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SKULL BASE CHORDOMAS AND CHONDROSARCOMAS: CLINICAL OUTCOME AND TOXICITY OF HIGH-DOSE PROTON BEAM THERAPY. ASSESSMENT OF PREDICTIVE FACTORS FOR TOXICITY THROUGH RADIOBIOLOGY MODELING

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ABSTRACT

Purpose:

The aim of our study is to report long term results on the use of pencil beam scanning PT for the treatment of skull base Chordoma and Chondrosarcoma, focusing on the factors influencing local control, overall survival and toxicity. We subsequently evaluated the occurrence of brain radionecrosis (RN) and potential predictive factors through radiobiological models and in particular on the role of specific physical properties of proton therapy treatment, such as RBE (Relative Biological Effectiveness), LET (Linear Energy Transfer), and dose rate (DR).

Methods and materials:

Between November 2014 and November 2024, 83 consecutive patients with skull base CH and CHS were irradiated. Sixty-three patients (76%) received PT after surgery with macroscopical residual disease, 10 patients (12%) after gross total resection, 3 (3.5%) patients with radical intent (after biopsy) and 7 patients (8.5%) were reirradiated. The median prescription dose was 72 GyRBE/36 fractions for post-operative intent, 66 GyRBE/33 fractions for definitive and 60 GyRBE/30 fraction for reirradiation. Treatment plans were optimized in RayStation using 3 or 4 fields with Single (SFO) or Multiple Field Optimization technique (MFO) and each plan was evaluated in terms of robustness. Adverse events were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 grading system. Response to treatment was defined according to RECIST 1.1 (Response Evaluation Criteria in Solid Tumors). We also analyzed the LET, RBE and DR distribution in each plan and their potential correlation with the onset of radionecrosis.

Results:

At the median follow up of 40.9 months (range 3-110 months) the 3-yr and 5-yr progression free survival (PFS) were 75.5% and 71.5% for the entire cohort. Based on histology, the 3- and 5-year PFS were 71.6% and 69% for CH, while they were 93% and 79% for CHS. The 3- and 5-year PFS decreases from 83% and 74% with a radical resection to 74% and 62% with a subtotal resection (i.e., with a macroscopic residual tumor) in CH histology and from 100% to 87.5% in CHS. The 3-yr and 5-yr OS were 88% and 79% for the entire cohort, respectively. Based on histology the 3-yr and 5-yr OS were 86% and 75% for CH and 100% for CHS. The 3- and 5-year OS for CH decreases from 100% and 83% with radical resection to 88% and 79% with

macroscopic residual tumor. On univariate analysis, the presence of pre-treatment optic compression and the dose received by 99% of the high-risk volume (D99 PTV HR) have a statistically significant impact on PFS and OS ($p<0.05$). High grade (G ≥3) acute toxicity was observed only in 1.5%, no high grade (G ≥3) late toxicity was observed. RN were reported in 18% of the cases (G1 RN 13%, G2 RN 5%). On univariate analysis, alcohol consumption, the presence of pre-treatment neurological deficits, and the volume of the temporal lobes (expressed in cc) receiving a dose greater than 60 Gy (V60) statistically significantly increase the risk of developing RN ($p < 0.05$). LET distribution, RBE-variable and DR seems to not correlate with RN.

Conclusions:

Our case series confirms the efficacy and safety of proton therapy for patients with CH and CHS of the skull base. The extent of the surgery was shown to be a factor impacting the local control and overall survival of patients. The RN rate is in line with historical data present in the literature, and only a minority of cases were symptomatic. This side effect appears instead to be more associated with clinical (alcohol consumption, presence of neurological deficits) and dosimetric variables (high doses to the temporal lobes) than physical properties of the treatment.

INTRODUCTION

Epidemiology and general aspects

Skull base Chordoma (CH) and Chondrosarcoma (CHS) are rare but locally aggressive bone tumors with a combined annual incidence of approximately 1/1,000,000 persons. [1] and they account for a very small percentage of all intracranial tumors, typically around 0.1% to 0.2%. The incidence in Italy mirrors the global figures, resulting in about 60 new cases annually, with median age of presentation usually in the third to fourth decade of life.

CH derive from remnants of the embryonic notochord, which extends from the Rathke pouch to the tip of the coccyx, representing the primitive longitudinal axis of the embryo. It most frequently arises in the midline, predominantly in the clivus and the spheno-occipital region. Four types of chordoma are recognized: conventional, chondroid, dedifferentiated, and poorly differentiated.

CHS are believed to occur from transformation of remnants of enchondral cartilage along petroclival or petrosphenoidal synchondroses. A minority of CHS result from transformation of a preexisting enchondroma or osteochondroma. The World Health Organization (WHO) grades conventional chondrosarcomas from 1 to 3 based on cellularity, cellular atypia, and mitotic activity. The nonconventional mesenchymal, clear cell, and dedifferentiated variants are much less common. [2] Skull base CH and CHS though rare, can cause a variety of symptoms due to their location near critical structures like the brainstem, cranial nerves, and major blood vessels. The clinical presentation often depends on the tumor's size, exact location, and how it's pressing on these surrounding structures. Common clinical presentations include headaches and cranial nerve dysfunction like diplopia, facial paralysis, trigeminal neuralgia, dysphagia and hearing loss. Although they have distinct origins and often different outcomes, their similar location and presentations, as well as their radiological findings, lead the two conditions to be considered together. [3]

Standard treatment for skull base chordoma and chondrosarcoma

Surgery

Surgical resection remains the first choice for CH and CHS of the skull base with the appropriate surgical approach based on tumor size and location. Complete surgical removal is the primary

treatment aim for both but this is often challenging due to their proximity to neurovascular structures at the skull base and this is compounded by disease rarity, leading to low surgical volumes.[4] Even though it is well established that the extent of resection influences progression-free and overall survival in patients with CH and CHS [5,6] surgery should aim towards maximally safe cytoreductive surgery with wide enbloc resection with preservation of neurological function and quality of life, even at the price of postoperative residual tumor. Within the constraints to safety and minimizing complications, a particular effort should be made to obtain the maximal surgical reduction of the lesion and clearance from eloquent structures even to repeating further surgery. The reduction of the burden of tumor and the abutting to critical structures can also favor the safer delivery of high doses of irradiation. These lesions have a broad surgical approach strategy that is based on the location of the tumor and the surgeon's preference. Transphenoidal, transanal, trans maxillary, anterior cervical retro pharyngeal, and transanal approaches have been well documented [7]. A variety of both open and endoscopic therapeutic approaches have evolved, with an emphasis on neurological preservation, increasing the rate of gross total resection and reducing morbidity. To exploit a total resection can be challenging because of difficult access, anatomic constraints, infiltrative nature of the lesion, and proximity to critical structures such as optic nerves, optic chiasm, cranial nerves, cochlea, brainstem, pituitary gland, and temporal lobes. The most challenging side effect with endoscopic approaches is the defect closure and prevention of Cerebrospinal Fluid (CSF) leak. With the increased experience with endoscopic skull-based techniques, improved instrumentation, and, if needed, the use of arterially based mucosal flaps for cerebrospinal fluid leak closure, the ability to approach resections of these lesions has significantly improved [8,9] permitting more thorough removal of tumor with less postoperative morbidity. CHS appear to be more indolent than CH, which may lead to favoring a more conservative initial surgery. Some small tumors and other select cases may be addressed with observation alone if of low-grade. In these cases, residual tumor can be observed closely without adjuvant treatment; being local recurrence rates and ability to metastasize less than CH.

Considering the high rate of local recurrence after surgery alone, postoperative radiotherapy plays a very important role in a global therapeutic approach; however, there is currently no clear consensus on the post-surgical radiation treatments that should be used after maximal resection.

Radiotherapy

Considering the difficulty to obtain a gross total resection and wide surgical margins, adjuvant Post-Operative Radiotherapy (PORT) is important or even essential for local tumor control even in these slowly growing tumors. In retrospective series aggressive upfront management with immediate PORT after surgery showed a 10- year survival rate of 65% versus 0% in comparison to those patients

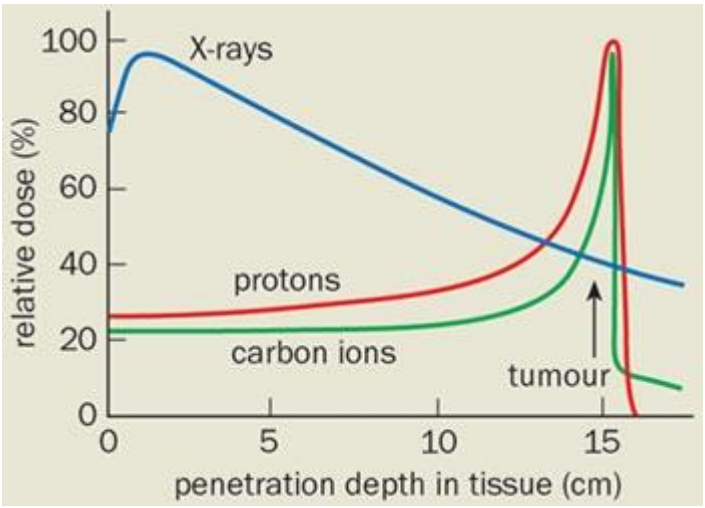
treated with RT at the time of recurrence [10]. The control of these radioresistant tumors requires doses more than 56-70 Gy, the dose level usually administered with photon beams. Doses of at least 74 Gy using conventional fractionation (1.8- 2 Gy per fraction) that are beyond the tolerance of several critical structures are recommended [11, 12]. This makes the treatment with X-ray difficult and the 5-year Progression Free Survival (PFS) reported with X-ray treatment is poor in the range of 17-39% [13, 14]. It is to note that most current series studying long-term outcome with conventional radiation therapy employed older techniques and may not apply to current management. Recently, the role of X-ray treatment, either SRT or SRS, in patients with chordomas or chondrosarcomas has been investigated in several systematic reviews [12, 15] In contrast with old studies reporting local control rates in the range of 17%–39% at 5 years following conventional RT, new radiation techniques offer improved clinical outcomes; however, the reported 5-year local control rates remain lower than those observed after Proton therapy (PT).

New X-ray radiotherapy techniques like conformal radiotherapy and intensity modulated radiation therapy (IMRT), stereotactic radiation therapy (SRT) and stereotactic radio surgery (SRS) have significantly improved the conformality and precision of radiation treatments and their potential efficacy have been suggested in a few studies; however, the reported 5-year survival is higher with PT than x-ray treatment. Using IMRT with a median dose of 76 Gy for CH and 70 Gy for CHS given in 2 Gy fractions, Sahgal et al. [16] reported 5-year survival rates of 85.6% and 84.1%, respectively, in 24 patients at a median follow-up of 36 months. For patients receiving SRS, local control rates of 21%–72% at 5 years have been observed in patients with small residual or recurrent chordomas and chondrosarcomas [17]. Complications associated with SRS are reported in 10% to 33% of patients, mainly represented by cranial nerve deficits and brain necrosis; however, grade 3 or more toxicities are reported in less than 10%.

Particles therapy

In comparison with conventional radiotherapy, particle beams such as PT and Carbon Ion Radiation Therapy (CIRT) have different physical and biological characteristics with better dose distribution. They deliver a lower entry dose, depositing the majority of their energy at the end of their path, yielding atypical narrow dose energy peak called "Bragg peak". *(fig. 1)*
This steep fall-off allows for delivery of high doses and sparing of tissue beyond the tumor. In the skull base, this feature is crucial, given the presence of several critical structures at risk.
Because of this physical property, particles are suitable for treating skull base tumors because high doses can be delivered to the target while preserving the surrounding normal tissue. In addition, because it is possible to make irregular target fields, they can deliver uniform doses to irregularly shaped tumors. Proton beams are categorized as low Linear Energy Transfer (LET) radiation with a biological effect of 1.1 times that of photon beams [18]. Radio biologically, carbon-ion beams result in two to three times the Relative Biological Effectiveness (RBE) of proton and conventional irradiation methods and they may be effective for treating highly radioresistant tumors [19].

Fig. 1: Particles therapy Bragg peak



Proton Therapy (PT)

PT was shown to be superior to photons in the seminal report of the Boston group for delivering higher doses to the tumor while keeping lower doses to normal tissues in the clival region [20]. Afterwards, PT has been considered the irradiation technique of choice in the treatment of these tumors and adjuvant therapy with CH and CHS is largely accomplished with proton EBRT, despite the limited number of available centers, but its exact role has not been fully established. New delivery techniques have developed and the recent introduction in the clinic of spot scanning PT technique (single pencil proton beams that can be modulated or conformed) to mimic current photon technique (i.e., IMRT) can offer very exciting results with high long term late grade >3 toxicity-free survival [21].

A few systematic reviews focusing on the efficacy and safety of PT in patients with chordoma and chondrosarcoma [22,23] showed, with a median dose ranging from 63 to 78.4 GyRBE, a 5-year local control rates range from 61% to 75% and from 93% to 96%, respectively, for CH and CHS and a 5-year OS rates range from 78% to 91% and 95%, respectively. Grade 3 or higher adverse radiation effects are reported in about 10% of patients; however, hypopituitarism may occur in up to 37% of patients. Regarding different PT techniques, clinical outcomes are similar for patients treated with pencil beam PT compared with those receiving passive scattering PT. Doses > 68–70 Gy in 2 Gy fractions are typically recommended, being slightly higher for chordomas (up to 73.8 Gy).

Carbon ion radiation therapy (CIRT)

In addition to PT, heavy ion beams have been used for the treatment of skull base CH and CHS and its use has been increasing, especially in Europe and Asia [24]. Heavy ions, most frequently carbon ions, have been theoretically postulated to have a biological advantage in terms of Relative Biological Effectiveness (RBE) over photon and proton therapy, particularly in slow-growing, usually radio resistant, tumors. The long-term results of irradiation with carbon ions using a raster scanning technique in patients with skull base Ch has been recently published [25]. A total of 155 patients were treated; at a median follow-up of 72 months, 5 and 10-year LC rates were 72% and 54%, respectively, whereas the 5-year - 10-year OS rates were 85%, and 75%, respectively. CIRT has been proposed also as a method of re-irradiation in cases with tumor recurrences with satisfactory outcome (survival after re-irradiation 86% at 24 months,

and 43% at 60 months) [26]. Moderate hypofractionation with 16-22 fractions of 3- 4.2 [36] GyE per fraction is feasible [27].

Systemic therapy

The role of systemic therapy in primary or advanced and metastatic CH has been traditionally limited because of the inherent resistance to cytotoxic therapies and lack of specific or effective therapeutic targets [28]. Despite resection and adjuvant radiation therapy, local recurrence rates in clival CH remain high and the risk of systemic metastases is not trivial, leading to significant morbidity and mortality.

Several cytotoxic therapies like topoisomerase inhibitors, anthracyclines, alkylating agents (e.g., temozolomide and cyclophosphamide), and microtubule inhibitors (e.g., paclitaxel) have been attempted in CH and CHS with little success [29, 30, 31].

Two categories of systemic therapies typically play a role in the modern treatment of advanced CH: targeted and immune-based therapies. Single-agent targeted therapies, such as the receptor tyrosine kinase (RTK) inhibitors imatinib and sorafenib and epidermal growth factor receptor (EGFR) inhibitor lapatinib, may be initiated in unresectable or distant metastatic disease, especially with PDGFR or EGFR activation [32]. Molecular targeted therapies (MTTs) may be more active and less toxic alternatives to cytotoxic chemotherapy agents. They act on cancer cell growth or survival pathways, relying on the presence of specific actionable targets like stem cell factor receptor (c-KIT), PDGFRA and PDGFR beta (PDGFRB), EGFR, hepatocyte growth factor receptor (MET), receptor tyrosine-protein kinase erbB-2 (HER2/neu), and vascular endothelial growth factor receptor (VEGFR), as well as the master regulators phosphatidylinositol 3-kinase (PI3K), signal transducer and activator of transcription 3 (STAT3), and mTOR [33,34,35]. Targeting the immunosuppressive tumor microenvironment in CH may be an effective strategy and is currently under investigation in preclinical studies and active clinical trials. Several immune checkpoint inhibitors (ICIs) were used as a single-agent therapeutic regimen, including pembrolizumab and nivolumab/bempegaldesleukin in select cases. Durvalumab, an anti– PD-L1 monoclonal antibody, and tremelimumab, an anti– CTLA-4 monoclonal antibody, were used as part of an investigational combination therapy in an institutional phase 2 trial (NCT02815995).

Chemotherapy has historically shown poor activity in conventional CHS and it is not a standard in the adjuvant/neoadjuvant setting, while it can be considered in the locally advanced or

metastatic disease, like anthracycline and gemcitabine-based combinations, ifosfamide, cisplatin [36,37]. With conventional cytotoxic chemotherapy cumulative objective response rate (ORR) was significantly dependent on the histotype, being 11% for conventional chondrosarcoma, with a median progression-free survival (PFS) of 5 months [36]. Several molecular targets have been identified in conventional CHS [38,39] but no targeted therapy has proven effective so far.

Dedifferentiated CHS are a high-grade tumor and they are often treated using the same combined treatment of osteosarcoma. Mesenchymal chondrosarcomas are characterized by an aggressive behavior and a peculiar chemosensitivity reported to be similar to Ewing sarcoma, and are often treated with a multimodal strategy including chemotherapy with Ewing-like regimens [40].

Aim of the Study

The aim of our study is to report long term results on the use of pencil beam scanning PT for the treatment of skull base CH and CHS, focusing on the factors influencing local control, overall survival and toxicity. We subsequently evaluated the occurrence of brain radionecrosis (RN) and potential predictive factors through radiobiological models.

MATERIALS AND METHODS

Patient characteristics

Between November 2014 and November 2024, 83 consecutive patients with skull base CH (n= 69, 83%) and CHS (n= 14, 17%) were irradiated with pencil beam scanning PT at our institution. Written informed consent was obtained from all patients and the study was approved by the local ethics committee (Ethics committee for clinical trials, Azienda Provinciale per I Servizi Sanitari, Trento, Italy). All patients were treated with curative intent and did not have metastases at diagnosis. Mean age at PT was 50 years (range: 3.7 - 84.1 years). Sixty-five patients were treated at first diagnosis and 18 subjects after one additional or several surgeries for tumor progression (recurrence disease). Sixty-three patients (76%) received PT after surgery with macroscopical residual disease, 10 patients (12%) after gross total resection, 3 (3.5%) patients with radical intent (after biopsy) and 7 patients (8.5%) were reirradiated. Patient baseline clinical and treatment characteristics are summarized in *Table 1*.

Table 1: Patient baseline clinical and treatment characteristics

Number of patients	***83***
Gender	
Male	*41 (49,4%)*
Female	*42 (50,6%)*
Age Proton therapy (years)	
Median	*50 years*
Range	*3.7 -84.1 years*
KPS Proton therapy	
Median	*90*
Range	*70-100*
Histology	
Chordomas	*69 (83,1%)*
Chondrosarcomas	*14 (16,9%)*
Skull base region	
Clivus	*76 (91.5%)*
Petro-clival	*5 (6%)*
Sellar	*2 (2.5%)*

Aim of the treatment	
Postoperative	*73 (87,9%)*
Exclusive	*3 (3,6%)*
Reirradiation	*7 (8,5%)*
Surgery number	
1	*55 (66,2%)*
> 1	*26 (31,3%)*
Resection status	
Complete	*10 (13%)*
Incomplete	*65 (87%)*
Brainstem compression	
Yes	*16 (19,2%)*
No	*67 (80,8%)*
Optic compression	
Yes	*10 (12%)*
No	*73 (88%)*
Neurological deficits before PT	
Yes	*58 (69,8%)*
No	*25 (30,2%)*
GTV, cm3, median (range)	*16,9 cc (0,2 – 148 cc)*
Dose, median	
Postoperative	*72 GyRBE (66 – 74 GyRBE)*
Exclusive	*66 GyRBE (66 – 72 GyRBE)*
Reirradiation	*60 GyRBE (54 – 60 GyRBE)*

Target Delineation and Treatment Planning

Each patient was treated in supine position and immobilized with a customized thermoplastic head mask. A simulation CT scan (1 mm slice thickness) was acquired for plan preparation and a diagnostic brain MRI was acquired within 7 days after planning CT (T2-weighted axial images, STIR images and post-contrast T1-weighted images were routinely acquired). Diagnostic brain MRI and preoperative brain MRI were rigidly registered with planning CT for target delineation. The gross tumor volume (GTV) encompassed any gross residual disease on CT and MRI images.

The high-risk clinical target volume (CTV-HR) included GTV with 3 mm safety margin modified according to both the anatomy and the surgical pathway, to include the areas of recurrence/residual tumor. The low-risk clinical target volume (CTV-LR) included the preoperative extension of disease, the surgical cavity and the surgical pathway, taking into account the postoperative changes.

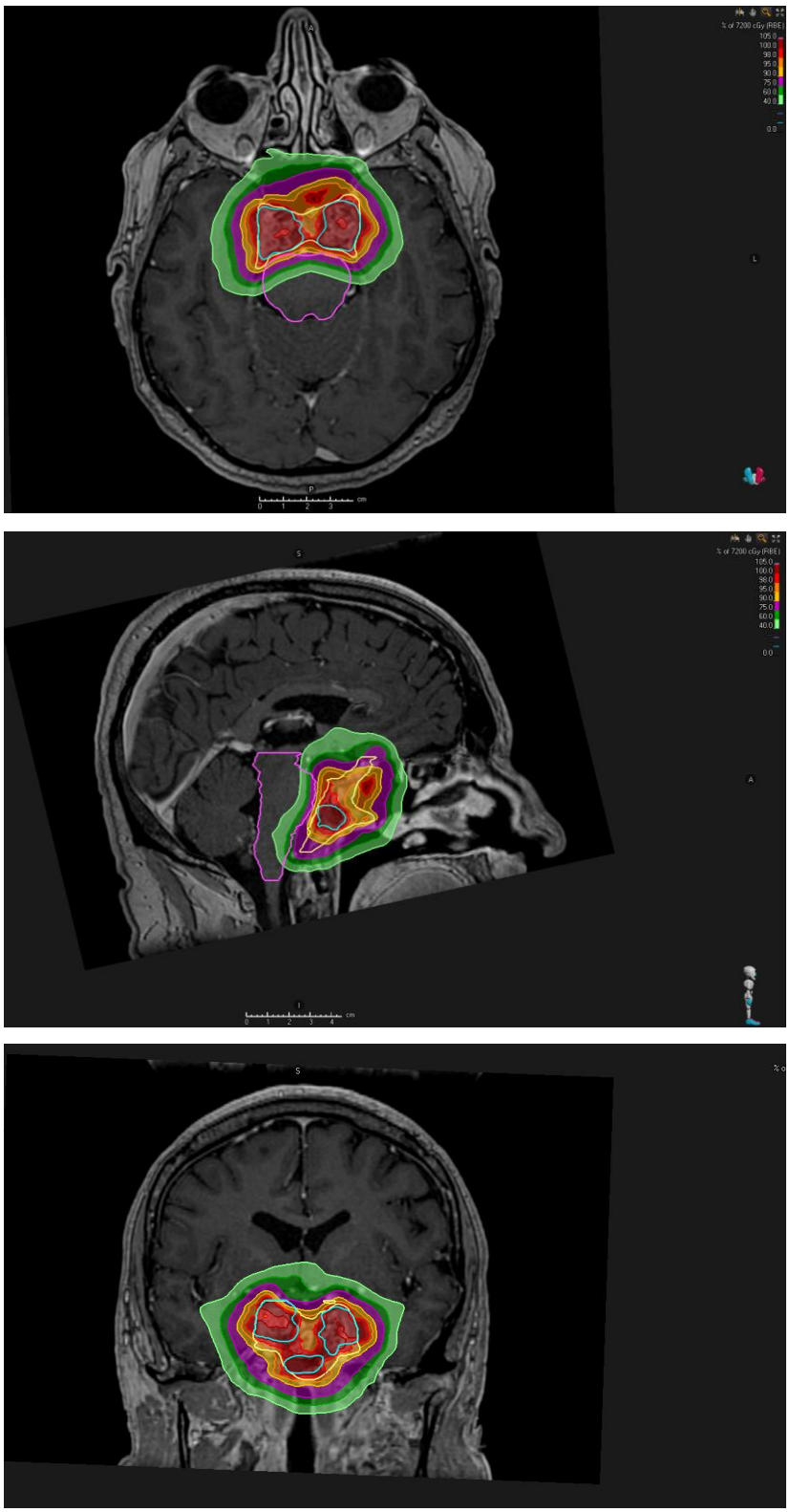
During the years the planning approach has been changed starting with a PTV-based optimization (where the PTV was obtained with a 3mm isotropic expansion of the CTV) passing through a hybrid approach (where the CTV was expanded of 2.0 mm to take into account for setup uncertainties while the range was explicitly considered during the robust optimization with a simulated uncertainty of 3.5%) until the current CTV-based full robust optimization approach (2mm for setup uncertainties and 3.5% for range uncertainties). With this last approach 16 scenarios were simulated during the optimization: 8 isocenter shifts along the diagonal direction's times two range uncertainties values.

Treatment plans were optimized in RayStation using 3 or 4 fields with Single (SFO) or Multiple Field Optimization technique (MFO). The dose grid was always cubic with a side length of 1.0 mm.

For CH, the median prescription dose was 72 GyRBE/36 fractions (range 60 – 74 GyRBE) for CTV-HR and 54 GyRBE/30 fractions (range 50 – 56 GyRBE) for CTV-LR, while for CHS the median prescription dose was 70 GyRBE/35 fractions (range 66 – 70 GyRBE) for CTV-HR and 54 GyRBE/30 fractions for CTV-LR (*fig.2*). In case of re-irradiation the median prescription dose to the CTV-HR was 60 GyRBE/30 fractions (range 54 – 66 GyRBE).

As for our clinical practice, each plan was evaluated in terms of robustness. Brain/base of skull treatments are evaluated by using the worst-case scenario approach implemented in our TPS using 1.0 mm for geometrical uncertainties and 3.5% for range uncertainty; details of the method and the motivation of these values can be found in Fracchiolla et al. [41].

Fig.2: Example of PT plan for skull base CH irradiated with a total dose of 72 GyRBE



Follow-up evaluation

Patients' follow-ups with brain MRI and clinical examination were planned every 3-6 months after the end of treatment for the first 2 years (regarding the intent of the treatment), every 6

months for the following 3 years, and then annually. Blood hormone assays and audiometric and visual examinations were performed every year. Adverse events were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 grading system. Response to treatment was defined according to RECIST 1.1 (Response Evaluation Criteria in Solid Tumors).

Statistical Analysis

For each of the three outcomes of interest (recurrence-free survival, overall survival, and radionecrosis), we derived survival probabilities using the Kaplan-Meier estimator and we identified significant risk factors using univariate Cox-proportional hazard models. End of proton therapy was chosen as baseline date. For the recurrence-free survival analysis, the index event was either recurrence or death. Candidate risk factors were: age at proton therapy, gender, comorbidities, histologic characterization (either chordoma or chondrosarcoma), chordoma subtype (conventional chondrosarcoma, conventional chordoma, chondroid chordoma, or dedifferentiated chordoma), intent of the proton therapy (radical, adjuvant, for residual cancer tissue after surgery, re-treatment), gross tumour volume (GTV), total dose in high risk (HR) volume (total dose-HR), D99 HR planning target volume (PTV) (D99- PTV-HR), brainstem compression, optic compression, and radionecrosis. Recurrence- free survival probability and the association with the proton therapy intent as risk factor were further calculated separately in the two histological subgroups (chordoma and chondrosarcoma). For the overall survival, the index event was death. We considered the same candidate risk factors as for recurrence-free survival. Overall survival probability and the association with the proton therapy intent as risk factor were further calculated separately in the two histological subgroups. For radionecrosis, the index event was occurrence of radionecrosis after proton therapy. Cumulative hazards were derived with the Nelson-Aalen estimator. Candidate risk factors were: age at proton therapy, gender, comorbidities, time from diagnosis, smoke habit, alcohol consumption, any surgery, number of surgeries, grade of last resection, neurological outcomes, location of the lesion (anterior cranial base, clivus, right petroclival, left petroclival), histologic characterization, chordoma subtype, proton therapy intent, Karnofsky Performance Status after proton therapy (KPS PT), GTV, HR clinical target volume (CTV) (CTV-HR), low-risk (LR) CTV (CTV-LR), PTV-HR, PTV-LR, proton therapy technique (multi-field optimization or single-field optimization), total dose- HR, total dose-LR, number of HR fractions, number of LR

fractions, D1-GTV, D1-PTV- HR, D99-PTV-HR, D-mean-PTV-HR, D1-PTV-LR, D99-PTV-LR, D-mean-PTV-LR, D1 right temporal lobe, V60 right temporal lobe, D1 left temporal lobe, V60 left temporal lobe, brainstem compression, optic compression, acute and late proton therapy side effects, neurological deficit. All analyses were run in the R statistical software (version 4.5.1).

RESULTS

Follow-up and clinical outcome

All patients but two (distant disease progression and general conditions decline) have completed their treatment without complications or interruptions. At the median follow up of 40.9 months (range 3-110 months) the 3-yr and 5-yr progression free survival (PFS) were 75.5% and 71.5% for the entire cohort. Based on histology, the 3- and 5-year PFS were 71.6% and 69% for CH, while they were 93% and 79% for CHS. As hypothesized, the extent of surgical resection impacts the risk of recurrence. In fact, the 3- and 5-year PFS decreases from 83% and 74% with a radical resection to 74% and 62% with a subtotal resection (i.e., with a macroscopic residual tumor) in CH histology and from 100% to 87.5% in CHS.

The 3-yr and 5-yr OS were 88% and 79% for the entire cohort, respectively. Based on histology the 3-yr and 5-yr OS were 86% and 75% for CH and 100% for CHS. Overall Survival is also influenced by the extent of surgical resection. Indeed, the 3- and 5-year OS for chordomas decreases from 100% and 83% with radical resection to 88% and 79% with macroscopic residual tumor. 14 patients died, 10 patients for the disease (8 for LR and distant progression, 2 patients for distant progression) and 2 patients for disease/treatment nonrelated cause.

On univariate analysis, the presence of pre-treatment optic compression and the dose received by 99% of the high-risk volume (D99 PTV HR) have a statistically significant impact on PFS and OS ($p<0.05$). Sex, age, histology, presence of comorbidity, and anatomic extension of the disease (upper/middle/lower clivus) had no influence on PFS and OS.

Toxicity

Toxicity profile was analyzed for the entire cohort of patients. Acute side effects are what we can expect when skull base lesions are irradiated. The most frequent toxicities observed were:

G1 asthenia (42%), G1 otitis (22%), G2 nausea (17%), G1 erythema (15%), G1 mucositis (15%) and pain (20%, median NRS score 4). High grade (G ≥3) acute toxicity was observed only in 1.5% of the cases (G3 erythema and G3 fatigue).

No high grade (G ≥3) late toxicity was observed. At a median follow-up of 43 months, the rate of hypopituitarism is 11.5% (G1 9% and G2 2.5%) and his was mainly manifested by an increase in prolactin and a reduction in GH, cortisol, and TSH. RN were reported in 18% of the cases (G1 RN 13%, G2 RN 5%). Acute and late toxicity profiles are summarized in *Table 2a/b*. The majority of RN cases were asymptomatic, and only 5% required steroid therapy, which led to the resolution or stabilization of radiological findings. No further interventions or bevacizumab use was necessary.

The most frequent site for the onset of RN is the temporal lobes, particularly the portion in close adjacency to the target (*fig. 3*). The median volume of RN was 2.3 cc (range 0,11 – 14,6 cc) and the median time of occurrence was 16 months after the end of PT (range 3,7 – 29 months).

On univariate analysis, alcohol consumption, the presence of pre-treatment neurological deficits, and the volume of the temporal lobes (expressed in cc) receiving a dose greater than 60 Gy (V60) statistically significantly increase the risk of developing RN ($p < 0.05$).

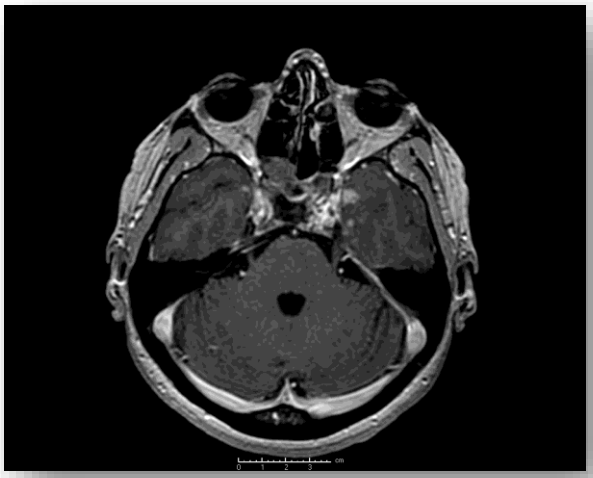
Table 2a: Acute toxicity

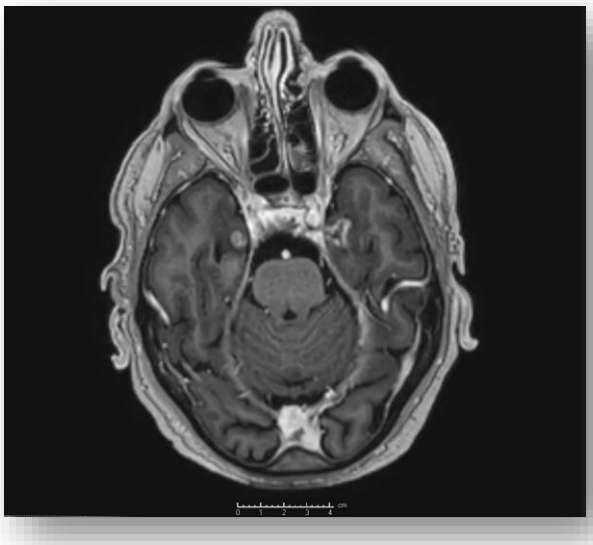
Side effect	***Grade 1***	***Grade 2***	***≥ Grade 3***
Skin erythema	*15%*	*2,5%*	*1,5%*
Dysphagia	*15%*	-	-
Otitis	*22%*	*2,5%*	-
Vomiting	*8,5%*	*2,5%*	-
Nausea	*20%*	*17%*	-
Fatigue	*42%*	*5%*	*1,5%*
Pain	*20% (Median NRS 4)*		
Mucositis	*15%*	*6%*	-
Diplopia	*5%*	*1,5%*	-
Seizure	*2,5%*	-	-

Table 2b: Late toxicity

Side effect	***Grade 1***	***Grade 2***	***≥ Grade 3***
Optic Neuropathy	-	-	-
Vascular disorders	4%	-	-
Hearing impaired	12,5%	1,5%	-
Hypopituitarism	9%	2,5%	-
Nausea	1,5%	2,5%	-
Fatigue	16%	4%	-
Diplopia	5%	1,5%	-
Radionecrosis	13%	5%	-

Fig.3: Example of temporal lobe radionecrosis





Impact of RBE variations on risk estimates of temporal lobe necrosis

The concept of relative biological effectiveness (RBE) has been introduced to account for the increased efficiency of different types of radiation to produce biological effects. RBE is defined as the ratio of a dose from the reference radiation, photons, to a dose from any other radiation quality (such as particles) to produce the same biological effect. Proton therapy currently relies on a constant RBE value of 1.1, which is a conceptual constant based on experimental data, as recommended worldwide [42]. This factor means that a given proton dose is expected to be equivalent to a 10% higher photon dose for all tumors, tissues and organs. However strong evidence exists that the RBE actually varies along the proton beam track and whether the increase of the RBE towards the distal edge is a clinical issue, or the use of a fixed RBE of 1.1 is

an adequate clinical solution is under debate, and there is an increasing awareness of clinical uncertainties in proton therapy arising from RBE issues [43]. There is growing interest in the scientific community to analyze the late side effects associated with proton therapy. Notably, in recent years, some side effects in skull base tumors have emerged with doses that were rarely reported with photon therapy, like RION (radiation induced optic neuropathy) [44] and a research direction aims to assess whether a variable RBE might partially account for this type of toxicity, with currently unclear and strong correlations [45].

RN after radiation treatment (particularly with particles) for skull base CH and CHS is a known and fairly common late side effect. Part of the reasons can be attributed to the high radiation doses delivered to the target (greater than 70 Gy) and the close proximity of brain tissue to the high-dose irradiated region. The temporal lobes are the region in closest contact with the irradiated area and thus at highest risk of radionecrosis. There is significant variation among reports, but some studies indicate that asymptomatic temporal lobe disorder occurred in about 40–50% of cases, at the maximum estimate, but Grade 3 or higher is considered to be 10% or less.

Several studies have attempted to evaluate various dosimetric parameters (Dmax, the maximum dose; D0.1cc, the maximum average dose delivered to a 0.1-cc volume, and D1cc, D2cc, D3cc, D5cc, D10cc and Dmean, the mean dose) and they indicated that Dmax was the most significant predictive dosimetric factor for brain necrosis after conventional fractionation [46].

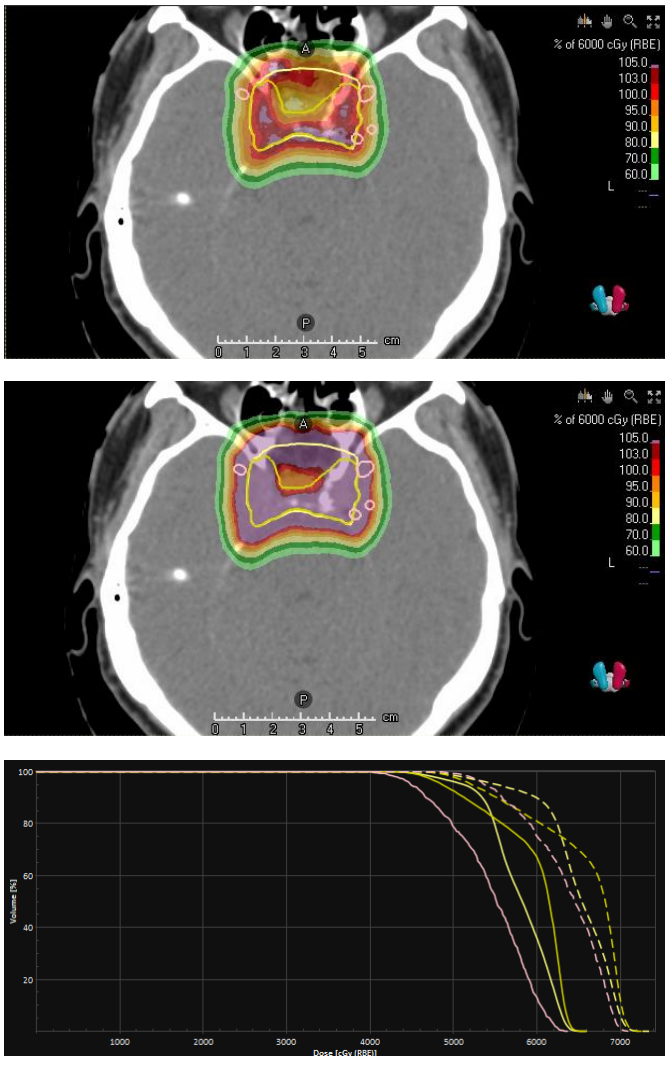
Moving beyond the standard dosimetric parameters mentioned above, we assessed in our population whether using a variable RBE in treatment planning might predict or justify the onset of radionecrosis.

Based on three variable RBE models we have recalculated, for each patient (cohort with radionecrosis and control group without radionecrosis), the plan doses. The three models rely on alfa/beta, fractional dose and LETd distribution. The calculation was performed with a voxel-wise based approach. [47,48,49].

In *Fig. 4*, a case (from the cohort with radionecrosis) is shown with the plan recalculated using a variable RBE model. Using a variable RBE model, we can observe a "hypothetical" increase in the delivered dose of about 8% compared to a standard proton therapy plan. This increase affects both the target area and the adjacent structures (organs at risk). This "hypothetical" increase is present in all treated cases (the radionecrosis cohort and the control cases) without

statistically significant differences. Furthermore, if we analyze the location where radionecrosis appeared, there is also a dose increase in this area due to the variable RBE model, but this dose increase does not differ statistically from other areas of the brain tissue where radionecrosis did not develop, both in the radionecrosis patient cohort and in the control cases. Therefore, in conclusion, we can establish that even when using variable RBE models for proton therapy planning in our population, the resulting dose increase does not appear to correlate with or justify the side effect of radionecrosis.

Fig. 4: Recalculated plan with RBE variable model in patient with radionecrosis

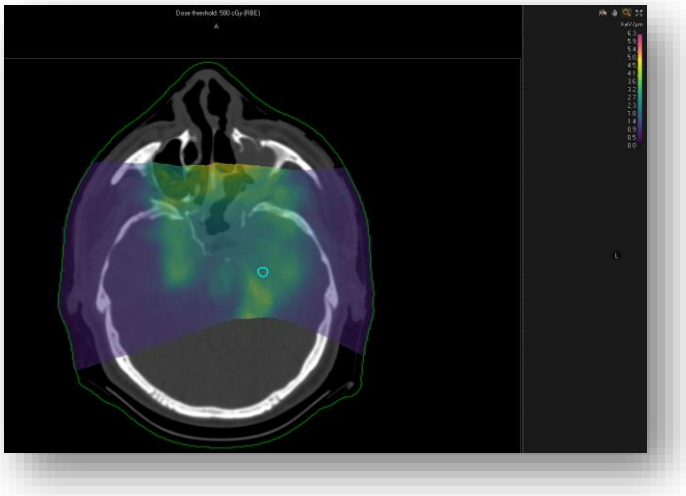


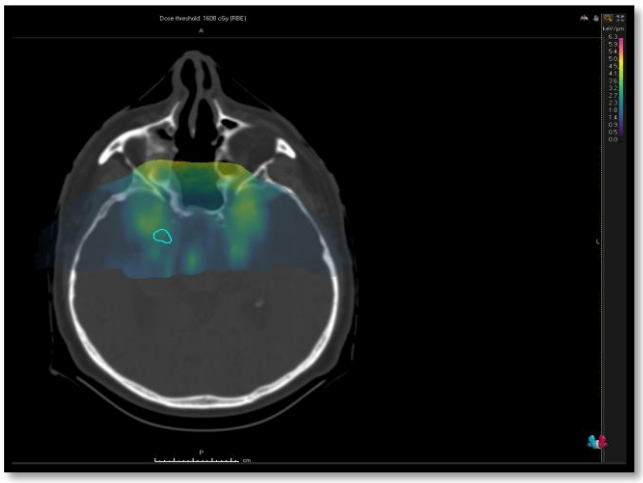
Impact of LET variations on risk estimates of temporal lobe necrosis

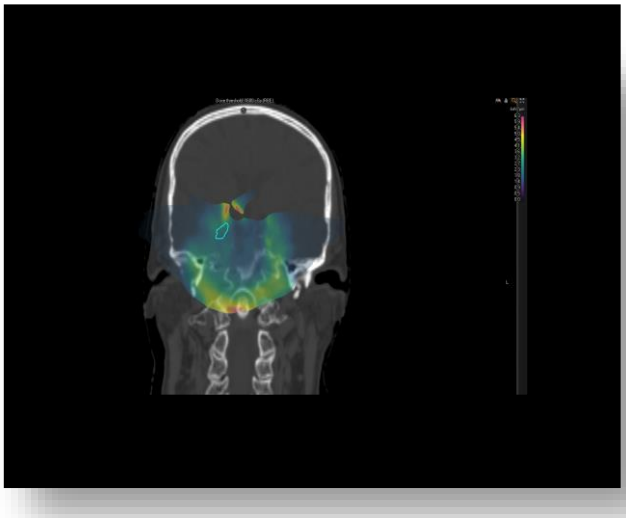
The rate at which a charged particle, such as an electron or proton deposits its energy along its track is described as its LET (Linear Energy Transfer) and its units are keV/µm.; the heavier the particle, the higher its LET. The LET largely determines the biological consequence of radiation exposure. Thus, electrons have a predominantly low LET, proton a slightly higher LET, neutrons an even higher LET, and heavily charged particles the highest LET of clinically used radiations. The rate of energy transfer increases as particles slow, which means that LET is only an average value that is little more than a useful guide to the radiation therapist. As the LET of beam increase, so does its relative biological effectiveness (RBE). As they slow down, the changing particle cross section (like proton) modifies their LET, generally increasing it to a Bragg peak just before achieving thermal equilibrium with the absorber, i.e., before the end of range. At equilibrium, the incident particle essentially comes to rest or is absorbed, at which point LET is undefined. For typical X-rays (which produce electrons), LET ranges from approximately 0.2 to 15 keV/µm−1; for fast neutrons (which produce protons), LET ranges from approximately 8 to 40 keV/µm−1; and for α particles, LET is greater than approximately 260 keV/µm−1. As mentioned before, for proton therapy, a fixed RBE of 1.1 is applied clinically, which likely oversimplifies the RBE model and underestimates RBE around high LET locations (eg, distal end of Bragg peak where LET is high, around 10 keV/µm). An underestimation of RBE will potentially increase the risk of toxicities in the nearby organs at risk. Hence, it is essential to develop an LET-based plan evaluation and optimization method for proton therapy. For example, for 2 Gy dose, an averaged RBE of 1.15 was found for LET values ranging from 1 keV/µm to 3 keV/µm. For LET values ranging from 6 keV/µm to 9 keV/µm, the average RBE was 1.35 which increased to 1.72 for even higher LET (9-12 keV/µm). The increase in RBE as a function of LET could extend biological range with up to 0.4 cm [47]. This issue is especially relevant in cancer treatment of disease sites such as head and neck or brain where there are many organs at risk such as brainstem and optic-nerve structures in the proximity [50].

Building on the points above and the understanding that an increase in LET, by leading to an increase in RBE, might be linked to higher toxicity, we generated a LET distribution map for all patients in our population and evaluated its relationship with the areas of RN (*figure 5*). Based on the analysis of these maps and their spatial distribution, no high LET values (typically > 10 keV/µm) were found in the areas of radionecrosis. Therefore, the onset of this side effect does not appear to be dependent on high LET values.

Fig.5: LET distribution and its relationship with RN







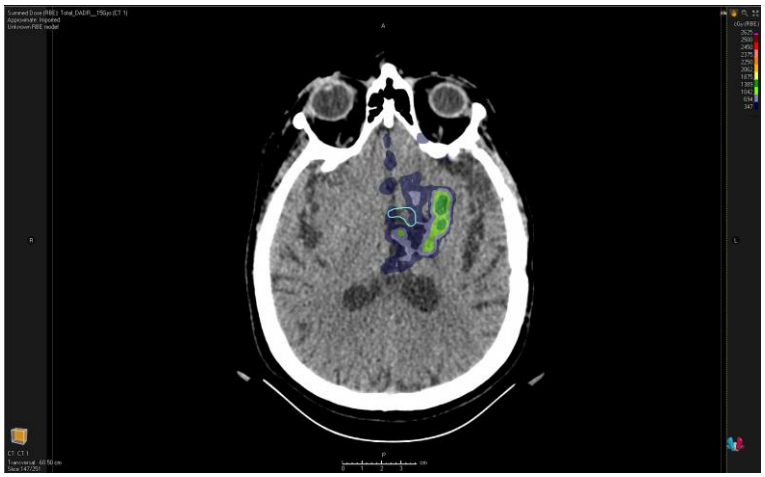
Impact of Dose-rate on risk estimates of temporal lobe necrosis

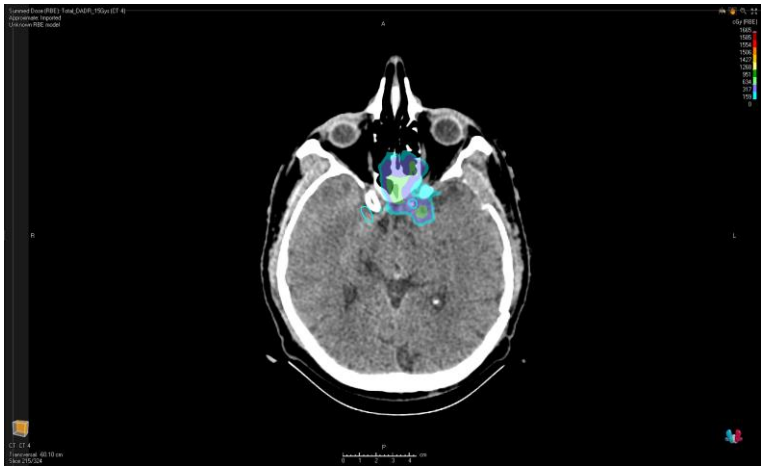
A dose rate (DR) is quantity of radiation absorbed or delivered per unit time and it is often indicated in micrograys per hour (μGy/h). When considering stochastic radiation effects, only the total dose is relevant; each incremental unit of dose increases the probability that the stochastic effect happens; when considering deterministic effects, the dose rate also matters. [51]. Depending on the range of variation, the DR is known to influence radiobiological effectiveness and radiochemical processes [Dale RG. Dose-rate effects in targeted radiotherapy. Phys Med Biol. 1996;41(10):1871-84]. There is evidence suggesting a potential correlation between DR and relative biological effectiveness (RBE) in conventional photon beams [52]. In contrast, such effects have not been identified in carbon ion beams and proton therapy. As mentioned before, rare, unexpected severe toxicities can occur in patients following proton therapy [53] often with relatively low dose levels compared to the dose constraints applied in conventional photon therapy. Meijers et al. for example, tried to investigate a possible correlation between radiation-induced optic neuropathy and DR delivered in the optic pathway [54] and they found that while optic structures of non-toxicity cases were exposed to DR of up to 1 to 3.2 GyRBE/s, the pre-chiasmatic optic nerves of the 2 toxicity cases were exposed to DR above 3.7 GyRBE/s.

Based on the assumption that high DR might be associated with an increased risk of toxicity, we extracted the instantaneous DR LOGFILES from our treatments and created a dose rate map for each treatment. Specifically, for each patient, we created a map of the delivered dose above a specific dose rate threshold (dose above DR), in particular above the dose rate value of 15 Gy/s. We selected this value, because, based on the article mentioned above, seems to correlate with an increased risk of toxicity. Subsequently, we focused on the areas of radionecrosis and evaluated whether doses with a DR value above 15 Gy/s had been delivered to these areas.

From our analysis, as you can see in *Fig. 6*, there do not appear to be any doses delivered with a DR greater than 15 Gy/s in the areas of radionecrosis. For this reason, the DR also does not seem to influence the onset of this side effect.

Fig.6: Dose distribution with DR > 15 Gy/s and its correlation with radionecrosis





DISCUSSION

CH and CHS of the skull base and cervical spine are reputed to be slow-growing processes with a definite propensity to local recurrence. However, pattern of failure following high radiation doses is poorly understood [55]. Due to tumor location within the base of the skull or cervical canal, a complete resection can rarely be achieved. Nonetheless, in expert hands, radical removal of the tumor has been reported in 62–79% [56]. In a 10-year meta-analysis of single institutional studies, a pooled Kaplan-Meier analysis showed that the 5-year PFS in patients who received GTR was 87% compared with 50% in patients with a subtotal resection, whereas the 5-year OS was 95% compared with 71%, respectively [6]. As a result, many patients can be offered higher dose adjuvant radiotherapy which provided the best chance of local control; however, the most effective modality and dose of radiotherapy, the specific patient populations in which radiotherapy may be more effective, and the benefits of radiotherapy after a complete resection remain to be elucidated. Proton beam therapy, which has superior dose-localization characteristics compared with conventional radiation and thus may prevent damage to adjacent tissue, has been considered the gold-standard modality of adjuvant radiotherapy for skull base CH and CHS thanks to superior local control and survival rates compared to photon treatment. This is due to the ability of proton therapy treatment to deliver higher doses to the target, especially when it is in close proximity to critical organs.

Our data set is one of the largest published concerning the treatment of skull base CH and CHS using active scanning proton therapy. The reported results confirm the efficacy and safety of high-dose proton therapy treatment. The 3- and 5-year PFS and OS are absolutely in line with other published proton therapy case series; in fact, the 5-year PFS for CH and CHS (including postoperative, radical, and re-irradiation treatment) is 69% and 80%, respectively, versus a range between 43% and 84% for CH and between 81% and 94% for CHS. The 5-yr OS is 75% for CH and 100% for CHS, versus a range between 69% and 84% for CH and 91-97% for CHS.

Our data confirm the importance of achieving the most radical surgical intervention possible. It emerged that the presence of postoperative disease residue negatively impacts disease control for both CH (5-yr PFS 74% vs 62.5%) and CHS (5-yr PFS 100% vs 87.5%).

The statistical analysis also showed that as the dose delivered to the high-risk volume (disease residue) increases (for every 1 Gy increment), there is a linear increase in both PFS and OS. On the other hand, the presence of pre-treatment optic pathway compression negatively affects

local control and survival. This association is likely due to the inability to deliver an optimal target dose in these patients in an effort to preserve visual function.

The treatment was well tolerated. The rate of acute toxicity ≥ Grade 3 was 1.5% (fatigue and skin erythema). The other side effects (like nausea, vomiting, otitis etc) were mild and transient. No late side effects ≥ Grade 3 were recorded. At a median follow-up of 43 months, the rate of hypopituitarism is 11.5% (G1 9% and G2 2.5%) and his was mainly manifested by an increase in prolactin and a reduction in GH, cortisol, and TSH. Hypopituitarism is a known side effect since the sellar region is irradiated in the majority of cases, and the rates reported in the literature range between 11% and 37% [57,58].

The radionecrosis rate was 18%, with the majority of cases (13%) being asymptomatic and self-resolving on subsequent MRI follow-ups without the need for specific therapy. The rate of radionecrosis is also in line with those reported in the literature, which range between 3% and 31% [59,60].

Numerous attempts have been made over the years to find clinical or dosimetric factors associated with the onset of radionecrosis in this patient setting, but without reaching definitive conclusions or demonstrating clear correlations. Mattke et al., in their case series of 244 patients affected by skull base CH and CHS, found that the maximum dose (Dmax) to the temporal lobes is a risk factor for the onset of radionecrosis and also the V60 (as the volume, which was irradiated with at least 60 Gy) showed a highly significant influence on the development of lesions; If V60 increased by 1 cc, the likelihood of developing a reaction increased by the factor of 1.395 [61].

The role of Dmax and D1cc in predicting temporal lobe radionecrosis risk in NPC patients undergoing 3D-CRT, IMRT, and VMAT is further confirmed by the review and meta-analysis by Dong et al [62].

The data from our analysis confirm the findings reported in the publications mentioned above. Indeed, the V60 also proved to be a risk factor for the onset of radionecrosis in our case series. Numerous clinical factors (age, sex, alcohol consumption, neurological deficits, etc.) were also analyzed to see if they had an impact on the incidence of radionecrosis.

Statistical analysis suggests that alcohol consumption ($p < 0.01$) and the presence of post-surgical neurological deficits ($p < 0.03$) appear to be predisposing factors for the onset of this side effect.

Proton beam therapy is often perceived, especially by photon therapy practitioners, as effective and full of potential, but also as a treatment associated with certain uncertainties or risks of adverse effects.

The presence of range uncertainty, a possibly variable rather than constant RBE, and LET values higher than anticipated, all increase the perception that this treatment might be more effective on one hand, but also potentially riskier on the other.

There are indeed historical case series, particularly in the pediatric population, which suggested that proton therapy treatment was accompanied by a higher risk of brainstem radionecrosis [63]. However, these data were subsequently refuted, because obsolete techniques were being used and these radionecrosis were predominantly asymptomatic.

Furthermore, the use of various technical strategies such as robust optimization, the use of proton arc therapy, and the modulated distribution of radiation beam angles significantly mitigates the presence of these uncertainties.

In addition to this, numerous other studies published subsequently have shown that the rate of radionecrosis in the brainstem is actually similar to that seen with photon radiation treatment [64].

Based on the above, we evaluated in our population whether certain factors intrinsic to the proton therapy technique, such as LET, RBE and dose rate, could correlate with the onset of radionecrosis.

Several publications have highlighted how LET values tend to increase near the distal end of the proton beam and in the corresponding lateral penumbra regions, and this leads to an increase in RBE compared to the defined 1.1 [65] with the resulting risk of increased side effects. Hence, it is essential to develop an LET-based plan evaluation and optimization method for proton therapy. Consequently, starting from the delivered treatment plans, we created a LET distribution map and evaluated the values within the areas of radionecrosis. The analysis did not show high LET values within the radionecrosis areas, or at least not higher values compared to the group in which this side effect did not occur.

Starting from the premise that the presence of a variable RBE may be associated with an increase in side effects, we recalculated the treatment plans using radiobiological models of variable RBE. Although the use of variable RBE causes an increase of about 8% in the delivered dose, there is no evidence that it is a determining factor in the onset of radionecrosis.

Finally, we analyzed the dose rate delivered in our plans and, in particular, we focused on the dose delivered with a dose-rate above a certain threshold (dose above dose-rate). Meijers et al. analyzed retrospectively a selected number of treatment plans for patients with and without visual toxicity and they found that while optic structures of non-toxicity cases were exposed to dose rates of up to 1 to 3.2 GyRBE/s, the pre-chiasmatic optic nerves of the 2 toxicity cases were exposed to dose rates above 3.7 GyRBE/s [54]. Moreover, Pham et al. in their analysis revealed that patients with a V40 chiasma greater than 75% had a shorter time to develop higher grades of toxicity compared to those with a lower V40 chiasma exposure [66]. In our cases, the absence of dose delivered with a high dose-rate in the radionecrosis areas tends to exclude a significant impact of this parameter on the onset of this side effect. Therefore, definitively, at least in our case series, there are no factors intrinsic to the proton therapy treatment that can explain the onset of cerebral radionecrosis.

CONCLUSIONS

Our case series confirms the efficacy and safety of proton therapy for patients with CH and CHS of the skull base, reinforcing the concept that proton therapy should be considered the gold standard treatment for these diseases.

The extent of the surgery was shown to be a factor impacting the local control and overall survival of patients. Indeed, the presence of a postsurgical residue is negatively associated with survival. The treatment was well tolerated and no significant side effects emerged. The radionecrosis rate is in line with historical data present in the literature, and only a minority of cases were symptomatic.

No elements emerged that would allow us to correlate specific properties of the proton therapy treatment (LET, RBE, DR) with the onset of radionecrosis. This side effect appears instead to be more associated with clinical (alcohol consumption, presence of neurological deficits) and dosimetric variables (high doses to the temporal lobes).

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