The role of radiation therapy in the management of head and neck paragangliomas: Impact of quality of life versus treatment response

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ABSTRACT

Purpose: To assess the impact of radiotherapy in paragangliomas (PGLs) with regard to overall survival, local control, volumetric response and particularly quality of life (QoL).
Materials and methods: From 1985 to 2010, 130 cases of head and neck (H&N) PGLs were managed at Bordeaux University Hospital. With a median follow-up of 7.6 years, we retrospectively present a cohort of 30 consecutive patients treated with radiation therapy for H&N PGLs. QoL was evaluated for 20 patients by the EORTC QLQ-C30 and H&N35 questionnaires through a cross-sectional study.
Results: The 5-year overall survival and local control were 95% and 96% respectively. QoL is altered following management of PGLs. The H&N35 score is lower after combined modality therapy (surgery ± embolization and radiation therapy) for speech and hearing ($p = 0.004$), trismus ($p = 0.003$) and total score ($p = 0.01$) than after radiotherapy alone. Tumor shrinkage was significant at 2 and 3 years after radiotherapy ($p = 0.018$; $p = 0.043$).
Conclusion: Ultimate QoL should be a major goal of any treatment strategy for this benign disease. Definitive radiotherapy should be considered as a reasonable alternative to multimodality treatment as it provides comparable disease control with an apparent improvement in QoL.

Paragangliomas (PGLs), also known as glomus tumors or chemodectomas, are benign neuroendocrine tumors arising from the paraganglia cells derived from the neural crest. Since 2004, the common World Health Organization (WHO) classification has designated "paraganglioma" as the medical term for the vascular tumor originating from the chromaffin extra-adrenal glands of the sympathic and parasympathetic systems. [1]. Cervical or cranial base PGLs are referred to by their site of origin [2].

Most of PGLs are slow growing tumors with a doubling time of 4.2 years [3]. However, aggressive or malignant tumors are observed in 8–30% of cases [4]. The majority of PGLs are sporadic and predominantly affect female patients [5]. Thirty percent have a familial component, and typically present as multifocal tumors in younger patients [6].

Surgery is currently considered the standard of care for primary treatment. Radiotherapy techniques such as External Beam Radiation Therapy (EBRT) [7] or Stereotactic RadioSurgery (SRS) [8] have been used in select unresectable tumors or in aggressive residual lesions. However, the potential benefit of each treatment is controversial [9–12]. The low prevalence of head and neck (H&N) PGLs makes randomized controlled studies almost impossible to plan, and only retrospective studies are available to guide treatment decisions. There are very few published studies [13,14] describing long-term local control, overall survival and especially quality of life (QoL) after radiotherapy. Overall and specific survival analysis reveals that most patients do not die of PGLs, and thus survival is not a meaningful end point for comparative decision making. Radiotherapy and surgery are both useful treatments of PGLs. The role of combined modality treatment (surgery ± embolization with adjuvant radiotherapy) is a matter of debate. [13,15–17]. A recent retrospective review [18] concludes that EBRT and SRS offer similar probabilities of tumor control with lower risks of morbidity compared with surgery. These results suggest that future decision making should integrate both local control and QoL.

In this report, we present data regarding the impact of management on QoL in these benign skull base tumors.

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Materials and methods

We report a unicenter retrospective study of response to EBRT in a cohort of 30 patients treated over 25 years. We included a cross sectional analysis of QoL from 20 patients with head and neck PGLs.

Patients, radiation technique

Thirty consecutive PGL patients receiving radiation therapy as a component of their treatment were identified between 1987 and 2010. Diagnosis was made through clinical presentation (pulsatile tinnitus, cranial nerves weakness, neck mass) and through CT imaging for patients treated from 1987 to 2000. After 2000, CT and MRI were used routinely in diagnosis. J-PGLs and V-PGLs were classified according to Fisch's grading system [19]. C-PGLs were graded according to the Shamblin's classification [20]. Radiation technique reflected the era in which patients were diagnosed: 2D radiotherapy (RT2D) used from 1987 to 1990, and 3D conformal planning (RT3D) from 1990 to the present day. One patient was treated with tomotherapy in 2009. MRI/CT image fusion was performed in all patients treated after 2004.

Clinical follow-up was done alternatively by the ENT surgeon and by the Radiation Oncologist. Patients diagnosed after 1990 underwent CT evaluations for follow up. MRI was performed yearly as a standard imaging follow-up for patients managed after 2000. The acute toxicity of radiotherapy was assessed by clinical examination during weekly treatment visits and 1 month after treatment. The late toxicity was estimated four times for the first and second year of treatment and after twice per year for the next follow-up visits.

Quality of life evaluation

Health-related QoL was performed using the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaires (EORTC QLQ-C30 and QLQ-H&N35).

The EORTC QLQ-C30 is a 30-item self-reported instrument. This questionnaire was developed in 1983 by Aaronson et al. [21] and specifically designed for patients with cancer in clinical trials. The questionnaire has been validated and widely accepted [22,23]. Each item has a Likert response scale whereby increasing scores indicate increasing burden. Three types of scales were evaluated: global QoL, functional score, and symptom score. Questionnaires are scored from 0 to 100 [24]. For the functional scales and global QoL, a score of 100 represents a perfect QoL (absence of burden), whereas for the symptom scales, a score of 100 indicates heavy burden.

The Head and Neck-specific module EORTC QLQ-H&N 35 contains 35 items evaluated 18 symptoms. For this questionnaire, a sub-group analysis was conducted between patients with H&N PGLs treated with "radiotherapy alone (group 1; $n = 9$) and those treated for H&N PGLs with combined modality therapy such as embolization and/or surgery (group 2; $n = 11$) prior to radiotherapy.

In our study, the EORTC-QLQ-C30 and EORTC QLQ-H&N 35 questionnaires were mailed to 21 patients and completed by patients without medical assistance. Evaluation, carried out as a cross-sectional study, was done once as a real time assessment in January 2011. Patients were required to have completed radiation at least 12 months prior to assessment.

As a control, a comparison with the EORTC Head and Neck Database was also performed. EORTC Head and Neck Database evaluated the QoL of 2,929 patients treated for squamous cell carcinoma with a range for age of 50–59 year old, and a male majority [25].

Tumor response

Volumetric analysis of tumor regression was done by Calliper's and Cavalier's methods [26,27]. Assuming the tumor volume as an ellipse, the Calliper's method uses the three greatest perpendicular lengths for the equation: $V = 4/3 \prod (1/2\ A \times 1/2\ B \times 1/2\ C) = A \times B \times C/6$ (V = volume, A = the largest dimension in the antero-posterior direction, B = the largest dimension in the mediolateral direction, and C = the largest dimension in the craniocaudal direction) [3]. The Cavalieri's method is applied by delineating of the tumor with treatment planning software. Spearman coefficient was used for comparison of the tumor volume using the two methods. Assessment of response was done for 15 tumors using manual delineation and volumetric estimation by images transferred to Eclipse® (Varian Medical Systems, CA, USA).

Overall survival, local control

Local control, overall survival, progression-free survival, and cause-specific-survival rate were calculated using the Kaplan–Meier method. Time to each end point was measured from the date of radiation therapy. A sub-group analysis was done comparing local control based on treatment modality.

Statistical methods

For QoL scores, analyses were performed by using the EORTC QLQ-C30 Scoring Manual and Addendum scoring instructions validated module, obtained after submission in November 2010 of our project to the EORTC QLQ C30 commission [25]. EORTC QLQ H&N 35 scores were compared between groups by using Student's t test and Wilcoxon test.

Regression of tumor volume was evaluated by the percent reduction of the initial volume at 1, 2 and 3 years. Parametric variables were compared with Student's t test. Non-parametric variables were compared with Wilcoxon test. Tests were considered as significant if value was lower than 0.05.

Results

Demographic and clinical characteristics are listed in Table 1. From July 1987 to September 2010, 30 consecutive patients (12 males and 18 females) with PGLs were referred to the department of radiation oncology. Pulsatile tinnitus (15/23) and hearing loss (16/23) were observed for jugular PGL. Sixty percent of the patients with carotid body PGL presented with a neck mass. Pharyngeal

Table 1
Patient characteristics.

Characteristics	Value	
Patients (n)	30	
Tumors (n)	42	
Age (years)		
Mean	50	
Range	11–81	
Gender (n, %)		
Male	12	40
Female	18	60
Type (n, %)		
Familial	5	16.7
Sporadic	25	83.3
WHO scale (n, %)		
0	23	76.7
1	4	13.3
>2	3	10
Tumor site (n, %)		
Jugulotympanic	23	54.8
Carotid body tumor	10	23.8
Vagal	9	21.4
Treatment		
Radiotherapy alone	16	53.3
Combined treatment	14	46.7