HPV impact on oropharyngeal cancer radiological staging: 7th vs 8th edition of AJCC TNM classification

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ABSTRACT

Purpose: To evaluate the agreement between pathological and radiological staging in oropharyngeal cancer by comparing the 7th and the 8th edition of the AJCC TNM system.
Methods: This retrospective cohort study included 57 cases of oropharyngeal cancer with lymph node metastases staged with the 7th and 8th editions of the AJCC TNM system. Comparison between clinical and radiological features and differences in agreement rates were calculated between radiological and pathological staging for the primary tumor (T) and lymph nodes (N) in HPVpos and HPVneg cases.
Results: Comparison of HPVpos and HPVneg revealed a significantly different distribution between early and advanced stages in the 8 th edition, with a relevant number of HPVpos patients redefined from advanced stages whit the 7 th ed. to early stages with 8 th ed. ($p < 0.01$); no significant differences were found when comparing all diagnostic methods for T and N.
Conclusions: The 8th edition of the AJCC TNM seems to lead to better pretreatment staging. For both HPVpos and HPVneg, the agreement between pretreatment radiological and pathological staging.

1. Introduction

The impact of human papillomavirus (HPV) in head and neck (HN) oncology has been dramatic. Although decreased tobacco and alcohol consumption has led to a decline in most head and neck squamous cell carcinomas (HNSCC), the incidence of oropharyngeal squamous cell carcinoma (OPSCC) has been increasing in many countries.[1–3] This unexpected trend has been attributed to the increase of HPV-positive (HPV^{pos}) OPSCCs, as molecular and epidemiologic data have established HPV as the causative agent for up to 80% of all OPSCC in the US and parts of Europe.[4] In Italy, the prevalence of HPV^{pos} OPSCC is lower but steadily increasing.[5,6] HPV^{pos} and tobacco- and alcohol-induced OPSCCs are distinct entities: demographically, HPV^{pos} OPSCCs occur more often in younger, healthier individuals with little or no classic risk factors; clinically, they often present with a small primary tumor (T) and relevant neck lymph node (LN) involvement; they usually are highly responsive to treatment and carry an excellent prognosis compared to HPV-negative (HPV^{neg}) form.[1,6–9]

In consideration of the evidence on the substantial differences between HPV^{pos} and HPV^{neg} OPSCC, the 8th edition of the American Joint Committee on Cancer (AJCC) staging system published in 2017 included a major modification: a distinct staging algorithm for HPV^{pos} OPSCC, defined by immunohistochemistry (IHC) for p16 as a surrogate marker for HPV-induced carcinogenesis.[11–13]

Concerning T staging, the p16-positive classification does not include carcinoma in situ or category T4b, and p16-negative cancers no longer include category T0.[11] As for nodal staging (N) categories, p16-positive cancers have a clinical staging (based on LN localization and dimension) and a pathological staging (based on the number of LN); the p16-negative cases are staged like other HNSCCs, with the upscaled role of extra-nodal extension (ENE).[11]

After clinical evaluation, a patient with OPSCC needs to undergo an initial complete radiological workup, aimed at providing the most accurate staging for T, nodal metastasis, distant metastasis, and possible synchronous cancers. According to the National Comprehensive Cancer Network (NCCN) guidelines, imaging assessment can be performed with

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computed tomography (CT) or magnetic resonance imaging (MRI) of the neck, with contrast if not contraindicated.[14]

There are known challenges in the radiological evaluation of HPV^{pos} OPSCC, which together with the complex anatomy of the upper aerodigestive tract and the effect of dental artifacts, make staging difficult[15,16]: normal lymphoid tissue enhances on CT and MRI in a manner similar to OPSCC, cancer may be small or even occult at presentation; nodal metastases are very common but often are clustered and cystic and, as such, can be misdiagnosed.[17–20]

This study aimed to evaluate whether the 8th edition of the AJCC TNM classification has led to an improvement in agreement between pathological and radiological staging, considering the impact of HPV status and the use of different imaging techniques.

2. Methods

This multicentric retrospective study included consecutive patients with a diagnosis of OPSCC with LN metastasis treated with surgical resection of cancer and neck dissection (ND) in two major Italian Cancer Care Centres (Department of Otorhinolaryngology and Head and Neck Surgery, Cattinara Hospital, Trieste, Italy; Department of Otorhinolaryngology, Head and Neck Surgery, Dell'Angelo Hospital, Mestre, Venice, Italy) between January 2004 and September 2020.

The local Ethics Committee (Trieste university ethical committee) approved this retrospective study (number 120.1522022). All procedures performed involving human participants were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Patients were selected based on the availability of HPV status, pre-treatment radiological evaluation with contrast-enhanced (CE) CT and/or MRI, clinical staging, T and N pathological staging after surgical treatment, in chronological order of diagnosis in the two centers. All patients with synchronous or previous HNSCC, or with a previous history of radiotherapy or neoadjuvant treatment or surgery on the head and neck area were excluded. Information regarding pre-treatment staging, risk factors, and treatment modality was collected.

Every patient was staged with both the 7th and the 8th editions of the AJCC TNM system[11,13] (Fig. 1).

Clinical staging for each patient was performed after a thorough clinical examination, including an endoscopic exam, by a specialist of our clinic with years of experience in head and neck cancer: the evaluation included a description of the primary tumor site and dimension, signs of extension to near anatomical structures, the clinical involvement of neck LN with bilateral neck palpation, and search of possible synchronous lesions in the upper aerodigestive tract.

Pre-treatment CT and/or MRI scans were collected for all patients. Contrast material was used for scanning unless contraindicated. All available imaging was used for radiological staging for T and N by an expert head and neck radiologist blinded to HPV status.

For each T and N stage, we defined "agreement" as the condition in which radiological staging matched the pathological staging, "disagreement" as the opposite condition; among the cases of "disagreement", we defined "over-staging" the condition in which the radiological stage was higher than the pathological stage, "under-staging" the opposite condition. Patients with stage I-II were classified as early stage and those with stage III-IV as an advanced stage.

HPV search and typing were performed on genomic DNA extracted from FFPE with MagCore genomic DNA FFPE One Step Kit and tested with PCR using HPV Sign, Sistema Pyro Mark Q96 IDTM, CE-IVD (Diatech pharmacogenetics), according to the manufacturer's instructions. The DNA quality of the samples was verified by amplification of the β-globin gene. $p16^{INK4a}$ was evaluated on FFPE sections by IHC

American Joint Committee on Cancer (AJCC) TNM Staging System
Prognostic Stage Groups

8th Edition

Oropharynx (p16+)

Clinical

Stage I	T0,T1,T2	N0,N1	M0
Stage II	T0,T1,T2	N2	M0
	T3	N0,N1,N2	M0
Stage III	T0,T1,T2,T3	N3	M0
	T4	N0,N1,N2,N3	M0
Stage IV	Any T	Any N	M1

Pathological

Stage I	T0,T1,T2	N0,N1	M0
Stage II	T0,T1,T2	N2	M0
	T3,T4	N0,N1	M0
Stage III	T3,T4	N2	M0
Stage IV	Any T	Any N	M1

Oropharynx (p16-)

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N0,N1,N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

7th Edition

Pharynx

Anatomic Stage/Prognostic Groups: Oropharynx

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Fig. 1. American Joint Committee on Cancer (AJCC) TNM Staging System for oropharyngeal cancer: Prognostic Stage Groups for 7th and 8th edition. T: primary tumor stage; N: nodal stage; M: distant metastasis.

and p16^{INK4a} positivity was evaluated by an expert pathologist and defined by strong and diffuse nuclear and cytoplasmatic staining of ≥70% of tumor cells.[13] We defined "HPV^{pos}," all cases with positive p16-IHC and HPV-DNA positivity; "HPV^{neg}," every other case.

Statistical analyses were performed with IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA). Clinical and radiological features were compared between HPV^{pos} and HPV^{neg} using the chi-square test and Fisher's exact test for categorical variables, and the Student's *t*-test for continuous variables. Concordance was defined as the reliability of defining the same T and N stage following the AJCC classification with different modalities (pathological evaluation, imaging) and was determined by generating contingency tables to calculate the proportion of agreement and Cohen's kappa (k) coefficient for inter-modality agreement. The k coefficient was calculated to estimate the agreement between MRI and CT for T and N staging in the HPV^{pos} and HPV^{neg} groups in TNM 7th and TNM 8th editions. K values <0.20 indicated poor agreement, values between 0.20 and 0.40 fair agreement, between 0.41 and 0.60 moderate agreement, between 0.61 and 0.80 good agreement, and between 0.81 and 1.00 almost perfect agreement.[21]

3. Results

A total of 57 patients (67% men; mean age 66 years, range 44–86) were included in this multicentric retrospective study. All 57 cases were histologically confirmed OPSCC, and the majority (67%) of cancers were identified in the palatine tonsil (Table 1). All patients were treated with surgical resection of cancer and neck dissection (ND); none of the patients had distant metastasis. 30 patients underwent adjuvant treatment (chemoradiotherapy 19%, radiotherapy 32%, chemotherapy 2%).

Thirty-six were HPV^{pos} (63%), all cases with positive p16-IHC and HPV-DNA positivity. HPV typing was possible in 34 patients: 31 HPV16, 1 HPV18, 1 HPV33, 1 HPV35. Risk factors were known for 52 patients (Table 1; Fig. 2). The prevalence of HPV^{pos} OPSCC was higher among never-smokers ($p < 0.01$) and never-drinkers ($p = 0.04$) (Table 1). No significant differences in sex distribution or mean age were noted considering the HPV^{pos} and the HPV^{neg} cases ($p > 0.05$) (Table 1).

Table 1
Patients characteristics. In bold, statistically significant p-value. M: man; F: female; HPV^{pos}: HPV-positive group; HPV^{neg}: HPV-negative group; ENE: extra-nodal extension; NS: not significant

Variable	Subset	Total	HPV^{pos}	HPV^{neg}	p-value
Number (%)		57	36	21	
Sex					
	M	38 (67)	25 (69)	13 (62)	NS
	F	19 (33)	11 (31)	8 (38)	
Age					
	Range	44–86	46–85	44–86	NS
	Mean	66	67	64	
Risk factors					
Smoke	Current	21 (42)	9 (28)	12 (63)	**>0.01**
	Former	15 (29)	8 (25)	7 (37)	
	Never	15 (29)	15(47)	0 (0)	
Alcol	Current	12 (24)	6 (19)	6 (32)	**0.04**
	Former	9 (18)	3 (10)	6 (32)	
	Never	29 (58)	22 (71)	7(36)	
Subsite					
	Tonsil	38 (67)	24 (66)	14 (67)	NS
	Base of tongue	12 (21)	6 (17)	6 (29)	
	Soft palate	2 (3)	1 (3)	1 (4)	
	T0	5 (9)	5 (14)	0 (0)	
ENE					
	Positive	20 (35)	13 (36)	7 (33)	NS
	Negative	37 (65)	23 (64)	14 (67)	
Stage					
7th ed	Early (I-II)	9 (16)	4 (11)	5 (24)	NS
	Advanced (III-IV)	48 (84)	32 (89)	16 (76)	
8th ed	Early (I-II)	39 (68)	34 (94)	5 (24)	**<0.01**
	Advanced (III-IV)	18 (32)	2 (6)	16 (76)	

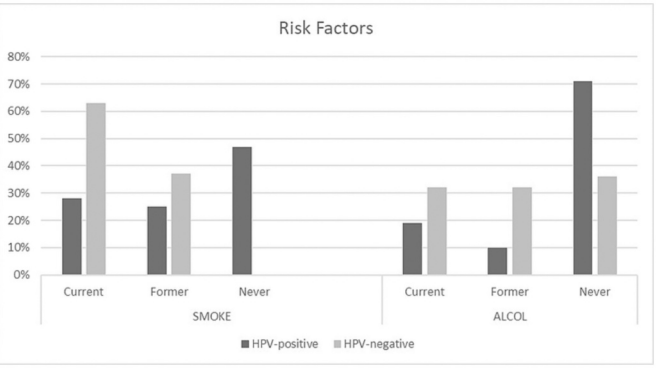

Fig. 2. Distribution of risk factor prevalence in HPV^{pos} and HPV^{neg}. HPV: human papillomavirus; HPV^{pos}: HPV-positive group; HPV^{neg}: HPV-negative group.

The extra-nodal extension was observed in 20 cases, 13 HPV^{pos} and 7 HPV^{neg}. Differences in cancer location and ENE were not statistically different between HPV^{pos} and 7 HPV^{neg} (Table 1).

Pathological staging with the 7th and 8th AJCC TNM classification is reported in Tables 2a and 2b. With the 7th edition, 9 patients presented at diagnosis with early-stage disease (24% of HPV^{neg}, 11% of HPV^{pos} cases), and 48 with advanced disease (76% in HPV^{neg}, 89% of HPV^{pos}). With the 8th edition, 39 patients presented at diagnosis with early disease (24% of HPV^{neg}, 94% in HPV^{pos}), and 18 presented with advanced disease (76% in HPV^{neg}, 6% of HPV^{pos}). When staged according to the 8th but not with the 7th edition (Table 1), the distribution of early and advanced stage OPSCCs at diagnosis differed significantly between HPV^{pos} and HPV^{neg} ($p < 0.01$).

All patients underwent pre-treatment radiological evaluation: in 40 cases CE-MRI, in 53 CE-CT; 37 patients had both. After a discussion in a multidisciplinary group for treatment options, all patients underwent surgical resection of cancer with free margins and ND.

Table 3 shows data on the rates of agreement between the pathological staging of T and N and radiological staging with MRI and CT in HPV^{pos} and HPV^{neg}, for both the AJCC TNM 7th and 8th editions.

Comparing radiological and pathological staging for T and N, there are no significant differences in agreement rates between HPV^{pos} and HPV^{neg}, for both the AJCC TNM 7th and 8th editions (Table 3).

Considering the 7th edition, for MRI versus CT, in HPV^{neg} cases the kappa values were moderate for T staging and good for N staging; in HPV^{pos} cases, they were good for T staging and moderate for N staging.

Considering the 8th edition, for MRI versus CT, in HPV^{neg} cases the kappa values were moderate for T staging and moderate for N staging; in HPV^{pos} cases, they were good for T staging and moderate for N staging.

Table 4 and Fig. 3 provide data and a visual representation of the specific distribution among disagreement rates, distinguishing under-staging and over-staging of clinical and radiological staging with MRI and CT versus pathological staging of T and N in HPV^{pos} and HPV^{neg}, both for the TNM 7th and 8th edition. Both in TNM 7th and 8th, for all diagnostic methods, there are no statistically significant differences between over-staging and under-staging between HPV^{pos} and HPV^{neg}.

4. Discussion

In our multicentric retrospective study, we evaluated the modification in the agreement between the pathological and radiological staging of the most recent 8th edition of the AJCC TNM, considering the impact of HPV status and the use of different imaging techniques.

We have found that 63% of patients had HPV^{pos} OPSCC; the distribution of HPV^{pos} and HPV neg cases showed no significant difference for age or sex groups, while smoke and tobacco consumption was

Table 2a
Pathological staging with 7th and 8th AJCC TNM (HPV^{neg}); cases with different staging between the 7th and 8th ed. are reported in bold type (part I). HPV: human papillomavirus; pT: pathological primary tumor stage; pN: pathological nodal stage

ID	HPV	7th TNM				8th TNM			
		pT	pN	Stage	Stage class	pT	pN	Stage	Stage class
TS03	NEGATIVE	1	2B	IVa	Advanced	1	2B	IAa	Advanced
TS04	NEGATIVE	1	0	I	Early	1	0	I	Early
TS09	NEGATIVE	1	0	I	Early	1	0	I	Early
TS10	NEGATIVE	3	0	III	Advanced	3	0	III	Advanced
TS17	NEGATIVE	2	**2B**	**IVa**	Advanced	2	**3B**	**IVb**	Advanced
TS18	NEGATIVE	2	**1**	**III**	Advanced	2	**2A**	**IVa**	Advanced
TS20	NEGATIVE	2	1	III	Advanced	2	1	III	Advanced
TS21	NEGATIVE	1	**2b**	**IVa**	Advanced	1	**3B**	**IVb**	Advanced
TS27	NEGATIVE	3	2B	IVa	Advanced	3	2B	IVa	Advanced
TS28	NEGATIVE	4A	2B	IVa	Advanced	4A	2B	IVa	Advanced
TS30	NEGATIVE	2	**2B**	**IVa**	Advanced	2	**3B**	**IVb**	Advanced
TS31	NEGATIVE	2	1	III	Advanced	2	1	III	Advanced
TS34	NEGATIVE	3	2A	IVa	Advanced	3	2A	IVa	Advanced
TS36	NEGATIVE	3	**2B**	**IVa**	Advanced	3	**3B**	**IVb**	Advanced
TS37	NEGATIVE	3	**2B**	**IVa**	Advanced	3	**3B**	**IVb**	Advanced
TS42	NEGATIVE	4A	**2C**	**IVa**	Advanced	4A	**3B**	**IVb**	Advanced
TS47	NEGATIVE	2	1	III	Advanced	2	1	III	Advanced
TS49	NEGATIVE	2	0	II	Early	2	0	II	Early
VE2017_2	NEGATIVE	1	**1**	**III**	Advanced	1	**2B**	**IVa**	Advanced
VE2018_1	NEGATIVE	2	0	II	Early	2	0	II	Early
VE2019_7	NEGATIVE	2	0	II	Early	2	0	II	Early

Table 2b
Pathological staging with 7th and 8th AJCC TNM (HPV^{pos}); cases with different staging between the 7th and 8th ed. are reported in bold type (part II). HPV: human papillomavirus; pT: pathological primary tumor stage; pN: pathological nodal stage

ID	HPV	7th TNM				8th TNM			
		pT	pN	Stage	Stage class	pT	pN	Stage	Stage class
TS01	POSITIVE	2	**2C**	**IVa**	Advanced	2	**2**	**II**	Early
TS02	POSITIVE	1	**2B**	**IVa**	Advanced	1	**2**	**II**	Early
TS05	POSITIVE	3	**2B**	**IVa**	Advanced	3	**1**	**II**	Early
TS06	POSITIVE	1	**2B**	**IVa**	Advanced	1	**1**	**I**	Early
TS07	POSITIVE	2	0	**IVa**	Advanced	2	0	**I**	Early
TS08	POSITIVE	3	0	**III**	Advanced	3	0	**II**	Early
TS11	POSITIVE	3	0	**III**	Advanced	3	0	**II**	Early
TS13	POSITIVE	3	**2C**	**IVa**	Advanced	3	**2**	**III**	Advanced
TS14	POSITIVE	2	0	**II**	Early	2	0	**I**	Early
TS15	POSITIVE	1	**2A**	**IVa**	Advanced	1	**1**	**I**	Early
TS16	POSITIVE	2	**2A**	**IVa**	Advanced	2	1	**I**	Early
TS22	POSITIVE	1	**2B**	**IVa**	Advanced	1	**2**	**II**	Early
TS23	POSITIVE	1	**2B**	**IVa**	Advanced	1	**1**	**II**	Early
TS24	POSITIVE	3	1	**III**	Advanced	3	1	**II**	Early
TS25	POSITIVE	2	1	**III**	Advanced	2	1	**I**	Early
TS26	POSITIVE	**4A**	**2B**	**IVb**	Advanced	**4**	**2**	**III**	Advanced
TS29	POSITIVE	2	**2B**	**IVa**	Advanced	2	**2**	**II**	Early
TS32	POSITIVE	2	**2B**	**IVa**	Advanced	2	**2**	**II**	Early
TS33	POSITIVE	3	1	**III**	Advanced	3	1	**II**	Early
TS35	POSITIVE	2	0	**II**	Early	2	0	**I**	Early
TS38	POSITIVE	0	**2B**	**IVa**	Advanced	0	**2**	**II**	Early
TS39	POSITIVE	0	**2B**	**IVa**	Advanced	0	**1**	**I**	Early
TS40	POSITIVE	0	**2B**	**IVa**	Advanced	0	**1**	**I**	Early
TS41	POSITIVE	0	**2B**	**IVa**	Advanced	0	**1**	**I**	Early
TS43	POSITIVE	2	**2B**	**IVa**	Advanced	2	**1**	**I**	Early
TS44	POSITIVE	3	**2B**	**IVa**	Advanced	3	**1**	**II**	Early
TS45	POSITIVE	2	**2A**	**IVa**	Advanced	2	**1**	**I**	Early
TS46	POSITIVE	3	**1**	**III**	Advanced	3	**1**	**II**	Early
TS48	POSITIVE	2	0	**II**	Early	2	0	**I**	Early
TS50	POSITIVE	1	1	**III**	Advanced	1	1	**I**	Early
VE2017_3	POSITIVE	1	**2B**	**IVa**	Advanced	1	**2**	**II**	Early
VE2018_2	POSITIVE	2	1	**III**	Advanced	2	1	**I**	Early
VE2018_3	POSITIVE	2	**2B**	**IVa**	Advanced	2	**1**	**I**	Early
VE2019_3	POSITIVE	0	1	**III**	Advanced	0	**1**	**I**	Early
VE2019_4	POSITIVE	1	0	**I**	Early	1	0	**I**	Early
VE2020_1	POSITIVE	1	1	**III**	Advanced	1	1	**I**	Early

significantly lower in HPVpos. This finding is in line with the literature and confirms the trend in our region and the fact that the main risk factor for HPV-positive tumors is sexual behavior[5,6,22–27] Table 1.

All patients in our study underwent surgical resection of cancer and ND, thus having a pathological staging for T and N in all patients of our cohort: this gives strength to accuracy data on staging. Each case was staged with both the 7th and 8th editions of the AJCC TNM classification and we were able to compare them. Dividing our cohort into two groups,

Table 3
Agreement rates for radiological and pathological staging TNM 7th and 8th edition (bold type for differences). HPV: human papillomavirus; HPV^{pos}: HPV-positive group; HPV^{neg}: HPV-negative group; NS: not significant; T: primary tumor stage; N: nodal stage; pT: pathological primary tumor stage; pN: pathological nodal stage; MRI: Magnetic Resonance Imaging; CT: computed tomography

TNM 7TH					TNM 8TH				
		HPV-POSITIVE	HPV-NEGATIVE	p-VALUE			HPV-POSITIVE	HPV-NEGATIVE	p-VALUE
Number (%)					Number (%)				
MRI T - pT	Agreement	13 (52)	10 (67)	NS	MRI T - pT	Agreement	13 (52)	10 (67)	NS
	Disagreement	12 (48)	5 (33)			Disagreement	12 (48)	5 (33)	
CT T - pT	Agreement	15 (44)	9 (45)	NS	CT T - pT	Agreement	15 (44)	9 (45)	NS
	Disagreement	**19 (56)**	**11 (55)**			Disagreement	**19 (56)**	**11 (55)**	
MRI N - pN	Agreement	9 (36)	9 (60)	NS	MRI N - pN	Agreement	14 (56)	7 (47)	NS
	Disagreement	**16 (64)**	6 (40)			Disagreement	11 (44)	**8 (53)**	
CT N - pN	Agreement	17 (50)	12 (60)	NS	CT N - pN	Agreement	21 (62)	13 (65)	NS
	Disagreement	17 (50)	8 (40)			Disagreement	13 (38)	7 (35)	

Table 4
distribution of disagreement rates between under-staging and over-staging of clinical and radiological staging with MRI and CT versus pathological staging of the primary tumor and neck metastasis in HPV^{pos} and HPV^{neg} for TNM 7th and 8th ed. HPV: human papillomavirus; MRI: Magnetic Resonance Imaging; CT: computed tomography

HPV-NEGATIVE TNM 7	Agreement	Disagreement	Over-staging	Under-staging
Number (%)				
MRI T	10 (67)	5 (33)	1 (7)	4 (26)
CT T	9 (45)	11 (55)	1 (5)	10 (50)
MRI N	9 (60)	6 (40)	4 (27)	2 (13)
CT N	12 (60)	8 (40)	7 (35)	1 (5)

HPV-POSITIVE TNM 7	Agreement	Disagreement	Over-staging	Under-staging
Number (%)				
MRI T	13 (52)	12 (48)	3 (12)	9 (36)
CT T	15 (44)	19 (56)	7 (21)	12 (35)
MRI N	9 (36)	16 (64)	13 (52)	3 (12)
CT N	17 (50)	17 (50)	11 (32)	6 (18)

HPV-NEGATIVE TNM 8	Agreement	Disagreement	Over-staging	Under-staging
Number (%)				
MRI T	10 (67)	5 (33)	1 (7)	4 (26)
CT T	9 (45)	11 (55)	1 (5)	10 (50)
MRI N	7 (46)	8 (54)	4 (27)	4 (27)
CT N	13 (65)	7 (35)	2 (10)	2 (25)

HPV-POSITIVE TNM 8	Agreement	Disagreement	Over-staging	Under-staging
Number (%)				
MRI T	13 (52)	12 (48)	3 (12)	9 (36)
CT T	15 (44)	19 (56)	7 (21)	12 (35)
MRI N	14 (56)	11 (44)	7 (28)	4 (16)
CT N	21 (62)	13 (38)	5 (15)	8 (23)

early (I and II) and advanced stage (III and IV), we found that with the 7th edition 84% of all patients presented with advanced disease at diagnosis, predominantly in the HPV^{pos} group (89%). Conversely, adopting the 8th edition, the majority of all patients were classified as early stage (68%) and notably, 94% of HPV^{pos} were early stage at diagnosis, inverting the 7th edition trend. The distribution between early and advanced stages in the 8th edition was significantly different between HPV^{pos} and HPV^{neg}.

This was expected: while the 7th edition adequately reflects the behavior of tobacco and alcohol-related cancers, it does not properly describe the prognosis or behavior of HPV-positive disease.[28] The 8th edition staging of HPV-positive OPSCC would give a more accurate and reasonable prediction of survival, denoting the good prognosis typically associated with HPV-positive OPSCC.[11,29,30] Fig. 4 is an example of HPV^{pos} squamous cell carcinoma of the base of the tongue with LN metastasis, staged as an advanced stage with 7th ed. and early stage with 8th ed.

Concerning the accuracy of radiological staging, we found disagreement in a considerable proportion of cases between the pathological and radiological staging, both with CT and MRI: the proportion of disagreement varied for CT and MRI in 7th and 8th ed., but it was never lower than 33%. More in detail, in the staging of the neck LN involvement with the 7th edition, the highest disagreement rate was found in the HPV^{pos} group for MRI. In HPV^{neg} the disagreement rates were generally slightly lower, but still between 40% and 58% in N staging with the different techniques.

Considering the 8th edition, in HPV^{pos} the disagreement rates were lower, mostly in N staging. The opposite happened in HPV^{neg}, with higher disagreement rates in N staging, particularly with MRI staging. This should be considered a meaningful finding, since the TNM 8th edition for OPSCC introduced major changes, mostly as regards N staging for oropharynx cancer.[22,30] Our results support previous claims that the 8th edition improves HPV-positive OPSCC staging: we showed that the new staging system yielded a better agreement between radiological and histological staging. On the other hand, in HPV^{neg} the disagreement rates for N, mostly with MRI and, to a lesser extent with CT, were higher with the 8th edition: this difference is not significant but could highlight the impact of the weight attributed to ENE in the 8th edition in HPV-negative OPSCC, where patients presenting ENE are upstaged as compared to similar cases without ENE.[11]

In our study, the relevance of ENE in the new staging system could explain the worse agreement rates between radiological and pathological staging in HPV^{neg}, with a trend towards under-staging. It is known that ENE is a critical issue in staging[32]: Patel et al. in 2018 found that pre-operative CE-CT imaging is not reliable in predicting major ENE (>2 mm) in OPSCC.[31] On the other hand, Park et al., found that both CT and MRI show worse results in HPV-positive cases, but not in HPV-negative OPSCC, comparing them to different subsites of HNSCC.[32,34–37]

In HPV^{pos}, in the 7th and 8th editions, MRI and CT agreement was "good" for T and "moderate" for N, with no difference between editions. In HPV^{neg}, between the 7th and 8th editions, the kappa value remained the same in T staging (moderate) but was worse in N staging with the 8th edition (from "good" to "moderate"). A possible interpretation could reside in the introduction and importance given to ENE itself in N staging in the 8th edition, as debated earlier. Accurate pre-treatment detection of ENE could identify those who could be offered primary chemoradiotherapy rather than surgery, avoiding a multiple modality treatment.[10,11,14,32,35]

The distributions of under-staging and over-staging among

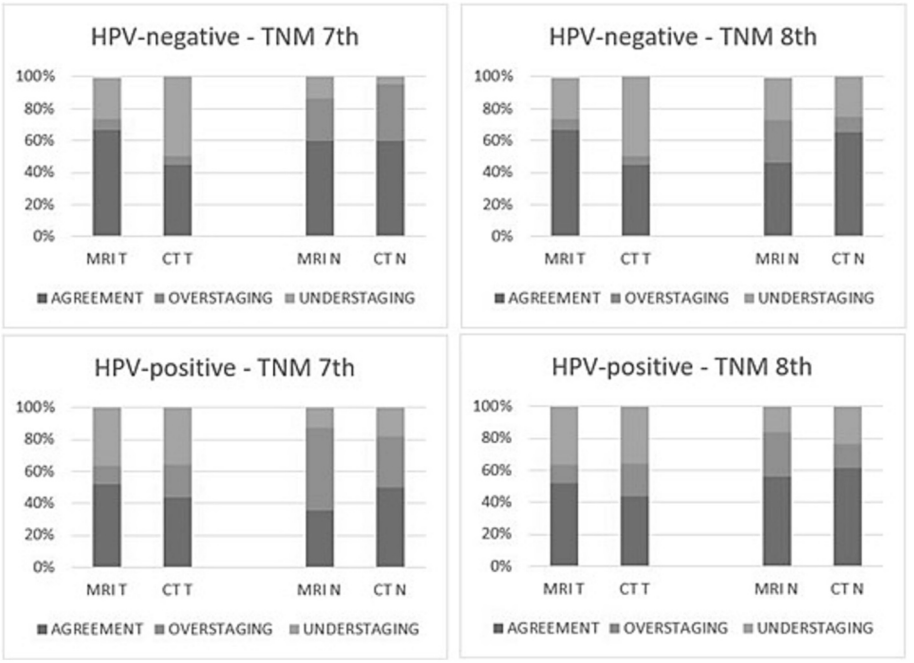

Fig. 3. Distribution among disagreement rates, distinguishing under-staging and over-staging of radiological staging with MRI and CT versus pathological staging of the primary tumor and neck metastasis in HPV^{pos} and HPV^{neg}, comparing TNM 7th ed. and TNM 8th ed. HPV: papillomavirus; HPV^{pos}: HPV-positive group; HPV^{neg}: HPV-negative group; T: primary tumor stage; N: nodal stage; pT: pathological primary tumor stage; pN: pathological nodal stage; MRI: Magnetic Resonance Imaging; CT: computed tomography.

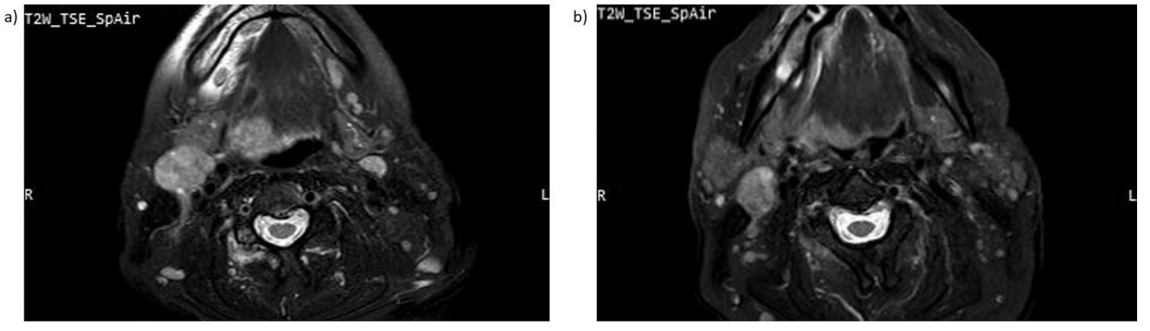

Fig. 4. T2W SPAIR MRI images of an HPV-positive oropharyngeal squamous cell carcinoma of the base of the tongue with multiple homolateral lymph nodes. With the 7th ed. of TNM, this would be an advanced stage IVa (cT2N2bM0); with the 8th edition, it is an early stage I (T2N1M0).

disagreement rates were analyzed. For HPV^{neg}, we can infer that there is a tendency for T under-staging mostly with CT; results for T staging are better with MRI, probably for a more accurate evaluation of primary tumor extension to surrounding anatomical structure (Fig. 5). Regarding the N stage, there is a trend towards over-staging when using the 7th edition, which is reversed in the 8th edition, where both MRI and CT tend to under-stage N. Giving the clinical and prognostic impact of these staging elements, it might suggest to radiologists to be as accurate as possible in assessing radiological images, even in smaller LN.[28,32–34]

For HPV^{pos} we found an improvement in agreement rates with the

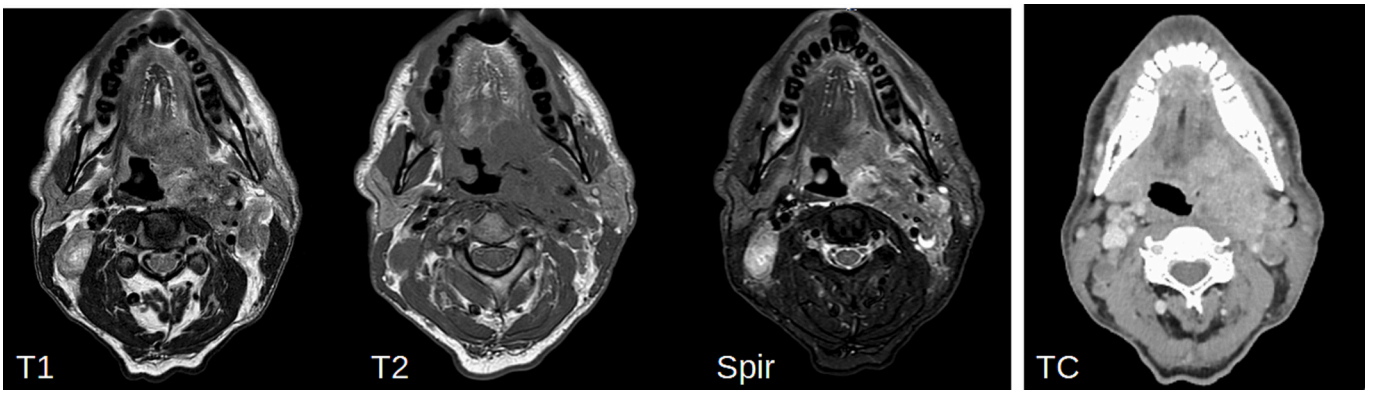

Fig. 5. Sequences of MRI (T1, T2, Spir) and CT scan images of a T4 HPV-positive squamous cell oropharyngeal cancer. MRI with different sequences can lead to a better analysis of tumor extension to anatomical surrounding structures, leading to a more precise T staging.

8th edition. There is a tendency towards T under-staging with all radiological techniques; on the other hand, the tendency to over-stage N using the 7th edition improved in the 8th, both with CT and MRI. Again, even though not statistically significant, we identified a trend towards a greater agreement between pre-treatment and pathological staging in HPV^{pos} with the 8th edition.

Limitations of this study are linked to biases of retrospective studies and a limited sample of patients: we recollected a large amount of data for each patient but limited access to clinical and radiological information was critical in the patient selection. Furthermore, another limitation is that only one radiologist evaluated the available imaging: it would surely be interesting to assess the inter-rater agreement between different physicians in imaging evaluation.

5. Conclusion

In this study, the 8th edition yielded better agreement between pre-treatment radiological staging and pathological staging for MRI assessment of the T parameter and CT assessment of the N parameter, in both HPV^{pos} and HPV^{neg} cases. Higher accuracy in pre-treatment staging for OPSCC carcinoma should be considered an important aim for clinicians, leading to better prognosis information for patients and more accurate discussion on treatment planning in multidisciplinary settings.

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