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Head & 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 (ND+RT) or definitive RT both commonly used. We aimed to characterize HNCUP and retrospectively compare outcomes for patients treated with ND+RT versus definitive RT.

Methods—From 1994-2009, 41 HNCUP patients underwent either ND+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 ND+RT and definitive RT in overall survival (OS), progression-free survival (PFS), or locoregional-relapse-free survival, freedom-from-locoregional failure, or freedom-from-distant failure. Among 17 ND+RT patients for whom human papillomavirus (HPV) status could be determined, HPV(+) patients trended towards improved OS ($p=0.06$) and PFS ($p=0.15$).

Conclusions—Neck dissection and post-op RT resulted in similar outcome as definitive RT. The prognostic implications of HPV(+) nodes in HNCUP are similar to those in oropharyngeal primary cancers.

Keywords

Unknown primary; neck dissection; radiation therapy; human papillomavirus

INTRODUCTION

The management of squamous cell carcinoma of unknown primary of the head and neck (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 risk of nodal recurrence, and control potential metastatic disease, with most published series advocating neck dissection followed with radiotherapy or, in recent years, chemo-radiotherapy⁽³⁻⁵⁾.

While neck dissection (ND) or radiotherapy (RT) alone provide similar locoregional control in HNCUP patients with N1 and selected N2a nodal classification without extracapsular extension, more advanced stage disease managed with up-front neck dissection requires additional adjuvant radiotherapy or chemoradiotherapy^(1, 6, 7). The use of multiple treatment modalities, however, may increase the toxicity and morbidity of therapy compared to single modality^(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 ND 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⁾.

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 (IRB) approved protocol. Patients with biopsy confirmed squamous cell carcinoma limited to the cervical lymph nodes without an identifiable primary tumor who received radiotherapy at the University of Michigan were eligible for the present analysis. Clinical neck classification was assigned retrospectively according to American Joint Committee on Cancer (AJCC) Cancer Staging Manual 7th edition.

Diagnostic Workup

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

Treatment

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

All patients received radiotherapy using either 3-dimensional conformal radiation therapy (3D-CRT) or intensity modulated radiation therapy (IMRT); IMRT was routinely used after 2002. Irrespective of radiotherapy technique, targets and organs at risk were outlined on the treatment planning CT. For definitive RT, the gross target volume (GTV) was defined as all known neck disease based on clinical examination and imaging. Clinical target volume-1 (CTV-1) was defined as GTV with typical margins of 0.5-1 cm. CTV-2 included potential primary mucosal sites, typically the bilateral base of 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-V in the ipsilateral neck and II-IV in the contralateral neck, with ipsilateral level IB included if level II neck node involvement was greater than N1. The planning target volume (PTV), 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 56-59 Gy to CTV-2, all delivered simultaneously over 35 fractions in the IMRT cases, while in the 3D cases all

targets received 50 Gy at 2 Gy/fractions and CTV1 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 CTV2. 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 extracapsular extension 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 (where level IB was not a target), contralateral glottic larynx (in cases where 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 (PRV).

Chemotherapy was administered concurrent with radiotherapy to patients with extracapsular extension (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 4µm 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 Inc., 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 human papillomavirus (HPV) was performed using the INFORM HPV ISH assay (Ventana Medical Systems Inc., Tucson, AZ), 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). In situ hybridization for Epstein-Barr virus (EBVR) encoded RNA (EBER; Ventana Medical Systems Inc., Tucson, AZ) was performed according to the manufacturer's protocol. Positive reactions for both in situ hybridization assays were detected using the ISH I View Blue Plus Detection Kit (Ventana Medical Systems Inc., Tucson, AZ) according to 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 EBER 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 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 ND+RT or definitive RT were identified and included in the present analysis. Twenty-two patients were treated with ND+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 ND+RT group. Of 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 ND+RT group, initial diagnosis of SCC was made by excisional biopsy in 4 patients (18%) and FNA in 18 patients (82%). In the RT group, 12 of 19 patients (63%) underwent excisional biopsy for diagnosis prior to 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 ND+RT and definitive RT groups, the most common site of nodal involvement at 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 ND+RT group, 12 patients had pathological evidence of ECE, while 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 ND+RT group (27%) than the definitive RT group (16%), this difference was not statistically significant ($p=0.62$).

Twenty eight patients (68.3%) received IMRT, 13 in the ND+RT group and 15 in the definitive RT group ($p=0.31$). Eleven patients (50%) in ND+RT group, and 14 patients (74%) in the definitive RT group received concurrent chemotherapy ($p=0.20$), consisting of cisplatin in 12 patients, carboplatin in 5 patients, 5-FU-carboplatin in 1 patient, and carboplatin-paclitaxel in 7 patients.

Four patients (18%) required feeding tube during the treatment in the ND+RT group compared with one patient (5%) in RT group ($p=0.43$). 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) than the ND+RT group (median 73 months, range 18-126) ($p=0.01$), due to the

more prevalent use of ND+RT in the earlier period of this study (median year of diagnosis for definitive RT group vs. ND+RT groups: 2006 vs. 2003). Overall, 4 patients died of disease: 3 in the ND + RT group, and one in the definitive RT group. OS at 2 and 4 years for the ND+RT group was 90.7% and 85.3%, compared to 93.3% and 85.6% in the definitive RT group, respectively, ($p=0.64$). PFS and LRFS (figure 1) were similar in the ND + RT and the definitive RT groups (PFS at 4 years: 67.9% vs. 70.1%, $p=0.82$; LRFS at 4 years: 76.1% vs. 75.0%, $p=0.99$; respectively). FFLRF was also not different between the ND + RT and definitive RT groups (90.9% vs. 88.8%, $p=0.84$), 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 ($p=0.21$ for OS, $p=0.69$ for PFS) or within each treatment group (ND+RT: $p=0.55$ for OS, $p=0.83$ for PFS; definitive RT: $p=0.21$ for OS, $p=0.35$ for PFS).

The emergence of a primary mucosal tumor occurred in two patients (5%), one 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 which received 50.4 Gy and 60 Gy, respectively. Two patients (11%) in the definitive RT group required salvage ND due to suspicious clinical or radiologic findings following therapy, but only in one 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 ND+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 ND+RT group (FFDF 88.8% vs. 71.9%, respectively, $p=0.26$). Metastatic sites were lung (4 patients), liver (2), and peritoneal and base of skull metastases in one each. Two cases of second primary tumours were observed in ND+RT group (one case with lung and one with hepatocellular carcinoma) and one case in the definitive RT group (melanoma).

Presence of HPV and EBV gene expression was assessed only for patients in the ND+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, while 7 (41%) were HPV-negative. HPV-positive patients were significantly more likely than HPV-negative patients to have non-keratinizing tumor histology (100% vs. 43%; $p=0.019$) and were younger (median age 52 vs. 61 yrs; $p=0.08$), but did not differ from HPV-negative patients in year of diagnosis ($p=0.38$), smoking status (history of >10 pack-years in 50% vs. 71%; $p=0.62$), nodal classification ($p=0.50$), cystic-type nodal presentation (78% vs. 71%; $p=1.00$) or tumor differentiation (poorly differentiated in 100% vs. 71%; $p=0.18$). Patients treated in the 2000's were numerically more likely to be HPV-positive than those treated in the 1990's (8/12 pts vs. 2/5 pts, $p=0.59$). HPV-positive patients had a trend toward superior PFS

(80.0% vs. 38.1% at 4 years; HR 0.29, $p=0.15$) and OS (100% vs. 53.6% at 4 years; HR 0.17, $p=0.06$) compared to HPV-negative patients. EBV status was determined for 7 patients in the ND+RT group who were not HPV-positive. One of the seven was EBV-positive; notably, this patient was of Caucasian ethnicity with nonkeratinizing, poorly differentiated squamous cell carcinoma.

DISCUSSION

Due to a lack of randomized trials, the management of patients with HNCUP remains a challenge regarding both the therapeutic options (surgery alone vs. surgery plus radiotherapy vs. radiotherapy) and the radiotherapy volumes (ipsilateral neck vs. bilateral neck and the putative mucosal sites) (1-3, 5, 12). Although neck dissection with post-operative radiotherapy 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 extracapsular extension 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. 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 (20). Wallace et al. similarly noted superior neck control and cause-specific survival in HNCUP patients undergoing neck dissection in addition to RT (21). In contrast, Colletier et al. 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 (3). Nguyen et. al further demonstrated no survival or regional control benefit with the use of neck dissection rather than excisional biopsy prior to RT, despite the presence of N2 or N3 disease in 91% of their HNCUP patient cohort (22). 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 one series of 277 HNCUP patients, Grau et al. demonstrated that while 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) (15). 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 be 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 non-smokers 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 Caucasian 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 one patient with non-keratinizing poorly differentiated squamous cell carcinoma, who notably was of Caucasian-American ethnicity, consistent with the reported occurrence of EBV-positive nasopharyngeal carcinoma in non-endemic 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 non-keratinizing 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 non-significant trend toward improved PFS ($p=0.15$) and OS ($p=0.06$), analogous to those for HPV-positive squamous cell carcinoma 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. As 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 ND+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 ND+RT, and the relatively small study cohort. As with any non-randomized 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 ND+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 ND+RT arm), the use of concurrent chemotherapy in 14 definitive RT patients compared to 11 ND+RT patients, and the presence of N3 disease in 3 definitive RT patients compared to 6 ND+RT patients. 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 ND+RT arm (28.1% vs. 11.2%), although this difference was not statistically significant ($p=0.26$) and no such trends were observed for the endpoints of LRFS ($p=0.99$), PFS ($p=0.82$), and OS ($p=0.64$). 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 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 be attributed to confounding or selection bias.

In recent years, combined modality therapy for locally advanced, known-primary head and neck squamous cell carcinoma 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 SCCUP, however, has not yet been conclusively established and could not be assessed in the current series, where 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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Figure 1. Progression-free survival (A) and locoregional relapse-free survival (B) after neck dissection and radiation therapy (ND + RT) or definitive radiotherapy (RT) in head and neck squamous cell carcinoma of unknown primary.

Table 1

Patient characteristics

	<u>Neck Dissection + Radiation Therapy</u>	<u>Definitive Radiation Therapy</u>
Age (years – median [range])	53 (37 – 72)	53 (38 – 76)
Year of Diagnosis (median [range])	2003 (1994 – 2008)	2006 (1994 – 2008)
Follow-up (months - median [range])	73 (18 – 126)	39 (11 – 98)

	<u>No. of patients (%)</u>	<u>No. of patients (%)</u>
<u>GENDER</u>		
Male	20 (90%)	17 (90%)
Female	2 (10%)	2 (10%)
<u>SMOKING HISTORY (>10 PACK-YEARS)</u>		
Past	5 (23%)	5 (26%)
Current	8 (36%)	5 (26%)
Smoking+alcohol	6 (27%)	5 (26%)
<u>TONSILLECTOMY</u>		
Childhood	4 (18%)	4 (21%)
Current	4 (18%)	7 (77%)

Table 2

Diagnostic and treatment modalities

	<u>Neck Dissection + Radiation Therapy</u>	<u>Definitive Radiation Therapy</u>
IMAGING TECHNIQUES		
	<u>No. of patients (%)</u>	<u>No. of patients (%)</u>
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%)

* Prior to neck dissection

Table 3

Distribution of involved nodes at presentation by clinical nodal stage

Neck Levels:	<u>I</u>	<u>II</u>	<u>III</u>	<u>IV</u>	<u>V</u>
NECK D SPECT ON + RAD AT ON THERAPY					
N1		2			
N2a		4	3		
N2b	1	7	4	2	1
N3		5	4	2	
DEFINITIVE RADIATION THERAPY					
N1		2			
N2a		4	1		
N2b	1	10	3	2	1
N3	1	3	2		

ND= Neck Dissection; RT = Radiation Therapy

Table 4

Tumor characteristics

	<u>Neck Dissection + Radiation Therapy</u>	<u>Definitive Radiation Therapy</u>
	No. of patients (%)	No. of patients (%)
<u>CLINICAL NODAL STAGE AT PRESENTATION</u>		
N1	2 (9%)	2 (10%)
N2a	6 (27%)	4 (21%)
N2b	8 (36%)	10 (53%)
N2c	0 (%)	0 (0%)
N3	6 (37%)	3 (16%)
<u>NODAL LEVELS INVOLVED AT PRESENTATION</u>		
Level I	1 (5%)	2 (11%)
Level II	18 (82%)	19 (100%)
Level III	11 (50%)	6 (32%)
Level IV	4 (18%)	2 (11%)
Level V	1 (5%)	1 (5%)
Multiple Levels	10 (45%)	7 (37%)
<u>EXTRACAPSULAR EXTENSION</u>		
No	5 (23%)	n/a
Yes	12 (55%)	n/a
N/A	5 (23%)	n/a
<u>HUMAN PAPILLOMAVIRUS STATUS</u>		
Positive	10 (32%)	n/a
Negative	7 (45%)	n/a
N/A	5 (23%)	n/a

N/A = not available

Table 5

Management paradigms and outcomes in SCCUP: a review of the literature

Author	N (no. of patients)	ND alone (no. of patients)	ND+RT (no. of patients)	Bx+RT (no. of patients)	Limited RT (no. of patients)	Extendend RT (no. of patients)	Locoregional Control (5-year)	Emergence of primary (5-year)
<i>Colletier et al. (3)</i>	136	0	97	39	16	120	Sx+RT: 88% RT:100%	8%
<i>Weir et al. (2)</i>	144	0		144	85	59	RT: 51%	7% (limited) vs. 1.7% (extended)
<i>Reddy et al. (5)</i>	52	0	31	21	16	36	Sx+RT: 90% RT: 48% ($p=0.0004$)	44% (limited) vs. 8% (extended) ($p=0.0005$)
<i>Aslani et al. (10)</i>	61	0	20	41	10	51	Sx+RT: 85% RT: 76.3% (NS)	7% (1 in Sx group and 3 in RT group)
<i>Wallace et al. (21)</i>	179	0	109	70	5	134	Sx+RT:93% RT+Sx:82% RT:73% ($p=0.029$)	8%
<i>Christiansen et al. (20)</i>	28	0	17	11	3	25	Sx+RT:90.9% RT: 40.9%	none
<i>Grau et al. (15)</i>	277	23	26	213	26	224	Sx: 29% Sx+RT: 59% RT: 44% (NS)	Sx: 54% RT: 23% (limited) RT: 13% (extended) ($p<0.05$)
<i>Demiroz et.al (Current study)</i>	41	0	19	22		41	Sx+RT:95.5% RT: 94.8% (NS) (4 yrs)	5%

Bx: Biopsy, ND: Neck dissection, NS: Not significant, RT: Radiotherapy, Sx=Surgery