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Original Article

Dosimetric Predictors of Dysphonia after Intensity-modulated Radiotherapy for Oropharyngeal Carcinoma

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Abstract

Aims: To investigate dosimetric predictors of voice changes after whole-field intensity-modulated radiotherapy (IMRT).
Materials and methods: Patients treated with whole-field IMRT for oropharyngeal/unknown primary tumours were selected for the present retrospective study having grossly uninvolved larynx at the time of radiotherapy and at least one follow-up visit. Voice changes were prospectively scored at each follow-up examination according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 scale and self-reported by two items (HN4 and HN10) of the Functional Assessment of Cancer Therapy-Head and Neck Scale (FACT-HN) questionnaire. Predictors of toxicity were investigated at logistic regression, including various patient and tumour characteristics, as well as individual dosimetric data.
Results: With a median follow-up of 18 months (range 3–46 months), peak CTCAE dysphonia was graded as 2 in 13 patients (10.5%), whereas 45 patients (36.3%) reported peak grade 0–1 voice changes according to FACT-HN4. Communication (FACT-HN10) was barely affected. At multivariate analysis, the mean laryngeal dose was an independent predictor of both grade 2 CTCAE dysphonia (odds ratio = 1.10, 95% confidence interval 1.01–1.20, $P = 0.025$) and grade 0–1 FACT-HN4 voice changes (odds ratio = 1.11, 95% confidence interval 1.04–1.18, $P = 0.001$). Further stratification optimised by a receiver operating characteristic (ROC) analysis showed that, to minimise the risk of grade 0–1 FACT-HN4 voice changes, the mean dose to the larynx has to be kept ≤49.4 Gy.
Conclusion: Voice changes after whole-field IMRT are common, but mild, and are strictly correlated to the dose received by the uninvolved larynx; in order to minimise the risk of side-effects, the mean dose to the larynx should be kept ≤50 Gy.

Key words: Dosimetric predictors; radiotherapy; voice changes

Introduction

One of the advantages of intensity-modulated radiotherapy (IMRT) for head and neck squamous cell carcinomas is to 'paint' the dose distribution around the target volume(s), minimising the irradiation of the nearby normal structures [1,2]. However, proper IMRT planning requires accurate *a priori* knowledge of which organs at risk surround the target(s) and their sensitivity to radiation. Relatively few data exist on the tolerance of the larynx [3,4]. With the standard conformal three-field technique (two opposed lateral beams to cover the upper neck and one anteroposterior beam for the mid/low neck), the incidental irradiation of the normal larynx was usually minimised by placing the field junction just above the arytenoids and by adding a laryngeal block on the anteroposterior field [5]. Whether to also maintain a similar approach for the lower neck with IMRT, in the so-called 'split-field IMRT', has been debated at length [6,7]. In specific circumstances (i.e. multiple neck nodes), it would be preferable to cover the whole target volume with IMRT (whole-field IMRT) minimising incidental irradiation of the larynx with a dose objective at planning.

Although there are multiple data in the literature on voice quality after successful radiotherapy for early glottic tumours [8,9], only two investigated and detailed long-term voice changes after incidental irradiation of the normal larynx [10,11]. However, due to the limited number of patients analysed and the lack of individual dosimetric data, these studies failed to provide recommendations on the dosimetric tolerance of the uninvolved larynx [10,11].

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Therefore, the only available data remain those presented as an abstract by Vineberg *et al.* [12] in 2009. In this study of 73 patients, mean laryngeal doses of 25, 40 or 55 Gy were associated with a 10, 20 or 40% risk of patient-reported long-term voice worsening after chemoradiation for oropharyngeal cancer. We had previously found a correlation between mean laryngeal dose (or alternatively V50) and the risk of laryngeal oedema after radiotherapy for non-laryngeal primaries [4]. In the present study, we analysed a novel group of patients with oropharyngeal/unknown primary tumours to assess the correlation between various dosimetric factors and the risk of both subjective and objective voice changes after treatment.

Materials and Methods

Patients

Patients with biopsy-proven head and neck squamous cell carcinomas and treated at a single institution with primary IMRT from August 2007 to December 2010 were considered for the present retrospective study, which was approved by the local Institutional Review Board (IRB).

Patients had to satisfy all the following three additional criteria:

(1) the larynx had to be uninvolved by cancer at both initial flexible fibreoptic examination and pre-treatment imaging studies (typically computed tomography);
(2) no major surgical operations in the head and neck region were allowed except for unilateral neck dissection and tonsillectomy. Patients had to be treated with definitive IMRT in 35 fractions and a simultaneous integrated boost approach, as previously reported [13]. Chemotherapy was allowed;
(3) Patients had to have at least one follow-up examination since the completion of radiotherapy.

Planning and Treatment

Our whole-field IMRT approach has been previously described in detail [13]. Briefly, plans were generated on Pinnacle^3 TPS v9.0 to be delivered by a nine-field static-gantry, step-and-shoot multileaf collimation technique and 6 MV photons. The prescription dose to the primary site was 70 Gy with the option to reduce the dose to 63 Gy and 68.25 Gy after R0 and R1 tonsillectomy, respectively. Unknown primary tumours were typically prescribed 63 Gy with the option to boost the putative/suspicious site of origin to 68.25 Gy. Regarding the neck, three dose levels were applied: 58.1 Gy for elective low risk (dissected negative or undissected clinically negative); 63 Gy for elective high risk (dissected positive and clinically suspicious) [14]; 70 Gy for gross nodal disease. All patients were treated comprehensively on both sides of the neck.

Each target was expanded by 5 mm to create the corresponding planning target volume. Dose constraints were put on the cord + 4 mm, brainstem, mandible, larynx (excluding cartilaginous framework) [4] and the mucosa of the upper gastrointestinal tract as appropriate. For the larynx, the V50 was tentatively kept $\leq$25% at planning (minor variation: V50 $\leq$ 30%). The constrictor muscles (superior, middle and inferior) were contoured but not constrained. All contours were generated under the supervision of the same doctor (GS).

Tabular differential dose–volume histogram (DVH) data for the larynx and the constrictor muscles were recomputed taking into consideration the dose actually delivered and recomputed as cumulative DVH data. From the DVH of each patient we extracted the mean laryngeal dose, the percentage of larynx receiving 50 Gy and the mean dose to the constrictor muscles considered as a whole.

Statistics

According to in-house guidelines, patients were also scheduled to be seen in the department of radiation oncology at regular follow-up intervals (3, 6, 12, 18, 24, 36, 48 and 60 months after treatment completion).

At each follow-up examination, voice changes were scored by one observer (GS) according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0: grade 1, mild or intermittent hoarseness or voice change, but fully understandable; grade 2, moderate or persistent voice changes, may require occasional repetition but understandable on telephone; grade 3, severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; requires voice aid (e.g. electrolarynx) for $\leq$50% of communication; grade 4, disabling; non-understandable voice or aphonic; requires voice aid (e.g. electrolarynx) for >50% of communication or requires >50% written communication. At each visit, patients were also asked to complete a quality of life questionnaire, the Functional Assessment of Cancer Therapy-Head and Neck Scale (FACT-HN) [15]. The FACT-HN v4 is a validated [16] self-reported instrument consisting of 27 general and 12 head and neck-specific items. For the purposes of the present study, only two questions were selected: 'My voice has its usual quality and strength' (HN4); 'I am able to communicate with others' (HN10). The patient was asked to give a response as it applies to the past 7 days and each item was rated on a 0–4 Likert-type scale: 0, not at all; 1, a little bit; 2, somewhat; 3, quite a bit; 4, very much. Observations obtained after locoregional failure were disregarded, with the exception of patients who underwent complementary neck dissection who were found to have residual disease and who continued to be followed up for dysphonia.

In order to run a logistic regression, we dichotomised both CTCAE and FACT-HN scores and considered the end point to be the development, at any follow-up, of grade 2–4 (CTCAE) and grade 0–1 (FACT-HN) toxicities, respectively. Apart from dosimetric data, various patient, tumour and treatment characteristics were also considered. Covariates with a P value lower than 0.2 at univariate analysis were entered into a logistic regression model at multivariate analysis. Covariates that were highly correlated were