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Original Article

Use of preoperative PET-CT and survival of p16-negative oropharyngeal cancer

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Abstract: No comparative study with a long-term follow-up period has evaluated the survival outcomes of preoperative 18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}FDG PET/CT) in patients with p16-negative OPSCC. We included patients with stage I-IVB p16-negative OPSCC undergoing surgery and categorized them into two groups based on whether they underwent preoperative ^{18}FDG PET/CT and compared their outcomes: the case group comprised patients who did not undergo preoperative ^{18}FDG PET/CT, whereas the control group comprised patients who underwent preoperative ^{18}FDG PET/CT. The findings of the multivariable Cox regression analysis revealed no association between preoperative ^{18}FDG PET/CT and overall survival (OS) in the case and control groups in the patients with stage I-III p16-negative OPSCC undergoing surgery (after multivariable adjustment, the hazard ratio [HR] was 1.12; 95% confidence interval [CI] = 0.86-1.48: $P = 0.4028$). However, we noted an association between preoperative ^{18}FDG PET/CT and OS in the case and control groups in the patients with stage IVA and IVB p16-negative OPSCC undergoing surgery (after multivariable adjustment, the HR of all-cause mortality for nonpreoperative PET/CT was 1.82 compared with preoperative PET/CT; 95% CI = 1.47-2.26; $P < 0.0001$). Preoperative ^{18}FDG PET/CT use was associated with a lower risk of mortality in the patients with stage IVA and IVB p16-negative OPSCC without metastasis.

Keywords: Preoperative, ^{18}FDG PET/CT, OPSCC, survival, clinical stages

Introduction

The incidence of human papilloma virus (HPV)-positive oropharyngeal squamous cell carcinoma (OPSCC) has gradually increased worldwide [1, 2]. The clinical behavior of HPV-positive OPSCC differs from that of HPV-negative OPSCC [3-10]. Compared with patients with HPV-negative OPSCC, most patients with HPV-positive OPSCC are younger, have smaller primary tumors and fewer synchronous or metachronous tumors, have a lower prevalence of cigarette smoking and mucosal lesions, exhibit a more favorable response to primary radiotherapy (RT) or concurrent chemoradiotherapy (CCRT), and have a higher overall survival (OS) rate [3-10]. Despite the increasing prevalence of HPV-positive OPSCC, HPV-negative OPSCC remains dominant in regions with a high prevalence of betel nut chewing, especially Taiwan [5]. The pathogenesis, oncological outcomes, and treatments differ between HPV-negative OPSCC and HPV-positive OPSCC in patients with smoking, alcohol drinking, and betel nut chewing habits [5, 6, 9, 10].

P16-positive OPSCC is considered a surrogate of HPV-positive OPSCC [11, 12].

Patients with p16-positive OPSCC exhibit superior oncological outcomes compared with those with p16-negative OPSCC [5, 13-15]. Indicating that p16-positive OPSCC is a single disease entity [5, 13-15]. The etiology of the disease differs between patients with p16-negative OPSCC and those with p16-positive OPSCC [5, 13-15]. Thus, the clinical outcomes of different therapeutic strategies would vary among these patients [15-17]. According to the National Comprehensive Cancer Network (NCCN) guidelines and reports from Taiwan [5, 17, 18]. primary surgery can be feasible and result in superior oncological outcomes compared with primary RT or CCRT for p16-negative OPSCC [18]. Surgical intervention can be considered as the primary therapeutic strategy for patients with p16-negative OPSCC with cigarette smoking and betel-nut chewing habits to achieve better locoregional control and prolong OS [18].

Preoperative ^{18}fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}FDG-PET/CT) has a high sensitivity for detecting occult lymph nodes in patients with head and neck cancer (HNC) [19]. Surgical treatment plans may be changed in approximately 22% of patients with HNC on the basis of preoperative positron emission tomography/computed tomography (PET/CT) findings [19]. Preoperative PET/CT may assist clinicians in determining the most suitable surgical plan or a more precise sequential adjuvant RT field for patients with HNC [19-29]. Therefore, the NCCN guidelines suggest the use of preoperative PET/CT for p16-negative OPSCC [17]. No study has examined the benefits of preoperative PET/CT for patients with p16-negative OPSCC undergoing surgery. Thus, the value of preoperative PET/CT for patients with p16-negative OPSCC undergoing curative surgery should be evaluated. This retrospective national cohort study investigated the effect of preoperative PET/CT on the survival of patients with p16-negative OPSCC.

Patients and methods

Study design and patient data source

This retrospective study was conducted using data from the Health and Welfare Data Center (HWDC) established by Taiwan's Ministry of Health and Welfare. The HWDC consolidates data gathered by the Taiwanese government from various sources. These data are then deidentified and made available for research purposes based on case-by-case approval. In particular, we used the Taiwan Cancer Registry, which provides detailed information on the staging and treatment of patients with cancer; the Cause of Death database, which lists all death certificates issued in Taiwan [30]; and the National Health Insurance (NHI) Research Database, which contains information on all NHI-reimbursed examinations, medications, and treatments. We are confident that no evidence of death is equivalent to evidence of life because all death certificates are issued by the government and are required for property inheritance, abandonment of inheritance in the court, and burial or cremation in Taiwan. The NHI program has been implemented since 1995 and covers more than 99% of Taiwan's population. Since July 2004, the NHI has been reimbursing ^{18}F-FDG-PET/CT performed for the initial staging of HNC when optimal staging is not achieved through conventional computed tomography. All databases in the HWDC are linked through a common but anonymized identifier to ensure privacy. The requirement for informed consent was waived due to the retrospective and deidentified nature of this study.

Study sample

We consecutively selected patients aged ≥ 20 years who underwent surgical resection of pathologically proven p16-negative OPSCC and had cigarette smoking, alcohol drinking, and betel nut chewing habits for over 10 years between January 1, 2009, and December 31, 2017. The preferred method for determining HPV tumor status is examining the expression of the surrogate marker p16 through immunohistochemistry [11, 12]. We determined p16 protein expression in HPV-negative OPSCC through immunohistochemistry in accordance with the College of American Pathologists guideline [11, 12].

Inclusion and exclusion criteria

Inclusion criteria were having nonmetastatic OPSCC underwent curative surgery and adjuvant treatments, such as adjuvant RT and CCRT, in accordance with the NCCN guidelines and patients' will or tolerance [17]. Resectability was verified by HNC surgeons, and surgery was performed in all patients in our study. The

index date was the date of surgery. Surgical procedures included tumor resection and neck dissection depending on clinical nodal and tumor stages. The diagnoses of enrolled patients were confirmed after reviewing their pathological data, and patients who were newly diagnosed as having p-16 negative OPSCC and confirmed to have no other cancer or distant metastasis were included in the present study. All patients with p-16 negative OPSCC underwent curative surgery. Patients were included in this study if they were aged ≥ 20 years, had a pathological stage I-IVB OPSCC without metastasis (determined in accordance with the American Joint Committee on Cancer [AJCC] criteria, 7th edition). Patients were excluded if they had a history of other cancers before the index date, an unknown pathological stage, missing sex data, unclear differentiation of tumor grade, p-16 positive, unclear margin status, missing extracapsular status, missing hospital levels, and unclear adjuvant treatments (like missing irradiation dose and unclear platinum dosage).

Covariates and outcome definition

We extracted data regarding sex, age, American Joint Committee on Cancer (AJCC) clinical stages, differentiation, surgical margin, extracapsular extension, adjuvant treatments, RT cumulative dose, platinum cumulative dose, CCI scores, diagnosis year, hospital levels (medical and nonmedical centers), and disease status at the last follow-up date from the Taiwan Cancer Registry. Clinical stages were based on the 8th edition of the AJCC for OPSCC. Age was analyzed as a continuous variable.

From the NHI Research Database, we identified patients who underwent ^{18}F-FDG PET/CT within 0 to 90 days before the index date (surgery). Patients with a record of ^{18}F-FDG-PET/CT were considered to have undergone preoperative PET/CT, whereas those without records were considered to have not undergone preoperative PET/CT. All patients in the control group (non-preoperative ^{18}FDG-PET/CT) underwent head and neck magnetic resonance imaging (MRI) or CT with contrast for primary tumor and nodal staging, abdominal ultrasound, whole-body bone scan, and chest X-ray for metastatic staging at least. The only difference is the addition of preoperative PET/CT in the case group. Professional nuclear medicine physicians and radiologists who were licensed in Taiwan officially interpreted and reported all images. The Taiwan Cancer Registry Database requires that all PET/CT reports are reviewed and reported by trained nuclear medicine physicians. Moreover, the Taiwan Cancer Registry Administration randomly reviews the reports of images by peer review to verify the accuracy of diagnoses, and hospitals with outlier chargers or practices may be audited and subsequently heavily penalized if malpractice or discrepancies are identified.

The primary outcome of interest was all-cause mortality, which was calculated from the initial date to the date of death. Information on OS was obtained from the Cause of Death database. Patients whose death records could not be found were considered alive and censored on the last day of the database record (December 31, 2019).

Medical center versus nonmedical center treatment

In Taiwan, medical centers have dedicated head and neck oncology treatment teams including radiologists, oncologists, radiation therapists, and HNC surgeons. However, nonmedical centers do not have such a team.

Statistical analysis

Continuous data are presented as the mean ± standard deviation or the median and interquartile range, as applicable, whereas categorical data are presented as the number and percentage. The distribution of patient characteristics was compared using the χ^2 test for categorical variables and two-tailed Student's *t* test or Kruskal-Wallis test for continuous variables.

Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. The adjusted Cox proportional hazards models were used to estimate the hazard ratio (HR) and 95% confidence interval (CI) and to estimate the correlation of covariates with OS. A stratified analysis was performed to determine the effect of preoperative PET/CT on various AJCC clinical stages (I-III and IVA and IVB) for determining the association of preoperative PET/CT with OS across various subgroups, because AJCC stages IVA and IVB without metastasis were identified as independent

prognostic factors for OS (**Table 2**). **Table 1** presents the sample size of patients with different AJCC clinical stages. All statistical analyses were performed using SAS (version 9.4; SAS Institute Inc.). A two-sided *P* value of < 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 1543 patients with p16-negative OPSCC met the inclusion criteria (**Table 1**). The final cohort included patients who underwent preoperative PET/CT (n = 1133, 1006 men and 127 women, mean age = 55.5±10.1 years) and those who did not undergo preoperative PET/CT (n = 410, 379 men and 31 women, mean age = 54.1±9.1 years). A total of 1133 and 410 patients with p16-negative OPSCC who underwent surgery were included in the case and control groups, respectively. A higher proportion of patients with OPSCC were men and older and had early stage I-III disease, a positive surgical margin, and no extranodal extension in the preoperative PET/CT group compared with the nonpreoperative PET/CT group. Other covariates were balanced between the preoperative PET/CT and nonpreoperative PET/CT groups. The crude all-cause mortality rates were 52.4% and 41.0% in the nonpreoperative PET/CT and preoperative PET/CT groups, respectively (*P* < 0.0001; **Table 1**).

Predictors of survival

The findings of the univariable and multivariable analyses revealed an association between preoperative PET/CT and improved survival (in the adjusted model, the HR [95% CI] for all-cause mortality was 1.55 [1.31-1.83] for the nonpreoperative PET/CT group compared with the preoperative PET/CT group; *P* < 0.0001; **Table 2**). Known prognostic factors, namely male sex (*P* < 0.0001), age > 70 years (*P* = 0.0006), AJCC stages IVA and IVB (*P* = 0.0122), a positive surgical margin (*P* = 0.0026), extranodal extension (*P* < 0.0001), no adjuvant treatments (*P* = 0.0002), and CCI score ≥ 1 (*P* < 0.0001), were associated with poor OS in the multivariable analysis.

Stratified analysis of the effect of preoperative PET/CT by stage

We performed a stratified analysis to investigate the effect of preoperative PET/CT on various AJCC clinical stages. We stratified the AJCC clinical stages (I-III and IV [no metastasis]) by using a Cox regression model and adjusted for age, AJCC clinical stages, differentiation, surgical margin, extracapsular extension, adjuvant treatments, RT cumulative dose, platinum cumulative dose, CCI scores, diagnosis year, and hospital levels (**Table 3**). The strongest correlation between preoperative PET/CT and all-cause mortality was observed in the patients with stage IVA and IVB OPSCC undergoing surgery (after multivariable adjustment, the HR [95% CI] was 1.33 [1.04-1.71]; *P* = 0.0122), followed by those with stage III and stage II OPSCC undergoing surgery (in the adjusted model, the HRs [95% CIs] were 1.09 [0.83-1.42] and 1.02 [0.74-1.41], respectively; **Table 2**). Therefore, we investigated the association between preoperative PET/CT and survival by stratifying different AJCC clinical stages. Among the patients with stage I-III p16-negative OPSCC undergoing surgery, we observed no association between preoperative PET/CT and OS in both the case and control groups (after multivariable adjustment, the HR [95% CI] was 1.12 [0.86-1.48]; *P* = 0.4028). Among the patients with stage IVA or IVB p16-negative OPSCC undergoing surgery, we observed an association between preoperative PET/CT and OS in both the case and control groups (after multivariable adjustment, the HR [95% CI] of all-cause mortality for the nonpreoperative PET/CT group was 1.82 [1.47-2.26] compared with the preoperative PET/CT group; *P* < 0.0001; **Table 3**).

We did not observe a progressive increase in the rate of PET/CT utilization for OPSCC staging in later years: 72.3% in 2011-2013 and 74.1% in 2014-2017 (**Table 1**). Furthermore, no association between PET/CT use and OS was noted in both the case and control groups over a period (**Tables 2** and **3**).

Change in stage (conversion of the clinical stage to pathological stage)

Table 4 presents the change in the stage (conversion of the clinical stage to pathological stage) in the patients with p16-negative OPSCC undergoing surgery. The more consistent clinical and pathologic stages for stage IVA-B in preoperative PET/CT group (83.6%) to reveal more accurate stages for advanced clinical stages than non-preoperative PET/CT group (61.6%) (**Table 4**).

Table 1. Demographic characteristics of patients newly diagnosed as having p16-negative oropharyngeal squamous cell carcinoma undergoing surgery

	Total N = 1543		Nonpreoperative PET/CT N = 410		Preoperative PET/CT N = 1133		*P* value
	n	(%)	n	(%)	n	(%)	
Sex							
Male	1385	(89.8)	379	(92.4)	1006	(88.8)	0.0368
Female	158	(10.2)	31	(7.6)	127	(11.2)	
Age							
Mean (SD)	55.1	(9.9)	54.1	(9.1)	55.5	(10.1)	0.0095
Median (IQR, Q1-Q3)	55	(48-62)	54	(47-60)	55	(49-62)	
≤ 40	88	(5.7)	22	(5.4)	66	(5.8)	0.0034
41-50	443	(28.7)	127	(31.0)	316	(27.9)	
51-60	577	(37.4)	175	(42.7)	402	(35.5)	
61-70	327	(21.2)	66	(16.1)	261	(23.0)	
> 70	108	(7.0)	20	(4.9)	88	(7.8)	
AJCC clinical stage							
I	269	(17.4)	60	(14.6)	209	(18.4)	0.0124
II	267	(17.3)	58	(14.1)	209	(18.4)	
III	215	(13.9)	54	(13.2)	161	(14.2)	
IVA and IVB	792	(51.3)	238	(58.0)	554	(48.9)	
Differentiation							
1	110	(7.1)	22	(5.4)	88	(7.8)	0.1210
2	878	(56.9)	242	(59.0)	636	(56.1)	
3	402	(26.1)	96	(23.4)	306	(27.0)	
4	15	(1.0)	5	(1.2)	10	(0.9)	
Missing	138	(8.9)	45	(11.0)	93	(8.2)	
Surgical margin							
Negative	1006	(65.2)	304	(74.1)	702	(62.0)	< 0.0001
Positive	537	(34.8)	106	(25.9)	431	(38.0)	
Extracapsular extension							
No	1155	(74.9)	286	(69.8)	869	(76.7)	0.0055
Yes	388	(25.1)	124	(30.2)	264	(23.3)	
Adjuvant treatments							
CCRT	750	(48.6)	220	(53.7)	530	(46.8)	0.1501
RT alone	293	(19.0)	67	(16.3)	226	(19.9)	
No adjuvant treatments	500	(32.4)	123	(30.0)	377	(33.3)	
RT cumulative dose, Gy							
Mean (SD)	66.0	(13.0)	65.6	(14.2)	66.2	(12.5)	0.1875
Median (IQR, Q1-Q3)	66.0	(64.0-70.0)	66.0	(62.7-70.0)	66.0	(64.0-70.0)	
< 70 Gy	694	(45.0)	201	(49.0)	493	(43.5)	0.1576
≥ 70 Gy	349	(22.6)	86	(21.0)	263	(23.2)	
no RT	500	(32.4)	123	(30.0)	377	(33.3)	
Platinum cumulative dose, mg							
Mean (SD)	484.8	(330.7)	464.2	(271.1)	493.4	(352.6)	0.5457
Median (IQR, Q1-Q3)	410.0	(300.0-600.0)	400.0	(300.0-600.0)	410.0	(300.0-600.0)	
< 500 mg	370	(24.0)	110	(26.8)	260	(22.9)	0.0941
≥ 500 mg	294	(19.1)	85	(20.7)	209	(18.4)	
No platinum	879	(57.0)	215	(52.4)	664	(58.6)	
CCI Scores							
Mean (SD)	0.7	(1.1)	0.6	(1.1)	0.7	(1.2)	0.0507
Median (Q1-Q3)	0	(0-1)	0	(0-1)	0	(0-1)	

0	939	(60.9)	268	(65.4)	671	(59.2)	0.0829
1	355	(23.0)	81	(19.8)	274	(24.2)	
2+	249	(16.1)	61	(14.9)	188	(16.6)	
Diagnosis year							
2011-2013	592	(38.4)	164	(39.0)	428	(37.7)	0.2108
2014-2017	951	(61.6)	246	(61.0)	705	(62.3)	
Hospital level							
Medical center	1019	(66.0)	285	(69.5)	734	(64.8)	0.0832
Nonmedical centers	524	(34.0)	125	(30.5)	399	(35.2)	
Mean follow-up time, months (SD)	54.9	(28.0)	58.2	(25.4)	57.3	(28.5)	0.1823
All-cause death	680	(44.1)	215	(52.4)	465	(41.0)	0.0001

PET/CT, Positron Emission Tomography/Computed Tomography; AJCC, American Joint Committee on Cancer; CCI, Charlson Comorbidity Index; IQR, Interquartile Range; SD, Standard Deviation; CCRT, Concurrent Chemoradiotherapy; RT, Radiotherapy; N, Number.

Table 2. Cox proportional hazard regression analysis of the risk of all-cause death in patients with p16-negative oropharyngeal squamous cell carcinoma undergoing surgery

Variable		Univariate			Multivariate		
		Crude HR	95% CI	*P* value	Adjusted HR*	95% CI	*P* value
Nonpreoperative PET/CT (Preoperative PET/CT as reference)		1.52	(1.29-1.79)	< 0.0001	1.55	(1.31-1.83)	< 0.0001
Sex	Female	1		< 0.0001	1		< 0.0001
	Male	2.74	(1.92-3.91)		2.68	(1.87-3.83)	
Age	≤ 40	1		0.0017	1		0.0006
	41-50	1.06	(0.68-1.34)		1.04	(0.62-1.23)	
	51-60	1.15	(0.68-1.32)		1.09	(0.64-1.25)	
	61-70	1.18	(0.69-1.40)		1.14	(0.66-1.34)	
	> 70	1.66	(1.12-2.46)		1.62	(1.08-2.43)	
Differentiation	1	1		0.1122	1		0.2026
	2	1.08	(0.65-1.20)		1.04	(0.62-1.15)	
	3 and 4	1.04	(0.61-1.19)		1.02	(0.58-1.15)	
AJCC clinical stages	I	1		0.0050	1		0.0122
	II	1.04	(0.62-1.13)		1.02	(0.74-1.41)	
	III	1.07	(0.75-1.26)		1.09	(0.83-1.42)	
	IVA and IVB	1.24	(1.01-1.51)		1.33	(1.04-1.71)	
Surgical margin	Negative	1		0.0946	1		0.0026
	Positive	1.14	(0.98-1.34)		1.29	(1.09-1.52)	
Extracapsular extension	No	1		< 0.0001	1		< 0.0001
	Yes	1.71	(1.45-2.01)		1.73	(1.43-2.10)	
Adjuvant treatment	RT alone	1		0.0206	1		0.0002
	CCRT	1.06	(0.86-1.30)		0.89	(0.71-1.11)	
	No adjuvant treatments	1.18	(1.15-1.47)		1.35	(1.07-1.70)	
CCI scores	0	1		0.0001	1		< 0.0001
	1	1.32	(1.10-1.58)		1.43	(1.19-1.73)	
	2+	1.45	(1.19-1.78)		1.43	(1.16-1.75)	
Diagnosis year	2011-2013	1		0.3836	1		0.7153
	2014-2017	1.07	(0.92-1.26)		1.03	(0.88-1.21)	
Hospital level	Medical center	1		0.5012	1		0.3494
	Nonmedical centers	1.06	(0.90-1.24)		1.08	(0.92-1.27)	

PET/CT, Positron Emission Tomography/Computed Tomography; HR, Hazard Ratio; aHR, adjusted Hazard Ratio; CI, Confidence Interval; AJCC, American Joint Committee on Cancer; CCI, Charlson Comorbidity Index; CCRT, Concurrent Chemoradiotherapy; RT, Radiotherapy. *All covariates mentioned in **Table 2** were adjusted.

Table 3. Cox proportional hazard regression analysis of the risk of all-cause death in patients with oropharyngeal squamous cell carcinoma undergoing surgery, stratified by the AJCC clinical stage

Variable		Clinical stage I-III			Clinical stage IVA and IVB		
		Adjusted HR	95% CI	*P* value	Adjusted HR*	95% CI	*P* value
Nonpreoperative PET/CT (preoperative PET/CT as reference)		1.12	(0.86-1.48)	0.4028	1.82	(1.47-2.26)	< 0.0001
Sex	Female	1		0.0026	1		< 0.0001
	Male	2.17	(1.31-3.60)		3.33	(1.98-5.60)	
Age	≤ 40	1		0.1134	1		0.1458
	41-50	1.00	(0.55-1.75)		1.01	(0.55-1.28)	
	51-60	1.05	(0.60-1.84)		1.03	(0.54-1.26)	
	61-70	1.06	(0.47-1.56)		1.07	(0.62-1.52)	
	> 70	1.86	(0.98-3.55)		1.34	(0.79-2.27)	
Differentiation	1	1		0.3175	1		0.3020
	2	1.02	(0.47-1.09)		1.00	(0.63-1.58)	
	3 and 4	1.03	(0.61-1.12)		1.03	(0.50-1.80)	
AJCC clinical stages	I	1		0.2962	-		
	II	1.03	(0.78-1.35)				
	III	1.09	(0.56-1.11)				
Surgical margin	Negative	1		0.0015	1		0.2611
	Positive	1.53	(1.18-1.99)		1.13	(0.91-1.40)	
Extracapsular extension	No	1		0.0012	1		< 0.0001
	Yes	2.17	(1.36-3.46)		1.63	(1.32-2.00)	
Adjuvant treatment	RT alone	1		0.0502	1		< 0.0001
	CCRT	0.95	(0.80-1.59)		0.90	(0.67-1.22)	
	No adjuvant treatment	1.18	(1.00-1.62)		1.86	(1.32-2.62)	
CCI scores	0	1		0.0169	1		0.0007
	1	1.43	(1.09-1.89)		1.46	(1.13-1.87)	
	2+	1.38	(1.02-1.89)		1.56	(1.18-2.06)	
Diagnosis year	2011-2013	1		0.3033	1		0.6499
	2014-2017	0.96	(0.89-1.48)		0.95	(0.77-1.18)	
Hospital level	Medical center	1		0.5213	1		0.0954
	Nonmedical centers	1.02	(0.72-1.19)		1.19	(0.97-1.47)	

PET/CT, Positron Emission Tomography/Computed Tomography; HR, Hazard Ratio; aHR, adjusted Hazard Ratio; CI, Confidence Interval; AJCC, American Joint Committee on Cancer; CCI, Charlson Comorbidity Index; CCRT, Concurrent Chemoradiotherapy; RT, Radiotherapy. *All covariates mentioned in **Table 2** were adjusted.

Kaplan-Meier OS ccurve

The 5-year OS in the preoperative and nonpreoperative PET/CT groups was 61.3% and 50.7%, respectively, for all disease stages ($P < 0.0001$; **Figure 1A**); 64.3% and 54.1%, respectively, for stage I-III disease ($P = 0.0011$; **Figure 1B**); and 57.8.3% and 49.7%, respectively, for stage IVA and IVB disease ($P = 0.0003$; **Figure 1C**).

Sensitivity analysis of the survival effect of nonpreoperative PET/CT by subgroup

The results of the sensitivity analysis of age, AJCC clinical stages, differentiation, surgical margin, extracapsular extension, adjuvant treatments, CCI scores, diagnosis year, and hospital levels determined using the inverse probability of treatment weighting for all-cause death in the patients with OPSCC undergoing surgery with and without preoperative PET/CT are presented as a forest plot in **Figure 1**. The adjusted HRs (95% CIs) for the preoperative PET/CT group were more significantly associated with longer OS compared with the nonpreoperative PET/CT group, irrespective of clinical stages, differentiation, surgical margin, extracapsular extension, adjuvant treatments, CCI scores, diagnosis year, and hospital levels, except for female sex, differentiation grade I, clinical stages I-III, and CCI score ≥ 2.

Table 4. Change in stages (consistency between clinical and pathological stages)

	Patient No.	Pathologic stage							
		I		II		III		IVA-B	
		n	(%)	n	(%)	n	(%)	n	(%)
Clinical stage I									
Nonpreoperative PET/CT	60	50	(83.0)	5	(8.3)	5	(8.3)	0	(0.0)
Preoperative PET/CT	209	181	(86.7)	19	(9.1)	6	(2.9)	3	(1.4)
Clinical stage II									
Nonpreoperative PET/CT	58	9	(15.5)	36	(62.1)	5	(8.6)	8	(13.8)
Preoperative PET/CT	209	33	(15.8)	152	(72.7)	16	(7.7)	8	(3.8)
Clinical stage III									
Nonpreoperative PET/CT	54	6	(11.1)	7	(13.0)	29	(53.7)	12	(22.2)
Preoperative PET/CT	161	13	(8.1)	18	(11.2)	97	(60.2)	33	(20.5)
Clinical stage IVA-B									
Nonpreoperative PET/CT	238	29	(12.2)	23	(9.7)	39	(16.4)	147	(61.8)
Preoperative PET/CT	554	24	(4.3)	23	(4.2)	44	(7.9)	463	(83.6)

PET/CT, Positron Emission Tomography/Computed Tomography; n, number.

Discussion

The pathogenesis of p16-negative OPSCC differs from that of p-16 positive OPSCC in patients with long-term smoking, alcohol drinking, and betel nut chewing habits [5, 6, 9, 10]. The oncological outcomes were poorer in patients with p16-negative OPSCC than in those with p16-positive OPSCC [5, 13-15]. Curative surgery can be a valuable therapeutic choice for patients with p16-negative OPSCC instead of primary RT or CCRT because of the high radioresistance of p16-negative OPSCC and the association of long-term smoking, alcohol drinking, and betel nut chewing habits with more gene variations [3, 5, 10, 17, 18]. The value of routine preoperative PET/CT should be reconsidered for patients with p16-negative OPSCC, although the NCCN guidelines suggest PET/CT before surgery for p16-negative OPSCC [17]. However, preoperative PET/CT does have limitations in terms of the nonspecific uptake of fluorodeoxyglucose in oropharyngeal areas and possible false-positive findings resulting from the normal physiological uptake of fluorodeoxyglucose in primary sites and regional lymph nodes in patients with OPSCC [31, 32]. In the current study, we investigated the effect of preoperative PET/CT on the survival of patients with p16-negative OPSCC. In the patients with stage I-III p16-negative OPSCC undergoing surgery, we observed no association between preoperative PET/CT and OS in both the case and control groups (after multivariable adjustment, the HR [95% CI] was 1.12 [0.86-1.48]; P = 0.4028). However, in the patients with stage IVA and IVB p16-negative OPSCC undergoing surgery, we observed an association between preoperative PET/CT and OS in both the case and control groups (after multivariable adjustment, the HR [95% CI] of all-cause mortality for nonpreoperative PET/CT was 1.82 [1.47-2.26] compared with preoperative PET/CT group; P < 0.0001).

Other prognostic factors for poor OS in the patients with p16-negative OPSCC receiving curative surgery were male sex, age > 70 years, AJCC stage IVA and IVB, a positive surgical margin, extranodal extension, no adjuvant treatments, and CCI score ≥ 1 (**Tables 2** and **3**). Similar to our findings, male sex, old age, and CCI score ≥ 1 were determined as poor prognostic factors for OS in patients with HNC in previous studies [33-37]. However, this is the first study to report male sex, age > 70 years, and CCI score ≥ 1 as prognostic factors for OS in the patients with p16-negative OPSCC undergoing surgery. In Taiwan, most patients with p16-negative OPSCC have habits of cigarette smoking and betel nut chewing [3, 5, 6, 9, 10]. Surgery is a more aggressive and curative treatment for these patients [18]. However, no study has identified prognostic factors for patients with p16-negative OPSCC undergoing surgery in regions with a high prevalence of betel nut chewing and smoking. This is the leading study to identify poor prognostic factors for patients

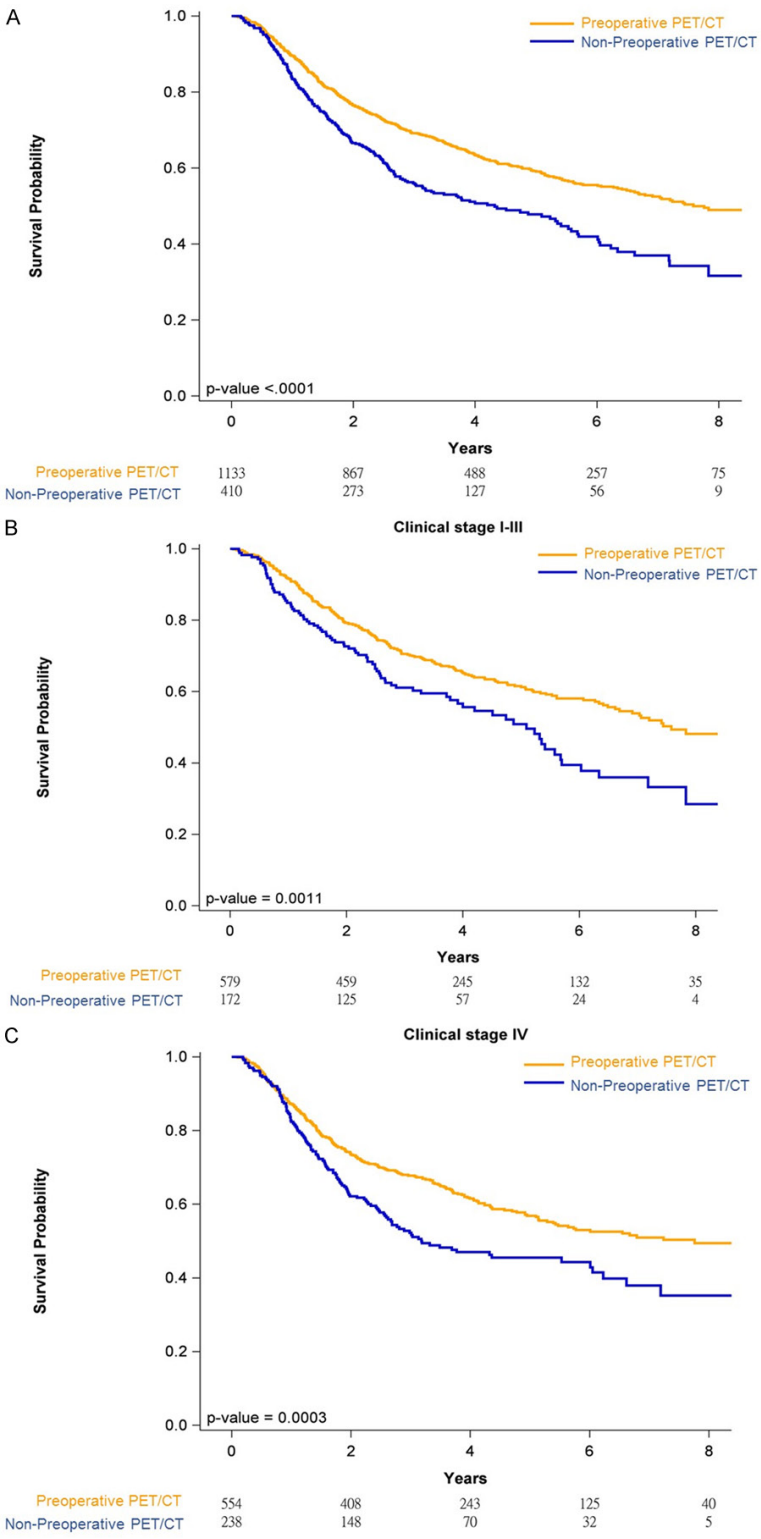

Figure 1. Kaplan-Meier overall survival curve of patients with p16-negative oropharynx cancer undergoing surgery with or without preoperative PET/CT. A. All Clinical stages. B. Clinical stages I-III. C. Clinical stage IVA and IVB.

with p16-negative OPSCC undergoing surgery (**Table 2**). In the Cox multivariable analysis, a positive surgical margin and extranodal extension were determined as poor prognostic factors for OS in the patients with p16-negative OPSCC; this finding is similar to that of previous studies indicating a positive surgical margin and extranodal extension as major risk factors for poor oncological outcomes in patients with HNC undergoing surgery [38, 39]. Not receiving adjuvant treatment was identified as a risk factor for mortality in patients with p16-negative OPSCC undergoing surgery (**Tables 2** and **3**). Furthermore, AJCC clinical stage IV was determined as an independent poor prognostic factor for mortality in the patients with p16-negative OPSCC undergoing surgery. This result might be attributable to the ease of performing R0 resection in stages I-III OPSCC but not in stages IVA and IVB OPSCC. After adjustment for adjuvant treatments and other covariates, only stages IVA and IVB but not stage II and III were identified as independent poor prognostic factors for mortality.

Prognostic factors for OS identified in the stratified analysis (**Table 3**) were similar to those determined in the nonstratified analysis (**Table 2**), except for preoperative PET/CT use. No significant difference between preoperative PET/CT use and nonpreoperative PET/CT use was noted in the patients with stage I-III p16-negative OPSCC undergoing surgery even after the sensitivity analysis (**Figure 2**). Although crude Kaplan-Meier OS curves for preoperative PET/CT use were significantly superior to those for nonpreoperative PET/CT use (**Figure 1B**), the adjusted HR (95% CI) of

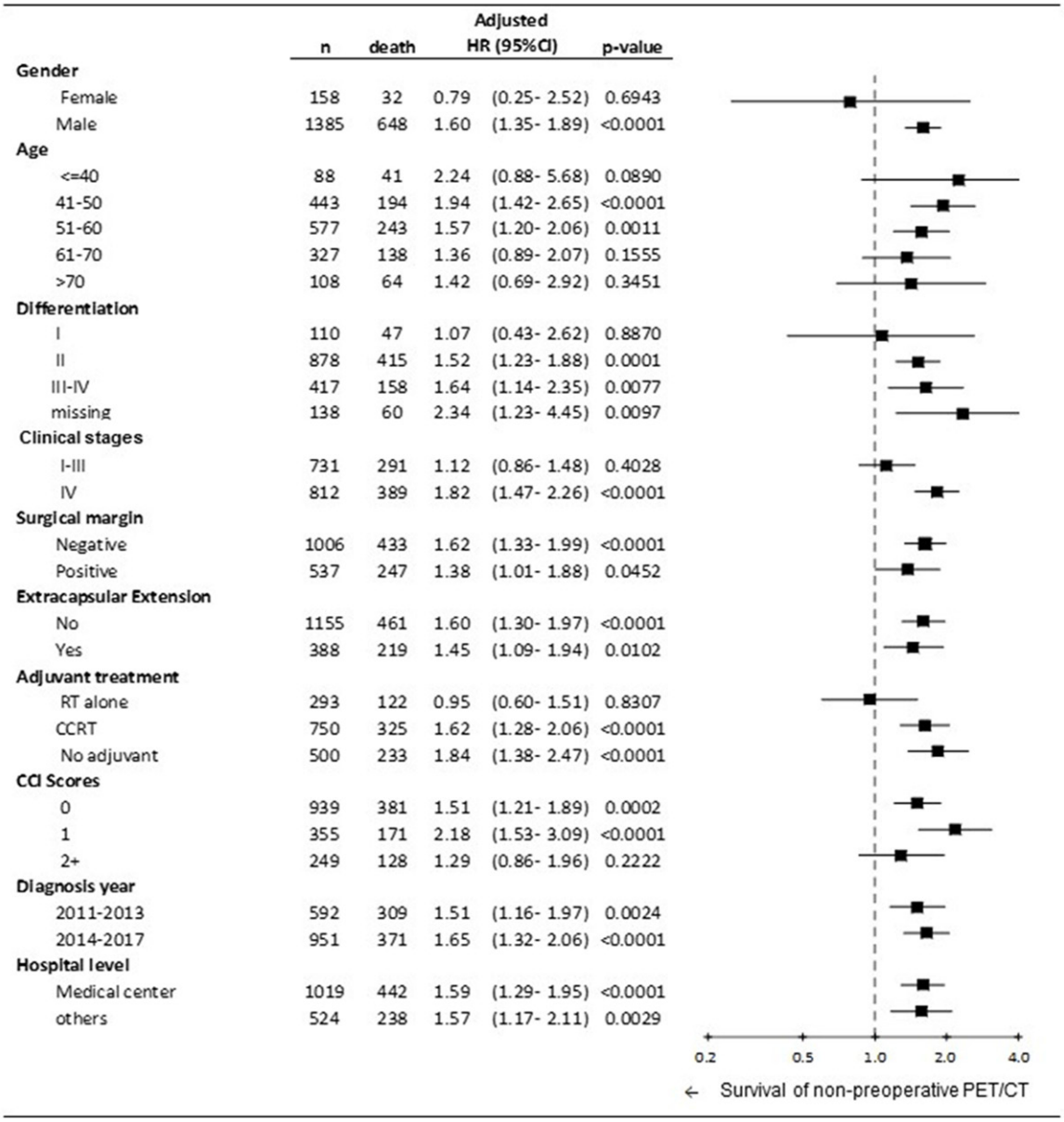

Figure 2. Sensitivity analysis for illustrating the impact of nonnpreoperative PET/CT on OS by subgroup.

mortality was 1.12 (0.86-1.48) for preoperative PET/CT use (**Table 3** and **Figure 2**). This finding can be due to risk factors for poor survival in the patients with stage I-III OPSCC, including a positive surgical margin and extranodal extension, being masked or adjusted by adjuvant RT or CCRT. However, the high risk of poor OS in the patients with stage IVA and IVB OPSCC could not be adjusted by adjuvant treatments. The current study indicated that the survival value of routine preoperative PET/CT use for the patients with stage I-III p16-negative OPSCC undergoing surgery should be reconsidered (**Table 3** and **Figure 2**). However, preoperative PET/CT might be necessary for patients with stage IVA and IVB OPSCC undergoing surgery because of the survival benefits of preoperative PET/CT use (**Table 3**; **Figures 1C** and **2**).

The survival benefits of preoperative PET/CT use in patients with stage IVA and IVB p16-negative OPSCC might be due to various factors. PET/CT was superior to both CT and magnetic resonance imaging (MRI) for detecting regional nodal metastases as well as distant metastases and second primary tumors in patients with

HNC [20-23]. A multicenter prospective study reported that PET/CT improved the staging of primary cancer and altered the management in 13.7% of patients with HNC [23]. When used for the initial staging of HNC, integrated PET/CT imaging appeared to be superior to CT, MRI, or PET alone [24]. These findings indicate that preoperative PET/CT is accurate for detecting occult cervical nodal metastases [20-24]. Although preoperative PET/CT does not have the sensitivity to replace neck dissection, it can be beneficial for planned neck dissection in terms of preventing residual occult neck lymph nodes in patients with OPSCC. The utility of PET/CT in detecting occult distant metastases and synchronous secondary primary tumors as well as altering sequential adjuvant radiation fields and doses in patients with p16-negative OPSCC undergoing neck dissection is compatible with the results of previous studies on patients with HNC [19-29]. The prevalence of occult lymph nodes or synchronous secondary primary tumors might be high in OPSCC [8, 40, 41]. Therefore, the use of preoperative PET/CT might be necessary for selected patients with OPSCC undergoing tumor removal and neck dissection (**Table 3** and **Figure 2**). The association of preoperative PET/CT use with prolonged survival in the patients with stage IVA and IVB p16-negative OPSCC undergoing surgery might be attributed to more accurate staging (**Table 4**). Irrespective of the clinical stage, preoperative PET/CT resulted in more accurate staging, and clinical stages were more consistent with pathologic stages in the preoperative PET/CT group than in the nonpreoperative PET/CT group. The more distinct differences of clinical stages and pathologic stages were stage IVA-B between preoperative PET/CT and non-preoperative PET/CT groups (**Table 4**). Taken together, preoperative PET/CT resulted in improved tumor, node, and metastasis staging, effectively detected occult cervical nodal metastases in patients undergoing planned neck dissection and synchronous secondary primary tumors, and altered sequential adjuvant RT fields; these factors might be responsible for better OS [19-29], especially in patients with resectable stage IVA and IVB disease (**Tables 3** and **4**; **Figures 1** and **2**).

The strength of our study is that this is the first study on preoperative PET/CT including a long-term follow-up cohort to examine the survival outcomes of patients with p16-negative OPSCC undergoing surgery stratified by different clinical stages. No comparative study with a long-term follow-up period has investigated the outcomes of preoperative ^{18}FDG PET/CT by different clinical stages. Preoperative ^{18}FDG PET/CT was associated with survival benefits only in the patients with stage IVA and IVB p16-negative OPSCC but not in those with stage I-III p16-negative OPSCC. Our results suggest that preoperative ^{18}FDG PET/CT is unnecessary for each patient with p16-negative OPSCC who will undergo curative surgery. Thus, we may not recommend preoperative ^{18}FDG PET/CT for every patient with p16-negative OPSCC. Preoperative ^{18}FDG PET/CT can be used for patients with stage IVA and IVB OPSCC (**Table 3** and **Figure 2**). Our findings can be incorporated into national health policies to reduce unnecessary medical expenditure.

This study has several limitations. First, all the patients with resectable p16-negative OPSCC were enrolled from an Asian population in Taiwan. Second, the reason for the use of preoperative PET/CT remained unclear in this retrospective analysis; this may lead to selection bias, although the NHI has been reimbursing ^{18}F-FDG-PET/CT performed for the initial staging of HNC since July 2004. Third, the effects of preoperative PET/CT might be underestimated because some of the patients were considered as non-PET/CT controls; although they may have undergone PET/CT, it was not recorded. Finally, although differences in clinical stages I-III between groups were not statistically significant ($P > 0.05$), the sample size of the intervention (preoperative PET/CT) for patients with stage I-III disease was small. To obtain crucial information on population specificity and disease occurrence, a large-scale randomized trial comparing carefully selected patients undergoing suitable treatments is essential. However, performing randomized controlled trials in daily practice might be difficult because not administering preoperative PET/CT to patients with advanced OPSCC for their inclusion in the control group would be unethical. Despite these limitations, a major strength of this study is the use of a nationwide population-based registry with detailed baseline and treatment information. Lifelong follow-up was possible through the linkage of the registry with the national Cause of Death database. Considering

the magnitude and statistical significance of the observed effects in the current study, the limitations are unlikely to affect our conclusions.

Conclusions

Our results demonstrated that preoperative ^{18}F-FDG PET/CT use was associated with a lower risk of mortality in the patients with stage IVA and IVB p16-negative OPSCC without metastasis. The use of this modality allowed for better staging concordance between clinical and final pathological stages. We observed no survival benefit of the use of preoperative ^{18}F-FDG PET/CT in the patients with stage I-III disease. A large randomized controlled trial would be necessary to confirm these findings.

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Disclosure of conflict of interest

None.

Abbreviations

PET/CT, Positron Emission Tomography/Computed Tomography; ^{18}FDG PET/CT, 18-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography; CT, Computed Tomography; HR, Hazard Ratio; aHR, adjusted Hazard Ratio; CI, Confidence Interval; FDG, Fluorodeoxyglucose; NCCN, National Comprehensive Cancer Network; AJCC, American Joint Committee on Cancer; CCI, Charlson Comorbidity Index; OS, Overall Survival; IQR, Interquartile Range; RT, Radiotherapy; CCRT, Concurrent Chemoradiotherapy; MRI, Magnetic Resonance Imaging; HPV, Human Papillomavirus; OPSCC, Oropharyngeal Squamous Cell Carcinoma; TCRD, Taiwan Cancer Registry Database; HNC, Head And Neck Cancers; HWDC, Health And Welfare Data Center; NHI, National Health Insurance.

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References

[1] Nasman A, Attner P, Hammarstedt L, Du J, Eriksson M, Giraud G, Ahrlund-Richter S, Marklund L, Romanitan M, Lindquist D, Ramqvist T, Lindholm J, Sparen P, Ye W, Dahlstrand H, Munck-Wikland E and Dalianis T. Incidence of human papillomavirus (HPV) positive tonsillar carcinoma in Stockholm, Sweden: an epidemic of viral-induced carcinoma? Int J Cancer 2009; 125: 362-366.

[2] Attner P, Du J, Nasman A, Hammarstedt L, Ramqvist T, Lindholm J, Marklund L, Dalianis T and Munck-Wikland E. The role of human papillomavirus in the increased incidence of base of tongue cancer. Int J Cancer 2010; 126: 2879-2884.

[3] Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tan PF, Westra WH, Chung CH, Jordan RC, Lu C, Kim H, Axelrod R, Silverman CC, Redmond KP and Gillison ML. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010; 363: 24-35.

[4] Gillison ML. HPV and prognosis for patients with oropharynx cancer. Eur J Cancer 2009; 45: 383-385.

[5] Al-Swiahb JN, Huang CC, Fang FM, Chuang HC, Huang HY, Luo SD, Chen CH, Chen CM and Chien CY. Prognostic impact of p16, p53, epidermal growth factor receptor, and human papillomavirus in oropharyngeal cancer in a betel nut-chewing area. Arch Otolaryngol Head Neck Surg 2010; 136: 502-508.

[6] Ringstrom E, Peters E, Hasegawa M, Posner M, Liu M and Kelsey KT. Human papillomavirus type 16 and squamous cell carcinoma of the head and neck. Clin Cancer Res 2002; 8: 3187-3192.

[7] Westra WH, Taube JM, Poeta ML, Begum S, Sidransky D and Koch WM. Inverse relationship between human papillomavirus-16 infection and disruptive p53 gene mutations in squamous cell carcinoma of the head and neck. Clin Cancer Res 2008; 14: 366-369.

[8] Licitra L, Perrone F, Bossi P, Suardi S, Mariani L, Artusi R, Oggionni M, Rossini C, Cantu G, Squadrelli M, Quattrone P, Locati LD, Bergamini C, Olmi P, Pierotti MA and Pilotti S. High-risk human papillomavirus affects prognosis in patients with surgically treated oropharyngeal squamous cell carcinoma. J Clin Oncol 2006; 24: 5630-5636.

[9] Kumar B, Cordell KG, Lee JS, Worden FP, Prince ME, Tran HH, Wolf GT, Urba SG, Chepeha DB, Teknos TN, Eisbruch A, Tsien CI, Taylor JM, D'Silva NJ, Yang K, Kurnit DM, Bauer JA, Bradford CR and Carey TE. EGFR, p16, HPV Titer, Bcl-xL and p53, sex, and smoking as indicators

of response to therapy and survival in oropharyngeal cancer. J Clin Oncol 2008; 26: 3128-3137.
[10] Sedaghat AR, Zhang Z, Begum S, Palermo R, Best S, Ulmer KM, Levine M, Zinreich E, Messing BP, Gold D, Wu AA, Niparko KJ, Kowalski J, Hirata RM, Saunders JR, Westra WH and Pai SI. Prognostic significance of human papillomavirus in oropharyngeal squamous cell carcinomas. Laryngoscope 2009; 119: 1542-1549.
[11] Lewis JS Jr, Beadle B, Bishop JA, Chernock RD, Colasacco C, Lacchetti C, Moncur JT, Rocco JW, Schwartz MR, Seethala RR, Thomas NE, Westra WH and Faquin WC. Human papillomavirus testing in head and neck carcinomas: guideline from the college of American pathologists. Arch Pathol Lab Med 2018; 142: 559-597.
[12] Lydiatt WM, Patel SG, O'Sullivan B, Brandwein MS, Ridge JA, Migliacci JC, Loomis AM and Shah JP. Head and neck cancers-major changes in the American Joint Committee on cancer eighth edition cancer staging manual. CA Cancer J Clin 2017; 67: 122-137.
[13] Lassen P, Eriksen JG, Hamilton-Dutoit S, Tramm T, Alsner J and Overgaard J. Effect of HPV-associated p16INK4A expression on response to radiotherapy and survival in squamous cell carcinoma of the head and neck. J Clin Oncol 2009; 27: 1992-1998.
[14] Fischer CA, Zlobec I, Green E, Probst S, Storck C, Lugli A, Tornillo L, Wolfensberger M and Terracciano LM. Is the improved prognosis of p16 positive oropharyngeal squamous cell carcinoma dependent of the treatment modality? Int J Cancer 2010; 126: 1256-1262.
[15] Galloway TJ, Zhang QE, Nguyen-Tan PF, Rosenthal DI, Soulieres D, Fortin A, Silverman CL, Daly ME, Ridge JA, Hammond JA and Le QT. Prognostic value of p16 status on the development of a complete response in involved oropharynx cancer neck nodes after Cisplatin-based chemoradiation: a secondary analysis of NRG oncology RTOG 0129. Int J Radiat Oncol Biol Phys 2016; 96: 362-371.
[16] Close LG, Brown PM, Vuitch MF, Reisch J and Schaefer SD. Microvascular invasion and survival in cancer of the oral cavity and oropharynx. Arch Otolaryngol Head Neck Surg 1989; 115: 1304-1309.
[17] NCCN Clinical practice guidelines in oncology: Head and Neck Cancer. In: National Comprehensive Cancer Network (NCCN) Version 1.2022. Harborside Press, LLC, 94 N Woodhull Rd, Huntington, NY 11743. 2022. 4/26/2022.
[18] Chuang HC, Chien CY, Huang TL, Chiu TJ, Lu H, Huang CC and Fang FM. Treatment of p16-negative advanced tonsil cancer: primary surgery or primary radiation? International Journal of Head Neck Science 2020; 4: 24-33.
[19] Lowe VJ, Duan F, Subramaniam RM, Sicks JD, Romanoff J, Bartel T, Yu JQM, Nussenbaum B, Richmon J, Arnold CD, Cognetti D and Stack BC Jr. Multicenter trial of [(18)F].fluorodeoxyglucose positron emission tomography/computed tomography staging of head and neck cancer and negative predictive value and surgical impact in the N0 neck: results from ACRIN 6685. J Clin Oncol 2019; 37: 1704-1712.
[20] Johnson JT and Branstetter BF 4th. PET/CT in head and neck oncology: state-of-the-art 2013. Laryngoscope 2014; 124: 913-915.
[21] Escott EJ. Role of positron emission tomography/computed tomography (PET/CT) in head and neck cancer. Radiol Clin North Am 2013; 51: 881-893.
[22] Xu G, Li J, Zuo X and Li C. Comparison of whole body positron emission tomography (PET)/PET-computed tomography and conventional anatomic imaging for detecting distant malignancies in patients with head and neck cancer: a meta-analysis. Laryngoscope 2012; 122: 1974-1978.
[23] Lonneux M, Hamoir M, Reychler H, Maingon P, Duvillard C, Calais G, Bridji B, Digue L, Toubeau M and Gregoire V. Positron emission tomography with [18F].fluorodeoxyglucose improves staging and patient management in patients with head and neck squamous cell carcinoma: a multicenter prospective study. J Clin Oncol 2010; 28: 1190-1195.
[24] Wong WL, Hussain K, Chevretton E, Hawkes DJ, Baddeley H, Maisey M and McGurk M. Validation and clinical application of computer-combined computed tomography and positron emission tomography with 2-[18F].fluoro-2-deoxy-D-glucose head and neck images. Am J Surg 1996; 172: 628-632.
[25] Zanation AM, Sutton DK, Couch ME, Weissler MC, Shockley WW and Shores CG. Use, accuracy, and implications for patient management of [18F].-2-fluorodeoxyglucose-positron emission/computerized tomography for head and neck tumors. Laryngoscope 2005; 115: 1186-1190.
[26] Ha PK, Hdeib A, Goldenberg D, Jacene H, Patel P, Koch W, Califano J, Cummings CW, Flint PW, Wahl R and Tufano RP. The role of positron emission tomography and computed tomography fusion in the management of early-stage and advanced-stage primary head and neck squamous cell carcinoma. Arch Otolaryngol Head Neck Surg 2006; 132: 12-16.
[27] Schwartz DL, Ford E, Rajendran J, Yueh B, Coltrera MD, Virgin J, Anzai Y, Haynor D, Lewellyn B, Mattes D, Meyer J, Phillips M, Leblanc M, Kinahan P, Krohn K, Eary J and Laramore GE. FDG-PET/CT imaging for preradiotherapy staging of head-and-neck squamous cell carcino-

ma. Int J Radiat Oncol Biol Phys 2005; 61: 129-136.
[28] Schoder H, Yeung HW, Gonen M, Kraus D and Larson SM. Head and neck cancer: clinical usefulness and accuracy of PET/CT image fusion. Radiology 2004; 231: 65-72.
[29] Fleming AJ Jr, Smith SP Jr, Paul CM, Hall NC, Daly BT, Agrawal A and Schuller DE. Impact of [18F].-2-fluorodeoxyglucose-positron emission tomography/computed tomography on previously untreated head and neck cancer patients. Laryngoscope 2007; 117: 1173-1179.
[30] Zhang J, Lu CY, Chen HM and Wu SY. Neoadjuvant chemotherapy or endocrine therapy for invasive ductal carcinoma of the breast with high hormone receptor positivity and human epidermal growth factor receptor 2 negativity. JAMA Netw Open 2021; 4: e211785.
[31] Werner MK, Pfannenberg C and Oksuz MO. Nonspecific FDG uptake in the tongue mimicking the primary tumor in a patient with cancer of unknown primary. Clin Imaging 2011; 35: 405-407.
[32] King KG, Kositwattanarerk A, Genden E, Kao J, Som PM and Kostakoglu L. Cancers of the oral cavity and oropharynx: FDG PET with contrast-enhanced CT in the posttreatment setting. Radiographics 2011; 31: 355-373.
[33] Chang CL, Yuan KS and Wu SY. High-dose or low-dose cisplatin concurrent with radiotherapy in locally advanced head and neck squamous cell cancer. Head Neck 2017; 39: 1364-1370.
[34] Liu WC, Liu HE, Kao YW, Qin L, Lin KC, Fang CY, Tsai LL, Shia BC and Wu SY. Definitive intensity-modulated radiotherapy or surgery for early oral cavity squamous cell carcinoma: propensity-score-matched, nationwide, population-based cohort study. Head Neck 2021; 43: 1142-1152.
[35] Lin KC, Chen TM, Yuan KS, Wu ATH and Wu SY. Assessment of predictive scoring system for 90-day mortality among patients with locally advanced head and neck squamous cell carcinoma who have completed concurrent chemoradiotherapy. JAMA Netw Open 2020; 3: e1920671.
[36] Chang JH, Wu CC, Yuan KS, Wu ATH and Wu SY. Locoregionally recurrent head and neck squamous cell carcinoma: incidence, survival, prognostic factors, and treatment outcomes. Oncotarget 2017; 8: 55600-55612.
[37] Liu WC, Liu HE, Kao YW, Qin L, Lin KC, Fang CY, Tsai LL, Shia BC and Wu SY. Definitive radiotherapy or surgery for early oral squamous cell carcinoma in old and very old patients: a propensity-score-matched, nationwide, population-based cohort study. Radiother Oncol 2020; 151: 214-221.
[38] Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefebvre JL, Greiner RH, Giralt J, Maingon P, Rolland F, Bolla M, Cognetti F, Bourhis J, Kirkpatrick A and van Glabbeke M; European Organization for Research and Treatment of Cancer Trial 22931. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004; 350: 1945-1952.
[39] Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, Kish JA, Kim HE, Cmelak AJ, Rotman M, Machtay M, Ensley JF, Chao KS, Schultz CJ, Lee N and Fu KK; Radiation Therapy Oncology Group 9501/Intergroup. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004; 350: 1937-1944.
[40] McMullen CP, Garneau J, Weimar E, Ali S, Farinhas JM, Yu E, Som PM, Sarta C, Goldstein DP, Su S, Xu W, Smith RV, Miles B and de Almeida JR. Occult nodal disease and occult extranodal extension in patients with oropharyngeal squamous cell carcinoma undergoing primary transoral robotic surgery with neck dissection. JAMA Otolaryngol Head Neck Surg 2019; 145: 701-707.
[41] Milliet F, Bozec A, Schiappa R, Viotti J, Modesto A, Dassonville O, Poissonnet G, Guelfucci B, Bizeau A, Vergez S, Dupret-Bories A, Garrel R, Fakhry N, Santini L, Lallemant B, Chambon G, Sudaka A, Peyrade F, Saada-Bouzid E, Benezery K, Jourdan-Soulier F, Chapel F, Sophie Ramay A, Roger P, Galissier T, Coste V, Ben Lakdar A, Guerlain J, Temam S, Mirghani H, Gorphe P, Chamorey E and Culie D. Synchronous primary neoplasia in patients with oropharyngeal cancer: impact of tumor HPV status. A GETTEC multicentric study. Oral Oncol 2021; 112: 105041.