Immunosuppression Impact on Head and Neck Cutaneous Squamous Cell Carcinoma: A Systematic Review with Meta-analysis

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract

Objective. The primary objective was to define and quantify the relationship between immunosuppression and prognosis in patients with cutaneous squamous cell carcinoma of the head and neck.

Data Sources. Ovid/medline, PubMed, Embase, and Scopus were searched from inception through June 5, 2017, with cross-referenced subject headings of squamous cell carcinoma, skin neoplasms, head and neck neoplasms, and prognosis. Additional gray literature was queried.

Review Methods. All prospective, retrospective, and cohort studies in the English literature investigating prognosis in patients with head and neck cutaneous squamous cell carcinoma were eligible for inclusion. Meta-analysis data were pooled using the fixed-effects model. The main outcome measures were hazard ratios detailing subgroup analysis between immunosuppressed and immunocompetent patients.

Results. Seventeen studies were eligible for inclusion; 317 of 2886 patients were immunosuppressed. Meta-analysis with pooled hazard ratios was performed for all outcome variables with at least 3 reported hazard ratios. Immunosuppression portended a worse prognosis across all outcome variables of interest: locoregional recurrence (2.20; 95% confidence interval [CI], 1.45-3.36), disease-free survival (2.69; 95% CI, 1.60-4.51), disease-specific survival (3.61; 95% CI, 2.63-4.95), and overall survival (2.09; 95% CI, 1.64-2.67).

Conclusion. This is the largest investigation into the impact of immunosuppression on head and neck cutaneous squamous cell carcinoma. Immunosuppressed patients experience worse recurrence and survival outcomes compared to immunocompetent counterparts. The data support formal inclusion of immunosuppression in head and neck cutaneous squamous cell carcinoma staging systems.

Keywords
cutaneous squamous cell carcinoma; immunosuppression; organ transplantation; cancer staging

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Cutaneous squamous cell carcinoma (cSCC) is the single most common neoplasm in organ transplant recipients (OTRs), with 75% of patients being diagnosed within 20 years of transplantation.¹,² Multiple studies report an increased incidence of cSCC among OTRs as well as patients with other forms of immunosuppression (IS) to include lymphoma and the human immunodeficiency virus (HIV).³,⁴ Cancer was noted to be the fourth most common cause of death in renal transplant patients, with cutaneous cancers being most common.⁵ Immunosuppressed patients carry a 100-fold increased incidence of cSCC compared to the general population,¹ along with a 7.2-fold increase in cancer recurrence.⁶

Whereas most patients with cSCC experience an excellent prognosis, IS is associated with decreased disease-specific survival (DSS) and overall survival (OS).⁷,⁹ In addition, immunosuppressed patients tend to develop poorly differentiated tumors.⁶,¹⁰,¹¹ Despite this association, IS was excluded from the most recent eighth edition of the American Joint Committee on Cancer (AJCC) staging system due to limited studies, patient heterogeneity, and small cohort numbers.¹²

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This systematic review of the literature with associated meta-analysis was performed to address the above AJCC concerns. The main study objective was to determine the relationship between IS and prognosis with respect to head and neck (H&N) cSCC recurrence and survival. In doing so, we aimed to elucidate the true impact of IS on H&N cSCC and to determine if immune status is a prognostic factor warranting consideration in patient counseling, treatment planning, and ultimately cancer staging.

Methods

Eligibility Criteria

The research protocol was designed a priori and based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology. All prospective, retrospective, and cohort studies in the English literature investigating prognostic factors and their relationship to outcomes in patients with H&N cSCC were eligible for inclusion. Studies were excluded if prognosis was not assessed, IS was not included as a prognostic factor, or if outcomes data were unavailable. Case reports and duplicate cohorts were excluded. Studies were excluded if data specific to H&N cSCC could not be extracted from other non-H&N subsites, eyelid malignancies, mucosal malignancies (including mucosal lip), cSCC in situ, verrucous carcinoma (based on its low metastatic potential), or other cutaneous malignancies such as basal cell carcinoma and melanoma.

Information Sources and Search Strategies

With guidance from an information specialist, a systematic review of the literature was designed to capture the maximal number of articles assessing prognosis in H&N cSCC. Four search engines were used: Ovid/Medline, PubMed, Embase, and Scopus. The databases were queried from inception through June 5, 2017. The search strategy included the cross-referenced subject headings of squamous cell carcinoma, skin neoplasms, head and neck neoplasms, and prognosis. The gray literature was searched via Google Scholar. All bibliographies of included articles were manually searched for relevant studies meeting inclusion criteria.

Data Extraction

A data spreadsheet was used to systematically record extracted information from eligible studies. Data captured included study design (study type, dates, location, inclusion/exclusion criteria, follow-up period), patient demographics (total number of patients, number of immunosuppressed patients, types of IS, age, sex), and treatment modalities (surgery and/or radiation therapy and/or chemotherapy). All data related to IS and prognosis were extracted. Outcome measures collected include local recurrence (LR), locoregional recurrence (LRR), regional recurrence (RR), distant recurrence (DR), disease-free survival (DFS), disease-specific survival (DSS), and overall survival (OS). Study authors were contacted for clarification in the event of unreported or insufficiently reported data.

Quality Appraisal

The quality of each research study was assessed by 2 investigators (A.N.E., Z.E.P.) using the validated Methodological Index for Non-Randomized Studies (MINORS) instrument. This instrument highlights 8 study attributes that are scored 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate) for a maximum possible score of 16.

Statistical Analysis

All studies meeting inclusion criteria were analyzed using descriptive statistics. The primary outcome measures were analyzed using hazard ratios (HRs) detailing subgroup analysis between immunosuppressed and immunocompetent patients. Hazard ratios were employed when the “time to event” was relevant for an outcome of interest, such as recurrence or survival. When HRs were available across at least 3 studies for a specific outcome, the data were weighted, pooled, and incorporated into the meta-analysis. When available, HRs derived from multivariate (vs univariate) analysis were used. When an HR was not reported, it was calculated, if possible, from provided summary statistics using established methods described by Tierney et al. Hazard ratios were pooled in Review Manager Version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) using the inverse variance method. Heterogeneity among studies was calculated using both the \( \chi^2 \) and \( I^2 \) tests, with heterogeneity defined as \( P < .10 \) or \( I^2 > 50\% \). In the event of homogeneity across the studies, the fixed-effect model was used; if heterogeneity was present, the random-effects model was to be employed.

Results

Article Selection

The results of the systematic review are outlined in a PRISMA flow diagram (Figure 1). Database searches returned a total of 1687 distinct articles. Manual search of gray literature and bibliographies from eligible articles identified an additional 18 articles for a total of 1705 potentially eligible articles. All abstracts were screened and reviewed by the authors (A.N.E., Z.E.P., C.E.S.), prompting thorough reading of 255 full-text articles. Ultimately, 17 articles met inclusion criteria for the systematic review. The articles were published between 1999 and 2016. Fifteen articles were prospective cohort studies, 1 article was a retrospective case control study, and 1 article was a prospective case control study. Most studies were published in Australia (9), followed by New Zealand (3), Germany (2), the United States (2), and Israel (1). Characteristics of each study are summarized in Table 2.

Systematic Review

Overall, 2886 patients were included in this systematic review. Sex was specified for 2715 patients: male (n = 2305; 85%) and female (n = 410; 15%). In 1078 patients, the presenting H&N cSCC was classified as primary in 916 (85%) patients and recurrent in 162 (15%) patients.
### Table 1. Methodological Index for Non-Randomized Studies (MINORS) Score for Studies Included in the Systematic Review.

<table>
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<tr>
<th>Study</th>
<th>Clear aim</th>
<th>Consecutive patients</th>
<th>Prospective data</th>
<th>Appropriate endpoints</th>
<th>Unbiased assessment</th>
<th>Appropriate follow-up</th>
<th>Appropriate retention</th>
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Abbreviations: HM, hematologic malignancy; IS, immunosuppression; NS, not specified; OTR, organ transplant recipient.

### Table 2. Characteristics of Studies Included in Systematic Review.³

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Dates</th>
<th>Total Patients⁴</th>
<th>Median Age, y</th>
<th>Patients with IS, No. (%)</th>
<th>Type(s) of IS</th>
<th>Median Follow-up, mo</th>
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<td>Bachar et al (2016)²³</td>
<td>Israel</td>
<td>NS</td>
<td>71</td>
<td>NS, mean: 71</td>
<td>6 (8)</td>
<td>OTR: 6</td>
<td>NS, minimum: 36</td>
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<td>Ch’ng et al (2013)⁷</td>
<td>New Zealand</td>
<td>1978-2010</td>
<td>239</td>
<td>68</td>
<td>33 (14)</td>
<td>NS</td>
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<td>Kreppel et al (2013)¹⁹</td>
<td>Germany</td>
<td>2003-2009</td>
<td>63</td>
<td>74</td>
<td>9 (14)</td>
<td>NS</td>
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<td>McLean et al (2013)⁸</td>
<td>Australia</td>
<td>1980-2010</td>
<td>95</td>
<td>NS, mean: 71</td>
<td>6 (6)</td>
<td>NS</td>
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</tr>
</tbody>
</table>

Abbreviations: HM, hematologic malignancy; IS, immunosuppression; NS, not specified; OTR, organ transplant recipient.

³"Other" types of immunosuppression encompass patients taking chronic immunosuppressant medications (eg, for rheumatologic disease).

⁴Indicates total number of patients with cutaneous squamous cell carcinoma.
Inclusion criteria for 13 studies (76%) specified patients with regional metastatic disease. Inclusion for the remaining 4 studies was not limited to patients with regional disease.10,18-20 Treatment modality was specified for 2109 patients as surgery alone (n = 535; 25%), surgery with adjuvant radiation (n = 1553; 74%), or definitive radiation therapy (n = 21; 1%). Fourteen patients (0.7%) were expressly identified as receiving chemotherapy in addition to surgery and/or radiation therapy.

In total, 317 (11%) patients were immunosuppressed. The immunosuppressed cohort included solid OTRs (n = 74; 23%), patients with lymphoproliferative disorders (n = 70; 22%), and patients otherwise on chronic immunosuppressive therapy (n = 12; 4%). In 161 immunosuppressed patients (51%), the etiology of IS was not specified. One study included patients with a uniform type of IS (cardiac and/or lung transplant patients).20 All other studies included patients with different etiologies or did not specify the reason for IS. The median number of immunosuppressed patients within each study was 17.

Several investigations included in the systematic review analyzed IS as a covariate when studying another prognostic variable. Local recurrence was assessed in 2 studies,6,20 RR in 3 studies,18,20,21 combined LRR in 4 studies,10,11,19,22 and DR in 2 studies.10,20 In addition to LR, 1 study investigated the risk of “any” recurrence.6 Regarding outcomes related to survival, DFS was assessed in 3 studies,10,23,24 DSS in 8 studies,6-9,11,22,25,26 and OS in 10 studies.6-8,10,11,19,20,23,25,27 One study reported “time to disease progression,” which included patients with either recurrence or death from disease.28

**Statistical Analysis**

When HRs were reported by study authors, they were derived from multivariate analysis in 12 of 17 cases (71%). Across all recurrence and survival outcomes variables, pooled HRs identified a meaningful relationship between IS and worse prognosis. Immunosuppressed patients with H&N cSCC were 2.20 times more likely to develop local or regional recurrence (LRR) compared to their immunocompetent counterparts (95% confidence interval [CI], 1.45-3.36). This analysis of HRs was available for LRR in 5 studies, including 2 studies analyzing RR18,21 and 3 studies reporting outcomes on combined LRR.10,19,22 The pooled HR for LRR was based on data from 144 immunosuppressed and 730 immunocompetent patients (Figure 2). The HR for isolated local, regional, or distant control could not be calculated due to insufficient data.

The pooled HR for DFS was statistically significant (2.69; 95% CI, 1.60-4.51). This was based on 3 studies encompassing 39 immunosuppressed and 204 immunocompetent patients (Figure 3).10,23,24 The pooled HR for DSS

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**Figure 1.** PRISMA flow diagram. cSCC, cutaneous squamous cell carcinoma; H&N, head and neck.
(3.61; 95% CI, 2.63-4.95) was also statistically significant and was based on 7 studies encompassing 145 immunosuppressed and 1557 immunocompetent patients (Figure 4).7-9,11,22,25,26 The statistically significant pooled HR for OS (2.09; 95% CI, 1.64-2.67) was based on 8 studies encompassing 140 immunosuppressed and 1201 immunocompetent patients (Figure 5).7,8,10,11,19,23,25,27

**Discussion**

Overall cSCC portends an excellent prognosis, with most patients successfully treated in the community. Consequently, most cSCC cases are never captured in a tumor database, and powering a meaningful prospective registry is cost prohibitive. For this reason, the AJCC disbanded its independent cSCC Task Force. In addition, the recently published eighth edition of the AJCC cancer staging manual removed the previously stand-alone cSCC chapter and changed it to a subsection within the H&N chapter.12 The current AJCC staging preserves the TNM system and incorporates factors such as extranodal extension and large-caliber nerve invasion. Despite strong consideration, IS is not included in the latest staging system due to limited studies, although AJCC authors do acknowledge the need for ongoing research and recommend IS designation with an “I” in tumor registries.

Smaller cohort studies have attempted to investigate the impact of IS on cSCC. This systematic review identified 3 that analyzed IS in the context of creating new prognostic tools for H&N cSCC.9,21,26 The prediction model proposed by Wermker et al21 was designed to assess the risk of lymph node metastasis in auricular cSCC. Regional recurrence was more common in patients with IS (15% vs 10%). Oddone et al26 analyzed patients with regional disease to propose a “prognostic score model,” incorporating IS
alongside treatment (ie, surgery with or without radiation therapy), extracapsular spread, and margin status. IS was included based on its meaningful relationship to DSS using multivariate analysis. Palme et al9 tested a staging system specifying regional metastasis to both the parotid and cervical echelons. Despite not being incorporated into this staging system, IS was again shown to be a significant predictor of DSS on multivariate analysis.

Although several H&N cSCC investigations demonstrate an association between IS and increased recurrence and/or worsened survival,6-11,18-28 studies such as the ones outlined above are limited to small cohorts with a median of only 17 immunosuppressed patients. The AJCC identified 1 prospective investigation of cSCC risk factors. This study was published in 2008, included all body sites, and analyzed 31 immunosuppressed patients.29 Such small numbers understandably limit the ability for the AJCC to meaningfully incorporate IS into the latest staging system.12

In an effort to address this limitation and to better elucidate the impact of IS on H&N cSCC patient outcomes, we used the study design of a systematic review of the literature specific to H&N cSCC and included a meta-analysis. Our investigation yielded 2886 patients with H&N cSCC, 317 (11%) of whom were immunosuppressed. This study marks the largest to date, surpassing prior median cohort size by 300 immunosuppressed patients. We attempted to overcome this variability using strict inclusion criteria, MINORS evaluation, and HRs when available across at least 3 studies for a specific outcome of interest. We also used HRs derived from multivariate as opposed to univariate analysis when available. In the event that the HR was not reported by the authors, we calculated it if data permitted.

Using an H&N cSCC-specific meta-analysis with pooled HRs, we demonstrated IS carries a statistically significant negative impact on all outcomes of interest to include LRR, DFS, DSS, and OS. Specifically, immunosuppressed patients with H&N cSCC were 2.20 times more likely to develop local or regional recurrence compared to their immunocompetent counterparts. Similarly, the IS cohort was 3.61 times more likely to die of their H&N cSCC.

One of the challenges in determining the true impact of IS on H&N cSCC outcomes is variability in study design and associated outcomes. In 3 studies from this systematic review, the relationship between IS and prognosis was the primary objective, but “time to event” was not the reporting means, thereby precluding inclusion in the meta-analysis. Manyam et al10 performed the only prospective case-control study included in this review, comparing immunosuppressed and immunocompetent patients. Progression-free survival and LRR and DFS were significantly lower in the 67 immunosuppressed patients, but the 2-year OS did not reach statistical significance. Southwell et al6 investigated the relationship between IS and prognosis via Kaplan-Meier analysis and odds ratios (ORs) instead of HRs. Immunosuppression carried a statistically significant increased risk of LR (OR, 7.2; 95% CI, 1.35-38.33) and “any recurrence” (OR, 5.3; 95% CI, 1.12-24.84) but did not reach statistical significance for DSS (OR, 2.4; 95% CI, 0.47-11.78). Kaplan-Meier analysis revealed worse 2-year OS, with no immunosuppressed patients surviving compared to 87% for immunocompetent patients’ counterparts. We attempted to overcome this variability using strict inclusion criteria, MINORS evaluation, and HRs when available across at least 3 studies for a specific outcome of interest. We also used HRs derived from multivariate as opposed to univariate analysis when available. In the event that the HR was not reported by the authors, we calculated it if data permitted.

The current review and meta-analysis supports incorporation of IS into the staging system for H&N cSCC but also highlights important knowledge gaps warranting further investigation to meaningfully do so. For example, over 50% of the patients included in the systematic review did not have specification of their immunosuppression category.
This knowledge gap supports the need for better documentation with respect to the specific IS etiology and immunosuppressant agents. Immunosuppression is a heterogeneous category comprising various modalities and medications. If significant differences are discovered based on the specific type of IS, the formal staging systems will need refining to include only those variants that truly affect patient prognosis and outcome. Importantly, IS should be considered a single component within the overall context of a patient’s oncologic staging schema. Incorporation into formal staging systems should enhance prognostication and should not lead to overtreatment, especially given the increased number of cutaneous lesions that IS patients experience. Increased disease burden may warrant more vigilant surveillance, but incorporation of IS into staging systems should lead to clinically meaningful benefits in treatment and associated prognosis.

One must also consider treatment bias and associated impact on prognosis. Immunosuppressed patients may be at risk for under- or overtreatment of their cSCC given the context of their comorbid conditions. Additional histopathologic studies such as the one included by Kreppel et al\textsuperscript{19} investigating podoplanin expression will be helpful in determining if prognosis in IS patients is in part related to more aggressive tumor biology such as lymphovascular invasion or extracapsular extension. Although most studies included within the present review used multivariate analysis to control for potentially confounding variables, further research focused on tumor characteristics specific to IS patients is warranted.

Last, this investigation includes limitations inherent to systematic reviews and meta-analyses. As mentioned previously, IS patients experience an increased burden of cSCC and may present with multiple primary lesions. Given the retrospective, pooled nature of the study, one potential limitation is the accurate classification of a separate primary lesion from a true recurrence. While this limitation can affect outcome measures related to recurrence and DFS, it should not affect overall survival rates.

Consideration must also be given to the effect of publication bias, in that studies demonstrating a strong relationship between a prognostic variable and an outcome are more likely to be published or reported.\textsuperscript{30} We attempted to minimize this bias through use of the gray literature and hand searching of all bibliographies. In addition, studies in which the H\&N subsite could not be extrapolated from trunk and extremity required exclusion. For example, the Brantsch et al\textsuperscript{86} article cited in the most recent AJCC edition included H\&N-specific data that could not be extrapolated from other included subsites and therefore did not meet inclusion criteria for this study. Given that the new staging system for cSCC is H\&N specific, we felt that a strict inclusion criterion limited to the head and neck region was justified.

This systematic review of the literature with meta-analysis represents the largest dedicated H\&N cSCC study to date investigating the impact of IS on recurrence and survival. Analysis of 2886 patients with H\&N cSCC, 317 of whom were immunosuppressed, demonstrated more aggressive tumor behavior in the setting of IS. Specifically, meta-analysis with pooled HRs demonstrated a significantly worse rate of LRR, DFS, DSS, and OS. This evidence illustrates the need for formal consideration of IS in future H\&N cSCC staging to allow for true prognostication, better patient counseling, and improved clinical decision making. The study also elucidates knowledge gaps within the existing literature and demonstrates the need for ongoing research, ideally using large prospective studies that will need to be multi-institutional.

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Author Contributions

Alhasan N. Elghouche, concept, study design, analysis/interpretation, draft, revisions, and final approval; Zachary E. Pflum, concept, study design, acquisition/content, draft, revisions, and final approval; Cecelia E. Schmalbach, concept, study design, analysis/interpretation, draft, revisions, and final approval.

Disclosures

Competing interests: Cecelia E. Schmalbach, teaching honorarium for nonprofit trauma consortium AO North America and deputy editor of Otolaryngology–Head & Neck Surgery.

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