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CLINICAL INVESTIGATION **Head and Neck**

INTENSITY-MODULATED RADIOTHERAPY FOR CERVICAL NODE SQUAMOUS CELL CARCINOMA METASTASES FROM UNKNOWN HEAD-AND-NECK PRIMARY SITE: M. D. ANDERSON CANCER CENTER OUTCOMES AND PATTERNS OF FAILURE

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Purpose: Conventional therapy for cervical node squamous cell carcinoma metastases from an unknown primary can cause considerable toxicity owing to the volume of tissues to be irradiated. In the present study, hypothesizing that using intensity-modulated radiotherapy (IMRT) would provide effective treatment with minimal toxicity, we reviewed the outcomes and patterns of failure for head-and-neck unknown primary cancer at a single tertiary cancer center.

Methods and Materials: We retrospectively reviewed the records of 52 patients who had undergone IMRT for an unknown primary at M.D. Anderson Cancer Center between 1998 and 2005. The patient and treatment characteristics were extracted and the survival rates calculated using the Kaplan-Meier method.

Results: Of the 52 patients, 5 presented with Stage N1, 11 with Stage N2a, 23 with Stage N2b, 6 with Stage N2c, 4 with Stage N3, and 3 with Stage Nx disease. A total of 26 patients had undergone neck dissection, 13 before and 13 after IMRT; 14 patients had undergone excisional biopsy and presented for IMRT without evidence of disease. Finally, 14 patients had received systemic chemotherapy. All patients underwent IMRT to targets on both sides of the neck and pharyngeal axis. The median follow-up time for the surviving patients was 3.7 years. The 5-year actuarial rate of primary mucosal tumor control and regional control was 98% and 94%, respectively. Only 3 patients developed distant metastasis with locoregional control. The 5-year actuarial disease-free and overall survival rate was 88% and 89%, respectively. The most severe toxicity was Grade 3 dysphagia/esophageal stricture, experienced by 2 patients.

Conclusion: The results of our study have shown that IMRT can produce excellent outcomes for patients who present with cervical node squamous cell carcinoma metastases from an unknown head-and-neck primary tumor. Severe late complications were uncommon.

INTRODUCTION

Head-and-neck cancer from an unknown site is rare, perhaps more so with the advent of sophisticated imaging technologies. Its rarity means that randomized prospective studies are unlikely to ever be conducted, and the optimal treatment remains somewhat controversial. The therapeutic philosophy has been to identify the therapy that gives the greatest control rates and the best quality of life after treatment (1). At the University of Texas M.D. Anderson Cancer Center, the treatment technique used for treating cervical node metastases from an unknown primary tumor site has consisted of parallel opposed fields to treat the upper neck and mid-neck nodal regions and the pharyngeal axis and an anterior low-neck field for the low-neck nodal regions. This technique has remained remarkably consistent from 1954, when Fletcher initiated megavoltage radiotherapy (RT) with ^{60}Co (1), and 1998. Although the use of RT in such cases substantially reduces the risk of regional failure (16% with neck dissection alone vs. 0% in patients with RT) (1), the risk of xerostomia from the dose required to prevent the appearance of a primary tumor and contralateral metastases has been considered unacceptable by many patients and clinicians.

In 1998, the RT technique was changed to incorporate a monoisocentric technique in which intensity-modulated RT (IMRT) was used to treat the upper neck cervical nodes and mucosal sites. The rationale for switching to IMRT was to exploit several potential advantages of IMRT compared with the conventional parallel opposed technique. First, dose modulation can minimize the excess radiation to

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normal structures such as the parotid glands, thereby reducing the risk of xerostomia. Second, a simultaneous boost can be incorporated into treatment planning, permitting accelerated fractionation to sites of gross disease while maintaining standard fractionation to mucosal sites that potentially harbor microscopic disease. The purpose of the present study was to evaluate the outcomes of patients who presented to the M. D. Anderson Cancer Center with an unknown primary and cervical node metastases who had undergone IMRT as a part of their overall treatment strategy.

METHODS AND MATERIALS

We retrospectively identified and reviewed the medical records of all patients with cervical node squamous cell carcinoma (SCC) metastases from an unknown primary site who underwent IMRT at the M.D. Anderson Cancer Center between 1998 and 2005 under an institutional review board–approved protocol. The requirement for informed consent was waived by this board. IMRT was given either as primary treatment or as postoperative adjuvant treatment.

All patients had a pathologically confirmed diagnosis of metastatic SCC; patients with papillary, basaloid, sarcomatoid, and undifferentiated subtypes were included. Patients with adenocarcinoma, melanoma, sebaceous gland carcinoma, leukemic infiltration, or soft tissue sarcoma were excluded, as were patients who had undergone surgery without RT and patients who had undergone previous RT at an outside facility.

IMRT was delivered using a linear accelerator producing 6-MV photons. Of the 52 patients, 35 (67%) were treated using a monoisocentric technique with an anteroposterior low-neck supraclavicular field matched to the IMRT fields, and 17 were treated with whole-neck IMRT. The IMRT fields generally consisted of nine static gantry beams with the following angles: 0°, 40°, 80°, 120°, 160°, 200°, 240°, 280°, and 320°. Three clinical target volumes (CTVs) were defined: CTV1, which included gross nodal disease with a margin; CTV2, the nodal volume at high risk of harboring microscopic disease; and CTV3, the nodal volume and mucosa deemed at low risk of harboring subclinical disease.

Follow-up information was obtained from the medical records, and the Kaplan-Meier method was used to calculate the probabilities of local, regional, and distant disease control and disease-specific and overall survival. For calculations of disease-specific survival, the following were scored as events: death from disease, death resulting directly or indirectly from treatment-related complications, and death from unknown causes that occurred <5 years after treatment.

RESULTS

Patient characteristics

A total of 52 patients had been treated with IMRT for SCC that had metastasized to the cervical lymph nodes from an unknown primary tumor site between 1998 and 2005. The median follow-up time for the entire cohort was 3.7 years (range, 1–7.6). The patient characteristics are listed in Table 1. Of the 52 patients, 44 (85%) presented with advanced Stage N2-N3 disease (Table 2); 25 patients were current smokers, 14 patients were former smokers, and 13 patients had never smoked.

Table 1. Patient and tumor characteristics

Characteristic	Value
Median age (y)	56
Median follow-up (y)	3.7
Gender	
Male	46
Female	6
Smoking history	
Yes	39
No	13
Pathologic type	
SCC	46
Basaloid SCC	3
Cystic SCC	1
Undifferentiated carcinoma	2
N status at presentation	
Nx	3
N1	5
N2a	10
N2b	18
N2c	6
N3	4

Abbreviation: SCC = squamous cell carcinoma.

The tumor histologic type had been confirmed by fine needle aspiration in 26 patients (50%), excisional node biopsy in 14 (27%), and neck dissection in 12 (23%). The findings at the central pathologic review were consistent with SCC in 46 patients, basaloid SCC in 3, cystic SCC in 1, and undifferentiated carcinoma in 2 patients. The tumor status by grade was Grade 1 in 1, Grade 2 in 5, Grade 3 in 25, and unknown in 21 patients.

After pathologic disease confirmation, the workup included physical examination, endoscopic evaluation, head-and-neck imaging (computed tomography or magnetic resonance imaging, with positron emission tomography [PET] in 26 patients), and examination under anesthesia with panendoscopy in all patients with or without directed biopsy cores taken. Also, 12 patients underwent bilateral tonsillectomies and 5 ipsilateral tonsillectomies during the examination under anesthesia.

Treatment

Surgery. Of the 14 patients whose tumors had been diagnosed by excisional biopsy, 11 had no measurable disease at IMRT. Extracapsular extension (ECE) was documented in 1 patient and not reported in 8 patients.

Thirteen patients (25%) had undergone neck dissection before RT, including selective neck dissection in 5, modified radical neck dissection in 5, and radical neck dissection in 3 patients. Pathologic evidence of ECE was documented in 7 (54%) of the 13 patients. Thirteen patients (46% of those irradiated with gross adenopathy) underwent selective neck dissection after RT because of the discovery of residual adenopathy on physical examination or diagnostic imaging at 6–8 weeks of follow-up. Only 1 patient (8%) had pathologic evidence of residual carcinoma. A total of 160 lymph nodes

Table 2. Presentation by radiographic nodal level involvement

Level	Retropharyngeal	I	II	III	IV*	V
N1			5			
N2a			9	3	1	
N2b	1	1	22	16	3	
N2c		1	4	2	1	
N3			4	2	2	
Nx			3			
Total	1 (2)	2 (4)	47 (90)	23 (44)	7 (13)	0 (0)

Data presented as numbers of patients, with percentages in parentheses.

* No patient with disease in Level IV nodes developed distant metastases.

Table 3. Treatment sequence according to nodal status at presentation

	Presenting nodal status					
Treatment sequence	Nx	N1	N2a	N2b	N2c	N3
Surgery, IMRT	1	1	2	4		
Surgery, CRT					2	2
IMRT, alone	2	2	8*	9*	1	
IMRT, surgery		1		5†	1	1
CRT			1			
CRT, surgery						1
CT, IMRT				2	1	
CT, CRT, surgery				2*†		
CT, surgery, IMRT		1				
CT, IMRT, surgery				1†‡	1	
Total	3 (6)	5 (10)	11 (21)	23 (44)	6 (11)	4 (8)

Abbreviations: IMRT = intensity-modulated radiotherapy; CRT = concurrent chemotherapy plus IMRT; CT = induction chemotherapy.

* Distant failure.

† Regional failure.

‡ Mucosal failure.

were removed after IMRT; only 1 node (<1%) was positive for disease.

Chemotherapy. A total of 14 patients (27%) had received systemic therapy. Of these, 8 patients (15%) had received induction chemotherapy with a taxane and carboplatin. The induction regimen included ifosfamide for 4 patients who had presented with advanced nodal disease (Stage N2b or greater) or low-neck disease and thus were considered at high risk of distant metastases. In addition, 8 patients, including 2 who had been treated with induction therapy, also received concurrent chemotherapy with RT. Of the 8 patients treated with concurrent chemoradiotherapy, 6 were treated with single-agent cisplatin, and 2 received carboplatin because of either a poor performance status or decreased renal function. Also, 4 of the 8 patients treated with concurrent chemoradiotherapy underwent RT after neck dissection. Of these 4 patients, 3 had had ECE. The details of treatment sequencing stratified by nodal stage at presentation are outlined in Table 3.

Intensity-modulated RT. IMRT was delivered in 30 fractions. The dose prescribed to the entire mucosa of the pharyngeal axis was 54 Gy at 1.8 Gy/fraction. The larynx and hypopharynx were not treated in 17 patients (33%), including all 13 nonsmokers. The neck treatment doses and volumes were determined by the presence or absence of nodal involvement. On the side of the neck containing disease, the uninvolved nodes at Levels IB and V were treated electively to 54–60 Gy. The median dose prescribed to the CTV for gross nodes with a margin (range, 0.5–1 cm) was 66 Gy (range, 60–72). The CTV for 5 patients who had presented after an excisional biopsy with no measurable nodal disease and no ECE was treated to a median dose of 64 Gy (range, 60–66). The median dose prescribed to the dissected necks was 60 Gy (range, 60–70). The prescribed dose to the uninvolved contralateral neck (46 patients) was 54 Gy; Level II–IV nodes were treated and included in either the IMRT fields or a separate low-neck. The nodes at Levels IB and V were not treated in the uninvolved sides of the neck. For patients treated with monoisocentric setups and IMRT, the prescribed dose to the uninvolved low-neck field was 50 Gy in 25 fractions. If the operative bed extended into the low-neck field, or if gross adenopathy was present within 1 cm of the junction, a boost dose of 6–10 Gy was delivered to the neck on the involved side using either an appositional electron beam or photons.

Outcomes

Primary mucosal and regional control. The 5-year actuarial rate of primary mucosal control was 98.1% (Fig. 1). Only 1 patient developed recurrent mucosal disease, which appeared at the base of the tongue, and 3 patients developed recurrence in the neck, for an actuarial 5-year regional control rate of 94.2% (Fig. 2). All recurrences occurred within 2 years after treatment. None of the patients with ECE developed recurrence in the neck.

All 3 patients with regional failure presented with Stage T0N2b disease. One patient had disease manifest in the base of tongue and had neck disease recur subsequently in contralateral Level 1B that was out of the radiation target volumes. The other 2 patients both had undergone post-RT neck dissection and developed recurrence in the involved neck. The neck recurrences developed at 7, 12, and 12 months, and all patients died of their disease within 3 years after salvage therapy.

Distant control. The 5-year actuarial rate of distant metastasis was 8.3% (Fig. 3). All distant metastases developed within 2 years of treatment. Five patients experienced distant failure, including 3 in whom locoregional control was maintained. Two patients had presented with Stage N2a disease and three with Stage N2b disease; none had had disease in the Level IV nodes or the supraclavicular fossa. The sites of metastasis were the lung in 2 patients, bone in 2, and axilla in 1 patient. The median time to death after the appearance of distant metastases was 4 months (range, 2–15).

Overall survival and disease-free survival. The 5-year actuarial disease-free and overall survival rate for the entire group was 88% and 81%, respectively. All 4 patients with

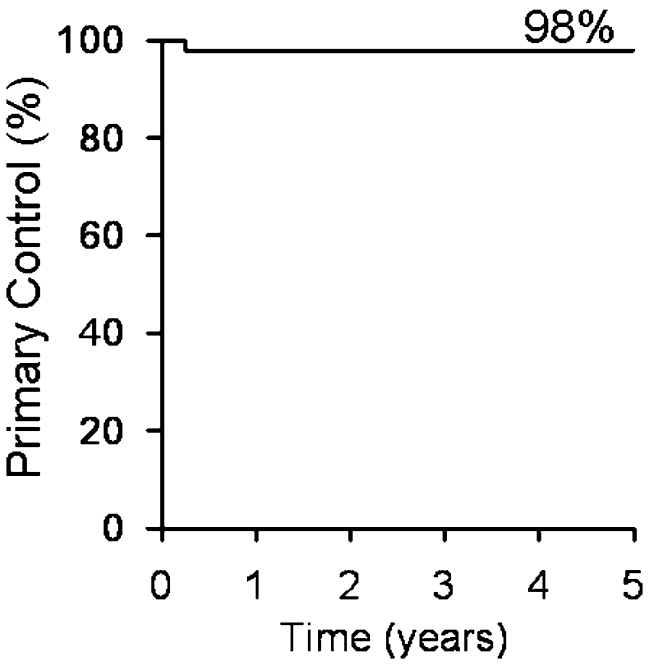

Fig. 1. Five-year actuarial rate of primary mucosal control (98.1%).

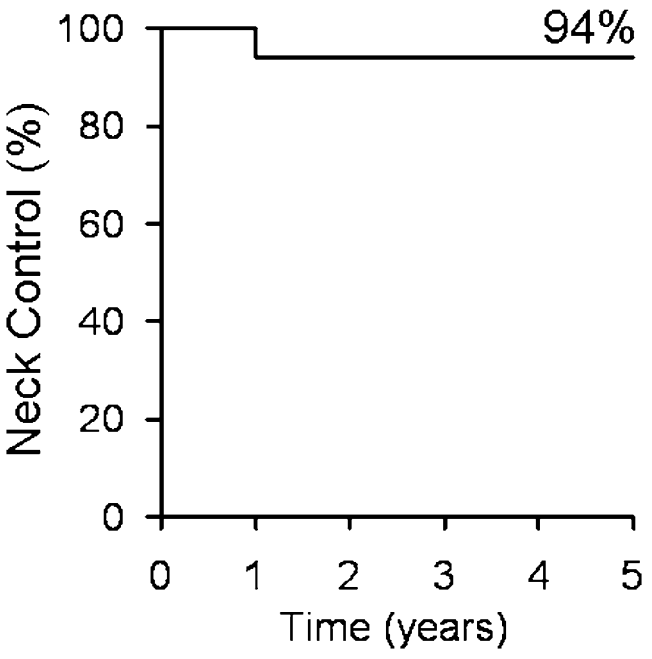

Fig. 2. Five-year actuarial rate of regional control (94.2%).

locoregional recurrence died of disease within 3 years after salvage therapy. Five patients developed six second primary tumors: four in the lung (small cell, adenocarcinoma, large cell carcinoma, and SCC), one in the prostate, and one basal cell carcinoma of the nose.

Complications

No Grade 4 complications were noted. Grade 3 esophageal toxicity occurred in 2 patients (1 with moderate to severe dysphagia who continued to require a percutaneous endoscopic gastrostomy tube and 1 with an esophageal stricture requiring dilation). The Grade 2 complications were hypothyroidism requiring oral medication in 1 patient and xerostomia in 3 patients. Grade 1 xerostomia was the most common complication, occurring in 6 patients.

DISCUSSION

The present study, the largest single-institution series reported to date, has demonstrated that IMRT can produce excellent disease-control and survival outcomes, with remarkably little toxicity, for patients presenting with cervical metastasis from an unknown head-and-neck primary cancer. The outcomes after IMRT in the present study were superior to those of historical control subjects treated with a parallel opposed technique (1–5). Our 5-year primary mucosal tumor control (98%), regional control (94%), disease-free survival (88%), and overall survival (89%) rates compare favorably with those from the Memorial Sloan-Kettering Cancer Center 2-year rates for progression-free survival (90%), distant metastasis-free survival (90%), and overall survival (85%) (6).

Given the rarity of head-and-neck cancer from an unknown primary site, randomized trials of various management strategies—and hence Level 1 evidence regarding the best such strategy—are unlikely. Thus, we undertook a retrospective review to determine how the treatment philosophy at the M.D. Anderson Cancer Center has evolved since the 1950s. During the past 60 years, the survival rate among patients with this type of cancer has gone from a few months (7, 8) to approximately 90% at 5 years. Such improvement evolved with the introduction of megavoltage irradiation with ^{60}Co in the 1950s at the M.D. Anderson Cancer Center, which provided a skin-sparing method to irradiate both the cervical node disease and mucosal areas of potential microscopic disease. In 1966, guidelines for the optimal treatment

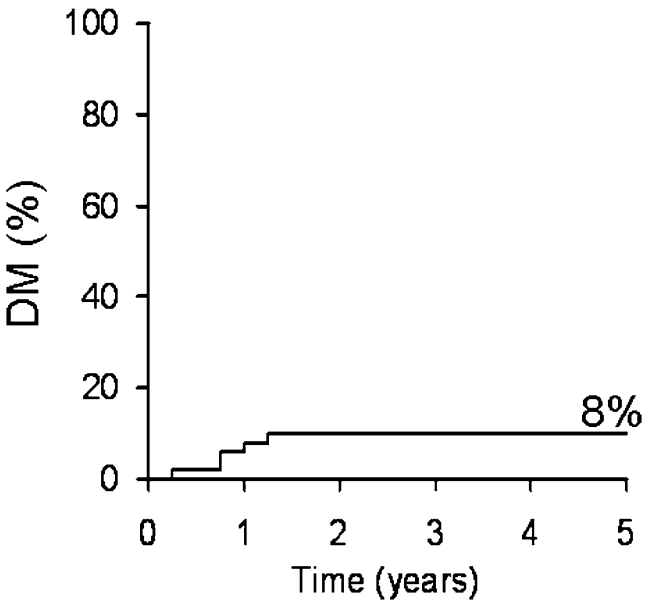

Fig. 3. Five-year actuarial rate of distant metastasis (DM) (8.3%).

of these patients included surgery or RT, or a combination of the two.

Jesse *et al.* (1) first reported the M.D. Anderson Cancer Center experience with 210 patients treated between 1954 and 1968. Within that group, 52 patients with advanced-stage, unresectable disease underwent primary RT using parallel opposed fields with ^{60}Co to the nasopharynx, oropharynx, hypopharynx, and both sides of the neck. At 3 years, the disease-free survival rate was 48% for the primary RT group and 47% for the combined surgery and postoperative RT group. In the primary RT group, 2 patients developed disease in the oral cavity and 1 patient in the hypopharynx. Disease recurred in the neck in 17% of patients with Stage Nx-N1 disease and in 22% of those with Stage N2-N3 disease. In that study, only 62% of patients had pathologically confirmed SCC, staging was performed by clinical examination, and RT planning was based on fluoroscopic images. Elective treatment of the mucosa of the upper respiratory and digestive tract along the pharyngeal axis was initiated when analysis revealed that 16% of patients developed subsequent primary tumors when only the neck had been addressed during treatment (1).

Carlson *et al.* (3) reported an update of the M.D. Anderson experience in 1986 in which 93 patients had been treated with RT between 1968 and 1980. The goal of that update was to investigate the results of a relatively consistent policy of treating both sides of the neck and the entire pharyngeal axis. Of the 79 patients presenting with head-and-neck SCC, the 10-year overall survival rate was 70% (3). Another modification to the treatment technique was instituted in 1973, when the hypopharynx, and later, the larynx were routinely excluded from the radiation field when the disease location or histologic findings almost certainly indicated a primary nasopharyngeal tumor. Otherwise, the larynx and hypopharynx were included in the treatment targets.

A subsequent report in 1990 (9) indicated that the treatment results reviewed at that time were superior to previous results from the M.D. Anderson Cancer Center. That report emphasized the importance of improving the quality of life for irradiated patients, because this treatment approach resulted in severe xerostomia (9). The advent of IMRT in the early to mid-1990s thus provided an appealing option for patients with neck disease, because it was thought to allow for the use of aggressive RT with lesser toxicity. As the results from the present study have indicated, the rates of severe xerostomia were quite low, and only 2 patients experienced Grade 3 toxicity.

Our comprehensive RT approach has been based on the premise that a significant proportion of patients with neck metastases have an occult malignancy in the pharyngeal axis. The excellent outcomes in the present series are comparable, not only to other series evaluating the outcomes of patients with Stage T0N+ head-and-neck cancer, but also similar to those from previous studies of IMRT used for oropharyngeal and nasopharyngeal cancer. We have previously described excellent results in a cohort of patients with Stage T1-T2 oropharyngeal cancer (10–16). Other randomized trials of patients with nasopharyngeal cancer have demonstrated less xerostomia in patients treated with IMRT than in those treated with more conventional treatment plans (17).

Although the results of the present series might be attributable to the use of IMRT, other factors, including more rigorous diagnostic workups, more aggressive treatment, and changes in the etiology of the disease, could also be responsible for the improvements in disease control and survival. Diagnostic radiologic techniques have improved greatly with the use of high-resolution computed tomography, magnetic resonance imaging, and, most recently, PET. Although PET/computed tomography has become more standard in our practice during the diagnostic workup, PET-directed tumor volume contouring for RT planning should not be used in clinical practice and is still considered investigational (18). Patients are also typically examined under anesthesia, and tonsillectomy is now recommended to identify occult malignancies in the tonsil.

Concurrent chemoradiotherapy has demonstrated good efficacy in locally advanced head-and-neck cancer. In the typical postoperative setting, chemotherapy is recommended if ECE is present (19). Few of the patients in our series had documented ECE, but 37% of all patients had been treated with concurrent chemoradiotherapy, and no patient with ECE had recurrent disease (compared with 16% of the patients in our previous report) (5). Concurrent chemotherapy might not be necessary when RT is to be delivered to the pharyngeal axis, even in patients with nodal disease (including ECE), because RT seems to be effective and the risk of additional toxicity is high.

The etiology of head-and-neck cancer is also changing. Oropharyngeal cancer is increasingly associated with human papilloma virus (HPV), and its incidence is also increasing among nonsmokers (20). The survival rates of patients with oropharyngeal cancer who are HPV-positive have been reported to be greater than those who do not have HPV (21). In the present study, approximately 30% of the patients were nonsmokers; therefore, to determine whether the improvement in outcomes was more closely linked to HPV-positive disease, we are obtaining the pathologic specimens of all patients in the present study for an analysis of HPV status in a future report.

Our current approach with respect to radiation volumes and dosage is as follows. The nodal targets in the head and neck include the retropharyngeal nodes and both sides of the neck. Inclusion of the neck node levels is determined by the involvement of that side of the neck. Specifically, we irradiate nodal Levels II–V on the involved side of the neck and consider irradiating Levels II–IV on the contralateral node-negative neck only if the primary is unlikely to be of nasopharyngeal origin. Level IB nodes are treated in the ipsilateral neck if patients present with disease in Levels II or III; however, we do not treat ipsilateral Level IB nodes when Levels II or III are not involved. Also, we do not treat the Level IB nodes in the uninvolved contralateral neck. IMRT allows treatment to be given within 6 weeks and

allows boost doses of hypofractionated radiation (2.2 Gy/fraction) to be given to gross nodal disease simultaneously with standard-fraction radiation (range, 1.8–2 Gy) to sites at risk of harboring microscopic disease. We recommend treating sites of gross nodal disease to 66 Gy in 30 fractions, with consideration of an electron boost to 70 Gy. Uninvolved, nonoperated lymph node–negative regions of the neck are treated to 54 Gy in 30 fractions. When RT is to be used after surgery, we treat the postoperatively positive neck to 60 Gy in 30 fractions and consider a boost to the involved site to 64 Gy if ECE is present.

Our approach to mucosal coverage has also evolved over time. The mucosal sites at risk are treated to 54 Gy in 30 fractions. Given the excellent mucosal control rate achieved, we disagree with the need to intensify therapy using either radiation dose escalation or the addition of concurrent chemotherapy (22). We treat the nasopharynx routinely using treatment of the retropharyngeal nodes. In the present series, the larynx and hypopharynx was excluded in 33% of the patients. The larynx and hypopharynx are highly amenable to adequate surgical diagnostic screening. In contrast to our previous report (3), we often omit the larynx and hypopharynx from the target volumes in patients who are nonsmokers or those presenting with Level II cystic nodes, because the risk of involvement is low but the morbidity associated with treatment is high (23).

CONCLUSION

At a single tertiary cancer center, we achieved excellent outcomes with IMRT for patients presenting with cervical node metastases from an unknown head-and-neck primary tumor. The survival rates were high, and late toxicity was minimal. Ideally, patients with this type of cancer should be treated in a setting that ensures that treatment of the neck and pharyngeal mucosa is balanced appropriately in terms of disease control and quality of life.

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