



# Pathological risk factors stratification in pN3b oral cavity squamous cell carcinoma: Focus on the number of positive nodes and extranodal extension

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## ABSTRACT

**Objective:** According to the AJCC 2017 Staging Manual, oral cavity squamous cell carcinoma (OCSCC) with pN2 disease (based on the AJCC 2010 criteria) and extra-nodal extension (ENE) should be classified as pN3b. We performed a detailed outcome analyses in this patient subgroup.

**Material and methods:** We retrospectively reviewed the clinical records of consecutive OCSCC patients who underwent radical surgery between 1996 and 2017. Patients with pN3b disease (n = 365) were divided into a pN+ ≥ 8/ENE ≥ 5 subgroup (defined by the presence of pN+ ≥ 8 nodes or ENE ≥ 5 nodes, n = 77) and a pN+ ≤ 7/ENE ≤ 4 subgroup (defined by the presence of pN+ ≤ 7 nodes and ENE ≤ 4 nodes, n = 288). Patients with pN0/pN1/pN2 (n = 1192/179/197) disease were included for comparison purposes.

**Results:** Patients in the pN+ ≥ 8/ENE ≥ 5 subgroup had less favorable 5-year outcomes than those in the pN+ ≤ 7/ENE ≤ 4/pN2/pN1/pN0 groups (local control, 64%/79%/86%/83%/88%, p < 0.001; neck control, 55%/75%/80%/86%/93%, p < 0.001; distant metastases, 67%/28%/20%/12%/3%, p < 0.001; disease-free survival, 21%/51%/64%/72%/82%, p < 0.001; disease-specific survival, 25%/55%/71%/82%/92%, p < 0.001; overall survival, 19%/40%/54%/64%/82%, p < 0.001; respectively). Among patients with pN3b disease, multivariable analysis identified the pN+ ≥ 8/ENE ≥ 5 subgroup, lower neck (level IV/V) metastases, and depth of invasion ≥ 25 mm as independent adverse prognostic factors for 5-year distant metastases and survival rates.

**Conclusions:** Patients in the pN+ ≥ 8/ENE ≥ 5 subgroup have an unfavorable prognosis and their classification as pN3b is advisable. In contrast, patients in the pN+ ≤ 7/ENE ≤ 4 subgroup should be classified as pN3a.

## Introduction

Pathological neck node metastases (pN+) are a well-known adverse prognostic factor in patients with oral cavity squamous cell carcinoma (OCSCC) [1–4]. Accordingly, the 5-year overall survival (OS) rates of patients with and without pN+ node(s) are 45% and 80%, respectively [5]. Among patients with pN+ disease, the presence of extra-nodal

extension (ENE) portends the poorest prognosis, with 5-year OS rates as low as 30–35% [6,7].

Compared with the American Joint Committee on Cancer (AJCC) Staging Manual, 7th edition (2010) [8], the most recent AJCC Staging System (8th edition, 2017) introduced significant changes in terms of ENE classification when determining the N-status of patients with oral malignancies. Specifically, the presence of ENE in pN1 and pN2 disease

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results in a disease upstaging to pN2a and pN3b, respectively [9]. However, the prognosis of OSCC patients with pN3b disease is not invariably poor. For example, patients with 10 nodes showing ENE or 20 pN+ nodes (eventually including at least one ENE) are expected to have much poorer clinical outcomes than those with only two pN+ nodes (eventually including one ENE). Remarkably, these two very different cases should both be equally staged as pN3b disease. Of note, pN3a disease according to the AJCC Staging Manual 8th edition

(presence of a single metastatic node > 6 cm in size without evidence of ENE; previously staged a pN3 disease according to the AJCC Staging Manual 7th edition) is extremely rare, accounting for < 0.1% of all OSCC cases [9,10].

We and others have previously shown that the number of pN+ is a prognostic predictor in OSCC patients [4,11–17]. In addition to the pN+ number, the outcomes of pN3b can be further stratified according to the presence of different clinicopathological risk factors (RFs; e.g., level

**Table 1**

Univariate analyses of 5-year outcomes in patients with pN3b oral cavity cancer (n = 365).

Risk factors (n, %)	5-year local control (% n event)	p	5-year neck control (% n event)	p	5-year DM (% n event)	p	5-year DFS (% n event)	p	5-year DSS (% n event)	p	5-year OS (% n event)	p
ENE number		0.117		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001
1–4 (310, 84.9)	79 (46)		74 (72)		31 (84)		49 (146)		53 (131)		39 (184)	
≥ 5 (55, 15.1)	66 (9)		53 (22)		68 (31)		20 (40)		23 (35)		18 (43)	
pN+ number		0.394		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001
≤ 7 (306, 83.8)	78 (47)		75 (70)		30 (78)		49 (143)		54 (125)		39 (179)	
≥ 8 (59, 16.2)	72 (8)		54 (24)		71 (37)		21 (43)		21 (41)		16 (48)	
Lower neck metastases		0.172		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001
No (325, 89.0)	78 (49)		75 (74)		33 (95)		48 (156)		52 (139)		38 (195)	
Yes (40, 11.0)	64 (6)		41 (20)		60 (20)		17 (30)		22 (27)		17 (32)	
pN2c disease		0.298		0.675		0.006		0.016		0.069		0.085
No (297, 81.4)	78 (44)		71 (76)		33 (85)		47 (145)		52 (129)		38 (179)	
Yes (68, 18.6)	72 (11)		70 (18)		51 (30)		34 (41)		39 (37)		28 (48)	
Sex		0.775		0.686		0.890		0.389		0.769		0.563
Male (340, 93.2)	78 (51)		71 (89)		36 (108)		44 (177)		49 (157)		36 (211)	
Female (25, 6.8)	70 (4)		69 (5)		35 (7)		52 (9)		51 (9)		28 (16)	
Age at disease onset		0.578		0.248		0.195		0.228		0.237		0.541
< 65 y (320, 87.7)	77 (48)		70 (86)		37 (106)		44 (169)		48 (152)		36 (200)	
≥ 65 y (45, 12.3)	76 (7)		79 (8)		25 (9)		54 (17)		61 (14)		36 (27)	
Alcohol drinking		0.147		0.984		0.698		0.512		0.830		0.412
No (108, 29.6)	81 (12)		70 (27)		39 (34)		45 (51)		47 (48)		31 (74)	
Yes (257, 70.4)	76 (43)		72 (67)		35 (81)		44 (135)		50 (118)		38 (153)	
Betel quid chewing		0.301		0.329		0.458		0.090		0.310		0.894
No (64, 17.5)	83 (7)		77 (13)		31 (17)		55 (25)		56 (24)		35 (41)	
Yes (301, 82.5)	76 (48)		70 (81)		37 (98)		43 (161)		48 (142)		36 (186)	
Cigarette smoking		0.544		0.786		0.811		0.613		0.819		0.737
No (55, 15.1)	76 (7)		67 (15)		34 (16)		44 (26)		47 (24)		30 (36)	
Yes (310, 84.9)	77 (48)		72 (79)		36 (99)		45 (160)		49 (142)		37 (191)	
Differentiation		0.384		0.148		< 0.001		0.025		0.002		0.016
Well/moderate (288, 78.9)	75 (49)		73 (72)		33 (81)		46 (143)		52 (124)		38 (174)	
Poor (77, 21.1)	90 (6)		65 (22)		50 (34)		38 (43)		38 (42)		28 (53)	
pT-status		0.005		0.065		0.218		0.003		0.001		< 0.001
pT1-2 (70, 19.2)	91 (4)		81 (13)		30 (20)		61 (26)		68 (21)		56 (30)	
pT3-4 (295, 80.8)	73 (51)		69 (81)		38 (95)		40 (160)		44 (145)		31 (197)	
Tumor depth (mm)		0.557		0.705		< 0.001		0.001		< 0.001		< 0.001
< 25 (293, 80.3)	78 (45)		72 (76)		31 (81)		48 (141)		53 (124)		40 (171)	
≥ 25 (72, 19.7)	79 (10)		71 (18)		58 (34)		29 (45)		31 (42)		19 (56)	
Margin status (mm)*		0.020		0.574		0.057		0.009		0.051		0.077
≤ 4 (54, 15.0)	54 (11)		75 (11)		43 (22)		26 (35)		41 (29)		29 (37)	
> 4 (306, 85.0)	82 (39)		72 (79)		35 (91)		48 (146)		51 (132)		37 (185)	
Perineural invasion		0.938		0.438		0.104		0.560		0.434		0.791
No (154, 42.2)	76 (23)		73 (37)		31 (41)		45 (76)		51 (67)		36 (96)	
Yes (211, 57.8)	78 (32)		70 (57)		40 (74)		44 (110)		48 (99)		36 (131)	
Lymphatic invasion*		0.525		0.772		0.010		0.047		0.052		0.004
No (295, 81.0)	79 (43)		72 (76)		33 (86)		48 (145)		52 (129)		39 (174)	
Yes (69, 19.0)	66 (11)		71 (17)		51 (29)		31 (40)		36 (36)		23 (52)	
Vascular invasion*		0.306		0.623		0.180		0.102		0.051		0.045
No (340, 93.4)	78 (49)		72 (86)		35 (105)		46 (169)		51 (150)		37 (207)	
Yes (24, 6.6)	58 (5)		67 (7)		50 (10)		25 (16)		30 (15)		21 (19)	
Skin invasion		0.276		0.247		0.116		0.008		0.013		0.048
No (319, 87.4)	78 (47)		72 (80)		35 (97)		47 (156)		52 (138)		38 (192)	
Yes (46, 12.6)	71 (8)		64 (14)		47 (18)		30 (30)		32 (28)		21 (35)	
Bone marrow invasion		0.293		0.478		0.612		0.862		0.444		0.014
No (287, 78.6)	79 (41)		70 (77)		36 (90)		44 (149)		51 (130)		38 (170)	
Yes (78, 21.4)	71 (14)		76 (17)		38 (25)		45 (37)		43 (36)		26 (57)	
Treatment modality		< 0.001		< 0.001		0.005		< 0.001		< 0.001		< 0.001
Surgery (26, 7.1)	45 (5)		39 (9)		53 (8)		28 (13)		17 (13)		4 (25)	
Surgery + RT/CCRT (339, 92.9)	78 (50)		73 (85)		35 (107)		46 (173)		51 (153)		38 (202)	

DM: distant metastases; DFS, disease-free survival; DSS, disease-specific survival; OS, overall survival; RT, radiotherapy; CCRT, concurrent chemoradiotherapy.

\* Unavailable data: margin status (n = 5), lymphatic invasion (n = 1), vascular invasion (n = 1).

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