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Characteristics and kinetics of cervical lymph node regression after radiation therapy for human papillomavirus-associated oropharyngeal carcinoma: Quantitative image analysis of post-radiotherapy response

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SUMMARY

Background and purpose: We sought to characterize the pattern of lymph node regression and morphology following definitive radiation therapy (RT) for human papilloma virus (HPV)-associated oropharyngeal carcinoma in patients with disease control.
Materials and methods: Radiographically positive cervical lymph nodes from patients treated with definitive RT for HPV-associated oropharyngeal carcinoma were segmented on initial pre- and subsequent post-RT contrast enhanced CT images. Pre-specified quantitative nodal parameters were calculated. Initial nodal parameter correlates of final nodal size, final nodal volume, and time to <1 cm short-axis diameter were determined.
Results: Sixty-six radiographically positive lymph node were analyzed in 36 patients. Lymph nodes exhibited initial volume decreases with size stabilization at ~4 months. Fifteen nodes (23%) underwent complete radiographic response (median 6.4 months following RT; range 2.9–25.6 months). On multivariate time-to-event analysis, initial hypodense/fat component, nodal volume, and short-axis diameter exhibited inverse association, while higher HU standard deviation exhibited a positive association, with reaching <1 cm short-axis diameter (all p <0.05).
Conclusions: Our results showed a substantial decrease in nodal volume within the first 1–2 months following RT. These findings support our current nodal imaging paradigm, propose a quantitative methodology, and describe a reference dataset for further validation and comparison studies.

Introduction

The incidence of oropharyngeal carcinoma in the United States is increasing, primarily due to human papillomavirus (HPV)-associated cases [1]. HPV-associated oropharyngeal carcinomas commonly presents with advanced regional lymph node (LN) involvement with heterogeneous nodal imaging characteristics [2]. Such nodes exhibit diverse morphologic components including solid, cystic, and necrotic elements [3,4]. Standard treatment paradigms for oropharyngeal carcinoma have centered on definitive radiation therapy (RT), often in sequence and/or in combination with systemic therapy. Surgery, specifically neck dissection, is typically reserved for evidence of residual nodal disease on follow up imaging [5].

Contrast enhanced computed tomography (CT) of the neck (CECTN) has been the primary imaging modality for initial cervical LN staging evaluation and subsequent treatment response assessment at our institution. Whole body FDG-PET/CT, MRI neck, US neck and US-guided FNA are also integrated in select cases [6,7]. Our current post-RT neck management paradigm includes consideration for neck dissections 8–12 weeks after RT completion and relies greatly on post-treatment CECTN imaging assessment [8–12].

We hypothesize that pretreatment cervical LN imaging characteristics influence the kinetics and pattern of radiographic LN

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regression and potentially impact the CECTN characteristics of the final nodal remnant. We undertook this study in order to establish a workflow to evaluate multi-parametric CT nodal regression characteristics and to create a reference dataset of radiographic LN regression patterns in a modern cohort of HPV-associated oropharyngeal carcinoma patients, with disease control following RT or concurrent chemoradiation alone (i.e. without neck dissection). The specific aims of the current study included: (1) quantitative characterization of radiographic nodal regression in HPV-associated oropharyngeal carcinoma radiation responders over time; (2) identification of quantitative imaging parameters as correlates of nodal regression; (3) generation of testable hypotheses for future comparison and prospective research.

Material and methods

Patients

Following Institutional Review Board approval, departmental databases were searched to identify adult patients irradiated at our institution for LN-positive HPV-associated oropharyngeal carcinoma. HPV status was determined by review of the medical records and pathology reports. Cases were considered HPV-associated if tested tumor specimens were positive for p16 by immunohistochemistry or high-risk HPV DNA by in-situ hybridization. Inclusion criteria were: (1) treatment with definitive RT with or without concurrent systemic therapy; (2) pre-treatment CECTN DICOM images available for evaluation; (3) clinical disease control with minimum of two years follow up post-RT; (4) at least two post-treatment diagnostic CECTN DICOM images over a minimum of 6 months follow up. Exclusion criteria were: (1) receipt of neo-adjuvant/induction or adjuvant systemic therapy; (2) receipt of pre- or post-RT neck dissection (pre-treatment excisional LN biopsies were allowed, given that at least one radiographically evident positive LN remained for evaluation); (3) development of local, regional, or distant recurrence following initial treatments; (4) prior RT to the head or neck; (5) distant metastatic or recurrent disease at presentation.

Imaging

Pre- and post-treatment CECTN DICOM images for all cases were transferred to the Pinnacle RT treatment planning system (ver. 9.4, Phillips, Andover MA). For this study, LNs analyzed were those reported as positive on diagnostic imaging reports, identifiable on the pre-treatment diagnostic CECTN, and generally met any of the following criteria: (1) size > 1.0 cm on short axis (while considering nodal level), (2) peripheral or irregular contrast enhancement, (3) presence of focal or central lucency or necrosis, (4) round rather than kidney/reniform shape, and (5) presence of radiographic extracapsular extension [10,13–16]. As per standard RT target delineation practice, individual positive cervical LNs were manually segmented/contoured, on a slice-by-slice basis and assigned a unique region of interest (ROI).

LNs included in this study were those described and annotated as positive in initial diagnostic radiology reports. Delineation of these nodes were corroborated in a peer fashion review at our departmental bi-weekly Head and Neck Development and Planning Clinic, as previously described [17]. Post-RT nodal volumes were delineated likewise (C.T.) with 15% of cases subjected to additional peer-review (G.B.G.).

Per institutional practice, the first post-RT follow-up CECTN was typically obtained 8 weeks following RT completion, then 3–4 months thereafter during the first two years of follow up, then every 6 months up to 5 years, and subsequently on an annual basis. Imaging follow-up at our institution generally consists of CECTN with PET and MRI reserved for equivocal findings and physician preference. CECTN images were typically obtained at our institution with 1.25-mm-section thickness and 25-cm FOV. Standard imaging generally used 120-mL iohexol (Omnipaque; GE healthcare, Princeton NJ) contrast, with imaging on a multi-slice scanner (Optima, GE Healthcare, Milwaukee WI). All follow up CECTNs and 33 of 36 (92%) baseline images were conducted at our institution.

CT parameters

Quantitative CT-based nodal characteristics were determined for segmented LNs ROI at each time-point using Pinnacle treatment planning system. Associated statistics were calculated using Matlab ver. 8.0 (MathWorks, Natick MA). Preselected nodal parameters included median and mean Hounsfield units (HU), HU standard deviation, and total nodal volume. CT intensity-volume histograms (i.e. plotting HU vs. ROI volume) were generated for each LN ROI. ROI volumes were segmented into four categories by HU: <0, 0–30, 30–170, and >170 HU. The proportion of the nodal ROI within these HU ranges were then labeled as follows: 0–30, fluid; 30–170 HU, soft tissue; <0 HU, hypodensity/fat; >170 HU, enhancement/calcification [4,18].

For all LNs, the involved anatomic nodal station was recorded based on consensus guidelines [19] and the greatest short axis dimension in the axial plane was measured. Nodes were scored as complete radiographic responders in the event that a treated nodal remnant could not be identified visually. In such instances all nodal parameters were set to zero.

Statistical analysis

Continuous and categorical variables were compared using Fisher's exact and Wilcoxon rank-sum tests, respectively. Univariate and multivariate linear regressions were utilized to associate initial CETCN parameters with final node short-axis diameter and final volume. Final short-axis diameter and nodal volume were considered the volumes on the final reviewed post-treatment scan.

To discretize continuous variables, optimal cutpoints were calculated utilizing X-Tile software [20]. As such an analysis assesses multiple cutpoints, Miller-Seigmund *P*-values to correct for multiple comparisons are reported in addition to log-rank *p*-values for univariate analyses. Univariate and multivariate time-to-event analyses were conducted via Kaplan–Meier and Cox regression for the *a priori* endpoint of LN regression to <1 cm short-axis diameter. This endpoint was chosen as a conservative benchmark frequently used in our institution. Tests were two-sided when appropriate with significance considered at $p < 0.05$. Statistical analyses were conducted using JMP v10 and SAS v9.3 (both SAS Institute Inc., Cary, NC).

Results

Patient and initial nodal characteristics

Between March 2004 to December 2011, 202 patients with oropharynx cancer with known HPV status were screened. Patients were excluded due to receipt of induction chemotherapy ($n = 125$), occurrence of locoregional failure, distant metastatic failure, or death ($n = 11$), N0 disease or excisional biopsy removing the only pathologic node ($n = 20$), and lack of pre-treatment CECTN, inadequate followup, imaging with modalties outside of CECTN ($n = 10$).

Within the remaining 36 patients, sixty-six radiographically positive LN ROIs were segmented and analyzed. Patient, disease,