Prognostic value of tumor volume in patients with head and neck squamous cell carcinoma treated with primary surgery

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Abstract

Background: Tumor volume in head and neck squamous cell carcinoma (HNSCC) was mainly measured in nonsurgically treated patients. We analyzed the influence of tumor volume on complete response (CR), overall survival (OS), and clear surgical margins also in primarily surgically treated patients.

Methods: In contrast-enhanced CTs, the tumor volumes of patients with incident HNSCC were measured.

Results: The tumor volumes of 259 patients were measured, of which 125 patients (48%) underwent primary surgery and 102 patients (84%) had clear margins. The tumor volume was not an independent factor for CR at the primary tumor site. Risk of death increased by 1.4% per mL of tumor volume (95% confidence interval [CI] 0.8%-2.0%; \(P < .001\)). The OS was better in patients treated with primary surgery, if the tumor volume was \(\leq 12\) mL (\(P < .001\)). Risk of involved margins increased by 4.5% per mL of tumor volume (95% CI 0.9%-8.3%; \(P = .003\)). The predicted probability of clear margins was \(\geq 80\%\) in tumor volumes \(\leq 16\) mL.

Conclusion: The tumor volume had an impact on CR, OS, and clear margins. The tumor volume may also aid in selecting HNSCC treatment.

Keywords
head and neck squamous cell carcinoma, prognosis, surgical therapy, survival, tumor volume

1 INTRODUCTION

Image-based tumor volumetry uses a summation of 2D tumor areas delineated slice by slice in order to approximate the true tumor volume. In head and neck squamous cell carcinoma (HNSCC), tumor volume may correlate better with treatment outcome than conventional tumor staging. Interestingly, tumor volume data from patients with HNSCC with primary surgical treatment is sparse. A likely reason for this is that tumor volumes are routinely calculated during radiotherapy (RT) planning but not before surgery. However, for patients treated with primary RT or primary concurrent radiochemotherapy, tumor volume was a powerful predictor of recurrence and overall survival (OS). Kneegjens and colleagues\(^1\) retrospectively measured tumor volume in 360 selected patients with advanced HNSCC treated with radiochemotherapy. The hazard for recurrence increased by 14% per 10 mL of additional tumor volume. The authors did not observe a comparable relation for T classification and concluded that tumor volume predicts recurrence more reliably than T classification in this specific setting.\(^1\) Similar observations have recently been reported for RT alone by Rutkowski\(^2\) in a literature review. A better correlation of tumor volume with treatment outcome compared to conventional T classification was observed by Strongin and co-authors.\(^3\) They retrospectively evaluated 78 patients with advanced
nonnasopharyngeal HNSCC treated with radiochemotherapy. A tumor volume of 35 mL was identified as the threshold at which survival decreased. In a prospective, randomized clinical trial including 101 patients, Plataniotis and colleagues investigated the prognostic impact of tumor volume in patients with locally advanced head and neck carcinoma treated with RT or radiochemotherapy. The addition of platinum compounds significantly improved the survival rate. A tumor volume < 22.8 mL was reported as the cutoff value at which local control decreased, resulting in a significantly higher median survival of 45 months compared with 12 months in tumor volume > 22.8 mL. A frequent clinical decision is whether curative intent surgery shall be part of the primary treatment in patients with incident HNSCC. The tumor volume may have some predictive value and aid in selecting surgical or nonsurgical primary treatment. In advanced hypopharyngeal cancer treated with primary radiochemotherapy, high tumor volumes were associated with poor outcome. Chen and co-authors retrospectively evaluated 76 patients for their 3-year cause-specific survival and tumor relapse-free survival after radiochemotherapy. The authors concluded that mainly patients with tumor volumes < 30 mL should be considered for laryngeal preservation in hypopharyngeal cancer. However, no data on surgically treated patients were presented in this study. In a literature review, Mendenhall and co-authors concluded that tumor volume may be a useful parameter to select patients for treatment with definitive RT, particularly for those with laryngeal squamous cell carcinomas. Mainly based on data on RT failures, the authors concluded that patients particularly with laryngeal HNSCC are likely better treated with surgery if the tumor volume is high. However, data on the outcome of primary surgical treatment were not systematically evaluated. In a retrospective study, Oemus and co-authors measured the tumor volumes in 275 unselected patients with head and neck carcinoma treated either surgically or nonsurgically. Larger tumor volumes were associated with decreased recurrence-free survival in univariate and multivariate analyses. A tumor volume of > 11 mL was reported as significantly less favorable in terms of survival. However, the authors did not evaluate their data for patients with primary surgical treatment and primary RT/radiochemotherapy separately. They also did not estimate a tumor volume threshold favoring either primary surgical treatment or primary RT/radiochemotherapy.

In short, the authors reasoned that patients with larger tumor volumes may benefit from surgical treatment with volume thresholds ranging between 11 mL and 30 mL. However, this hypothesis is mainly based on RT/radiochemotherapy treatment failures in high-volume tumors but not on face-to-face comparisons of patients treated with primary surgery or primary RT/radiochemotherapy. Furthermore, most data available on the predictive impact of tumor volumes in HNSCC was obtained in advanced disease. In this analysis, patients with local and advanced HNSCC treated with primary curative intent surgery or with primary RT/radiochemotherapy were included. The purpose of this study was to explore how tumor volume influences the rates of complete response (CR) at the primary tumor site and OS in total and grouped by primary treatment modality. Moreover, we were interested in the association of tumor volumes and clear margin rates.

2 | MATERIALS AND METHODS

2.1 | Registry population

Patients referred to the Department of Otorhinolaryngology - Head and Neck Surgery, Medical University of Innsbruck, Austria, between 2008 and 2016 with incident histologically confirmed HNSCC were retrospectively evaluated. Disease was staged according to the seventh edition of the Union for International Cancer Control (UICC) TNM classification system by an interdisciplinary board. Inclusion criteria comprised histologically proven incident HNSCC from the oral cavity, oropharynx, hypopharynx or larynx, any UICC stage, and any oncologic treatment, including surgery. Cancers of the thyroid, nasopharynx, nose, and paranasal sinuses or cancer of unknown primary were excluded. Also excluded were patients with recurrent disease or receiving best supportive care as a primary treatment modality. Furthermore, patients were excluded if no contrast-enhanced CT scans were available before treatment. The American Society of Anesthesiologists (ASA) Physical Status Classification System served as a measure of comorbidity. The ASA grading was done according to the instructions outlined online. The institutional review board of the Medical University of Innsbruck had approved the study (UN4590) and informed consent was obtained from all study participants.

2.2 | Patient sample

Even using a simple approximation, tumor volume calculation is a considerable effort and could not be performed in the whole patient population. To obtain a reasonable patient subset, the number of covariates needed for multivariate analysis was estimated. From previous studies, tumor stage, tumor site, ASA score, and cyclin-dependent kinase inhibitor 2A (p16) were known relevant prognostic factors. It was also considered relevant, if first line treatment included curative intent surgery and if the resection margins were clear. Age and sex were included as basic demographic characteristics, resulting in 8 factors. At least 15 events were considered appropriate per factor and a death proportion of 0.5 was assumed resulting in a sample size of 240 patients. Based on a smaller subset from a previous publication, a patient
sample was shaped as similar to the whole patient population as possible. This required some more patients than initially calculated. Ethnic factors were considered less relevant because the vast majority of patients in Central Europe are white. Data for socioeconomic status were not available.

### 2.3 CT scans and tumor volume approximation

Diagnostic CT scans were performed following the standardized CT head and neck imaging protocols at the Department of Radiology, Medical University of Innsbruck. A GE Medical Systems Light Speed VCT or Light Speed 16 CT Scanner (GE Medical, Vienna, Austria) was used. The scan area ranged from the frontal sinus to the upper mediastinum with a resolution of $512 \times 512$ pixels. Slices were calculated from raw data with 2 mm thickness, collimation of $24 \times 1.2$ mm, and 0.45 pitch. Additional sagittal and coronal images were reconstructed. At contrast medium, Jopamiro 370 (Bracco Austria GmbH, Vienna, Austria) was administered intravenously, adjusted to the patient’s body weight. The images were exported in Digital Imaging and Communications in Medicine format using IMPAX EE (Agfa Healthcare, Bonn, Germany) picture archiving and communication system (Cerner, Kansas City, KS). Maximum orthogonal diameters in millimeters were manually measured, as previously described, in anterior-posterior, mediolateral, and craniocaudal planes in diagnostic axial and coronal CT scans using a picture archiving and communication system software. Tumor volumes were approximated using an ellipsoid formula $(\text{volume} = \pi \times \frac{x \times y \times z}{1000})/6)$. Calculation of tumor volumes was performed by the first author (D.D.). Raw results were divided by 1000 to obtain volumes in milliliters. Previously reported intraclass correlation coefficients within raters and between raters were $0.95 (P < .01)$ and $0.99 (P < .01)$, respectively. Calculated volume estimates were reliable over a wide range of tumor sizes. However, volume approximation resulted in an underestimation bias of approximately $8\%$ compared to the reference method of manual slice-by-slice segmentation volumetry.

### 2.4 Cyclin-dependent kinase inhibitor 2A expression

Surgical specimens were collected in $4\%$ buffered formalin, fixed overnight, and embedded using the ethanol (isopropanol) wax quick $4\$ mm protocol of Histos 5 Embedding Processor (Milestone, Bergamo, Italy). Five-micrometer-thick paraffin sections were dewaxed and antigen retrieval was performed in a Discovery Automated Staining System (Ventana, Tucson, AZ), p16INK4 (catalog number 6595294001; Ventana). Primary antibodies were added to the sections by automatic dispensing. The immunohistochemical staining was completed by the Discovery Automated Staining System using universal secondary antibody solution, hematoxylin counterstaining, and the DAB MAP Kit (all Ventana products), as published previously. The cutoff for p16-positivity was $70\%$ or more positive tumor cells.

### 2.5 Treatment

Individual treatment plans were devised by a multidisciplinary team, including specialists for head and neck surgery, radiation oncology, medical oncology, diagnostic radiology, and pathology. Primary treatment modality was grouped in primary surgical treatment or primary RT/radiochemotherapy. Treatment was categorized in primary surgical treatment if the patients received curative intent surgery first, either as the sole treatment or followed by RT or radiochemotherapy. Surgical procedures were aimed at achieving clear surgical margins. Debulking or emergency procedures were not counted as primary surgical treatments. Depending on the stage and site of the tumor, transoral laser microsurgery or conventional external approaches were performed. Selective or comprehensive neck dissections were performed in accordance with National Comprehensive Cancer Network practice guidelines in the head and neck. If considered favorable, reconstruction was achieved mainly by free tissue transfer. Treatment was categorized as primary RT/radiochemotherapy if patients first received curative intent RT or radiochemotherapy. In stages I and II of HNSCC, 3D-conformal RT was performed as nonsurgical treatment. The gross tumor volume encompassed all visible primary and nodal diseases and was delineated on the planning CT scans at the Department of Radiation Oncology with the PROSOMA Workstation (Oncology System Limited, Shrewsbury, UK), as previously described. An $8\ mm$ 3D margin was generated for defining the clinical target volume for gross disease, irradiated up to $70\ Gy$. Comprehensive elective nodal irradiation was undertaken by defining the high-risk (irradiated up to $60\ Gy$) and low-risk (irradiated up to $50\ Gy$) volumes in the neck according to the consensus guidelines depending on the primary site, T classification, N classification, and expected patterns of regional nodal metastases. An isotropic margin of $5\ mm$ was applied to the respective clinical target volume to generate planning target volumes. In advanced-stage HNSCC, primary radiochemotherapy with mitomycin and 5-fluorouracil was performed with a target definition similar to nonsurgical treatment in stages I and II described above. Mitomycin C ($10\ mg/m^2$) was administered as a single intravenous bolus in the first and third week of radiochemotherapy for its tumoricidal activity in hypoxic cells. The 5-fluorouracil ($1000\ mg/m^2/d$ with a maximum of $1500\ mg/d$) was administered as a continuous infusion for $24\ hours$ in the first and third week of radiochemotherapy as a radiosensitizer. Postoperative RT was
administered in patients with advanced-stage HNSCC after complete surgical resection with clear margins and without extranodal spread, as describe for RT in stages I and II HNSCC. Postoperative radiochemotherapy was performed if the surgical margins were not clear or if extracapsular spread was present in histopathological neck specimens, as described for radiochemotherapy in advanced HNSCC.18

### 2.6 | Outcome parameter

The CR at the primary tumor site, OS, and clear margin rate in surgical procedures served as the outcome parameters. To assess CR at the primary tumor site, a restaging, including contrast-enhanced CT scans of the head and neck, chest and abdomen and endoscopy, including control biopsies from the primary tumor site, were performed 6-8 weeks after completion of the primary treatment modality. The CR at the primary tumor site was assumed if no residual primary tumor was detected at this 6-week posttreatment workup. Any salvage procedures were performed if recommended by the interdisciplinary tumor board, but were not considered in this evaluation (ie, the CR at the primary tumor site results of primary treatment without salvage procedures are presented). For OS, the time interval from HNSCC diagnosis to the last follow-up observation was calculated in months. Death was registered based on the clinical information systems of all departments of the central Tyrolean Hospital in Innsbruck. Moreover, death data were yearly obtained from the epidemiologic tumor registry of the state of Tyrol and finally by telephone calls to the patients’ general practitioners, if the last nondeath observation was more than 2 years. Surgical resection margins were grouped based on the pathologist’s reports into clear and involved. For the clear margin rate, clear surgical margins were defined as a minimum distance from the invasive tumor front from the resection margin of 5 mm or more in the histopathological specimen with the exception of glottic tumors treated with laser surgery. Here, a minimal distance of 3 mm was used.18

### 2.7 | Data analysis

Frequency data were presented in tabular form. For continuous data, means and SDs or medians and 25th and 75th percentiles were provided. Extreme tumor volumes > 120 mL were trimmed. Logarithmic transformation was used to analyze volumetric data in regression models. The ASA score9 was dichotomized into ASA I/II and ASA III/IV. The median follow-up time was calculated as described by Schemper and Smith.19 The Mann-Whitney and Kruskal-Wallis tests were used to evaluate the univariate influence of various factors on tumor volume. Influence of tumor volume on CR at the primary tumor site was assessed with the Mann-Whitney test and a simple logistic regression model with clear margin rates as outcome variables, and tumor volumes and primary treatment modalities as factors.

For survival analysis, the Kaplan-Maier and Cox regression models were used. For Kaplan-Meier plots, tumor volumes were categorized into 3 volume groups, each occurring in approximately one third of the study sample. Because 50% of death was frequently not reached during the observation period, 75% OS rates were provided. To evaluate the question if larger tumor volumes should rather be treated with primary surgery or primary RT/radiochemotherapy, a Cox regression model was used with tumor volume and primary treatment modality as covariates. If the interaction term surgical treatment versus tumor volume yielded a P value > .05, no advantage of surgery as a part of primary treatment was assumed. Additional factors in this model included age, sex, ASA score, p16, and tumor site.

To assess the influence of tumor volumes on the clear margin rates, a logistic regression model with clear versus involved margins as the dependent variable and tumor volume as a covariate was used. The predicted probabilities for clear margins were plotted against tumor volume and the tumor volume with 20% or higher probability for involved tumor margins was marked. All calculations were performed with SPSS 23.0 (IBM, Armonk, NY).

### 2.8 | Registry population

Between 2008 and 2016, 802 patients with incident HNSCC were treated at the Department of Otorhinolaryngology - Head and Neck Surgery, Medical University of Innsbruck. For a representative sample of 276 patients, tumor volumes were calculated. Of these, 17 patients were excluded because their primary tumor sites were not in the oral cavity, oropharynx, hypopharynx, or larynx. Of the finally included 259 patients, 54 were women. The mean (+ SD) age was 61 years (+ 10 years), with a minimum of 28 years and a maximum age of 87 years (Table 1). Clinical data of the finally included 259 patients did not differ from the total patient population of 802 patients (all P > .05; Table 1). Median follow-up time was 45 months (95% confidence interval [CI] 42-48 months).

### 3 | RESULTS

#### 3.1 | Tumor volumes

Distribution of the tumor volumes was right skewed. Mean tumor volume was 17 mL (+/- 47 mL) with a minimum of 0.02 mL and a maximum of 680 mL. After trimming of the extreme volumes above 120 mL to a maximum of 120 mL for further analysis, the mean tumor volume was 15 mL (+/- 23 mL). Logarithmic-normalization resulted in an approximately symmetric unimodal distribution. The
maximum tumor diameter correlated with the cubic root of the tumor volume ($r = 0.9; P < .001$). In line with predominantly ellipsoid tumor shapes, the average ratio of maximum and minimum tumor diameter was 1.7 ($+/− 0.7$). Sex had no influence on tumor volume ($P > .5$), but age had ($P = .011$) with significantly smaller tumor volumes below the age of 50 years and above the age of 80 years (Table 2).

The ASA score had a highly significant impact on the tumor volumes ($P < .001$). Patients with ASA scores I and II had significantly smaller primary tumor volumes than patients with ASA scores III and IV (Table 2; $P < .001$). The tumor volumes were influenced by tumor site. Although the tumor volumes did not significantly differ between HNSCC of the oral cavity, oropharynx, and hypopharynx (Table 2; $P > .5$), laryngeal tumor volumes were significantly smaller (Table 2; $P < .001$). The p16 status had no significant influence on the

<table>
<thead>
<tr>
<th>TABLE 1 Clinical data of patient samples with tumor volume measurements</th>
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<tr>
<td>Variables</td>
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<td>Primary treatment modality</td>
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<td>Primary surgical</td>
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<td>Primary RT/radiochemotherapy</td>
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</table>

Abbreviations: ASA, American Society of Anesthesiologists; p16, cyclin-dependent kinase inhibitor 2A; RT, radiotherapy; UICC, Union for International Cancer Control.

The clinical parameters of these 259 included patients did not significantly differ from the total registry population of 802 patients treated between 2008 and 2016 (all $P > .05$).

*Absolute number of patient samples for each clinical parameter. The number after the solidus sign provides the total number of data available for each clinical parameter.

*Absolute number of registry population for each clinical parameter. The number after the solidus sign provides the total number of data available for each clinical parameter.
3.2 | Influence of tumor volumes on complete response rates of the primary tumors

Patients with CR at the primary tumor site 6 weeks after the end of treatment (194/259; 75%) had significantly smaller median tumor volumes (5.0 mL; 25th percentile = 1.0 mL; 75th percentile = 14.7 mL) before treatment than patients without CR at the primary tumor site (65/259; 25%) in whom the median pretreatment tumor volume was 9.2 mL (25th percentile = 3.6 mL; 75th percentile = 26.7 mL; \( P = .005 \)). However, this result is confounded by the high CR at the primary tumor site rate of surgically treated patients who had significantly lower pretreatment tumor volumes than patients treated without surgery. In a logistic regression model on CR with treatment group as a factor and tumor volume as a covariate, the effect of the tumor volume was not significant \( (P > .5) \), indicating that tumor volume is not an independent predictor of CR. This applied for both patients treated with and without surgery.

3.3 | Tumor volumes and survival

The tumor volume had a significant impact on OS. In a simple Cox regression model with tumor volume as the only covariate, the risk of death increased by 1.4% per mL of tumor volume (95% CI 0.8%-2.0%; \( P < .001 \)). In addition, if age, sex, ASA score, p16, and tumor site were added as covariates, tumor volume had a significant impact on OS \( (P = .008) \). For Kaplan-Meier analyses, tumor volumes were categorized into 3 volume groups \(( \leq 2 \text{ mL}; > 2 - 12 \text{ mL}, \text{ and } > 12 \text{ mL} \)\), each occurring approximately in one third of the patient sample \((n = 79, 92, \text{ and } 88, \text{ respectively}) \). The 3 tumor volume groups revealed distinct and parallel survival curves with approximately 46, 17, and 10 month’s 75% survival \((P < .001) \). If stratified by tumor volume group, patients with tumor volumes \( \leq 12 \text{ mL} \) had a significant benefit from primary surgical treatment \((P < .001) \). No survival benefit of primary surgical treatment was observed for tumor volumes \( > 12 \text{ mL} \) \((P = .5) \). This was consistent with the results of a Cox regression model, including the 3 tumor volume

![FIGURE 1](image-url) Overall survival (OS) grouped by 3 volume groups. Kaplan-Meier plots comparing OS in 259 patients with head and neck squamous cell carcinoma grouped by 3 volume groups with small primary tumor volumes \( \leq 2 \text{ mL} \) (black continuous line), medium primary tumor volumes 2 to 12 mL (black dotted line) and large primary tumor volumes \( > 12 \text{ mL} \) (black dashed line). The 3 tumor volume groups revealed distinct and parallel survival curves. A significant difference in survival was observed between all 3 tumor volume groups \((P < .001) \). For small-sized primary tumor volumes 75% OS (horizontal black dotted line) was 46.0 months \((n = 79; 95\% \text{ confidence interval } [CI] 29.4-62.2 \text{ months}) \), for medium-sized primary tumor volumes 75% OS was 17.0 months \((n = 92; 95\% \text{ CI } 18.3-25.3 \text{ months}) \), and for larger primary tumor volumes 75% OS was 10.0 months \((n = 88; 95\% \text{ CI } 6.0-14.0 \text{ months}; \text{ all log-rank } P < .001) \).
groups, primary treatment modality, age, sex, ASA score, p16, and tumor site as covariates. In this model, the interaction term tumor volume group primary treatment modality was significant for tumor volumes $\leq 12$ mL ($P < .002$) but not for tumor volumes $> 12$ mL. This suggests that, also in a multivariate model, the OS in patients treated with primary surgical treatment was better than primary RT/radiochemotherapy in patients with tumor volumes $\leq 12$ mL, whereas primary treatment modality had no influence on OS in patients with tumor volumes $> 12$ mL.

### 3.4 Influence of tumor volumes on surgical resection margins

Of 259 patients, a total of 125 (48%) were treated with primary surgery. In 121 patients, resection margins were available. In 102 of 121 patients (84%), clear margins were obtained. The median tumor volumes of clear margin resections was 2.0 mL (25th percentile = 0.7 mL; 75th percentile = 6.6 mL) compared to 9.5 mL (25th percentile = 3.6 mL; 75th percentile = 28.1 mL) for resections with involved margins (Mann-Whitney $P = .003$). The odds ratios (ORs) for involved margins increased by 4.5% (95% CI 0.6%-8.3%) per mL tumor volume. In a logistic regression model with clear versus involved margins as the dependent variable and tumor volume as a covariate, the predicted probability of involved margins was $< 20\%$ (ie, the predicted probability for clear margins was $\geq 80\%$), up to a tumor volume of 16.1 mL (Figure 3). When broken down by tumor site, the number of events (involved margins) in some site-specific subgroups was too low for reasonable logistic regressions and the results are just presented to give an idea. In 26 of 45 patients (58%) with tumors of the oral cavity treated with primary surgery, 3 of 26 patients had involved margins. The calculated ORs for involved margins increased by 8.7% (95% CI 7.4%-12.0%) per mL tumor volume. The calculated predicted probability of clear margins was 80% at a tumor volume of 16.2 mL (Figure 4A). In 45 of 105 surgically
treated patients with oropharyngeal tumors, 8 of 45 patients had involved margins. The calculated ORs for involved margins increased by 14.6% (95% CI 5.0%-25.0%) per mL tumor volume. The calculated predicted probability of clear margins was 80% at a tumor volume of 13.9 mL (Figure 4B). In patients with hypopharyngeal tumors, 11 of 43 (26%) were treated with primary surgery. In 2 of 11 patients, involved margins were obtained. The calculated ORs for involved margins increased by 10.2% (95% CI 9.2%-13.2%) per mL tumor volume. The calculated predicted probability of clear margins was 80% at a tumor volume of 9.5 mL (Figure 4C).

In patients with laryngeal tumors, 39 of 66 (59%) were treated with primary surgery. In 6 of 39 patients, involved margins were obtained. The calculated ORs for involved margins decreased by 98.4% (95% CI 90.5%-107.0%) per mL tumor volume. The predicted probability of clear margins was 80% at a tumor volume of 31.6 mL (Table 3; Figure 4C).

4 | DISCUSSION

Tumor volumes may provide relevant information in HNSCC in addition to conventional staging systems. A better correlation of tumor volume with survival, treatment outcome, and rate of recurrences for patients treated with RT and radiochemotherapy was reported by several authors.1-7 Some authors proposed volumetric cutoffs, which may aid in selecting surgical or nonsurgical treatment modalities.3-5 The authors mutually reasoned that patients with larger tumor volumes may benefit from surgical treatment rather than RT or radiochemotherapy.
Most studies used contrast-enhanced CT to calculate tumor volumes. Contrast-enhanced CT of the head, neck, thorax, and abdomen is the standard diagnostic modality in patients with head and neck cancer at our department due to its good accuracy, availability, and comparatively low costs. This resulted in a high availability of CT scans in the studied patient population. Depending on various specific adjustment parameters, MRI is a highly valuable alternative imaging modality for tumor volume measurements.\(^1,2\) Compared to CT, MRI has various advantages but also some disadvantages.\(^6\) If tumor volume is delineated from positron emission tomography scans, it is defined as metabolic tumor volume, which may differ from anatomic tumor volume. The metabolic tumor volume was reported as a strong prognosticator for OS for patients treated with RT or radiochemotherapy.\(^2\) In most of these studies, no surgically treated patients were included. Rather, the superiority of surgical therapy in patients with large tumor volumes was only suspected because the patients with large tumor volumes treated with primary RT/ radiochemotherapy had a poor outcome. In fact, tumor volume data from patients with primary surgical treatment is rare. A likely reason for this is that tumor volumes are routinely calculated during RT planning, but not before surgery. In this retrospective analysis, we analyzed the influence of tumor volume on CR at the primary tumor site, OS, and clear margin rates also in patients treated with primary surgery. In 259 patients with incident HNSCC treated between 2008 and 2016 at the Department of Otorhinolaryngology - Head and Neck Surgery, Medical University of Innsbruck, tumor volumes were measured and calculated in contrast-enhanced CT scans before treatment by 1 single operator, as previously reported\(^1\) and recommended by Mendenhall and colleagues.\(^6\)

Tumor volumes were right skewed and leptokurtic with a median of 6 mL. The observed mean tumor volume of 17 mL (\(1/24\) 47 mL) differs from previous observations: Chen and co-authors\(^5\) reported a mean tumor volume of 33.4 mL (3.8-152.4 mL) in 76 patients with advanced hypopharyngeal cancer. Knegjens and colleagues\(^1\) reported a mean tumor volume for advanced HNSCC of all common tumor sites of the head and neck of 37.0 mL (2.1-182.7 mL). In these studies, only patients with advanced tumors were included, which might explain this difference. Oemus and co-workers\(^7\) also included patients with limited disease and reported a median tumor volume 11.4 mL in a register-based study including 275 patients. However, in contrast to the present collective, almost half of the patients included in the Oemus et al\(^7\) study were measured from MRI scans. Apparently, tumor volume data are substantially subjected to patient selection bias.

Sex had no significant influence on tumor volume (\(P > .5\)) but age and ASA score had. Patients below 50 and above 80 years of age had smaller tumor volumes than patients between 50 and 80 years old. However, the number of patients above 80 years was small (\(n = 7\)). The ASA scores I/II showed significantly lower median tumor volumes

<table>
<thead>
<tr>
<th>Tumor site</th>
<th>Margins</th>
<th>No. of patients</th>
<th>Median, mL</th>
<th>p25, mL</th>
<th>p75, mL</th>
<th>Change in OR per additional mL of tumor volume(^a) (%; 95% CI)</th>
<th>Predicted probability, mL(^b)</th>
</tr>
</thead>
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<tr>
<td>All sites</td>
<td>Clear</td>
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<td>2.0</td>
<td>0.7</td>
<td>6.6</td>
<td>+4.5 (0.6%-8.3%)</td>
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<td></td>
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<td>9.5</td>
<td>3.6</td>
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<td>Oral cavity(^d)</td>
<td>Clear</td>
<td>23</td>
<td>3.9</td>
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<td>10.9</td>
<td>+14.6 (5.0%-25.0%)</td>
<td>13.9</td>
</tr>
<tr>
<td></td>
<td>Involved</td>
<td>8</td>
<td>17.4</td>
<td>9.5</td>
<td>28.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypopharynx(^e)</td>
<td>Clear</td>
<td>9</td>
<td>3.2</td>
<td>0.9</td>
<td>7.4</td>
<td>+10.2 (9.2%-13.2%)</td>
<td>9.5</td>
</tr>
<tr>
<td></td>
<td>Involved</td>
<td>2</td>
<td>21.2</td>
<td>4.3</td>
<td>23.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Larynx(^e)</td>
<td>Clear</td>
<td>33</td>
<td>0.8</td>
<td>0.2</td>
<td>5.6</td>
<td>−98.4 (90.5%-107.0%)(^d)</td>
<td>31.6(^d)</td>
</tr>
<tr>
<td></td>
<td>Involved</td>
<td>6</td>
<td>2.0</td>
<td>0.3</td>
<td>4.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio; p25, 25th percentile; p75, 75th percentile.

\(^a\)Change in OR per additional mL of tumor volume in percent. The 95% CIs are provided.

\(^b\)Predicted probability for \(\geq 80\%\) clear margins.

\(^c\)Number of events (involved margins) in site-specific subgroups is too low for reasonable logistic regressions. Results are presented to give an idea. The 95% CIs are provided to estimate accuracy of presented results.

\(^d\)Predicted probability for \(> 80\%\) clear margins increased with additional tumor volumes (see Discussion section).
compared with higher ASA scores III/IV (Table 2; \(P < .001\)). The reason for this observation is unclear. The tumor volume depended on the tumor site. Although tumor volumes did not significantly differ among HNSCC of the oral cavity, oropharynx, and hypopharynx \((P > .5)\), laryngeal tumor volumes were significantly smaller (Table 2; \(P < .001\)). The \(p16\) positivity had no significant influence on tumor volume \((P = .1)\) but a trend for larger tumor volumes in \(p16\)-positive tumors with a median tumor volume of almost 9 mL compared to 5 mL in \(p16\)-negative tumors was observed. If only oropharyngeal tumors were considered, this trend could not be observed \((P = .7)\). Similar results were recently reported by Davis and co-authors.\(^{25}\)

In patients with incident HNSCC, CR is the desired outcome of primary treatment. Treatment response was assessed 6 to 8 weeks after the end of primary treatment before any salvage treatment was initiated. Only the CR at the primary tumor site was assessed, because only volumes of primary tumors were analyzed. Overall, CR at the primary tumor site was achieved in 194 of 259 patients (75%). Patients with CR at the primary tumor site 6 weeks after the end of treatment had smaller pretreatment median tumor volumes (approximately 5 mL) than patients with residual disease at the primary tumor site (approximately 10 mL; \(P < .01\)). This result is severely biased by the treatment modality (with/without surgery). The CR at the primary tumor site was more often achieved in surgically treated patients (87%) with smaller tumor volumes than in patients treated without surgery with larger tumor volumes (68%). If adjusted for treatment modality in a logistic regression model, the tumor volume revealed no power to predict CR at the primary tumor site \((P > .5)\). In this evaluation, tumor volume was not an independent predictor of CR at the primary tumor site. One reason why only 87% and not almost 100% CR at the primary tumor site was observed in surgically treated patients is that patients with T1 and T2 glottic cancer treated with transoral laser microsurgery were frequently resected closely for functional reasons. Treatment response evaluation of CR at the primary tumor site 6 weeks after primary surgical treatment often resulted in additional surgical intervention to obtain clear margins. However, these patients were not categorized as CR at the primary tumor site.

Tumor volume had a significant effect on OS. Per milliliter of additional tumor volume, the risk of death increased by almost 1.5%. This increase is surprisingly similar to previous investigations.\(^1\) To evaluate the question if patients with larger tumor volumes benefit from curative intent surgery as primary treatment modality instead of primary RT/radiochemotherapy, tumor volume was categorized into 3 volume groups. Up to a tumor volume of 12 mL, patients with HNSCC experienced a significant survival benefit from surgical treatment. For tumor volumes < 2 mL, the 75% OS was almost 6 times higher for patients with curative intent surgery as part of primary treatment compared to RT or radiochemotherapy alone. Up to a tumor volume of 12 mL, 75% OS remained 3.5 times higher for surgically treated patients. However, in patients with tumor volumes larger than 12 mL, treatment modality did not significantly influence OS. This was in line with the results of a Cox regression analysis, including age, sex, ASA score, \(p16\), and tumor site. This result conflicts with previous reports that rather suggest that patients with large tumor volumes benefit from surgical treatment.\(^5,6\) A possible reason for this discrepancy is that, in these studies, no patients treated with primary surgery were included. The hypothetical advantage of surgical treatment in patients with large tumor volumes was assumed based on poor outcome of primary RT/radiochemotherapy. However, in line with the results reported by Kazmi and co-workers,\(^26\) larger tumor volumes were also associated with poor outcome in patients treated with primary surgery.

For surgically treated patients, the rate of patients with clear resection margins is a relevant outcome parameter. For all tumor sites, clear margins were observed in 102 of 125 patients (84%) with primary surgical treatment. For any additional milliliter of tumor volume, the risk of involved margins increased by 4%. Up to a tumor volume of 16 mL, the predicted probability of involved margins was <20% (Figure 3). The number of patients is too small for a site-specific analysis; however, if interpreted with appropriate caution, the calculated results are considered interesting. Predicted probabilities for clear margins ranged between 16 mL for patients with tumors of the oral cavity and approximately 10 mL for patients with hypopharyngeal tumors (Figure 4A–C). In contrast, the predicted probability of clear margins for patients with laryngeal tumors increased with additional tumor volumes (ie, larger laryngeal tumors had a better chance to be resected with clear margins (Figure 4D). This unusual result is probably due to the practice to resect small glottis tumors with small safety margins for functional reasons. Laryngeal tumors at other laryngeal subsites are frequently larger than glottic tumors and are treated more aggressively. Particularly large tumors are frequently treated with laryngectomy resulting in high clear margin rates.

### 5 | CONCLUSION

In patients with HNSCC, tumor volumes may easily be approximated from routine staging CT scans and adds valuable information. The tumor volume provided no relevant information if CR will be obtained and if treatment, including surgery, is superior to achieve CR when compared to treatment without surgery. Tumor volume was an independent factor to predict OS, the risk of death increased by 1.4% per mL tumor volume. The OS was better in patients treated with primary surgery if the tumor volume was \(\leq 12\) mL.
Except for laryngeal tumors, tumor volume provided valuable information if clear margins will be obtained in tumor resections. Although the UICC tumor stages are ranked on an ordinal scale, tumor volumes provide data on a ratio scale offering more flexibility for data analysis. This may allow the definition of the cutoff values that can support clinicians in making treatment decisions.

CONFLICT OF INTEREST
None of the authors named in the submitted work have any conflict of interest including no financial or personal relationships that inappropriately bias his or her actions within 3 years of the beginning of the work. No financial support for any of the work presented in the present article was obtained.

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