BENEFIT OF POSTOPERATIVE CHEMORADIOOTHERAPY FOR
PATIENTS WITH UNKNOWN PRIMARY SQUAMOUS CELL
CARCINOMA OF THE HEAD AND NECK

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Abstract: Background. Postoperative adjuvant chemoradiotherapy recently became an established modality for patients with selected high-risk locally advanced head and neck cancers. The optimal treatment of unknown primary squamous cell cancer of the head and neck (SCCHN) continues to be controversial, since major randomized studies excluded those patients.

Methods. We conducted a retrospective review of patients treated during 1995 to 2002 for unknown primary SCCHN. All patients were treated with a neck dissection followed by concurrent high-dose cisplatin (100 mg/m²) and bilateral neck radiotherapy.

Results. Thirty-seven patients were identified with nodal disease distribution of N1 (5%), N2a (22%), N2b (41%), N2c (8%), N3 (22%), and Nx (3%). Modified neck dissection was done on the majority (30/37 = 81%) of patients. With a median follow-up of 42 months among the survivors, very few patients had regional recurrence (5%) or distant failure (11%), and 89% of patients were alive. The actuarial 5-year overall survival rate could not be estimated because there were no deaths beyond 20 months after surgery. Substantial yet acceptable acute and late morbidities were demonstrated in this cohort of patients.

Conclusions. Postoperative chemoradiotherapy is of potential benefit to patients with unknown primary SCCHN by improving survival and reducing failures. This treatment warrants further prospective evaluation.

Keywords: chemoradiotherapy; head and neck cancer; unknown primary; neck dissection; squamous cell cancer

Cervical adenopathy is a very common presentation in head and neck cancer. In 2% to 4% of all new patients who present with enlarged cervical
lymph nodes, the primary tumor cannot be found, even after extensive evaluation. The diagnostic procedures for cervical squamous cell carcinoma of unknown primary (SCCUP) include physical examination with thorough evaluation of the head and neck mucosa using fiberoptic endoscopy, biopsies from all suspicious sites or from the sites of possible origin of the primary, CT, and recently 18F-flouro-2-deoxy-D-glucose positron emission tomography (18-FDG-PET).

The optimal treatment of cervical SCCUP has not yet been defined and remains controversial. Controversy stems from the fact that patients with cervical SCCUP are often excluded from major randomized clinical trials; studies reported are usually single-institution retrospective series, and patients are treated with heterogeneous treatments. Recommendations for treatment vary and include surgical excision of the involved lymph node alone, neck dissection, radiotherapy, or combinations. Moreover, varying sequences of treatment modalities have been used in previously reported retrospective series.

Concurrent chemoradiotherapy has now become an integral part of standard nonsurgical treatment of patients with locally advanced head and neck cancer, and postoperative treatment in pathologically high-risk patients. However, the role of chemoradiotherapy for cervical SCCUP has not yet been established.

We report here the outcome of a specific cohort of cervical SCCUP patients treated uniformly with neck dissection followed by concurrent chemoradiotherapy using high-dose cisplatin and radiation to bilateral neck fields.

PATIENTS AND METHODS

Patient Population. Patients diagnosed with cervical SCCUP during 1995 to 2002 were identified through a search of the Detroit's Surveillance, Epidemiology, and End Results (SEER) registry and the Wayne State University Head and Neck Oncology multidisciplinary group database. A thorough review of medical records was conducted for patients who had squamous cell carcinoma or undifferentiated cancer histology, treatment with neck dissection followed by concurrent chemoradiotherapy, and a minimum follow-up of 12 months after surgery. Human Investigation Committee (HIC) and Institutional Review Board (IRB) approval was obtained to review patients' charts.

Diagnostic Workup. A patient with metastatic carcinoma in cervical nodes was classified to have an unknown primary tumor if investigations failed to detect a primary tumor site. For this report, N status for all patients was classified retrospectively according to the American Joint Committee for Cancer Staging (AJCC) 1997 classification. All patients were treated by members of the multidisciplinary Head and Neck Oncology Group at the Karmanos Cancer Institute.

The initial diagnosis was made by a fine-needle aspiration. Three patients who had excisional biopsies at outside hospitals were referred to our institution for further management. Panendoscopy was done on each patient by a head and neck surgeon and included nasopharyngoscopy, laryngoscopy, bronchoscopy, and esophagoscopy. Random biopsies were obtained from the nasopharynx, oropharynx, and hypopharynx, and biopsies were obtained from suspicious areas. Tonsillectomy was not done routinely as part of the diagnostic work-up unless indicated by the examination. Imaging studies included head and neck CT, chest radiography and CT, and PET scan after 2002.

Treatment Methods.

Surgery. The majority of patients had modified comprehensive neck dissection, while radical dissection was done for 7 patients. A selective neck dissection or nodal excision alone was never performed. A wide local excision of the scar was performed if an excisional biopsy was previously done.

Chemotherapy. Three to 5 weeks after surgery, patients underwent concurrent chemoradiotherapy. Chemotherapy was cisplatin at 100 mg/m² intravenously and was planned to be given concurrently with radiotherapy every 3 weeks to a total of 3 cycles on day 1, 22, and 43, unless treatments were delayed by low blood counts or increased creatinine. Patients demonstrated adequate hematological, renal, and liver function prior to cisplatin chemotherapy. A few patients were switched to carboplatin secondary to renal dysfunction. Patients were admitted to the hospital for 24 hours to ensure adequate mannitol volume expansions, hydration, and control of emesis. When necessary, an aggressive outpatient hydration protocol was followed after treatment. Feeding tubes were not placed prophylactically but were placed if indicated during the treatment course.

Radiotherapy. At Wayne State University and Karmanos Cancer Institute, the radiotherapy of...
patients with cervical SCCUP had been delivered by linear accelerator (4 MV photon) through lateral opposed fields to both sides of the neck and the potential primary sites, including the nasopharynx, base of tongue, tonsillar fossa, and hypopharynx. The supraclavicular area was also included in the anterior radiation field. An initial 5000 cGy was given to ports encompassing all potential primary sites and bilateral neck with opposed bilateral fields with a 4-MV photon and 9-MeV electron beam. The involved neck was then boosted with an ipsilateral 9- to 12-MeV electron beam to total dose of 6000 to 6400 cGy, depending on location, number of nodes involved, and presence or absence of extracapsular extension (ECE). Radiation was given in standard 200 cGy per fraction, standard 5 fractions per week. In the absence of radiographically visible tumor, intensity-modulated radiation treatment (IMRT) planning was not employed in order to avoid marginal miss and cold areas in potential risk areas. CT-PET was not available in our institution during treatment periods for patients on this study.

**Follow-Up.** All patients were seen routinely on a monthly basis in year 1, bimonthly in year 2, and quarterly in years 3 and 4 in the multidisciplinary head and neck clinic. During each clinic visit, each patient was seen by a head and neck surgeon and a medical oncologist. A radiation oncologist saw the patients separately at the Radiation Oncology Center. At each visit, the patient had a thorough physical examination, endoscopy, and periodic imaging studies (neck and chest CT) determined by the treating physicians.

**Endpoints and Statistics.** Endpoints of this study were regional recurrence, distant recurrence, any recurrence, and overall survival. Four time-to-event variables were computed: regional recurrence–free survival (RRFS); distant recurrence–free survival (DRFS); freedom from any recurrence, termed recurrence-free survival (RFS); and overall survival (OS). All 4 of these time-to-event variables were measured from the date of neck dissection. RFS was calculated from the time of neck dissection surgery to the time of regional failure, salvage surgery, distant metastases, or second primary, whichever came first. Any tumor recurrence in the neck or development of second primary was documented by biopsy. A 60-month cutoff period was used to differentiate regional recurrence from second primary tumor. OS was measured from the date of surgery to the last day of follow-up or to death. Standard Kaplan-Meier estimates of the censored RRFS, DRFS, RFS, and OS functions were computed. Because of the small sample sizes, survival statistics (eg, 6-month or 12-month rates) were estimated more conservatively using linear interpolation among successive event times on the Kaplan-Meier curves. Both point and 90% confidence interval estimates were computed. All follow-up data collected as of April 1, 2004, were analyzed for this report.

**RESULTS**

**Patient Characteristics.** Baseline demographic and clinical data are listed in Table 1. The majority of patients were white males. Seventy-one percent and 68% of patients, respectively, had N2b lymph node status and ECE. Positive nodal margins were seen in 6 patients (16%), and margins could not be documented in 4 patients (11%). Seven patients (19%) had radical neck dissection, whereas the rest underwent modified neck dissection. The decision to do bilateral neck dissection was based on the clinical assessment of the neck, as suggested by the discrepancy between the number of bilateral neck dissections and pN2c patients. Level I and II lymph nodes were involved in the majority of patients, while level V nodes were involved in 5 patients.
The mean times from diagnosis to neck dissection and from neck dissection to chemoradiotherapy were 1.5 months (range, 0–5.9 months), and 1.0 month (range, 0.4–2.1 months), respectively.

Delivered Treatment. Twenty-nine patients (78%) received 3 cycles of cisplatin on days 1, 22, and 43 without delay (see Table 2). Chemotherapy was delayed in 6 patients, secondary to transient renal insufficiency or low blood count. Eight patients were given carboplatin instead of cisplatin at some time during their treatment. Substitution of carboplatin for cisplatin was due to renal insufficiency and intractable nausea and vomiting. Severe mucositis delayed radiotherapy in 5 patients. The radiation therapy was given in 200-cGy fractions, 5 times a week for total doses that are shown in Table 2.

Toxicity. The majority of patients reported varying degrees of acute mucositis and delayed xerostomia. The major toxicities are shown in Table 3. No patients died from treatment-related causes. Two of the 3 patients with esophageal stricture required long-term intermittent dilatation. One year from treatment, 9 patients who required nutritional support were free of feeding tubes. Postoperative shoulder dysfunction was not measured.

Efficacy Data

Regional Recurrence. With a median follow-up of 39 months among the 37 patients still censored for this endpoint, 2 (5%) regional recurrences were observed. One patient had a recurrence in the skin and the neck at 6 months, and a second patient had a relapse in the neck ipsilaterally at 9 months. Both patients had N3 disease and pathology showed ECE. Their overall survival was 12 and 11 months, respectively. The actuarial 5-year regional control rate cannot be estimated in this cohort because no regional recurrences were detected beyond 12 months after surgery. The Kaplan-Meier graph of RRSF is shown in Figure 1. One patient developed a second, primary early-stage tongue cancer 90 months from his initial diagnosis. He was treated by surgical excision and was still alive after a follow-up of 106 months.

Distant Failure. Four of 37 (11%) patients developed distant failure. Three patients had lung recurrence, 1 had axillary metastasis, and 1 had brain metastasis. The median follow-up time among the 33 patients still free of distant recurrence was 39 months (range, 9–106 months). The Kaplan-Meier curve for DRFS is depicted in Figure 2. Since all distant failures occurred within 23 months from neck dissection, the confidence limits of the DRFS cannot be calculated thereafter.

Overall Survival and Recurrence-Free Survival. The median follow-up time for any cause mortality was 42 months (range, 9–106 months) among the 33 of 37 (89%) patients who were still alive. Four patients died during that period, 1 secondary to metastatic well-differentiated adenocarcinoma of the colon 18 months from the original head and neck cancer diagnosis. Two patients died of distant metastases, and 1 died of regional recurrence, with survival times of 12, 20, and 11 months, respectively. The actuarial 5-year OS could not be estimated because of no events beyond 20 months after surgery. Figure 3 shows the Kaplan-Meier curve for OS, and Figure 4 shows Kaplan-Meier curve for any recurrence (RFS).

DISCUSSION

Carcinoma of unknown primary is defined as histologic diagnosis of metastasis without the detection of a primary tumor. The failure to detect the primary tumor could be explained by spontaneous

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Table 2. Delivered treatment.

<table>
<thead>
<tr>
<th>Treatment profile</th>
<th>No.</th>
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<tbody>
<tr>
<td>Chemotherapy, no. of patients</td>
<td>No.</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>29</td>
</tr>
<tr>
<td>Cisplatin and/or carboplatin × 2 cycles</td>
<td>6</td>
</tr>
<tr>
<td>Cisplatin or carboplatin × 1 cycle</td>
<td>2</td>
</tr>
<tr>
<td>Radiotherapy median dose, cGy</td>
<td>No.</td>
</tr>
<tr>
<td>Potential primary sites</td>
<td>5000</td>
</tr>
<tr>
<td>Involved neck</td>
<td>6400</td>
</tr>
<tr>
<td>Uninvolved neck</td>
<td>5000</td>
</tr>
<tr>
<td>Supraclavicular neck region</td>
<td>5000</td>
</tr>
<tr>
<td>Delay of treatment, no. of patients</td>
<td>No.</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>6</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 3. Toxicity for 37 patients.

<table>
<thead>
<tr>
<th>Toxicity (grade III/IV)</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucositis</td>
<td>17 (46)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Renal</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>7 (19)</td>
</tr>
<tr>
<td>Feeding tube</td>
<td>9 (24)</td>
</tr>
<tr>
<td>Xerostomia</td>
<td>11 (30)</td>
</tr>
<tr>
<td>Esophageal stricture</td>
<td>3 (8)</td>
</tr>
</tbody>
</table>
regression or immune-modulated destruction of the primary tumor, faster growth rate of the nodal metastasis, or sloughing of the necrotic tumor. The level of the involved lymph nodes may suggest the location of the primary site and may guide the diagnostic evaluation.

The incidence of cervical SCCUP is becoming less common with the recent advancements in imaging and diagnostic procedures for head and neck tumors. Molecular assays have recently been proposed to help identify a potential primary site such as in the detection of Epstein-Barr virus (EBV) by in situ hybridization in cervical SCCUP of nasopharyngeal origin. Moreover, 18-FDG-PET imaging of the head and neck area has increased the possibility of detecting the primary site when traditional imaging modalities have failed to do so. Some authors advocate bilateral tonsillectomy because of the fact that level II and III are the most involved groups of lymph nodes and the emergence of a subsequent primary tumor was commonly seen in the oropharynx including tonsils.

Various therapeutic approaches have been employed in the treatment of cervical SCCUP. All published studies have been retrospective series with heterogeneous patient populations (different histopathology) and different treatment and diagnostic modalities, leaving optimum treatment for these patients uncertain. Some general conclusions, however, could be drawn from recent larger series.

Surgery remains the mainstay of management of SCCUP with acceptable clinical outcomes and side effects. The comprehensive neck dissection (removing all 5 cervical levels) has been widely accepted, especially since a predictable pattern of regression or immune-modulated destruction of the primary tumor, faster growth rate of the nodal metastasis, or sloughing of the necrotic tumor. The level of the involved lymph nodes may suggest the location of the primary site and may guide the diagnostic evaluation.

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nodal metastasis does not exist with SCCUP. Although modified comprehensive neck dissections have mostly been performed for larger nodes, a radical comprehensive neck dissection may be required. Other reported surgical approaches include selective neck dissection, lymph node excision, or a planned or salvage neck dissection. Other authors suggest that local control and survival are equivalent between excisional biopsy and neck dissection if adjuvant radiotherapy was given.\textsuperscript{5,22} We remain concerned that excisional biopsy alone is inadequate treatment (due to lack of accurate staging), even if followed by radiotherapy. Surgery with neck dissection has the advantage of accurate lymph node staging as well as identifying poor pathologic features like ECE and close margins which could predict higher recurrence rate.\textsuperscript{23,24} Planned neck dissections performed after irradiation showed persistence of nodal disease in up to 44% of patients.\textsuperscript{25,26} This high rate of residual disease could be explained by selection bias, since most patients who received radiotherapy prior to surgery have advanced unresectable disease. Surgery alone is associated with high failure rate, although some authors postulate that surgery alone may be adequate for patients with N1 disease without ECE and with no history of violated neck.\textsuperscript{27,28} However, Coster et al\textsuperscript{8} found a lymph node recurrence rate of 30% in patients treated by surgery alone in a series of 24 patients, 14 of whom had N1 disease.

Postoperative radiotherapy is frequently used in the treatment of advanced head and neck cancer. The use of radiotherapy in cervical SCCUP has been described in multiple series with some differences in the sequence and the field of radiotherapy. Most studies used radiotherapy as adjuvant modality and less frequently, alone\textsuperscript{29,30} or before surgery.\textsuperscript{25,26} The optimal field of radiotherapy remains controversial with respect to inclusion of the potential primary site and contralateral neck. The benefit from extensive radiotherapy to the large areas of the mucosa and bilateral neck should be weighed against acute and late toxicities and the difficulties of reirradiation in case of emergence of a second primary tumor. Bilateral neck irradiation improved the local control and prevented emergence of other mucosal primaries,\textsuperscript{6,31–33} and in some series, improved survival as compared with ipsilateral neck treatment.\textsuperscript{34} Some authors suggest limiting mucosal irradiation to the nasopharynx and oropharynx for lower probability of occult carcinoma located in hypopharynx and larynx and higher involvement rate of level II and III lymph nodes.\textsuperscript{35,36} The role of chemotherapy and the role of adjuvant chemoradiotherapy in the management of cervical SCCUP have not been adequately investigated as described in many retrospective series. Since the mid-1990s, at Karmanos Cancer Institute and Wayne State University, we have treated patients with cervical SCCUP with neck dissection followed by concurrent chemoradiotherapy. We report a cohort of 37 such patients in whom there is homogeneity in the diagnostic and therapeutic approach. The regional control is excellent (only 2 events) in this cohort of patients in whom 70 and 68% have >N2b disease and ECE, respectively. The results of the current series (27% had N1 or N2a and 73% had greater than N2a disease) are favorably compared to recent series in which radiotherapy was delivered to bilateral sides of the neck. Colletier et al\textsuperscript{5} reported a regional control rate of 81% in a series of 136 patients (59% had N1 or N2a) treated with surgery followed by bilateral neck radiotherapy. In another series (52 patients) reported by Reddy et al,\textsuperscript{32} regional control was achieved in 86% of patients (48% had N1 or N2a) treated with surgery and radiotherapy. We cannot estimate the actuarial 5-year regional control rate in this cohort because of no events occurred beyond 12 months after surgery. Moreover, due to the small number patients with events, further prognostic factor analysis cannot be performed. The pattern of failure in which we see more distant metastasis (4 patients) compared with regional failure (2 patients) in this cohort is consistent with the trend seen in recent trials employing concurrent chemoradiotherapy.\textsuperscript{11,12,37} Chemotherapy in addition to bilateral neck irradiation could explain the very low rate of emergence of the primary tumor as well as lower rate of second primary appearance. Series with adjuvant bilateral neck irradiation reported emergence of the primary tumor in 7% to 20% of patients.\textsuperscript{6,32,38} We have to be very cautious in comparing these series given their retrospective design and possible inherent biases.

To the best of our knowledge, only 2 small series with cervical SCCUP treated with chemoradiotherapy have been reported in the literature. In these, chemoradiotherapy was not uniform, which makes it difficult to compare the results. De Braud et al\textsuperscript{3} from Wayne State University reported on 16 patients treated with different chemotherapy regimens before, during, or after radiotherapy. Neck dissection was done in 3 patients before concurrent chemotherapy. The historical control group consisted of 25 patients...
treated by radiotherapy alone (16 patients) or neck dissection followed by radiotherapy (9 patients). The median survival was 37 months in the chemotherapy group versus 25 months in the surgery and radiotherapy group despite lower N3 disease in the latter group. In a second series, Argiris et al. reported on 25 patients with cervical SCCUP treated in 5 different protocols of chemoradiotherapy in which radiotherapy was administered to the bilateral neck. Chemotherapy used concurrently with RT included paclitaxel, 5-fluorouracil (5-FU), and hydroxyurea. Some of these protocols used different induction chemotherapy as well. Neck dissection was done in 22 patients, with 14 of them receiving adjuvant chemoradiotherapy. The 5-year progression-free and overall survival rates were 87 and 75%, respectively. We could not calculate the actuarial 5-year OS for our series because of no deaths beyond 20 months after surgery, which makes the comparison with other series more difficult.

The encouraging results of our series come with a price in terms of more acute toxicities and late morbidities including xerostomia and esophageal stricture (Table 3). Bilateral neck radiotherapy with chemotherapy could explain the higher but acceptable rate of late adverse effects. On the other hand, treatment of the involved side of the neck alone may have a detrimental effect on the patient's outcome because potential sites of occult primaries in the head and neck mucosa and any subclinical diseases in the contralateral side of the neck are left untreated. In our current cohort, every patient regardless of the N classification received the same planned dose of chemotherapy and the same field/dose of radiotherapy which might be excessive for N1 and N2a patients without poor pathologic features as has recently been shown in comparative analysis of the concurrent postoperative radiation plus chemotherapy trials of the European Organization for Research and Treatment of Cancer (EORTC) and Radiation Therapy Oncology Group (RTOG). For that subset of patients, some authors recommend surgery or radiotherapy. In addition, recently reported studies using concurrent chemoradiotherapy in known head and neck primaries suggest that elective neck dissection should be part of the treatment. The positive results of the recent adjuvant chemoradiotherapy in resectable head and neck cancer argue that patients with cervical SCCUP should be treated in a similar fashion. The treatment of this group of patients may continue to evolve in the future as more advancements are made in the treatment of resectable and unresectable head and neck can-

<table>
<thead>
<tr>
<th>Author (year), ref. no.</th>
<th>No. of patients</th>
<th>Treatment (no. of patients)</th>
<th>N status (% of patients)</th>
<th>5-yr actuarial OS</th>
<th>Metachronous primaries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colletier et al (1988)</td>
<td>136 S ≥ RT (136)</td>
<td>N1, N2a (59) N2b, N2c (19) N3 (13)</td>
<td>60% 10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grau et al (2000)</td>
<td>277 S (23) RT (224) RT ≥ S (26)</td>
<td>N1 (17) N2 (49) N3 (34)</td>
<td>36% 12%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reddy and Marks (1997)</td>
<td>52 RT (13) S ≥ RT (39)</td>
<td>N1, N2a (48) N2b, N2c (23) N3 (29)</td>
<td>51% 19%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argiris et al (2003)</td>
<td>25 5 diff. protocols CRT (3) S + CRT (22)</td>
<td>N2a (20) N2b, N2c (56) N3 (24)</td>
<td>75% 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current series</td>
<td>37 S ≥ CRT</td>
<td>N1, N2a (28) N2b, N2c (48) N3 (22)</td>
<td>NR 3%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: S, surgery; RT, radiotherapy; CRT, chemoradiotherapy; NR, not reported.

*Median survival of 37 months in the chemotherapy group and 24 months in the non-chemotherapy group.
†See overall survival curve. 5-yr actuarial OS cannot be estimated due to the low number of events.
cancer, particularly with the encouraging results from recent trials using induction chemotherapy prior to chemoradiotherapy. 56,47

We conclude that the addition of concurrent cisplatin chemotherapy to adjuvant radiotherapy given after neck dissection in cervical SCCUP results in high rates of regional disease control, may prolong survival and compares favorably with previous reports that used radiotherapy alone postoperatively (Table 4). Our results warrant testing this approach in a prospective setting with a larger number of patients.

REFERENCES


Chemoradiotherapy in SCCHN of Unknown Primary


