



Computed tomography evaluation after induction chemotherapy for T3 laryngeal cancer: Does response correlate with vocal cord mobility?

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ABSTRACT

Objectives: After induction chemotherapy (IC) for laryngeal cancer, Computed Tomography (CT) is used to assess tumor response but lacks rationalized methods for measurement of this response. In T3 laryngeal cancer, remobilization of an initially fixed vocal cord (VC) is a major sign of tumor response. We compared the performances of RECIST1.1, WHO and volumetric methods of evaluating response with laryngeal remobilization to determine if these measurements could objectively assess tumor response.

Material and Methods: This monocentric retrospective cohort study included patients treated with T3 laryngeal cancer with initial VC fixation treated with an organ preservation protocol with IC between 1999 and 2012. Tumors were measured with CT using RECIST1.1, WHO and volumetric methods by two radiologists blinded to VC remobilization (VCR), before and after induction chemotherapy and VC mobility was clinically assessed. Radiologic tumor shrinkage was compared to VCR. AUCs of ROC curves were compared. Inter-reader reliability, sensitivity and specificity of optimal cutoffs were determined.

Results: Seven females and thirty-six males with a mean age of 59 years were included. AUCs were 0.759, [95%CI 0.614; 0.904] for RECIST1.1, 0.763, [95%CI 0.617; 0.909] for WHO and 0.752, [95%CI 0.608; 0.896] for volumetric evaluations with no significant difference among the three techniques. Inter-reader reliabilities were good (RECIST1.1) to excellent (WHO and volumetric methods).

Conclusion: RECIST1.1, WHO and volumetric measures match with VCR after IC in patient with T3 laryngeal cancer. WHO criteria combine accuracy, reproducibility and practical use; they may be best adapted for response assessment and protocol design.

Introduction

Head and neck squamous cell carcinomas (HNSCC) represent 5% of new cancer cases worldwide and involve the larynx in 24% of newly diagnosed patients [1].

Due to its fast acquisition time and its good performances to assess the head, the neck and the chest, post contrast CT-scanner is the first line imaging tool for tumor staging in laryngeal carcinomas. It is also recommended for post therapeutic assessment and follow-up [2].

Laryngeal squamous cell carcinoma (SCC) treatment options,

especially induction chemotherapy protocols, are still debated and under clinical trials. Initial responses to non-surgical therapies are variable, with impact on long-term survival [3].

Induction chemotherapy has been employed as a tool to select patients likely to respond to definitive radiotherapy or chemo-radiotherapy. Head and neck induction chemotherapies have mostly been described and studied in T3 laryngeal SCC for larynx preservation protocols. In the literature, tumor shrinkage is clinically [4–6] and most of time radiologically assessed [7] and clinical vocal cord remobilization appears to be a major prognostic factor [8] and a main clinical

Abbreviations: IC, induction chemotherapy; VC, vocal cord; VCR, vocal cord remobilization

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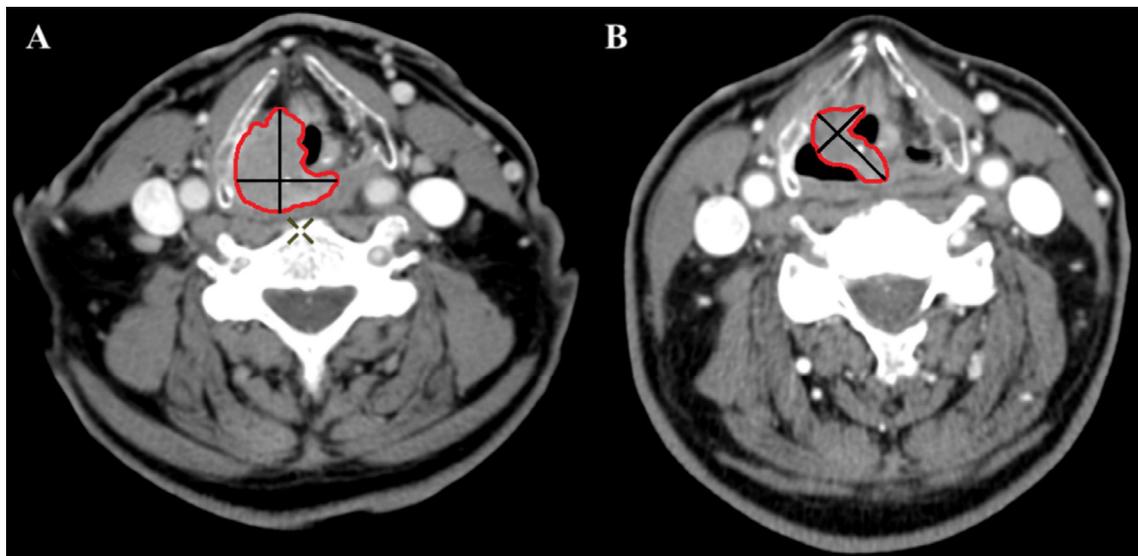


Fig. 1. Pre (A) and post (B) induction chemotherapy contrast enhanced CT-scanner with tumor contouring and automatically determined axial largest diameter and largest dimension perpendicular to the largest diameter according to RECIST 1.1 and WHO guidelines.

criterion to assess tumor response to induction chemotherapy [6]. Although CT is also widely used to evaluate this response [7], there are various cutoffs in the literature and a lack of precise definitions of clinically significant measurements [5,7]. The goal of our study was to assess how CT response evaluation matched with vocal cord remobilization after induction chemotherapy in patients with T3 laryngeal squamous cell carcinoma and an initially fixed vocal fold, in order to determine objective thresholds for further studies.

Material and methods

Population

The Institutional Review Board at Gustave Roussy Cancer Center approved this study.

In this retrospective study we screened all patients with histologically proven T3 squamous cell carcinoma treated in our institution between 1999 and 2012 eligible to a curative treatment (patients with distant metastases were excluded).

We included all patients with initial hemilarynx fixation treated with induction chemotherapy in an organ preservation protocol. Hemilarynx fixation was defined as a fixation of the vocal fold and a fixation of the arytenoid cartilage. We thus excluded the patients with isolated vocal fold fixation due to a tumor limited to the cord itself. A post contrast CT evaluation before and after induction chemotherapy had to be available for the patient to be included.

Induction treatment

Induction chemotherapy was comprised of three courses of a combination of cisplatin and fluorouracil (CDDP-5FU) or more recently cisplatin, fluorouracil and docetaxel (TPF) administered every three weeks.

Clinical evaluation

For each patient, initial and post-chemotherapy clinical evaluation with fiberoptic laryngoscopy determined vocal cord mobility. Vocal cord remobilization was defined as normal or impaired mobility after induction chemotherapy. Response was judged insufficient when the hemilarynx remained fixed two weeks after the second or third cycle and/or tumor volume shrinkage at physical examination was less than

50%. Response was judged sufficient when vocal cord remobilization occurred within two weeks after the second or third cycle and tumor volume shrinkage at physical examination was more than 50%.

Definitive treatment

Radiotherapy was delivered at a dose of 70 Gray to good responders to induction chemotherapy. Patients with an insufficient response underwent a total laryngectomy with adjuvant radiotherapy according to pathological features and the patient's clinical status. When indicated, radiosensitizing agents (e.g. platinum-based chemotherapy or targeted therapy) were used.

Imaging

All patients included had initial and post induction chemotherapy neck contrast-enhanced CT with protocols dedicated to the evaluation of the laryngeal tumor. Every patient underwent a free-breathing contrast-enhanced CT with biphasic injection of iodinated contrast agent consisting in a double injection (40 mL, 1 mL/s – delay 180 s – 50 mL, 1.5 cc/s, acquisition after 35 s). Head and neck acquisitions covered from the pulmonary apex to the top of frontal sinuses (standard acquisition parameters were 120 kV, 100 to 400 mAs with automatic exposure control system). Slice thickness was inferior or equal to 3 mm and acquisitions were performed without gap (25/43) or with overlaps (18/43).

Analysis

Two radiologists FB and GG respectively with a 13-year and 1-year experience in head and neck tumor imaging evaluated tumor size and volume on both CT's, before and after induction chemotherapy, for each patient. They evaluated three types of measurement methods (Fig. 1)

- One dimensional (1D) measurement according to the *Response Evaluation Criteria in Solid Tumors 1.1* (RECIST1.1) [9], consisting in assessing the largest diameter of the tumor in an axial plane.

- Two dimensional (2D) measurement according to the World Health Organization (WHO) standards [10], which calculates the product of the largest diameter by the largest dimension perpendicular to this largest diameter, in an axial plane.

- Volumetric (3D) measurement, assessing tumor volume using the Advantage Windows workstation (Advantage Workstation 4.7 – Volume

Share 7, GE Healthcare) semi-automatic volume tools, adding free-hand correction. Delineation of the lesion was initiated with the automatic process, then every slice was checked by the radiologists and contouring was refined, if needed, according to morphology and enhancement. In case of major discordance between the two readers (more than 29% of difference between the two measurements), we reviewed the case and reached a collegial agreement. In case of minor discordance, the mean value of their measurements was taken as the final value.

For each patient the radiologists measured the modification in tumor size after induction chemotherapy as compared to pretreatment assessment and computed the percentage of tumor reduction or growth:

$$\text{Percentage of tumor evolution} = (\text{Size after ICT} - \text{Size before ICT}) * 100 / \text{Size before ICT}$$

Negative values corresponded to reduction of tumor size. This percentage was calculated for each type of measurement (1D, 2D, volumetric).

Statistics

Statistical analysis was carried out using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, N.Y., USA). To assess the performance of CT-scanner to predict vocal cord remobilization after induction chemotherapy, the sensitivity and specificity of this method were calculated for different thresholds and plotted in a receiver operating characteristic curve (ROC). Areas under the curve (AUCs) and confidence intervals were determined. The Hanley & Mc Neil method was used to test differences between AUC values.

The Youden index was used to determine the optimal shrinkage thresholds.

The inter-reader reliability was analyzed by intra-class correlation coefficients (two-way mixed-effects model) calculated using the percentage of tumor evolution for each measurement method.

The significance threshold used in this study was $P < .05$.

Results

We screened 262 consecutive patients with T3 laryngeal SCC. Forty-three patients (7 females and 36 males) met the inclusion criteria. The mean age was 59 years (± 21). Data on post-chemotherapy CT-scanner and clinical evaluation was available after two (24/43) or three cycles (19/43) independent of the chemotherapy regimen (CDDP-5FU or TPF).

After 2 cycles of induction chemotherapy, vocal cord remobilization was observed in 24/43 patients (56%).

CT performance to predict vocal cord remobilization is shown for the three types of measurements in Fig. 2. The RECIST1.1 method (1 dimension) showed an area under the curve (AUC) of 0.759, [95%CI 0.614; 0.904]. The AUC for the 2 dimensional evaluation (WHO) was 0.763, [95%CI 0.617; 0.909] and for the volumetric evaluation 0.752, [95%CI 0.608; 0.896]. There were no significant differences between the AUCs (1D versus 2D $P = .47$; 2D versus 3D $P = .6$; 1D versus 3D $P = .56$). Percentages of tumor reduction cutoffs with the best compromise between sensitivity (Se) and specificity (Sp) to predict vocal cord remobilization were for 1D measurements (RECIST 1.1): -34% (Se = 54%; Sp = 79%), for 2D measurements (WHO): -56% (Se = 67%; Sp = 74%) and for 3D measures: -68% (Se = 63%; Sp = 69%).

The intra-class correlation coefficients for the percentage of tumor evolution after induction chemotherapy were: 0.723 (95%CI [0.544; 0.839]) for RECIST1.1, 0.902 (95%CI [0.826; 0.935]) for WHO criteria and 0.965 (95%CI [0.936; 0.981]) for the volumetric measurement.

Discussion

We demonstrate in this study that tumor shrinkage evaluation by CT, with intravenous biphasic injection of iodinated contrast agent, is significantly correlated with vocal cord remobilization after induction chemotherapy among patients treated for T3 squamous cell carcinoma with initial vocal fold fixation. These results define an imaging response level that we can expect after induction chemotherapy, which has until now remained unclear in the currently published literature.

The CT-scanner response assessment thresholds we propose are precisely described and calculated, even if the statistical power remains moderate due to our small sample size. To date, thresholds used in the literature are heterogeneous. Tumor response is sometimes evaluated only clinically, histologically [4], or radiologically [7]. Cutoffs to define response vary among studies from 50% [3] to 80% [5]. Radiologic evaluation is used as a sole criterion for response or is combined with other criteria such as vocal cord mobility, depending on the studies [3,5]. Thus the present study has the advantage of evaluating 3 methods of radiologic assessment in addition to vocal fold mobility.

Interestingly we noticed that the cutoffs we found for 1D and 2D measurements that were related to tumor response (-34% and -56% respectively) were very close to the tumor response-to-treatment cutoffs defined in international criteria for clinical trials in solid tumors. Indeed, in the one dimensional RECIST1.1, the definition of partial tumor response is a decrease of at least 30% while for the WHO criteria (using 2D measures) the cutoff for response is a 50% decrease [9,10]. We suggest that using RECIST1.1 or WHO criteria could be a simple way to evaluate T3 laryngeal squamous cell carcinoma after induction chemotherapy, in addition to fiberoptic laryngoscopy assessment.

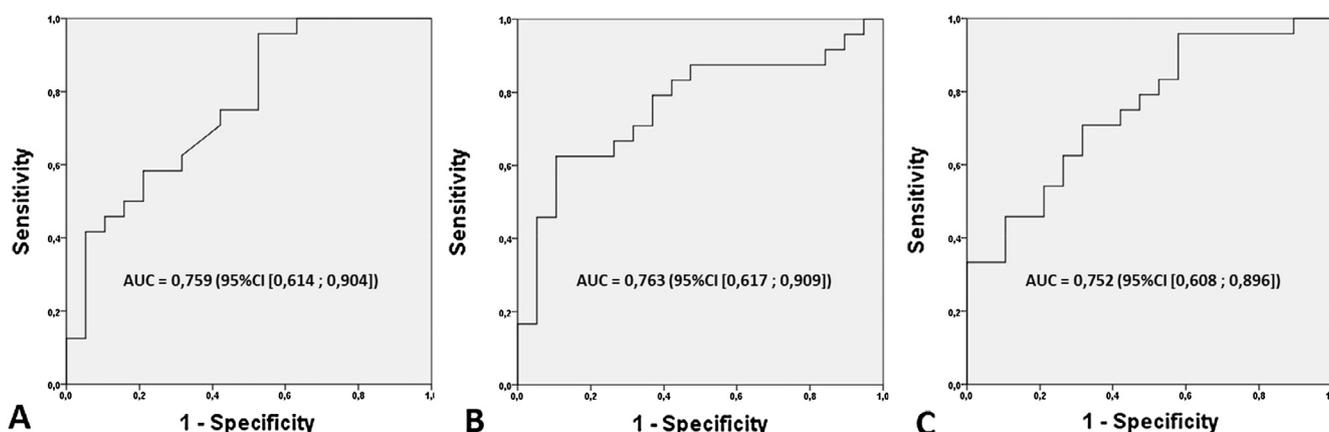


Fig. 2. ROC curves showing the diagnostic performances of the percentage of tumor reduction for three types of measures (1 dimension (A), 2 dimensions (B) and 3 dimensions (C)) as predictor of vocal cord remobilization. AUC and 95% confidence intervals are given for each type of measure.

Nevertheless, due to the small sample size these data require further validation. Our data also show that RECIST1.1 and WHO are just as efficient as 3D volumetric assessment for evaluating the response of T3 laryngeal squamous cell carcinoma after induction chemotherapy, while being much simpler to use in daily practice or in the design of clinical trials. Moreover, there is no difference in terms of performances between RECIST1.1 and WHO criteria. One argument in favor of using WHO criteria is the excellent inter-reader reliability of this method.

The question of laryngeal preservation using concurrent chemoradiation or protocols with selection by induction chemotherapy remains a debate [11]. In our opinion, the role of induction chemotherapy in larynx preservation mainly depends on the relevance of response evaluation criteria to assess as precisely as possible IC efficacy.

Clinically, vocal cord mobility is a landmark in laryngeal tumor evaluation and an important prognostic factor [6,8], which is why we use it as a gold standard to assess the response to induction chemotherapy. As about 25% patients treated for laryngeal T3 tumors do not present with vocal cord fixation [12] (for example supraglottic tumors invading the pre epiglottic space), our CT-scanner cutoffs may also be able to provide imaging landmarks that could be used later among these patients who do not have initial vocal cord fixation.

The main limitations in our study were the lack of power and the retrospective design. There is heterogeneity in CT-scanner acquisition parameters over the course of time, but none of the exams had a slice thickness above 3 mm, which is the maximum acceptable thickness according to the most recent guidelines [2].

We have shown that CT tumor measurement guidelines (dimension and cutoff) can be useful to evaluate response after induction chemotherapy in patients with T3 laryngeal squamous cell carcinoma and initial vocal fold fixation. 2D measurements (WHO criteria) have the same performance as the two other methods we tested but combines an excellent inter-reader reliability with an easier use in practice, which leads us to prefer this method. Cutoffs found suggest that using RECIST1.1 or WHO guidelines in tumor response evaluation could be a good way to define response assessment after induction chemotherapy. Extending these results we could suggest using these cutoffs when designing head and neck clinical trials in oncology and when evaluating the response to induction chemotherapy in patients with T3 laryngeal squamous cell carcinoma but with no initial vocal cord fixation. For patients with initial cord fixation, a clinical-radiologic score merging the data of laryngoscopic vocal cord mobility and radiologically assessed tumor shrinkage could be developed and tested in further studies.

RECIST1.1, WHO and volumetric measures correlate with vocal cord remobilization after IC in patient with T3 laryngeal cancer and initial vocal fold fixation. The 2-dimensional WHO criteria combine accuracy, reproducibility and easy use in daily practice; they may be best adapted for response assessment and protocol design.

Conflict of interest statement

The author Gabriel Garcia is prepared to take responsibility for the

integrity of the content of the manuscript. The material is original research, has not been previously published and has not been submitted for publication elsewhere while under consideration. There was no affiliations or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials of the research discussed in the manuscript. We certify that we have no affiliation with or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials discussed in the manuscript (e.g., employment, consultancies, stock ownership, honoraria). Co-authors have read and approved the paper.

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