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Extracapsular extension is associated with worse distant control and progression-free survival in patients with lymph node-positive human papillomavirus-related oropharyngeal carcinoma

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ABSTRACT

Objectives: To determine the prognostic utility of pathologic extracapsular extension (ECE) in human papillomavirus (HPV) associated oropharyngeal squamous cell carcinoma (OPSCC).

Materials and Methods: Retrospective analysis was performed on patients who underwent surgery for primary HPV-related OPSCC and received adjuvant radiotherapy (RT) between 2006 and 2015. Locoregional control (LRC), distant control (DC), progression-free survival (PFS) and overall survival (OS) were compared between the groups with and without ECE using univariate Kaplan-Meier and multivariate Cox regression survival analyses.

Results: 75 patients were identified and ECE was demonstrated on the surgical pathology of 26 patients. ECE(+) patients more frequently received chemotherapy (76.9% vs. 32.7%; $p < 0.0001$) and RT doses > 66 Gy (76.9% vs. 16.3%; $p < 0.001$). With a median follow-up of 29 months, patients with ECE had a significantly worse 5-year DC rate than those without ECE (76.7% vs. 97.9%; $p = 0.046$), and patients with ECE had a significantly worse 5-year PFS (54.5% vs. 93.6%; $p = 0.021$) than those without ECE. On multivariate Cox regression analysis, ECE was independently prognostic of worse DC (hazard ratio: 8.26; 95% confidence interval: 1.24–55.21; $p = 0.029$) and worse PFS (HR: 4.64; 95% CI: 1.18–18.29; $p = 0.028$). There was no statistically significant difference in 5-year LRC (93.3% vs. 95.7%) or OS (66.9% vs. 97.0%) between ECE(+) and ECE(−) patients, respectively.

Conclusion: This study suggests that ECE is independently prognostic of worse DC and PFS in patients who undergo surgery prior to adjuvant RT for primary HPV-related OPSCC.

Introduction

The presence of extracapsular extension (ECE) in lymph node-positive head and neck squamous cell carcinoma (HNSCC) leads to poor locoregional control (LRC), distant control (DC) and overall survival (OS) [1–8]. Due to its poor prognosis, histologically identified ECE is an indication for more aggressive adjuvant treatment, with both an increased dose of post-operative radiotherapy (RT) and concurrent chemotherapy [9]. Evidence supporting this approach largely stems from two contemporaneous, separately designed and run, phase III randomized trials, EORTC 22931 and RTOG 95–01, and the meta-analysis of their pooled data [10–12]. The pooled data demonstrated that there was a survival benefit of post-operative concurrent chemoradiation (CRT) over RT alone in patients with pathologic evidence of either ECE or positive surgical margins.

However, data regarding the prognostic importance of ECE in HNSCC is prior to the human papillomavirus (HPV) era. It is now well known that HPV is an important oncogenic factor in oropharyngeal squamous cell carcinoma (OPSCC) [13,14]. Not only is HPV an important etiologic factor, but it is also an important prognostic factor. HPV-related OPSCC carries a more favorable prognosis for both disease-free survival (DFS) and overall survival (OS) when compared with tobacco and alcohol related OPSCC [13–17]. Due to differences in cancer mechanisms, survival, disease progression and even sites of distant

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metastasis (DM) between HPV-related and non-HPV-related OPSCC, it is evident they are two biologically distinct entities [18]. Therefore, studies questioning the prognostic importance of ECE in HPV/p16(+) tumors have been performed, demonstrating that ECE lacks the same prognostic value in determining outcomes in patients with HPV/p16(+) OPSCC [19–26]. Recently, a meta-analysis including some of these studies found no association between ECE and disease-free survival (DFS) [27]. Our goal was to analyze the effect of ECE on disease control and survival of HPV(+) OPSCC in patients who underwent definitive surgery followed by adjuvant (chemo) radiation determined by pathology at our institution.

Patients and methods

Patient eligibility

Patients were selected from an Institutional Review Board approved database of head and neck cancer patients treated in the Department of Radiation Oncology at our institution. Preliminary inclusion for this study was based on disease site and treatment modality. Only patients who underwent primary definitive surgery for pathologic lymph node-positive, HPV(+) OPSCC (base of tongue, tonsil or soft palate) followed by adjuvant RT/CRT as indicated based on surgical pathology, or those patients who underwent neck dissection followed by definitive RT or CRT were included [9]. Patients were excluded if they received definitive RT, CRT or induction chemotherapy prior to definitive surgery. Patients were also excluded if they had prior head and neck irradiation, prior OPSCC or were undergoing palliative treatment. After initial therapy, patients were followed routinely by an otolaryngologist, medical oncologist and/or radiation oncologist with physical exam, in-office laryngoscopy and imaging (CT Neck and/or PET scans). Suspicious masses were biopsied to evaluate for recurrence.

Pathologic tumor data

All pathologic data were determined at the time of initial biopsy and surgery, and were gathered from electronic medical records at our institution. Paraffin-embedded, formalin-fixed pretreatment tissue from biopsy or resection specimens were tested for HPV using p16 immunohistochemical expression and/or HPV-16/18 genotyping. P16 positivity was defined as diffuse nuclear and cytoplasmic staining in > 70% tumor cells. ECE of the metastatic lymph nodes was determined by pathologists at the time of surgery, and was listed as positive or negative. ECE was defined by carcinoma infiltrating through the lymph node capsule into the perinodal soft tissue. The extent/grade of ECE was not routinely reported, and tumor specimens were not available for grading. Tumor stage, nodal stage, positive surgical margins, close surgical margins defined as ≤5 mm, lymphovascular space invasion (LVSI), and perineural invasion (PNI) were all recorded from the pathology reports at the time of surgery.

Statistical analysis

Baseline patient and tumor characteristics (Table 1) were compared using chi-squared and Fisher-exact tests for categorical variables and student's *t*-test for continuous variables. Primary endpoints of the study were locoregional control (LRC), distant control (DC), progression free survival (PFS) and overall survival (OS) following (C)RT. Patients were divided into two cohorts based on their ECE status, and all primary endpoints were evaluated using Kaplan-Meier plots and Cox proportional hazard ratios for univariate and multivariate survival analysis, respectively. Log-rank tests were used to determine significance in survival difference for univariate analysis. Endpoints of LRC, DC, PFS and OS were calculated using data from the last day of RT until the most recent follow-up for each endpoint. Cox regression analyses were then performed using a stepwise method with an entry probability of 0.05 and removal probability of 0.10. Parameters initially included in the regression analysis were ECE, positive surgical margins, significant smoking history (defined as ≥10-pack years smoking history), tumor stage (T3-T4 vs. T0-T2), nodal stage (N1-2a vs. N2b-N3), number of positive lymph nodes, presence of a close margin, LVSI, PNI, RT dosing, and whether or not concurrent chemotherapy was used. Significant smoking history was categorized as 10-pack years or greater, as has been done elsewhere when risk-stratifying patients [24,28,29]. Statistical significance was set at < 0.05, and all hypothesis tests were 2-sided. Baseline clinicopathologic factors were compared using SAS statistical package (version 9.3; SAS Institute Inc., Cary, NC). Survival statistics were performed using Statistical Package for the Social Sciences version 20 (IBM, Armonk, NY).

Table 1
Baseline patient and tumor characteristics.

Variable, No. (%)	ECE(+) (n = 26)	ECE(−) (n = 49)	P value
Mean age (range)	57 (41–84)	58 (39–85)	0.954[a]
Male sex	23 (88.5)	42 (85.7)	0.269[b]
pT stage			0.347[b]
0–2	24 (92.3)	46 (93.9)	
3	1 (3.9)	3 (6.1)	
pN stage			0.129
1-2a	8 (30.8)	24 (49.0)	
2b-3	18 (69.2)	25 (51.0)	
Bilateral nodes	2 (7.7)	2 (4.1)	0.508
Mean positive nodes (range)	2.53 (1 −6)	2.29 (1 −8)	0.532[a]
> 10 pack years smoking history	3 (11.5)	9 (18.4)	0.205[b]
Positive margins	9 (34.6)	10 (20.4)	0.178
Close margins	5 (19.2)	15 (30.6)	0.289
LVI	9 (34.6)	17 (34.7)	0.995
PNI	5 (19.2)	8 (16.3)	0.234[b]
Concurrent chemotherapy	20 (76.9)	16 (32.7)	**< 0.001**
Chemotherapy Agent			0.973[b]
Cisplatin based	14 (53.9)	13 (26.5)	
5-FU/hydroxyurea based	3 (11.5)	2 (4.1)	
Cetuximab	1 (3.9)	0 (0.0)	
Carboplatin/paclitaxel	1 (3.9)	1 (2.0)	
Docetaxel/cetuximab	1 (3.9)	0 (0.0)	
RT dosing (Gy)			**< 0.001**[b]
≥70	2 (7.7)	2 (4.1)	
66	18 (69.2)	6 (12.2)	
60–64	3 (11.5)	31 (63.3)	
< 60	3 (11.5)	10 (20.4)	
HPV test			0.262[b]
p16 only	4 (15.4)	7 (14.3)	
HPV DNA	22 (84.6)	42 (85.7)	

[a] Denotes student's T-test.
[b] Denotes fisher-exact test.

Results

In total, 75 patients with a median follow-up of 29 months (range 2–115 months) underwent adjuvant RT in the Department of Radiation Oncology at our institution for pathologic lymph-node positive, HPV(+) OPSCC following surgery from 2006–2015 and were included in this analysis. There were 26 patients with ECE, and 49 without. The only statistically significant differences in baseline patient or tumor characteristics between the ECE(+) and ECE(−) cohorts included treatment modality, with a much higher proportion of ECE(+) patients receiving CRT and a higher dose of RT when compared with ECE(−) patients (Table 1). These differences are expected, since the presence of ECE is an indication for CRT and a higher postoperative RT dose. Six patients with ECE did not receive concurrent chemotherapy for the following reasons: 4 patients were offered but declined chemotherapy, 1 patient was not a candidate for chemotherapy given his age and comorbidities, and 1 patient did not receive chemotherapy for unknown reasons.