Preoperative Positron Emission Tomography for Node-Positive Head and Neck Cutaneous Squamous Cell Carcinoma

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

Abstract

Objectives. Surgery is the primary treatment modality for node-positive cutaneous squamous cell carcinoma of the head and neck with no distant disease (HNcSCC-M0). The role of preoperative positron emission tomography/computed tomography (PET/CT) scan for these patients is unclear. We compared preoperative PET/CT with final histopathology among patients undergoing lymphadenectomy and/or parotidectomy for HNcSCC-M0.

Study Design. Case series with chart review.

Setting. Single Australian center.

Subjects and Methods. Investigation included disease parameters and preoperative CT and PET/CT findings of 64 patients with node-positive HNcSCC without distant metastatic disease. Fisher’s exact test was used to test for a difference in the proportion of patients with chronic lymphocytic leukemia between the false- and true-negative PET/CT subgroups.

Results. Of 64 patients who underwent PET/CT prior to surgery for node-positive HNcSCC-M0, 56 underwent a neck dissection and 30, a parotidectomy. Of these, 13 neck dissections and 2 parotidectomies were performed in the absence of FDG-avid (18F-fludeoxyglucose) nodes in these nodal fields. The PET/CT positive predictive value of the neck was 91.1%. The negative predictive values in the neck and parotid regions were 60%. Of the false-negative subgroup, 66.7% had chronic lymphocytic leukemia, compared with 11.1% of the true-negative subgroup (P = .09). Based on PET/CT findings, surgical plans according to preoperative CT were changed for 6.25% of patients.

Conclusion. Use of PET/CT for surgical candidates with node-positive HNcSCC-M0 has high specificity and positive predictive value with relatively low sensitivity and negative predictive value. A statistical trend toward a higher rate of chronic lymphocytic leukemia among patients with false-negative results is suggested.

Keywords

cutaneous squamous cell carcinoma, radiology, PET/CT scan, accuracy analysis, chronic lymphocytic leukemia

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The incidence of nonmelanoma skin cancer is increasing steadily,¹,² and Australia has the highest incidence worldwide.³ The second-most common nonmelanoma skin cancer is cutaneous squamous cell carcinoma, with more than half of these cases located in the head and neck region (HNcSCC).⁴ The current HNcSCC staging system (American Joint Committee on Cancer, seventh edition)⁵ takes into account the primary skin tumor size and invasiveness, the nodal status (size, number, laterality), and distant spread. Treatment of patients with node-positive HNcSCC without distant spread (M0) consists of skin lesion excision (for patients presenting with synchronous primary disease) and lymphadenectomy for nodal involvement, followed by regional postoperative radiation treatment.⁶

Limited data demonstrate a role for preoperative positron emission tomography/computed tomography (PET/CT) for patients with high-risk primary skin squamous cell carcinoma (SCC), regardless of nodal status.⁷ There are no data to describe the use of preoperative PET/CT among patients

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planning to undergo lymphadenectomy with node-positive HNcSCC. This study compares findings from PET/CT with CT alone and describes the additional information from PET/CT. Furthermore, we describe various predictive factors associated with false-negative (FN) rates.

Materials and Methods

This study is a retrospective cohort analysis of patients with skin-origin SCC of the head and neck region (HNcSCC) with nodal involvement and no distal spread who were treated surgically at a single tertiary Australian center (Peter MacCallum Cancer Center) between August 1, 2005, and August 1, 2014 (10-year period). Information collected included demographic data, disease parameters, treatment modalities, various survival metrics, and preoperative PET/CT and CT scan findings. A PET/CT scan was considered positive where the maximum standardized uptake value was $>3$ without an obvious physiologic explanation as interpreted by an experienced nuclear medicine physician. The study was conducted following the approval of the local ethical committee at Peter MacCallum Cancer Center (approval 15/03R), governed by the National Health and Medical Research Council of the Australian government according to the World Medical Association Declaration of Helsinki (2008).

Inclusion Criteria

Patients included those with HNcSCC and nodal spread (palpable disease or demonstrated on anatomic imaging modalities) who proceeded to lymph node dissection and underwent preoperative PET/CT scan during the study period.

Exclusion Criteria

Patients with synchronous cutaneous and mucosal SCC, patients undergoing salvage operations or palliative intent surgery, or patients with distant spread (mainly to the lung) were excluded.

Patient Identification

From our cohort of 138 patients who underwent lymph node dissection for HNcSCC-M0, 64 (46.4%) underwent PET/CT scan prior to surgery.

Statistics

All statistical analyses were performed in the R statistical software package with standard and validated statistical procedures. In accordance with institutional policy, all statistical analysis results and their interpretation were independently reviewed by a qualified statistician.

The overall survival and freedom from regional recurrence were estimated via the Kaplan-Meier method with corresponding 95% CIs. Time to regional recurrence was measured from the date of nodal dissection until the date of documented nodal recurrence where death was a censoring event.

Among cases of elective lymphadenectomy ($n = 15$), Fisher's exact test was used to test for a difference in the proportion of patients with chronic lymphocytic leukemia between the FN and true-negative (TN) PET/CT subgroups. A $P$ value of .05 was considered significant.

Results

The demographic data and disease parameters of the 64 patients with HNcSCC-M0 and nodal spread who had preoperative PET/CT are described in Table 1. The median age was 78.7 years, and the majority of patients (84.4%) were men. Fifty-two patients had radiation treatment following the operation (90.4% completion rate), whereas 12 had surgery alone.

Overall, 34 patients underwent neck dissection alone; 22 patients, parotidectomy with neck dissection; and the remaining 8 patients, parotidectomy alone. Of the patients undergoing parotidectomy and neck dissection, 13 had FDG-avid (18F-fludeoxyglucose) disease in the parotid alone and underwent elective neck dissection, and 2 had high FDG-avid disease in a periparotid node and underwent elective parotidectomy.

The lymphatic disease burden is presented in Table 2. A median of 2 involved lymph nodes was found in the parotid and neck specimens (range, 1-27 nodes); necrotic nodes were seen in 60% of patients. The rates of overall survival and freedom from regional recurrence are shown in Figure 1. The plateaus for overall survival and freedom from regional recurrence after 4 years were 52% and 86%.
respectively. To analyze the accuracy of PET/CT, extent of dissection was divided into 2 nodal regions (parotid and neck; Table 3). PET/CT scan identified disease in 1 or both of these stations, and patients underwent dissection of 1 or both of these nodal regions. Of the 43 scans with high FDG uptake in the neck, 42 (97.6%) had SCC on histologic evaluation. Conversely, of the 13 scans without FDG uptake in the neck, 4 cases (30.7%) had histologically confirmed metastatic SCC on the final pathology report. The concordance of the increased FDG uptake with pathology nodal status in the neck was based on a matched level between the preoperative imaging and operative specimen.

All 28 patients with increased preoperative FDG uptake in the parotid and both patients undergoing elective parotidectomy (with no preoperative FDG uptake) had nodal involvement on histologic examination. Overall (Table 4), 57 patients with high FDG uptake (neck or parotid) proved to have SCC on histology. This group is considered the true-positive group. The TN group consists of 9 cases with no FDG uptake (neck or parotid) and no SCC on histologic evaluation. All patients with a TN nodal basin had uptake in another basin and were therefore also a true-positive subgroup, as 9 of the 57 patients had therapeutic dissection in 1 site (neck or parotid) and elective dissection in the other site. Six patients had no FDG uptake in any nodal basin but had postoperative histologic confirmation of nodal involvement.

For patients with FN PET/CT imaging, the disease burden in the dissected nodes (PET/CT negative) was significant: the diameter of the smallest node was 8 mm; 3 patients had extra capsular extension; and 4 had N2 stage (1 involved lymph node). None of the FN patients had anatomically suspicious nodes on the contrast CT performed in conjunction with the FDG/PET scan.

One patient had false-positive disease with no malignancy identified in neck nodes despite high preoperative FDG uptake. This 76-year-old man underwent parotidectomy and removal of local aggressive squamous cell carcinoma of his cheek with neck dissection for high FDG-avid neck nodes, which turned out to be all negative (0 of 17).

**Table 2. Nodal Description Following Head and Neck Lymphadenectomy for Skin-Origin Squamous Cell Carcinoma with Regional Metastasis.**

<table>
<thead>
<tr>
<th>Description</th>
<th>Median (Range) or n (%)</th>
</tr>
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<tbody>
<tr>
<td>Disease stagea</td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td>21 (32.8)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>43 (67.2)</td>
</tr>
<tr>
<td>Neck nodal burden (n = 56)</td>
<td></td>
</tr>
<tr>
<td>Positive nodes</td>
<td>2 (1-26)</td>
</tr>
<tr>
<td>Total nodes</td>
<td>23 (1-85)</td>
</tr>
<tr>
<td>Parotid nodal burden (n = 30)</td>
<td></td>
</tr>
<tr>
<td>Positive nodes</td>
<td>1 (1-13)</td>
</tr>
<tr>
<td>Total nodes</td>
<td>2 (1-43)</td>
</tr>
<tr>
<td>Parotid and neck positive nodes (n = 64)</td>
<td></td>
</tr>
<tr>
<td>Positive nodes</td>
<td>2 (1-27)</td>
</tr>
<tr>
<td>Total nodes</td>
<td>23 (1-86)</td>
</tr>
<tr>
<td>Histologic nodal features</td>
<td></td>
</tr>
<tr>
<td>Necrotic nodes (n = 64)</td>
<td>20 (3.125)</td>
</tr>
<tr>
<td>Presence of extracapsular extension (n = 54)</td>
<td>40 (74.1)</td>
</tr>
<tr>
<td>Nodal maximal diameter, mm (histologic measurement)</td>
<td>15 (3-65)</td>
</tr>
<tr>
<td>Unknown</td>
<td>10</td>
</tr>
</tbody>
</table>

aDisease stage according the American Joint Committee on Cancer, seventh edition.

**Figure 1.** Analyses are presented for overall survival and freedom from regional recurrence (Kaplan-Meier method) for patients with head and neck cutaneous squamous cell carcinoma and nodal spread who underwent preoperative positron emission tomography/computed tomography scan. Dotted lines represent the limits of the 95% CI.
No histologic signs of acute or chronic inflammation (eg, granulation) were demonstrated, which could explain preoperative high FDG uptake.

The sensitivity and specificity of PET/CT for nodal disease in the neck were 91.3% and 90%, respectively. The positive and negative predictive values for lymphatic spread in the neck, as dictated by preoperative PET/CT, were 91.1% and 69.2%, respectively. For neck and parotid cases that had no FDG uptake (15 elective operations), the negative predictive value was 60% (6 FNs of 15 elective operations).

Of the 6 patients in the FN subgroup, 4 (66.7%) had chronic lymphocytic leukemia, compared with only 1 (11.1%) of the 9 patients in the TN subgroup (P = .09). A necrotic component was demonstrated in 60% of the nodal specimens (of 64 patients), as opposed to only 1 necrotic node (16.6%) in the FN subgroup (of 6 patients).

In a comparison of PET/CT and CT scan findings of the entire study group (N = 64), 4 patients (6.25%) had PET/CT findings that changed the surgical plan. Those 4 patients were part of the true-positive subgroup. One patient had contralateral neck nodal spread, and the other 3 had regional spread to sites (parotid, posterior triangle) not demonstrated on contrast-enhanced CT scan, which would not have otherwise been included in the surgical plan.

**Table 3.** Basin Preoperative PET/CT Scan Accuracy Analysis: Separated for the Neck and the Parotid.

<table>
<thead>
<tr>
<th>Histopathology, n</th>
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<tr>
<td></td>
</tr>
<tr>
<td>SCC</td>
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<tr>
<td>Neck nodes (n = 56)</td>
</tr>
<tr>
<td>High FDG uptake within the neck (therapeutic neck dissection)</td>
</tr>
<tr>
<td>No FDG uptake with in the neck (elective neck dissection)</td>
</tr>
<tr>
<td>Parotid nodes (n = 30)</td>
</tr>
<tr>
<td>High FDG uptake within the parotid (therapeutic parotidectomy)</td>
</tr>
<tr>
<td>No FDG uptake within the parotid (elective parotidectomy)</td>
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</tbody>
</table>

Abbreviations: FDG, 18F-fludeoxyglucose; PET/CT, positron emission tomography/computed tomography; SCC, squamous cell carcinoma.

**Table 4.** Preoperative PET/CT Scan Accuracy Analysis: Combined Neck and Parotid of 64 patients.

<table>
<thead>
<tr>
<th>Histopathology, n</th>
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<tr>
<td></td>
</tr>
<tr>
<td>SCC</td>
</tr>
<tr>
<td>High FDG uptake</td>
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<tr>
<td>No FDG uptake (elective dissection)</td>
</tr>
</tbody>
</table>

Abbreviations: FDG, 18F-fludeoxyglucose; FN, false negative; FP, false positive; PET/CT, positron emission tomography/computed tomography; SCC, squamous cell carcinoma; TN, true negative; TP, true positive.

*All TN cases were TP as well in another basin.

Discussion

The role of PET/CT scan prior to lymph node dissection (neck dissection, parotidectomy or both) for HNeSCC-M0 with nodal spread is ill-defined. Cho et al described a small cohort of patients undergoing preoperative PET/CT for the workup of cutaneous SCC tumors; however, only 12 patients in this study were node positive. The authors described a high level of accuracy for primary lesions and nodal metastases; however, a lack of calculations of accuracy metrics and no mention of the follow-up period render these conclusions vague. The low rate of nodal metastases with the undetermined benefit and high expense of this investigative tool may explain the infrequent use of PET/CT scan for HNeSCC.

Recently, another retrospective analysis compared PET/CT with anatomic imaging modalities (CT, magnetic resonance imaging) among 31 patients node-positive HNeSCC-M0. The number of patients where the management dramatically changed (classified as high impact) following PET/CT scan was 10% (3 of 31), with FN scans in 13% of cases (4 of 31). On the basis of these results, the authors suggested that PET/CT has a limited role in HNeSCC. Again, the small population, with only 25 patients proceeding to surgery, make it difficult to draw conclusions from this study.

The use of PET/CT scans is becoming increasingly common, with greater experience reported in the literature, even among subgroups with complex clinical patterns of disease. The survival curves for overall survival and freedom from regional recurrence, which plateau after 4 years at 52% and 86%, respectively, are similar to published survival curves, suggesting that the current patient cohort is a representative population without obvious selection bias.

The findings from this series demonstrate a change in extent of dissection for 6.25% of patients based on the preoperative PET/CT findings. As such, 16 patients require PET/CT to benefit 1 patient. We suggest that the lymph node dissection incorporate all sites with high FDG uptake, as well as sites of high clinical suspicion (clinical judgment) despite negative preoperative findings.

Despite the obvious benefits of functional imaging, financial considerations cannot be ignored. The correlation between high FDG uptake and pathology status of dissected nodes was based on matched neck level; however, we could not compare the number of nodes on PET/CT with the number of involved nodes, because of the difficulty distinguishing a large involved lymph node from matted smaller nodes on preoperative PET/CT. Importantly, a major limitation of this study is the inability to capture those patients for whom surgery was abandoned due to the discovery of metastatic disease at the time of PET/CT; this undefined group of patients clearly benefited from the preoperative imaging modality, as the PET/CT scan led to the abandonment of curative intent surgical resection. As such, it is expected that the actual TN and FN subgroups are larger than what is reported here. This is an inevitable weakness of a retrospective analysis.
Potential explanations for FN lymph nodes include nodal necrosis or low-volume metastatic disease. Neither of these scenarios was noted in the current series. The FN subgroup included patients with lymph nodes $>8$ mm in diameter, including patients with N2 disease and extracapsular extension but not patients with nodal necrosis. The low negative predictive value of PET/CT scans highlights the importance of elective dissection beyond the nodal disease seen on PET/CT scan. Unfortunately, the small size of the “true positive” (n = 57) and “false negative” (n = 6) subgroups meant that a comparative outcome analysis could not be performed to elucidate the effect of FDG uptake levels in metastatic nodes.

Patients with chronic lymphocytic leukemia are more likely to have a FN preoperative PET/CT scan, which should be considered in planning the extent of surgery.

**Conclusion**

PET/CT scan prior to lymph node dissection for HNcSCC-M0 with nodal spread has high specificity and positive predictive values with relatively low sensitivity and negative predictive values. The PET/CT FN rate is higher among patients with chronic lymphocytic leukemia.

**Author Contributions**

Nir Hirshoren, conception and design, data acquisition, analysis, interpretation of data, drafting and revision and final approval and agreement to be accountable for the manuscript; Elizabeth Olayos, data acquisition, drafting and revision and final approval and agreement to be accountable for the manuscript; Alan Herschtal, analysis, interpretation of data, drafting and revision and final approval and agreement to be accountable for the manuscript; Aravind S. Ravi Kumar, analysis, interpretation of data, drafting and revision and final approval and agreement to be accountable for the manuscript; David E. Gyorki, conception and design, analysis, interpretation of data, drafting and revision and final approval and agreement to be accountable for the manuscript.

**Disclosures**

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**References**