IS PLANNED NECK DISSECTION NECESSARY FOR HEAD AND NECK CANCER AFTER INTENSITY-MODULATED RADIOTHERAPY?

MIN YAO, M.D., PH.D.,*† HENRY T. HOFFMAN, M.D.,*† KRISTI CHANG, M.D. † GERRY F. FUNK, M.D.,*† RUSSELL B. SMITH, M.D.,*† HUAMING TAN, M.S.,§ GERALD H. CLAMON, M.D.,† KEN DORNFIELD, M.D., PH.D.,*† AND JOHN M. BUATTI, M.D.*†

*Departments of Radiation Oncology, †Otolaryngology, and §Medical Oncology, Holden Comprehensive Cancer Center, University of Iowa Health Care, Iowa City, IA; and †Department of Biostatistics, College of Public Health, The University of Iowa, Iowa City, IA

Purpose: The objective of this study was to determine regional control of local regional advanced head and neck squamous cell carcinoma (HNSCC) treated with intensity-modulated radiotherapy (IMRT), along with the role and selection criteria for neck dissection after IMRT.

Methods and Materials: A total of 90 patients with stage N2A or greater HNSCC were treated with definitive IMRT from December 1999 to July 2005. Three clinical target volumes were defined and were treated to 70 to 74 Gy, 60 Gy, and 54 Gy, respectively. Neck dissection was performed for selected patients after IMRT. Selection criteria evolved during this period with emphasis on post-IMRT [18F] fluorodeoxyglucose positron emission tomography in recent years.

Results: Median follow-up for all patients was 29 months (range, 0.2–74 months). All living patients were followed at least 9 months after completing treatment. Thirteen patients underwent neck dissection after IMRT because of residual lymphadenopathy. Of these, 6 contained residual viable tumor. Three patients with persistent adenopathy did not undergo neck dissection: 2 refused and 1 had lung metastasis. Among the remaining 74 patients who were observed without neck dissection, there was only 1 case of regional failure. Among all 90 patients in this study, the 3-year local and regional control was 96.3% and 95.4%, respectively.

Conclusions: Appropriately delivered IMRT has excellent dose coverage for cervical lymph nodes. A high radiation dose can be safely delivered to the abnormal lymph nodes. There is a high complete response rate. Routine planned neck dissection for patients with N2A and higher stage after IMRT is not necessary. Post-IMRT [18F] fluorodeoxyglucose positron emission tomography is a useful tool in selecting patients appropriate for neck dissection. © 2007 Elsevier Inc.

INTRODUCTION

Many locoregionally advanced head and neck squamous cell carcinoma (HNSCC) patients are now treated with radiation, with or without concurrent chemotherapy, to achieve organ preservation. The management of nodal disease postradiation is controversial. It is generally agreed that patients with N1 disease with complete response postradiation do not require neck dissection. However patients with N2 or N3 disease have routine, planned neck dissections in many institutions, regardless of treatment response. Planned neck dissection has been incorporated into organ preservation protocols in clinical trials. This strategy evolved in the early 1970s because the rate of ipsilateral neck recurrence was lower in those treated with combined radiation and surgery compared with those treated with either modality alone (1, 2). With the advance in radiation techniques and the addition of concurrent chemotherapy, however, a high proportion of patients achieve complete response. Many patients who have neck dissection following (chemo)radiation often have no residual viable cancer in the resected lymph nodes. The risk of isolated neck recurrence in patients with complete response has also been reported to be low, even without neck dissection (3–9). These findings support the practice of determining the need for neck dissection based on postradiation findings rather than preradiation staging. Controversy continues because of reports of high regional recurrence rates for those patients who do not

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receive a neck dissection predetermined by the clinical stage before treatment, and lack of clinical parameters for patient selection (10, 11). This has been reviewed recently by Mendenhall et al. (12) and Pellitteri et al. (13).

Patients in previous studies were treated with conventional radiotherapy with two opposed lateral fields that matched to one anterior lower neck field. Radiation techniques have advanced in past decade, particularly with the use of intensity-modulated radiotherapy (IMRT). An advanced form of three-dimensional conformal radiation technique, IMRT uses multiple beams of nonuniform intensity, conforming high-dose radiation to the gross tumor, bulky lymph nodes, and high-risk microscopic areas yet sparing adjacent normal structures. For head-and-neck cancers, IMRT is the ideal radiation treatment: several studies published recently documented IMRT can potentially improve local regional control (14–18), reduce side effects (especially xerostomia) (19, 20), and improve quality of life (21–23) for patients with head-and-neck cancer.

In this retrospective study, we reviewed treatment outcomes of patients with stage N2 and higher HNSCC treated with definitive IMRT. We focus on regional control, and discuss the role of neck dissection and its selection criteria after definitive IMRT.

METHODS AND MATERIALS

A total of 237 patients with HNSCC (excluding skin and parotid) were treated with IMRT with curative intent from December 1999 to July 2005 at the University of Iowa. Of these, 143 patients had stage N2 or N3 disease, and 100 were treated with definitive IMRT. Excluded were 4 patients with nasopharyngeal carcinoma and 5 who had neck dissection before radiation. One patient, lost to follow-up 9 months postradiation, was also excluded. This patient was alive with no evidence of locoregional disease but with lung metastasis at last follow-up. Thus, the remaining 90 patients were analyzed for this study. Approval was sought and granted before treatment, and lack of clinical parameters for patient selection (10, 11). This has been reviewed recently by Mendenhall et al. (12) and Pellitteri et al. (13).

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**METHODS AND MATERIALS**

A total of 74 patients received cisplatin-based chemotherapy; 73 concurrently with radiation and 1 with induction chemotherapy.

**RESULTS**

**Patient characteristics**

Patient characteristics are given in Table 1, and stage distribution is summarized in Table 2. The most common site was the oropharynx, accounting for 71% (64/90) of patients in this study. This lack of balance reflects our policy that oropharyngeal cancers are generally treated with primary radiation and oral cavity cancers are treated with primary surgery followed by postoperative radiation if indicated. Of the 64 oropharyngeal cancer patients, 32 had base-of-tongue cancer, 26 tonsil cancer, 1 pharyngeal wall cancer, and 5 tumor that involved two or more subsites for which the origin could not be differentiated.

**RESULTS**
Outcomes of patients with and without neck dissection

In all, 14 neck dissections were performed in 13 patients (1 patient had bilateral neck dissection). Types of neck dissection included selective neck dissection (6), modified radical neck dissection (6), and radical neck dissection (2). Neck dissections were performed at a median time of 17 weeks from radiation completion (range, 9–34 weeks). Six hemineck dissections contained residual viable tumor, whereas the remaining 8 were pathologically negative. One patient, who had a stage T4AN2B oral tongue cancer, also had residual tumor in the primary site and underwent resection of the primary tumor and free-flap reconstruction at the time of the neck dissection. He had bulky tumor that crossed the midline, extended to base of tongue and deep muscle of the tongue. Along with current chemotherapy, IMRT was given as neoadjuvant treatment to downstage the tumor to avoid the morbidity associated with a total glossectomy. With a median follow-up of 28.8 months (range, 11.4–48.9 months), 1 patient developed local recurrence, but none had regional recurrence.

A total of 77 patients did not have neck dissection. One patient died of chemotherapy-induced neutropenia 6 days after completing treatment. Three patients with residual cancer did not have surgery. Of these, 1 patient had stage T4AN2B buccal mucosa cancer and 1 had stage T4AN2B laryngeal cancer. Both refused the recommended treatment of primary surgical resection followed by postoperative radiation and then refused salvage surgery despite persistent disease after IMRT. Both died from locoregional disease progression. The third patient had stage TxN2A of an unknown primary. She did not have neck dissection because she was found to have lung metastasis after the primaries were controlled. It was not possible to find the primary site.

Overall treatment outcomes

Median follow-up for all patients was 29 months (range, 0.2–74 months). All living patients were followed at least 9 months after completing treatment. Accounting for the 3 patients who did not have salvage surgery for persistent disease after IMRT, the 2-year local control, regional control, distant metastasis-free survival, overall survival is 96.3%, 95.4%, 81.8%, and 80.4%, respectively. The 3-year local control, regional control, distant metastasis-free survival, overall survival is 96.3%, 95.4%, 80.0%, and 67.5%, respectively (Figs. 1–4).

FDG PET as selection criteria for neck dissection

Of the 13 patients who had neck dissection after IMRT, 12 had PET and CT studies 7 to 16 weeks after IMRT (median 14 weeks) before neck dissection. All had residual lymph nodes ranged from 1.2 to 3.5 cm in the CT study. Eight had positive FDG uptake in the residual lymph node; 5 of them contained residual viable tumor, whereas in 3 results were pathologically negative at neck dissection. Four patients had negative PET study, and all had pathologically negative results.

All 3 patients with residual cancer who did not have surgery had positive post-IMRT FDG PET study results. Of 73 patients observed, 64 patients had an FDG PET scan 5 to 29 weeks (median 15 weeks) after completing IMRT. Only 1 of these PET studies demonstrated FDG uptake in the cervical lymphatic regions. This patient had a residual lymph node of 0.7 cm with a maximum standardized uptake value (SUVmax) of 2.6. Ultrasound-guided fine-needle aspiration of this lymph node revealed reactive changes. This patient did not receive further treatment and

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**Table 2. American Joint Committee on Cancer stage distribution of 90 patients**

<table>
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<tr>
<th>T stage</th>
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<td>28</td>
<td>12</td>
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* These patients with nasal cavity cancer presented with cervical lymph node metastasis after the primaries were controlled.
had no evidence of disease recurrence 21 months after completing IMRT. Of the 63 patients who had negative post-IMRT PET study, 1 had regional recurrence as mentioned above, representing a false-negative result.

The results of FDG PET in correlation of pathologic results at neck dissection and clinical outcomes are summarized in Table 3. The sensitivity, specificity, positive predictive value, and negative predictive value of post-IMRT PET in prediction of pathologic status/clinical outcome are 88.9%, 94.3%, 66.7%, and 98.5%, respectively.

CT study results as selection criterion for neck dissection

All patients who had neck dissection had residual lymph nodes in the CT studies. The 3 patients with residual cancer and did not have surgery also had residual lymph node involvement.

Of the 73 patients observed, 61 had CT of the head and neck after IMRT. Most commonly the CT imaging was obtained concurrently with the FDG PET imaging. In all, 38 patients did not have any residual lymph nodes in the CT; 1 of these patients, who also had a negative post-IMRT PET study, had regional recurrence as mentioned above. A total of 23 patients had residual lymph nodes, 19 with residual lymph nodes of \( \sim 1.0 \) cm (range, 0.8–1.5 cm). In 4 patients who had residual adenopathy (range, 2.4–4.0 cm), FDG uptake was not shown in the PET study. Three had adhesion/encasement of carotid artery by the residual adenopathy and did not have neck dissection; the remaining patient chose to remain under observation. None of these patients had regional recurrences.

DISCUSSION

In this report, we demonstrate a high regional response rate of cervical lymphadenopathy after IMRT treatment of 90 patients with stage N2 or greater HNSCC. Only 10 of these patients had persistent viable cancer in the regional lymphatic basin after IMRT; 6 had neck dissection with persistent viable disease in the residual lymph node, 3 had

<table>
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Table 3. Summary of positron emission tomography (PET) results in correlation with pathologic findings at neck dissection and clinical outcomes
persistent disease without neck dissection and had disease progression, and 1 had regional recurrence, who had an initial complete response and did not have neck dissection. The remaining 80 patients either had negative pathology at neck dissection or had no regional recurrence without neck dissection. Similar high nodal response rates after IMRT have also been reported. Garden et al. (24) summarized the experience from M. D. Anderson Cancer Center in treatment of 80 oropharyngeal cancer patients with IMRT. The investigators reported that 26 of 69 patients with gross nodal disease at the time of irradiation underwent postirradiation selective neck dissections, and 21 (81%) had negative pathologic specimen results. They showed a 2-year regional control rate of 94%. de Arruda et al. (25) reported 50 patients with oropharyngeal cancer (92% with Stage III and IV disease) treated with IMRT at Memorial Sloan-Kettering Cancer Center. Of these, only 1 in 10 patients who had a planned neck dissection after therapy had a pathologically positive test result for the neck.

The high regional response rate is caused by better dose delivery in IMRT to the nodal disease. Stenson et al. (26) showed the incidence of viable cancer in the neck dissection specimen increased as radiation dose decreased. Because of technical difficulties in avoiding high dose to the spinal cord and the larynx, when using conventional radiation, bulky lymph nodes and lymph nodes in the lower neck are often underdosed with this radiation technique. For example, to avoid unnecessary irradiation to the normal larynx, at the University of Florida the opposed lateral fields are matched to the anterior lower neck field at the level of thyroid notch, even when the adenopathy is at the matched line (27). Abnormal lymph nodes at and below the matched line would be underdosed and neck dissection after radiation is therefore necessary to achieve regional control. However, in IMRT, the abnormal lymph nodes are included in the target volume as the primary tumor and are treated to a high dose as that to the primary tumor, and thus, expected to have similar response to the treatment as the primary tumor. The cervical lymphatic region that receives elective irradiation is also better covered in IMRT than conventional radiation. By dosimetric comparison of IMRT to conventional radiation, Sanguineti et al. (28) demonstrated that a significant portion of the volume of some lymph node levels will not be covered by the conventional radiation and the dosimetric coverage of any level by conventional radiation would have been below that pursued by IMRT. With better dose delivery to the bulky adenopathy and better dose coverage of elective irradiated cervical regions, better regional control is expected with IMRT compared standard conventional radiation.

Our data supports the concept that after appropriately delivered IMRT neck dissection should be based on post-treatment assessment and re-staging rather than pretreatment clinical staging. Neck dissection should play a selective role in the management of patients with documented residual disease after IMRT. Neck dissection contributes to high regional control rates when applied to this selected group of patients.

How to select patients to have neck dissection is controversial. In our practice, the selection criteria for neck dissection continue to evolve. Historically, our evaluation based on physical examination and CT study for persistent adenopathy. Recently, we have shown that FDG PET is highly accurate in the detection of persistent and recurrent disease for head-and-neck cancer patients after IMRT (29). We have also shown that the postradiotherapy FDG PET correlates to pathologic status of the residual lymph node; negative FDG PET highly predicts negative pathology (30–32). The results reported here further confirm that many residual lymph nodes do not contain viable tumor when posttreatment FDG PET is negative, and neck dissection may be withheld in these patients. Figure 5 summarizes our current policy using FDG PET in selecting patients for neck dissection after IMRT (32). Many patients reported here were evaluated following this algorithm. The results reported here support such practice; only 1 patient developed regional recurrence, giving a 2-year and 3-year regional control of 95.4% (accounting for 3 patients who did not have neck dissection even with known residual disease at the neck).

However, Rogers et al. (33) reported a different experience when using FDG PET in the decision regarding neck dissection after definitive radiation. The authors reported on 12 patients who had FDG PET imaging 1 month after completing radiotherapy and underwent neck dissection. Six of the 7 patients with a negative one-month FDG PET had positive pathologic disease results found at neck dissection; this correlated to a negative predictive value of 14%. This low predictive value can be attributed to multiple factors, as we pointed out before (34), the most significant of which is the timing of the PET study after radiation. Greven et al. (35) studied FDG PET imaging obtained 1 month and 4, 12, and 24 months postradiation and showed a high false-negative rate for scans obtained 1 month after treatment. The investigators found that 7 of 25 patients (28%) with a negative 1-month PET developed local recurrence 3 to 12 months after treatment. The PET obtained 4 months after treatment was more accurate: none of 18 patients with negative 4-month scan developed local recurrence. Lowe et al. (36) prospectively performed FDG PET scans in 44 patients with Stage III or IV head-and-neck cancer at 2 and 10 months after radiation. They found that 3 of 21 (14%) scans obtained at 2 months after radiation were false negatives. Based on these studies, we routinely obtain PET and CT 3 to 4 months after radiation.

Recently, investigators from several institutions have reported their experiences supporting the role of FDG PET in decision making for neck dissection after radiation. Porceddu et al. (37) reported 39 patients with residual lymph node involvement after radiation, and 32 of them had negative postradiation PET. Five patients with negative PET had neck dissection, and had pathologically negative results. The remaining 27 patients were followed closely.
without neck dissection. With a median follow-up of 34 months, there was only 1 patient who failed simultaneously at the primary site and in the neck. No patient had an isolated neck failure. Brkovich et al. (38) reported correlation of postradiation PET and pathology at neck dissection of 21 patients after radiation. They found a negative predictive value of 91.7%, suggesting a negative PET be a reliable predictor of the absence of residual tumor. Nayak et al. (39) reported 30 patients with stage N2 to N3 HNSCC who had posttreatment PET/CT within 5 months after chemoradiation. Patients with positive PET/CT underwent confirmatory biopsy and, if positive, neck dissection. Patients with negative PET/CT were followed clinically and radiographically for a median of 20 months (minimum 9 months). They found 8 patients had positive posttreatment PET/CT; 6 of them had positive biopsy and underwent neck dissection. Twenty-two patients had negative PET/CT and no recurrence was identified during the study. Thus, 80% of patients (24/30) were spared neck dissection without evidence of recurrent disease in the neck. However, multiinstitutional prospective clinical trials are necessary to determine whether such an approach is universally feasible.

Of note, in our current study, the majority of patients had oropharyngeal cancer. We and others have shown that, for head-and-neck cancer patients treated with IMRT, oropharyngeal cancer has better local regional control than cancer from other sites (14–16). For oral cavity cancer, we generally offer primary surgery and postoperative radiation for indicated patients (40). We reported 3 patients with involvement of the oral cavity who had primary IMRT. Two of them had residual tumor both at the primary site as well as the lymphatic regions. Therefore, it remains prudent to exercise caution in the use of the approach of neck dissection based on postradiation restaging for patients with primary sites other than the oropharynx.

In conclusion, we have demonstrated excellent regional control of locoregionally advanced HNSCC after IMRT treatment. We propose that routine neck dissection after IMRT is not necessary, especially for oropharyngeal squamous cell carcinoma. Post-IMRT FDG PET is useful in selecting patients who might have residual disease and in whom neck dissection would be necessary to achieve regional control.

REFERENCES


