Confirmation of the 8th edition of the AJCC/UICC TNM staging system for HPV-mediated oropharyngeal cancer in Japan

Takatsugu Mizumachi

Akihiro Homma

Tomohiro Sakashita

Satoshi Kano

Hiromitsu Hatakeyama

Satoshi Fukuda

Department of Otolaryngology- Head and Neck Surgery, Hokkaido University Graduate School of Medicine, Kita 15, Nishi 7, Kita-ku, Sapporo 060-8638, Japan

Corresponding author: Takatsugu Mizumachi

Mailing address: Department of Otolaryngology- Head and Neck Surgery, Hokkaido University Graduate School of Medicine, Kita 15, Nishi 7, Kita-ku, Sapporo 060-8638, Japan

Phone: +81-11-706-5958

Fax: +81-11-717-7566

E-mail: mizumati@med.hokudai.ac.jp

Abstract

Background: Several studies have demonstrated that the 7th edition of the AJCC/UICC TNM staging classification system does not consistently distinguish between prognostic subgroups for human papillomavirus (HPV)-mediated oropharyngeal squamous cell carcinoma (OPSCC). The 8th edition of the AJCC/UICC TNM staging came into effect for use with HPV-mediated OPSCC on or after January 1, 2017. This study confirms that the 8th edition of the AJCC/UICC TNM staging system for HPV- mediated OPSCC accurately reflects disease outcomes.

Patients and methods: We retrospectively analyzed 195 patients with OPSCC treated at Hokkaido University Hospital, Sapporo, Japan between 1998 and 2015. HPV status was evaluated by immunohistochemical analysis of p16.

Results: Of the 195 OPSCC patients, 111 (56.9%) were p16 positive, and 84 (43.1%) were p16 negative. The 3-year overall survival rate (OS) was significantly lower in the p16-negative patients with stage III-IV in comparison with those with stage I-II (55.0% vs 93.1%, $p<0.01$). The 3-year OS did not differ significantly between stage I-II and stage III-IV in the p16-positive patients (86.7% vs 87.7%). According to the 8th edition of the AJCC/UICC TNM staging system, stage I-II and stage III could be differentiated on the basis of the 3-year OS in the p16-positive patients (90.9% vs 70.2%, $p<0.01$).

Conclusions: The 7th edition of the AJCC/UICC TNM staging system is suitable for use with p16-negative patients; however, it does not effectively discriminate between p16-positive patients. Therefore, the 8th edition of the AJCC/UICC TNM staging system is more suitable for HPV-mediated OPSCC in Japan.

Key Words

AJCC/UICC TNM staging system

Head and neck cancer

Human papillomavirus

Oropharynx

p16

Introduction

Oropharyngeal squamous cell carcinoma (OPSCC) was traditionally associated with smoking and alcohol consumption [1]. Recently, human papillomavirus (HPV) has been recognised as another primary cause of OPSCC [2]. The incidence of OPSCC has been increasing in the United States and Western Europe, while the prevalence of smoking- and alcohol-induced cancers has been declining [3-5].

HPV-mediated OPSCC has distinct epidemiologic, clinical, and molecular features in comparison with HPV-unrelated OPSCC. Patients with HPV-mediated OPSCC are more likely to present with a small primary tumor and more extensive nodal disease [6]. Despite this tendency to present with more advanced nodal disease, HPV-mediated OPSCC has a better prognosis and better response to treatment than HPV-unrelated OPSCC [2, 7].

Several studies have demonstrated that the 7^{th} edition of the AJCC/UICC TNM staging system does not consistently distinguish between prognostic subgroups for OPSCC as it was established before HPV-mediated OPSCC was classified as a disease entity [8, 9]. The International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S) study, which involves the largest dataset from five North America and two European centers, represented an international effort to develop a pretreatment TNM

clinical staging classification and proposed a novel staging system for HPV-mediated OPSCC [10]. This study showed that the traditional N0 to N2b nodal stages are homogeneous for outcome within T1 and T2 categories (creating Stage I), that N2c and T3 represent an intermediate stage (Stage II), and T4 and N3 are the least favorable group (Stage III). Stage IV is reserved for distant metastases.

The 8th edition of the AJCC/UICC TNM staging system came into effect for use with HPV-mediated OPSCC on or after January 1, 2017, with HPV-mediated OPSCC treated separately from HPV-unrelated OPSCC. The T categories remain the same as in the 7th edition, except that the HPV-mediated classification does not include a Tis category and there is no T4b within T4 (Table 1). There are three categories of clinically involved nodes for HPV-mediated OPSCC: N1, N2, and N3 (Table 2). N1 represents one or more ipsilateral lymph node metastases, none larger than 6 cm; N2 represents contralateral or bilateral lymph nodes, none larger than 6 cm, and N3 represents lymph node(s) larger than 6 cm. Clinical stage groups are classified as stage I (T1-T2N0-N1), stage II (T1-T2N2 or T3N0-N2), and stage III (T4 or N3) (Table 3). Metastatic disease (M1) is classified as stage IV.

In this study, we evaluated whether the 8th edition of the AJCC/UICC TNM staging system was able to differentiate more effectively between patients with HPV-mediated

OPSCC in Japan.

Patients and methods

Patients

After institutional research ethics board approval, we retrospectively analyzed consecutive assembled patients without distant metastatic OPSCC undergoing definitive treatment at Hokkaido University Hospital, Japan, between 1998 and 2015. All patients were staged according to the AJCC/UICC TNM staging system (seventh and eighth edition) using physical and endoscopic examinations as well as computed tomography (CT), magnetic resonance imaging, and/or FDG PET-CT imaging.

Therapy

All patients were managed by a multidisciplinary team, including head and neck surgeons, radiation oncologists, and medical oncologists. The patients with early T and N classifications received surgery, radiotherapy or concurrent chemoradiotherapy with a total dose of 65-70 Gy. The patients with an advanced T or N classification received concurrent chemoradiotherapy, using platin-based or docetaxel-based chemotherapy. Therapy for these patients was decided without consideration of their p16 status.

p16 immunohistochemistry (IHC)

All histological samples were reviewed by expert head and neck pathologists to confirm the diagnosis. IHC for p16 was carried out as described previously [11]. The cut-off point for the determination of p16-positivity by IHC was nuclear expression with ≥ +2/+3 intensity and ≥ 75% distribution [12].

Statistical analysis

Factors associated with p16 status, including gender, age, tumour subsites, alcohol consumption and second primary tumour status, were analysed by cross-tabulations using the two-tailed Fisher's exact test. Statistical significance was set at $p<0.05$. Smoking status was analysed by Mann-Whitney U-test with statistical significance set at $p<0.05$.

Overall survival curves were calculated using the Kaplan-Meier method. Survival was calculated from the date of the start of treatment until either death or the last date on which the patient was known to be alive. Probabilities of overall survival, which included death from any cause computed from the beginning of treatment to either death or the last date on which the patient was known to be alive, were calculated by the Kaplan–Meier method and compared using the log-rank test. Statistical significance was set at $p<0.05$.

Results

Patient population and p16 IHC

A total of 195 patients with OPSCC were treated with definitive treatment between 1998 and 2015. The demographic and clinicopathological characteristics of patients are listed in Table 4. The median follow-up time was 41.6 months (range, 4 to 150 months) for surviving patients. In total, 111 of 195 (56.9%) OPSCC patients were p16 positive. The rate of p16-positive diagnosis rose from 43.9% in 1998-2005 to 63.9% in 2011-2015. P16-positive patients had a significantly lower level of smoking and alcohol consumption, and less second primary tumors than the p16-negative patients. The 3-year overall survival rate for the p16-positive patients was significantly better than that for p16-negative patients (87.5% vs 68.0%, $p<0.001$).

The 7th edition of the AJCC/UICC TNM staging system in p16-positive OPSCC

The distributions of T and N classifications based on the 7th edition of the AJCC/UICC TNM stage in p16-positive and -negative OPSCC are shown in Table 5 and 6, respectively. Of the 111 patients with p16-positive OPSCC, 3 (2.7%), 11 (9.9%), 17 (15.3%), and 80 (72.1%) were diagnosed as stage I, II, III, and IV, respectively. On the

other hand, of the 84 patients with p16-negative OPSCC, 17 (20.0%), 15 (17.9%), 16 (19.0%), and 36 (42.9%) were diagnosed as stage I, II, III, and IV, respectively. Overall survival rates for p16-positive and -negative OPSCC are shown in Figure 1. For the patients with p16-negative OPSCC, the overall survival for those diagnosed as with stage III-IV was significantly worse than that for stage I-II patients (3-yr OS: 93.1% of stage I-II vs. 55.0% of stage III-IV, $p<0.01$). However, for the patients with p16-positive OPSCC, there was no difference in survival between stage I-II and III-IV (3-yr OS: 86.7% of stage I-II vs. 87.7% of stage III-IV, $p<0.01$).

The 8th edition of the AJCC/UICC TNM staging system in p16-positive OPSCC

The distributions of T and N classifications based on the 8th edition of the AJCC/UICC TNM stage in p16-positive OPSCC are shown in Table 7. Of the 111 patients with p16-positive OPSCC, 67 (60.4%), 25 (22.5%), and 19 (17.1%) were diagnosed as stage I, II, and III, respectively. Most of the p16-positive patients were diagnosed as stage I when using the 8th edition of the AJCC/UICC TNM staging system, despite the fact that most of them were diagnosed as stage IV when using the 7th edition. Figure 2 shows the shift in stage classification from the 7th edition to the 8th edition. All patients diagnosed as stage I and II using the 7th edition were diagnosed as stage I using the 8th edition. Of

the 17 patients diagnosed as stage III using the 7th edition, 8 were stage I and 9 were stage II. Of the 80 patients diagnosed as stage IV using the 7th edition, 45 patients were diagnosed as stage I and 16 as stage II. More than half of the patients diagnosed as stage IV using the 7th edition were diagnosed as stage I when using the 8th edition.

Survival analysis using the 8th edition of the AJCC/UICC TNM staging system in p16-positive OPSCC (Figure 3)

Survival analysis was performed using the 8th edition of the AJCC/UICC TNM staging system in p16-positive OPSCC. The 3-year overall survival for stage I, II, and III were 90.9%, 90.9%, and 70.2%, respectively. Survival for patients diagnosed as stage III was significantly worse than that for stage I- II patients (p<0.01). Of the 19 patients with stage III, 6 died. All patients received chemoradiotherapy. Five patients died due to recurrence at the primary site, and one patient died due to the distant metastasis.

Discussion

This study shows that the 8th edition of the AJCC/UICC TNM staging system was able to effectively discriminate between patients with p16-positive OPSCC in this case series.

The present study, in agreement with other recent studies, showed that the rate of HPV-mediated OPSCC was increasing in Japan. Maruyama et al. reported that the prevalence of HPV increased from 36.8% during the period from 1995 to 1999, to 39.0% during the period from 2000 to 2009, and 48.3% between 2010 and 2012 [13]. Further, in the multicenter study in Japan, HPV was detected in 50.3% of cases between 2008 and 2010 [14]. These results suggest that, as in Western Europe and North America, HPV-mediated OPSCC is increasing in Japan.

The N criteria in HPV-mediated OPSCC have been revised in the 8th edition. Historically, nodal stage has been a dominant prognostic factor in OPSCC [15]. HPV-mediated OPSCC has a tendency to metastasize early to lymph nodes regardless of early T-stage, so that most patients with HPV-mediated OPSCC are diagnosed as N2b and then stage IV using the 7th edition. In an era of rising HPV prevalence, the impact of the N stage on prognosis has declined in the population-based cohort [16]. In HPV-mediated OPSCC, patients classified as N1-N2b using the 7th edition are classified as N1 using the 8th edition. In the present study, most of the HPV-mediated OPSCC patients were diagnosed as N2b using the 7th edition; however, a majority of patients were diagnosed as N1 using the 8th edition. The distribution of clinical stages has shifted due to the revision of N categories. We found that most of the HPV-mediated OPSCC

patients were diagnosed as stage IV using the 7th edition; however, this shifted to stage I when the 8th edition was used.

Several studies have shown that the 7th edition of the AJCC/UICC TNM staging system was not ideal for risk stratification for patients with HPV-mediated OPSCC [16-19]. In the present study, we did not observe any statistical difference in survival between stage I-II and III-IV using the 7th edition for patients with p16-positive OPSCC. When using the 8th edition, however, there was statistical difference in survival between stage I-II and III patients. These results suggest that the 8th edition is more effective in discriminating among patients with HPV-mediated OPSCC in Japan, in the same manner as in Western Europe and North America.

There are several limitations related to the use of the 8th edition in HPV-mediated OPSCC. IHC for p16 overexpression is used to classify HPV-mediated OPSCC in the 8th edition. As p16 is upregulated when high-risk HPV oncoproteins degrade p53 and pRB, p16 is a surrogate marker for HPV DNA testing. Direct detection of HPV is not used as a defining factor due to its problems associated with its universal availability and applicability, cost, and failure to stratify survival as well as p16 overexpression [12]. However, due to other genetic perturbations, several patients overexpress p16 without any relation to HPV. The rate of HPV-negativity among p16-positive patients was

reported to be around 10-20% [2, 20-22],. The prognosis for p16-positive/HPV-negative OPSCC remains unclear. Lewis et al. reported that patients with p16-positive/HPV-negative OPSCC had significantly better survival than those with p16-negative OPSCC [23]. However, several reports showed that p16-positive/HPV-negative OPSCC patients had poorer survival than those with p16-positive/HPV-positive OPSCC [24, 25]. Perrone et al. recommend that HPV should be assessed by some method in addition to p16 IHC [24]. Taken together, these reports suggest that we need to remember that there are a small number of patients with p16-positive/HPV-negative OPSCC, and that these patients have worse survival than those with p16-negative OPSCC.

The 8th edition of the AJCC/UICC TNM staging system introduces the use of extranodal extension (ENE) in categorizing “N” for neck node metastasis. ENE is one of the most important nodal characteristics influencing prognosis [26]. However, ENE is not categorized in p16-positive OPSCC. Spector et al. reported that matted nodes, which were defined as 3 nodes abutting one another with loss of the intervening fat plane that is replaced with evidence of ENE, were a prognostic factor for a poor outcome in HPV-positive OPSCC [27]. Vainshtein et al. also reported that matted nodes portended dramatically increased distant failure and risk of death in HPV-positive

OPSCC [28]. These reports suggest that we need to take particular care with p16-positive OPSCC patients with matted nodes.

The patients with HPV-mediated OPSCC have favorable clinical outcomes in comparison with the HPV-negative patients. However, the treatment for the HPV-mediated OPSCC patients is currently the same as that for HPV-negative OPSCC patients. The current standard of care for OPSCC is derived from older trials of head and neck cancer patients with predominately HPV-negative disease, potentially representing the overtreatment of patients with favorable risk, HPV-mediated OPSCC [29]. A number of clinical trials are now underway to investigate strategies for the de-intensification of treatment in HPV-mediated OPSCC patients in order to minimize morbidity while maintaining excellent outcomes. The National Comprehensive Cancer Network guidelines stated that the results of HPV testing should not change management decisions except in the context of a clinical trial [30].

In conclusion, we demonstrated that the 7th edition of the AJCC/UICC TNM staging system is inadequate for predicting survival patients, and that the 8th edition of the AJCC/UICC TNM staging system is able to effectively discriminate among Japanese patients with p16-positive OPSCC.

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Conflict of Interest

No author has any conflict of interest.

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Figure Legends

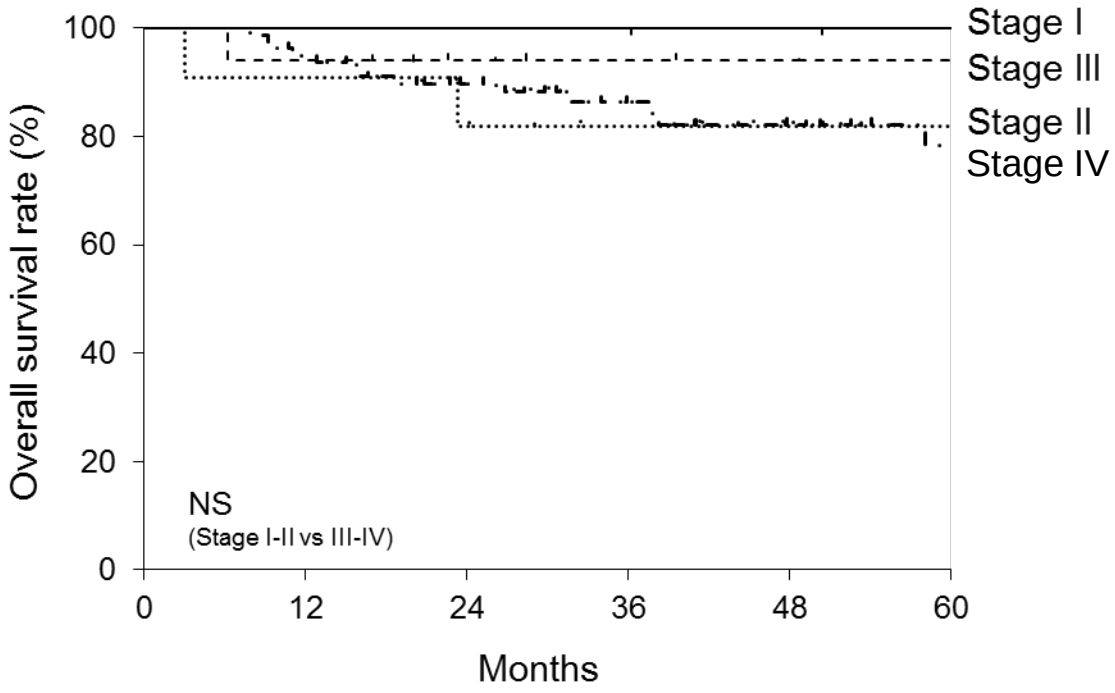
Figure 1 Kaplan-Meier curves for overall survival for patients with p16-positive (a) and p16-negative (b) OPSCC patients using the 7th edition of AJCC/UICC TNM staging system

Figure 2 The shift in clinical stage among patients with p16-positive OPSCC from the 7th to the 8th edition of the AJCC/UICC TNM staging system

Figure 3 Kaplan-Meier curves for overall survival for patients with p16-positive OPSCC patients using the 8th edition of the AJCC/UICC TNM staging system

Figure 1

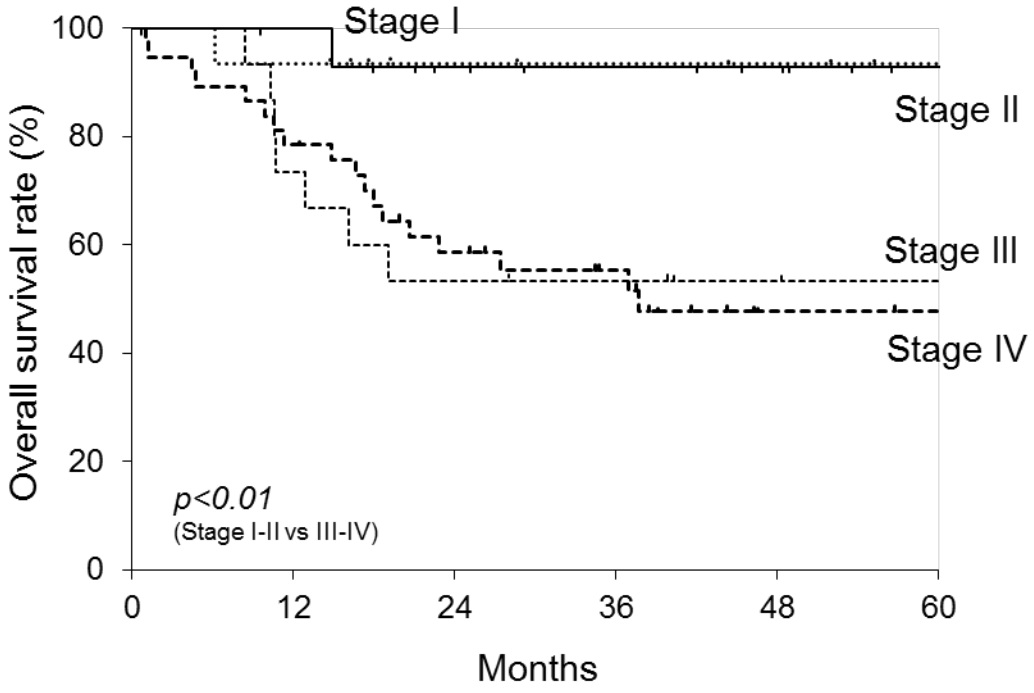
a



Number at Risk

I	3	3	3	3	2	1
II	11	10	9	6	5	1
III	17	16	12	10	9	8
IV	80	75	60	43	28	20

b



Number at Risk

I	17	15	11	9	6	2
II	15	14	10	9	8	6
III	16	11	8	7	5	4
IV	36	29	20	15	6	5

Figure 2

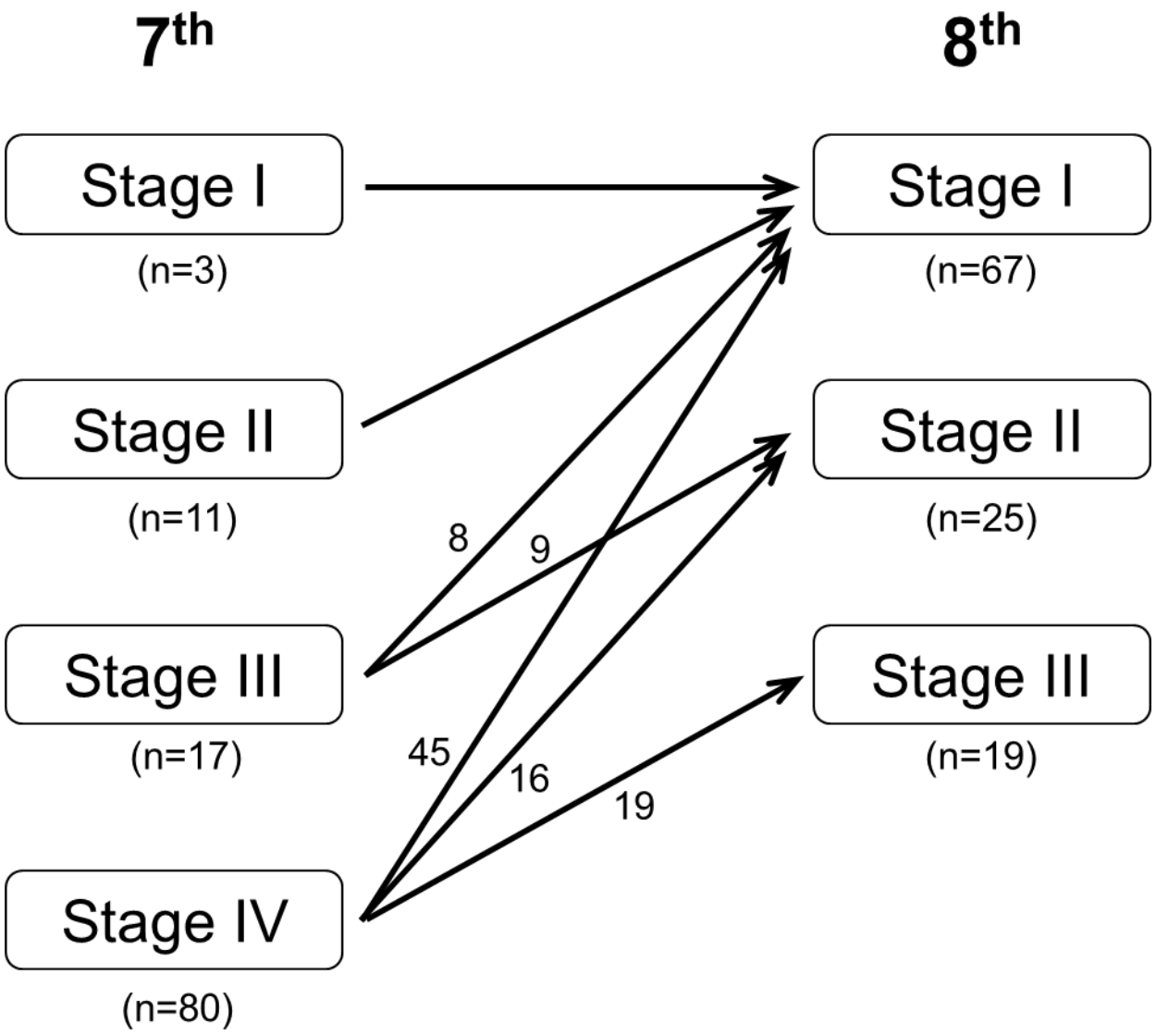
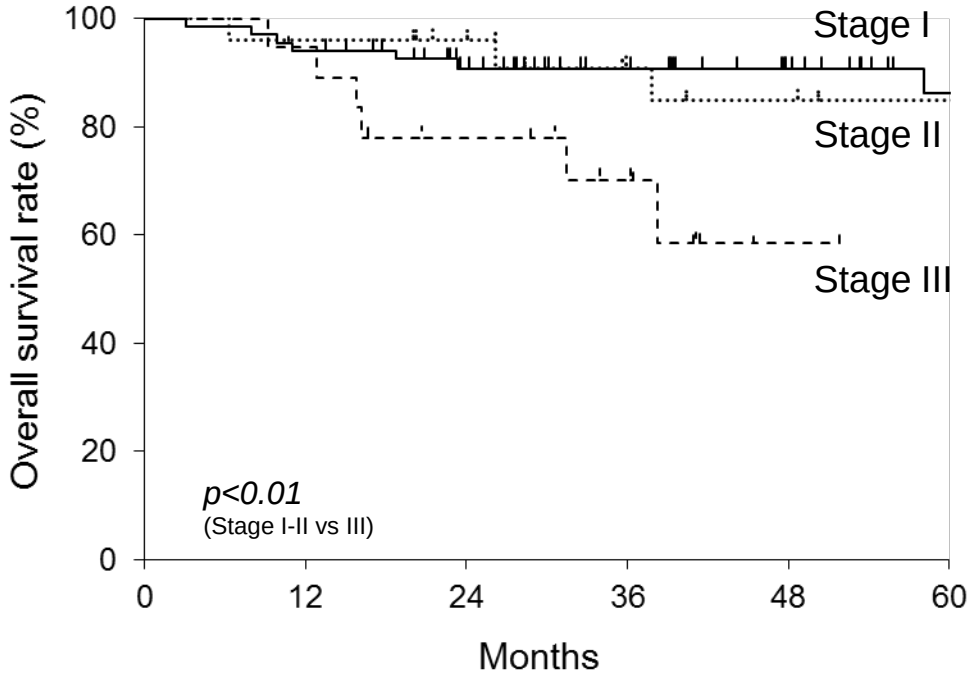

7th
8th
Stage I
(n=3)
Stage II
(n=11)
Stage III
(n=17)
Stage IV
(n=80)
Stage I
(n=67)
Stage II
(n=25)
Stage III
(n=19)
8
9
45
16
19

Figure 3



Number at Risk

I	67	63	47	39	30	19
II	25	24	21	15	13	11
III	19	17	12	8	1	0

Table 1 Definition of primary tumor in p16-positive oropharyngeal cancer in the 8th edition of the AJCC/UICC TNM staging system

T Category	T Criteria
T0	No primary identified
T1	Tumor 2 cm or smaller in greatest dimension
T2	Tumor larger than 2 cm but no larger than 4 cm in greatest dimension
T3	Tumor larger than 4 cm
T4	Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond

Table 2 Definition of regional lymph node in p16-positive oropharyngeal cancer in the 8th edition of the AJCC/UICC TNM staging system

Clinical N Category	Clinical N Criteria
N0	No regional lymph node metastasis
N1	One or more ipsilateral lymph nodes, none larger than 6 cm
N2	Contralateral or bilateral lymph nodes, none larger than 6 cm
N3	Lymph node(s) larger than 6cm

Table 3 Definition of clinical stage in p16-positive oropharyngeal cancer in the 8th edition of the AJCC/UICC TNM staging system

Stage I	T1, T2	N0, N1	M0
Stage II	T1, T2	N2	M0
	T3	N0, N1, N2	M0
Stage III	T1, T2, T3	N3	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

Table 4 Demographic and clinicopathological characteristics of OPSCC patients according to p16 status

	Patients n=195	p16-positive n=111	p16-negative n=84	*p* value
Gender				NS
Male	170	95	75	
Female	25	16	9	
Age at diagnosis (median =64)				0.002
<64 years	96	65	31	
≥64 years	99	46	53	
Year of diagnosis				0.030[a]
1998-2005	41	18	23	
2006-2010	47	25	22	
2011-2015	107	68	39	
Tumor subsite				*p* <0.001[b]
Lateral wall	108	77	31	
Anterior wall	56	25	31	
Superior wall	22	8	14	
Posterior wall	9	1	8	
Smoking				*p* <0.001
Median pack-years	30±25.2	22.5±24.3	41±22.6	
Alcohol consumption				*p* <0.001[c]
current	122	56	66	
occasional	23	15	8	
past	6	6	0	
none	29	26	3	
unknown	15	8	7	
Second primary tumor				*p* <0.001
No. of patients	50	14	36	
Management				
Surgery	54	26	28	
Radiotherapy	28	14	14	
Chemoradiotherapy	113	71	42	

3-Year overall survival, %	79.4	87.5	68.0	p <0.001

NS not significant

[a] 1998-2005 versus 2011-2015

[b] Lateral wall versus all other subsites

[c] Current versus others

Table 5 Distribution of T and N classification in p16-positive OPSCC using the 7th edition of the AJCC/UICC TNM staging system

	T1	T2	T3	T4
N0	3	11	7	2
N1	1	7	2	2
N2a	2	4	1	0
N2b	12	27	10	9
N2c	1	3	1	4
N3	0	1	1	0

Table 6 Distribution of T and N classification in p16-negative OPSCC using the 7th edition of the AJCC/UICC TNM staging system

	T1	T2	T3	T4
N0	17	15	8	2
N1	1	4	3	2
N2a	0	2	0	0
N2b	4	1	5	4
N2c	1	0	3	8
N3	0	2	0	2

Table 7 Distribution of T and N classification in p16-positive OPSCC using the 8th edition of the AJCC/UICC TNM staging system

	T1	T2	T3	T4
N0	3	11	7	2
N1	15	38	13	11
N2	1	3	1	4
N3	0	1	1	0