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Value of two-cycle docetaxel, cisplatin, and 5-fluorouracil induction chemotherapy in hypopharyngeal carcinoma

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Various studies have investigated laryngeal function and survival after induction chemotherapy in hypopharyngeal carcinoma, but potential factors to help predict response rates after induction chemotherapy remain unknown. This retrospective study evaluated which factors are related to an ineffective response to two-cycle docetaxel, cisplatin, and 5-fluorouracil (TPF) induction chemotherapy in hypopharyngeal carcinoma to determine potential candidates for this treatment in clinical practice. From Jan 2005 to Dec 2015, 81 patients diagnosed with hypopharyngeal squamous cell carcinoma based on a pathological examination were analyzed. They were administered two-cycle TPF induction chemotherapy, and magnetic resonance imaging was performed before and after induction chemotherapy. The mean survival time was 5.7 years (95% confidence interval, 5.1–6.2 years). The 1, 3, 5 and 6-year survival rates were 98.8%, 80.1%, 64.5%, and 54.2%, respectively. TPF induction chemotherapy was well tolerated; the main adverse effects resolved with symptomatic treatment. A response to TPF induction chemotherapy was associated with lymph node size, tumor grade, invasion region, T stage, and primary tumor. The following issues were significantly associated with an increasing non-response rate to two-cycle induction chemotherapy: increasing lymph node size, moderately differentiated squamous cell carcinoma, invasion of the esophagus along with the thyroid cartilage, and primary tumor in the piriform sinus. Lymph nodes of ≥2.15 cm, moderately differentiated tumor grade, or thyroid cartilage invasion were the best cutoff values for patients who did not respond to induction chemotherapy. However, the initial cancer site, cancer stage, and degree of cancer differentiation were not closely related to the efficacy of induction chemotherapy.

Key words: hypopharyngeal carcinoma, induction chemotherapy, effectiveness, prediction

Cancer of the hypopharynx is rare and accounts for 3% to 5% of the malignancies in the upper aerodigestive tract; early diagnosis of hypopharyngeal cancer seldom occurs, as patients usually present late, with some studies reporting that 50% of patients already have neck lymph node metastases; 60–80% of these patients have ipsilateral lymph node metastases, and ≤40% of these patients have contralateral occult lymph node tumor deposits [1–3]. Unfortunately, patients with early-stage hypopharyngeal carcinoma are usually asymptomatic, and significant neck lymph node and distant metastases are not easily palpated upon physical examination, because no physical barrier exists to prevent the cancer from disseminating into soft neck tissues [4]. In fact, when patients develop pain, pharyngeal obstructions, and neck lymph node metastases, the hypopharyngeal cancer is often at a late stage [5]. Thus, most patients with hypopharyngeal cancer have a poor prognosis and low survival rate [4].

Submucosal invasion and neck lymph node metastasis are two characteristics of hypopharyngeal cancer. Given these two major characteristics, surgery and postoperative radiotherapy have been recommended as a standard therapy for hypopharyngeal cancer [6]. However, if focal invasion is evident in hypopharyngeal cancer, surgery is conducted at the expense of laryngeal function. In this scenario, patients have a 5-year survival rate of 18–50% [7–9].

According to the National Comprehensive Cancer Network (NCCN) guidelines, to help preserve laryngeal function, docetaxel, cisplatin, and 5-fluorouracil (TPF) induction chemotherapy is one of the recommended treatment options for locally advanced hypopharyngeal cancer in patients who have T2-3, any N, or T1/N+ disease [10]. For patients who have a complete response and stable or improved disease in the neck secondary to induction chemotherapy, non-surgical treatment could be considered,

including combined systemic chemotherapy and radiation therapy [10]. If patients do not achieve a partial response, NCCN guidelines recommend surgery [10]. However, we believe that physicians cannot determine whether a patient will be sensitive to induction chemotherapy or experience a partial response or better prior to treating a patient with induction chemotherapy.

Physicians treat patients with induction chemotherapy combined with radiotherapy for late-stage head and neck cancer because induction chemotherapy may reduce the tumor size and increase survival rates, help preserve pharyngeal function and have prognostic value [11]. To date, the efficacy of induction chemotherapy has varied among studies, and about 10–40% of patients are non-responsive to induction chemotherapy [5,12,13]. We believe one risk of administering induction chemotherapy is that if patients have an ineffective response to induction chemotherapy, they would unnecessarily experience the side effects of chemotherapy and could lose their best opportunity for surgery. However, the benefit of induction chemotherapy is that patients who experience a good response to induction chemotherapy may preserve their laryngeal function and have improved survival outcomes [14].

In our hospital, induction chemotherapy with a two-course TPF regimen has been used to treat patients with late-stage hypopharyngeal cancer since 2005. We use a two-cycle TPF regimen because in our experience patients demonstrated a better tolerance and clear or specific responses to two-cycle TPF induction chemotherapy. If patients experience a bad response to two cycles of induction chemotherapy, they usually experience a bad response to a third cycle, in our experience. However, we have also seen that the physical body of patients becomes weak after three cycles of induction chemotherapy, ultimately affecting subsequent surgical treatment. For patients achieving favorable efficacy after induction chemotherapy, we treat them with radiotherapy combined with chemotherapy. Conversely, for patients who are non-responsive to induction chemotherapy, we recommend surgical resection combined with postoperative radiotherapy.

The purpose of our study was to ascertain which factors are related to an ineffective response to two-cycle TPF induction chemotherapy to help determine which patients with hypopharyngeal carcinoma may or may not be candidates.

Patients and methods

Patients and inclusion and exclusion criteria. This study was approved by the institutional review board of Guangdong General Hospital. Because of the retrospective nature of the study, the requirement of informed patient consent was waived. A total of 92 patients who were administered induction chemotherapy were studied; 81 were included in the analysis. The remaining 11 patients did not meet the inclusion criteria and were excluded. Of these 11 patients, six patients did not have complete data from their imaging examinations, and five patients were administered only one course of induction chemotherapy.

The inclusion criteria for this study were as follows. First, patients were diagnosed with hypopharyngeal cancer using a pathological or cytological examination such as fibrolaryngoscopy, lymph node biopsy, or other examinations. Second, magnetic resonance imaging (MRI) indicated objective and measurable lesions, and the maximal diameter could be measured. Third, the Karnofsky score was >70. Lastly, patients could not have any contradictions to surgery or chemotherapy after obtaining liver and kidney function tests, routine blood tests, and electrocardiography.

Patients were excluded from this study if any of the following conditions were met: incomplete data from imaging examinations after patients were administered two-cycle TPF induction chemotherapy, and if the patients had poor treatment compliance or were lost to follow-up after only one cycle of induction chemotherapy.

Therapeutic regimen and efficacy evaluation. Of the 81 patients, the majority was diagnosed with late-stage hypopharyngeal cancer; only two patients who asked to undergo surgical treatment had stage II hypopharyngeal cancer. All patients were administered TPF induction chemotherapy: docetaxel (75 mg/m^2), cisplatin (75 mg/m^2; d1), and fluorouracil (750 mg/m^2; d1–d5). During chemotherapy, antiemetic therapy, hydration therapy, and intravenous dexamethasone infusion (5 mg) were administered, accompanied by a normal saline infusion (2000 ml) to reduce vascular responses. Induction chemotherapy was administered, and one cycle was administered for 21 days; each patient was administered two cycles of induction chemotherapy. Routine blood tests were performed once or twice weekly, including liver and kidney function tests and blood electrolyte and glucose levels. Lymph node measurements were performed based on the RECIST measurement method. Three physicians measured the maximum diameter of the solid portion of the lymph nodes on MRI cross-sections, and the means were calculated.

Evaluation of the therapeutic efficacy was based on WHO criteria for measurable lesions. After two-cycle induction chemotherapy, imaging examinations were performed to evaluate therapeutic efficacy. The following definitions were used to assess therapeutic efficacy: complete remission (CR), complete absence of cancer upon clinical examination; partial remission (PR), the product of the maximal diameter and vertical diameter was reduced by >50%; stable disease (SDz), the product of the maximal diameter and vertical diameter was reduced by <50% or had increased by <25%; and progressive disease (PD), the product of the maximal diameter and vertical diameter had increased by >25%. In this study, effectiveness was defined if CR or PR was present; ineffectiveness was defined if SDz or PD was observed.

For patients responsive to induction chemotherapy, radiotherapy and chemotherapy were administered during the

same period, and salvage surgery was performed if residual cancer was observed 6 months after the termination of therapy. For patients who were non-responsive to induction chemotherapy, surgery was performed, followed by postoperative radiotherapy.

Observation index. The clinical characteristics of patients achieving a therapeutic response and no response were analyzed, including gender, age, initial site of hypopharyngeal cancer (the sinus piriformis, posterior hypopharyngeal wall, and postcricoid), tumor stage, degree of tumor differentiation, distal metastasis, neck lymph node size, and site of tumor invasion (the esophagus, tongue base, and thyroid cartilage). These characteristics were analyzed to explore the relationship among these factors with the efficacy of induction chemotherapy.

Statistical analysis. Patient demographic and clinical characteristics are summarized as means ± standard deviation (SD) for age and lymph node size and n (%) for categorical variables such as total and post-induction chemotherapy response. An univariate analysis was performed using a binary logistic regression analysis and is presented as an odds ratio (OR) with corresponding 95% confidence intervals (95%CI) and P value. Variables with a significance level of <0.1 in the univariate analysis were selected and then assessed in a multivariate logistic analysis using a backward selection method. Furthermore, a receiver operating characteristic (ROC) curve analysis was performed to identify pre-diagnostic performance for those variables significantly associated with a response in the multivariate logistic regression model. Results are represented by an ROC curve and area under the ROC curve (AUC) with 95% CIs and P values. Kaplan-Miere survival curves including all patients in this study were created, and survival times were assessed.

The best cutoff value for patient responses to induction chemotherapy (PD and SDz) was derived according to the maximization of the Yunden index (= sensitivity + specificity – 1). Diagnostic performance for sensitivity and specificity was calculated using the corresponding best cutoff value. McNemar's test was also applied for identifying the significance of diagnostic performance. All statistical assessments were two-tailed and considered significant with a p-value of <0.05. All statistical analyses were performed using SPSS (released 2008; SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc).

Results

General characteristics. In this retrospective study, a total of 81 patients with hypopharyngeal cancer were administered induction chemotherapy. One woman and 80 men were included in the analysis. Their ages ranged from 40 to 78 years, with a mean age of 57.72 years (SD = 9.98). Patient demographic and clinical characteristics are summarized in Table 1. For these patients, the main clinical manifestations included pharyngeal foreign body sensation, neck mass, bloody sputum, difficulty swallowing, hoarseness, and dyspnea.

Imaging examinations were performed before and after induction chemotherapy. The patients had the following tumor grades: well-differentiated squamous cell carcinoma (28 patients), moderately differentiated squamous cell carcinoma (43 patients), and poorly differentiated squamous cell carcinoma (10 patients) (Table 1). According to the TNM staging system by the Union for International Cancer Control (UICC2002), our patients had the following cancer stages: stage II, two patients; stage III, five patients; and stage IV, 74 patients (Table 1).

Treatment response. Among the 81 patients, 38 patients experienced a therapeutic response (CR and PR), and 43 were considered non-responsive (PD and SDz). The univariate analysis results for post-induction chemotherapy response while considering patient demographic and clinical characteristics are shown in Table 1. The univariate analysis showed that lymph node size, moderately differentiated tumor grade, invasion such as thyroid cartilage invasion and invasion of both the esophagus and thyroid cartilage, T3 + T4 stage, N3 stage, and primary tumor including piriform sinus and postcricoid region were associated with a posttreatment response to induction chemotherapy.

Variables with a significance level of <0.10 were selected and assessed in a multivariate analysis using a backward selection method as shown in Table 2. In the multivariate analysis, model, age, lymph node size, tumor grade, invasion region, and primary tumor were retained. This analysis revealed that patients with an increasing lymph node size, moderately differentiated squamous cell carcinoma, invasion of both the esophagus and thyroid cartilage, and primary tumor in the piriform sinus were significantly associated with increasing non-response rates (OR = 1.729, 4.373, 5.881, and 9.223, respectively; all p≤0.026) (Table 2).

The four above mentioned clinical characteristics (an increasing lymph node size, moderately differentiated squamous cell carcinoma, invasion of both the esophagus and thyroid cartilage, and primary tumor in the piriform sinus) that were associated with posttreatment response to induction chemotherapy were also assessed in a ROC curve analysis to identify pre-diagnostic performance or the factors most associated with posttreatment responses, CR/PR versus non-response, and PD/SDz to induction chemotherapy. The ROC curve analysis revealed that lymph node size, tumor grade, and invasion region were significant for determining responses prior to administering induction chemotherapy regarding the patients' post-induction chemotherapy response (Table 3; Figure 1).

MRI was used to assess response to induction chemotherapy in this study. MRI scans were obtained before and after induction chemotherapy, and MRI scans from two representative cases are shown in Figure 2A–D.

The Yunden index helped to demonstrate the best cutoff values for patients who did not have a response to two-cycle

Table 1. Patient demographic and clinical characteristics and univariate analysis of posttreatment response (n=81).

Variables	Total (n=81)	PD + SDz (n=43)	CR + PR (n=38)	OR (95% CI)	p-value
Age, y	57.72 ± 9.98	55.72±9.28	59.97±10.38	0.956 (0.913–1.002)	0.059
Gender					N/A
Male	80 (98.8)	42 (52.25)	38 (47.5)		
Female	1 (1.2)	1 (100)	0 (0)		
Lymph node size (cm)	2.51 ± 1.72	3.15±1.90	1.79±1.11	1.831 (1.272–2.637)	0.001*
Tumor grade					
Well differentiated	28 (34.6)	9 (32.1)	19 (67.9)	1	
Moderately differentiated	43 (53.1)	28 (65.1)	15 (34.9)	3.941 (1.434–10.832)	0.008*
Poorly differentiated	10 (12.3)	6 (60.0)	4 (40.0)	3.167 (0.711–14.096)	0.130
Invasion region					
No invasion	26 (32.1)	8 (30.8)	18 (69.2)	1	
Thyroid cartilage	24 (29.6)	15 (62.5)	9 (37.5)	3.750 (1.160–12.122)	0.027*
Esophagus with thyroid cartilage	31 (38.3)	20 (64.5)	11 (35.5)	4.091 (1.347–12.429)	0.013*
Distant metastasis					
No	73 (90.1)	37 (50.7)	36 (49.3)	1	
Yes	8 (9.9)	6 (75)	2 (25)	2.919 (0.552–15.425)	0.207
Clinical stage					
II	2 (2.5)	1 (50)	1 (50)	1	
III	5 (6.2)	2 (40)	3 (60)	0.667 (0.025–18.059)	0.810
IV	74(91.4)	40 (54.1)	34 (45.9)	1.176 (0.071–19.527)	0.910
T stage					
T1+T2	41 (50.6)	14 (34.1)	27 (85.9)	1	
T3+T4	40 (49.4)	29 (72.5)	11 (27.5)	5.084 (1.917–13.118)	0.001*
N stage					
N0-1	23 (28.4)	8 (18.6)	15 (39.5)	1	
N2a/2b	51 (63.0)	29 (67.4)	22 (57.9)	2.472 (0.890, 6.864)	0.083
N3	7 (8.6)	6 (14.0)	1 (2.6)	11.250 (1.146, 110.46)	0.038*
Primary tumor					
Piriform sinus	63 (77.8)	36 (57.1)	27 (42.9)	4.444 (1.114–17.725)	0.035*
Posterior hypopharynx	13 (16.0)	3 (23.1)	10 (76.9)	1	
Postcricoid region	5 (6.2)	4 (80)	1 (20)	13.333 (1.048–169.56)	0.046*

Data are summarized as mean ± SD for age and lymph node size and n (%) for categorical variables for total and posttreatment response status. An univariate analysis was performed using a binary logistic regression analysis and is represented with an odds ratio (OR) and corresponding 95% confidence interval (CI) and p-value. PD, progressive disease; SDz, stable disease; CR, complete remission; PR, partial remission; *p<0.05, indicates significantly associated with posttreatment response.

induction chemotherapy (PD/or SDz), including lymph nodes of ≥2.15 cm, moderately differentiated tumor grade, or thyroid cartilage invasion. The corresponding sensitivity and specificity based on the cutoff values were as follows: lymph node size, 76.70% and 73.00%, respectively; tumor grade, 79.10% and 50.00%, respectively; and invasion region, 81.40% and 47.40%, respectively (Table 3). The McNemar test indicated that lymph node or tumor grade (both p>0.05) might not be relevant factors to determine which patients may benefit from induction chemotherapy prior to treatment when applying the best cutoff values for diagnosis (Table 3).

A survival curve was created from the time of treatment to December 2015 for all 81 patients included in this study who were administered induction chemotherapy (Figure 3). Their mean survival time was 5.7 years, with a 95% CI of 5.1 to 6.2 years. More than 50% of the patients were alive during follow-up. The 1, 3, 5 and 6-year survival rates were 98.8%, 80.1%, 64.5%, and 54.2%, respectively.

A summary of adverse events related to two-cycle TPF induction chemotherapy is shown in Table 4. The most common adverse events included gastrointestinal events such as nausea and vomiting, transient myelosuppression, and alopecia. None of the patients experienced a loss of taste. Further, none of the patients experienced intolerance to the two-cycle induction chemotherapy, and the treatment was well tolerated. The main adverse effects resolved with symptomatic treatment.

Discussion

In this retrospective study, we studied patients who underwent two-cycle TPF induction chemotherapy to determine which factors are associated with a response or no response to induction chemotherapy, so patients can avoid unnecessary induction chemotherapy if they would not benefit from it. A lack of response to induction chemotherapy was associated with an increased lymph node size, moderately differentiated squamous cell carcinoma, invasion of both the esophagus and thyroid cartilage, and primary tumor in the piriform sinus. Further, this study demonstrates that the best cutoff values for induction chemotherapy in patients who had a posttreatment non-response included a lymph node size of ≥2.15 cm, moderately differentiated tumor grade, or invasion of the thyroid cartilage. In our analysis, the corresponding sensitivity and specificity were 76.7% and 73%, respectively, for lymph node size; 79.1% and 50%, respectively, for tumor grade; and 81.4% and 47.4%, respectively, for invasion region.

Considering all head and neck squamous cell carcinomas, hypopharyngeal cancer is highly malignant. Hypopharyngeal cancer has often progressed by the time of initial diagnosis, and thus, a total or partial laryngectomy or total hypopharyngeal resection combined with neck lymphadenectomy is warranted. Therefore, most patients will permanently

Table 2. Multivariate logistic regression analysis of posttreatment response.

Variables	OR (95%CI)	p-value
Age, y	0.943 (0.886–1.003)	0.064
Lymph node size (cm)	1.729 (1.153–2.593)	0.008*
Tumor grade		
Well differentiated	1	
Moderately differentiated	4.373 (1.193–16.025)	0.026*
Poorly differentiated	1.516 (0.219–0.473)	0.673
Invasion region		
No invasion	1	
Thyroid cartilage	2.882 (0.657–12.646)	0.161
Esophagus with thyroid cartilage	5.881 (1.373–25.200)	0.017*
Primary tumor		
Piriform sinus	9.223 (1.776–47.880)	0.008*
Posterior hypopharynx	1	
Postcricoid region	15.726 (0.758–326.203)	0.075

Variables with a significance level of <0.1 in the univariate analysis were selected and assessed in a multivariate analysis using a backward selection method. OR, odds ratio; 95%CI, 95% confidence interval. *p<0.05.

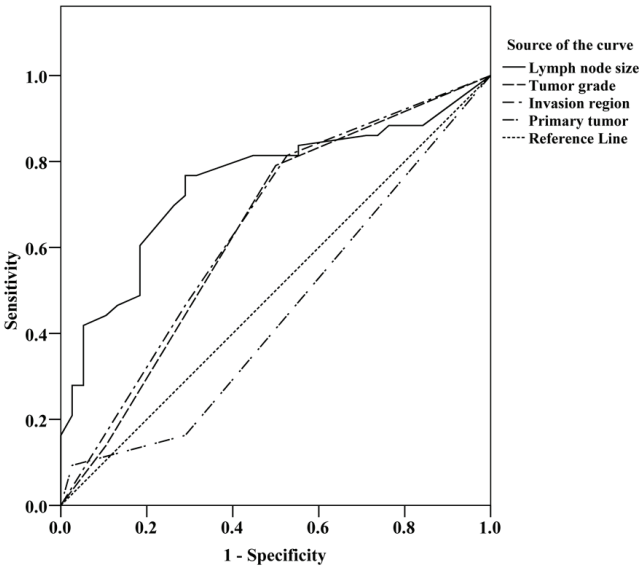

Figure 1. ROC of lymph node size, tumor grade, invasion region, and primary tumor to identify non-response.

Table 3. Summary of the ROC curve analysis and pre-diagnostic performance.

Variables	ROC curve analysis		Pre-diagnostic performance			
	AUC (95%CI)	p-value	Best cutoff	Sensitivity	Specificity	McNemar test p-value
Lymph node size	0.750 (0.641 to 0.859)	<0.001	≥2.15 cm	76.70%	73.00%	1
Tumor grade	0.639 (0.516 to 0.762)	0.032	Moderately differentiated	79.10%	50.00%	0.087
Invasion region	0.648 (0.527 to 0.770)	0.022	Thyroid cartilage invasion	81.40%	47.40%	0.036
Primary site	0.448 (0.321 to 0.575)	0.421	–			

AUC, area under the receiver operating curve (ROC); 95%CI, 95% confidence interval.

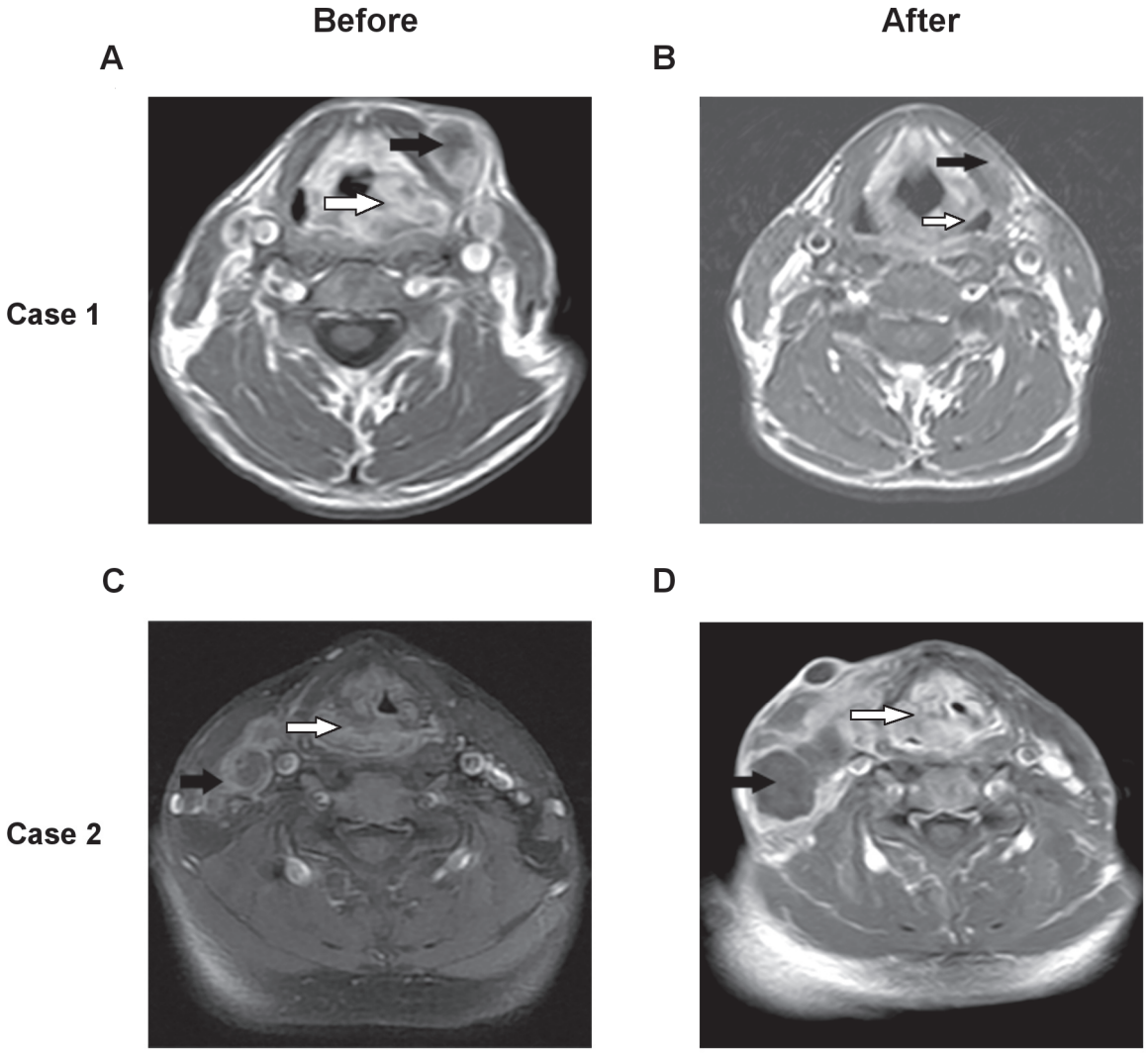

Figure 2. MRI scans were obtained before and after induction chemotherapy; images from two cases are shown. (A) Case 1: Before induction chemotherapy. The primary tumor is marked by a white arrow, and metastasis to a lymph node in the neck is marked by a black arrow. (B) Case 1: After induction chemotherapy. The primary tumor is marked by a white arrow, and metastasis to a lymph node in the neck is marked by a black arrow. Both, the primary and metastatic tumors were significantly reduced after induction chemotherapy. (C) Case 2: Before induction chemotherapy. The primary tumor is marked by a white arrow, and metastasis to a lymph node in the neck is marked by a black arrow. (D) Case 2: After induction chemotherapy. The primary tumor is marked by a white arrow, and metastasis to a lymph node in the neck is marked by a black arrow. Both, the primary and metastatic tumors had increased in size after induction chemotherapy.

lose their laryngeal function. Cisplatin and fluorouracil (PF) induction chemotherapy has been used in neck and head cancer since the 1980s and has significantly changed this condition [15, 16]. To that end, PF induction chemotherapy has been demonstrated to have a significant survival benefit and has helped with the preservation of laryngeal function when administered before radiotherapy [17]. More recently, TPF has been demonstrated to be superior to PF; in fact, patients who were administered TPF experienced significantly greater laryngeal preservation and laryngectomy-free survival than those administered PF induction chemotherapy [18–20]. Therefore, TPF induction chemotherapy is the gold standard of induction chemotherapy in this cancer type [20]. Studies have shown that patients who are responsive to induction chemotherapy are sensitive to radiotherapy [21]. Thus, induction chemotherapy may help physicians screen for patients with hypopharyngeal cancer who are sensitive to chemotherapy and for whom radiotherapy could be used to preserve laryngeal function and help induce remission.

Two-cycle induction chemotherapy has become a recommended therapy for progressive hypopharyngeal cancer as it could decrease tumor burden, improve tumor-associated

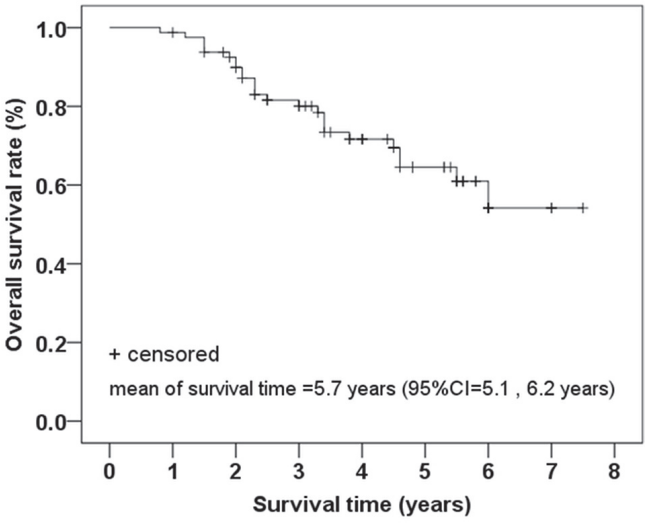

Figure 3. A survival curve for 81 patients who were all administered two-cycle TPF induction chemotherapy. The survival time was calculated from the time of treatment to the end in December 2015.

Table 4. Posttreatment adverse events.

Adverse events	WHO grade			
	0	1	2	3
Lymphopenia	30 (37)	20 (24.7)	26 (32.1)	5 (6.2)
Erythrocytopenia	45 (55.6)	28 (34.6)	8 (9.9)	–
Thrombocytopenia	58 (71.6)	19 (23.5)	4 (4.9)	–
Nausea and vomiting	1 (1.2)	13 (16)	61 (75.3)	6 (7.4)
Diarrhea	57 (70.4)	22 (27.2)	2 (2.5)	–
ALT	54 (66.7)	8 (9.9)	19 (23.5)	–
BUN	66 (81.5)	15 (18.5)	–	–
Higher creatinine level	73 (90.1)	7 (8.6)	1 (1.2)	–
Drug fever	66 (81.5)	15 (18.5)	–	–
Hypersensitivity	76 (93.8)	5 (6.2)	–	–
Alopecia	4 (4.9)	49 (60.5)	28 (34.6)	–
Heart function	81 (100)	–	–	–
Nervous system	81 (100)	–	–	–

Data are summarized as n (%). BUN, blood urea nitrogen; ALT, alanine aminotransferase.

symptoms, and ameliorate surgical outcomes [22]. Further, TPF has been demonstrated to improve outcomes, as compared with PF alone, but more recent phase III studies did not show a benefit in survival when TPF induction was followed by chemotherapy and radiation, as compared with chemotherapy and radiation alone [6].

However, studies have revealed that two-cycle induction chemotherapy increases acute toxic effects in clinical practice [23]. Thus, some investigators have speculated whether induction chemotherapy helps preserve laryngeal function and whether it is safe and effective [3, 14, 24]. For patients responsive to induction chemotherapy, subsequent radiotherapy and chemotherapy may achieve a laryngeal function rate as high as 83.6%, with a 5-year survival rate of 54% that is similar to those experienced after traditional therapies [14]. In the present study comprising 81 patients, 38 patients experienced a CR plus PR, and 43 patients experienced a PR plus SDz (>50%). TPF regimen has demonstrated superior outcomes to a PF regimen regarding laryngeal function preservation [25].

Regarding therapeutic regimens, the GORTEC (Groupe Français d'Oncologie Radiothérapie Tête et Cou) study enrolled 213 patients with laryngeal or hypopharyngeal squamous cell carcinoma and demonstrated that patients administered TPF had an overall response rate of 80%, and those patients administered PF had an overall response rate of only 59.2%, with a 3-year laryngeal function preservation rate of 70.3% with TPF that was significantly higher than that achieved with PF (57.3%). However, the survival rate was comparable between the two regimens [3]. In fact, no survival benefit has been demonstrated between TPF and PF induction chemotherapy regimens followed by chemotherapy versus chemotherapy alone [6].

As for toxicity experienced with chemotherapy, patients can tolerate both TPF and PF; several phase III clinical trials have demonstrated manageable toxicity with TPF regimens [6]. Consequently, with a PF regimen and sequential chemotherapy and radiotherapy, less acute severe mucositis was seen, as compared with cisplatin and radiotherapy alone. However, TPF sequential therapy has been demonstrated to be well tolerated but has a higher hematologic adverse event rate than PF [26]. In this study, patients had good tolerance with the TPF regimen, and the main adverse effects were reversible and included gastrointestinal events, transient myelosuppression, and alopecia. These adverse effects resolved after symptomatic treatments were administered, and no patient was intolerant to two-cycle induction chemotherapy because of adverse effects. None of the patients experienced a loss of taste with two-cycle induction chemotherapy.

To our knowledge, no good index currently exists to predict the efficacy of induction chemotherapy. Some patients are insensitive to induction chemotherapy. Thus, induction chemotherapy may decrease their immunity, lessen their opportunity to obtain optimal therapy, and increase the economic burden. In this study, after clinical characteristics were assessed, we aimed to explore the factors affecting induction chemotherapy and screen clinical indicators that could be used to determine sensitivity to chemotherapy before treatment. This assessment could help guide clinical decision-making. The present study demonstrates that the efficacy of TPF induction chemotherapy is closely

related to neck lymph node size and site of cancer involvement in patients with hypopharyngeal cancer. If the neck lymph node was larger than 2.15 cm, the efficacy of induction chemotherapy was reduced (OR = 1.661). If the cancerous tumor had invaded the esophagus and thyroid cartilage, the risk of non-response to induction chemotherapy was 15.803-fold higher than that of patients without involvement of both sites. In a previous study, patients who were deemed suitable for induction treatment included patients with the following traits: a good performance status, no contraindications to taxanes or cisplatin, and locally advanced laryngeal, hypopharyngeal, or oropharyngeal cancer [26]. In addition, in the present study, the efficacy of induction chemotherapy had no relationship with cancer stage, age, initial site of cancer, or degree of cancer differentiation.

This study had some limitations. First, the sample size in this study was small, therefore additional study with a larger sample size is warranted in the future. This was only a preliminary study, so more studies with a larger sample size are required to confirm our findings and to explore more accurate indexes to predict the efficacy of induction chemotherapy. Given that different studies use varying definitions of laryngeal function preservation, it is difficult to directly compare results among studies [3]. Lastly, given the nature of retrospective studies, data were collected in past medical records, but these medical records were designed without the purpose of this particular study in mind; as such, data on potential confounding factors may be lacking. Therefore, future studies are necessary to further explore two-cycle induction chemotherapy in hypopharyngeal carcinoma.

Induction chemotherapy with a TPF regimen is clinically important for the non-surgical treatment of focal progressive hypopharyngeal cancer. This therapy may be safe and effective for the preservation of laryngeal function. However, the accurate use of a therapeutic protocol is important to reduce the potential for unnecessary side effects such as gastrointestinal reactions, hair loss, and bone marrow suppression that patients experience with induction chemotherapy, particularly if they are not candidates for induction chemotherapy. This study aimed to determine some prognostic factors that may help physicians determine which patients would benefit from induction chemotherapy prior to initiation. If patients are not candidates for induction therapy, they could avoid this treatment and have surgical management sooner when their tumors are smaller. In our study, some factors affecting the efficacy of induction chemotherapy were investigated, and the results revealed that surgery was the preferred therapy for patients with neck lymph nodes of >2.15 cm, thyroid cartilage invasion, and moderately differentiated tumor grade.

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