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Oncologic Outcomes of Selective Neck Dissection in HPV-Related Oropharyngeal Squamous Cell Carcinoma

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Objectives: To examine outcomes of selective neck dissection (SND) in patients with human papillomavirus (HPV)-related oropharyngeal squamous cell carcinoma (OPSCC) who present with clinical neck disease.

Study Design: Multi-institutional retrospective review.

Methods: Two institutional databases of patients with HPV-related OPSCC were reviewed to identify patients with clinical (c) N1-N3 neck disease who underwent SND ± adjuvant therapy.

Results: Three hundred and twenty-four patients were identified with a median follow-up of 49 months (range 3–199 months). All patients underwent transoral resection of the primary tumor and SND, including levels II–IV and ± levels I or V, with resection of additional nonlymphatic tissue (extended SND) as indicated by extent of disease, including the spinal accessory nerve (7%), the internal jugular vein (13%), and the sternocleidomastoid muscle (8%). Two hundred and seventy (83%) patients underwent adjuvant radiation. There were 13 (4%) regional recurrences and 19 (6%) distant recurrences. Regional control following salvage was 98%. On univariable analysis, absence of radiation was associated with regional recurrence (odds ratio [OR] 9.2, 95% confidence interval [CI] 2.9–29.4). On multivariable analysis, adjuvant radiation was associated with improved disease-free survival (DFS) (OR 0.27, 95% CI 0.14–0.53) but lost significance for overall (OS) and disease-specific survival (DSS) ($P > 0.05$). Five-year Kaplan-Meier estimates for OS, DSS, and DFS were 88% (95% CI 84%–92%), 93% (95% CI 89%–96%), and 83% (95% CI 78%–87%), respectively.

Conclusion: In HPV-related OPSCC presenting with clinical neck disease, a SND ± additional tissue resection and adjuvant therapy, when indicated, provides excellent long-term regional control. Omission of radiotherapy increases the risk of regional recurrence, although it may not significantly impact OS or DSS. It appears unnecessary to routinely perform a comprehensive neck dissection.

Key Words: Neck dissection, squamous cell carcinoma, oropharynx, HPV.

Level of Evidence: 4.

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INTRODUCTION

In the early 1900s, radical neck dissection, as described by Crile, became the standard of care for squamous cell carcinoma of the upper aerodigestive tract presenting with gross clinical neck disease.[1] Through the influence of Martin, this paradigm persisted into the 1960s.[2] In the 1970s, Suarez, championed a modified radical neck dissection (MRND), removing levels 1 through 5, while sparing when possible—as a less morbid and comparable oncologic operation—at least one of the following: sternocleidomastoid, internal jugular vein, and spinal accessory nerve.[3] Further studies from the 1980s and 1990s investigated the distribution of cervical metastases in large series of patients undergoing comprehensive neck dissection and demonstrated which lymph node levels could be safely omitted for certain primary tumors, giving rise to the concept of the selective neck dissection (SND).[4] Randomized trials have supported the oncologic equivalence and lower complication rates of SND in the elective setting,[5,6] but its use for gross regional metastases has been more controversial.

Although several studies support the oncologic safety of SND for clinical neck disease,[7,8] current National Comprehensive Cancer Network guidelines continue to recommend a MRND in the therapeutic setting.[9] Some reports have shown regional recurrence rates as high as 30% with SND for advanced neck disease, even in conjunction with postoperative radiotherapy.[10] Importantly, no studies have evaluated the oncologic efficacy and safety of SND for treatment of clinical neck disease in

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patients with HPV-related OPSCC. The latter cohort frequently presents with regional lymphadenopathy. The incidence of removing additional nonlymphatic structures (extended SND) in these patients with bulky lymph node metastases has also not been described. With the increase in human papillomavirus (HPV)-related oropharyngeal squamous cell carcinoma (OPSCC) and the growing number of patients who present with small primary tumors and gross clinical neck disease,[11] investigating the oncologic efficacy and safety of a SND approach in an effort to decrease patient morbidity is imperative. The objectives of this study were to determine, in patients with HPV-related OPSCC with clinical neck metastasis, the oncologic outcomes and complication rates of resection of nodal levels 2 to 4, with additional lymphatic or nonlymphatic tissue as indicated by the extent of regional disease.

MATERIALS AND METHODS

A retrospective review of institutional databases at both Washington University and Mayo Clinic was performed to identify patients with p16-positive squamous cell carcinoma of the oropharynx with clinical neck disease who were treated with SND between 1998 and 2013. All data collection was approved by the institutional review board at Washington University and Mayo Clinic. In this study, p16 immunohistochemistry was used as a marker for HPV-related disease, as previously described.[12] Inclusion criteria were patients with cN1-cN3 neck disease, p16-positive immunohistochemistry from either a biopsy of the neck or the oropharyngeal primary site, transoral surgical treatment of the primary site, and SND(s), without or without adjuvant therapy. Patients were excluded if they had prior treatment for a cancer of the upper aerodigestive tract, distant metastatic disease on presentation, or were treated with noncurative intent.

The selective neck dissection included levels 2 to 4 and was extended to other lymphatic or nonlymphatic structures, as determined by the surgeon. To be considered selective, either levels 1 or 5, or both, were not dissected. Neural, vascular, and muscle structures were preserved whenever possible, with extent of resection determined intraoperatively by patterns of tumor invasion. If extralymphatic tissue required resection, this was designated an *extended* selective neck dissection. Contralateral elective neck dissection was performed at the discretion of the surgeon based on the location of the primary tumor and risk of occult metastasis. Adjuvant therapy use was determined by the presence of pathology-derived risk factors, in consultation with patients and a multidisciplinary discussion, although these criteria changed over time based on evolving data.[13,14]

Of the two institutions in this study, dosing and fields of adjuvant radiotherapy differ slightly. For both, in well-lateralized T1 to T2 tonsil primaries, if adjuvant radiotherapy is indicated based on pathologic criteria from the neck dissection, only the unilateral neck is treated. If there is base of tongue involvement, however, adjuvant radiotherapy is given to the contralateral neck if not dissected. At one institution, if the contralateral neck is clinically N0, it is generally not dissected and treated with adjuvant radiotherapy if indicated. At the second institution, if the contralateral neck is clinically N0, it is often dissected; if pathologically N0 and on a study protocol, adjuvant radiotherapy will be omitted to that neck. For radiotherapy dosing, at one institution the entire dissected neck receives 60 gray (Gy) units; however, at the second institution the involved nodal levels will get 60 Gy, whereas the uninvolved ipsilateral nodal levels receive 54 Gy. Both institutions treat the contralateral uninvolved neck to 54 Gy if not dissected. For both institutions, gross tumor volumes (GTVs) were contoured-based on preoperative physical examination, nasopharyngoscopy, and fluorodeoxglucose-positron emission tomography (PET)/computed tomography (CT) scans, as well as operative and pathology reports. Computed tomography simulation scans were fused with preoperative CT and/or PET-CT scans. The high-risk clinical target volume (CTV1) was defined as the primary tumor (pGTV +1.5–2.0 cm) and positive lymph nodes (nGTV +0.5–1.0 cm). The low-risk or elective clinical target volume (CTV2) was defined as the uninvolved elective neck. These volumes were then expanded by 0.5 cm to obtain a planning target volume (PTV).

Data collected included demographics, tumor characteristics, treatment details, and outcomes. Comorbidities, as measured by the Adult Comorbidity Evaluation Index 27 (ACE-27),[15] were available for the Washington University cohort. Clinical N-stage was determined by the operative surgeon based on physical exam and imaging. In the case of an unknown primary tumor, if the primary lesion was not identified after surgical intervention, it was staged as T0. Age was dichotomized around the mean. ACE-27 score was dichotomized to no or mild comorbidities (0 or 1) versus moderate or severe comorbidities (2 or 3) given the previously reported negative prognostic value of an ACE-27 score of 2 or more in patients with head and neck cancer.[16] Smoking was dichotomized at 10 pack years given its prognostic importance in prior studies.[17] Nodal disease was dichotomized by early (N0–N2a) versus advanced (N2b–N3) nodal stage because this has also been shown to be prognostic in p16-positive disease.[18] The presence of five or more pathologically positive lymph nodes was also documented given the known association with decreased survival in previous reports.[19] The primary endpoint to evaluate the efficacy of selective neck dissection for clinically positive neck disease was regional recurrence. Secondary endpoints included overall (OS), disease-specific (DSS), and disease-free survival (DFS), as well as complications of the neck dissection. DFS events were the first of either recurrence, or death of any cause.

Statistical analysis was performed using SPSS (SPSS v22, IBM, Chicago, IL). Descriptive statistics were used to define the study population. To determine risk factors associated with regional recurrence, a univariable analysis was performed with a chi-square test or Fisher's exact test for categorical variables and a t test or Mann-Whitney U-test for continuous data, depending on data normality. Given the limited number of regional recurrences, a multivariable analysis of predictive factors could not be performed. Variables associated with survival outcomes were also investigated, and those that were statistically significant in univariable analysis were included in a multivariable Cox survival analysis.

RESULTS

Three-hundred twenty-four cN1-cN3 patients were identified who underwent selective neck dissection for p16-positive clinical neck disease. Median follow-up was 49 months (range 3–199 months). All patients were treated with transoral laser or robotic resection of the primary tumor in conjunction with a SND. In the case of an unknown primary, an ipsilateral palatine and lingual tonsillectomy were performed, as previously described.[20] The contralateral neck dissection was performed concurrently or staged at the discretion of the surgeon.

Demographics and clinical staging are shown in Table I. No pretreatment characteristics were predictive of regional recurrence, including clinical N-stage.

TABLE I.
Preoperative Characteristics.

	All Patients (n = 324)	No Regional Recurrence (n = 311)	Regional Recurrence (n = 13)	*P* Value
Gender				0.650
Male	287 (89%)	276 (89%)	11 (85%)	
Female	37 (11%)	35 (11%)	2 (15%)	
Age (years)				0.540
Mean	55.9	56.4	58.3	
Standard deviation	9.6	9.7	10.6	
Smoking				0.224
Less than 10 pack years	197 (61%)	187 (60%)	10 (77%)	
10 or more pack years	127 (39%)	124 (40%)	3 (23%)	
ACE-27*				0.999
0–1	150 (88%)	144 (88%)	6 (100%)	
2–3	20 (12%)	20 (12%)	0	
Oropharyngeal subsite				0.265
Base of tongue	145 (45%)	142 (46%)	3 (23%)	
Tonsil	178 (55%)	168 (54%)	10 (77%)	
Soft palate	1 (<1%)	1 (<1%)		
Clinical T-stage				0.999
T0–2	277 (86%)	266 (85%)	11 (85%)	
T3–4	47 (15%)	45 (15%)	2 (15%)	
Clinical N-stage				0.999
N1–2a	148 (46%)	142 (46%)	6 (46%)	
N2b–3	176 (54%)	169 (54%)	7 (54%)	
Clinical N3	20 (6%)	20 (100%)	0	0.345

*Data available only for patients treated at Washington University.
ACE-27 = Adult Comorbidity Evaluation Index 27; N = node; T = tumor.

Treatment details are shown in Table II. Extent of the SND, including additional lymphatic, neurovascular, or muscular structures, was not predictive of regional recurrence. Lymph node yield from the neck dissection, number of pathologically positive nodes, and extracapsular spread were also not associated with regional recurrence. Twenty patients had clinical N3 disease and 23 had pathological N3 disease; none had regional failure. The omission of adjuvant radiotherapy, however, was associated with significantly increased the risk of regional recurrence (odds ratio [OR] 9.2, 95% confidence interval [CI] 2.9–29.4, $P = 0.001$). Adjuvant chemoradiation did not decrease the risk of regional recurrence over radiation alone (OR 1.2, 95% CI 0.2–7.6, $P = 0.999$).

Treatment outcomes are described in Table III and regional recurrence details in Table IV. There were 13 (4%) regional recurrences: 12 isolated and one associated with a local recurrence. Salvage treatment with curative intent was subsequently delivered in 10 (77%) of these cases, of which five (38% of all regional recurrences) cases were alive and disease-free at last follow-up. Surgical salvage neck dissection was attempted in eight patients and was successful in four. Definitive chemoradiation without salvage surgery was attempted in two patients and was successful in one. This yielded final regional control in 316 (98%) of patients in the study cohort.

In a multivariable analysis (Table V), the two factors most strongly associated with improved DFS included early T-stage and the addition of adjuvant radiation. Although not associated with regional recurrence, the presence of five or more pathologically positive lymph nodes was strongly associated (hazard ratio = 3.76) with decreased DSS. The extent of neck dissection was not a significant prognostic factor for DFS in the multivariable model. The addition of adjuvant radiation lost prognostic significance for overall and disease-specific but maintained significance for DFS.

DISCUSSION

The results of this study demonstrate that for patients with HPV-related OPSCC and clinical evidence of neck metastasis, a SND approach incorporating levels 2 to 4 plus resection of additional tissue as indicated, with postoperative adjuvant therapy, provides excellent long-term regional control. These findings are significant in light of the current epidemic of HPV-associated oropharyngeal squamous cell carcinoma. Patients with this disease often have advanced clinical neck metastasis at initial presentation, and deescalation of treatment without

TABLE II.
Treatment Details.

	All Patients (n = 324)	No Regional Recurrence (n = 311)	Regional Recurrence (n = 13)	*P* Value
Pathologic T-stage				0.999
T0–2	269 (83%)	258 (83%)	11 (85%)	
T3–4	55 (17%)	53 (17%)	2 (15%)	
Pathologic N-stage				0.775
N0–2a	118 (36%)	114 (37%)	4 (31%)	
N2b–3	206 (64%)	197 (63%)	9 (69%)	
Pathologic N3	23 (7%)	23 (100%)	0	0.309
Neck dissection				0.729
Unilateral	259 (80%)	249 (80%)	10 (77%)	
Bilateral	65 (20%)	62 (20%)	3 (23%)	
Ipsilateral neck dissection levels				0.505
II–IV	151 (47%)	147 (47%)	4 (31%)	
I–IV	153 (47%)	145 (47%)	8 (62%)	
II–V	20 (6%)	19 (6%)	1 (8%)	
Ipsilateral neck dissection: structures resected				
Spinal accessory nerve	21 (7%)	21 (7%)	0	0.999
Internal jugular vein	42 (13%)	41 (13%)	1 (8%)	0.999
Sternocleidomastoid muscle	26 (8%)	26 (8%)	0	0.610
Other*	16 (5%)	15 (5%)	1 (8%)	0.489
Ipsilateral neck dissection				
Lymph node yield				
Median	28	25	30	0.261
Range	2–78	2–78	24–38	
Number of pathologically positive nodes				
Median	2	2	2	0.430
Range	0–40	0–40	1–4	
Five or greater	41 (13%)	38 (12%)	3 (23%)	0.249
Extracapsular spread (ECS)†				
ECS present	214 (71%)	207 (71%)	7 (58%)	0.341
ECS absent	88 (29%)	83 (29%)	5 (42%)	
Contralateral neck dissection				
Lymph node yield				
Median	21	21	22	0.820
Range	0–78	0–78	14–32	
Number of pathologically positive nodes				
Median	1	1	0	0.270
Range	0–19	0–19	0–1	
Adjuvant radiation	270 (83%)	265 (85%)	5 (39%)	**0.001**
Adjuvant radiation dosage (Gy)				0.312
Median	60	60	66	
Range	0–70	0–70	60–66	
Adjuvant chemotherapy	148 (46%)	145 (47%)	3 (23%)	0.095
No adjuvant therapy	54 (17%)	46 (15%)	8 (61%)	**0.001**

*Other structures include deep neck musculature, thyroid, and the vagus and hypoglossal nerves.
†The presence or absence of ECS in the ipsilateral neck was unknown in 10 patients, and the neck dissection was pathologically negative in 12 patients.
ECS = extracapsular spread; Gy = gray; N = node; T = tumor.

compromise of oncologic outcomes is the concept behind current HPV-OPSCC–related research.[21] In this report, complications of the neck dissection were low and prior authors have shown that both perioperative[5] and long-term complications, particularly related to shoulder morbidity,[22,23] are significantly lower for SND than MRND.

TABLE III.
Outcomes.

	n = 324
Recurrence	
Local	5 (2%)
Regional	12 (4%)
Locoregional	1 (<1%)
Distant	19 (6%)
5-year Kaplan-Meier survival estimates (95% CI)	
Overall survival	88% (84%–92%)
Disease-specific survival	93% (89%–96%)
Disease-free survival	83% (78%–87%)
Complications of the neck dissection	
Overall complications	23 (7%)
Surgical site infection	8 (3%)
Chyle leak	5 (2%)
Inadvertent cranial nerve injury	3 (1%)
Neck hematoma	4 (1%)
Other*	3 (1%)

*Other complications include two neck seromas managed with percutaneous drainage, and one pneumothorax that resolved spontaneously.
CI = confidence interval.

The oncologic safety of a SND in the therapeutic setting, however, has been controversial.[24] Many authors support the use of SND for patients with regional metastasis from head and neck squamous cell carcinoma because regional recurrence rates are generally below 10% and comparable to historical data for MRND.[8,25–32] A recent meta-analysis of five studies, which directly compared outcomes for SND and MRND in patients with clinical neck disease from oral cavity primary tumors, found no significant difference in regional recurrence between neck dissection types.[33] These studies contain few patients with oropharyngeal primary tumors and are not stratified by HPV status. In addition, they either include very few or no patients with N3 disease. The majority of authors advocate SND only in the case of N1 or limited N2 disease.[32,34–36] In one of the largest studies specifically dedicated to the expanded use of SND for advanced nodal disease, Pellitteri et al.[37] reported 12% regional recurrence with multiple positive nodes but included only two patients with N3 disease. Higher rates of regional failure with SND have been associated with advanced nodal stage and extracapsular spread in some reports, and these authors caution against SND in patients with bulky metastatic adenopathy.[10,38,39] The current study contained 20 patients with clinical N3 and 23 patients with pathological N3 staging and found no regional failures in any of these patients. This finding is of particular interest in the context of HPV OPSCC, for which patients managed via the nonsurgical approach demonstrate an independent association between N3 disease and reduced survival, and emerges as a criterion for inclusion in the highest locoregional stage.[40–42]

In addition to advanced nodal disease, few studies of SND in the therapeutic setting examine the oncologic

TABLE IV.
Regional Recurrences.

Initial Clinical Stage	Side of Recurrence	Neck Level	Recurrence In-Field of Previous Dissection	Received Adjuvant Radiation	Treatment of Recurrence	Outcome at Last Follow-up
T2N2b tonsil	Ipsilateral	Retropharyngeal	No	Yes	Palliative	Dead of disease
T2N2a tonsil	Ipsilateral	Retropharyngeal	No	No	Definitive chemoradiation	No evidence of disease
T4N2c tonsil	Contralateral	II, IV, V	Yes (II, IV)	No	Neck dissection, radiation	Alive with disease
T1N2b base of tongue	Ipsilateral	V	Yes	No	Neck dissection, radiation	No evidence of disease
T2N1 tonsil	Ipsilateral	V	No	Yes	Neck dissection	Dead of disease
T1N2a tonsil	Ipsilateral	I, V, parotid	No	No	Neck dissection, parotidectomy, radiation	Dead of disease
T1N2b tonsil	Contralateral	II	No	Yes	Neck dissection	No evidence of disease
T2N2b tonsil	Ipsilateral	Parotid	No	Yes	Palliative	Alive with disease
T1N1 tonsil	Contralateral	III	No	No	Neck dissection, radiation	Dead of disease
T2N1 tonsil	Ipsilateral	II, IV, V	Yes (II, IV)	Yes	Palliative	Dead of disease
T4N2b base of tongue	Ipsilateral	Retropharyngeal	No	No	Unknown	Alive with disease
T0N2a	Bilateral	II (contralateral) IV, parotid (ipsilateral)	No (contralateral) Yes (ipsilateral IV)	No	Neck dissection, parotidectomy, radiation	No evidence of disease
T2N2b tonsil	Contralateral	II	No	No	Neck dissection, radiation	No evidence of disease

N = node; T = tumor.

TABLE V.
Univariable and Multivariable Cox Survival Analysis for Disease-Free Survival.

	Overall Survival HR (95% CI)	*P* Value	Disease-Specific Survival HR (95% CI)	*P* Value	Disease-Free Survival HR (95% CI)	*P* Value
Univariable						
Age (younger than 56 vs. 56 or older)	0.36 (0.17–0.73)	**0.005**	0.45 (0.18–1.12)	0.088	0.43 (0.24–0.78)	**0.005**
Gender (male vs. female)	2.08 (0.50–8.64)	0.315	1.24 (0.29–5.31)	0.775	2.07 (0.65–6.64)	0.221
Smoking (10 or more pack years)	1.31 (0.69–2.51)	0.409	1.37 (0.58–3.22)	0.475	1.10 (0.64–1.90)	0.721
ACE-27 (0–1 vs. 2–3)*	0.60 (0.22–1.61)	0.311	0.89 (0.20–3.94)	0.876	0.75 (0.29–1.96)	0.557
Oropharyngeal subsite (base of tongue vs. tonsil)	1.49 (0.78–2.86)	0.230	1.63 (0.69–3.86)	0.270	1.20 (0.70–2.06)	0.505
Clinical T-stage (0–2 vs. 3–4)	0.25 (0.13–0.49)	**0.001**	0.24 (0.10–0.58)	**0.002**	0.28 (0.16–0.48)	**0.001**
Clinical N-stage (1–2a vs. 2b–3)	0.61 (0.31–1.20)	0.155	0.70 (0.29–1.70)	0.432	0.58 (0.33–1.02)	0.057
Neck dissection levels (II–IV vs. additional levels)	0.73 (0.38–1.41)	0.349	1.06 (0.45–2.51)	0.889	0.66 (0.38–1.14)	0.134
Neck dissection (resection of nonlymphatic structures)	1.91 (0.94–3.89)	0.075	3.04 (1.26–7.37)	0.14	1.75 (0.95–3.23)	0.075
Five or more positive lymph nodes	3.08 (1.49–6.38)	**0.002**	4.13 (1.66–10.24)	**0.002**	2.89 (1.57–5.32)	**0.001**
Extracapsular spread	1.17 (0.53–2.58)	0.697	1.17 (0.43–3.20)	0.761	1.29 (0.66–2.53)	0.454
Adjuvant radiation	0.59 (0.26–1.35)	0.209	0.62 (0.21–1.84)	0.387	0.41 (0.22–0.75)	**0.004**
Adjuvant chemotherapy	1.16 (0.60–2.24)	0.651	0.60 (0.24–1.49)	0.273	0.88 (0.51–1.51)	0.634
Multivariable						
Clinical T-stage (0–2 vs. 3–4)	0.31 (0.16–0.60)	**0.001**	0.30 (0.12–0.76)	**0.010**	0.31 (0.18–0.55)	**0.001**
Adjuvant radiation	0.50 (0.21–1.18)	0.111	0.42 (0.13–1.33)	0.139	0.27 (0.14–0.53)	**0.001**
Five or more positive lymph nodes	2.72 (1.26–5.87)	**0.011**	3.76 (1.41–10.01)	**0.008**	2.86 (1.48–5.54)	**0.002**
Age (younger than 56 vs. 56 or older)	0.43 (0.21–0.90)	**0.026**	0.57 (0.23–1.44)	0.234	0.54 (0.30–0.99)	**0.046**

*Data available only for patients treated at Washington University.
ACE-27 = Adult Comorbidity Evaluation Index 27; CI = confidence interval; HR = hazard ratio; T = tumor.

safety of an extended SND, including removal of nonlymphatic structures, and none examine the frequency in HPV-related OPSCC. The concept of an extended SND has been incorporated into previous classification systems.[43,44] Data regarding this technique is limited, however, and its use remains controversial.[45] The most recent consensus statement from the American Head and Neck Society did not officially classify or address the validity of an extended SND approach.[46] Several reports mention the need for an extended SND in certain cases but do not analyze the effect on recurrence and survival.[28,31,37] In one of the only reports to specifically address outcomes of patients treated with an extended SND, Dhiwakar et al.[30] reported on 16 patients and found no regional recurrences. The current study expands on this finding because 55 patients required resection of nonlymphatic tissue due to extent of disease, and only two (4%) of these patients experienced a regional recurrence.

The excellent regional control found in this report for SND in patients with advanced nodal disease and those requiring extended SND is likely related to three factors: HPV-associated disease, meticulous technique and adjuvant radiation therapy. Human papillomavirus-related OPSCC is well-known to have an improved prognosis over non-HPV–related squamous cell carcinoma.[12] In addition, for surgically treated patients, prognosis has been associated primarily with T classification and not N classifcation.[18] Node number, specifically five or greater, but *not* extracapsular spread has been prognostic in these patients, a finding we confirmed in this study.[19] Although node number was not associated with regional recurrence in the current study, it did portend significantly worse OS,DSS and DFS, likely due to the increased rate of regional recurrence and distant metastasis in the high-node number group.

Finally, omission of adjuvant radiotherapy was associated with a significantly increased risk of regional recurrence. The benefit of postoperative radiation for advanced clinical nodal disease has been recognized for over 30 years,[47] and criteria for adjuvant therapy are now well-defined.[9] Several recent studies support the need for adjuvant radiation after SND for advanced neck disease.[27,48] Wolff et al.[27] performed SND for 318 patients with N2 disease and found regional recurrence in less than 10% of those who received adjuvant radiation but over 35% of those who underwent surgery alone. Despite the increased risk of regional recurrence

in patients who do not receive adjuvant radiation, its prognostic significance was lost for DSS and OS because a proportion of patients who recurred regionally were successfully salvaged. Our finding of no significantly associated benefit from the use of adjuvant chemotherapy in a p16+ OPSCC population corroborates previous work.[14]

The outcomes of surgical management in this study fare well in comparison to recent nonsurgical series. Garden et al.[49] reported on 401 patients with lymph node-positive HPV-related OPSCC and with 20% undergoing neck dissection, still found a neck recurrence rate of 8%, twice as high as the current study. These authors did not discuss survival outcomes, however. In one of the largest reported primary nonsurgical studies of advanced stage OPSCC, Garden et al.[40] reported a 5-year overall survival of 78%, but for N3 disease this estimate dropped below 60%. In the current report, overall survival for all study patients was 88%, and for patients with pathological N3 disease the estimated 5-year overall survival was 91%.

There are several limitations of the study. Firstly, there are no comparison groups available, either for MRND or HPV-negative tumors. In addition, several variables that may have prognostic significance could not be retrieved, including tumor volume, number, and extent of breaks in adjuvant therapy. Finally, retrospective data collection is subject to the omissions and inaccuracies of the medical record, and also hampered by a lack of 11th nerve functional data, an important outcome in neck dissection.

CONCLUSION

In patients with clinical neck disease from HPV-related oropharyngeal squamous cell carcinoma, a SND approach incorporating levels 2 to 4 with extension to adjacent tissue as indicated, ± adjuvant therapy provides excellent long-term regional control with low associated morbidity. This remains true even in select patients with N3 adenopathy who are otherwise candidates for neck dissection. Adjuvant radiotherapy, when indicated based on accepted pathological characteristics, is associated with a decreased risk of regional recurrence.

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