Efficacy of Targeted Chemoradiation and Planned Selective Neck Dissection to Control Bulky Nodal Disease in Advanced Head and Neck Cancer

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Purpose: To determine the efficacy of targeted chemoradiation with the radiation plus platinum (RADPLAT) protocol and planned selective neck dissection in patients with N2 to N3 nodal disease associated with upper aerodigestive tract carcinoma.

Methods: Analysis of 52 patients with N2a, N2b, or N3 disease involving 60 heminecks treated with intra-arterial cisplatin, 150 mg/m², and intravenous sodium thiosulfate, 9 g/m², on days 1, 8, 15, and 22; radiation therapy, 180 to 200 cGy per fraction for 35 fractions (total dose, 68-74 Gy); and planned neck dissection (33 of 35 procedures were selective).

Results: Of the 56 evaluable heminecks, a clinical complete response was achieved in 33 (59%). Within this group, 16 neck dissections were performed, none of which yielded disease on pathological examination. A clinical partial response was obtained in 21 heminecks, of which 18 subsequently had a neck dissection, yielding disease on pathological examination in 14. In all cases, it was possible to completely excise all adenopathy with clear margins on pathological examination. The rate of regional disease control among the 56 evaluable heminecks was 91% (51/56) (median follow-up, 36 months). Four failures were associated with uncontrolled disease at other sites, and 1 was an isolated neck recurrence.

Conclusion: Selective neck dissection appears to be an effective adjunct to targeted chemoradiation in controlling N2 to N3 neck disease.

PATIENTS AND METHODS

Between June 1, 1993, and August 31, 1995, 52 patients with squamous cell carcinoma of the upper aerodigestive tract and associated bulky (N2-N3) nodal disease were treated with a targeted chemoradiation protocol known as RADPLAT.² All of the patients with evaluable data were offered planned neck dissection 8 weeks after completion of radiation. Selective neck dissection was done whenever possible, thus reserving radical and modified radical neck dissection for patients who had residual adenopathy that involved multiple levels and/or invaded nonlymphatic structures.

Thirty-three of the patients were included in an earlier report in which the response to treatment and preliminary survival data were analyzed for the first 50 patients treated at the University of Tennessee, Memphis, between June 1, 1993, and September 30, 1994.³ In this current larger series, which includes only patients with bulky nodal disease, the emphasis of the analysis is on regional disease control, to determine whether planned lymphadenectomy is necessary and whether selective neck dissection is efficacious.

All patients entered into the study underwent a clinical staging of disease at both the primary and the regional sites with the use of information based on physical examination, endoscopic findings, and radiological studies (computed tomography and/or magnetic resonance imaging). Nodes that were considered to be positive by means of radiological criteria included those with central radiolucencies (necrosis, keratosis), nodes of which the smallest diameter was greater than 1.5 cm, and nodes with poorly defined borders indicating extracapsular spread. Only a few patients in the group actually had their nodal stage increased on the basis of radiological studies, and the vast majority of patients who had N2 disease did so on the basis of physical examination findings.

Patients in this series were analyzed to determine the response of the neck disease to chemoradiation as determined by clinical criteria (physical examination and computed tomographic studies) and pathological examination after neck dissection. Other end points included site of recurrence, survival, the type of neck dissection performed, and the need for additional treatment to the neck. Although the study consisted of 52 patients, the analysis was done on 60 heminecks because in 8 patients the bulky disease also affected the opposite side of the neck.

The targeted chemoradiation protocol (RADPLAT) involved the use of intra-arterial cisplatin chemotherapy combined with systemic chemoneutralization. Cisplatin (150 mg/m² weekly for 4 weeks) was rapidly infused during 3 to 5 minutes through a microcatheter placed angiographically to selectively encompass only the dominant blood supply of the targeted tumor. In each patient, the goal was to infuse the component of the disease considered to be bulky and/or infiltrative and in which radiotherapy alone was likely to fail. In the majority of patients, it was possible to cover the full extent of the primary disease with the cisplatin infusion, whereas in a small number of patients, only the radiotherapy field permitted this. In the patients whose bulky nodes involved the upper part of the neck, some of the drug was delivered to this region if the superior thyroid artery was included in the targeted infusion. Simultaneous with starting the intra-arterial infusion of cisplatin, sodium thiosulfate (9 g/m² during 30 minutes, followed by 12 g/m² during 6 hours) was given intravenously. This allowed the tumor bed to initially receive the full dose of cisplatin before the neutralizing agent, and for the systemic organs to receive the neutralizing agent before the cisplatin.⁴ Patients received pre-treatment intravenous hydration during 2 hours, which consisted of 2 L of isotonic saline solution containing 20 mEq of potassium chloride and 2 g of magnesium sulfate. The cisplatin was dissolved in 400 mL of isotonic saline solution. Posttreatment hydration consisted of 1 L of isotonic saline solution containing 20 mEq of potassium chloride and 2 g of magnesium sulfate during 6 hours. Dexamethasone sodium phosphate was also administered intravenously or orally, 4 mg every 6 hours until the following morning. All of the arterial catheterizations were accomplished transcutanously through the femoral artery, and catheters were removed immediately after infusion.

Conventional external beam irradiation was used in daily fractions (180-200 cGy per fraction) to a total dose of 68.5 to 74.0 Gy given during 7 to 8 weeks to the primary tumor. Thus, nodal disease lying within the portals covering the primary lesion also received the same total dose. Nodal disease lying outside the field to the primary tumor received 50 Gy plus a boost, for a total dose of at least 60 Gy. The chemotherapy infusions were given concurrently on days 1, 8, 15, and 22 of radiotherapy.

is also a belief among surgeons that patients who have bulky nodal disease should undergo a comprehensive neck dissection (removal of levels I-V), and, in most cases, the non-lymphatic structures (spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle) should also be removed, ie, through radical neck dissection.

In a previous pilot study done at another site with the use of the same targeted chemoradiation protocol as in this study,⁵ the rate of disease control and recurrence in the neck for patients with N2 to N3 disease was 20 of 22, and only 1 patient developed a regional recurrence (median follow-up, 24 months). The majority of patients in this series had a neck dissection for residual disease confirmed by fine needle aspiration (salvage), whereas the policy in our study was to perform planned neck dissection for all patients regardless of the clinical response. The purpose of this analysis was to confirm the efficacy of the radiation plus platinum (RADPLAT) program for patients with bulky nodal disease to determine whether planned selective neck dissection provided effective regional disease control for patients found to have residual tumor in the neck. We were also interested in analyzing the yield of positive disease for patients who did and did not have a clinical complete response (CR) to the chemoradiation to determine whether neck dissection should be routinely carried out for complete responders as well as partial responders.

The median age of the patients was 59 years (range, 38-84 years). There were 42 men and 8 women. The median

RESULTS
length of follow-up was 36 months (range, 20-46 months). The distribution by T and N classification is shown in Table 1. Classification of disease in the primary site included 4 patients with T2 lesions, 17 patients with T3, and 31 with T4. Classification of the nodal disease included 7 patients with N2a lesions, 14 with N2b, 23 with N2c, and 8 with N3. The 23 patients with N2c nodal disease were further subclassified according to each side of the neck (hemineck) as follows: N0, 1; N1, 14; N2a, 8; N2b, 21; and N3, 2. The 15 heminecks that did not have bulky disease (ie, N0 and N1) were excluded from the subsequent analysis. Thus, the distribution by N classification of the total number of heminecks analyzed was as follows: N2a, 15; N2b, 35; and N3, 10 (total of 60 heminecks with bulky disease).

Planned neck dissections were actually carried out on 35 of the 60 heminecks that contained bulky nodal disease before treatment. The remaining 25 necks were not dissected for the following reasons: 3 patients did not complete therapy; 6 patients died in the interval between the completion of radiotherapy and the time for restaging (2 months); 12 patients had a clinical CR to the chemoradiation and subsequently refused surgery; 1 patient had progressive disease at the primary site (this patient had bilateral bulky nodal disease and thus counted for 2 heminecks); and 2 patients developed distant metastases before restaging biopsy and planned neck dissection could be completed.

Among the 35 planned neck dissections performed, 33 were selective (ie, preservation of 1 or more levels of lymph node groups), and 2 were comprehensive (ie, removal of all 5 levels of lymph nodes) (Table 2). Table 2 gives the combinations of lymph node levels removed in the selective neck dissections. Eight selective neck dissections were performed during which it was necessary to remove 1 or more of the nonlymphatic structures routinely included in the radical neck dissection (ie, sternocleidomastoid muscle, internal jugular vein, or spinal accessory nerve). In the 2 comprehensive neck dissections, it was necessary to remove the sternocleidomastoid muscle in 1 procedure (ie, modified radical neck dissection) and all 3 nonlymphatic structures in the other (ie, radical neck dissection).

Figure 1 outlines the treatment results for disease response in the regional nodes. There were a total of 60 heminecks (32 patients) containing N2 to N3 disease, 4 of which could not be evaluated for reasons outlined previously. Three of the patients who had a partial response were not operated on for the following reasons: 2 patients died of disease and 1 patient died of an unrelated cause. In the subset of neck dissections performed for disease showing a clinical partial response, it was possible to completely excise all adenopathy with pathologically clear margins.

The single recurrence involved a patient with a T4 N2b piriform sinus cancer who had a level II to IV dissection after a CR in the primary site and a partial re-
response in the regional lymph nodes. The recurrent lymphadenopathy was noted in level V approximately 4 months after the planned neck dissection. Retrospective review of the computed tomographic scan of the neck obtained 2 months after chemoradiation showed that the positive node had been present before the neck dissection but it had not been noted clinically. The patient was subsequently rendered disease free after a dissection of level V. The 2 heminecks (1 patient) that showed no response to initial treatment had no subsequent neck dissection because the patient also had no disease response in the primary site. This patient had massive unrespectable tumor extending from the hypopharynx to the nasopharynx, and he subsequently died of progressive locoregional disease.

Acute wound complications after neck dissection developed in 6 of the 35 patients (17%); the complications included chyle fistula (2 patients), flap necrosis (1 patient), wound dehiscence (2 patients), and hematoma (1 patient). Late complications, all of which were related to excessive soft tissue fibrosis, occurred in 5 patients.

The pathological CR rate to the targeted chemoradiation in the regional lymph nodes among the 35 dissected necks was 57% (20/35). With a median follow-up of 36 months (range, 20-46 months), the rate of disease control among the 55 evaluable heminecks was 50/55 (91%). Among the 50 patients rendered disease free after initial treatment (chemoradiation with or without neck dissection), the rate of disease recurrence within the regional lymph nodes was 2% (1/50), and with subsequent salvage surgery it was 0% (0/50). In addition to the 1 patient who had persistent disease at the primary site, local recurrence developed in 1 (2%) of 54 patients and distant metastases in 14 (26%) of 54. The Kaplan-Meier projected 3-year overall and disease-specific survival for the group was 32% and 47%, respectively. The rate of locoregional disease control at 3 years was 77% (Figure 2).

**COMMENT**

The data from this study indicate that the protocol of intraarterial supradose cisplatin and concomitant radiation therapy is highly effective for controlling bulky regional disease associated with carcinomas of the upper aerodigestive tract. Among the 56 heminecks that were treated, only 1 had evidence of recurrence, which was subsequently successfully treated by further surgery. In comparison, the neck control rates after radiation therapy and radical neck dissection reported in 3 large series were as follows: N2 disease, 29 of 37 (78%), 54 of 66 (82%), and 45 of 45 (100%); N3 disease, 1 of 5 (20%), 14 of 23 (61%), and 21 of 28 (75%).9-11

It is unclear from other studies whether the use of chemotherapy combined with radiation and neck dissection further improves the rate of regional disease control for N2 to N3 disease. Wolf and Fisher12 reported neck recurrence in 6 of 18 patients with N2 to N3 disease who had a CR in the neck after chemoradiation, whereas 5 of 19 patients who had a neck dissection for persistent disease died of neck recurrence. They suggested performing a planned neck dissection in all patients who had less than a CR in the neck after induction chemotherapy. However, Armstrong et al,13 reviewing records of patients treated with various regimens of induction chemotherapy, recommended that patients who had a CR after chemoradiation need not undergo planned neck dissection. They reported a neck failure rate of 5 of 32 among patients with node-positive disease who had a major neck response after chemoradiation compared with 11 of 19 for those who did not. With regard to concomitant chemoradiation as opposed to induction chemotherapy, little data are available to determine whether its effects on the regional disease are better than those of radiation alone. Wanebo et al,14 using preoperative cisplatin and accelerated hyperfractionated radiation, reported a pathological CR rate of 15 (44%) of 34 in the neck for the subset that underwent neck dissection, a rate that was less than half of that in the primary site. Follow-up was too short (median, 12 months) to interpret the rate of failure in the nodes. In a more recent study, Lavertu et al15 reported a CR in 17 of 26 patients with N2 to N3 disease receiving concomitant chemoradiation vs 13 of 27 for those receiving radiation alone. Among the 91 patients with N0 to N3 disease at risk for recurrence, 8 did have recurrences, 2 of whom had received radiation alone whereas 6 had received chemoradiation. These findings suggest that there is minimal advantage for adding chemotherapy to the radiotherapy regimen, and it is probably the planned neck dissection that markedly improves regional control.

The main purpose for developing this novel drug delivery technique was to control advanced unresectable tumor within the primary site. The drug delivery technique combined with concomitant radiation therapy has proved to be very effective for unresectable tumors as well.
as resectable disease that would have required loss of major organ function.7,10 We were surprised to find that the treatment was also very effective for control of regional disease. Only 14 of the 56 heminecks with N2 to N3 disease that completed treatment were subsequently found to have evidence of residual disease. This rate of response to chemoradiation is higher than that reported for radiation alone and other chemoradiation trials.10,12,14,15,17 Although the associated nodal disease was not the preferential targeted site for the cisplatin infusions, it is likely that some uptake directly into the neck was achieved whenever the superior thyroid artery was included as one of the targeted vessels. In the few selected patients who had bulky nodal disease associated with small primary lesions, the infusate was purposely targeted toward the nodal disease through the lower branches of the external carotid artery and/or the thyrocervical trunk. Although such manipulations may account for the high response rate in the regional lymphatics in some patients, it is also possible that others benefited solely from smaller concentrations of nonneutralized cisplatin circulating systemically that may have been sufficient to enhance the regional effects of radiotherapy.

To achieve the ultimate high response rate in the neck, it was necessary to incorporate a planned neck dissection. Whereas the protocol required doing this for all heminecks with bulky disease, the failure to find evidence of residual disease in the 16 heminecks showing a clinical CR to chemoradiation suggests that it is unnecessary for this subset. However, the yield of positive disease for the heminecks that had evidence of clinically residual tumor (14/18) strongly supports the practice of performing planned neck dissection for this group. This approach, posttreatment neck dissection only for residual disease, has also been recommended after radiotherapy for oropharyngeal cancer with advanced neck metastases17 and in the management of the clinically positive neck as part of a larynx preservation protocol.13 However, Lavertu et al15 reached the opposite opinion on the basis of a yield of 4 of 18 patients having positive neck disease after a CR to radiation or chemoradiation. Using another approach, Weisman et al3 used positive cytologic findings as the indication for postchemoradiation neck dissection. Only 1 of 20 patients with bulky nodal disease who had a CR developed a recurrence in the neck (median follow-up, 24 months).

Thirty-three of the 35 neck dissections performed were of the selective type.18 With the exception of 1 case, this more conservative approach proved to be an effective operation for controlling any residual adenopathy after the chemoradiation. Selective neck dissection is primarily indicated for patients who have a high risk of occult metastases and for whom there is a predictable pattern of lymph node involvement. The goal of the neck surgery done for patients in our study was to remove all of the lymph node groups that were initially involved by gross disease or at high risk for involvement by occult disease. However, decisions were made not to dissect certain lymph node levels on the basis of the assumption that there was a minimal risk of occult disease to remain in lymph node groups that were initially negative and had received a full course of radiation therapy. In essence, trimodality therapy (chemoradiation plus surgery) was administered to the lymph node levels in patients who were clinically positive or were at highest risk for harboring occult disease, whereas bimodality therapy (chemoradiation) was used to treat the lymph node levels that were at low risk of having metastatic tumor. The postchemoradiation assessment to exclude the presence of such occult disease included a computed tomographic scan as well as physical findings.

In general, the goal when the neck was dissected was to remove all lymph node groups containing gross disease at the time of initial evaluation plus any levels that had an initial high risk of harboring occult disease. For adenopathy associated with mucosal lesions arising in the oropharynx, hypopharynx, and larynx, levels II through IV were routinely dissected for each neck that contained bulky lymphadenopathy. Thus, the submandibular and posterior triangles (levels Ia and V) were rarely dissected unless there was initial involvement by gross disease. For the patients whose bulky nodal disease was associated with mucosal primary tumors in the oral cavity, levels I through III were routinely dissected, whereas levels IV and V were not, unless initially involved by gross disease. The manner in which perinodal connective-tissue disease was handled during the neck dissection was in keeping with the oncological principles followed when the radical neck dissection was performed. Whenever the surgeon encountered tumor and/or scar tissue extending into the surrounding connective tissue, every effort was made to completely excise all involved tissue with a clear margin. In our series, this was possible in every case, although in some instances it required removal of 1 or more of the nonlymphatic structures routinely preserved in the modified radical and selective neck dissection procedures. In a few instances, it also necessitated excision of overlying cutaneous structures. Although there were several cases in which the lymphadenopathy was adherent to the carotid sheath, it was possible in every procedure to remove the disease from the common and/or internal carotid artery without resecting or grafting the vessels.

For several of the patients in our series who were determined to have pathological evidence of residual tumor in the neck dissection specimen, the diagnosis was based on 1 or 2 foci of malignant-appearing cells representing an extremely small volume of disease. Under these circumstances, the tiny nests of tumor cells were usually surrounded by tissue that was extensively necrotic or undergoing intense hyalinization. It is highly probable that in some of these cases, these malignant cells were no longer viable or would eventually undergo cell death. Thus, one cannot assume that intervention with neck dissection was the sole reason for no subsequent regional recurrence for patients whose necks were considered to have residual pathologically positive disease.

The rate of surgical complications after procedures on patients treated with chemoradiation is high.14 In our series, the acute events (chyle leak, incision breakdown,
flap necrosis, hematoma) occurred in 17%. Both of the chyle leaks resolved spontaneously. None of the patients required reoperation for complications related to the neck dissection. The late complication of soft-tissue fibrosis was more problematic. This was markedly severe in 5 patients, causing them to complain of limited neck movement, tightness and soreness of their neck muscles, and esthetic alterations. This problem has yet to be resolved. We are currently studying the effects of pentoxifylline as a potential mitigating agent. It is intuitive that the use of selective neck dissection with its more limited surgical bed also reduces the extent of fibrosis.

We conclude that targeted chemoradiation with the use of intra-arterial supradose cisplatin and concomitant radiation therapy followed by planned selective neck dissection for patients with squamous cell carcinoma of the upper aerodigestive tract with N2 to N3 neck nodes is highly effective for controlling regional disease. The major cause of failure among this group of patients is distant metastases, an event that is well known to be highly associated with advanced nodal disease. Future studies are under way that specifically address the problem of distant metastases as well as alleviating the late soft tissue effects of neck fibrosis.

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