

Lymph Node Ratio and Depth of Invasion in cN0 Oral Tongue Squamous Cell Carcinoma: A Retrospective Review

Michael Xie, MD¹; Peter Dziegielewski, MD, FRCSC²; Nhu-Tram Nguyen, MDCM, FRCPC³; Hadi Seikaly, MD, MAL, FRCSC⁴; Jeffrey Harris, MD, FRCSC⁴; Dan O’Connell, MD, FRCSC⁴; Vince Biron, MD, PhD, FRCSC⁴; Stuart D. Archibald, MD, FRCSC¹; B. Stanley Jackson, MD, FRCSC¹; James Edward Massey (Ted) Young, MD, FRCSC, FACS¹; and Michael K. Gupta, MD, MSc, FRCSC¹; Han Zhang, MD, FRCSC¹

¹Division of Otolaryngology—Head and Neck Surgery; McMaster University; Hamilton, Ontario, Canada

²Department of Otolaryngology-Head and Neck Surgery, University of Florida.

³Division of Radiation Oncology; McMaster University; Hamilton, Ontario, Canada

⁴Division of Otolaryngology—Head and Neck Surgery; University of Alberta; Edmonton, Alberta, Canada



Introduction

Oral cavity cancer has a 354 000 world wide annual incidence

- >90% SCC
- 40-50% oral tongue subsite, higher cause specific mortality

Cervical nodal metastasis is the most important factor in oral cavity SCC (OCSCC)

- Occult nodal metastasis rates range from 8-49%
- Elective neck dissection (END) has a diagnostic/staging and therapeutic role in OCSCC

Depth of invasion (DOI) is a novel well established prognostic factor and guides END

$$\text{Lymph node ratio (LNR)} = \frac{\# \text{ lymph nodes positive (tumor factor)}}{\# \text{ lymph nodes dissected (treatment factor)}} \times 100$$

Both DOI and LNR predict survival and locoregional control

Objective: Examine the relationship between DOI and LNR as prognostic factors in oral tongue SCC (OTSCC)

- Does LNR provide additional prognostic information?

Methods

Recruitment population: Consecutive, newly diagnosed OTSCC patients treated at McMaster University, University of Alberta, or University of Florida from 2004-2018

Study Design: Multi-institutional retrospective review of head and neck cancer databases

Study Population: 356 cN0 OTSCC out of 394 eligible patient

Inclusion Criteria: (1) >18yo, (2) pathologic diagnosis of OTSCC, (3) cT(1-4)N0, primary surgery with curative intent

Exclusion Criteria: (1) palliative intent, (2) previous oncologic head and neck surgery/radiotherapy, (3) incomplete data sets

Outcomes: Association between DOI and LNR>median (5.7), overall **survival (OS)**, **disease specific survival (DSS)**

Statistics: Descriptive statistics, chi squared for discrete variables, ANOVA for continuous variables, multivariate analysis, time to event analysis (KM, log rank, multivariate cox regression. Level of significance at p<0.05. Statistics performed using SPSS 26.0 (SPSS Inc, Chicago, IL.)

Results: Validation of Previous Evidence

DOI was associated with higher than median LNR (β 1.811, 95% CI 1.213-4.441) on MVA

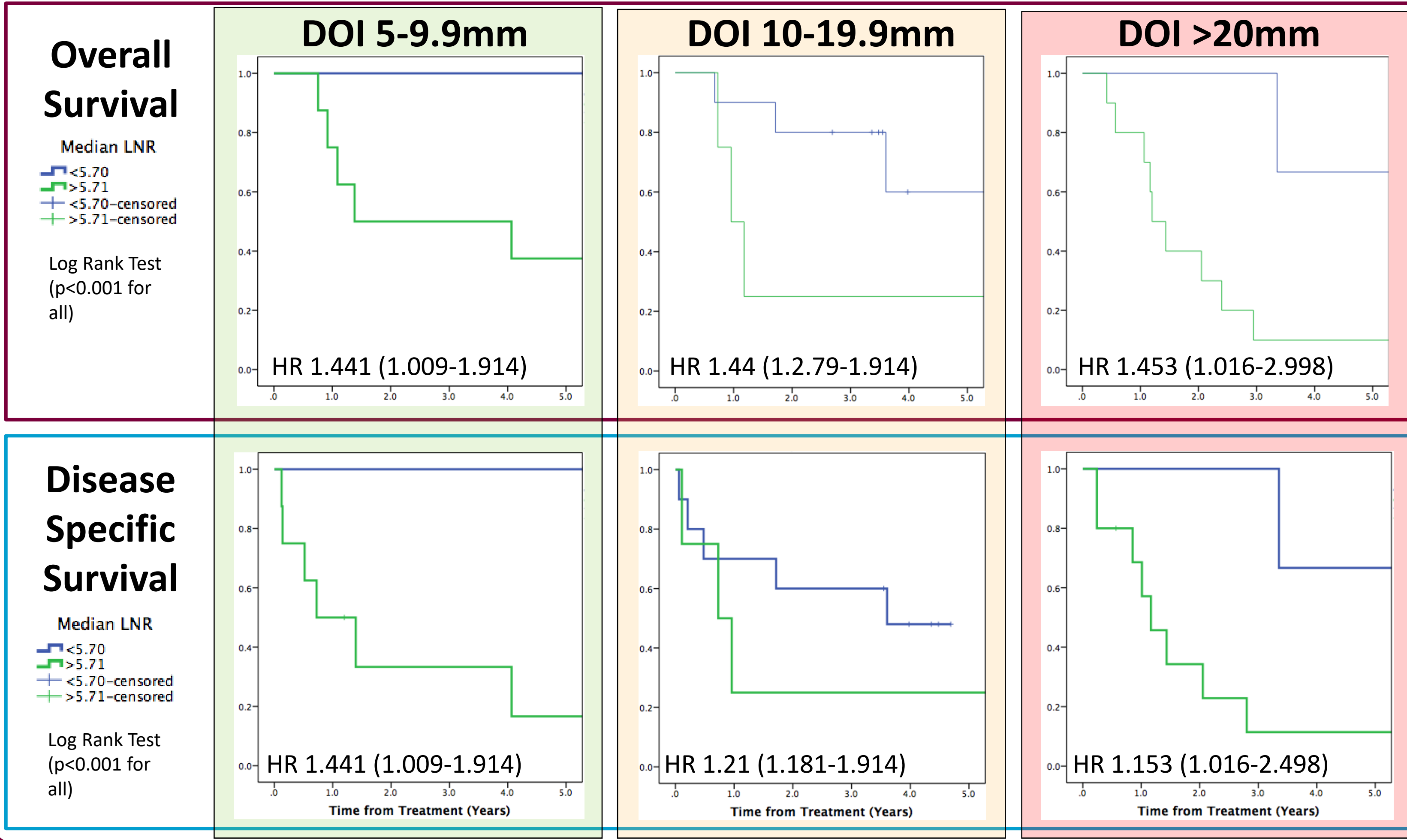
Both DOI and LNR were prognostic for OS and DSS

- pN, LN+, LN sampled, age, gender, PNI, LVI, ECS, margin, smoking status, adjuvant therapy

Results

Variable	DOI <5mm	DOI 5-9.9mm	DOI 10mm-19.9mm	DOI > 20mm	p-Value
N	227 (63.9)	55 (15.5)	51 (14.4)	23 (6.5)	
Age					0.109
Gender [‡]					0.973
Female	68 (30.0)	16 (29.1)	15 (29.4)	7 (30.4)	
Male	159 (70.0)	39 (70.9)	36 (70.6)	16 (69.6)	
Charlson Comorbidity Index [‡]	1.2 (1.0-2.1)	1.1 (1.0-2.2)	1.1 (1.0-2.2)	1.1 (1.0-2.2)	0.974
Tumour Size [‡]					<0.0001
< 2 cm	221 (97.4)	31 (56.3)	0	0	
2-4 cm	6 (2.6)	20 (36.4)	20 (39.2)	2 (8.7)	
> 4 cm	0	4 (7.3)	31 (60.8)	21 (91.3)	
Margin [‡]					0.134
< 1mm	0 (0.0)	0 (0.0)	4 (7.8)	3 (13.0)	
1mm-4mm	159 (70.0)	24 (43.6)	24 (47.1)	14 (60.9)	
>5mm	68 (30.0)	31 (56.4)	23 (45.1)	6 (26.1)	
PNI [‡]	32 (14.1)	24 (43.6)	47 (92.2)	22 (95.7)	0.001
LVI [‡]	1 (0.04)	34 (61.8)	46 (90.2)	22 (95.7)	0.001
Neck Dissection Levels [‡]					0.024
Levels 1-3	143 (63.0)	31 (56.4)	12 (23.5)	9 (39.1)	
Levels 1-4	84 (37.0)	24 (43.6)	35 (68.6)	11 (47.8)	
Levels 1-5	0 (0.0)	0 (0.0)	3 (5.9)	1 (4.3)	
Bilateral	0 (0.0)	0 (0.0)	1 (2.0)	2 (8.7)	
Lymph Nodes Sampled [‡]	32.01 (11-64)	33.14 (14-44)	37.9 (28-61)	32.2 (24-55)	0.095
Lymph Nodes Positive ^a	0.08	1.24	3.14	4.8	0.001
Lymph Node Ratio ^a	0.21	3.74	8.41	14.44	0.001
ECS [‡]	1 (0.4)	5 (9.1)	7 (13.7)	12 (52.2)	0.001
pN-Stage [‡]					0.001
N0	219 (96.5)	8 (14.5)	0 (0.0)	0 (0.0)	
N+	8 (3.5)	47 (85.5)	51 (100.0)	23 (100.0)	
Adjuvant Therapy [‡]					0.001
RT	24 (10.6)	31 (56.4)	2 (3.9)	2 (8.7)	0.001
CRT	4 (1.8)	17 (30.9)	46 (90.2)	21 (91.3)	0.001

[‡]Mean (Range), [‡]Frequency (%), ^aMean



Discussion

Existing literature demonstrates association between DOI and LNR on MVA (Ding et al, 2019)

No established median LNR cut-off (~6, range 6-10)

Meta-analysis shows that LNR is an independent predictor of OS and DSS (Huang et al, 2019)

LNR further stratifies survival outcome in DOI subgroups

- Particularly in DOI 5-9.9mm
- May have a role for guiding treatment escalation N1 disease with less than 18 dissected LNs

Limitations

- Retrospective
- Small stratified sample sizes
- Although multi-institutional, we were unable to collect/control for site related heterogeneity (e.g. surgical and pathology department practices)

Conclusion

Within cN0 OTSCC

- Validated LNR associated with DOI
- Validated DOI and LNR alone have prognostic value
- LNR used sequentially in DOI >5mm subgroups further predicts OS and DSS

Bray, F. *et al.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA. Cancer J. Clin.* **68**, 394–424 (2018).
Brennan, S. *et al.* Prospective trial to evaluate staged neck dissection or elective neck radiotherapy in patients with CT-staged T1-2 no squamous cell carcinoma of the oral tongue. *Head Neck* **32**, 191–198 (2010).
Capote, A. *et al.* Elective neck dissection in early-stage oral squamous cell carcinoma - Does it influence recurrence and survival? *Head Neck* **29**, 3–11 (2007).
Chinn, S. B. & Myers, J. N. Oral cavity carcinoma: Current management, controversies, and future directions. *Journal of Clinical Oncology* vol. 33 3269–3276 (2015).
Ding, D. *et al.* Association between Lymph Node Ratio and Recurrence and Survival Outcomes in Patients with Oral Cavity Cancer. *JAMA Otolaryngol. - Head Neck Surg.* **145**, 53–61 (2019).
El-Naaj, I. A., Leiser, Y., Shveis, M., Sabo, E. & Peled, M. Incidence of oral cancer occult metastasis and survival of T1-T2N0 oral cancer patients. *J. Oral Maxillofac. Surg.* **69**, 2674–2679 (2011).
Farhood, Z., Simpson, M., Ward, G. M., Walker, R. J. & Osazuwa-Peters, N. Does anatomic subsite influence oral cavity cancer mortality? A SEER database analysis. *Laryngoscope* **129**, 1400–1406 (2019).
Gil, Z. *et al.* Lymph node density is a significant predictor of outcome in patients with oral cancer. *Cancer* **115**, 5700–5710 (2009).
Ho, A. S. *et al.* Metastatic lymph node burden and survival in oral cavity cancer. *J. Clin. Oncol.* **35**, 3601–3609 (2017).
Hosni, A. *et al.* Lymph node ratio relationship to regional failure and distant metastases in oral cavity cancer. *Radiother. Oncol.* **124**, 225–231 (2017).
Huang, T. H., Li, K. Y. & Choi, W. S. Lymph node ratio as prognostic variable in oral squamous cell carcinomas: Systematic review and meta-analysis. *Oral Oncology* vol. 89 133–143 (2019).
Johnson, N. W., Jayasekara, P., Amarasinghe, A. A. & Hemantha, K. Squamous cell carcinoma and precursor lesions of the oral cavity: Epidemiology and aetiology. *Periodontol.* **2000** **57**, 19–37 (2011).
Kim, S. Y., Nam, S. Y., Choi, S. H., Cho, K. J. & Roh, J. L. Prognostic value of lymph node density in node-positive patients with oral squamous cell carcinoma. *Ann. Surg. Oncol.* **18**, 2310–2317 (2011).
National Comprehensive Cancer Network. Head and Neck Cancer (Version 2.2020). https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf.
Patel, S. G. *et al.* Lymph node density in oral cavity cancer: Results of the International Consortium for Outcomes Research. *Br. J. Cancer* **109**, 2087–2095 (2013).
Ren, Z. H. *et al.* Elective versus therapeutic neck dissection in node-negative oral cancer: Evidence from five randomized controlled trials. *Oral Oncology* vol. 51 976–981 (2015).
Tam, S., Amit, M., Zafereo, M., Bell, D. & Weber, R. S. Depth of invasion as a predictor of nodal disease and survival in patients with oral tongue squamous cell carcinoma. *Head Neck* **41**, hed.25506 (2018).
Warnakulasuriya, S. Global epidemiology of oral and oropharyngeal cancer. *Oral Oncology* vol. 45 309–316 (2009).