The Role of Neck Dissection After Chemoradiotherapy for Oropharyngeal Cancer With Advanced Nodal Disease

Gary L. Clayman, DDS, MD; Chad Jeffery Johnson II; William Morrison, MD; Lawrence Ginsberg, MD; Scott M. Lippman, MD

Objective: To analyze and compare the effectiveness of sequential platinum-based chemotherapy and radiotherapy with and without selective neck dissection in patients with N2a and greater stage node-positive squamous cell carcinoma of the oropharynx.

Design: Nonrandomized controlled trial.

Setting: Tertiary referral center.

Patients: Sixty-six patients with squamous cell carcinoma of the oropharynx staged N2a or greater.

Interventions: Platinum-based induction chemotherapy followed by definitive radiation therapy; and selective neck dissections 6 to 10 weeks following the completion of radiation therapy in patients with radiographic evidence suggesting residual neck disease.

Main Outcome Measures: Locoregional recurrence and disease-free survival.

Results: Of 66 patients, 24 (36%) had complete responses in the primary local tumor (oropharynx) and regional disease (neck nodes), as assessed clinically and radiographically. These patients had lower rates of locoregional recurrence than did patients showing no or partial responses, but the differences were not significant (P > .05). Of 18 patients undergoing neck dissection, 10 (56%) had pathological evidence of residual tumor. Patients showing a complete response of regional and neck disease had significantly improved disease-specific and overall survival (P = .01 for both) compared with patients showing no or partial responses of their neck disease. Patients with no or partial responses who underwent neck dissections had significantly improved overall survival compared with similar patients who did not undergo neck dissections (P = .002).

Conclusions: Even in patients with bulky nodal disease, a complete response in the neck to sequential chemotherapy and radiotherapy may indicate that neck surgery is not necessary for good locoregional control and improved disease-free survival. Neck dissection is recommended for patients with no or partial radiographic responses.

PATIENTS AND METHODS

Between July 1, 1990, and April 1, 1995, 66 patients with squamous cell carcinoma of the oropharynx with associated advanced nodal disease (N2-N3) were treated with platinum-based induction chemotherapy followed by definitive radiotherapy. Platinum-based chemotherapy was given at a dose of 100 mg/m² for a median of 3 cycles (range, 1-4 cycles), and consisted of cisplatin plus fluorouracil in 37 patients (86%), cisplatin plus paclitaxel in 6 patients (9%), and other platinum-containing combinations in 3 patients (5%). Radiation therapy was given in a concomitant boost fractionation schedule to a median dose of 72 Gy (range, 68-74 Gy) in 42 fractions over 6 weeks.

Clinical response, particularly in the primary sites of the tonsil and tongue base, may be difficult to assess radiographically with computed tomography (CT) or magnetic resonance imaging (MRI) because of lymphoid tissue enhancement. In those equivocal cases, clinical impression was the determining factor in response. Complete response (CR) was defined as the disappearance of all evidence of tumor. Partial response (PR) was defined as a decrease of 30% or more in tumor size as determined by clinical examination, CT scan, or MRI scan.

Patients with incomplete responses in the neck following completion of treatment or who were otherwise recommended by the Multidisciplinary Head and Neck Oncology Program, The University of Texas M. D. Anderson Cancer Center, Houston, underwent neck dissections 6 to 10 weeks following the completion of definitive radiation therapy. Selective neck dissections were performed when minimal residual disease within lymph nodes was detected. Modified radical or radical neck dissections were performed on patients who exhibited substantial residual adenopathy that had invaded nonlymphatic structures.

Disease control, disease-specific survival, and overall survival curves were produced using the Kaplan-Meier product limit method. All patients were followed up for survival until time of death or study termination. Proportions of patients who exhibited the response variables of interest in the various treatment groups were compared by χ² analysis. Statistical analysis was performed using Statistica for Windows (StatSoft, Inc, Tulsa, Okla).

The inclusion of neck dissection as part of standard therapy for patients treated with either radiation therapy alone or radiation therapy plus chemotherapy has been controversial. Although it is clear that selective neck dissection is needed in node-positive patients who fail to respond to prior therapy, it is less clear whether patients who achieve complete or partial clinical responses in the neck will benefit by surgical intervention.

The goals of the present study were as follows: (a) to analyze the effectiveness of sequential platinum-based chemotherapy and radiotherapy on locoregional recurrence (LRR) and disease-free survival in patients with N2a and greater stage node-positive oropharyngeal cancer and (b) to determine the value of selective neck dissection in this patient group.

RESULTS

PATIENTS

The study population included 52 men (79%) and 14 women (21%). The median patient age was 52.5 years (range, 26-75 years). Most patients had primary tumors in either the base of the tongue (n=37 [56%]) or the tonsil (n=22 [33%]), and the remaining 7 (11%) had tumors of the pharyngeal wall. The tumor and node classifications are shown in Table 1.

Of the 66 patients eligible for this study, clinical evaluations of treatment response were available for 65 after the completion of induction chemotherapy alone and for 59 after the completion of chemotherapy and radiotherapy. (No data were available for 1 patient, and 6 received subtherapeutic doses of radiotherapy.) Evaluations based on either CT or MRI scans after completion of chemotherapy and radiotherapy were available for the primary local tumors of 48 patients and for the regional neck disease of 50 patients. Sixteen patients with favorable T1 and T2 primary tumor responses underwent posttherapy ultrasonographic evaluations of the neck.

RESPONSE TO SEQUENTIAL CHEMOTHERAPY AND RADIATION THERAPY

As expected, a significant increase in clinical CRs occurred in patients undergoing sequential chemotherapy and radiation therapy vs those undergoing induction chemotherapy alone (76.3% vs 49.2% for the primary tumor [P=.002] and 59.3% vs 30.8% for the neck disease...
[P = .001] (Table 2). These differences were verified by the results of CT or MRI studies performed in a selected, smaller test group of patients.

**LRR AFTER SEQUENTIAL CHEMOTHERAPY AND RADIATION THERAPY AS RELATED TO THERAPY RESPONSE**

To determine if a CR to sequential chemotherapy and radiation therapy was a predictor of local control, we analyzed rates of LRR as a function of treatment response, as determined by CT or MRI after sequential treatment with chemotherapy and radiotherapy (Table 3). The median follow-up time was 26.7 months (range, 3.0-108.5 months). Although there were no significant differences in rates of LRR in patients with a CR compared with those with a PR (P > .10), there was a strong trend toward decreased LRR in patients with a CR either in the primary tumor alone or in the primary tumor and the neck together (P = .08). Of 24 patients who had CRs of the primary tumor and the neck by clinical and radiographic analysis, 2 had local recurrences, 1 had a distant metastasis, and 0 had regional recurrences. There were no isolated regional recurrences. None of the 29 patients who had a CT- or MRI-documented CR in the neck subsequently experienced a recurrence in the neck.

**LRR IN PATIENTS WHO DID AND DID NOT UNDERGO SALVAGE SURGERY AFTER COMPLETION OF SEQUENTIAL CHEMOTHERAPY AND RADIATION THERAPY**

Eighteen patients underwent neck dissections, including 14 who underwent neck dissections only and 4 who underwent neck dissections and regional resections of the neck. Of these 24 patients, 1 (4%) had a distant metastasis.

**DISEASE-FREE AND OVERALL SURVIVAL AFTER SEQUENTIAL CHEMOTHERAPY AND RADIATION THERAPY**

Overall and disease-free survival of patients with N2a and greater stage node-positive cancer of the oropharynx treated with sequential chemotherapy and radiotherapy was 49.2% and 78.4%, respectively (Figure 1A-B). There was a significant difference in disease-free and overall survival (P = .01 for both) in patients showing a CR in the neck to sequential chemotherapy and radiotherapy compared with patients showing only a PR (Figure 2A-B). There also was a significant improvement in disease-specific survival associated with salvage neck dissection (vs no dissection) in patients with a primary site CR but only a neck or regional PR to sequential chemotherapy and radiotherapy (P = .02) (Figure 3).
Despite important advances in organ preservation and survival with platinum-based chemotherapy and radiotherapy,11,12 the failure to achieve locoregional control remains a major cause of treatment failure and death in patients with locally advanced head and neck cancer. The role of neck dissection after chemoradiotherapy for head and neck cancer (eg, in respect to initial node stage and locoregional response13,14) is unclear. To address this important clinical management issue, we focused this study on a single head and neck subsite (oropharynx), to limit disease heterogeneity, and on advanced nodal disease (N2-N3), a clinical setting in which the role of neck dissection after chemoradiotherapy is extremely relevant.

We found that LRR rates were consistently lower in patients with a CR than in those with a PR to sequential chemoradiotherapy, as assessed by CT or MRI scan. Locoregional recurrences occurred in only 2 (8%) of the 24 patients with a CR of the primary tumor and neck disease (which were only local in both cases) vs in 3 (38%) of the 8 patients with a PR. No patient with a CR in the neck subsequently experienced a recurrence. A primary site CR (with or without a CR in the neck) was associated with a trend toward fewer LRRs ($P = .08$). (Treatment response after chemotherapy alone in our study apparently did not affect the LRR rates.)

Overall, the patients with a CR in the neck (as assessed by CT, MRI, or ultrasonography) had significantly improved rates of disease-free and overall survival compared with the patients with no response or a PR. Of the 29 patients with a CR in the neck, 25 did not undergo neck dissections; only 3 (10.3%) of the 29 experienced LRR, 2 of whom did not undergo surgery. Among patients with no response or a PR in the neck, those who underwent neck dissections had significantly improved overall survival compared with those who did not ($P = .02$). Indeed, the disease-specific survival rate
in the subgroup of patients who underwent neck dissections after no response or a PR in the neck was not significantly different from that seen in patients who had a CR in the neck. Patients with residual disease in primary and regional sites following induction chemotherapy and definitive radiotherapy were never successfully salvaged surgically.

Our findings (especially that no patient with a CR in the neck subsequently experienced a recurrence in the neck) suggest that, even in patients with bulky nodal disease, a CR in the neck to chemoradiotherapy may indicate that neck surgery is not necessary to achieve local control and improved disease-free survival. This is consistent with the conclusions reached in several previous studies. Armstrong and colleagues' tested a chemoradia- tion protocol (similar to that used in the present study) in 80 patients with locally advanced resectable cancer of the larynx, hypopharynx, and oropharynx. Among patients who did not undergo neck dissection, a neck recurrence occurred in only 1 of 17 with a CR in the neck. Peters et al.15 reported that the risk of neck relapse in patients who did not undergo neck dissection, a neck recurrence in 1 of 3 with a CR in the neck subsequently experienced a recurrence in the neck, we do not recommend neck dissection in this group. Nevertheless, because of the potential of microscopic persistent disease, patients with a CR at the 6- to 8-week postchemoradiotherapy evaluation should have a second evaluation 2 to 3 months later. If gross disease is found in the latter evaluation, the patient should be considered for neck salvage surgery. We continue to recommend neck dissection in patients with oropharyngeal cancer achieving no response or a PR to chemoradiotherapy.

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Corresponding author and reprints: Gary L. Clay- man, DDS, MD, Department of Head and Neck Surgery, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Campus Box 441, Houston, TX 77030 (e-mail: gclayman@mdanderson.org).

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