The Laryngoscope

Carcinoma of Unknown Primary and the 8th Edition TNM Classification for Head and Neck Cancer

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Objective: In the 8th Edition TNM Classification for Head and Neck Cancer, the classification for carcinoma of unknown primary (CUP) changed in addition to oropharyngeal carcinomas. The current classification considers extranodal extension (ENE), determination of p16 (surrogate marker for human papillomavirus), and detection of Epstein-Barr virus (EBV). The aim of this study was to investigate the influence of the new classification on the prognosis of p16-positive and p16-negative CUP and the impact of EBV proof.

Methods: Clinical and pathological data from patients with CUP of the head and neck between 2009 and 2018 were evaluated. The 7th (UICC7) and 8th (UICC8) edition of the Union for International Cancer Control staging system were applied and compared.

Results: There were 97 patients treated, 26.8% women and 73.2% men. The average age at initial diagnosis was 64.6 years. Of which, 58.8% had a documented history of smoking, 37.1% were positive for p16, 4.1% were positive for EBV, and 66% had ENE. Most of the patients were at stage III/IVa (78.4% according to UICC7). According to UICC8, p16+ patients were mainly at stage I (86.1%), and p16− at stage IVb (56.1%). P16 status ($P = .002$), ENE ($P = .001$), nodal category (TNM7, $P < .001$), UICC stage (TNM7, $P < .001$) and UICC stage (TNM8, $P < .001$) had a significant impact on survival in the univariate analysis. The 8th TNM classification resulted in a downstaging of p16-positive CUP syndromes and an upstaging of p16-negative syndromes.

Conclusion: The 8th TNM classification shows the lower UICC stage in p16-positive CUP syndromes. The prognostic significance for survival has improved from the 7th to the 8th TNM classification.

Key Words: CUP, TNM, P16, EBV.

Level of Evidence using the 2011 OCEBM: Level 3.

***Laryngoscope*, 131:E2534–E2542, 2021**

INTRODUCTION

Head and neck cancer of unknown primary (HNCUP) is diagnosed in cases of cervical metastasis with no identifiable primary tumor. With a proportion of approximately 1% to 5% of all head and neck cancers, HNCUP makes up a relatively low number of head and neck cancer (HNC) patients.[1–4] The most frequent histological subtype in 75% to 90% of cases is squamous cell carcinoma (SCC).[4–6] With approximately 40% prevalence in European HNC, persistent human papillomavirus

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Additional supporting information may be found in the online version of this article.

Editor's Note: This Manuscript was accepted for publication on febraury 20, 2021.

I.P. and A.C. contributed equally.

Meeting information: 91st Annual German Conference of the German Society for Otolaryngology (President Andreas Dietz). Berlin, Germany (05/22/2020)

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DOI: 10.1002/lary.29499

(HPV) infection (e.g., HPV-16) is a major risk factor for developing HNC.[7,8] Further risk factors are smoking, heavy drinking, and Epstein-Barr virus (EBV) infection, especially for the development of nasopharyngeal cancer (NPC).[9–11]

HPV-positive oropharyngeal cancers (OPCs) have been shown to have a better overall survival rate (OS) compared with HPV-negative OPCs.[12] In 2016, a multicenter cohort study (O'Sullivan et al. including 2603 patients) proposed a new staging system for HPV-positive OPC.[13] These findings led to a staging systems revision by the American Joint Committee on Cancer and the Union for International Cancer Control (UICC) in 2016.[14,15] The 8th edition of the UICC's TNM Classification of Malignant Tumors dedicates a whole chapter to HNCUP, considering the same surrogate marker p16 for HPV-related HNC as the OPC classification plus EBV status to assign patients to different nodal categories and UICC stages of HNCUP.[16] Further factors besides size, number of nodes, and ipsi-, contra-, or bilateral lymph node manifestation are the extranodal extension (ENE) in p16– HNCUP patients.[15]

In a retrospective study with 978 patients, Cheraghlou et al. showed that HPV-associated HNCUP indicates superior survival compared with HPV- HNCUP patients.[17] Other recent studies concluded the same impact on the OS and longer disease-free survival (DFS) of HPV+ HNCUP patients.[18,19] Because EBV as a favorable prognostic factor has only been described in NPC,[20] similar studies indicating the impact and relevance of EBV in the prediction of OS of HNCUP patients are missing.

To date, there has been no study verifying the 8th TNM Classification of Malignant Tumors in its current form to determine HNCUP patients' nodal categories and UICC stages and evaluating the changes made from the 7th to the 8th edition (e.g., prognostic value). Therefore, the objective of the present study is to assess the applicability of UICC's TNM Classification of Malignant Tumors 8th Edition for HNCUP in comparison to the 7th Edition and to investigate the role of both HPV and EBV in HNCUP.

MATERIAL AND METHODS

Patient Inclusion Criteria

Patients treated for HNCUP at Charité—Universitätsmedizin Berlin between 2009 and 2018 were included and reviewed. The Institutional Review Board approved this study (application no. EA2/005/18). Their diagnoses were histologically confirmed in all cases by the pathological institution of the university.

Patient and Treatment Assessment

Each patient with HNCUP underwent a diagnostic assessment including medical history, physical examination, and imaging studies including computed tomography (CT) scan or magnetic resonance imaging of the neck and CT scan of the thorax and abdomen. Positron emission tomography–CT was performed in 53 patients to further investigate the primary tumor. Each patient underwent panendoscopy, for primary tumor search, biopsies were taken from the nasopharynx and tongue base, and tonsillectomies were performed bilaterally. The lymph node was removed or biopsied for histopathological evaluation.

Each patient's specific data were individually discussed by a multidisciplinary tumor board consisting of head and neck surgeons, radio-oncologists, pathologists, medical oncologists, and radiologists. Therapy recommendations are based on UICC stage and medical condition. The National Comprehensive Cancer Network guideline was used as guidance for treatment regimens.[21] The treatment included neck dissection followed by adjuvant radiotherapy (RT) or chemoradiotherapy (CRT). Neck dissection was performed as modified radical neck dissection or radical neck dissection depending on the tumor infiltration of surrounding structures, usually unilateral or bilateral in clinical susceptive tumor growth bilaterally.

RT was usually performed using 54 to 70 Gy, but >70 Gy was used in cases with ENE. Chemotherapy was applied in patients with ENE and consisted of cisplatin (5×20 mg/m^2) ± 5-fluorouracil (5FU, 5×600 mg/m^2 c.i.), mitomycin C (1×10 mg/m^2) ± 5FU, or cetuximab in the first and fifth week of RCT.

Definite RT/CRT was considered in advanced nodal categories. In patients with advanced UICC stages with distal metastases and impaired medical conditions, palliative chemotherapy or immunotherapy (e.g., cetuximab and nivolumab) was offered. In addition, these patients received the best supportive care.

The medical records of all patients were reviewed for medical history, imaging studies, and surgical and histopathological protocols, and the UICC stage was classified according to TNM 7th and 8th edition.

Immunohistochemistry

Immunohistochemical staining was performed using tissue microarrays. For this, representative tumor areas of SCC samples were marked on the hematoxylin and eosin–stained section of all included patients. Two cores of 1.5-mm diameter were punched from different areas of each patient sample using a tissue microarray (Beecher Instruments, Woodland, CA) and were embedded in a new paraffin block. For immunohistochemistry, slides were deparaffinized in xylol, rehydrated in graded alcohol, and then boiled for 5 minutes in citrate buffer (pH = 6) using a pressure cooker. Immunohistochemical staining was performed on a BenchMark ULTRA autostainer (Ventana, Tucson, AZ), using the monoclonal rabbit antibody p16INKA4 (CINtec Histology Kit; Ventana Medical Systems, Inc., Innovation Park Drive, Tucson, AZ) according to the manufacturer's instructions. P16 was used as a surrogate marker to confirm HPV relation.[22] Overexpression of p16 was defined as medium to strong (2+/3+) intensity of the nuclear staining with a distribution of ≧ 75% (of the tumor cells; Fig. S1). In situ hybridization of EBV was performed on a Leica BOND

MAX stainer (Leica Biosystems, IL) using the fluorescein-conjugated oligonucleotide (EBER Probe ASR; 1700 Leider Lane, Buffalo Grove, IL) according to the manufacturer's instructions.

Statistical Analysis

According to the statistical analyses and methods in the published literature (SAMPL) guidelines, normally distributed, continuous variables were expressed as mean with standard deviation.[23] For categorical variables, counts and percentages were reported.

Analysis of variance testing was used to compare group means of continuous variables, and Fisher's exact test, to investigate whether two categorical variables were associated.

The primary outcome of the study was the OS, which was defined as the time from the initial diagnosis of HNCUP to the date of death or last follow-up. The Kaplan-Meier method was used to determine OS. Investigated clinicopathological variables included gender (male *vs*. female), age (<65 *vs*. ≥65 years), tobacco exposure (never smoked *vs*. smoking history), additional cancers except HNCUP (yes *vs*. no), p16 status (positive *vs*. negative), EBV status (positive *vs*. negative), ENE (yes *vs*. no), nodal category TNM7 (N1 *vs*. N2 *vs*. N3), UICC stage TNM7 (III/IVa *vs*. IVb *vs*. IVc), and UICC stage TNM8 (I/II *vs*. III/IVa *vs*. IV *vs*. IVb *vs*. IVc). The impact of the variables on OS was investigated using the logrank test. Variables with a significant influence on OS ($P < .05$) in the univariate analysis were further investigated using Cox multivariate proportional hazard models with backward elimination. P values <.05 were considered statistically significant. All P-values are exploratory. No adjustment for multiple testing was performed.

Statistical analyses were performed using IBM SPSS statistics, version 25.2 (SPSS; IBM Corp., Armonk, NY).

RESULTS

Patient Characteristics and Treatment

Between 2009 and 2018, 110 patients were diagnosed with HNCUP at the current center. Analyses were limited to 97 patients who had available tissue for p16 and EBV staining and no history of head and neck SCC. The clinicopathological data are summarized in Table 1. The mean age at the initial diagnosis of HNCUP was 64.6 years. The study population consisted of 71 men (73.2%) and 26 women (26.8%). Of which, 49.5% were current smokers, and of the 42 patients with documented pack years (PY), the average was 48.8 PY; and 14.4% of the study patients had previously been diagnosed with cancer (e.g., breast, prostate, melanoma, hepatocellular carcinoma).

Neck dissection was performed in 61% of patients; in 17% of the cases, neck dissection was performed bilaterally; 96% of the patients underwent modified radical neck dissection; and 4% underwent radical neck dissection. In 28% of patients, definite RT or CRT was performed; 6% with palliative chemotherapy; and 5% with the best supportive care only.

HNCUP Characteristics

All tumors were histologically confirmed HNSCC. Sixty-six percent showed ENE, and two patients (2.1%) had an unknown ENE status. Using the 7th edition of the TNM classification, most patients were at advanced categories or stages (77.3% N2, 69.1% UICC IVa) at the initial HNCUP diagnosis (Table 1). Distant metastases were found in 10 patients, who subsequently were classified as UICC stage IVc. Using the 8th edition of the TNM classification, p16+ patients were downstaged and p16– patients were upstaged. Patients with distant metastases remained in UICC stage IV in p16+ HNCUP and UICC IVc in p16– HNCUP.

According to immunohistochemistry staining, the patients were subdivided into a p16+/EBV– group (n = 36), p16–/EBV– group (n = 57), and p16–/EBV+ group (n = 4). There were no significant differences in the constitution of the groups except for nodal category ($P < .001$), M status (0.008), and UICC stage according to TNM 8th edition ($P < .001$). P16– patients had more advanced nodal categories and UICC stages regardless of their EBV status (p16–/EBV–: 64.9% N3b and 56.1% UICC IVb; EBV+: 75% N3 and 75% UICC stage IVa) compared with p16+ patients (94.4% N1 and 86.1% UICC I).

Long-Term Survival

After a maximum follow-up time of 60 months, 49 of the 97 patients (50.5%) had died. The 1-, 3-, and 5-year OS rates of all HNCUP patients (n = 97) were 74.2%, 59.8%, and 49.5%.

The long-term OS of the three subgroups differed significantly. P16+/EBV– patients had a significantly improved 5-year OS (66.7%) compared with both p16–/EBV– and p16–/EBV+ patients (40.4% and 25%, respectively). The latter two groups of p16– patients did not significantly differ ($P = .459$, Fig. 1).

The OS in patients with a less extensive nodal category and less advanced UICC stage was significantly improved compared with that in patients with more advanced nodal categories or UICC stages according to both TNM 7th and 8th editions (nodal category TNM7: $P < .001$, UICC stage TNM7: $P < .001$, UICC stage TNM8/p16+: $P = .001$, and UICC stage TNM8/p16–: $P < .001$; Fig. 2). The mean OS of stage IVb and IVc did not significantly differ according to TNM7 (16 *vs*. 12 months, $P = .401$). However, mean OS of stage IVb improved significantly compared with that of IVc according to TNM8 (29 *vs*. 5 months, $P = .001$) (Fig. 2).

Figure 3 summarizes the alterations of the tumor staging from UICC7 to UICC8. The OS of patients with a downstaging and an upstaging according to the 8th edition was superior compared to those who remained at the same stage (5-year OS of patients with downstaging: 66.7%, upstaging: 46.2%, and same stage: 34.3%). Patients with changed stages included mainly UICC stage III or IVa according to the TNM 7th edition. Here, 33 p16+ HNCUP patients were downstaged to UICC I or II, and 26 p16– HNCUP patients were upstaged to UICC IVb because of ENE. All patients with distant metastases

Table 1.
Patient Characteristics of the Study Patients and Their Tumors According to p16/EBV Detectability.

Variable	Total n = 97	p16+/EBV– n = 36	p16–/EBV– n = 57	p16–/EBV+ n = 4	*P* Value*	Test
Sex, no. (%)					.814	FET
Male	71 (73.2)	27 (75.0)	41 (71.9)	3 (75.0)		
Female	26 (26.8)	9 (25.0)	16 (28.1)	1 (25.0)		
Age at initial diagnosis of HNCUP, yr					.146	ANOVA
Mean (SD)	64.6 (11.0)	63.0 (11.4)	66.3 (10.1)	54.5 (15.1)		
Tobacco exposure, no. (%)					.523	FET
Never smoked	10 (10.3)	4 (11.1)	5 (8.8)	1 (25.0)		
Former smoker	9 (9.3)	5 (13.9)	4 (7.0)	0 (0.0)		
Current smoker	48 (49.5)	16 (44.4)	29 (50.9)	3 (75.0)		
Unknown	30 (30.9)	11 (30.6)	19 (33.3)	0 (0.0)		
Smoking history, no. of pack years					.149	ANOVA
Mean (SD)	48.8 (23.4)	40.3 (18.7)	51.1 (24.0)	73.3 (25.2)		
Cancers before HNCUP diagnosis, no. (%)					.582	FET
Yes	14 (14.4)	5 (13.9)	8 (14.0)	1 (25.0)		
No	83 (85.6)	31 (86.1)	49 (86.0)	3 (75.0)		
HNCUP characteristics						
Extranodal extension					.359	FET
Yes	64 (66.0)	21 (58.3)	40 (70.2)	3 (75.0)		
No	31 (32.0)	14 (38.9)	16 (28.1)	1 (25.0)		
Unknown	2 (2.1)	1 (2.8)	1 (1.8)	0 (0.0)		
Nodal category (7th edition TNM classification), no. (%)					.187	FET
N1	9 (9.3)	5 (13.9)	4 (7.0)	0 (0.0)		
N2a	27 (27.8)	12 (33.3)	14 (24.6)	1 (25.0)		
N2b	43 (44.3)	16 (44.4)	26 (45.6)	1 (25.0)		
N2c	5 (5.2)	2 (5.6)	3 (5.3)	0 (0.0)		
N3	13 (13.4)	1 (2.8)	10 (17.5)	2 (50.0)		
Nodal category (8th edition TNM classification), no. (%)					<.001 [1]	FET
N1	36 (37.1)	34 (94.4)	1 (1.8)	1 (25.0)		
N2	2 (2.1)	2 (5.6)		0 (0.0)		
N2a	8 (8.2)		8(14.0)			
N2b	8 (8.2)		8(14.0)			
N2c	0 (0.0)		0 (0.0)			
N3	3 (3.1)			3 (75.0)		
N3a	3 (3.1)		3 (5.3)			
N3b	37 (38.1)		37 (64.9)			
Distant metastasis, M1, no. (%)	10 (10.3)	3 (8.3)	7 (12.3)	0 (0.0)	.008	FET
UICC stage (7th edition), no. (%)					.217	FET
III	9 (9.3)	5 (13.9)	4 (7.0)	0 (0.0)		
Iva	67 (69.1)	27 (75.0)	38 (66.7)	2 (50.0)		
IVb	11 (11.3)	1 (2.8)	8 (14.0)	2 (50.0)		
IVc	10 (10.3)	3 (8.3)	7 (12.3)	0 (0.0)		
UICC stage (8th edition), no. (%)					<.001 [2]	FET
I	31 (32.0)	31 (86.1)				
II	3 (3.1)	2 (5.6)		1 (25.0)		
III	1 (1.0)		1 (1.8)	0 (0.0)		
IV	3 (3.1)	3 (8.3)				
Iva	20 (20.6)		17 (29.8)	3 (75.0)		
IVb	32 (33.0)		32 (56.1)	0 (0.0)		
IVc	7 (7.2)		7 (12.3)			

*Comparison of patients with p16+/EBV– and p16–/EBV–.
[1]N1 vs. N2 vs. N3.
[2]UICC stage I vs. II vs. III vs. IV.
ADJ = adjuvant treatment; CRT = chemoradiation; EBV = Epstein-Barr virus; FET = Fisher's exact test; HNCUP = Head and neck cancer of unknown primary; ND = neck dissection; RT = radiotherapy; UICC = Union for International Cancer Control.

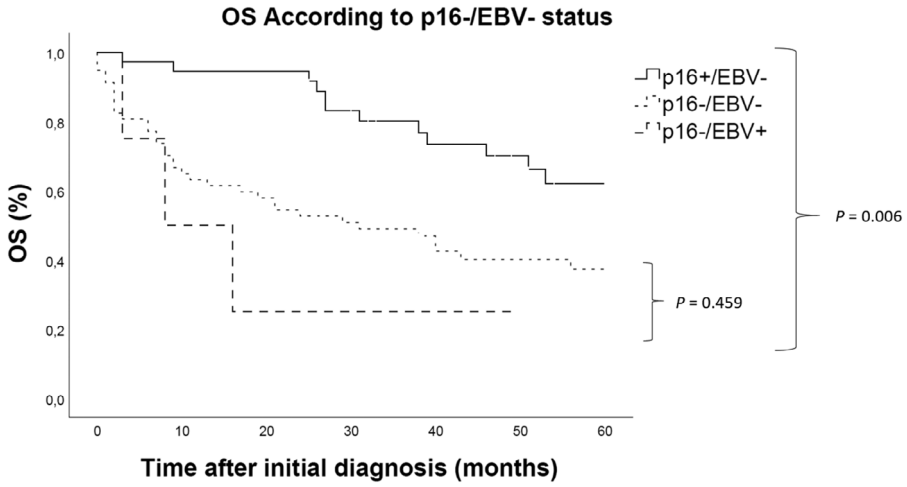

Fig. 1. Overall survival of the 97 patients according to p16 and EBV status.

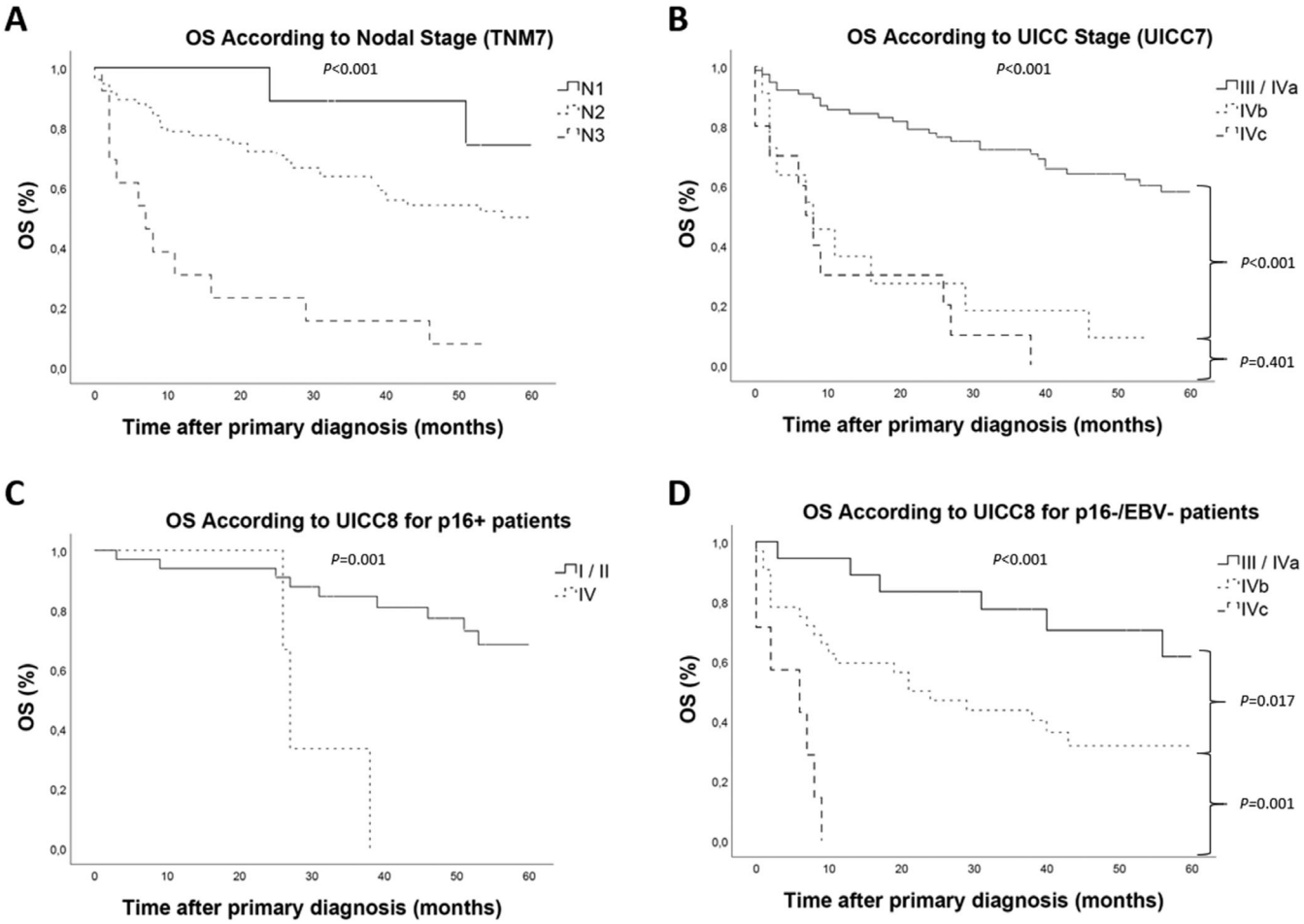

Fig. 2. Overall survival (OS) of the patients according to UICC staging systems. (A) OS of the 97 patients according to their TNM 7th edition nodal category. (B) OS of the 97 patients according to their TNM 7th edition UICC stage. (C) OS of the p16-positive patients (n = 36) according to their TNM 8th edition UICC stage. (D) OS of the p16-negative/EBV-negative patients (n = 57) according to their TNM 8th edition UICC stage.

remained unchanged in the highest stage possible (UICC IV in p16+ HNCUP and UICC IVc in p16– HNCUP) and had therefore the lowest OS.

Predictors of Overall Survival

Positive predictors of OS are summarized in Table 2 and included p16 (P = .002), no ENE (P = .001), less

A

UICC7 * Up- or Downstaging

		Downstaging	Upstaging	Same Stage	Total
UICC 7 Stage	III/IVa	33 (34.0%)	26 (26.8%)	17 (17.5%)	76 (78.4%)
	IVb	3 (3.1%)	0	8 (8.2%)	11 (11.3%)
	IVc	0	0	10 (10.3%)	10 (10.3%)
Total		36 (37.1%)	26 (26.8%)	35 (36.1%)	97 (100%)

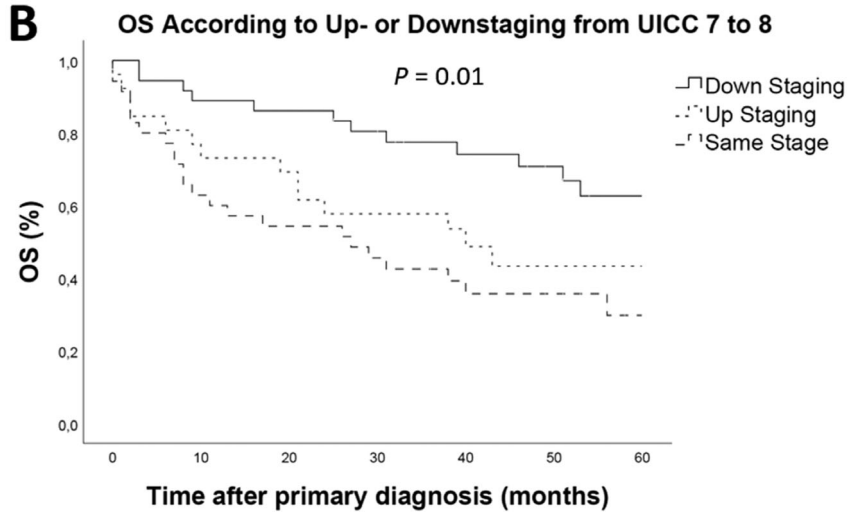

Fig. 3. Classification of the study patients according to up- and downstaging from TNM7 to UICC8. (A) Number of patients who were up- or downstaged based on the individual UICC7 stage. (B) Overall survival of the patients according to their change in UICC stage from UICC7 to UICC8.

extensive nodal categories according to TNM7 ($P < .001$), and less advanced UICC stages according to both UICC 7th ($P < .001$) and 8th edition ($P < .001$).

In multivariate analysis, only the UICC stage according to TNM 8th edition ($P = .003$) showed significant impact on OS. P16 status and ENE are both used to determine UICC staging according to TNM 8th edition. When multivariate analysis was performed without 8th edition UICC stage, p16 status ($P = .004$, $HR = 0.399$, $CI = 0.207–0.769$) and ENE ($P < .001$, $HR = 3.536$, $CI = 1.65–7.58$) both showed significant impact.

In p16+/EBV– HNCUP patients, lower UICC stages according to both TNM 7th ($P = .001$) and 8th edition ($P = .001$) were associated with a significantly better OS.

In p16–/EBV– HNCUP patients, significant factors included no ENE ($P = .005$), lower nodal category ($P = 0.004$) and UICC stage according to TNM 7th edition ($P < .001$), and less advanced UICC stages according to TNM 8th edition ($P < .001$) (Table 2).

In the small subgroup of four p16–/EBV+ HNCUP patients, there was no significance for any of the clinicopathological variables.

DISCUSSION

This study analyzed the OS of patients with HNCUP, who were assigned to nodal categories and UICC stages according to the TNM Classification of Malignant Tumors 7th and 8th edition. The latest classification considered the HPV, EBV, ENE, and number of lymph nodes. The lymph node classification is based on the p16+ and p16– oropharyngeal squamous cell carcinoma (OPSCC). So far, the classification has not been examined for HNCUP, even though it is known that HPV has a positive predictive value.[17,19] Therefore, the present study investigated whether the changes made in the 8th edition are also valid for HNCUP. Therefore, the study reviewed the data of 97 patients diagnosed with HNCUP between 2009 and 2018. The study shows that the TNM 8th edition is well applicable to HNCUP and improves the prognostic significance of the UICC stages for patients.

In the current study, the average patient age was 64.6 years and the proportion of p16+ HNCUP patients was 37.1%. These data correlate highly with those published by Sivars et al.[18] However, the patients from the database from Sweden and United States differed. Here, the average patient age was 60 years, and the proportion of p16+ HNCUP patients was 69%.[4,17] In the present study, 58.8% of the patients have a smoking history, which is less than the 76% and 79% in other studies.[5,18] The number of male patients was three times higher than that of female patients; however, the male proportion was lower compared with older studies.[4,5,17,18]

The role of HPV in HNCUP has been investigated in multiple studies in the past years.[4,5,17–19,24] A review of the Swedish Cancer Registry including 68 patients and

Table 2.
Kaplan-Meier Analysis of Clinicopathologic Variables Associated with Overall Survival.

Variable		Kaplan-Meier Analysis All Patients n = 97	Mean OS (Mo/%[1])	P	Kaplan-Meier Analysis (Subgroups) p16+/EBV− n = 36	Mean OS (Mo/%[1])	P	p16−/EBV− n = 57	Mean OS (Mo/%[1])	P	p16−/EBV+ n = 4	Mean OS (Mo/%[1])	P
Age (yr)	< 65	49	42/57.1	.147	19	51/73.7	.487	27	37/48.1	.201	3	20/33.3	.918
	≥ 65	48	35/41.7		17	48/58.8		30	28/33.3		1	16/0.0	
Sex	Male	71	37/46.5	.272	27	47/59.3	.092	41	31/39.0	.567	3	23/33.3	.515
	Female	26	43/57.7		9	56/88.9		16	37/43.8		1	8/0.0	
Tobacco exposure	Never smoker	10	51/80.0	.106	4	52/75.0	.644	5	49/80.0	.247	1	49/100.0 †	.182
	Smoking history	57	38/49.1		21	47/61.9		33	36/45.5		3	9/0.0	
Other cancer diagnoses*	No	83	38/49.4	.809	31	50/64.5	.476	49	32/40.8	.796	3	20/33.3	.918
	Yes	14	39/50.0		5	49/80.0		8	35/37.5		1	16/0.0	
p16	Negative	61	32/39.3	.002	—	—	—	—	—	—	—	—	—
	Positive	36	50/66.7		—	—		—	—		—	—	
EBV	Negative	93	39/50.5	.147	—	—	—	—	—	—	—	—	—
	Positive	4	19/25.0		—	—		—	—		—	—	
ENE	Yes	64	32/37.5	.001	21	46/57.1	.233	40	26/30.0	.005	3	9/0.0	.182
	No	31	53/74.2		14	55/78.6		16	50/68.8		1	49/100.0 †	
Nodal category (7th)	1	9	55/77.8	<.001	5	57/80.0	.465	4	51/75.0	.004	—	—	.433
	2	75	41/53.3		30	49/66.7		43	35/44.2		2	29/50.0	
	3	13	14/7.7		1	46/0.0		10	12/10.0		2	10/0.0	
UICC 7th	III/IVa	76	45/61.8	<.001	32	51/75.0	.001	42	40/52.4	<.001	2	29/50.0	.433
	IVb	11	16/9.1		1	46/0.0		8	14/12.5		2	10/0.0	
	IVc	10	12/0.0		3	30/0.0		7	5/0.0		—	—	
UICC 8th	I/II	34	50/70.6	<.001	33	52/72.7	.001	—	—	<.001	1	8/0.0	.515
	III/IVa	21	45/61.9		—	—		18	48/66.7		3	23/33.3	
	IV	3	30/0.0		3	30/0.0		—	—		—	—	
	IVb	32	29/34.4		—	—		32	29/34.4		—	—	
	IVc	7	5/0.0		—	—		7	5/0.0		—	—	

*Diagnosed cancers before initial HNCUP diagnosis.
†Patient censored.
[1]Proportion of patients alive after a maximum follow-up time of 60 months.
EBV = Epstein-Barr virus; ENE = extranodal extension; HNCUP = head and neck cancer of unknown primary; UICC = Union for International Cancer Control.

the National Cancer Database in the United States including 978 patients found significant advantages in the OS for HPV-related HNCUP.[4,17] The present study confirms the positive predictive value of the HPV surrogate marker p16. The OS of p16+ HNCUP patients was significantly increased compared with that of p16− patients (P = .002). The OS of p16−/EBV− and p16−/EBV + patients did not significantly differ (Fig. 1); however, that only four patients tested EBV+ questions the usefulness of the EBV determination for HNCUP. According to the International Agency for Research on Cancer, EBV is a well-established carcinogenic agent.[20,25,26] The evidence of EBV can be understood as an indication for possible primaries in the nasopharynx.[27,28] In the current center, the detection of both p16 and EBV has no therapeutic relevance. Ruuskanen et al. suggested a prognostic benefit for EBV+ NPC, and Carpén et al. were unable to show the same significant effect for OPC.[20,29] For HNCUP, no resilient data surveying the effect of EBV on OS are available. The present study is one of the largest monocenter studies for HNCUP, which has determined EBV for HNCUP in contrast to other studies. However, due to the low prevalence of 4.1% EBV+ HNCUP patients, no conclusions can be drawn to distinguish it from p16−/EBV− HNCUP.

The 8th edition of the TNM Classification of Malignant Tumors by the UICC is applicable to HNCUP. The current study shows that UICC stages according to the 8th edition have a significant impact on OS (Table 2), and 95% of the patients who changed stage were at UICC stage III or IVa according to TNM7 (Fig. 3). This corresponds with the N category having improved in p16+

HNCUP and worsened in p16-negative HNCUP from TNM7 to TNM8. For p16+ HNCUP and p16+ OPC, a lack of prognostic significance of the N categories could be confirmed considering localization and ENE according to TNM7.[30,31] Greater impact on OS was reported for nodal categories including both localization and ENE in p16– OPC.[30] The present study confirms that ENE has a significant influence on the OS in p16–/EBV– HNCUP patients (Table 2). This is consistent with previous studies, describing ENE and p16 as major prognostic factors and emphasizes the validity of the current staging system.[24,32] Thus, ENE should be considered in the p16– HNCUP classification but not in the p16+ HNCUP classification of the TNM 8th edition.[15]

UICC stages according to TNM 7th and 8th edition significantly influence the outcome. However, the OS between UICC stage IVb and IVc became significantly different in p16– HNCUP patients after using TNM8 (Fig. 2). This was caused by p16– HNCUP patients with distant metastases who stayed in UICC stage IVc, whereas patients with ENE were classified IVb or III/IVa without ENE.

The improvement in the prognostic significance of TNM Classification of Malignant Tumors 8th edition should drive the discussion about changes in treatment modalities for p16+ HNCUP. Despite multiple studies having underlined the benefit of p16+ for OS, therapy regimens do not differ between p16+ and p16– HNCUP patients.[21,33,34] Recent studies have tried to reduce patient side effects by reducing treatment intensity.[35–38] Ultimately, the search for the primary remains the patients' best chance of being assessed and referred to an appropriate therapy with multiple studies emerging in this field over recent years.[39–42] Karni *et al* have shown that transoral laser microsurgery reveals the primary oropharyngeal carcinoma in 94% of patients (37% palatine tonsil, 63% tongue-base).[43]

This study's limitations are clearly associated with its retrospective approach. Smoking status, therapeutic details, and follow-up data were not documented consistently. Furthermore, the relatively small number of patients with HNCUP limits the statistical power of studies investigating this disease. Conversely, due to its low incidence, prospective studies for HNCUP are difficult to design.

CONCLUSION

The 8th edition of the TNM classification is applicable to HNCUP. Prognostic significance is given in every single UICC stage from UICC I to IVc. ENE should be considered in the p16– HNCUP classification but not in the p16+ HNCUP classification.

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