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Patterns of failure in high-metastatic node number human papillomavirus-positive oropharyngeal carcinoma

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ABSTRACT

Background: The 8th edition American Joint Committee on Cancer staging system for resected HPV-positive oropharynx carcinoma (HPV+ OPC) highlights high node number as a critical determinant of survival. We sought to characterize outcomes and patterns of failure in patients with high pathologically involved node number oropharynx cancer.

Methods: We retrospectively identified 116 HPV+ OPC patients sequentially treated with neck dissection and either resection or intraoperative brachytherapy of the primary tumor between 2010 and 2016. External beam radiation was given based on the pathologic findings. Cox proportional hazards regression was used for multivariate analysis.

Results: With a median follow-up of 27 months, the 3-year overall survival and progression free survival (PFS) were 89% and 81%, respectively. On multivariate analysis, ≥5 involved lymph nodes was significantly associated with worse PFS (hazard ratio 4.3, 95% confidence interval (CI) 1.5–12.0, $P = 0.001$). Rates of 3-year locoregional recurrence (LRR) in patients with ≤4 vs ≥5 were 6% and 22% (log-rank $P = 0.12$). Rates of 3-year distant metastases (DM) were 12% and 53% between ≤4 and ≥5 (log-rank $P < 0.001$).

Conclusion: Our findings confirm that patients with 5 or more involved lymph nodes appear to have substantially worsened rates of disease recurrence. While these patients appear to be at high risk of both LRR and DM, the predominant mechanism of failure is distant, and the rate of DM in this group was over 50%. Dedicated clinical trials in this patient population are warranted with a focus on mitigating the high DM rate.

Introduction

Human papillomavirus-positive (HPV+) oropharyngeal carcinoma (OPC) compromises over 70% of all newly diagnosed OPC cases and exhibits more favorable survival outcomes compared to HPV-negative disease. Survival rates with HPV+ disease are approximately 30% higher at 5 years than with HPV-negative disease [1], which has led to the design of different staging systems for both HPV+ and HPV-negative disease. Additionally, amongst HPV+ patients, a separate staging system has been adopted for clinically staged versus pathologically staged patients [2]. In the new pathologic staging system, the number of involved nodes, as opposed to laterality or size, is a key determinant of stage in resected cancers. In the study that formed the basis for the American Joint Committee on Cancer (AJCC) 8th edition staging system, the presence of ≥5 pathologically positive nodes was associated with worsened 5-year overall survival (OS) 71% vs 84% [3]. Yet, the patterns of failure within this high-risk group were not specifically elucidated—an important aspect for developing therapeutic strategies to counteract the worsened survival rates. We sought to further examine outcomes within a cohort of patients treated surgically with neck dissections and either resection or intraoperative brachytherapy of the primary site to examine risk factors for recurrence, validate the ≥5 node cutoff, characterize the role of salvage therapy in patients with recurrence, and, most importantly, examine patterns of failure in high (≥5) node number versus low (≤4) node number patients.

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Methods

Patient population

HPV-associated OPC patients from 2010 to 2016 at Yale New Haven Hospital (YNHH) who underwent neck dissection were included in this retrospective study. Those with previous head and neck cancer or cancer treatment to the head and neck region were excluded. Yale University's IRB approved the protocol and written consent was waived. Pathologic data, HPV status, and clinicodemographic features were extracted from patient records. HPV status was determined using p16 immunohistochemistry and/or HPV in situ hybridization (ISH).

Study endpoints

Progression free survival (PFS) was defined as time from primary surgery to progression or death from any cause. OS was defined as time from primary surgery to death of any cause. Distant metastases (DM) were defined as disease outside of the head and neck region and was confirmed by imaging and/or biopsy-proven disease consistent with the primary when possible. Locoregional recurrence (LRR) was defined as recurrence within the head and neck.

Statistical analysis

Statistical analysis was performed using STATA/IC software package (version 14.2; StataCorp, College Station, TX). Multivariable analysis (MVA) was conducted using backwards-exclusion with the Cox proportional hazards model. The inclusion cut-off was $P < 0.20$. Proportionality was confirmed using time-dependent covariates. Survival analysis was conducted using the Kaplan-Meier method and log-rank test.

Results

Patient and tumor characteristics

One hundred and sixteen patients were included with a median follow-up of 27 months (range: 1 to 63 months). Patient and tumor characteristics are described in Table 1. The median patient age was 60, and 101 (87%) patients were male. 64 (55%) of patients had a tonsil primary while 52 (45%) had a base of tongue primary. Ninety-eight (85%) were cT1-2, and 83 (72%) were 7th Ed. AJCC pN1-2b. 11.2% had greater than 4 pathologically involved lymph nodes (range 0 to 14). The median number of lymph nodes dissected was 34 (range: 5–97). Fifty-nine patients (51%) had pENE. Forty-one patients (35%) received intraoperative brachytherapy (IOBT) to the primary site without resection while 75 patients (65%) received primary tumor resection. Of the resected patients, 35 underwent transoral robotic surgery (TORS). There was a strong trend for patients undergoing primary brachytherapy to having more advanced T stages than patients undergoing primary surgery (Supp. Table A). Ten patients (24%) receiving IOBT were cT3-4 while eight patients (11%) receiving primary tumor resection were cT3-4 (p = 0.051). Patients undergoing IOBT were treated with palladium-103 with a median dose of 25.74 Ci (range: 17.75–44.4 Ci). Of those receiving resection, 11 had positive margins (14%). Overall, 64 patients (55%) received post-operative chemoradiation (CRT), 38 (33%) received adjuvant RT alone, and 13 (11%) received no post-operative therapy. Within those receiving no post-operative therapy, eight were Stage I-II and pN0 on neck dissection. Of those receiving chemotherapy, 48 (74%) received cisplatin, six (9%) received carboplatin, four (6%) received a combination, and eight (12%) were not definitively specified due to treatment at an outside facility. Adjuvant RT was delivered with IMRT at a median dose of 58 Gy (range: 50–70 Gy) in 30 fractions (median; range: 20–38). Amongst the 63 patients with radiation fields that were available for review, 59 patients received radiation to the tumor bed and bilateral neck, while 4 patients received radiation to the tumor bed and ipsilateral neck only.

Table 1
Patient demographics.

Characteristic	Total (%)	≤4 pN+ (%)	≥5 pN+ (%)	P
Total	116	103 (88.8)	13 (11.2)	
Age: median [range], y	60 [36–87]	59 [36–87]	62 [48–81]	0.14
Sex				0.21
Male	101 (87.1)	88 (85.4)	13 (100)	
Female	15 (12.9)	15 (14.6)	0 (0)	
Disease Site				0.49
Tonsil and Soft Palate	64 (55.2)	58 (56.3)	6 (46.2)	
Base of Tongue	52 (44.8)	45 (43.7)	7 (53.8)	
Smoking				0.71
Never smoker	45 (38.8)	39 (37.9)	6 (46.2)	
Former smoker	40 (34.5)	37 (35.9)	3 (23.1)	
Current smoker	31 (18.7)	27 (26.2)	4 (30.8)	
Smoking dose, pys[a]				0.27
≤10, Light	62 (54.9)	53 (51.5)	9 (69.2)	
> 10, Heavy	51 (45.1)	47 (45.6)	4 (30.8)	
cT[b]				0.68
T1	40 (34.5)	37 (35.9)	3 (23.1)	
T2	58 (50.0)	50 (48.5)	8 (61.5)	
T3	12 (10.3)	10 (9.7)	2 (15.4)	
T4	6 (5.2)	6 (5.8)	0 (0)	
pN (AJCC 7th)[c]				< 0.001
N0	16 (13.8)	16 (15.5)	0 (0)	
N1	10 (8.6)	10 (9.7)	0 (0)	
N2a	24 (20.7)	24 (23.3)	0 (0)	
N2b	49 (42.2)	42 (40.8)	7 (53.8)	
N2c	12 (10.3)	6 (5.8)	6 (46.2)	
N3	5 (4.3)	5 (4.9)	0 (0)	
Primary Treatment				0.06
Brachytherapy	41 (35.3)	33 (32)	8 (61.5)	
Resection	75 (64.7)	70 (68)	5 (38.5)	
pENE				0.08
Negative	59 (50.9)	49 (47.6)	10 (76.9)	
Positive	57 (49.1)	54 (52.4)	3 (23.1)	
Surgical margins				> 0.99
Negative	62 (86.1)	57 (83.8)	5 (1 0 0)	
Positive	11 (13.9)	11 (16.2)	0 (0)	
Adjuvant Therapy[d]				> 0.99
None	13 (11.2)	52 (50.5)	12 (92.3)	
Chemotherapy	1 (0.9)	1 (1.0)	0 (0)	
RT	38 (32.8)	38 (36.9)	0 (0)	
CRT	64 (55.2)	12 (11.7)	1 (7.7)	

y = year. pys = pack-years. cT = clinical T stage. pN = pathologic N stage. AJCC = American Joint Committee on Cancer. pN+ = number of pathologically positive lymph nodes.

[a] Incomplete smoking data.

[b] Comparison of cT1-2 v cT3-4.

[c] Comparison of pN0-2a v pN2b-3.

[d] Comparison of any adjuvant therapy to none. *P* values determined by Fisher's exact test, chi-square, or student *t*-test where appropriate.

Survival outcomes

For all patients, the 3-year PFS and OS were 81% and 89% respectively. Of the 103 patients with ≤4 nodes, the 3-year PFS was 86%, while for the 13 patients with ≥5 involved nodes the 3-year PFS was 47% (Fig. 1; log-rank $P = 0.002$). However, 3-year OS was not significantly different in patients with ≤4 nodes at 90% and ≥5 nodes at 81% (log-rank $P = 0.26$).

We found no significant difference in 3-year OS between patients with pENE (91%) and those without pENE (86%) (log-rank $p = 0.30$) or 3-year PFS (pENE+ 83% and 77%, log-rank $P = 0.89$). Among patients with resection of the primary tumor, there was no difference in 3-year