Original Article

The efficacy and safety of the addition of programmed cell death protein 1 inhibitor to preoperative chemotherapy in locoregionally advanced oropharyngeal carcinoma

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Background: Immune checkpoint inhibitors have shown promise in improving the survival rates for recurrent and/or metastatic head and neck cancers. However, their impact on curative outcomes in head and neck cancers remains undefined, especially for those with locoregionally advanced oropharyngeal carcinoma (LAOPC), a subtype of head-and-neck malignancy closely associated with human papillomavirus infection. This study aimed to clarify the efficacy and safety of the addition of programmed cell death protein 1 (PD-1) inhibitor into preoperative chemotherapy in LAOPC.

Methods: We retrospectively included patients with LAOPC who underwent preoperative immunochemotherapy between 2021 and 2024. Statistical analyses were conducted using chi-square tests. The efficacy was assessed using Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1). Safety was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) 5.0.

Results: A total of 23 patients were identified, and 11 (47.8%) had P16-positive tumors. There were 22 patients (95.7%) who completed two cycles of preoperative treatment. Among the 23 patients, the response to primary tumors and neck metastatic lymph nodes could be assessed in 21 and 22 patients, respectively. Additionally, 13 (61.9%) patients had a major pathologic response to the primary tumor, including 12 patients (57.1%) who achieved a pathologic complete response (PCR). In addition, 11 (50.0%) patients had a PCR in the metastatic cervical lymph nodes, while 11 (50.0%) patients still had residual tumors in the lymph nodes. The combined positive score and P16 status were not significantly associated with PCR to the primary tumor or neck metastatic lymph nodes. Moreover, 19 (82.6%) patients experienced treatment-related adverse effects, with the majority being grade 1–2 toxicities, and only 2 (8.7%) patients had grade 3 or higher toxicities. No treatment-related deaths occurred.

Conclusions: The incorporation of a PD-1 inhibitor into preoperative chemotherapy may be an effective approach for treating LAOPC and involve acceptable toxicity.

Keywords: Oropharyngeal carcinoma; immunotherapy; chemotherapy; response; surgery

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Introduction

Oropharyngeal squamous cell carcinoma is a subtype of head-and-neck malignancy closely associated with human papillomavirus (HPV) infection. In 2022, there were 106,313 new cases of oropharyngeal squamous cell carcinoma reported globally (1). Over 40% of patients are diagnosed with locally advanced disease, and the treatment for locoregionally advanced oropharyngeal carcinoma (LAOPC) is typically multimodal (2-4). For patients with LAOPC, the advent of robotic and minimally invasive surgical techniques has enabled surgery followed by postoperative adjuvant therapy to emerge as a viable alternative to concomitant chemoradiation. Approximately 30% of patients with LAOPC can achieve organ-sparing results following neoadjuvant chemotherapy. However, the efficacy of neoadjuvant therapy in attaining postoperative control and long-term survival in patients with LAOPC remains controversial (5,6), and tumor progression after comprehensive treatment has been observed in 42–67% of patients (7,8). Therefore, there is an urgent need to investigate combined treatment modalities that can reduce the incidence of posttreatment failure.

Patients with head-and-neck squamous cell carcinoma (HNSCC) may experience varying degrees of benefit from immunotherapy, which can be influenced by the genetic and cellular heterogeneity within the tumor microenvironment (9). The KEYNOTE-048 trial demonstrated that the programmed cell death protein 1 (PD-1) inhibitor pembrolizumab, with or without chemotherapy, provided a survival advantage over cetuximab chemotherapy in patients with recurrent and metastatic HNSCC (rmHNSCC) (10). In addition, studies on neoadjuvant immunotherapy in HNSCC have shown that combined chemotherapy and immunotherapy can improve tumor response rates from 30% to 67% (11-13). However, these studies included a limited number of patients with LAOPC. Earlier study on LAOPC has demonstrated that neoadjuvant chemotherapy alone achieves a pathologic complete response (PCR) rate of around 15% (14). A recent study involving 73 patients with HPV-positive LAOPC reported that neoadjuvant nivolumab plus chemotherapy achieved a deep response (50% tumor shrinkage) in 70.8% of evaluable patients (15). However, only 12.3% of these patients underwent surgical treatment, which complicates the accurate assessment of tumor response. In light of this, we conducted this real-world study to evaluate the efficacy and safety of preoperative immunochemotherapy followed by surgery for patients with LAOPC. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-2025-202/rc).

Highlight box

Key findings

- The incorporation of a programmed cell death protein 1 inhibitor into preoperative chemotherapy holds promise as an effective approach for treating locoregionally advanced oropharyngeal carcinoma (LAOPC) and has acceptable toxicity.

What is known and what is new?

- The limited enrollment of patients with LAOPC in clinical trials and the small number of these patients who have undergone surgical treatment following preoperative immunochemotherapy represent a barrier to define the role of this approach in OPC subsite.
- Our findings indicated that patients undergoing this combined treatment achieved a higher pathologic complete response rate, with tolerable adverse reactions during the treatment period.

What is the implication, and what should change now?

- Preoperative immunochemotherapy is a promising strategy for enhancing tumor response in patients with LAOPC.
- Future studies should focus on identifying biomarkers to better predict response to preoperative immunochemotherapy.

Methods

Patients

We retrospectively included patients with resectable LAOPC who received preoperative immunochemotherapy at our institution from March 2021 to March 2024. Patients were eligible for the analysis if they met the following inclusion criteria: (I) stage T3–4 and/or N2–3

LAOPC according to the eighth edition of the American Joint Committee on Cancer (AJCC) staging system; (II) administration of preoperative immunochemotherapy followed by surgical treatment; and (III) adequate hematologic, liver, and renal function. Patients lacking histopathological or pathological evidence of non-squamous cell carcinoma were excluded. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the First Affiliated Hospital of Xiamen University (No. XMYY-2024KY237) and informed consent was taken from all the patients.

Variables

The study analysis included the following variables: gender, age, smoking history, alcohol consumption history, primary tumor site, P16 status, TNM staging, chemotherapy regimens, immunotherapy regimens, surgical procedure, response to preoperative immunochemotherapy, and treatment-related toxicities. P16 status was used as a surrogate marker for HPV association in oropharyngeal cancer (16). The combined positive score (CPS) was defined as the ratio of programmed cell death ligand 1 (PD-L1)-positive cells (including tumor cells, lymphocytes, and macrophages) to the total number of tumor cells (17).

Treatment

A multidisciplinary team (MDT) at our institution reviewed the condition of each patient to formulate an overall treatment plan. During the preoperative phase, patients received two cycles of preoperative chemotherapy combined with a PD-1 inhibitor. The chemotherapy regimen included nab-paclitaxel and platinum under the following dosages: 220–260 mg/m^2 of nab-paclitaxel on day 1, 75 mg/m^2 of cisplatin on days 1–3, or carboplatin at a dose sufficient to achieve an area under the concentration-time curve of 5 mg/min/mL on day 1. The immunotherapy regimen included one of the following PD-1 inhibitors: camrelizumab (200 mg on day 1), pembrolizumab (200 mg on day 1), nivolumab (200 mg on day 1), tislelizumab (200 mg on day 1), and or sintilimab (200 mg on day 1). Preoperative immunochemotherapy was administered as an intravenous infusion every 3 weeks. The final determination of the preoperative treatment regimen was made collaboratively by the treating physician and the patient.

Surgical intervention was scheduled approximately four weeks after the final cycle of preoperative immunochemotherapy. Imaging examination, including computed tomography (CT), magnetic resonance imaging (MRI), or 18-fluorodexoyglucose positron emission tomography with computed tomography (^{18}FDG-PET/CT), was used to determine the extent of the primary tumor and cervical lymph nodes. The scope of surgical resection was determined according to the discussion from the MDT.

Evaluation of the efficacy of preoperative immunochemotherapy

All patients underwent CT, MRI, or PET/CT before and after treatment to define the extent of primary tumors and cervical lymph nodes and to assess the tumor response to preoperative therapy. Tumor response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria 3 weeks after the final cycle of preoperative immunochemotherapy, with responses being categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The PCR of primary lesions and cervical metastatic lymph nodes was established separately. PCR was defined as the absence of residual tumor tissue in either primary lesions or cervical metastatic lymph nodes (18). Major pathologic response (MPR) was defined as less than 10% residual tumor in the primary site upon pathological examination (18). An incomplete pathologic response (IPR) was defined as the presence of 10% or more viable tumor cells in the primary lesion.

Assessment of adverse reactions

Follow-up data on adverse reactions were collected through outpatient visits and telephone consultations. Adverse events of the preoperative immunochemotherapy were monitored and recorded throughout the preoperative treatment and continued for 30 days after the last treatment dose. Throughout the treatment period, patients receive weekly evaluations of hematological, hepatic, renal, cardiac, and gastrointestinal functions, along with thyroid function assessments conducted every three weeks. These events were graded using the Common Terminology Criteria for Adverse Events (CTCAE) 5.0.

Follow-up

All patients were regularly followed up every 3 months after

Table 1 Patient baseline characteristics

Variable	N (%)
Age (years)	
<65	18 (78.3)
≥65	5 (21.7)
Gender	
Male	21 (91.3)
Female	2 (8.7)
Smoking history	
Yes	18 (78.3)
No	5 (21.7)
Alcohol history	
Yes	12 (52.2)
No	11 (47.8)
Tumor location	
Base of tongue	12 (52.2)
Tonsillar fossa	7 (30.4)
Soft palate	1 (4.3)
Pharyngeal oropharynx	3 (13.0)
Tumor stage	
T1–2	1 (4.3)
T3–4	22 (95.7)
Nodal stage	
N1	3 (13.0)
N2	5 (21.7)
N3	15 (65.2)
P16 status	
Positive	11 (47.8)
Negative	12 (52.2)
CPS	
≥20	11 (47.8)
0–19	12 (52.2)
PD-1 inhibitor	
Tislelizumab	12 (52.2)
Camrelizumab	1 (4.3)
Pembrolizumab	6 (26.1)
Nivolumab	3 (13.0)
Sintilimab	1 (4.3)

CPS, combined positive score; N, nodal; PD-1, programmed cell death protein 1; T, tumor.

treatment. The follow-up included physical examination, endoscopy, neck CT or MRI examination, chest CT examination, and routine hematological and thyroid function tests. For patients suspected of disease progression, PET/CT examination or pathological biopsy was performed to further clarify the diagnosis if necessary.

Statistical analysis

Descriptive statistics were used to analyze patient baseline characteristics. The chi-square test was employed to evaluate intergroup differences in PCR. All statistical analyses were performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA), and a P value of <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 23 patients were included in this study. The median age of the patients was 55 years (range, 33–77 years) (*Table 1*). The majority of the patients were male (n=21, 91.3%). The tumor locations were primarily in the tongue base (n=12, 52.2%), followed by the tonsil (n=7, 30.4%), multiple sites in the oropharynx (n=3, 13.0%), and the soft palate (n=1, 4.3%). Among the 23 patients, 12 (52.2%) had P16-negative tumors, and 11 (47.8%) had P16-positive tumors. In the preimmunochemotherapy imaging staging, 22 patients (95.7%) were classified with stage T3–4 disease, and 20 patients (86.9%) were classified with stage N2–3 disease. In addition, 11 patients (47.8%) had a CPS ≥20. During preoperative immunochemotherapy, 1 patient (4.3%) received only one cycle of treatment due to intolerance, while 22 patients (95.7%) completed two cycles of preoperative treatment.

Surgical interventions

An MDT determined the surgical approaches. Of the 23 patients, 20 (87.0%) underwent radical surgery consisting of a lateral oropharyngectomy or a base of tongue resection for the primary lesion and neck dissection after preoperative immunochemotherapy. Two (8.7%) patients initially underwent diagnostic tonsillectomy, followed by preoperative immunochemotherapy and subsequent neck lymphadenectomy. One patient (4.3%) underwent only radical resection of the primary lesion without

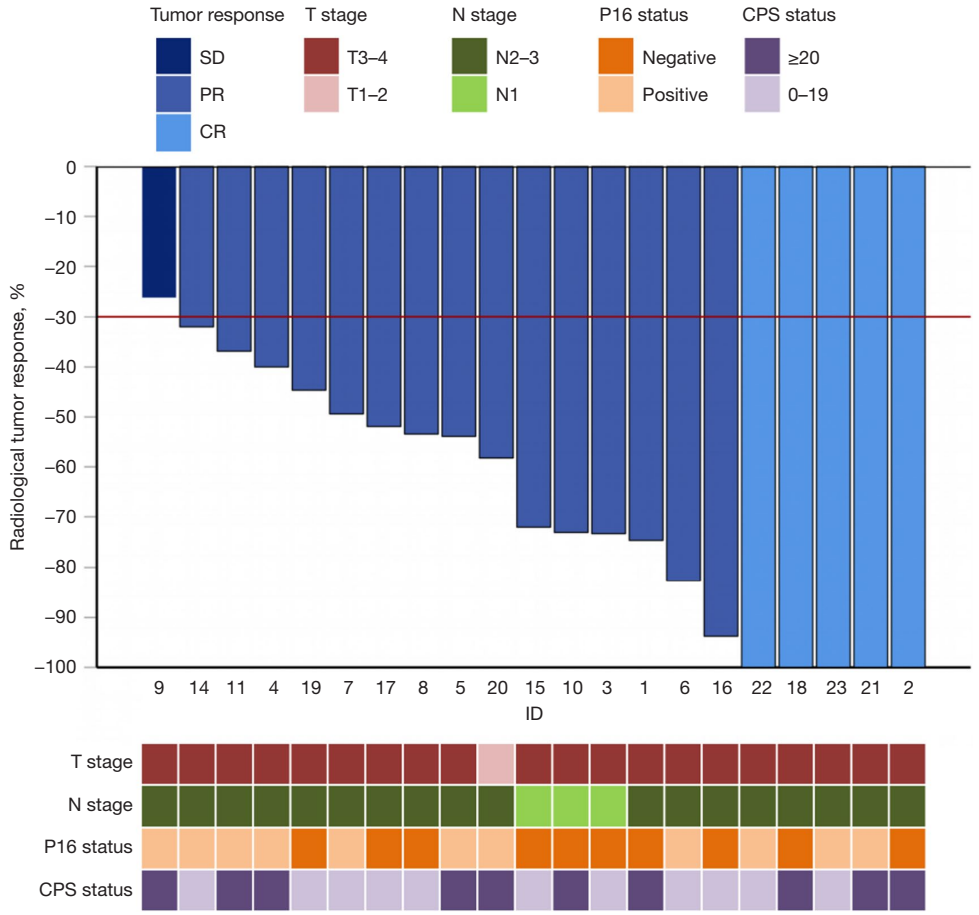

Figure 1 Imaging evaluation of the treatment response to the primary tumor of patients who underwent resection of the primary lesion (n=21). CPS, combined positive score; CR, complete response; ID, identification; N, nodal; PR, partial response; SD, stable disease; T, tumor.

lymphadenectomy after immunochemotherapy. After surgery, 17 (73.9%) patients received postoperative adjuvant radiotherapy, while 6 (26.1%) did not receive postoperative adjuvant radiotherapy.

Imaging-based response to preoperative immunochemotherapy

Figure 1 illustrates the imaging evaluation of the primary tumor in 21 patients who underwent radical resection of the primary lesion after preoperative immunochemotherapy. Among the 20 patients who underwent surgery for both the primary tumor and neck metastatic lymph nodes, 5 (25%) achieved CR, 14 (70%) achieved PR, and 1 (5%) had SD, resulting in an overall response rate (ORR) of 95%. For the primary tumor (n=21), 5 (23.8%) patients achieved CR, 15 (71.4%) achieved PR, and 1 (4.7%) was classified as SD. For the neck metastatic lymph nodes (n=22), all target lymph nodes demonstrated shrinkage after preoperative immunochemotherapy, with 9 (40.9%) patients achieving CR and 13 (59.1%) achieving PR. *Figure 2* shows the treatment response of a patient after two cycles of preoperative immunochemotherapy. The patient was diagnosed with HPV-related tongue-base cancer and underwent PET/CT before preoperative therapy (*Figure 2A*,*2C*), which revealed hypermetabolic lesions in the right tongue base and right neck. After two cycles of therapy, preoperative imaging (*Figure 2B*,*2D*) confirmed CR in both the primary tumor and neck metastatic lymph nodes.

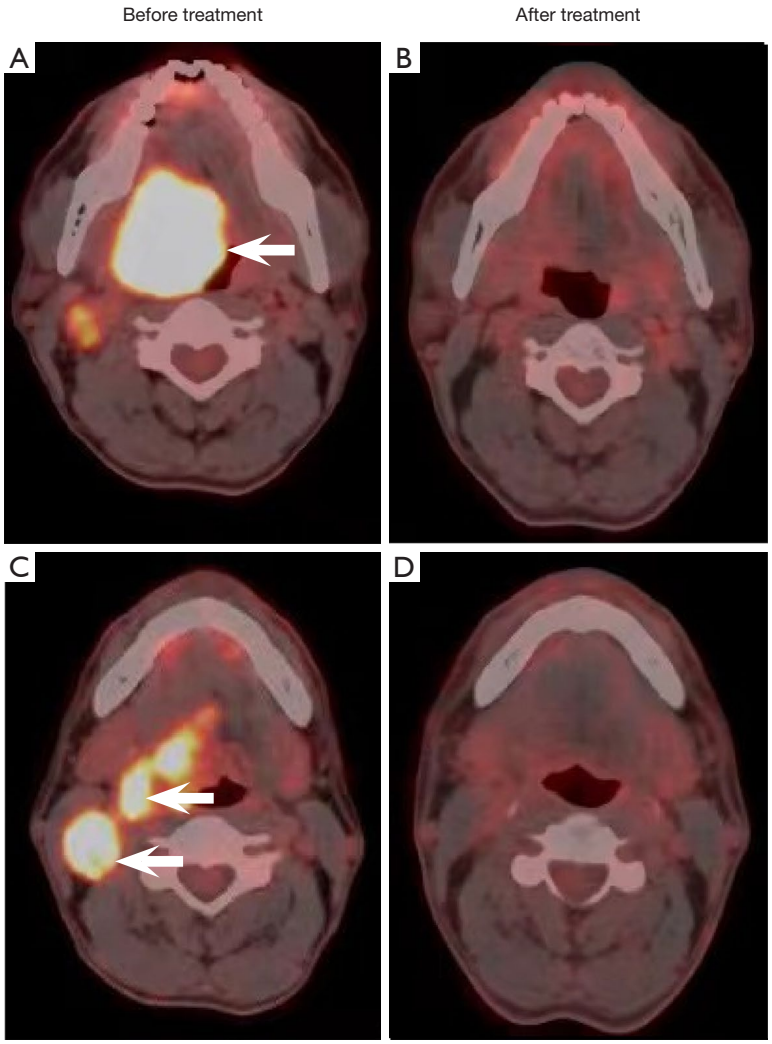

Figure 2 The primary lesion and cervical metastatic lymph nodes (A,C) before and (B,D) after preoperative immunochemotherapy, exhibit a complete response to the preoperative immunochemotherapy using ^{18}FDG-PET/CT scan (white arrows indicate the oropharyngeal lesions and neck metastatic lymph nodes before preoperative immunochemotherapy). ^{18}FDG-PET/CT, ^{18}fluorodeoxyglucose-positron emission tomography/computed tomography.

Pathological response to preoperative immunochemotherapy

Figure 3 illustrates the pathological evaluation of the primary tumor in 21 patients who underwent radical resection of the primary lesion after preoperative immunochemotherapy. Among these patients, 13 (61.9%) had an MPR to the primary tumor, including 12 (57.1%) who achieved a PCR, and 8 (38.1%) patients had IPR to the primary tumor. The assessment of the 22 patients who underwent unilateral or bilateral lymph node dissection after preoperative immunochemotherapy showed that 11 (50.0%) had a PCR to the cervical metastatic lymph nodes, while 11 (50.0%) still had residual tumors in the lymph nodes.

The relationship between PCR and biomarkers

Figure 4 presents the correlation between PCR to the primary tumor and different levels of CPS expression. The results showed that the PCR to the primary tumor was not associated with CPS status, including for cutoff points of 10 (*Figure 4A*), 20 (*Figure 4B*), 30 (*Figure 4C*), 40 (*Figure 4D*),

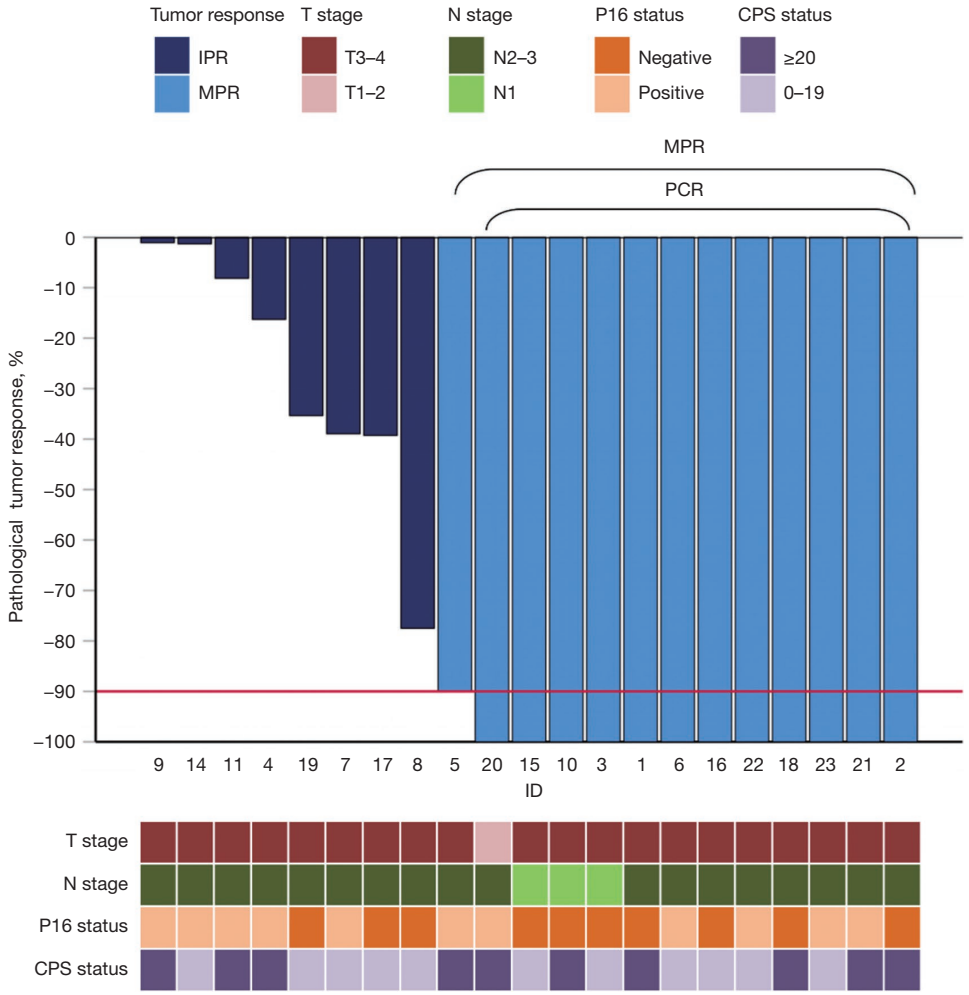

Figure 3 Pathological evaluation of the treatment response of the primary tumor in patients who received resection of the primary lesion (n=21). CPS, combined positive score; ID, identification; IPR, incomplete pathologic response; MPR, major pathologic response; N, nodal; PCR, pathologic complete response; T, tumor.

50 (*Figure 4E*), and 60 (*Figure 4F*). Similarly, no significant associations were found between PCR and neck metastatic lymph nodes and different levels of CPS expression (*Figure 5*).

We also investigated the association of PCR in the primary tumor or metastatic neck lymph nodes with P16 status. The results showed that P16 status was not significantly associated with PCR in the primary tumor (*Figure 6A*) or metastatic neck lymph nodes (*Figure 6B*).

Toxicity

Of the 23 patients, 19 (82.6%) experienced treatment-related adverse effects, and most of them were grade 1–2 toxicities. Only 2 (8.7%) patients had grade 3 or higher toxicities (*Table 2*). Hematological toxicity included anemia (n=11, 47.8%), lymphocytopenia (n=9, 39.1%), leukopenia (n=8, 34.8%), and neutropenia (n=8, 34.8%), with 2 patients (8.7%) experiencing grade 3 or higher neutropenia. Thyroid dysfunction was the most common non-hematological reaction (n=11, 47.8%), with hypothyroidism in 1 patient (4.3%) and hyperthyroidism in 10 (43.5%). Alanine aminotransferase (ALT) levels increased in 5 patients (21.7%), and aspartate aminotransferase (AST) levels increased in 6 (26.7%). Moreover, 3 patients (13.0%) experienced renal toxicity. No treatment-related deaths occurred.

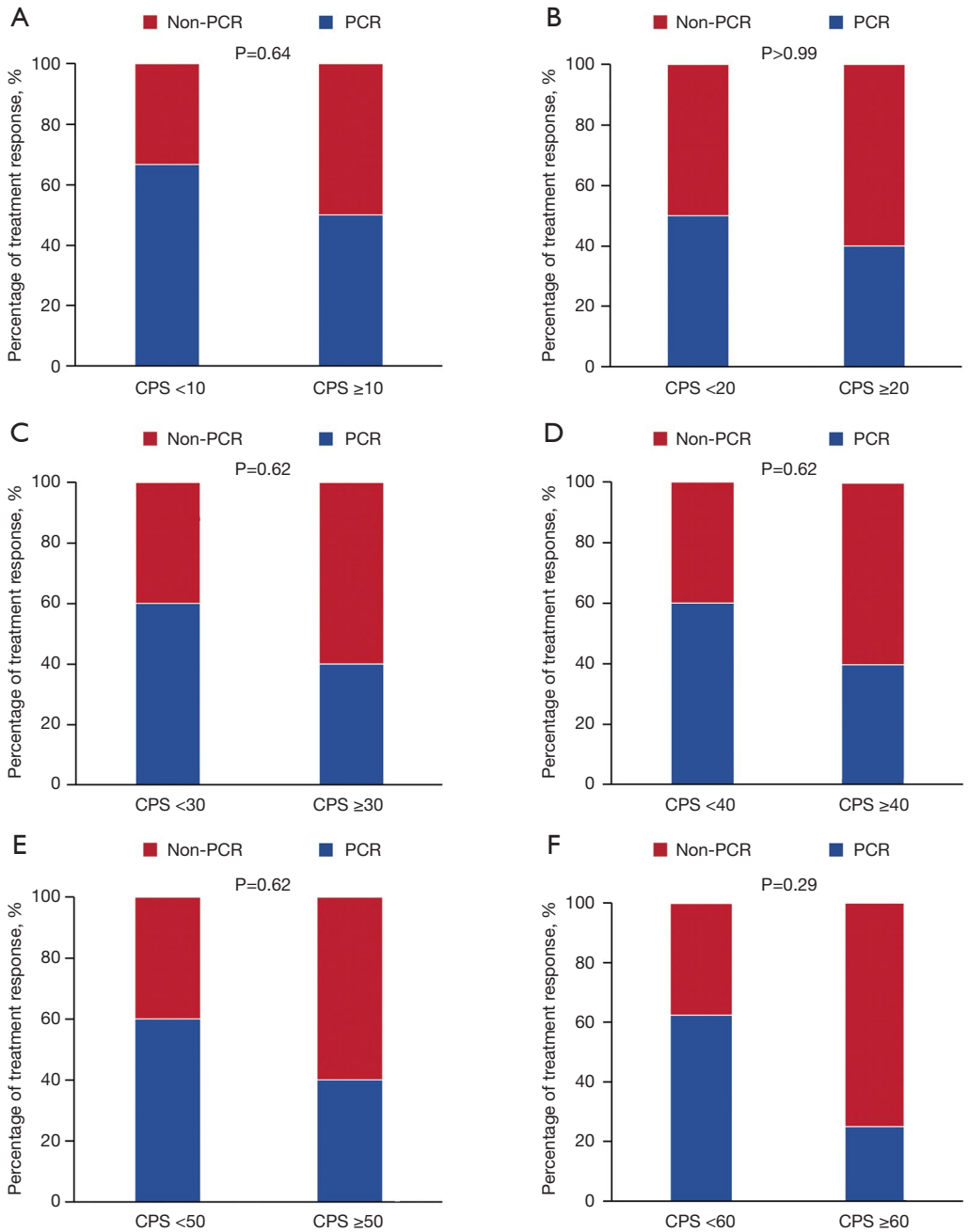

Figure 4 The correlation between PCR in the primary tumor and different levels of CPS expression. Cutoff points of CPS status: (A) 10, (B) 20, (C) 30, (D) 40, (E), 50, and (F) 60. CPS, combined positive score; PCR, pathologic complete response.

Survival

The median follow-up period was 11.83 months (range, 3.7–40.4 months). Three patients (13.0%) experienced disease progression, and 2 patients (8.7%) died. The first patient developed esophageal cancer during follow-up after treatment and died of esophageal cancer at 33.3 months of follow-up without evidence of oropharyngeal cancer progression. The second patient developed extensive bone metastases 14.2 months postdiagnosis and died due to bone metastasis 18.5 months after diagnosis. The third patient

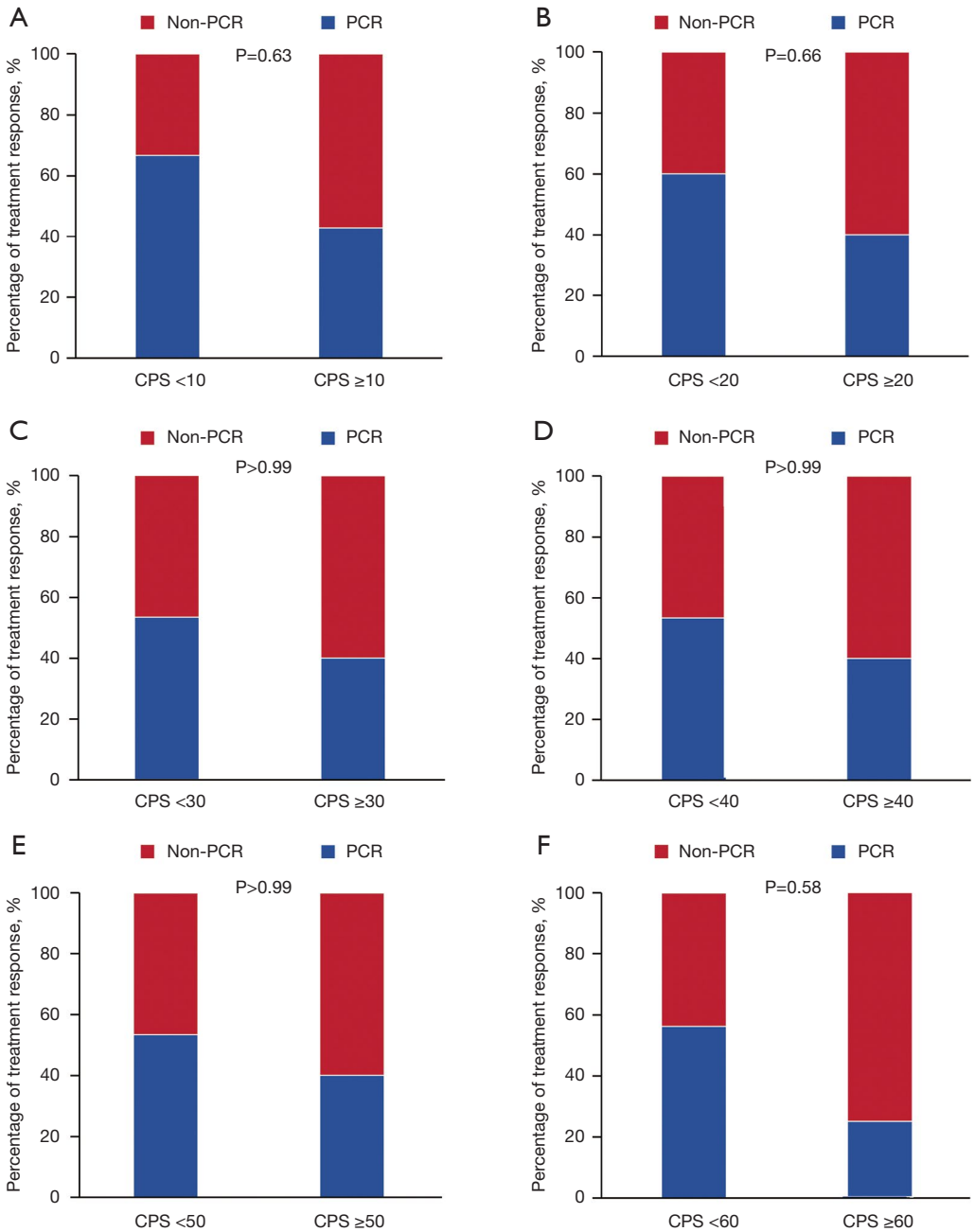

Figure 5 The correlation between PCR in the metastatic neck lymph node and different levels of CPS expression. Cutoff points of CPS status: (A) 10, (B) 20, (C) 30, (D) 40, (E), 50, and (F) 60. CPS, combined positive score; PCR, pathologic complete response.

was diagnosed with extensive bone metastasis 13.1 months postdiagnosis and remains under treatment.

Discussion

In this study, we investigated the initial efficacy and safety of combining preoperative immunochemotherapy in patients with LAOPC. Our findings indicated that patients undergoing this combined treatment achieved a higher PCR rate, with tolerable adverse reactions during the treatment period.

A previous study on LAOPC has reported a PCR rate of

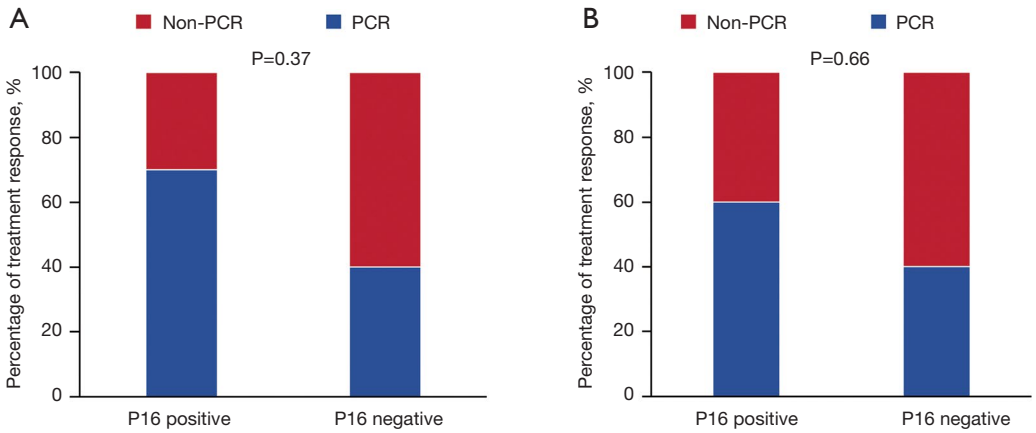

Figure 6 The correlation between PCR in the (A) primary tumor and (B) neck metastatic lymph nodes and P16 status. PCR, pathologic complete response.

Table 2 Acute toxicities during preoperative immunochemotherapy (n=23)

Toxicity	N (%)	Grade 1–2	Grade 3	Grade 4
Hematologic				
Leukopenia	8 (34.8)	8 (34.8)	0	0
Neutropenia	8 (34.8)	6 (26.1)	2 (8.7)	0
Anemia	11 (47.8)	11 (47.8)	0	0
Thrombocytopenia	0	0	0	0
Lymphocytopenia	9 (39.1)	9 (39.1)	0	0
Non-hematologic				
Alanine aminotransferase increase	5 (21.7)	5 (21.7)	0	0
Aspartate aminotransferase increase	6 (26.1)	6 (26.1)	0	0
Blood creatinine increase	3 (13.0)	3 (13.0)	0	0
Hyperthyroidism	10 (43.5)	10 (43.5)	0	0
Hypothyroidism	1 (4.3)	1 (4.3)	0	0
Nausea	3 (13.0)	3 (13.0)	0	0
Vomiting	3 (13.0)	3 (13.0)	0	0

N, number.

approximately 15% following neoadjuvant chemotherapy alone (14). However, integrating immunotherapy may raise the PCR rate in patients with locally advanced HNSCC, with PCR rates ranging from 16.7% to 55.6% (18,19-22). In the study by Wu *et al.*, which included 14 patients with LAOPC, the imaging CR rate after neoadjuvant immunotherapy plus chemotherapy was 28.6% (4/14). However, only 9 of these patients underwent surgical treatment, making it difficult to accurately assess the PCR status (23). Additionally, in the study by Zhang *et al.*, among the 13 patients with LAOPC out of the enrolled patients with HNSCC, 11 received surgical treatment after neoadjuvant immunochemotherapy, and 7 (63.6%) achieved MPR, including 3 (27.3%) who achieved PCR and another 4 (36.4%) who had an IPR (20). Without postoperative pathological results, it is impossible to determine the PCR

status of patients. Therefore, after MDT discussions, the majority of our patients underwent surgical treatment for the primary lesion and the neck to confirm the PCR status. Our research showed that patients with LAOPC who underwent preoperative immunochemotherapy exhibited optimal responses in both the primary tumor and neck lymph nodes. Among the 20 patients who received surgery for both primary tumor and neck lymph nodes, the PCR rate for the primary lesion was 57.1%, and the PCR rate for the metastatic lymph nodes in the neck was 50.0%. The high ORR observed in our study is consistent with the findings from the above-mentioned studies on neoadjuvant immunotherapy with chemotherapy in LAOPC, further supporting the effectiveness of this treatment modality. Therefore, neoadjuvant immunochemotherapy is a promising strategy for enhancing tumor response in patients with LAOPC. These results are particularly encouraging, as they suggest a significant reduction in tumor burden and the potential for improved local control and survival outcomes with longer follow-up.

The presence of HPV is an important predictor of survival in patients with oropharyngeal carcinoma, with HPV-positive tumors associated with superior survival outcomes compared to HPV-negative tumors (24). Sadeghi *et al.* reported a PCR rate of 43.6% for patients with HPV-related LAOPC treated with neoadjuvant chemotherapy and surgery (25). Conversely, Park *et al.* reported that the overall survival did not differ significantly for patients with LAOPC treated with neoadjuvant chemotherapy regardless of HPV status (26). In our study, no statistically significant disparity was found in PCR rates between HPV-positive and HPV-negative patients. This may be due to the lower tumor mutation burden in HPV-positive LAOPC, which generally correlates with a poorer response to immunotherapy (27,28). A recent study included 73 patients with HPV-positive LAOPC and found that neoadjuvant nivolumab and chemotherapy achieved a deep response (50% tumor shrinkage) in 70.8% of the evaluable patients (15). However, these patients primarily received treatment regimens consisting of subsequent chemoradiotherapy, making it challenging to accurately assess the tumor response. Further studies are needed to examine the variations in immune responses according to HPV status.

Several studies on rmHNSCC have indicated a significant correlation between CPS status and the efficacy of immunotherapy (15,29). The role of CPS status in predicting the efficacy of neoadjuvant immunotherapy in LAOPC remains unclear. Several prospective phase II studies have found neither CPS status nor HPV status to be significantly associated with the CR rate or ORR (20-23). The results from Rosenberg *et al.* found that PD-L1 expression was not significantly associated with deeper responses or improved progression-free survival (PFS) for patients with HPV-positive LAOPC who received neoadjuvant nivolumab and chemotherapy. However, circulating tumor HPV DNA clearance was significantly associated with improved PFS (15). Our study found no significant difference in the PCR rates between patients with LAOPC with varying CPS and P16 status. Therefore, more studies are required to identify biomarkers beyond CPS for predicting the efficacy of neoadjuvant immunotherapy in this patient population.

In the KEYNOTE-048 trial, 22% of patients experienced thyroid dysfunction following single-agent immunotherapy, with 18% developing hyperthyroidism and 4% developing hypothyroidism (30). Similar findings were observed in the KEYNOTE-040 and CheckMate-141 trials, in which approximately 10% of patients exhibited thyroid dysfunction (31,32). Our results aligned with these findings, with thyroid dysfunction being the predominant nonhematological toxicity. Notably, 43.5% of our patients exhibited with hyperthyroidism, a finding consistent with the previous studies in patients with locally advanced nasopharyngeal carcinoma treated with immunotherapy, which is likely due to the variable use and type of PD-1 regimens (33,34). In several advanced solid tumors, thyroid dysfunction has been correlated with better immunotherapy responses (35,36). Further investigation is needed to better understand the relationship between therapeutic efficacy in patients with LAOPC and thyroid dysfunction. In addition, although only 8.7% of patients had grade 3 or higher toxicities in our study, 82.6% of patients experienced treatment-related adverse effects. These findings suggest that the neoadjuvant immunochemotherapy regimen has a manageable toxicity profile, although careful monitoring and supportive care remain essential.

This study involved several limitations which should be acknowledged. First, we employed a retrospective design, which may introduce biases related to patient selection and could lead to an underestimation of immune-related adverse reactions. Second, the limited number of patients in our study precluded detailed analysis of the relationship between PCR and a variety of factors. Third, the short follow-up period did not allow for the comparison of survival between patients with different responses to treatment. In addition, the distinction between patients who were candidates for

upfront resection versus those with non-resectable disease was not analyzed. Finally, the heterogeneity in treatment regimens, including different chemotherapy protocols and the use of immunotherapy, introduces variability that could confound the interpretation of outcomes. Standardizing treatment approaches or stratifying analyses based on treatment modalities would enhance the robustness of the findings.

Conclusions

Incorporating a PD-1 inhibitor into the preoperative chemotherapy regimen demonstrated promise as an effective approach for treating LAOPC and had acceptable toxicity. Future studies should focus on identifying biomarkers to better predict response to preoperative immunochemotherapy, personalizing treatment regimens based on individual patient characteristics, and clarifying the role of maintenance therapy in preventing disease recurrence. Additionally, long-term follow-up is essential to fully determining the impact of this treatment on overall survival and quality of life.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-2025-202/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-2025-202/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-2025-202/coif). S.G.W. serves as an unpaid editorial board member of *Translational Cancer Research* from November 2024 to October 2025. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the First Affiliated Hospital of Xiamen University (No. XMYY-2024KY237) and informed consent was taken from all the patients.

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