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Occult Primary Head and Neck Squamous Cell Carcinoma: Utility of Discovering Primary Lesions

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Abstract

Objective—Cancer of an unknown primary (CUP) squamous cell carcinoma metastatic to cervical lymph nodes is a challenging problem for the treating physician. Our aim is to determine if identification of the primary tumor is associated with improved oncologic outcomes and/or tumor characteristics including human papilloma virus (HPV) status.

Study Design—Retrospective, matched-pairs analysis contrasting 2 cohorts based upon discovery of primary lesion.

Setting—Tertiary teaching hospital.

Subjects and Methods—Records of 136 patients initially diagnosed as carcinoma of unknown primary were retrospectively reviewed (1980–2010) and divided into 2 cohorts based on discovery of the primary lesion. Primary outcome measures were overall survival and time to recurrence

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Author Contributions

Kara S. Davis, data collection, statistics, data analysis and interpretation, manuscript preparation, manuscript revisions; **J. Kenneth Byrd**, concept and design, acquisition of data, revision of manuscript; **Vikas Mehta**, concept and design, acquisition of data, revision of manuscript; **Simon I. Chiosea**, concept and design, acquisition of pathologic data; **Seungwon Kim**, interpretation of data, final approval of version to be published; **Robert L. Ferris**, concept and design, interpretation of data, final approval of version to be published; **Jonas T. Johnson**, concept and design, interpretation of data, final approval of version to be published; **Umamaheswar Duvvuri**, concept and design, interpretation of data, final approval of version to be published.

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according to Kaplan-Meier analysis. A nested subset of 22 patients in which the primary was discovered were matched to 22 patients remaining undiscovered according to nodal stage and age.

Results—Discovered lesions were more likely to exhibit HPV positivity ($P < .001$). Matched-pairs analyses demonstrated that discovery of the primary was associated with better overall survival (HR = 0.125; 95% confidence interval [CI], 0.019–0.822; $P = .030$). Discovery of the primary was associated with improved cause-specific survival (HR = 0.142; 95% CI, 0.021–0.93; $P = .0418$) and disease-free survival (HR = 0.25; 95% CI, 0.069–0.91; $P = .03$).

Conclusion—HPV positivity is associated with discovery of the primary tumor. Discovery of the primary lesion is associated with improved overall survival, cause-specific survival, and disease-free survival in patients initially presenting as CUP in matched-pair and cohort comparison analyses.

Keywords

unknown primary tumor; oropharyngeal; HPV; cervical metastases; squamous cell carcinoma; unknown primary; human papilloma virus; base of tongue; tonsil; oropharyngeal cancer

Introduction

Management of patients presenting with cancer of an unknown primary (CUP) for squamous cell carcinoma metastatic to the cervical lymph nodes is a challenging problem. Initially, care is directed toward discovery of the occult primary lesion. Complete head and neck examination, flexible nasolaryngoscopy, and cross-sectional mucosal imaging by contrasted computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and/or PET/CT are considered standard initial evaluation. If the primary lesion remains undiscovered, patients are traditionally taken to the operating room for examination, direct laryngoscopy, biopsies of the base of tongue, and bilateral tonsillectomy. This operative approach is successful for discovery of the occult primary tumor in 17% to 50% of patients.^{1–3} With the introduction of transoral laser microsurgery (TLM) and transoral robotic surgery (TORS), the ability to discover the primary lesion is improving, however, and may be as high as 94%.^{2,4}

Cervical lymph node metastases of squamous cell carcinoma from unknown primary sites are being increasingly discovered to have arisen from the oropharynx, especially in association with human papillomavirus (HPV)-positive status.^{5,6} In addition, patients with oropharyngeal squamous cell carcinoma (OPSCC) have been shown to have distinct posttreatment outcomes based on characteristics such as HPV status and smoking history.⁷

Whether the discovery of the primary tumor improves oncologic outcomes in the era of HPV is currently unknown. Furthermore, the impact of HPV positivity on discovery of the primary tumor is not described. Therefore, our primary objective was to determine if identification of the primary is associated with improved oncologic outcomes. Second, we aimed to evaluate the influence of HPV positivity on discovery of occult lesions and the subsequent relationship with survival.

Materials and Methods

Patient Population

This study was approved by the University of Pittsburgh Medical Center Institutional Review Board (PRO12010335). Patients diagnosed with CUP were identified through the University of Pittsburgh Medical Center Department of Otolaryngology Head and Neck Tumor Registry between 1980 and 2011. The medical records, radiographic imaging and reports, pathology reports, and operative reports of 136 patients initially identified as CUP were retrospectively reviewed (1980–2010). Inclusion criteria were met if the occult tumor was not discovered after the initial workup, which included complete head and neck examination, including flexible nasolaryngoscopy, and cross-sectional mucosal imaging (contrasted CT, MRI, and/or PET/CT). Cervical metastases were pathologically confirmed squamous cell carcinoma in all patients.

All patients were then taken to the operating room for attempted discovery of the primary tumor by either traditional methods, which included direct laryngoscopy and bilateral tonsillectomy, or TORS. Patients with an obvious lesion upon direct laryngoscopy were excluded. Patients were divided into 2 cohorts based on discovery of the primary lesion: identified or unidentified. From these cohorts, each patient with a discovered primary lesion was matched with one patient with an undiscovered primary lesion. Matching variables were age (± 5 years), clinical nodal stage (N1 vs N2 vs N3), and treatment received (surgery alone; radiation therapy; surgery and radiation therapy; chemotherapy and radiation therapy; or chemotherapy, radiation therapy, and surgery). Forty-four patients underwent matching, yielding 22 matched pairs. All patients were treated for curative intent and had 2-year follow-up information.

Pathologic Evaluation

All patients undergoing matching had HPV testing by either p16 immunohistochemistry (IHC) or HPV in situ hybridization. IHC for p16 (G175–405; BD Pharmingen, San Diego, California) as a surrogate marker for HPB was performed as per the manufacturer's protocol. Cases were considered positive if $>80\%$ of tumor cells showed diffuse strong cytoplasmic and nuclear positivity staining. HPV detection was performed by in situ hybridization using probes targeting a wide spectrum of HPV strains including 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, and 52 (Y1404; Dako, Carpinteria, California). Cases with punctate nuclear signal were considered positive. The majority of patients had either of the HPV testing as part of the initial diagnostic evaluation. There were 8 patients without this information. The original tissue blocks for these cases were retrieved and tested by IHC for p16. In the event of discordant HPV detection and p16 results, the p16 IHC was used to determine HPV positivity.

Statistical Methods

Overall survival (OS), cause-specific survival (CSS), and disease-free survival (DFS) between the discovered and never-discovered patient cohorts were compared using Kaplan-Meier estimates and the log-rank test for equality of survival curves. A matching variable was used in the analysis to account for matching based on age, clinical nodal stage, and

treatment. Matched-pair analysis was further compared using the stratified Cox regression model. Analysis was completed for date of diagnosis to date of most recent oncologic follow-up, with death and first recurrence as censoring variables. Death was subdivided into death secondary to disease or due to other causes. Patient characteristics that were not matched were evaluated by the χ^2 test. SPSS software package version 21.0 (SPSS Inc, Chicago, Illinois) and STATA software package version 13.0 (StataCorp, College Station, Texas) were used for statistical computation.

Results

Demographics

The characteristics of the matched pairs are listed in Table 1. The pairs were matched by age (± 5 years), nodal status (N1 vs N2 vs N3), and treatment modality (data not shown). There were no significant differences between the 2 groups with respect to the matching variables or smoking status ($P < .05$). Individual cases were reviewed to match pairs with equivalent treatment regimens. The patients in which the primary tumor was discovered did not differ from the undiscovered patients with regard to use of TORS at the initial operation ($P = .216$), performance of neck dissection on the ipsilateral side of metastasis ($P = .97$), performance of neck dissection on the contralateral side of metastasis ($P = .367$), use of traditional external beam radiation (XRT) versus intensity-modulated radiation therapy (IMRT) ($P = .62$), or chemotherapy ($P = .329$). Selected data are highlighted in Figure 1. All matched patients received definitive radiation $\pm$ chemotherapy to radiation doses of 60–74 Gy (mean = 67.3 Gy, = SD 4.1, median dose = 70 Gy). Overall, the matched patients ranged in age from 37 to 78 years, with an average age of 57.05 years (SD = 9.51). This was not different than the entire study population average age of 57.35 years (range, 39–85, SD = 10.29). Patients with the primary tumor unidentified were more likely to be of white ethnicity ($P = .015$).

Among the 22 patients in which the primary tumor was discovered, 4 were clinically N1, 2 were N2a, 11 were N2b, 1 was N2c, and 4 patients presented with N3 disease. Among the 22 patients in which the primary tumor was undiscovered, 4 were clinically N1, 2 were N2a, 9 were N2b, 1 was N2c, 4 were N3, and 2 were N2 with conflicting evidence to further classify the nodal status.

As compared with patients with discovered primary lesions included in the matched-pairs analysis, the patients with undiscovered primary lesions were more likely to be HPV negative ($P < .001$). Conversely, discovered lesions were more likely to show HPV positivity ($P < .001$). When a neck dissection was performed, there was no difference in the presence of extracapsular extension of the resected presenting metastases ($n = 16$; $P = .838$).

Analysis of Oncologic Outcomes

Follow-up time ranged from 5 to 146 months, with an average of 35.9 months for the patients with undiscovered tumors and 51.6 months for the patients with discovered tumors ($P = .12$). One patient had an adverse event associated with attempted surgical discovery of

the primary tumor that required embolization for control of postoperative oropharyngeal hemorrhage.

Discovery of the occult primary ($n = 136$) was associated with improvement in overall survival (mean survival 10.19 vs 8.83 years, $P < .001$), when stratified across N1-N2c disease (data not shown). In the entire unknown primary cohort, HPV positivity was associated with improved overall survival (95% confidence interval [CI], 99.65–196.348; $P < .001$). Of the 44 matched patients, 10 patients died: 9 died of disease (DOD) and 1 from an unrelated accident. Only 1 of these patients (DOD) was in the discovered group. Overall survival is shown by the Kaplan-Meier curves in Figure 2 for patients with discovered and undiscovered lesions. Discovery of the primary tumor was associated with improved overall survival (HR = 0.125; 95% CI, 0.019–0.822; $P = .030$). Five-year overall survival in the identified group was 95.7%. Patients in which the primary tumor remained undiscovered at the initiation of primary therapy had a 5-year overall survival of 52%.

In the overall unknown primary cohort of 136 patients, there were 74 patients in which the primary was never discovered. Of these, 66 had sufficient data to determine the mode of radiation therapy used during treatment. Forty patients were treated with XRT, and 26 were treated with IMRT. Comparison of Kaplan-Meier analysis revealed no difference in overall survival in comparing undiscovered patients treated with XRT versus IMRT (95% CI, 68.91–109.37 months, $P = .925$). In the 22 undiscovered patients used in matched-pairs analysis, only 2 were treated with XRT. The remaining 20 were treated with IMRT, precluding any meaningful analysis.

Eleven patients had documented disease persistence or recurrence following primary therapy. In the group of discovered patients, 2 had persistent disease following therapy and 1 of these went on to successful salvage surgical therapy. There were no other locoregional or distant recurrences in this group. In those patients with an unidentified primary, 4 patients had persistent disease following primary treatment. Three patients developed locoregional recurrence, and 2 patients had evidence of distant metastases. Figure 3 shows the Kaplan-Meier curves for cause-specific survival (HR = 0.142; 95% CI, 0.021–0.93; $P = .0418$). Identification of the primary tumor was associated with improved cause-specific survival. Similarly, discovery of the primary was also associated with improved disease-free survival (HR = 0.25; 95% CI, 0.069–0.91; $P = .03$) as shown in Figure 4. When stratified by HPV status, each survival curve remained significant, OS and CSS: Exp(B) 10.294, $P = .046$; 95% CI, 1.045–101.427; DFS: Exp(B) = 6.664, $P = .031$; CI 95%, 1.185–37.475).

Discussion

Although our ability to identify previous occult primary lesions is greatly improving with new technology, no studies have primarily examined whether discovery of the primary tumor in patients presenting as CUP has any benefit to the patient with regards to oncologic outcomes in the era of HPV.^{2,4} In the 1990s, and again in the 2000s, 2 separate groups suggested improved survival with discovery of the primary tumor during exam under anesthesia (EUA).^{1,8} In a recent study of the effect of TLM on the discovery of the occult primary tumor, Karni et al² corroborated this evidence. The authors observed improved

disease-free survival in patients undergoing TLM versus patients undergoing traditional EUA without TLM. The primary goal of this study, therefore, was to examine the association of successful identification of the primary tumor (either EUA or TORS) with improved survival and to describe the potential influence of HPV status on the interpretation of such findings.

In the current study, identification of the primary tumor was associated with improved overall, disease-free, and cause-specific survival versus patients in which the primary tumor remained unidentified at the initiation of primary treatment. There are likely several contributing factors to this observation. Most notably, there was a significant association with HPV positivity and successful discovery of the primary lesion with nearly all discovered tumors being HPV positive. There was no difference in overall survival between undiscovered unknown primary patients treated with XRT versus IMRT. This may be secondary to the fairly wide, comprehensive, IMRT plans used to treat unknown primary patients at our institution.

Cervical lymph node metastases of squamous cell carcinoma from unknown primary sites are being increasingly discovered to have arisen from the oropharynx, especially in association with HPV-positive status.^{7,9,10} As such, these unknown primary neoplasms are expected to behave and respond to treatment as HPV-positive OPSCC. The 5-year disease-free survival rate of 86% in the patients with identified primary lesions is similar to survival rates observed in HPV-positive oropharyngeal tumors.¹¹ The phenotype of HPV-positive OPSCC is distinct from OPSCC not associated with HPV and likely affords the excellent prognosis of HPV-positive OPSCC.^{6,11,12} A retrospective analysis of a Radiation Therapy Oncology Group phase III trial (RTOG 0129) established better overall and progression-free survival for patients with HPV-positive tumors versus those with HPV-negative tumors.⁶ This has been confirmed and validated in subsequent literature based on both HPV status and p16 status. Furthermore, the usual presentation of these patients is nodal metastases in the neck from a small primary, similar to the presentation of identified CUP patients in the current study, which leads to higher staging in the current TNM staging system. Despite the advanced nodal stage of these tumors, HPV-positive OPSCCs are expected to have an excellent prognosis independent of stage due to increased treatment susceptibility.

There are several limitations to this study beyond the flaws associated with a retrospective review. Patients with identified primary lesions may be more likely to undergo targeted treatment with less treatment-related side effects, thereby affording improved outcomes. Matching attempted to control for treatment differences by considering the modality of treatment used, but treatment specifics, such as radiation dosage, may have been variable. At our institution, however, radiation dose of 60 to 74 Gy is the standard prescribed dose, regardless of whether or not the primary tumor was discovered. De-escalation to IMRT doses less than 70 Gy in identified T1/T2 primary oropharyngeal tumors with negative margins has only recently been used at our institution and is outside the timeframe of this study. In addition, 13 of the 22 patients who underwent surgical procedures in which the primary lesion were discovered were found to have negative resection margins. In effect, such patients have undergone primary ablative surgery of the primary tumor. There is

inherently no way to match for this type of difference, and the resultant decrease in overall tumor burden may be contributing to improved survival in such patients.

In a recent analysis evaluating the incidence of HPV in the neck metastasis of unknown primary tumors after complete workup, there was not a significant survival advantage observed in HPV-positive versus HPV-negative tumors.¹³ This may have been attributed to the high rate of tobacco use in the study population, which has been shown to decrease survival in the HPV-positive OPSCC. In the current study, 73% of matched patients had at least a 10 pack-year smoking history with similar rates in the discovered versus not discovered patients. This may have equivocated the effect smoking had on our survival comparison versus previously published literature.^{6,13} With the effect of smoking status attenuated between groups, the influence of HPV status may be more pronounced in the present study. With regards to stratifying OS, CSS, and DFS by HPV status, only 1 patient in the group with the primary lesion identified was HPV-positive and died of disease. Therefore, these data must be interpreted cautiously.

HPV positivity may have accounted for the majority of the differences in oncologic outcomes regardless of successful identification of the primary lesion. The association of HPV positivity with improved oncologic outcomes is well delineated in the literature, although the mechanism underlying this association remains to be fully defined. The oncogenic pathobiology in virally mediated cancers is seemingly detached from “traditional” carcinogens such as cigarette smoking and alcohol. The incorporation of HPV DNA into the cell may alter the balance of certain cell cycle proteins, with a propensity toward a makeup that is more easily treated with current regimens. Additionally, the HPV virus may compromise DNA repair mechanisms, yielding an increased response to radiation with a proclivity toward apoptosis.^{14–17} HPV-positive tumors have been shown to have differential response rates to primary irradiation with HPV-positive tumors having a larger volume of tumor response during the early days of radiation.¹⁸

HPV is thought to trigger increased host immune surveillance, which may also be a modifier of overall survival in HPV positive patients. The virus is thought to induce tumor clearance mechanisms.¹⁹ In vitro resistance to radiation and cisplatin was demonstrated to resolve in an in vivo, immunocompetent mouse model. This was negated in immunocompromised mice enhanced with adenovirus vector vaccine of E6 and E7 proteins.¹⁹ These murine studies may in part predict the survival advantages seen in discovered patients. A primary tumor sizeable enough to be discovered may be more likely to induce such immune surveillance mechanisms and prime the patient for improved response to CRT.

Furthermore, the reason for the higher incidence of HPV positivity in the discovered group is unknown, but interesting. Likely there is something inherent to the pathology and oncogenesis of HPV-positive oropharyngeal squamous cell carcinoma that produces a more focal, discrete primary tumor, which may be more easily identified grossly and on histology. Differences in field cancerization may contribute to this. A recent retrospective review by Rietbergen et al²⁰ of 20 surgically treated patients evaluated 97 resection margins. The specimens were analyzed for tumor and presence of transcriptionally active HPV by detection of HPV16-E6-mRNA. All negative resection margins were found to be negative

for HPV16-E6-mRNA, which was thought to support the absence of field effect in these tumors.²⁰

Conclusions

Discovery of the primary lesion is associated with improved overall survival in patients initially presenting as CUP, both in matched-pair and cohort comparison analyses. Within a matched-pairs subset accounting for age, nodal status, and primary treatment, improved locoregional control with discovery of the primary was suggested by improved cause-specific and disease-free survival. These differences are most likely secondary to improved discovery of the primary tumor in association with HPV positivity. HPV-positive SCC is expected to have an excellent prognosis, likely due to the immunology of HPV-driven tumors being more susceptible to treatment. Further studies may clarify treatment discrepancies and molecular differences.

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References

1. Haas I, Hoffman TK, Engers R, Ganzer U. Diagnostic strategies in cervical carcinoma of an unknown primary. *Eur Arch Otorhinolaryngol*. 2002; 259:325–333. [PubMed: 12115082]
2. Karni RJ, Rich JT, Sinha P, Haughey BH. Transoral laser microsurgery: a new approach for unknown primaries of the head and neck. *Laryngoscope*. 2011; 121:1194–1201. [PubMed: 21495044]
3. Strojan P, Ferlito A, Medina JE, et al. Contemporary management of lymph node metastases from an unknown primary to the neck: I. a review of diagnostic approaches. *Head Neck*. 2013; 35:123–132. [PubMed: 22034046]
4. Mehta V, Johnson P, Tassler A, et al. A new paradigm for the diagnosis and management of unknown primary tumors of the head and neck: a role for transoral robotic surgery. *Laryngoscope*. 2013; 123:146–151. [PubMed: 23154813]
5. El-Mofty SK, Zhang MQ, Davila RM. Histologic identification of human papillomavirus (HPV)-related squamous cell carcinoma in cervical lymph nodes: a reliable predictor of the site of an occult head and neck primary carcinoma. *Head Neck Pathol*. 2008; 2:163–168. [PubMed: 20614311]
6. Ang K, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med*. 2010; 363:24–35. [PubMed: 20530316]
7. Begum S, Gillison ML, Ansari-Lari MA, et al. Detection of human papillomavirus in cervical lymph nodes: a highly effective strategy for localizing site of tumor origin. *Clin Cancer Res*. 2003; 9:6469–6475. [PubMed: 14695150]
8. McQuone SJ, Eisele DW, Lee D, et al. Occult tonsillar carcinoma in the unknown primary. *Laryngoscope*. 1998; 108:1605–1610. [PubMed: 9818813]
9. Goldenberg D, Begum S, Westra WH, et al. Cystic lymph node metastasis in patients with head and neck cancer: an HPV-associated phenomenon. *Head Neck*. 2008; 30:898–903. [PubMed: 18383529]
10. Issing WJ, Taleban B, Tauber S. Diagnosis and management of carcinoma of unknown primary in the head and neck. *Eur Arch Otorhinolaryngol*. 2003; 260:436–443. [PubMed: 12684829]
11. Fakhry C, Westra W, Li S, et al. Improved survival of patients with human papilloma—positive head and neck squamous cell carcinoma in a prospective clinical trial. *J Natl Cancer Inst*. 2008; 100:261–269. [PubMed: 18270337]
12. Marur S, D'souza G, Westra WH, Forastiere AA. HPV-associated head and neck cancer: a virus-related cancer epidemic. *Lancet Oncol*. 2010; 11:781–789. [PubMed: 20451455]

13. Compton AM, Moore-Medlin T, Herman-Ferdinandez L, et al. Human papillomavirus in metastatic lymph nodes from unknown primary head and neck squamous cell carcinoma. *Otolaryng Head Neck*. 2011; 145:51–57.
14. Kong CS, Narasimhan B, Cao H, et al. The relationship between human papillomavirus status and other molecular prognostic markers in head and neck squamous cell carcinomas. *Int J Radiat Oncol Biol Phys*. 2009; 74:553–561. [PubMed: 19427557]
15. Worden FP, Kumar B, Lee JS, et al. Chemoselection as a strategy for organ preservation in advanced oropharynx cancer: response and survival positively associated with HPV16 copy number. *J Clin Oncol*. 2008; 26:3138–3146. [PubMed: 18474879]
16. Lassen P. The role of human papillomavirus in head and neck cancer and the impact on radiotherapy outcome. *Radiother Oncol*. 2010; 95:371–380. [PubMed: 20493569]
17. Kimple RJ, Smith MA, Blitzer GC, et al. Enhanced radiation sensitivity in HPV-positive head and neck cancer. *Cancer Res*. 2013; 73:4791–4800. [PubMed: 23749640]
18. Chen AM, Li J, Beckett LA, et al. Differential response rates to irradiation among patients with human papillomavirus positive and negative oropharyngeal cancer. *Laryngoscope*. 2013; 123:152–157. [PubMed: 23008061]
19. Williams R, Lee DW, Elzey BD, et al. Preclinical models of HPV+ and HPV- HNSCC in mice: an immune clearance of HPV+ HNSCC. *Head Neck*. 2009; 31:911–918. [PubMed: 19283850]
20. Rietbergen MM, Braakhuis BJM, Moukhtari N, et al. No evidence for active human papillomavirus (HPV) in fields surrounding HPV-positive oropharyngeal tumors. *J Oral Pathol Med*. 2014; 43:137–142. [PubMed: 24118314]

Figure 1. Baseline treatment characteristics between discovered ($n = 22$) and undiscovered ($n = 22$) primary tumors used in matched-pairs analysis.

Figure 2. Kaplan-Meier curves for overall survival of discovered versus undiscovered primary tumors. Discovery was associated with improved overall survival (HR = 0.125; 95% confidence interval, 0.019–0.822; $P = .030$).

Figure 3.

Kaplan-Meier curves for cause-specific survival. Identification of the primary tumor was associated with improved cause-specific survival (HR = 0.142; 95% confidence interval, 0.021–0.93; $P = .0418$).

Figure 4.

Kaplan-Meier curves for disease-free survival. Discovery of the primary was also associated with improved disease-free survival (HR = 0.25; 95% confidence interval, 0.069–0.91; $P = .03$).

Table 1

Characteristics of Matched Patients.

	Identified (n = 22)		Unidentified (n = 22)	
	Number of Patients	%	Number of Patients	%
Age, years				
Mean	56.00		58.09	
Standard deviation	8.94		10.15	
Sex				
Female	1	4.5	2	9.1
Male	21	95.5	20	90.9
Nodal stage				
N1	4	18.2	4	18.2
N2	14	63.7	14	63.7
N3	4	18.2	4	18.2
Smoking status				
Never-less 10 PY	7	31.82	5	22.7
Greater than 10 PY	14	63.64	17	77.3
HPV status				
Positive	21	95.5	8	36.3
Negative	1	4.5	14	63.7

Abbreviations: PY, pack-years; HPV, human papilloma virus.