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Original Article

Efficacy and toxicity of PD-1 inhibitor combined with induction chemotherapy for locally advanced laryngeal and hypopharyngeal cancers

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Abstract: Objective: To evaluate the efficacy, toxicity, and voice rehabilitation outcomes of PD-1 inhibitors combined with induction chemotherapy (PCIC) compared to induction chemotherapy (IC) alone. Methods: A retrospective analysis was conducted on 250 patients with stage III/IVA squamous cell carcinoma of the larynx/hypopharynx treated between June 2021 and December 2023. After 1:1 propensity score matching, 216 patients (108 per group) were analyzed. Both groups received platinum-based induction chemotherapy, with the PCIC group receiving an additional PD-1 inhibitor, toripalimab. Efficacy was evaluated based on response rates and survival outcomes, while toxicity profiles and voice rehabilitation were assessed. Results: The PCIC group had significantly higher complete remission rates (81.48% vs. 65.74%; P = 0.021) and improved 1-year overall survival (62.96% vs. 49.07%; P = 0.040). The incidence of neutropenia and nausea was higher in the PCIC group (P < 0.05). Voice quality assessments showed worse objective vocal grade but better patient-perceived vocal quality in the PCIC group (both P < 0.05). Conclusion: The combination of PD-1 inhibitors with induction chemotherapy improve remission rates and survival in patients with locally advanced laryngeal and hypopharyngeal cancers. However, increased toxicity and voice rehabilitation challenges highlight the need for comprehensive patient support during treatment.

Keywords: PD-1 inhibitors, induction chemotherapy, laryngeal cancer, hypopharyngeal cancer, survival outcomes, toxicity profiles

Introduction

Laryngeal and hypopharyngeal cancers, primarily squamous cell carcinomas, represent challenging malignancies due to their complex anatomical locations, functional impact, and propensity for both local and distant spread [1-3]. These cancers are often diagnosed at advanced stages, which significantly affects patient prognosis and quality of life. Conventional treatment regimens typically involve a combination of surgery, radiotherapy, and chemotherapy, with the primary goals being tumor eradication, larynx preservation, and maintenance of voice and swallowing functions. Despite aggressive treatments, the prognosis for advanced-stage laryngeal and hypopharyngeal cancers remains suboptimal, with 5-year survival rates ranging from 50% to 60% [4, 5].

In recent years, immunotherapy has ushered in a new era in cancer treatment, significantly altering the therapeutic landscape. Among immunotherapeutic agents, PD-1 inhibitors, such as pembrolizumab and nivolumab, have shown promise in enhancing antitumor immunity by blocking the checkpoint pathways that tumors use to evade immune detection [6, 7].

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These inhibitors have demonstrated efficacy in recurrent or metastatic head and neck cancers, supporting their potential role in managing earlier stages of the disease, potentially in combination with traditional therapies [8, 9].

The rationale for combining PD-1 inhibitors with chemotherapy lies in their ability to enhance the immune response against tumor cells. While chemotherapy reduces tumor burden through cytotoxic action, it also induces immunogenic cell death, releasing tumor antigens and promoting immune activation. PD-1 inhibitors can enhance this effect by preventing the negative regulatory interactions that suppress T-cell responses, thereby improving the immune system's ability to target cancer cells [10, 11].

Despite these theoretical benefits, the combination of PD-1 inhibitors and chemotherapy raises several critical questions. While this combination could improve overall survival and locoregional control, it may also increase toxicity, affecting patient tolerance and quality of life [12]. Notable toxicities such as myelosuppression, gastrointestinal disturbances, and fatigue may compromise the efficacy of chemotherapy regimens [13]. Therefore, understanding the balance between efficacy and toxicity is essential when designing treatment protocols for these patients.

Furthermore, preserving laryngeal function, which is crucial for speech and swallowing, remains a key goal in the treatment of laryngeal and hypopharyngeal cancers [14, 15]. The integration of combination therapies necessitates evaluating not only oncological outcomes but also functional outcomes, including voice quality and laryngeal preservation. Rehabilitation strategies for voice and function are essential adjuncts to treatment, and their integration with immunotherapy presents both challenges and opportunities.

Several studies have investigated the use of PD-1 inhibitors in combination with induction chemotherapy for head and neck cancers. However, most of these studies are limited by small sample sizes or single-center designs, which can introduce biases and limit the generalizability of their findings [16-18]. Additionally, few studies have specifically addressed laryngeal and hypopharyngeal cancers, where organ preservation is a critical concern. This study aims to address these gaps by evaluating the efficacy and safety of PD-1 inhibitors combined with induction chemotherapy in a larger, multicenter cohort.

This study investigates the relationship between efficacy, toxicity, and functional outcomes in patients with locally advanced laryngeal and hypopharyngeal cancers receiving a combination of PD-1 inhibitors and induction chemotherapy. Specifically, we aim to determine whether the addition of a PD-1 inhibitor to induction chemotherapy improves complete remission rates, overall survival, and local control, without unacceptable increases in treatment-related toxicity.

Materials and methods

Study design

A retrospective analysis was conducted on 250 patients with locally advanced laryngeal and hypopharyngeal cancers treated at Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences between June 2021 and December 2023. General information, including gender, age, BMI, disease stage, comorbidities, and treatment details, was extracted from electronic medical records.

Patients were categorized into two groups: those receiving PD-1 inhibitors combined with induction chemotherapy (PCIC, n = 116) and those receiving induction chemotherapy (IC, n = 134) alone. To adjust for baseline imbalances, propensity score matching (PSM) was performed using a 1:1 nearest-neighbor algorithm with a caliper width of 0.2. Matching covariates included age, sex, BMI, clinical stage (III/IVA), T/N stage, histology, and comorbidities. After PSM, 216 patients (108 per group) were included in the comparative analysis.

The study was approved by the Institutional Review Board and Ethics Committee of Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences. Informed consent was waived due to the retrospective use of de-identified patient data.

Study objectives: The primary objective of this study was to evaluate improvements in survival outcomes with the addition of a PD-1 inhibitor

to induction chemotherapy. Secondary objectives included assessing the reduction in treatment failure due to secondary tumors and exploring the effects on voice rehabilitation.

Treatment decision-making process: Treatment decisions were made by attending physicians based on clinical guidelines. Patients provided informed consent after being thoroughly briefed on the potential benefits and risks associated with each treatment option.

Eligibility and grouping criteria

Inclusion criteria: i. Participants aged 18 to 70 years. ii. Histologically confirmed locally advanced (Stage III or IV), non-metastatic squamous cell carcinoma (T2-4, any N, M0) of the hypopharynx or larynx as the primary tumor site. iii. Diagnosis must meet the World Health Organization Classification of Head and Neck Tumors criteria [19]. iv. At least one measurable lesion in one dimension according to RECIST guidelines [20]. v. Adequate bone marrow function (neutrophils > 1.5 × 10^9/L, platelets > 100 × 10^9/L, hemoglobin > 10.0 g/dL). vi. Adequate liver function: bilirubin < 1.5 mg/dL, SGOT, SGPT < 3 × ULN, GGT < 5 × ULN. vii. Adequate renal function (glomerular filtration rate > 70 mL/min). viii. Expected survival of at least six months. ix. Completion of a full course of chemoradiotherapy, with complete case records.

Exclusion criteria: i. Diagnosis of any cancer within the past five years, except adequately treated basal cell carcinoma of the skin or cervical intraepithelial neoplasia. ii. Pregnancy or breastfeeding. iii. Serious illness such as myocardial infarction, severe arrhythmia, cerebrovascular disease, peptic ulcer, poorly controlled diabetes, or severe psychiatric disorders. iv. Prior systemic chemotherapy or radiotherapy, surgery for head and neck or laryngeal cancer, or diagnosis of nasopharyngeal carcinoma. v. Distant metastasis (M1), prior exposure to PD-1 inhibitors, or recent surgery within 30 days prior to treatment. vi. Known allergies or hypersensitivity to study drugs, active infection, symptomatic peripheral neuropathy (Common Terminology Criteria [CTC] grade 2 or higher), or ototoxicity (CTC grade 2 or higher). vii. Severe neurological or psychiatric disorders (e.g., dementia or seizures). viii. Drug abuse problems or cognitive dysfunction.

Patient selection criteria are shown in **Figure 1**.

Induction chemotherapy

All patients underwent two to three cycles of platinum-based IC. The modified TPF regimen consisted of intravenous administration of 260 mg/m^2 nab-paclitaxel (H20067345, Jiangsu Taxus Pharmaceuticals Co., Ltd., China), 80 mg/m^2 cisplatin (H37021358, Qilu Pharmaceutical Co., Ltd., China), and 3 mg/m^2 raltitrexed (H20223017, Guangdong Starpharm Holdings Co., Ltd., China) on the first day, with treatments spaced at 3-week intervals for a total of 2 to 3 cycles. Additionally, patients in the PCIC group received 240 mg of intravenous toripalimab (S20180015, Suzhou Zelgen Biopharmaceuticals Co., Ltd., China) on the first day of each IC cycle.

Radiotherapy

Following the completion of IC, all patients received platinum-based concurrent chemoradiotherapy (CCRT), consisting of 100 mg/m^2 cisplatin (H37021358, Qilu Pharmaceutical Co., Ltd., China) administered every three weeks. Patients in the PCIC group continued anti-PD-1 immunotherapy with 240 mg of toripalimab (S20180015, Suzhou Zelgen Biopharmaceuticals Co., Ltd., China) for 2 to 3 cycles during radiotherapy. Radiotherapy was delivered using volumetric modulated arc therapy (VMAT).

The gross tumor volume (GTV) included the primary tumor and enlarged lymph nodes, specifically the primary site and retropharyngeal lymph nodes (GTVnx), as well as clinically involved cervical lymph nodes (GTVnd). The high-risk clinical target volume (CTV1) was defined as areas with metastasis-positive lymph nodes and their adjacent lymphatic drainage regions. The low-risk lymphatic drainage area (CTV2) encompassed cervical regions requiring prophylactic irradiation outside of CTV1. The planning target volumes (PTVs) for GTVnx, GTVnd, CTV1, and CTV2 received total radiation doses of 69.96 Gy, 69.96 Gy, 60.06 Gy, and 54.45 Gy, respectively, over 33 frac-

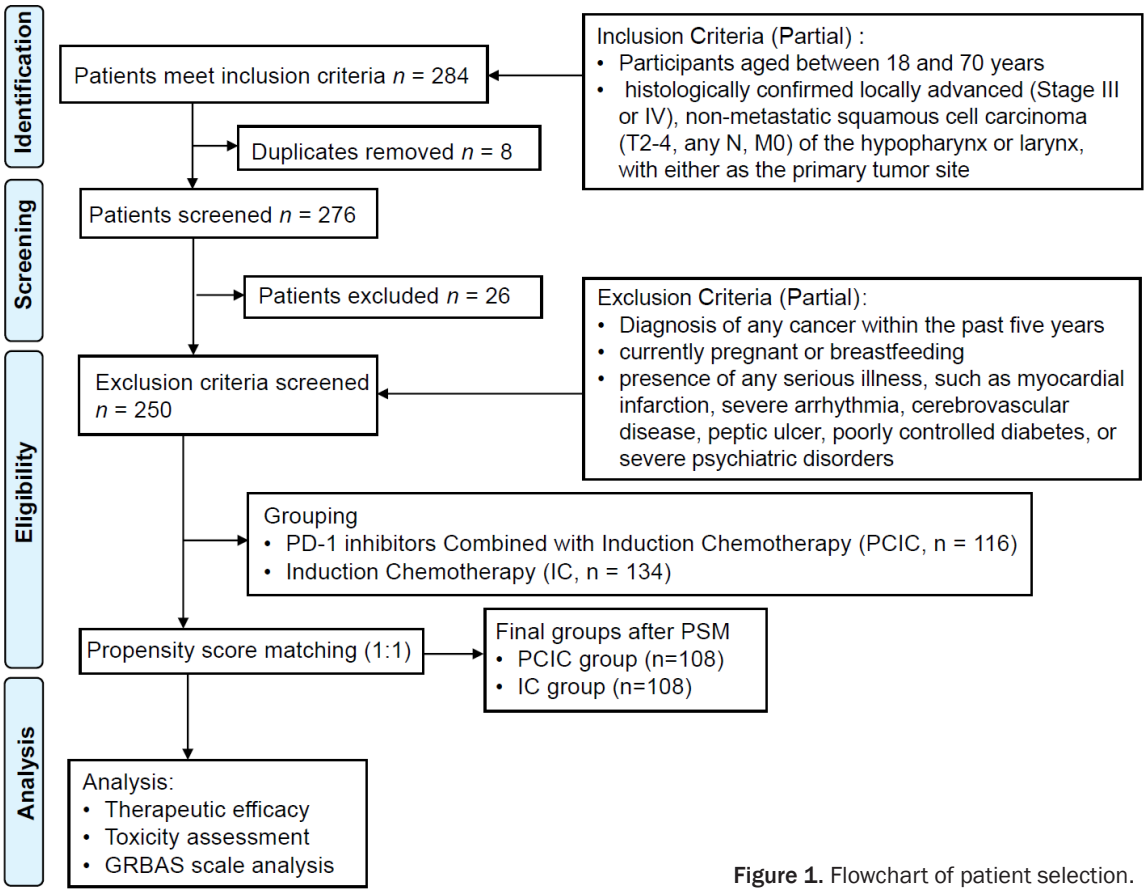

Figure 1. Flowchart of patient selection.

tions, administered five times per week, beginning on the first day of the first CCRT cycle.

Therapeutic efficacy and toxicity assessment

Short-term efficacy was evaluated at the conclusion of IC and one month following the completion of the overall treatment. This assessment involved physical examinations, nasopharyngeal fiberscope examinations, and magnetic resonance imaging (MRI) of the nasopharynx and neck. The efficacy of treatment on cervical lymph nodes and primary nasopharyngeal lesions was categorized according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) [20] into complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD).

Acute hematological and non-hematological toxicities observed during IC and CCRT were graded based on the Common Terminology Criteria for Adverse Events version 5.0.

Voice rehabilitation outcomes

One month after completing the overall treatment, patients' voices were recorded. The recordings included reading a standard paragraph and repeating the maximum sustained vowel /a/ three times. A headset microphone (Sennheiser MKE 2-p; Sennheiser Electronic Corporation, Old Lyme, CT) was positioned 12 cm from the corner of the mouth for the recordings. Sound was captured using a Panasonic Professional Digital Audio Tape (DAT) recorder (SV-3800, Panasonic Corporation, Osaka, Japan) at a sampling frequency of 44.1 kHz. Before analysis, all recordings were transferred as audio files (.wav) from the DAT to a computer hard drive using the Swell Soundfile Editor version 4.5 (Sävén Hightech, Täby, Sweden).

Two speech-language pathologists, each with at least two years of experience in voice assessment, conducted a perceptual analysis of the voice samples while blinded to the patients'

demographic details, diagnoses, and recording time points. The perceptual analysis was performed using the Grade, Roughness, Breathiness, Asthenia, and Strain (GRBAS) scale, achieving a kappa of 0.74 [21]. Each of the five voice qualities on the GRBAS scale was rated on a four-point scale: 0.5 = normal, 1.5 = mildly impaired, 2.5 = moderately impaired, 3.5 = severely impaired.

Before treatment, patients were assessed using the Voice Handicap Index-30 (VHI-30) and re-evaluated one month after the completion of the overall treatment using the same tool. The VHI-30 scale consists of 30 items divided into three dimensions: (1) Functional: assessing the impact of voice disorders on daily life and social functioning; (2) Physical: evaluating physiological symptoms and discomfort associated with voice; (3) Emotional: assessing the impact of voice problems on emotional or psychological state. Each item is rated on a 5-point scale ranging from 0 (never) to 4 (always). The Cronbach's α for the total VHI-30 score and its three subscales ranged from 0.788 to 0.944, indicating high internal consistency reliability of the scale [22].

Statistical analysis

Sample size calculation: Given the retrospective nature of this study, all eligible patients treated between June 2021 and December 2023 were included (n = 250). A post hoc power analysis was conducted using G*Power 3.1.9.7 to evaluate the adequacy of the post-propensity score matching (PSM) cohort. With the final matched sample size (n = 216, 108 per group), a two-tailed independent t-test assuming a medium effect size (d = 0.5) and α = 0.05 achieved a statistical power of 96.9%, confirming sufficient sensitivity to detect clinically meaningful differences.

PSM: To minimize confounding bias inherent in retrospective comparisons, PSM was performed using SPSS version 29.0 (IBM Corp., Armonk, NY, USA). Propensity scores were estimated via logistic regression, incorporating covariates clinically relevant to laryngeal/hypopharyngeal cancer outcomes: age, sex, BMI, clinical stage (III/IVA), T stage (T1-4), N stage (N1-3), histology (differentiated/undifferentiated), and malnutrition status. A 1:1 nearest-neighbor matching algorithm with a caliper width of 0.2 standard deviations of the logit propensity score was applied without replacement. Balance between matched groups was assessed using standardized mean differences (SMD < 0.1 for all covariates) and χ^2 tests ($P > 0.05$). Visual inspection of the propensity score distributions before and after matching was also conducted to ensure successful matching.

Data analysis: Data analysis was conducted using SPSS version 29.0 statistical software (IBM Corp., Armonk, NY, USA). Categorical data were presented as frequencies and percentages [n (%)]. Continuous data with a normal distribution were presented as mean ± standard deviation (SD). Chi-square tests or Fisher's exact tests were used for categorical variables, while independent t-tests were applied for continuous variables. A *p*-value of less than 0.05 was considered statistically significant.

Multivariate logistic regression: The primary outcome of this study was to assess whether adding a PD-1 inhibitor to induction chemotherapy significantly improved survival outcomes in patients with locally advanced laryngeal/hypopharyngeal cancers. This was evaluated using the 1-year overall survival (OS) metric. Patients who died within one year of treatment were classified into the Death group, while those who survived beyond one year were classified into the Survival group. The 216 enrolled patients were divided into the Death group (n = 119) and the Survival group (n = 97). Variables showing significant differences in differential analysis and correlation analysis were included as covariates in the logistic regression analysis. These covariates included Treatment Group (PCIC vs. IC), CR after induction chemotherapy, CR after overall treatment, 1-year LRRFS (Locoregional Recurrence-Free Survival), second primary tumor, neutropenia, nausea, vomiting, grade of auditory-perceptual voice, and asthenia.

Results

Comparison of baseline characteristics before PSM

Before PSM, 239 patients were included in the analysis (IC group: n = 134; PCIC group: n = 116). Baseline characteristics revealed significant imbalances between the groups (Table

Table 1. Baseline characteristics after propensity score matching

Parameters	IC Group (n = 108)	PCIC Group (n = 108)	t/χ^2	P
Male/Female	84 (77.78%)/24 (22.22%)	82 (75.93%)/26 (24.07%)	0.104	0.747
Age (years)	40.15 ± 6.24	39.87 ± 6.02	0.334	0.739
BMI (kg/m^2)	19.36 ± 2.07	19.22 ± 2.15	1.457	0.147
Current Smoking (Yes/no)	85 (78.7%)/23 (21.3%)	78 (72.22%)/30 (27.78%)	1.225	0.268
Marital status (Married/Others)	92 (85.19%)/16 (14.81%)	97 (89.81%)/11 (10.19%)	1.058	0.304
Clinical stage			0.180	0.672
III	38 (35.19%)	41 (37.96%)		
IVA	70 (64.81%)	67 (62.04%)		
T stage			0.215	0.975
T1	14 (12.96%)	13 (12.04%)		
T2	0 (9.26%)	9 (8.33%)		
T3	38 (35.19%)	41 (37.96%)		
T4	46 (42.59%)	45 (41.67%)		
N stage			0.220	0.896
N1	17 (15.74%)	15 (13.89%)		
N2	54 (50%)	57 (52.78%)		
N3	37 (34.26%)	36 (33.33%)		
Histology (nonkeratinizing)			0.381	0.537
Differentiated	15 (13.89%)	12 (11.11%)		
Undifferentiated	93 (86.11%)	96 (88.89%)		
Swallowing Difficulty	83 (76.85%)	79 (73.15%)	0.395	0.530
Hoarseness	64 (59.26%)	58 (53.7%)	0.678	0.410
Malnutrition	71 (65.74%)	69 (63.89%)	0.081	0.776
Dyspnea (Breathing Difficulty)	39 (36.11%)	42 (38.89%)	0.178	0.673
Family History of Cancer	14 (12.96%)	16 (14.81%)	0.155	0.694
Personal History of Cancer	16 (14.81%)	13 (12.04%)	0.358	0.549

BMI: Body Mass Index; T stage: Tumor stage; N stage: Node stage; IC: Induction Chemotherapy.

Table 2. Short-term efficacy after induction chemotherapy

Variable	IC Group (n = 108)	PCIC Group (n = 108)	χ^2	P
CR	9 (8.33%)	15 (13.89%)	10.985	0.004
PR	79 (73.15%)	88 (81.48%)		
SD	20 (18.52%)	5 (4.63%)		
PD	0 (0.00%)	0 (0.00%)		

CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease.

Table 3. Short-term efficacy after overall treatment

Variable	IC Group (n = 108)	PCIC Group (n = 108)	χ^2	P
CR	71 (65.74%)	88 (81.48%)	7.716	0.021
PR	33 (30.56%)	16 (14.81%)		
SD	4 (3.70%)	4 (3.70%)		
PD	0 (0.00%)	0 (0.00%)		

S1). The PCIC group had a higher proportion of stage IVA disease (68.10% vs. 55.97%; P = 0.049) and a greater prevalence of undifferentiated histology (90.52% vs. 79.85%; P = 0.019). In contrast, the IC group had a higher proportion of T1 tumors (14.18% vs. 7.76%) and differentiated histology (20.15% vs. 9.48%), as well as a significantly higher rate of malnutrition (68.66% vs. 55.17%; P = 0.028). No significant differences were observed in age, sex, BMI, smoking status, marital status, T2-3/N stage, swallowing difficulty, hoarseness, dyspnea, or family/personal cancer history (P > 0.05 for all). These imbalances necessitated propensity score matching to mitigate confounding effects.

Comparison of baseline characteristics after PSM

After 1:1 propensity score matching, 216 patients were included (n = 108 per group). The

Table 4. Long-term efficacy after overall treatment

Variable	IC Group (n = 108)	PCIC Group (n = 108)	χ^2	P
1-year OS	53 (49.07%)	68 (62.96%)	4.228	0.040
1-year PFS	45 (41.67%)	52 (48.15%)	0.917	0.338
1-year LRRFS	43 (39.81%)	58 (53.7%)	4.184	0.041
1-year DMFS	51 (47.22%)	53 (49.07%)	0.074	0.785
1-year LP rate	94 (87.04%)	101 (93.52%)	2.585	0.108

OS: overall survival; DFS: disease free survival; LRRFS: locoregional recurrence-free survival; DMFS: distant metastasis-free survival; LP rate: larynx-preservation rate.

Table 5. Comparison of causes of treatment failure and complication after treatment between the two groups

Variable	IC Group (n = 108)	PCIC Group (n = 108)	χ^2	P
Locoregiona	38 (35.19%)	30 (27.78%)	1.374	0.241
Distant metastases	11 (10.19%)	7 (6.48%)	0.970	0.325
Locoregional and distant metastases	4 (3.70%)	1 (0.93%)	0.819	0.365
Second primary tumor	12 (11.11%)	2 (1.85%)	7.638	0.006
Complication			1.033	0.998
None	85 (78.70%)	83 (76.85%)		
Bleeding	1 (0.93%)	2 (1.85%)		
Aspiration	2 (1.85%)	2 (1.85%)		
Aspiration pneumonia	1 (0.93%)	2 (1.85%)		
Necrosis of the flap	1 (0.93%)	1 (0.93%)		
Fistula	10 (9.26%)	10 (9.26%)		
Wound healing problems	4 (3.70%)	3 (2.78%)		
General	2 (1.85%)	3 (2.78%)		
Other	2 (1.85%)	2 (1.85%)		

matched cohorts demonstrated balanced baseline characteristics (**Table 1**). No significant differences were observed in age, sex, BMI, clinical stage, T/N stage, or comorbidities (P > 0.05 for all), confirming successful covariate adjustment.

Comparison of efficacy

This study demonstrated significant improvements in both short-term and long-term outcomes with the addition of PCIC for patients with locally advanced laryngeal and hypopharyngeal cancers. Short-term efficacy after induction chemotherapy showed a higher CR rate in the PCIC group compared to the IC group (13.89% vs. 8.33%; P = 0.004), with fewer SD cases (4.63% vs. 18.52%) (**Table 2**). Following overall treatment, the PCIC group achieved a significantly higher CR rate (81.48% vs. 65.74%; P = 0.021) (**Table 3**). For long-term outcomes, the PCIC group exhibited improved 1-year OS (62.96% vs. 49.07%; P = 0.040) and 1-year LRRFS (53.7% vs. 39.81%; P = 0.041) compared to the IC group (**Table 4**). The 1-year larynx preservation rate was numerically higher in the PCIC group (93.52% vs. 87.04%), though not statistically significant (P = 0.108). Treatment failure due to second primary tumors was significantly reduced in the PCIC group (1.85% vs. 11.11%; P = 0.006), while the rates of locoregional and distant metastasis did not differ significantly (**Table 5**). Regarding complications, no significant differences were found across all specified categories, including bleeding, aspiration, aspiration pneumonia, necrosis of the flap, fistula, wound healing problems, general issues, and others (χ^2 = 1.033; P = 0.998).

Comparison of toxicities

Analysis of toxicities between the IC and PCIC groups revealed significant differences in some

Table 6. Toxicities between two groups

Variable	IC Group (n = 108)	PCIC Group (n = 108)	χ^2	P
Leukopenia			1.890	0.169
G1 + 2	91 (84.26%)	83 (76.85%)		
G3 + 4	17 (15.74%)	25 (23.15%)		
Neutropenia			6.034	0.014
G1 + 2	87 (80.56%)	71 (65.74%)		
G3 + 4	21 (19.44%)	37 (34.26%)		
Hemoglobin			2.395	0.122
G1 + 2	100 (92.59%)	105 (97.22%)		
G3 + 4	8 (7.41%)	3 (2.78%)		
Thrombocytopenia			0.750	0.386
G1 + 2	94 (87.04%)	98 (90.74%)		
G3 + 4	14 (12.96%)	10 (9.26%)		
ALT/AST elevated			0.464	0.496
G1 + 2	105 (97.22%)	102 (94.44%)		
G3 + 4	3 (2.78%)	6 (5.56%)		
Skin			0.000	1.000
G1 + 2	92 (85.19%)	92 (85.19%)		
G3 + 4	16 (14.81%)	16 (14.81%)		
Mucositis			0.245	0.621
G1 + 2	86 (79.63%)	83 (76.85%)		
G3 + 4	22 (20.37%)	25 (23.15%)		
Nausea			4.888	0.027
G1	105 (97.22%)	97 (89.81%)		
G2	3 (2.78%)	11 (10.19%)		
Vomiting			5.315	0.021
G1	101 (93.52%)	108 (100%)		
G2	7 (6.48%)	0 (0.00%)		

G: Grade.

adverse events (**Table 6**). Notably, Grade 3-4 neutropenia occurred more frequently in the PCIC group (34.26% vs. 19.44%; P = 0.014). Grade 2 nausea was more frequent in the PCIC group (10.19% vs. 2.78%; P = 0.027), while Grade 2 vomiting was absent in the PCIC group compared to 6.48% in the IC group (P = 0.021) (**Table 6**). Other toxicities, including leukopenia, thrombocytopenia, and mucositis, showed no significant differences between the groups (P > 0.05). Overall, while the PCIC regimen was associated with certain increased toxicities, the overall safety profile remained broadly similar between the two treatment groups.

Comparison of voice rehabilitation outcomes

The comparison of auditory-perceptual voice assessments and patient perceptions between the IC and PCIC groups revealed several notable differences. The overall voice grade was significantly higher in the PCIC group compared to the IC group (1.86 ± 0.54 vs. 1.71 ± 0.32; P = 0.015), indicating a perceived worse voice quality in the PCIC group. Similarly, the asthenia parameter showed a statistically significant difference, with the IC group scoring slightly higher than the PCIC group (0.11 ± 0.04 vs. 0.1 ± 0.03; P = 0.032) (**Figure 2**). No significant differences were found between groups for functional, physical, emotional, or total scores, both before and after treatment (P > 0.05 for all) (**Table 7**). Despite the lack of significant differences between groups for all scores, it is important to note that within each group, there was a significant improvement from before to after treatment across all categories (functional, physical, emotional, and total scores), as indicated by highly significant t-tests (P < 0.001 for all comparisons).

Multivariate logistic regression analysis

In the multivariate logistic regression analysis of factors influencing survival outcomes in patients with locally advanced laryngeal and hypopharyngeal cancer, several significant associations were identified. In multivariate analysis, after adjusting for clinical covariates, patients receiving PD-1 inhibitor plus induction chemotherapy (PCIC) had a higher probability of 1-year survival compared to IC alone (Coefficient = 1.892, Standard Error = 0.532, Wald = 12.642, P < 0.001) (**Table 8**). The Grade of Auditory-Perceptual Voice was significantly associated with improved outcomes (Coefficient = 2.793, Standard Error = 0.494, Wald = 5.654, P < 0.001), with an odds ratio (OR) of 16.328 (95% CI: 6.201-42.995), indicating that higher grades of voice quality are linked to better survival outcomes. In contrast, asthenia showed a strong negative association

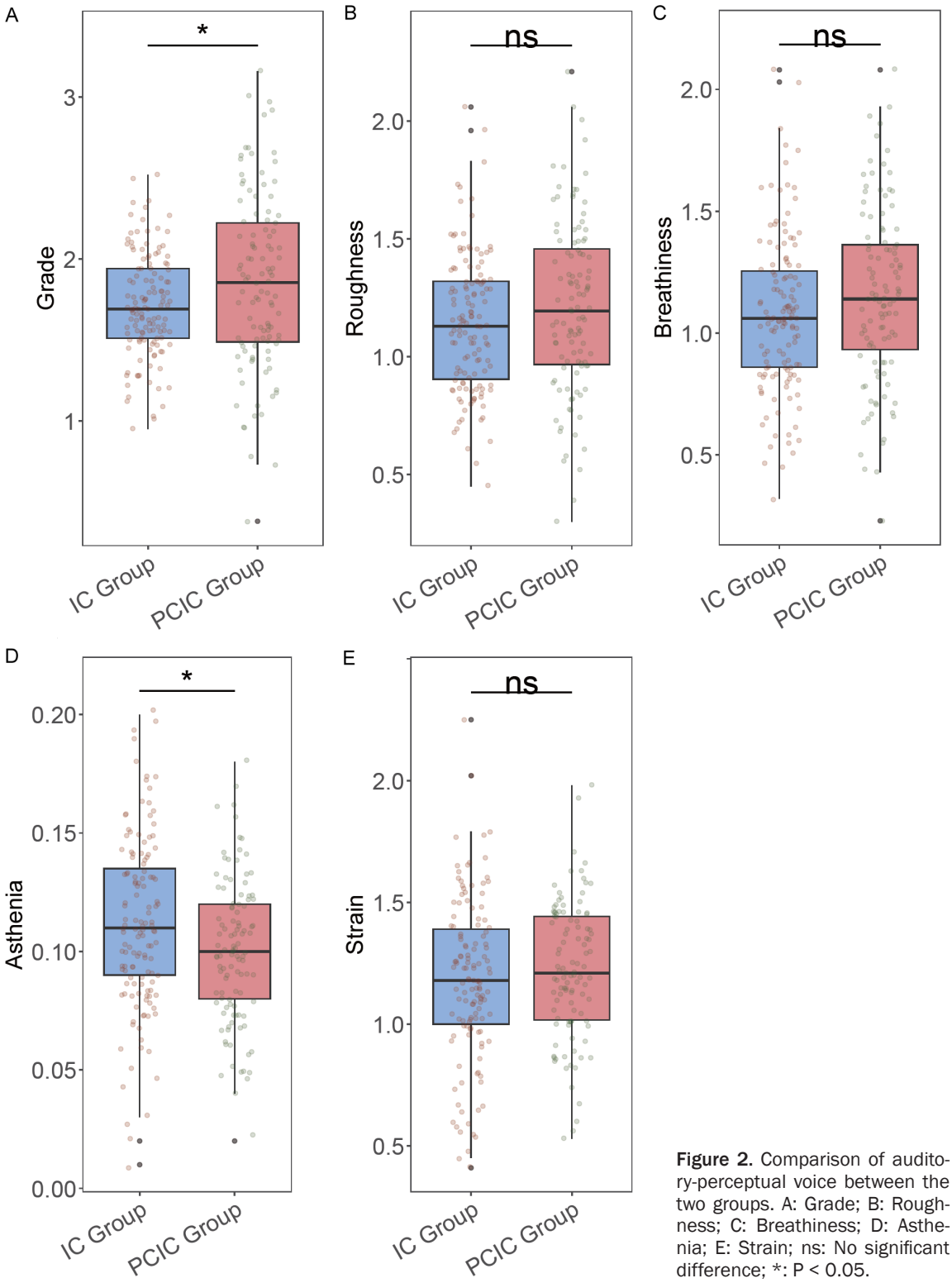

Figure 2. Comparison of auditory-perceptual voice between the two groups. A: Grade; B: Roughness; C: Breathiness; D: Asthenia; E: Strain; ns: No significant difference; *: P < 0.05.

(Coefficient = -39.061, Standard Error = 7.734, Wald = -5.050, P < 0.001). However, the reported OR was incorrectly calculated or reported as 0.000 (95% CI: 0.000-0.000), likely indicating an issue with the data or its interpretation. Complete response (CR) after overall treatment also showed a significant positive association with survival outcomes (Coefficient = 1.354,

Table 7. Comparison of patient perceptions between the two groups

Variable	IC Group (n = 108)	PCIC Group (n = 108)	t	P
Functional score				
Before treatment	11.88 ± 4.41	10.72 ± 4.53	1.911	0.057
After treatment	8.09 ± 2.01	7.95 ± 2.13	0.48	0.632
t	8.127	5.751		
P	< 0.001	< 0.001		
Physical score				
Before treatment	14.78 ± 4.29	14.61 ± 4.60	0.277	0.782
After treatment	10.29 ± 2.81	9.71 ± 2.42	1.623	0.106
t	9.099	9.797		
P	< 0.001	< 0.001		
Emotional score				
Before treatment	9.45 ± 2.88	9.36 ± 2.52	0.259	0.796
After treatment	7.89 ± 2.57	7.56 ± 2.75	0.906	0.366
t	4.200	5.015		
P	< 0.001	< 0.001		
Total score				
Before treatment	41.81 ± 9.39	39.73 ± 9.54	1.615	0.108
After treatment	35.02 ± 9.71	33.26 ± 9.65	1.338	0.182
t	5.224	4.955		
P	< 0.001	< 0.001		

Standard Error = 0.501, Wald = 2.702, P = 0.007), with an OR of 3.874 (95% CI: 1.450-10.346). Neutropenia was significantly negatively associated with survival outcomes (Coefficient = -1.203, Standard Error = 0.538, Wald = -2.234, P = 0.025), with an OR of 0.300 (95% CI: 0.105-0.863), suggesting that the occurrence of neutropenia adversely impacts patient survival rates. Other variables, including CR after induction chemotherapy, 1-year LRRFS, second primary tumors, nausea, and vomiting, did not show statistically significant associations with survival outcomes (P > 0.05 for all).

Discussion

In this study, we observed significant improvements in outcomes with the addition of a PD-1 inhibitor to induction chemotherapy. These findings align with the growing body of evidence supporting the use of immunotherapy in the treatment of head and neck cancers, particularly in enhancing the benefits of conventional chemotherapy.

The enhanced CR rates in the PCIC group can be attributed to the synergistic effects of immunotherapy and chemotherapy. PD-1 inhibitors, such as toripalimab, work by blocking the interaction between PD-1 and its ligands, thereby reactivating T-cell mediated tumor cell killing [23, 24]. This can potentiate the cytotoxic effects of chemotherapy, which often induces immunogenic cell death, releasing tumor antigens and enhancing immune recognition. For instance, Shi et al. reported that PD-1 inhibitors enhance chemotherapy-induced immunogenic cell death by promoting tumor antigen release and dendritic cell activation, leading to increased T-cell infiltration in the tumor microenvironment [25]. This synergy likely underlies the higher CR rates observed in both short-term and long-term assessments.

The improved OS and LRRFS in the PCIC group over one year further support this hypothesis. Immunotherapy's ability to generate a sustained immune response could lead to prolonged tumor surveillance, reducing the likelihood of recurrence [26]. However, the lack of significant differences in progression-free survival and distant metastasis-free survival suggests that while local control is enhanced, systemic control remains a challenge. This highlights the need for further research into combination regimens that may include additional systemic agents to address micrometastatic disease [27].

One area where the anticipated benefit was not statistically significant was in larynx preservation. Although the rate was higher in the PCIC group, the difference did not reach statistical significance. This suggests that while immunotherapy may aid in tumor control, it does not necessarily contribute to organ preservation in the absence of significant tissue-sparing effects. Future studies could explore the integration of organ-preserving surgical techniques alongside PCIC to potentially increase preservation rates. Notably, Wang et al. proposed that PD-1 inhibitors may indirectly preserve organ

Table 8. Multivariate logistic regression analysis of the impact of inhibitors on survival outcomes in patients with locally advanced laryngeal/hypopharyngeal cancer

Variable	Coefficient	Stand Error	Wald	P	OR (95% CI)
Treatment Group (PCIC vs. IC)	1.892	0.532	12.642	< 0.001	6.630 (2.341-18.792)
Grade of Auditory-Perceptual Voice	2.793	0.494	5.654	< 0.001	16.328 (6.201-42.995)
Asthenia	-39.061	7.734	-5.050	< 0.001	0.000 (0.000-0.000)
CR after induction chemotherapy	1.169	0.813	1.439	0.150	3.220 (0.655-15.834)
CR after overall treatment	1.354	0.501	2.702	0.007	3.874 (1.450-10.346)
1-year LRRFS	0.493	0.462	1.066	0.286	1.637 (0.662-4.048)
Second primary tumor	-2.954	1.829	-1.615	0.106	0.052 (0.001-1.878)
Neutropenia	-1.203	0.538	-2.234	0.025	0.300 (0.105-0.863)
Nausea	-1.783	1.807	-0.987	0.324	0.168 (0.005-5.806)
Vomiting	-1.599	1.249	-1.280	0.201	0.202 (0.017-2.338)
Grade of Auditory-Perceptual Voice	2.793	0.494	5.654	< 0.001	16.328 (6.201-42.995)

function by reducing post-treatment fibrosis through immune-mediated suppression of TGF-β signaling [28], a mechanism that warrants validation in future studies.

The study also revealed favorable reductions in treatment failure due to secondary primary tumors in the PCIC group. This is an intriguing finding, suggesting that immune modulation may play a role in reducing second primary tumor risks, possibly through early detection and clearance of preneoplastic lesions by an activated immune system. This potential benefit could represent a significant advantage of immunotherapy and merits further investigation [29, 30].

The PCIC regimen demonstrated significant improvements in survival outcomes and secondary tumor prevention in patients with locally advanced laryngeal and hypopharyngeal cancers. However, it also led to increased incidences of specific toxicities, such as neutropenia and nausea. The exacerbation of neutropenia could be attributed to the immunomodulatory effects of PD-1 inhibitors, which, while beneficial for tumor control, may also enhance the myelosuppressive effects of chemotherapy. This underscores the need for vigilant monitoring and possibly preemptive supportive care to mitigate these adverse effects without compromising chemotherapy's dose intensity [31, 32]. Interestingly, the absence of higher-grade vomiting in the PCIC group suggests that while nausea was more prevalent, vomiting was better managed, potentially due to effective supportive care protocols.

Regarding voice rehabilitation outcomes, the perceptual voice analysis revealed slightly inferior voice quality in the PCIC group. This highlights the complexity of balancing oncologic control with functional outcomes. The paradoxical findings-worse objective vocal grade but better patient-perceived quality-may be related to immune-mediated mucosal changes [33]. The effects of PD-1 inhibitors on mucosal and neural structures involved in phonation could explain these findings [34]. While the PCIC group reported better vocal quality, potentially reflecting psychosocial factors such as improved survival or reduced tumor burden, increased feelings of shame regarding voice issues emphasize the need for comprehensive rehabilitative support, addressing both physiological and psychological recovery aspects.

The GRBAS scale outcomes highlighted potential concerns with voice-related asthenia and overall voice grade. These results may reflect the combined impact of therapy on the neuromuscular components of voice production, particularly considering the extensive involvement of neck structures in both the disease and treatment. The slightly higher asthenia scores raise questions about the impact of systemic treatments on muscle function, suggesting the need for targeted rehabilitation strategies to mitigate these side effects [35].

Given the multifaceted impact of PD-1 inhibitors observed in our study, several future research avenues emerge. One critical area is the identification of biomarkers that can predict the response to PCIC, aiding patient selection

and personalizing treatment regimens. Integrating advanced imaging and molecular profiling could uncover mechanisms of resistance and guide future interventions to consolidate treatment gains [36-38]. Additionally, optimizing dosing schedules and supportive measures to minimize toxicity while preserving efficacy is crucial. The integration of adjunct therapies, such as radioprotectors or tailored antiemetics, could prove valuable in immunotherapy-chemotherapy regimens [39].

Multivariate logistic regression analysis identified auditory-perceptual voice grade and complete response post-treatment as positive predictors of survival outcomes in patients with locally advanced laryngeal/hypopharyngeal cancers, while asthenia and neutropenia emerged as significant negative predictors. Meanwhile, our analysis confirms that PD-1 inhibitors synergize with induction chemotherapy to significantly improve survival, likely through enhanced tumor response. However, the association of PCIC with higher-grade toxicity and voice rehabilitation challenges underscores the need for vigilant supportive care. These findings highlight potential areas for targeted interventions to improve patient outcomes by addressing these key factors. However, the unusual result regarding asthenia requires further investigation to clarify its true impact.

Our findings emphasize the importance of a multidisciplinary approach in managing laryngeal and hypopharyngeal cancers, integrating oncologic, rehabilitative, and supportive care strategies. Incorporating voice therapy and psychological support as part of routine care could enhance post-treatment quality of life by addressing the nuanced needs highlighted by patient-reported outcomes.

Despite these promising findings, several limitations must be considered. The retrospective design introduces inherent biases (e.g., selection and recall bias) that may limit the generalizability of the results. The single-center cohort and modest sample size restrict the applicability of these findings to broader populations. Additionally, the absence of biomarker analysis (e.g., PD-L1 expression) precludes the identification of predictive subgroups. Finally, despite propensity score matching, residual confounding from unmeasured variables (e.g., socioeconomic factors) may persist, and the lack of multivariable analysis limits causal inferences.

To address these limitations, future studies should prioritize prospective, multicenter trials with larger cohorts to validate our findings. Incorporating molecular profiling (e.g., tumor mutational burden, immune microenvironment markers) could provide insight into the mechanisms of response heterogeneity. Advanced statistical approaches, such as machine learning or causal inference models, may help control for complex confounders. Additionally, embedding patient-reported outcomes (PROs) and functional rehabilitation metrics (e.g., longitudinal voice assessments) into trial designs would offer a holistic evaluation of treatment impact. These efforts will clarify the role of PD-1 inhibitors in laryngeal preservation strategies, while balancing efficacy, toxicity, and functional outcomes.

In conclusion, the combination of PD-1 inhibitors with induction chemotherapy offers promising enhancements in survival outcomes and secondary tumor prevention for patients with locally advanced laryngeal and hypopharyngeal cancers, though it presents specific toxicity challenges and impacts voice rehabilitation. The insights from this study pave the way for continued innovation in treatment paradigms, aiming for optimal oncologic and functional outcomes, while emphasizing the importance of holistic patient-centered care in the era of personalized medicine.

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Disclosure of conflict of interest

None.

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Table S1. Baseline characteristics before propensity score matching

Parameters	IC Group (n = 134)	PCIC Group (n = 116)	t/χ^2	P
Male/Female	87 (64.93%)/47 (35.07%)	89 (76.72%)/27 (23.28%)	4.154	0.042
Age (years)	41.27 ± 6.83	40.94 ± 6.49	0.390	0.697
BMI (kg/m^2)	19.42 ± 2.13	19.18 ± 2.24	0.856	0.393
Current Smoking (Yes/no)	109 (81.34%)/25 (18.66%)	85 (73.28%)/31 (26.72%)	2.328	0.127
Marital status (Married/Others)	113 (84.33%)/21 (15.67%)	99 (85.34%)/17 (14.66%)	0.050	0.823
Clinical stage			3.870	0.049
III	59 (44.03%)	37 (31.9%)		
IVA	75 (55.97%)	79 (68.1%)		
T stage			5.564	0.135
T1	19 (14.18%)	9 (7.76%)		
T2	16 (11.94%)	11 (9.48%)		
T3	53 (39.55%)	41 (35.34%)		
T4	46 (34.33%)	55 (47.41%)		
N stage			0.318	0.853
N1	21 (15.67%)	17 (14.66%)		
N2	68 (50.75%)	63 (54.31%)		
N3	45 (33.58%)	36 (31.03%)		
Histology (nonkeratinizing)			5.488	0.019
Differentiated	27 (20.15%)	11 (9.48%)		
Undifferentiated	107 (79.85%)	105 (90.52%)		
Swallowing Difficulty	103 (76.87%)	86 (74.14%)	0.251	0.617
Hoarseness	79 (58.96%)	65 (56.03%)	0.217	0.641
Malnutrition	92 (68.66%)	64 (55.17%)	4.818	0.028
Dyspnea	50 (37.31%)	47 (40.52%)	0.269	0.604
Family History of Cancer	18 (13.43%)	15 (12.93%)	0.014	0.907
Personal History of Cancer	20 (14.93%)	14 (12.07%)	0.432	0.511

BMI: Body Mass Index; T stage: Tumor stage; N stage: Node stage; IC: Induction Chemotherapy.