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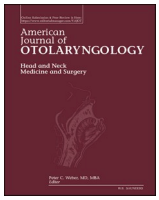

Impact of time-to-surgery on survival and quality of life in oral cancer

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ABSTRACT

Purpose: To investigate the association between time-to-surgery (TTS) and overall survival (OS), disease specific survival (DSS) and quality of life (QoL) in patients with oral squamous cell carcinoma (OSCC).
Materials and methods: 116 patients with OSCC candidate to surgery were examined. TTS intervals starting from diagnosis (*TTS-clinical-based*) and from histological reports (*TTS-biopsy-based*) were calculated. The effects of TTS intervals and prognostic factors on 5-year OS and DSS were explored.
Results: In our cohort advanced T-categories OSCCs with TTS < 30 days showed a trend to have higher DSS rate ($p = 0.049$). Patients with *TTS-clinical-based* < 30 days showed better postoperative QoL. Positive surgical margins, nodal involvement (pN+), DOI >10 mm, invasive surgery and extra-capsular extension in pN+ were found to be significantly associated with a poor OS and DSS.
Conclusions: TTS ≥ 30 days can adversely affect DSS, especially in the advanced T categories. Short TTS intervals resulted associated with a better postoperative QoL.

1. Introduction

Despite significant progress in research and treatment, oral squamous cell carcinoma (OSCC) is still a highly aggressive tumour with a 5-year overall survival (OS) rate of approximately 50 % [1].

Among disease-unrelated factors that may negatively influence the survival of cancer patients and may be at least partially the cause for these disappointing results, the time to treatment initiation (TTI) has been advocated by several researchers [1–3]. The complexity of the OSCC population, the high prevalence of frailty and comorbidities, the increasing complexity of modern diagnostic procedures and multimodal treatment strategies, as well as waiting lists for radiotherapy have been counted among the possible causes of treatment delay [4,5].

TTI has been generically defined as "time between diagnosis and the start of definitive treatment" but there is a lack of consensus on the definition of diagnosis in this context, e.g. clinical-based versus biopsy-based diagnosis.

Some authors [2,6] reported extensive analysis based on national cancer database showing that a longer TTI, independently of treatment platform, negatively impact on OS in patients with head and neck squamous cell carcinomas (HNSCCs) [7,8]. Although these data show the damaging effect of delayed treatment on patients' outcome, some authors highlighted the need to separately analyse the prognostic impact of the different primary treatments (upfront surgery and upfront (chemo)-radiotherapy) and adjuvant treatment (post-operative (chemo)-radiotherapy) [8].

In HNSCC, *Tumour Volume Doubling Time* (TVD) has been estimated to be around 90 days, with differences according to subsites and histology [9]. There is, therefore, a rising need to separately consider head and neck subsites because of different speed of growth and biological behaviour of tumours [6–8,10]. Additionally, it is important to include in the outcome evaluation both the OS and the disease specific survival (DSS) to more precisely weigh the impact of cancer on mortality.

Since current pandemic events have led to delays in surgical care of oncologic patients [6], clinicians are wondering about how long can surgery be postponed and when delay becomes significant for patient survival.

Therefore, surgically treated OSCC were retrospectively analysed to calculate two different time-to-surgery (TTS) measurements: one based on clinical diagnosis time ("*TTS-clinical-based*") and the second based on biopsy diagnosis time ("*TTS-biopsy-based*"), aiming to investigate their impact on OS and DSS. Finally, the association between TTS intervals and postoperative Quality of Life (QoL) has been tested.

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2. Material and methods

2.1. Patient selection

This is a retrospective cohort study on patients who underwent up-front surgery for OSCC at the Clinic of Otolaryngology at the XXX Hospital (University of XXX, XXX).

Inclusion criteria were: age ≥ 18 years, histological diagnosis of OSCC, and a minimum follow-up of 5 years Exclusion criteria were: non-squamous histology, tumour site different from oral cavity, lip cancer, presence of distant metastases, pre-operative (chemo)-radiotherapy, incomplete anamnestic data.

2.2. Data collection

Data were anonymously collected, after obtaining the patients' informed consent and in full compliance with ethical values and Italian privacy law (Law Decree n.196/2003).

We collected prognostic factors divided into four categories:

1. Patient-related data: sex and age, considered as a binary variable with a cut-off of 65 years;
2. Tumour-related data: oral subsites and tumour classification. We adopted the 8th edition of the pTNM stage system by the American Joint Committee on Cancer. The different subsites were grouped into two categories, "tongue" and "other oral cavity subsites" to reduce data spread.
3. Treatment-related data: surgical approach, neck dissection, use of microvascular flap, adjuvant (chemo)-radiotherapy, if any.
4. Histology-related data: grading, presence of vascular, lymphatic or perineural invasion; depth of invasion (DOI), microscopic status of surgical margins, and extra nodal extension (ENE).

Two different TTS have been calculated: "*TTS-clinical-based*" is the interval between the date of clinical diagnosis and surgery; while "*TTS-biopsy-based*" started from the date of histological diagnosis; for each measurement, the impact on 5-years OS, DSS and QoL was analysed. According to literature [2–4], TTS was firstly divided into two groups with a cut-off of 30 days, and then it was categorized into four groups: <30 days, from 30 to 44 days, from 45 to 89 days, ≥90 days. Upstaging from clinical-to-pathological classification for T and N categories was calculated.

2.3. QoL assessment

The QoL was evaluated using the University of Washington Quality of Life Questionnaire [10] that patients routinely complete 12 months after surgery. This specific questionnaire is composed of 12 questions, each of them with between 3 and 6 possible responses. The final score is between 0 and 100. The 12 questions are about pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder, taste, saliva, mood and anxiety. Furthermore, there are 4 global questions that investigate overall QoL considering not only physical and mental health, but also other social factors. The final score is a percentage as result of a weighted average. Score 0 represents the worst QoL and 100 the best.

2.4. Statistical analysis

OS and DSS were estimated using Kaplan-Meier method, and the Log-Rank test (Mantel-Cox) was used to compare differences in OS and DSS in relation to the variables considered in this study. Cox regression models were applied to investigate the main predictors of survival and results were expressed as hazard ratios (HRs) with their 95 % confidence intervals (CIs). 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 and analysis

116 patients (44 women and 72 men) affected by OSCC who were surgically treated between 2008 and 2015 and met the inclusion criteria, were identified and included in the study. The mean age at diagnosis was 64 years (range 35–85). Tables 1 and 2 show tumour- and treatment-/histology-related data, respectively. We observed 10 (8.6 %) cases of clinical-to-pathologic upstaging for T and 11 (9.4 %) for N; the re-distribution of categories is presented in Supplementary Table.

3.1. TTS distribution

The medians [interquartile range] of the *TTS-clinical-based* and *TTS-biopsy-based* were 28.5 [20.8–41.3] and 26.0 days [19.0–36.5], respectively.

In our cohort we found 4 patients with TTS longer than 90 days: two cases had comorbidities (one suffered from acute pneumonia and the other had a femur fracture) requiring specific treatment; one patient was skeptical about surgery and needed more time to get a second opinion in a different hospital; one patient was a foreigner who returned to his country of origin between the first clinical evaluation and surgery.

Since TTS was >90 days only in these 4 cases, we modified the

Table 1
Tumour-related data. Subsites were re-grouped into two categories "tongue" and "oral cavity" and stages were categorized in two groups "early stage" and "advanced stage", as it is shown in the column on the right. AJCC: American Joint Committee on Cancer.

	Number (n)	*Percentage (%)*	
Age			
<65 years	53	45.7 %	
≥65 years	63	54.3 %	
Subsite			
Tongue	51	44.0 %	*Tongue*: 52 (44.8 %)
Tongue + floor of the mouth	1	0.9 %	
Cheek	15	12.9 %	*Oral cavity*: 64 (55.2 %)
Floor of the mouth	32	27.6 %	
Hard palate	5	4.3 %	
Retromolar trigone	12	10.3 %	
pT AJCC 8th Edition			
pT1	41	35.4 %	
pT2	28	24.1 %	
pT3	34	29.3 %	
pT4	13	11.2 %	
pN AJCC 8th Edition			
pN0	83	71.6 %	
pN1	10	8.6 %	
pN2	11	9.5 %	
pN3	12	10.3 %	
Stage AJCC 8th Edition			
I	41	35.3 %	*Early stage*: 63 (54.3 %)
II	22	19 %	
III	24	20.7 %	*Advanced stage*: 53 (45.7 %)
IV	29	25.0 %	
Recurrence			
Yes	29	25.0 %	
No	87	75.0 %	
Subsite recurrence			
Oral cavity	20	69.0 %	
Neck	8	27.6 %	
Tongue + neck	1	3.4 %	

Table 2
Treatment-related and histology-related data. G1,2 are well or moderately differentiated tumours while G2,3 are moderately or poorly differentiated tumours. R0 means free margins, R1 means there's a presence of malignant cells.

	Number (n)	*Percentage (%)*
Surgical approach		
Transoral	80	69 %
Conservative transmandibular	10	8.6 %
Marginal transmandibular	14	12 %
Segmental transmandibular	9	7.8 %
Pull-through	3	2.6 %
Neck dissection		
Yes	85	73.3 %
No	31	26.7 %
Use of microvascular flaps		
Yes	51	44 %
No	65	56 %
Adjuvant radiotherapy or radio-chemotherapy		
Yes	37	31.9 %
No	79	68.1 %
Grading		
G 1,2	54	46.6 %
G 2,3	22	19 %
Not available	40	3.4 %
Vascular invasion		
Yes	2	1.7 %
No	114	98.3 %
Lymphatic invasion		
Yes	1	0.9 %
No	115	99.1 %
Perineural invasion		
Yes	1	0.9 %
No	115	99.1 %
Depth of invasion (DOI)		
<5 mm	61	52.6 %
5–10 mm	26	22.4 %
>10 mm	29	25 %
Microscopic status of resected margins		
R0	96	82.8 %
R1	20	17.2 %
Presence of metastatic nodes		
Yes (N+)	34	29.3 %
No (N−)	82	70.7 %
Extra nodal extension (ENE)		
Yes	14	41.2 %
No	20	58.8 %

intervals as follows: <30 days, from 30 to 44 days, from 45 to 60 days, ≥60 days.

3.2. Survival analysis

At the time of analysis 28 of the 116 patients died (24.1 %). Fourteen of the deaths were cancer-related, data regarding 4 patients were not available and one patient has been lost during follow-up.

Overall, 5-year OS estimate was 76.5 % (95 % IC 67.6–83.2 %). No significant differences in both OS and DSS were observed according to *TTS-clinical-based* and *TTS-biopsy-based* (Fig. 1). Also, when stratifying patients bases on stage, no difference in terms of OS and DSS were found for neither *TTS-clinical-based* nor *TTS-biopsy-based*, both for patients with stage I-II disease and stage III-IV diseases. Conversely, in patients with pT3–4 disease but not in those with pT1–2 disease, *TTS-clinical-based* ≥ 30 days resulted significantly correlated with worse DSS ($p = 0.049$) (Figs. 2 & 3).

3.3. Quality of life (QoL)

Patients treated later than 30 days after clinical diagnosis showed a significantly lower global QoL score at the Washington questionnaire, than those patients treated within 30 days from diagnosis ($p = 0.01$). There are no differences in the distribution of pT categories within the groups. The in-depth comparison of the questionnaire showed that there were some significant differences between patients treated before and after 30 days from the clinical diagnosis in terms of pain, anxiety, mood and social activities ($p = 0.045$). Considering the well-known effects induced on QoL by RT, we specifically investigated the subgroup of 37 patients who underwent adjuvant therapy (31.9 %) who reported a lower QoL scores in comparison with not-radiated patients (68.1 %) but the difference in scores resulted not statistically significant ($p > 0.05$). In particular, saliva, swallowing and anxiety were found to be lower. The distribution within the two groups was homogeneous, 21 patients with TTS < 30 days and 17 with TTS ≥ 30 days.

3.4. Impact of prognostic factors on survival

Table 3 summarizes the prognostic factors in relation to OS and DSS. As result of the univariate analysis, the presence of positive surgical

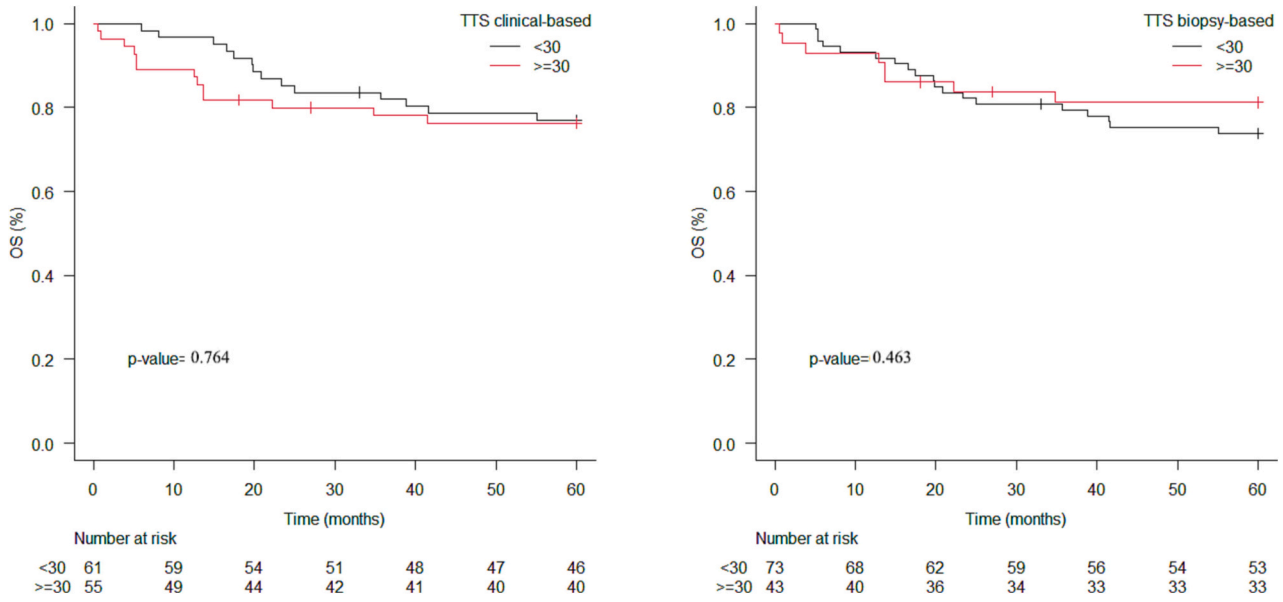

Fig. 1. 5-Year OS considering *TTS-clinical-based* on the left and *TTS-biopsy-based* on the right; <30 days (black line) and ≥30 days (red line). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

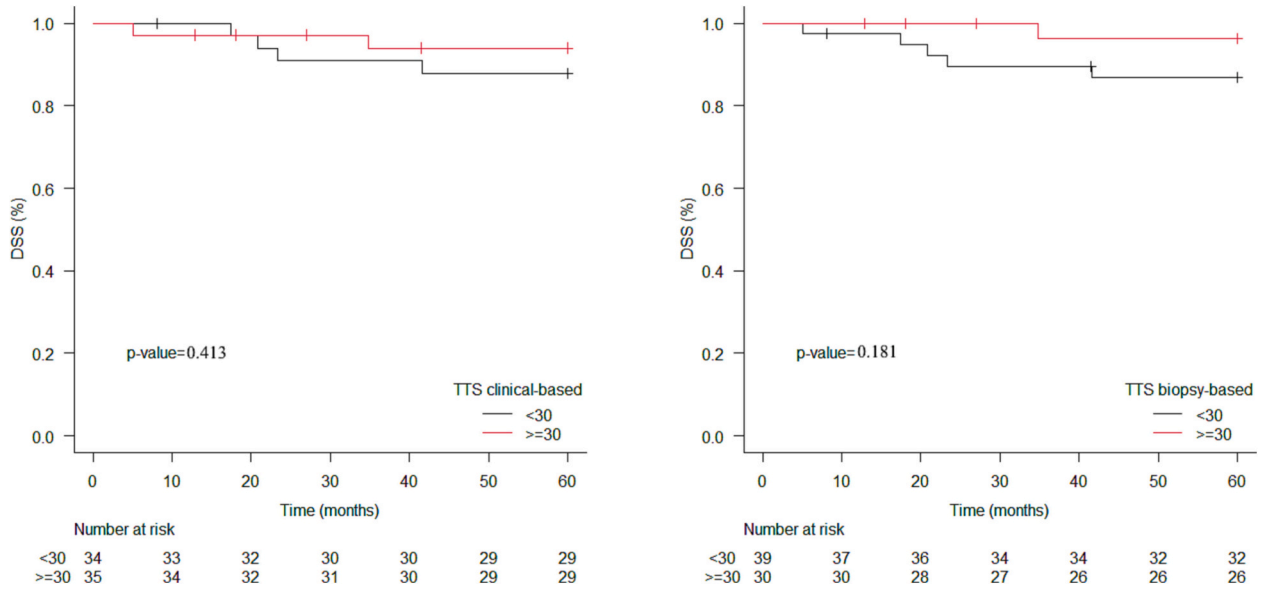

Fig. 2. 5-Year DSS in the subgroup of pT1–2 categories comparing *TTS-clinical-based* on the left and *TTS-biopsy-based* on the right. <30 days (black line) and ≥30 days (red line). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

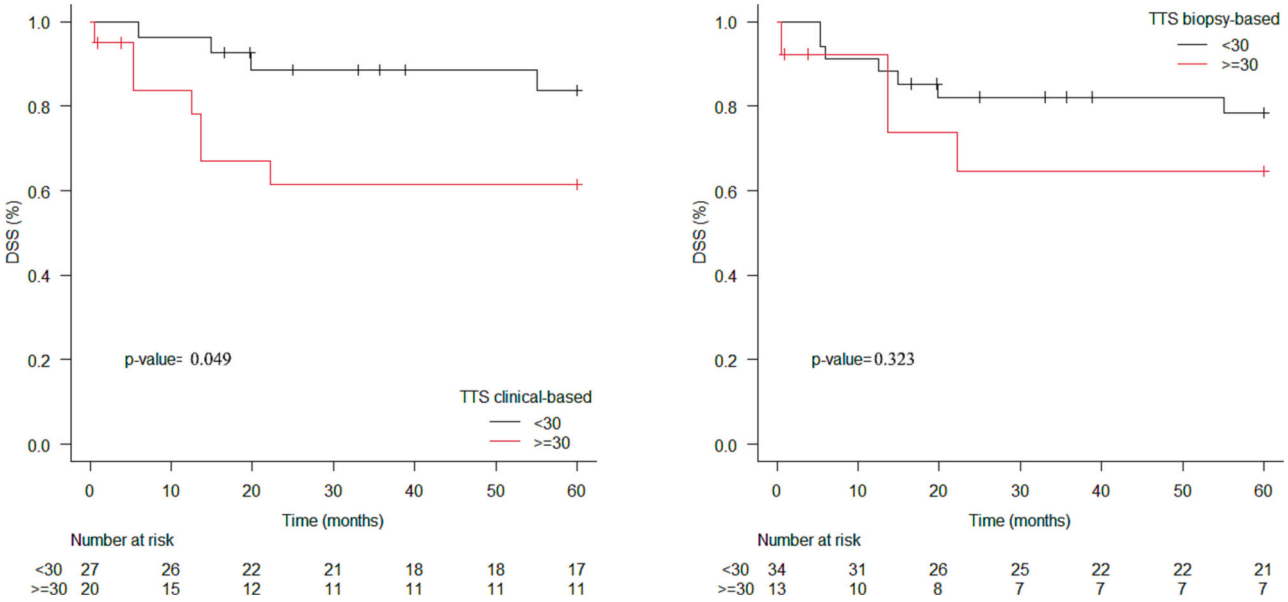

Fig. 3. 5-Year DSS in the subgroup of pT3–4 categories comparing *TTS-clinical-based* on the left and TTS-*biopsy-based* on the right. <30 days (black line) and ≥30 days (red line). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

margins, nodal involvement (pN+), DOI >10 mm, invasive surgical approach and presence of ECE were found significant prognostic factors for OS (Table 3). These parameters resulted significantly associated also with a higher risk of death for OSCC while advanced pT categories affected only OS.

4. Discussion

This retrospective cohort-study investigated the association between delayed surgical treatment with survival and quality of life in OSCC.

Though assuming different time partitions, neither *TTS-clinical-based* nor *TTS-biopsy-based* affected OS and DSS rate. However, advanced pT-categories subgroup showed a significant worse DSS when *TTS-clinical-based* interval was longer than 30 days (Figs. 2 and 3). Moreover, patients with *TTS-clinical-based* interval longer than 30 days, reported a significantly lower global QoL score.

The most recent literature has highlighted the importance of time between diagnosis to treatment in the determination of prognosis [11,12]. A recent review by Graboyes et al. reported that delay in treatment for HNSCC was associated with poor survival, stressing that a huge heterogeneity exists among definitions of diagnosis to treatment interval and surgery-to-adjuvant therapy time [13]. There should be specify that considering together the waiting time before surgery and before adjuvant therapy (CT/RT) lead to a clear misinterpretation of data because the TTI for adjuvant treatments is inevitably prolonged. [14].

Moreover, most studies [2,3,11,15] have used national cancer registries to provide large sample sizes to increase statistical power. However, as the populations are heterogeneous, the outcomes may not correspond with the experience of individual institutions. Also, these

Table 3
Prognostic factors related to overall survival (OS) and disease specific survival (DSS).

	OS		DSS	
	Hazard ratio (95 % C·I)	*p-value*	*Hazard ratio (95%C·I)*	*p-value*
Age				
<65 years	1.00 (Reference)		1.00 (Reference)	
≥65 years	1.31 (0.61–2.83)	0.49	1.02 (0.3935–2.646)	0.97
Subsite				
Tongue	1.00 (Reference)		1.00 (Reference)	
Oral cavity	1.42 (0.65–3.11)	0.38	1.1 (0.45–3.12)	0.73
pT AJCC 8th Edition				
pT1 (47,4 %)	1.00 (Reference)		1.00 (Reference)	
pT2 (29,3 %)	3.21 (1.19–8.68)	**0.02**	2.7870 (0.91–8.52)	0.07
pT3 (12,1 %)	2.95 (0.83–10.45)	0.09	0.8903 (0.10–7.62)	0.91
pT4 (11,2 %)	5.07 (1.63–15.72)	**0.005**	3.0230 (0.72–12.66)	0.13
pN AJCC 8th Edition				
pN0 (71,6 %)	1.00 (Reference)		1.00 (Reference)	
pN1 (8,6 %)	6.82 (2.47–18.86)	**<0.001**	18.98 (4.51–79.86)	**<0.001**
pN2 (9,5 %)	6.97 (2.52–19.29)	**<0.001**	18.91 (4.49–79.53)	**<0.001**
pN3 (10,3 %)	4.32 (1.47–12.65)	**<0.001**	11.53 (2.58–51.55)	**0.001**
Stage S AJCC 8th Edition				
Early (54,3 %)	1.00 (Reference)		1.00 (Reference)	
Advanced (45,7 %)	6.76 (2.56–17.87)	**0.0001**	7.108 (2.04–24.77)	**0.002**
Surgical approach				
Transoral (69 %)	1.00 (Reference)		1.00 (Reference)	
Segmental mandibulectomy/ pull-through (10,4 %)	2.74 (0.98–7.70)	**0.05**	5.018 (1.59–15.83)	**0.006**
Marginal/ conservative transmandib. (20,6 %)	2.65 (1.13–6.21)	**0.02**	2.708 (0.86–8.54)	0.09
Depth of invasion (DOI)				
<5 mm (52,6 %)	1.00 (Reference)		1.00 (Reference)	
5–10 mm (22,4 %)	2.25 (0.82–6.21)	0.12	3.434 (0.77–15.35)	0.11
>10 mm (25 %)	4.06 (1.65–9.94)	**0.002**	8.988 (2.47–32.72)	**<0.001**
Microscopic status of resected margins				
Negative (R0) (82,8 %)	1.00 (Reference)		1.00 (Reference)	
Positive (R1) (17,2 %)	2.26 (0.99–5.16)	**0.05**	2.929 (1.08–7.92)	**0.03**
Extra nodal extension (ENE)				
pN0 (40,5 %)	1.00 (Reference)		1.00 (Reference)	
ENE+ (12,1 %)	3.54 (1.19–10.53)	**0.02**	16.45 (1.84–147.30)	**0.01**
ENE− (20,7 %)	4.48 (1.76–11.41)	**0.002**	25.78 (3.29–201.80)	**0.001**
Neck dissection not performed (26,7 %)	0.43 (0.09–2.05)	**0.29**	2.97 (0.27–32.83)	0.37
Adjuvant therapy (CT/ RT)				
No	1.00 (Reference)		1.00 (Reference)	
Yes	0.89 (0.39–2.04)	0.79	1.47 (0.56–3.83)	0.43
TTS_BIOPSY-BASED				
<30 day	1.00 (Reference)		1.00 (Reference)	
≥30 day	0.99 (0.97–1.01)	0.45	0.99 (0.96–1.02)	0.58
TTS_CLINICAL-BASED				
<30 day	1.00 (Reference)		1.00 (Reference)	
≥30 day	1.00 (0.98–1.02)	0.78	1.00 (0.98–1.03)	0.74

Significant *p-values* ($p < 0.05$) are marked in bold.

types of studies generally lack information on surgical outcomes, recurrence, and reasons for treatment delay.

To overcome this heterogeneity, we sought to validate the results obtained from a national cancer registry [2], analysing a case series from our institution that included strictly selected patients affected by OSCC and referred to a unique tertiary health care hospital. The tumour site is an independent predictor associated with a late-stage observed at the moment of diagnosis [16]. Nevertheless, the optimal timeframe within which patients should be treated is still undefined just as an optimal TTS-cut-off remains indeterminate. Murphy et al. [11] reported that a TTS longer than 46 days was associated with a significant increase in mortality in HNSCC. A Taiwanese national study focused only on OSCC observed an inverse association between diagnosis-to-treatment interval and OS [3]. Interestingly, the authors noted that subgroups with <20 days and <30 days diagnosis-to-treatment intervals showed the lowest rate of upstaging (from c-staging to p-staging) in comparison with other subgroups with longer intervals. This is an important observation knowing that in the head and neck district the Tumour Volume Doubling Time (TVD) can be equal to just 30 days if the cancer is poorly differentiated [9], and a modification in volume leads to an upstaging and a change in treatment indications, with consequent changes both in prognosis and QoL.

In our cohort an upstaging between clinical and pathological based TNM occurred similarly to what was reported in literature [26] that is nearly 10 % for both T- and N-upstaging. The upstaging phenomenon is a crucial event in OSCC that is regulated by different factors: the relationship between increasing TTS and mortality is probably influenced by tumour progression, so the waiting time for treatment represents a correctable variable. Xiao et al. [17], in fact, noted significant relationship between TTI and T, N, and stage upstaging but there was a subsequent lack of significant association between TTI and mortality, appearing that time-to-treatment itself is not a significant predictor of mortality independent of upstaging, suggesting that there may be additional factors contributing to the complex relationship between TTI and mortality [17].

Several studies only analysed as outcome endpoint the OS and this may lead to the risk to overlook important influences on survival made by adjuvant therapies and comorbidities.

For these reasons, we considered also DSS, that reflects the cancer specific mortality, and we adopted a 30-day categorization method in a cohort with longitudinal 5-year follow-up. Moreover, *TTS-clinical-based* and *TTS-biopsy-based* almost overlapped, meaning that in our cohort diagnosis and histological response usually happened close in time.

Our results are in line with other studies in which the association between time-to-treatment and prognosis in OSCC resulted weak. Similarly, Jensen et al. [18] found that TTI does not have a statistically

significant impact on outcome in their large personal series, as long as patients, in general, are treated relatively fast, reporting a median TTI of 27 days.

Liao et al. [19] reported a median TTI of 40 days and an association with decreased OS for TTI-biopsy > 60 days in HNSCC. However, this association was lost when the analysis was restricted to patients with OSCC.

Several authors found that a longer biopsy-to-surgery waiting time significantly influenced the appearances of metastases with no significant impact on OS [20–24] probably because untreated cancer is more likely to lead to an upstaging that affects DSS prior than OS [21]. We so investigated the association between delayed TTS and both OS and DSS within categories of T, stratifying the patients based on primary tumour stage according to the TNM edited by AJCC.

Adopting the 8th edition of the TNM staging system, advanced pT categories resulted significantly associated with poor survival when *TTS-clinical-based* was ≥30 days, consistent with Van Harten et al. [1].

Aware of the limited number of cases, TTS >30 days did not significantly affect OS but it appears to have a significant influence on QoL: given equal OS and DSS rates, patients who had TTS < 30 days perceived a better global QoL. pT categories were equally distributed within the groups, confirming that in our cohort early pT category and advanced pT category were homogenously treated before or after 30 days, and that both early and advanced pT categories benefit from being treated earlier than a month in terms of QoL. Furthermore, also the percentage of patients undergoing adjuvant therapy was homogeneously distributed within the groups. To the best of our knowledge, no previous studies have investigated the impact of treatment delay on QoL [10,25]. Thus, the longer we wait, the higher is the possibility of tumour growth, with a consequent change in surgical indication switching often towards a more invasive surgical approach that notoriously compromises QoL [10,26]. In addition, as cancer diagnosis is itself cause of stress and worries [27], a delay in treatment might increase the patient psychological distress and uncertainty [1,28].

A paradox arose from the observation that patients treated after 15 days from the biopsy showed a better prognostic trend than those treated earlier, although the difference was not significant. After stratifying for *stage*, patients treated within 15 days were mostly affected by *advanced stage* disease while those treated after were in an *early stage*. [29] A possible explanation could be that patients with advanced stage disease are prioritized, due to the increased risk of becoming unresectable. Similarly, Van Harten [15] and by Coca-Pelaz [29] have hypothesized that more aggressive tumours are generally planned faster but still have a worse prognosis, a sort of "waiting time paradox" [30].

This study has some limitations: firstly, the retrospective design of the research. Then, the limited sample size could lead in misinterpretations of differences in OS and DSS based on treatment intervals, while a larger prospective cohort would improve to discriminate changes. Unfortunately, considering the low number of events for DSS outcome, a multivariate analysis was not performed to confirm the independent role of delayed TTS in predicting a poor prognosis.

Even if the relatively small sample size used in this study to evaluate the impact of TTS ≥ 30 days on DSS, the outcomes revealed a trend of significance, especially considering advanced T-categories. In our opinion, the strengths of this study are the strict inclusion criteria adopted assuring homogeneity of the sample and the study design tightly focused on surgery; although in limited sample, the results help to delineate this issue within a larger field that is oncologic surgery. Moreover, a well-designed study, even if small, might contribute to meta-analysis in evaluating the impact of surgery delay on survival in head and neck cancers. In the light of the above, our future plan is to carry on this research observing if developments in diagnostic methods and surgical techniques can lead to shorter TTS and further improvements in QoL.

In conclusion, according to our findings, TTS longer than 30 days can determine a lower DSS in advanced T-categories. Short TTS intervals were associated with a better QoL in surgically treated OSCC patients. This outcome gives the awareness that surgeons can have a fundamental role in improving the QoL from both a physical and a psychological point of view.

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CRediT authorship contribution statement

Giancarlo Tirelli: Conceptualization, Supervision, Validation, **Paolo Boscolo-Rizzo:** Methodology, Supervision, Validation, Writing - review & editing **Ludovica Pelloso:** Data Curation **Nicoletta Gardenal:** Data Curation, Investigation **Fabiola Giudici:** Software, Formal analysis, review and editing **Alberto Vito Marcuzzo:** Writing - Original Draft preparation – review and editing **Margherita Tofanelli:** Data Curation, Writing - Original Draft preparation and review & editing.

Declaration of competing interest

None.

References

[1] Van Harten MC, De Ridder M, Hamming-Vrieze O, Smeele LE, Balm AJM, Van Den Brekel MWM. The association of treatment delay and prognosis in head and neck squamous cell carcinoma (HNSCC) patients in a Dutch comprehensive cancer center. Oral Oncol 2014;50:282–90. https://doi.org/10.1016/j.oraloncology.2013.12.018.

[2] Polesel J, Furlan C, Birri S, Giacomarra V, Vaccher E, Grando G, et al. The impact of time to treatment initiation on survival from head and neck cancer in north-eastern Italy. Oral Oncol 2017;67:175–82. https://doi.org/10.1016/j.oraloncology.2017.02.009.

[3] Liao C, Chen H, Wen Y, Lee SR, Ng SH, Liu TW, et al. Association between the diagnosis-to-treatment interval and overall survival in Taiwanese patients with oral cavity squamous cell carcinoma. Eur J Cancer 2017;72:226–34. https://doi.org/10.1016/j.ejca.2016.11.010.

[4] Schoonbeek RC, de Vries J, Bras L, Sidorenkov G, Plaat BEC, Witjes MJH, et al. The effect of treatment delay on quality of life and overall survival in head and neck cancer patients. Eur J Cancer Care (Engl) 2022;31:e13589. https://doi.org/10.1111/ecc.13589.

[5] Boscolo-Rizzo P, Gava A, Marchiori C, Baggio V, Da Mosto MC. Functional organ preservation in patients with locoregionally advanced head and neck squamous cell carcinoma treated by platinum-based multidrug induction chemotherapy and concurrent chemoradiotherapy. Ann Oncol 2011;22:1894–901. https://doi.org/10.1093/annonc/mdq681.

[6] Rygalski CJ, Zhao S, Eskander A, Mroz EA, Brock G, Silverman DA, et al. Time to surgery and survival in head and neck cancer. Ann Surg Oncol 2020;13:1–9. Ann Surg Oncol 2021;28:877–85. https://doi.org/10.1245/s10434-020-09326-4.

[7] Graboyes EM, Garrett-Mayer E, Ellis MA, Sharma AK, Wahlquist AE, Lentsch EJ, et al. Effect of time to initiation of postoperative radiation therapy on survival in surgically managed head and neck cancer. Cancer 2017;123:4841–50. https://doi.org/10.1002/cncr.30939.

[8] Harris JP, Chen MM, Orosco RK, Sirjani D, Divi V, Hara W. Association of survival with shorter time to radiation therapy after surgery for U.S. patients with head and neck cancer. JAMA Otolaryngol Head Neck Surg 2018;144:349–59. https://doi.org/10.1001/jamaoto.2017.3406.

[9] Jensen AR, Nellemann HM, Overgaard J. Tumor progression in waiting time for radiotherapy in head and neck cancer. Radiother Oncol 2007;84:5–10. https://doi.org/10.1016/j.radonc.2007.04.001.

[10] Tirelli G, Gatto A, Bonini P, Tofanelli M, Arnez ZM, Piccinato A. Prognostic indicators of improved survival and quality of life in surgically treated oral cancer. Oral Surg Oral Med Oral Pathol Oral Radiol 2018;126:31–40. https://doi.org/10.1016/j.oooo.2018.01.016.

[11] Murphy CT, Galloway TJ, Handorf EA, Egleston BL, Wang LS, Mehra R, et al. Survival impact of increasing time to treatment initiation for patients with head and neck cancer in the United States. J Clin Oncol 2016;34:169–78. https://doi.org/10.1200/JCO.2015.61.5906.

[12] Jafari A, Najafi Sh, Moradi F, Kharazifard M, Khami M. Delay in the diagnosis and treatment of oral cancer. J Dent (Shiraz) 2013;14:146–50 [PMID: 24724136; PMCID: PMC3927673].

[13] Graboyes EM, Kompelli AR, Neskey DM, Brennan E, Nguyen S, Sterba KR, et al. Association of treatment delays with survival for patients with head and neck

cancer a systematic review. JAMA Otolaryngol Head Neck Surg 2019;145:166–77. https://doi.org/10.1001/jamaoto.2018.2716.
[14] Lauritzen BB, Jensen JS, Grønhøj C, Wessel I, von Buchwald C. Impact of delay in diagnosis and treatment-initiation on disease stage and survival in oral cavity cancer: a systematic review. Acta Oncol 2021;60:1083–90. https://doi.org/10.1080/0284186X.2021.1931712.
[15] van Harten MC, Hoebers FJ, Kross KW, van Werkhoven ED, van den Brekel MW, van Dijk BA. Determinants of treatment waiting times for head and neck cancer in the Netherlands and their relation to survival. Oral Oncol 2015;51:272–8. https://doi.org/10.1016/j.oraloncology.2014.12.003.
[16] Adrien J, Bertolus C, Gambotti L, Mallet A, Baujat B. Why are head and neck squamous cell carcinoma diagnosed so late? Influence of health care disparities and socio-economic factors. Oral Oncol 2014;50:90–7. https://doi.org/10.1016/j.oraloncology.2013.10.016.
[17] Xiao R, Ward MC, Yang K, Adelstein DJ, Koyfman SA, Prendes BL, et al. Increased pathologic upstaging with rising time to treatment initiation for head and neck cancer: a mechanism for increased mortality. Cancer 2018;124:1400–14. https://doi.org/10.1002/cncr.31213.
[18] Jensen JS, Jakobsen KK, Mirian C, Ghanizada M, Håkansson K, Wessel I, et al. Impact of time to treatment initiation for patients with oral cavity squamous cell carcinoma: a population-based, retrospective study. Acta Oncol 2021;60:491–6. https://doi.org/10.1080/0284186X.2020.1863462.
[19] Liao DZ, Schlecht NF, Rosenblatt G, Kinkhabwala CM, Leonard JA, Ference RS, et al. Association of delayed time to treatment initiation with overall survival and recurrence among patients with head and neck squamous cell carcinoma in an underserved urban population. JAMA Otolaryngol Head Neck Surg 2019;145:1001–9. https://doi.org/10.1001/jamaoto.2019.2414.
[20] Fujiwara RJ, Judson BL, YarbroughWG Husain Z, Mehra S. Treatment delays in oral cavity squamous cell carcinoma and association with survival. Head Neck 2017;39:639–46. https://doi.org/10.1002/hed.24608.
[21] Tumati V, Hoang L, Sumer BD, Truelson JM, Myers LL, Khan S, et al. Association between treatment delays and oncologic outcome in patients treated with surgery and radiotherapy for head and neck cancer. Head Neck 2019;41:315–21. https://doi.org/10.1002/hed.25457.
[22] Caudell JJ, Locher JL, Bonner JA. Diagnosis-to-treatment interval and control of locoregionally advanced head and neck cancer. Arch Otolaryngol Head Neck Surg 2011;137:282–5. https://doi.org/10.1001/archoto.2011.20.
[23] Huang J, Barbera L, Brouwers M, Browman G, Mackillop WJ. Does delay in starting treatment affect the outcomes of radiotherapy? A systematic review. J Clin Oncol 2003;21:555–63. https://doi.org/10.1200/JCO.2003.04.171.
[24] Ho AS, Kim S, Tighiouart M, Mita A, Scher KS, Epstein JB, et al. Quantitative survival impact of composite treatment delays in head and neck cancer. Cancer 2018;124:3154–62. https://doi.org/10.1002/cncr.31533.
[25] Valdez JA, Brennan MT. Impact of oral cancer on quality of life. Dent Clin N Am 2018;62:143–54. https://doi.org/10.1016/j.cden.2017.09.001.
[26] Chandu A, Smith AC, Rogers SN. Health-related quality of life in oral cancer: a review. J Oral Maxillofac Surg 2006;64:495–502. https://doi.org/10.1016/j.joms.2005.11.028.
[27] Posluszny DM, Dougall AL, Johnson JT, Argiris A, Ferris RL, Baum A, et al. Posttraumatic stress disorder symptoms in newly diagnosed patients with head and neck cancer and their partners. Head Neck 2015;37:1282–9. https://doi.org/10.1002/hed.23760.
[28] Mendes CM, Batista Bde A, Paixao SP, Santos Tde S, Martins-Filho PR. Anxiety and depression during expecting time for oral cancer treatment. J Craniofac Surg 2015;26:998–9. https://doi.org/10.1097/SCS.0000000000001668.
[29] Coca-Pelaz A, Takes RP, Hutcheson K, Saba NF, Haigentz Jr M, Bradford CR, et al. Head and neck cancer: a review of the impact of treatment delay on outcome. Adv Ther 2018;35:153–60. https://doi.org/10.1007/s12325-018-0663-7.
[30] Crawford SC, Davis JA, Siddiqui NA, de Caestecker L, Gillis CR, Hole D, et al. The waiting time paradox: population based retrospective study of treatment delay and survival of women with endometrial cancer in Scotland. Br Med J 2002;325:196. https://doi.org/10.1136/bmj.325.7357.196.