

Protontherapy to maintain local control of head and neck paragangliomas

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Introduction

Paragangliomas are rare vascular neuroendocrine tumors that develop in neuroendocrine cell groups located along vascular and nervous axes of the head, neck and neck. Their annual incidence is estimated at 2–8/1,000,000 [1]. Parasympathetic paragangliomas of the head and neck account for 3% of all paragangliomas, but are the most common middle-ear tumors. Despite their benign and localized nature in 90% of cases, aggressive local extension remains responsible for significant symptoms due to cranial nerve involvement.

Given their low incidence, therapeutic strategies vary according to the extent of the disease. In tumors with local evolution, surgical resection combined or not with radiotherapy is recommended. However, the radiotherapy strategy is preferred in tumors with a high risk of post-operative complications and functional sequelae [2]. Conventional radiation therapy was initially used and provided a high local control rate, but carried a risk of secondary cancers and neurocognitive disorders. Protontherapy delivers a maximal dose of energy (Bragg peak) followed by a rapid decline just before the proton comes to rest [3]. Protontherapy, by modulating this Bragg peak, can thus target tumors precisely and thereby attenuate the risk of toxicity to surrounding healthy tissues.

Following Ioannides' study [4], our team published in 2018 one of the first single-center studies suggesting that proton beam therapy is an effective and well-tolerated treatment for skull-base paragangliomas, with documented functional benefits [5]. The present study reports updated data with a longer follow-up on the efficacy, and acute and long-term toxicities of protontherapy in paragangliomas of the head and neck.

Material and methods

Patients

We retrospectively analyzed 18 patients, with newly diagnosed or recurrent paraganglioma of the head and neck

treated with protontherapy between July 2001 and May 2020, in the Institut Curie Proton Therapy Center in Orsay (ICPO). One patient was excluded from our study because he received photon-proton radiotherapy and died shortly afterwards from chronic uncontrolled hepatitis. Therefore, seventeen patients were actually included in our study. Patients' baseline characteristics are reported in Table 1. Ten patients were treated for newly diagnosed paragangliomas, whereas five patients had recurrent disease after surgery, and two patients received adjuvant protontherapy for a residual tumor after surgery. One patient had an initial stable oligo-metastatic expansion with hypermetabolic uptake in the occiput and acetabulum: he received protontherapy to the primary lesion and conventional radiotherapy to the secondary lesions; no systemic treatment was given. Fifteen patients had initial hearing loss.

Protontherapy

Proton beam therapy was delivered by a cyclotron in the Institut Curie Proton therapy Center of Orsay, France (ICPO), with an energy of 201 MeV and a double-scattering technique. Magnetic resonance imaging (MRI) with thin-slice (2.0 or 3.0 mm) was required to delineate organs at risk and target volumes. Gross target volume delineation matched the visible tumor on MRI. The clinical target volume was built by adding to the gross target volume a margin of 3 to 5 mm, depending on the adjacency of organs at risk. A margin of 2 mm was added around the clinical target volume to create the planning target volume (PTV). Treatment plans were designed so that at least 95% of the PTV received at least 95% of the prescribed dose. The main dose constraints for organs at risk used are detailed in Supplementary Table 1 and were consistent with European recommendations [6]. All seventeen patients included in this retrospective study received a complete proton-only based treatment according to the double-scattering technique. Prescribed median dose for the PTV was 50.4 Gy RBE (Relative Biological Effectiveness = 1.1) (IQR 25–75%: 50.4–50.4 Gy) (1.8 Gy RBE/fraction). Median treatment

Table 1. Baseline characteristics in this cohort ($N=17$) of patients undergoing protontherapy of head and neck paragangliomas.

Patients' characteristics at baseline	
Median age [range]	52.6 years [16.0–68.2]
Sex, $n(\%)$	
Male	7 (41%)
Female	10 (59%)
Initial Karnofsky index, $n(\%)$	
100	7 (41%)
90	4 (24%)
80	5 (29%)
≤ 70	1 (6%)
Site of disease, $n(\%)$	
Jugulotympanic glomus	15 (88%)
Vagal Glomus	2 (12%)
Tumor side, $n(\%)$	
Left	9 (53%)
Right	8 (47%)
Status of disease, $n(\%)$	
Newly diagnosed	10 (59%)
Recurrence after surgery	5 (29%)
Residual tumor after surgery	2 (12%)

duration was 42.0 days (IQR 25–75%: 40.0–43.0 days). Median number of fields was three. Treatment characteristics are detailed in [Supplementary Table 2](#).

Statistical analysis

Baseline characteristics were summarized as numbers and percentages for qualitative data, and as medians with the inter-quartile ranges for continuous variables. Follow-up was calculated from the date of the end of the protontherapy to the date of last news. The Kaplan-Meier method has been chosen to estimate the median follow-up, the local-recurrence-free survival (LRFS), the progression-free survival (PFS) and overall survival (OS) rates. Excel version 2016 was used for the statistical analysis.

Results

Local control and survival

Median follow-up was 50.1 months (IQR 25–75%: 29.9–88.0 months). At the time of data closure, local-recurrence-free survival was 100%, with radiological stability in fourteen patients (82%) including the metastatic patient and a slight reduction of tumor size in three patients (18%). No recurrences were observed. At the last news, no deaths had been reported among the seventeen patients. Follow-up continued for 15 patients, whereas two patients were lost to follow-up. During the paraganglioma follow-up, one patient developed breast cancer.

Toxicity and functional benefit of protontherapy

Adverse events had been classified according the Common Terminology Criteria for Adverse Event (CTCAE) v.5 [7]. Protontherapy was well tolerated: nausea (53%), localized alopecia (41%) and headache (47%) were the most common acute symptoms in our cohort, with the need to introduce transient corticosteroid corticotherapy in three cases for headache. Acute adverse events of grade 2 or less occurred

Table 2. Protontherapy of head and neck paragangliomas: acute toxicity according to CTCAE v.5.

Acute toxicity	Grade 1	Grade 2	Grades 3–4
Nausea	9 (53%)	0	0
Headache	8 (47%)	1 (6%)	0
Alopecia	7 (41%)	1 (6%)	0
Radiodermatitis	6 (35%)	0	0
Otitis	4 (24%)	0	0
Dysphagia	3 (18%)	0	0
Hearing loss	0	1 (6%)	0
Dizziness	2 (12%)	0	0

CTCAE: Common Terminology Criteria for Adverse Events.

Table 3. Protontherapy of head and neck paragangliomas: late toxicity according to CTCAE v.5.

Late toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Fatigue	10 (59%)	0	0	0
Headache	2 (12%)	0	0	0
Dizziness	3 (18%)	0	0	0
Impaired hearing	0	1 (6%)	1 (6%)	0
Cataract	0	1 (6%)	1 (6%)	0
Lagophthalmos	1 (6%)	0	0	0
Alopecia	1 (6%)	0	0	0

CTCAE: Common Terminology Criteria for Adverse Events.

in 94% of patients, with mainly grade 1 adverse events and only 18% of grade 2 adverse events. No grade 3 or 4 toxicities, hospitalization or discontinuation occurred during treatment. One of the fifteen patients with initial hearing impairment, experienced a deterioration in hearing function (grade 1 to grade 2), which was concomitant with serous otitis. Details on acute toxicities are reported in [Table 2](#).

Among the seventeen patients, ten (59%) reported at least a partial functional benefit from protontherapy, with mainly an attenuation of tinnitus, dizziness and headaches. Fatigue was the most widely late-reported symptom. Grade 2 to 3 late toxicities occurred in 24% of patients, while no grade 4 or 5 toxicity was reported. No patients showed pituitary deficiency. Hearing ability was stable in thirteen patients; two patients had a significant deterioration in their hearing, while two patients experienced an improvement. The two patients with deteriorated hearing (one grade 2 and one grade 3 toxicity) had hearing loss initially, which had worsened by one grade at follow-up. The maximal doses received by the ipsilateral cochlea due to dosimetric constraints were 52.9 Gy and 54.4 Gy, respectively. Swallowing disorders disappeared, while dizziness and tinnitus remained stable or disappeared. Details on late toxicities are reported in [Table 3](#).

Discussion

In the current therapeutic arsenal of head and neck paragangliomas, radiotherapy is preferred to excisional surgery when the surgical procedure cannot be completed or when significant functional sequelae are expected [2]. Over the years, conventional radiotherapy has repeatedly proven to be effective, like in the Lassen-Ramshad's study, with an LRFS of greater than 90% [8–13] and an OS of 93% at 48 months (range 1–456) [13]. Few data exist on the place of protontherapy in this indication, and are exclusively based on retrospective studies ([Supplementary Table 3](#)). As suggested

in a previous report in 2017 [5], the present study with a longer follow-up of 50.1 months (IQR 25–75%: 22.9–88.0) confirms the efficacy of protontherapy in achieving local tumor control. All 17 patients experienced local disease control with volume stability obtained in 82% of cases and significant volumetric shrinkage in 18% of cases. These results were concordant with Ioannides' study of 7 patients [4] and Kang's retrospective review of 37 patients in which the 5-year recurrence-free and OS rates were higher than 97% [14]. Nevertheless, variable PTV doses (35.0 Gy RBE in Ioannides' study versus 50.4 Gy RBE in our study) remain a methodological obstacle to the comparison of the different methods of irradiation from one study to another. The minimum necessary dose is controversial: 45 Gy (Dupin's [11] and Rougier's studies [15]) vs. 50 Gy [14]. More investigations are required. Unfortunately, at this time, no randomized study is under way or even planned [16]. The question arises as to whether the advantages of protontherapy are sufficient to promote it over modern techniques such as IMRT.

As paragangliomas are benign tumors with prolonged life expectancy, limiting the toxicities induced by the irradiation of healthy tissues is an essential consideration. The physical characteristics of protons make them an ideal vector for the irradiation of new lesions. Indeed, concerning the irradiation of organs at risk close to the PTV (cochlea, vessels, cranial nerves), protontherapy does not seem to generate significant benefits compared with IMRT [11]. Organs at risk far from the PTV receive a significantly different dose, from a very low dose with IMRT to no dose with protontherapy, but as yet there is little evidence that these few Gray have a significant clinical impact. The issue appears to be more pronounced for structures at an intermediate distance (hypothalamic–pituitary–adrenal axis and cognitive function), which are sensitive to radiation-induced toxicity. Indeed, among the 200 patients with low-grade and benign brain tumors studied by Jalali et al. [17], neurocognitive scores were significantly higher over a period of 5 years and new neuroendocrine dysfunctions were lower (31% vs 51%; $p = 0.01$) with stereotactic conformal radiotherapy compared with conventional radiotherapy. This was also observed in Lassen-Ramshad's study [13]. With most adverse events being grade 2 or less and only two cases of grade 3 toxicity in this current study, protontherapy seems to generate lower long-term toxicity. Indeed, the reduced risk of endocrine impairment, stroke, memory impairment, and cognitive impairment seems to be gradually confirmed. Protontherapy also seems to reduce the risk of secondary brain tumors by 38% [18] to 54% [19], as compared with photon therapy (relative risk of 10.5 in the Minniti's study [20]). A functional benefit of protontherapy was reported in 59% of our patients and was most pronounced for tinnitus, vertigo and headaches. This clinical benefit is similar to the results reported by Kang and his team in 2020 [14], with an improvement in symptoms in 70% of patients.

The main limitation of this study is its small size, a parameter that is not very expandable in real life due to the rare prevalence of this disease and the use of a state-of-the-art

technique such as protontherapy. The long median follow-up of this homogeneous cohort makes the strength of our study. Therefore, with the development of protontherapy centers all over the world, indications for protontherapy, although always discussed, are becoming more numerous, like for paragangliomas of the head and neck, and the therapy seems to be gaining a privileged place among other modern radiotherapy techniques.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

Data available on request due to privacy/ethical restrictions.

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