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Prognostic Factors for Survival, Recurrence, and Metastasis in Early-Stage Tongue Cancer: An Overview

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Abstract: ***Early-stage tongue squamous cell carcinoma demonstrates variable clinical behavior that cannot be fully explained by conventional TNM staging alone. This narrative review synthesizes evidence on primary tumor-related prognostic factors influencing survival, recurrence, and metastatic risk, including tumor subsite, size, depth of invasion, histologic differentiation, perineural and lymphovascular invasion, invasion pattern, host immune response, and surgical margin status. The reviewed literature highlights depth of invasion, worst pattern of invasion, and margin status as consistently influential determinants, while other parameters provide additional stratification in selected contexts. Variability in definitions and reporting practices remains a major limitation across studies, underscoring the need for standardized assessment to support individualized treatment planning in early-stage tongue carcinoma.***

Keywords: tongue squamous cell carcinoma, depth of invasion, prognostic factors, surgical margins, nodal metastasis

1. Introduction

Oral squamous cell carcinoma (OSCC) is the most common malignancy of the oral cavity, and cancers of the tongue represent one of the most frequent and clinically aggressive subsites. Tongue squamous cell carcinoma (TSCC) is associated with higher rates of cervical lymph node metastasis, lower overall survival, and increased disease-specific mortality compared with other oral cavity locations [1–4]. Although early-stage tumors (Stage I–II) are generally managed with surgery alone, a substantial proportion of patients experience local recurrence or develop regional metastases, which significantly worsens prognosis [4,5].

Several population-based and institutional studies have demonstrated that tumor subsite within the tongue influences both metastatic patterns and survival outcomes. Tumors located in the posterior third of the tongue exhibit higher rates of bilateral and contralateral nodal metastases and worse prognosis compared with tumors of the anterior two thirds, likely due to bilateral lymphatic drainage and technical limitations of surgical excision in this region [6,7]. These findings indicate that anatomical factors alone may contribute to biologically and clinically distinct behavior even within early-stage disease.

While tumor size remains a fundamental component of TNM staging [8], it does not fully explain the variability in outcomes among patients with comparable clinical stages. Tumor diameter has been associated with survival, local recurrence, and nodal metastasis [9–14], and tumors measuring 2–4 cm carry more than twice the risk of disease-related mortality compared with tumors ≤2 cm [15]. Nevertheless, size-based classification does not adequately reflect the depth and pattern of tissue infiltration that underlie metastatic potential.

Depth of invasion (DOI) has emerged as one of the most robust predictors of nodal metastasis, local recurrence, and survival in TSCC [16,17–22]. Rates of occult cervical metastases increase markedly with increasing DOI, reaching over 50% in tumors with DOI greater than 10 mm [16]. These observations led to the incorporation of DOI into the AJCC 8th edition staging system, with cut-off values of 5 mm for T1 and 10 mm for T2 tumors based on ICOR models [17]. Tumor thickness, although related to DOI, represents a distinct measurement and may have independent prognostic value, particularly in exophytic or ulcerated tumors [23–27]. However, inconsistent definitions and cut-off values have limited its routine clinical application.

Beyond dimensional parameters, histopathological indicators of aggressive tumor biology play a critical role in prognosis. Tumor differentiation grade has been associated with pathological stage, extranodal extension, recurrence, and risk of occult nodal disease, although conflicting results exist across studies [28–32]. Similarly, perineural invasion (PNI) and lymphovascular invasion (LVI) are recognized markers of tumor spread, associated with increased risks of cervical metastasis, recurrence, and reduced survival [33–39]. In early-stage tumors, the presence of PNI alone may increase the risk of nodal metastases by up to sixfold [35], while LVI has been linked to significantly higher recurrence rates and poorer survival outcomes [38,39], though not all studies demonstrate consistent prognostic value [40,41].

The pattern of tumor invasion, particularly the worst pattern of invasion (WPOI), reflects loss of cellular cohesion and increased infiltrative capacity [42]. High-risk invasion patterns (WPOI-4 and WPOI-5) are independently associated with nodal metastasis, locoregional recurrence, and decreased survival, even in patients with T1–T2N0 disease [43–46]. Moreover, aggressive invasion patterns are strongly linked to deep margin involvement and the need for wider surgical excision to achieve adequate local control [7,47,48]. These observations suggest that microscopic invasion architecture may be as clinically relevant as traditional macroscopic tumor measurements.

Finally, surgical margin status remains a cornerstone prognostic factor for local disease control [49]. Close or involved margins are associated with higher rates of local recurrence and frequently prompt consideration of adjuvant therapy [25, 50- 53]. However, definitions of "close" and "positive" margins vary considerably across studies, leading to wide discrepancies in reported risk and management strategies [25, 48, 51, 52]. In addition, the method of margin assessment- whether from the main specimen or from the tumor bed- has been shown to influence local control outcomes in early TSCC [49, 54].

Despite the abundance of published data, the prognostic relevance of individual tumor-related factors and their optimal integration into clinical decision-making remain incompletely standardized. Variability in pathological definitions, measurement techniques, and reporting practices contributes to inconsistent risk stratification and potentially suboptimal treatment selection. Therefore, a comprehensive synthesis of current evidence is required to clarify the relative importance of anatomical, dimensional, and microinvasive tumor characteristics in early TSCC.

The aim of this review is to critically analyze and summarize the available literature on primary tumor–related prognostic factors for survival, recurrence, and metastatic risk in early-stage squamous cell carcinoma of the tongue. By integrating data on tumor subsite, size, depth of invasion, histological differentiation, perineural and lymphovascular invasion, invasion pattern, and surgical margins, this review seeks to support more accurate risk assessment and to inform individualized therapeutic strategies in early TSCC.

2. Overview

Prognostic significance of tumor subsite

Farr et al. [55] report a gradual decrease in 5-year survival and an increase in the frequency of metastasis with more distal tumor location. Squamous cell carcinoma of the oral tongue shows a higher risk of metastasis, lower overall survival, and higher disease-specific mortality compared with other sites in the oral cavity [1- 4]. In other studies, the highest mortality has been reported for carcinoma of the floor of the mouth [56]. Oral tongue SCC can be subdivided into subsites (onco-anatomical locations). When survival is analyzed across different subsites- lateral border, ventral surface, and dorsum of the tongue- no statistically significant difference is observed [57]. Regarding distal tumor location, a higher frequency of contralateral and bilateral nodal metastases is observed in tumors of the posterior one-third of the tongue, along with a significantly worse prognosis compared with tumors of the anterior two-thirds [6]. Possible reasons include bilateral lymphatic drainage of this region, as well as anatomical limits of excision and difficult surgical access, which in turn are associated with increased rates of involved resection margins [6,7].

Primary tumor size

Within the TNM staging system, the size of the primary tumor- defined as the largest superficial diameter of the tumor mass- plays a critical role in both clinical (cT) and pathological (pT) staging [8]. Tumor size is an established significant prognostic indicator of overall survival [9,10]. Tumor diameter is also a prognostic factor for disease metastasis [5,11], for the development of local recurrence [12,13], and for the technical achievement of negative resection margins [14,7].

In tongue carcinoma with tumor size between 2 cm and 4 cm, the risk of death is 2.2-fold higher compared with tumors up to 2 cm (T1) [15]. In multivariable analysis, tumor size is an independent predictor of disease-specific survival [15].

Depth of invasion and tumor thickness

Depth of invasion (DOI) is defined as the distance from the level of the basement membrane of the adjacent normal mucosa to the deepest point of tumor invasion [23,16]. Tumor thickness is defined as the distance from the surface of the tumor to the deepest invasion into tissues [58–60,16].

DOI is an established independent predictor of survival [12] and of local and locoregional recurrence [17–20]. In tongue carcinoma, reported rates of occult metastases are 23% for DOI < 5 mm, 34% for DOI 6–10 mm, and 53% for DOI > 10 mm [16]. DOI > 5 mm is associated with decreased survival and a high risk of cervical metastases [21]. A statistically significant difference in the development of cervical metastases has been reported between cases with DOI up to 4 mm and those with DOI up to 5 mm [22] (meta-analysis).

In TNM8, based on models developed by ICOR [17], the DOI cut-off is defined as 5 mm for T1 and 10 mm for T2 tumors.

DOI and tumor thickness have different meanings and are not always the same measurement [23,16], because tumor thickness tends to be greater in exophytic tumors and smaller in ulcerated tumors [25]. DOI and tumor thickness have often been incorrectly treated as equivalent, interchangeable concepts [23].

The prognostic significance of tumor thickness has been discussed in the literature [24,60], with different critical values suggested for different subsites [24,26]. For tongue cancer, proposed cut-offs range between 3 mm, 5 mm, and 8 mm [24]. Tumor thickness has been described as a more important predictor of survival than the superficial tumor size [27].

Tumor differentiation grade

The differentiation grades of epithelial tumors were described by Broders in 1920, based on a subjective assessment of keratinization, cellular and nuclear polymorphism, and mitotic activity [61]. Based on these criteria, the World Health Organization categorizes tumor differentiation as G1 (well differentiated), G2 (moderately differentiated), and G3 (poorly differentiated) [62]. Differentiation grade has been reported to be significantly associated with pathological tumor stage, extranodal extension, and recurrence [28,29]. In early tongue carcinomas, higher rates of occult metastases have been reported in moderately and poorly differentiated tumors [15,30]. Other authors have found no association between tumor differentiation and the development of cervical lymph node metastases [58,31,32].

Perineural invasion

Perineural invasion (PNI) was first described in 1835 and

1862 by authors observing the ability of tumors to spread along nerve fibers [63- 65]. The first definition of PNI was provided by Batsakis as invasion of tumor cells into, around, or through nerve fibers [66]. Because this definition allows variability in interpretation, many authors propose adding that the tumor should involve at least 33% of the nerve circumference or that tumor cells should be identified within any of the three nerve layers [63].

Reported PNI rates vary widely from 6% to 82% [33,67,13,68], likely due to lack of standardization and the use of different methods, including immunohistochemistry for S100 [69]. With routine H&E examination, reported rates are 52% and 62% [33,67]. PNI frequency depends on tumor stage, DOI, and differentiation. In early carcinomas, PNI is approximately two-fold lower, with reported rates of 23–31.1% in T1 and T2 lesions [34,68].

PNI is associated with an increased risk of cervical lymph node metastases, local recurrence, and worse disease-specific mortality [33,34]. In T1 tumors, the presence of PNI increases the risk of cervical lymph node metastases six-fold [35]. In univariable analyses, PNI is associated with increased risk of local, regional, and distant recurrence [36]. Patients with PNI have a worse prognosis: 5-year disease-specific survival is 94.6% in patients without PNI versus 56.6% in patients with PNI [36].

Lymphovascular invasion

In lymphovascular invasion (LVI), tumor cells invade small-caliber blood or lymphatic vessels, preferentially those lined by a single layer of endothelial cells and lacking a smooth muscle layer [37,38]. Its prognostic significance for cervical metastasis and survival was first discussed by Poleksic [70] in 1978 and by Batsakis [71] in 1984.

Reported LVI rates range from 2% to 51% on H&E staining, and the frequency increases with higher tumor category [72]. Cassidy et al. [39] report an LVI rate of 20% on H&E staining. With immunohistochemistry (S100, CD34, CD31), LVI rates increase substantially—42% [67], 69% [73], and 76% [74].

An association between LVI and cervical metastasis as well as worse survival in early oral cancer has been reported (Huang et al.) [38]. A significantly higher recurrence rate has been reported in patients with LVI (87%) compared with those without LVI (54.9%), and 3-year overall survival was 71.3% versus 90.3% [39]. Other studies have not found prognostic value for LVI [40,41].

Lymphoplasmacytic infiltration

The degree of lymphoplasmacytic infiltration (LPI) is an established prognostic factor in oral cavity carcinoma [75]. The lymphocytic response is assessed at the tumor–host interface and is classified as strong, moderate, or limited based on the presence of lymphoid nodules/aggregates in the field of view [76]. LPI is a three-level variable [77] and may also be described as (type 1) a dense, continuous rim of lymphoid tissue; (type 2) patchy lymphoid aggregates with interruptions; and (type 3) absence of lymphoid aggregates or no lymphocytic response [77]. LPI is not included as a mandatory reporting element in College of American Pathologists recommendations [78]. In the latest Royal College of Pathologists dataset, LPI is also absent from mandatory variables [79].

LPI is significantly associated with overall survival and the risk of local recurrence [77]. In early oral cancer, univariable analyses show that LPI is significantly associated with 5-year disease-specific survival [80]. In multivariable analyses, moderate and marked lymphoplasmacytic reaction is an independent predictive factor for overall and disease-specific survival [80,81]. In a cohort of early, poorly differentiated tongue tumors with weak LPI, lower survival (42.9%) has been reported compared with advanced tongue tumors (46.6%) [80].

A key immunologic factor reflecting tumor biology is the presence of tumor-infiltrating lymphocytes (TILs) [82]. Low TILs at the invasive front (<20%) is a negative prognostic factor [82].

Pattern of tumor invasion

An unfavorable pattern of invasion is a proven negative predictive factor in oral cavity carcinoma [83]. It reflects loss of intercellular cohesion, increased motility, enzymatic secretion, and loss of contact inhibition [42]. Assessment is performed at the invasive front. Jakobsson et al. [84] described four patterns as part of a malignancy grading system. Anneroth et al. [85] described four invasion patterns:
Grade 1: a pushing, well-defined border;
Grade 2: infiltrating solid cords/strands;
Grade 3: infiltration by thin strands or large groups (>15 cells per group);
Grade 4: marked diffuse infiltration as single cells or small groups (<15 cells), extending up to 1 mm beyond the tumor front.

In the AJCC Cancer Staging Manual (8th ed.) [83], Brandwein-Gensler et al. [77] proposed a fifth pattern (Grade 5): small tumor cell groups (<15 cells) separated by >1 mm; scattered extratumoral PNI or extratumoral LVI also corresponds to Grade 5.

The invasion pattern can be assessed as worst pattern of invasion (WPOI)- the most adverse pattern present- or predominant pattern of invasion (PPOI)- the most common pattern across slides [77]. Prognostic significance has been shown for WPOI, but not for PPOI [77]. High-risk patterns with independent prognostic value are WPOI-4 and WPOI-5 [43–45].

Prognostic significance: Unfavorable WPOI is associated with increased risk of local recurrence, metastasis, and mortality [43,72,84,86,87]. Crissman et al. [10] found invasion pattern to be the only significant predictive factor for 5-year survival in regression analysis. In early tumors, invasive WPOI-4/5 is associated with reduced overall survival [45]. In early oral cancer (Stage I/II), invasion pattern correlates with risk of metastasis [46]. WPOI-4/5 are significant independent predictors of locoregional recurrence; the risk of nodal metastatic recurrence in WPOI-5 is 42% [44]. In patients with T1/T2N0M0 oral tongue SCC, WPOI is an independent negative prognostic factor [43].

Impact of WPOI on margin width: Close or involved margins are associated with more aggressive invasion patterns [48]. Invasive patterns (WPOI-4/5) are the most common cause of involved deep margins [7]. Optimal margin width is influenced by invasion pattern: 1.7 mm is considered optimal for WPOI-1/2/3, whereas 7.8 mm is optimal for WPOI-4/5 [47]. Unfavorable invasion pattern and close margins (1–5 mm) are associated with higher risk of local recurrence [25].

Resection margins

Resection margins include peripheral/mucosal and deep margins [25,48]. They are assessed histologically by measuring the distance between the tumor front and the margin; commonly, >5 mm is considered clear, and 1–5 mm close [25]. The definition of an involved margin remains controversial: some define involvement as <1 mm [25], while others define it as tumor present at the margin (true transection) [88,48,77,51]. Depending on the definition, reported involved-margin rates range from 23% to 4.5% [48,7,51]. The deep margin is most commonly involved (87%), while superficial peripheral margins are less often involved (16%) [7]. In tongue carcinoma, margin involvement of 11% has been reported [7]. Higher pathological stage predicts margin involvement [7]. Risk factors for mucosal margin involvement include superficially spreading tumors without gross visibility, multiple invasion foci, carcinoma in situ at the periphery, and a second primary tumor; risk factors for deep margin involvement include invasion patterns 3- 5, perineural/intraneural invasion, vascular emboli, and perivascular extension [7].

Prognostic significance: Margin width is an accepted prognostic factor for local control [49]. Margin status predicts local recurrence (evidence level B/C) and supports consideration of adjuvant therapy [25]. Loree et al. [50] and Sutton et al. [48] define <5 mm as close and report significant differences among clear, close, and involved margins. Yamada et al. [51] found significant differences when “close” was defined as <4 mm, but no difference between close and clear when “close” was defined as <5 mm. Zanoni et al. [52] reported higher local recurrence when the margin was ≤2.2 mm, but no difference between 2.3–5 mm and >5 mm [52]. Liao et al. [53] reported <7 mm as an independent negative prognostic factor. Conversely, some studies did not find an association between margin status and local recurrence or overall survival [77].

Method of margin assessment: Several surgical approaches are used: (1) margins assessed on the main specimen and (2) margins assessed from the tumor bed [49,54]. In early oral tongue cancer (pT1/pT2), assessing margins on the main specimen improves local control compared with assessment from the tumor bed [49,54].

3. Conclusion

Early-stage tongue squamous cell carcinoma demonstrates substantial biological heterogeneity, and outcomes cannot be reliably predicted by TNM staging alone. Evidence consistently supports the prognostic value of depth of invasion, perineural and lymphovascular invasion, worst pattern of invasion, and surgical margin status, while tumor subsite, differentiation grade, and host immune response may further refine risk stratification in selected patients [6,7,16,17,33–41,43–49,75–82]. Standardized definitions, measurement methods, and routine reporting of these parameters are essential to improve comparability across studies and to support individualized decisions regarding elective neck management, adjuvant therapy, and follow-up intensity [25,48,49,54,77–79]. Future research should focus on validated multivariable models integrating key histopathologic and microenvironmental features to enable more precise, clinically actionable prognostication in early TSCC [43–46,75–82].

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