REDUCED PROGNOSTIC IMPACT OF NODAL STATUS IN HPV-ASSOCIATED OROPHARYNGEAL SQUAMOUS CELL CARCINOMA

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INTRODUCTION:

In Head and Neck Squamous Cell Carcinoma, nodal metastasis generally has a negative impact on prognosis. Human Papilloma Virus (HPV)-associated oropharyngeal SCC (OPSCC) has been shown repeatedly to confer better prognoses than HPV-negative oropharyngeal SCC, despite a high frequency of nodal metastases. We hypothesized that nodal metastasis has a reduced impact on survival in HPV-positive OPSCC than it does in HPV-negative OPSCC.

METHODS:

This was a retrospective study that included 126 patients with node positive (N+) OPSCC diagnosed and/or treated at an NCCN Comprehensive Cancer Care Center between 2007 and 2013. Tumor tissue from all these patients was evaluated for high risk HPV types 16 and 18 using in-situ hybridization (ISH) and divided into two groups, either HPV-positive or HPV-negative. Cox-regression survival analysis and log-rank test were conducted to compare the overall survival (OS) and disease-specific survival (DSS) between the two groups. A p-value of <=0.05 was considered significant for all analyses.

RESULTS:

Among the 126 N+ OPSCC patients, the HPV positivity rate was 69% (N=87). There was no statistically significant difference in nodal staging between the HPV-positive and HPV-negative patients (p-value: 0.14). Median overall survival (OS) time for HPV-positive patients was >60 months and for HPV-negative patients was 48 months. The 1 year, 2 year and 3 year OS rates for HPV-positive, N+ tumors were 92%, 83% and 75%. The 1 year, 2 year, and 3 year OS for HPV-negative, N+ tumors were 67%, 59% and 59%. The difference in DSS [Hazard Ratio: 0.39 (0.17 - 0.93), p-value: 0.03] and OS [Hazard Ratio: 0.42 (0.20 - 0.89), p-value: 0.02] between HPV-positive and HPV-negative, N+ OPSCC was statistically significant, even after adjusting for the N stage.

CONCLUSION:

These data suggest that nodal status carries significantly less prognostic importance to overall survival in HPV-associated OPSCC as compared to HPV-negative OPSCC. This may well have implications for future TNM staging classifications -- and potentially for therapeutic decision making in the management of OPSCC.
Background:

Human papillomavirus (HPV) has emerged as an important causative agent and indicator of improved prognosis in oropharyngeal head and neck squamous cell carcinomas (SCC), but its prognostic implication in unknown primary head and neck SCC is less clear. In patients without a primary tumour on initial assessment, many are subsequently found in the oropharynx on panendoscopy, tonsillectomy, and more recently, with transoral robotic or laser lingual tonsillectomies. Thus, we hypothesize that unknown primary head and neck SCC behave similarly to oropharyngeal SCC. The current study investigates the prognostic value of HPV status in the unknown primary head and neck SCC.

Methods:

We conducted a retrospective review of patients with SCC in a cervical lymph node without an identifiable primary tumour treated at Princess Margaret Hospital between 2004 and 2013. Patients with documented p16INK4a immunohistochemistry (IHC), HPV polymerase chain reaction (PCR), or in situ hybridization (ISH) were included in the analysis. HPV status was defined by PCR or ISH when available and by p16 IHC for the remainder of patients. Survival analysis was performed using Kaplan Meier methods with the log-rank test for univariable analysis. Cox proportional hazards models were used for multivariable survival analysis.

Results:

Of a total of sixty-four patients with known HPV status, 40 patients (62.5 %) were HPV positive and 24 (37.5%) were HPV negative. The mean age of the HPV positive group was 59.0 (SD 8.7), and 55.6 (SD 8.5) for the HPV negative group. There were 36 (90%) and 22 (91.7%) males in the HPV positive and HPV negative groups respectively. Twenty-five patients (62.5%) and 21 patients (87.5%) had a smoking history in each group respectively. The HPV negative group had more advanced nodal disease with a higher proportion of N2c and N3 disease (50% vs 12.5%, p = .003). Treatment included primary (chemo)radiotherapy in 92.5% and 90.0% in the HPV positive and HPV negative groups respectively, or neck dissection followed by adjuvant (chemo)radiotherapy in 7.5% or 10% respectively. Three year overall survival was 91% in HPV positive and 68% in HPV negative patients (Figure 1, p=0.01). Three-year progression free survival was 88% in HPV-positive and 34% in HPV-negative patients (Figure 2, p<0.001). In multivariable analysis, HPV negative status (p=0.003) and advanced nodal status (p=0.05) were independent predictors for poorer progression-free survival.

Conclusions:
HPV mediated unknown primary head and neck SCC have an improved prognosis in comparison to those that are not related to HPV. The present series is the largest series investigating HPV status and prognostic significance in head and neck unknown primary squamous cell carcinomas.

Figure 1. Kaplan Meier curve illustrating a significant difference in three year overall survival between HPV positive and HPV negative patients

Figure 2. Kaplan Meier curve illustrating a significant difference in three year progression free survival between HPV positive and HPV negative patients
Objective: Precise use of prognostic parameters is critical for surgically-treated p16+ oropharyngeal squamous cell carcinoma (OPSCC), to guide adjuvant treatment. Traditionally in head and neck cancer, the most common negative prognosticators and determinants of adjuvant therapy are extracapsular spread (ECS) and high nodal stage. Recent evidence of non-prognostication from these nodal parameters in surgically managed p16+ OPSCC necessitates new, more reliable prognosticators. Our objective is to compare the prognostic significance of metastatic node number to other adverse features in surgically-treated p16+ OPSCC including traditionally negative nodal predictors.

Design: Observational study of prospectively assembled p16+ OPSCC patients treated with primary transoral surgery (TOS) and neck dissection +/- adjuvant therapy from 10/1996-7/2012.

Methods: Of 269 TOS-treated primary OPSCC patients, 220 p16+ cases were found eligible. Logistic regression was used to identify significant predictors of recurrence. Kaplan-Meier and Cox proportional hazard regression analyses were used to identify factors predictive of disease-specific survival (DSS) and disease-free survival (DFS) and to calculate hazard ratios (HR). C-statistic was used to determine the discriminative power of the models that included nodal parameters.

Results: Median follow-up was 59 (12-189) months; 85% had a minimum of 24 months follow-up. Adjuvant radiotherapy was administered in 44% and chemoradiotherapy in 34%. Recurrence developed in 22 patients (10%); 4 local, 5 regional, 2 regional and distant and 11 distant. 3- and 5-year DSS were 94.6% and 93%; 3-and 5-year DFS were 89% and 86%. Distribution of metastatic nodes was: 0 in 21 (9.5%), 1 in 74 (33.6%), 2 in 38 (17%), 3 in 32 (14.5%), 4 in 18 (8.2%), and >= 5 in 37 (17%). Thirty-eight (17%) had pN2c-pN3 disease while 159 (80%) had ECS. Median ipsilateral lymph node ratio (Pathologic nodes/Dissected nodes) was 0.07 (0-0.93). Multivariable logistic regression identified >= 5 nodes as a predictor of recurrences along with pT3-T4 disease. In multivariate Cox analyses, metastatic node number, pT3-T4 and margins were prognostic for DSS. Metastatic node number, pT3-T4, and any adjuvant therapy were prognostic for DFS. ECS, pN2c-N3 stage and smoking were not prognostic for recurrence, DSS or DFS. The cut-off for increased risk of poorer DSS and DFS occurred at 3 metastatic nodes (HR=3.32, 95% CI: 1.02-10.84, p=0.046; HR=3.09, 95% CI: 1.42-6.71, p=0.004 respectively) but a stronger association was observed for >= 5 nodes (HR=4.81, 95% CI: 1.59-14.56, p=0.005; HR=3.79, 95% CI: 1.60-8.97, p=0.002 respectively).

Conclusions: Metastatic node number is the strongest nodal predictor of outcomes in surgically-treated p16+ OPSCC patients. This further confirms recent evidence that ECS and advanced nodal stage (pN2c-N3) are not significant prognosticators and may not be reliable to determine use or intensity of adjuvant therapy in p16+ OPSCC, nor contribute to accurate stratification for clinical trials. A closer surveillance for recurrence is recommended for patients with more than 3 nodes but especially those with >= 5 metastatic nodes.
Background: Extracapsular extension of lymphatic metastases (ECE) has been shown to be a prognostic marker for poor outcome among patients with advanced head and neck squamous cell carcinoma. Recent reports have suggested that ECE is not associated with poor outcome among patients with p16-positive/HPV-associated oropharynx squamous cell cancer (OPSCC).

Objective: To compare the prognostic value of ECE between patients with p16-positive OPSCC and other patients with head and neck squamous cell carcinoma (HNSCC)

Methods: The study cohort included patients with newly diagnosed HNSCC between 2002-2013 enrolled in a prospective IRB-approved study who underwent neck dissection as part of their primary treatment. Patients with and without ECE were assessed for overall survival, disease-specific survival, and disease recurrence, defined as the development of either loco-regional or distant metastasis. Demographic and clinicopathologic factors were also collected at enrollment. OPSCC patients were further stratified into groups with p16-positive or p16-negative disease. Differences in the clinical outcome between HNSCC with and without ECE were assessed by Kaplan-Meir analyses and log-rank tests.

Results: Eighty-two HNSCC patients underwent primary surgical resection and had neck dissection with data reported for ECE. Distribution by anatomic site included: 36 (44%) oral cavity, 26 (32%) oropharynx, 17 (21%) larynx, and 2 (2%) hypopharynx cancers. The majority of cases (n=72, 88%) presented with Stage III or IV disease. Among patients with OPSCC, 16 patients (62%) had confirmed p16-expression in their tumor. Median follow-up for the cohort was 43 months. Among patients with either non-OPSCC or p16-negative OPSCC (n=62), those with ECE were significantly more likely to develop a loco-regional recurrence or distant metastasis compared to patients without ECE (log-rank p = 0.006). Furthermore, the ECE group trended toward reduced overall survival compared to the non-ECE group (median survival = 87 months vs. 32 months, respectively, log-rank p = 0.14). There was no detectable difference in overall survival between p16-positive OPSCC patients with and without ECE (log-rank p = 0.44), and no difference in time to disease recurrence, with a trend toward earlier recurrence in the group without ECE (log-rank p = 0.15). Among all patients with ECE (n = 32) the estimated 5 yr disease-free rate was 90% in the p16-positive OPSCC group vs. 57% among the remainder of the cohort (log rank p = 0.15).

Conclusion: ECE is a risk factor for poor outcome among patients with p16-negative OPSCC and HNSCC from other sites, however an association of ECE with poor outcome among patients with p16-positive OPSCC was not demonstrated in our cohort.
Purpose: Metastases from unknown primary are considered a distinct clinical entity in NCCN head and neck guidelines, with peculiar issues for the clinician. Diagnosis is based on the careful exclusion of a primary carcinoma arising mainly from the upper aerodigestive tract and from the skin. On the whole, neck node metastasis from clinically undetectable primary squamous cell carcinoma (SCC) accounts for 1% to 9% of head and neck malignancies. In the present study, we evaluate the prevalence of HPV and EBV oncogenic viruses in neck metastases from unknown primary SCC.

Patients and Methods: We evaluated fresh samples from a consecutive series of 22 neck dissections for metastases from unknown primary SCC obtained between 2010 and 2012 at a single institution. The samples were tested for the presence of HPV E6 and E7 mRNA and EBV DNA. All the patients underwent comprehensive neck dissection followed by adjuvant radio+chemotherapy.

Results: Oncogenic viral infections were detected in 12 cases (54% total; 2 HPV18, 5 HPV16, 2 EBV infection, and 3 EBV/HPV16 coinfections). The most frequent primarily involved neck level in our series was IIA (70%), in which the prevalence of viral infection was significantly higher (66%). We did not find any other significant correlations between virus detection and the clinicopathological parameters or prognosis.

Conclusion: The viral infection rate in the present series of metastases from unknown primary is even higher than what observed among nasopharyngeal and oropharyngeal carcinomas. If we consider, as NCCN guidelines, occult primary tumors to be a distinct pathological entity, the present findings lead us to consider such disease, particularly when in the presence of a bulky IIA node, to be a virus-related disease, similar to oropharyngeal and nasopharyngeal carcinoma. In general, the prognosis does not seem to be affected by the presence of any oncogenic virus, in contrast to the expectations based upon data from the nasopharynx and oropharynx. Nevertheless, the small number of patients and the short follow-up period did not allow us to draw definitive conclusions about this matter, and the hypothesis that a better prognosis is associated with viral detection remains rational and deserves to be tested again in a wider series with a longer follow-up time because, if confirmed, this finding could facilitate treatment selection in clinical practice. In any case, virus detection would have a decisive impact on diagnostic/decisional algorithms, especially if detection methods are implemented on cytological samples (e.g., thin-prep). In fact, the detection of an oncogenic virus in a FNAB or histological sample compatible with SCC would certainly be helpful when searching for the primary tumor, would guide the biopsy site choice and would indicate a bilateral tonsillectomy if high-risk HPV is detected.
LEARNING CURVE FOR ROBOT-ASSISTED NECK DISSECTION IN HEAD AND NECK CANCER: A 3-YEAR SUBSET ANALYSIS OF SEVERANCE ROBOT-ASSISTED NECK DISSECTION TRIAL

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Background: The introduction of robotic surgical systems expanded the role of minimally invasive surgery for head and neck cancer. With transoral robotic surgery (TORS) for the removal of primary tumors, robot-assisted neck dissection (RAND) for the management of regional metastases has been applied to maximize the concepts of minimally invasive surgery since 2010. Here, we intended to evaluate the learning curve and clinical outcomes of RAND in a single tertiary care institution.

Materials and Methods: Fifty cases of modified radical neck dissections (MRND) and 40 cases of supraomohyoid neck dissections (SOND) were performed with the help of robotic system to treat head and neck cancer between May 2010 and April 2013. The MRND and the SOND groups were subdivided into 5 and 4 consecutive subgroups of 10 patients each, respectively. Perioperative parameters were analyzed and compared, including mean operation time, duration and amount of drainage, length of hospital stay, and postoperative complications.

Results: Significant decreases in mean operation time were observed as experience performing RAND increased in both the MRND and the SOND groups. The mean operation time for the MRND group decreased by 29% over the course of our study (initial subgroup, 298.1 minutes; last subgroup, 212.4 minutes). The mean operation time for the SOND group decreased by 53% over the course of our study (initial subgroup, 226.5 minutes; last subgroup, 106.1 minutes). There were no significant differences between subgroups for the length of hospital stay, duration and amount of drainage, or postoperative complications.

Conclusions: This is the first report on the learning curve for RAND used to treat head and neck cancer. We explored the learning curve in a single institution over a 3-year period. This study can be used as a timeline reference for institutions where the RAND procedure will be adopted as a standard procedure.
This study aims to introduce our surgical experience of robot-assisted neck dissection (RAND) via a retroauricular approach (RA) in head and neck cancer and evaluate its surgical feasibility, which is expected to maximize the post-treatment cosmesis and functional outcome of the patients' neck. One hundred and seven patients (29 oral cavity, 39 oropharynx, 11 hypopharynx, 2 nasopharynx, 9 larynx, 10 salivary gland, 1 paranasal sinus, 1 primary mandible, 2 eye origin, 3 metastasis of unknown origin) who underwent treatment of primary lesion followed by RAND of cN0 or cN+ neck for biopsy proven head and neck cancer from May 2010 to December 2013 were enrolled and analyzed (Range of follow-up period: 1-43 months). Demographic, clinicopathological, and treatment characteristics were measured as well as incidence of perioperative complications. All endoscopic operations of RAND were successfully performed, without any significant intraoperative complications or conversion to open surgery. 10 patients received bilateral RANDs and the most common type of RAND (n=42) performed was selective neck dissection (SND) (II-V). Other types were SND(I-III) 38, SND(II,II) 11, SND(II-IV) 10, MRND 12, SND(III-V) 2, SND(II-IV) 1 and retropharyngeal lymph node dissection in 9 patients. Approach methods for the RANDs were as follows; transaxillary-retroauricular (TARA) 6, RA 61, modified facelift (MFL) 49. Fifty-seven out of all the patients received transoral robotic surgery (TORS) to remove the primary lesion. Twenty five patients received free flap reconstruction through the single incision port to restore the surgical defect. Based on patient-reported outcome questionnaires, most patients were satisfied with their cosmetic surgical outcomes. In terms of adjuvant treatment, 41 patients received concurrent chemoradiotherapy and 23 received radiotherapy. The average follow up period was 12.9 months (range 1-43 months). The estimated 3-year overall survival rate of the population was 83% and the 3-year disease free survival rate was 79.9%. RAND via RA in head and neck cancer were feasible and showed a clear cosmetic benefit, although longer operation time remains the drawback of this procedure. Further study of considerable number of patients with long period of follow-up should be conducted in order to evaluate long-term oncologic and functional outcomes in more detail.
S283 CLINICAL OUTCOME AND PROGNOSTIC FACTOR ANALYSIS AFTER SALVAGE SURGERY OF ISOLATED REGIONAL RECURRENTNES
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Objective The aim of this study was to evaluate the outcome and predictive factors for salvage surgery of isolated regional recurrence for head and neck squamous cell carcinoma.

Subjects and Methods A retrospective study was conducted with 55 patients with isolated neck recurrence. Thirty-one patients (56.4%) were treated with surgery alone. Surgical treatment was followed by postoperative radiotherapy in 5 patients (9.1%), and chemoradiation in 19 patients (34.5%). Eight patients underwent a bilateral neck dissection. Selective neck dissections were performed in 7 patients. Twenty-five patients underwent (modified) radical neck dissections and extended radical neck dissections were performed in 23 patients.

Results The 5-year overall and disease-specific survival rates were 61.8% and 60%, respectively. Recurrent disease developed in 22 patients (40%), with local recurrence in 3 patients, regional recurrence in 9 patients, and distant metastasis in 9 patients; 1 patient had both local and regional recurrence. Multivariate analysis revealed that extracapsular spread (p = 0.039, odds ratio 2.972) was independent factor associated with worse disease-specific survival. The patients who had advanced N stage (p = 0.032, odds ratio 3.322), disease free time less than six months (p = 0.047, odds ratio 0.399), extracapsular spread (ECS; p = 0.005, odds ratio 6.073), and in-field recurrence (p = 0.004, odds ratio 4.51) had significantly worse overall survival rate with the multivariate analysis.

Conclusion Salvage surgery for isolated regional recurrence had favorable oncological and functional outcome. Successful surgical salvage is most probable in late recurrence (>= 6 months) patients with recurrent N1 stage (no evidence of ECS) in the out-of-previous treatment field.
CLINICAL NODAL STAGE IS A SIGNIFICANT PREDICTOR OF OUTCOME IN PATIENTS WITH ORAL CAVITY SQUAMOUS CELL CARCINOMA AND PATHOLOGICALLY NEGATIVE NECK METASTASES: RESULTS OF THE INTERNATIONAL CONSORTIUM FOR OUTCOME RESEARCH.

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BACKGROUND:

We aimed to study the importance of clinical N classification (cN) in a subgroup of patients with oral cavity squamous cell carcinoma (OSCC) and pathologically negative neck nodes (pN-).

METHODS:

A total of 2,258 patients from 11 cancer centers who underwent neck dissection for OSCC (1990-2011) had pN- disease. The median follow-up was 44 months. 5-year overall survival (OS), disease-specific survival (DSS), disease free survival, local control, locoregional control, and distant metastasis rates were calculated by the Kaplan-Meier method. cN classification and tumor, node, metastasis classification system staging variables were subjected to multivariate analysis.

RESULTS:

A total of 345 patients were preoperatively classified as cN+ and 1,913 were classified as cN-. The 5-year OS and DSS of cN- patients were 73.6 and 82.2 %, respectively. The 5-year OS and DSS of cN+ patients were 64.9 and 76.9 %, respectively (p < 0.0001 each). A cN+ classification was a significant predictor of worse OS (p = 0.03) and DSS (p = 0.016), regardless of treatment, depth of invasion, or extent of neck dissection. cN classification was associated with recurrence-free survival (p = 0.01) and locoregional (neck and primary tumor) control (p = 0.004), but not with local (p = 0.19) and distant (p = 0.06) recurrence rates.

CONCLUSIONS:

Clinical evidence of neck metastases is an independent predictor of outcome, even in patients with pN- nodes.