Ann Surg Oncol (2019) 26:547–554
https://doi.org/10.1245/s10434-018-6806-x

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – HEAD AND NECK ONCOLOGY

Does p16+ Predict a Favorable Prognosis for Oropharyngeal Cancer? Risk Factors for Treatment Failure for Patients Who Underwent Surgery-Based Therapy

Young Min Park, MD, PhD, Min Seok Kang, MD, Yoon Woo Koh, MD, PhD, Eun Chang Choi, MD, PhD, and Se-Heon Kim, MD, PhD

Department of Otorhinolaryngology, Yonsei University College of Medicine, Seoul, Korea

ABSTRACT

Background. This study aimed to identify prognostic clinicopathologic factors that could predict treatment failure and to analyze clinical data from p16+ oropharyngeal squamous cell carcinoma (OPSCC) patients who underwent surgery.

Methods. Data from p16+ OPSCC patients who underwent surgery at Severance Hospital of Yonsei University were retrospectively reviewed.

Results. The average smoking history was 14.6 pack-years (range 0–94 pack-years). Of the 188 patients, 73 (38.8%) underwent transoral robotic surgery (TORS) for surgical treatment of their primary lesions, and the remaining 115 patients (61.2%) underwent conventional surgery. Extracapsular nodal spread was detected in 87 patients (46.3%). At histologic examination, 67 patients (35.6%) showed positive surgical margins, and 121 patients (64.4%) had negative surgical margins. Postoperative adjuvant treatment was performed for 167 patients (88.8%). During the follow-up period, there were 18 recurrences including 2 local recurrences, 10 regional recurrences, and 6 distant metastases. During the study period, 17 deaths occurred. The univariate analysis showed that the American Joint Committee on Cancer (AJCC) 8th-edition staging system, lymphovascular invasion, more than four metastatic lymph nodes, and a smoking history of more than 10 pack-years were significantly associated with treatment failure. In the multivariate analysis, only the AJCC 8th-edition staging system was significantly associated with the patient's survival.

Conclusion. Surgical treatment methods including TORS for p16+ OPSCC patients showed excellent oncologic results, and many previously known clinicopathologic factors did not show a significant relationship with patient prognosis. Only the newly revised AJCC 8th-edition staging system showed a significant relationship with patient survival, and this should be considered in the setting of p16+ OPSCC treatment guidelines in the future.

Traditionally, the main causes of head and neck squamous cell carcinoma (HNSCC) are smoking and drinking, and the overall incidence of HNSCC has declined due to a decades-long anti-smoking campaign. On the other hand, the incidence of oropharyngeal squamous cell carcinoma (OPSCC) is increasing due to the increase in OPSCC associated with human papilloma virus (HPV).[1] About 70% of the OPSCC cases in the United States are reported to be associated with HPV, and the increase in HPV-associated OPSCC is common in other developed countries.[2–5] Findings show that HPV-positive OPSCC differs significantly from HPV-negative OPSCC in terms of prognosis and response to therapy.[6–8]

The new revised American Joint Committee on Cancer (AJCC) 8th-edition staging system is divided into p16+ OPSCC and p16− OPSCC depending on the presence or absence of p16 expression, which represents HPV status. Although p16+ OPSCC generally is known to have a good prognosis, 5–10% of these patients eventually experience disease recurrence, and their prognosis is poor.[9,10] If we can predict p16+ OPSCC patients with an exceptionally poor prognosis, a more aggressive treatment strategy can be established for these patients. However, the previously

First Received: 15 March 2018;
Published Online: 1 October 2018

S.-H. Kim, MD, PhD
e-mail: shkimmd@yuhs.ac

known prognostic factors for HNSCC are not suitable for predicting the prognosis of patients with p16+ OPSCC.[11,12]

Recently, one of the major changes associated with OPSCC due to the emergence of HPV as a new etiology is the introduction of transoral robotic surgery (TORS). The use of TORS has the advantage of less morbidity than radiation therapy or concurrent chemoradiotherapy because of rapid patient recovery after treatment and loss of function.[13,14] Therefore, the frequency of surgical treatment for OPSCC is increasing, and the incidence of chemoradiotherapy is decreasing. In addition, there is the advantage of being able to establish a treatment strategy tailored to individual patients by analyzing pathologic and molecular characteristics based on the obtained specimen of the lesion. Thus, the rapid increase in p16+ OPSCC.

The wide adoption of TORS with excellent outcomes in the treatment of OPSCC requires new treatment guidelines for these patients. However, no established guidelines specific for p16+ OPSCC patients exist to date. To establish such a treatment strategy, it is necessary to analyze the postoperative pathologic findings and treatment outcomes for p16+ OPSCC patients and to clarify the prognostic factors of these patients. Therefore, we aimed to identify clinical and pathologic prognostic factors that could predict treatment failure and to analyze the clinical data of p16+ OPSCC patients who underwent surgery.

MATERIALS AND METHODS

We retrospectively reviewed data from patients with a diagnosis of OPSCC at Severance Hospital of Yonsei University who underwent surgery between November 2005 and November 2015. The current study included only patients who had received follow-up evaluation for at least 30 months. The mean follow-up period was 61.8 months (range 30–150 months).

All the patients underwent a complete head and neck physical examination, including endoscopy, computed tomography, magnetic resonance imaging, and positron emission tomography, to assess the extent of the disease before treatment. Since 2005, we have routinely conducted p16 immunohistochemistry tests to investigate the HPV status of patients with a diagnosis of OPSCC, and only p16+ OPSCC patients were included in this study. All staging of patients was evaluated by the newly revised AJCC 8th-edition staging system and an old version of the AJCC 7th-edition staging system. Because this study investigated only patients who underwent surgery-based therapy, the tumor-node-metastasis (TNM) staging system used in this study was pathologic staging based on pathologic findings of surgical specimens.

We retrospectively analyzed the medical records from 188 patients with p16+ OPSCC to collect data on the patients' personal information, tumor location and stage, operation record, hospital record, recurrence of disease, and survival. All the patients underwent surgery of the primary site and cervical lymph nodes as a first-line treatment. Surgical treatment of the primary site also included conventional surgical treatment or TORS. The recurrence and distant metastasis were confirmed on histologic examination of the lesions or based on imaging studies in cases wherein the histologic examination of the lesions was difficult.

The surgical treatment method for the primary site was chosen based on the preference of the operator and the state of the patient. Surgical treatment of the cervical lymph nodes was performed simultaneously with treatment of the primary site using elective selective neck dissection for the negative neck and therapeutic radical neck dissection for the positive neck.

Adjuvant treatment (radiotherapy or chemoradiotherapy) was performed for the following adverse pathologic features: positive margin, extracapsular nodal spread (ECS), pT3 or pT4 primary tumor, N2 or N3 nodal disease, perineural invasion (PNI), vascular embolism, and lymphatic invasion. Systemic concurrent chemotherapy was considered in cases with a positive margin, ECS, or both.

When the malignant tumor cells were observed in the margin of the surgical specimen on pathologic examination, we defined it as a positive surgical margin. In pathologic analysis of cervical lymph nodes, ECS was defined as malignant tumor cells that had spread outside the capsule of lymph node. Also, irradiation of the primary site and bilateral neck irradiation were performed for patients who required adjuvant therapy. Adjuvant treatment was started 4–6 weeks after surgery.

The primary end points of the study were recurrence-free survival and overall survival. In this study, recurrence was defined as locoregional recurrence and distant metastasis detected 6 months after the end of treatment. The Chi square test or Fisher's exact test was used to evaluate differences in categorical variables between two independent groups. An independent two-sample t test was used to assess differences in continuous variables between two independent groups. Multivariate logistic regression analysis was performed to model dichotomous variables. The Kaplan–Meier curve was used to analyze recurrence-free survival and overall survival, and the survival outcomes were assessed using a log-rank test. A p value lower than 0.05 was considered to indicate statistical significance. The statistical analyses were performed using SPSS 18.0 for Windows (SPSS, Chicago, IL, USA).

TABLE 1 Information on all p16+ oropharyngeal carcinoma (OPC) patients who underwent surgery

Variables	All surgical patients (n = 188) No. of patients (%)	Smoking ≤ 10 pack-years (n = 104) No. of patients (%)	Smoking > 10 pack-years (n = 84) No. of patients (%)	p value
Males	159 (84.6)	75 (72.1)	84 (100)	< 0.001
Age (years)				0.507
Mean (range)	57.2 (30–81)	56.8 (30–81)	57.7 (39–77)	
Smoking history (pack-years)				< 0.001
Mean (range)	14.6 (0–94)	1.3 (0–10)	31.3 (12–94)	
Alcohol use	115 (61.2)	49 (47.1)	66 (78.6)	< 0.001
Location				0.383
Tonsil	160 (85.1)	88 (84.6)	72 (85.7)	
BOT	24 (12.8)	15 (14.4)	9 (10.7)	
Soft palate	4 (2.1)	1 (1)	3 (3.6)	
TNM stage (AJCC 7th ed)				0.833
1	8 (4.3)	5 (4.8)	3 (3.6)	
2	17 (9)	9 (8.7)	8 (9.5)	
3	36 (19.1)	22 (21.2)	14 (16.7)	
4	127 (67.6)	68 (65.4)	59 (70.2)	
TNM stage (AJCC 8th ed)				0.109
1	143 (76.1)	85 (81.7)	58 (69)	
2	39 (20.7)	17 (16.3)	22 (26.2)	
3	6 (3.2)	2 (2)	4 (4.8)	
Surgery				0.295
TORS	73 (38.8)	44 (42.3)	29 (34.5)	
Others	115 (61.2)	60 (57.7)	55 (65.5)	
ECS				0.770
Yes	87 (46.3)	47 (45.2)	40 (47.6)	
No	101 (53.7)	57 (54.8)	44 (52.4)	
Margin				0.448
Positive	67 (35.6)	35 (33.7)	33 (39.3)	
Negative	121 (64.4)	69 (66.3)	51 (60.7)	
Adjuvant treatment				0.999
Yes	167 (88.8)	92 (88.5)	75 (89.3)	
No	21(11.2)	12 (11.5)	9 (10.7)	
Recurrence				0.630
Local	2 (1)	0 (0)	2 (2.4)	
Regional	10 (5.3)	8 (7.7)	2 (2.4)	
Distant metastasis	6 (3.2)	3 (2.9)	3 (3.6)	
Death	17 (9)	9 (8.7)	8 (9.5)	0.999

BOT base of tongue, *TNM* tumor-node-metastasis, *AJCC* American Joint Committee on Cancer, *TORS* transoral robotic surgery, *ECS* extra-capsular spread

RESULTS

The study enrolled 188 patients with p16+ OPSCC, including 159 men (84.6%) and 29 women (15.4%). The mean age of the patients was 57.2 years (range 30–81 years). The average smoking history was 14.6 pack-years (range 0–94 pack-years), and 115 patients (61.2%) had a history of drinking. The primary site was the tonsils in 160 cases (85.1%), the base of the tongue in 24 cases (12.8%), and the soft palate in 4 cases (2.1%).

TABLE 2 Incidence of recurrence and death events according to tumor-node-metastasis (TNM) stage

Subgroup	No. of patients	%
Recurrence		
TNM stage (AJCC 7th ed)		
1	0	0
2	2	11.8
3	1	2.8
4	15	11.8
TNM stage (AJCC 8th ed)		
1	12	8.4
2	4	10.3
3	2	33.3
Death		
TNM stage (AJCC 7th ed)		
1	0	0
2	1	5.9
3	0	0
4	16	12.6
TNM stage (AJCC 8th ed)		
1	8	5.6
2	5	12.8
3	4	66.7

AJCC American Joint Committee on Cancer

According to the AJCC 7th-edition staging system, 8 patients (4.3%) had stage 1 disease, 17 patients (9%) had stage 2 disease, 36 patients (19.1%) had stage 3 disease, and 127 patients (67.6%) had stage 4 disease. Based on the newly revised AJCC 8th-edition staging system, 85 patients had stage 1 disease (76.1%), 17 patients had stage 2 disease (20.7%), and 2 patients had stage 3 disease (3.2%).

Of the 188 patients, 73 (38.8%) underwent TORS for surgical treatment of their primary lesions, and the remaining 115 patients (61.2%) underwent conventional surgery. In 87 patients (46.3%), ECS was detected. Of the 188 patients, 67 (35.6%) showed positive surgical margins in the histologic examination, and 121 patients (64.4%) had negative surgical margins. Postoperative adjuvant treatment was performed for 167 patients (88.8%).

During the follow-up period, there were 18 recurrences, including 2 local recurrences, 10 regional recurrences, and 6 distant metastases. During the study period, 17 deaths occurred. Other patient information is summarized in Table 1.

The 188 patients were divided into two groups according to smoking habits: one group with a history of 10 pack-years or fewer and another group with a history of 10 pack-years or more. Of the 188 patients, 84 had a history of 10 pack-years, and 104 had a history of fewer than 10 pack-years of smoking. The percentage of men was significantly higher in the group that had a history of more than 10 pack-years of smoking. The remaining clinicopathologic factors showed no significant difference between the two groups (Table 1).

The incidence of recurrence and death events was analyzed according to TNM stage (Table 2). Based on the AJCC 7th-edition staging system, the recurrence event rate was 11.8% for the stage 2 patients disease, 2.8% for the stage 3 patients, and 11.8% for the stage 4 patients. Based on the AJCC 8th-edition staging system, the recurrence event rate was 8.4% for the stage 1 patients, 10.3% for the stage 2 patients, and 33.3% for the stage 3 patients. Compared with the 7th-edition system, use of the 8th-edition system confirmed that the rate of recurrence increased numerically with stage.

Death events occurred for 5.9% of the stage 2 patients and 12.6% of the stage 4 patients classified according to the AJCC 7th-edition staging system. In contrast, according to the AJCC 8th-edition staging system, the death rate was 5.6% for the stage 1 patients, 12.8% for the stage 2 patients, and 66.7% for the stage 4 patients. Compared with the 7th-edition system, use of the 8th-edition system confirmed that death events increased numerically with stage.

The univariate analysis evaluated various clinicopathologic factors including the AJCC 7th-edition staging system, the AJCC 8th-edition staging system, surgical treatment method, ECS, number of metastatic lymph nodes (LNs) (≤ 4 or > 4), lymphovascular invasion (LVI), PNI, surgical margin status, and adjuvant treatment to determine the relationship between these factors and 5-year recurrence-free survival (Table 3). Only the number of metastatic LNs and LVI were significantly associated with 5-year recurrence-free survival, and the remaining factors showed no significant relationships (Fig. 1). We next performed univariate analysis of the relationship between these factors and 5-year overall survival. The univariate analysis showed that the AJCC 8th-edition staging system, the number of metastatic LNs, LVI, and pathologic T classification were significantly associated with 5-year overall survival (Fig. 2).

The multivariate logistic regression analysis showed that LVI was the only statistically significant factor associated with disease recurrence ($p = 0.039$). In particular, for the risk of regional recurrence, the AJCC 8th-edition staging system ($p = 0.041$) and smoking history of more than 10 pack-years ($p = 0.049$) were the only statistically significant factors associated with lymph node recurrence. Finally, the AJCC 8th-edition staging system was the only factor that showed a statistically significant relationship with overall patient survival ($p = 0.005$). The presence of ECS, surgical margin status, and adjuvant treatment, which

TABLE 3 Univariate analysis of risk factors predicting 5-year recurrence-free survival (RFS) and overall survival (OS)

Variables	No. of patients	%	5-year RFS (%)	*p* value	5-year OS (%)	*p* value
Gender				0.062		0.253
Males	159	84.6	88.7		92.1	
Females	29	15.4	100		95.8	
Age (years)				0.298		0.111
≤ 50	44	23.4	86.4		77.7	
> 50	144	76.6	91.7		93.7	
Smoking history (pack-years)				0.573		0.886
None	85	45.2	90.6		89.9	
≤ 10	19	10.1	84.2		94.7	
> 10	84	44.7	91.7		88.4	
Alcohol use				0.989		0.742
Yes	115	61.2	90.4		91.5	
No	73	38.8	90.4		86.8	
Location				0.509		0.815
Tonsil	160	85.1	89.4		92.6	
BOT	24	12.8	95.8		91.7	
Soft palate	4	2.1	100		100	
Pathologic T classification				0.709		0.003
T1–2	152	80.9	90.8		92.3	
T3–4	36	19.1	88.9		69.5	
TNM stage (AJCC 7th ed)				0.755		0.354
1–2	25	13.3	92.0		94.7	
3–4	163	86.7	90.2		92.3	
TNM stage (AJCC 8th ed)				0.060		< 0.001
1	143	76.1	91.6		94.5	
2	39	20.7	89.7		85.3	
3	6	3.2	66.7		44.4	
Surgical treatment				0.617		0.141
TORS	73	38.2	91.8		95.9	
Others	115	61.2	89.6		88.0	
ECS				0.741		0.787
Yes	87	46.3	89.7		89.7	
No	101	53.7	91.1		91.9	
Metastatic LN				0.050		0.008
≤ 4	140	74.5	92.9		94.3	
> 4	48	25.5	83.3		72.1	
LVI				0.017		0.029
Yes	65	34.6	83.1		79.6	
No	123	65.4	94.1		94.4	
PNI				0.393		0.391
Yes	22	11.7	95.5		86.4	
No	166	88.3	89.4		93.2	
Margin				0.068		0.123
Positive	67	35.6	85.1		80.4	
Negative	121	64.4	93.4		93.5	
Adjuvant treatment				0.419		0.147
Yes	167	88.8	95.2		100	
No	21	11.2	89.8		91.7	

BOT base of tongue, *TNM* tumor-node-metastasis, *AJCC* American Joint Committee on Cancer, *TORS* transoral robotic surgery, *ECS* extracapsular spread, *LN* lymph node, *LVI* lymphovascular invasion, *PNI* perineural invasion

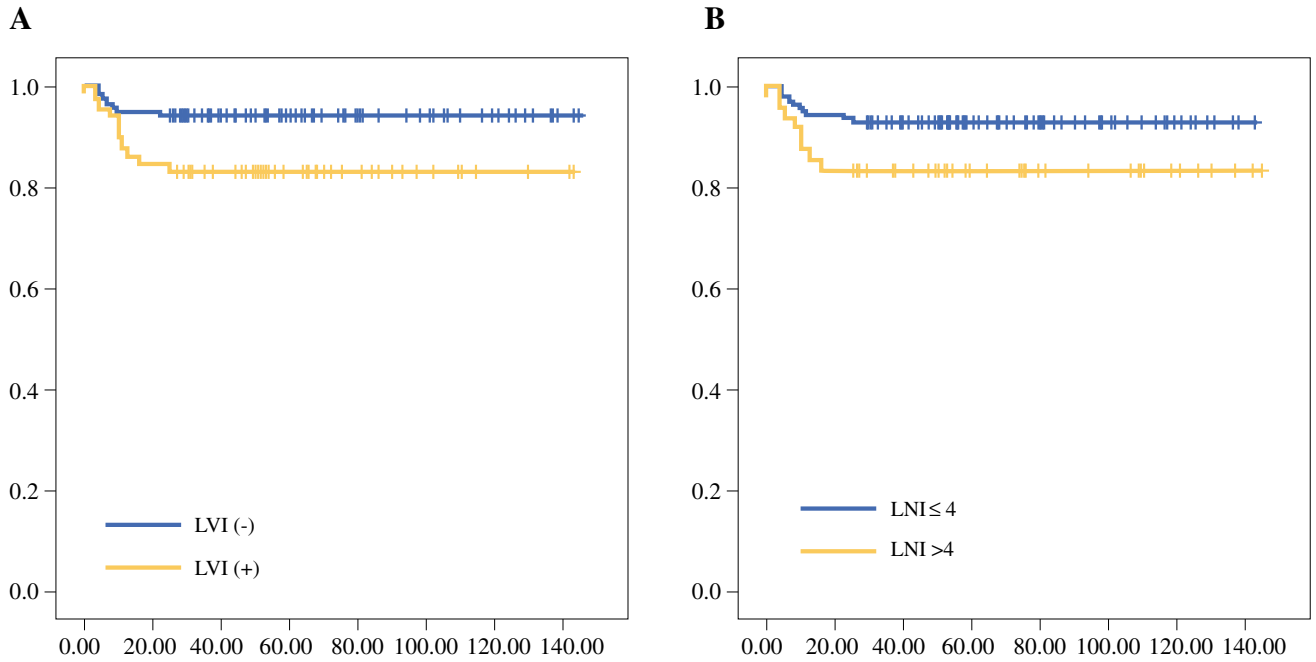

FIG. 1 The 5-year recurrence-free survival of p16+ oropharyngeal squamous cell carcinoma (OPSCC) patients according to **a** lymphovascular invasion and **b** number of metastatic lymph nodes (≤ 4 or > 4)

are known to be prognostic factors for HNSCC, did not show any significant relationship with disease recurrence or overall survival.

DISCUSSION

This study analyzed prognostic factors related to disease recurrence and overall survival. In the univariate analysis, more than four metastatic LNs and LVI had a significant relationship with disease recurrence, but only LVI was significantly associated with disease recurrence in the multivariate analysis. Of 18 disease recurrences, 55.6% were regional recurrences. In the multivariate analysis, the AJCC 8th-edition staging system and a smoking history of more than 10 pack-years were significantly associated with regional LN recurrence. In terms of overall survival, only the AJCC 8th-edition staging system showed a statistically significant relationship in the multivariate analysis.

Previously known adverse features such as ECS, surgical margin status, and PNI did not show a statistically significant relationship with treatment failure in this study.[15] Although previous studies have reported that adjuvant radiation is a significant factor related to disease recurrence, this study did not show a statistically significant relationship between this factor and disease recurrence.[16]

The most significant prognostic factor for patient survival was the newly revised AJCC 8th-edition staging system. As seen in this study, the AJCC 8th-edition staging system resulted in downstaging for a large number of patients compared with the AJCC 7th-edition staging system. Disease recurrence and death events according to TNM staging increased numerically as use of the AJCC 8th-edition staging system increased, which was not the case for the AJCC 7th-edition staging system. Previous known adverse factors such as ECS, margin status, LVI, PNI, and adjuvant therapy were not associated with patient prognosis. This suggests that new treatment guidelines are needed to determine the indications for adjuvant therapy after surgery for p16+ OPSCC patients. However, the current National Comprehensive Cancer Network (NCCN) guideline, widely applied in clinical practice, defines adverse pathologic features such as ECS, positive margins, pT3 or pT4, N2 or N3, PNI, and vascular embolism and recommends adjuvant treatment for patients with these factors. It does not reflect the different clinical features and prognosis of p16+ OPSCC and does not even reflect the AJCC 8th-edition staging system.

The mean follow-up period of this study was 60 months, which was relatively long compared with other previous studies, and it included a relatively large number of patients ($n = 188$). However, the retrospective design of this study was a limitation, and selection bias was a problem because only patients who underwent surgery were included in the study. In addition, some p16+ OPSCC patients treated with surgery and adjuvant therapy could have avoided adjuvant therapy considering their

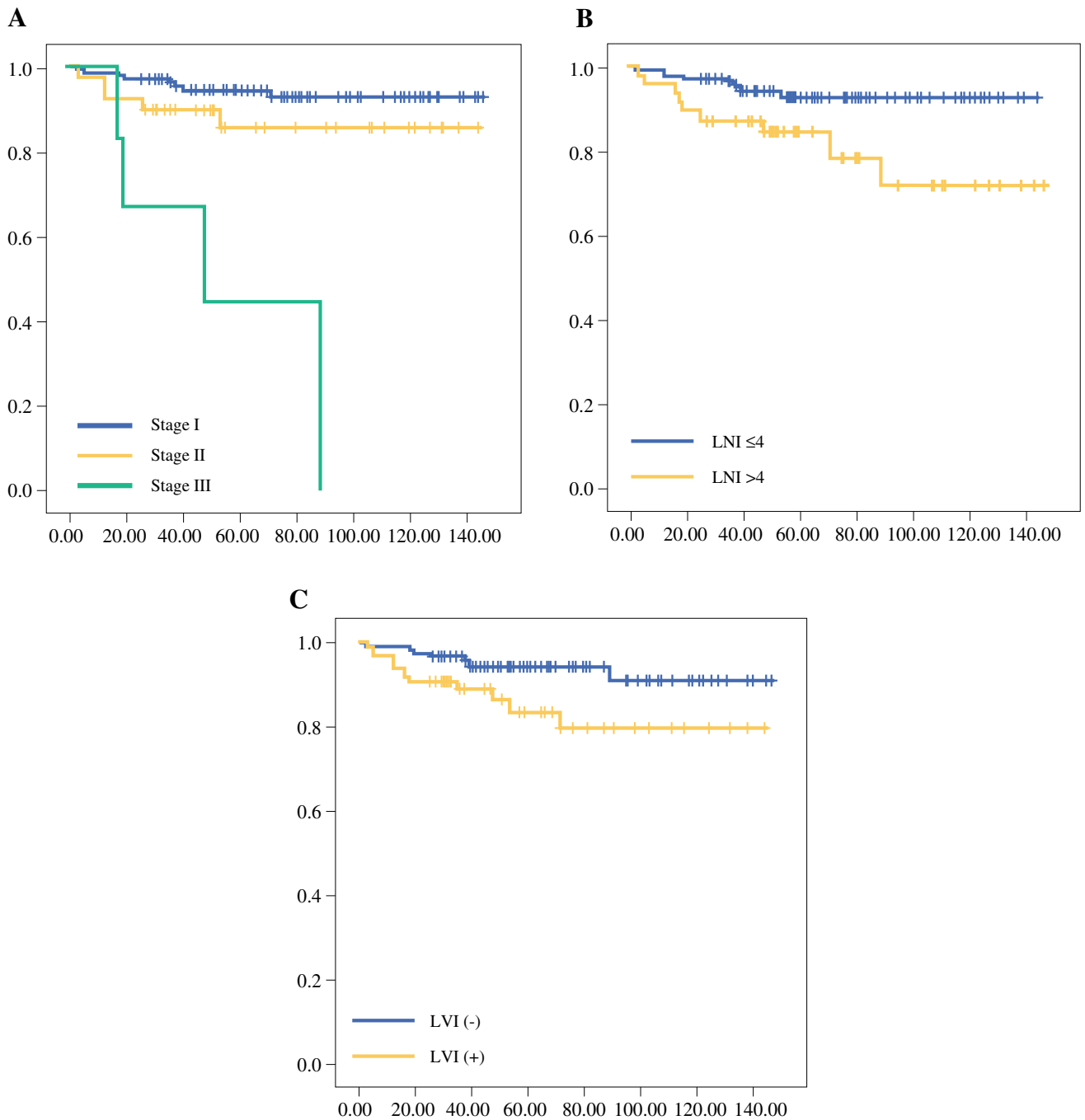

FIG. 2 The 5-year overall survival of p16+ oropharyngeal squamous cell carcinoma (OPSCC) patients according to **a** the AJCC 8th-edition staging system **b** number of metastatic lymph nodes (≤ 4 or > 4), and (**c**) lymphovascular invasion. AJCC, American Joint Committee on Cancer

favorable results. However, we recommended and performed adjuvant therapy based on the old-fashioned indications of previous guidelines. Further studies should establish de-intensified treatment strategies based on the prognostic factors identified in these patients and present their indications.

Surgical treatment methods, including conventional surgery and TORS, for p16+ OPSCC patients showed excellent oncologic results, and many previously known clinicopathologic factors did not show a significant relationship with patient prognosis. Only the newly revised AJCC 8th-edition staging system showed a significant

relationship with patient survival, and this should be considered in the setting of p16+ OPSCC treatment guidelines in the future.

DISCLOSURES There are no conflicts of interest.

REFERENCES

1. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. *J Clin Oncol.* 2008;26:612–9.
2. Ramqvist T, Dalianis T. Oropharyngeal cancer epidemic and human papillomavirus. *Emerg Infect Dis.* 2010;16:1671–7.
3. Sturgis EM, Ang KK. The epidemic of HPV-associated oropharyngeal cancer is here: is it time to change our treatment paradigms? *J Natl Compr Canc Netw.* 2011;9:665–73.
4. Nguyen NP, Ly BH, Betz M, Vinh-Hung V. Importance of age as a prognostic factor for tonsillar carcinoma. *Ann Surg Oncol.* 2010;17:2570–7.
5. Panwar A, Batra R, Lydiatt WM, Ganti AK. Human papilloma virus positive oropharyngeal squamous cell carcinoma: a growing epidemic. *Cancer Treat Rev.* 2014;40:215–9.
6. Smith EM, Wang D, Rubenstein LM, Morris WA, Turek LP, Haugen TH. Association between p53 and human papillomavirus in head and neck cancer survival. *Cancer Epidemiol Biomark Prev.* 2008;17:421–7.
7. Ang KK, Sturgis EM. Human papillomavirus as a marker of the natural history and response to therapy of head and neck squamous cell carcinoma. *Semin Radiat Oncol.* 2012;22:128–42.
8. Granata R, Miceli R, Orlandi E, et al. Tumor stage, human papillomavirus, and smoking status affect the survival of patients with oropharyngeal cancer: an Italian validation study. *Ann Oncol.* 2012;23:1832–7.
9. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med.* 2010;363:24–35.
10. Rietbergen MM, Brakenhoff RH, Bloemena E, et al. Human papillomavirus detection and comorbidity: critical issues in selection of patients with oropharyngeal cancer for treatment de-escalation trials. *Ann Oncol.* 2013;24:2740–5.
11. O'Sullivan B, Huang SH, Su J, Garden AS, Sturgis EM, Dahlstrom K, et al. Development and validation of a staging system for HPV-related oropharyngeal cancer by the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S): a multicentre cohort study. *Lancet Oncol.* 2016;17:440–51.
12. Haughey BH, Sinha P, Kallogjeri D, Goldberg RL, Lewis JS Jr, Piccirillo JF, et al. Pathology-based staging for HPV-positive squamous carcinoma of the oropharynx. *Oral Oncol.* 2016;62:11–9.
13. Cohen MA, Weinstein GS, O'Malley BW Jr, Feldman M, Quon H. Transoral robotic surgery and human papillomavirus status: oncologic results. *Head Neck.* 2011;33:573–80.
14. Weinstein GS, O'Malley BW Jr, Cohen MA, Quon H. Transoral robotic surgery for advanced oropharyngeal carcinoma. *Arch Otolaryngol Head Neck Surg.* 2010;136:1079–85.
15. O'Sullivan B, Huang SH, Siu LL, et al. Deintensification candidate subgroups in human papillomavirus-related oropharyngeal cancer according to minimal risk of distant metastasis. *J Clin Oncol.* 2013;31:543–50.
16. Kaczmar JM, Tan KS, Heitjan DF, et al. HPV-related oropharyngeal cancer: risk factors for treatment failure in patients managed with primary transoral robotic surgery. *Head Neck.* 2016;38:59–65.