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# Prevalence, prognosis, and treatment implications of retropharyngeal nodes in unknown primary head and neck carcinoma

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ABSTRACT

*Objective:* (1) To estimate the prevalence of radiographically positive Retro-Pharyngeal Lymph Nodes (RPLN) in unknown primary carcinoma of the head and neck and (2) to determine the prognostic implications of radiographically positive RPLN and other radiographic features (3) to identify patients at low risk for retropharyngeal metastasis.

*Materials and methods:* The medical records of all 68 eligible patients treated at the Princess Margaret Cancer Centre between 2000 and 2014 were retrospectively reviewed for demographic, clinical, pathologic, and radiologic data. Radiologic data included: RPLN, extra capsular spread (ECS), neck staging and cystic/necrotic or matted neck nodes. LRR, DR, DFS and OS were estimated using the competing risk methods and the Kaplan-Meier method.

*Results:* Seven patients had concerning RPLN (10.3%). Forty-four patients were p16 positive (65%). RPLN status did not have any effect on LRR, DFS, DR and OS. Radiological ECS and p16 (neg.) status were found to be significant predictors of LRR ($p = 0.023$; $p = 0.014$). Matted nodes, radiological ECS and p16 (neg.) status were found to be significant predictors of DFS ($p = 0.012$; $p < 0.001$; $p = 0.014$). Matted nodes and radiological ECS were found to be significant predictors of OS ($p = 0.017$; $p = 0.0036$). Only radiological ECS was found to be a significant predictor of distant recurrence ($p = 0.0066$).

*Conclusions:* 10% of CUP patients will harbor radiological positive RPLN. A large proportion of CUP patients are positive for p16. Radiologic features such as ECS and matted nodes can predict worse outcomes.

## Introduction

Despite diagnostic efforts to locate a primary tumor, roughly 3 percent of patients presenting with metastatic squamous cell carcinoma (SCC) to the neck will have no identifiable primary site [1]. Patients who initially present with metastatic lymph node(s) usually undergo a diagnostic work-up that includes physical examination, diagnostic imaging, which may include PET/CT, as well as pan-endoscopy and biopsy of suspicious mucosal primary sites and palatine tonsillectomy. This historical approach may identify as many as 44% of primary tumors [2]. Of those tumors identified at the time of pan-endoscopy, as many as 89% are oropharyngeal carcinomas [3].

Patients with primary tumors in the pharyngeal axis may develop metastatic nodes to the retro-pharyngeal nodal basin in addition to metastatic nodes to the lateral neck. In a large series of patients with oropharyngeal carcinoma, the prevalence of radiographically positive retropharyngeal lymph nodes (RPLN) was 10 percent [4]. However, the prevalence of retropharyngeal nodes in patients with unknown primary carcinoma is currently unknown.

In patients who were treated with primary surgery for early T

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category oropharyngeal squamous cell carcinoma, one study demonstrated a pathologically positive retropharyngeal nodal rate of 11% (14% in tonsil primaries vs 0% in base of tongue primaries) among 72 patients [5]. In this study, the negative predictive value with pre-operative computed tomography was 93% and that of PET-CT was 92.6% suggesting the presence of occult positive nodes. The authors noted that in patients with either a single node or no nodes on pre-operative clinical staging (N0-N2a), there were no positive retropharyngeal nodes. In another study in which patients were managed with primary surgery, the rate of occult positive retropharyngeal nodes in the absence of radiographically positive features was 7.4% [6].

The presence of radiographically enlarged RPLNs is a harbinger of poor outcomes and is associated with a lower recurrence free survival (81% vs. 51%, $p < 0.001$) and overall survival (82% vs. 52%, $p < 0.001$) in patients diagnosed with oropharyngeal carcinoma [4]. In addition to the presence of RPLN, other radiographic features of lymphatic regional disease have been shown to be associated with better or worse outcomes in patients with oropharyngeal carcinoma: These include the radiographic N category [7], the presence of cystic nodes [8], necrotic nodes [9], and extracapsular spread [10]. To date, there is little data showing the prognostic implication of these adverse radiographic features in patients with unknown primary carcinomas (CUP).

The treatment of patients with CUP varies by institution with treatment approaches ranging from neck dissection with or without adjuvant therapy to definitive radiotherapy with or without chemotherapy. Similarly, management of the retropharyngeal region is variable depending on patient features and institutional practice. More recently, Trans-oral Robotic Surgery (TORS) or Trans-oral laser microsurgery (TLM) have been utilized in the identification or resection of small volume primary tumors that may have otherwise escaped identification [11–13]. Often these procedures are combined with lateral neck dissection. To better understand the need and extent of adjuvant therapy after such procedures, it is imperative to define the at-risk lymph node basins. The goals of the present study are (1) to estimate the prevalence of radiographically positive RPLN in unknown primary carcinoma of the head and neck and (2) to determine the prognostic implications of radiographically positive RPLN and other radiographic features (3) to identify patients at low risk for retropharyngeal metastasis who may not require prophylactic treatment.

## Materials and methods

Patients with a final diagnosis of CUP treated at Princess Margaret Cancer Centre between 2000 and 2014 were identified from a prospective *Head and Neck Cancer Anthology of Outcome Database* [14]. Institutional Research Ethics Board approval was obtained prior to conducting the study. Patients were excluded for the following reasons: unavailable pre-treatment imaging, previous head and neck cancer, and unknown p16/HPV status. Demographic, clinical, pathologic, and radiologic data were recorded on included patients. Patient smoking status was classified as current smoker, past smoker or never smoker. Past and current smokers were further categorized based on a smoking pack year history of greater than or less than ten pack years. The initial pretreatment diagnostic imaging studies were reviewed by a dedicated head and neck radiologist (EY) for the presence or absence of radiographically positive RPLN. For the purposes of this study, the boundaries of the retro-pharynx were defined cranially by the upper edge of the body of C1/hard palate; caudally by the cranial edge of the body of the hyoid bone; anteriorly by the posterior edge of the superior or middle pharyngeal constrictor muscle; posteriorly by the longus capitis muscle and longus colli muscle; laterally by the medial edge of the internal carotid artery; and medially by a line parallel to the lateral edge of the longus capitis muscle [15]. Patients with any of the following RPLN imaging characteristics were considered to have radiographically positive RPLN: minimal axial diameter > 5 mm or a maximal axial diameter of 10 mm; presence of central necrosis or hypodensity; Presence of > 1 lateral RPLN or hyper-metabolic activity on PET (maximum standardized uptake value > 4.5). In addition, any identifiable median RPLN on imaging was considered positive [4].

We collected information pertaining to other prognostic variables that may confound the prognostic effect of RPLN. These prognostic variables included other imaging features, such as radiographic extranodal extension (ENE), the presence of cystic nodes, the presence of necrotic nodes, radiographic N category on imaging. Radiographic ENE was defined as a thick-walled, enhancing nodal margin with loss of outer nodal margin definition and infiltration of the adjacent fat planes around portions of the node [16]. Cystic nodes were defined as round or ovoid masses with a thin (< 2 mm) enhancing capsule, homogeneous fluid content, and no internal complex, irregular, or solid area [17]. Necrotic nodes were defined as nodes with thicker solid walls and irregular, complex central low attenuation [17]. N category was defined according to the AJCC TNM Staging System for Head and Neck Tumors (AJCC 7th edition, 2010) [18]. In addition, all patients had known p16 status. p16 status was defined as positive when there was moderate to strong diffuse cytoplasmic and nuclear staining in ≥ 50% of tumor cells and tumor displayed basaloid or non-keratinizing morphology.

Dosimetry parameters were retrieved from radiotherapy plans that were delivered as part of the treatment course. Right and left parotid mean doses were obtained from the clinical radiotherapy treatment planning system (Pinnacle).

Demographic variables were analyzed using descriptive statistics using SAS. Predictors of the presence of retropharyngeal nodes (nodal category, radiographic ENE, cystic nodes, necrotic nodes, matted nodes) were examined in univariate analysis using logistic regression. Failure in the pharyngeal axis was defined as disease emergence in the nasopharynx, oropharynx, hypopharynx, or larynx. Loco-regional recurrence (LRR) was defined as either emergence of primary site or recurrence in the lymph nodes of the neck including the retropharyngeal lymph node basin. Distant recurrence (DR) was defined as any clinical or radiographic evidence of disease outside of the head and neck region. Disease free survival (DFS) was defined as survival without any evidence of disease at any site, and as such, both deaths and disease recurrence represented events. Overall survival (OS) was defined as death due to any cause. Treatment finish date was used as time point zero. LRR and DR were estimated using the competing risk methods. DFS and OS were estimated using the Kaplan–Meier method. The significance of predictors of loco-regional control, distant control, OS and DFS was assessed in univariate analysis using Cox proportional hazard models. Dosimetry parameters were compared using unpaired t-tests. A two-sided *p*-value of less than 0.05 was considered statistically significant for all measures.

## Results

Of 146 consecutive patients diagnosed with CUP during the study period, 68 patients, 60 males (88%) and 8 females (12%) met the inclusion criteria. The mean age was 60.4 (Median 58.5; range 42.1–87.2). Forty-four patients (65%) were p16 positive. Fourteen patients (20%) had an N1 nodal disease, 16 patients (24%) N2a nodal disease, 34 patients (50%) N2b nodal disease, 1 patient (1.5%) N2c nodal disease and 3 patients (4.5%) N3 nodal disease. Baseline clinical and treatment details can be found in Table1.

Seven patients had radiographically positive RPLN (10.3%). Of these 3 of 44 (7%) p16 positive patients and 4 of 24 (17%) p16 negative patients had RPLN (HR = 0.37 for p16+, $p$ = NS) and 1 of 30 (3%) with N1-N2a disease and 6 of 38 (16%) with N2b-N3 disease (HR = 3.22 for N2b-N3, $p$ = NS). Six of the seven patients had RPLN ipsilateral to the lateral neck disease and one patient had bilateral RPLN. The rates of radiographic ENE, cystic, necrotic, or matted nodes were 28%, 37%, 60%, and 13%, respectively. In univariate analysis, all tested variables, including nodal status, p16 status, presence of cystic or