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Original article

Protontherapy of head and neck paragangliomas: A monocentric study

Protonthérapie des paragangliomes de la tête et du cou : expérience monocentrique

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ABSTRACT

Purpose. – The aim of this study was to assess efficacy and safety of proton beam therapy of paragangliomas of the head and neck, rare benign tumours developed close to crucial structures such as cranial nerves and vascular tissues.
Patients and methods. – Ten patients with a paraganglioma of the head and neck were treated from 2001 to 2014 with image-guided proton therapy. Neurological and ear nose throat symptoms were collected in addition to audiometric testing, before and after the treatment. Acute and late toxicities were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.
Results. – Median age at diagnosis was 52.6 years (range: 18.2–65.8 years). Proton therapy was the exclusive treatment in six patients and four patients had a postoperative radiotherapy. Median dose was 50.4 Gy relative biological effectiveness (RBE; range: 45.0–67.0 Gy). With a median follow-up of 24.6 months (range: 6.7–46.2 months), local tumour control rate was 100% (stable, $n = 10$). No upper grade 2 acute toxicity was reported. To the latest news, seven patients had controlled symptoms (improved, $n = 1$, stabilized, $n = 6$). One patient out of seven with initial tinnitus had a decrease in his symptoms, while the six other patients had a sustained stabilization.
Conclusion. – Proton beam therapy is an effective and well-tolerated treatment modality of skull base paragangliomas, with documented functional benefit. A longer follow-up is planned in order to assess local control and long-term toxicities.

Mots clés :
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RÉSUMÉ

Objectif. – L'objectif de l'étude était d'évaluer l'efficacité et la tolérance de la protonthérapie des paragangliomes de la tête et du cou, des tumeurs rares développées à proximité de structures vasculaires et nerveuses à risque.
Patients et méthodes. – Dix patients atteints d'un paragangliome de la tête et du cou ont été pris en charge de 2001 à 2014 par protonthérapie guidée par l'image. Les symptômes neurologiques et ORL étaient recueillis en complément d'un suivi audiométrique avant, pendant et après l'irradiation. La toxicité aiguë et tardive a été évaluée selon la Common Terminology Criteria for Adverse Events (CTCAE) v4.
Résultats. – L'âge médian au moment du diagnostic était de 52,6 ans (extrêmes : 18,2–65,8 ans). La protonthérapie était exclusive chez six patients et postopératoire chez quatre autres. La dose totale médiane était de 50,4 Gy EBR (efficacité biologique relative ; extrêmes : 45,0–67,0 Gy). Avec un suivi médian de

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24,6 mois (extrêmes : 6,7–46,2 mois), le taux de contrôle local était de 100 % (maladie stable, $n = 10$). Aucune toxicité aiguë de grade 2 ou plus n'a été rapportée. Aux dernières nouvelles, sept patients avaient des symptômes contrôlés (améliorés, $n = 1$; stabilisés, $n = 6$). Parmi les sept patients souffrant initialement d'acouphènes, un a constaté une amélioration et six une stabilisation durable.
Conclusion. – La protonthérapie est une modalité thérapeutique efficace et bien tolérée pour les paragangliomes de la tête et du cou, avec un bénéfice fonctionnel documenté. Un suivi prolongé est engagé afin d'évaluer le contrôle local et la toxicité éventuelle à plus long terme.

1. Introduction

Paragangliomas are rare neuroendocrine tumours in adults with an annual incidence estimated at approximately 2–8/1,000,000. They develop along parasympathetic and sympathetic ganglia, from the skull base to the pelvic area. Paragangliomas from the parasympathetic system affect the head and neck area in about 3% of cases, and are generally not functional (non secreting). Anatomic sites involved are located in the carotid body along with the jugulotympanic glomus and the vagal glomus. Most of paragangliomas are benign (90%), but high morbidity of these tumours is explained by vascular (carotid axis) and functional organ involvement (cranial nerves, hearing system). In 30 to 40% of cases, a genetic predisposition is identified [1,2]. Most of hereditary paragangliomas relate to germinal mutation of the succinate dehydrogenase mitochondrial complex II gene, which is a tumour-supressor gene composed of three subunits (SDHD, SDHC, SDHB). Other genetic mutations are: neurofibromatosis of type I (NFI), multiple endocrine neoplasia (MEN1, MEN2) and Von Hippel Lindau syndrome [3,4]. Paragangliomas of head and neck have a long natural history with low growth rates, estimated at 0.8 mm per year and a median doubling time of 4.2 years in a historical epidemiological study [5].

Surgical resection and radiation therapy are preferential treatments options for these tumours characterized by a local extension. Radiation therapy is privileged over surgery when there is a high risk of post-operative complications [6]. Conventional radiation therapy has been used initially, with high local control rates. Dosimetric gain of proton therapy compared to three-dimensional (3D) radiation therapy is based on the Bragg peak. The dose is maximal just before the proton ion stops its path, with a rapid falloff of the energy deposit after this "peak" (minimal exit dose). The proton beam can be modulated using a conformal compensator, building a spread-out Bragg peak, along the tumour penetration. This allows an improved depth-dose distribution compared to photon-based therapy. Proton therapy allows targeting tumours very precisely, especially in the skull base area, and aims to reduce the risk of toxicities on immediately surrounding healthy tissues. The objectives of this study were to present preliminary clinical results of protontherapy of head and neck paragangliomas and to introduce dosimetric considerations.

2. Patients and methods

Institutional review board approval was obtained for this retrospective study. All patients consecutively treated between 2000 and 2014 by protontherapy for newly diagnosed or recurrent paragangliomas of the head and neck were included in this study. Patients were identified from the electronic cancer registry. All treatment decisions were reviewed and validated by a multidisciplinary expert committee. Clinical data treatment details and outcomes were collected from electronic health records.

2.1. Population

Eleven patients (six males, five females) were treated between July 2001 and December 2014 for paragangliomas in the head and neck area. One patient was excluded from the study since radiation therapy was interrupted at 9 Gy (patient's refusal without medical indication). As a result, ten patients were included in our study.

2.2. Proton therapy

Three-dimensional proton beam therapy was performed using a cyclotron of 201 MeV. relative biological effectiveness (RBE) of protons was 1.1 Gy Eco [7]. A personalized thermoplastic three-points mask was used for immobilization. Target volumes and organs at risk were defined on thin-slice MRI (2.0–3.0 mm) (T2, T1 with and without gadolinium sequences). gross target volume was defined as the visible tumour on angio-MRI. A margin of 3 to 5 mm has been added to the gross target volume to define the clinical target volume, depending on proximity to the organs at risk and bone structures. Planning target volume was defined as the clinical target volume with a surrounding margin of 2 mm. A standardized list of the organs at risk was used for delineation: chiasma, cochlea, hypophysis, temporal lobes, optical nerve, eye, internal auditory canal, inner ear, spinal cord and brain stem. Main dose constraints used are displayed in Table S1. Dosimetric data were extracted from Isogray treatment planning system (Dosisoft).

The patient with the largest paraganglioma was selected as a model for a dosimetric comparison. Proton radiotherapy and two photon intensity-modulated radiation therapy techniques were compared: volumetric arc therapy (6 MV) and helical tomotherapy (6 MV). Volumes of low doses were considered as structures and collected on the treatment plans: V2, V5, V10, V15, and V20 were used (Vx: volume receiving at least x Gy). Volumetric arc therapy and helical tomotherapy plans were performed in April 2015 by an experienced dosimetrist, who did not work on the proton therapy plan.

2.3. Follow-up

A weekly medical consultation was required for each patient during the treatment period. After the proton therapy period, patients were reviewed for neurological and ear, nose and throat (ENT) symptoms, with systematic ophthalmologic examination and audiometric testing, every six months. Tumoral response was assessed by annual angio-MRI (T2, T1 with and without gadolinium sequences). Local control was defined as a stabilization or a reduction of the symptoms without radiologic progression. Acute toxicities were defined as toxicities within 90 days after the end of radiation therapy, and late toxicities occurring after this delay, according to the Radiation Therapy Oncology Group (RTOG) definition. All toxicities were collected according to the Common Terminology Criteria for Adverse Events (CTCAE) v.4. Follow-up

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