J Chin Med Assoc

ORIGINAL ARTICLE

Enhancing regional control in p16-negative oropharyngeal cancer: A propensity score-matched analysis of upfront neck dissection and definitive chemoradiotherapy

Tsung-Lun Lee[a,b], Wei-Chen Fang[a,b], I.-Cheng Lee[b,c], Jiing-Feng Lirng[b,d], Chia-Fan Chang[a,b], Yen-Bin Hsu[a,b], Pen-Yuan Chu[a,b], Yi-Fen Wang[a,b], Muh-Hwa Yang[b,e], Peter Mu-Hsin Chang[b,e], Ling-Wei Wang[b,f], Shyh-Kuan Tai[a,b,g,*]

[a]Department of Otolaryngology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [b]School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; [c]Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [d]Department of Radiology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [e]Division of Medical Oncology, Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [f]Division of Radiation Oncology, Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [g]Infection and Immunity Research Center, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC

Abstract

Background: The presence of p16 and neck disease is important predictors of prognosis for oropharyngeal squamous cell carcinoma (OPSCC). Patients who are p16-negative and have clinically node-positive (cN+) disease generally have worse oncologic outcomes. This study aimed to investigate whether upfront neck dissection (UFND) could provide potential benefits for patients with cN+ p16-negative OPSCC.

Methods: Through this retrospective study, 76 patients with cN+ p16-negative OPSCC were analyzed, those who received either definite concurrent chemoradiotherapy (CCRT group) or UFND followed by chemoradiotherapy (UFND group). The primary endpoints were regional recurrence-free survival (RRFS), disease-specific survival (DSS), and overall survival (OS). Factors associated with survival were evaluated by univariate and multivariate analysis. Survival between the two groups was compared by propensity score-matched analysis.

Results: Matched 23 patients in each group through propensity analysis, the UFND group showed a significantly better 5-year RRFS (94.1% vs 61.0%, $p = 0.011$) compared to the CCRT group. Univariate analysis revealed that UFND was the sole factor associated with regional control (hazard ratio [HR] = 0.110; 95% CI, 0.014-0.879; $p = 0.037$). Furthermore, the study found that the CCRT group was associated with a higher dose of radiotherapy and exhibited a significantly higher risk of mortality due to pneumonia.

Conclusion: The study indicated that UFND followed by CCRT may be a potential treatment option for patients with cN+ p16-negative OPSCC, as it can reduce the risk of regional recurrence. Additionally, the study highlights that definite CCRT is connected to a larger dose of radiotherapy and a higher risk of fatal pneumonia. These findings could be beneficial in informing clinical decision-making and improving treatment outcomes for patients with OPSCC.

Keywords: Concurrent chemoradiotherapy; Neck dissection; Oropharyngeal squamous cell carcinoma; Prognosis; Propensity score

1. INTRODUCTION

Oropharyngeal squamous cell carcinoma (OPSCC) is often associated with the presence of human papillomavirus (HPV), and p16 is a commonly used surrogate marker for HPV.[1–3] The prevalence of p16-positive OPSCC varies across different countries and regions and may change with time. The recent approval of the HPV vaccine by the United States Food and Drug Administration for oropharyngeal cancer prevention, as well as the implementation of universal HPV immunization programs, may lead to a decrease in the incidence of p16-positive OPSCC. Nevertheless, the treatment of p16-negative OPSCC should not be overlooked. Investigations into the treatment of this subtype of OPSCC remain crucial to improving oncologic outcomes.

The main distinction between p16-positive and p16-negative OPSCC lies in their response to chemoradiotherapy. Compared to p16-positive OPSCC, p16-negative OPSCC tends to be a poor responder to chemoradiotherapy, which can have a detrimental effect on oncologic outcomes.[4] Intensified multimodality treatment can enable better management of p16-negative OPSCC.

* *Address correspondence. Dr. Shyh-Kuan Tai, Department of Otolaryngology, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: sktai.tw@gmail.com (S.-K. Tai).*

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article

Journal of Chinese Medical Association. (2024) 87: 516-524.

Received October 12, 2023; accepted January 18, 2024.

doi: 10.1097/JCMA.0000000000001085

Aside from p16, neck stage is another significant prognostic factor for OPSCC. Patients with advanced neck stage have been found to exhibit poorer response to radiotherapy, likely due to the relatively lower responsiveness of large and/or hypoxic lymph node metastases compared to the primary tumor. To address this issue, planned neck dissection (ND) has been included in treatment protocols either independently of treatment response or as a salvage procedure for residual or recurrent nodal disease following chemoradiotherapy for advanced head and neck squamous cell carcinoma. The potential benefits and role of upfront ND (UFND) in patients with clinically node-positive (cN+) p16-negative OPSCC have not been widely explored in the current literature. The available literature on this topic is limited and primarily focuses on head and neck cancer, with a particular emphasis on hypopharyngeal and OPSCC cases, regardless of p16 status.[5–7] Therefore, the aim of the present study is to investigate the possible advantages of UFND in patients with cN+ p16-negative OPSCC.

2. METHODS

The retrospective study was approved by the institutional research ethics committee of Taipei Veterans General Hospital (TPEVGH IRB No.: 2020-04-013AC), and the requirement for informed consent from patients was waived. Between January 1, 2011, and September 30, 2019, the medical records of 213 newly diagnosed patients with p16-negative OPSCC who received curative treatment at Taipei Veterans General Hospital, a single tertiary referral hospital in Taipei, Taiwan were reviewed. Among these patients, 114 had clinical neck metastasis. We excluded patients who did not complete the entire treatment course or were not followed up for more than 3 months (n = 10), had simultaneous or prior head and neck malignancy (n = 17), or had distant metastasis (n = 11) at the time of diagnosis. Ultimately, data from 76 patients with cN+ p16-negative OPSCC were included in the analysis. The mean follow-up duration was 50.4 months (range: 5.6-140.6 months). Clinicopathological data and tumor characteristics were recorded from hospital registries.

All patients underwent standard pretreatment evaluations for staging, which were determined by a multidisciplinary team comprising radiologists, medical oncologists, radiation oncologists, and head and neck surgeons using the seventh edition of the American Joint Committee on Cancer/Union for International Cancer Control TNM staging classification. During the meeting, the largest diameters of lymph nodes were measured in the long axis and recorded as the maximal neck size in this review. Based on the image study, necrotic metastatic nodes are characterized by thicker walls and irregular, complex central low attenuation. In contrast, the definition of cystic nodes entails homogeneous fluid content without internal complex, irregular, or solid areas, and an enhancing capsule <2 mm in thickness.[8]

The curative treatment was determined using a shared decision-making approach involving the patients, their families, and attending physicians. The treatment plan for neck disease was concluded based on the patient's preference, either definite concurrent chemoradiotherapy (CCRT group) or upfront surgery including ND followed by chemoradiotherapy (UFND group). The extent of ND was determined based on preoperative imaging studies and the conclusion of a multidisciplinary meeting.

Standard radiotherapy performed at our hospital includes intensity-modulated radiation therapy (IMRT) with standard fractionation according to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for Head and Neck Cancer. The planned total dose of radiotherapy was >60 Gy (2.0 Gy/d) to the primary tumor region and involved nodal stations. For the purposes of this review, the radiation dose for the primary tumor was defined as the total dose of radiotherapy to the primary tumor region (primary tumor site or postoperative tumor bed), and the dose for the neck metastasis was defined as the total dose to the involved nodal stations.

IMRT was combined with cisplatin-based triweekly chemotherapy or weekly targeted therapy with cetuximab in this review. Targeted therapy with cetuximab is covered by National Health Insurance for patients aged 70 years and older and those with serum creatinine clearance <50 mL/min, hearing impairment, or intolerance to cisplatin-based chemotherapy.

After treatment completion, regular follow-up was performed once a month in the first year, once every 2 months in the second year, and once every 3 months after the third year. The first imaging follow-up was conducted 2 to 3 months after the completion of CCRT. After that, follow-up imaging was scheduled every 6 to 12 months until 5 years after completion of CCRT. Functional results were determined based on the patient's dependence on feeding and tracheostomy tubes at their last follow-up.

The causes of death are ultimately documented and categorized into locoregional disease, distant metastasis, second primary malignancy, and pneumonia. As local and regional diseases can sometimes be difficult to distinguish, they are grouped together under the same cause of death. Furthermore, if a patient passes away due to carotid blowout syndrome, this too will be attributed to a locoregional disease-related cause of death.

2.1. Statistical analysis

Categorical variables across groups were compared using the Pearson Chi-squared test or Fisher exact test when the number was <5. Parametrically distributed continuous data were compared using the unpaired Student's *t* test. Cumulative regional recurrence-free survival (RRFS), disease-specific survival (DSS), and overall survival (OS) were determined using the Kaplan-Meier method, and these three survivals were measured from the start of treatment. The Log-Rank test was used to statistically compare the survival curves between the UFND and CCRT groups.

Variables that achieved statistical significance ($p < 0.05$) or those that were close to significance ($p < 0.1$) by univariate Cox proportional hazard model were subsequently included in the multivariate analysis using a forward stepwise Cox regression model.

To address potential confounding factors, a propensity analysis was performed using logistic regression to generate a propensity score for patients who received UFND or CCRT. The propensity model included variables that were associated with treatment decisions. The model was then used to match UFND and CCRT groups on a one-to-one basis using the nearest-neighbor matching method. Survival analysis was repeated for each matched subgroup to evaluate the effect of UFND on oncologic outcomes while adjusting for confounding factors. Statistical significance was set at a two-tailed $p < 0.05$. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS 20 for Windows, SPSS Inc., Chicago, IL).

3. RESULTS

3.1. Patient demographics and tumor-related characteristics

Of the 76 patients reviewed, 96.1% (73/76) were male, with a mean age of 56.3 years (range 38-89 years). The majority of patients had a history of cigarette smoking (90.8%) and alcohol consumption (73.7%). Approximately half had the habit of betel-quid chewing (52.6%). The most common location of the primary tumor was the palatine tonsil (67.1%, 51/76), followed by the tongue base (18.4%, 14/76), soft palate (9.2%, 7/76), posterior pharyngeal wall (3.9%, 3/76), and vallecula (1.3%, 1/76).

Based on the treatment modality, the CCRT group consisted of 49 patients, while the UFND group had 27 patients. Within the UFND group, 92.6% (25/27) of cases underwent ipsilateral NDs, while only 7.4% (2/27) underwent bilateral NDs. After undergoing ND, 40.7% (11/27) of patients were diagnosed with a higher pathologic N stage than their original clinical N stage. Pathological reports of 11 out of 27 patients (40.7%) showed extranodal extension (ENE). Among these 11 cases, only 45.5% (5/11) were initially diagnosed with ENE through staging imaging.

Among the cohort of 73 patients who underwent systemic treatment, the majority (78.1%, 57/73) received cisplatin-based chemotherapy, while a subset of 12 patients (16.4%) were treated with cetuximab-targeted therapy. Two patients (2.7%) received a combination of targeted therapy and cisplatin-based chemotherapy, and the remaining two patients (2.7%) were administered cisplatin in conjunction with immunotherapy.

The baseline characteristics of the patients in the two treatment groups are presented in the left column of Table 1. The UFND group had a statistically significant higher proportion of male patients (88.9% vs 100%) and significantly earlier clinical T stage (T1-2, 100% vs 46.9%). Additionally, the UFND group received significantly lower radiation doses over the primary tumor and neck field (both $p = 0.000$). However, other factors, including age, personal habits, clinical N stage, overall staging, maximal size of neck metastasis, ENE, necrotic or cystic nodal change of lymph nodes shown on the image, and functional outcomes (long-term tube feeding and tracheostomy tube), did not reach statistical significance.

Due to significant differences in clinical T stage between the UFND and CCRT groups, propensity analysis using a one-to-one nearest-neighbor matched method was conducted to minimize selection bias. The variables entered in the propensity model were age, sex, clinical T stage, and N stage. The propensity analysis matched 23 patients in each group, and the aforementioned confounding factors were well-matched between the two groups (Table 1, right column).

3.2. Causes of death

Table 2 displays the causes of death for each group following propensity score-matched analysis. In the UFND group, 17.4% (4/23) of patients died due to distant metastasis, while 4.3% of patients died of locoregional disease. Out of the four cases that died of distant metastasis, 50% (2/4) had ENE upon pathological analysis. In the CCRT group, 21.7% of patients died due to aspiration pneumonia, 8.7% of patients died of locoregional disease, and 4.3% died of distant metastasis. No patients in either group died as a result of a second primary malignancy. It is noteworthy that patients in the CCRT group had a significantly higher risk of dying from aspiration pneumonia ($p = 0.049$), while there was no significant difference in other factors between the two groups.

3.3. Oncologic and survival outcomes

The median follow-up duration for all cases was 53.3 months (range, 5.6-140.6) in the UFND group and 45.6 months (range, 6.7-130.7) in the CCRT group. In the UFND group, 25.9% (7/27) of cases experienced relapse, including seven cases of local recurrence (25.9%), one case of regional recurrence (3.7%), and five cases of distant recurrence (18.5%). In contrast, 38.8% (19/49) of cases in the CCRT group experienced relapse, including eight cases of local recurrence (16.3%), 13 cases of regional recurrence (26.3%), and six cases of distant recurrence (12.2%).

The comparative analysis revealed a statistically significant difference in the 5-year RRFS rate between the UFND and CCRT groups (95.0% vs 70.1%, $p = 0.017$) (Fig. 1A). However, there were no statistically significant differences in the 5-year DSS and OS rates between the two groups (5-year DSS: 80.8% vs 74.8%, $p = 0.656$; 5-year OS: 70.4% vs 60.1%, $p = 0.549$) (Figs. 2A and 3A).

After propensity score-matched analysis, 5-year RRFS was still better in the UFND group (94.1% vs 61.0%, $p = 0.011$) (Fig. 1B). There were still no statistically significant differences in the 5-year DSS and OS rates between the two groups (5-year DSS: 77.3% vs 64.8%, $p = 0.482$; 5-year OS: 73.9% vs 61.7%, $p = 0.515$) (Figs. 2B and 3B).

3.4. Factors associated with survival by univariate and multivariate analyses

Among all of the 76 p16-negative OPSCC patients, univariate analysis revealed that UFND was the sole factor associated with regional control, as shown in Table 3. Clinical T stage, N stage, primary tumor excision, ENE, and necrotic or cystic lymph nodes shown on image were not found to be significantly associated with RRFS. Given that all other factors had a $p > 0.1$, multivariate analysis was not performed. After propensity score matching analysis of the 46 patients, univariate analysis also revealed that UFND was the only factor related to regional control. Furthermore, none of the specific factors were associated with DSS in the univariate Cox proportional hazard model (Table 4). Similarly, no factors were found to be linked to OS in all p16-negative OPSCC patients. After propensity score matching analysis, only clinical T stage was found to have an impact on OS (Table 5). Similarly, because none or only one factor had a $p < 0.1$ in the univariate Cox proportional hazard model, multivariate analysis was not conducted.

3.5. Functional outcomes

According to the latest follow-up records, 15 out of 76 patients (19.7%) required tube feeding, while 5 (6.6%) required tracheostomy. Although the UFND group had a lower rate of long-term feeding tube dependence (n = 3, 11.1%) than the CCRT group (n = 12, 24.5%), the difference was not statistically significant ($p = 0.231$). Similarly, the rate of long-term tracheostomy dependence was lower in the UFND group (n = 1, 3.7%) than in the CCRT group (n = 4, 8.2%), but without statistical significance ($p = 0.436$) (Table 1). The same trend was observed after propensity score-matched analysis.

4. DISCUSSION

Treating cN+ in p16-negative OPSCC remains a challenge, and controlling lymph node metastasis is a critical issue that needs to be addressed. In this group of patients with less radio-sensitive disease, several factors might be related to poor disease control, including increased tumor load, hypoxic change,[9] or intrinsic biological features of lymph node metastasis. All of these factors may contribute to radio-resistance, and surgical removal of the clinical lymph node disease before CCRT is a reasonable hypothesis to achieve better oncological outcomes. However, there is little literature discussing the role of UFND specifically in this group of patients. Two relevant prospective trials have been conducted to investigate treatment modalities for head and neck cancer and evaluate their oncological outcomes. One prospective study was carried out by Carinci et al[10] to assess the impact of UFND followed by CCRT on DSS rate in patients with unresectable advanced head and neck carcinoma. The results of this study showed that UFND followed by CCRT can provide a significantly higher DSS rate. The other prospective study[11] primarily evaluated patients with a radio-curable pharyngolaryngeal primary along with large lymph nodes and demonstrated that UFND followed by radiotherapy is a feasible treatment option that can achieve adequate disease-free survival and OS.

Table 1

Patient demographics and tumor-related characteristics in the UFND and CCRT groups before and after matching by propensity analysis

	Before propensity score matching			After propensity score matching		
	UFND (n = 27)	CCRT (n = 49)	*p*	UFND (n = 23)	CCRT (n = 23)	*p*
Gender (n, %)			0.042			NA
Female	3 (11.1)	0 (0)		0 (0)	0 (0)	
Male	24 (88.9)	49 (100)		23 (100)	23 (100)	
Age (mean ± SD)	55.6 ± 10.0	56.6 ± 11.0	0.665	55.1 ± 9.5	56.5 ± 9.3	0.607
Alcohol consuming (n, %)			0.786			0.491
No	8 (29.6)	12 (24.5)		7 (30.4)	4 (17.4)	
Yes	19 (70.4)	37 (75.5)		16 (69.6)	19 (82.6)	
Betel-quid chewing (n, %)			0.635			0.767
No	14 (51.9)	22 (44.9)		11 (47.8)	9 (39.1)	
Yes	13 (48.1)	27 (55.1)		12 (52.2)	14 (60.9)	
Cigarette smoking (n, %)			0.694			1.000
No	3 (11.1)	4 (8.2)		1 (4.3)	2 (8.7)	
Yes	24 (88.9)	45 (91.8)		22 (95.7)	21 (91.3)	
Clinical T stage (n, %)			<0.001			1.000
1-2	27 (100)	23 (46.9)		23 (100)	22 (95.7)	
3-4	0 (0)	26 (53.1)		0 (0)	1 (4.3)	
Clinical N stage (n, %)			0.149			0.135
1-2a	9 (33.3)	8 (16.3)		7 (30.4)	2 (8.7)	
2b-3	18 (66.7)	41 (83.7)		16 (69.6)	21 (91.3)	
AJCC stage (n, %)			0.183			0.346
III	6 (22.2)	5 (10.2)		4 (17.4)	1 (4.3)	
IV	21 (77.8)	44 (89.8)		14 (82.6)	22 (95.7)	
Maximal size of neck metastasis (n, %)			0.810			1.000
<3 cm	14 (51.9)	28 (57.1)		11 (47.8)	11 (47.8)	
≧3 cm	13 (48.1)	21 (42.9)		12 (52.2)	12 (52.2)	
ENE on image (n, %)			0.122			0.189
No	22 (81.5)	31 (63.3)		19 (82.6)	14 (60.9)	
Yes	5 (18.5)	18 (36.7)		4 (17.4)	9 (39.1)	
Necrotic nodal metastasis (n, %)			0.474			0.556
No	11 (40.7)	25 (51.0)		10 (43.5)	13 (56.5)	
Yes	16 (59.3)	24 (49.0)		13 (56.6)	10 (43.5)	
Cystic nodal metastasis (n, %)			0.786			1.000
No	21 (77.8)	36 (73.5)		17 (73.9)	16 (69.6)	
Yes	6 (22.2)	13 (26.2)		6 (26.1)	7 (30.4)	
RT dose, primary tumor, cGy (mean ± SD)	6628.2 ± 67.5	6952.5 ± 31.7	<0.001	6597.4 ± 71.0	6935.7 ± 43.8	<0.001
RT dose, neck, cGy (mean ± SD)	6124.4 ± 90.1	6781.6 ± 58.6	<0.001	6118.3 ± 83.4	6846.8 ± 79.0	<0.001
Duration of treatment, d (mean ± SD)	83.6 ± 2.9	77.7 ± 3.7	0.213	83.8 ± 3.3	70.7 ± 5.3	0.044
Tube feeding (n, %)			0.231			0.608
No	24 (88.9)	37 (75.5)		22 (95.7)	20 (87.0)	
Yes	3 (11.1)	12 (24.5)		1 (4.3)	3 (13.0)	
Tracheostomy tube (n, %)			0.650			1.000
No	26 (96.3)	45 (91.8)		22 (95.7)	23 (100)	
Yes	1 (3.7)	4 (8.2)		1 (4.3)	0 (0)	

CCRT = concurrent chemoradiotherapy; cGy = centigray; ENE = extranodal extension; RT = radiotherapy; UFND = upfront neck dissection.

Recently, Sato et al[12] conducted a study to investigate the impact of UFND followed by CCRT on oncologic outcomes in patients with hypopharyngeal cancer with advanced neck involvement. The results of this study showed that the treatment modality could provide satisfactory regional control, but had no impact on DSS and OS. The management of OPSCC is especially controversial due to the nature of p16, which divides the disease into two distinct diseases. In earlier studies, the most authors did not divide patients according to the p16 status.[13–15] More recent studies have mostly focused on p16-positive OPSCCs.[16–18]

We conducted a review of 76 patients with cN+ p16-negative OPSCC at our tertiary medical center, and our study presented surgery followed by CCRT and definitive CCRT as treatment options with curative intent. Although both approaches demonstrated comparable oncologic outcomes, UFND followed by CCRT allowed for better regional control with significantly reduced radiation dose. Similar results were also observed in a previous study published in 2019 that utilized the Surveillance, Epidemiology, and End Results (SEER) Head and Neck with HPV Status Database.[19] This study showed that upfront surgery did not have a significant impact on OS or cause-specific survival in patients with HPV-negative OPSCC.

Previous literature has pointed out that ND may have a negative impact on patients' quality of life, including shoulder drop, pain, or feeding tube dependence, especially when trimodal treatment is performed.[20–22] However, according to our study,

Table 2

Causes of death in the UFND and CCRT groups after propensity score-matched analysis

Cause of death, No. (%)	UFND group (n = 23)	CCRT group (n = 23)	Total (n = 46)	*p*
Locoregional disease-related	1 (4.3)	2 (8.7)	3 (6.5)	1.000
Die of distant metastasis	4 (17.4)	1 (4.3)	5 (10.9)	0.346
Die of second primary malignancy	0 (0)	0 (0)	0 (0)	
Aspiration pneumonia	0 (0)	5 (21.7)	5 (10.9)	0.049
Unknown or unspecified due to loss of follow-up	0 (0)	1 (2.0)	1 (1.3)	

CCRT = concurrent chemoradiotherapy; UFND = upfront neck dissection.

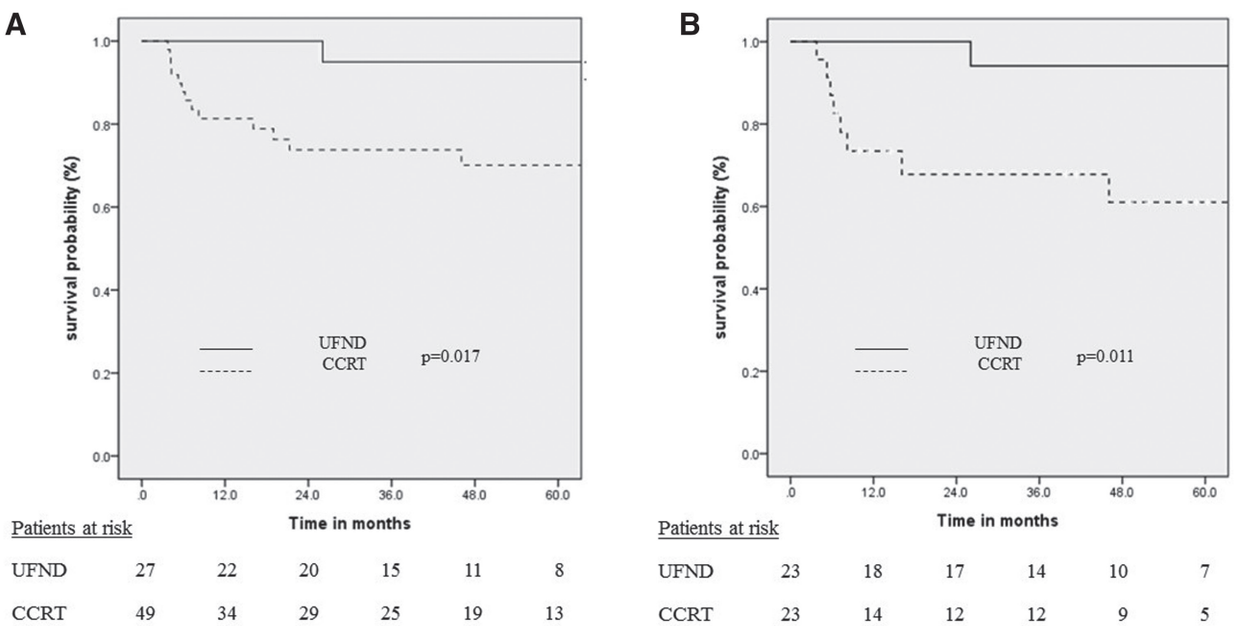

Fig. 1 A comparative analysis of the 5-y regional recurrence-free survival of cN+ p16-negative OPSCC revealed a statistically significant difference in the UFND or CCRT groups before (95.0% vs 70.1%, $p = 0.017$) (A) and after propensity score matching (94.1% vs 61.0%, $p = 0.011$) (B). CCRT = concurrent chemoradiotherapy; cN+ = clinically node-positive; OPSCC = oropharyngeal squamous cell carcinoma; UFND = upfront neck dissection.

long-term feeding tube dependence and tracheostomy tube dependence were lower in the UFND group, although without statistical significance. It is noteworthy that patients in the CCRT group exhibited a significantly higher risk of mortality due to pneumonia ($p = 0.049$). This result might have been a consequence of most patients (71%) receiving selective ND in our hospital, with preservation of the three functional structures. Besides, the dose of radiotherapy was lower in the UFND group. Common adverse effects of irradiation, such as decreased saliva and damage to pharyngeal constrictors, were closely correlated to the dose volume for organs at risk.[23,24] The comparable functional outcomes could be attributed to the type of surgery and the dose of radiation.

Another benefit of the surgery is that UFND allows for level-specific mapping of nodal disease and provides a definite pathological diagnosis. These information can be used to tailor the dose and volume of RT, potentially reducing the total dose delivered to the postoperative target volumes based on different risks. Our study found that patients who underwent UFND received significant lower doses to the neck, which may have contributed to the group's lower risk of death from aspiration pneumonia. In addition, certain indicators of poor prognostic outcomes, such as microscopic ENE and lymph node density, can only be confirmed through ND. In our series, 40.7% of the patients had an upstaged pathologic N stage after ND compared with the original clinical N stage, and in 54.4% of patients, microscopic ENE was only detected after ND. The presence of advanced regional metastasis and ENE plays a crucial role in determining the survival outcomes of patients. The poor prognosis associated with the presence of ENE is attributed to a higher risk of both regional and distant failures when compared to encapsulated lymph node metastasis.[25] It is worth noting that ENE emerges as the most significant predictive factor for regional recurrence, distant metastatic progression, and OS.[26] Furthermore, a comprehensive meta-analysis[27] has been conducted to investigate the association between ENE and the occurrences of locoregional recurrence as well as distant metastasis progression. The results of this analysis unequivocally confirm the substantial impact of ENE on the development of distant metastasis, further emphasizing its clinical significance in the patients' oncologic outcomes. ND can help stratify patients through a definitive pathological diagnosis and allow for targeted or intensified postoperative chemoradiation and posttreatment follow-up for better disease control.[28–30]

Furthermore, UFND can be used to avoid further treatment and irradiation of the neck after a full course of radiotherapy or CRT in cases of persistent or recurrent nodal disease. A

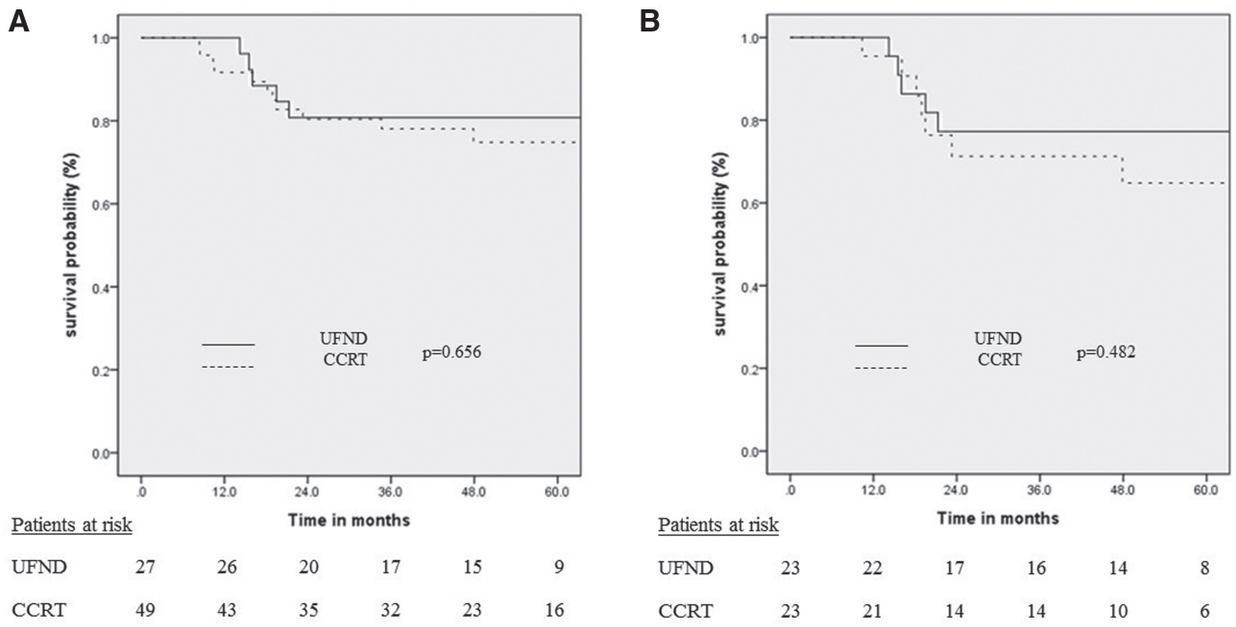

Fig. 2 The comparative analysis of the 5-y disease-specific survival rates between the UFND and CCRT groups, respectively, revealing no statistically significant differences (80.8% vs 74.8%, $p = 0.656$) (A). The results of propensity score-matched analysis still demonstrated no statistically significant differences between the two groups (77.3% vs 64.8%, $p = 0.482$) (B). CCRT = concurrent chemoradiotherapy; UFND = upfront neck dissection.

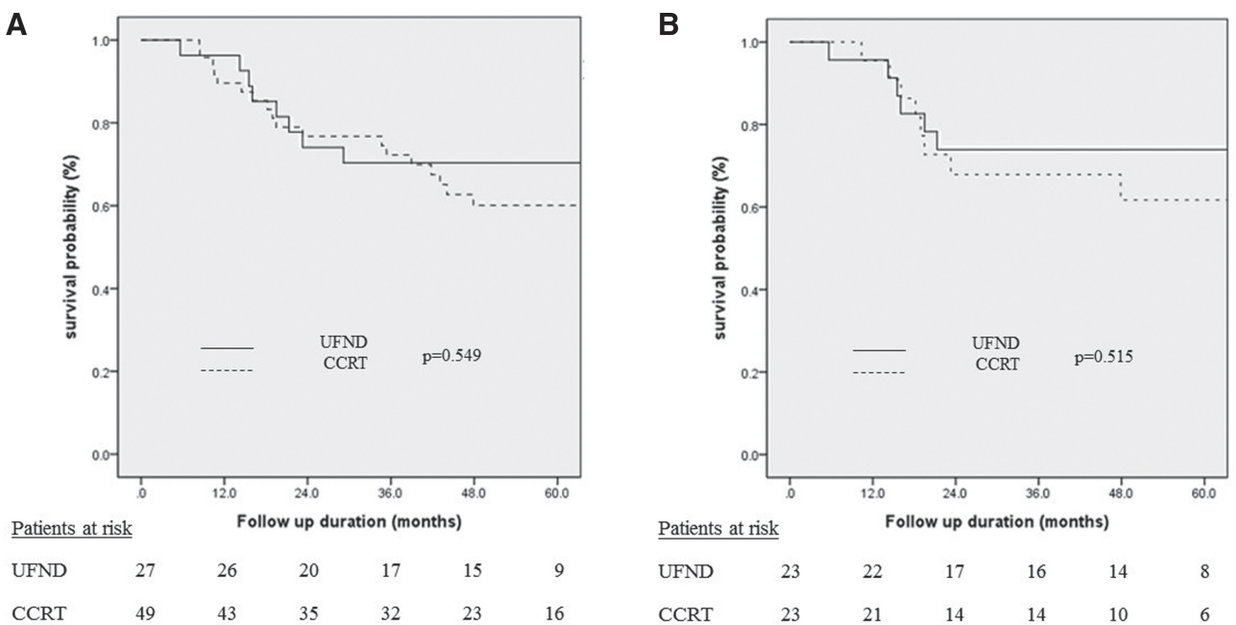

Fig. 3 In the comparative analysis of the 5-y overall survival rates between the UFND and CCRT groups, no statistically significant differences were observed (70.4% vs 60.1%, $p = 0.549$) (A). The results of propensity score-matched analysis also demonstrated no statistically significant differences between the two groups (73.9% vs 61.7%, $p = 0.515$) (B). CCRT = concurrent chemoradiotherapy; UFND = upfront neck dissection.

study by Stenson et al[31] found that 35% of ND specimens contained microscopic residual tumor in lymph nodes following CRT. As a result, planned ND used to be performed after primary CCRT for large neck disease of OPSCC,[32] but the benefits and risks were controversial.[33,34] Previous high-dose irradiation delivered to the neck during CCRT considerably increases the risk of postoperative complications after ND. Soft tissue fibrosis and decreased vascularization can lead to impaired wound healing, secondary hemorrhage, infections, soft tissue necrosis, and higher vulnerability of large vessels, potentially leading to ruptures of the carotid artery in worst-case scenarios.[35–37] Two studies have compared the postoperative complications between patients treated with UFND and those with salvage ND after oncological failure, and the results showed a much higher complication rate in the latter group.[38,39]

Table 3

Factors associated with regional recurrence-free survival by univariate Cox proportional hazard model before and after matching by propensity analysis

	Before propensity score matching		After propensity score matching	
	Univariate		Univariate	
Variables	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Clinical T stage				
T1-T2	Reference		Reference	
T3-T4	1.092 (0.366-3.261)	0.875	1.000 (0.000-686946.909)	1.000
Clinical N stage				
N1-N2a	Reference		Reference	
N2b-N3	4.390 (0.574-33.598)	0.154	28.933 (0.029-29301.862)	0.341
Overall staging				
3	Reference		Reference	
4	2.362 (0.309-18.065)	0.408	23.701 (0.002-303289.761)	0.512
Treatment group				
CCRT	Reference		Reference	
UFND	0.126 (0.016-0.960)	0.046	0.110 (0.014-0.879)	0.037
Primary tumor excision				
No	Reference		Reference	
Yes	0.432 (0.120-1.550)	0.198	0.274 (0.057-1.322)	0.107
ENE upon image				
No	Reference		Reference	
Yes	2.047 (0.709-5.911)	0.186	1.402 (0.350-5.611)	0.633
Necrotic lymph node				
No	Reference		Reference	
Yes	1.609 (0.539-4.804)	0.394	1.181 (0.317-4.401)	0.805
Cystic lymph node				
No	Reference		Reference	
Yes	0.438 (0.098-1.960)	0.280	0.699 (0.145-3.371)	0.656

CCRT = concurrent chemoradiotherapy; ENE = extranodal extension; HR = hazard ratio; UFND = upfront neck dissection.

Table 4

Factors associated with disease-specific survival by univariate Cox proportional hazard model before and after matching by propensity analysis

	Before propensity score matching		After propensity score matching	
	Univariate		Univariate	
Variables	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Clinical T stage				
T1-T2	Reference		Reference	
T3-T4	0.920 (0.319-2.649)	0.877	1.000 (0.000-514646.247)	1.000
Clinical N stage				
N1-N2a	Reference		Reference	
N2b-N3	4.716 (0.623-35.711)	0.133	2.659 (0.343-20.602)	0.349
Overall staging				
3	Reference		Reference	
4	2.525 (0.333-19.121	0.370	1.054 (0.136-8.171)	0.960
Treatment group				
CCRT	Reference		Reference	
UFND	0.787 (0.273-2.265)	0.657	0.664 (0.211-2.095)	0.485
Primary tumor excision				
No	Reference		Reference	
Yes	0.550 (0.177-1.706)	0.301	0.492 (0.148-1.636)	0.248
ENE upon image				
No	Reference		Reference	
Yes	2.341 (0.877–6.245)	0.089	1.720 (0.546-5.426)	0.355
Necrotic LN				
No	Reference		Reference	
Yes	1.044 (0.389-2.805)	0.931	1.245 (0.395-3.924)	0.708
Cystic LN				
No	Reference		Reference	
Yes	0.622 (0.177-2.185)	0.459	0.795 (0.215-2.937)	0.730

CCRT = concurrent chemoradiotherapy; ENE = extranodal extension; HR = hazard ratio; LN = lymph node; UFND = upfront neck dissection.

Table 5

Factors associated with overall survival by univariate Cox proportional hazard model before and after matching by propensity analysis

	Before propensity score matching		After propensity score matching	
	Univariate		Univariate	
Variables	HR (95% CI)	*p*	HR (95% CI)	*p*
Clinical T stage				
T1-T2	Reference		Reference	
T3-T4	1.241 (0.563-2.737)	0.592	43.989 (2.751-703.395)	0.007
Clinical N stage				
N1-N2a	Reference		Reference	
N2b-N3	1.764 (0.607-5.120)	0.297	1.448 (0.324-6.471)	0.628
Overall staging				
3	Reference		Reference	
4	0.935 (0.322-2.714)	0.902	0.590 (0.132-2.637)	0.489
Treatment group				
CCRT	Reference		Reference	
UFND	0.776 (0.337-1.785)	0.550	0.705 (0.244-2.033)	0.517
Primary tumor excision				
No	Reference		Reference	
Yes	0.490 (0.197-1.221)	0.126	0.552 (0.185-1.647)	0.287
ENE upon image				
No	Reference		Reference	
Yes	2.093 (0.967-4.532)	0.061	1.358 (0.455-4.054)	0.584
Necrotic LN				
No	Reference		Reference	
Yes	1.139 (0.523-2.480)	0.744	1.198 (0.415-3.453)	0.738
Cystic LN				
No	Reference		Reference	
Yes	0.641 (0.241-1.700)	0.371	0.961 (0.301-3.066)	0.947

CCRT = concurrent chemoradiotherapy; ENE = extranodal extension; HR = hazard ratio; LN = lymph node; UFND = upfront neck dissection.

In the future, larger series of assessments and systematic validations should be considered to further investigate the role of UFND in different subgroups with poorer prognostic factors of the neck, such as ENE and higher lymph node density. It is important to acknowledge that our study has some limitations, including its retrospective design and limited number of cases. The limited number of cases is attributed to the fact that only patients with p16-negative cN+ lesions were included. Additionally, ND tended to be performed with the excision of the primary tumor in clinical practice, resulting in ND being performed more frequently in operable tumors. As a result, the T and N stages would be earlier in the UFND group than in the CCRT group.

In conclusion, our retrospective review with a propensity score-matched analysis found that UFND reduces regional recurrence in patients with p16-negative cN+ OPSCC. Furthermore, this treatment modality could achieve comparable oncological outcomes with significantly reduced doses of radiotherapy and result in a definitive pathologic diagnosis. Although there were no significant differences in long-term dependence on feeding or tracheostomy tube between the CCRT group and UFND group, patients in the CCRT group exhibited a significantly higher risk of mortality due to pneumonia. These findings can help devise a suitable treatment plan when encountering p16-negative OPSCC and highlight the difference in treatment between p16-negative and p16-positive OPSCC.

ACKNOWLEDGMENTS

This work received financial support from the Taipei Veterans General Hospital (V109C-184).

REFERENCES

1. Chen AY, Zhu J, Fedewa S. Temporal trends in oropharyngeal cancer treatment and survival: 1998–2009. *Laryngoscope* 2014;124:131–8.
2. Reuschenbach M, Tinhofer I, Wittekindt C, Wagner S, Klussmann JP. A systematic review of the HPV-attributable fraction of oropharyngeal squamous cell carcinomas in Germany. *Cancer Med* 2019;8:1908–18.
3. Windon MJ, D'Souza G, Rettig EM, Westra WH, van Zante A, Wang SJ, et al. Increasing prevalence of human papillomavirus–positive oropharyngeal cancers among older adults. *Cancer* 2018;124:2993–9.
4. Lassen P, Primdahl H, Johansen J, Kristensen CA, Andersen E, Andersen LJ, et al; Danish Head and Neck Cancer Group (DAHANCA). Impact of HPV-associated p16-expression on radiotherapy outcome in advanced oropharynx and non-oropharynx cancer. *Radiother Oncol* 2014;113:310–6.
5. Chen WY, Chen TC, Lai SF, Liang TH, Huang BS, Wang CW. Outcome of bimodality definitive chemoradiation does not differ from that of trimodality upfront neck dissection followed by adjuvant treatment for >6 cm lymph node (N3) head and neck cancer. *PLoS One* 2019;14:e0225962.
6. Elicin O, Albrecht T, Haynes AG, Bojaxhiu B, Nisa L, Caversaccio M, et al. Outcomes in advanced head and neck cancer treated with up-front neck dissection prior to (chemo)radiotherapy. *Otolaryngol Head Neck Surg* 2016;154:300–8.
7. Elicin O, Nisa L, Dal Pra A, Bojaxhiu B, Caversaccio M, Schmucking M, et al. Up-front neck dissection followed by definitive (chemo)-radiotherapy in head and neck squamous cell carcinoma: rationale, complications, toxicity rates, and oncological outcomes—a systematic review. *Radiother Oncol* 2016;119:185–93.
8. Goldenberg D, Begum S, Westra WH, Khan Z, Sciubba J, Pai SI, et al. Cystic lymph node metastasis in patients with head and neck cancer: an HPV-associated phenomenon. *Head Neck* 2008;30:898–903.
9. Nordsmark M, Bentzen SM, Rudat V, Brizel D, Lartigau E, Stadler P, et al. Prognostic value of tumor oxygenation in 397 head and neck tumors after primary radiation therapy. An international multi-center study. *Radiother Oncol* 2005;77:18–24.

10. Carinci F, Cassano L, Farina A, Pelucchi S, Calearo C, Modugno V, et al. Unresectable primary tumor of head and neck: does neck dissection combined with chemoradiotherapy improve survival? *J Craniofac Surg* 2001;12:438–43.
11. D'Cruz AK, Pantvaidya GH, Agarwal JP, Chaukar DA, Pathak KA, Deshpande MS, et al. Split therapy: planned neck dissection followed by definitive radiotherapy for a T1, T2 pharyngolaryngeal primary cancer with operable N2, N3 nodal metastases—a prospective study. *J Surg Oncol* 2006;93:56–61.
12. Sato MP, Otsuki N, Kitano M, Ishikawa K, Tanaka K, Kimura T, et al. Up-front neck dissection followed by chemoradiotherapy for T1-T3 hypopharyngeal cancer with advanced nodal involvement. *Head Neck* 2021;43:3810–9.
13. Sakashita T, Homma A, Hayashi R, Kawabata K, Yoshino K, Iwae S, et al. The role of initial neck dissection for patients with node-positive oropharyngeal squamous cell carcinomas. *Oral Oncol* 2014;50:657–61.
14. Van Abel KM, Moore EJ. Focus issue: neck dissection for oropharyngeal squamous cell carcinoma. *ISRN Surg* 2012;2012:547017.
15. Paximadis PA, Christensen ME, Dyson G, Kamdar DP, Sukari A, Lin HS, et al. Up-front neck dissection followed by concurrent chemoradiation in patients with regionally advanced head and neck cancer. *Head Neck* 2012;34:1798–803.
16. Pedro C, Mira B, Silva P, Netto E, Pocinho R, Mota A, et al. Surgery vs. primary radiotherapy in early-stage oropharyngeal cancer. *Clin Transl Radiat Oncol* 2017;9:18–22.
17. Kelly JR, Park HS, An Y, Yarbrough WG, Contessa JN, Decker R, et al. Upfront surgery versus definitive chemoradiotherapy in patients with human papillomavirus-associated oropharyngeal squamous cell cancer. *Oral Oncol* 2018;79:64–70.
18. Zenga J, Jackson RS, Graboyes EM, Sinha P, Lindberg M, Martin EJ, et al. Oncologic outcomes of selective neck dissection in HPV-related oropharyngeal squamous cell carcinoma. *Laryngoscope* 2017;127:623–30.
19. Sanford NN, Hwang WL, Pike LRG, Lam AC, Royce TJ, Mahal BA. Trimodality therapy for HPV-positive oropharyngeal cancer: a population-based study: trimodality therapy for HPV+ OPC. *Oral Oncol* 2019;98:28–34.
20. Laverick S, Lowe D, Brown JS, Vaughan ED, Rogers SN. The impact of neck dissection on health-related quality of life. *Arch Otolaryngol Head Neck Surg* 2004;130:149–54.
21. Donatelli-Lassig AA, Duffy SA, Fowler KE, Ronis DL, Chepeha DB, Terrell JE. The effect of neck dissection on quality of life after chemoradiation. *Otolaryngol Head Neck Surg* 2008;139:511–8.
22. Lango MN, Egleston B, Ende K, Feigenberg S, D'Ambrosio DJ, Cohen RB, et al. Impact of neck dissection on long-term feeding tube dependence in patients with head and neck cancer treated with primary radiation or chemoradiation. *Head Neck* 2010;32:341–7.
23. Mortensen HR, Jensen K, Aksglaede K, Behrens M, Grau C. Late dysphagia after IMRT for head and neck cancer and correlation with dose-volume parameters. *Radiother Oncol* 2013;107:288–94.
24. Jensen K, Lambertsen K, Grau C. Late swallowing dysfunction and dysphagia after radiotherapy for pharynx cancer: frequency, intensity and correlation with dose and volume parameters. *Radiother Oncol* 2007;85:74–82.
25. Johnson JT, Myers EN, Bedetti CD, Barnes EL, Schramm VL, Jr, Thearle PB. Cervical lymph node metastases. Incidence and implications of extracapsular carcinoma. *Arch Otolaryngol* 1985;111:534–7.
26. Myers JN, Greenberg JS, Mo V, Roberts D. Extracapsular spread. A significant predictor of treatment failure in patients with squamous cell carcinoma of the tongue. *Cancer* 2001;92:3030–6.
27. Mermod M, Tolstonog G, Simon C, Monnier Y. Extracapsular spread in head and neck squamous cell carcinoma: a systematic review and meta-analysis. *Oral Oncol* 2016;62:60–71.
28. Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). *Head Neck* 2005;27:843–50.
29. Cooper JS, Zhang Q, Pajak TF, Forastiere AA, Jacobs J, Saxman SB, et al. Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys* 2012;84:1198–205.
30. Sher DJ, Adelstein DJ, Bajaj GK, Brizel DM, Cohen EEW, Halthore A, et al. Radiation therapy for oropharyngeal squamous cell carcinoma: executive summary of an ASTRO evidence-based clinical practice guideline. *Pract Radiat Oncol* 2017;7:246–53.
31. Stenson KM, Haraf DJ, Pelzer H, Recant W, Kies MS, Weichselbaum RR, et al. The role of cervical lymphadenectomy after aggressive concomitant chemoradiotherapy: the feasibility of selective neck dissection. *Arch Otolaryngol Head Neck Surg* 2000;126:950–6.
32. Wolf GT, Fisher SG. Effectiveness of salvage neck dissection for advanced regional metastases when induction chemotherapy and radiation are used for organ preservation. *Laryngoscope* 1992;102:934–9.
33. Clayman GL, Johnson CJ, 2nd, Morrison W, Ginsberg L, Lippman SM. The role of neck dissection after chemoradiotherapy for oropharyngeal cancer with advanced nodal disease. *Arch Otolaryngol Head Neck Surg* 2001;127:135–9.
34. Goenka A, Morris LG, Rao SS, Wolden SL, Wong RJ, Kraus DH, et al. Long-term regional control in the observed neck following definitive chemoradiation for node-positive oropharyngeal squamous cell cancer. *Int J Cancer* 2013;133:1214–21.
35. Steinbichler TB, Golm L, Dejaco D, Riedl D, Kofler B, Url C, et al. Surgical rescue for persistent head and neck cancer after first-line treatment. *Eur Arch Otorhinolaryngol* 2020;277:1437–48.
36. Davidson BJ, Newkirk KA, Harter KW, Picken CA, Cullen KJ, Sessions RB. Complications from planned, posttreatment neck dissections. *Arch Otolaryngol Head Neck Surg* 1999;125:401–5.
37. Slijepcevic AA, Roh J, Pipkorn P, Lipsey K, Bradley JP. Carotid blowout syndrome in head and neck cancer patients: management of patients at risk for CBS. *Laryngoscope* 2023;133:576–87.
38. Liu XK, Li Q, Zhang Q, Su Y, Shi YX, Li H, et al. Planned neck dissection before combined chemoradiation in organ preservation protocol for N2-N3 of supraglottic or hypopharyngeal carcinoma. *ORL J Otorhinolaryngol Relat Spec* 2012;74:64–9.
39. Peters LJ, Weber RS, Morrison WH, Byers RM, Garden AS, Goepfert H. Neck surgery in patients with primary oropharyngeal cancer treated by radiotherapy. *Head Neck* 1996;18:552–9.