Squamous Cell Carcinoma From an Unknown Head and Neck Primary Site

A “Selective Treatment” Approach

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Objective: To assess the efficacy of limiting treatment to the involved neck by way of neck dissection and adjuvant radiotherapy and reserving other therapies for salvage in the management of metastatic cervical squamous cell carcinoma from an unknown head and neck primary site.

Design: Retrospective study of patients whose clinico-pathological data had been prospectively collected in a comprehensive head and neck database.

Setting: A tertiary referral university hospital.

Patients: The study population comprised 70 patients with metastatic cervical squamous cell carcinoma from an unknown head and neck primary site.

Interventions: Neck dissection alone in patients with pN1 disease confined to the lymph node. All remaining patients received neck dissection and adjuvant postoperative irradiation of the involved (dissected) neck.

Main Outcome Measures: Incidence of primary, regional, and distant recurrence and disease-specific and overall survival.

Results: Nodal stage was pN1 in 5 patients (7%); pN2a in 13 (19%); pN2b in 30 (43%); pN2c in 4 (6%); and pN3 in 18 (26%). Neck dissection alone was performed in 10 patients (14%), while 60 patients (86%) underwent neck dissection and adjuvant irradiation. Median follow-up was 45 months. The primary tumor site emerged in 8 patients (11%). The 5-year control rates were 84% in the ipsilateral (dissected) neck and 93% in the contralateral (undissected) neck. The 5-year disease-specific and overall survival rates were 62% and 56%, respectively. Macrophscopic extracapsular spread was the only statistically significant adverse prognostic factor (P < .001).

Conclusions: The results of our selective treatment approach compare favorably with the results of other reported protocols using comprehensive irradiation or concurrent chemoradiation. However, patients with extracapsular spread and pN2 or pN3 disease were at high risk of treatment failure and may benefit from adjuvant chemoradiation. Although our protocol spares patients of potentially morbid therapies, salvage is rarely successful.


Cervical lymph node metastasis from mucosal squamous cell carcinoma (SCC) is a relatively common head and neck presentation. However, approximately 5% of patients presenting with cervical lymph node metastasis of SCC have no identifiable primary site despite extensive diagnostic workup, including physical examination, fiberoptic endoscopy, examination with general anesthesia and targeted biopsies of potential primary sites, computed tomography or magnetic resonance imaging, and more recently fludeoxyglucose F18 positron emission tomography (PET).1,2

The optimal treatment of metastatic cervical SCC arising from an unknown primary site (SCCUP) in the head and neck is controversial. Patients with cervical SCCUP are usually excluded from randomized trials, leaving clinicians with the difficult task of interpreting small retrospective series with heterogeneous populations with respect to nodal distribution and treatment delivery. Several institutions have recommended aggressive therapeutic protocols for cervical SCCUP. These approaches include neck dissection with postoperative irradiation of bilateral necks and extended irradiation to potential primary mucosal sites in the head and neck (comprehensive irradiation)3,6 and more recently neck dissection with adjuvant postoperative chemoradiation.7,9

Over the last 20 years, the Sydney Head and Neck Cancer Institute, Sydney, Australia, has adopted a selective treatment approach with the intent of minimizing mor-
bidity and reserving additional treatment for salvage. Treatment has been focused on the clinically involved neck only by way of ipsilateral neck dissection and adjuvant postoperative neck irradiation in selected cases. Comprehensive irradiation has been reserved for patients with bilateral disease or in whom an occult primary nasopharyngeal primary tumor is suspected. The primary aim of this study was to analyze recurrence and survival following our treatment protocol, with particular reference to patterns of treatment failure.

STUDY COHORT

Since 1987, all clinicopathological data concerning patients treated at the Sydney Head and Neck Cancer Institute, Royal Prince Alfred Hospital, have been entered prospectively into a computerized database. By December 2006, 942 patients with SCC had undergone neck dissections. Of these, the primary mucosal or cutaneous cancer was not identified in 70 previously untreated patients (7%), who had no evidence of distant disease. The study cohort comprised these patients with metastatic cervical SCCUP treated with curative intent. There were 37 men and 13 women, with a median age of 62 years (range, 38-86 years). All patients were treated by members of the multidisciplinary Head and Neck Oncology team at Royal Prince Alfred Hospital.

DIAGNOSTIC WORKUP

A patient was classified as having metastatic cervical SCCUP if diagnostic workup confirmed metastatic cervical SCC and failed to identify a primary head and neck cancer site. In general, patients had cervical SCC proven by fine-needle aspirate biopsy. However, 2 patients were referred following open excision biopsy. A search for a head and neck primary site included physical examination and fiberoptic nasopharyngoscopy with the patient awake, which was repeated in the multidisciplinary head and neck clinic; computed tomography and/or magnetic resonance imaging from skull base to clavicles; and examination using general anesthesia, with rigid pharyngolaryngoscopy and targeted biopsies of the most likely primary sites, including ipsilateral tonsillectomy and biopsies of the tongue base and nasopharynx. Other sites were biopsied only if the mucosa was macroscopically abnormal. Chest computed tomography was used to evaluate for distant metastasis and following the availability of PET in 1999, 14 patients underwent PET as part of their diagnostic workup. In all cases, the neck disease was clearly demonstrated on PET, and in 3 of the 14 patients, PET revealed a potential primary mucosal site, which was later proven negative following an examination with general anesthesia and biopsy evaluation.

TREATMENT PROTOCOL AND CLINICAL REVIEW

The primary treatment modality in all patients was neck dissection, the extent of which was determined by the location and extent of disease. Of the 70 patients, 64 patients underwent unilateral neck dissection, and 6 patients with bilateral cervical disease underwent bilateral synchronous neck dissection (Table 1). Following histopathological assessment, each patient was assigned a pathological neck stage, according to the American Joint Committee on Cancer 2002 staging classification, and the sites of malignant nodal involvement were recorded (Table 2 and Table 3). Levels I and II of the neck were involved in 74% of neck dissection specimens. Macroscopic extracapsular spread (ECS) of tumor beyond the capsule of an involved lymph node was evident in 26 patients (37%), all of whom also had pN2 or pN3 disease. Microscopic ECS was present in 17 patients (24%), and all but 1 of these patients also had pN2 or pN3 disease.

Indications for adjuvant postoperative neck irradiation included previous open biopsy, ECS, and advanced neck disease (pN2 or pN3). The dose and fractionation schedules, treatment fields, and target volumes varied during the course of the study. Earlier in this series the standard postoperative dose was 50 Gy (to convert to rads, multiply by 100) in 25 fractions. Later, total doses of 54 to 60 Gy were more commonly used. A total of 60 patients received surgery and adjuvant postoperative radiotherapy. Of these 60 patients, 49 patients (82%) received irradiation to the dissected neck alone, while 11 patients had comprehensive irradiation that aimed to encompass both sides of the neck as well as potential mucosal sites in the nasopharyngeal, oropharyngeal, hypopharyngeal, and laryngeal regions.

Eight patients did not receive adjuvant radiotherapy. Of these, 2 patients had a single positive node with no ECS and radiotherapy was not recommended, 4 patients declined postoperative radiotherapy, and 2 patients died prior to the commencement of their postoperative radiotherapy. The radiotherapy records of 2 patients were incomplete.

Table 1. Summary of Neck Dissections Performed

<table>
<thead>
<tr>
<th>Neck Dissection</th>
<th>No. of Neck Dissections</th>
</tr>
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<tbody>
<tr>
<td>Comprehensive</td>
<td></td>
</tr>
<tr>
<td>Extended radical</td>
<td>11</td>
</tr>
<tr>
<td>Radical</td>
<td>19</td>
</tr>
<tr>
<td>Modified radical</td>
<td>28</td>
</tr>
<tr>
<td>Selective</td>
<td></td>
</tr>
<tr>
<td>Level I-III</td>
<td>3</td>
</tr>
<tr>
<td>Level I-IV</td>
<td>2</td>
</tr>
<tr>
<td>Level II-V</td>
<td>7</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>76</td>
</tr>
</tbody>
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Table 2. Incidence of Pathological Nodal Stage

<table>
<thead>
<tr>
<th>Nodal Stage</th>
<th>Patients, No. (%)</th>
</tr>
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<tbody>
<tr>
<td>pN1</td>
<td>5 (7)</td>
</tr>
<tr>
<td>pN2a</td>
<td>13 (19)</td>
</tr>
<tr>
<td>pN2b</td>
<td>30 (43)</td>
</tr>
<tr>
<td>pN2c</td>
<td>4 (6)</td>
</tr>
<tr>
<td>pN3</td>
<td>18 (26)</td>
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</tbody>
</table>

Table 3. Incidence of Malignant Nodal Involvement by Neck Level

<table>
<thead>
<tr>
<th>Neck Level</th>
<th>Incidence of Malignant Nodal Involvement, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>25</td>
</tr>
<tr>
<td>II</td>
<td>53</td>
</tr>
<tr>
<td>III</td>
<td>36</td>
</tr>
<tr>
<td>IV</td>
<td>26</td>
</tr>
<tr>
<td>V</td>
<td>16</td>
</tr>
</tbody>
</table>
Following treatment, patients were reviewed by the surgeon at 6-week intervals. The median duration of follow-up for the patients alive at the last point of contact was 45 months (range, 2-138 months).

STUDY END POINTS

Outcome data were prospectively collected at the time of clinical review and entered onto the comprehensive head and neck database by our database manager. The following clinical end points were evaluated: the rate of emergence of the primary cancer (defined as a mucosal primary located in a site consistent with the initial metastatic cervical disease and emerging within the first 5 years of follow-up); regional disease control in the ipsilateral (dissected) and contralateral (undissected) neck; incidence of distant metastases; and disease-specific and overall survival. In the presence of bilateral neck disease, the side with the greater volume of disease was considered to be the ipsilateral neck. Time to recurrence was measured from the date of neck dissection to the date of the relevant clinical event. Disease-specific and overall survival were measured from the date of surgery to the date of most recent clinical review or to death. All follow-up data collected to December 31, 2006, were analyzed for this report.

STATISTICAL ANALYSIS

Cumulative primary control, neck control, and survival rates were calculated by the Kaplan-Meier method. Each study end point was analyzed according to pathological stage, extent of ECS, type of neck dissection, and postoperative radiotherapy. Univariable comparisons were assessed by the log-rank test. The χ² test was used to determine the significance of differences between proportions. Multivariable analysis was performed using the Cox proportional hazards model. P < .05 was considered statistically significant.

RESULTS

RECURRENT

Primary tumor sites subsequently emerged in 8 patients (11%), at a median of 18 months (range, 5-36 months) after neck dissection. Postoperative adjuvant radiotherapy was planned for all of these patients according to our treatment protocol. However, 2 patients refused irradiation. The sites of local recurrence included base of tongue in 4 patients, larynx in 2, and oral tongue in 2. At the time of initial presentation, 1 patient underwent PET, which did not demonstrate a primary site. Three patients had undergone biopsy with negative results of what later proved to be the primary site. Salvage treatment was undertaken in 6 of the 8 patients and included surgery and adjuvant radiotherapy in 4 patients and surgery alone in 2 patients. Of the 6 patients who received salvage treatment, 3 are alive and free of disease at a median of 2 months (range, 2-3 months) following salvage treatment and 3 patients died of disease at a median of 44 months (range, 25-75 months) following salvage treatment. One patient died 2 months after treatment with palliative intent following local recurrence and lung metastases. The eighth patient with local recurrence declined further treatment and was lost to follow-up.

A total of 14 patients (20%) experienced recurrence in the neck, with a median time to neck recurrence of 9 months (range, 2-63 months). Histologic examination demonstrated ECS in all but 1 of these 14 patients (9 with macroscopic ECS and 4 with microscopic ECS). Ipsilateral (dissected) neck failure occurred in 9 patients (3 with pN2a, 2 with pN2b, and 4 with pN3), and contralateral (undissected) neck failure occurred in 5 patients (4 with pN2b and 1 with pN3). Thus, the crude risk of neck failure in patients with macroscopic ECS in the presence of pN2 or pN3 disease was 35%, since 9 of 26 patients with both of these prognostic factors failed in the neck. Conversely, only 4% of patients (1 of 27) with no ECS and pN2 or pN3 disease failed in the neck. All the patients in whom treatment had failed in the neck had received postoperative adjuvant neck irradiation. The 5-year actuarial ipsilateral (Figure 1A) and contralateral (Figure 1B) regional control rates were 84% and 93%, respectively. There was a nonsignificant trend toward worse 5-year ipsilateral regional control of 83% in patients with multiple nodes compared with 5-year ipsilateral regional control of 100% in those with solitary nodal involvement (log rank test P = .36) (Figure 1C and D).

Salvage treatment was attempted in 8 patients and consisted of neck dissection alone in 2, neck dissection and adjuvant postoperative irradiation in 4, and radiotherapy alone in the remaining 2 patients. Two patients remain disease-free at 13 and 45 months following salvage therapy, and 1 patient is alive with disease 2 months following salvage treatment. The remaining 5 patients died of disease at a median of 10 months (range, 2-20 months) following salvage therapy. Salvage was unsuitable because of advanced regional and distant disease in 5 patients, 4 of whom died within 1 month and the other within 3 months of recurrence.

Five patients experienced recurrence at distant sites at a median of 9 months (range, 3-12 months) following initial treatment, and 4 of these patients have died. Thus, of the total study cohort of 70 patients, 27 patients (39%) experienced recurrence following initial treatment. Of these, 5 remain disease-free following salvage treatment.

SURVIVAL AND MORBIDITY

Disease-specific survival and overall survival at 5 years were 62% and 56%, respectively (Figure 2A and B). While there was a nonsignificant trend toward worse disease-specific survival in those patients with pN3 stage (P = .07) (Figure 2C), this was statistically significant in patients with macroscopic ECS (P < .001) (Figure 2D).

In total, 12 of 70 patients (17%) had complications, with wound-related problems being the most frequent. All irradiated patients had varying grades of acute mucositis and xerostomia. One patient had laryngeal necrosis requiring total laryngectomy 47 months after irradiation. Death occurring as a complication of treatment was not observed.

COMMENT

In contrast to other sites,^10 cervical SCCUP has a relatively good prognosis, with disease-specific survival rates approaching 70%^1. An unknown head and neck primary tumor site is assumed based on well-documented patterns of cervical lymphatic spread of head and neck...
Therefore, many centers adopt aggressive locoregional treatment directed against the most likely mucosal sites based on the location of involved nodes. Such an approach involves extended field mucosal and bilateral neck irradiation (comprehensive irradiation). Advocates of this aggressive approach contend that treatment reduces the subsequent rate of emergence of primary tumors and improves control in the contralateral neck. Those opposed to this approach argue that in the absence of a significant survival advantage, the early and late treatment-related morbidity of comprehensive irradiation is excessive. Furthermore, salvage options are severely restricted in patients in whom a primary tumor emerges.
Several authors have documented high rates of control using neck dissection alone in patients with limited disease (ie, N1, N2a, and ECS negative) and suggest that adjuvant radiotherapy is not indicated. Coster et al\(^1\) reported locoregional control rates in 24 patients with N1 and N2a disease of 92% and 75%, respectively, while Iganej et al\(^2\) reported an 81% locoregional control rate in 41 patients with N1 and N2a disease with no ECS.

Although adjuvant irradiation may improve locoregional control in patients with advanced disease, there is no conclusive evidence that comprehensive radiotherapy is superior to irradiation of the ipsilateral neck alone. Weir et al\(^3\) retrospectively analyzed a series of 144 patients and found no difference in survival based on the extent of neoadjuvant radiotherapy. Although Reddy and Marks\(^4\) found the same result with respect to survival in their cohort of 52 patients, they found that bilateral neck irradiation improved contralateral neck control and the subsequent emergence of occult primary disease. In their review of 136 patients undergoing a comprehensive treatment protocol, Collette et al\(^5\) reported an impressive survival rate of 74% for the whole group, 69% for those with N2 disease, and 71% for N3 disease.

Although landmark studies have established concurrent chemoradiotherapy as an integral component in the treatment of patients with locally advanced SCC of the head and neck,\(^6\)-\(^10\) its role in cervical SCCUP remains unproven. To date, only 3 small retrospective series evaluating chemoradiotherapy in this setting have been published.\(^11\)-\(^13\) de Braud et al\(^11\) reported a median survival of 37 months in 16 patients receiving chemotherapy delivered before, during, or after radiotherapy vs 25 months in their historical control group. In the second series, Argiris et al\(^12\) reported 5 different chemotheraphy protocols in 25 patients receiving adjuvant chemoradiotherapy. They reported 5-year progression-free and overall survival rates of 87% and 75%, respectively. However, the small patient populations and highly heterogeneous treatment regimens used in these studies make interpretation difficult. The third series reported by Shehadeh et al\(^13\) comprised 37 patients treated with neck dissection followed by concurrent chemoradiotherapy. The regional control and overall survival rates were 95% and 89%, respectively, with a median follow-up of 42 months.

Encouraging results following concurrent chemoradiotherapy schedules should be considered in context of associated early and late treatment-related toxic effects. Argiris et al\(^12\) reported 1 treatment-related death, and 16% of patients were gastrostomy tube dependent 1 year after therapy.\(^8\) Shehadeh et al\(^13\) reported that 19% of the study cohort required hospitalization for management of treatment-related morbidity, and 8% had chronic esophageal stricture requiring intermittent dilatation.

The predominant pattern of treatment failure in our study cohort was regional recurrence within the dissected neck or contralateral metastases to the undissected neck, which occurred in 20% (n=14) of patients and accounted for 52% (14 of 27) of all treatment failures. All patients had adverse pathological prognostic factors, namely ECS and/or advanced nodal disease (pN2 or pN3), and underwent adjuvant neck irradiation. Comprehensive irradiation is not supported by our results, since the reported emerging primary rate of 11% and contralateral neck control rate of 93% are within the range of those series using the more aggressive treatment protocols detailed previously.\(^3\)-\(^9\) However, outcomes were particularly poor in patients with macroscopic ECS and pN2 or pN3 disease, with treatment failing in the neck in 35% of these patients. These selected patients may benefit from more aggressive treatment, in particular postoperative chemoradiation. This is particularly important given the low rate of successful salvage experienced in patients with recurrent disease in our series.

Another area of controversy is the optimal extent of cervical lymphadenectomy for SCCUP. The majority of patients treated in the early part of this series underwent comprehensive neck dissection, mainly because of the difficulty in predicting patterns of lymphatic spread. However, recent trends in mucosal SCC have been evolving toward more selective approaches in the surgical management of malignant cervical lymphadenopathy,\(^12\)-\(^13\) and we believe it is reasonable to apply these concepts to SCCUP, relying on adjuvant radiotherapy for microscopic residual disease. Accordingly, 24% of lymph node dissections performed in our study cohort were selective neck dissections. We were unable to evaluate whether the extent of neck dissection influenced outcomes because of heterogeneity and inadequate sample size. Nevertheless, we did not detect any tendency toward worse outcome in those undergoing selective neck dissection.

It was not possible, nor was it the aim of the present study, to determine the accuracy of PET in the diagnostic workup of SCCUP. Published studies report that the detection rate of a head and neck SCCUP by PET does not exceed 25% and has an overall staging accuracy of 69% to 78%.\(^2\) Positron emission tomography is useful for detection of regional and distant disease, particularly when treatment is homolateral.

In conclusion, comprehensive irradiation is not supported by our results as the emerging primary and contralateral failure rates were low. However, more aggressive therapy should be offered to selected patients, namely, those with bulky neck disease (pN2 and pN3) and, in particular, patients with macroscopic ECS. The morbidity associated with concurrent chemoradiation supports a selective approach based on risk of regional failure. The concept of reserving additional therapy for salvage is not supported by the low rate of successful salvage in our series. Cure is most likely to be achieved following initial therapy.

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Author Contributions: Dr Patel had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Patel. Acquisition of data: Patel, Wyten, and Gao. Analysis and interpretation of data: Patel, Clark,
REFERENCES


