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Additional immunotherapy to standard of care for unresectable locally advanced head and neck squamous cell carcinoma: a meta-analysis

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 January 2025 and was last updated on 24 January 2025.

INTRODUCTION

Review question / Objective The role of immunotherapy in the treatment of locally advanced head and neck squamous cell carcinoma (LA HNSCC) remains uncertain, particularly in cases of unresectable LA HNSCC. This meta-analysis aims to evaluate the efficacy of immunotherapy in patients with unresectable LA HNSCC through a systematic review of the existing literature.

Condition being studied Head and neck squamous cell carcinomas rank as the sixth most prevalent type of cancer globally, accounting for approximately 830,000 new cases and 430,000 fatalities annually. The anatomical sites affected by HNSCC encompass the larynx, hypopharynx, oropharynx, nasopharynx, oral cavity, nasal cavity, and paranasal sinuses. Notably, around 60% of HNSCC patients are diagnosed with locally advanced disease. Standard treatment regimens typically include radical surgical intervention followed by adjuvant therapies, such as induction chemotherapy, adjuvant radiotherapy, or CCRT. Postoperative chemoradiotherapy has been shown to significantly enhance clinical outcomes compared to postoperative radiotherapy alone in patients presenting with high-risk factors, such as positive surgical margins and extracapsular involvement in lymph nodes. Induction chemotherapy holds substantial value for patients with LA HNSCC, with the TPF regimen (paclitaxel, cisplatin, and 5-fluorouracil) being widely utilized to improve PFS. The current standard of care for unresectable patients with locally advanced HNSCC is high-dose cisplatin-based CCRT. For patients who are unsuitable for cisplatin-based CCRT due to advanced age or compromised medical conditions, the alternative SOC is a combination of radiotherapy and cetuximab. Despite advancements in treatment, the prognosis for patients with locally advanced HNSCC remains poor, with 50% of patients experiencing

locoregional recurrence or distant metastasis, which significantly contributes to HNSCC-related mortality. Consequently, it is imperative to investigate novel treatment regimens to enhance patient outcomes.

The primary targets of cancer immunotherapy include PD-1 receptors, PD-L1 receptors, and CTLA-4. There is an increasing body of evidence supporting the use of immunotherapy across various malignancies, including lung cancer, colorectal cancer, and melanoma, among others. The efficacy of immunotherapy in HNSCC has also been extensively investigated[8]. Nivolumab and pembrolizumab, both immune checkpoint inhibitors, have been approved for the treatment of platinum-refractory recurrent/metastatic HNSCC. Pembrolizumab, either as monotherapy for patients with a PD-L1 combined positive score ≥1 or in combination with chemotherapy, has been approved for first-line treatment of recurrent/metastatic HNSCC based on the significant findings from the KEYNOTE-048 study. Inspired by the success observed in recurrent/metastatic HNSCC, numerous studies have investigated the potential benefits of incorporating immunotherapies into the standard of care for patients with unresectable locally advanced recurrent/metastatic HNSCC patients, aiming to enhance disease control and patient survival. However, to date, the integration of immunotherapy with standard of care has not yielded significant advancements and has not altered clinical diagnostic and treatment practices. Further research is required to identify the specific patient population that may benefit from the combination of immunotherapy and standard of care. The objective of this systematic review is to collate evidence from published clinical trials that compare the efficacy of immunotherapy combined with the standard of care versus standard of care alone in patients with unresectable locally advanced HNSCC. This review aims to evaluate and synthesize findings from studies investigating the use of immune checkpoint inhibitors in locally advanced HNSCC, either as monotherapy or in combination with chemotherapy, radiotherapy, or other checkpoint inhibitors.

METHODS

Participant or population

(1) ≥18 years old;
(2) histologically proven squamous-cell carcinoma;
(3) patients with unresectable stage III-IVB HNSCC of oral cavity, oropharynx, hypopharynx or larynx.

Intervention Immunotherapy + concurrent chemoradiotherapy; Immunotherapy + radiotherapy.

Comparator High-dose cisplatin-based concurrent chemoradiotherapy; Cetuximab + radiotherapy.

Study designs to be included Randomized controlled trials, cohort study, and single-arm studies.

Eligibility criteria Inclusion and exclusion criteria. Included studies fulfilled the following criteria: (1) ≥18 years old; (2) histologically proven squamous-cell carcinoma; (3) patients with unresectable stage III-IVB HNSCC of oral cavity, oropharynx, hypopharynx or larynx; (4) immunotherapy + CCRT or immunotherapy + RT; (5) CCRT or Cetuximab + RT; (6) available PFS or OS. Exclusion criteria: (1) recurrent and metastatic HNSCC; (2) operable LA HNSCC; (3) data were not available for analysis; (4) animal experiments, cell research, reviews, meta-analysis, duplicates, case reports, or letters; (5) studies with patient number less than 10.

Information sources This systematic review and meta-analysis adhered to the PRISMA reporting guidelines. A comprehensive search was conducted across several electronic databases, including PubMed, Embase, Medline, the Cochrane Library, and Google Scholar, up to August 2023. The search strategy employed a combination of standardized search terms and keywords, such as head and neck squamous cell carcinoma, head and neck cancer, head and neck malignant tumor, locally advanced head and neck squamous cell carcinoma, immunotherapy, immune checkpoint inhibitor, PD-1, PD-L1 and CTLA-4.

Main outcome(s) PFS and OS.

Quality assessment / Risk of bias analysis The risk of bias was evaluated by two independent investigators utilizing the Cochrane Risk of Bias tool prior to the execution of statistical analyses. Each included study was assessed based on seven criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias.

Strategy of data synthesis We used the Review Manger, Stata and R software to conduct statistical analysis. PFS and OS reported as hazard ratio with 95% confidence interval were regarded as primary

endpoints. The longer follow-up outcomes of clinical trials aiming the same population of subjects would be selected. In the single-group rate meta-analysis, cohort study and randomized controlled trials were divided into two single-arm studies to conduct analysis.

Subgroup analysis We divided the patients into different subgroups based on clinical characteristics in specific studies.

Sensitivity analysis Sensitivity analysis was performed to analyze the stability and reliability of the pooled results.

Country(ies) involved China.

Keywords unresectable; LA HNSCC; immunotherapy; meta-analysis.

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