Original Article

Outcomes of Patients Diagnosed With Carcinoma Metastatic to the Neck From an Unknown Primary Source and Treated With Intensity-Modulated Radiation Therapy

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BACKGROUND: There are few published studies to guide the treatment of carcinoma metastatic to the neck from an unknown primary (CUP). In this regard, the objective of the current study was to share the authors' current experience treating patients with CUP using intensity-modulated radiation therapy (IMRT), which principally targeted both sides of the neck, the nasopharynx, and the oropharynx. **METHODS:** This was a retrospective study in which an institutional database search was conducted to identify patients with CUP who received IMRT. Data analysis included frequency tabulation, survival analysis, and multivariable analysis. **RESULTS:** Two-hundred sixty patients met inclusion criteria. The most common lymph node category was N2b (54%). IMRT volumes included the entire pharyngolaryngeal mucosa in 78 patients, the nasopharynx and oropharynx in 167 patients, and treatment limited to the involved neck in 11 patients. Eighty-four patients underwent neck dissections. The 5-year overall survival, regional control, and distant metastases-free survival rates were 84%, 91%, and 94%, respectively. Over 40% of patients had gastrostomy tubes during therapy, and 7% patients were diagnosed with chronic radiation-associated dysphagia. Higher lymph node burden was associated with worse disease-related outcomes, and in subgroup analysis, patients with human papillomavirus-associated disease had better outcomes. No therapeutic modality was statistically associated with either disease-related outcomes or toxicity. **CONCLUSIONS:** Comprehensive IMRT with treatment to both sides of the neck and to the oropharyngeal and nasopharyngeal mucosa results in high rates of disease control and survival. The investigators were unable to demonstrate that treatment intensification with chemotherapy or surgery added benefit or excessive toxicity. ***Cancer*** **2018;124:1415-27**. *© 2018 American Cancer Society.*

KEYWORDS: head and neck neoplasms, intensity-modulated radiation therapy, squamous cell carcinoma, unknown primary neoplasms.

INTRODUCTION

Carcinoma of unknown primary (CUP) accounts for approximately 3% of head and neck (HN) cancer diagnoses,[1] the majority of which are squamous cell carcinomas (SCCs). Because of this relatively low incidence of HNCUP, there is a dearth of strong evidence-based guidance for management. Thus, the National Comprehensive Cancer Network guidelines are relatively broad,[2] recommending surgery (with adjuvant therapy, as indicated by the surgical findings), radiation, or systemic therapy and radiation. Guidelines regarding the specifics of radiation are also vague, particularly with regard to treatment volumes. The National Comprehensive Cancer Network guidelines recommend treating suspected sites of subclinical spread, based on primary lymph node drainage patterns and the subsequent risk of recurrence, and advocate irradiating presumed mucosal sites, although others favor treating the involved neck only.[3,4]

On the basis of work by Jesse and colleagues[5] at The University of Texas MD Anderson Cancer Center, when analyzing patterns of mucosal and regional recurrence, if radiation was to be used, then coverage of both sides of the neck and the entire pharyngeal axis and larynx was recommended with few exceptions. Subsequent analyses validated the

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approach[6,7] with regard to a low incidence of mucosal and regional relapse, although a modest incidence of late swallowing toxicity and high rates of xerostomia were noted. In 1 of the largest series on CUP, Grau et al validated the findings that treatment to both sides of the neck and the entire pharyngolaryngeal mucosa resulted in lower rates of disease recurrence and suggested that patients who received this comprehensive approach had better survival expectations that those who received radiation to the involved neck only.[8] Although those authors recommended a prospective trial to address the appropriate volumes to irradiate in patients with CUP, and an international multiinstitutional cooperative trial was planned,[9] a trial was never conducted.

Frank et al[10] reported our initial experience using intensity-modulated radiation therapy (IMRT) to treat patients diagnosed with CUP. We began using this technology in the early 2000s to capitalize on the xerostomia reduction that IMRT can achieve while still delivering comprehensive radiation to both sides of the neck and the pharyngeal mucosa. At that time, we were not fully aware of the implications of disease associated with human papillomavirus (HPV), but we subsequently began to modify our treatment by omitting coverage of the larynx and hypopharynx in nonsmokers. In the 52 patients who received treatment through 2005, disease control rates were very high, and the toxicity profile was very encouraging.[10]

Subsequent to this initial experience, our radiation approach for patients with HNCUP has remained fairly comprehensive. However, because we increasingly encountered patients with limited smoking history and/or HPV-associated disease, as well as performing more comprehensive evaluations (including positron emission tomography scans, examinations under anesthesia, and adequate examinations of the thin mucosa in the larynx and hypopharynx, assuring that there was no primary tumor), we more frequently omitted the larynx and hypopharynx from our treatment fields. In addition, because many patients presented with a significant lymph node burden, with the accompanying increased risk of extracapsular extension (ECE), there was increased interest in the integration of systemic therapies into our approach.

To this end, we undertook the current retrospective study to update our experience of IMRT for patients with HNCUP. In particular, we wanted to: 1) identify patient and treatment parameters associated with oncologic outcomes of interest, 2) investigate the outcomes of radiation monotherapy versus combination approaches involving surgery and/or chemotherapy for HNCUP, 3) evaluate outcomes based on the degree of mucosal coverage, and 4) identify toxicity profiles for HNCUP in the modern treatment era.

MATERIALS AND METHODS

Patient Characteristics

This was a retrospective analysis of patients who had cervical lymph node SCC metastases from CUP and received IMRT in the Department of Radiation Oncology at The University of Texas MD Anderson Cancer Center from 2000 through 2015. The study was conducted under an institutional review board-approved protocol.

All patients had a pathologically confirmed diagnosis of metastatic cervical lymph node SCC without an identified mucosal primary tumor. Individuals with a known diagnosis of SCC of the skin either before or concurrent with the lymph node presentation, for which the lymph nodes were consistent with metastatic spread from skin cancer, were excluded. The medical records of patients were reviewed to assess patients' demographic, clinical, radiologic, and pathologic data. All patients were restaged retrospectively using criteria of the seventh edition of American Joint Committee on Cancer staging system.

Radiotherapy Treatment

IMRT was delivered using a linear accelerator producing 6-MV photons. The initial IMRT planning system (Corvus; North American Scientific, Inc, Cranberry Township, PA) was used from 2000 to 2003; in 2003, we transitioned to the Pinnacle planning system (Philips Medical Systems, Andover, MA).

Treatment was delivered with a static gantry approach. The IMRT fields generally consisted of 9 static gantry beams with the following angles: 0, 40, 80, 120, 160, 200, 240, 280, and 320 degrees for patients who received treatment to both sides of the neck and 7 beams equidistant through a 190-degree arc for those who received treatment to only 1 side of the neck. General treatment strategies included defining 3 clinical target volumes (CTVs). CTV1 included gross lymph node disease with a margin or, in postoperative situations, the preoperative tumor bed with margin. A virtual gross target volume (GTV) was created for patients who received chemotherapy before radiation, and margins similar to those used in patients who had true GTVs were added to create CTV1 in this setting. CTV2 was a neck volume at high risk of harboring microscopic disease but without clinical, radiographic, or pathologic evidence of lymph node disease; and CTV3 was the lymph node volume and

mucosa deemed at low risk of harboring subclinical disease. Lymph node levels 1 through 5 were treated in the lymph node-positive neck, and lymph node levels 2 through 4 were treated when the lymph node-negative neck was included. The retropharyngeal lymph nodes were treated. All CTVs were treated simultaneously, with fractional doses ranging from 1.7 to 2.2 Gray (Gy), depending on the number of fractions and the total dose prescribed to each respective CTV.

During this 15-year time frame, we used 2 separate IMRT techniques. The first, colloquially referred to as *split-field*, treated the mucosa and upper neck with IMRT, while the lower neck was treated with an appositional photon field. When using the split-field technique in patients for whom only the nasopharyngeal and oropharyngeal mucosa were treated, the inferior extent of the IMRT portals was 1 to 2 cm inferior to the hyoid. The lower neck field had a larynx block, which shielded the glottic and subglottic larynx as well as the adjacent hypopharynx. The epiglottis within the IMRT portals was not included in the CTV and was not delineated as an avoidance structure. For those patients who received split-field irradiation and who had the larynx and hypopharynx included, level 3 lymph nodes also were included in the IMRT field. The junction was at the inferior aspect of the cricoid cartilage, and the low neck field had a small central block at the superior border to avoid excess dose to the spinal cord at the junction.

In *whole-field* IMRT, if treatment was limited to the nasopharyngeal and oropharyngeal mucosa, the larynx and adjacent hypopharynx were delineated as an avoidance structure. The superior border for this avoidance was at the superior aspect of the thyroid cartilage.

TABLE 1. Patient and Disease Characteristics

Characteristic	No. of Patients (%)
Sex	
Men	221 (85)
Women	39 (15)
Age: Median [range], y	58 [19-84]
Smoking status	
Current	88 (34)
Former	91 (35)
Never	77 (30)
Unknown	4 (1)
Alcohol status	
Current	160 (61)
Former	30 (12)
Never	60 (24)
Unknown	10 (4)
Method of diagnosis	
Fine-needle aspiration	119 (46)
Excisional biopsy	119 (46)
Core biopsy	22 (8)
Tonsillectomy	
Yes	143 (55)
No	113 (43)
Unknown	4 (1)
Lymph node status	
Nx	1 (<1)
N1	25 (10)
N2a	40 (15)
N2b	141 (54)
N2c	31 (12)
N3	22 (8)
Size of largest lymph node: Mean [range], cm	3.2 [0.8-12]
No. of involved neck levels	
1	136 (52)
≥2	123 (47)
Unknown	1 (<1)
Solitary lymph node	
Yes	69 (27)
No	190 (73)
Unknown	1 (<1)

Abbreviation: y, years.

Statistical Analyses

Studied parameters included patient and tumor characteristics, management data, response to treatment, and patient survival. The chi-square test was used to determine the statistical significance of associations between clinicpathologic variables. Binary logistic regression was used to test the relation between continuous variables and binary responses. The Kaplan-Meier method was used to calculate the probabilities of local, regional, and distant disease control and disease-specific survival and overall survival (OS). Patients who had gross neck disease at the time of their radiation and either did not have a post-treatment radiographic re-evaluation or had a radiographic evaluation that revealed persistent disease were coded as neck recurrence for the purpose of statistical analysis. However, patients who underwent neck dissection within the first 6 months after radiation without evidence of new lymph node disease and with no subsequent recurrence were not considered to have regional recurrence in this analysis, even if the neck dissection specimen had evidence of microscopic disease.

Comparisons between survival curves were made using the log-rank test. Multivariable analysis was performed with the Cox proportional-hazards model. A forward selection technique was used in which variables that had P values $< .1$ were included in the model. For continuous variables that had a significant association with outcome endpoints, recursive partitioning analysis was done to identify optimal cutoff points. For comparison of model performance when adding lymph node status or the size of the largest lymph node to the base model without lymph node staging or size information, we used Bayesian information criterion (BIC). A lower BIC indicates improved model performance and parsimony using

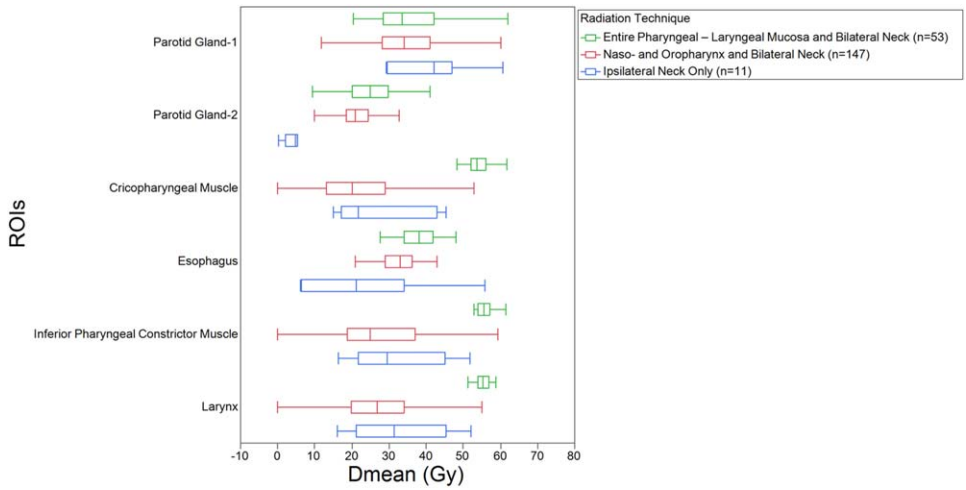

Figure 1. Box-and-whisker plots illustrate the mean dose (D_{mean}) in gray (Gy) for regions of interest (ROIs) grouped by the 3 radiation techniques. For each patient, parotid gland-1 is the parotid gland that received the higher dose, and parotid gland-2 is the gland that received the lower dose.

the BIC evidence grades presented by Raftery,[11] with the posterior probability of superiority of a lower BIC model based on the difference between the tested model and the base model. All analyses were performed using JMP Pro statistical software (version 11.2.0; SAS Institute Inc, Cary, NC). *P* values $< .05$ were considered significant.

Toxicity tabulation included feeding tube (gastrostomy) use and chronic radiation-associated dysphagia (RAD). RAD was defined as having either of the following more than 1 year after radiation: videofluoroscopy/endoscopy-detected aspiration or stricture and gastrostomy tube and/or aspiration pneumonia.[12] Grade 3 or greater osteoradionecrosis events were also recorded.

RESULTS

Patient Demographics and Lymph Node Characteristics

Two hundred sixty patients met the inclusion criteria, including 221 men and 39 women (6:1 ratio). The median age was 58 years (range, 19-84 years). Most patients had N2b disease (n = 141; 54%). The lymph node stage distribution is provided in Table 1. One hundred thirty-six patients had lymph node(s) confined to 1 cervical lymph node level (52%), and 123 (47%) had lymph nodes at multiple levels.

Diagnoses were made by fine-needle aspiration in 119 patients (46%), excisional biopsy in 119 (46%), and core biopsy in 22 (8%). All patients had at least 1 examination under anesthesia, 184 (71%) had a positron emission tomography scan as part of the radiologic workup, and 143 (55%) underwent tonsillectomy.

Forty-two patients (16%), including 20 diagnosed by fine-needle aspiration and 22 diagnosed by biopsy, underwent subsequent surgical neck dissections before radiation treatment (Table 1). Twenty-one of those 42 patients (50%) presented to our center after their neck dissection. Documentation of the number of pathologically involved lymph nodes identified at neck dissection was available for 39 patients. Nineteen patients had a solitary lymph node, 14 had 2 or 3 lymph nodes, and 5 had >3 lymph nodes (range, 4-14 lymph nodes). One patient underwent a negative neck dissection after diagnosis and induction chemotherapy. Forty-five of 144 patients who underwent either excisional biopsy or neck dissection had lymph node ECE.

Radiation Treatment

Seventy-nine patients (30%) who presented after either excisional biopsy or neck dissection had no gross disease at the time of radiation. The median prescribed dose of radiation to CTV1 in these patients was 60 Gy (range, 60-66 Gy). The median prescribed dose of radiation to CTV1 of the remaining 181 patients with gross disease was 66 Gy (range, 63-72 Gy). All but 2 patients completed treatment as prescribed. Radiation treatment was delivered to putative mucosal primary sites in 245 patients (94%). The entire pharyngolaryngeal mucosa was treated in 78 patients (30%), whereas the nasopharynx and oropharynx, excluding the hypopharynx and larynx, were treated in 167 patients (63%). The choice of the extent of mucosal treatment evolved over the years of the study. Fifty-four patients (44%) who received treatment before

TABLE 2. Treatment Characteristics

Characteristic	No. of Patients (%)
Pre-RT neck dissection	
Yes	42 (16)
No	218 (84)
Type of pre-RT neck dissection[a]	
Selective	18 (43)
Modified	17 (0)
Radical	6 (14)
Not specified	1 (2)
IMRT technique	
Split-field	180 (69)
Whole-field	80 (31)
Mucosal site targeted	
Entire pharyngolaryngeal mucosa	78 (30)
Nasopharynx, oropharynx	167 (64)
Mucosa not targeted	11 (4)
Not specified	4 (2)
Overall RT time [IQR], d	41 [39-43]
Induction chemotherapy	
Yes	63 (24)
No	197 (76)
Type of induction chemotherapy[a]	
Taxane + platinum-based	47 (75)
Platinum + cetuximab-based	15 (24)
Not specified	1 (<1)
Concurrent chemotherapy[a]	
Yes	65 (25)
No	195 (75)
Type of concurrent chemotherapy[a]	
Taxane + platinum-based	2 (3)
Cisplatin	29 (45)
Carboplatin	18 (28)
Cetuximab	12 (18)
Not specified	4 (6)

Abbreviations: d, days; IMRT, intensity-modulated radiation therapy; IQR, interquartile range; RT, radiation therapy; WF-IMRT, whole-field intensity-modulated radiation therapy.
[a] Percentages of patients who received the specified treatment are indicated.

2009 had radiation to the entire pharyngolaryngeal mucosa, compared with 24 patients (17%) who received treatment since 2009. Putative mucosal primary sites were treated to a median planned dose of 54 Gy (range, 50-66 Gy). Only 6 patients received ≥60 Gy, and 75% were planned to receive 54 Gy.

Eleven patients (4%), had treatment to the involved neck with no directed attempt at treating mucosal sites. The reasons for not treating the mucosa in these patients were lymph node location in 7 patients, large-volume N3 disease in 2 patients, and poor performance status in 2 patients. Among the 7 patients for whom lymph node location influenced the decision, 3 had substantial level 1 disease, and 4 had significant lymph node burden in level 4 and the supraclavicular fossa. Specifics of radiation sites treated were missing in 4 patients.

Although all patients received IMRT to the upper neck (and to mucosal sites in 245 patients), 176 (69%) received split-field IMRT, and 80 (31%) received whole-field IMRT. Among those who received IMRT to both sides of the neck and to the nasopharyngeal and oropharyngeal mucosa, 148 (89%) received split-field IMRT; and, among those who received treatment to the entire pharyngolaryngeal mucosa, 24 received split-field IMRT (31%).

Mean doses for several normal tissues are illustrated in Figure 1. Dose-volume histograms were only available for 211 patients. The main avoidance structures throughout the time frame of the study were the parotid glands. The superior and middle constrictor muscles received the dose prescribed to the mucosa.

Chemotherapy

Sixty-three patients (24%) received induction chemotherapy, including 47 who received taxane/platinum-based induction chemotherapy and 15 who received platinum and cetuximab. The specifics of induction chemotherapy were missing in 1 patient (Table 2). Sixty-two of these 63 patients (98%) had N2b or greater disease at presentation.

Sixty-five patients received concurrent chemotherapy (25%), of whom 63 (97%) received a single concurrent drug and 2 received a taxane-platinum doublet (Table 2). Forty-seven patients had N2 disease, and 14 had N3 disease. Sixteen of the 45 patients (36%) who had lymph node ECE received concurrent chemotherapy. Forty-four of the 181 patients who had gross lymph node disease (24%) received concurrent chemotherapy, including 8 of the 11 patients (67%) who received radiation only to the neck. Twenty patients who received concurrent therapy also received induction therapy. Among the 57 patients who received concurrent chemotherapy and mucosal irradiation, 12 had treatment that included the larynx and the hypopharynx.

Postradiation Neck Dissections

Forty-two patients (23% of the 181 with gross adenopathy who received radiation) underwent neck dissection after IMRT at 1 to 5 months postradiation. Three patients underwent a planned neck dissection (having received 63-66 Gy to CTV1), and the remaining 39 patients had post-treatment clinical and radiographic findings concerning for residual disease. Ten of 42 patients (24%) had pathologic evidence of residual carcinoma.

Outcomes

Two hundred five patients (79%) were alive at last contact. The median follow-up for surviving patients was 61

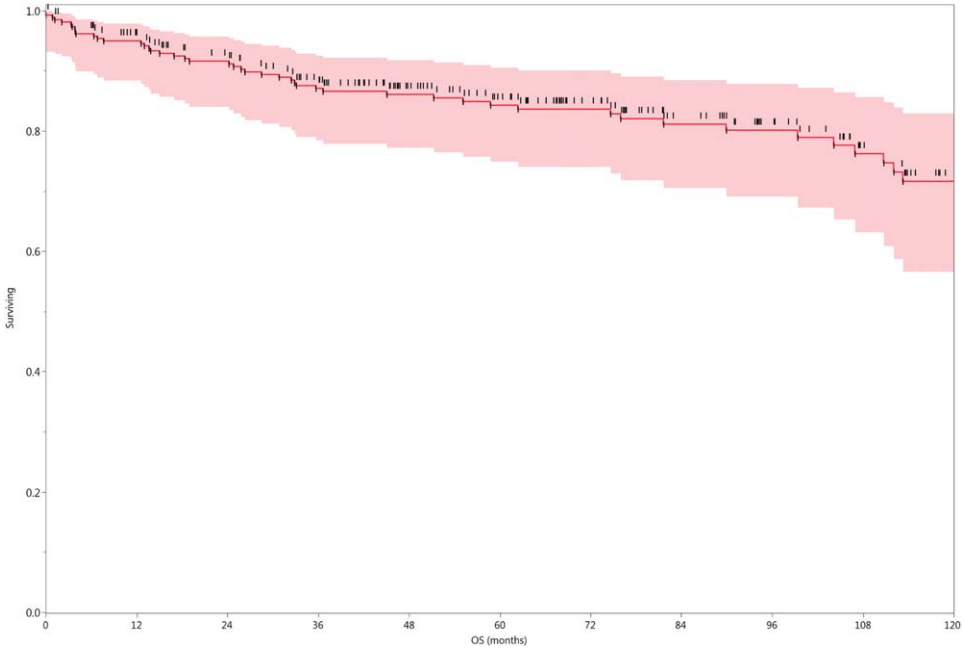

Figure 2. Actuarial overall survival (OS) is illustrated for the entire cohort (n = 260).

months (range, 0-176 months). Thirty-one living patients (14%) had a follow-up of less than 2 years.

Overall survival

Fifty-five patients (21%) were dead at the time of analysis, and 28 had evidence of disease at the time of death. Forty-five of the 55 patients who died presented with N2b disease or greater, including 10 of the 22 patients who presented with N3 disease. The 2-year, 5-year, and 10-year actuarial OS rates for the entire cohort of 260 patients were 92%, 84%, and 72%, respectively (Fig. 2). OS and recurrence-free survival rates subgrouped by radiation technique are illustrated in Figure 3.

In multivariate analysis, the OS rate was negatively associated with older age ($P < .0001$) and treatment to the neck only ($P = .02$). Because only 11 patients received treatment to the neck alone, the model was rerun without this variable. Only older age was significant in the new model.

There were no statistical differences in survival between patients who did and did not undergo neck dissection. Analyses included all patients who underwent neck dissection and separate analyses limited to those who underwent pre-IMRT and post-IMRT dissections. An analysis of patients who received radiation without evidence of gross lymph node disease (including patients who underwent pre-IMRT neck dissections or excisional biopsies), compared with those who had lymph node disease, revealed an improved survival rate for the former group, with comparative 5-year OS rates of 92% versus 82%, respectively ($P = .02$). However, this variable was not significant in the multivariate analysis ($P = .45$).

No differences in OS were observed with the receipt of either concurrent or induction chemotherapy. Because induction chemotherapy was received almost exclusively by patients who had higher lymph node burden, a subgroup analysis limited to patients with N2b disease or greater was performed and did not reveal any differences.

Neck control

Twenty-four patients (9%) had recurrent or persistent disease in the neck. The actuarial 2-year and 5-year neck control rates were 92%, and 91%, respectively. Twenty-one patients developed neck recurrences in CTV1, 2 developed neck recurrences in CTV2, and 1 developed a neck recurrence in the unirradiated contralateral neck.

In univariate analysis, the neck control rate was negatively associated with older age ($P < .01$), women ($P < .01$), and larger lymph node burden. The latter was analyzed by several variables, including: lymph node category (Nx and N1-N2a vs N2b-N3; $P = .015$), size of the largest lymph node as a continuous variable ($P = .0015$), size of the largest lymph node as either $\geq$5.2 or <5.2 cm ($P = .001$), or lymph node multiplicity (solitary vs multiple lymph nodes; $P = .05$). The 5-year and 10-year lymph node control rate by lymph node status and size of the largest lymph node affected are illustrated in Figure 4. Twenty-two of the 24

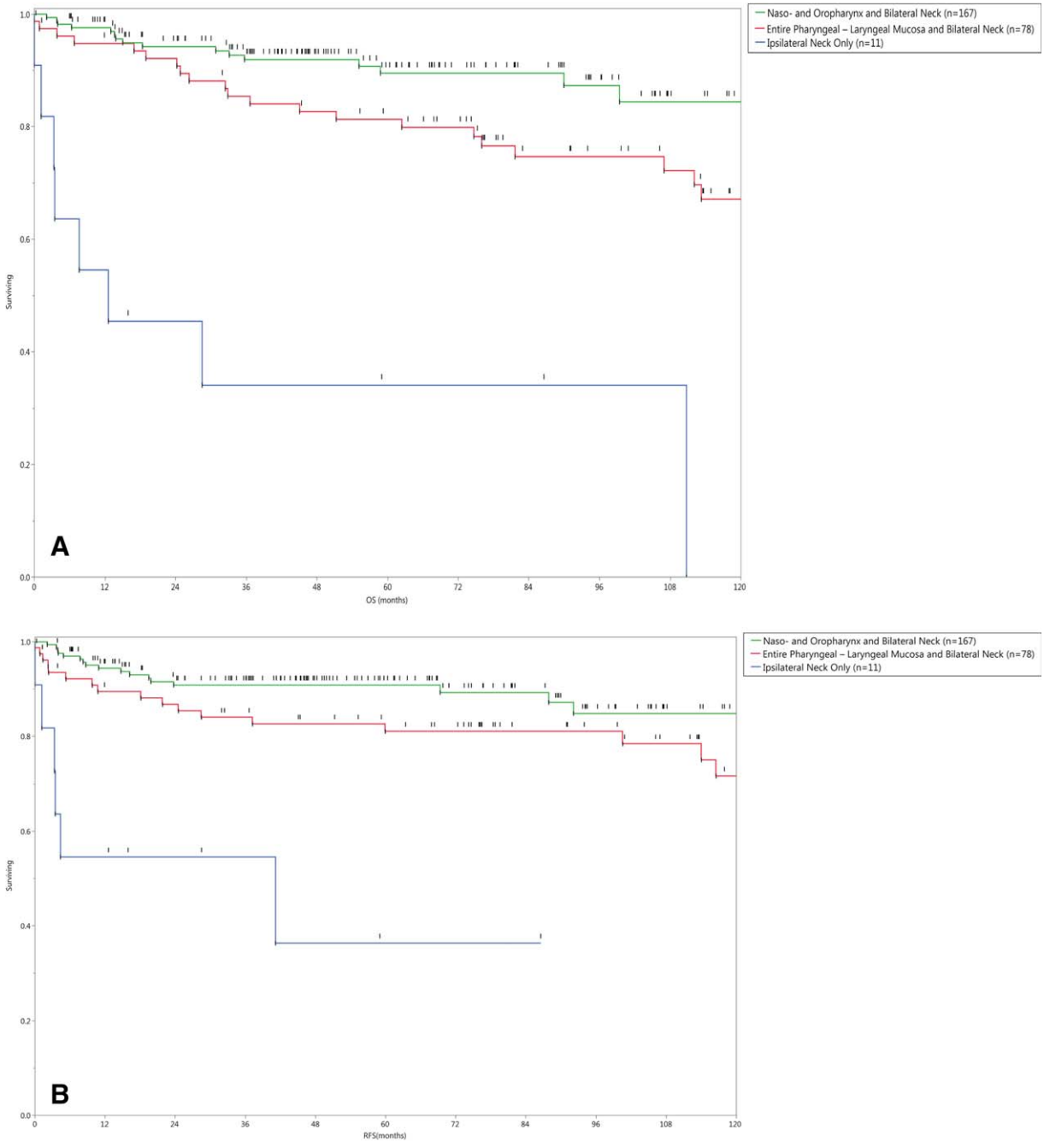

Figure 3. (A) Overall survival and (B) recurrence-free survival are illustrated according to radiation technique.

patients (92%) who developed neck recurrences originally presented with N2b disease or greater. All variables that were statistically significant in univariate analysis maintained statistical significance ($P < .05$) in multivariate analysis. There was no statistical association between the number of involved lymph node levels (1 level vs multiple levels) nor between the location of the involved lowest lymph node level and regional failure.

Distant metastases

The 2-year, 5-year, and 10-year actuarial distant metastases-free survival (DMFS) rates were 95%, 94%, and 90%, respectively. Sixteen patients (6%) developed distant metastases. The most common site of metastases was the lung (9 of 16 patients; 56%). Eleven of 16 patients (69%) had isolated distant disease without evidence of disease above the clavicles. Original lymph

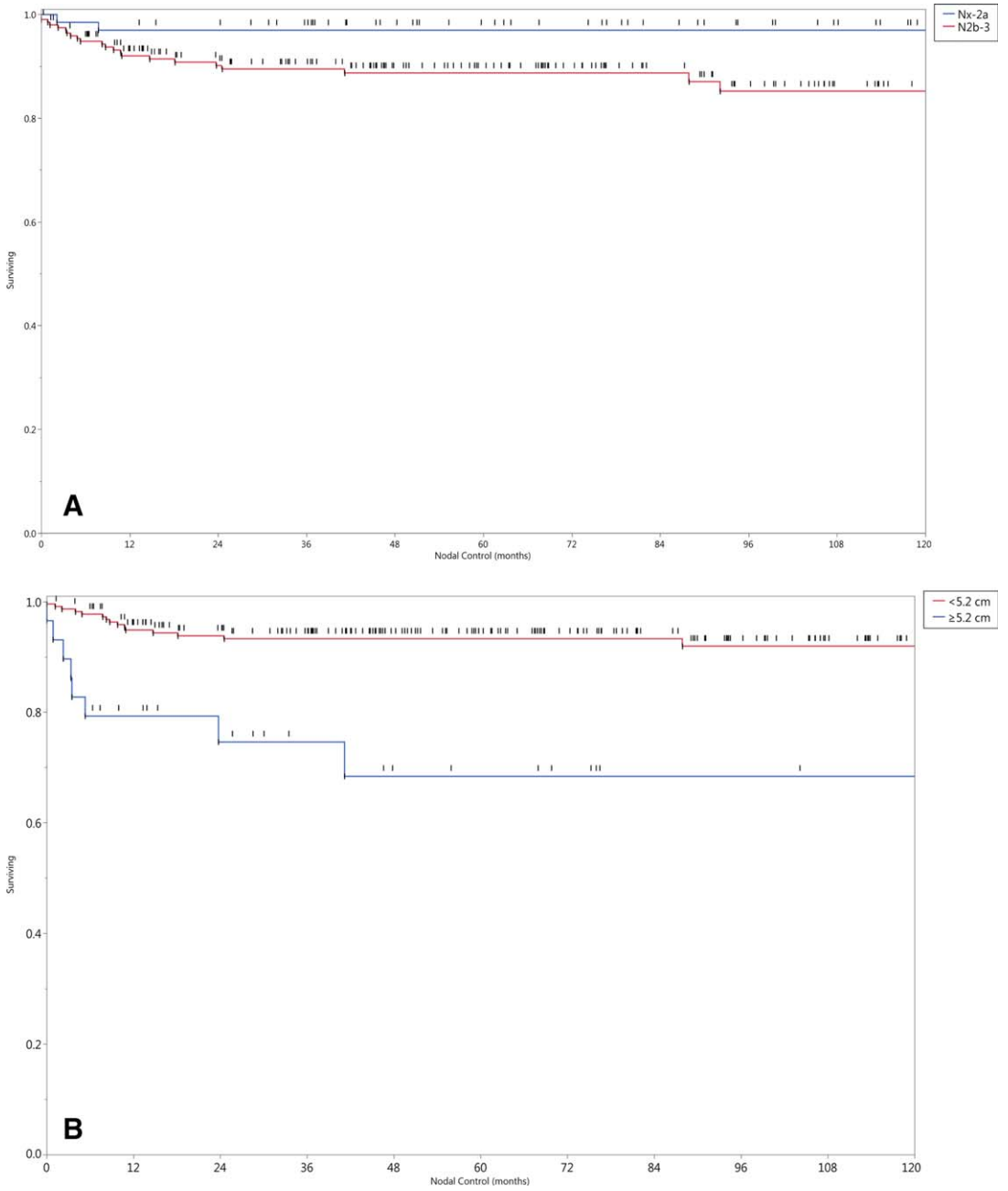

Figure 4. Lymph node control is grouped according to (A) lymph node category and (B) the size of the largest lymph node (in centimeters).

node staging in these 16 patients was N2b in 13 patients and N3 in 3 patients. Four patients had disease in level IV/V lymph nodes. Univariate analysis revealed that older age, female sex, and increased lymph node burden were significantly associated with a higher rate of distant failure. In multivariate analysis, the higher distant failure rate was associated with being female ($P < .01$).

Primary tumor development

Fourteen patients (5%) manifested a primary tumor. Ten tumors developed in an HN mucosal site, including 5 in the oropharynx, 3 in the larynx, 1 in the nasopharynx, and 1 in the oral cavity. Eight of these 10 patients, including 6 who received treatment to the entire pharyngolaryngeal mucosa, developed mucosal primary tumors within targeted, radiated mucosal sites. Of the 3 patients who

developed laryngeal cancer, only 1 had his larynx included in the mucosal coverage. Only 3 of the 178 patients (1%) who received treatment to both sides of the neck and to the naso-oropharyngeal mucosa developed a primary tumor. There were 4 nonmucosal primary tumors; 1 arose in the skin of the chest wall, 1 was diagnosed as a primary squamous cell of the ipsilateral parotid, and 2 were lung SCCs. It is feasible that the latter 3 were metastases rather than primary lesions. Seven of these 14 primary tumors occurred within the first 2 years of follow-up, and 5 developed more than 5 years after treatment.

HPV/P16 subgroup analysis

HPV/P16 status was known for 113 patients. HPV association was considered positive if testing for either HPV or p16 was positive. Ninety patients had HPV-associated disease, and 23 did not. Five HPV-negative patients had N3 disease. Only 12% and 17% of patients who had HPV-positive and HPV-negative disease, respectively, received treatment to the entire pharyngolaryngeal mucosa, and 87% of HPV-positive patients received treatment to the nasopharynx and oropharynx. Patient and treatment characteristics for patients with known HPV/P16 status are summarized in Table 3.

HPV-positive patients had improved rates of OS ($P = .002$), neck control ($P = .035$), and DMFS ($P = .047$). The 5-year actuarial rates of OS, neck control, and DMFS were 91%, 94%, and 95%, respectively, for HPV-positive patients and 70%, 73%, and 77%, respectively, for HPV-negative patients (Fig. 5).

Toxicities

One hundred eight patients (42%) had a percutaneous gastrostomy tube placed either before or during radiation treatment. Ninety-five of those patients (88%) had their tubes removed by 6 months after they completed radiation. There were no significant differences in the incidence of gastrostomy placement in patients who received treatment to the entire pharyngolaryngeal mucosa compared with those who received only partial pharyngeal treatment ($P = .8$), nor were there differences in gastrostomy rates between patients who did or did not receive concurrent systemic therapy ($P = .3$).

Eighteen patients (7%) had chronic RAD[12] at last follow-up, including 10 patients who still had gastrostomy tubes. Of the 18 patients with chronic RAD, 8 (5%) received treatment to the oropharynx and nasopharynx, and 10 (13%) received treatment to the entire pharyngolaryngeal mucosa ($P = .2$). There was no difference in the incidence of chronic RAD in patients who did or did not receive concurrent chemotherapy. Five patients (2%) developed osteoradionecrosis of the mandible requiring surgical intervention.

DISCUSSION

Our objective was to update a preliminary analysis of 52 patients who were diagnosed with HNCUP and received treatment with comprehensive IMRT. The current study, consisting of 260 patients who had a median follow-up >5 years, confirmed that excellent disease-related outcomes were achieved, with 5-year lymph node control, DMFS, and OS rates of 91%, 94%, and 84%, respectively, even though >57% of the cohort had advanced-stage lymph node disease at presentation. In addition, with an approach of using comprehensive radiation that included the treatment of putative mucosal sites, only 4% subsequently developed an HN mucosal tumor. This low rate of primary tumor development was achieved even after omitting the larynx and hypopharynx in the majority of patients.

The excellent oncologic outcomes in our patients with HNCUP who received IMRT are consistent with those reported in many other small series.[1,13-16] Patients in those series also typically received treatment to mucosal sites. The large number of patients in our cohort, along with the relatively long follow-up, should add to the confidence that excellent disease control can be achieved with comprehensive radiation for patients with HNCUP. Furthermore, the survival rates reported in this study are similar to those in our patients with known disease sites. Over the past decade in particular, most of our patients with oropharyngeal cancer have had HPV-associated disease. Similarly, in patients for whom we had material for testing p16 and/or HPV, 80% were positive. The 5-year OS for this subgroup was 90%, which is similar to the 84% observed in our patients with oropharyngeal cancer.[17]

To better explain our outcomes, we performed multivariate analysis. Older age was associated with worse OS, and increased lymph node burden was associated with an increased rate of disease recurrence. In subgroup testing, also consistent with known findings, patients with HPV-associated disease fared better. One surprising finding was the poorer outcome of female patients. Other than the vagaries of statistical analysis, we cannot offer an explanation for this finding.

One aim of the study was to assess the impact of other therapies (surgery and chemotherapy) added to radiation. With regard to disease outcome, the use of pretreatment neck dissection did not correlate with disease recurrence. The role of neck dissection is controversial,

TABLE 3. Patient, Disease and Treatment Characteristics in Patients With Known Human Papillomavirus/P16 Status

Characteristic	No. of Patients (%)	
	HPV/P16-Positive, n = 90	HPV/P16-Negative, n = 23
Sex		
Men	79 (88)	15 (65)
Women	11 (12)	8 (35)
Age: Median [range], y	57 [38-83]	60 [26-84]
Smoking status		
Current	16 (18)	8 (36)
Former	41 (48)	9 (41)
Never	29 (34)	5 (23)
HPV status, ISH		
Positive	82 (91)	0 (0)
Negative	8 (9)	22 (95)
P16, IHC		
Positive	84 (93)	0 (0)
Negative	2 (2)	23 (100)
Lymph node status		
N1	7 (8)	1 (4)
N2a	11 (12)	1 (4)
N2b	60 (66)	11 (48)
N2c	5 (6)	5 (22)
N3	7 (8)	5 (22)
Mucosal site targeted		
Entire pharyngolaryngeal mucosa	11 (12)	4 (17)
Nasopharynx, oropharynx	78 (87)	17 (74)
Mucosa not targeted	1 (1)	2 (9)
Induction chemotherapy		
Yes	28 (31)	7 (31)
No	62 (69)	16 (69)
Concurrent chemotherapy		
Yes	26 (29)	10 (43)
No	64 (71)	13 (57)
Treatment outcomes		
Distant failures	4 (4)	4 (17)
Neck failures	5 (5)	6 (26)
Primary developed in HN mucosa	3 (3)	1 (4)

Abbreviations: HN, head and neck; HPV, human papillomavirus; IHC, immunohistochemistry; ISH, in situ hybridization; P16, tumor-suppressor protein.

and the existing literature does not give clear guidance that a neck dissection improves outcome.[1] Similar to our report, all series are retrospective and thus subject to selection bias. Furthermore, older series in particular do not account for the changing epidemiology and impact of an increase in patients with HNCUP having HPV-associated disease. Examples from the literature highlighting the controversy include reports by Wallace et al[18] and Aslani et al.[19] The former investigators demonstrated a significant improvement in neck control among patients who underwent preradiotherapy neck dissection compared with those who underwent either postradiotherapy neck dissection or no neck surgery. The latter investigators did not detect a benefit to disease control in their patients who underwent surgery. However, similar to our findings, regardless of treatment approach, lymph node burden seemed to be the better predictor of outcome. Shoustari et al[14] reported a series of patients who underwent preradiotherapy neck dissection. Disease control at 5 years for patients who had nonbulky disease was 100% compared with 67% for those who had large-volume disease.

Also, we were unable to demonstrate a benefit from either neoadjuvant or concurrent systemic therapy. Even when we restricted the analysis of induction therapy to those who we thought would be at higher risk of recurrence (N2b or higher), differences in outcomes were not observed. The lack of benefit from induction chemotherapy is consistent with recent reports in patients who had HN cancer with known primaries,[20,21] whereas the lack of benefit from concurrent therapy appears to be contrary to a benefit observed in prospective, randomized studies in those who had HN cancer with known primaries.[22] However, this body of evidence, believed to reflect a benefit for all patients with stage III through IVb HN cancer, is based largely on patients with advanced T-classification. The vast majority of studies investigating the role of concurrent chemotherapy for patients with advanced HN cancer principally accrued patients who had T3 and T4 disease, often excluding those who had small primary tumors, and not recruiting patients with T0 disease (CUP). Therefore, the lack of a benefit in our trial may be due to the modest size and retrospective nature of the cohort, or it could be a function of the statistics, wherein not disproving the null hypothesis does not mean it is true. However, it also may suggest that patients who have small or nondetectable primary tumors, particularly with HPV-associated disease, may not gain much benefit in disease control by the addition of chemotherapy to radiation. This concept has been recently tested by NRG Oncology (NRG HN-002), and the results of this trial are eagerly awaited.

Although there was no obvious benefit from the addition of systemic therapy, there was also no apparent excess toxicity, neither acute nor late. This is contrary to a report by Sher et al.[23] Nearly all patients in their study received mucosal radiation and concurrent chemotherapy. However, one-half of those patients received a platinum-taxane doublet. Anticipating toxicity, all patients who received this treatment approach had prophylactic gastrostomy tubes, and 46% had late grade 3 esophageal toxicity. Whether this high rate of toxicity is related to the addition of chemotherapy, or the radiation techniques (including dose and volume), or both is speculative. However, we believe our lower rates of toxicity may be explained by mostly using only a single agent of systemic

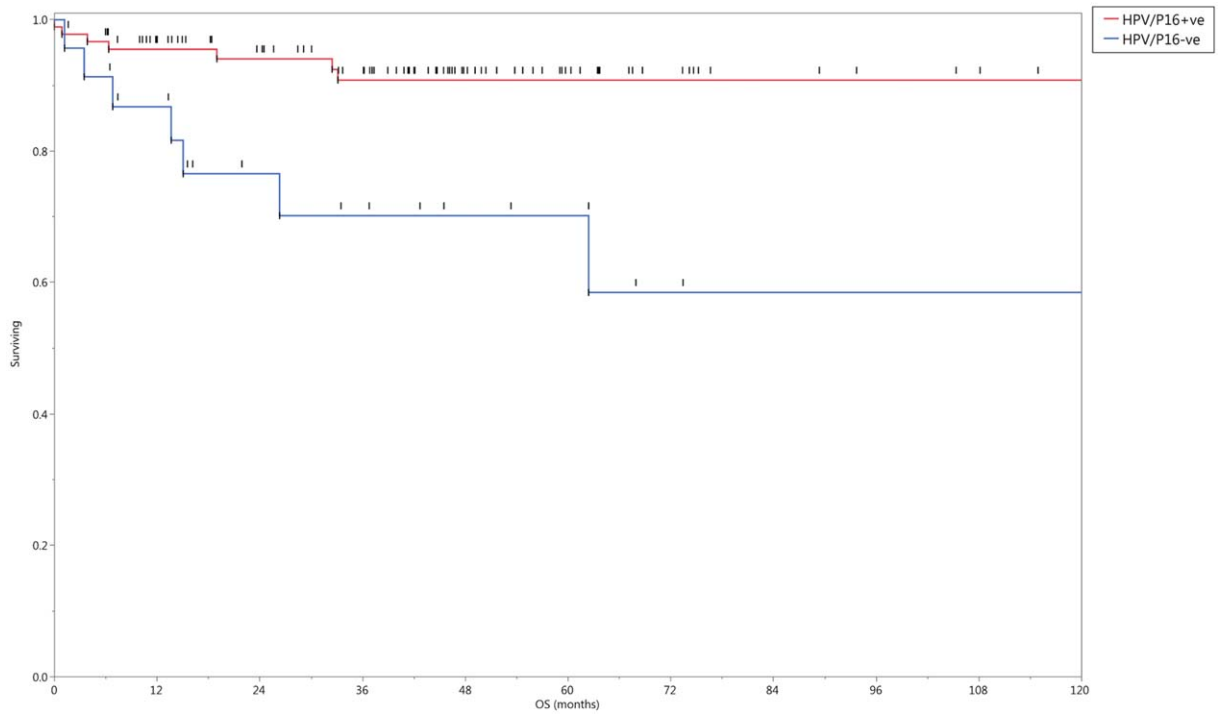

Figure 5. Overall survival (OS) is illustrated according to tumor human papillomavirus/tumor-suppressor protein (HPV/p16) status (+ve indicates positive; −ve, negative).

therapy, only dosing the pharynx to 54 Gy, limiting the volume to include only the oropharynx and nasopharynx, minimizing the dose to the esophagus to $\leq$40 Gy, and proactive models of supportive care with avoidance of prophylactic gastrostomy.

Excluding the hypopharynx and larynx was a major change in our radiation approach. This change was based on the observation that more patients had limited smoking histories; and, ultimately, many of our patients had HPV-associated disease. The development of mucosal primary tumors remained uncommon with this change. The incidence of chronic RAD in patients who received treatment to the oropharyngeal and nasopharyngeal mucosa was 5%. However, we were unable to demonstrate that more aggressive therapy with larger fields led to increased toxicity.

Others have described limiting the irradiated mucosal volume. Wallace et al described omitting the hypopharynx and larynx,[18] and none of their 28 patients developed a mucosal primary. Mourad et al reported an initial experience of 68 patients in whom they targeted only the oropharynx, bilateral retropharyngeal lymph nodes, and bilateral cervical lymph nodes.[24] Only 1 patient in that study later developed a mucosal primary. Because we also treat retropharyngeal lymph nodes and have observed evidence of HPV-associated nasopharyngeal cancer,[25] we still include the nasopharyngeal mucosa. We limit the elective radiation dose to 54 Gy (at 1.8 Gy per fraction) and believe that this combination of only modest dose and more limited target volume results in limited late toxicity.

The major limitation of this work is its retrospective nature. However, for this uncommon presentation of HN cancer, stronger evidence-based trials are nonexistent. An international cooperative trial investigating the volume to irradiate[9] was terminated because of extremely poor accrual. Our large series is consistent with disease-related outcomes reported in smaller trials with shorter follow-up. However, the retrospective nature of this study can lead to underreporting of events, particularly toxicity events (especially grade 1 xerostomia and dysphagia).

Ultimately, the optimal management of patients with CUP is similar to that of patients who present with HN SCC and known mucosal sites. With regard to managing HN cancers, there are 2 basic questions. The first question is how to best control the disease we know, which, in patients with CUP, is solely the gross lymph node disease. Our data suggest that radiation is an effective therapy, and gains in controlling this disease by the routine use of neck dissection and/or systemic therapy are

likely small, but similarly toxicity profiles are not greatly altered by additional therapies. We still consider a preoperative neck dissection for patients who have low lymph node burden (ie, a solitary lymph node without radiographic ECE), because, if pathology confirms the clinical impression, then neck dissection alone should suffice. Similar to controversies in oropharyngeal cancer, the need for the addition of concurrent chemotherapy in all patients remains unclear. We are more selective in patients who have undergone surgery, adding concurrent therapy only for patients who have extensive ECE. In patients who present with gross disease, the lymph node burden is influential in decision making, because it is likely that we will still add a systemic agent to the treatment for patients who have N3 disease, those who have multilevel bulky disease, and those who have radiographic evidence of extensive ECE.

The second question is: How necessary is it to treat disease that is not clearly evident, and even may not exist? This question mainly relates to the volume to irradiate. Our approach has been relatively aggressive, treating mucosal sites and uninvolved regions of the neck. This approach was successful, with few patients developing disease outside of the radiation-targeted tissues. Late toxicity was not excessive; however, even in the best case, there was still an approximate 5% rate of severe late effects, and over 40% of patients required gastrostomy tube use for up to 6 months. The alternative is to limit the treatment to the involved neck only. Studies have suggested that, with regard to survival, neck-only therapy is as effective as more comprehensive radiation.[3,4,9] However, balancing an increased risk of disease recurrence versus a lower toxicity profile remains a complex question in this era, when much of the research is in discovering less toxic and ideally noninferior therapies.

In conclusion we report on 260 patients who received IMRT for CUP, including 245 who received radiation to both sides of the neck and to putative mucosal sites (which was limited to the oropharynx and nasopharynx in 167 patients). Excellent rates of disease control were observed, and the 5-year OS rate was 84% for all patients and 92% for those who had known HPV-associated disease.

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AUTHOR CONTRIBUTIONS

Mona Kamal: Conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing–original draft; writing–review and editing, visualization, and supervision. **Abdallah S. R. Mohamed:** Conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing–review and editing, visualization, and supervision. **Clifton David Fuller** and **Faye M. Johnson:** Conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing–review and editing, visualization, and supervision. **Erich M. Sturgis**, **William H. Morrison**, **G. Brandon Gunn**, **Katherine A. Hutcheson**, **Jack Phan**, **Stefania Volpe**, **Sweet Ping Ng**, **Renata Ferrarotto**, **Steven J. Frank**, **Heath D. Skinner**, and **David I. Rosenthal:** Conceptualization, methodology, validation, investigation, resources, data curation, writing–review and editing, visualization, and supervision. **Adam S. Garden:** Conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing–original draft; writing–review and editing, visualization, supervision, and project administration.

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