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REVIEW ARTICLE / ПРЕГЛЕДНИ РАД

Potential pitfalls within the AJCC 8th Edition Staging System for Salivary Gland Carcinoma

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SUMMARY
Salivary gland carcinomas (SGCs) are uncommon malignancies, representing less than 5% of all head and neck cancers. They exhibit marked variation in their histological types, as well as in clinical and biological behavior. According to the 5th edition of the World Health Organization (WHO) Classification of Head and Neck Tumours (5th ed.), in the chapter on salivary gland tumors, there are 21 recognized types of SGCs. The prognosis of patients with SGCs is currently assessed using the Tumor, Nodes, Metastasis staging system established by the American Joint Committee on Cancer (AJCC). However, recent evidence indicates that this system may lack sufficient sensitivity in predicting treatment response and survival outcomes, particularly with respect to cervical nodal involvement. Notably, the 8th edition of the AJCC staging protocol applies the same N-classification to both human papillomavirus-negative squamous cell carcinoma of the upper aerodigestive tract and SGCs, despite marked differences in biological behavior, therapeutic strategies, and clinical outcomes between these entities. The pitfalls in the 8th AJCC N-staging system for SGCs include the lack of prognostic significance of extranodal extension, the lack of consideration of parotid lymph nodes, and the significance of bilateral neck metastases, which are extremely rare in SGCs. The aim of the present narrative review was to highlight the unresolved limitations of the AJCC 8th edition.
Keywords: salivary gland carcinoma; staging; classification; pathological nodal status; depth of invasion

INTRODUCTION

Salivary gland carcinomas (SGCs) are rare malignancies, representing less than 5% of all head and neck cancers [1, 2]. According to the World Health Organization (WHO) – Global Cancer Observatory, in 2020 the global incidence was 0.59 and the mortality rate 0.23 per 100,000 per year [1, 2]. Despite their rarity, SGCs display remarkable heterogeneity in histological subtypes, with diverse clinical and biological behavior. The 5th edition of the WHO classification of SGCs recognizes 21 distinct primary malignant entities [3]. Approximately 80% of SGCs arise in the parotid gland, whereas carcinomas of the submandibular, sublingual, and minor salivary glands of the upper aerodigestive tract account for the remaining 20% [1, 2, 3]. Management typically involves surgical excision of the primary tumor, neck dissection in cases of cervical lymph node involvement, and adjuvant radiotherapy or concurrent chemoradiotherapy in advanced cases to improve overall survival and locoregional control [4].

The survival of patients with SGCs is estimated using the Tumor, Nodes, Metastasis (TNM) staging system developed by the American Joint Committee on Cancer (AJCC) [5] (Table 1). The 8th edition of the AJCC staging system for SGCs aimed to convey disease extent and stage, enabling physicians to plan treatment modalities and evaluate prognosis and outcomes [5]. Thus, the primary role of the TNM staging system is to predict survival rates and treatment outcomes. Recent evidence indicates that the current staging system for SGCs may lack sufficient sensitivity in predicting treatment and survival outcomes. The aim of the present narrative review was to highlight the unresolved pitfalls of the AJCC 8th edition.

DEPTH OF INVASION

Staging of minor SGCs of the upper aerodigestive tract currently parallels that of squamous cell carcinoma arising in the same sites, despite substantial differences in their clinical and biological behavior. In the 8th edition of the AJCC TNM classification, depth of invasion was incorporated into T-staging and introduced as a key prognostic factor for oral squamous cell carcinoma, strongly correlated with overall survival [5, 6]. Depth of invasion, defined as the vertical distance from the reconstructed mucosal surface to the deepest point of tumor invasion, is considered the primary predictor of lymph node metastasis in early-stage oral cancer [5, 6]. However, the application of depth of invasion to staging minor SGCs remains controversial. Calabrese et al. argued that, as minor SGCs are typically submucosal in origin, the concept of depth of invasion is not applicable in cases where the tumor does not infiltrate the

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Table 1. The AJCC TNM Classifications for Salivary Gland Carcinomas

Primary tumor (T)	
Primary tumor (T) – major salivary glands (parotid, submandibular, and sublingual)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤ 2 cm in greatest dimension without extraparenchymal extension*
T2	Tumor > 2 cm but not more than 4 cm in greatest dimension without extraparenchymal extension*
T3	Tumor > 4 cm and/or tumor having extraparenchymal extension*
T4	Moderately advanced or very advanced disease
T4a	Moderately advanced disease; Tumor invades the skin, mandible, ear canal, and/or facial nerve
T4b	Very advanced disease; Tumor invades skull base and/or pterygoid plates and/or encases carotid artery
Primary tumor (T) – minor salivary glands	
Minor salivary gland carcinomas are staged, by convention, using the mucosal tumor staging classification, according to the anatomical site of the tumor	
Regional lymph nodes – pathological N	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node ≤ 3 cm in greatest dimension and no extranodal extension (ENE [-])
N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE (+); or a single ipsilateral lymph node > 3 cm but not more than 6 cm in greatest dimension and ENE (-); or metastases in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension and ENE (-); or in bilateral or contralateral lymph nodes, none > 6 cm in greatest dimension and ENE (-)
N2a	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE (+); or a single ipsilateral lymph node > 3 cm but not more than 6 cm in greatest dimension and ENE (-)
N2b	Metastasis in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension and ENE (-)
N2c	Metastasis in bilateral or contralateral lymph node(s), none > 6 cm in greatest dimension and ENE (-)
N3	Metastasis in a lymph node > 6 cm in greatest dimension and ENE (-); or in a single ipsilateral node > 3 cm in greatest dimension and ENE (+); or multiple ipsilateral, contralateral, or bilateral nodes, any with ENE (+); or a single contralateral node of any size and ENE (+)
N3a	Metastasis in a lymph node > 6 cm in greatest dimension and ENE (-)
N3b	Metastasis in a single ipsilateral node > 3 cm in greatest dimension and ENE (+); or multiple ipsilateral, contralateral, or bilateral nodes, any with ENE (+); or a single contralateral node of any size and ENE (+)
Distant metastases (M)	
M0	No distant metastasis
M1	Distant metastasis

basement membrane [7]. These authors suggested that applying the AJCC 8th edition TNM classification to minor SGCs of the oral cavity may result in overstaging and, consequently, overtreatment [7]. Conversely, Das and Misra emphasized that the submucosal location of minor SGCs facilitates invasion into adjacent structures (e.g., bone, muscle, deep neck spaces), thereby supporting the role of depth of invasion in guiding radical surgical management, with excision extending beyond the greatest depth regardless of basement membrane or mucosal involvement [8]. In the absence of prospective evidence linking depth of invasion to survival in minor SGCs, its applicability as a staging parameter remains unclear. Nonetheless, depth of invasion assessment may aid surgical planning aimed at optimizing locoregional disease control. To address the paucity of evidence regarding the prognostic value of depth of invasion in minor SGCs, imaging-based evaluation – taking into account glandular anatomy and site-specific invasion patterns – may serve as a useful adjunct in preoperative planning [9, 10].

PATHOLOGICAL CLASSIFICATION AND MOLECULAR CHARACTERIZATION: THE IMPORTANCE OF HIGH-GRADE DEDIFFERENTIATION

Recent immunological advances have considerably refined the classification and treatment of both benign and malignant head and neck lesions [11, 12, 13]. Within this context, salivary gland pathology remains one of the most complex areas in head and neck surgical pathology, where novel genetic and molecular insights have driven substantial revisions in the 5th edition of the WHO Classification of Head and Neck Tumors [3, 14]. The key updates in this edition include: 1) the integration of molecular data to define new entities; 2) the incorporation of cytological evaluation in accordance with the Milan system; and 3) the recognition of high-grade transformation as a significant adverse prognostic factor [3, 14].

Given the marked heterogeneity of SGCs, accurate classification is crucial for selecting appropriate treatment strategies and for determining survival and prognostic

outcomes. Notable revisions have been made in the classification of adenocarcinoma, not otherwise specified, which has now been subdivided into microsecretory carcinoma, sclerosing microcystic adenocarcinoma, mucinous adenocarcinoma, salivary carcinoma not otherwise specified, and several emerging entities [3, 14]. In the 5th edition of the WHO classification, molecular alterations were incorporated into the definitions of multiple malignancies, including mucoepidermoid carcinoma, adenoid cystic carcinoma, secretory carcinoma, polymorphous adenocarcinoma, hyalinizing clear cell carcinoma, mucinous adenocarcinoma, and microsecretory adenocarcinoma [3, 14].

Histological grading is considered one of the most important and reliable prognostic factors in SGCs. Grading is based on the cellular and morphological characteristics of individual tumors, as well as the recognition of entity-specific features [15–20]. A high histological grade has been identified as an independent predictor of poor overall survival, increased risk of locoregional recurrence, and higher likelihood of distant metastasis. Brajković et al. reported that perineural invasion was frequently associated with high-grade tumors, correlating with a 32% reduction in overall survival and an 80% increase in the risk of local recurrence [16]. To date, a universal histological grading system for SGCs has not been recommended [3], and evaluation remains particularly challenging in tumors with minimal cellular atypia [3, 14]. In this context, molecular diagnostics play an increasingly important role, providing insights into tumor biology and informing the suitability of patients with recurrent or metastatic disease for targeted therapies.

Furthermore, recent findings suggest that the number of positive lymph nodes, rather than extranodal extension or nodal diameter, may represent a more reliable independent predictor of survival and treatment outcomes in SGCs.

Nodal involvement is widely recognized as one of the most significant prognostic factors influencing survival and treatment outcomes in SGCs [1–4]. In the current 8th edition of the AJCC staging system, the same N-classification is applied to both human papillomavirus-negative squamous cell carcinoma of the upper aerodigestive tract and SGCs, despite the biological and clinical differences between these entities [5]. For squamous cell carcinoma, extranodal extension (ENE) and the largest nodal diameter have been identified as the most critical nodal prognostic indicators, strongly associated with survival and treatment outcomes. However, recent trials reported pitfalls in the AJCC N-staging system for SGCs, including the lack of prognostic significance of ENE, the lack of consideration of parotid lymph nodes, and the significance of bilateral neck metastases, which are extremely rare in SGCs [21–25].

Brajković et al. [16, 24] reported that the number of pathologic lymph nodes, rather than ENE or nodal size, was associated with survival rates and treatment outcomes in SGCs. The prognosis was statistically significantly worse in patients with multiple nodal metastases (pN2 and pN3) than in those with absent or limited nodal involvement (pN0 and pN1) [16, 24]. Lombardi et al. [25] identified both the number and the maximum diameter of nodal metastases as major prognostic determinants of survival. Based on these findings, the authors proposed novel N-classifications stratified according to the number of metastatic nodes (0 *vs*. 1–3 *vs*. ≥ 4) and/or their maximum diameter (< 20 mm *vs*. > 20 mm) [25]. According to Aro et al. [26], the number of positive lymph nodes represents an independent nodal prognostic factor, and patients were stratified into different stages: N0, N1 (1–2 pN+), N2 (3–21 pN+) and N3 (> 22 pN+ or ENE+). Similarly, Lee et al. [27] stratified patients with intermediate- and high-grade SGCs into three nodal stages: N0, N1 (one positive lymph node), and N2 (≥ 2 positive nodes and/or ENE+). In addition, the lymph node ratio, defined as the ratio of positive lymph nodes to the total number of dissected nodes, has been proposed as an independent prognostic factor for survival [28]. Notably, prognostic stratification based on these proposed modifications to pN staging demonstrated superior predictive value compared with the current TNM staging system.

The current AJCC staging system does not recognize parotid lymph nodes as a distinct prognostic category in parotid gland carcinomas (PGCs). However, several studies have highlighted their potential importance. Brajković et al. [24] reported pathologic parotid lymph node involvement in 36% of high-grade PGCs, which was associated with an increased risk of locoregional relapse and lateral neck involvement. Similarly, Lombardi et al. [25] demonstrated that disease localization to parotid lymph nodes significantly increased the risk of cervical nodal metastases and adversely impacted survival. The presence of metastatic parotid nodes in parotidectomy specimens may therefore serve as a predictive marker for cervical metastases in clinically node-negative (cN0) cases, particularly in high-grade tumors. Lim et al. reported a 38% incidence of parotid node metastasis in cN0 cases, which correlated with occult cervical nodal disease and a higher risk of locoregional recurrence [29]. Klussmann et al. [30] further observed that 80% of patients with occult cervical metastases also had involved parotid nodes. Consequently, several authors advocate total parotidectomy as the optimal surgical approach for PGCs, even in early-stage tumors (T1/T2) [31]. In contrast, others have questioned the prognostic significance of parotid lymph nodes, citing the underdeveloped lymphatic network of the gland, which may not reliably harbor metastatic deposits [32]. Taken together, parotid node status may help identify high-risk patients who could benefit from elective neck dissection or adjuvant radiotherapy.

Regional lymph node involvement is widely recognized as an adverse prognostic factor in salivary gland malignancies, underscoring the importance of detecting patients at high risk for regional metastasis. The standard treatment for clinically node-positive (cN+) neck disease consists of neck dissection tailored to the number, size, and extranodal spread of metastatic nodes, followed by adjuvant radiotherapy [4]. In contrast, management of the clinically node-negative (cN0) neck remains controversial and is generally individualized. Elective neck dissection is usually

recommended when the risk of occult nodal metastasis exceeds 15–20% for a given tumor type [33, 34]. Several studies of elective neck dissection in high-grade major SGCs have reported occult metastases in 20–40% of cases [4, 16, 24]. In a large cohort of 2807 patients with adenoid cystic carcinoma of major salivary glands, Xiao et al. [35] demonstrated that elective neck dissection improved overall survival in pT3–pT4 tumors. Similarly, Zbären et al. [36] found that patients with parotid carcinoma who underwent elective neck dissection had a significantly lower rate of locoregional recurrence compared with those managed without elective neck dissection. Occult metastases following surgical resection of SGCs were most frequently identified in cervical levels II, III, and V [37, 38].

DISTANT METASTASES

Distant metastases (DM) represent the leading cause of treatment failure and mortality in patients with SGCs. High-grade histology, advanced TNM stage, and nodal metastases are the principal prognostic factors associated with DM development. Brajković et al. reported a 35% incidence of DM in high-grade SGCs and demonstrated that, among the TNM stage components, pathological nodal status was the independent predictor of both regional and distant metastases as well as poor overall prognosis [39]. Importantly, the number of pathological nodes – but not ENE or nodal size – was significantly associated with the risk of DM. Despite excellent locoregional disease control, the rate of DM remains high, particularly in patients with high-grade tumors. Freitag et al. [15] and Haderlein et al. [40] reported five-year distant metastasis-free survival rates of 62.7% and 56.5%, respectively, in previously treated patients with high-grade SGCs. The treatment of metastatic disease is particularly complicated by tumor heterogeneity.

The National Comprehensive Cancer Network guidelines list multiple management options for patients with distant metastases, including observation, metastasectomy, chemotherapy, concurrent chemoradiotherapy, hormone therapy, and targeted immunotherapy [41, 42]. Selected patients with oligometastatic disease and good performance status may benefit from surgical resection; metastasectomy has been associated with significantly improved five-year survival, reduced overall mortality, and lower cancer-specific mortality compared with non-surgical approaches [41, 43]. Stereotactic body radiation therapy offers a non-invasive alternative for patients with oligometastatic disease who are not candidates for surgery [44, 45]. In contrast, patients with multiple metastases or a high tumor burden are typically managed with systemic therapy, targeted immunotherapy, or observation [41]. In cases of indolent adenoid cystic carcinoma, observation is often appropriate, with treatment initiated only upon disease progression [41, 43]. Conventional platinum-based systemic therapy has demonstrated limited efficacy, providing modest survival benefit while inducing significant systemic toxicity [39, 41, 46].

Table 2. Pitfalls in the current 8th Edition AJCC Staging for Salivary Gland Carcinomas

T	• Prospective trials on the correlation between depth of invasion and survival in minor SGCs; • Significance of tumor grade due to the variable biological and clinical behavior of histological subtypes
N	• Unclear prognostic significance of extranodal extension and nodal size; • No consideration of parotid lymph nodes; • The occurrence of contralateral nodal metastases in major SGCs is extremely uncommon; • Prospective trials on the prognostic significance of major nodal factors (extranodal extension, nodal size, the number of pathological nodes) are needed

Emerging targeted therapies have shown promising results, offering comparable or superior efficacy with lower toxicity relative to conventional chemotherapy [39, 41]. Patients with recurrent or metastatic disease are therefore encouraged to participate in clinical trials. Specific molecular alterations may guide treatment selection, such as RET and NTRK gene fusions, which can be targeted with selpercatinib or pralsetinib (RET inhibitors) and entrectinib or larotrectinib (NTRK inhibitors) [17, 18]. Similarly, androgen receptor (AR) overexpression in salivary duct carcinoma (SDC) may be managed with androgen-deprivation therapy, while human epidermal growth factor receptor 2 (HER2) overexpression or amplification is amenable to trastuzumab and potentially other HER2-targeted agents [19, 20]. In a phase II clinical trial, Takahashi et al. [47] reported a 70.2% response rate in AR-positive and HER2-positive SDC treated with trastuzumab and docetaxel. By contrast, several phase II trials investigating targeted agents such as cetuximab, imatinib, bortezomib, nelfinavir, and dovitinib demonstrated only modest activity in metastatic SGC, with no significant differences in response rates between adenoid cystic carcinoma and non-adenoid cystic carcinoma cases [48].

CONCLUSION

SGCs represent a rare and heterogeneous group of tumors with substantial variability in histological features as well as locoregional and distant metastatic potential. Tumor histological grade, AJCC tumor stage, and nodal status are consistently identified as the most powerful predictors of survival and treatment outcomes. However, further studies are required to clarify the prognostic role of depth of invasion in minor salivary gland carcinomas. Emerging evidence indicates that the current N-classification, particularly the inclusion of ENE, may lack specificity in predicting outcomes for salivary gland malignancies. Given that the primary function of any staging system is to stratify prognosis, the clinical relevance of ENE and nodal dimension in SGC staging warrants further investigation. Recent studies highlight the increasing number of pathologic cervical nodes as a more reliable prognostic factor for survival and treatment outcomes. Additionally, the current AJCC staging system does not account for positive parotid lymph

nodes, despite growing evidence linking their involvement with locoregional treatment failure.

DM remain the leading cause of mortality and treatment failure in SGCs. Overall survival in metastatic disease is generally poor, as only a minority of patients present with operable metastases, while conventional platinum-based systemic therapies confer limited benefit and considerable toxicity. Novel targeted therapies directed at specific molecular alterations have demonstrated encouraging preliminary results; however, these findings remain in the early stages of clinical evaluation (Table 2).

Ethics: The authors affirm that the manuscript has been written in compliance with the ethical standards of the *Serbian Archives of Medicine* and with the institutional ethical regulations applicable to each author.

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Потенцијални недостаци осме ревизије класификације тумора пљувачних жлезда Америчког заједничког комитета за рак

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САЖЕТАК

Карциноми пљувачних жлезда (КПЖ) су ретки малигнитети, који чине мање од 5% свих малигнитета главе и врата. Одликују се значајном разноликошћу хистолошких подтипова, са различитим клиничким и биолошким понашањем. У петој ревизији класификације Светске здравствене организације за болести пљувачних жлезда издваја се 21 тип примарних малигнитета ових жлезда. Преживљавање болесника са КПЖ процењује се коришћењем TNM (тумор, нодус, метастазе) система стадијума болести 8. ревизије Америчког заједничког комитета за рак. Нова истраживања указују на то да тренутни систем одређивања стадијума болести за КПЖ није довољно осетљив да би предвидео исход лечења и преживљавања болесника, посебно у вези са регионалним лимфним метастазама. Наиме, актуелни протокол предлаже исту нодалну класификацију за *HPV*-негативни сквамоцелуларни карцином горњег аеродигестивног тракта и КПЖ, упркос значајним разликама у биолошком понашању, модалитетима лечења и исходима између ова два ентитета. Недостаци у одређивању нодалног статуса код КПЖ укључују нејасан прогностички значај екстранодалног ширења за КПЖ, неодређен статус паротидних лимфних чворова и упитан значај контралатералних метастаза на врату, које су изузетно ретке код КПЖ. Циљ овог наративног прегледног чланка је да укаже на недостатке у актуелној TNM класификацији болести за КПЖ.

Кључне речи: карциноми пљувачних жлезда; стадијум болести; класификација; патолошки нодални статус; дубина инвазије тумора