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# Metastatic Squamous Cell Carcinoma of Known and Unknown Primary Origin Treated with Axillary or Inguinal Lymphadenectomy

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## Abstract

**Background:** Metastatic squamous cell carcinoma (SCC) to the axillary or inguinal lymph nodes from an unknown primary source is rarely encountered. We sought to evaluate a cohort of patients with metastatic SCC managed by lymphadenectomy to determine their survival, and to determine which clinicopathologic factors were associated with outcome.

**Methods:** All patients undergoing axillary or inguinal lymphadenectomy for SCC at our institution were identified retrospectively. Patients were stratified by unknown primary (UP) vs known skin primary (KP) tumors. Pertinent data on patient, tumor, and treatment variables was collected.

**Results:** We identified 51 patients who met inclusion criteria. Of those, 20 patients (39%) had UP metastatic SCC and 31 patients (61%) had KP. The 5-year overall survival for UP was 65%, as compared to 49% for KP (p=0.16). Cumulative incidence of recurrence was 46%. Cox regression failed to demonstrate a significant association between KP vs UP, HPV status, chemotherapy, or radiation with survival.

**Conclusions:** Nearly two-thirds of patients undergoing axillary or inguinal lymphadenectomy for metastatic SCC of unknown primary were alive five years following the procedure.

## INTRODUCTION

Non-melanoma skin cancer (NMSC) is the most common human malignancy with a prevalence exceeding that of all other cancers combined.[1–3] An estimated 5.4 million Americans are treated for NMSC each year, and the incidence is projected to continue rising through 2040.[3,4] Of the two predominant types of NMSC, squamous cell carcinoma (SCC)



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is more aggressive and has a greater propensity for metastatic spread than basal cell cancer. The rates of SCC metastasis are reported as low as 1.9%, but can be as high as 40% in certain high-risk subtypes.[5–7] Risk factors for metastasis include immunosuppression and certain characteristics of the primary tumor, including depth of penetration, diameter, growth rate, differentiation, histological subtype, and lymphovascular or perineural invasion.[7–10] Metastasis typically occurs first through regional lymphatics, and nodal status is the primary prognostic indicator for mortality.[11–12] Although five-year overall survival for cutaneous SCC is generally excellent (>90%), it has been reported to be as low as 26-34% in the setting of clinical nodal metastases.[8,11] On rare occasion, SCC presents as lymphadenopathy without an apparent primary source. The most appropriate treatment strategy and outcomes for these patients are unclear.

In contrast to the paucity of data for patients with SCC of unknown primary site metastatic to the axilla or groin, the natural history of patients with head-and-neck SCC metastases of unknown primary site is well-documented. Around 4% of head and neck SCC present as nodal metastases with an unknown primary.[13] Workup of these tumors in the head and neck setting involves a thorough evaluation of the nasal and oropharynx, as well as testing for Human Papillomavirus (HPV).[13] In the last two decades, HPV positive head-and-neck SCCs have emerged as a clinically distinct subgroup, associated with markedly better responses to chemotherapy and radiation, and improved overall survival.[14,15] However, the role of HPV in non-head and neck cancers is less well-understood.

Predictions about tumor behavior and determination of appropriate therapy are typically based on the primary tumor site. As such, the absence of a primary tumor poses diagnostic and therapeutic challenges. [20,21] In this study, we sought to evaluate patients with axillary and inguinal lymph node metastases from SCC of unknown primary site to better define outcomes for patients managed with lymphadenectomy for this uncommon clinical scenario. Our primary objectives were to determine the recurrence risk and overall survival of patients undergoing axillary and inguinal lymphadenectomies for metastatic SCC with no known head-and-neck or anogenital primary, and to determine which clinicopathologic factors (including HPV status), or treatment factors were associated with improved outcome.

## METHODS

### Patients and Tissue Collection

The study was approved by the Institutional Review Board prior to initiation. The records of all patients treated at our institution from 1990 to 2015 with the diagnosis of metastatic SCC of unknown primary were identified using procedural codes for axillary and inguinal lymphadenectomy as well as pathology reports. All patients undergoing axillary and inguinal lymphadenectomies for metastatic SCC with known skin primary tumors were included for comparative purposes. Patients with known anogenital or head and neck cancers were excluded from this study. Pertinent clinical data on patient, treatment, and pathologic variables were collected retrospectively utilizing our institutional electronic medical record system. Prior to treatment, all patients underwent full skin examination, and investigation with CT and/or PET scan. Those with inguinal disease underwent full anogenital evaluation

and proctoscopy to rule out potential SCC originating from those sites. Outcomes were assessed by review of the electronic medical record.

### HPV Genotyping

Formalin-fixed paraffin-embedded (FFPE) tumor tissue was retrieved for HPV genotyping on the subset of patients with available tissue who were consented to protocols enabling tumor molecular interrogation. All samples were derived from lymphadenectomy specimens. A dermatopathologist (MP) confirmed tissue diagnosis of metastatic SCC using H&E staining for all cases submitted to HPV genotyping.

DNA was extracted from FFPE tissues using QIAamp DNA FFPE Tissue Kit (Qiagen Inc, Valencia, CA). HPV genotyping was performed using the INNO-LiPA HPV Genotyping *Extra kit* (Innogenetics, Belgium). In brief, 100 ng of DNA was utilized for PCR amplification of a short fragment (65-bp) of the HPV L1 region with biotinylated primers ($SPF_{10}$) using the MJ PTC-200 DNA engine thermocycler. PCR products were hybridized to the AutoBlot 3000H 20 Strip, a probe-specific nitrocellulose test strip, placed on an adhesive LiPA-Scan Reading template and analyzed using the LiRAS for LiPA HPVE v2.01 software (Innogenetics, Belgium). All assays included the amplification of a 270 bp fragment of HLA-DPB1 as a positive control for human DNA. All PCR runs met quality control standards, with all samples positive for internal positive controls and negative for internal negative controls for each run. This system detects 28 HPV types (HPV 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 66, 68, 70, 73, and 82). High-risk HPV types were defined as the 12 high-risk types classified as group 1 carcinogens (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59).

### Statistics

Patient characteristics were described overall and broken down by known and unknown primaries. Differences in patient characteristics between those with known and unknown primaries were compared with the Fisher’s Exact test and the Wilcoxon Rank Sum test where appropriate. Overall survival (OS) was estimated from the time of surgery until death. Disease specific survival (DSS) was estimated from the time of surgery until death from disease. Patients alive at last follow up were censored, regardless of disease status. Patients who died from other causes were censored when calculating DSS. OS and DSS were estimated using Kaplan Meier (KM) methods and curves. Median and annual estimates were provided with 95% confidence intervals. KM estimates and curves were provided stratified by known primary status, and the log-rank test was performed. Univariable Cox proportional hazards regression assessed the relationship between risk factors and OS and DSS. P-values less than 0.05 were considered statistically significant. All analyses were performed using SAS 9.4 (The SAS Institute, Cary, NC).

## RESULTS

### Patients

Our patient population consisted of 51 patients with a median age of 67 years (range: 37-89 years). Most of the population was male (n=35, 69%) and Caucasian (n=43, 84%). The

cohort consisted of patients with metastatic SCC to axillary and inguinal LN, and either a known skin primary tumor (KP, n=31, 61%) or unknown primary tumor (UP, n=20, 39%). Patient demographics were similar irrespective of the presence of a known primary tumor, although patients with UP were more likely to have a history of non-squamous cell cancer (55% vs 21%, p=0.02, Table 1).

HPV status was available for 24 patient tumors. Six tumors were positive for HPV (KP=2, UP=4), while 18 tumors were negative for HPV (KP=13, UP=5, Table 2). Of the KP tumors that were HPV positive, one was in the inguinal basin and the other in the axilla while all four UP tumors that were positive were found in the inguinal basin. Of note, HPV genotyping revealed that all four tumors in patients with UP were positive for HPV type 16, while one tumor from the KP was positive for HPV type 16 and the other was positive for HPV type 52.

## Treatment

All patients had clinical lymphadenopathy and were managed with therapeutic lymphadenectomy, with a median of 15 (range 1-33) nodes removed. A median of 2 (range: 1-17) positive nodes were identified. Most patients did not receive chemotherapy or radiation. Only 16% (n=5) of patients with KP and 5% (n=1) of patients with UP received neoadjuvant chemotherapy, while 19% (n=6) with KP and 0% (n=0) with UP received neoadjuvant radiation. Similarly, postoperative adjuvant chemotherapy was employed in only 10% (n=3) of patients with KP and 15% (n=3) of patients with UP. However, 29% (n=9) of patients with KP and 40% (n=8) of patients with UP received postoperative adjuvant radiation therapy. Treatment characteristics of each cohort can be found in Table 2.

## Recurrence and Survival

The median follow-up time for survivors was 74 months (range: 1-213 months). Twenty-three patients (46%) recurred, all within the first three years of follow-up. Those patients with recurrence underwent a variety of further treatments with some receiving additional chemotherapy or radiation, some of the treatment naïve patients receiving these therapies for the first time, and still a small portion undergoing additional surgical procedures. Of note, we observed no recurrences after three years. Univariate analysis detected no association between gender, age, KP vs UP, number of positive nodes, neoadjuvant chemotherapy, or neoadjuvant radiation and the probability of disease recurrence (Table 3).

Three-year cumulative incidence of recurrence was 46% (95%CI: 31-59%) with no recurrences after 3 years. Of the patients who recurred, fourteen (27%) died for reasons directly attributable to metastatic SCC. The estimated five-year OS for the entire cohort was 56% (95% CI: 40-69%). The 5-year overall survival rate was 49% for patients with KP (95% CI: 29-66%) and 65% for patients with UP (CI 40-81%) (p=0.16, Figures 1a and b). The estimated three-year DSS for the entire cohort was 70% (95%CI: 55-81%). Of the 14 patients that died of metastatic SCC, 11 had KP tumors and 3 had UP tumors. The five-year DSS was 60% for patients with KP tumors (95% CI 39-76%) and 84% for patients with UP tumors (95% CI 59-95%) (p=0.11, Figure 1b). No deaths due to metastatic SCC occurred after three years post operation during the follow-up period.

Cox regression failed to demonstrate an association between HPV status, KP vs UP, number of positive nodes, neoadjuvant chemotherapy, and neoadjuvant radiation with OS or DSS (Table 4). Not surprisingly, advanced age was associated with higher risk of death (HR 1.08, 95%CI 1.03 – 1.12, p<0.001).

## DISCUSSION

Patients presenting with metastatic SCC of unknown primary to the axillary or inguinal lymph nodes are an unusual, poorly characterized population with regard to management and outcomes. We have identified a cohort of patients treated with therapeutic lymphadenectomy at our institution over a 25-year period. To our knowledge, this represents the largest single series of such patients with adequate outcome information. We found that nearly two-thirds of UP patients managed with lymphadenectomy (with or without pre/postoperative chemotherapy or radiotherapy) will be alive and free of disease five years after the operation. Among patients in whom we were able to assess viral status, HPV was detectable in a minority of tumors evaluated, although we were unable to ascribe any prognostic significance to this finding.

Metastatic SCC with a known primary skin tumor has been previously reported to be associated with a poor overall five-year survival rate of 26-34%.[8,11] In contrast, the five-year survival of patients included in this study with known skin primary lesions was 49%. Patients included in our study were selected to undergo an operation, which may explain the improved survival as compared to what has been previously published. Interestingly, the survival data of patients with unknown primary tumors reported in the study (65% five-year OS) were higher than previous estimates in a similar cohort of patients (39%).[22] Again, this could potentially be explained by the fact that all our patients were treated with lymphadenectomy (a treatment approach not reported in the previous studies) or potentially due to better detection and/or treatment methods developed in the years since the earlier data were collected.

We found no statistically significant improvement in survival for patients with UP compared to KP: If a biologically relevant difference does truly exist, our lack of significance may be attributed to the limited power of our study given the sample size. If a survival advantage does indeed exist for UP, it may be related to immunogenic reactivity of the individual tumors in these patients and better overall host defense influencing survival.

In the melanoma literature, patients with melanoma of unknown primary (MUP) presenting with lymphadenopathy appear to have improved overall survival compared to those with known primary (55% vs 44% at 5 years, p=.002)[25]. Stronger endogenous immune response against the tumor has been hypothesized to be one factor responsible for primary tumor regression and ultimately improved survival. Disease in lymph nodes could have acquired different mutations affecting immunogenic reactivity and thus evaded regression itself. Indeed, other studies of regressed melanomas have demonstrated circulating factors that potentiated lymphocytic cytotoxicity and also found increased lymphocytic infiltrates in the tumors[25–28]. A similar mechanism could potentially be taking place with unknown primary SCC.

Interestingly in our series, no patient recurred or died of disease after three years post lymphadenectomy. This is similar to previous reports of patients with UP metastatic SCC in which no patient died of disease after 2.5 years of follow-up.[22,23] Intriguingly, this is also comparable to studies in MUP which demonstrated a prolonged and durable survival in patients that live beyond three years.[25,26] This observation carries important prognostic implications for patients and provides interesting insight into the underlying biology of the disease. It supports that endogenous immune response may have produced a lasting durable response towards the tumor, and that lymphadenectomy provided therapeutic benefit for the remaining disease in the lymph node basins.

Advanced age was found to be the only statistically significant factor associated with overall survival, while number of positive nodes, neoadjuvant chemotherapy, and neoadjuvant radiation were not associated with any difference in either overall or disease specific survival. This is consistent with the existing literature.[22–24] The role for these therapies in this disease presentation remains unclear.

While HPV status identifies a distinct favorable subgroup of patients associated with improved outcomes in locally and regionally metastatic SCC in the head and neck,[14,15] our study was unable to demonstrate any significant difference for SCC in the axillary or inguinal nodes. HPV status was established in 24 of our patients, with only six being positive. The majority of the HPV positive tumors (5/6) were found in the inguinal region and of these, the four UP tumors were all positive for HPV serotype 16. This potentially indicates that the unknown primary could have instead been from an unrecognized anogenital SCC that spontaneously regressed rather than a skin source. HPV positive status was not associated with OS nor rate of recurrence, although there were too few HPV+ patients to detect a significant difference. The question of whether HPV status may play some role in patients with metastatic SCC to the axilla or inguinal nodal basins remains unanswered by this study.

Our study on unknown primary metastatic SCC represents a contribution to the understanding of the nature and prognosis of this largely unreported group. However, our work represents a single center retrospective review and thus carries the associated limitations. The sample size in this study was small, and likely underpowered to detect potentially important biologic differences among endpoints. There was also lack of uniformity in utilization of adjuvant therapies that could have affected outcomes. Finally, HPV analysis was limited because HPV status was not established on every individual tumor due to consent issues and retrospective confines.

## Conclusions

Nearly two-thirds of patients with metastatic SCC of unknown primary to axillary and inguinal LNs selected for lymphadenectomy were alive five years following the procedure. Moreover, no patients experienced disease recurrence beyond three years, offering interesting insight into the tumor biology. HPV was detected in a minority of patients who could be evaluated for it, and as such, we cannot draw any conclusion as to its clinical

relevance in patients with non-head-and-neck, non-anogenital metastatic SCC of known or unknown primary.

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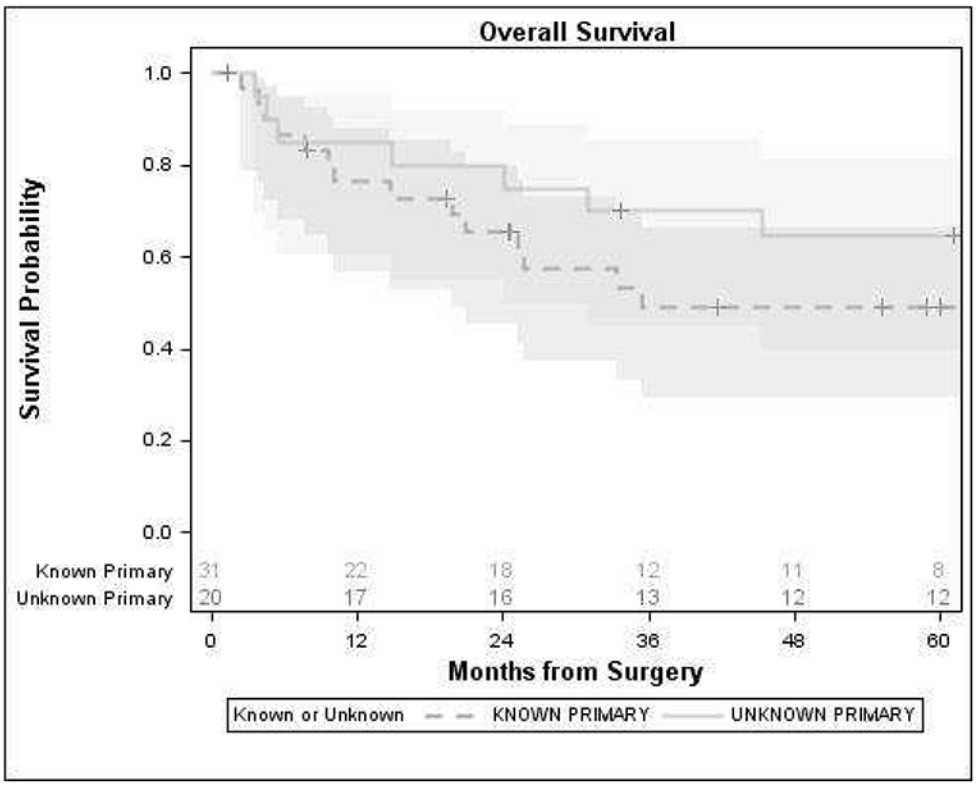
## Research Highlights

- Patients with metastatic squamous cell carcinoma to the axillary or inguinal lymph nodes were treated with lymphadenectomy.
- A sub-group was identified that had an unknown primary source of disease.
- We sought to further define recurrence risk and survival in this population.
- The 5-year overall survival for Unknown Primary patients was 65%, as compared to 49% for Known Primary patients (p=0.16).
- Analysis failed to demonstrate a significant association between KP vs UP or HPV status with survival.




| | OS | | | | DSS | | | |
|---|---|---|---|---|---|---|---|---|
| Primary Site | N (#D) | 3 yr. KM Est | [95% CI] | p-value | N (#D) | 3 yr. KM Est | [95% CI] | p-value |
| Known | 31 (17) | 0.49 | [0.29 - 0.66] | 0.16 | 31 (11) | 0.60 | [0.39 - 0.76] | 0.11 |
| Unknown | 20 (8) | 0.65 | [0.40 - 0.81] | | 20 (3) | 0.84 | [0.59 - 0.95] | |

**Figure 1a and 1b. OS Stratified by Known Primary Status**

Kaplan Meier methods and curves for Overall Survival of patients with Metastatic SCC treated by axillary or inguinal lymphadenectomy and stratified based on an unknown primary source of disease versus a known skin primary source of disease. P-value of 0.16 indicating no difference of statistical significance.

**Table 1.**

Patient Characteristics

| | | Entire Population | Known Primary Population | Unknown Primary Population | p-value |
|---|---|---|---|---|---|
| Age at Surgery, years | Median (range) | 67 (37-89) | 67 (37-82) | 64 (41-89) | 0.56 |
| Gender | Male | 35 (69) | 23 (74) | 12 (60) | 0.36 |
| | Female | 16 (31) | 8 (26) | 8 (40) | |
| Race | White | 43 (84) | 27 (87) | 16 (80) | >0.95 |
| | Hispanic | 2 (4) | 1 (3) | 1 (5) | |
| | Asian | 2 (4) | 1 (3) | 1 (5) | |
| | Missing | 4 (8) | 2 (6) | 2 (10) | |
| History of Cancer | Yes | 17 (33) | 6 (19) | 11 (55) | **0.017** |
| | No | 32 (63) | 23 (74) | 9 (45) | |
| | Unknown | 2 (4) | 2 (6) | 0 (0) | |
| History of Smoking | Yes | 20 (39) | 12 (39) | 8 (40) | >0.95 |
| | No | 27 (53) | 16 (52) | 11 (55) | |
| | Unknown | 4 (8) | 3 (10) | 1 (5) | |
| Tumor Location | Axilla | 33 (65) | 21 (68) | 12 (60) | 0.76 |
| | Groin | 18 (35) | 10 (32) | 8 (40) | |

Characteristics of patient groups stratified by known vs unknown primary. Numbers represent frequency with percent in parentheses unless otherwise specified. Percents may not add up to 100% due to rounding. Patients with unknown values were not included in formal comparisons. History of Cancer indicates a past diagnosis of any histology excluding SCC.

**Table 2.**

Tumor and Treatment Characteristics

| | | Entire Population | Known Primary Population | Unknown Primary Population | p-value |
|---|---|---|---|---|---|
| # Positive Nodes | Median (range) | 2.0 (1.0-17.0) | 2.0 (1.0-17.0) | 1.0 (1.0-15.0) | 0.22 |
| # Total Nodes Identified | Median (range) | 15.0 (1.0-33.0) | 15.0 (1.0-33.0) | 15.5 (4.0-33.0) | 0.29 |
| HPV Status | Positive | 6 (12) | 2 (6) | 4 (20) | 0.15 |
| | Negative | 18 (35) | 13 (42) | 5 (25) | |
| | Missing | 27 (53) | 16 (52) | 11 (55) | |
| Tumor Grade | Poor | 13 (25) | 8 (26) | 5 (25) | 0.85 |
| | Moderate | 9 (18) | 5 (16) | 4 (20) | |
| | Well | 3 (6) | 1 (3) | 2 (10) | |
| | Missing | 26 (51) | 17 (55) | 9 (45) | |
| Neoadjuvant Chemotherapy | Yes | 6 (12) | 5 (16) | 1 (5) | 0.38 |
| | No | 45 (88) | 26 (84) | 19 (95) | |
| Neoadjuvant Radiation | Yes | 6 (12) | 6 (19) | 0 (0) | 0.07 |
| | No | 45 (88) | 25 (81) | 20 (100) | |
| Adjuvant Chemotherapy | Yes | 6 (12) | 3 (10) | 3 (15) | 0.67 |
| | No | 44 (86) | 27 (87) | 17 (85) | |
| | Unknown | 1 (2) | 1 (3) | 0 (0) | |
| Adjuvant Radiation | Yes | 17 (33) | 9 (29) | 8 (40) | 0.76 |
| | No | 31 (61) | 19 (61) | 12 (60) | |
| | Unknown | 3 (6) | 3 (10) | 0 (0) | |

Characteristics of tumors and subsequent treatment strategies for patient groups stratified by known vs unknown primary. Numbers represent frequency with percent in parentheses unless otherwise specified. Percents may not add up to 100% due to rounding.

Patients with unknown values were not included in formal comparisons.

**Table 3:**

Univariate Analysis for Recurrence

| | Odds Ratio | 95% Confidence Interval | p-value |
|---|---|---|---|
| Age at Surgery | 0.99 | 0.96 – 1.02 | 0.55 |
| Female (ref: Male) | 0.66 | 0.27 – 1.60 | 0.36 |
| Known Primary (ref: Unknown Primary) | 1.33 | 0.62 – 2.85 | 0.47 |
| Positive HPV (ref: Negative HPV) | 0.48 | 0.17 – 1.40 | 0.18 |
| Number of Positive Nodes | 1.01 | 0.91 – 1.12 | 0.86 |
| Neoadjuvant Chemotherapy | 3.02 | 0.95 – 9.59 | 0.06 |
| Neoadjuvant Radiation | 1.74 | 0.47 – 6.51 | 0.41 |

Univariate Analysis of Factors influencing recurrence of metastatic SCC after axillary or inguinal lymphadenectomy.

**Table 4:**

Cox Regression for Overall and Disease Specific Survival

| | Overall Survival | | | Disease Specific Survival | | |
|---|---|---|---|---|---|---|
| | **Hazard Ratio** | **95% Confidence Interval** | **p-value** | **Hazard Ratio** | **95% Confidence Interval** | **p-value** |
| Age at Surgery | 1.08 | 1.03 – 1.12 | <0.001 | 1.03 | 0.98 – 1.08 | 0.24 |
| Female (ref: Male) | 0.44 | 0.17– 1.18 | 0.10 | 0.14 | 0.02 – 1.08 | 0.06 |
| Known Primary (ref: Unknown Primary) | 1.83 | 0.78 – 4.28 | 0.16 | 2.75 | 0.77 – 9.88 | 0.12 |
| Positive HPV (ref: Negative HPV) | 0.30 | 0.07 – 1.35 | 0.12 | N/A | N/A | N/A |
| Number of Positive Nodes | 1.03 | 0.94 – 1.14 | 0.49 | 1.01 | 0.89 – 1.16 | 0.86 |
| Neoadjuvant Chemotherapy (ref: No Neoadjuvant Chemo) | 0.96 | 0.22 – 4.09 | >0.95 | 1.62 | 0.36 – 7.24 | 0.53 |
| Neoadjuvant Radiation (ref: No Neoadjuvant Rad) | 0.98 | 0.23 – 4.20 | >0.95 | 1.69 | 0.38 – 7.56 | 0.49 |

Cox Regression Analysis for patient and treatment factors influencing survival outcome in metastatic SCC treated with axillary or inguinal lymphadenectomy. N/A indicates that an estimate could not be obtained due to low sample size.