Is there a role for tumor volume in prediction of prognosis for oral cancer?

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ABSTRACT

Purpose: New prognostic factors in oral squamous cell carcinoma (OSCC) (tumor-, host-, and environment-related) have been introduced recently to complete those traditionally considered. Among them, tumor volume (TV) could be the most interesting and applicable in clinical practice, considering the routine use of computed tomography in tumor staging. In this retrospective study we aimed to investigate whether a correlation exists among these new prognostic factors and survival outcomes.
Meterials and methods: We collected data about 140 patients affected by OSCC who underwent primary surgery. Prognostic factors were collected and Overall Survival (OS), Disease Specific Survival (DSS) and Disease Free Survival (DFS) were estimated using Kaplan-Meier method; the Log-Rank test (Mantel-Cox) and Cox regression models were applied to investigate predictors of survival.
Results: The 5-year OS, DSS and DFS were 73.6 %, 89.2 % and 75.2 % respectively. Nodal metastasis (pN+), relapse and American Society of Anesthesiologists ASA-II were found independent prognostic factors for OS, and significantly associated to worst DSS ($p < 0.001$). TV significantly correlated with higher relapse occurrence ($p = 0.03$).
Conclusions: In our experience, lymph-node status, ASA classification and relapse significantly influenced DSS on univariate analysis. TV could represent an interesting additional parameter, since it significantly influenced DFS. However, prospective studies with standardized TV measurements and a greater number of patients are needed to validate this result.

1. Introduction

Oral cancer is the seventh most common human neoplasia [1], with a worldwide estimated incidence of 275,000 new cases per year: 90 % of all cases are oral squamous cell carcinoma (OSCC) [2].

Despite the developments in diagnosis and treatment, these tumors are still characterized by a poor prognosis, with a 5-year survival rate around 50 % [2]. This could be influenced by the lack of clarity in factors affecting OSCC prognosis.

Many different prognostic factors have been considered so far, with the aim of identifying which potential parameters could influence patients' overall survival (OS) and disease specific survival (DSS) [3].

In particular, the stage of tumor (T) is a controversial prognostic factor because it represents a dimensional parameter for which exophytic tumors have been classified as advanced, even though there was not a parallel infiltrative growth. For this reason, the histopathologic parameters depth of invasion (DOI) for tumors, and extra capsular extension (ECE) for lymph node, that resulted inversely related to survival, have been added to the 8th edition of the tumor staging [4]. This has, however, been reported to be an imperfect prognostic indicator [5,6] with clinicians requiring new diagnostic tools to help them tailor management to the individual patient's needs.[5].

The *Union for International Cancer Control* (UICC) [7] has recently integrated the conventional prognostic factors (tumor –T- and node —N— category, extra capsular extension (ECE) and surgical resection margin) with other uncommon variables, categorized into host-related,

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Table 1
Classification of prognostic factors in OSCC according to the 9th edition of the UICC Manual.

Prognostic factors	Tumor related	Host related	Environment related
Essential	T category N category Extra capsular extension (ECE) Surgical resection margin	Performance status Tobacco/ alcohol/betel	Dose of chemoradiotherapy
Additional	Tumor volume Hypoxia	Age Comorbidity	Overall treatment time/ radiation treatment time Interval from surgery to start of postoperative radiotherapy
New and promising	EGFR mutation TP53 mutation Bcl-2 ERCC1	Swallowing-related quality of life Global quality of life	

tumor-related and environment-related factors distinguishing them into essential, additional and new-promising factors (Table 1), introducing among them the evaluation of tumor volume (TV). There is an increasing evidence in the literature [8] that supports the role of TV as a prognostic marker in the glottis, supraglottis, hypopharynx and nasopharynx while, concerning oropharynx, primary TV was not predictor of OS, and it may not be used as prognostic factor in this type of tumor. In OSCC, TV is routinely calculated in patients undergoing radiotherapy (RT): Janmunee et al. [9] showed that TV had an influence on the overall survival of locally advanced oral cancer (67 patients treated with concurrent chemoradiotherapy). Conversely, evidences regarding TV role in surgery are rare [10–12].

Furthermore, the evaluation of preoperative volume can be challenging and is not so standardized. Tarsitano et al. [13] used a 3D digital model to obtain TV and showed that it was larger in patients with tumor recurrence than in patients who were disease free.

Traditionally, the role of essential OSCC's prognostic factors has been investigated. Recently, Kuznetsov et al. [14] have analyzed the association between radiographic TV in OSCC and tumor stages, margins status, chemo/radiation use and recurrence in a small sample size, but none have considered both conventional and new prognostic factors globally. This consideration led us to investigate whether a correlation exists among TV together with prognostic parameters globally and 5-years survival outcomes.

Therefore, the aim of this study was to analyze if TV could be added to classic prognostic factors affecting overall, disease-specific and disease-free survivals to address clinicians in the preoperative prognostication and therapeutic decision making.

2. Materials and methods

In this retrospective cohort study, we collected data about 140 patients affected by OSCC who underwent primary surgery carried out by the same medical team from January 2008 to December 2015.

Exclusion criteria were: RT as first choice treatment, histologic type other than OSCC, advanced disease staged as unresectable or unfit for surgery according to the most recent international guidelines [15]. Patients gave their consent for the anonymous use of their data. The study protocol was approved by the University Ethics Committee on Clinical Investigation (N.89/2018) in compliance with the Helsinki Declaration.

Tumor-, host- and environment- related factors were collected.

2.1. Tumor-related factors

The 8th edition of TNM staging system accordingly to NCCN guidelines 2019, was used to define clinical (cTNM) and pathological (pTNM) staging [15]. The histopathological specimens were re-evaluated by a single pathologist, to measure DOI and verify the presence of ECE in those cases where that data was lacking. The pathologic staging of primary tumor was considered as a binary variable and divided as follows: early T (pT1 and pT2) and advanced T (pT3 and pT4); analogously, pathologic nodes staging was classified as pN0 and pN+ (that includes pN1, pN2 and pN3).

According to NCCN guidelines, surgical margins were considered "free" when histopathological examination showed at least 5 mm of healthy tissue between the invasive tumor front and the surgical margin, "infiltrated" and "close" in our study, were unified into the same category, re-called as "positive".

To complete tumor related factors, we collected the presence of relapse (local or loco-regional) as follow up data.

Tumor volume (TV) was estimated using pre-operative computed tomography (CT) scan applying cuboid ($V = abc$) and ellipsoid ($V = abc\pi/6$) formulae [16,17].

2.2. Host-related factors

Tobacco and alcohol consumption were considered together as the presence or absence of exposure.

Age was considered a binary variable with a cutoff point of 65 years.

To conjugate performance status evaluation and comorbidities as unique prognostic factor, we adopted the *American Society of Anesthesiologists* (ASA) - *Physical Status Classification System*.

2.3. Environment-related factors

According to NCCN guidelines, adjuvant RT or chemo-radiotherapy (CRT) were indicated in case of advanced primary tumor, positive surgical margins, ECE, pN2–3, nodal disease in level IV or V, perineural, vascular and lymphatic invasions [15].

Specifically, adjuvant RT dosage was 60Gy, divided into 30 fractions of 2Gy each. Standard chemotherapy (CT) was performed using cisplatinum 100 mg/mq g1° q 21 × 3 cycles [15].

In our cohort, we analyzed overall survival (OS), disease specific survival (DSS) and disease free survival (DFS).

2.4. Statistical analysis

A descriptive analysis was performed on age, gender, tumor characteristics, surgical therapy, adjuvant therapy and recurrences rate. Continuous variables are expressed as mean and standard deviation or median (range: min-max) according to data distribution.

Outcome definitions were based on the time elapsed from the date of surgery to the date of the event of interest (death for OSCC for DSS, death for all causes for OS, and recurrence for DFS) or censored on the date of the last follow-up. Patients who did not have any event, have been censored at the end of the follow-up period, updated to May 31st, 2020. The median follow-up (reported with interquartile range) was computed for censored patients, excluding patients with the events of interest (reverse Kaplan-Meier method).

OS, DSS and DFS were estimated using Kaplan-Meier method, and the Log-Rank test (Mantel-Cox) was used to compare differences in OS, DSS and DFS in relation to the variables considered in this study. Cox regression models were applied to investigate the main independent predictors of survival and results were expressed as hazard ratios (HRs) with their 95 % confidence intervals (CIs). All of the variables subjected to univariate analysis with a p-value <0.10 were entered as covariates into multivariate analysis (applied only to OS and DFS and not to DSS due to the low number of events).

Table 2
Distribution of demographic, tumor characteristics, data regarding surgical therapy, adjuvant therapy and follow-up in this sample.

Sex	
Male	86 (61.4%)
Female	54 (38.6%)
Age	
Mean, SD, range	65±11 (35-92)
<65	61 (43.6%)
≥ 65	79 (56.4%)
Death	62 (44.2%)
Neoplastic disease	17 (12.1%)
Other cause	45 (32.1%)
Tobacco and alcohol	
Yes	83 (59.3%)
No	20 (14.3%)
Not available	37 (26.4%)
ASA[a] Physical Status Classification System	
ASA I	19 (13.6%)
ASA II	83 (59.3%)
ASA III	38 (27.1%)
Tumor subsite	
Alveolar ridge	1 (0.7%)
Lip	5 (3.6%)
Tongue	57 (40.7%)
Buccal mucosa	14 (10%)
Floor of mouth	40 (28.6%)
Hard palate	7 (5%)
Retromolar trigone	16 (11.4%)
pathological tumor staging (pT)[b]	
pT1	48 (34.3%) } Early 85 (60.7%)
pT2	37 (26.4%) }
pT3	42 (30%) } Advanced 55 (39.3%)
pT4	13 (9.3%) }
Depth of Invasion	
<5mm	76 (54.3%)
5-10mm	26 (18.6%)
>10mm	38 (27.1%)
Tumor volume ellipsoid	
Median, range	1.86cm^3 (0.05 – 40.96cm^3)
Tumor volume cuboid	
Median, range	3.55cm^3 (0.1 – 78.26cm^3)
pathological node staging (pN)[b]	
pN0	104 (74.3%)
pN1	11 (7.9%)
pN2	13 (9.3%) } N+ 36 (25.7%)
pN3	12 (8.5%)
Local relapse within 5 years	
Yes	37 (26.4%)
No	103 (74.6%)
Surgical approach	
Trans-oral	93 (66.4%)
Trans-mandibular	44 (31.4%)
Pull-trough	3 (2.2%)
Mandibulectomy	
No	108 (77.2%)
Marginal	16 (11.4%)
Segmental	16 (11.4%)
Reconstruction	
Direct closure/local flap	65 (46.4%)
Graft	13 (9.3%)
Flap	62 (44.3%)
- Free	31
- Pedicle	31
Neck dissection	
No	34 (24.3%)
Unilateral	79 (56.4%)
Bilateral	27 (19.3%)
Extra Capsular Extension	
Yes	14 (10%)
No	126 (90%)
Surgical margins	
Negative	119 (85%)
Positive	21 (15%)
Adjuvant treatment	
Yes	38 (27.1%)
No	102 (72.9%)
Overall treatment time (OTT)	
Median, range whole sample	22.5 days (1 – 193)
Median, range exclusive surgical therapy	12 days (1 – 105)
Median, range combined therapy (surgery + adjuvant)	96.5 days (53 – 193)
Interval from surgery and start of postoperative radiotherapy (38 patients undergone to adjuvant treatment)	
Median, range	55.5 days (14 – 142)
Radiation treatment time (38 patients undergone to adjuvant treatment)	
Median, range	41.5 days (7 – 57)

[a]ASA American Society of Anaesthesiologists.
[b]Tumor (pT) and nodes (pN) pathological staging according the 8th ed. as reported in NCCN 2019 guidelines.

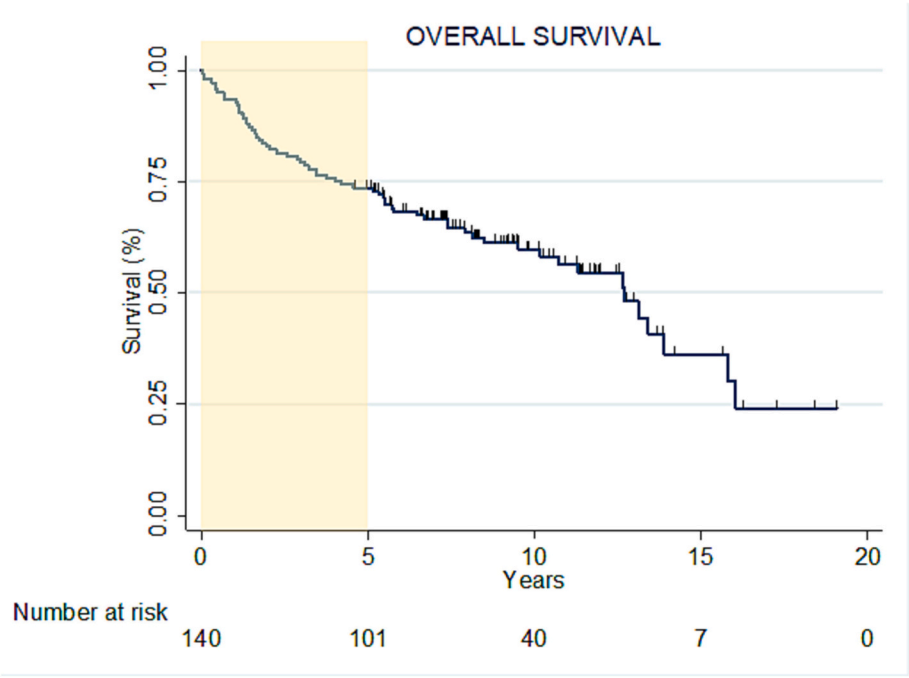

Fig. 1. Kaplan-Meier plots showing overall survival (OS) of the entire cohort: the observation period of 5-years is highlighted in light yellow. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

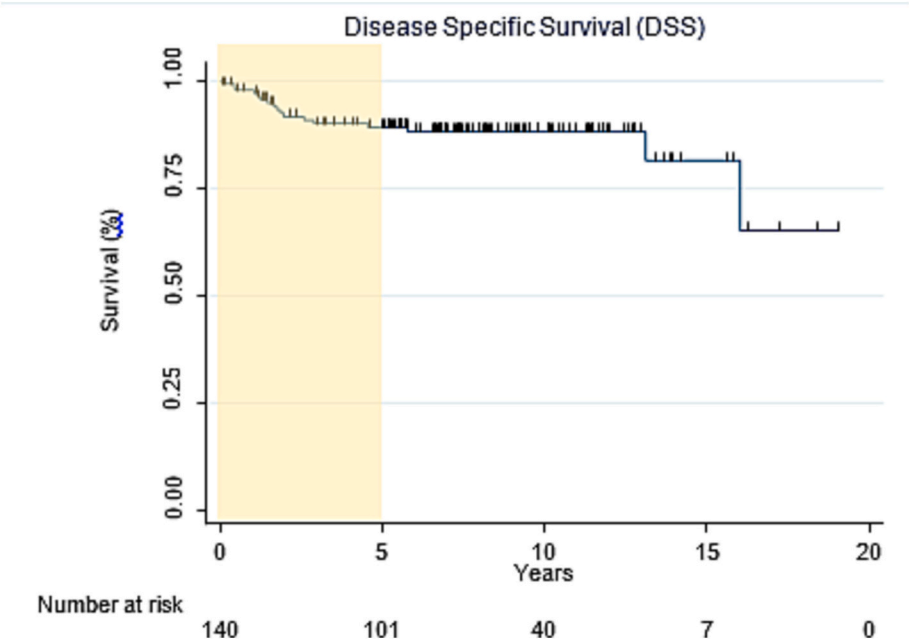

Fig. 2. Kaplan-Meier plots showing disease-specific survival (DSS) of the entire cohort: the observation period of 5-years is highlighted in light yellow. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Statistical analysis was performed using the software R (the R Foundation for Statistical Computing; Version 4.0.0). All *p*-values were calculated from 2-sided tests using 0.05 as the significance level.

3. Results

A total of 140 patients treated for OSCC met the inclusion criteria and were considered in the statistical analysis; data about tumor volume were available in 110 patients, in that 30 patients (21.4 %) performed imaging elsewhere, thus TV could not be calculated.

Table 2 reports the distribution of demographic, tumor characteristics and data about surgical therapy, adjuvant treatment and follow-up.

The 5 year OS was 73.6 % (95 % CI: 65.4 %–80.1 %) (Fig. 1), the 5 years DSS was 89.2 % (95 % CI: 82.40 %–93.40 %) (Fig. 2), and the 5 years DFS was 75.2 % (95 % CI: 66.70 %–81.80 %) (Fig. 3). Median follow-up was 7.23 [4.87–10.27] years: during this observation period, a total of 62 deaths occurred, of which 17 due to oral cancer, while local relapses occurred in 37 cases.

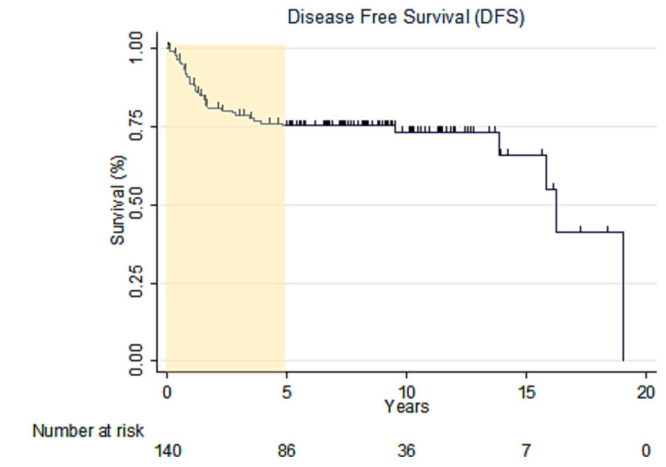

Fig. 3. Kaplan-Meier plots showing disease-free survival (DFS) of the entire cohort: the observation period of 5-years is highlighted in light yellow. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

As reported in Table 3, in the univariate analysis we noted that age ≥ 65, tumor staging (pT early/advanced), nodal involvement (pN+) and relapse occurrence resulted associated to a higher risk of death for all causes (OS). ASA Score II resulted as a protective factor compared to ASA I. As result of the multivariate analysis, nodal involvement (pN+), relapse and ASA II were found independent prognostic factors for OS.

According to the univariate analysis, these parameters significantly affected also DSS, as reported in Table 4. The variables positive surgical margins and TV (calculated with both cuboid and ellipsoid formulae), resulted just over the limits of statistical significance ($p = 0.06$) in univariate analysis for DSS (see Table 4). Due to the paucity of events, meaning death for disease ($N = 17$), we cannot proceed with the multivariate analysis for DSS.

Since the relapse occurrence in our cohort significantly affected both OS and DSS, we conducted univariate and multivariate analysis for prognostic factors of DFS (see Table 4). In our sample, 37 (26,4 %) patients suffered a local relapse, of whom 26 (70.3 %) died: 14 (53.8 %) from cancer, and 12 (46.2 %) from other causes. The univariate analysis showed that no prognostic factors significantly affected DFS; multivariate model was performed including parameters assessed in the univariate analysis with a p value of less than the cut-off of 0.10 and adjusted for age. Since both ellipsoid and cuboid volumes were highly

Table 3
Univariate and multivariate Cox regression analysis regarding prognostic factors for OS. Multivariable model was performed including parameters assessed in the univariable analysis with a p value of less than the cut-off of 0.10.

	Univariate Cox regression		Multivariate Cox regression	
	HR (95 % CI)	p-Value	HR (95 % CI)	p-Value
Sex				
F	1.00 (Reference)			
M	1.12 (0.67–1.90)	0.66		
Age				
<65	1.00 (Reference)			
≥65	2.16 (1.25–3.74)	0.006	1.62 (0.91–2.88)	0.10
pT[aa]				
Early	1.00 (Reference)			
Advanced	1.84(1.11–3.04)	0.02	1.28 (0.68–2.40)	0.44
pN[bb]				
N0	1.00 (Reference)			
N+	2.82 (1.68–4.75)	<0.001	2.98 (1.58–5.62)	<0.001
Extra capsular extension				
No	1.00 (Reference)			
Yes	1.65 (0.78–3.45)	0.192		
Surgical margins				
Negative	1.00 (Reference)			
Positive	1.46 (0.76–2.81)	0.2538		
ASA[c] classification				
I	1.00 (Reference)			
II	0.28 (0.14–0.51)	<0.001	0.24 (0.12–0.49)	<0.001
III	0.83 (0.44–1.57)	0.57	0.65 (0.33–1.30)	0.28
Adjuvant therapy				
No	1.00 (Reference)			
Yes	1.10 (0.63–1.93)	0.2352		
Volume ellipsoid (30 data missing)	1.01 (0.97–1.05)	0.57		
Volume cuboid (30 data missing)	1.00 (0.99–1.00)	0.566		
Relapse				
No	1.00 (Reference)			
Yes	2.21 (1.32–3.68)	0.002	2.23 (1.33–3.75)	0.002
Overall treatment time (38 cases treated with RT)				
<100 days	Reference			
≥100 days	0.81 (0.30–2.17)	0.67		
Alcohol and tobacco exposure				
No	1.00			
Yes	0.81 (0.35–1.87)	0.62		
Radiation treatment time (38 cases treated with RT)	0.96 (0.92–1.01)	0.10		
Interval from surgery and start of postoperative radiotherapy (38 cases treated with RT)	1.00 (0.98–1.02)	0.83		

[a] Early tumor (pT1 and pT2), advanced tumor (pT3 and pT4): pathological staging according the 8th ed. as reported in NCCN 2019 guidelines.
[b] N+ includes pN1, pN2 and pN3: pathological staging according the 8th ed. as reported in NCCN 2019 guidelines.
[c] ASA American Society of Anaesthesiologists.

Table 4
Univariate Cox regression analysis regarding prognostic factors for DSS and univariate and multivariate Cox regression analysis regarding prognostic factors for DFS. Multivariable model was performed including parameters assessed in the univariable analysis with a p value of less than the cut-off of 0.10 and adjusted for age.

	Univariate Cox Regression DSS		Univariate Cox Regression DFS		Multivariate Cox Regression DFS	
	HR (95 % CI)	p-Value	HR (95 % CI)	p-Value	HR (95 % CI)	p-Value
Sex						
F	1.00 (Reference)		1.00 (Reference)			
M	1.55 (0.54–4.45)	0.41	1.35 (0.68–2.69)	0.39		
Age						
<65	1.00 (Reference)		1.00 (Reference)			
≥65	0.83 (0.32–2.19)	0.71	1.43 (0.74–2.72)	0.29		
pT						
Early	1.00 (Reference)		1.00(Reference)			
Advanced	1.53 (0.58–3.75)	0.3887	0.94 (0.48–1.85)	0.86		
pN						
N0	1.00 (Reference)		1.00 (Reference)			
N+	5.32 (1.96–14.46)	0.001	1.63 (0.81–3.32)	0.17		
Extra capsular extension						
No	1.00 (Reference)		1.00 (Reference)			
Yes	2.58 (0.73–9.14)	0.142	0.92 (0.28–3.00)	0.89		
Surgical margins						
Negative	1.00 (Reference)		1.00 (Reference)		2.10	
Positive	2.72 (0.96–7.76)	0.06	1.99 (0.91–4.35)	0.08	(0.95–4.60)	0.06
ASA[a] classification						
I	1.00 (Reference)		1.00 (Reference)			
II	0.10 (0.03–0.35)	<0.001	0.60 (0.24–1.50)	0.27		
III	0.39 (0.13–1.19)	0.10	0.94 (0.35–2.50)	0.90		
Adjuvant therapy						
No	1.00 (Reference)		1.00 (Reference)			
Yes	1.59 (0.58–4.30)	0.36	1.21 (0.60–2.45)	0.59		
Volume ellipsoid (30 data missing)	1.05 (0.99–1.00)	0.06	1.02 (0.99–1.04)	0.09	1.05 (1.01–1.10)	0.03
Volume cuboid (30 data missing)	1.00 (0.99–1.00)	0.06	1.04 (0.99–1.08)	0.09		
Relapse						
No	1.00 (Reference)		–	–		
Yes	13.41 (3.84–46.87)	<0.001				
Overall treatment time (38 cases treated with RT)						
<100 days	1.00 (Reference)		Reference			
≥100 days	1.04 (0.21–5.17)	0.96	0.86 (0.26–2.81)	0.80		
Alcohol and tobacco exposure						
No	1.00	0.23	1.00	0.98		
Yes	Non calculable[b]		0.99 (0.38–2.60)			
Radiation treatment time (38 cases treated with RT)	0.96 (0.90–1.03)	0.30	0.98 (0.92–1.04)	0.50		
Interval from surgery and start of postoperative radiotherapy (38 cases treated with RT)	1.00 (0.97–1.03)	0.85	0.98 (0.96–1.01)	0.23		

[a] ASA American Society of Anaesthesiologists.
[b] Including all patients who had the event.

correlated, to correct collinearity, only the ellipsoid one was included in multivariate model. Multivariate analysis showed that TV significantly correlates with higher relapse occurrence ($p = 0.03$), while positive surgical margins shows only a trend toward significance ($p = 0.06$).

The majority of patients (66.4 %) underwent transoral approach with margin mapping system and intraoperative frozen sections, allowing to obtain 85 % negative margins. Among the 21 patients (15 %) with positive margins, 38 % had a loco-regional recurrence; conversely in those who had microscopically negative margins, the percentage of recurrence was lower (24,4 %).

Although it was not significant (p-value = 0.23), patients not exposed to tobacco nor alcohol had 100 % DSS.

In our cohort, 38 patients (27.1 %) underwent adjuvant RT or CRT; only one had to stop the treatments because of acute toxicity.

4. Discussion

Clinicians have already attempted to identify predictive factors to stratify the prognosis of OSCC; histological and biological features have been studied alongside the classic factors related to cancer, patient and treatment [5].

In our experience, from multivariate analysis for OS and univariate analysis of DSS, pN stage together with ASA classification (the system we used to combine performance status evaluation and comorbidities) resulted the two most consistent independent predictors of outcome for OSCC treated with primary surgery and appropriate adjuvant therapy. Moreover, the recurrences negatively affected both OS and DSS, thus we investigated the parameters in relation to the risk of recurrence (DFS). The multivariate analysis showed that TV was an independent prognostic factor affecting DFS ($p = 0.03$), while surgical margins showed only a trend toward significance ($p = 0.06$).

What emerges is that the pN+ stage significantly affected both OS and DSS. This result is widely supported in literature [3,4]: as early as 1981 Johnson et al. [18] introduced the role of ECE on patients' survival and recently Matos [19] and Tirelli [4] have confirmed the negative impact of lymph node involvement on prognosis, even after the introduction of ECE in the staging criteria. Otherwise, ECE alone did not result an independent prognostic factor, probably due to the paucity of the event in our sample (10 %).

A still controversial parameter remains the T stage: the univariate analysis showed that advanced pT was related to a worse OS but did not significantly increase the occurrence of cancer-related death (DSS). This

result is hardly surprising, giving that although it may be intuitive that as tumor stage increases, TV increases accordingly, the stage of T is a dimensional parameter that might not perfectly reflect the biological behavior of the tumor that is better revealed by the N stage. Therefore, tumor infiltration and depth of invasion, which also implies a greater risk of nodal metastasis [20] clearly appears to be an important prognostic factor, more than the superficial extension of the neoplasm [4]. For these reasons, DOI and ECE have been added in the clinical and pathological classifications of T and N respectively.

We agree with Kuznetsov et al. [14] that stated despite DOI has been incorporated as a variable determining T stage, a 3-dimensional analysis as TV evaluation would integrate T staging system, improving the prognostication ability.

Tarsitano et al. [13] investigated in a small number of patients the value of TV measurement and sphericity for oral carcinomas in relation to OS and DFS, confirming they both could be considered when formulating prognoses for patients with oral cancer.

In our experience TV represents an interesting "additional" prognostic factor [7] that resulted significantly related to DFS ($p = 0.03$) and at the limits of significance for DSS ($p = 0.06$). This measurement has not been standardized and it can be calculated using slice-by-slice segmentation volumetry, or approximated considering maximum diameters (a, b, c) assessed in antero-posterior, cranio-caudal and latero-lateral directions on preoperative CT scans, applying the cuboid ($V = abc$) or the ellipsoid ($V = abc\pi/6$) formulae, respectively [16,17]. Differences between these three methods of calculating TV have been investigated in 2015 by Dejaco et al. [16] and they concluded that, by comparison with slice-by-slice segmentation considered the most accurate, ellipsoid approximation underestimates the volume by −8 %, whereas the cuboid approximation overestimates it up to +50 %.

Considering the paucity of studies analyzing the differences among alternative measurements, we estimated TV considering the three maximum diameters, detected by a specialized radiologist on CT scans, and applying both cuboid and ellipsoid formulae.

Usually, TV is routinely calculated in patients undergoing RT because the greater the TV, the greater the RT-dose required. Classification of tumors according to the volume cannot replace TNM staging in daily practice, but it can guide planning the ideal dose for individual patients [21–23].

On the other hand, evidences regarding TV role in surgery are rare: Joo et al. [10] found that a volume >20 mL jeopardized DSS and implied a higher risk of nodal involvement confirming that an increase in oral cancer volume was associated with a worse survival [24,25]. Dejaco et al. [26] described that increase of 1 mL tumor volume corresponds to 1.4 % risk of death over. Thus, TV assessment might represent an interesting additional prognostic factor that has the major limitations represented by the lack of a uniform measurement method: the evaluation is commonly based on tumor thickness and not on DOI, although the latter is a more accurate measurement that relates to patients' prognosis. Piazza et al. [27] reported the prediction of preoperative DOI by imaging but this method required a universally adopted protocol avoiding potential bias for high inter-operator variability, as Locatello et al. reported [28].

Another factor still under discussion remains the value of surgical margins status on survival.

In our cohort, the univariate analysis did not point out a significant association between surgical margins and OS, while the correlation with DSS and DFS was at limits of significance ($p = 0.06$); however, we noted a lower incidence of recurrence (24.4 % vs 38 %) in patients with negative margins. We would underline that, following the transoral mini-invasive surgery, the removal of the tumor is performed with a piecemeal resection and the presence of positive margins is expected to be more frequent than adopting an en-bloc resection. However, the intraoperative margin mapping by using frozen sections allows a real time assessment of resection margins, with the possibility of immediate surgical enlargement, and finally negative margins [29,30]. This result has been verified in our cohort with 66.4 % of transoral resection and 85 % of negative surgical margins.

Moreover, the development of mini-invasive transoral surgical technique showed a radical treatment using a more conservative approach, even in more advanced stages [31].

Concerning host-related factors, patients included in ASA II category had an unexpected better OS and DSS compared to ASA I, probably due to a non-homogeneous distribution of patients affected by early or advanced stage tumor between ASA I and II categories. Since our study is retrospective, we had 26.4 % missing data about tobacco and alcohol consumption. Considering this limit, exposure to tobacco or alcohol did not shown a significant influence on OS, nor on DSS and DFS, differently from expected [32,33]. However, we noted a trend because patients who were not exposed to tobacco nor alcohol had 100 % DSS.

Experiencing a recurrence within the first 5 years after primary treatment is a well-known negative factor [24,25,34] that in our cohort affected OS and DSS. The multivariate analysis of DFS, highlighted that the independent prognostic factors that significantly affected the relapse in our cohort was the TV. Recurrence rate for OSCC ranges between 13 % and 30 % [35] and, accordingly, in our sample was 26 %. It is plausible to suppose that patients who suffered a relapse, had a highly aggressive primary tumor; however, neoplastic characterization in clinical practice is usually defined by macroscopic, histologic and cytological criteria, which allow clinicians to partially identify subjects with a more aggressive tumor and, therefore, a higher risk of recurrence. In future prospective, we could consider the expression of some biomarkers as new and promising tumor related factors, such as EGFR or TP53 mutations, Bcl-2 and ERCC1expressions.

The main limitations of this study are the retrospective design and the missing data on tumor volume for the 30 patients who underwent radiologic imaging elsewhere; we could not proceed with the multivariate analysis for DSS due to the paucity of events. A standardization on TV measurement is still lacking, nevertheless we try to overcome this inconvenience using both available mathematic formulae (cuboid and ellipsoid) and we found no great difference between the two results. On the other hand, the strengths of this work are the prolonged follow-up on a medium-large cohort of patients, the standardized treatments performed by the same staff, and the analyses made by a single pathologist and a single radiologist to align the interpretations.

In our opinion, TV could represent an interesting prognostic factor among new emergent features with the following issues that remain to be addressed: how should we measure it in a standard way and which kind of relationship exists between TV and DOI.

5. Conclusions

In our experience, lymph node status, ASA classification and relapse significantly influenced DSS on univariate analysis. The newly introduced TV could represent an interesting additional parameter in the global prognostic stratification, since it significantly influenced DFS. However, prospective studies with standardized TV measurements and a greater number of patients are needed to validate this result.

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Declaration of competing interest

None.

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