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Pretreatment tumor volume and tumor sphericity as prognostic factors in patients with oral cavity squamous cell carcinoma

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ABSTRACT

Purpose: This study was designed as a retrospective observational study, focusing on the correlation between the preoperative CT-scan tumor volume, tumor sphericity, and the disease-related prognosis.
Methods: A total of 30 consecutive patients, affected by primary oral cancer, were retrospectively identified from our oral cancer database. The preoperative images (DICOM data) for the study population were uploaded into a modular software package designed to convert patients' medical images into 3D digital models. Multislice interpolation and threshold segmentation tools were used to segment the tumor mass. This was then converted into a 3D mesh and exported in STL format, in order to calculate the corresponding volume. We applied the concept of sphericity — a measurement of how closely the shape of an object approaches that of a mathematically perfect sphere — to the segmented tumor mass.
Results: Mean tumor volume was larger in patients with tumor recurrence and/or who had died than in patients who were disease free/alive. Tumor sphericity was influential on clinical outcomes. It appeared to be lower in patients who had tumor recurrence and/or who had died (0.54 ± 0.09 and 0.53 ± 0.05) than in patients who were disease free/alive (0.65 ± 0.07). This difference was statistically significant ($p < 0.05$). Cumulative recurrence-free survival was 86.2% for patients with a tumor volume lower than the cut-off value. Otherwise, it was 0% for those with a tumor volume higher than the cut-off value ($p < 0.01$; log rank test). Cumulative recurrence-free survival was 86.3% for patients with a higher sphericity index, compared with 13.6% for those with a lower sphericity index.
Conclusion: The prognostic model, based on a tridimensional, CT-based characterization of the tumor size, which includes both tumor volume and tumor sphericity, uses readily available information and could be considered when formulating prognoses for patients with oral cancer.

1. Introduction

Squamous cell carcinoma is the most common malignant neoplasm involving the oral mucosa. Surgery with or without radiation and chemotherapy is the established treatment for oral carcinoma (Shah and Gil, 2009).

The TNM system of the American Joint Committee on Cancer is the most widely used tumor staging tool. According to the TNM system, the T defines the greater linear tumor dimension, varying from T1 to T3, while T4 tumors invade adjacent structures, regardless of size. In addition to the maximum diameter and anatomical extent of the primary tumor, TNM classification is based on the number and size of the involved regional lymph nodes, and the presence of distant metastases. TNM is universally accepted as a prognostic system for head and neck cancer (Edge and Compton, 2010).

The recently published 8th Edition of the *AJCC Cancer Staging Manual* introduced both the depth of primary tumor invasion and the extracapsular extension of lymph node metastases as prognostic criteria. This seems to result in an improvement in terms of evaluation of prognostic outcomes compared with the AJCC 7th Edition (Pollaers et al., 2018). However, the maximum diameter and

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anatomical extents used for the TNM classification are non-volumetric measures, being measured in a single axis clinically and/or pathologically, therefore they do not take into account the tridimensional (3D) extent of the tumor.

Tumor volume can be estimated by different methods, using either imaging scans (Cavalcanti et al., 2004) or measurements of surgical specimens (Nixon et al., 2013; Lin et al., 2017), when surgery represents the primary treatment choice. However, volume estimation methods are not routinely practiced.

Although efforts have been made to use tumor volumetric measurements as a predictive characteristic of the response to treatment, in particular for laryngeal cancer (Hermans, 2006; Kraas et al., 2001; Shiao et al., 2017), very little experience has been reported in the literature of volumetric evaluation of head and neck tumors. In a few studies, tumor volume has been already reported as a predictor of survival or treatment response for head and neck tumors, in particular for those tumors in which surgical treatment is not the primary indication (Been et al., 2008; Dubben et al., 1998). The prognostic value of tumor volume has also been previously studied in hypopharyngeal and laryngeal tumors (Chen et al., 2009; Mukherji et al., 2005). In these studies, a greater pretreatment tumor volume was associated with a higher chance of recurrence after radiotherapy (Chen et al., 2009; Doweck et al., 2002). Despite the possibility that tumor volume may be a prognosticator, tumor volume measuring techniques and cutoff values vary widely. While considering the response to treatment of the diverse anatomical sites of invasion, site-specific and stage-specific studies are fundamental in establishing the role of tumor volume in treatment outcomes for surgical and nonsurgical modalities.

Given these considerations, we hypothesize that tumor volume may be a prognostic factor for survival in patients with oral cavity squamous cell carcinoma. To our knowledge, no studies have been previously carried out on the prognostic value of tumor volume based on pretreatment CT scans for oral cavity cancers, using the present protocol. Moreover, we also introduced the 'sphericity index' as a surface regularity parameter of the tumor. This study was designed to evaluate the impact of 3D characterization of tumor size, in terms of both tumor volume and tumor sphericity, on disease control and survival, in a uniform cohort of patients treated for oral cavity cancer.

2. Materials and methods

2.1. Study design and ethics

Our Institutional Review Board approved the study under the code 217/2017/O/Sper.

This study was designed as a retrospective observational study, focusing on the correlation between the preoperative CT-scan tumor volume/tumor sphericity and the disease-related prognosis.

2.2. Study population and treatment characteristics

A study population of 30 consecutive patients was retrospectively identified from the oral cancer database of the Head and Neck Department, Division of Maxillofacial Surgery of S. Orsola-Malpighi Teaching Hospital in Bologna. All patients were surgically treated for primary oral squamous cell carcinoma (OSCC). Patient treatment consisted of composite resection, including excision of the primary tumor with ipsilateral or bilateral neck dissection. Microvascular reconstruction was performed in relation to the tumor stage. Postoperative radiotherapy or concomitant radiochemotherapy was performed when indicated, i.e. for locally advanced stage (T3–T4 tumors), positive or close surgical margins, multiple positive nodes, and/or extranodal spread. The mean follow-up time was 42 months (range 20–67).

2.3. 3D characterization of tumor sizes

Tumor volume (V_t) calculation

The preoperative images (DICOM data) of the study population were uploaded into D2P™ software (3D Systems Inc., Rock Hill, SC), a modular software package designed to convert patients' medical images into 3D digital models (Fig. 1) (See supplementary materials).

Multi-slice interpolation and threshold segmentation tools were used to segment the tumor volume, which was then converted to a 3D mesh and exported in STL format. For each 3D mesh of the segmented tumor mass the corresponding volume (V_t) was calculated.

Tumor sphericity (S_t) calculation

The concept of sphericity (S) was applied to the segmented tumor mass.

Sphericity (S) is a measurement of how closely the shape of an object approaches that of a mathematically perfect sphere: the sphericity of a particle (p) is the ratio of the surface area of a sphere (with the same volume as the given particle) to the surface area of the particle (see Equation 1) (Wadell, 1935).

$$S = \frac{\pi^{\frac{1}{3}}(6V_p)^{\frac{2}{3}}}{A_p} \quad (1)$$

where V_p is the volume of the particle (p) and A_p is the surface area of the particle.

The sphericity of a sphere is a unit by definition, so any particle that is not a sphere will have sphericity less than 1. Examples of sphericity of common tridimensional objects are shown in Fig. 2.

2.4. Statistical analysis

For calculating the categorical variables, the frequencies and percentages were reported. For the continuous variables, the means and SDs were calculated. For the comparison of continuous variables, a Student's t-test was used.

Kaplan–Meier and post-hoc, log-rank tests were used to compare the survival statuses between different groups. The cut-off predictive values for continuous variables were calculated using the ROC curve method and the Youden index. For survival analysis, the Cox regression method was also performed.

All analyses were made using SPSS version 23.0 (IBM SPSS, New York, NY) and a p value of 0.05 was chosen as significant.

3. Results

3.1. Descriptive analysis

According to T staging, 10 patients (33%) were classified as early stage (T1–T2), while 20 patients (67%) were classified as advanced stage (T3–T4). 19 patients (63%) were found negative for nodal metastases (N−) and 11 patients (37%) had nodal neck metastases (N+).

Positive or close margins were identified in three patients (10%). 27 patients (90%) had disease-free surgical margins after histological examination.

Demographic, clinical, and outcome measures from our 3D characterization of tumor size (V_t, S_t) are shown in Table 1.

3.2. Correlates of survival

Tumor volume and tumor sphericity assessment.

The mean tumor volume (V_t) for all 30 patients was 13.3 cm^3 (SD 18.9).

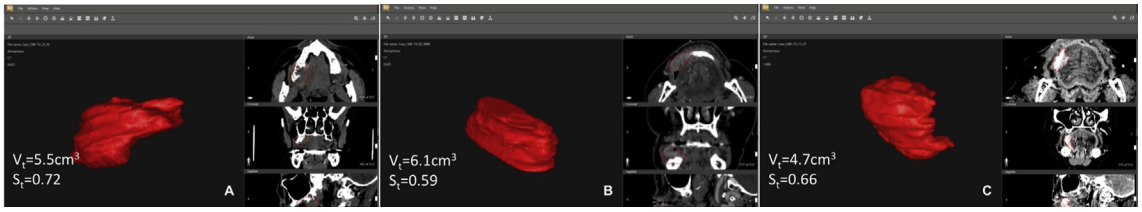

Fig. 1. CT scans of examples of segmented tumors, obtained using D2P™ software, for different anatomical regions: a) upper alveolar gingiva; b) lower alveolar gingiva; c) tongue. V_t = tumor volume; S_t = tumor sphericity.

Solid	sphere	dodecahedron	Cube	tetrahedron
Sphericity	1	~0.910	~0.806	~0.671

Fig. 2. Examples of tridimensional shapes with different sphericity values: from high (left side) to low (right side).

Mean tumor volume (V_t) was found to be larger in those patients with tumor recurrence and/or who had died (24.5 ± 26.9 cm^3, 20.6 ± 12.7 cm^3) compared with patients who were disease free/alive (6.8 ± 7.4 cm^3), even if these differences were not statistically significant according to the Student's t-test ($p = 0.057$, $p = 0.207$).

The mean tumor sphericity (S_t) for all 30 patients was 0.61 (SD 0.09).

Results from comparisons of the continuous variables among subgroups of patients showed that S_t was influential on clinical outcomes. It appeared to be lower in patients who had tumor recurrence and/or died (0.54 ± 0.09 and 0.53 ± 0.05) than in patients who were disease free/alive (0.65 ± 0.07). This difference was statistically significant ($p < 0.05$).

3.3. Kaplan–Meier analysis

The overall survival rate was 73.3%. The survival rate for early (T1–T2) and advanced (T3–T4) stage was 100% and 60%, respectively. Overall 5-year disease-free survival rate was 63.3%. Furthermore, stratifying according to stage, for early and advanced tumors, disease-free survival was 90% and 50%, respectively.

Measurements for both S_t and V_t were further stratified according to cut-off values obtained from the ROC curve and the Youden index. The cut-off values indicate the best discriminative predictive values for both recurrence-free survival and for overall survival.

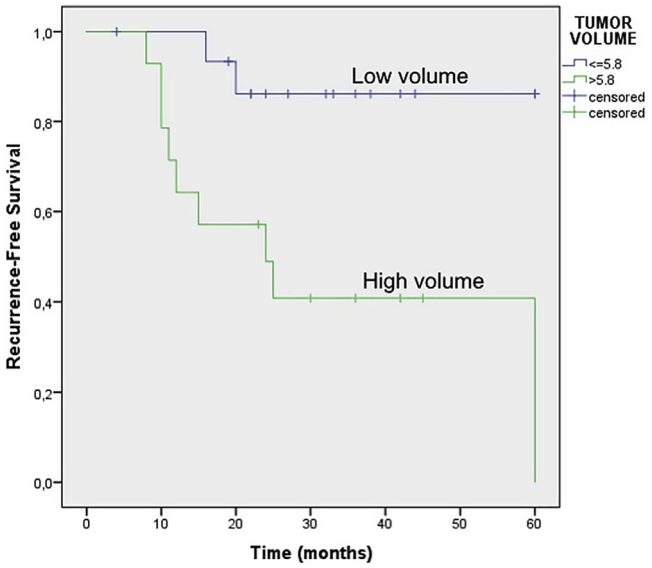

Fig. 3. Kaplan-Meyer curves demonstrating worse recurrence-free survival in patients with a V_t value higher than 5.8 cm^3 (0.0% vs 86.2%; $p < 0.01$; log rank test). For larger tumors (V_t > 5.8 cm^3) the median survival was 24 months.

Cut-off values for V_t of 5.8 cm^3 and 10.0 cm^3 were obtained for recurrence-free survival and for overall survival, respectively.

Cumulative recurrence-free survival was 86.2% for patients having a V_t lower than the cut-off value. Otherwise, it was 0% for those having a V_t higher than the cut-off value ($p < 0.01$; log rank test). For tumor volumes larger than 5.8 cm^3, the median recurrence-free survival was 24 months (Fig. 3).

Cumulative overall survival was 94.1% for patients having a V_t lower than the cut-off value. Otherwise, it was 0% for those having a

Table 1
Outcome data from the study population.

	Total 30 (100%)	Alive, disease free 19 (63%)	Recurrence 11 (37%)	Dead 8 (27%)
Male (%)	15 (50)	9 (47)	6 (55)	4 (50)
Age (SD)	71,2 (14,1)	71,2 (13,9)	71,4 (15,3)	70,6 (15,9)
T classification				
T1-T2 (%)	10 (33)	9 (47)	1 (9)	0 (0)
T3-T4 (%)	20 (67)	10 (53)	10 (91)	8 (100)
N classification				
N– (%)	19 (63)	13 (68)	6 (55)	4 (50)
N+ (%)	11 (37)	6 (32)	5 (45)	4 (50)
Positive margins (%)	3 (10)	1 (5)	2 (18)	2 (25)
V_t(SD)	13,3 (18,9)	6,8 (7,4)	24,4 (26,9)	20,6 (12,7)
S_t(SD)	0,61 (0,09)	0,65 (0,07)	0,54 (0,09)	0,53 (0,05)

Categorical variables are reported as frequencies (percentages), while continuous variables are reported as mean (SD). V_t = tumor volume (measured in cm^3); S_t = tumor sphericity (adimensional).

V_t higher than the cut-off value ($p < 0.01$; log rank test). For tumor volumes larger than 10.0 cm^3, the median overall survival was 24 months (Fig. 4).

For S_t, a cut-off value of 0.58 was obtained for both recurrence and death.

Cumulative recurrence-free survival was 86.3% compared with 13.6% (Fig. 5), and overall survival was 100.0% compared with 15.6% (Fig. 6) ($p < 0.001$; log rank test). For less spherical tumors ($S_t < 0.58$) the median recurrence-free survival was 15 months.

3.4. Cox regression analysis

For the Cox regression analysis, we calculated the percent of tumor sphericity ($\%S_t$) and applied the Cox regression to it.

Results showed that $\%S_t$ was associated with both recurrence and death. For every increase of one $\%S_t$ percentage point, the hazard of recurrence during follow-up decreased to 0.893 of its previous value ($p = 0.003$), and the hazard of death decreased to 0.886 of its previous value ($p = 0.006$) (Table 2).

Similar results were found for V_t and recurrence. For every increase of 1 cm^3 in V_t there was an increase in the hazard of recurrence during the follow-up of 1.032 times ($p = 0.006$), while there was no significant association between a V_t increase and the hazard of death (Table 2).

4. Discussion

TNM classification is the best available staging system for OSCC. It is widely available and accepted as an important tool for establishing nomenclature, and it uses robust parameters for prognostic prediction (Pollaers et al., 2018). It allows division into prognostic subgroups and delivery of stage-specific therapies, and it facilitates meaningful discussions between physicians and patients regarding management and expected outcomes (Shah and Gil, 2009). The purpose of the tumor, node, metastasis (TNM) classification system is to facilitate the treatment planning, the prognosis, and the uniform assessment of treatment, results, and research (Shah and Gil, 2009; Kreppel et al., 2013).

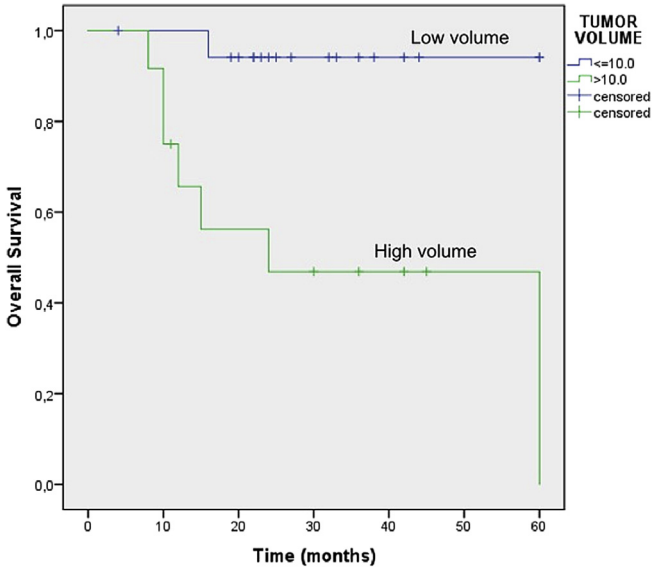

Fig. 4. Kaplan-Meyer curves demonstrating worse overall survival in patients with a V_t value higher than 10.0 cm^3 (0.0% vs 94.1%; $p < 0.01$; log rank test). For larger tumors ($V_t > 10.0$ cm^3) the median survival was 24 months.

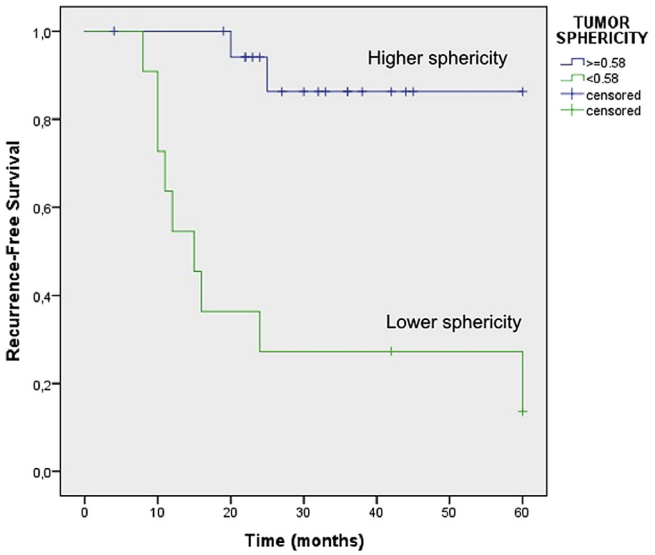

Fig. 5. Kaplan-Meyer curves demonstrating worse recurrence-free survival in patients with an S_t value lower than 0.58 (13.6% vs 86.3%; $p < 0.001$; log rank test). For less spherical tumors ($S_t < 0.58$) the median survival was 15 months.

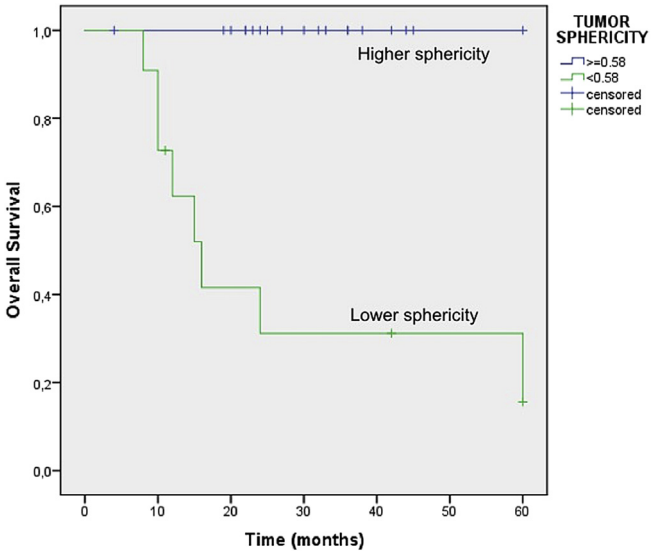

Fig. 6. Kaplan-Meyer curves demonstrating worse overall survival in patients with an S_t value lower than 0.58 (15.6% vs 100.0%; $p < 0.001$; log rank test).

Despite being a user-friendly, universally applicable classification of tumor burden, the TNM system for OSCCs is based on maximum tumor length, which fails to take into account for the overall tridimensional extent of the tumor (Van der Schroeff et al., 2009; Zafereo, 2013). Indeed, small or superficial tumors (T1 or T2 stage) can especially be overestimated by the TNM classification, and would better fit into a classification based on a volumetric evaluation of the tumor size.

In addition, T4 tumors are classified according to their invasion to adjacent structures, which can occur with tumors of varying volumetric extent. However, the literature suggests that infiltration into adjacent structures (i.e. the mandible, the maxilla, or muscle) is not always associated with a worse prognosis (Mücke et al., 2008).

For these reasons, and because it has been shown in this study to be of prognostic value, we believe that the 3D evaluation of tumor size could be considered as an improvement to the present TNM classification.

Table 2
Results of Cox regression analysis for both recurrence and death.

	Recurrence HR	Death HR
Tumor volume (V_t)	1.032 (1.009–1.055) $p = 0.006$ (<0.05)	1.025 (0.996–1.054) $p = 0.088$
Tumor percent sphericity (%S_t)	0.893 (0.830–0.961) $p = 0.003$ (<0.05)	0.886 (0.813–0.966) $p = 0.006$ (<0.05)

HR = hazard ratio.

The measurement of tumor volumes by imaging methods is known to be useful for treatment decision making, and it has been tested successfully for nonsurgical treatment modalities for tumors of the oropharynx and larynx (Mendenhall et al., 2014; Paulino et al., 2005; Rutkowski et al., 2014).

To our knowledge, only a few studies have investigated the value of tumor volume measurement for oral carcinomas in relation to overall survival. Chen et al. found that overall tumor volume influenced the treatment outcomes, with larger tumor volumes being associated with poorer overall survival in a group of patients with pT4a tongue carcinomas (Chen et al., 2011). Mücke et al. reported that tumor volume was significantly associated with overall survival in patients with squamous cell carcinoma of the tongue (Mücke et al., 2015). Lin et al. described the correlation existing between tumor volume and prognosis for patients affected by T4a oral cavity SCCs who had undergone surgical treatment (Lin et al., 2017).

Both the Chen et al. and Mücke et al. studies used an imaging-based tumor volume model to investigate tongue cancer only. Chen identified the tumor volume using preoperative MRI. He enrolled only advanced-stage (pT4a stage) patients, and concluded that volume represented an important prognostic factor, although some procedural limits could be identified (Chen et al., 2011). Mücke performed the tumor volume assessment using preoperative CT-scans on patients affected by tongue cancer tumors of every T-stage (Mücke et al., 2015).

In the study by Lin et al., the volumes of primary cancers were calculated by multiplying three macroscopic dimensions of the surgical specimens, and these were then related to recurrence and death (Lin et al., 2017).

These studies are not comparable in terms of methodology of volume calculation, or the cohort of patients enrolled.

Our study reports the influence of both tumor volume and tumor sphericity as prognostic predictors in patients with OSCCs. Our results are based on a cohort of 30 patients with surgically treated cancer, who underwent CT-scan segmentation for the calculation of both tumor volume and tumor sphericity, according to our new CT-based protocol. A dedicated modular software package was used to convert patients' medical images into 3D digital models. Multislice interpolation and threshold segmentation tools were used to segment the tumor extent tridimensionally. This was then converted into a 3D mesh and exported in STL format for further calculation of tumor volume (V_t) and tumor sphericity (S_t).

Regarding tumor volume cut-offs, Chen suggested that patients with a primary tumor volume above 23 ml had poor prognosis and needed more aggressive treatment (Chen et al., 2011).

Mücke reported that a large tumor volume (above 18.3 cm^3) was associated with a significantly poorer overall survival (Mücke et al., 2015). In a study published by Lin et al., the value used as a cut-off for volume measurement stratification was 33.6 cm^3 (Lin et al., 2017). In our study, cut-off values of 5.8 cm^3 and 10.0 cm^3 were obtained for recurrence-free survival and overall survival, respectively. These data are quite different from those previously discussed. Possible reasons for these differences are: 1) the modality of volume assessment; 2) the characteristics of the enrolled patients (all stages vs only advanced stages).

Regarding the first aspect, the modality of assessment of the tumor volume was very different among the studies discussed. MRI and CT scans can potentially differ in terms of tumor volume segmentation results. Recent studies indicate that the evaluation of edema surrounding the tumor remains difficult, and that MRI may slightly overestimate the tumor size in these cases (Lee et al., 2014; Mortuaire et al., 2017). In the study published by Lin et al., the volumes of primary cancers were calculated by multiplying three macroscopic dimensions of the surgical specimen (Lin et al., 2017). This method is not comparable in terms of measurement accuracy with a CT- or MRI-based method, due to the assessment method itself and tissue shrinkage.

Regarding the second aspect, all the studies discussed considered only advanced-stage tumors and registered high tumor volumes. This aspect significantly influenced the average value of tumor volume cut-offs obtained.

Our study also investigated the prognostic value of tumor sphericity in patients with oral cancer. Results showed that, alongside the standard TNM parameters, an improvement in prognosis can be achieved by assessment of tumor sphericity (S_t), measured on a 3D mesh obtained from CT data. S_t is a novel and very useful parameter for tumors, which are characteristically irregular in shape, as in the case of primary tumors.

This is, to our knowledge, the first such report in the existing literature regarding oral cancer patients.

Only two studies published in head and neck literature have reported the value of sphericity in patients who underwent FDG PET. They concluded that sphericity of pre-therapeutic FDG uptake in the primary tumor provides independent and significant prognostic information in patients with head and neck cancer (Hofheinz et al., 2015; Apostolova et al., 2014).

The rationale for defining this new parameter, sphericity (S_t), is that prominent intratumoral spatial variations in cellularity, pattern of invasion, and tumor–host interface are expected to result from the irregularity of the 3D shape of the external surface of the tumor itself. Geometrically, these shape irregularities increase the surface area-to-volume ratio of the tumor.

The study has some limitations. Firstly, it was of retrospective design, so there may have been a selection bias. Secondly, our study involved a small number of patients. Finally, some errors in estimating tumor volume may have occurred due to inaccuracy of segmentation.

5. Conclusion

In conclusion, our prognostic model based on a tridimensional CT characterization of tumor size, which includes both tumor volume and tumor sphericity, provides readily available information that could be complementary to the existing staging system, and a useful tool when formulating a prognosis for patients with oral cancer.

Validation of our proposed method and cut-off values is required in future studies, by enrolling a larger number of patients affected by OSCC.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcms.2018.12.019.

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