European Archives of Oto-Rhino-Laryngology (2019) 276:1183–1189
https://doi.org/10.1007/s00405-019-05323-w

HEAD & NECK

Tumor volume as a predictive parameter in the sequential therapy (induction chemotherapy) of head and neck squamous cell carcinomas

M. Bohlen[1] · C. -J. Busch[1] · S. Sehner[2] · F. Forterre[3] · J. Bier[1] · C. Berliner[4] · L. Bußmann[1] · A. Münscher[1]

Received: 14 December 2018 / Accepted: 30 January 2019 / Published online: 6 February 2019

Abstract

Purpose Tumor volume in locally advanced head and neck squamous cell carcinomas (LAHNSCC) treated by induction chemotherapy (ICT) and followed by radiochemotherapy (RCT) was measured. The presence of potential correlation of initial tumor volume and volume reduction after ICT and RCT with remission status, overall survival (OS) and disease-free survival (DFS) were investigated. Furthermore, reliability of approximation of the tumor volume relying on its diameter to manual three-dimensional measurement was assessed.

Methods Data of patients with LAHNSCC treated by ICT consisting of docetaxel, cisplatin, and 5-fluorouracil (TPF) followed by definite RCT were retrospectively analyzed. The tumor volume was calculated slice-by-slice in contrast-enhanced CT or MRI before and after ICT as well as after complete treatment. The volume was compared to radiologic remission status, correlated with OS and DFS, and to volume estimation using tumor diameter.

Result 65 patients were included. Primary tumor volume did not correlate with complete remission rate (CR) after ICT and RCT, OS or DFS. The change in tumor volume between baseline imaging and post-RCT had a significant impact on OS ($p = 0.026$) and DFS ($p = 0.028$). The agreement between tumor volume and radiologic remission was 72.14%.

Conclusion The initial tumor volume had no influence on CR, OS or DFS. A severe response to ICT did not predict a powerful RCT outcome. The change in tumor volume post-RCT had an impact on OS and DFS. Tumor volume estimation using its diameter seems to be a reliable method.

Keywords Head and neck neoplasms · Induction chemotherapy · Remission status · Treatment outcome

M. Bohlen and C. -J. Busch contributed equally and share first authorship.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00405-019-05323-w) contains supplementary material, which is available to authorized users.

✉ M. Bohlen
Marielin.Bohlen@t-online.de

[1] Department of Otorhinolaryngology, Head and Neck Surgery and Oncology, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20251 Hamburg, Germany

[2] Department of Medical Biometry and Epidemiology, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20251 Hamburg, Germany

[3] Department of Veterinary Medicine, Small Animal Surgery, Vetsuisse Faculty Bern, Länggassstrasse 120, 3012 Bern, Switzerland

[4] Department of Diagnostic and Interventional Radiology and Nuclear Medicine, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20251 Hamburg, Germany

Introduction

HNSCC is the sixth most common cancer worldwide [1]. The 5-year OS rate is stagnating at about 42% in adults. Patients with LAHNSCC require a multidisciplinary treatment regime. Currently, the standard treatment for these patients is surgery with or without risk adapted radio(chemo) therapy (R(c)T) or concurrent cisplatin-based RCT. Furthermore, ICT remains a relevant treatment alternative for selected patients traditionally used for organ preservation or in patients with a high tumor burden. In the NCCN Guidelines, ICT is accepted as a treatment option for patients with LAHNSCC [2]. Studies show that in particular larynx and hypopharynx generate higher preservation rates with sequential therapies such as ICT [3]. In addition, ICT can also provide superior OS, DFS and loco regional control [4]. Certainly, the high toxicity along with TPF often impairs the use of ICT but also provides superior results versus PF alone [5, 6]. Consequently, the dispose of ICT is considered

as very controversial. Therefore, the selection of patients who have a benefit from the ICT treatment should be in focus. Tumor volume could have an impact on CR and OS in LAHNSCC [7–9]. A relation between tumor volume and nodular [10, 11] or distant spread [8, 12] has been described. Nevertheless, there are limited data correlating the primary tumor volume, response to ICT with OS and DFS in patients with LAHNSCC. The predictive value of the primary tumor volume and the change in tumor volume under treatment are the major concerns of this analysis. Furthermore, accuracy of a simple method of tumor volume evaluation was investigated.

Materials and methods

Study population

A retrospective image data analysis of patients with LAHNSCC at our university medical center for the work-up of the predictive value of the primary tumor volume and the change in tumor volume under treatment for OS and DFS was performed. Tumor volume before and after ICT as well as after therapy (6 weeks and 3 months after therapy) was measured. All procedures were in accordance with the standards of act for healing professions of Hamburg, Germany, and with the principles of the 1964 Declaration of Helsinki and its later amendments. Informed consents for the Clinical Cancer Registry and all examinations were obtained from each patient. All clinical and imaging data were anonymized.

We extracted and reviewed charts from our institutional database of all consecutive patients with LAHNSCC who were curatively treated with an ICT and a following RCT between June 2008 and February 2016. Subjects were selected according to the following inclusion and exclusion criteria. Inclusion criteria: previously untreated histologically squamous cell carcinoma arising from the oral cavity, oropharynx, hypopharynx, nasopharynx or larynx; treatment between 2008 and 2016 with three cycles of a triple chemotherapy regimen consisting of TPF and a following RCT; full diagnostic work-up with CT/MRI and clinical examination before treatment. Exclusion criteria: not available initial MRI or CT image, strong artifacts of images so that these could not be evaluated accordingly, patients who did not return after the first performance. Deviations and abortions within the ICT or RCT are not considered exclusion criteria and, therefore, also incorporated in the analysis. Of 75 treated patients, a total of 65 patients met the inclusion criteria. 10 patients could not be included in this retrospective study due to incompleteness of charts: (6 = not available MRI or CT image), (2 = strong artifacts), (2 = patient who did not return after the first performance).

MR imaging

MR imaging was performed using two different 1.5-T scanners (Magnetom Symphony, Siemens, Erlangen, Germany and Achieva, Philips Medical System, Best, The Netherlands) and two different 3-T scanners (Intera and Ingenia, Philips Medical System, Best, The Netherlands). Standard diagnostic sequences were performed in all patients scanned in supine position. Sample parameters are provided in Appendix 1.

CT imaging

CT scans were performed following the standardized CT head and neck imaging protocols at the Department of Diagnostic and Interventional Radiology and Nuclear Medicine, University Medical Center Hamburg-Eppendorf (UKE) using a multi-slice CT scanner (Brillance 64 MX 8000 IDT 16; Philips, The Best, Netherlands). For the measurement, axial and sagittal CT images in diagnostic CT scans were used. Slices were calculated from data with 3 mm thickness. FA average applied doses are provided in Appendix 2.

Image evaluation

Two readers independently analyzed image data. Exact anatomical location of the lesions was determined by T1 weighted imaging. In questionable cases or severe artifacts, additional information was subsequently used from T2-weighted imaging to allow better tumor delineation. Volumetric analysis was conducted in contrast-enhanced axial T1w sequences. Tumor volume was computed independently using AW Server version 3.2 (GE Healthcare, Chicago, IL, USA) by a doctoral candidate and a radiologist. Finally, the volume of all measured slices containing tumor was summed up for the total tumor volume and compared to the estimation of the tumor volume using its diameter.

Tumor volume before and after ICT as well as after therapy (6 weeks and 3 months after therapy) was evaluated. The remission status was calculated based on RECIST v1.1 as well as the radiologic one.

Statistics

Sample characteristics are given as absolute and relative frequencies, mean ± standard deviation or median with interquartile range (IQR), whichever is appropriate.

At every follow-up (post-ICT, post-RCT), the percentage change of tumor volume in comparison with the primary tumor volume was calculated. This change in tumor volume was also categorized into four usual defined remission

stages: 100% reduction as 'complete remission', 30% to < 100% reduction as 'partial remission', < 30% reduction to 20% growth as 'stable disease' and more than 20% growth as 'progress'.

The correlation coefficient was estimated to describe the agreement between the two different volume/length measures. The agreement between the different remission stage measures (radiology versus volume change) was also estimated and the kappa coefficient was reported.

Survival analysis was performed using baseline adjusted a Cox proportional hazards model; the starting time was the date of diagnosis. Kaplan–Meier curves were used to visualize the processes and hazard ratios (HR) with corresponding 95% confidence intervals were reported to quantify the effects.

All of the models present available case analyses. A two-tailed $p < 0.05$ was considered to be statistically significant. Nominal p values are reported without correction for multiplicity. All of the analyses were performed using StataCorp Stata 15.1.

Results

The study included 65 patients with LAHNSCC treated with ICT and following RCT.

Pretreatment tumor volume

The initial tumor volume measured slice-by-slice was almost identical (correlation coefficient 0.964) with the tumor volume approximated by the maximum tumor diameter. The distribution of the primary tumor volume is shown in Fig. 1 and ranged between 0.04 and 214 cc. The median resp. mean tumor volume was 19.05 cc/33.38 cc resp before primary treatment. After ICT it represented 3.32 cc resp. 13.99 cc. 81% (53) of the patients indicated a response to the induction chemotherapy, while 15 of these patients showed a CR and 38 a partial remission. (BL $n = 65$/post-ICT $n = 63$).

Depending on remission status, the median pre-therapeutic tumor volume was 11.19 cc for patients with CR; 15.98 cc for patients with partial remission; 38.21 cc for patients with stable disease and 28.86 cc for patients with progressive disease. The primary tumor volume was not a significant predictor for the odds of CR ($p = 0.255$).

Almost 10 of the 15 patients, who revealed a CR after ICT, showed also a CR after treatment (66.6%). 4 patients could not be assessed, because they did not return after treatment (three) or died (one).

At the time of interpretation, 17 patients had died. The median follow-up time was 43 months (95% CI 34–53). For the total cohort, the 5-year OS and DFS rates were 65.5% and 53.8%.

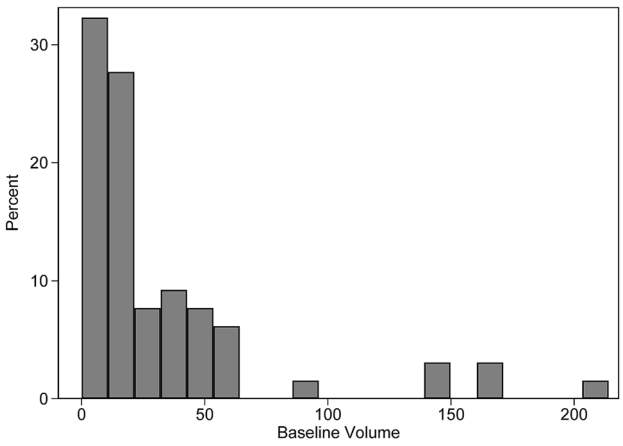


Fig. 1 Diagram depicting distribution of the measured tumor volume (measured in cm^3) in 65 patients with LAHNSCC. Most of tumor patients included presented a low tumor volume (median resp. mean tumor volume 19.05 cc/33.38 cc resp)

The primary tumor volume had a non-crucial effect on OS ($p = 0.384$) and DFS ($p = 0.966$).

Change in tumor volume under treatment

The change of tumor volume between baseline and post-ICT did not show any significant effect on OS ($p = 0.589$) or DFS ($p \leq 0.485$).

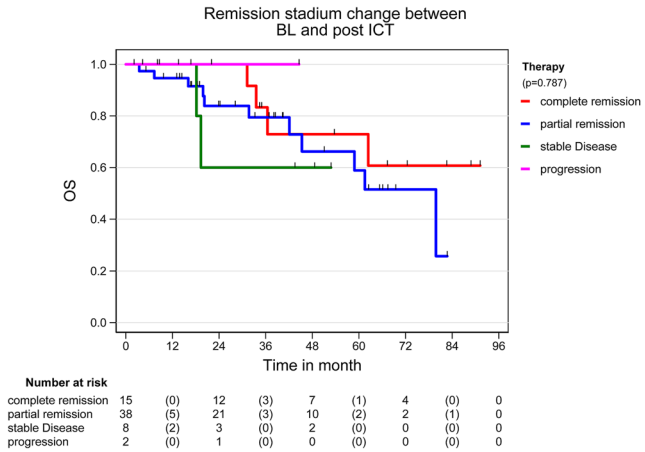
The change in tumor volume between baseline and post-RCT had a significant impact on OS ($p = 0.026$) and DFS ($p = 0.028$). The patients who had a stable disease after RCT had a 20-fold higher risk to die than those with a CR ($p = 0.014$). Patients with a progressive disease had a fourfold higher risk ($p = 0.095$). Analogous patients with a stable disease or progression after RCT had a ninefold ($p = 0.048$) or sevenfold ($p = 0.023$) higher risk to get a relapse (Figs. 2, 3).

Comparison of volume and common radiologic remission status

The compatibility between radiologic and volume remission degrees was high at 72.14% (Kappa 0.56) overall time points of measurement.

TNM status

The N-Stage correlated significantly with OS ($p = 0.020$; $HR_{N0\ vs\ N3} = 9.0$, $p = 0.011$, 95% CI 1.7; 49.1, all other comparisons to N0 are insignificant) and DFS ($p = 0.031$; 8.0, $p = 0.016$, 95% CI 1.5; 43.9, all other comparisons to N0 are insignificant). Both effects are adjusted for the T-Stage of the patient; all patients had M0-stage.



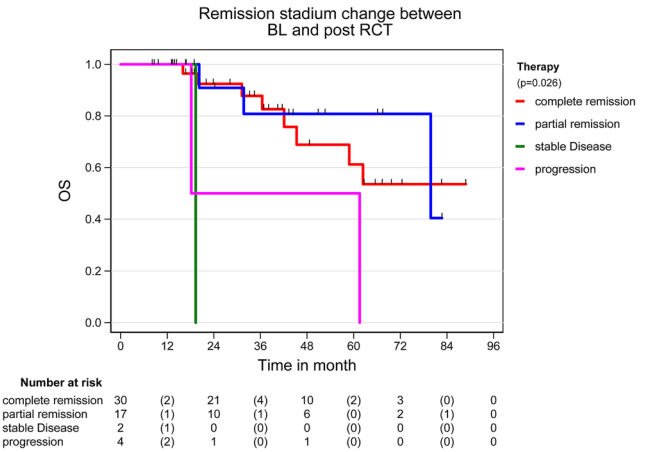
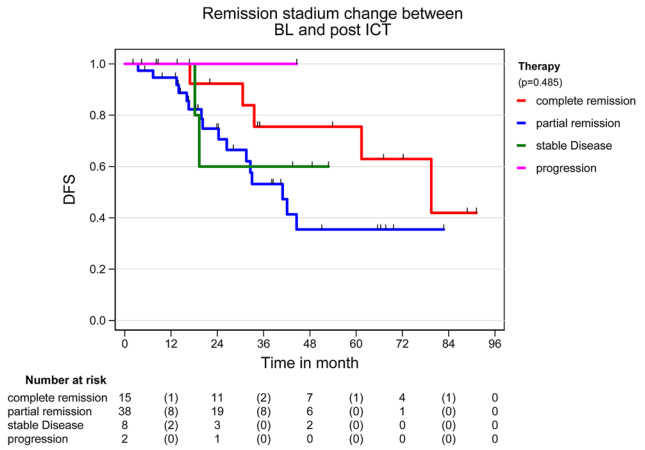


Fig. 2 Diagram depicting effect of changes in tumor volume on overall survival. Left diagram: change of tumor volume between baseline (BL) and post-ICT, right diagram: change of tumor volume between baseline (BL) and post-RCT. The change of tumor volume between baseline and post-ICT did not affect OS ($p=0.589$). The change in tumor volume between baseline and post-RCT had a significant impact on OS ($p=0.026$)



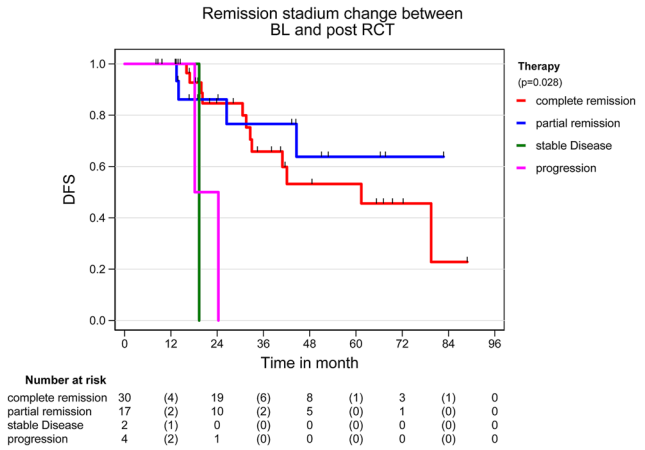


Fig. 3 Diagram depicting effect of changes in tumor volume on disease-free survival. Left diagram: change of tumor volume between baseline (BL) and post-ICT, right diagram: change of tumor volume between baseline (BL) and post-RCT. The change of tumor volume between baseline and post-ICT had no effect on DFS ($p \leq 0.485$). The change in tumor volume between baseline and post-RCT had a significant impact DFS ($p=0.028$)

Discussion

In this study, we investigated the predictive value of the primary tumor volume and the change in tumor volume under sequential (ICT) treatment for CR, OS and DFS in patients with LAHNSCC. Ideally, initial tumor volume should help as an indicator for ICT, to identify which patients might benefit from the ICT treatment. Two methods of volume calculation were compared after ICT as well as after completed therapy. The three-dimensional measurement was used as the reference method and required time-consuming slice-by-slice manual segmentation. Parallel on the same scans, the maximum orthogonal diameter was measured and used for volume estimation. A good agreement between both methods was observed (correlation coefficient 0.964). The agreement between radiologic and volume remission was at around 72.14% after ICT and RCT. A further study dealing with cervical cancer also reported that small (< 40 cc) and large (> 100 cc) initial tumor volume for the prediction of treatment outcome can be estimated by diameter in MRI scans. However, for intermediate size (40–99 cc) tumors a slice-by-slice measurement was more accurately [13]. Furthermore, it was found that the difference between both measurements was large enough to have an impact on the response to therapy [14].

In addition, an underestimate (− 8%) of tumor volumes by ellipsoid approximations using maximum orthogonal diameters in CT scans has been described [15]. In contrast to the above-mentioned studies, our results show that the majority of patients had a small (< 40 cc) initial tumor volume. We also evaluated tumors after therapy, at a stage where they often present a mixed density with irregular and diffuse borders, because of the intense edema. These characteristics will of course prevent accurate volume calculation and give some support for the use of the simple tumor diameter-based volume estimation. This might also be one explanation to the high agreement found between both measurements in our study.

In the present work, the primary tumor volume did not statistically correlate with the probability of a CR. One reason might be the small number of patients with stable and progressive disease included, but other factors cannot be excluded. One study focusing on primary RCT, reflects our observation [9]. Only one single further publication indicated that primary tumor volume was significantly different between patients with and those without CR in LAHNSCC treated with ICT [16]. Therefore, initial tumor volume cannot be used as a valuable tool to recommend ICT.

Several studies worked out that tumor volume is an even better predictor of treatment outcome after RCT than TNM system [8, 17]. In this trial, TNM stage is a predictor for OS and DFS, but we could not reveal a correlation between tumor volume and these mentioned points. Few studies have demonstrated that tumor volume for patients with advanced LAHNSCC treated with RCT is a valuable prognostic factor for OS [7–9] and DFS [8]. Dejaco and colleagues [7–9] also found out that the risk of death increases by 1.4% per mL of tumor volume. In contrast to our study, patients with any UICC (Union Internationale Contre le Cancer) stage were included which might explain this mean tumor difference. Two of the above-listed studies excluded cancer of thyroid, nasopharynx, nose and paranasal sinuses. The included cancer types and the highly toxic ICT treatment could have been contributing to the fact that no correlation between primary tumor volume and OS or DFS was found.

Also interesting is the assumption that tumor volume has an impact on the efficacy of RCT and, therefore, on OS and organ preservation. The radioresistant influencing factors such as clonogenic cells [18] increase linearly with the tumor volume [19]. Consequently, a strong reduction in tumor volume after ICT [20] could improve the efficacy of RCT. This assumption is used in clinical practice and a decrease of at least 30% will result in a RCT [21] (sometimes at least 50%) [22]. As an argument in favor of an intense radio-effectivity, as a rule, only in cases of lower response, patients will be considered for an early surgical treatment. In our investigation, almost 75% of the patients who were tumor free after ICT remained also tumor free after treatment. Nevertheless, we could not work out that a severe response to ICT resulted in a better OS. One study observed that patients which were treated with ICT have shown higher organ preservation rates [3] but this was not associated with improved OS compared with RCT alone [23–25]. Only one study reported that ICT can provide superior OS [4]. The high toxicity proceeding from the ICT could influence negatively the OS rates. This may be one reason why no improved OS for patients with a rapid reduction in tumor volume could be observed.

One benefit of ICT is supposed to be the significantly reduced rate of distant metastasis [3, 23]. It is assumed that strong reduction of tumor burden after ICT [20] has a positive influence on the probability of metastasis. Several studies observed for oropharyngeal, hypopharyngeal and laryngeal cancers a severe correlation between tumor volume and lymph node [10, 11] or distant metastasis [8, 12]. However, in our study the change of tumor volume did not show any impact on DFS.

Therefore, the investigation of other powerful prognostic biomarkers is important. Resistance to chemotherapy is a relevant factor in the treatment of HNSCC and was investigated in three large studies including the 65 cases from the current study. The first study with 453 cases of HNSCC analyzed the impact of core proteins in the nucleotide excision repair pathway, especially excision repair cross-complementing group 1 (ERCC1), Xeroderma pigmentosum group F (XPF) and a (XPA) on overall survival or response rates to chemo-and radiotherapy. Considering the overall patient cohort no statistical significant association could be detected [26].

The second and third studies from Nienstedt and colleagues verified the evidence for a significant role of ßIII-tubulin (TUBB3) with regard to chemotherapeutic resistance and the prognostic impact of enhancer of zeste homolog 2 (EZH2) expression. Their results demonstrated a statistical significant association could be detected that the overexpression of TUBB3 and the EZH2 expression had no impact on overall survival [27, 28].

We worked out that the key point was post-RCT (6 weeks or 3 months). Changes detected at this stage had an impact on OS and DFS. Patients who had a good response post-RCT had a stronger probability for a superior OS and DFS. As mentioned before, this result should be considered cautiously, because of the small number of patients with stable and progressive disease. All these patients died after 60 months at the latest. The size of the two groups was too small, giving deceased people a very strong weighting. This potential bias could be excluded using a large cohort of patients.

Limitations

The main flaw of the present study is the small size of the cohort. Further, since lymph node metastasis was not included in the measurements, we were not able to correctly calculate the complete tumor burden. In some cases, CT and MRI images were used assorted to represent tumor change. Moreover, the influence of the human papilloma virus status in this rather small cohort could not be taken into account.

Conclusion

In the present study, we found a good agreement between diameter-based and accurate manual tumor volume calculation. Primary tumor volume in ICT regimes was not a predictor for OS and DFS in patients with LAHNSCC treated with ICT followed by RCT. A severe response to ICT did not attend with a powerful RCT outcome. The change in tumor volume between baseline and post-RCT was a prognostic factor for OS and DFS. This result should be interpreted cautiously due to the small size and heterogeneity of the studied cohort.

Funding This study was not funded by any grant.

Compliance with ethical standards

Conflict of interest M. Bohlen declares that she has no conflict of interest. CJ Busch declares that she has no conflict of interest. S. Sehner declares that she has no conflict of interest. F. Forterre declares that he has no conflict of interest. JC. Bier declares that he has no conflict of interest. C. Berliner declares that he has no conflict of interest. L. Bussmann declares that she has no conflict of interest. A. Münscher declares that he has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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