Examining the Need for Neck Dissection in the Era of Chemoradiation Therapy for Advanced Head and Neck Cancer

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Objectives: To (1) determine clinical factors that predict pathologic complete response (pCR) on neck dissection after sequential chemoradiotherapy (SCRT) for advanced head and neck cancer and (2) compare survival parameters between those who underwent neck dissection and those who did not among those patients with a clinical complete response (cCR) in the neck after SCRT, thus assessing the benefit of neck dissection in patients with a cCR in the neck.

Design: Retrospective review with a mean follow-up of 3.5 years.

Setting: Regional cancer center.

Patients: The study population comprised 55 patients undergoing SCRT for advanced head and neck cancer with N2 or N3 neck disease. Three patients developed progressive disease and were excluded, and 28 patients underwent neck dissection.

Interventions: Patients were assessed by physical examination and radiographically after SCRT.

Main Outcome Measures: Physical examination and radiographic assessments of residual neck disease were compared with pathologic findings in those patients who underwent neck dissection. Survival comparisons were made between patients with a cCR in the neck who underwent neck dissection and those who did not.

Results: Of 28 patients who underwent neck dissection, 8 had persistent pathologically positive nodal disease: 5 (45%) of 11 had N3 and 3 (18%) of 17 had N2 disease. Individual clinical neck assessments after SCRT were fairly predictive of a negative pathologic finding at neck dissection. The negative predictive values were physical examination (75%), computed tomography or magnetic resonance imaging (71%), and positron emission tomography (75%). However, when physical examination, imaging studies, and positron emission tomography all indicated a complete response, this accurately predicted a pCR on neck dissection. There appeared to be no improvement in survival parameters when a neck dissection was performed on patients with a cCR in the neck.

Conclusions: Patients with N3 disease are at high risk for residual neck metastasis after SCRT. Patients with N2 disease can be assessed with physical examination, imaging studies, and positron emission tomography. If these all indicate a cCR, then neck dissection is likely not needed. Neck dissection did not appear to further improve survival parameters for patients with a cCR in the neck.

Arch Otolaryngol Head Neck Surg. 2006;132:526-531

H E A D A N D N E C K C A N C E R globally afflicts 500 000 individuals per year. Since the early 1990s, chemoradiotherapy (CRT) has been used for “organ preservation.” These regimens have proven effective in achieving disease control at the primary site, hence organ preservation, while yielding excellent survival rates.\(^1\)\(^-\)\(^3\) The ability of CRT to treat regional nodal metastases has been less clear. A wide variety of strategies for neck management has been advocated. Some recommend neck dissection for all N2 and N3 disease regardless of the response to therapy.\(^4\)\(^-\)\(^8\) Others recommend neck dissection only for those with less than a complete response to CRT.\(^9\)\(^-\)\(^16\) and this is the approach we have generally followed. This report reviews our experience with neck management in patients with advanced head and neck cancer treated uniformly with protocol-based sequential CRT (SCRT) at the Dana Farber Cancer Institute, Boston, Mass.\(^17\)

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The study aims were 2-fold: first, to determine clinical factors that predict a pathologic complete response (pCR) on neck dissection after CRT, and second, to compare survival parameters between
those who underwent neck dissection and those who did not among those patients with a clinical complete response (cCR) in the neck after SCRT, thus assessing the benefit of neck dissection in patients with a cCR in the neck.

METHODS

This study reviews 55 patients with advanced stage III or IV head and neck cancer and N2 or N3 nodal disease without distant metastases, who began protocol-based SCRT between June 1999 and December 2002.17 All patients had squamous cell carcinoma of the head and neck; unknown primary cancer and primary cancer sites in the sinonasal cavity, nasopharynx, and salivary glands were excluded. Three patients were excluded because they developed progressive disease while undergoing treatment. This report analyzes the remaining 52 patients.

Sequential CRT consisted of 3 cycles of platinum-based induction chemotherapy, followed by concurrent CRT with once-daily radiation therapy and weekly carboplatin at an area under the curve of 1.5.17 The induction chemotherapy regimen included cisplatin and fluorouracil with or without docetaxel given for 3 cycles every 21 days. Radiation to the neck was delivered at a dose of 2 Gy per day. Involved nodal regions received at least 60 Gy and uninvolved nodal regions at least 50 Gy. Neck dissections were planned between 6 and 12 weeks after SCRT. Potential candidates for neck dissection after SCRT were those patients with less than a cCR to therapy, N3 disease, pretreatment open lymph node biopsy, and initial fixed neck lymph node.

Response to therapy was assessed at the primary site and the neck by physical examination, computed tomography (CT) or magnetic resonance imaging (MRI), and positron emission tomography (PET) performed after induction chemotherapy and after CRT. The protocol principal investigator (M.R.P.) oversaw the treatment responses. Physical examination assessments were performed by the authors (L.A.G., M.R.P., R.B.T., L.J.W., C.M.S., and R.I.H.). Physical examination assessment of the neck’s response to treatment was based on comparison of the largest dimension of the neck lymph node. Assessment by CT or MRI of the neck’s response to treatment was based on the sum product of the perpendicular diameters of the nodal disease. As defined by the protocol, a complete response in the neck was indicated by no residual identified disease, a partial response by a greater than 50% reduction in the nodal disease, and no change by a 50% or less reduction in the nodal disease. Progressive disease was indicated by a 25% or greater increase in the nodal disease. A cCR in the neck was defined as all available clinical assessments demonstrating a complete response, including physical examination and/or imaging studies, and/or PET. Less than a cCR in the neck was defined as at least 1 clinical assessment indicating a partial response, no change, or progressive disease. The follow-up period, overall survival, and progression-free survival were calculated from the date of treatment initiation. Physical examination and appropriate imaging evaluated patients monthly during the first year, every other month in the second year, and every 3 to 6 months thereafter.

Univariate analysis was performed using the Kruskal-Wallis or χ² test. The power of the study was limited owing to the small sample size and small number of events. When appropriate, Kaplan-Meier survival curves were used. In addition, positive predictive value and negative predictive values were obtained using the formula as described by Brizel et al.²

Table 1. Characteristics of 52 Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, range (median), y</td>
<td>38-75 (54)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
</tr>
<tr>
<td>Male</td>
<td>41</td>
</tr>
<tr>
<td>Primary site</td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td>3</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>39</td>
</tr>
<tr>
<td>Larynx</td>
<td>7</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>3</td>
</tr>
<tr>
<td>Primary stage</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>9</td>
</tr>
<tr>
<td>T2</td>
<td>16</td>
</tr>
<tr>
<td>T3</td>
<td>15</td>
</tr>
<tr>
<td>T4</td>
<td>12</td>
</tr>
<tr>
<td>Neck stage</td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>40</td>
</tr>
<tr>
<td>N3</td>
<td>12</td>
</tr>
<tr>
<td>Patients who underwent neck dissection</td>
<td>28</td>
</tr>
<tr>
<td>Positive neck dissection findings</td>
<td>8</td>
</tr>
<tr>
<td>Follow-up duration, mean (median), mo</td>
<td>41.3 (38.4)</td>
</tr>
</tbody>
</table>

RESULTS

PATIENT DATA AND TREATMENT OUTCOME

As given in Table 1, the median patient age of the 52 evaluable patients was 54 years, with a range of 38 to 75 years. Eleven patients were female and 41 were male. Primary tumor location and tumor and neck stage are given in Table 1. Neck dissections were performed on 28 of the 52 patients after completion of SCRT. At the time of analysis, the follow-up duration for surviving patients ranged 16.9 to 69.3 months, with a mean of 41.3 months and a median of 38.4 months.

Of the 52 patients, there has been no recurrent disease in 45 (83%), and 46 (88%) are survivors. The mean overall survival is 37.0 months or longer, with a median of 37.9 months or longer. The mean progression-free survival is 36.3 months or longer, with a median of 37.7 months or longer.

CLINICAL FACTORS THAT PREDICT A pCR ON NECK DISSECTION AFTER SCRT

Cancer Stage

Neck dissection identified residual metastatic disease in 3 (18%) of 17 patients with N2 disease and 5 (45%) of 11 patients with N3 disease. There was no significant difference in risk for residual nodal disease between N2a, N2b, or N2c neck stages. One patient (patient 32) had N3 disease and less than cCR after SCRT but developed distant metastases before his planned neck dissection and died of disease. Persistent pathologically positive adenopathy was found in the following primary stage tumors that underwent neck dissection: T1 (0/3), T2 (2/7; 29%), T3 (3/11; 27%), and T4 (3/7; 43%).
Table 2. Adverse Oncologic Events in 20 Patients With a cCR in the Neck After SCRT

<table>
<thead>
<tr>
<th>N Stage/Neck Management</th>
<th>ND Pathologic Finding</th>
<th>Recurrent Disease</th>
<th>DOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N2 (n = 17)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underwent ND (n = 4)</td>
<td>pCR (n = 4)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Did not undergo ND (n = 13)</td>
<td>NA</td>
<td>DM (n = 1 [patient 31])</td>
<td>Patient 31</td>
</tr>
<tr>
<td>N3 (n = 3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underwent ND (n = 3)</td>
<td>pCR (n = 2); pPR (n = 1 [patient 5])</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: cCR, clinical (physical examination and radiologic examination) complete response; DM, distant metastases; DOD, dead of disease; NA, not applicable; ND, neck dissection; SCRT, sequential chemoradiation therapy (induction chemotherapy, then chemoradiation therapy); pCR, pathologic complete response (no residual neck disease at ND); pPR, pathologic partial response (residual neck disease at neck dissection).

Findings After SCRT

Neck Physical Examination. Findings from physical examination of the neck suggested a complete response in 16 of the 28 patients who later underwent neck dissection. Neck dissection found a pCR (no residual viable nodal adenopathy) in 12 of 16 patients. The negative predictive value of physical examination was 75%. The positive predictive value of physical examination was 33% (4/12). There was no significantly different predictive pattern among the different neck stages.

Imaging Study. Computed tomography or MRI was performed on 22 of the 28 neck dissection patients. Imaging studies found a complete response in the neck in 7 of 22 patients. In patients who later underwent neck dissection, a pCR was found in 5 of the 7 patients. The negative predictive value of neck CT or MRI was 71%. The positive predictive value of CT or MRI was 33% (5/15). There was no significantly different predictive pattern among the different neck stages.

Positron Emission Tomography. Positron emission tomography was performed on 21 of the 28 patients who later underwent neck dissection. The findings from PET included a complete response in 12 of 21. In patients who later underwent neck dissection, a pCR was found in 9 of the 12. The negative predictive value of PET was 75%. The positive predictive value of PET was 22% (2/9). There was no significantly different predictive pattern among the different neck stages.

Combination Physical Examination and Imaging Studies (CT or MRI). Neck physical examination and imaging study findings were available for 22 of the 28 patients who later underwent neck dissection. Both neck physical examination and imaging studies found a complete response in 6 of 22. Three patients had N2b disease, and 3 patients had N3 disease. Neck dissection findings were pCR in 5 of 6. The negative predictive value was 83% when both physical examination and imaging studies demonstrated a complete response. The 1 patient with residual neck disease had N3 disease.

Combination Physical Examination, Imaging Studies (CT or MRI), and PET. Neck physical examination, imaging studies, and PET evaluation were available for 19 of the 28 patients who later underwent neck dissection. Of the 19 patients, 5 had a complete response on all 3 assessments, and all 5 also had negative neck dissection findings. Three patients had N2b disease, and 2 patients had N3 disease. The negative predictive value for all 3 modalities combined was 100%.

Summary

Patients at greatest risk for residual neck disease after SCRT were those patients with initial N3 disease. Of the 11 patients with N3 disease who underwent neck dissection, 5 (45%) had residual pathologically positive neck disease.

Individual clinical neck assessments that suggested a complete response did a modest job of predicting negative pathologic findings at neck dissection. The individual negative predictive values were physical examination, 75%; imaging studies, 71%; and PET, 75%. When assessments were combined, the ability of a cCR to predict a pCR on neck dissection increased. When physical examination and imaging studies together demonstrated a complete response, the negative predictive value was 83%. When physical examination, imaging studies, and PET all demonstrated a complete response, the negative predictive value was 100%.

SURVIVAL PARAMETERS AMONG PATIENTS WITH A cCR IN THE NECK AFTER SCRT

Among those patients with a cCR in the neck after SCRT, we compared survival parameters between those who underwent neck dissection and those who did not, thus assessing the benefit of neck dissection in the patient with a cCR in the neck.

Of the 52 patients, 20 (38%) had a cCR in the neck that was demonstrated by all available clinical data after SCRT. The available clinical data included findings from combined physical examination/imaging studies (CT or MRI) and PET (n = 14), combined physical examination and imaging studies (CT or MRI) (n = 4), and physical examination only (n = 2). As given in Table 2, 7 patients underwent neck dissection and 13 patients did not. Patients with a cCR in the neck after SCRT did well. Among the 20 patients with a cCR in the neck, there were only 2 with any adverse oncologic events. One patient (patient 5) with N3 disease was found to have residual neck disease at neck dissection and did well thereafter. The second patient (patient 31) with N2 disease had an
initial fixed lymph node and was scheduled to have a neck dissection but developed distant metastases while awaiting surgery and died of disease. All 20 patients maintained locoregional control. The 7 patients who had a cCR in the neck and underwent neck dissection, at a mean follow-up of 46.4 months, had a median progression-free survival of 43.2 months or longer, an overall survival of 46.4 months or longer, and a median overall survival of 43.2 months or longer. The 13 patients who had a cCR in the neck and who did not undergo neck dissection, at a mean follow-up of 40.6 months, had a median progression-free survival of 37.9 months or longer and a median overall survival of 37.9 months or longer. Among patients with a neck cCR, the number of adverse oncologic events was similar, and survival parameters did not seem improved with the addition of neck dissection.

Comparisons were made between patients who had a cCR in the neck after SCRT and those who had less than a cCR (ie, partial response, no change, or progressive disease) in the neck in terms of progression-free survival and overall survival. The cCR group had a significantly improved progression-free survival ($P = .04$, log rank test) and overall survival ($P = .04$, log rank test) compared with the group that had less than a cCR.

**COMMENT**

This study aimed to better understand the role of neck dissection after SCRT. The study goals were 2-fold. First to determine clinical factors that predict pCR on neck dissection after CRT, and second, among those patients with cCR in the neck after CRT, to compare survival parameters between those who underwent neck dissection and those who did not, thus assessing the benefit of neck dissection in the patient with a cCR in the neck. In this small series of patients who were treated with aggressive and highly successful SCRT, in whom there were a limited number of adverse oncologic events, the following trends emerged. First, N3 nodal stage was the single best predictor of persistent nodal disease at neck dissection. Second, when findings from combined post-therapy clinical assessments including physical examination, imaging studies (CT or MRI), and PET all indicate a complete response in the neck, this accurately predicts a pCR and no neck relapse, particularly in patients with N2 disease. Third, patients who obtain a cCR in the neck, whereby all available clinical assessments indicate a complete response, have improved overall survival and progression-free survival compared with patients who had less than a cCR. Neck dissection in patients who had a cCR in the neck did not appear to further reduce the risk of adverse oncologic events or enhance survival parameters. Patients with a cCR in the neck did well and sustained only 2 adverse oncologic events, none of which were locoregional failure. There were no neck relapses in this group, and all patients with N2 disease who underwent neck dissection had a pCR. Based on these observations, we advocate that patients with N2 disease who had a neck cCR after aggressive SCRT do not require neck dissection.

The management of head and neck cancer has changed significantly over the past half century. Since the publication of the study for laryngeal preservation by the Department of Veterans Affairs, there has been a continuous shift toward chemoradiation in managing head and neck cancer and applying it toward other primary sites including the oropharynx and hypopharynx. The success rate at the primary site has been excellent, but there continues to be controversy regarding how to manage the neck in patients who are treated with initial CRT.

The slow acceptance and ongoing resistance to non-surgical neck management is based on several concerns and is in part historically based. Radiation therapy trials in the 1970s and 1980s established that patients with neck disease with nodes larger than 3 cm were at high risk for residual disease at the completion of therapy. Mendenhall et al reported that neck dissection was not needed in patients with N1 disease treated by radiation therapy but added that neck dissection improved neck control in patients with N2 and N3 disease. In addition, fibrosis from radiation therapy made future clinical assessments of neck recurrence difficult, and salvage surgery was rarely successful. For these reasons neck dissection was routinely performed after radiation therapy for patients with N2 and N3 disease. This thinking has persisted into the CRT era. Others have further argued that the functional morbidity from neck dissection is far less than that of primary resection, and the complication rate from neck dissection when performed within 4 to 12 weeks after completion of CRT is low. Also, neck dissection is regarded as less morbid compared with death from uncontrollable neck disease.

To determine the role of neck dissection in this era of CRT, the following questions need to be answered: (1) How often is a cCR in the neck achieved after CRT? (2) How accurately does a cCR in the neck predict a pCR at neck dissection or no regional relapse if neck dissection is not performed? (3) In patients with a cCR in the neck, does neck dissection yield any additional progression-free survival or overall survival benefit? Prior reports examining the role of neck dissection after CRT are difficult to compare for several reasons. The study objectives are often different. Various treatment regimens have been used with differing chemotherapy agents and varying radiation schemes. Patient exclusion criteria vary. The timing and type of clinical assessments are often different. The definition of complete response is not always consistent. Indications for neck dissection are not constant. Many of the studies, including ours, are limited statistically because of the low number of patients with critical findings (ie, N2 disease and cCR in the neck) and the low number of events (ie, residual neck disease at neck dissection, neck recurrence, distant metastasis, and death from disease). This creates findings of reduced significance. Among the various studies, it is often difficult to track neck stage, response to treatment, findings at neck dissection, and later development of adverse oncologic events in any comparable fashion.

With these reservations in mind, reviewing the literature yields the following observations. Combining the findings from prior articles on neck dissection and ours reveals a range of rates between 38% and 73% for a cCR
in the neck after CRT, with an average of 56%.\textsuperscript{4-5,7-9,11,14,16} The incidence of a cCR in the neck yielding positive findings at neck dissection (pPR/cCR) ranged between 14% and 39%, with an average of 25%.\textsuperscript{4-5,7-9,11} Many investigators combined N2 and N3 disease to keep the sample size robust. Our low rate of 14% with the combination of those with N2 and N3 disease and 0% for those with N2 disease only reflects the successful nature of our SCRT regimen. We found that all patients with N2 disease who had a cCR had a negative neck dissection finding and no regional relapse. Our results indicate the following trend: when findings from combined clinical assessments including physical examination, imaging studies (CT or MRI), and PET all indicate a complete response in the neck, this accurately predicts a pCR at neck dissection. Others have found that physical examination and/or imaging studies (CT or MRI) did not have a significant ability to predict a pCR at neck dissection.\textsuperscript{5,8,9} We and others\textsuperscript{7,9} have also found that patients with a cCR in the neck who underwent neck dissection had no survival benefit compared with those who had a cCR in the neck and did not undergo neck dissection. Brizel et al\textsuperscript{8} were the only group to report a survival advantage for those patients who underwent a neck dissection.

The literature consistently indicates that there is no clear advantage to neck dissection in patients with N0 or N1 disease after CRT.\textsuperscript{7} At present, most investigators agree that N3 neck disease should be managed with neck dissection following CRT regardless of the clinical response to treatment.\textsuperscript{4-5,7-9,14} The rate of residual pathologic neck disease in patients with N3 disease after CRT has been reported to be between 42% and 50%.\textsuperscript{6,8} Our rate was consistent with this at 45%, and N3 disease was the single best predictor of persistent tumor in the neck. Argiris et al\textsuperscript{9} postulates that perhaps microscopic disease in the neck, yet it is not customary to mandate resection of the primary site in patients with a cCR at the primary site after CRT to prove that they have a pCR, and it is accepted that a small fraction of these will recur locally.\textsuperscript{20,21} The risk of pathologic partial response and regional relapse in patients with N2 disease who have a cCR is low, and we advocate that neck dissection is not required in this patient group.

These study patients were part of an international phase 3 protocol originating at the Dana Farber Cancer Institute. As all of the data become available from this protocol, these neck management issues will be reexamined in a larger patient population.

In conclusion, in this small series with a limited number of events, a number of trends were noted. In patients undergoing aggressive SCRT, when findings from combined clinical assessments, including, physical examination, imaging studies, and PET scans, all indicate a cCR in the neck, this accurately predicts no residual neck disease on neck dissection, particularly in patients with N2 disease. Patients with cCR in the neck have improved overall survival and progression-free survival compared with patients with less than a cCR, and these survival advantages do not seem to be further improved by neck dissection. Therefore, patients with N2 disease who have a cCR in the neck do not need neck dissection.

Submitted for Publication: July 18, 2005; final revision received October 25, 2005; accepted January 9, 2006.

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Financial Disclosure: None.

REFERENCES


(REPRINTED) ARCH OTOLARYNGOL HEAD NECK SURG/VOL 132, MAY 2006 WWW.ARCHOTO.COM

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