and the influence of the local tumor on tooth development. However, radiological findings showed that the tumor-coated bone was capable of adaptive functions such as maintaining the condyle-fossa relationship despite significant dystrophy, and that the emergence of permanent teeth was an indicator of the preservation of the local differentiation capacity of the hard tissue, which must be ensured over many years to be successful.

**Conclusion:** The analysis of jaw dysmorphia and the examination of the stages of dentition are valuable diagnostic aids for assessing the dysplastic component of an often-disfiguring facial tumor, which in rare cases can transform into a malignant peripheral nerve sheath tumor. In individual cases, dental findings can provide clues for estimating the timing of the interaction between PNF and hard tissues which can apparently date back to the prenatal phase. The skeletal findings can already be identified on plain radiographs of the skull.

**Keywords:** Neurofibromatosis type 1, mandible, plexiform neurofibroma, bone dysplasia, MPNST, dentition, aplasia, timing of oral plexiform neurofibroma development.

\*These Authors contributed equally to this work.



Prof. R.E. Friedrich, MD, DMD, PhD, FEBOMFS, Department of Oral and Craniomaxillofacial Surgery, Eppendorf University Hospital, University of Hamburg, Martinist. 52, 20246 Hamburg, Germany. Tel: +49 40741053259, e-mail: rfriedrich@uke.de

Received January 15, 2026 | Revised February 2, 2026 | Accepted February 19, 2026



This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

©2026 The Author(s). Anticancer Research is published by the International Institute of Anticancer Research.

## Introduction

Neurofibromatosis type 1 (NF1), an autosomal dominant hereditary tumor predisposition syndrome, is a relatively common human disease with an incidence of 1:2500 to 1.3000 live births (1). The characteristic nerve sheath tumor (neurofibroma) of NF1 occurs particularly frequently and often very conspicuously in the integument causing considerable aesthetic and functional disturbances (2). However, NF1 is also characterized by changes in the skeletal system, both systemically in bone maintenance (osteoporosis) (3) or smaller than average total body height (4), and locally through deformities of individual bones (*e.g.*, tibial pseudarthrosis), as well as larger bone segments (*e.g.*, elongation of an extremity) (5). In the skull region, in addition to sphenoid dysplasia (6), which is an osseous lesion listed as a diagnostic criterion for NF1 (7, 8), further deformities of the facial skull have been described (9), which usually occur on one side (10), and are topographically related to a nerve sheath tumor that is considered pathognomonic for the disease, the plexiform neurofibroma (PNF) (11). PNF is considered a congenital tumor (12) or at least a tumor manifesting in early childhood (4, 13). On the other hand, PNFs were also diagnosed late, although it was pointed out that craniofacial tumors had been identified in the first year of life and the diagnosis of the entity had been confirmed very early on (13, 14). PNF develops from Schwann cells or their precursors, probably like all neurofibromas (15, 16). Craniofacial PNF often develops in the peripheral branches of the 5th cranial nerve (17).

*Facial bones.* The skeletal findings associated with trigeminal PNF in NF1 patients have been summarized by Sailer *et al.* in a diagnostic list (18, 19) (Table I), which has been confirmed and further elaborated in later studies (20-22). While clinical findings accessible for inspection (*e.g.*, facial swelling) may vary (10, 18, 19) and thus may escape initial diagnosis (23), the coincidence of radiological findings of the jaws was considered diagnostically relevant (18, 19), meaning that a suspected diagnosis of a

craniofacial PNF can be made based on their simultaneous detection (24), even in children (25, 26, 27). However, the findings are subject to considerable variability in individual cases. Bone alterations may severely influence the individual phenotype thus confirming the initial diagnosis through conspicuous findings (25-27) but on the other hand may escape initial assessment in cases of less conspicuous tumors or bone deformities (10, 28). In terms of phenotype expression, time of occurrence (29) and the spatial characteristics (25) of tumor-associated bone deformation during childhood and adolescence can have a significant influence on the respective constellations of hard tissue findings, *e.g.*, facial symmetry and dentition (23, 30). The characteristic bone changes in the jaws are related not to volume but to the extent of invasive craniofacial PNF (30). The spatiotemporal variability of skeletal findings requires careful monitoring of the findings over time (4, 25, 29, 30, 31-34). The influence of tumorous changes in the masticatory muscles on the shape of the affected side of the mandible, which appears to be predominantly effective during the development phase of the bone and is an unilateral finding in most cases, probably varies depending on the time of tumor development and the extent of the masticatory muscles affected by the lesion(s) in each case (34). The variable spatiotemporal tumor spread into the masticatory muscles and the functional impact on muscles and bone probably contributes to the wide variety of bone deformities of the lower jaw, as has been addressed in recent publications (18-29).

*Teeth.* Studies of dentition in NF1 patients have shown that the tooth shape, size and emergence of the permanent dentition of the PNF-affected jaw regions correspond to those of the unaffected side (35). However, an oral lesion may cover an already emerged tooth, especially permanent molar (36). The soft tissue tumors covering the teeth were often identified as oral neurofibromas (25, 36). Orally growing neurofibromas are to be expected in extensive facial PNF that have infiltrated the cutaneous terminal territories of the second and/or third trigeminal nerve branch(es) and are often continuous with externally visible tumors (4, 37).

Table I. Review of the characteristic findings for facial plexiform neurofibroma according to Sailer et al. (18, 19) for the patient between the ages of 2.75 and 15.3 years.

Diagnostically relevant clinical and radiological findings as reported by Sailer et al. (1988)	Patient (Age) 2 years 9 months	Patient (Age) 5 years, 6 months	Patient (Age) 6 years, 10 months	Patient (Age) 15 years, 4 months
1. Center of the chin is shifted toward the affected side.	N.d.	Yes	Yes	Yes
2. Usually slight swelling of the cheek or intraoral soft tissue.	Yes	Yes	Yes	Yes
3. (Deeply) retracted incisura semilunaris (coronoid notch)	(Yes)	Yes	Yes	Yes
4. Coronoid notch retraction results in pseudo-elongation of the condylar and/or muscular processes.	Yes	Yes	Yes	Yes
5. Mandibular ramus is deformed or hypoplastic and often shows perforating defects (Bruns, 1891).	Yes	Yes	Yes	Yes
6. The jaw angle is flat or absent.	Yes	Yes	Yes	Yes
7. Hypoplastic or absent mandibular corpus	Yes	Yes	Yes	Yes
8. Tooth retention on the affected side of the lower jaw	No	Yes (first molar)	Yes (first molar)	No
9. Hypoplastic upper jaw and zygomatic area on same side as mandibular deformity	No: Tuber region Yes: Zygomatic arch	No: Tuber region Yes: Zygomatic arch	No: Tuber region Yes: Zygomatic arch	Yes: Tuber region Yes: Zygomatic arch
10. Tooth retention on the affected side of the upper jaw	No (deciduous teeth)	No (mixed dentition)	Yes (soft tissue mass)	No (emergence of first molar)
11. Restricted forward movement in the affected joint	N.d.	N.d.	N.d.	N.d.
12. All patients depicted in the literature and all of our patients have a low position of the auricle on the affected side.	N.d.	N.d.	N.d.	Yes

N.d.: No data.

In contrast to permanent dentition, the emergence of teeth of the first dentition in NF1 patients with oral neurofibroma appears to be not hindered by oral PNF (35). Overall, the shape and structure of the teeth in NF1 is inconspicuous and consistent with anthropological data (36). However, commonly known anomalies of the occlusal surfaces can be observed somewhat more frequently in NF1 patients (38).

Numerous reports have contributed to describing the NF1 craniofacial skeletal phenotype of patients affected by extensive facial PNF (24, 25, 39). Many practitioners have sought to alleviate the often severely impaired orofacial features through surgical interventions (40-43). However, little data is available on the progression of dental and skeletal findings from childhood to adulthood (26, 27, 29). This report aims to contribute to the radiological and clinical characterization of tumor-associated jaw changes and phases of dentition during the period from childhood to adolescence in an NF1 patient with extensive PNF both to distinguish between tumorous and dysplastic components of orofacial manifestations of the disease in

this region and to illustrate interrelationships between an infiltratively growing soft tissue tumor and associated osseous changes over time.

### Case Report

*Early diagnostic features. Medical history.* Since birth, swelling of the right upper eyelid and a protruding right eye had been noticed. Two months after birth, hydrophthalmia was diagnosed and treated repeatedly with surgery (angulocision, trabeculotomy) during the first few months, followed by gum changes on the same side at the age of 6 months. At the age of 2 years, swelling of the right lip was observed and the child was referred for further treatment.

*General findings.* The young patient was first presented at the outpatient clinic of the Department of Oral and Maxillofacial Surgery at the age of 2 years 9 months because facial asymmetry with soft tissue excess on

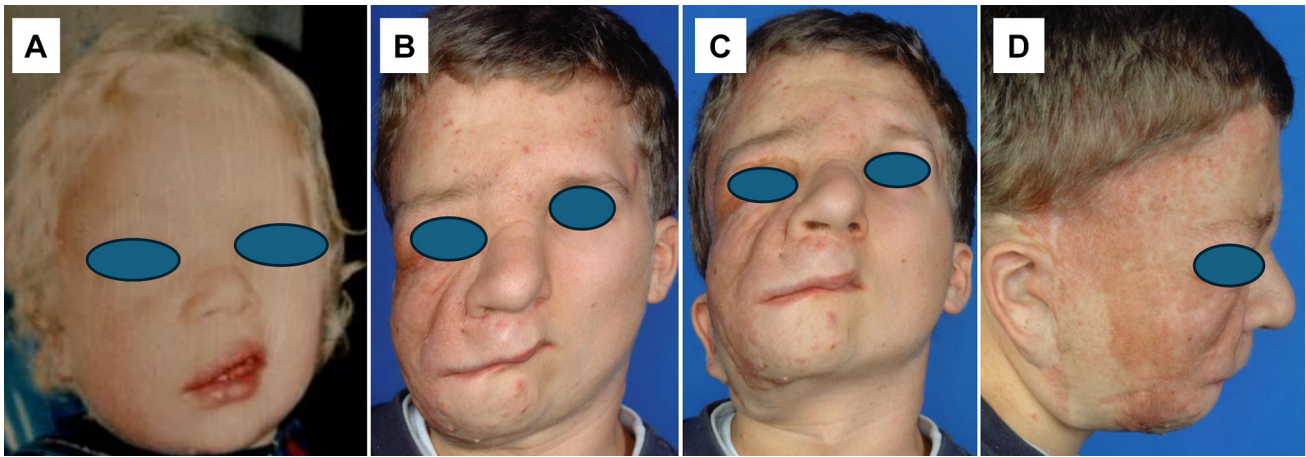


Figure 1. Development of facial plexiform neurofibroma. (A) During the initial examination, the following are noticeable on the right side of the face: right-sided ptosis, especially lateral (“lying paragraph shape” of eyelid), enlarged and laterally lowered nostril, enlarged lips (which appear to extend slightly beyond the midline to the opposite side), drooping corner of the mouth, and voluminous cheek. (B) Image of the 15-year-old boy. Soft tissue drooping from the brow region to the chin, enlarged right nostril and right side of the lips, deviation of the chin region toward the tumor side. The excess tissue in the right cheek region is no longer visible after multiple surgical procedures. (C) The view from the front-bottom clearly shows the lower attachment of the pinna on the tumor side. (D) The side view shows the characteristic pigment disorders of the facial skin, which partially mark the diffuse neurofibroma, the multitude of scars as residues of the correction of the facial disfigurement, and the tumor infiltration of the external ear, which is conspicuous in the lower part of it.

the right side raised suspicion of a tumor or dysplasia (Figure 1). During the initial examination, the enlarged cheek region was noticeable, as was asymmetry of the eyelids, *i.e.*, tumor mass of lateral upper lid [so-called lying paragraph form of the lid edge (4)]. Further physical examination revealed café-au-lait spots on the skin and discrete axillary freckling.

**Oral cavity and teeth.** The oral findings showed a complete set of deciduous teeth. Noteworthy was the wide gap between the first and second deciduous molars of the right jaws’ side and soft tissue swelling in the right retromolar region of the lower jaw (Figure 1A). The X-ray taken using the panoramic view (PV) technique confirmed the complete development of the first dentition on both sides of the body and the comparatively more distal position of the two right second deciduous molars [*i.e.*, less mesial migration of the tooth germ and thus dystopic (distal) tooth development within the jaw ridge]. This revealed the outline of the permanent lower right first molar in the jaw angle with a transition to the ramus, and the permanent upper right first molar had a widened bone bridge to the

second deciduous molar. Both teeth were in the stage of completed crown formation. Compared to the unaffected side with close contact between the most distal deciduous teeth and the first permanent molars, there was a distinct gap on the right side between the retained first molars and the second deciduous molars in both jaws (Figure 2A).

Regarding anterior teeth of the permanent dentition, the frontal teeth had symmetrically emerged and tooth buds 34-44 were present. The antimeres of permanent teeth of both jaws were at the same stage of development and position to replace the respective deciduous teeth (35). On the side of the facial tumor swelling, the bone surrounding the mandibular permanent first molar’s crown was radio-translucent compared to the unaffected side. Around the crown of the tooth, the lesion was assessed as a cyst-like osteolysis (23), which had dissolved the cortical boundary of the lower jaw to the oral cavity. There was no cyst-like formation like the mandibular situation in the right distal maxilla.

**Facial bones. Jaws.** Panoramic view. In the upper jaw, the right tuber area appeared hypoplastic on the radiograph,

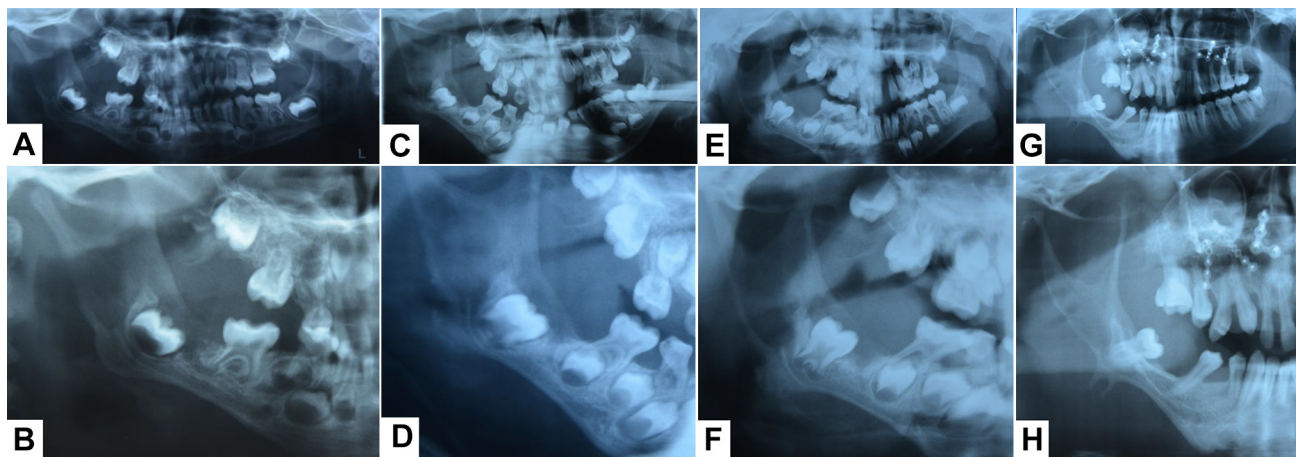


Figure 2. A series of panoramic images of the jaw in a case of right-sided facial plexiform neurofibroma. (A), (C), (E), and (G) show overview images of the jaw, while (B), (D), (F), and (H) show the diagnostic relevant details of the right jaw regions. (A) The child's fully erupted primary dentition. The overview already clearly shows the distalization of both first molars of the permanent dentition and a deeper semilunar notch on the right side. The second deciduous molar of the lower jaw on the right side is further distal in the tooth row than its corresponding tooth on the other side of the jaw. (B) Detail from (A): shows complex skeletal malformation and preservation of anatomical landmark (mental foramen). (C) The illustration shows the development of permanent teeth. The lower second permanent premolar on the right side is developing more distally than on the opposite side and is following the position of its predecessor. (D) Due to the distalization, the bone gap ("spacing") between the lower two premolars is significantly larger on the right than on the left. The right outer jaw angle has interrupted continuity of cortical hyperdensity compared to the preliminary image. (E) Further development of the teeth, with tooth 46 emerging. (F) Above the crown of tooth 46 is extensive oral soft tissue shadowing. The right outer angle of the jaw appears to be developing a superficially blurred bone proliferation. (G) In the meantime, both processes have thinned and extended caudally, the coronoid notch is deep and wide, and the jaw angle has been replaced by two spine-like exostoses. (H) Tooth 46 has emerged with the formation of an alveolar process. Over the entire time interval (B, D, F, H), the compacted bone area dorsal to tooth 46 has been preserved. This bone density defines the transition to the translucency of the ramus. Tooth 45 has emerged into the dental arch and is located further distally than the second premolar on the other side of the jaw (G). The mental foramen is located between the two premolars (H). [Age: 2 years, 10 months (A,B), 5 years, 6 months (C,D), 6 years, 10 months (E,F), 15 years, 4 months (G,H)].

*i.e.*, rounded cranially and slightly shortened, so that the existing tooth buds (permanent first and second molars with the direction of emergence toward the oral bone surface) were oriented more distally than the antimeres on the opposite side (Figure 2A and B). In the lower jaw, mesial to the retained crown of tooth 46, the mandibular corpus was hypoplastic in the vertical dimension and basal shape formed an arch between the outer jaw angle and the canine region, so that an antegonial notch had developed on the tumor side, which was absent on the unaffected side. The dorsal aspect of the ramus appeared somewhat shortened, so that the transition to the jaw angle was slightly further cranial on the right than on the left. Furthermore, the distal parts of the right mandible showed further abnormalities, such as a smaller sagittal extension (narrowing) of the ramus, and an extensive translucency of the ramus starting above the deeper

situated right mandibular foramen and extending to just below the semilunar *incisura* or notch (a.k.a. as 'coronoid notch'). On the right side, the mandibular foramen was located just below the occlusal plane of the impacted first molar. Other notable features were a deepened coronoid notch with a noticeably narrow articular process and a capitulum that was barely distinguishable in shape from the collum. At this point in time, the right muscle process appeared normal and symmetrical in position and outline compared to the left. The lateral cephalogram revealed the difference in the basal limitation of the mandible with unilateral development of an antegonial notch. The contours of the rami largely overlapped in the frontal part. However, a sagittal shortening of the tumor side was already apparent in the comparison of the posterior edge and jaw angle of the rami, with a unilateral wide-open outer jaw angle (Figure 2). A continuous basal

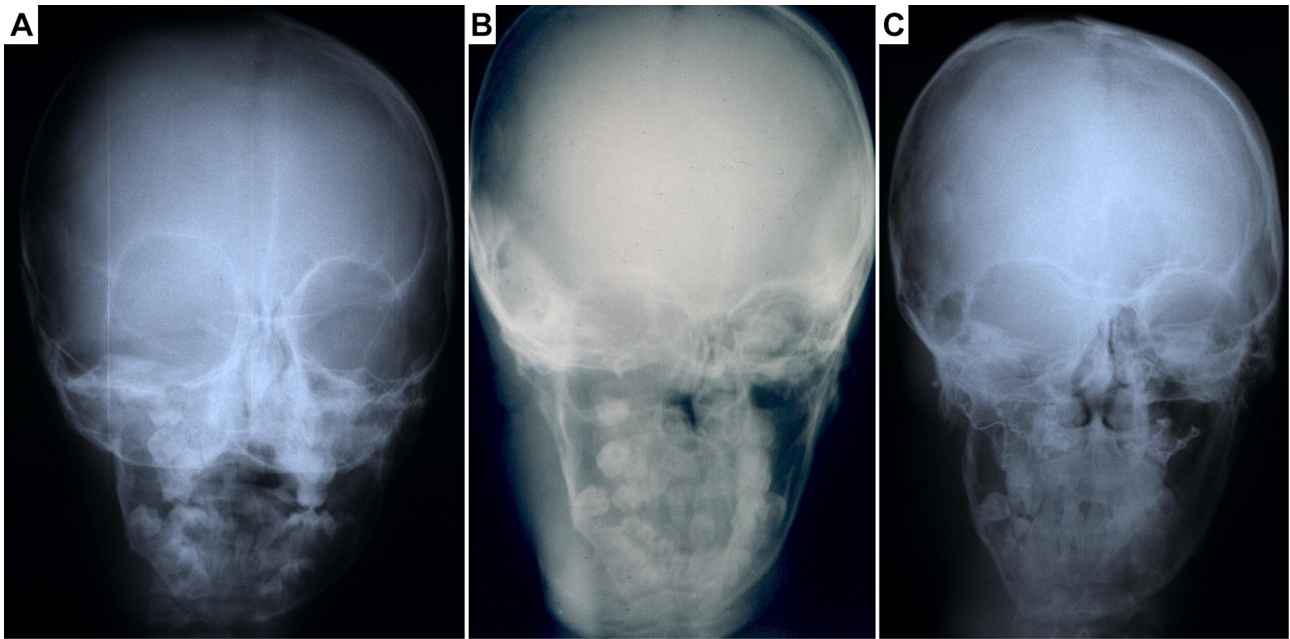


Figure 3. Posterior-anterior cephalograms of the patient. (A) Even the first overview shows the enlarged orbital opening on the right side. The upper orbital rim is above the left one. The center of the lower jaw deviates slightly to the right. There is a retraction of the right corpus base (antegonial notch) (5 years, 6 months). (B) The right retained permanent first molar is surrounded by a cyst-like radiolucency that extends into the ramus. The right curvature of the mandibular body is flattened. There is a noticeable soft tissue shadow in the right temporal-frontal region (6 years, 10 months). (C) The image after Le Fort I osteotomy shows the slightly outward-facing, arcuate deformation of the ramus. After the procedure, the mandible continues to deviate toward the tumor side (15 years, 4 months).

cortical line of compaction had developed on both sides of the mandible (22). The PVs, selected projections, lateral and posterior-anterior cephalograms illustrated the development of dysmorphia over time, which was particularly noticeable in the lower jaw (Figure 2, Figure 3, Figure 4, and Figure 5).

In summary, the overall appearance of the lower jaw showed distinct hypoplastic regions on the right side, exclusively located in distal parts, *i.e.*, in the jaw angle and ramus region. This combination of findings is often seen in NF1-patients with FPNF (24) but rarely noticed in small children (33, 34, 45). Taking into account the soft tissue and hard tissue findings of the face, the findings suggested that the child had NF1.

For further diagnosis, an oral biopsy was taken from the soft tissue tumor. The diagnosis of the tissue sample confirmed an oral neurofibroma and supplemented the findings already recorded to arrive at a final diagnosis of NF1.

*Follow-up.* In the following years, four facial surgeries were performed to reduce the cheek tumor with a facelift, correction of ptosis, and reduction of the nasolabial tumor and lip corner tightening. An ophthalmological examination performed at the age of 5 confirmed that the right eye could only perceive exposure to light.

*5 Years, 6 months.* On plain radiographs, the basal horizontal margin of the corpus merged almost imperceptibly at the outer angle of the jaw into the raised posterior margin of the ramus, *i.e.* there was a wide open jaw angle. The outer jaw angle was significantly larger on the tumor side than on the unaffected side. This outer frame of the ramus-corpus angulation correlated with a wide-open inner jaw angle. The upper branch of the jaw angle was formed by a mesial shift of the subcondylar part of the ramus, while the joint-bearing section of the ramus maintained its relationship to the glenoid fossa. This caused the joint neck to shift basally

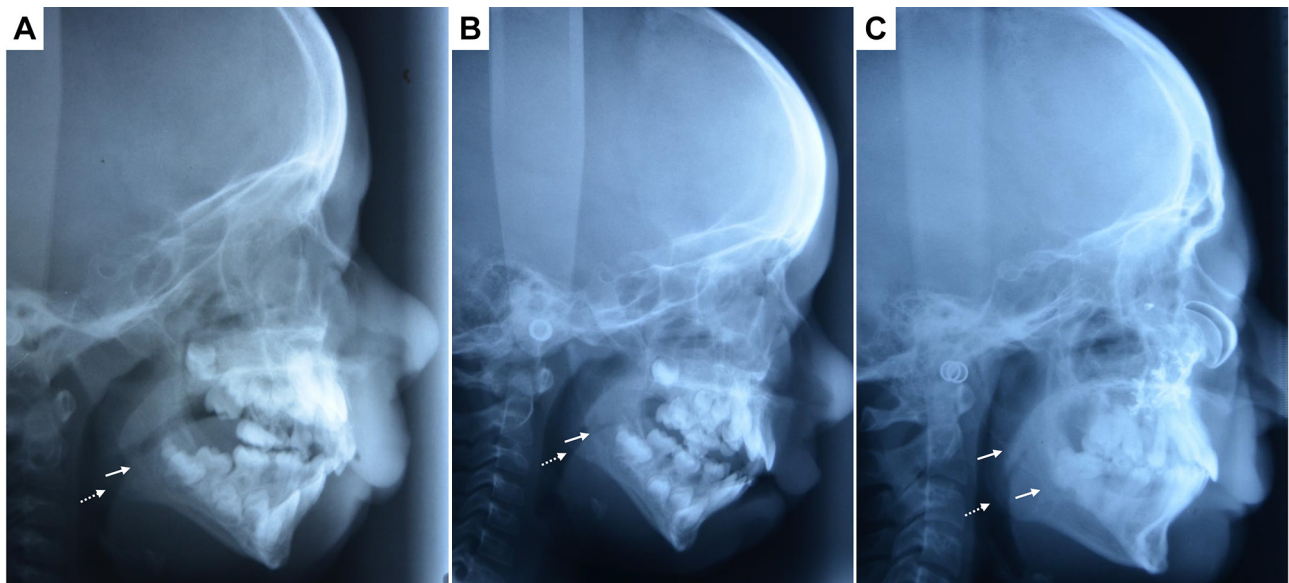


Figure 4. Lateral cephalograms of the patient. (A) The posterior edge of the ramus on the tumor side (solid arrow) is significantly more anterior than that on the healthy side (dotted arrow) (5 years, 6 months). (B) The conditions remain constant in the follow-up examination (solid arrow: jaw angle on the affected side; dotted arrow: jaw angle on the healthy side) (6 years, 10 months). (C) As the patient has grown significantly older, a prominent jaw angle has developed on the healthy side (dotted arrow). In contrast, the jaw angle (lower solid arrow) and ramus (upper solid arrow) on the affected side remain hypoplastic. Additional finding: Pneumatization of the sphenoid sinus extends into the postsellar region (46) (15 years, 4 months).

towards the mesial while the joint process maintained its position in the fossa. Thus, the dorsal, linear relationship between the muscular process and the ramus remained unchanged. However, bending of the condylar process to the fossa increased the intercondylar distance between the two process tips, and this sagittal difference in the relationship between the bone segments was noticeable when comparing the sides (22). Whereas enlarged intercondylar distance was noticeable, the narrowing of the articular process was constant to the previous radiograph, as was the line-like tapered, caudally curved contour of the zygomatic arch and the wide, flat glenoid fossa. At this point, there was no obvious difference in the root development of the permanent first molars of the lower jaw. In contrast to the left side, no permanent second molar anlage was recorded on the right (25). The permanent right lower molar bordered directly on the flat translucency of the ramus, which was interpreted as a concave thinning of this bone segment (22, 25). An indistinct radiopaque lesion was visible at the angle of the jaw, the basal end of which

was confluent with the angle of the jaw below the crown of the right molar. In this area, the basal cortical continuous radiopacity of the bone margin was interrupted. This uneven bone margin could represent both signs of initial bone apposition.

*Midface and skull base.* The skull overview image confirmed the clinical impression of a right-sided orbit with caudal displacement of the infraorbital rim (44) and sphenoid dysplasia. The contour of a very thin zygomatic arch, curved caudally, was visible on the right side. In line with the patient's age, there had been no pneumatization of the sphenoid bone to date (LC, OPG) and the sphenoid-occipital junction was open (39).

*6 Years, 10 months.* On PV, the radiological findings of the teeth and jaws were like those of the previous year. A striking finding was the now obvious slowdown in root growth of the first molar on the affected side, which was embedded in an enlarged pericoronal translucency. This

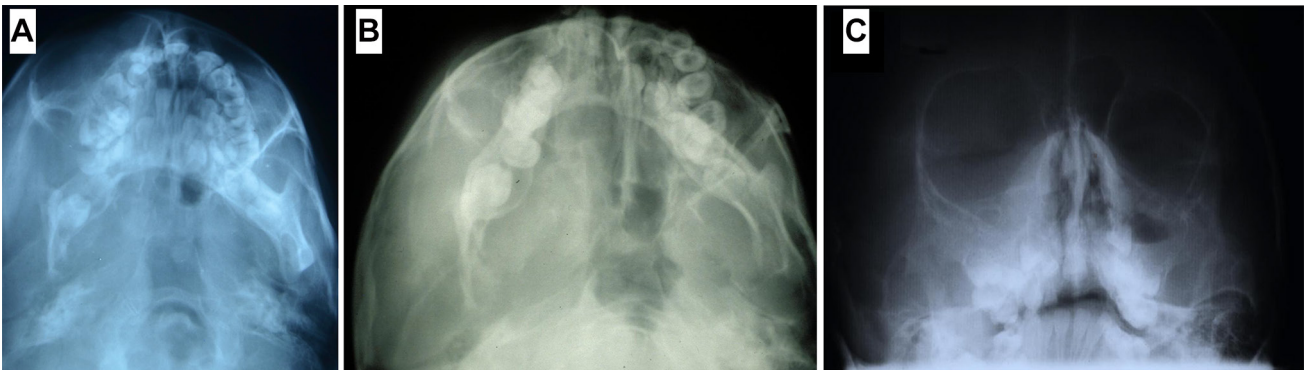


Figure 5. Axial (A, B) and anterior-posterior midface overview image (C) of the patient. (A) The axial image shows the transversely tapered ramus area on the right side. Pericoronar brightening around tooth 46 (5 years, 6 months). (B) With a slightly altered projection, the ramus, which is flattened in the corpus region and slightly curved laterally in the ramus region, appears virtually unchanged several years later (15 years, 4 months). (C) The orbital view shows that the right anterior frame of the orbital bones opening is both higher cranially and extends further down caudally. The right infraorbital foramen appears enlarged (6 years, 10 months).

translucency of the angular bone segment was separated disto-cranially from the extensive ramus translucency by a bone bridge, that is, both bone findings of distinct radiotranslucencies still were spatially separated (Figure 2). The soft tissue shadows of the oral tumors covering the retained molars were constant in extent. The posterior edge of the right ramus was deformed anteriorly into a slightly convex arch segment. The deformation was apparently the result of mesial translation of the right-sided shortened ramus-corporum segment while maintaining the condyle-fossa relationship in the joint, *i.e.*, an adaptive deformation of the shortened tumor-side, joint-bearing bone. Now, a spur-like bone extension defined the outer angle of the jaw. In retrospect, the present bone findings were already marked by irregular bone border of the dorsal jaw angle in the X-ray taken 14 months ago. The lateral cephalogram confirmed the unilateral dysplasia of the right ramus contour seen in the preliminary X-ray. The almost linear transition from the posterior edge of the ramus to the basal border of the body was clearly visible.

In summary, follow-up examinations of the child showed progressive dentition, deepening of the coronoid notch, and deformation of the posterior wall of the ramus with suspected exophytic bone formation at the outer angle of the jaw on the tumor side.

15 Years, 4 months. The PV illustrated that in the meantime, the patient's right eye had been enucleated as a result of tumor destruction and replaced with a prosthesis. The current treatment was aimed at correcting the PNF-associated facial scoliosis (25), which had caused a complex malposition of the jaws and was corrected by Le Fort I osteotomy of the upper jaw with adjustment to improve occlusal contact between the rows of teeth (Figure 2G and H, Figure 3C, Figure 4C). On postoperative X-ray (PV) of the jaws both right processes were significantly lengthened and narrowed (Figure 2G and H). The coronoid notch was located almost in the middle of the ramus. The radio-translucency of the ramus on the affected side now affected the entire anterior to posterior plane of the bone segment. The bone spur previously observed on the flattened outer jaw angle had transformed into two spurs. The first molar was fully developed and covered by the tumor. The right mandibular foramen was located caudal to the dorsal root of the first molar (22). Between the tooth socket and the surrounding jaw sections, the bone bridge between the peri-molar translucency and the ramus concavity - already documented on previous recordings - continued to exist. The emergence of the tooth into the oral tumor had promoted periodontal osteogenesis and vertical dimension of alveolar process, so that the

tilted tooth was firmly anchored in bone and its occlusal surface followed Spee’s curve. Thus, physiological bone formation of the alveolar process had been able to proceed completely in a tumorous soft tissue environment and showed radiological bone density corresponding to that of the unaffected side. Furthermore, radiopaque trajectories had developed in the thin corpus segment between the first molar and second premolar, replacing the previously obvious radiotranslucent region. The second premolar, which did not migrate adequately in mesial direction, had emerged. The mental foramen was located between the two premolars that were separated by “spacing” (36). In the upper jaw, there was spontaneous mesial migration, eruption, and approximal contact of tooth 16 on the tumor side (tooth 17 was removed prior to LeFort I osteotomy). Noteworthy were the positional abnormalities of teeth (spacing), vertical bone deficiency of the alveolar process, and tumorous soft tissue shadows on the right maxillary alveolar process side, which was also affected. Like the PV, the lateral cephalogram illustrated the deepened coronoid notch (Figure 2H, Figure 4C). The outer jaw angle on the tumor side became larger over time, while the angle on the healthy side straightened up (Table II). Following dysgnathic surgery, the rows of teeth were aligned in occlusion up to the terminal premolars. The ocular prosthesis used to replace the tumor-destroyed eyeball was displaced caudally (Figure 2G and H, Figure 3C, Figure 4C). The pneumatization of sphenoid sinus reached for the post-sellar region (46) and was dorsally defined by the clivus’ surface (39).

*Histology.* Tissue examination of resected specimens at various stages of treatment consistently confirmed the diagnosis of diffuse plexiform neurofibroma.

**Discussion**

The report shows the rapid aggravation of the soft tissue tumor with early *exenteratio orbitae* on the tumor side and typical findings in the orbital and cheek area, which point to a tumor manifesting in early childhood. The radiologically

Table II. Changes in the external jaw angle between the ages of 2.5 and 15.3 years on lateral cephalograms.

Age (years/months)	Mandibular angle (°)		
	Right side (R)	Left side (L)	Difference R-L
2/9	146.7	126.7	20
5/6	144.9	128.8	16.1
6/10	152.5	129.3	23.2
15/4	162	114.4	47.6

detectable changes in the jaws, especially the mandible, were initially not very pronounced. In contrast, the child showed early signs of soft tissue findings on the eyelids and cheek on the right side, caudally including the corner of the mouth. The external local findings were initially non-specific to address NF1, but the radiological course of the skeletal deformation of the facial skull and orbit showed the pathognomonic combination of enlarged orbital entrance, incomplete dorsal limitation of the orbit, bowl-shaped caudally bent zygomatic arch, and progressive dysplasia of the mandible in the jaw area so that the suspected diagnosis could be made.

However, at the time of first investigation the facial and jaw deformities in relationship to local nerve sheath tumor were hardly noticeable in early childhood. However, only few years later, characteristic deformities such as deep coronoid notch and restricted mesial movement of the first molars were evident in overview images of the jaw. The full picture of unilateral facial tumor development was apparent in adolescence. Follow-up examinations show that bone and tooth development and positional changes in the jaw in the area of trigeminal PNF occurred over time and were associated with the development of hard tissue and facial growth in general. The effects of the hemifacial diffuse PNF on jaw growth were thus visible during the period that is considered both, the phase with the highest tumor growth rate and associated bone deformities, and the stage of life in which the greatest growth dynamics are generally observed (8). During this growth phase, the interaction between muscles and

musculature is particularly important for the development of the phenotype. In the case of a topographically adjacent neurogenic tumor, it is plausible to assume that both the neural and functional control of the affected bone may be affected, especially in the case of diffuse plexiform neurofibromas with invasive growth characteristics. In this respect, the bone changes likely can be interpreted in part as a local growth impediment resulting from insufficient or misdirected muscular effects on the bones to be moved, which influence skeletal homeostasis during the growth period (25, 33, 45). In addition, effective tumor infiltration into the periosseous soft tissues may result in alterations of the bony surface (47). With this hypotheses of tumor-dependent changes on the bones' shape, the parallel is obvious to sphenoid dysplasia in NF1, which is the mainly analyzed skeletal anomaly of the skull and used for clinical diagnostic purposes of the entity (7). Sphenoid dysplasia often occurs adjacent to intraorbital PNF (44). However, local physical effects (pressure) and circulatory disturbances of the cerebrospinal fluid appear to play a role in bone shaping at this site (31, 48).

On the other hand, observations have been reported showing that typical NF1-related mandibular deformation can also begin only with adolescence (29). The spatial correlation between bone dysplasia, which primarily affects ramus and processes, and noticeable changes in signal behavior and the structure of the masticatory muscles medial to the ramus on MRI has been described in detail (28). Some authors suspect that hypoplasia or even destruction of the masticatory muscles in NF1, as seen in imaging, is not caused by a tumor but rather by fatty degeneration of the muscles (22). In fact, morphological evidence of tumor in destroyed muscle can require considerable diagnostic effort (28). However, the hypotheses of neurodegenerative or tumor-infiltrative muscle destruction should not be considered mutually exclusive explanations for the soft tissue findings. It cannot be ruled out that PNF has developed in the branches of the mandibular nerve's motoric branches that are innervating the pterygoid muscles, causing neural dysfunction and fatty degeneration. On the other hand,

invasive PNF can both induce the local development of fatty tissue and destruction of parenchyma (11).

Surgical explorations have shown that extensive and invasive PNF extending to the skull base, the entire masticatory muscles of the region may form a diffuse soft mass surrounding dysplastic proximal sections of the mandible (47). The coincidence of nerve sheath tumor and osseous dysplasia has been confirmed by imaging, surgical exploration and histology providing evidence of diffuse PNF and structural abnormalities of the bone surfaces to which the masticatory muscles were attached (47). The characteristic, albeit individually variable pattern of mandibular deformation supports the hypothesis of tumor-associated skeletal dysplasia (25).

*Pseudo-elongation of the condyle.* Sailer *et al.* (18, 19) introduced the term "pseudo-elongation" for changes in the articular processes in vertical dimension in neurofibromatosis patients with facial PNF (Table I). Some authors' X-rays presented NF1 case collections showed an elongated articular process on the tumorous facial side and discussed this delicate osseous alteration as pseudo-elongation (22). The argument for assuming that this is only an apparent ("pseudo") elongation could be that the joint process only appears elongated because of an imaging effect (plain radiograph), for example due to the frequently observed strong translucency of the thinned bone below the condyles and in the ramus area between the coronoid notch and the mandibular foramen (24-27). On the other hand, the deepened *incisura* may look like a secondary osteolysis, leading to the conclusion that the elongation of the processes was caused by central substance loss in the ramus. This interpretation of the findings would correspond to the assumption that the thinned ramus, especially between the mandibular foramen and the coronoid notch, is dissolving in a defined direction due to unknown causes. However, follow-up examinations of individual cases suggest that it is more likely to be a growth restriction of the ramus in all three dimensions, which is partially compensated for by elongation of the (dysplastic) joint process. This

alternative interpretation is also supported by the fact that the articulating joint process regularly migrates mesially with its basal end (49). The hypothesis of pseudoelongation of the processes is also contradicted by the finding that the muscle process on the tumor side may be longer and extended cranially in cases of facial PNF, an objective finding of the extended vertical dimension of the bone segment (47).

However, a simple measurement of the length of the condyle (posterior edge) of the presented case shows that the process indeed is elongated, although this finding is only clearly noticeable in images of the aged individual. Hypoplasia of the ramus is highlighted as a common finding in NF1-associated mandibular dysplasia (see diagnostic criterion no. 5, Table I). In the case of shortened/hypoplastic ramus, lengthening of the articular process would further shift the ratio of condyle to ramus in favor of the condyle. The follow-up examination of the presented case suggests that this is a finding that manifests over a longer period and may also be associated with changes in the shape of the process or capitulum and coronoid process.

Based on this and earlier observations that have documented an elongated articular process in PNF-affected individuals, it seems reasonable to assume that the process is genuinely elongated in these cases. The cause of this phenomenon has been hypothesized to be adaptive processes of sagittal elongation of the condyle in cases of shortened growth of the mandibular body on the tumor-affected side in this direction (49). In this respect, the elongation of the joint process would be a compensatory mechanism in the known hemifacial PNF-associated facial scoliosis, which leads to a shortening of the corpus on the tumor side and causes this bone segment to deviate toward the tumor side (25). It is likely that residual functionality of the lateral pterygoid muscle (49) is necessary for this compensatory action of the process.

The assessment that this is a real elongation of the *condylus articularis* can be verified in numerous documents (25, 29, 30). After evaluating the findings, the term “pseudoelongation” should no longer be used

to describe PNF-associated mandibular dysplasia in NF1 patients, because it does not correspond to the measurement of bone segment dimensions and obscures the adaptive nature of the growth disorder. There appears to be a limited growth capacity of the articular process, which partially compensates for the apparently reduced capacity of the distal corpus and subcondylar ramus to achieve symmetrical development of the affected half of the mandible (30). These adaptive processes, *i.e.*, basal extension of the joint process with potential preservation of joint function (49), must be distinguished from progressive bone loss, that affects the ramus-mandibular angle region and potentially the articular process (34). Both processes, *i.e.*, preservation of joint function (articulation) and dysplasia of the joint process, can occur together (25) or independent from each other (49). In order to assess the pathogenesis of tumor-related mandibular changes outlined here arising in the developmental phase of the affected children and adolescents, a study of a larger group in a long-term follow-up should be undertaken. Long-term observations such as those presented here are essential in order to detect both late tumor destruction of the bone (35) and to document the stability of skeletal deformation (50).

*Timing of osseous lesions.* In the present case, the development of tumor-associated jaw dysplasia could already be observed in the first years of life. Apparently, jaw dysplasia is linked to the growth phase and causes bizarre changes in the lower jaw, especially the distal lower jaw and its processes. The typical constellation of clinical and skeletal findings (18, 19, Table I) was already reached within the first 7 years of life in this case. This period is the lifetime in which the greatest growth potential is observed in many NF1 patients (8). The skeletal deformation pattern of the case presented here resembles a case in the study by Visnapuu *et al.* (29). However, in that case, the radiological findings were unremarkable until the onset of puberty. It can therefore be concluded that similar jaw malformation patterns can occur at different stages of physical development in

NF1 patients with trigeminal PNF (third branch affected) including congenital noticeable jaw deformities (12, 13, 33, 45). Indeed, the time window for these characteristic bone shape alterations during childhood and adolescence may be relatively wide. The obvious conclusion from the sum of the reports is a presumably wide interval in which jaw malformations can occur predominantly restricted to the growth phase (12, 13, 29, 33, 45) and, in rare cases, may persist beyond (34). The summary of these findings confirms the assessment of experts that the findings of the disease do not necessarily follow a linear course and that children and adolescents with NF1 therefore require short-term monitoring of their findings (50).

*Neuro-osteological and musculoskeletal relations in the development of NF1-associated jaw deformities.* The development of the mandible begins lateral to Meckel's cartilage (51). The first ossification is recorded in the area of the mental foramen, *i.e.*, neural development (inferior alveolar nerve) precedes ossification slightly (52). In sync with the ossification of the early mandible, the dental lamina sinks into the bone and the deciduous tooth germs are positioned in relation to the terminal nerve branches. This temporospatial sequence defines the relationship between the deciduous molars and the foramen at an early stage. Typically, the mental foramen is located between the anlagen and later the roots of the two deciduous molars (52). Deviations in the relationship between the foramen and the apices of the deciduous molars or their permanent successors (lower premolars) have been described many times as anatomical variations and mainly affect the relationship between these landmarks (including the root tips of the adjacent teeth) in the sagittal (mesio-distal) dimension (53).

In the present case, the relationship between the osseous ostium and the tooth roots has been preserved on both sides. Although the mesial migration of the right second premolar is slightly shorter than that of the left side, this slight difference has no influence on the position of the foramen as defined dorsal to the root of the first premolar and between the roots of the premolars. In this

respect, the X-ray findings indicate largely undisturbed postnatal neuroosteological control of tooth development in a discreetly dysmorphic bone. However, if the positions of the premolars after tooth eruption are compared with their positions during intraosseous development, no difference in the vertical positional relationship of the teeth between the mandibular sides is visible in the early stage (*vide supra*). However, even in the 2 years 9 months old child, there was a slightly wider bone bridge between the permanent premolars' crowns on the tumor side compared to the unaffected side (Figure 1A and B).

These observations on tooth development and nerve canal formation suggest that the facial PNF, classified as congenital, can only have had a formative effect after the mandible had developed and the tooth buds had become embedded in the bone. In fact, the precursor of the first premolar is located above the inferior alveolar nerve in the shell-shaped ossified mandible located basally (fetus 47 mm long) and, at a length of 64 mm, on both sides – at a distance – surrounded by bone, to find a developed mental foramen laterally (53).

An influence of the lesion on sequential tooth formation is evident from the incomplete mesial migration and long retention phase of the first molar. Similarly, the absence of the second permanent molar on the tumor side probably indicates an influence of the nerve on tooth formation, which can be used to determine the timing of functionally effective tumor growth. The formation of the first molar is associated with intrauterine life, while the second molar develops only postnatally (54). Based on the analysis of the dental findings, it is likely that the influence of PNF only began after the formation of the first permanent molar [histological evidence of mineralization 7–8 months after ovulation (54)], potentially hindering the mesial migration of the developing tooth and subsequently preventing the formation of the second molar anlage. Aplasia of the second molars is considered a rare finding (25). However, changes in tooth number in NF1 are not limited to aplasia (25) but also include supernumerary teeth. Interestingly, the dorsal region of the dental arch is more frequently affected by this finding (55). With

reference to the known phases of tooth development (54) the influence of the disease on tooth development points to a late phase of the prenatal life and may include the postnatal period, like in this case, during which PNF could have been effective for tooth development: enamel organ of the second molar is expected approx. 6 months after birth (55).

It is known from previous reports that the functional impairment of the masticatory muscles caused by PNF of the third trigeminal branch is highly variable (25-28, 49). However, the tumor infiltration of masticatory muscles, especially pterygoid muscles, and the tumor mass located at their site and interpreted as fatty degeneration of the masticatory muscles were located directly on the concave lingual ramus side (23). The lesions were ending at the displaced mandibular foramen (23, 25-27). However, the signal indicating fat close to the lingual side of the mandibular ramus was not identified in the nerve canal (23, 25-27). It is not yet clear whether the enlarged nerve canal described repeatedly in NF1 patients (29) represents the radiological equivalent of a tumorous inferior alveolar nerve. However, it has been pointed out that at no point during the early development of the inferior alveolar nerve the branch completely fills the encircling bone canal (52). It therefore remains open to interpretation whether the enlarged nerve canal (as well as the enlarged foramina) on radiographs is sign of tumor-related or non-tumorous mandibular differentiation disorder in NF1 patients (26). This interpretation would be consistent with findings that enlarged nerve canals and *mental* foramina have been observed in NF1 patients who did not develop trigeminal PNF (29).

The *mandibular* foramen on the tumor side typically differs from that on the unaffected side in terms of its cranial position: the foramen on the tumor side is frequently located deeper (23). This finding is also clearly evident in the present case. However, the difference in cranial position only develops into a clear discrepancy during clinical follow-up of the child. It is likely that this complex anomaly is related to the general dysplasia of the ramus and the masticatory muscles attached to it

(34). This assumption is supported by the very narrow thickness of the ramus and the typical concavity of the bone segment (23).

The observations show that the developmental disorder of the dentition on the tumor side primarily affects the distal teeth, especially those that have no precursors. Although consistent with other descriptions of dental and skeletal conditions in congenital trigeminal PNF [3rd branch (25)], the individual findings allow only very limited generalizations. It can be assumed that facial PNF, in this case primarily that of the third trigeminal nerve with involvement of the motor branches, only influences the dentition and the outline of the bone, especially the distal parts close to the joints, towards the end of the prenatal period. The postnatal course of tumor growth is characterized by the extent of tumorous transformation of the nerve and the organs it supplies, especially the masticatory muscles, as well as unknown factors that determine tumor biology (56-59). However, tumor volume only seems to be significant if impairment of several functional units (especially masticatory muscles) corresponds to this measurement (30). The tumor-associated changes affect the outline and volume of the bone as well as the number and position of the teeth but show no progressive changes in the terminal section of the affected nerve, as far as can be deduced from the constancy of the nerve canals and the *mental* foramen's image on plain radiographs.

*PNF-associated mandibular alterations in NF1 and hemifacial microsomia.* The combined occurrence of tumor-associated fatty degeneration of the masticatory muscles due to infiltration with a PNF and dysplasia of the jaws on the same side, especially the mandible, allows a comparison with current concepts of the interdependence of muscle degeneration and mandibular deformation in hemifacial microsomia (60). The deformities of the affected mandibular side in hemifacial microsomia correlated primarily with dysplasia of the pterygoid muscles and the temporal muscle (60). Based on their own observations, the authors concluded that communication between

neural crest cells and cephalic myogenic mesodermal cells begins early in physical development. In contrast to hemifacial microsomia, the facial PNF of NF1 patients has the characteristics of a neoplasm. Nevertheless, the similarities in the topographically and functionally related hard and soft tissue developments of both diseases are striking and indicate that in facial PNF, the characteristic, albeit variable, skeletal morphology of the jaw is probably to a significant extent a consequence of musculoskeletal dysplasia. This makes it all the more important in these cases to differentiate the transformation of PNF from dysplasia into malignant peripheral nerve sheath tumor (MPNST) (32).

*Jaw changes and diagnostic criteria for NF1.* The current recommendations for age-adapted diagnostic evaluation and criteria for NF1 in childhood and adolescence lack references to facial skeleton malformations as an indicator of tumor suppressor gene disease (50), which, according to numerous reports in the literature, can already be detected in childhood (25). Recommendations for the developmentally appropriate examination of children and adolescents with NF1 and craniofacial PNF should include, in addition to standardized neurological and ophthalmological examinations (8), specialist examinations of facial findings, which can cover a wide spectrum of neoplastic manifestations, dysplasias and functional disorders. The skeletal findings are frequently associated with a craniofacial PNF, a precancerous lesion that rarely transforms into MPNST in the craniofacial region (13). However, the pathogenesis is well documented for the syndrome and has already been diagnosed in childhood and adolescence. Distinguishing between dysplastic and neoplastic findings can be difficult in these individuals. The care of these patients is supported by regular expert follow-up examinations applying known diagnostic criteria in the field of interest (61-63).

*PNF-associated mandibular alteration and MPNST.* Neurofibromas occurring after the developmental phase of the jaw do not appear to result in mandibular dysplasia

(64). Bone erosion should be considered an indication of an PNF (24, 25). Rapid bone resorption with an increase in the volume of the soft tissue tumor may indicate malignancy (65). In the latter case, the complete dissolution of the mandibular ramus and jaw angle, which is observed in rare cases with extensive facial PNF and associated complex skeletal deformities, can make it difficult to distinguish between malignant (66-68) and functional causes of organ destruction (34). PNF can lead to cyst-like enlargements of the jaw in relation to impacted teeth (22) and may thus be interpreted as an oral mass invading the intraosseous space from the oral cavity (67).

## Conclusion

Skeletal findings in the jaw region can often be detected on plain radiographs of NF1 patients, and changes in the bone and dentition can be monitored over time using readily available examination techniques. Follow-up examinations show that, using the example of jaw deformities, the interaction of neoplastic and dysplastic forces eventually can be traced in NF1.

These imaging techniques provide detailed information about the bones and dentition of NF1 patients with low radiation exposure. They are suitable for helping to differentiate between tumor-associated and development-specific changes in these hard tissues and provide valuable information for the diagnosis of the disease in these patients during the course of treatment.

## Conflicts of Interest

The Authors declare that there are no conflicts of interest with respect to this publication.

## Authors' Contributions

R.E. Friedrich: Treatment of the patient, conceptualization, draft and corrections of the manuscript. F. K. Kohlrusch: Literature research, draft and correction of the manuscript. C. Hagel: Histologic diagnosis, draft and

corrections of manuscript. M. Giese: Literature research, draft and correction of the manuscript. All Authors have agreed to the release of the manuscript for publication.

## Funding

This research received no external funding.

## Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

## References

- Ly KI, Blakeley JO: The diagnosis and management of neurofibromatosis type 1. *Med Clin North Am* 103(6): 1035-1054, 2019. DOI: 10.1016/j.mcna.2019.07.004
- Lammert M, Friedman JM, Roth HJ, Friedrich RE, Kluwe L, Atkins D, Schooler T, Mautner VF: Vitamin D deficiency associated with number of neurofibromas in neurofibromatosis 1. *J Med Genet* 43(10): 810-813, 2006. DOI: 10.1136/jmg.2006.041095
- Tucker T, Schnabel C, Hartmann M, Friedrich RE, Frieling I, Kruse H, Mautner V, Friedman JM: Bone health and fracture rate in individuals with neurofibromatosis 1 (NF1). *J Med Genet* 46(4): 259-265, 2009. DOI: 10.1136/jmg.2008.061895
- Riccardi VM: Neurofibromatosis. Phenotype. Natural History, and Pathogenesis. 2nd edition, The Johns Hopkins University Press, Baltimore and London, p.31 (congenital presence of craniofacial diffuse PNF); pp. 37-39 (short stature); pp. 110-112 (oral involvement in facial PNF), 1992.
- Stevenson DA, Viskochil DH, Carey JC: Neurofibromatosis type 1 is a genetic skeletal disorder. *Am J Med Genet A* 143A(17): 2082-2083, 2007. DOI: 10.1002/ajmg.a.31758
- Friedrich RE, Hagel C: Malignant peripheral nerve sheath tumor (MPNST) arising from orbital plexiform neurofibroma in a small child with neurofibromatosis type 1. *Cancer Diagn Progn* 5(2): 244-254, 2025. DOI: 10.21873/cdp.10436
- Legius E, Messiaen L, Wolkenstein P, Pancza P, Avery RA, Berman Y, Blakeley J, Babovic-Vuksanovic D, Cunha KS, Ferner R, Fisher MJ, Friedman JM, Gutmann DH, Kehrer-Sawatzki H, Korf BR, Mautner VF, Peltonen S, Rauen KA, Riccardi V, Schorry E, Stemmer-Rachamimov A, Stevenson DA, Tadini G, Ullrich NJ, Viskochil D, Wimmer K, Yohay K, International Consensus Group on Neurofibromatosis Diagnostic Criteria (I-NF-DC), Huson SM, Evans DG, Plotkin SR: Revised diagnostic criteria for neurofibromatosis type 1 and Legius syndrome: an international consensus recommendation. *Genet Med* 23(8): 1506-1513, 2021. DOI: 10.1038/s41436-021-01170-5
- Carton C, Evans DG, Blanco I, Friedrich RE, Ferner RE, Farschtschi S, Salvador H, Azizi AA, Mautner V, Röhl C, Peltonen S, Stivaros S, Legius E, Oostenbrink R, ERN GENTURIS NF1 Tumour Management Guideline Group: ERN GENTURIS tumour surveillance guidelines for individuals with neurofibromatosis type 1. *EClinicalMedicine* 56: 101818, 2023. DOI: 10.1016/j.eclinm.2022.101818
- Rittersma J, Ten Kate LP, Westerink P: Neurofibromatosis with mandibular deformities. *Oral Surg Oral Med Oral Pathol* 33(5): 718-727, 1972. DOI: 10.1016/0030-4220(72)90439-2
- Cohen MM Jr: Perspectives on craniofacial asymmetry. IV. Hemi-asymmetries. *Int J Oral Maxillofac Surg* 24(2): 134-141, 1995. DOI: 10.1016/s0901-5027(06)80086-x
- Scheithauer BW, Woodruff JM, Erlandson RA: Tumors of the Peripheral Nervous System. Atlas of Tumor Pathology, Third Series, Fascicle 24, Armed Forces Institute of Pathology, Washington, pp. 177-218, 385-405, 1997.
- Cacchione A, Carboni A, Lodi M, Vito R, Carai A, Marrazzo A, Macchiaiolo M, Voicu IP, Mastronuzzi A, Colafati GS: Congenital craniofacial plexiform neurofibroma in neurofibromatosis type 1. *Diagnostics (Basel)* 11(2): 218, 2021. DOI: 10.3390/diagnostics11020218
- Waggoner DJ, Towbin J, Gottesman G, Gutmann DH: Clinic-based study of plexiform neurofibromas in neurofibromatosis 1. *Am J Med Genet* 92(2): 132-135, 2000.
- Huson SM: The neurofibromatoses: classification, clinical features and genetic counselling. *Monogr Hum Genet* 16: 1-20, 2008. DOI: 10.1159/000126500
- Recklinghausen FD: Ueber die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuomen: Festschrift zur Feier des fünfundzwanzigjährigen Bestehens des pathologischen Instituts zu Berlin. Berlin, Hirschwald, 1882.
- White EE, Rhodes SD: The NF1+/- immune microenvironment: dueling roles in neurofibroma development and malignant transformation. *Cancers (Basel)* 16(5): 994, 2024. DOI: 10.3390/cancers16050994
- Korf BR: Plexiform neurofibromas. *Am J Med Genet* 89(1): 31-37, 1999. DOI: 10.1002/(sici)1096-8628(19990326)89:1<31::aid-ajmg7>3.0.co;2-w
- Sailer HF: Mandibular asymmetry associated with perimandibular hemangiomas. *J Maxillofac Surg* 1: 104-109, 1973. DOI: 10.1016/S0301-0503(73)80022-0
- Sailer HF, Künzler A, Makek MS: Neurofibrohemangiomas soft tissue changes with pathognomonic mandibular deformity. *Fortschr Kiefer Gesichtschir* 33: 84-86, 1988.
- Shapiro SD, Abramovitch K, Van Dis ML, Skoczylas LJ, Langlais RP, Jorgenson RJ, Young RS, Riccardi VM: Neurofibromatosis: Oral and radiographic manifestations. *Oral Surg Oral Med Oral Pathol* 58(4): 493-498, 1984. DOI: 10.1016/0030-4220(84)90350-5

- 21 D'Ambrosio JA, Langlais RP, Young RS: Jaw and skull changes in neurofibromatosis. *Oral Surg Oral Med Oral Pathol* 66(3): 391-396, 1988. DOI: 10.1016/0030-4220(88)90252-6
- 22 Lee L, Yan YH, Pharoah MJ: Radiographic features of the mandible in neurofibromatosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 81(3): 361-367, 1996. DOI: 10.1016/s1079-2104(96)80338-6
- 23 Overdiek A, Feifel H, Schaper J, Mayatepek E, Rosenbaum T: Diagnostic delay of NF1 in hemifacial hypertrophy due to plexiform neurofibromas. *Brain Dev* 28(5): 275-280, 2006. DOI: 10.1016/j.braindev.2005.10.001
- 24 Friedrich RE, Reul A: A combination of skeletal deformations of the dorsal mandible and temporomandibular region detected in orthopantomograms of patients with neurofibromatosis type 1 indicates an associated ipsilateral plexiform neurofibroma. *J Craniomaxillofac Surg* 46(7): 1091-1104, 2018. DOI: 10.1016/j.jcms.2018.04.018
- 25 Friedrich RE, Giese M, Schmelzle R, Mautner V, Scheuer HA: Jaw malformations plus displacement and numerical aberrations of teeth in neurofibromatosis type 1: a descriptive analysis of 48 patients based on panoramic radiographs and oral findings. *J Craniomaxillofac Surg* 31(1): 1-9, 2003. DOI: 10.1016/s1010-5182(02)00160-9
- 26 Friedrich RE, Kohlrusch FK, Hagel C: Facial diffuse plexiform neurofibroma-associated mandibular deformities: surgical interventions and monitoring of treatment results in a patient for over 40 years. *Cancer Diagn Progn* 5(3): 319-329, 2025. DOI: 10.21873/cdp.10444
- 27 Friedrich RE, Kohlrusch FK, Hagel C: Recurrent diffuse neurofibroma of the mandibular anterior lingual alveolar process associated with dental and skeletal changes in neurofibromatosis type 1. *Cancer Diagn Progn* 5(3): 330-343, 2025. DOI: 10.21873/cdp.10445
- 28 Hisatomi M, Asaumi J, Konouchi H, Yanagi Y, Kishi K: Bone deformity showing a deep coronoid notch of the mandible in a patient with neurofibromatosis type 1. *Dentomaxillofac Radiol* 34(6): 380-383, 2005. DOI: 10.1259/dmfr/46427075
- 29 Visnapuu V, Peltonen S, Tammissalo T, Peltonen J, Happonen RP: Radiographic findings in the jaws of patients with neurofibromatosis 1. *J Oral Maxillofac Surg* 70(6): 1351-1357, 2012. DOI: 10.1016/j.joms.2011.06.204
- 30 Friedrich RE, Christ G, Scheuer HA: Mandibular symmetry on posterior-anterior cephalograms of neurofibromatosis type 1 patients with facial plexiform neurofibroma. *GMS Interdiscip Plast Reconstr Surg DGPW* 12: Doc11, 2023. DOI: 10.3205/iprs000181
- 31 Jacquemin C, Bosley TM, Svedberg H: Orbit deformities in craniofacial neurofibromatosis type 1. *AJNR Am J Neuroradiol* 24(8): 1678-1682, 2003.
- 32 Soltaninia O, Dehghan A, Fatehi F, Naderi H: Malignant peripheral nerve sheath tumor, a rare intraosseous malignancy in the mandible of a patient with neurofibromatosis type 1: a case report. *Indian J Otolaryngol Head Neck Surg* 75(4): 3839-3842, 2023. DOI: 10.1007/s12070-023-03885-0
- 33 Aloyouny AY, Albagieh HN, Alweteid AS, Alsheddi MA: Mandibular neurofibroma with osseous deformities in a 3-year-old child with neurofibromatosis type 1: A case report presentation and diagnosis. *Niger J Clin Pract* 24(11): 1755-1757, 2021. DOI: 10.4103/njcp.njcp\_421\_20
- 34 Friedrich RE, Scheuer HA: Unilateral creeping destruction of deformed mandibular ramus and angle associated with extensive facial plexiform neurofibroma in neurofibromatosis type 1: a case report with analysis of the literature for diagnosing osteolytic events of the mandible in tumor-suppressor gene syndrome. *Anticancer Res* 38(7): 4083-4091, 2018. DOI: 10.21873/anticancer.12698
- 35 Friedrich RE, Schön M: Dental developmental stages and decayed, missing, and restored teeth in neurofibromatosis type 1-affected children and adolescents. *J Clin Exp Dent* 16(3): e300-e322, 2024. DOI: 10.4317/jced.61363
- 36 Friedrich RE, Giese M, Stelljes C, Froeder C, Scheuer HA: Size of tooth crowns and position of teeth concerning the extension of facial plexiform neurofibroma in patients with neurofibromatosis type 1. *Anticancer Res* 32(5): 2207-2214, 2012.
- 37 Friedrich RE, Schmelzle R, Giese M, Mautner VF: Zur Häufigkeit intraoraler weichgeweblicher Raumforderungen bei Neurofibromatose Typ 1. *Dtsch Z Mund Kiefer GesichtsChir* 18: 207-209, 1994.
- 38 Santoro R, Santoro C, Loffredo F, Romano A, Perrotta S, Serpico R, Lauritano D, Lucchese A: Oral clinical manifestations of neurofibromatosis type 1 in children and adolescents. *Appl Sci* 10(14): 4687, 2020. DOI: 10.3390/app10144687
- 39 Lilienthal EK, Scheuer HT, Scheuer HA, Friedrich RE: The skull base in NF1 phenotypes on lateral cephalograms. *J Craniomaxillofac Surg* 53(12): 2118-2132, 2025. DOI: 10.1016/j.jcms.2025.09.011
- 40 Arnaudow M: Neurofibromatose und Zahnersatz. *Zahnärztliche Praxis (München)* 14: 49-50, 1963.
- 41 Smith GC, Smith RJ: Multiple neurofibromatosis (von Recklinghausen's disease). Case report. *Aust Dent J* 24(4): 253-255, 1979. DOI: 10.1111/j.1834-7819.1979.tb02934.x
- 42 Delay A, Varazzani A, Bouland C, Brochet L, Bouletreau P, Cousin AS: Temporomandibular joint ankylosis following bimaxillary surgery in a patient with neurofibromatosis type 1: a case report. *Oral Maxillofac Surg* 29(1): 184, 2025. DOI: 10.1007/s10006-025-01486-5
- 43 Friedrich RE, Reul A: Decayed, missing, and restored teeth in patients with Neurofibromatosis Type 1. *J Clin Exp Dent* 10(2): e107-e115, 2018. DOI: 10.4317/jced.54561
- 44 Friedrich RE, Rother J, Christ G, Lehmann M, Eulenburg CG, Giese M, Scheuer HA: Analysis of orbital plain radiographs for orbital deformities in neurofibromatosis type 1 patients, with special reference to alterations of the orbital rim as indicators of adjacent plexiform neurofibroma. *Anticancer Res* 33(3): 1081-1090, 2013.

- 45 Rath R, Kaur S, Baig SA, Pati P, Sahoo S: Multifocal head and neck neurofibromas with osseous abnormalities and muscular hypoplasia in a child with neurofibromatosis: Type I. *Case Rep Radiol* 2016: 3980270, 2016. DOI: 10.1155/2016/3980270
- 46 Friedrich RE, Scheuer HT, Kersten JF, Scheuer HA: Sphenoid bone pneumatization on lateral cephalograms of patients with neurofibromatosis type 1. *In Vivo* 35(1): 349-361, 2021. DOI: 10.21873/invivo.12266
- 47 Friedrich RE, Kohlrusch FK, Hagel C: Surgical measures improving functional limitations of the masticatory system, aesthetic deficits, and skeletal malformations in neurofibromatosis type 1-associated hemifacial diffuse plexiform neurofibroma complicated by rapidly growing midfacial peripheral nerve sheath tumor. *Cancer Diagn Progn* 5(5): 566-582, 2025. DOI: 10.21873/cdp.10471
- 48 Rijken BFM, van Veelen-Vincent MLC, Mathijssen IMJ: Sphenoid dysplasia in patients with neurofibromatosis type 1: Clinical features and imaging findings including cerebrospinal fluid alterations. *Eur J Paediatr Neurol* 42: 28-33, 2023. DOI: 10.1016/j.ejpn.2022.11.006
- 49 Friedrich RE, Kohlrusch FK, Hagel C, Giese M: Long-term stable unilateral mandibular deformity associated with ipsilateral skull-base soft-tissue lesion and degenerated pterygoid muscles in neurofibromatosis type 1. *Cancer Diagn Progn* 6(1): 160-178, 2026. DOI: 10.21873/cdp.10516
- 50 Farschtschi S, Vaassen P, Kluwe L, Hartung T, Salamon J, Rosenbaum T: Age-adapted diagnostic evaluation and treatment of patients with type 1 neurofibromatosis in Germany. *Dtsch Arztebl Int* 122(3): 71-76, 2025. DOI: 10.3238/arztebl.m2024.0257
- 51 Kjær I: Neuro-osteology. *Crit Rev Oral Biol Med* 9(2): 224-244, 1998. DOI: 10.1177/10454411980090020501
- 52 Radlanski RJ, Renz H, Tsengelsaikhon N, Schuster F, Zimmermann CA: The remodeling pattern of human mandibular alveolar bone during prenatal formation from 19 to 270mm CRL. *Ann Anat* 205: 65-74, 2016. DOI: 10.1016/j.aanat.2016.01.005
- 53 Currie CC, Meehan JG, Whitworth JM, Carr A, Corbett IP: Determination of the mental foramen position in dental radiographs in 18-30 year olds. *Dentomaxillofac Radiol* 45(1): 20150195, 2016. DOI: 10.1259/dmfr.20150195
- 54 Pasler HE: *Orale Strukturbiologie*, Thieme, Stuttgart, pp.27-37, 1992.
- 55 Friedrich RE, Scheuer HT, Kersten JF, Scheuer HA: Supernumerary teeth of permanent dentition in patients with neurofibromatosis type 1. *J Craniomaxillofac Surg* 48(1): 98-104, 2020. DOI: 10.1016/j.jcms.2019.12.006
- 56 Kossler N, Stricker S, Rödelsperger C, Robinson PN, Kim J, Dietrich C, Osswald M, Kühnisch J, Stevenson DA, Braun T, Mundlos S, Kolanczyk M: Neurofibromin (Nf1) is required for skeletal muscle development. *Hum Mol Genet* 20(14): 2697-2709, 2011. DOI: 10.1093/hmg/ddr149
- 57 Sullivan K, El-Hoss J, Quinlan KG, Deo N, Garton F, Seto JT, Gdalevitch M, Turner N, Cooney GJ, Kolanczyk M, North KN, Little DG, Schindeler A: NF1 is a critical regulator of muscle development and metabolism. *Hum Mol Genet* 23(5): 1250-1259, 2014. DOI: 10.1093/hmg/ddt515
- 58 Kühnisch J, Seto J, Lange C, Stumpp S, Kobus K, Grohmann J, Elefteriou F, Fratzl P, Mundlos S, Kolanczyk M: Neurofibromin inactivation impairs osteocyte development in Nf1Prx1 and Nf1Col1 mouse models. *Bone* 66: 155-162, 2014. DOI: 10.1016/j.bone.2014.06.012
- 59 Heude E, Rivals I, Couly G, Levi G: Masticatory muscle defects in hemifacial microsomia: A new embryological concept. *Am J Med Genet A* 155A(8): 1991-1995, 2011. DOI: 10.1002/ajmg.a.34095
- 60 Riccardi VM: Neurofibromatosis type 1 is a disorder of dysplasia: The importance of distinguishing features, consequences, and complications. *Birth Defects Res A Clin Mol Teratol* 88(1): 9-14, 2010. DOI: 10.1002/bdra.20616
- 61 Koblin I, Reil B: Changes in the facial skeleton in cases of neurofibromatosis. *J Maxillofac Surg* 3: 23-27, 1975. DOI: 10.1016/s0301-0503(75)80009-9
- 62 Lorson EL, DeLong PE, Osborn DB, Dolan KD: Neurofibromatosis with central neurofibroma of the mandible: Review of the literature and report of case. *J Oral Surg* 35(9): 733-738, 1977.
- 63 Giese M: Die Veränderungen der Kiefer und der Zahnstellung bei Neurofibromatose Typ 1 (Morbus Recklinghausen). *Med. Dissertation, University of Hamburg*, p. 34, 1995.
- 64 Inoue T, Elaskary M, Shima A, Hirai H, Suzuki F, Matsuda M: Trigeminal neurofibroma in the infratemporal fossa arising from the inferior alveolar nerve: A case report. *Mol Clin Oncol* 7(5): 825-829, 2017. DOI: 10.3892/mco.2017.1410
- 65 de Oliveira MG, Pozatti Moure S, Sérgio Batista P, Moraes Chaves AC, Rados PV, Sant'Ana Filho M: NF1 diagnosis criteria and associated sarcomatous tumor review of the literature and case report. *Oral Maxillofac Surg* 12(4): 231-235, 2008. DOI: 10.1007/s10006-008-0137-1
- 66 Che Z, Nam W, Park WS, Kim HJ, Cha IH, Kim HS, Yook JI, Kim J, Lee SH: Intraosseous nerve sheath tumors in the jaws. *Yonsei Med J* 47(2): 264-270, 2006. DOI: 10.3349/ymj.2006.47.2.264
- 67 Lozouet M, Paul L, Kallel M, Braux G, Leclerc A, Emery E: Trigeminal malignant peripheral nerve-sheath tumor: Systematic review, and case report treated by proton-beam therapy. *Neurochirurgie* 71(2): 101621, 2025. DOI: 10.1016/j.neuchi.2024.101621
- 68 Colmenero C, Rivers T, Patron M, Sierra I, Gamallo C: Maxillofacial malignant peripheral nerve sheath tumours. *J Craniomaxillofac Surg* 19(1): 40-46, 1991. DOI: 10.1016/s1010-5182(05)80270-7