CANCER DIAGNOSIS & PROGNOSIS
3: 457-462 (2023) doi: 10.21873/cdp.10239

WPOI-4/5 Correlates With Lymph Node Recurrence and Poor Prognosis in Early-stage Tongue Squamous Cell Carcinoma

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Abstract. *Background/Aim: Neck management in patients with early-stage tongue cancer remains controversial. The worst pattern of invasion (WPOI) of the primary tumor has been associated with the incidence of regional metastasis. We investigated the prognostic role of WPOI, especially in relation to regional lymph node recurrence and disease-specific survival (DSS). Patients and Methods: We retrospectively reviewed medical records and evaluated tumor specimens of 38 patients with early-stage tongue cancer who underwent primary tumor resection without elective neck dissection. Results: Regional lymph node recurrence rates were significantly higher in patients with WPOI-4/5 compared with WPOI-1 to -3. The 5-year DSS rates were significantly higher for WPOI-1 to -3 than for WPOI-4/5. Notably, patients with WPOI-1 to -3 achieved a 100% 5-year DSS rate with salvage neck dissection and postoperative treatment, even those with cervical lymph node recurrence, whereas patients with WPOI-4/5 had a poorer prognosis. Conclusion: Patients with WPOI-1 to -3 tumors can be followed up without neck dissection until regional lymph node recurrence is detected, with a good course after salvage treatment. In contrast, patients with WPOI-4/5 tumors who are followed up until the appearance of regional lymph node recurrence have a poor prognosis, even with adequate treatment for recurrent disease.*

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Key Words: Early-stage tongue cancer, worst pattern of invasion (WPOI), elective neck dissection, depth of invasion.

Cancers of the lip and oral cavity represent the 16th most common neoplasm worldwide. The optimal neck-management strategy in patients with early-stage cT1-T2 and clinically node-negative (cN0) oral tongue squamous cell carcinoma (OTSCC) remains controversial. The occult metastasis rate of early-stage OTSCC is reported to be around 20%-40% (1-3), with the presence of nodal metastasis being the main prognostic factor. According to the "watchful-waiting" approach, neck dissection should not be performed in patients with early-stage OTSCC. Alternatively, elective neck dissection (END) may be conducted at the time of surgery for the primary tongue lesion to reduce the risk of regional failure due to subclinical occult lymph node metastasis. Although carrying out END for all patients has been shown to be associated with a higher survival rate, 60%-80% of patients without potential metastases may undergo unnecessary surgery, potentially resulting in neurological complications, dysphagia, and other problems. However, adopting a watchful-waiting policy, in which neck dissection is limited to those patients who develop regional recurrence, means that lymph node metastasis may be uncontrollable by the time the recurrence is detected.

A prospective randomized controlled trial in patients with cT1-T2N0M0 oral cancer revealed that END resulted in higher overall and disease-free survival rates compared with a watchful-waiting approach (4). However, the trial was designed based on the previous 7th TNM staging system, which only considered tumor diameter and not tumor thickness or depth of invasion (DOI). Tumor thickness and DOI of the primary oral cancer have been associated with the incidence of regional metastasis (5). The 8th edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) staging system added DOI to the criteria for T classification in patients with oral

Table I. *Clinicopathological features*.

	(n=38)
Males, n (%)	25 (66)
Age, years	
Median	61
Range	34-82
Follow-up, months	
Median	70
Q1-Q3	56-80
pT Stage UICC (8th), n (%)	
pT1	19 (50)
pT2	19 (50)
WPOI, n (%)	
WPOI-1	3 (7.9)
WPOI-2	7 (18)
WPOI-3	19 (50)
WPOI-4	8 (21)
WPOI-5	1 (2.6)

UICC: Union for International Cancer Control; WPOI: worst pattern of invasion.

Table II. *Five-year regional lymph node recurrence and disease-specific survival*.

n=38	LN recurrence, n (%)	DSS, n (%)
pT stage		
pT1 (n=19)	6 (32)	17 (89)
pT2 (n=19)	11 (58)	17 (89)
WPOI		
WPOI-1 (n=3)	0	3 (100)
WPOI-2 (n=7)	1 (14)	7 (100)
WPOI-3 (n=19)	9 (47)	19 (100)
WPOI-4 (n=8)	6 (75)	5 (63)
WPOI-5 (n=1)	1 (100)	0
WPOI-1 to -3 (n=29)	10 (34)	29 (100)
WPOI-4/5 (n=9)	7 (78)	5 (56)

WPOI: Worst pattern of invasion; LN: lymph node; DSS: disease-specific survival.

cancer. However, the survival benefit of END in patients with revised early-stage OTSCC are still under investigation including a randomized multicenter phase III study (6).

In addition to DOI, various histopathological prognostic factors, including invasive tumor front (7) where the laminin 2 chain is highly expressed in tumor cells (8), tumor budding (9), mode of invasion (10), and worst pattern of invasion (WPOI) (11) have been evaluated. WPOI was proposed by Brandwein-Gensler *et al*. (11) by modifying and expanding the concept of pattern of invasion (12). The WPOI is the highest score of the pattern of invasion present in the surgical specimen, no matter how focal. This grading system was added to the International Collaboration on Cancer Reporting dataset as a mandatory pathology reporting element for oral cavity squamous cell carcinoma (13). The AJCC staging manual 8th edition indicates that WPOI type 5 is an important prognosticator in patients with oral cancer (14). The five patterns of invasion are as follows: Type 1, pushing borders; Type 2, finger-like growth; Type 3, large separate islands, >15 cells per island; Type 4, small tumor islands, ≤15 cells per island; and Type 5, tumor satellites, ≥1 mm from the main tumor or next closest satellite (15).

In this study, we aimed to investigate the prognostic role of WPOI, especially in relation to regional lymph node recurrence and disease-specific survival (DSS).

Patients and Methods

Study cohort. We conducted a retrospective study of consecutive patients with early-stage OTSCC who underwent transoral resection without END. We reviewed medical records and evaluated tumor specimens. The cases were re-staged according to the AJCC/UICC classification 8th edition. The inclusion criteria were: 1) patients who underwent primary surgery by transoral approach without END at our institution between January 2005 and December 2017, 2) a diagnosis of pT1-T2, cN0M0 OTSCC, and 3) availability of slides of primary resection for pathologic review. The primary lesion was treated by a transoral approach, unless the safety margin of 1.5 cm from the macroscopic tumor involved the mylohyoid muscle, which required pull-through resection. The exclusion criteria were: 1) prior treatment of the reference carcinoma, 2) adjuvant radiotherapy for the primary surgery, and 3) patients who dropped out before their 36-month follow-up visit. Patients who developed regional lymph node recurrence underwent either salvage surgery followed by adjuvant chemoradiotherapy in the case of extranodal extension, or chemoradiotherapy when the patient refused to undergo surgical treatment. Thirty-eight patients were included in this study. This study was approved by the Institutional Review Board of Saga University (approval number 2021-11-R-05).

Pathologic review. A pathologic review was conducted by a head and neck pathologist (AM) without access to the individual clinical data. WPOI was assessed according to previous descriptions of sections stained using hematoxylin-eosin (11, 15).

Statistical analysis. Survival analyses were performed using the Kaplan-Meier method and compared using the log-rank test for each group, and $p<0.05$ was considered statistically significant. All statistical analyses were carried out using JMP Pro 17.0.0 (JMP Statistical Discovery LLC, Cary, NC, USA).

Results

Clinicopathological characteristics. The study included 38 patients with pT1-T2, cN0M0 OTSCC (Table I). The median patient age was 61 years (range=34-82 years), and there were 25 male and 13 female patients. The median duration of follow-up was 70 (Q1-Q3=56-80) months. The pT stage was pT1 in 19 cases (50%) and pT2 in 19 cases (50%). The distribution of WPOI among our cohort was as follows:

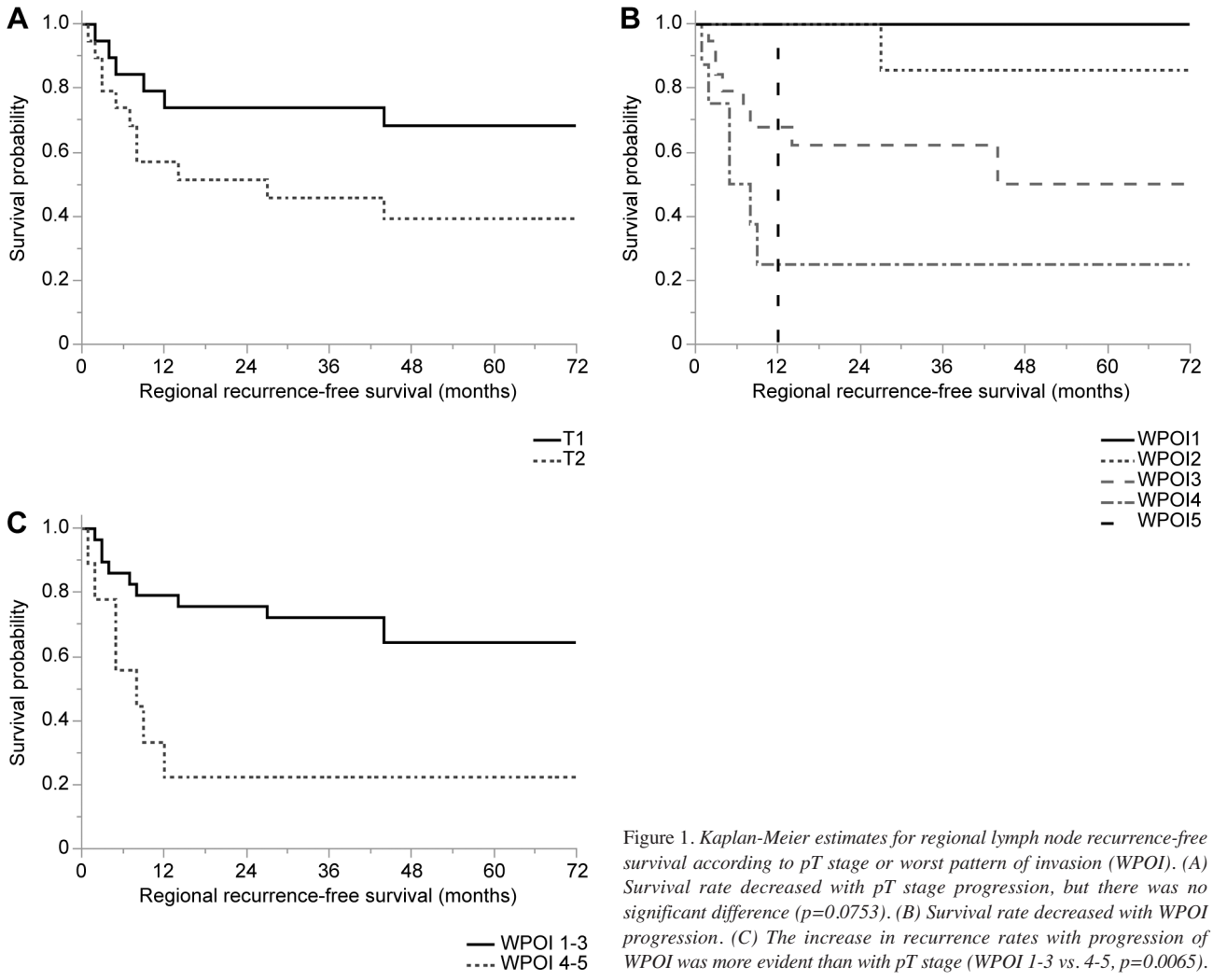

Figure 1. *Kaplan-Meier estimates for regional lymph node recurrence-free survival according to pT stage or worst pattern of invasion (WPOI). (A) Survival rate decreased with pT stage progression, but there was no significant difference (p=0.0753). (B) Survival rate decreased with WPOI progression. (C) The increase in recurrence rates with progression of WPOI was more evident than with pT stage (WPOI 1-3 vs. 4-5, p=0.0065).*

WPOI-1 in three (7.9%), WPOI-2 in seven (18%), WPOI-3 in 19 (50%), WPOI-4 in eight (21%), and WPOI-5 in one (2.6%) case. All WPOI-1 and -5 cases were pT1, and WPOI-2 to -4 cases were either pT1 or pT2 (data not shown).

Risk of regional recurrence according to pT stage and WPOI. Seventeen patients (45%) had regional lymph node recurrence at the time of last follow-up. The regional lymph node recurrence rates for patients with pT1 and pT2 were 32% and 58%, respectively, and increased with progressive pT stage (Table II). Interestingly, while the WPOI varied from WPOI-1 to -5, 16 of 17 patients (94%) with regional lymph node recurrence had ≥WPOI-3, and seven of nine cases (78%) with highly invasive type of WPOI-4 or -5 developed regional lymph node recurrence. The Kaplan-Meier curve for regional lymph node recurrence-free survival is shown in Figure 1A-C. Although the survival rate appeared to decrease with pT stage progression, the difference was not significant (p=0.0753) (Figure 1A). However, in line with WPOI, the increase in regional lymph node recurrence rates was more evident than that for pT stage (Figure 1B), with lymph node recurrence rates of 34% and 78% for WPOI-1 to -3 and -4/5 respectively (Figure 1C). Regional lymph node recurrence rates were significantly higher for WPOI-4/5 than for WPOI-1 to -3 (p=0.0065), and correlated more strongly with WPOI than with pT staging.

Survival risks according to pT stage and WPOI. We examined DSS rates in relation to pT stage and WPOI (Figure 2A-C). Of the 38 cases, four patients died from the disease, with a 5-year DSS of 89%. The survival rates for pT1 and pT2 were comparable (p=0.9208) (Figure 2A). The survival rate decreased with WPOI progression (Figure 2B). The 5-year DSS rates for WPOI-1 to -3 and -4/5 were 100% and 56%,

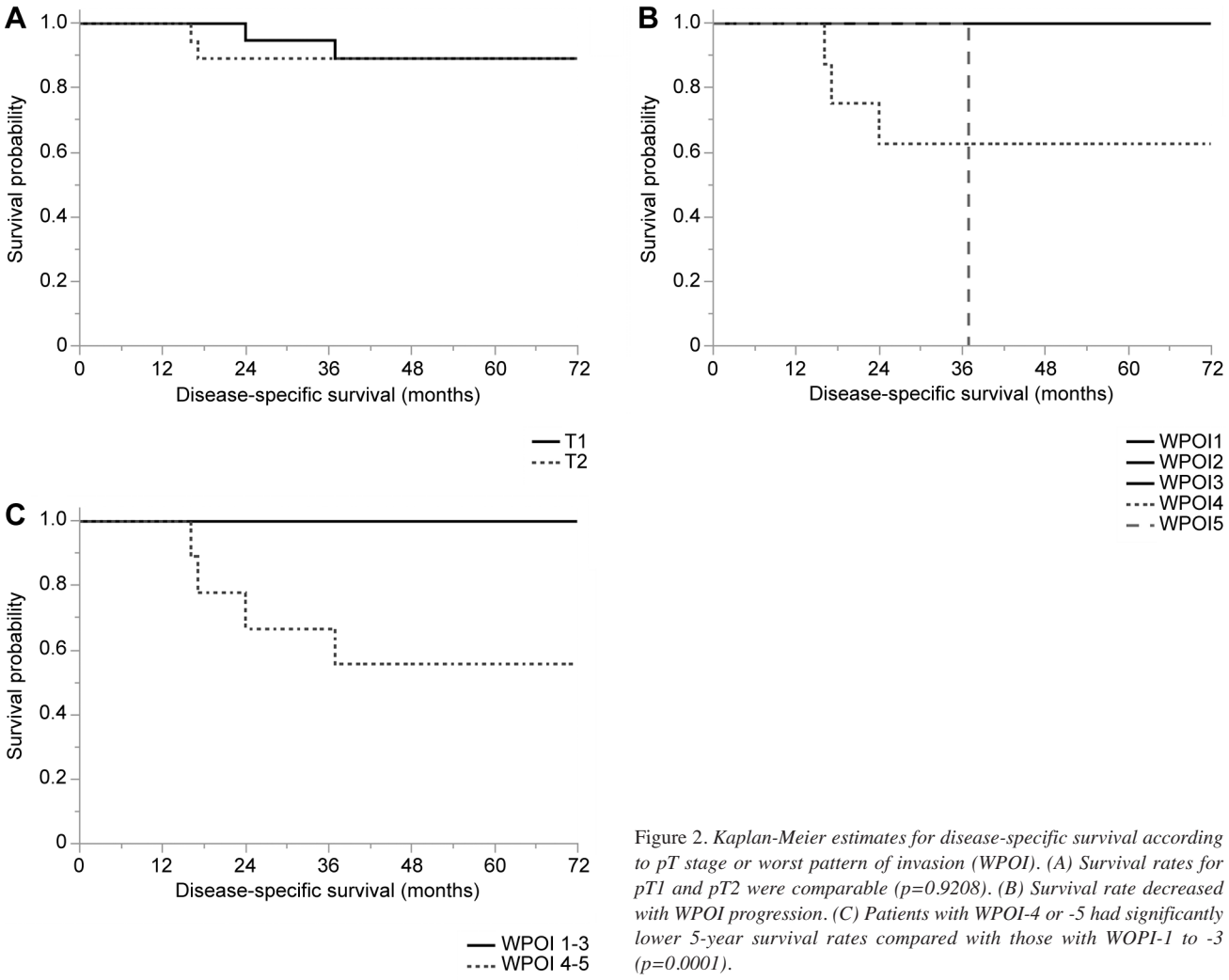

Figure 2. *Kaplan-Meier estimates for disease-specific survival according to pT stage or worst pattern of invasion (WPOI). (A) Survival rates for pT1 and pT2 were comparable (p=0.9208). (B) Survival rate decreased with WPOI progression. (C) Patients with WPOI-4 or -5 had significantly lower 5-year survival rates compared with those with WOPI-1 to -3 (p=0.0001).*

respectively, with significantly lower 5-year survival rates for WPOI-4/5 compared with WOPI-1 to -3 (p=0.0001) (Figure 2C). Notably, salvage treatment for regional lymph node recurrence resulted in 100% 5-year DSS in patients with WPOI-1 to -3. Thus, WPOI-4/5 was associated with a poorer prognosis after treatment for recurrent disease.

Discussion

The present study of 38 patients with early-stage OTSCC showed that WPOI correlated more strongly with prognosis than pT stage. Notably, highly invasive WPOI-4/5 tumors had a high rate of regional lymph node metastasis after initial transoral resection, and developed uncontrollable recurrence even after neck dissection and postoperative treatment for recurrent disease, indicating a poor prognosis. The regional lymph node recurrence rates appeared to increase in line with pT stage progression, but the differences were not significant, possibly due to the small number of cases. However, even with this limited number of cases, the correlation between WPOI progression and regional lymph node recurrence rate was stronger than that for pT stage. There was no difference in 5-year DSS rate between pT1 and pT2 tumors. In contrast, in relation to WPOI, the 5-year DSS rate for WPOI-1 to -3 was 100%, which was significantly higher than 56% for highly invasive tumors with WPOI-4/5. Notably, the 5-year DSS rate for the 29 patients with WPOI-1 to -3 was 100%, although one WPOI-2 and nine WPOI-3 cases had regional lymph node recurrence. Therefore, in the case of the watchful-waiting policy for early-stage OTSCC, neck dissection can be limited to cases with regional lymph node recurrence up to WPOI-3, and a high survival rate can be expected with a good course after salvage treatment of recurrent disease. In contrast, the prognosis for highly

invasive OTSCC with WPOI-4/5 is poor with this watchful-waiting policy, and a change in treatment strategy is required to improve the prognosis. Regional lymph node recurrence occurred in seven cases with WPOI-4/5 disease, and four patients died from recurrent disease. These results suggest that a policy of no treatment until regional lymph node recurrence appears is inappropriate in case of WPOI-4/5 disease. When adopting a watchful-waiting policy, patients with WPOI-4/5 tumors might need to undergo neck dissection as soon as possible, without waiting for the appearance of regional lymph node metastasis to improve prognosis. When the tumor was preoperatively suspected highly invasive disease, such as WPOI-4/5, the patient should undergo pull-through resection and prophylactic neck dissection, which may also improve survival. Although preoperative evaluation of invasiveness at the invasion front would help in establishing a treatment strategy for early-stage OTSCC, there is currently no established method. Further studies are needed to examine the relationship between invasion-front patterns and the results of imaging techniques, such as magnetic resonance imaging and positron emission-computed tomography, as well as the development of new diagnostic techniques.

This study has some limitations. It is a retrospective study with a small sample size, performed at a single institution. The results of this study should be evaluated in a sub-analysis of the ongoing randomized study (6). Despite these limitations, the results presented in this study may contribute to the development of new treatment strategy for proactive cervical control depending on the pathologic findings after transoral resection of the primary lesion, and thus add a new dimension to the controversy of END for early-stage OTSCC.

The use of transoral resection as initial treatment for early-stage OTSCC allows the histopathological evaluation of the invasive potential at the invasion front of the resected cancer tissue. Patients with mild-to-moderately invasive tumors, such as WPOI-1 to -3, can be followed up without neck dissection until regional lymph node recurrence is detected, with a good course after salvage treatment. In contrast, patients with highly invasive tumors such as WPOI-4/5 who are followed up until the appearance of regional lymph node recurrence have a poor prognosis, even with adequate treatment for recurrent disease. These patients should thus undergo intensified treatment, including neck dissection as early as possible after transoral resection in the case of highly invasive OTSCC, or pull-through surgery and prophylactic neck dissection if highly invasive OTSCC is suspected preoperatively.

Conflicts of Interest

The Authors have no conflicts of interest to disclose with respect to the publication of this paper.

Authors' Contributions

All Authors contributed to the study conceptualization. Tomoya Ishida and Moriyasu Yamauchi contributed to data curation. Akimichi Minesaki and Moriyasu Yamauchi contributed to formal analysis and investigation. Yuichiro Kuratomi and Moriyasu Yamauchi contributed to methodology, project administration, supervision and validation. Moriyasu Yamauchi contributed to funding acquisition. The first draft of the manuscript was written by Moriyasu Yamauchi and all Authors commented on previous versions of the manuscript. All Authors read and approved the final manuscript.

Acknowledgements

This work was supported by JSPS Grant-in-Aid for Scientific Research (C) [grant number 20K09734]. The Authors thank Susan Furness, PhD, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

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Received March 26, 2023
Revised April 4, 2023
Accepted April 5, 2023