Peri-neural Invasion is An Important Prognostic Factor of T2N0 Oral Cancer

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Abstract

Purpose: To determine the prognostic factors of T2N0 oral cancer patients who have received radical surgery.

Materials and Methods: From January 2012 to December 2017, a total of 166 T2N0 oral cancer patients who had received radical surgery were analyzed. Thirty-one of them received postoperative adjuvant therapy. The endpoints were disease-specific survival (DSS), and disease-free survival (DFS). The associated factors of survival according to pathologic results and treatment, including perineural invasion (PNI), angiolymphatic invasion (ALI), and adjuvant therapy, were analyzed.

Results: The median follow up time was 43.5 months. The 3-year rates of DSS, and DFS were 86.1% and 80.1%, respectively. The 3-year DSS for perineural invasion (PNI) negative and PNI positive patients was 90.8% and 57.0%, respectively ($p=0.0006$), with the 3-year DFS for PNI negative and PNI positive patients being 84.2% and 54.6%, respectively ($p=0.001$).

A multivariate analysis revealed PNI was an independent prognostic factor of DSS (Hazard Ratio [HR] = 3.29; 95% Confidence Interval [CI] = 1.35-8.02; $p = 0.009$), and DFS (HR = 4.68; 95% CI = 1.77-12.3; $p = 0.002$). Adjuvant therapy was also an independent prognostic factor of DSS (HR = 0.26; 95% CI = 0.08-0.78; $p = 0.017$), and DFS (HR = 0.27; 95% CI = 0.07-0.96; $p = 0.044$).

Conclusion: PNI was an independent prognostic factor and adjuvant therapy improved the clinical outcomes for T2N0 oral cancer patients.

Introduction

Oral squamous cell carcinoma (OSCC) is one of the most common malignancies worldwide [1]. Surgery is the mainstay treatment for OSCC, particularly for early stage disease. Locoregional recurrence occurs frequently after radical surgery, particularly for patients with positive margins and extranodal extension [2, 3]. Postoperative adjuvant therapy is used to treat advanced head and neck squamous cell carcinoma patients who have pathological adverse features [2–4]. For T2N0 OSCC patients, the important prognostic factors and the role of adjuvant therapy still remain controversial. Previous studies [5, 6] have revealed that the local recurrence rate was 23% after 31 months follow up, with a 5-year survival rate of 63.5% for T2N0 OSCC. These clinical reports are reminders that some pathological adverse features and occult diseases may affect clinical outcomes in T2N0 OSCC patients. The rate of salvage surgery for recurrent disease is poor [7, 8], therefore identifying the patients who have the potential risk for disease recurrence in order to give them adequate advice is important. To the best of our knowledge, there has been limited available data which has discussed the poor prognostic predictors of T2N0 disease and guided the followed clinical treatment.

The primary purpose of this study is to evaluate the prognostic factor in T2N0 OSCC, while its secondary purpose is to learn whether adjuvant therapy improves clinical outcomes or not.

Materials And Methods

Patients

There were 287 newly diagnosed OSCC patients from January 2012 to December 2017 who were chosen from the database at Taichung Veterans General Hospital. The inclusion criteria for patients included: (1) completed pretreatment staging workup; (2) no distant metastasis at diagnosis; (3) received radical tumor excision and neck dissection, as well as pathologically confirmed SCC; (4) pathologic proved tumor size of 2–4 cm with no lymph node metastasis; and (5) without secondary malignancy. Afterwards, there were 166 eligible patients eligible for this study. The staging was performed according to the American Joint Committee on Cancer (AJCC) TNM classification system 7th edition.

The study was approved by the Institutional Review Board of Taichung Veterans General Hospital.

Adjuvant therapy

Patients who received adjuvant therapy were given so according to adverse features, including margin status, perineural invasion (PNI), angiolymphatic invasion (ALI), and tumor cell differentiation grade. Thirty-one patients underwent external beam radiotherapy, while a linear accelerator with a 6-MV photon beam and source-axis distance technique was used. A total radiation dose of 60.0–66.0 Gy, 1.8-2.0 Gy per fraction, at 5 fractions per week was delivered. Twenty-five of the 31 patients were scheduled to receive concurrent chemotherapy, which used a cisplatin-base regimen.

Adjuvant therapy was delivered within 4–6 weeks after radical surgery.

Statistical analysis

The endpoints were both disease-specific survival (DSS) and disease-free survival (DFS). DSS was calculated from the date of radical surgery to the date of disease-related death or last follow-up. DFS was measured from the date of radical surgery to the date of any evidence of recurrence or last follow-up. Survival times were estimated using the Kaplan-Meier method, while the Log-rank test was used for the comparison between the groups. A Cox regression model was used for multivariate analysis. The statistical analyses were performed using SPSS software, version 12.0. A p value of less than 0.05 was considered statistically significant.

Results

Table 1 summarizes the patients' characteristics. There were 148 males and 18 females within a range of 33–92 years of age, with the median age being 56 years. Histopathologic examinations revealed that 20 patients showed margin positive, 24 patients had PNI positive, and 6 patients had ALI positive.

Table 1
patients' characteristics and univariate analysis (n = 166)

characteristics	Numbers (%)	3-year DSS	p value	3-year DFS	p value
Age	33–92				
	Median:56				
≤56	83 (50)	85.7%		86.4%	
> 56	83 (50)	84.6%	p = 0.22	74.0%	p = 0.25
Gender					
Male	148 (89.2)	85.7%		80.1%	
Female	18 (10.8)	88.8%	p = 0.56	80.4%	p = 0.85
Grade					
1	14 (8.4)	100%		84.4%	
2	132 (79.6)	85.8%		81.2%	
3	20 (12.0)	70.1%	p = 0.56	70.0%	p = 0.53
PNI					
positive	24 (14.4)	57.0%		54.6%	
negative	142 (85.6)	90.8%	p = 0.0006	84.2%	p = 0.001
ALI					
positive	6 (3.6)	50.0%		50.0%	
negative	160 (96.4)	87.5%	p = 0.01	82.2%	p = 0.0009
Margin					
positive	20 (12.0)	72.3%	p = 0.25	68.8%	
negative	146 (88.0)	86.9%		81.6%	p = 0.33
Adjuvant therapy					
Yes	31 (18.7)	89.4%		93.5%	
No	135 (81.3)	83.8%	p = 0.16	77.0%	p = 0.15
Abbreviations: PNI: Perineural invasion; ALI: angiolymphatic invasion; DSS: Disease-specific survival; DFS: Disease-free survival.					

The median follow-up time was 43.5 months, with a range of 2.3-101.6 months. The 3-year rates of DSS and DFS were 86.1% and 80.1%, respectively. Table 1 summarizes the univariate analysis. The 3-year DSS

rates for PNI positive and PNI negative were 57.0% and 90.8%, respectively ($p = 0.0006$, Fig. 1), and the 3-year DSS rates for ALI positive and ALI negative were 50.0% and 87.5%, respectively ($p = 0.01$, Fig. 2), and 3-year DSS rates for patients who had received adjuvant therapy and those who hadn't were 89.4% vs. 83.8%, respectively ($p = 0.16$). The 3-year DFS rates for PNI positive and PNI negative were 54.6% and 84.2%, respectively ($p = 0.001$, Fig. 3), 3-year DFS rates for ALI positive and ALI negative were 50.0% and 82.2%, respectively ($p = 0.0009$, Fig. 4), and the 3-year DFS rates for patients who had received adjuvant therapy and those who had not were 93.5% vs. 77.0% ($p = 0.15$). In the subgroup analysis, 8 of 24 PNI positive patients received adjuvant therapy, while 16 did not. Patients who received adjuvant therapy experienced both better DSS (100% vs. 35%, $p = 0.005$) and DFS (100% vs. 29.1%, $p = 0.005$).

Table 2 summarizes the multivariate analysis. Multivariate analysis revealed that PNI (Hazard Ratio [HR] = 3.29; 95% Confidence Interval [CI] = 1.35–8.02; $p = 0.0009$), ALI (HR = 6.86; 95% CI = 1.25–37.5; $p = 0.026$) and adjuvant therapy (HR = 0.26; 95% CI = 0.08–0.78; $p = 0.017$) were all independent prognostic factors for DSS. Age (HR = 1.04; 95% CI = 1.01–1.07; $p = 0.012$), PNI (HR = 4.68; 95% CI = 1.77–12.3; $p = 0.002$) and adjuvant therapy (HR = 0.27; 95% CI = 0.07–0.96; $p = 0.044$) were all independent prognostic factors for DFS. ALI (HR = 7.08; 95% CI = 0.95–52.8; $p = 0.056$) had a borderline significant effect on DFS.

Table 2
Multivariate analysis for DSS and DFS

Variables	HR(95%CI)	P value
DSS	1.02 (0.99–1.05)	0.189
Age		
Gender	0.33 (0.06–1.70)	0.188
Grade	1.70 (0.79–3.66)	0.172
PNI	3.29 (1.35–8.02)	0.009
ALI	6.86 (1.25–37.5)	0.026
Margin	0.92 (0.81–1.03)	0.179
Adjuvant therapy	0.26 (0.08–0.78)	0.017
DFS	1.04 (1.01–1.07)	0.012
Age	0.13 (0.01–1.17)	0.070
Gender	1.17 (0.53–2.59)	0.684
Grade	4.68 (1.77–12.3)	0.002
PNI	7.08 (0.95–52.8)	0.056
ALI	0.88 (0.76–1.02)	0.096
Margin	0.27 (0.07–0.96)	0.044
Adjuvant therapy		
Abbreviations: DSS: Disease-specific survival; DFS: Disease-free survival;		
PNI: Perineural invasion; ALI: angiolymphatic invasion.		

Discussion

It is important to distinguish the T2N0 OSCC patients with poorer outcomes from the others, and subsequently guide them using the followed treatment.

PNI is widely considered to be a predictor of poor prognosis, and is related to aggressive tumor behavior, tumor recurrence, and poor clinical outcomes in oral cancer patients [9–12]. PNI is a way for tumor cell spread to occur in and along the nerve bundle beyond the local tumor. In a previous study, OSCC was recognized as a neurotropic cancer, where approximately 30% of patients had PNI positive [13]. In this study, we revealed that PNI was an independent prognostic factor of T2N0 OSCC patients.

Sparano et al. [14] showed that ALI was a predictor correlated to occult lymph node metastasis in clinical T1/T2N0 oral cancer patients. Additionally, Aires et al. [15] found that ALI was a predictor for distant metastasis. In this trial, we demonstrated that ALI positive patients had poorer DSS, and also tended to have poorer DFS. In our study, too few positive ALI patients may affect the ability to determine the difference between patients with ALI positive and patient with ALI negative.

Postoperative radiotherapy was scheduled for oral cancer patients who had experienced intermediate risk disease after surgery, while radiotherapy with concurrent chemotherapy was given to patients who had a high risk of disease after surgery. Previous studies [2–4] defined the adverse features, while isolating PNI as an intermediate risk factor. Nair et al. [16] demonstrated that PNI worsened survival rates and required patients to receive adjuvant therapy. For T2N0 oral cancer patients, the survival benefit of adjuvant therapy is controversial. Luryi et al. [17] reviewed stage I and II OSCC and revealed that adjuvant therapy did not improve survival. In the Luryi study, stage I disease was included and the team did not consider the pathologic adverse factors. For stage I disease, patients experienced a lower risk of disease relapse, with the treatment-related side effects possibly counteracting the benefits of adjuvant therapy. Rubin et al. [18] did not find any survival benefit of T2N0 oral cancer patients. In the Rubin study, pathological adverse factors such as PNI and ALI were not included in their analysis. In subgroup analysis in our study, we recruited 24 PNI positive patients and revealed that the patients who had received adjuvant therapy experienced both better DSS (100% vs. 35%, $p = 0.005$) and DFS (100% vs. 29.1%, $p = 0.005$). After several pathological and treatment factors were incorporated into multivariate analysis, we determined that adjuvant therapy offered better results.

This retrospective study did have certain limitations. First, margin status did not show any significant difference on DSS and DFS. We reviewed the pathology reports, but margin status may often be affected by different surgical procedures and re-excision in the surgery process. Second, the staging was according to the AJCC 7th edition, and did not consider tumor invasion depth, which is considered in the AJCC 8th edition. The first advantage of this study was that we selected T2N0 OSCC in order to exclude the effect of tumor size. The second advantage was that we excluded any patients who had a second malignancy in order to eliminate the influences between primary oral cancer and second malignancy. Further studies are still required in order to clarify the adverse features, as well as to find more patients who require adjuvant therapy so as to improve future clinical outcomes.

Conclusion

PNI is an independent prognostic factor of T2N0 OSCC, and adjuvant therapy for patients with adverse factors improves their clinical outcomes. For T2N0 OSCC patients, adverse features were incorporated in order to guide adjuvant therapy.

Abbreviations

DSS

disease-specific survival.

DFS

disease-free survival.

PNI

perineural invasion.

HR

Hazard Ratio.

CI

Confidence Interval.

OSCC

Oral squamous cell carcinoma.

ALI

angiolymphatic invasion.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Taichung Veterans General Hospital.

Not applicable for consent to participate.

Consent for publication

Not applicable.

Availability of supporting data

All data and material are available in the article.

Competing interests

The authors declare that there are no competing of interest.

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None.

Authors' contributions

Study concepts: CSC

Study design: CCC

Data acquisition: CCC and YSC

Quality control of data and algorithms: YCL

Data analysis and interpretation: CCC and CCW

Statistical analysis: CCC

Manuscript preparation: CSC and CCC

Manuscript editing: CCC and CCW

Manuscript review: CCW

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Figures

Figure 1

Disease-specific survival according to peri-neural invasion status.

Figure 2

Disease-specific survival according to angiolymphatic invasion status.

PNI
p=0.001

Figure 3

Disease-free survival according to peri-neural invasion status.

ALI
p=0.0009

Figure 4

Disease-free survival according to angiolymphatic invasion status.