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Malignant melanoma in the head and neck region - A systematic review.

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Abstract

Background
Malignant melanoma of the head and neck (HNM) is a rare but aggressive neoplasm with significant heterogeneity in clinical presentation, biological behavior, and outcomes. This systematic review evaluated the clinical, prognostic, and therapeutic aspects of cutaneous and mucosal HNM, with emphasis on survival outcomes, treatment strategies, and molecular markers such as nicotinamide N-methyltransferase (NNMT).

Methods
A systematic literature search was conducted using PubMed, Scopus, Web of Science, and Google Scholar for studies published from 1977 to March 2024. Inclusion criteria comprised original clinical studies and systematic reviews evaluating HNM patients, including tumor subtypes, survival, treatment modalities (surgery, radiotherapy, or both), and molecular characteristics. Extracted data included demographic distribution, anatomical subsite prevalence, pathological staging, treatment outcomes, and prognostic factors.

Results
Cutaneous HNM was more common in elderly males and frequently involved sun-exposed facial regions, with poorer overall survival than melanomas at other anatomical sites. Mucosal melanoma of the head and neck (MMHN), especially sinonasal and oral variants, demonstrated high local recurrence and distant metastasis rates with limited survival improvement. Combined surgery and radiotherapy (SRT) improved local control and moderately enhanced survival compared to surgery or radiotherapy alone. NNMT overexpression was associated with adverse clinical outcomes across multiple HNM subtypes, suggesting its value as a prognostic biomarker and therapeutic target.

Conclusion
Head and neck melanomas are biologically distinct malignancies with aggressive behavior and challenging management outcomes. Multimodal treatment approaches and integration of molecular biomarkers such as NNMT may improve prognostication and individualized therapy.

Need for future research
Large-scale prospective studies are required to refine staging systems, validate emerging biomarkers, and evaluate targeted therapeutic strategies for improved management of HNM.

Keywords: *Head and Neck Melanoma, Mucosal Melanoma, Cutaneous Malignant Melanoma, Radiotherapy and Surgery, Nicotinamide N-Methyltransferase (NNMT)*
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Introduction

Malignant melanoma is a highly aggressive neoplasm of melanocytic origin characterized by a marked propensity for local invasion and distant metastasis.[1] Although melanoma predominantly arises in cutaneous sites, a subset occurs within the head and neck region, involving both cutaneous and mucosal surfaces.[1,2] Head and neck melanomas (HNMs) present unique diagnostic and therapeutic challenges because of their anatomical complexity, proximity to vital structures, and poorer survival outcomes compared to melanomas arising at other anatomical locations.[4,5]

Cutaneous malignant melanoma (CMM) of the head and neck demonstrates distinct epidemiological and histopathological characteristics when compared with melanomas of the trunk and extremities.[2] These tumors predominantly affect elderly individuals and are strongly associated with chronic ultraviolet (UV) radiation exposure, particularly in sun-exposed facial regions.[2,4] Lentigo maligna melanoma and nodular melanoma are among the most frequently encountered histological subtypes in this region.[2]

Mucosal melanomas of the head and neck (MMHN), although rare, are highly aggressive neoplasms associated with advanced-stage presentation, frequent local recurrence, and early distant metastasis.[3] These lesions commonly arise in the nasal cavity, paranasal sinuses, and oral mucosa and are biologically distinct from cutaneous melanoma because they lack a clear association with ultraviolet radiation exposure.[3,6]

Despite advances in surgical management and adjuvant therapies, the prognosis of HNM remains poor, particularly for mucosal variants.[3,5] Recent studies have evaluated the role of multimodal treatment approaches, including the combination of surgery and radiotherapy, to improve local disease control and survival outcomes.[6] Emerging molecular research has also identified nicotinamide N-methyltransferase (NNMT) as a potential biomarker associated with tumor progression, invasiveness, and poor prognosis in head and neck tumors.[7]

Given the clinical heterogeneity and aggressive biological behavior of HNM, a comprehensive synthesis of the available evidence is necessary. This systematic review aims to evaluate the clinicopathological features, prognostic factors, treatment outcomes, and molecular characteristics of malignant melanoma occurring in the head and neck region, with emphasis on differences between cutaneous and mucosal subtypes, multimodal therapeutic strategies, and the prognostic significance of NNMT.

Methodology

Information sources and search strategy

A systematic literature search was conducted using PubMed, Scopus, Web of Science, and Google Scholar for studies published from January 1977 to March 2024. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords including "head and neck melanoma," "cutaneous malignant melanoma," "mucosal melanoma," "treatment outcomes," "radiotherapy," "surgery," and "nicotinamide N-methyltransferase (NNMT)." Boolean operators ("AND," "OR") were applied to optimize search sensitivity and specificity. Manual screening of reference lists from relevant articles was also performed to identify additional eligible studies.

Eligibility criteria

Studies were included if they:

Involved human subjects diagnosed with malignant melanoma of the head and neck region, including cutaneous and mucosal variants.

Reported clinicopathological, therapeutic, survival, prognostic, or molecular findings related to head and neck melanoma.

Included original research articles such as retrospective studies, prospective studies, population-based analyses, systematic reviews, or meta-analyses.

Were published in the English language.

Studies were excluded if they:

Were case reports, editorials, conference abstracts without full-text availability, letters to editors, or narrative opinions.

Did not specifically analyze head and neck melanoma separately from melanomas of other anatomical sites.

Had unclear methodology or insufficient outcome data.

Selection process

All identified records were independently screened by two reviewers in a stepwise manner involving title screening, abstract evaluation, and full-text assessment. Duplicate studies were removed before screening. Studies meeting the predefined eligibility criteria were included for qualitative synthesis. Any disagreements regarding study inclusion were resolved through discussion and consensus between the reviewers.

Data collection process

Data extraction was independently performed by two reviewers using a standardized data extraction format. Extracted information was cross-verified to ensure consistency and accuracy. In cases of unclear or incomplete information, clarification was obtained

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through consensus interpretation of the published data. No direct contact with study investigators was undertaken.

Data items

The primary outcomes assessed included:

- Overall survival (OS)
- Cancer-specific survival (CSS)
- Local recurrence
- Regional nodal metastasis
- Distant metastasis
- Treatment effectiveness of surgery, radiotherapy, or combined therapy

Secondary outcomes included:

- Demographic characteristics
- Tumor location and anatomical subsite
- Histopathological subtype
- Tumor thickness and staging
- Molecular marker expression, particularly NNMT
- Prognostic indicators associated with survival outcomes

Where multiple outcome measures or time points were reported, the most clinically relevant and clearly defined results were extracted. Missing or unclear information was interpreted conservatively based on available study data.

Study the risk of IAS assessment.

Methodological quality and risk of bias were independently assessed by two reviewers. Observational studies were evaluated using the Newcastle-Ottawa Scale (NOS), while systematic reviews and meta-analyses were assessed using the AMSTAR 2 tool. Studies demonstrating moderate to high methodological quality were included in the review. Disagreements in scoring were resolved through consensus.

Effect measures

Effect measures extracted from the included studies consisted primarily of hazard ratios (HRs), relative risks (RRs), odds ratios (ORs), confidence intervals (CIs), and survival percentages where available. These measures were used for qualitative comparison and synthesis of prognostic and therapeutic outcomes.

Synthesis methods

Due to substantial heterogeneity among the included studies in terms of study design, patient population, treatment modalities, and reported outcomes, a quantitative meta-analysis was not performed. Instead, a narrative synthesis approach with tabulated summaries was used to compare epidemiological characteristics, prognostic factors, treatment outcomes, and molecular findings across studies.

Reporting bias assessment

Potential reporting bias was minimized through comprehensive database searching and inclusion of studies from multiple sources. However, formal assessment of publication bias using funnel plots or statistical testing was not feasible because of the heterogeneity and the limited number of studies included for each outcome category.

Certainty assessment

The certainty of evidence was assessed qualitatively based on study design, methodological rigor, consistency of findings, and risk of bias assessment outcomes. Greater weight was assigned to population-based studies, systematic reviews, and meta-analyses with robust methodology.

Results

Study selection

The systematic database search identified 436 records from PubMed, Scopus, Web of Science, and Google Scholar published between January 1977 and March 2024. After the removal of 98 duplicate records, 338 articles underwent title and abstract screening. Among these, 287 records were excluded because they were unrelated to head and neck melanoma, lacked relevant therapeutic or prognostic outcomes, were case reports/editorials, or failed to provide site-specific analysis of head and neck lesions. Fifty-one full-text articles were assessed for eligibility. Following a detailed full-text review, 44 studies were excluded due to inadequate methodological quality, insufficient survival data, overlapping datasets, lack of head and neck-specific analysis, or unclear study design. Finally, seven studies fulfilled the eligibility criteria and were included in the qualitative synthesis.

Studies excluded after full-text review

Studies excluded after full-text assessment primarily consisted of:

- Case reports and small case series
- Non-English publications
- Studies without a separate head and neck melanoma analysis
- Molecular studies lacking clinical correlation
- Studies with incomplete survival or treatment outcome data
- Conference abstracts without an accessible full text

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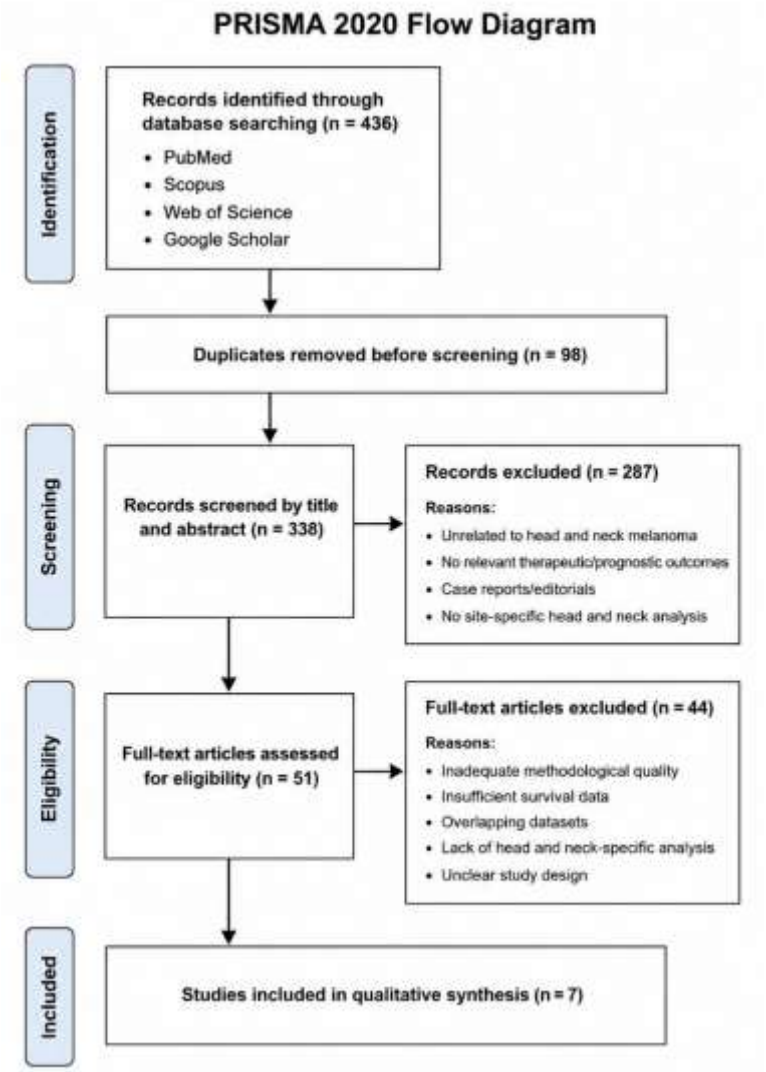

Figure 1. PRISMA flow diagram demonstrating study identification, screening, eligibility assessment, and inclusion process.

Study characteristics

The included studies comprised retrospective cohort studies, population-based analyses, systematic reviews, and meta-analyses evaluating epidemiological patterns, prognostic factors, treatment outcomes, and molecular biomarkers in head and neck melanoma. Publication years ranged from 1977 to 2023. Sample sizes varied substantially, from 59 patients in institutional mucosal melanoma cohorts to over 178,000 patients in population-based registry analyses. Both cutaneous and mucosal melanoma subtypes were represented.

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Table 1. Epidemiological and clinicopathological characteristics of head and neck melanoma

Authors	Study Design	Sample Size	Major Findings
Conley and Hamaker (1977)	Retrospective review	772 patients	The majority of tumors showed deep invasion (Clark Levels III-V). The face was the most common site. Mucosal melanoma demonstrated markedly poorer survival compared to cutaneous melanoma.
Gillgren et al. (1999)	Population-based study	756 patients	Lentigo maligna melanoma occurred significantly more frequently on facial skin. Patients with head and neck melanoma were older than those with melanoma at other sites.
Ding et al. (2021)	Population-based study	70,605 patients	Head and neck melanoma showed poorer overall survival and cancer-specific survival compared to body melanoma. Older age, male sex, ulceration, and metastasis were adverse prognostic factors.
Shannon et al. (2023)	Cross-sectional SEER analysis	178,892 patients	Head and neck melanoma had the highest mortality risk among all anatomical melanoma sites, with significantly worse overall survival.

Table 2. Therapeutic outcomes and prognostic factors in mucosal head and neck melanoma

Authors	Treatment Modality	Key Outcomes	Prognostic Factors
Patel et al. (2002)	Surgery with/without radiotherapy	High local recurrence and distant metastasis rates despite treatment. Five-year disease-specific survival was 44%.	In the advanced stage, tumor thickness >5 mm, vascular invasion, and distant metastasis predicted poor survival.
Grant-Freemantle et al. (2021)	Systematic review and meta-analysis	Combined surgery and radiotherapy reduced local recurrence and moderately improved survival compared to surgery alone.	Improved local control associated with multimodal therapy. Radiotherapy alone demonstrated poorer survival outcomes.

Table 3. Molecular biomarkers in head and neck melanoma

Authors	Biomarker	Biological Significance	Clinical Relevance
Togni et al. (2021)	Nicotinamide N-methyltransferase (NNMT)	NNMT overexpression promoted tumor proliferation, migration, and invasion.	Associated with poor prognosis, lymph node metastasis, and locoregional recurrence. Potential prognostic biomarker and therapeutic target.

Risk of bias in studies

Risk of bias assessment demonstrated that the majority of included observational studies were of moderate-to-high methodological quality according to the Newcastle-Ottawa Scale. Population-based studies utilizing SEER registry data demonstrated lower selection bias because of large patient cohorts and standardized reporting methods. The included systematic review and meta-analysis showed moderate-to-high methodological quality based on AMSTAR 2 assessment. However, several studies exhibited limitations, including retrospective design, heterogeneity in treatment protocols, inconsistent follow-up duration, and variability in reporting survival outcomes.

Results of individual studies

Conley and Hamaker reported that deeply invasive tumors constituted the majority of head and neck melanoma cases, with mucosal melanoma demonstrating substantially lower cure rates compared to cutaneous variants. Gillgren et al. identified distinct epidemiological characteristics in cutaneous head and neck melanoma, particularly the increased prevalence of lentigo maligna melanoma in chronically sun-exposed facial regions.

Patel et al. demonstrated high local recurrence, nodal metastasis, and distant failure rates in mucosal melanoma of the head and neck despite aggressive surgical management. Ding et al. showed significantly lower 5-year cancer-specific survival and overall survival in head and neck melanoma compared to body melanoma.

Shannon et al. identified head and neck location as an independent adverse prognostic factor with a hazard ratio of 1.90 (95% CI: 1.85-1.96). Grant-Freemantle et al.

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demonstrated that combined surgery and radiotherapy significantly reduced local recurrence (RR 0.63; 95% CI: 0.48-0.82) and moderately improved survival compared to surgery alone.

Togni et al. consistently reported NNMT overexpression across multiple head and neck tumor subtypes, correlating with poor clinical outcomes and aggressive biological behavior.

Results of syntheses

Collectively, the included studies demonstrated that head and neck melanoma possesses distinct clinicopathological and prognostic characteristics compared to melanoma at other anatomical locations. Cutaneous variants were strongly associated with chronic ultraviolet exposure and older age, while mucosal melanomas exhibited aggressive biological behavior with frequent recurrence and distant metastasis.

Evidence from therapeutic studies supported surgery as the primary treatment modality, with combined surgery and radiotherapy providing superior local disease control compared to single-modality approaches. Molecular evidence suggested that NNMT overexpression may contribute to tumor progression and adverse clinical outcomes.

Substantial heterogeneity was observed across studies with respect to patient populations, tumor subtypes, treatment protocols, and reported outcome measures, limiting direct quantitative comparison.

Reporting biases

Formal statistical assessment of publication bias was not feasible because of the limited number of included studies and substantial methodological heterogeneity. Potential reporting bias may exist due to the preferential publication of studies demonstrating statistically significant clinical findings and the underreporting of studies with negative outcomes.

Certainty of evidence

The certainty of evidence was considered moderate for epidemiological and prognostic findings derived from large population-based studies and systematic reviews. Evidence supporting multimodal treatment strategies was also considered moderate because of consistent findings across multiple studies.

The certainty of evidence regarding molecular biomarkers such as NNMT was considered low-to-moderate due to limited prospective validation, small sample sizes in molecular studies, and variability in laboratory methodologies.

Discussion

Malignant melanoma in the head and neck region (HNM) represents a unique clinical entity due to its aggressive behavior, complex anatomical location, and varying histological subtypes, which include both cutaneous and mucosal melanomas. The included studies in this systematic review collectively highlight the epidemiological, pathological, prognostic, and therapeutic complexities of HNM, providing critical insights into its management and outcomes.

Epidemiological Patterns and Subtype Distribution

Several studies emphasized distinct epidemiological characteristics of HNM compared to melanoma at other anatomical sites. Gillgren et al. (1999) and Ding et al. (2021) both noted that HNM predominantly affects older adults, with a higher incidence in males. Lentigo maligna melanoma—a subtype associated with chronic sun exposure—was found to occur up to 74 times more frequently on the face, highlighting the role of cumulative UV exposure. The study by Shannon et al. (2023) further corroborated that HNM is associated with worse overall survival than melanomas at other body sites, even after adjusting for major clinicopathological factors.

Prognostic factors and tumor biology

The studies by Conley and Hamaker (1977) and Patel et al. (2002) underscore the importance of tumor stage, depth of invasion, and anatomical subsite as strong prognostic indicators. For example, Conley's analysis of 772 HNM cases highlighted that deeply invasive tumors (Clark's Levels III–V) were predominant and were associated with poorer outcomes. Elective neck dissection showed a higher 5-year cure rate compared to therapeutic approaches, suggesting early surgical intervention improves prognosis. Patel et al. further differentiated between oral and sinonasal mucosal melanomas, with oral melanomas demonstrating a higher rate of regional nodal involvement (42% vs. 20%) and worse patterns of failure. However, both subtypes showed poor outcomes due to high rates of local recurrence and distant metastasis, reinforcing the aggressive nature of mucosal melanomas.

Impact of anatomic location on survival

Shannon et al. (2023) conducted a robust analysis of over 178,000 cases and determined that melanomas in the head and neck region confer the highest risk of death compared to other anatomical sites, with a hazard ratio of 1.90. This supports the notion that anatomical constraints, difficulties in achieving wide surgical margins, and a propensity for earlier metastasis contribute to the poor prognosis of HNM.

Treatment strategies: Surgery vs. radiotherapy

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The meta-analysis by Grant-Freemantle et al. (2021) demonstrated that while surgery remains the cornerstone of treatment for HNM, combining surgery with radiotherapy (SRT) significantly reduced the risk of death (RR 0.93) and local recurrence (RR 0.63) compared to surgery alone. Importantly, radiotherapy alone was associated with worse survival outcomes, indicating that monotherapy may be insufficient for optimal control. These findings suggest that while radiotherapy plays a crucial adjunctive role—particularly in mucosal melanoma—it should not replace surgical resection when feasible.

Molecular insights and future directions

The review by Togni et al. (2021) adds a molecular dimension to the understanding of HNM by highlighting the role of nicotinamide N-methyltransferase (NNMT). NNMT overexpression was consistently observed across various HNM subtypes and was associated with enhanced tumor invasiveness, metastatic potential, and poor prognosis. Functional studies suggested that NNMT silencing could inhibit tumor proliferation and promote apoptosis, pointing to its potential as a prognostic biomarker and therapeutic target. However, the lack of consensus on its role in oral squamous cell carcinoma indicates the need for further validation across larger and more diverse cohorts.

Limitations

Several limitations should be considered while interpreting the findings of this review. First, most included studies were retrospective in nature, introducing potential selection bias, reporting bias, and variability in follow-up duration. Considerable heterogeneity existed among studies regarding patient demographics, tumor subtypes, staging systems, treatment protocols, and reported outcome measures, limiting direct comparison across studies. The inclusion of both cutaneous and mucosal melanoma studies further contributed to clinical heterogeneity because of their distinct biological behavior and prognostic profiles.

The review was also limited by the relatively small number of studies specifically addressing head and neck melanoma, particularly mucosal variants, which remain rare malignancies. Some included studies lacked standardized reporting of survival metrics, confidence intervals, and treatment outcomes. Formal quantitative meta-analysis and publication bias assessment were not feasible because of methodological heterogeneity and limited outcome uniformity across studies.

In addition, only English-language publications were included, which may have introduced language bias. Despite comprehensive database searching, the possibility of missing relevant unpublished studies or gray literature cannot be excluded.

Clinical and policy implications

The findings of this review emphasize the aggressive clinical behavior and poor prognosis associated with head and neck melanoma, particularly mucosal subtypes. Early diagnosis and prompt multidisciplinary management remain essential for improving patient outcomes. The consistently poorer survival observed in head and neck melanoma compared to melanoma at other anatomical sites supports the need for closer surveillance strategies and individualized treatment planning.

The evidence supporting combined surgery and radiotherapy suggests that multimodal treatment approaches should be considered in appropriate patients, especially for mucosal melanoma, where local recurrence rates remain high. Integration of molecular biomarkers such as NNMT into future diagnostic and prognostic frameworks may facilitate risk stratification and the development of targeted therapeutic approaches.

From a policy perspective, the findings highlight the importance of standardized reporting systems, multicenter collaboration, and prospective registry-based studies for rare head and neck melanomas. Incorporation of anatomical site-specific prognostic factors into melanoma staging guidelines may improve clinical decision-making and optimize resource allocation for high-risk patients. Further investment in translational research and targeted therapy trials is warranted to improve survival outcomes in this challenging disease entity.

Conclusion

Malignant melanoma of the head and neck is a biologically and clinically distinct entity with a poorer prognosis compared to melanomas at other anatomical sites. The evidence from this review underscores the multifactorial nature of outcome determinants, including anatomical site, histological subtype, stage at diagnosis, and treatment strategy. Cutaneous melanomas in the head and neck are commonly diagnosed in older patients and exhibit a unique histopathological spectrum influenced by UV exposure. Mucosal melanomas, although less common, are notably more aggressive, with high recurrence and metastasis rates despite multimodal treatment.

Surgery remains the primary treatment modality, but the addition of radiotherapy (SRT) appears to improve local control and moderately enhance survival in mucosal variants. Emerging biomarkers like NNMT offer promising avenues for molecular classification and targeted therapy, but require further investigation.

Given the complex behavior and poor outcomes associated with HNM, a multidisciplinary approach incorporating early surgical intervention, adjuvant

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therapy, and molecular profiling is essential. Future studies should focus on personalized treatment strategies, enhanced staging models incorporating anatomical site and biomarkers, and prospective trials evaluating targeted therapies to improve survival in this challenging malignancy.

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List of abbreviations
HNM: Head and Neck Melanoma
MMHN: Mucosal Melanoma of the Head and Neck
CMM: Cutaneous Malignant Melanoma
NNMT: Nicotinamide N-Methyltransferase
OS: Overall Survival
CSS: Cancer-Specific Survival
RR: Relative Risk
HR: Hazard Ratio
CI: Confidence Interval
SEER: Surveillance, Epidemiology, and End Results
SRT: Surgery and Radiotherapy
NOS: Newcastle-Ottawa Scale
AMSTAR 2: A Measurement Tool to Assess Systematic Reviews 2

Registration and protocol
This systematic review was not prospectively registered in any international review registry such as PROSPERO. A formal review protocol was not prepared before the conduct of the study.

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The authors received no external financial support for the conduct, authorship, or publication of this review. No funding agency or sponsor had any role in study design, literature search, data extraction, interpretation of findings, manuscript preparation, or the decision to submit the manuscript for publication.

Competing interests
The authors declare that they have no competing interests related to this work.

Availability of data, code, and other materials
All data generated or analyzed during this review are included within the manuscript and its supplementary materials. No external analytic code was used. Data extraction forms and synthesized study data are available from the corresponding author upon reasonable request.

Author contributions
Dr. Karthik Shunmugavelu: Conceptualization, study design, literature review, data interpretation, manuscript drafting, critical revision, and supervision.
Dr. Evangeline Cynthia Dhinakaran: Literature screening, data extraction, methodological assessment, manuscript editing, and interpretation of findings.
Dr. Rufus Ranjitsingh Edwin: Data analysis, review of clinical content, manuscript revision, and final approval of the submitted version.
All authors read and approved the final manuscript.

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