Head and neck squamous cell carcinoma of unknown primary: Neck dissection and radiotherapy or definitive radiotherapy

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ABSTRACT: *Background.* Management of head and neck carcinoma from unknown primary (HNCUP) remains controversial, with neck dissection and radiotherapy (RT) or definitive RT both commonly used. The purpose of this study was to characterize HNCUP and retrospectively compare outcomes for patients treated with neck dissection + RT versus definitive RT.

Methods. From 1994 to 2009, 41 patients with HNCUP underwent either neck dissection + RT ($n = 22$) or definitive RT ± concurrent chemotherapy ($n = 19$) at our institution. Treatment outcomes were compared using Kaplan–Meier methods and log-rank test.

Results. There were no differences between patients treated with neck dissection + RT and definitive RT in overall survival (OS), progression-free survival (PFS), locoregional relapse-free survival (LRFS), freedom from locoregional failure (FFLRG), or freedom from distant failure (FFDF). Among 17 patients who underwent neck dissection + RT for whom human papillomavirus (HPV) status could be determined, HPV(+) patients trended toward improved OS ($p = .06$) and PFS ($p = .15$).

Conclusion. Neck dissection and postoperative RT resulted in similar outcomes as definitive RT. The prognostic implications of HPV(+) nodes in HNCUP are similar to those in oropharyngeal primary cancers. © 2013 Wiley Periodicals, Inc. *Head Neck* **36:** 1589–1595, 2014

KEY WORDS: unknown primary, neck dissection, radiation therapy, human papillomavirus

INTRODUCTION

The management of head and neck carcinoma from unknown primary (HNCUP) remains a therapeutic dilemma. Treatment options consist of surgery alone, radiotherapy (RT) alone, or combined-modality treatment.[1,2] The primary objectives are to treat mucosal surfaces at highest risk of harboring the primary tumor, eliminate the risk of nodal recurrence, and control potential metastatic disease, with most published series advocating neck dissection followed with RT or, in recent years, chemoradiotherapy.[3–5]

Although single modality therapy with either neck dissection or RT alone provide similar locoregional control in patients with HNCUP with N1 and selected N2a nodal classification without extracapsular extension (ECE), more advanced stage disease managed with up-front neck dissection requires additional adjuvant RT or chemoradiotherapy.[1,6,7] The use of multiple treatment modalities, however, may increase the toxicity and morbidity of therapy compared to single modality therapy.[8,9] Few retrospective studies have been published investigating the use of definitive RT, either with or without concomitant chemotherapy, in the treatment of advanced neck stage HNCUP.[3,10] We examined our institutional experience to assess whether neck dissection has an additional benefit to RT in these patients, and assessed human papillomavirus (HPV) in available nodal tissue to assess whether the presence of HPV infection in HNCUP is associated with favorable outcomes analogous to those observed in HPV-associated oropharyngeal cancer.[11]

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MATERIALS AND METHODS

The medical records of all patients with head and neck cancer treated in the departments of otolaryngology–head and neck surgery and radiation oncology at the University of Michigan between January 1994 and January 2009 were queried under an Institutional Review Board approved protocol. Patients with biopsy-confirmed squamous cell carcinoma (SCC) limited to the cervical lymph nodes without an identifiable primary tumor who received RT at the University of Michigan were eligible for the present analysis. Clinical neck classification was assigned

retrospectively according to the American Joint Committee on Cancer Staging Manual 7th edition.

Diagnostic workup

SCC in the cervical lymph nodes was biopsy proven in all patients by either fine-needle aspiration or excisional biopsy. Pretreatment initial diagnostic workup included physical examination, chest X-ray, direct endoscopic examination under anesthesia, panendoscopy with random biopsies, and CT and/or MRI of the head and neck. In recent years, positron emission tomography (PET)/CT and tonsillectomy were routinely performed in an effort to identify the primary tumor.

Treatment

After diagnosis and staging, patients were treated with either a combination of neck dissection and adjuvant RT or definitive RT. The choice of treatment modality was according to physician preference, as no uniform policy existed. All patients in the neck dissection + RT group underwent either radical or modified radical neck dissection.

All patients received RT using either 3-dimensional conformal radiation therapy or intensity-modulated radiation therapy (IMRT); IMRT was routinely used after 2002. Irrespective of RT technique, targets and organs at risk were outlined on the treatment planning CT. For definitive RT, the gross target volume was defined as all known neck disease based on clinical examination and imaging. Clinical target volume-1 (CTV-1) was defined as gross target volume with typical margins of 0.5 to 1 cm. CTV-2 included potential primary mucosal sites, typically the bilateral base of the tongue and ipsilateral tonsillar fossa, larynx, hypopharynx, and nasopharynx, with the oral cavity and the contralateral larynx typically excluded. Primary mucosal site targets, however, were individualized according to risk factor profile; in patients without a history of smoking, for example, the hypopharynx and larynx were omitted from the targets. CTV-2 also included lymph node levels at risk of microscopic disease, typically levels I to V in the ipsilateral neck and II to IV in the contralateral neck, with ipsilateral level IB included if level II neck node involvement was >N1. The planning target volume, aimed to accommodate setup uncertainties, was typically obtained by adding a 5-mm volumetric expansion to the CTVs. This expansion was reduced in recent years to 3 mm, as daily imaging was introduced to assess and correct setup errors. Prescription doses were typically 70 Gy to CTV-1 and 56 to 59 Gy to CTV-2, all delivered simultaneously over 35 fractions in the IMRT cases, whereas in the 3D cases, all targets received 50 Gy at 2 Gy/fractions and CTV-1 was subsequently boosted with an additional 20 Gy to a total of 70 Gy.

For adjuvant cases, CTV-1 encompassed the neck levels, which contained grossly and pathologically involved lymph nodes and adjacent levels considered to be at highest risk for microscopic disease. Potential primary mucosal sites and lymph nodes levels at lower risk were included in CTV-2. Prescription doses were typically 60 Gy to CTV-1 and 54 Gy to CTV-2, all given in 30 fractions over 6 weeks. Sites of ECE received 66 Gy, either by an electron beam boost of 3 additional fractions or, in more recent years, as boost integrated into the IMRT plan. Organs at risk included the brainstem, spinal cord, bilateral parotid and submandibular salivary glands (in which level IB was not a target), contralateral glottic larynx (in cases in which the ipsilateral larynx or hypopharynx were targets), oral cavity, and lips. Spinal cord contours were expanded by 3 mm to create a planning organ at risk volume.

Chemotherapy was administered concurrent with RT in patients with ECE at neck dissection or for advanced nodal disease in patients receiving definitive RT.

In situ hybridization and immunohistochemical staining

Immunohistochemical (IHC) stains and in situ hybridization (ISH) studies were performed on 4-μm sections from paraffin-embedded tissue blocks containing a representative sample of untreated tumor for patients with tissue blocks available in the Department of Pathology at our institution. No ISH or IHC analysis was performed in the definitive RT group, as tissue blocks for the majority of these patients were not accessible from the outside institution where the original diagnostic procedure had been performed.

IHC staining for p16INK4a was performed per protocol supplied by the manufacturer's kit (CINtec Histology Kit; MTM Laboratories, Heidelberg, Germany) and visualized using the ultraView polymer detection system (Ventana Medical Systems, Tucson, AZ) on a Ventana Benchmark Ultra Autostainer. Tumors with >75% staining in both the nucleus and cytoplasm were considered positive. ISH for high-risk HPV was performed using the INFORM HPV ISH assay (Ventana Medical Systems), which consists of a cocktail directed against a subset of high-risk HPV genotypes (HPV 16, 18, 33, 35, 39, 45, 51, 52, 56, and 66). ISH for Epstein–Barr virus (EBV)-encoded RNA (Ventana Medical Systems) was performed in accord with the manufacturer's protocol. Positive reactions for both ISH assays were detected using the ISH I View Blue Plus Detection Kit (Ventana Medical Systems) in accord with the manufacturer's instructions. For HPV scoring, tumors were classified as positive if any dot-like nuclear signal was present in tumor cell nuclei and negative when no nuclear signal was present. For EBV-encoded RNA scoring, tumors were considered positive when tumor cell nuclei demonstrated diffuse staining.

Statistical analysis

Baseline characteristics between groups were compared using the independent samples *t* test for continuous variables, the Mann–Whitney test for ordinal variables, and either the Fisher's exact test or chi-square test for categorical variables. Clinical endpoints for this study were overall survival (OS), progression-free survival (PFS), locoregional relapse-free survival (LRFS), freedom-from-locoregional failure (FFLRF), and freedom-from-distant failure (FFDF), and were all calculated from the start date of RT using Kaplan–Meier methods. The log-rank test was used to evaluate statistical differences in survival outcomes between groups. A significance level of 0.05 was

TABLE 1. Patient characteristics.

	Neck dissection + RT	Definitive RT
Age, y, median (range)	53 (37–72)	53 (38–76)
Year of diagnosis, median (range)	2003 (1994–2008)	2006 (1994–2008)
Follow-up, mo, median (range)	73 (18–126)	39 (11–98)
	No. of patients (%)	No. of patients (%)
Sex		
Male	20 (90)	17 (90)
Female	2 (10)	2 (10)
Smoking history, >10 pack-years		
Past	5 (23)	5 (26)
Current	8 (36)	5 (26)
Smoking + alcohol	6 (27)	5 (26)
Tonsillectomy		
Childhood	4 (18)	4 (21)
Current	4 (18)	7 (77)

Abbreviation: RT, radiation therapy.

used for all comparisons. All analyses were performed using MedCalc (v12.4.0.0, MedCalc Software, Mariakerke, Belgium).

RESULTS

Forty-one patients diagnosed with HNCUP and treated with either neck dissection + RT or definitive RT were identified and included in the present analysis. Twenty-two patients were treated with neck dissection + RT, and 19 were treated with definitive RT. Two patients underwent definitive RT followed by planned neck dissection within 3 months and are included in the neck dissection + RT group. Of a total of 41 patients, 37 were men (90%). Median age at diagnosis was 53 years (range, 38–72 years) for both groups. Patient characteristics are listed in Table 1.

In the neck dissection + RT group, the initial diagnosis of SCC was made by excisional biopsy in 4 patients (18%) and fine-needle aspiration in 18 patients (82%) (Table 2). In the RT group, 12 of 19 patients (63%) underwent excisional biopsy for diagnosis before RT; of these, ECE was present in 5, absent in 4, and not specified in 3. Either ECE or gross residual tumor after excisional biopsy was present in 8 of these 12 patients (67%).

In both the neck dissection + RT and definitive RT groups, the most common site of nodal involvement at the time of presentation was level II (90%), followed by level III (41%). Approximately 50% of patients with level II and 20% with level III nodes presented with isolated involvement at these levels; the remainder of patients had involvement of additional levels. No patient presented with isolated involvement at other neck levels. In the neck dissection + RT group, 12 patients had pathological evidence of ECE, whereas 5 patients had no ECE; no information regarding ECE was available for the remaining 5 patients. The distribution of nodal involvement at presentation by clinical nodal classification and nodal characteristics was similar between groups and is detailed in Tables 3 and 4. Although there was a higher prevalence of N3 disease in the neck dissection + RT group (27%) than the definitive RT group (16%), this difference was not statistically significant ($p = .62$).

Twenty-eight patients (68.3%) received IMRT, 13 in the neck dissection + RT group and 15 in the definitive RT group ($p = .31$). Eleven patients (50%) in the neck dissection + RT group, and 14 patients (74%) in the definitive RT group received concurrent chemotherapy ($p = .20$), consisting of cisplatin in 12 patients, carboplatin in 5 patients, 5-fluorouracil-carboplatin in 1 patient, and carboplatin-paclitaxel in 7 patients.

Four patients (18%) required feeding tubes during the treatment in the neck dissection + RT group compared with 1 patient (5%) in the RT group ($p = .43$). No patient required a long-term (>6 months) feeding tube.

Follow-up for living patients was shorter in the definitive RT group (median, 39 months; range, 11–98 months) than the neck dissection + RT group (median, 73 months; range, 18–126 months; $p = .01$) because of the more prevalent use of neck dissection + RT in the earlier period of this study (median year of diagnosis for definitive RT group vs neck dissection + RT groups: 2006 vs 2003, respectively). Overall, 4 patients died of disease: 3 in the neck dissection + RT group, and 1 in the definitive RT group. OS at 2 and 4 years for the neck dissection + RT group was 90.7% and 85.3%, compared to 93.3% and 85.6% in the definitive RT group, respectively ($p = .64$).

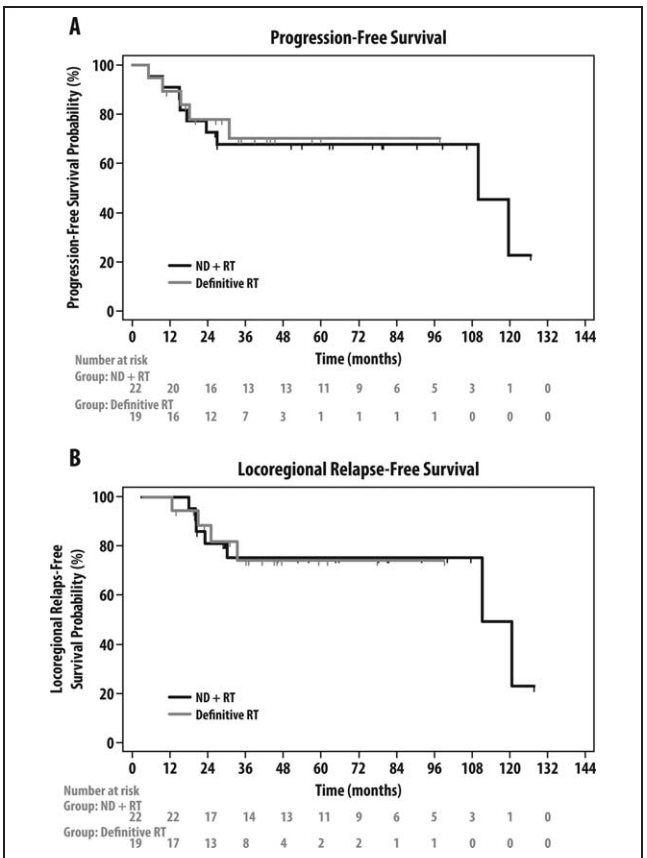

FIGURE 1. Progression-free survival (A) and locoregional relapse-free survival (B) after neck dissection (ND) and radiation therapy (RT) or definitive RT in head and neck squamous cell carcinoma of unknown primary.

PFS and LRFS (Figure 1) were similar in the neck dissection + RT and the definitive RT groups (PFS at 4 years, 67.9% vs 70.1%; $p = .82$; LRFS at 4 years, 76.1% vs 75.0%; $p = .99$; respectively). FFLRF was also not different between the neck dissection + RT and definitive RT groups (90.9% vs 88.8%; $p = .84$), with no locoregional recurrences observed after 19 months. OS and PFS did not differ between patients who did and did not undergo PET/CT staging either in the overall cohort ($p = .21$ for OS; $p = .69$ for PFS) or within each treatment group (neck dissection + RT, $p = .55$ for OS; $p = .83$ for PFS; definitive RT, $p = .21$ for OS; $p = .35$ for PFS).

Emergence of a primary mucosal tumor occurred in 2 patients (5%), 1 patient in each group, at 9 and 15 months after completion of RT. Both occurred in the ipsilateral tonsillar fossae, within the previously irradiated CTVs that received 50.4 Gy and 60 Gy, respectively. Two patients (11%) in the definitive RT group required salvage neck dissection because of suspicious clinical or radiologic findings after therapy, but only in 1 patient was cancer found in the dissected specimen.

One patient in each group (5% overall) experienced ipsilateral neck recurrence. The patient in the definitive RT group presented with initial N3 disease in level II and experienced an in-field nodal recurrence in the same level 19 months after completion of RT. He was successfully salvaged by radical neck dissection. The patient in the neck dissection + RT group was initially treated for N2b disease in level II with definitive RT followed by planned neck dissection, and experienced recurrence 16 months after completion of RT in the subcutaneous fat of ipsilateral level IB, outside of the CTV. He underwent successful surgical excision and remains without evidence of disease at last follow-up.

Distant metastases were observed in 11.2% in the RT group and in 28.1% in the neck dissection + RT group (FFDF 88.8% vs 71.9%, respectively, $p = .26$). Metastatic sites were lung (4 patients), liver (2 patients), and peritoneal and base of skull metastases (1 patient each). Two cases of second primary tumors were observed in the neck dissection + RT group (1 case with lung and 1 with hepatocellular carcinoma) and 1 case in the definitive RT group (melanoma).

Presence of HPV and EBV gene expression was assessed only for patients in the neck dissection + RT group (Table 4), as adequate material was not available for the definitive RT group. For 17 patients with assessable HPV status, 10 (59%) were HPV-positive, whereas 7 (41%) were HPV-negative. HPV-positive patients were significantly more likely than HPV-negative patients to have nonkeratinizing tumor histology (100% vs 43%; $p = .019$) and were younger (median age 52 vs 61 years; $p = .08$), but did not differ from HPV-negative patients in year of diagnosis ($p = .38$), smoking status (history of [ge]10 pack-years in 50% vs 71%; $p = .62$), nodal classification ($p = .50$), cystic-type nodal presentation (78% vs 71%; $p = 1.00$), or tumor differentiation (poorly differentiated in 100% vs 71%; $p = .18$). Patients treated in the 2000s were numerically more likely to be HPV-positive than those treated in the 1990s (8 of 12 patients vs 2 of 5 patients; $p = .59$). HPV-positive patients had a trend toward superior PFS (80.0% vs 38.1% at 4 years; hazard ratio, 0.29; $p = .15$) and OS (100% vs 53.6% at 4 years; hazard ratio, 0.17; $p = .06$) compared to HPV-negative patients. EBV status was determined for 7 patients in the neck dissection + RT group who were not HPV-positive. One of the 7 patients was EBV-positive; notably, this patient was of white ethnicity with nonkeratinizing, poorly differentiated SCC.

TABLE 2. Diagnostic and treatment modalities.

	Neck dissection + RT	Definitive RT
	No. of patients (%)	No. of patients (%)
Imaging techniques		
CT	19 (86)	18 (94)
MRI	1 (5)	2 (10)
PET/CT	12 (55)	15 (79)
Surgical modalities		
Excisional biopsy	4 (18)*	12 (63)
Radical	5 (23)	N/A
Modified radical	17 (77)	N/A
Chemotherapy		
Concurrent	11 (50)	14 (74)

Abbreviations: RT, radiation therapy; PET, positron emission tomography; N/A, not available.
*Before neck dissection.

DISCUSSION

Because of a lack of randomized trials, the management of patients with HNCUP remains a challenge regarding both the therapeutic options (surgery alone vs surgery plus RT vs RT) and the RT volumes (ipsilateral neck vs bilateral neck and the putative mucosal sites).[1–3,5,12] Although neck dissection with postoperative RT is the most common treatment approach, the results of this retrospective study suggest that primary RT, mostly concurrent with chemotherapy with surgery reserved for salvage of locoregional failure, may achieve similar therapeutic results.[3,5,13] The presenting characteristics of our patient population are consistent with those in prior reports on HNCUP, with typical features including unilateral neck involvement and level II as the most frequent site of cervical metastasis.[6,14–16]

Surgery alone is typically the preferred primary approach in patients with early-stage neck disease without radiographic evidence of ECE and no history of surgical violation of the neck, with high rates of regional control demonstrated after neck dissection alone in a number of studies.[1–3,17–19] For example, Christiansen et al[20] observed significantly higher 5-year survival and neck control rates (55.6% vs 18.2% and 90.9% vs 40.9%, respectively) for patients treated with neck dissection and adjuvant RT compared with biopsy plus RT. Wallace et al[21] similarly noted superior neck control and cause-specific survival in patients with HNCUP undergoing neck dissection in addition to RT. In contrast, Colletier et al[3] observed no regional recurrences after excisional biopsy and definitive RT despite the presence of N2 disease or ECE in 41% and 25% of these patients, respectively. Nguyen et al[22] further demonstrated no survival or regional control benefit with the use of neck dissection rather than excisional biopsy before RT, despite the presence of N2 or N3 disease in 91% of their patients with

TABLE 3. Distribution of involved nodes at presentation by clinical nodal stage.

	Distribution by neck level				
	I	II	III	IV	V
Neck dissection + RT					
N1		2			
N2a		4	3		
N2b	1	7	4	2	1
N3		5	4	2	
Definitive RT					
N1		2			
N2a		4	1		
N2b	1	10	3	2	1
N3	1	3	2		

Abbreviation: RT, radiation therapy.

HNCUP cohort. Our results are in line with the latter series demonstrating similar tumor control rates in the surgery + RT compared with the definitive RT groups.

Control of the unknown primary mucosal site is another important consideration in management of HNCUP. In 1 series of 277 patients with HNCUP, Grau et al[15] demonstrated that whereas neck control was similar between patients treated with surgery alone, definitive RT alone, or surgery with adjuvant RT, emergence of the mucosal primary was significantly higher in patients treated with surgery alone (54% vs 15% at 5 years). Similar results have been consistently reported in a number of studies.[3,5,6,16,23] A review of the literature, shown in Table 5, demonstrates 5-year locoregional control and emergence of mucosal primary tumor rates ranging from 29% to 100% and 2% to 54%, respectively. The reasons for these wide ranges are likely related to the different management strategies, as summarized above. In the present study, all patients received extended field RT irrespective of treatment group; accordingly, no difference in control of the primary mucosal site was observed.

Emergence of a primary mucosal tumor in the hypopharynx and larynx has been reported to occur less frequently than in the nasopharynx and oropharynx, leading some to suggest that these sites may be safely excluded from the extended RT fields to reduce treatment toxicity in selected patients with HNCUP.[21,24] This consideration is especially relevant to nonsmokers and patients with HPV-positive nodal metastases, in whom the primary tumor is highly likely to be oropharyngeal.[25–27] HPV expression has additionally been demonstrated in significant proportion of white patients with nasopharyngeal carcinomas, implying that the ipsilateral nasopharynx should remain included in the target volume in patients with HPV-positive EBV-negative HNCUP.[28,29] Patients with EBV-expression in metastatic lymph nodes, on the other hand, are highly likely to have occult nasopharyngeal primary tumors, and, in these patients, the hypopharynx, larynx, and oropharynx can be excluded.[30–33] In our series, EBV-RNA was detected in 1 patient with nonkeratinizing poorly differentiated SCC, who notably was of white-American ethnicity, consistent with the reported occurrence of EBV-positive nasopharyngeal carcinoma in nonendemic populations.[29]

In our present study, 59% of patients for whom HPV status could be determined were HPV-positive. Although HPV status was strongly associated with nonkeratinizing tumor histology, as in other studies, it was not associated with year of diagnosis, cystic node presentation, tumor differentiation, or smoking status, in contrast to previous reports.[25,27,34] HPV expression was also associated with a nonsignificant trend toward improved PFS ($p = .15$) and OS ($p = .06$), analogous to those with HPV-positive SCC of known oropharyngeal origin.[11,26,30,34,35]

One important source of potential confounding in our study is the lack of information on HPV status in the definitive RT group. Because the definitive RT group was treated in more recent years, over which time the incidence of HPV-associated oropharyngeal cancer has increased, it is possible that a greater proportion of less favorable HPV-negative patients in the neck dissection + RT group could have masked any potential benefit of adding neck dissection to RT.[36] Additional limitations of our study design include its retrospective design, which precludes reliable estimation of functional outcomes for comparison between patients who received definitive RT and neck dissection + RT, and the relatively small study cohort. As with any nonrandomized retrospective study, the possibility of selection bias as a source of confounding between treatment groups cannot be excluded, which may mask potential differences in efficacy between neck dissection + RT and definitive RT. This remains an important consideration, even despite the fact that no statistical differences in baseline characteristics were observed. Examples of such potential sources of imbalance between arms include the fact that excisional biopsy at diagnosis removed all gross nodal disease in 9 of 19 patients in the definitive RT arm (compared with use of excisional biopsy in 4 of 22 patients of the neck

TABLE 4. Tumor characteristics.

	Neck dissection + RT, no. of patients (%)	Definitive RT, no. of patients (%)
Clinical nodal stage at presentation		
N1	2 (9)	2 (10)
N2a	6 (27)	4 (21)
N2b	8 (36)	10 (53)
N2c	0 (0)	0 (0)
N3	6 (37)	3 (16)
Nodal levels involved at presentation		
I	1 (5)	2 (11)
II	18 (82)	19 (100)
III	11 (50)	6 (32)
IV	4 (18)	2 (11)
V	1 (5)	1 (5)
Multiple	10 (45)	7 (37)
ECE		
No	5 (23)	N/A
Yes	12 (55)	N/A
N/A	5 (23)	N/A
HPV status		
Positive	10 (32)	N/A
Negative	7 (45)	N/A
N/A	5 (23)	N/A

Abbreviations: RT, radiation therapy; ECE, extracapsular extension; N/A, not available; HPV, human papillomavirus.

TABLE 5. Management paradigms and outcomes in squamous cell carcinoma of unknown primary: a review of the literature.

Author	No. of patients	Neck dissection alone, no. of patients	Neck dissection + RT, no. of patients	Bx + RT, no. of patients	Limited RT, no. of patients	Extended RT, no. of patients	Locoregional control (5 y)	Emergence of primary (5 y)
Colletier et al[3]	136	0	97	39	16	120	Sx + RT: 88% RT: 100%	8%
Weir et al[2]	144	0		144	85	59	RT: 51%	7% (limited RT) vs 1.7% (extended RT)
Reddy et al[5]	52	0	31	21	16	36	Sx + RT: 90% RT: 48% ($p = .0004$)	44% (limited RT) vs 8% (extended RT) ($p = .0005$)
Aslani et al[10]	61	0	20	41	10	51	Sx + RT: 85% RT: 76.3% (NS)	7% (1 in Sx group and 3 in RT group)
Wallace et al[21]	179	0	109	70	5	134	Sx + RT: 93% RT + Sx: 82% RT: 73% ($p = .029$)	8%
Christiansen et al[20]	28	0	17	11	3	25	Sx + RT: 90.9% RT: 40.9%	None
Grau et al[15]	277	23	26	213	26	224	Sx: 29% Sx + RT: 59% RT: 44% (NS)	Sx: 54% RT: 23% (limited RT) RT: 13% (extended RT) ($p < .05$)
Demiroz et al (current study)	41	0	19	22		41	Sx + RT: 95.5% RT: 94.8% (NS) (4 y)	5%

Abbreviations: RT, radiation therapy; Bx, biopsy; Sx, surgery; NS, not significant.

dissection + RT arm), the use of concurrent chemotherapy in 14 definitive RT patients compared to 11 patients who underwent neck dissection + RT, and the presence of N3 disease in 3 patients who underwent definitive RT compared to 6 patients who underwent neck dissection + RT. It is similarly possible that selection of poorer prognosis patients for more aggressive therapy may account for the higher observed frequency of distant metastases in the neck dissection + RT arm (28.1% vs 11.2%), although this difference was not statistically significant ($p = .26$) and no such trends were observed for the endpoints of LRFS ($p = .99$), PFS ($p = .82$), and OS ($p = .64$). Nevertheless, these potential sources of imbalance, as well as the relatively small number of included patients and observed events, may limit the statistical power of our study to detect the difference in outcomes between treatment modalities, warranting the inclusion of larger numbers of patients in a randomized prospective study that can appropriately stratify for such prognostic factors and background treatment. Given the high rates of survival and locoregional control in both groups of our study, however, it is unlikely that a significantly larger study of similar retrospective design would demonstrate a difference in outcome between treatment modalities that could not be at least in part attributed to confounding or selection bias.

In recent years, combined-modality therapy for locally advanced, known primary head and neck SCC has been shown to yield outcomes superior to RT alone in both the definitive and adjuvant settings.[37–39] The role of concurrent chemotherapy in SCC of unknown primary, however, has not yet been conclusively established and could not be assessed in the current series, in which most patients in both arms received concurrent chemotherapy. Extrapolating from the demonstrated benefits in studies of known primary cancers, the administration of concurrent chemotherapy with definitive RT for locally advanced disease and with adjuvant RT for patients with ECE at neck dissection is advised.

In summary, comprehensive extended field RT delivered either as definitive therapy or adjuvantly after neck dissection produced high rates of mucosal and neck control in patients with HNCUP. Patients treated with the combination of neck dissection and RT had similar outcomes to those treated with definitive RT without neck dissection. Our results suggest that definitive RT either with or without concomitant chemotherapy is sufficient for the up-front management of HNCUP, with neck dissection reserved for salvage of regional failure.

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