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Meta-analysis

Regression and local control rates after radiotherapy for jugulotympanic paragangliomas: Systematic review and meta-analysis

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ABSTRACT

The primary treatment goal of radiotherapy for paragangliomas of the head and neck region (HNPGLs) is local control of the tumor, i.e. stabilization of tumor volume. Interestingly, regression of tumor volume has also been reported. Up to the present, no meta-analysis has been performed giving an overview of regression rates after radiotherapy in HNPGLs. The main objective was to perform a systematic review and meta-analysis to assess regression of tumor volume in HNPGL-patients after radiotherapy. A second outcome was local tumor control. Design of the study is systematic review and meta-analysis. PubMed, EMBASE, Web of Science, COCHRANE and Academic Search Premier and references of key articles were searched in March 2012 to identify potentially relevant studies. Considering the indolent course of HNPGLs, only studies with $\geqslant$12 months follow-up were eligible. Main outcomes were the pooled proportions of regression and local control after radiotherapy as initial, combined (i.e. directly post-operatively or post-embolization) or salvage treatment (i.e. after initial treatment has failed) for HNPGLs. A meta-analysis was performed with an exact likelihood approach using a logistic regression with a random effect at the study level. Pooled proportions with 95% confidence intervals (CI) were reported. Fifteen studies were included, concerning a total of 283 jugulotympanic HNPGLs in 276 patients. Pooled regression proportions for initial, combined and salvage treatment were respectively 21%, 33% and 52% in radiosurgery studies and 4%, 0% and 64% in external beam radiotherapy studies. Pooled local control proportions for radiotherapy as initial, combined and salvage treatment ranged from 79% to 100%. Radiotherapy for jugulotympanic paragangliomas results in excellent local tumor control and therefore is a valuable treatment for these types of tumors. The effects of radiotherapy on regression of tumor volume remain ambiguous, although the data suggest that regression can be achieved at least in some patients. More research is needed to identify predictors for treatment success.

Head and neck paragangliomas (HNPGLs) are rare tumors of paraganglia. They consist of chromaffin tissue and are associated with the parasympathetic autonomic nervous system. HNPGLs are named according to site of origin. The most common HNPGLs are the carotid body tumor, vagal body tumor and jugulotympanic tumor (i.e. paraganglioma of the temporal bone) [1,2]. Due to their location in close proximity to important neurovascular structures, tumor growth may lead to serious morbidity and cranial nerve impairment, however the majority of HNPGLs are notoriously benign, indolent tumors and a "wait and scan" policy may be advisable in appropriate cases [2,3]. Therefore, if treatment is commenced, this should focus on reducing morbidity rather than increasing survival.

With surgical treatment, it is possible to remove the tumor without recurrence. Surgery however, leads to neurovascular complications in up to 60% of cases; especially cranial nerve injury and, less frequently, carotid artery lesions [4,5]. Radiotherapy is an alternative treatment in HNPGL-patients. Irradiation produces fibrosis and vascular sclerosis rather than eradication of the tumor cells [6,7]. Its main objective is long-term local control, i.e. no progression of tumor volume. Interestingly, it can also lead to tumor regression, which may result in reduction of HNPGL-associated symptoms [8,9].

The effect of radiation is difficult to assess given the indolent natural course of HNPGLs. Only long-term follow-up might provide evidence that radiotherapy is a beneficial treatment in these patients. Since HNPGLs almost never show spontaneous tumor volume reduction, tumor regression is probably a better marker for radiotherapy effect than local tumor control.

Objective of the study

A few systematic reviews and meta-analyses of the effects of radiotherapy on HNPGLs have been published [10–12]. However,

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these reviews assessed the effect of radiotherapy by local control rates rather than regression rates and up until now, a meta-analysis assessing regression of tumor volume has not been performed. The main aim of the present study was to perform a comprehensive systematic review and meta-analysis of tumor regression following different types of radiotherapy in HNPGLs.

Materials and methods

Eligibility criteria

Studies assessing the effect of radiotherapy on tumor volume of HNPGLs were eligible for inclusion. The analysis aimed to assess the proportion of HNPGL-patients with tumor regression after radiotherapy, with local control rates as second outcome. According to the "Response evaluation in solid tumors (RECIST) criteria", a partial treatment response is defined as "at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters" [13]. However, the RECIST criteria have not (yet) been widely accepted in the field of paragangliomas. More importantly, the primary intention of treatment for HNPGLs is to reduce morbidity and relief of HNPGL-associated symptoms has been observed after a regression of tumor volume of less than 30% [8,14]. In view of this clinical relevance, we broadened our definition and defined tumor regression as any tumor volume less than the tumor volume before radiotherapy. Local control was defined as a tumor volume equal to or less than the tumor volume at start of radiotherapy.

We aimed to stratify tumor regression and local control rates for radiotherapy as initial treatment (i.e. without prior therapy), combined treatment (i.e. directly post-operatively or post-embolization) or salvage treatment (i.e. after initial treatment has failed). Studies regarding radiotherapy preoperatively were not included. In addition, we tried to stratify for type of radiotherapy (i.e. radiosurgery/stereotactic radiotherapy (RS) or external beam radiotherapy (EBRT)). In our analyses, we combined the results of the two types of high precision radiotherapy: stereotactic radiotherapy and radiosurgery.

To accurately assess regression and local control rates, firstly, only studies determining treatment response (tumor volume) by radiologic evaluation were eligible for inclusion. Secondly, considering the indolent nature of HNPGLs [3], only studies with $\geqslant$12 months follow-up were eligible.

Studies concerning patients with malignant HNPGLs were excluded, unless data for patients with benign HNPGLs could be extracted separately. We defined malignant HNPGL as the presence of metastases, i.e. the presence of chromaffin tissue in nonchromaffin organs, distant from the primary tumor [15–17].

In case of multiple studies describing the same cohort, the study which comprised the highest number of subjects and/or the longest duration of follow-up was included. Furthermore, only studies reporting a population of more than 10 HNPGL-patients were included. Eligible studies were restricted to languages familiar to the authors (English, French, German and Dutch). When reported data were not sufficient for accurate data extraction, we tried to contact the authors for clarification.

Search strategy

In March 2012, PubMed, EMBASE, Web of Science, COCHRANE and Academic Search Premier were searched to identify potentially relevant studies (Appendix 1). References of key articles were assessed for additional relevant articles.

Data extraction

All studies obtained from the search strategy were entered into reference manager software (Reference Manager version 12, Thomson Reuters, Philadelphia, PA) and were screened on title and abstract. Potentially relevant studies were retrieved for detailed assessment. For eligible studies, data were independently extracted by two reviewers (L.v.H. and E.C.). Disagreements between reviewers were resolved by consensus, but when doubt remained, a third reviewer (O.D.) decided.

Risk of bias assessment

The present meta-analysis is based on observational studies. Risk of bias assessment was based on study components that potentially bias an association between the intervention under study (radiotherapy) and the outcomes (regression and local control). The following elements were assessed for all studies:

1. Risk of selection bias. Inclusion of consecutive exposed patients or a random sample of the inception cohort was considered a low risk of bias.
2. Adequacy of reporting of intervention (radiotherapy). When type and dose of radiotherapy were reported, this was considered adequate.
3. Adequacy of measurements for regression and local control. The effect of radiotherapy on tumor volume should have been measured by either sequential MRI or CT scanning.
4. Adequacy of result stratification per treatment modality (i.e. initial, combined or salvage treatment).
5. Adequacy of follow-up. Loss to follow-up <5% was considered to represent a low risk of bias.

Statistical analysis

The main outcome of the present meta-analysis was the pooled proportion of HNPGLs with regression after radiotherapy. The pooled proportion of HNPGLs with local control after radiotherapy was the secondary outcome. For all studies, the proportion of HNPGLs with tumor regression was calculated as the number of HNPGLs with tumor regression divided by the total number of HNPGLs treated with radiotherapy. The same procedure was applied to the proportion of HNPGLs with local control. For all proportions exact 95% confidence intervals (95% CI) were calculated.

Meta-analysis was performed using an exact likelihood approach. The method used was a logistic regression with a random effect at the study level. Given the expected clinical heterogeneity a random effects model was performed by default and no fixed effects analyses were performed. For meta-analysis of proportions the exact likelihood approach based on a binomial distribution has advantages compared to a standard (DerSimonian and Laird) random effects model that is based on normal distributions. Firstly, estimates from a binomial model are less biased than estimates from models based on a normal approximation. This is especially the case for proportions that are close to 0 or 1. Secondly, no assumptions are needed for the exact approximation when dealing with zero-cells, whereas the standard approach needs to add an arbitrary value (often 0.5) when dealing with zero-cells. Adding values to zero-cells is known to contribute to the biased estimate of the model. All analyses were performed with STATA 12.0 (Stata Corp., Texas, USA).

Results

Study selection

The initial search resulted in 1371 unique records; 137 were selected for detailed assessment (Fig. 1). After detailed assessment, 122 articles were excluded for following reasons: no original data ($n = 4$), no radiologic evaluation ($n = 51$), inclusion of patients with