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Review

Chordoma in children: Case-report and review of literature

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ABSTRACT

We report an exceptional case of a very late local failure in a 9-year-old boy presenting with a chordoma of the cranio-cervical junction. The child was initially treated with a combination of surgical resection followed by high dose photon–proton radiation therapy. This aggressive therapy allowed a 9-year remission with minimal side-effects. Unfortunately, he subsequently presented with a local failure managed with a second full-dose course of protons. The child died one year later from local bleeding of unclear etiology.

1. Introduction

Chordomas (CH) are rare low grade malignancies that represent approximately 1% of all intra cranial tumors and 4% of bony primaries.[1–3] They develop from notochordal embryonic residues,[4] an origin supported by the association with the brachyury gene, a gene involved in the notochord development.[5,6] In the adults, they are located typically in the sacrococcygeal (SC) (50%), the intra cranial (IC), at the skull base (SB) (35%), and the intermediate spinal (S) regions (15%). Only 5% of cases have been described in the pediatric age, with unclear specificities concerning presentation, and outcome. We report in this paper a clinical case of skull base CH in a child, and we summarize through the English literature peculiarities of CH in this age group.

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2. Case report

Antonio M., a 9-year-old boy, was referred to the Department of Neurosurgery in San Giovanni Rotondo (Italy), following a couple of month-history of posterior cervical pains. On MRI, an extensive tumor process was visualized. It extended from the lower clivus, through the foramen magnum, down to C2, inclusive. The tumor was abutting the medulla and cervical cord anteriorly and laterally, right side. It extended substantially in the soft tissues anteriorly, with a visible protrusion, on physical examination, through the posterior aspect of the nasopharynx. Estimated dimensions were 35 mm × 15 mm. The child was operated on through two successive approaches, in March and April 2000. The tumor bed was filled with fatty and muscular tissue. Pathological examination was consistent with a CH. On histopathological study, the tumor was positive for epithelial (KL1+, EMA+), and mesenchymal (PS100) antigens. Post-operative MRI was of a difficult interpretation, due to the interposition of soft tissue although multiple small residual foci were suspected within the canal. The patient was referred to the Institut Gustave-Roussy, in Villejuif (France) where high dose, high precision post-operative radiotherapy was recommended. A combined photon–protontherapy program was implemented in collaboration with the Institut Curie-Proton Therapy Center, in Orsay (ICPO, France). It delivered, from January 2001 through March 2001, a total of 68.4 Gy (RBE) in 5 daily fractions of 1.8 Gy each per week (Gy (RBE) corresponds to the physical dose times an estimated 1.1 mean RBE value). Half was delivered using 3D conformal 15 MV photons, and half using 201 MeV protons, with a fixed horizontal beam, on a passive scattering mode (Fig. 1). Acute tolerance was satisfactory with mild headaches, nauseas, and mucositis, managed with a short course of steroids and mouthwash. Follow-up was alternated between France and Italy and uneventful until January 2010. At that time, 106 months following radiotherapy, performance status was excellent, with only a slight permanent neck deviation, related with mild radiation-induced atrophy of C1, and of the occipital bone (Fig. 2). C1 deformation was attributed retrospectively to left to right vertebral body dose-gradient that ranged between 9 and 48 Gy. Unfortunately, MRI also evidenced a local tumor progression along the pharyngeal wall. A grossly subtotal resection was performed abroad in the same neurosurgical department, in May 2010, followed by a second course of conventionally fractionated protons, at ICPO, up to 70 Gy (RBE) (Fig. 3). The cumulative biologically equivalent dose (BED) was estimated retrospectively to 165 Gy_{10} for tumor, and 270 Gy_2 for late CNS reactions. These theoretical estimates do not take into account the extensive delay between treatments. The patient could resume normal life for almost a year, when a cataclysmic hemorrhage was exteriorized through the mouth.

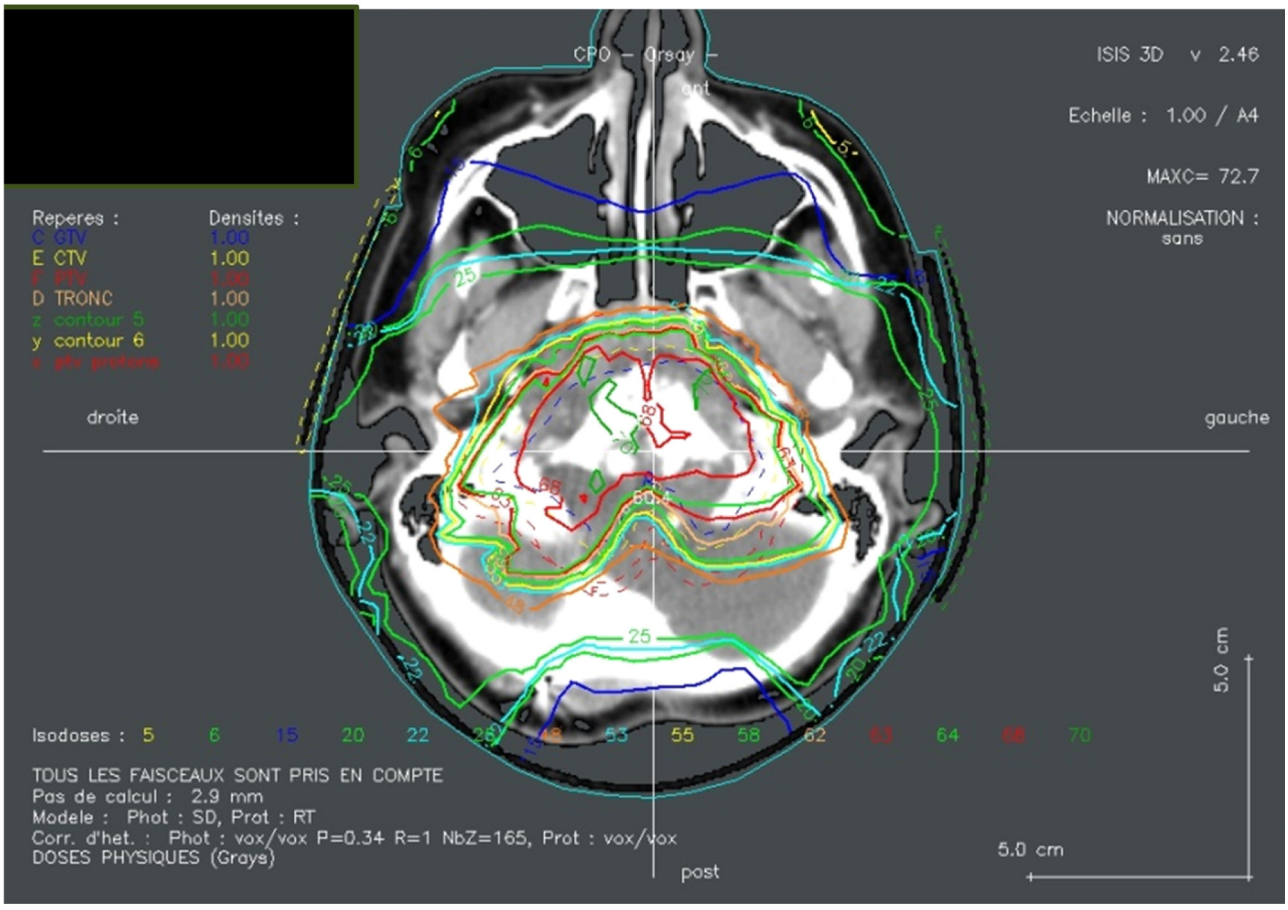

Fig. 1 – 9 year-old boy with skull base-cervical canal chordoma. Post-operative photon-proton radiotherapy mid-plane dose-distribution. Prescribed dose: 68.4 Gy (RBE) (*personal coll.*).

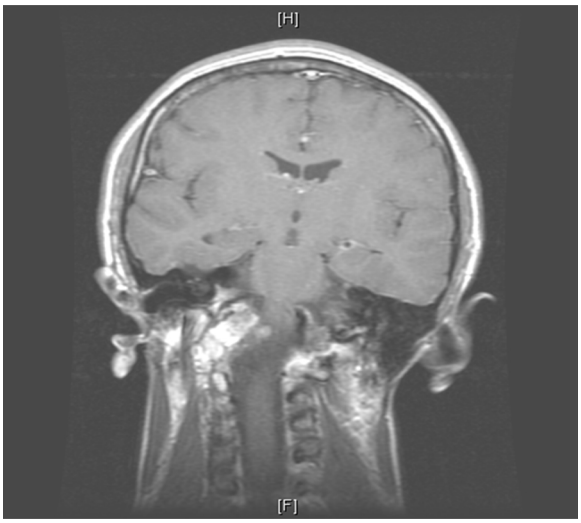

Fig. 2 – Same patient as Fig. 1. MRI aspect at 84 months follow-up, showing radiotherapy-related bony alterations at C1-C2 (*personal coll.*).

Despite his referral to the emergency unit of the local hospital, the patient died shortly thereafter. No autopsy was performed. It was impossible retrospectively to assess whether the cause of death was tumor progression, radionecrosis of the internal carotid artery or of one of its branches, or a combination of both.

3. Review of literature

Cranial CH is a very rare entity in the pediatric population, since it represents less than 1% of intra cranial malignancies and 5% of all CHs.[7–9] Mean age varies according to series between 8 and 12 years, most approaching 10 years.[10,11] There are case-reports of newborns affected with CHs.[12] Sex ratio is close to 1, although some series evidence a slight female predominance.[13,14] Several factors differ between adults and children at presentation, and following therapy. They concern anatomical sites, extension, tolerance to therapy, and outcome.

As far as anatomical sites are concerned, several authors have evidenced that the proportion of lower sites was inferior in children compared with adults: SB: 54% vs. 35%; S: 23% vs. 15% and SC: 22% vs. 50%.[7,11,14] But this proportion seems superior in younger children, which could explain, in part, a worse outcome.[15,16] Interestingly, multiple reports concern unusual presentations in youngsters, such as: extra clival cranial, intra cerebral, mediastinal, gluteal, etc.[17–29]

Symptoms at presentation depend on the tumor site, and are not specific to children. If they are IC, cranial nerve palsies are seen in 60% or so.[10,30] Non specific symptoms of hydrocephalus are present in one-third of cases.[31] Cervical-S sites or extension include also frequently stiff neck and nasal obstruction. Physical examination is generally positive for a retro pharyngeal mass. SC sites are frequently revealed by pains in the lower back, associated or not with a sacral mass when the tumor is located posteriorly; when the lesion extends anteriorly, diagnosis is frequently late and revealed by symptoms of digestive or cauda equina compression.[32–34]

As for metastases, they are rare at presentation in all age-groups (<5%, except SC ≤25%).[11,14,30,35] Dissemination within the CNS, similar to the natural history of medulloblastomas, has been exceptionally reported.[36] Many practitioners with limited experience in this tumor type point out to their patients that CH is a benign process. Metastases are more common in the course of the disease with a pediatric

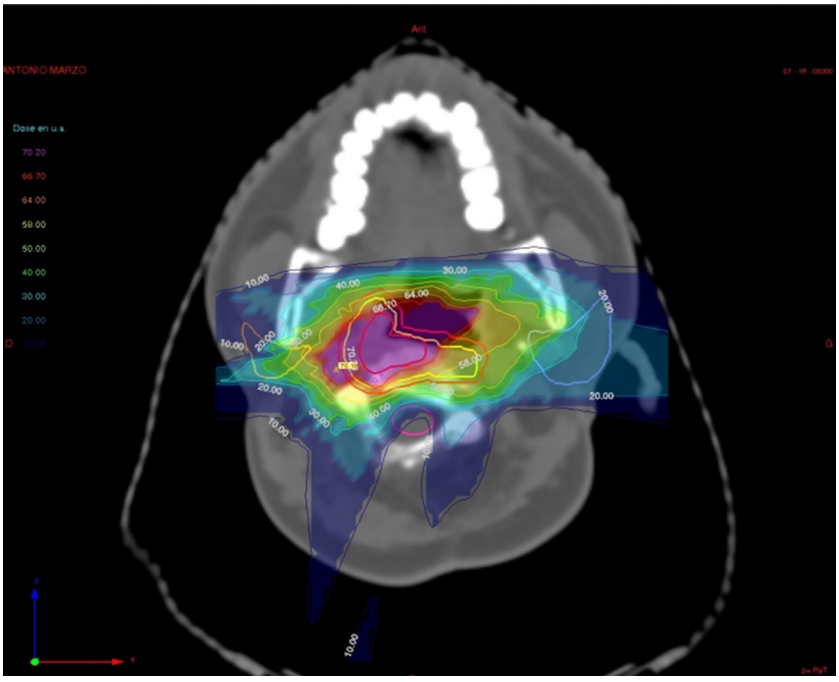

Fig. 3 – Same patient as Fig. 1. Re-irradiation for local failure at 106 months. Prescribed dose: 70.2 Gy (RBE) (*personal coll.*).

predominance compared with adults: 9–58% range vs. 7–40%.[10,31,37] In these situations, they are frequently associated with a local failure.[38] Some patterns of such "combined" failures are more frequently reported such as local + nodal or local + surgical route. Distant metastases are mainly pulmonary.[31,37] This pattern has been correlated with a higher proportion of atypical pathological variants compared with adults especially those <5 years of age (approx 65% vs. 20%). This age group is also remarkable for a higher proportion of SC sites (25% vs. 6%), compared with older children. The worse prognosis associated with SC sites could be correlated with the density of the venous drainage in this anatomical region. Associated morbid conditions have also been reported in a very early childhood: among them, the tuberous sclerosis is a neurofibromatosis associated with benign and malignant primaries. These conditions have been associated with tyrosine kinase pathways impairments, including anomalies of the mTOR pathway, responsible for uncontrolled cellular proliferation.[2,39–41] Epidermal growth factors inhibitors and mTOR inhibitors have been tested with remarkable but transient responses in both recurrent and metastatic presentations (see below).

Treatment strategy is common with that in adults: maximal surgical resection followed by high-dose, high-precision radiation therapy. Children must be operated on by pediatric surgical teams with experience in SB and S management. Multidisciplinary teams (neurosurgical, otolaryngological, orthopedic) are frequently mobilized for such sophisticated approaches, through national, and international collaborations. Multiple successive procedures are routinely requested for SB CH: through anterior (trans oral, trans palatine), posterior, and lateral approaches. The extension down through the foramen magnum needs a separate, generally anterior-lateral approach. Quality of resection based on modern imaging techniques (MRI, neuronavigation, endoscopy) and on modern surgical techniques (laser, microsurgery) has been substantially improved, but incomplete resection remains frequent in children: 0–36% in literature.[7,11,30,35] Metallic fixations can be requested for spinal consolidation. As they call for metallic material (rods, screws, cages) they can pose additional challenges to particle therapy, both at the time of simulation (requesting a MV CT simulator), and in treatment (multiple beam-angle restrictions, related with potential alterations of the particles path).

While a complete surgical resection remains crucial for long term local control,[42] the difficulties at performing a complete surgical resection have stimulated the interest in additional radiation therapy.[43] CH has the reputation of a highly radio-resistant process that is confirmed by disappointing outcome of a series dealing with 2D and 3D conventionally fractionated photon therapy: 17–40% long term survivors, following doses ≤55–60 Gy.[44] Results with stereotactic mono or pauci fractionated photon therapy have also been brought out with interesting results in highly selected patients.[44] The introduction of high dose, high precision protontherapy in the mid-seventies at Massachusetts General Hospital, Boston, turned out to be a breakthrough, with approximately two-third of patients remaining alive with NED at 3–4 years in SB, and cervical-S locations.[45] This favorable outcome has been reproduced by multiple teams in US, Europe and Japan.[46–48] Doses were progressively upgraded to 75 Gy (EBR) (Gy (EBR) = physical dose × an estimated mean 1.1 RBE) and more, conventionally fractionated, at the price of an acceptable toxicity. Recently, carbon ions have also been advocated in place of protons.[42,49] In children, the combination of surgery and radiotherapy is also recommended,[50,51] with no dose-alteration, despite the increased risks of severe side-effects following higher doses.[52] But dose adaptations can be proposed according to age, patient's conditions, and size of the residues.

In children, long term risks can be conveniently stratified in two groups, whether 1 – they are shared with adults at approximately the same dose-levels, or 2 – are observed at significantly different dose levels or totally unrelated: the first group is represented by: brain matter radionecrosis, affecting supra tentorium (esp. temporal lobes, close to the skull base), infra tentorium (brain stem, and cerebellum), spinal cord, and cranial neuropathies (rather uncommon, except for the II and VIII nerves). The second group is represented by: pituitary failure affecting growth hormone and spurt, cognitive impairments related with the inclusion of large white matter sectors, or of sensitive structures such as hippocampus; bone and cartilage plates growth delays inducing shortening of long bones, facial deformities, etc. In this group, a dose gap between adults and children is also correlated with younger age at therapy. As a rule, dose range associated with damages is inferior to curative doses recently recommended in CHs (i.e. 70–75 Gy fractionated, total dose). We will mention brain and spinal cord necrosis >55 Gy and >48 Gy respectively, in the first group (approx. 5% risk at 5 years, both in adults and children). But the most challenging situations concern the organs, and physiologic functions pertaining to the second group; cartilage arrest >15 Gy, and GH pituitary hormone failure >25 Gy, in children. Concomitant chemotherapy can further alter radiation tolerance. If tolerance of the second group organs remains a major concern (high frequency of pituitary hormones replacement, and cosmetic deformities, such as in our own case), tolerance of the first group organs is not trivial (substantial risk of internal auditory failure).

In adults, high-dose high-precision proton-based radiotherapy yields a long term disease-free survival (or local control) and overall survival between 55–87%, and 55–94%, respectively.[45–48,51,53] Pediatric CHs seem to fare better compared with their adult counterparts: 60–100% and 80–100%, respectively.[13,30,50,54,55] Nonetheless, younger children were frequently excluded in earlier series dealing with protons (since they require special attention, such as general anesthesia). Younger patients (i.e. <5 years of age) behave actually less favorably.[10,11,31,37,54] This seems to be related with a higher rate of undifferentiated histologies, and a more rapid pace of the disease, related with upfront or secondary metastases. These tumors are also more frequently located in the SC region with frequent advanced presentation that pose highly challenging surgical decisions (especially in case of S3 invasion). Furthermore, unlike the adults, the chondroid subtype does not seem to have a favorable impact on prognosis.[7,56]

In the case of a local-regional failure, re-irradiation is increasingly considered a reasonable option, especially in the context of modern technologies. It still remains complex due

to the subtle balance between a tumor dose level associated with a prolonged local control expectancy and a relatively safe dose to critical organs. This concept deals with poorly documented factors, especially alterations of tumor cells and micro-environment radiosensitivity following a second course of irradiation, and influence of delay between both courses. Dose fractionation and target volume are also important to consider. In a Canadian survey, most radiation oncologists kept away from CNS primaries re-irradiation, and recommended low-dose conventionally fractionated regimes (i.e. 20 Gy in 10 fractions).[57] For Ang, based on spinal cord experiments on a monkey, a three year-delay seemed optimal for full recovery of radiation injuries following a first course of 44 Gy fractionated, allowing supposedly a full dose administration, at second course.[58] Expert consensus consider that a cumulative dose of 90 Gy remains on the safe side, in adults affected with recurrent gliomas.[59] BED is a useful prognosticator of "biological" dose that takes into account cellular sensitivity (i.e. α/β value of the linear quadratic survival curve model), and dose per fraction.[59] When $\alpha/\beta = 2$ Gy (a commonly accepted value for cell populations involved in late responses), the 2 Gy-equivalent dose (EQ_2) equals half that value. In our case-report, despite a high cumulative BED of 270 Gy_2, and $QD_2 = 135$ Gy (for late responding tissues), we estimated a 10 year-interval to be sufficient for full recovery of anatomical critical structures. We also recommended a stereotactic approach, based on the use of protons alone, along with fiducial markers alignment and a minimal target-volume for re-irradiation based on GTV + 2 mm safety margin or so. This was supposed to virtually take out all sensitive CNS structures from the beams' path.

Chemotherapy is also commonly used in pediatric malignancies, but episodically only in CHs.[7,11,30,60] Polychemotherapy regimens have been administered with drugs similar to soft part sarcomas (ifosfamide, doxorubicin, etoposide), and again mainly indicated where local treatment had failed previously. Few very young children have been managed with upfront chemotherapy, due to an extensive presentation of the disease locally and/or distantly. In adults, targeted therapy has also drawn attention: Imatinib Mesylate, a tyrosin kinase receptor inhibitor (CKIT), and Sirolimus, an inhibitor of the MTOR kinase pathway, have been tested in advanced local or metastatic presentations or as a salvage program at the time of a failure with documented objective responses. For example, in one phase II Italian-Swiss study of 50 patients, median progression-free survival was 9 months with 64% patients experiencing a clinical benefit.[61–63]

4. Conclusion

Our case represents an exceptionally delayed local failure in a child affected with a cranio-cervical chordoma. Despite the excellent outcome reported in the literature in children with chordomas using high dose high precision particle therapy, a protracted follow-up in excess of 10 years is warranted. Following a surgical salvage program, re-irradiation should be considered a challenging option in the head and neck region. The BED concept could help define dose-constraints to the tumor and normal tissues, whereas target volume should be confined to macroscopic residues only, with no or minimal safety margins. Alternative approaches combining sub-optimal radiation doses, along with sensitizing agents, are also warranted.

Conflict of interest

None declared.

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None declared.

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