Preoperative Chemotherapy-Sensitized Radiation Therapy for Cervical Metastases in Head and Neck Cancer

Matthew M. Puc, MD; Francis A. Chrzanowski, Jr, MD; Hoang S. Tran, MD; Li Liu, MD; Arvin S. Glicksman, MD; Christine Landman, MD; Gus J. Slotman, MD

Objective: To determine the efficacy of concurrent preoperative cisplatin chemotherapy and radiotherapy (CT/RT) for patients with advanced head and neck cancer and cervical metastatic disease.

Design: Retrospective analysis.

Setting: University hospitals.

Patients: Eighty-eight patients with operable stage III and IV squamous cell carcinoma of the head and neck and palpable cervical lymphogenous metastases received preoperative concurrent CT/RT followed by planned neck dissection.

Interventions: All patients undergoing CT/RT received concomitant continuous infusions of cisplatin (20 mg/m²) on days 1 to 4 and 22 to 25 of CT/RT. Thirty-nine patients underwent single-fraction (1.8-Gy) radiotherapy to 45.0 Gy, and 49 patients received 10 single-fraction (1.8-Gy) treatments, which were hyperfractionated (1.2-Gy twice a day) to 46.8 Gy.

Main Outcome Measures: The 71 patients for whom complete post-CT/RT data were available were evaluated for clinical response in addition to survival. Histologic complete response (HCR) was confirmed from planned neck dissection specimens (n = 48) after clinical complete response (CCR) from initial CT/RT. Kaplan-Meier statistical analysis for disease-specific survival and overall survival was performed on all 88 patients who received CT/RT.

Results: A CCR and an HCR were noted in 78% (18/23) and 59% (10/17) of patients with N1 lesions, respectively, and in 60% (29/48) and 45% (14/31) of patients with N2-3 lesions, respectively. The percentage of patients with CCR who also had HCR was 67% (10/15) for patients with N1 lesions and 54% (14/26) for patients with N2-3 lesions. With a median follow-up of 18.5 months, the Kaplan-Meier disease-specific survival rate at 54 months (n = 88) was 70% (21/30) for patients with N1 lesions, 60% (24/40) for patients with N2 lesions, and 39% (7/18) for patients with N3 lesions. The overall survival and disease-specific survival rates at 5 years for all nodal groups combined were 36% (32/88) and 59% (52/88), respectively.

Conclusions: A CCR to CT/RT was achieved in nearly two thirds of patients with head and neck cervical lymphogenous metastases, independent of nodal tumor load. Most patients (59% [24/41]) with CCR were pathologically tumor free before neck dissection.
PATIENTS AND METHODS

The patients included in this study were participants in 2 sequential clinical trials investigating the simultaneous preoperative use of concomitant CT/RT for advanced, operable stage III and stage IV squamous cell carcinoma of the head and neck (Roger Williams Medical Center–Brown University, Providence, RI; University of Medicine & Dentistry of New Jersey–Robert Wood Johnson Medical School, Camden; and Kantoyspital Hospital, Basel, Switzerland).

Patients who were referred for these trials underwent careful clinical assessment for pretreatment staging. They were first assessed preoperatively by clinical examination, panendoscopy (direct laryngoscopy, bronchoscopy, and esophagoscopy), directed biopsies of suspicious lesions, imaging studies (computed tomography and chest radiography), and biochemical studies (complete blood cell count, liver function tests, renal function tests, and determination of electrolyte levels). No patients were noted to have distant metastatic disease at initial presentation. At the time of esophagoscopy, a percutaneous endoscopic gastrostomy tube was placed for patients who presented with a 10% or greater weight loss or who subsequently developed a 10% or greater weight loss during the treatment regimen. The patients were referred to a nutritionist for diet care and were also seen by a dentist.

During the initial evaluation and staging, the patients were seen by the radiation oncologist, medical oncologist, and surgical team prior to final assessment. They were deemed eligible if they had a potentially resectable squamous cell carcinoma of the head and neck, were an acceptable risk for surgery, had adequate renal function for chemotherapy, and signed an informed consent form.

Before surgery, all patients received a continuous infusion of cisplatin (20 mg/m² divided into 3 L of 3% glucose in water), which infused continuously over a 24-hour period. The infusions were administered on days 1 to 4 and were repeated on days 22 to 25 of concurrent radiotherapy. Group 1 patients (n = 39) received single-fraction radiotherapy to 45.0 Gy at 1.8 Gy per day for 5 weeks. Group 2 patients (n = 49) received single-fraction radiotherapy to 45.0 Gy at 1.8 Gy per day for 5 weeks. Radiotherapy consisted of treatment to the entire pharyngeal tube in most patients, with the addition of the oral cavity for those patients for whom it was appropriate. Cervical nodes were treated from the base of the skull to the clavicle in all patients. In patients with clinically positive cervical adenopathy, the supraclavicular fossa on both sides were also treated. The primary tumor site and the neck received the same dose of radiation.

The patients were admitted to the hospital during weeks 1 and 4 for therapy or for treatment of toxic effects, as needed. Toxic effects according to the criteria of the Eastern Cooperative Oncology Group were previously reported for each entire treatment group, inclusive of N0 disease (n = 175). Comprehensively, the majority of the acute toxic effects (89% [155/175]) were either grade 1 or grade 2; only 11% (20/175) of the toxic effects were grade 3, with no grade 4 toxic effects reported. One hundred fifty-seven patients (90%) completed the total preoperative treatment regimen.

At the completion of either regimen, patients were reassessed within approximately 2 to 4 weeks. The primary tumor site and the neck were examined for CCR by manual palpation. Group 1 patients were all scheduled to undergo a radical resection of the primary tumor regardless of the clinical response. If patients had a large amount of residual tumor at resection or did not undergo surgery, they underwent additional CT/RT therapy. The CT/RT included 1.8 Gy per day for 27.0 Gy (total dose, 72.0 Gy) plus another course of cisplatin (20 mg/m²) for 4 days. For group 2 patients, if a complete or near-complete response was noted at the primary site after extensive biopsies, they continued with additional CT/RT without formal surgical resection of the original primary tumor site (organ preservation). The CT/RT included 1.2 Gy twice per day for 12 days, for an added dose of 28.8 Gy (total, 75.6 Gy) plus a concurrent infusion of carboplatin (25 mg/m²) twice per day with each fraction of radiation.

All patients with cervical adenopathy were initially scheduled to undergo a planned neck dissection, including N1 disease that responded to preoperative therapy. Neck dissection alone (group 2 patients with a histologic complete response [HCR] at the primary site) or neck dissection along with definitive surgical resection of the primary site (group 1 and group 2 patients with residual disease at the primary site) was performed 4 to 8 weeks after the end of the initial CT/RT (either 45.0 or 46.8 Gy). Usually, a radical neck dissection was performed on these patients. Select patients had preservation of the 11th nerve, if it allowed complete removal of the original tumor-bearing volume. Most commonly, functional dissection was reserved for N1 disease that had undergone a CCR. The choice of neck resection (standard radical vs modified radical) was based on the original tumor load. If bilateral dissections were performed, a unilateral radical neck was complemented by a contralateral modified neck dissection, with preservation of the jugular vein on that same side. Generally, access to the neck was gained through a hockey-stick incision or a modified MacFee incision to minimize carotid exposure. Twenty-three patients did not undergo neck dissection because of medical contraindication, refusal, or death before the scheduled operative date. Clinical complete response within the neck was determined on physical examination. Confirmation of CCR by radiologic imaging studies was done when indicated clinically. Histologic complete response within the cervical nodes was verified by pathologic examination of the contents from the neck dissection.

Statistical analysis included disease-specific survival and overall survival using the Kaplan-Meier product limit method and χ² analysis, when appropriate.

Subsequently, numerous studies have evaluated the concurrent use of chemotherapy and radiation therapy to exploit any possible synergistic effects. These studies have mainly focused on survival rates, toxic effects of chemotherapy, organ preservation, and distant metastatic disease. Few of them, however, have specifically dealt with the role of neck dissection in patients with advanced head and neck cancers and cervical metastases who receive preoperative simultaneous chemotherapy and radiotherapy.

There are 2 critical issues that arise with the use of chemoradiation in the management of cervical lymphog...
Of the 88 patients who presented with cervical lymph node involvement, 71 had available data for documenting CCR and 48 had data available for evaluation of HCR. Fourteen patients (20%) had stage III disease, and 57 patients (80%) had stage IV disease. Twenty-three patients had N1 lesions, and 48 patients had N2-3 lesions (Table 1). The primary tumor sites are listed below:

<table>
<thead>
<tr>
<th>Site</th>
<th>No. (%)</th>
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<tbody>
<tr>
<td>Oral cavity</td>
<td>15 (21)</td>
</tr>
<tr>
<td>Larynx</td>
<td>15 (21)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>20 (28)</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Total</td>
<td>71</td>
</tr>
</tbody>
</table>

Seventy-one patients had data available for evaluating CCR. Eighteen (78%) of the 23 patients with N1 disease, and 29 (60%) of the 48 patients with N2-3 disease had CCR (P = .20). Forty-eight patients eventually underwent a planned neck dissection for documentation of HCR. The other 23 patients either refused surgery, were medically unfit to undergo surgery, or died of their disease or other causes before surgery could be performed. Ten (59%) of 17 patients with N1 disease and 14 (45%) of 31 patients with N2-3 disease who underwent neck dissection had HCR (P = .50). The most important datum is the percentage of patients with CCR who also had HCR. Three patients with N1 disease and 3 patients with N2-3 disease all had CCR but did not undergo a neck dissection, so they were excluded. Therefore, 10 (67%) of 15 patients with N1 disease and 14 (54%) of 26 patients with N2-3 disease who initially had CCR were confirmed as being tumor free by histologic examination of the surgically resected cervical lymph nodes (P = .60). Thus, for the combined group (N1 and N2-3) with CCR, there was a 59% (24/41) HCR rate to the preoperative concurrent chemosensitized radiotherapy. In terms of tumor stage, 6 patients (55%) with stage III disease compared with 18 patients (49%) with stage IV disease had HCR (P > .99). Since the extent of nodal disease did not significantly affect histologic response, it is important to see if the histologic response of the lymphogenous metastases was in any way related to the primary tumor size (T stage). As shown in Table 2, the results indicate that no individual T stage had a significantly increased percentage of HCR (P = .20). Similarly, in terms of primary tumor sites, no specific location had a statistically greater percentage of HCR (Table 3).

The current status of patients with histologic evaluation is shown in Table 4. It is important to note the significant difference in outcome between the histologic and nonhistologic responders. Seventy-one percent of the patients with HCR showed no evidence of disease on follow-up, while only 33% of the patients without HCR had no evidence of disease (P = .01). There was also a statistical difference between the 2 groups in the percentage of patients who died of their disease: 4 (17%) of the patients with HCR and 13 (54%) of the patients without HCR (P = .01).

Twenty-five (52%) of the 48 patients who underwent neck dissection after concurrent CT/RT were alive.
with no evidence of disease and 17 patients (36%) died of their disease. Of the 23 patients who did not follow their CT/RT with a neck dissection, 9 (39%) had no evidence of disease, while 10 patients (44%) died of their disease, neither of which was significantly different from patients with neck surgery ($P = .40$ and $P = .70$, respectively). A similar analysis was done with CCR patients. Of the CCR patients who underwent a neck dissection, 54% had no evidence of disease on follow-up, which was not statistically improved over the CCR patients (17%) who had no evidence of disease on follow-up, which was not statistically improved over the CCR patients (17%) who did not have a neck resection ($P = .20$). It should be noted that the difference in the extent of nodal disease between the patients with a neck dissection (N1, n = 19; N2-3, n = 29) and the patients without a neck dissection (N1, n = 4; N2-3, n = 19) was not statistically different ($P = .11$). Also, the percentage of CCR patients who died of their disease was statistically identical regardless of whether or not a neck dissection was performed ($P > .99$).

Major complications from neck dissections occurred in 7 patients (15%): carotid blowout (n = 1), fistula (n = 3), cellulitis (n = 1), delayed healing (n = 1), and wound infection (n = 1). The total incidence of cervical recurrence during this follow-up period occurred in 4 patients (Table 5). Three of the 4 patients died of their disease, and 1 patient is alive with disease. Also, 3 (75%) of the patients who developed cervical recurrences did not have a CCR to the simultaneous preoperative CT/RT. The 1 patient with the primary tumor in the larynx was noted to have a recurrence at that site, along with his neck recurrence. Four other patients had distant metastases, 2 of which were located in the lung and 3 in the bone. Four other patients had local recurrence only. Three of these primary tumors were located in the hypopharynx and 1 in the larynx. Of the 4 patients with local recurrence, 3 underwent a neck dissection. Two were non-histologic responders and have since died of their disease. The other patient had HCR and after undergoing local resection has no evidence of disease.

The Kaplan-Meier survival rates for disease-specific survival at 54 months (n = 88) were 70% (21/30) for patients with N1 disease, 60% (24/40) for patients with N2 disease, and 39% (7/18) for patients with N3 disease ($P > .20$). The overall survival and disease-specific survival rates at 5 years for all nodal groups combined were 36% (32/88) and 59% (52/88), respectively. Disease-specific survival at 36 months (n = 88) comparing each nodal stage individually between the 2 treatment groups was calculated. Comparing group 1 with group 2, patients with N1 disease had disease-specific survival rates of 70% (14/20) and 79% (8/10), respectively ($P = .33$), patients with N2 disease had disease-specific survival rates of 80% (8/10) and 57% (17/30), respectively ($P = .47$), and patients with N3 disease had disease-specific survival rates of 63% (5/8) and 30% (3/10), respectively ($P = .27$).

**Table 5. Cervical Recurrence in 4 Patients**

<table>
<thead>
<tr>
<th>TNM Stage, Site</th>
<th>CCR</th>
<th>HCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3 N1, oropharynx</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>T4 N2, larynx</td>
<td>−</td>
<td>No surgery</td>
</tr>
<tr>
<td>T4 N2, oropharynx</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>T2 N1, hypopharynx</td>
<td>−</td>
<td>DOD</td>
</tr>
</tbody>
</table>

*CCR indicates clinical complete responder; HCR, histologic complete responder; plus sign, present; minus sign, absent; DOD, died of disease; and AWD, alive with disease.

This review of patients with advanced squamous cell carcinoma of the head and neck who initially presented with cervical involvement provides insight into the efficacy of planned neck dissection after concurrent CT/RT. A majority of the patients had stage IV disease, with the oropharynx being the most common location of the primary tumor. The preoperative treatment regimen was well tolerated, and the postoperative morbidity in our study was minimal compared with that in previously published reports. Approximately two thirds of the patients, independent of nodal tumor load, had CCR after the initial CT/RT regimen. Also, 20 (59%) of the 41 patients who had CCR and underwent neck dissection had HCR confirmed by pathologic examination of the resected neck contents. The patients with HCR had a significantly improved outcome compared with nonhistologic responders. These results demonstrate that physical examination of the neck after CT/RT did not accurately predict whether there was residual tumor within the cervical lymph nodes. Finally, there was no clear evidence that a planned neck dissection improved patient survival after CT/RT.

The majority of patients in this study had N2-3 lesions, and 60% (29/48) of them had CCR to the initial preoperative treatment. The patients with N1 lesions had a slightly better, but not statistically different ($P = .20$), CCR rate (78% [18/73]). The 2 groups combined had a 66% CCR rate (47/71), which is comparable to the 69% CCR rate initially reported by Al-Sarraf and associates. In terms of HCR, the combined group had a 50% HCR (24/48). More importantly, 24 (59%) of the 41 patients who exhibited a CCR to the initial CT/RT and subsequently underwent neck dissection were found to be free of regional involvement on pathologic examination. This signifies that CCR in the majority of our patients translated into a lack of pathologic presence of cancer cells, in essence an excellent response of the cervical nodes to concurrent preoperative CT/RT.

In this study, the patients who were identified as having no histologic evidence of cancer within the cervical
nodes had a significantly better outcome than nonhistologic responders. This finding was similar to the previous findings of Goodman and associates, who showed that patients with advanced head and neck primary tumors who received preoperative cisplatin-sensitized radiotherapy and had HCR also had a significantly improved disease-specific survival at 5 years compared with nonhistologic responders. Our findings with CT/RT complement these results with regard to cervical lymphogenous metastases. Therefore, patients who respond favorably to concurrent CT/RT, either locally or regionally, have a significantly improved chance of long-term survival. Our review of the literature indicates that HCR of lymphogenous metastases from squamous cell carcinoma of the head and neck with significantly improved disease-free survival has not been reported previously and is an important finding of this study.

At 54 months, the disease-specific survival rates for the individual nodal stages in the combined groups were favorable. Although we did not find a statistical difference between the nodal stages, prior studies have shown an improved survival for patients with N1 lesions compared with patients with N2 or N3 lesions.

When groups 1 and 2 were compared in terms of individual nodal stage, there were again no statistical differences (patients with N1 lesions, \( P = .33 \); patients with N2 lesions, \( P = .47 \); and patients with N3 lesions, \( P = .27 \)). Also, it is important to note that the histologic response within the cervical nodes was not significantly related to the primary tumor site (Table 2).

The decision for neck surgery must also be tempered with the impact of concurrent CT/RT on the incidence of wound complications after neck dissection. Sasser and associates reported a major surgical complication rate of 61% after induction chemotherapy followed by radiation therapy. Also, Newman and colleagues reported a 35% total complication rate in 17 patients who underwent chemoradiation therapy, but they observed only 3 major complications (18%). In essence, this complication rate is similar to our findings, which demonstrated only a 15% major complication rate, one that compares favorably with the complication rates mentioned in most published reports. A difference that may account for this finding is that the neck dissections in our patients were routinely performed 4 to 8 weeks after radiation therapy that consisted of a total dose of less than 50.0 Gy. The majority of the studies reported used higher total doses of radiation (>50-74 Gy). Therefore, further studies are needed, not only to see if concurrent CT/RT is equal to or better than standard therapy (irradiation and surgery) in controlling the node-positive neck but also to establish the true risk of postoperative complications.

Sixty-seven percent (10/15) of the patients with N1 lesions and 34% (14/42) of the patients with N2-3 lesions who had CCR were later found to have HCR on subsequent neck dissection, which raises the question of whether or not routine neck dissection is warranted in all patients who present with cervical lymphogenous metastases. If preoperative CT/RT renders the cervical nodal basin free of disease, the necessity of a routine neck dissection is brought into question. Using a cisplatin-sensitized radiotherapy regimen, our data lend support for avoiding neck dissection in a majority of patients with CCR, especially patients with N1 lesions. Patients who have only a partial response or no response at all usually have a poor outcome, and in these patients the need for neck dissection takes on a different significance. In such cases, salvage neck dissection may be beneficial only if the primary tumor is well controlled.

**Our results** with patients who did not undergo a planned neck dissection after CT/RT provide some insight into the idea of limiting the role of routine neck dissections in patients with cervical metastases after CT/RT. These patients had a statistically similar clinical outcome compared with patients who did undergo a planned neck dissection, independent of nodal response to CT/RT. Additionally, patients with CCR who underwent a neck dissection had a statistically similar clinical outcome to patients with CCR who did not undergo a neck dissection. These findings bring into question the traditionally assumed correlation between a planned neck dissection and improved disease-free or overall survival.

Another point to mention is that 2 (29%) of the 7 patients who were categorized as nonclinical responders and who underwent neck dissection were found to have no pathologic evidence of tumor. At the same time, 7 (41%) of the 41 patients with CCR had evidence of residual tumor on subsequent neck dissection. These 2 findings bring into question the issue of clinically evaluating the neck after CT/RT. We used manual palpation; however, this can obviously lead to a misdiagnosis. Our data show that basing a patient’s response to a CT/RT regimen on the findings of physical examination alone is inaccurate and provides a poor assessment of potential metastatic disease within the neck. There will be instances after CT/RT when fibrosis or scar tissue in the neck will clinically resemble residual lymphogenous metastases and will therefore erroneously indicate incomplete response to therapy. The ability to correctly identify the tumor status within the neck without the need for a radical neck dissection would be of great benefit to case management.

To our knowledge, there is no randomized trial that evaluates this issue. It may be beneficial, then, to test the ability of a noninvasive procedure, such as ultrasonography, computed tomography, magnetic resonance imaging, or a minimally invasive procedure, such as fine-needle aspiration, used either individually or in combination to accurately document the response in the neck. Weissman et al used fine-needle aspiration, magnetic resonance imaging, computed tomography, and physical findings to identify persistent neck masses that were suggestive of malignancy and that therefore required a neck dissection. Interestingly, of 5 patients with a fine-needle aspirate or imaging study that was suggestive of malignancy, 4 did not have viable tumor cells identified in the resected neck contents. If the neck could be accurately investigated without the need for a comprehensive neck dissection, a more efficient approach to the treatment of the neck in advanced squamous cell carcinoma of the head and neck could be established.
REFERENCES


