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Low-Dose Nivolumab Added to Neoadjuvant Chemotherapy in Locally Advanced Head and Neck Squamous Cell Carcinoma: Study from a Resource-Constrained Setting

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ABSTRACT

Background: Head and neck squamous cell carcinoma (HNSCC) remains a major cause of cancer-related morbidity and mortality, particularly in low- and middle-income countries where patients frequently present with locally advanced unresectable disease. Although immune checkpoint inhibitors improve survival in recurrent and metastatic settings, their high-cost limits routine use in resource-constrained environments. We evaluated the clinical outcomes and cost implications of incorporating low dose nivolumab into neoadjuvant chemotherapy for locally advanced unresectable or borderline resectable HNSCC.
Methods: In this prospective single-center study, 50 patients with AJCC stage III–IVA non-metastatic HNSCC were treated between April 2023 and March 2024. Patients received paclitaxel and carboplatin combined with nivolumab 40 mg every three weeks as induction therapy. The primary endpoint was overall response rate (ORR) assessed by RECIST v1.1. Secondary endpoints included conversion to definitive therapy, pathological complete response (pCR), progression-free survival (PFS), overall survival (OS), treatment-related toxicity (CTCAE v5.0), and drug cost comparison.
Results: Forty-four patients were evaluable for response. The ORR was 88.6% (complete response 4.5%, partial response 84%). Among oral cavity tumors, 27.7% were rendered resectable, and 40% of those undergoing surgery achieved pCR. In non-oral cavity tumors, 84.6% proceeded to radical chemoradiotherapy. At a median follow-up of 12 months, one-year PFS and OS were 79.5% and 90.9%, respectively. Grade ≥3 adverse events occurred in 31.5% of patients, with manageable immune-related toxicities. The low-dose regimen reduced nivolumab drug cost per patient by approximately 88.9% compared to standard dosing.
Conclusion: Low dose nivolumab combined with induction chemotherapy demonstrated high response rates and acceptable toxicity in this real-world cohort. This dose-modified approach may represent a practical strategy to improve access to immunotherapy in resource-limited settings. Further randomized studies are warranted.

Keywords*: head and neck squamous cell carcinoma; Concurrent chemoradiotherapy; pathological complete response; hazard ratio; complete response.*

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is among the most common malignancies globally, with rising incidence in developing countries [1]. In India and South-Central Asia, oral cavity cancers predominate, largely due to tobacco exposure [1].

Concurrent chemoradiotherapy (CRT) remains the standard of care for unresectable locally advanced disease. The MACH-NC meta-analysis demonstrated that concomitant chemotherapy improves five-year overall survival by 6.5% in non-metastatic HNSCC [4]. Induction chemotherapy has demonstrated minimal survival advantage, notwithstanding enhanced response rates [4, 5].

Immune checkpoint inhibitors targeting PD-1 have transformed treatment of recurrent/metastatic HNSCC. The CheckMate 141 trial demonstrated improved overall survival with nivolumab versus standard therapy [2], and the KEYNOTE-048 trial established pembrolizumab as first-line therapy in recurrent/metastatic disease [3].

Recent studies suggest that neoadjuvant chemoimmunotherapy may improve pathological response and downstaging [6–9]. The phase III KEYNOTE-689 trial recently demonstrated event-free survival benefit with perioperative pembrolizumab in resectable HNSCC [10].

Pharmacodynamic studies indicate that PD-1 receptor occupancy occurs at doses substantially lower than approved regimens, suggesting a biologic rationale for dose de-escalation [11, 12]. Given cost constraints in LMICs, exploring low-dose strategies is clinically relevant.

We conducted a prospective study to evaluate the clinical outcomes, safety, and cost impact of adding low dose nivolumab to induction chemotherapy in patients with locally advanced unresectable or borderline resectable HNSCC.

PATIENTS AND METHODS

Study design and patient selection

We conducted a single-center prospective study of patients with HNSCC treated at our institution, a 650-bed tertiary hospital in North India, who attended the Oncology OPD of our institution from April 2023 to March 2024. A detailed record of clinical examination and investigations of each patient was compiled. Patients diagnosed with locally advanced (AJCC stage III-IVA) non-metastatic HNSCC and deemed unresectable/borderline resectable at initial presentation were included in the present study. All the patients were discussed in the multidisciplinary tumor board. Eligibility criteria included patients aged ≥ 18 years with histologically confirmed squamous cell carcinoma and an ECOG performance status of 0–2. Only those who received at least three doses of low dose nivolumab as part of the neoadjuvant regimen were included in the present study. The criteria for inoperability used at our institution for HNSCC are extensive involvement of the skin or diffuse peritumoral edema, high infratemporal fossa involvement, significant involvement of the posterior third of the tongue, skull base invasion, fixation to the spine or prevertebral fascia or muscles, and carotid and/or brachial plexus encasement. Exclusion criteria included prior systemic therapy or radiotherapy for HNSCC, recurrent or metastatic disease, active autoimmune disease requiring immunosuppression, uncontrolled intercurrent illness (grade ≥ 2 heart failure, active hepatitis B/C, HIV with CD4 < 200 cells μL^{-1}), baseline grade ≥ 2 peripheral neuropathy, pregnancy or lactation, and any contraindications to chemotherapy or immunotherapy.

- The collected data encompassed baseline demographic information, disease characteristics, treatment details, dates of key events, toxicity data (CTCAE v5.0), and status at outpatient follow-up.
- This study was conducted in accordance with the guidelines approved by the Institutional Review Board Ethics Committee. The study was prospective and involved data collected during routine clinical care and follow-up.

Sample size estimation

A sample size of 50 patients was selected based on the patient influx and the feasibility and availability of nivolumab for poor patients. It was a single-arm, prospective study.

Treatment protocol

Patients received neoadjuvant chemotherapy combined with low dose nivolumab. The primary chemotherapy regimen was a combination of paclitaxel and carboplatin in most patients. Nivolumab was administered at low doses, defined as 40 mg every 3 weeks.

Inj 40 mg of nivolumab IV in normal saline over 30 minutes, Inj Paclitaxel 175 mg per m^2 in Normal Saline over 3 hours, Inj Carboplatin AUC 5 in 5% dextrose over 1 hour with standard premedication were administered.

Outcome measures

The main efficacy outcome we studied was overall response rate (ORR). The other outcomes assessed were progression-free survival (PFS), overall survival (OS), toxicity profile, and cost analysis. PFS was defined as the time from diagnosis to disease progression or death due to any cause, while OS was calculated from diagnosis to the last available follow-up. For patients who underwent surgical resection, the pathological complete response (pCR) was assessed. Toxicity was

evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Response assessment

Tumor response was assessed using RECIST v1.1 criteria [13]. Toxicity was graded using CTCAE version 5.0 [14]. A consensus meeting resolved any discrepancies after two independent radiologists assessed the response. During the meeting, both radiologists looked at the scans together, talked about how their assessments were different, and came to an agreement on the final response classification. If the two senior radiologists couldn't agree, a third senior radiologist was asked to make the final decision.

Cost analysis was conducted to assess the direct costs of utilizing a low dose nivolumab regimen compared to standard dosing. The median absolute dose of nivolumab administered per patient was calculated based on the dosing frequency and total number of doses received. The median cost per patient was derived by multiplying the median dose by the cost per milligram, which was determined based on the current pricing at our center for available vial sizes (40 mg and 100 mg). The percentage reduction in drug cost per patient when using the low-dose approach versus standard regimens was also calculated.

Statistical analysis

Descriptive statistics were used to summarize patient demographics and clinical characteristics. Categorical variables were compared using chi-square or Fisher's exact tests, while continuous variables were compared using independent t-tests. Normality of continuous variables was assessed visually with histograms and Q–Q (quantile–quantile) plots.

Survival outcomes, including progression-free survival (PFS) and overall survival (OS), were estimated using the Kaplan–Meier method, with comparisons between groups performed using the log-rank test. A p-value of < 0.05 was considered statistically significant. All statistical analyses were conducted using IBM SPSS Statistics v26 and R v4.1. 2. Graphs and figures were generated using the *ggplot2* and *survminer* packages in R v4.1. 2.

RESULTS

Patient Characteristics

Between April 2023 and March 2024, a total of 50 patients with locally advanced unresectable or borderline resectable non-metastatic head and neck squamous cell carcinoma were enrolled [Table 1]. The median age at diagnosis was 54 years. The cohort was predominantly male (42 patients, 84%), reflecting the known epidemiologic distribution of HNSCC in the region. A history of tobacco exposure was documented in 40 patients (80%).

With respect to disease stage, 14 patients (28%) had stage III disease, and 36 patients (72%) had phase IVA disease at presentation. The oral cavity was the most common primary site, accounting for 21 cases (41%). Other primary sites included hypopharynx (10 patients, 20%), larynx (10 patients, 20%), and oropharynx (9 patients, 18%). All patients were deemed unresectable or borderline resectable at baseline following multidisciplinary tumor board assessment.

Table 1. Baseline Patient Characteristics (n=50)

Characteristic	N (%)
Total patients	50
Median age	54 years
Male sex	42 (84%)
Tobacco exposure	40 (80%)
Stage III	14 (28%)
Stage IVA	36 (72%)
Oral cavity	21 (41%)
Hypopharynx	10 (20%)
Oropharynx	9 (18%)
Larynx	10 (20%)

Radiologic Tumor Response

Radiologic response assessment according to RECIST v1.1 criteria was available for 44 patients [Table 2]. Six patients were not evaluable due to inadequate baseline imaging or loss to follow-up prior to the first radiologic reassessment; however, all patients were included in survival analyses.

Table 2. Radiologic Response (RECIST v1.1) (n=44)

Response	N (%)
Complete response	2 (4.5%)

Partial response	37 (84.1%)
Stable disease	4 (9.1%)
Progressive disease	1 (2.3%)
Overall response rate (CR+PR)	39 (88.6%)

Among evaluable patients, complete response (CR) was observed in 2 patients (4.5%), partial response (PR) in 37 patients (84.1%), stable disease (SD) in 4 patients (9.1%), and progressive disease (PD) in 1 patient (2.3%). The overall response rate (ORR; CR + PR) was therefore 88.6% (39 of 44 patients), indicating substantial tumor regression following induction chemoimmunotherapy.

Site-specific response patterns were observed. Laryngeal primaries demonstrated a 100% radiologic response rate, whereas oral cavity tumors exhibited an ORR of 72.2%. These findings suggest differential responsiveness across anatomic subsites, though subgroup numbers were limited.

Conversion to Definitive Radical Therapy

Following induction therapy and multidisciplinary reassessment, 27 of 50 patients (54%) proceeded to definitive radical treatment [Table 3]. Of these, 5 patients (10% of the total cohort) underwent surgical resection, and 22 patients (44%) received radical chemoradiotherapy. The remaining 23 patients (46%) did not proceed to radical treatment due to persistent unresectability, disease progression, or clinical ineligibility.

Table 3. Conversion to Definitive Radical Therapy (n=50)

Category	N (%)
Definitive surgery	5 (10%)
Radical chemoradiotherapy	22 (44%)
Total radical therapy	27 (54%)
No radical therapy	23 (46%)

Among patients with oral cavity tumors, 5 of 18 initially unresectable cases (27.7%) were rendered operable following induction therapy. Notably, 2 of these 5 patients (40%) achieved pathological complete response (pCR) on surgical histopathologic examination, representing 11.1% of the total oral cavity subgroup.

In contrast, among 26 patients with non-oral cavity tumors, 22 patients (84.6%) proceeded to radical chemoradiotherapy, reflecting a high conversion rate in these subsites.

Survival Outcomes

At a median follow-up of 12 months, a total of 10 progression events were recorded among the 50 enrolled patients. Median progression-free survival (PFS) and overall survival (OS) were not reached at the time of analysis. The estimated one-year PFS rate was 79.5%, and the one-year OS rate was 90.9%. Kaplan–Meier survival curves are presented in Figure 1. Patients undergoing radical therapy had significantly improved PFS (HR 0.09; 95% CI 0.01–0.68; $p < 0.001$). Survival details are summarized in Table 4.

Table 4. Progression-Free Survival by Radical Therapy Status

Group	n	Events	Median PFS	HR (95% CI)
Radical therapy	27	1	Not reached	0.09 (0.01–0.68)
Non-radical therapy	23	9	10.9 months	
Adjusted HR				0.12 (p=0.03)

Impact of Definitive Radical Therapy on PFS

Survival outcomes differed markedly according to receipt of definitive radical therapy. Among the 27 patients who underwent radical treatment, only 1 patient (3.7%) experienced disease progression during follow-up. In contrast, 9 of 23 patients (39.1%) in the non-radical group developed progression events.

Median PFS was not reached in the radical therapy group, whereas it was 10.9 months in the non-radical group. Univariable Cox proportional hazards regression analysis demonstrated that receipt of radical therapy was associated with a substantially reduced risk of progression (hazard ratio [HR] 0.09; 95% confidence interval [CI], 0.01–0.68), corresponding to an approximate 91% relative reduction in risk [Figure 2].

Multivariable Cox regression analysis adjusting for clinical stage (III vs IVA), primary tumor site (oral cavity vs non-oral cavity), and tobacco exposure confirmed that definitive radical therapy remained independently associated with improved

PFS (adjusted HR 0.12; p = 0.03). Stage IVA disease showed a non-significant trend toward inferior PFS, while tumor site and tobacco exposure were not independently predictive after adjustment. Given the limited number of events (n = 10), the multivariable analysis was considered exploratory.

Toxicity Analysis

Treatment-related adverse events were evaluated using CTCAE version 5.0 criteria [Table 5]. Hematologic toxicities were common but manageable. Neutropenia occurred in 18 patients (36%), with grade ≥3 neutropenia in 7 patients (14%). Anemia was observed in 16 patients (32%), including grade ≥3 anemia in 3 patients (6%). Thrombocytopenia occurred in 10 patients (20%), with 2 cases (4%) classified as grade ≥3.

Non-hematologic toxicities included fatigue (20 patients, 40%), nausea/vomiting (14 patients, 28%), and peripheral neuropathy (12 patients, 24%). Grade ≥3 fatigue and gastrointestinal toxicity occurred in 3 patients (6%) and 2 patients (4%), respectively. Grade ≥3 peripheral neuropathy was documented in 2 patients (4%).

Immune-related adverse events were infrequent and manageable. Hypothyroidism occurred in 4 patients (8%) and was grade 1–2 in all cases. Immune-related hepatitis occurred in 2 patients (4%), including one grade 3 event (2%) that required corticosteroid therapy. One patient (2%) developed grade 3 pneumonitis. Overall, grade ≥3 adverse events occurred in 31.5% of patients. No treatment-related deaths were observed.

Cost Analysis

A cost comparison between standard nivolumab dosing regimens (240 mg every two weeks or 3 mg/kg weight-based dosing) and the fixed 40 mg dosing strategy was performed. The low-dose regimen resulted in an approximate 88.9% reduction in per-patient nivolumab drug expenditure. This substantial reduction in drug cost significantly improves treatment affordability in resource-constrained settings and may enhance access to immunotherapy in LMIC populations.

Overall, the addition of low dose nivolumab to induction chemotherapy resulted in high radiologic response rates, enabled conversion to definitive radical therapy in more than half of patients, demonstrated acceptable toxicity, and produced encouraging early survival outcomes while markedly reducing treatment cost.

DISCUSSION

This prospective study demonstrates that the addition of low-dose nivolumab to induction chemotherapy yields high radiologic response rates, facilitates conversion to definitive radical therapy, and achieves encouraging early survival outcomes in patients with locally advanced unresectable or borderline resectable head and neck squamous cell carcinoma (HNSCC). Importantly, this clinical activity was achieved alongside an approximately 85–90% reduction in drug cost compared with conventional dosing strategies. These findings suggest dose-optimized immunotherapy in resource-constrained contexts is biologically plausible and practicable.

Clinical efficacy and response depth

The ORR of 88.6% in this cohort is impressive and compares favourably to prior induction chemotherapy studies, which have shown response rates between 60% and 75% [4,5]. Cross-trial comparisons must be approached with caution; nevertheless, this degree of tumour reduction aligns with neoadjuvant chemoimmunotherapy studies, indicating synergistic effects of cytotoxic treatment and PD-1 inhibition [6–9,15–18].

Meta-analyses from 2024 to 2025 support neoadjuvant HNSCC chemoimmunotherapy. The pooled pathological response rates of Cao and Zhu et al. were much greater than chemotherapy alone [15,16]. Widjaja et al.'s updated analysis and Frontiers in Oncology's collaborative pooled data validated early survival signals and enhanced downstaging rates with immunotherapy-based induction techniques [17,18]. ORR and conversion rates in our data match these pooled findings.

The high transition rate to definitive radical therapy (54%), however, was the most therapeutically important outcome. The goal of curative-intent treatment for locally progressed HNSCC is crucial. Radical treatment greatly enhanced progression-free survival. The progression hazard ratio was 0.09 in univariable analysis and 0.12 in multivariable correction, showing a clear correlation between conversion and survival benefit.

Although radical therapy allocation was not randomized and likely reflects tumour biology and response depth, the amount of survival separation shows that induction chemoimmunotherapy may dramatically alter chosen patients' therapeutic trajectory. Thus, radical therapy conversion is a clinically actionable intermediate endpoint.

Pathologic Response and Biological Activity

The achievement of pathological complete response (pCR) in 40% of resected oral cavity tumours provides additional evidence of biological efficacy. Pathologic response has increasingly been recognized as a surrogate marker for long-term

outcomes in multiple solid tumours, including HNSCC [6,15–18]. Despite the modest number of resected cases in this investigation, the pCR subgroup's absence of recurrence at last follow-up indicated disease elimination.

A moderate but statistically significant inverse connection was seen between cumulative nivolumab dose and tumour size decrease. Despite caution, this study supports the idea that biological activity may be sustained at lower doses due to receptor saturation kinetics rather than linear dose-response dynamics.

Biological Reasons for Dose De-Escalation
Pharmacodynamic studies show that PD-1 receptor occupancy on circulating T cells approaches saturation at low drug concentrations, supporting low-dose nivolumab [11,12]. Early-phase studies demonstrate receptor occupancy at dosages below recommended regimens, suggesting immune checkpoint blockade plateaus [11,12]. Once receptor binding is biologically sufficient, dosage escalation may not increase T-cell activation correspondingly.

This nonlinear pharmacodynamic profile supports dosage optimization scientifically. This work shows that lower fixed doses can induce therapeutic immune activation with preserved clinical efficacy, acceptable toxicity, and robust survival signals. No recent meta-analyses of neoadjuvant immunotherapy [15–18] have examined dose-optimization techniques, underscoring their novelty.

Safety Profile
Its safety profile matched paclitaxel, carboplatin, and PD-1 inhibitor toxicities [2,11]. About one-third of patients experienced Grade ≥3 adverse events, mostly due to hematologic damage. Without treatment-related death, immune-related adverse events were rare and treatable.

Importantly, dose decrease did not reduce immunologic activity or immune-related damage. The incidence of hypothyroidism, hepatitis, and pneumonitis matches pivotal trial PD-1 blockade characteristics [2,11].

Survival and Prognosis
At median follow-up of 12 months, one-year PFS and OS were 79.5% and 90.9%. We missed median survival targets. These early survival estimates are consistent with survival signals reported in neoadjuvant immunotherapy trials and pooled analyses [15–17].

Multivariable Cox regression demonstrated that receipt of radical therapy remained independently associated with improved PFS after adjustment for stage, tumour site, and tobacco exposure. Although the limited number of events constrains statistical robustness, the consistency of effect strengthens the inference that successful conversion to radical therapy is the dominant prognostic determinant in this setting.

Pharmacoeconomic Impact in LMIC Context
The economic implications of this strategy are particularly significant. Conventional nivolumab dosing regimens impose substantial financial burden in LMIC settings. In contrast, the 40 mg fixed-dose regimen reduced per-patient induction drug cost by approximately 85–90%.

Financial toxicity frequently limits access to immunotherapy in LMIC environments. Recent global oncology policy discussions have emphasized the need for cost-optimized strategies without compromising clinical efficacy. Modern meta-analyses [15–17] show strong biological activity, therefore dose de-escalation techniques that preserve therapeutic benefit while reducing cost should be considered.

Health systems savings per responder exceeded 80% compared to typical dosage settings. Reductions may enhance adherence, minimize catastrophic health costs, and increase equal access within public oncology resources.

Recent 2024–2025 meta-analyses show that neoadjuvant chemoimmunotherapy enhances HNSCC pathological response and downstaging [15–17]. These studies focused on high-income standard-dose immune checkpoint inhibitor regimens.

The present investigation shows that considerably decreased nivolumab exposure can provide equivalent biological and clinical signals. By integrating pharmacodynamic rationale with pharmacoeconomic evaluation, this study introduces a novel and globally relevant dimension to neoadjuvant immunotherapy research.

Limitations
This was a single-centre prospective cohort without a randomized comparator arm. The contribution of low-dose nivolumab cannot be definitively separated from chemotherapy effects. The sample size was modest, and the number of progression

events was limited, restricting multivariable modelling stability. Follow-up remains relatively short, and biomarker analyses such as PD-L1 expression were not incorporated.

Despite these limitations, the magnitude of response, conversion rate, survival separation, and cost reduction provide compelling hypothesis-generating evidence. Future studies should include randomized comparisons of standard-dose versus low-dose PD-1 blockade in induction settings. Formal cost-effectiveness modelling incorporating quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) would strengthen economic conclusions. Biomarker-driven patient selection strategies may further optimize benefit. Longer follow-up is essential to confirm durability.

CONCLUSION

In this prospective cohort of patients with locally advanced unresectable HNSCC, low-dose nivolumab combined with induction chemotherapy achieved high radiologic response rates, enabled conversion to definitive radical therapy in more than half of patients, maintained acceptable toxicity, and reduced drug cost by nearly 90%. Downstaging techniques are useful in the clinic, as shown by the strong link between conversion and longer progression-free survival.

This method is safe for living things and smart for the economy. It could change the way immunotherapy is provided in places with few resources. Randomized validation is needed to be sure that the medicine works, lasts, and is worth the money in the long run.

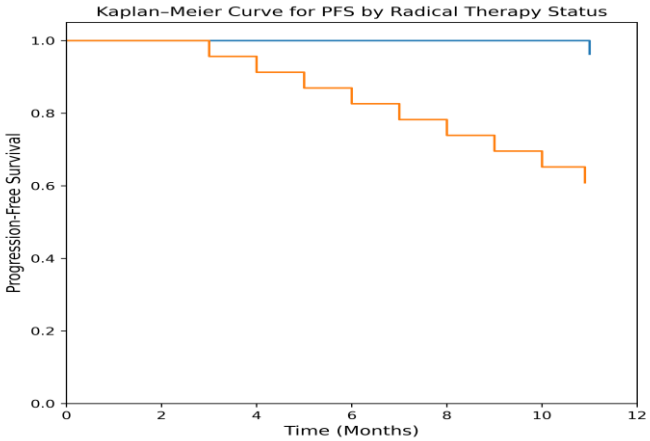

Figure 1. Kaplan–Meier Curve for Progression-Free Survival According to Radical Therapy Status

The Kaplan–Meier plot shows the difference in progression-free survival (PFS) between people who had definitive radical treatment (surgery or radical chemoradiotherapy) and those who did not have definitive radical therapy. The PFS of patients who got radical therapy was much better than that of patients who did not get radical therapy. The median PFS for the non-radical group was 10.9 months, while it was not met in the radical therapy group. The risk of progression is 0.09 (95% CI: 0.01-0.68). Log-rank $p < 0.001$.

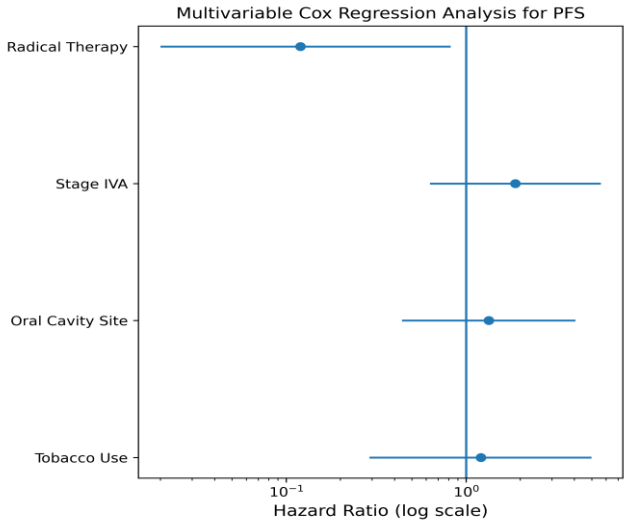

Figure 2. Multivariable Cox Proportional Hazards Regression Analysis for Progression-Free Survival

A forest plot shows a multivariable Cox regression study that looks at factors linked to progression-free survival (PFS). Acceptance of definitive radical treatment was linked to a longer PFS (adjusted HR 0.12; p = 0.03). After taking everything into account, clinical stage IVA, main tumour site (oral cavity vs. non-oral cavity), and smoking history were not linked to PFS on their own. The horizontal bars show 95% confidence intervals, and the straight line shows that HR = 1.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F: Global cancer statistics. 202036185, 2021:209-249. 10.3322/caac.21660
2. Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L, et al.: Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med. 2016:1856-1867. 10.1056/NEJMoa1602252
3. Burtness B, Harrington KJ, Greil R, Soulières D, Tahara M, de Castro G Jr, et al.: Pembrolizumab alone or with chemotherapy vs cetuximab with chemotherapy in recurrent/metastatic HNSCC (KEYNOTE-048). Lancet. 2019:1915-1928. 10.1016/S0140-6736(19)32591-7
4. Pignon JP, le Maître A, Maillard E, Bourhis J; MACH-NC Collaborative Group: Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): update of 107 randomized trials. Radiother Oncol. 2009:4-14. 10.1016/j.radonc.2009.04.014
5. Cohen EEW, Karrison TG, Kocherginsky M, Mueller J, Egan R, Huang CH, et al.: DeCIDE: phase III randomized trial of induction chemotherapy in locally advanced head and neck cancer. J Clin Oncol. 2014:2735-2743. 10.1200/JCO.2013.54.6309
6. Uppaluri R, Campbell KM, Egloff AM, Zolkind P, Skidmore ZL, Nussenbaum B, et al.: Neoadjuvant and adjuvant pembrolizumab in resectable locally advanced HNSCC. Clin Cancer Res. 2020:5140-5152. 10.1158/1078-0432.CCR-20-1695
7. Wise-Draper TM, Old MO, Worden FP, O'Neill A, Cohen EEW, Chau N, et al.: Neoadjuvant nivolumab in resectable HNSCC. J Clin Oncol. 2022:138-149. 10.1200/JCO.21.01391
8. Zhang C, Chen YP, Jiang W, Liu X: Zhang J, Zhou GQ, et al. Neoadjuvant camrelizumab plus chemotherapy in locally advanced HNSCC. J Clin Oncol. 2021:2784-2792. 10.1200/JCO.21.00385
9. Leidner R, Sanmamed MF, Young K, et al.: Neoadjuvant immunoradiotherapy in head and neck cancer. Nat Med.2021. 27:1046-1052.10.1038/s41591-021-01320-x
10. Harrington KJ, et al.: KEYNOTE- 689: Phase III trial of perioperative pembrolizumab in resectable HNSCC. Presented at ASCO Annual Meeting. 2024,
11. Brahmer JR, Drake CG, Wollner I: Powderly JD, Picus J, Sharfman WH, et al. Phase I study of anti-PD-1 antibody nivolumab. J Clin Oncol. 2010:3167-3175. 10.1200/JCO.2009.26.7609
12. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al.: Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012:2443-2454. 10.1056/NEJMoa1200690
13. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al.: New response evaluation criteria in solid tumours: RECIST guideline (version 1.1). Eur J Cancer. 2009:228-247. 10.1016/j.ejca.2008.10.026
14. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. 2017, //ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm:
15. Cao LM, Yu YF, Li ZZ, Wang GR, Xiao Y, Luo HY, et al.: Neoadjuvant chemoimmunotherapy for resectable head and neck squamous cell carcinoma: systematic review and meta-analysis. Ann Surg Oncol. 2025:5206-5217. 10.1245/s10434-025-17195-y
16. Zhu X, Qiu J, Zhang Y, Lin C, Wang X, Shi X, et al.: Neoadjuvant chemoimmunotherapy for locally advanced squamous cell carcinoma of the head and neck: systematic review and meta-analysis. Pharmacol Res. 2025212, 107598. 10.1016/j.phrs.2025.107598
17. Widjaja W, Ng I, Shannon N, Iyer NG: Neoadjuvant immunotherapy in resectable HNSCC: updated systematic review and meta-analysis. Ann Surg Oncol. 202532, 2713-2724. 10.1245/s10434-024-16587-w