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Staging of oropharyngeal squamous cell carcinoma of the head and neck: Prognostic features and power of the 8th edition of the UICC staging manual

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ABSTRACT

Introduction: Recognizing the prognostic power differentiating HPV-associated oropharyngeal squamous cell cancer (OPSCC) from OPSCC with other causes, the UICC Cancer Staging Manual 8th edition realizes significant changes from the 7th edition. Purpose of this study was to evaluate the differences of prognostic impact between the 7th and the latest edition of TNM Classification as well as to examine risk factors like extranodal extension (ENE) and lymph node ratio (LNR) for HPV-mediated OPSCC.

Material and methods: The study includes 255 patients with OPSCC and initial diagnosis between 2008 and 2015. HPV status was determined according to p16 immunohistochemistry (IHC) and all patients were classified as defined by 7th and 8th edition of UICC. Prognostic influence of ENE and LNR was analyzed for patients with HPV-mediated OPSCC.

Results: 41.2% of the OPSCC were p16-positive. Implementation of the 8th edition of the UICC lead to a better differentiation between the respective stages. Regarding HPV-positive OPSCC, Kaplan-Meier survival curves showed a significantly better overall survival (OS) for patients with a LNR $\leq$10% as well as for patients with negative ENE status ($p = 0.004$, $p = 0.008$).

Conclusion: 8th edition of UICC achieves to differentiate properly between the UICC stages. However, the staging rule of ignoring ENE in HPV-mediated OPSCC should be further analyzed. Moreover LNR might be a possible additional prognostic factor – especially regarding HPV-positive tumors.

Introduction

Recognizing the prognostic power differentiating HPV-associated oropharyngeal squamous cell cancer (OPSCC) from OPSCC with other causes, the UICC Cancer Staging Manual 8th edition realizes significant changes from the 7th edition and distinguishes two different types of OPSCC [2–4]. Significant work has been performed to refine TNM stage and prognostic groups of OPSCC according to HPV status [5–7]. The 7th edition failed to differentiate properly between UICC stages [7–9], reducing the predictive feature of any specific stage [4]. The significantly better local-regional control and survival after therapy of patients with HPV-mediated OPSCC was not adequately taken into account [1,6,9].

The prognostic factor of extranodal extension (ENE) has been integrated in 8th edition staging system for HPV-negative tumors (N3b category) as several studies had shown that ENE leads to a significantly worse survival in HPV-negative OPSCC and represents one of the most important predictors of regional recurrence and distant metastases [10]. However, numerous studies failed to confirm this prognostic importance of ENE in HPV-positive tumors [5,10,12]. A factor that is not integrated in the TNM staging is the prognostic value of the lymph node ratio (LNR). Several studies evaluated LNR as potential prognostic factor for risk stratification in

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head and neck cancer (HNSCC) [11,13,14]. However, the prognostic impact of LNR in HPV- positive OPSCC has not been analyzed sufficiently so far. Purpose of this study was to evaluate the differences of prognostic impact between the 7th and the 8th edition of TNM Classification as well as to investigate risk factors such as ENE and LNR for HPV-mediated OPSCC.

Materials and methods

This retrospective study includes all patients with initial diagnosis of OPSCC between 01.01.2008 and 31.12.2015. Suitable patients were identified by International Classification of Diseases for Oncology (C01, C05.1, C05.2, C05.8, C05.9, C09.0-C09.9, C10.0–10.9, C14.0, C14.8). We furthermore verified all cases and collected anonymous data by studying the patient files including histopathology reports, doctor's reports, anesthesia protocols, operation reports and imaging. Exclusion criteria were prior treatment of HNSCC, recurrent tumors, insufficient tumor samples and lack of complete follow-up. Patients that quit the follow-up program and for which no survival data could be provided by cancer registry were excluded from survival analyses. OPSCC have been treated by surgery alone, surgery combined with adjuvant radiation/chemoradiation, primary radiation/chemoradiation or induction chemotherapy followed by radiation/chemoradiation. To evaluate history of cigarette smoking we included data on current or ever consumption as well as total smoking exposure measured by pack years (py: 0; <20; >20). Alcoholic consumption was according to the documented amount grouped as none, moderate, high or unknown. Regarding analysis of ENE and LNR, only patients with primary surgery and neck dissection were included. ENE was determined by histopathology reports. For LNR analysis a minimum of 10 lymph nodes had to be dissected and we excluded patients with pN0 (LNR = 0) as well as patients with pN3 neck metastases for which a conglomerate of lymph node metastases could not be excluded at any certainty. All analysis of LNR were performed with a cut off value of low and high LNR, ≤10 and > 10% (in following also referred to as LNR 1) [11,14]. Additionally we examined a cut off value of 13.6% as it represented our median LNR (in following also referred to as LNR 2). Pathological and clinical staging of OPSCC was done using the 7th edition of UICC TNM Classification (2010). In a second step all carcinomas were reclassified according to the 8th edition (2017). Immunohistochemistry (IHC) of the tumor suppressor protein p16 (cyclin-dependent kinase 2 A) is recommended as surrogate marker for HPV-mediated carcinogenesis [4,15–17] and was therefore performed using formalin-fixed, paraffin-embedded tumor specimens and a mouse monoclonal antibody (anti-$p16^{INK4a}$) to determine the HPV status. P16-IHC was classified positive on condition of strong and diffuse nuclear and cytoplasmatic staining in 70% or more of the tumor cells [18]. To detect p16-expression we used the CINtec p16-Histology kit (Roche Diagnostics, Mannheim, Germany). Tissue samples were provided by the tissue bank of the University Medical Center Mainz in accordance with the regulations of the tissue biobank and the approval of the ethics committee of University Medical Center Mainz [No. 837.360.16 (10679)].

Statistical analysis

Statistical analysis was carried out using SPSS Statistics for Windows, Version 25.0 (NY: IBM Corp., 2017). Two-sided statistical tests and a *p*-value less than 0.05 were regarded significant. Chi-square-test was used to compare HPV-positive and HPV-negative patients regarding demographic and clinicopathological parameters as well as tumor localization and furthermore to compare the distribution of patients among UICC categories according to the 7th vs. 8th edition of UICC classification. Chi-square test and fisher's exact test were used to analyze ENE-positive and ENE-negative patients. Kaplan-Meier estimates were carried out with 95% confidence intervals (95% CI) for overall survival (OS) which was measured from the date of initial histo-pathological diagnosis to the death of the patient or the time the patient was lost to follow-up. The significance was tested using the log-rank test. Mann-Whitney test was used as non-parametric test to analyze if HPV-status affects the absolute number of lymph nodes dissected. Potential prognostic variables for OS were evaluated by Kaplan-Meier estimates as well as Cox regression model using univariate and multivariate analysis (95% CI) to estimate hazard ratio (HR).

Results

255 patients with OPSCC met inclusion criteria with a majority of male patients (n = 178, 69.8%). Table 1 gives an overview of relevant descriptive data of the study population, risk factors and UICC classification of the 7th and 8th edition in relation to HPV status.

The median and mean age was 61 ± 9.6 years. In 41.2% of the cases (n = 105) p16-IHC was positive. With 32.9% the tonsils were the most frequent tumor localization (Table 2).

The majority of patients were smokers (84.6%) and most of them were classified in the highest category of >20 py (71.4%) (Table 1). In the majority of cases the patients' alcohol consumption was classified as moderate (25.1%) or high (36.1%). 60% of the patients were treated with primary surgery. Referring to the 7th edition, the majority of patients were staged UICC IVA (52.5%) followed by UICC III (16.5%). After reclassification according to the 8th edition, most of the patients present with stage I (27.5%) followed by stage IVA (20.4%).

HPV and 8th edition of UICC

For the period under consideration the prevalence of HPV-mediated tumors showed a trend of steady increase from 21.1% in 2008 to 42.9% in 2011 and up to 55.3% in 2015 ($p = 0.089$). OPSCC of the tonsil were in 65.5% p16-positive (Table 2). While HPV-status was independent of gender and age, the category of alcohol consumption as well as the patients smoking behavior showed a significant association to HPV-status ($p < 0.001$): 77.2% of patients being classified with “high alcohol consumption” and 72.0% of patients with a history of smoking of >20 py presented with HPV-negative OPSCC (Table 1). With exception of grading ($p < 0.001$), the histopathological prognostic factors of lymphovascular, vascular or perineural invasion showed no significant differences in the distribution between p16-negative and -positive OPSCC.

Fig. 1 illustrates the change of UICC stages I-IV when reclassifying all patients according to 8th edition of the UICC.

After applying the 8th edition the percentage of UICC I increases from 10.6% to 27.5%. Notably 24 of these patients were staged UICC IV before. While 134 patients were classified UICC IVA when applying the 7th edition, only 50 remained stage IVA according to the current version. However, the percentage of UICC IVB increased from 1.6% to 9.4% as the prognostic impact of ENE is now integrated in TNM classification for HPV negative tumors. HPV status was associated with 7th edition UICC stage ($p = 0.005$) and particularly of 8th edition UICC stage ($p < 0.001$) (Table 1): HPV-positive tumors are classified in the lower UICC stages I or II if the 8th edition is applied. According to 7th edition 81.5% of the tumors being classified UICC I were p16-negative. Applying the 8th edition 70.0% of OPSCC with UICC stage I are now p16-positive (Table 1).

Fig. 2 presents the Kaplan-Meier survival curves according to 7th (A) and 8th (B) edition of the UICC respectively ($p < 0.001$).

Table 1
Overview of study population in relation to HPV status.

		HPV negative		HPV positive		p-value	Total
		150	58.8%	105	41.2%		n = 255
Gender	male	106	59.6%	72	40.4%	0.720	178
	female	44	57.1%	33	42.9%		77
Age	>60 years	81	60.9%	52	39.1%	0.481	132
	≤60 years	69	56.6%	53	43.4%		123
Alcoholic consumption	none	20	58.8%	14	41.2%	**<0.001**	34
	moderate	30	46.9%	34	53.1%		64
	high	71	77.2%	21	22.8%		92
	unknown	29	45.3%	35	54.7%		64
Smoking	no	7	19.4%	29	80.6%	**<0.001**	36
	yes	138	69.7%	60	30.3%		198
Smoking categories	0	7	19.4%	29	80.6%	**<0.001**	36
	≤20 py	9	64.3%	5	35.7%		14
	>20 py	90	72.0%	35	28.0%		125
Primary surgery	no	64	62.7%	38	37.3%	0.299	102
	yes	86	56.2%	67	43.8%		153
LNR 1	<= 10%	19	50.0%	19	50.0%	1.000	38
	>10%	22	50.0%	22	50.0%		44
LNR 2	<= Median	20	48.8%	21	51.2%	1.000	41
	> Median	21	51.2%	20	48.8%		41
ENE	no	24	53.3%	21	46.6%	0.153	45
	yes	19	38.0%	31	62.0%		50
UICC 7th edition	I	22	81.5%	5	18.5%	**0.005**	27
	II	15	71.4%	6	28.6%		21
	III	22	52.4%	20	47.6%		42
	IVA	67	50.0%	67	50.0%		134
	IVB	3	75.0%	1	25.0%		4
	IVC	21	77.8%	6	22.2%		27
UICC 8th edition	I	21	30.0%	49	70.0%	**<0.001**	70
	II	15	34.1%	29	65.9%		44
	III	19	47.5%	21	52.5%		40
	IVA	50	100.0%	0	0.0%		50
	IVB	24	100.0%	0	0.0%		24
	IVC	21	77.8%	6	22.2%		27
Grading	1	2	66.7%	1	33.3%	**0.001**	3
	2	103	68.2%	48	31.8%		151
	3	39	43.3%	51	56.7%		90

py: pack years, LNR: lymph node ratio, ENE: extranodal extension.

Table 2
Localization of oropharyngeal primary tumors and HPV status.

		Total (n)	HPV	
			p16- (n)	p16+ (n)
Localization	Tonsilla palatina	32.9% (84)	34.5% (29)	65.5% (55)
	Base of the tongue	22.7% (58)	51.7% (30)	48.3% (28)
	Palatum molle/uvula	11.8% (30)	90% (27)	10% (3)
	Posterior pharyngeal wall	3.9% (10)	100% (10)	0% (0)
	Vallecula/lingual epiglottis	2.4% (6)	66.7% (4)	33.3% (2)
	Glossotonsillar fold	1.2% (3)	100% (3)	0% (0)
	Oropharynx not otherwise specified	25.1% (64)	73.4% (47)	26.6% (17)
total		100% (255)	58.8% (150)	41.2% (105)

$Chi^2(6) = 48.619$, $p < 0.001$.

Median follow-up was 33.9 months. Regarding the 8th edition the intention of a better discrimination between the four different stages is confirmed.

Analyzing variables with potential prognostic impact in OPSCC, patients with HPV-mediated tumors, age <60 years (trend), more moderate alcoholic consumption, non-smokers and patients with a history of <20 py showed significantly better OS rates ($p < 0.001$, $p = 0.068$, $p < 0.001$, $p = 0.003$, $p = 0.004$). In addition to that, patients with a LNR ≤10% (LNR1), LNR ≤13.6% (LNR 2) and patients with negative ENE status had significantly better OS rates ($p = 0.006$, $p = 0.002$, $p = 0.004$). The 5-year OS of HPV-associated OPSCC was 70.4% compared to 42.8% in HPV-negative tumors ($p < 0.001$) (Table 3).

Primary surgery resulted in a better 5-year-OS (66.7% vs. 32.4%, $p < 0.001$) – however, lower T levels got preferred primary surgical treatment (Table 3). Comparing 7th and 8th edition, 8th edition UICC stage IV had a significantly worse overall survival rate (30.4% vs. 45.4%, $p = 0.014$), reflecting the worse prognostic effect of ENE as well as the down-staging of HPV-positive tumors.

When analyzing the subgroup of HPV-positive OPSCC, lower category of alcoholic consumption, primary surgery, LNR ≤10%, LNR ≤13.6% and negative ENE status resulted in a significant better OS ($p = 0.001$, $p < 0.001$, $p = 0.003$, $p = 0.002$, $p = 0.008$). No significant differences were found between smokers and non-smokers

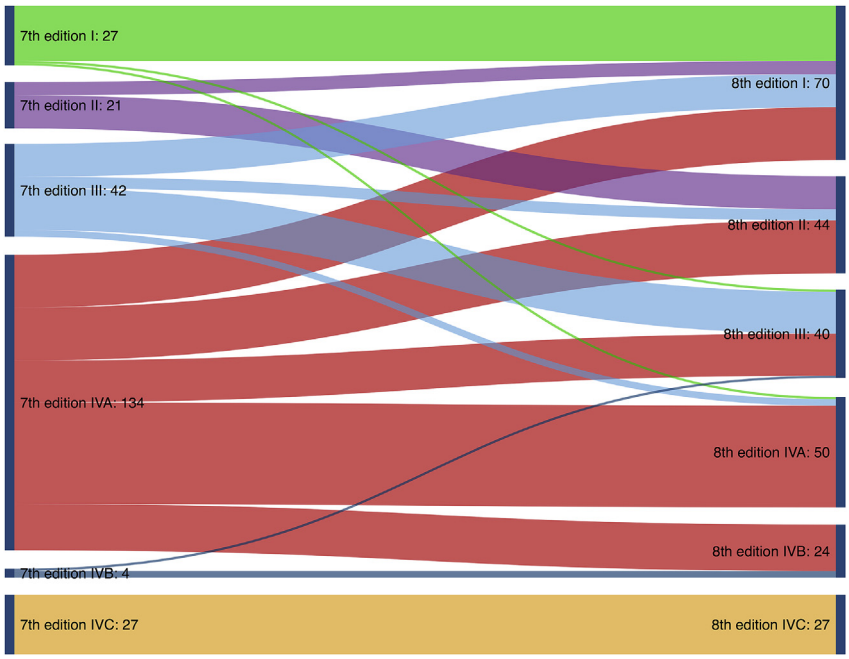

Fig. 1. Illustration of the change of UICC stages I-IV reclassified according to 8th edition of the UICC.

($p = 0.154$) and between the different categories of smoking ($p = 0.081$). All data concerning OS of p16 positive OPSCC is presented in the supplementary.

Variables with possible prognostic potential were further analyzed and evaluated by multivariate analysis using Cox' proportional hazards regression. HPV status, age and primary surgery were found as independent predictors for OS in patients with OPSCC ($p = 0.025$, $p = 0.001$ and $p < 0.001$) (Table 3). Cox multivariate analysis of OS furthermore confirmed age and primary surgery as independent predictors in HPV-mediated tumors ($p = 0.017$ and $p = 0.018$). These results need to be interpreted carefully as all T1 tumors but only 9.1% of T4 tumors have been treated surgically. Furthermore we analyzed the prognostic impact of ENE, LNR 1, grouped T-status (1/2 vs 3/4) as well as N-status in a multivariate analysis including all p16-positive cases. As a consequence of the inclusion criteria the remaining number of cases was too small with only a few death events (e.g. only one death in the group p16 positive and ENE negative). As consequence ENE and LNR did not reach significance in multivariate analysis ($p = 0.929$, HR:1.05; $p = 0.915$, HR 2.25).

Extranodal extension

A total number of 95 patients met inclusion criteria for analysis of ENE and 52.6% of them were ENE-positive. Regarding patients with ENE a median of 17 ± 11.9 lymph nodes were dissected compared to a median of 19 ± 10.8 lymph nodes for patients without ENE. The cases with positive ENE were not significantly different distributed between p16-positive and p16-negative tumors (59.6% vs. 44.2%, $p = 0.153$). Higher rates of ENE were seen in patients with positive smoking status (75.0% vs. 44.3%, $p = 0.050$).

To evaluate the prognostic impact of ENE in HPV-positive patients we analyzed OS (Fig. 3A). Remarkably Kaplan-Meier survival estimates demonstrate a significantly better OS in p16-positive OPSCC without ENE (ENE-positive: OS = 92.9%, ENE-negative: OS = 68.0%, $p = 0.008$).

Lymph node ratio

Regarding analysis of LNR firstly we examined all patients treated with primary surgery and uni- or bilateral neck dissection (138 patients). The absolute number of positive lymph nodes showed a significant difference between p16-positive and p16-negative OPSCC in Mann-Whitney-test ($p = 0.010$) with a higher number of positive lymph nodes in p16-positive tumors (mean 3.68 vs. 2.24 and median 2.00 vs. 1.00 lymph node metastases). For the following statistical analysis only patients with a minimum of 10 lymph nodes dissected were included: A median of 22 lymph nodes were dissected (mean 23.66) - with a median of 3 and a mean of 4.33 metastases. The median LNR was 13.6%. 46.34% of the patients presented with a LNR $\leq$10% and 53.66% with a LNR >10% and this distribution was similar in HPV-positive and HPV-negative OPSCC. Kaplan-Meier survival estimates including HPV-positive and −negative tumors demonstrated a significant better OS for patients with a LNR $\leq$10% compared to patients with a LNR >10% ($p = 0.006$) as well as a significant better OS for patients with a LNR $\leq$ 13.6% compared to patients with a LNR > 13.6% ($p = 0.002$). LNR was further analyzed by examining HPV-mediated and HPV-negative tumors. In the subgroup of HPV-positive OPSCC, patients with a LNR $\leq$10% as well as patients with a LNR $\leq$13.6% presented with a significantly better OS ($p = 0.004$, $p = 0.003$) (Fig. 3B). Remarkably in HPV-negative OPSCC, there was no significant difference in the OS between patients with a LNR $\leq$10% and a LNR >10% ($p = 0.116$) or between patients with a LNR $\leq$ 13.6% and a LNR > 13.6% ($p = 0.054$).

Discussion

HPV and UICC 8th edition

Our data confirmed that HPV-positive OPSCC showed a significantly improved 5-year OS of 70.4% compared to 42.8% in patients with HPV-negative tumors. Applying the 8th edition 70% of OPSCC with UICC stage I are now p16 positive tumors, keeping in mind that a large proportion of these cases has been classified advanced

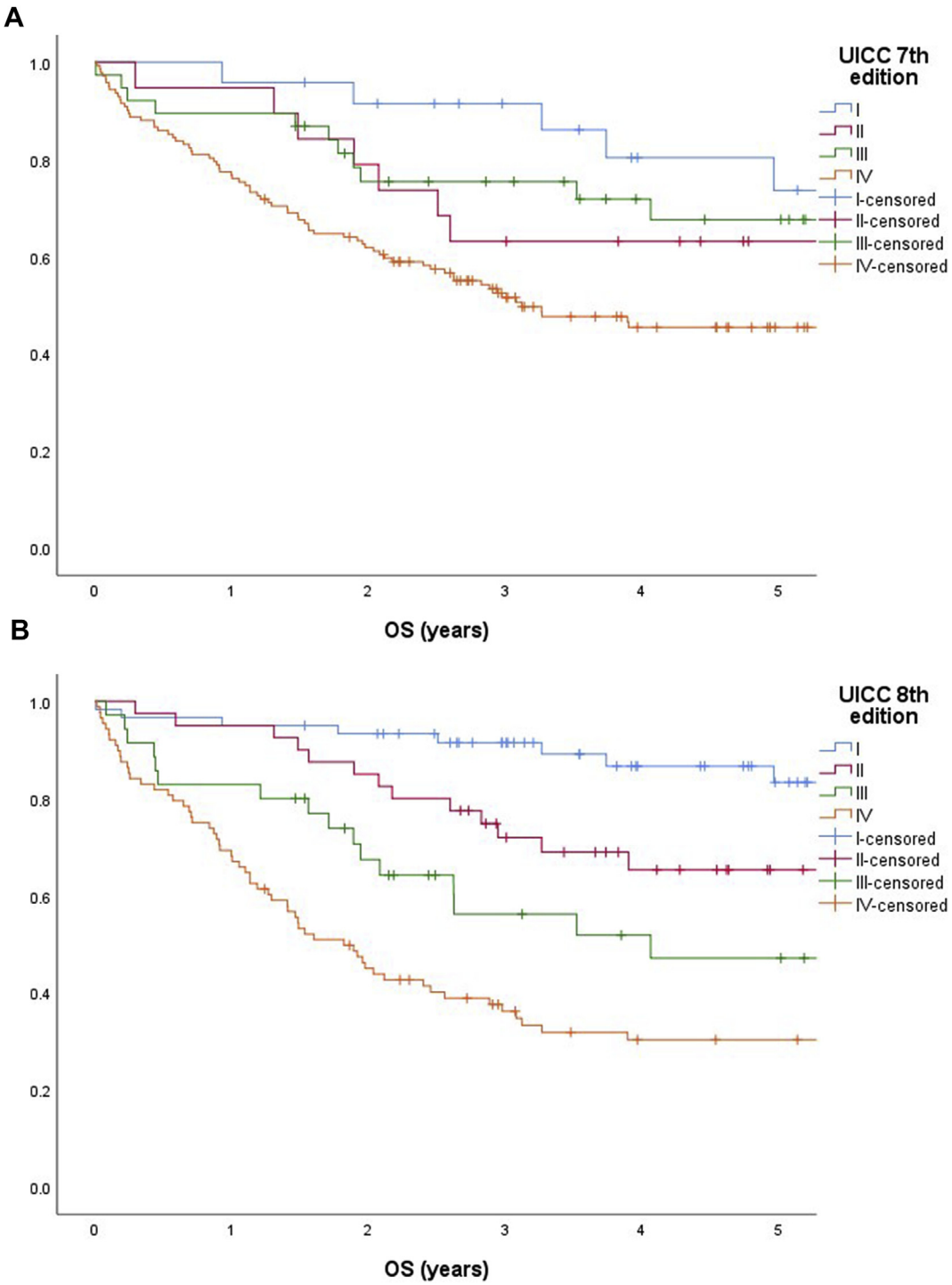

Fig. 2. Kaplan-Meier 5-year survival estimates according to 7th (A) and 8th (B) edition of the UICC
OS = overall survival.

stage before (Fig. 1). This is in concordance with recent results of Gronhoj et al. demonstrating a better OS of approximately 30% for HPV-mediated OPSCC [19]. Furthermore our results are concordant with the aim of 8th edition to better differentiate between the four UICC stages. In a large multicentric study of the International Collaboration on Oropharyngeal Cancer Network for Staging (ICON-S), which served to develop and validate TNM criteria for the 8th edition, only 2% of the HPV-positive patients and 2% of the HPV-negative patients were treated with primary surgery [7]. In our opinion it is therefore important to evaluate the changes of the 8th edition in a patient cohort with 57.3% of HPV-negative and 63.8% of HPV-positive patients being treated with primary surgery.

In fact the prognostic down-staging of HPV-OPSCC anticipates evidence based international recommendations and standards in therapy of OPSCC [9]. The applied treatment strategies for the management of OPSCC are traditionally diverse and the choice between primarily surgical and non-surgical approaches is often dependent on regional preference [9]. Due to favorable outcomes

Table 3
Prognostic impact on overall survival (all patients).

		N	Survival (univariate)			Univariate Analysis (Cox)		Multivariate Analysis (Cox)	
			2-year OS (%)	5-year OS (%)	p-value	HR	p-value	HR	p-value
HPV	negative	133	57.3	42.8	<**0.001**	0.379	<**0.001**	0.560	**0.025**
	positive	90	85.6	70.4					
Gender	male	154	67.2	50.4	0.344	0.807	0.335	0.940	0.793
	female	69	72.4	60.7					
Age	>60	115	61.3	47.8	0.068	0.693	0.069	0.487	**0.001**
	≤60	108	76.9	59.7					
Alcoholic consumption	none	31	77.4	69.9	<**0.001**	0.965	0.931	0.695	0.398
	moderate	61	77.0	67.5		0.950	0.883	0.658	0.271
	high	81	56.2	28.5		2.879	<**0.001**	1.720	0.101
	unknown	50	73.7	69.0					
Smoking	no	33	84.8	78.3	**0.003**	3.068	**0.004**	2.008	0.883
	yes	171	63.4	46.5					
Smoking categories	0	33	84.8	78.3	**0.004**	0.329	**0.006**		
	≤20 py	13	53.8	26.9		1.523	0.268		
	>20 py	109	63.9	47.7					
LNR 1	<= 10%	36	88.9	83.7	**0.006**	0.314	**0.010**		
	>10%	38	60.3	50.1					
LNR 2	<= Median	38	89.5	84.5	**0.002**	0.279	**0.004**		
	> Median	36	58.1	47.5					
ENE	no	45	88.9	85.0	**0.004**	0.310	**0.006**		
	yes	39	59.0	51.8					
Primary surgery	no	85	51.2	32.4	<**0.001**	0.354	<**0.001**	0.377	<**0.001**
	yes	138	79.6	66.7					
Primary surgery T1	no	0	–	–	–	–	–		
	yes	54	83.3	70.3					
Primary surgery T2	no	13	53.8	46.2	**0.050**	0.414	0.058		
	yes	50	84.0	72.4					
Primary surgery T3	no	22	54.5	26.2	0.094	0.534	0.100		
	yes	29	64.6	48.4					
Primary surgery T4	no	50	49.5	31.3	0.089	0.209	0.124		
	yes	5	80.0	80.0					
UICC I	7th	24	91.5	73.7	0.633	1.278	0.639		
	8th	60	93.3	83.3					
UICC II	7th	19	78.9	63.2	0.707	1.191	0.709		
	8th	40	85.0	65.3					
UICC III	7th	38	75.4	67.6	0.190	0.624	0.202		
	8th	35	67.4	47.2					
UICC IV	7th	142	61.9	45.4	**0.014**	0.655	**0.015**		
	8th	88	45.0	30.4					
UICC 7th edition	I	24	91.5	73.7	**0.009**	0.336 0.546 0.548	**0.010** 0.127 **0.046**		
	II	19	78.9	63.2					
	III	38	75.4	67.6					
	IV	142	61.9	45.4					
UICC 8th edition	I	60	93.3	83.3	<**0.001**	0.151 0.311 0.581	<**0.001** <**0.001 0.048**		
	II	40	85.0	65.3					
	III	35	67.4	47.2					
	IV	88	45.0	30.4					

py: pack years, LNR: lymph node ratio, ENE: extranodal extension.

after combined chemo-radiation in HPV-associated OPSCC [18] and a lack of evidence for the benefit of surgery, the management with ablative surgery has been already questioned [20]. In the National Comprehensive Cancer Network (NCCN) Guidelines (2.2018 version; June 20, 2018), the prognostic factors HPV-status as well as ENE are now incorporated in the treatment algorithms but there is currently no evidence that the new staging criteria published in the 8th edition should drive clinical decision-making. Thus, the treatment algorithms are almost identical. The results of upcoming research studies or ongoing trials such as the EORTC 1420 phase III study [21] will have to reveal the extent to which single radiotherapy instead of primary surgery for small OPSCC, reduced radiation dosages, radiotherapy alone instead of chemoradiation, less invasive surgical methods, or immunotherapy may lead to de-escalation in the treatment of p16-positive OPSCC.

Lymph node ratio

Our results of univariate analysis of LNR showed that a LNR of ≤10% leads to significant better OS in patients with HPV-mediated OPSCC and analysis with a cut-off value of 13.6% as our median LNR showed comparable results. However, LNR ≤10% as well as LNR ≤13.6% did not serve as predictor of better OS for HPV-negative OPSCC. Our results of LNR analysis are contrary to the current system of N-classification of p16-positive OPSCC. In primarily surgically treated HPV-positive OPSCC it is the number of affected lymph nodes (cut-off pN1/pN2 ≥ 5) that has a decisive prognostic influence determining the pN-category of 8th edition [5]. Taking LNR into account as a relevant prognostic factor, a minimum number of 40 lymph nodes had to be resected to achieve LNR ≤10% in a patient with e.g. 5 lymph node metastases. As Jacobi et al. and Kuenzel et al. already discussed critically LNR represents a valuable prognostic parameter for OPSCC and it should be interpreted in its

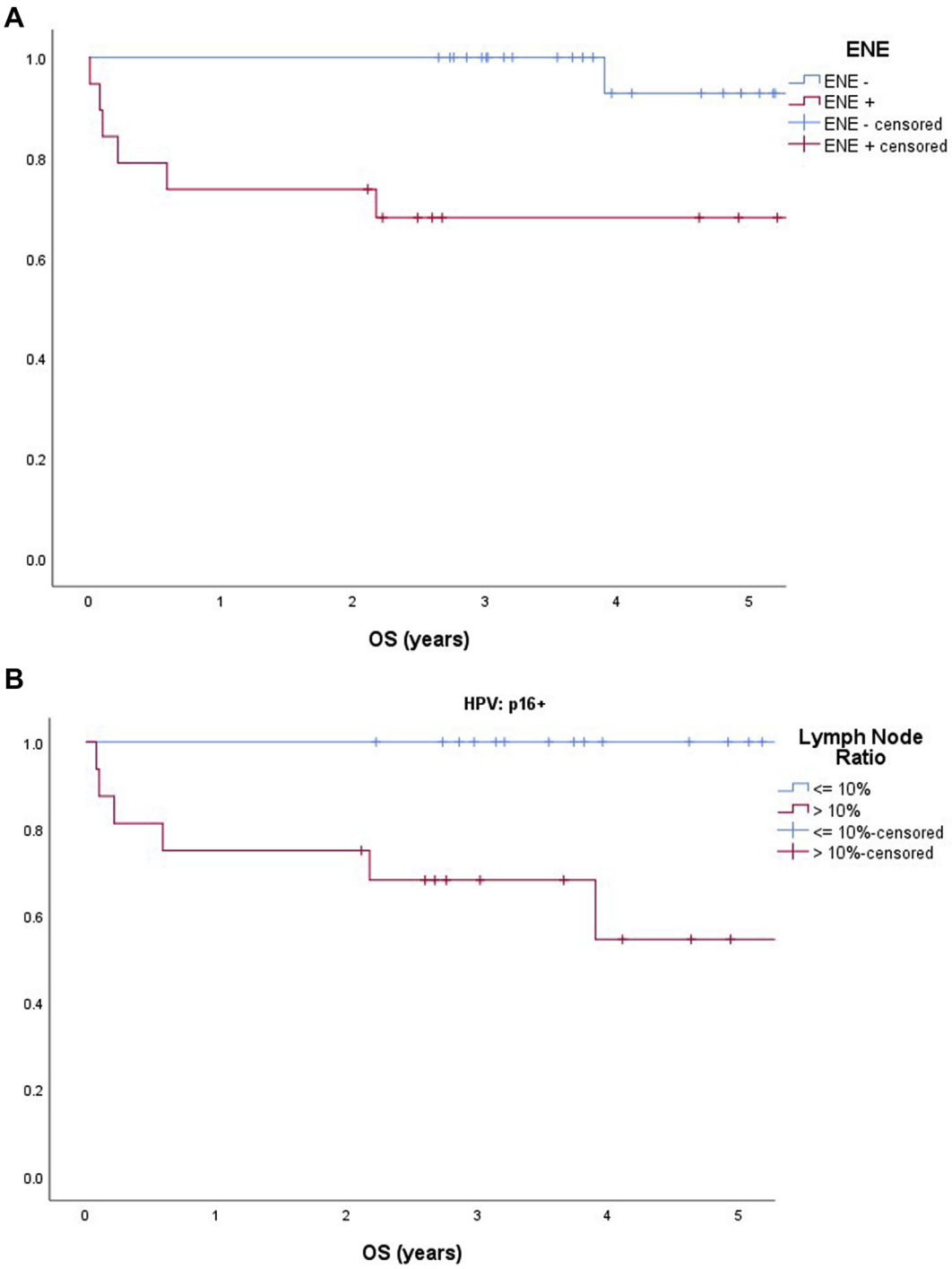

Fig. 3. Prognostic impact of extranodal extension (A) and lymph node ratio (B) in patients with HPV-associated oropharyngeal cancer
ENE = extranodal extension; OS = overall survival; HPV: human papilloma virus.

full context [11,14]. As recommended in the latest TNM edition we tried to standardize the extent of neck dissection retrospectively in so far that only patients with a minimum of 10 lymph nodes dissected met inclusion criteria of LNR analysis. However, LNR is dependent on several factors such as surgical techniques, selective vs. radical procedure, uni-vs. bilateral neck dissection, histopathological examination with rate of detected metastases as well as general institutional standards [11,14,22–25]. A formula that contains both the LNR and the lymph node yield ("LNR^{LNY}") as it is discussed by Jacobi et al. could improve interpretation of LNR [14]. Nevertheless, LNR and its cut-off value of 10% seems to represent a valuable prognostic factor in HPV-mediated OPSCC and its prognostic importance should be analyzed in further prospective investigations to generate the necessary evidence.

Extranodal extension

It is predominantly the prognostic factor of HPV-status that has been analyzed by recent studies which investigated the application of the 8th edition of UICC [9,26]. Therefore we focused on

evaluating the prognostic impact of ENE for p16-positive OPSCC. As positive ENE leads to a distinct up-staging in HPV-negative OPSCC we analyzed Kaplan-Meier survival estimates to examine if ENE is really completely negligible in HPV-positive tumors. The presence of ENE (52.6.%) was in concordance with rates reported in previous studies (59.2%, 52% and 43.5% respectively) [27–29]. Kaplan-Meier estimates could demonstrate a significantly worse OS of patients with ENE and HPV-mediated tumors ($p = 0.008$). This is concordant to An et al. that analyzed the prognostic value of ENE in 1043 patients with HPV-associated OPSCC and demonstrated that positive ENE showed an inferior OS (3-year OS: 89.3% vs. 93.6%, $p = 0.01$) [28]. They furthermore stated that not the presence of $\geq$5 lymph nodes but positive ENE was significantly associated with worse OS on multivariate Cox regression ($p < 0.05$) [28]. Further subdivision of pathological proven ENE into several categories – such as microscopic ($\leq$0.2 cm beyond the lymph-node capsule) versus macroscopic ENE (>0.2 cm beyond the lymph-node capsule) and soft-tissue metastases – is also a matter of debate [4]. However, the rationale in the revised TNM classification is that microscopic and macroscopic ENE is considered as ENE-positive for its definition.

Summary

The 8th edition of the UICC staging system achieves better differentiation between the respective UICC stages improving the predictive feature of any specific stage. However, HPV-status remains without any consequence for decision making so far. Whether ENE is completely negligible in HPV-positive OPSCC has to be scrutinized. Furthermore, the stratification algorithm of the pathological N-classification of p16-positive OPSCC is at least debatable taking into account the prognostic value of LNR. Investigations in large prospective trials are required to generate valid evidence clarifying the prognostic impact of ENE and LNR in HPV-positive tumors.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.02.032.

References

[1] Carlander A-LF, Grønhøj Larsen C, Jensen DH, Garnæs E, Kiss K, Andersen L, et al. Continuing rise in oropharyngeal cancer in a high HPV prevalence area. Eur J Cancer 2017;70:75–82. https://doi.org/10.1016/j.ejca.2016.10.015.
[2] Edge SB, Compton CC. The American joint committee on cancer. Ann Surg Oncol 2010;17:1471–4. https://doi.org/10.1245/s10434-010-0985-4.
[3] Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The eighth edition AJCC cancer staging manual, CA cancer. J Clin 2017;67:93–9. https://doi.org/10.3322/caac.21388.
[4] Lydiatt WM, Patel SG, O'Sullivan B, Brandwein MS, Ridge JA, Migliacci JC, et al. Head and Neck cancers-major changes in the American Joint Committee on cancer eighth edition cancer staging manual. Ca - Cancer J Clin 2017;67:122–37. https://doi.org/10.3322/caac.21389.
[5] Huang SH, O'Sullivan B. Overview of the 8th edition TNM classification for head and neck cancer. Curr Treat Options Oncol 2017;18:40. https://doi.org/10.1007/s11864-017-0484-y.
[6] Huang SH, Xu W, Waldron J, Siu L, Shen X, Tong L, et al. Refining American Joint Committee on Cancer/Union for International Cancer Control TNM stage and prognostic groups for human papillomavirus-related oropharyngeal carcinomas. J Clin Oncol 2015;33:836–45. https://doi.org/10.1200/JCO.2014.58.6412.
[7] 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). Lancet Oncol 2016;17:440–51. https://doi.org/10.1016/S1470-2045(15)00560-4.
[8] Marur S, Forastiere AA. Head and neck squamous cell carcinoma. Mayo Clin Proc 2016;91:386–96. https://doi.org/10.1016/j.mayocp.2015.12.017.
[9] Würdemann N, Wagner S, Sharma SJ, Prigge E-S, Reuschenbach M, Gattenlöhner S, et al. Prognostic impact of AJCC/UICC 8th edition new staging rules in oropharyngeal squamous cell carcinoma. Front Oncol 2017;7:129. https://doi.org/10.3389/fonc.2017.00129.
[10] Mermod M, Tolstonog G, Simon C, Monnier Y. Extracapsular spread in head and neck squamous cell carcinoma. Oral Oncol 2016;62:60–71. https://doi.org/10.1016/j.oraloncology.2016.10.003.
[11] Künzel J, Psychogios G, Mantsopoulos K, Grundtner P, Waldfahrer F, Iro H. Lymph node ratio as a predictor of outcome in patients with oropharyngeal cancer. Eur Arch Oto-Rhino-Laryngol 2014;271:1171–80. https://doi.org/10.1007/s00405-013-2513-1.
[12] Klozar J, Koslabova E, Kratochvil V, Salakova M, Tachezy R. Nodal status is not a prognostic factor in patients with HPV-positive oral/oropharyngeal tumors. J Surg Oncol 2013;107:625–33. https://doi.org/10.1002/jso.23292.
[13] Künzel J, Mantsopoulos K, Psychogios G, Grundtner P, Koch M, Iro H. Lymph node ratio as a valuable additional predictor of outcome in selected patients with oral cavity cancer. Oral Surg Oral Med Oral Pathol Oral Radiol 2014;117:677–84. https://doi.org/10.1016/j.oooo.2014.02.032.
[14] Jacobi C, Rauch J, Hagemann J, Lautz T, Reiter M, Baumeister P. Prognostic value of the lymph node ratio in oropharyngeal carcinoma stratified for HPV-status. Eur Arch Oto-Rhino-Laryngol 2018;275:515–24. https://doi.org/10.1007/s00405-017-4833-z.
[15] El-Naggar AK, Westra WH. p16 expression as a surrogate marker for HPV-related oropharyngeal carcinoma. Head Neck 2012;34:459–61. https://doi.org/10.1002/hed.21974.
[16] Westra WH. Detection of human papillomavirus (HPV) in clinical samples. Oral Oncol 2014;50:771–9. https://doi.org/10.1016/j.oraloncology.2014.05.004.
[17] Lewis JS. p16 Immunohistochemistry as a standalone test for risk stratification in oropharyngeal squamous cell carcinoma. Head Neck Pathol 2012;6(Suppl 1):S75–82. https://doi.org/10.1007/s12105-012-0369-0.
[18] Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363:24–35. https://doi.org/10.1056/NEJMoa0912217.
[19] Grønhøj C, Jensen DH, Dehlendorff C, Marklund L, Wagner S, Mehanna H, et al. Development and external validation of nomograms in oropharyngeal cancer patients with known HPV-DNA status. Br J Canc 2018;118:1672–81. https://doi.org/10.1038/s41416-018-0107-9.
[20] Lybak S, Ljøkjel B, Haave H, Karlsdottir À, Vintermyr OK, Aarstad HJ. Primary surgery results in no survival benefit compared to primary radiation for oropharyngeal cancer patients stratified by high-risk human papilloma virus status. Eur Arch Oto-Rhino-Laryngol 2017;274:477–87. https://doi.org/10.1007/s00405-016-4203-2.
[21] Clinical Trials Database. EORTC-1420 clinical trial details. https://www.eortc.org/research_field/clinical-detail/1420/. [Accessed 4 February 2019].
[22] Feng Z, Qin LZ, Huang X, Li JZ, Su M, Han Z. Nodal yield. J Oral Maxillofac Surg 2015;73:1851–9. https://doi.org/10.1016/j.joms.2015.03.027.
[23] Friedman M, Lim JW, Dickey W, Tanyeri H, Kirshenbaum GL, Phadke DM, et al. Quantification of lymph nodes in selective neck dissection. Laryngoscope 1999;109:368–70.
[24] Norling R, Therkildsen MH, Bradley PJ, Nielsen MB, von Buchwald C. Nodal yield in selective neck dissection. Acta Otolaryngol 2013;133:965–71. https://doi.org/10.3109/00016489.2013.799290.
[25] Lörincz BB, Langwieder F, Möckelmann N, Sehner S, Knecht R. The impact of surgical technique on neck dissection nodal yield. Eur Arch Oto-Rhino-Laryngol 2016;273:1261–7. https://doi.org/10.1007/s00405-015-3601-1.
[26] Sano D, Yabuki K, Arai Y, Tanabe T, Chiba Y, Nishimura G, et al. The applicability of new TNM classification for humanpapilloma virus-related oropharyngeal cancer in the 8th edition of the AJCC/UICC TNM staging system in Japan. Auris Nasus Larynx 2018;45:558–65. https://doi.org/10.1016/j.anl.2017.07.010.
[27] Sinha P, Lewis JS, Piccirillo JF, Kallogjeri D, Haughey BH. Extracapsular spread and adjuvant therapy in human papillomavirus-related, p16-positive oropharyngeal carcinoma. Cancer 2012;118:3519–30. https://doi.org/10.1002/cncr.26671.
[28] An Y, Park HS, Kelly JR, Stahl JM, Yarbrough WG, Burtness BA, et al. The prognostic value of extranodal extension in human papillomavirus-associated oropharyngeal squamous cell carcinoma. Cancer 2017;123:2762–72. https://doi.org/10.1002/cncr.30598.
[29] Maxwell JH, Ferris RL, Gooding W, Cunningham D, Mehta V, Kim S, et al. Extracapsular spread in head and neck carcinoma. Cancer 2013;119:3302–8. https://doi.org/10.1002/cncr.28169.