



Squamous cell carcinoma of the head and neck with unknown primary: trends and outcomes from a hospital-based registry

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Background: Squamous cell carcinoma of unknown primary of the head and neck region is a known entity described mainly by retrospective reports. We searched a hospital-based registry to better describe the changing incidence, and to assess diagnostic and treatment strategies.

Methods: The National Comprehensive Cancer Database was queried for head and neck cancers from oropharynx, tonsil, tongue, larynx, hypopharynx primary sites with a designation of clinical T0, representing an unknown primary. Kaplan Meier, Cox multivariate models, and propensity matched cohorts were used to assess significant factors for overall survival.

Results: There were 964 cases that met the criteria, and 468 cases with known treatments, staging, and survival data. The incidence increased over time, with the highest rates supported in the last 5 years. In patients who underwent HPV testing, 72% were positive. Patients with AJCC 7th clinical N2c or N3 disease had significantly worse outcomes despite the majority receiving neck dissection, radiation, and chemotherapy. Local surgery, compared to incisional or excisional biopsy, had the highest diagnostic yield of finding a primary tumor. In multivariate models, no combination of surgical approach, radiation, or systemic therapy was significantly associated with improved survival. This remained true in 1:1 propensity matched cohorts for age, comorbidities, and clinical nodal burden. In a subset of cN1 patients, combined chemoradiation therapy after excisional biopsy or local surgery was associated with (not statistically significant) improved survival compared to radiation alone (P=0.054).

Conclusions: The incidence of unknown primary head and neck carcinoma is increasing, and current cases have a high proportion of HPV positivity. HPV positivity predicts strongly for a tonsil primary. Local surgery was associated with the highest diagnostic yield. Clinical nodal burden strongly predicts for overall outcome, and type of treatment facility is an important driver of survival. A subset of cN1 patients may benefit from the addition of chemotherapy to radiation.

Keywords: Unknown primary; squamous cell carcinoma head and neck; radiation therapy

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Introduction

Squamous cell carcinoma of the head and neck of unknown primary is a rare diagnosis which represents 3–9% of all squamous cell malignancies of the head and neck region (1). Typical clinical presentation comprises cervical nodal metastasis in the absence of an identifiable primary lesion by imaging or pathologic confirmation, described in multiple retrospective reports (2–5). In the absence of prospective trials to guide treatment recommendations, the National Comprehensive Cancer Network (NCCN) currently recommends surgery, systemic therapy, radiation, or the combination of these treatments (6). We sought to better characterize the incidence, diagnostic strategies, and treatment using a hospital-based patient registry. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-4631>).

Methods

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study (STUDY00005643) was approved by our university's institutional review board, and individual consent for this retrospective analysis was waived as we utilized a nationally available, de-identified, and hospital-based data set. The National Cancer Database (NCDB) (7) was queried for head and neck cases with a clinical T0, node-positive squamous cell carcinoma of the larynx, oropharynx, tonsil, floor of mouth, tongue, and hypopharynx diagnosed between 2004 and 2015. Patients were over 18 years of age, and those with metastatic disease were excluded. Primary sites for all patients were recorded in the database reflecting the best clinical judgement of the records per data input staff of the NCDB. Staging was based on the American Joint Committee on Cancer (AJCC) 7th edition. All eligible patients were included for overall assessment of trends and diagnostic work up, and patients with complete survival data were included in survival analyses (Figure 1). The primary end point recorded in NCDB files is overall survival. Patient characteristics, stage, and treatments are recorded per NCDB guidelines, published at their website (7).

Statistical analysis

T-test, Chi-squared test, and Kruskal Wallis tests compared characteristics between groups. Survival was evaluated by

Kaplan Meier and log-rank tests. Cox proportional hazard models were constructed to describe factors affecting survival. Inverse probability of treatment weighting was constructed to assess the average treatment effects. Propensity score matched 1:1 cohorts were constructed using the STATA (College Station, TX) psmatch2 package with a caliper size of 0.2 to account for mismatches in patient characteristics (8). A two-sided P value of 0.05 was set as significant. In survival analyses, patients with missing categorical data were dropped from analysis.

Results

Demographics and characteristics of entire population

A total of 964 subjects met the inclusion criteria as shown in Figure 1, with characteristics as described in Table 1. Half of all cases were designated as a 'tonsil' or 'oropharynx' primary, and 29% classified as 'tongue' by NCDB subset coding. ICD-0 (version 3) primary site codes are captured in the database, and the most common were tonsil (n=305, code C09.X), base of tongue (n=177, code C01.X), and oropharynx not otherwise specified (n=164, code C10.9). Human papillomavirus (HPV) results were available for 412 patients, with 306 being positive. Pathologic nodal staging was recorded in patients who received regional nodal surgery or at least an incisional biopsy. Five hundred fifty-five patients were designated as having received 'regional nodal therapy', which was considered to be a neck dissection. Two hundred ninety-eight patients were designated cT0 cN0, but 112 of these received radiation or both radiation and chemotherapy, illustrating the difficulty in stage identification. Due to these initial uncertainties, only limited analysis of the overall population was performed.

To assess if HPV status was predictive of tumor site, a subgroup of 165 patients with HPV testing results and a pathologic T stage diagnosis was formed, which would represent those with clinically occult primaries who were eventually identified. In 31 patients with HPV negative disease, 13 (42%) were tonsil followed by 11 (35%) as tongue. In 134 patients with HPV positive disease, 101 (75%) were tonsil followed by 25 (19%) as tongue. This proportion was significantly different (P=0.0005).

Treatment breakdown of the 964 patient cohort

There was a broad distribution of treatments. One hundred sixty-four patients (17%) received either an incisional or

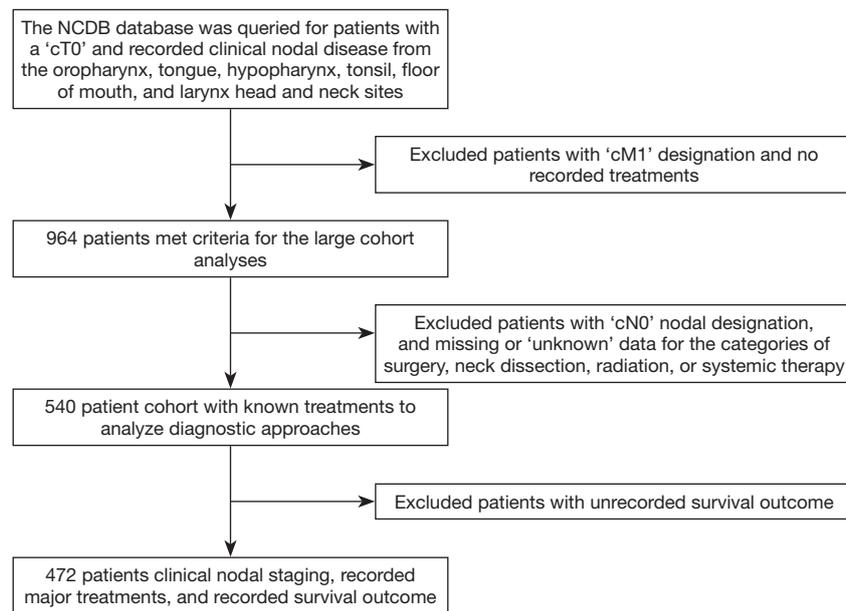


Figure 1 Flowchart of patient selection and subgroups.

Table 1 Patient and disease characteristics of the entire cohort

	Median (range) or N
Age (yrs)	57 (22–90)
Sex	
Male	753
Female	211
Charlson Deyo Score	
0	806
1	136
2+	22
HPV status	
Pos	306
Neg	96
Unknown/not reported	562
Facility type	
Community Ca program	75
Comprehensive community Ca program	370
Academic/research program	382
Integrated Network Cancer program	122
Year of diagnosis	
2004–2009	296
2010–2015	668

Some cells will not add up to 964 due to missing fields in database

excisional biopsy with no further therapy. Five hundred fifty-five patients (58%) received regional nodal surgery, and 318 (33%) of these patients had removal of five or more nodes. Fifty-eight patients (6%) received a definitive primary surgery, with 35 (60%) subsequently undergoing adjuvant radiation or chemoradiation. Excluding the 58 patients who received radical surgery (n=906), 175 patients (19%) received radiation alone after biopsy or local excision, and 449 (50%) received chemoradiation therapy.

Survival analysis

Five-year overall survival (5-yr OS) was 77%. Patients who received chemoradiation had a 5-yr OS of 81%, 74% for those who received radiation alone, and 70% for those who received neither (P=0.054). In a multivariate Cox model including clinical stage group, HPV status, Charlson-Deyo score, receipt of nodal surgery, receipt of local or radical surgery, and receipt of radiation or chemoradiation, only HPV positive disease (HR =0.45, 95% CI: 0.22–0.94, P=0.04) and increasing Charlson-Deyo score (HR =1.5, 95% CI: 1.16–1.93, P=0.002) were significantly associated with improved and worse OS, respectively.

Population excluding cN0 with known treatments

A population excluding cN0 nodal designation, and

Table 2 Patient and disease characteristics of the cohort with recorded nodal stage and known treatments (n=540)

	Median (range) or N
Clinical nodal stage	
N1	145
N2/N2a	143
N2b	172
N2c	33
N3	47
HPV status	
Pos	224
Neg	48
Unknown	268
Neck dissection	
No	145
Yes	395
Surgical investigation of primary site	
Incisional biopsy only	318
Excisional biopsy	51
Local surgery	152
Radical surgery	19
Radiation and chemotherapy	
No radiation	63
Radiation alone	93
Radiation and chemotherapy	384
Time from diagnosis to treatment (days)	
First surgical procedure	0 (0–352)
Radiation	62 (12–456)
Systemic therapy	56 (5–835)

missing data or 'unknown' for surgery to the primary site, regional nodal surgery, radiation therapy, or systemic therapy was constructed. This produced a cohort of 540 patients (Table 2). Survival data was available for 472 of these patients. The incidence of unknown primary diagnosis per these criteria increased over time, from nine cases entered in 2004 to 89 cases in 2014, and 72 cases in 2015. Ninety-three percent of patients were Caucasian. HPV testing was performed in 272 patients, of which 224 were positive (72%).

Surgical approach to primary tumor and rate of pathologic discovery

In the cohort of 540 patients, 429 (79%) had a recorded pathologic T-stage. Of these 429 patients, 216 (50%) underwent an incisional biopsy of a potential primary or nodal site only, 46 (11%) underwent excisional biopsy, 148 (35%) underwent local surgery (defined by site specific codes, such as tonsillectomy), and 19 (4%) underwent radical surgery. The most rigorous staging procedure per patient was recorded for the following analysis (for instance if both excisional biopsy and local surgery were performed, the patient was designated as receiving local surgery as his or her diagnostic approach). If a pathologic T-stage was coded this was treated as success of the diagnostic procedure to estimate diagnostic yield. The diagnostic yield of incisional biopsy only was 5% (10 of 216 patients had pathologic confirmation of a primary tumor), for excisional biopsy 65% (30 of 46 patients), and for local surgery 86% (126 of 148 patients), respectively. Almost all pathologic primary tumors were pT1 (129 patients, 73%) or pT2 (38 patients, 21%) regardless of the surgical procedure used.

Surgical approach to regional nodes

Three hundred ninety-five of the 540 patients (73%) received regional lymph node surgery. In 108 of these patients (27%), the number of lymph nodes removed was 1–5, and in 203 (51%) the number was greater than 5, with the remaining 84 patients designated as having undergone node directed surgery but with an unknown number of nodes removed. There were significant differences in the extent of clinical nodal disease in patients who did or did not have regional nodal surgery ($P=0.0004$ KW). Compared to those who did not receive regional nodal surgery, patients who underwent regional nodal surgery were more likely to be cN1 (29% vs. 21%) or cN2a (29% vs. 19%), and less likely to be cN2c (5% vs. 8%) or cN3 (6% vs. 16%, $P=0.001$).

Receipt of radiation and systemic therapy

Four hundred seventy-seven of 540 patients (88%) received radiation therapy. Three hundred ninety-four patients (73%) received systemic therapy, 286 of whom (73%) were designated as single agent and 108 (27%) designated multiagent. Overall, 384 patients (71%) received radiation and chemotherapy, 93 (17%) received radiation alone,

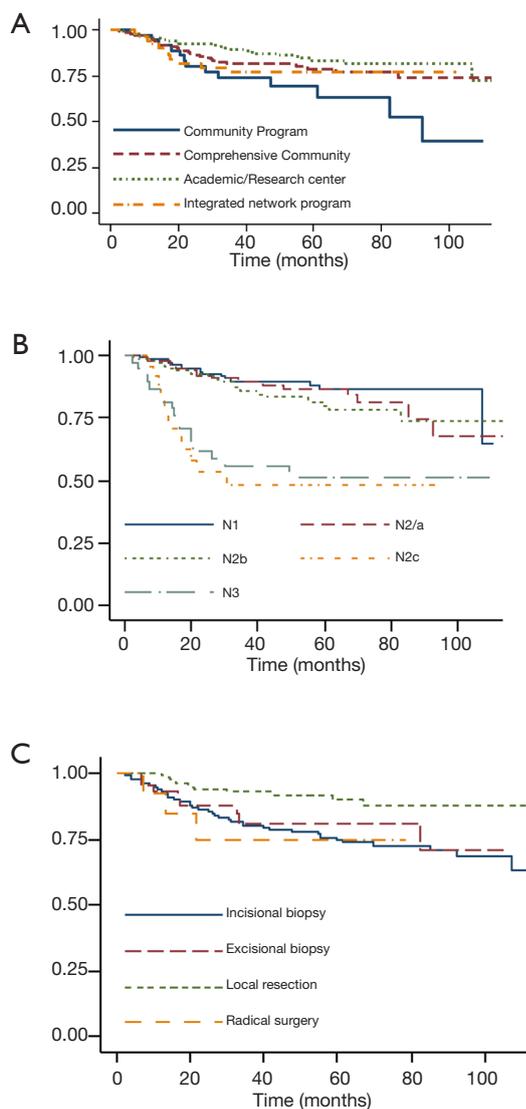


Figure 2 Kaplan-Meier curves of overall survival for (A) facility type, (B) clinical nodal stage, and (C) extent of local surgery for patients with survival data.

and 63 (12%) received neither. Of these 63 patients who received neither, 40 received incisional biopsy only as the highest form of treatment and were essentially untreated.

Survival analysis

Five-year OS for the group of 472 patients was 79% and median survival was greater than 144 months. On univariate Cox analysis, increasing age (HR =1.05, 95% CI: 1.03–1.07, P=0.0001), clinical nodal status of cN2c or cN3 (HR =6.4,

95% CI: 3.02–13.86, P=0.0001 and HR =5.08, 95% CI: 2.71–10.70, P=0.0001) and increasing Charlson Deyo score (for 1, HR =1.91, 95% CI: 1.13–3.23, P=0.02, and for 2, HR =3.73, 95% CI: 1.17–11.97, P=0.03) were associated with worse OS. HPV status was not significant in the group of 224 patients with known HPV status (HR =0.39 for positive versus negative, 95% CI: 0.13–1.18, P=0.095), though only 15 failures occurred in this population. In a stepwise comparison in reference to treatment at a community cancer program, treatment at an academic/research center was associated with improved overall survival (HR =0.33, 95% CI: 0.19–0.72, P=0.004), while treatment at a comprehensive community cancer center was borderline (HR =0.53, 95% CI: 0.30–1.06, P=0.053). Kaplan-Meier curves are shown in *Figure 2*.

Comparing surgical approaches to a potential primary site with incisional biopsy alone as reference, local surgery (i.e., tonsillectomy) was associated with improved OS (HR =0.37, 95% CI: 0.21–0.73, P=0.003) while excisional biopsy or radical surgery were not (HR =0.92, 95% CI: 0.46–1.85, P=0.81). OS differed by pathologic T stage, with 5-yr OS for patients with pT0, pT1, and pTX designations 75%, 92%, and 75% respectively (P=0.0001 by log rank).

On univariate analysis, neither receipt of regional neck surgery (HR =0.72, 95% CI: 0.45–1.12, P=0.15), radiation therapy (HR =0.84, 95% CI: 0.45–1.59, P=0.59), or systemic therapy (HR =1.04, 95% CI: 0.64–1.71, P=0.68) were associated with improved OS. Neck dissection remained non-significant when analyzed as number of nodes removed as a continuous variable (HR =1.00, 95% CI: 0.99–1.01, P=0.3), or when examination of ≥ 18 nodes was used as a cut off (HR =1.22, 95% CI: 0.93–1.58, P=0.12). Radiation fields were defined as head and neck without further specification in 51% of patients, a ‘limited’ head and neck field in 31% of patients, and neck radiation only in 2% of patients. Of the patients who received systemic therapy, 73% received a single agent. In a similar comparison of no radiation, radiation, or radiation and chemotherapy, no factor was associated with OS (HR =0.85, P=0.654). Similarly, receipt of regional nodal surgery was not significant by log-rank in each subset of clinical nodal stage analyzed separately (data not shown). Multivariate Cox analysis is shown in *Table 3*. While patient, disease, and clinical nodal burden is correlated with outcomes, no treatment was significantly associated with survival.

To help address that sequence of therapy could affect treatment choice, and thus its impact on survival, a 6-bin treatment assignment of incisional/excisional biopsy, biopsy

Table 3 Multivariate analysis of factors affecting survival in the cohort of 468 patients with survival data available

	Hazard ratio (95% CI)	P value
Age	1.05 (1.02–1.07)	0.00001
Charlson Deyo (0 as reference vs. all others)	1.92 (1.14–3.23)	0.01
Facility type (community as reference)		
Integrated community	0.51 (0.26–1.00)	0.05
Academic	0.39 (0.20–0.77)	0.007
Integrated network	0.64 (0.28–1.46)	0.29
Clinical nodal (N1 as reference)		
N2/a	1.31 (0.65–2.63)	0.65
N2b	1.55 (0.80–3.01)	0.19
N2c	6.28 (2.84–13.9)	<0.00001
N3	4.55 (2.17–9.51)	<0.00001
Regional nodal surgery	0.94 (0.55–1.61)	0.83
Surgery to primary site (incis bx as reference)		
Excisional biopsy	1.19 (0.55–2.58)	0.67
Local surgery	0.58 (0.30–1.15)	0.12
Radical surgery	1.80 (0.53–6.08)	0.34
Loco-regional therapy (neither as reference)		
Radiation	1.53 (0.68–3.47)	0.67
Radiation and chemotherapy	0.98 (0.47–2.06)	0.97

+ RT, biopsy + CRT, local surgery or greater alone, surgery + RT, and surgery + CRT was constructed. No single treatment group produced significantly improved survival, though local surgery plus chemoradiation achieved the best results (HR =0.42, 95% CI: 0.16–1.08, P=0.07). A similar analysis restricted to patients with positive HPV results showed no difference in survival by treatment approach.

No treatment modality was significantly correlated with facility type (Kruskal Wallis, P=0.06 for neck dissection, P=0.44 for radiation or chemotherapy and radiation, P=0.19 for extent of local surgery).

A subgroup of cN1 patients (n=131) was analyzed, as this group is of particular interest in optimal management strategies. In multivariate analysis using the six bins of therapy, the treatment regimens of biopsy followed by CRT (HR =0.26, 95% CI: 0.06–1.04, P=0.06) or local surgery plus followed by CRT (HR =0.11, 95% CI: 0.01–1.03, P=0.054) trended toward improved survival; however there were only 15 deaths in this cohort.

Propensity matched cohorts

Propensity matched cohorts were constructed using facility type, age at diagnosis, Charlson-Deyo score, and clinical nodal burden as matching patient and disease variables. Specific cohorts matching surgery type, neck dissection, and radiation versus chemoradiation were made to evaluate the impact on survival of treatment type. No significant treatment selection was associated with improved overall survival (data not shown).

Discussion

To our knowledge, this is the largest series of patients with squamous cell carcinoma of unknown primary of the head and neck with a description of multiple interventions in work up and treatment. The data show that the incidence of unknown primary cancer is increasing, HPV positive patients have a high likelihood of tonsil primaries and improved OS compared to the whole cohort, and that

specialization of the treating facility may impact outcomes. While there was no statistically significant improvement in survival with adding chemotherapy to radiation overall, cN1 patients may benefit.

The incidence of unknown primary of the head and neck in this hospital-based registry increased over time, an era in which PET-CT, though not recorded in this hospital-based data set, was more widely adopted and available for staging (9,10). A recent single institution series reported similar findings with a more than doubling of cases from 2005–2008 to 2012–2014 (11). One explanation is the increasing incidence of HPV positive disease (12), which can present with smaller tonsillar primaries and more extensive anatomic cervical nodal disease. Both in this report and other series (11,13), a large majority of patients who received testing were HPV positive.

In this analysis, all patients had clinically undetectable disease, but a portion subsequently had a tumor found through work up. We included this group, which falls outside the traditional definition of true unknown primary, to analyze utility of different diagnostic methods. Patients who received HPV testing and had a reported pathologic tumor stage, positive disease status was significantly associated with a higher rate of tonsil primaries than other subsites. Series prior to the HPV investigation era suggested that tonsillectomy found a primary site in 10–35% of patients sampled (2,14). Current NCCN guidelines support tonsillectomy in patients with higher level cervical nodal disease (6). HPV status in the entire 964 population was associated with improved survival, in agreement with work by Cheraghlou *et al.* (5).

Local surgery, such as tonsillectomy, had the highest diagnostic yield in identifying a primary. With the revision in AJCC 8th staging to classify unknown primary tumors that are p16+ as oropharynx, which is also bolstered by this data, this data supports recommendations for tonsillectomy as part of standard work up in these patients. In the multivariate Cox analysis, receipt of local surgery may have improved OS for N1 patients (P=0.054). This is consistent with an analysis of the SEER database which showed that addition of tonsillectomy to radiation improved survival (15). Additionally, identification of the primary may allow better delineation of radiation fields (16–18).

Interestingly, facility type had a significant impact on survival. Patients treated at community centers had significantly worse OS compared to academic centers (P=0.007) or even integrated community centers (P=0.05). Lassig *et al.* reported similar findings of improved outcomes

with advanced head and neck cancers at ‘academic’ compared to ‘community’ centers despite no significant differences in treatment selection, duration, or completion (19); however, they noted differences in rates of current smoking which is known to be an important risk factor (20), but was not available in our analysis.

Unfortunately, no clear conclusions about management of the neck can be drawn. Outcomes of N2c and N3 disease remained poor; this persisted in multivariate models. The NCCN guidelines note ‘consider systemic therapy/RT’ for this situation in either the p16+ or occult primary sections (6). Cheraghlou *et al.* reported a survival advantage for chemoradiation in N2c/N3 HPV negative disease (5).

Chemoradiation therapy did not show a significant benefit over radiation across all groups. A model attempting to control for other surgical interventions nearly showed improved survival in cN1 disease with addition of chemotherapy to radiation (P=0.054). Previous series have reported 75–92% control using neck dissection alone for N1/N2a disease when no extracapsular extension is present (21,22). A retrospective trial of pN1 disease utilizing mostly unilateral radiation after neck dissection reported 100% in N1 disease (23). A series of 66 patients published in abstract form showed that neck dissection followed by adjuvant therapy had lower local failure compared to upfront chemoradiation, but noted that the CRT patients had more advanced neck disease and no OS or PFS difference (24).

We acknowledge the limitations of this report, including its retrospective nature, limited HPV testing results, variability in staging work up inherent to any multiple center series, and the inherent difficulties of retrospective registry recorded data with a diagnosis of ‘unknown primary’ of any disease site. Analyses that provide data on local regional control may be more informative for treatment modality. However, utilizing these data sets allows for analyses of a larger population of this rare entity than any single institution series can allow.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study (STUDY00005643) was approved by our university's institutional review board, and individual consent for this retrospective analysis was waived as we utilized a nationally available, de-identified, and hospital-based data set.

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