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ORIGINAL ARTICLE

Volumetric regression ratio of the primary tumor and metastatic lymph nodes after induction chemotherapy predicts overall survival in head and neck squamous cell carcinoma: a retrospective analysis

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Summary

Purpose: *We looked for any predictive value of change in primary tumor and metastatic lymph node volumes after induction chemotherapy (IC) on oncologic outcome in head and neck squamous cell carcinoma (HNSCC).*

Methods: *Nineteen patients with stage IVA/B HNSCC treated between 2004 and 2010 with at least one cycle of IC (docetaxel, cisplatin and 5-fluorouracil / TPF) and concomitant chemoradiotherapy (CRT) with cisplatin were retrospectively analyzed. Volumes were calculated separately for primary tumor (Vtm), lymph node metastases (Vln) and their sum (Vsum) on computed tomography (CT) images before and after IC. The effect of volumetric changes on locoregional failure (LRF), distant metastasis (DM) and overall survival (OS) was assessed. P values <0.05 were considered as statistically significant.*

Results: *The median follow-up of surviving patients was 25 months (range: 10.7-83.3). The median number of cycles and duration of TPF was 3 (range: 1-4) and 44 days (range: 4-116), respectively. Empirical area under the curve (AUC) analyses for death, LRF and DM revealed optimal cut-off values of Vtm diminution (30.54%, AUC: 87%) and Vsum decrease (35.45%, AUC: 64.55%) only for OS (p <0.05). Among those, a reduction in Vsum more than 35.4% between pre- and post-IC was significantly correlated with better OS (100 vs 43% at 2 years, p <0.05).*

Conclusion: *Volumetric shrinkage of the tumor load after IC assessed with CT seems to predict OS. The assessment of volumetric shrinkage upon IC might be used to decide whether to offer patients alternative strategies like palliative/de-intensified treatments or more aggressive combined modalities after IC.*

Key words: *computed tomography, head and neck squamous cell carcinoma, induction chemotherapy, survival, volume*

Introduction

Concomitant CRT is the standard therapeutic strategy for unresectable locoregionally advanced HNSCC [1]. When IC is administered, TPF chemotherapy has been shown to be superior to cisplatin and 5-fluorouracil only [2-4]. However, the debate whether to add IC prior to CRT is still ongoing.

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The updated MACH-NC meta-analysis [1] and the recently presented meta-analysis by Budach et al. [5] did not show any superiority of IC followed by CRT over CRT alone. Recently published randomized trials did not present consistent results favoring IC [6-9]. The only new positive trial by Ghi et al. [9] had a 2x2 factorial design and concomitant treatment arms contained either cisplatin or cetuximab as systemic agent (full text not published), which makes it difficult to draw a sound conclusion. The multidisciplinary Head and Neck Tumor Board of the University Hospital of Bern selected only patients indicated for TPF IC before CRT in case of locoregionally advanced disease with inoperable tumor and/or nodal masses which would also require extremely large target volumes and frequent adaptive re-planning in case of definitive CRT.

In HNSCC, the routinely used basic standard to estimate the outcome is the TNM stage. It takes the largest diameter and the anatomical local extent of disease, the number and size of involved lymph nodes and the presence or absence of distant metastases into account. On the other hand, it is also shown that the volumetric staging can be superior to TNM staging regarding prediction of outcome and TNM staging is not always correlated with the extent of disease burden [10-12].

Several studies were published demonstrating the predictive value of pre-treatment volume of primary tumor and/or involved lymph nodes on outcome in locoregionally advanced HNSCC treated with either surgery, CRT or radiation alone [13,14]. In addition, the ratio of volumetric change during CRT might also be predictive for local failure [15]. However, there is no consensus about any standard volumetric cut-off value to be used for volumetric staging.

In the past 10 years, some centers have begun to use IC routinely either as a standard protocol for locoregionally advanced HNSCC or just for selected cases having very advanced disease. Bisdas et al. [16] have associated tumor volume with CT prior to IC on 19 patients to disease-free survival (DFS).

The goal of this study was to look for any predictive value of volumetric change in primary tumor and metastatic lymph nodes due to IC on LRF, DM and OS in patients with locoregionally advanced HNSCC definitively treated with CRT after induction therapy. To our knowledge no article has yet been published regarding any predictive value of volumetric changes after IC on oncological outcome.

Methods

Between 2004 and 2010, 389 cases diagnosed with oral, oropharyngeal, laryngeal and hypopharyngeal primary cancer were treated with definitive CRT. In this cohort, 40 patients with stage IVA/B (UICC/AJCC 7th edition) biopsy-proven HNSCC treated with at least one cycle of IC and definitive CRT were retrospectively analyzed. The study was approved by the local Ethics Committee in accordance with the Helsinki Declaration. Clinical staging was based on ENT-examination, panendoscopy and head and neck CT with or without ^{18}F-Fluorodeoxyglucose positron emission tomography (^{18}FDG-PET)-CT (thoracic CT in case of no ^{18}FDG PET-CT). Twenty-one patients were excluded: 19 had missing digitalized imaging or data, 1 had a previously treated disease with lymph node recurrence, and another one received 5 cycles of IC due to patient related reasons.

IC consisted of docetaxel 75 mg/m^2 as infusion over one hour followed by cisplatin 75 mg/m^2 as infusion over one hour on day 1, followed by fluorouracil 1000 mg/m^2 as continuous infusion for 4 days. Concomitant chemotherapy consisted of 2-3 cycles of cisplatin 100 mg/m^2 3-weekly. Cetuximab or carboplatin were used alternatively in patients in whom cisplatin was contraindicated. All patients were irradiated using intensity-modulated radiotherapy (IMRT) technique up to 72 Gy with 2 Gy per fraction, 5 times per week as we have described in detail in a previous article [17].

To compare the volumetric change in tumor burden after IC, Vtm, Vln and Vsum before and after the completed course of IC were calculated as follows: initial pre-IC images were imported into our radiotherapy treatment planning system (Eclipse version 11.0, Varian, Palo Alto CA, USA). CT images performed before CRT for treatment planning were already stored in our system. The primary tumor and metastatic lymph nodes were contoured by the same radiation oncologist separately in each image set (Figure 1). Metastatic lymph nodes were defined as nodes with a diameter of ≥10 mm in short axis (except for the jugulodigastric and retropharyngeal nodes in which ≥15 mm and ≥8 mm were considered as malignant, respectively). At the end, all volumes were revised by a radiologist to avoid possible errors and improve accuracy. Volumes in cm^3 (mL) were calculated with the volume calculation algorithm of the treatment planning software and recorded separately for Vtm, Vln and Vsum on the pre-IC and post-IC image sets for comparison.

Statistics

Descriptive statistics for patient characteristics were calculated. All time-to-event endpoints were calculated from the start of IC. Difference of volumes pre- to post-IC was assessed with paired Sign test. Ratios of volumetric change after IC were calculated for Vtm, Vln and Vsum respectively. Receiver operating

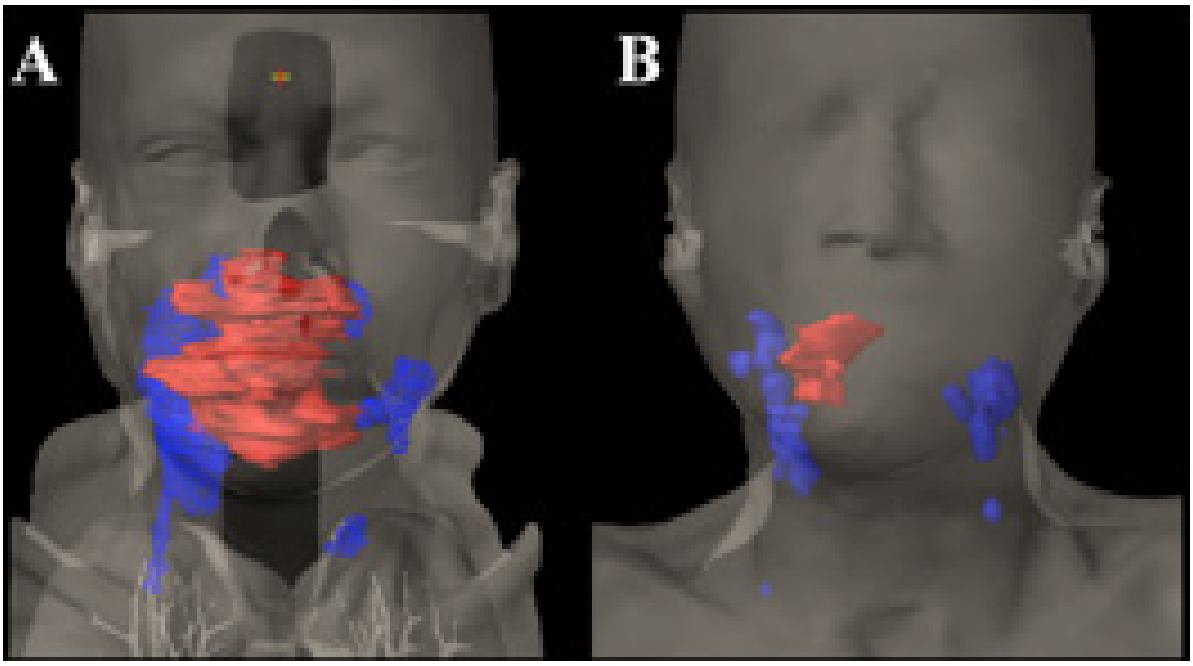

Figure 1. Primary tumor (red) and metastatic lymph node (blue) structures pre-(**A**) and post-IC (**B**) based on CT delination.

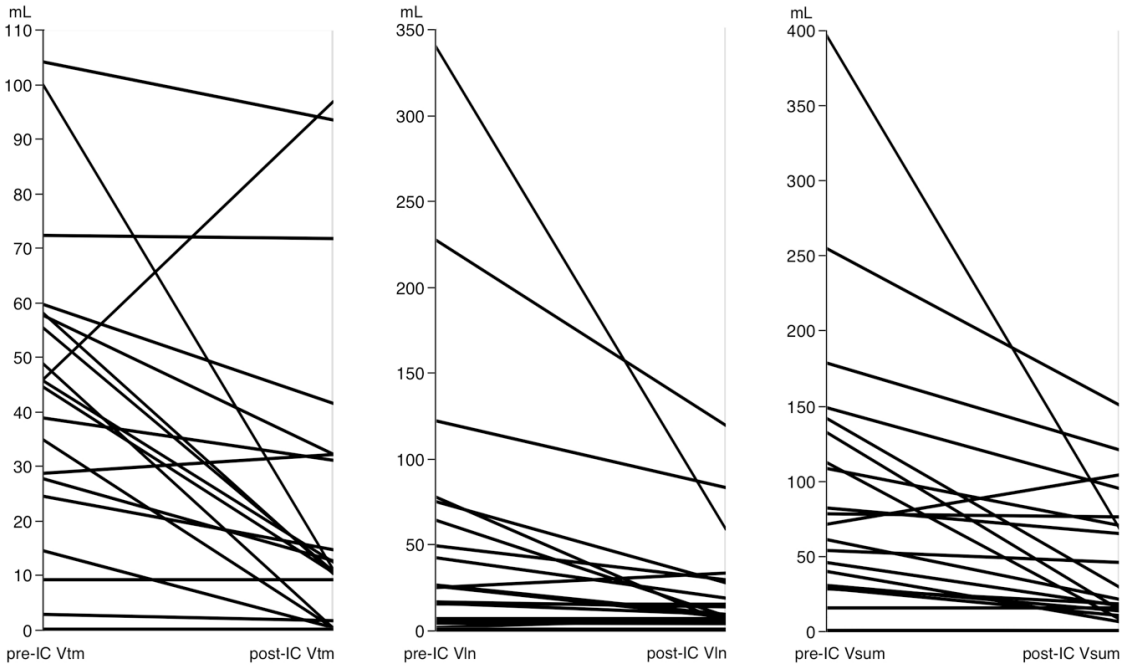

Figure 2. Change in volumes of primary tumor, involved lymph nodes and their sum.
IC: Induction chemotherapy, Vtm: Volume of the primary tumor, Vln: Volume of metastatic lymph nodes, Vsum: Vtm + Vln

characteristic (ROC) analyses were done for endpoints of LRF, DM and OS with an optimized sensitivity and specificity defined cut-off with the largest AUC. Survival curves for LRF, DM and OS were constructed with the Kaplan-Meier method and predictive value of cut-off ratios regarding survival, LRF and DM were tested with log-rank test. P values <0.05 were considered as statistically significant. SPSS software version 15 (IBM, Chicago IL, USA) and JMP 9.0 (SAS Institute Inc. North Carolina, US) were used for statistical analyses.

Results

The median patient age was 60 years (range: 41-73). Ten patients had their primary tumors

arising from the oropharynx, 6 from larynx and 3 from hypopharynx. The median number of cycles and duration of TPF was 3 (range: 1-4) and 44 days (range: 4-116), respectively. Five patients were administered 1-2 cycles of TPF, 11 received 3 cycles and 3 received 4 cycles based on multidisciplinary tumor board decision. Six patients had interruptions of CRT related to acute toxicity for a median of 2 days (range: 1-5). The median follow-up of surviving patients was 25 months (range: 10.7 – 83.3). Statistically, none of those parameters were associated with survival.

Initial and post-IC mean volumes and related mean changes in percent are given in Table 1 and Figure 2. One patient did not have any lymph node metastases but only an extensive primary tumor.

Empirical AUC analyses for death, LRF and DM revealed significant optimal cut-off values of Vtm reduction (-30.54%, AUC: 87%) and Vsum reduction (-35.45%, AUC: 64.55%) only for OS ($p < 0.05$). To predict the OS, the 35.45% decrease of Vsum was statistically significant in log-rank test (Figure 3). If the total radiological visible volume containing tumor and involved lymph node mass shrunk at least 35.45% after IC, OS at 2 years was significantly higher (100 vs 43%, $p < 0.05$).

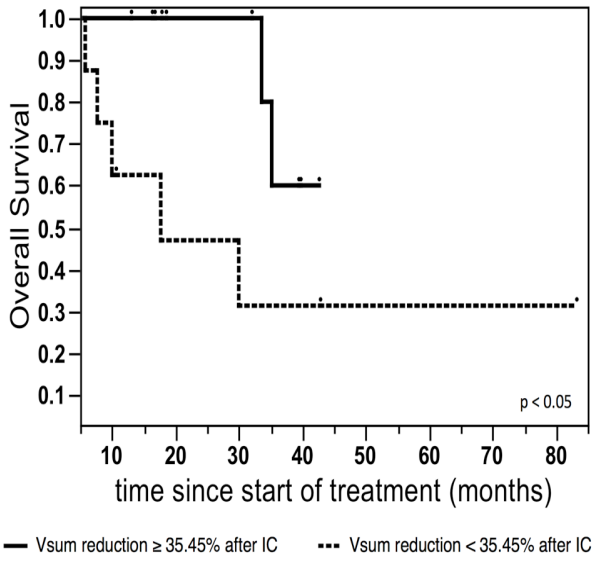

Figure 3. Overall survival stratified according Vsum reduction after IC. IC: Induction chemotherapy, Vsum: Sum of the primary tumor and metastatic lypmh node(s).

Discussion

Several studies and review articles have been published about the significant predictive value of primary tumor volume, metastatic lymph node volume and their sum on varying endpoints of outcome (local control, LRC, DM, OS and DFS) [13,14]. However, there is no consensus about the volume thresholds to be used. Only Studer et al. [12,18-20] extensively studied this issue and consistently used a classification system divided by three thresholds.

Before the development and widespread use of software which enables 3D measurement of the volumes on images, cuboid and ellipsoid volume formulas (a×b×c and 1/6 xπ×a×b×c, respectively) were used to estimate the tumor and metastatic lymph node volumes [21-23]. Thanks to advances in imaging technologies some authors also included CT-based radiological indicators like lymphatic extracapsular spread [24], central nodal necrosis [21,25] or perfusion parameters [26] for predicting outcome and found significant results related to those factors. But in our study we did not include criteria other than simple volumetric parameters in standard contrast enhanced CT.

Almost all studies published on this subject evaluated the tumor burden before CRT or radiotherapy alone. Few articles about the value of tumor volume before IC were mostly focused on the correlation of volume with chemotherapy effects like tumor remission [27] or negative biopsy results [28]. Bisdas et al. [16] measured primary tumor volume with CT before IC and found a significant correlation with decreased DFS. Seol et al. [29] and Yu et al. [30] used metabolic primary tumor volume prior to IC measured with ^{18}FDG-PET-CT and found significant correlation

Table 1. Measured volumes of primary tumor, metastatic lymph nodes and their sum

Measured volume	*Mean pre-IC volume in mL (range)*	*Mean post-IC volume in mL (range)*	*Mean relative change (%)*
Vtm	45.3 (2.4-103.1)	25.4 (0-95.8)	-43.6
Vln	58.1 (0-334.7)	22.7 (2.26-116.6)	-39.0
Vsum	103.3 (13.81-392)	48.2 (4.8-148.1)	-39.7

IC: Induction chemotherapy, Vtm: Volume of the primary tumor, Vln: Volume of metastatic lymph nodes, Vsum: Vtm + Vln

with DFS. The methodologically most similar attempt to our current study was from Yoon et al. [31] where they demonstrated the correlation of the percentage of maximum standardized uptake value (SUVmax) decrease regarding primary tumor or metastatic lymph nodes after IC with the outcomes including clinical complete response, LRF and OS in a cohort of 21 patients. It was a study showing a relation between outcome and a quantitative ratio measurable from the start of IC to its end before CRT. However, the IC regimen was a non-standard protocol used in East Asia and the volumetric assessment was done with metabolic response and not with morphological changes.

Detailed results and treatment related toxicities of this cohort is published previously [17]. To our knowledge, the present study is the first to evaluate the volumes before and after IC using proportional change in morphology, taking both primary tumor and metastatic lymph nodes into consideration. We evaluated the predictive value of total locoregional tumor shrinkage of at least -35% after IC on OS. It is also interesting to see, that our cut-off value is close to the partial response threshold of -30%, defined by the widely accepted RECIST guideline [32] where the use of one-dimensional longest diameter but not a 3D volumetric assessment is required. On the other hand, it is interesting to observe a significant effect of volume change on OS without being able to find any optimal cut-off value for LRF or DM. The underlying reason for this lack of significance might be the limited sample size or another parameter we are not aware of.

The major limitation of our study besides its retrospective nature is the heterogeneity and the limited number of the patient cohort. In addition, the number of IC cycles varied due to toxicity. Moreover, patients responding to one or two cycles could typically continue to respond during the next cycles. The cut-off value what we defined should be 'fine-tuned' with future studies having larger sample sizes. HNSCC, even with the same histopathology, follows different clinical courses regarding the primary tumor site. This is why it will be impossible to generate a uniform algorithm for all subsites of the head and neck area. Therefore it is important to have cases with homogeneous disease sites or stratified large cohorts in studies like this.

Today, administering TPF IC for locoregionally advanced HNSCC is justified and widely accepted, based on a high level of evidence only for larynx preservation purposes [33,34]. On the other hand, to choose IC for cases having extensive bulky disease remains to be an option.

By using these simple volumetric measurements to calculate the volume reduction of the tumor mass after IC, it may be possible to assess patients who may be offered modalities combined with radical and morbid surgical options and closer follow-up, or on the contrary, offer those poor responders less aggressive palliative approaches with modified radiation dose/fractionation/volume concepts (e.g. less total dose, split course, no elective irradiation), no or less toxic CRT. The CT-based method to calculate the volumes may be implemented in countries and healthcare settings where resources for other imaging techniques like ^{18}FDG-PET-CT are limited.

Conclusion

Primary tumor together with metastatic lymph node volume reduction after IC with a cut-off value of at least -35.45% seems to be predictive on OS in patients with stage IVA/B HNSCC. Shrinkage of the total locoregional tumor volume less than this cut-off value has an OS of 43% in comparison to a higher volume reduction with an OS of 100% at 2 years. However, these results need to be validated in future prospective studies with larger sample sizes to allow establishing their value as a measurement tool of stratification and allocation to treatment strategies.

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