INPLASY

Understanding the Lymph Node Microenvironment in Metastatic and Non-Metastatic Head and Neck Squamous Cell Carcinoma: A Systematic Review

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Completed but not published.

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 17 August 2026 and was last updated on 17 August 2026.

INTRODUCTION

Review question / Objective Population
The population consisted of patients diagnosed with HNSCC, with or without lymph node involvement. All tumor localizations of HNSCC, including oropharyngeal, lar-yngeal, hypopharyngeal, oral, and nasopharyngeal squamous cell carcinoma (SCC), were included.

Intervention
Assessment of the immune microenvironment in cervical lymph nodes of patients with HNSCC, with or without lymph node involvement. Additionally, reports exploring the dialogue and immunological communication pathways between the primary tumor and lymph nodes.

Comparison
Comparisons between metastatic and non-metastatic lymph nodes were considered whenever available. Studies comparing tumor-draining lymph nodes with non-tumor-draining lymph nodes, or lymph node tissue with primary tumor tissue were also eligible.

Outcomes
The primary outcome of this study was to investigate the infiltration of immune cells (including innate immune cells – macrophages, dendritic cells, neutrophils, and natural killer cells and adaptive immune cells – T helper cells, cytotoxic T cells, regulatory T cells, B cells, lymphocytes) in the lymph nodes of HNSCC, both with and without lymph node metastasis. The secondary outcome aimed to examine tumor characteristics (TNM staging, histopathology) and survival outcomes such as overall survival (OS) and disease-free survival (DFS) to evaluate the impact of the lymph node microenvironment on the prognosis of HNSCC.

Timing
Extensive research was performed and relevant articles published between 1990 and 2025 were eligible for inclusion.

Setting
Prospective and retrospective clinical trials investigating the immune microenvironment in cervical lymph nodes of patients with HNSCC were included.

The following criteria were used for exclusion:
(1) Studies that did not investigate the lymph node immune microenvironment and cell infiltration in HNSCC.
(2) Studies focusing on indicators other than immune cells, such as cytokines, chemokines, gene expression, growth factors, endothelial cells, and fibroblasts.
(3) Papers that were not available or not written in English, as well as reviews, public communications, posters, personal opinions, or letters.

Condition being studied Head and neck squamous cell carcinoma (HNSCC) ranks as the sixth leading cause of cancer worldwide. The five-year survival rate remains poor and has not improved in the past 20 years. In addition to primary treatments such as surgery, chemotherapy, and radiotherapy, immunotherapy has shown promising results. However, identifying which patients will benefit from these novel approaches remains a major clinical challenge. There is limited information and significant uncertainty regarding disease progression. The TNM system has been widely used, but offers limited guidance in predicting treatment response or guiding therapeutical de-escalation.
There is increasing evidence suggesting that the immune microenvironment strongly influences disease prognosis and treatment response. Recent research on immune checkpoint inhibitors has proven that the immune cells surrounding tumor cells are able to combat cancer. The specific distribution of immune cells in the tumor microenvironment (TME) of HNSCC has been shown to significantly impact their favorable prognosis.

METHODS

Participant or population The population consisted of patients diagnosed with HNSCC, with or without lymph node involvement. All tumor localizations of HNSCC, including oropharyngeal, laryngeal, hypopharyngeal, oral, and nasopharyngeal squamous cell carcinoma (SCC), were included.

Intervention Assessment of the immune microenvironment in cervical lymph nodes of patients with HNSCC, with or without lymph node involvement. Additionally, reports exploring the dialogue and immunological communication pathways between the primary tumor and lymph nodes.

Comparator Comparisons between metastatic and non-metastatic lymph nodes were considered whenever available. Studies comparing tumor-draining lymph nodes with non-tumor-draining lymph nodes, or lymph node tissue with primary tumor tissue were also eligible.

Study designs to be included Prospective and retrospective clinical trials.

Eligibility criteria Prospective and retrospective clinical trials investigating the immune microenvronment in cervical lymph nodes of patients with HNSCC were included.

Information sources Electronic searches were conducted in PubMed, Scopus, and the Cochrane Library to identify studies investigating the immune microenvironment of cervical lymph nodes in patients with head and neck squamous cell carcinoma.

Main outcome(s) The primary outcome of this study was to investigate the infiltration of immune cells (including innate immune cells – macrophages, dendritic cells, neutrophils, and natural killer cells and adaptive immune cells – T helper cells, cytotoxic T cells, regulatory T cells, B cells, lymphocytes) in the lymph nodes of HNSCC, both with and without lymph node metastasis.

Quality assessment / Risk of bias analysis We collected qualitative data on potential sources of bias in each of the studies. The bias in each study was analyzed using the recommended approach for assessing the risk of bias in non-randomized studies through the Newcastle-Ottawa Scale (NOS) tool. For each domain of bias, studies were classified into one of the three following categories: low, high, unclear risk of bias.

Strategy of data synthesis Due to the heterogeneity of study designs, immune markers, outcomes, and re-porting, quantitative analysis of the data was not performed and considered inappropriate. Consequently, a meta-analysis was not feasible, and a narrative synthesis was conducted. Given these limitations, the certainty of the evidence was not formally assessed.

Subgroup analysis When data were available, subgroup analyses were performed according to lymph node status (metastatic versus non-metastatic), lymph node type (tumor-draining,

sentinel, and control lymph nodes), immune cell populations (macrophages, dendritic cells, neutrophils, natural killer cells, T-helper cells, cytotoxic T cells, regulatory T cells, B cells, and total lymphocytes), HPV status, and survival outcomes, including overall survival and disease-free survival.

Sensitivity analysis No formal sensitivity analysis was performed because a quantitative synthesis was not feasible.

Country(ies) involved Belgium.

Keywords lymph node microenvironment; innate immune system; adaptive immune system; head and neck squamous cell carcinoma; immunological pathways; immune cell distribution.

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