American Head and Neck Society - Journal Club
Volume 31a, May 2020

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Investigating the Effect of Thyroid Nodule Location on the Risk of Thyroid Cancer

Sina Jasim, Thomas J. Baranski, Sharlene A. Teefey, and William D. Middleton.

*from **Thyroid**, March 2020*

Background: Thyroid nodules are routinely evaluated with ultrasound. Our aim was to determine if thyroid nodule location was a useful feature to predict thyroid cancer.
Materials and Methods: Retrospective review of patients with thyroid nodules from six referral centers from 2006 to 2010. A total of 3313 adult patients with thyroid nodules and confirmed benign or malignant thyroid diagnoses were included.

Results: Mean patient age was 54.2 (18–97) years, and the majority were women (n = 2635, 79.8%). A total of 3241 nodules were analyzed, 335 (10.3%) of which were malignant. Thyroid nodule location was an independent risk factor in predicting thyroid cancer (p = 0.005). Thyroid cancer odds were highest in the isthmus (odds ratio [OR] = 2.4, 95% confidence interval [CI] 1.6–3.6, p < 0.0001). In a multivariate regression model adjusting for age, sex, family history of thyroid cancer, radiation exposure, nodule size, and American College of Radiology (ACR) TI-RADS (Thyroid Imaging Reporting and Data System) score, the isthmus nodules had the highest risk of malignancy (OR = 2.4 [CI 1.5–3.9], p = 0.0007), followed by upper thyroid nodules (OR = 1.8 [CI 1.2–2.7], p = 0.005) and then middle thyroid nodules (OR = 1.5 [CI 1.1–2.0], p = 0.01) compared with lower thyroid nodules. Isthmus nodules were significantly smaller in size compared with middle (p < 0.0001) and lower (p = 0.0004), but not upper nodules (p = 0.25), with a mean size of 15.5mm (–10.7).

Conclusions: Thyroid nodule location is an independent risk factor in predicting the risk of thyroid cancer. Isthmic nodules carry the highest risk of cancer diagnosis and lower lobe nodules carry the lowest risk.

Summary:
Compared with lower lobe nodules, isthmus nodules continued to demonstrate the highest risk of malignancy in a multivariate regression model (OR = 2.4 [CI 1.5–3.9], p = 0.0007), followed by

upper lobe nodules (OR = 1.8 [CI 1.2–2.7], p = 0.005) and then middle lobe nodules (OR 1.5 [CI1.1–2.0], p = 0.01).

Malignant thyroid nodules located in the isthmus were significantly smaller in size compared with other locations.

In looking into the points contributing to the ACR TI-RADS, they confirmed that the risk of thyroid cancer increased by 73% with each increase in the score by one point (OR = 1.73 [CI 1.6–1.8], p < 0.0001).

Strengths
The strength of the study relies on the large sample size that included comprehensive data points gathered from multiple academic institutions with sonographic expertise, allowing the authors to adjust for various confounding factors when studying the risk of thyroid nodule location in predicting thyroid cancer. The diagnosis of thyroid cancer was confirmed by cytology and/or surgical pathology.

Weaknesses
The limitation of the study is the retrospective nature, which introduces the risk of selection bias. We did not factor in the margin of error that might be associated with cytology results, or adjust for solitary versus multiple thyroid nodules in the analysis; the rationale is that thyroid nodules can carry a similar risk of malignancy regardless of whether the patient has a solitary nodule or multiple nodules.

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Comorbidity in head and neck cancer: Is it associated with therapeutic delay, post-treatment mortality and survival in a population-based study?

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*From **Oral Oncology**, January 2020*

Objectives*:* This study aims to investigate the relationship between comorbidities and therapeutic delay, post- treatment mortality, overall and relative survival in patients diagnosed with squamous cell carcinoma of the head and neck (HNSCC).

Patients and Methods*:* 9245 patients with a single HNSCC diagnosed between 2009 and 2014 were identified in the Belgian Cancer Registry. The Charlson Comorbidity Index (CCI) was calculated for 8812 patients (95.3%), distinguishing patients having none (0), mild (1–2), moderate (3–4) or severe comorbidity (>4). The re- lationship between CCI and therapeutic delay was evaluated using the Spearman correlation. Post-treatment mortality was modelled with logistic regression, using death within 30 days as the event. The association be- tween comorbidity and survival was assessed using Cox proportional hazard models.

Results*:* Among 8812 patients with a known CCI, 39.2% had at least one comorbidity. Therapeutic delay in- ceased from 31 to 36 days when the CCI worsened from 0 to 4 (rho = 0.087). After case-mix adjustment, higher baseline comorbidity was associated with increased post-surgery mortality (mild, OR 3.52 [95% CI 1.91–6.49]; severe, OR 18.71 [95% CI 6.85–51.12]) and post-radiotherapy mortality (mild, OR 2.23 [95% CI 1.56–3.19]; severe, OR 9.33 [95% CI 4.83–18.01]) and with reduced overall survival (mild, HR 1.39, [95% CI 1.31–1.48]; severe, HR 2.41 [95% CI 2.00–2.90]). That was also the case for relative survival in unadjusted analyses (mild, EHR 1.77 [95% CI 1.64–1.92]; severe, EHR = 4.15 [95% CI 3.43–5.02]). *Conclusion:* Comorbidity is significantly related to therapeutic delay, post-treatment mortality, 5-year overall and relative survival in HNSCC patients. Therapeutic decision support tools should optimally integrate co- morbidity.

Summary:

- Comorbidity at the time of a HNSCC diagnosis was associated with therapeutic delay, with an increased risk of 30-day post-treatment mortality and with lower survival, even after adjusting for several prognostic factors and potential confounders (including age, sex, anatomic site, cancer stage, WHO performance status and previous hospital stay).
- A statistically significant association between comorbidities and time-to-treatment was found in this study.
- While chronological age itself is not an argument to offer a less intense treatment to HNC patients, providing major surgery or radiotherapy to a patient with comorbidities puts this patient at a high risk of having post-treatment complications or dying.

Strengths:

- Large dataset from a single institution (9245 patients) with >5 year follow up
- Includes surgical and non-surgical treatment plans
- Highlights the fact that there is an almost 5-fold increased risk of 30-day post-surgical mortality between patients with mild and severe comorbidity index.

Weaknesses:

- HPV status not known for oropharyngeal tumors (30% of dataset)
- Not all comorbidities are captured in the comorbidity index (renal dysfunction for example), which can impact treatment choices.
- Severity of each individual comorbidity is not measured and incorporated on the comorbidity index

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Impact of routine surveillance imaging on detecting recurrence in human papillomavirus associated oropharyngeal cancer

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From ***Oral Oncology****, April 2020*

Objectives*:* This study examines the utility of surveillance imaging in detecting locoregional failures (LRF), distant failures (DF) and second primary tumors (SPT) in patients with human papillomavirus (HPV) associated oropharyngeal cancer (OPC) after definitive chemoradiotherapy (CRT).

Methods and materials*:* An institutional database identified 225 patients with biopsy proven, non- metastatic HPV+ OPC treated with definitive CRT between 2004 and 2015, whose initial post-treatment imaging was negative for disease recurrence (DR). Two groups were defined: patients with <2 scans/year Group 1 and patients with ≥2 scans/year Group 2. The Mann-Whitney test or Chi-square was used to determine differences in baseline characteristics between groups. Fine & Gray regression was used to detect an association between imaging frequency, DR and diagnosis of SPT.

Results*:* Median follow up was 40.8 months. 30% of patients had ≥T3 disease and 90% had ≥ N2 disease (AJCC 7th edition). Twenty-one failures (9.3%) were observed, 7 LRF and 15 DF. Six LRF occurred within 24 months and 14 DF occurred within 36 months of treatment completion. Regression analysis showed Group 2 had increased risk of DR compared to Group1 (HR 10.3; p = 0.002) albeit with more advanced disease at baseline. Five SPT were found (2 lung, 2 esophagus, and 1 oropharynx) between 4.5 and 159 months post-CRT.

Conclusion*:* Surveillance imaging seems most useful in the first 2-3 years post treatment and is particularly important in detecting DF. Surveillance scans for SPT has a low yield but should be considered for those meeting lung cancer screening guidelines.

Summary

- Nearly all local recurrences and distant failures happened within the first two and three years respectively, after the completion of definitive chemoradiotherapy.
- After two years and three years respectively, imaging to detect locoregional and distant recurrences appears unnecessary
- Current guidelines that allow for a single surveillance imaging in the first six months post treatment would have missed the majority of recurrences in this series.

Strengths

- Relatively uniform cohort of HPV+ patients – confirmed with HPV ISH
- Identified a time frame (2-3 years) after which the utility of surveillance imaging is low

Weaknesses

- Smaller cohort (225 patients) with retrospective data.
- Scans were not all obtained using a well-defined time protocol
- Groups 1 and 2 were subject to provider selection bias as patients with more advanced disease had more scans

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Sentinel Lymph Node Biopsy for High-Risk Cutaneous Squamous Cell Carcinoma of the Head and Neck

Wu, M; Sethi, R.; Emerick, K., 2019; 130: 108-114.

*From **Laryngoscope**, January 2020*

Objectives: To describe outcomes of a single institution experience with sentinel lymph node biopsy (SLNB) for high-risk cutaneous squamous cell carcinoma of the head and neck.

Study Design: Retrospective case series.

Methods: Chart review was performed for patients who presented with clinically node negative cutaneous squamous cell carcinoma of the head and neck between December 2007 and May 2018. Patients who met high-risk criteria underwent SLNB and excision, with or without adjuvant therapy. Patients who underwent prior neck dissection were excluded. The main outcomes were SLNB result, lymph node spread, recurrence-free survival, disease-specific survival, and overall survival.

Results: Eighty-three patients underwent successful SLNB, and one patient underwent selective neck dissection for intraoperatively identified occult lymph node metastasis. Five patients (6%) had a sentinel node positive for tumor, of whom 4/5 received further treatment (neck dissection, radiation, and/or systemic therapy) with no further recurrence at the time of last follow-up. SLNB had a negative predictive value of 95% to 100%. Recurrent tumor at presentation, tumor arising from an area of chronic inflammation, and immunosuppression were significantly associated with increased risk of subsequent recurrence, with a mean follow-up of 19.9 months.

Conclusions: SLNB can be used to identify regional lymph node metastases in cutaneous squamous cell carcinoma of the head and neck with a high negative predictive value (95%–100%). Factors associated with recurrence were tumor being locally recurrent at presentation, arising from an area of chronic inflammation, and immunosuppression.

Summary

- Patients with clinically or imaging N0 cSCCA of the head and neck with at least two high-risk features (size >2 cm, poorly differentiated histology, perineural invasion, and depth beyond the subcutaneous fat) were offered SLNB.
- Primary tumor was treated with Mohs micrographic surgery or wide local excision.
- SLNB technique included intradermal injection of technetium-99 m sulfur colloid tracer and a radionuclide lymphoscintigram and/or low-dose single photon emission computed tomography and intraoperative gamma-probe.
- Kaplan-Meier curves and multivariate Cox proportional hazards model were used for the analysis.
- 89 patients were included and in 83 the SNLB was feasible.
- Most common sites were scalp, cheek and ear (62%) with tumors <4 cm (76%) and 96% were classified as T3 by the AJCC. 67% of patients were treated with wide local

excision. 6/84 (7%) had a positive SLNB and 4/78 (5%) patients of the negative SLNB, developed regional recurrence.

- The overall and disease-specific survival at 19.9 months was 89% and 94%, respectively. No statistically significant difference in recurrence and survival was noted between patients with (+) SLNB versus (-) SLNB. After multivariable analysis, immunosuppression, recurrent tumors and origin in an area of chronic inflammation were significantly associated with recurrence.

Strengths

- Single-institution cohort of patients
- Specific definition of high-risk patients
- Homogeneous technique of SLNB

Weaknesses

- Low number of events of (+) SLNB and recurrence
- Heterogeneity of primary and adjuvant treatment (Mohs and wide resection and RT indications)
- Statistical analysis of low power due to the small sample size and low number of events.
- The controversy about the specific weight of elements to define a high risk cSCCA is still open.

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Risk and Rate of Occult Contralateral Nodal Disease in Surgically Treated Patients with Human Papillomavirus-Related Squamous Cell Carcinoma of the Base of the Tongue

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*From **JAMA Otolaryngology Head & Neck Surgery**, November 2019*

Importance: The optimal treatment strategy for patients with human papillomavirus (HPV)-related oropharyngeal squamous cell carcinoma (OPSCC) of the base of the tongue (BOT) has not been sufficiently studied.

Objective: To investigate the rate of and risk factors for occult contralateral nodal disease in patients with HPV-related BOT OPSCC undergoing transoral surgery and bilateral neck dissections.

Design, setting, and participants: This retrospective case series reviewed the medical records of patients with HPV-related BOT OPSCC who underwent transoral surgery and bilateral neck dissections from January 1, 2002, through December 31, 2018, at the tertiary care center of Washington University School of Medicine in St Louis. Patients had a median follow-up of 30.0 months (interquartile range, 11.0-60.4 months). Patients with recurrent disease or multiple

synchronous OPSCC primary tumors were excluded for a total of 89 patients. Data were analyzed from January 1 through June 1, 2019.

Main outcomes and measures: The primary outcome was the rate of contralateral occult nodal disease. Secondary outcomes were potential risk factors for contralateral occult nodal disease and regional recurrence rates.

Results: Eighty-nine patients were included in the series, of whom 81 (91.0%) were men. The mean (SD) age was 60 (9) years. Overall, 34 patients (38.2%) had pathologic contralateral nodal metastases. Seventy patients had no clinical evidence of contralateral nodal disease. Of these 70, occult nodes were identified in 15 (21.4%). Risk of contralateral disease was higher when the primary tumor crossed midline (odds ratio, 6.23; 95% CI, 1.71-22.77). Of the 55 patients with no occult disease identified, only 2 (3.6%) received radiotherapy to the contralateral neck, and no regional recurrence of disease was noted.

Conclusions and relevance: Given the rate of occult contralateral nodal disease of 21.4%, it appears that contralateral elective neck dissection or radiotherapy should be recommended in patients with HPV-related BOT OPSCC. Patients with a pathologically negative result of contralateral neck dissection may not benefit from radiotherapy to that nodal basin. Future prospective investigations should evaluate functional and oncologic outcomes of contralateral elective neck dissection compared with elective radiotherapy in the contralateral neck for HPV-related BOT OPSCC.

Summary

- N=202 p16+ BOT SCCA. 114 underwent unilateral neck dissection and 89 (44%) underwent bilateral neck dissection. Of the 89 that underwent bilateral neck dissection, 19 had preoperative clinical evidence of contralateral neck disease. 21% of the remaining 70 patients had occult contralateral neck disease. In total, 34 (38%) had pathologic positive contralateral nodes.

Table 3. Risk Factors for Contralateral Nodal Disease in All Patients

Risk Factor	Patient Population[a] Contralateral pN0 Neck Finding (n = 55)[b]	Contralateral pN1+ Neck Finding (n = 34)[c]	Univariate Analysis, OR (95% CI)
Tumor location			
Lateralized	34 (61.8)	8 (23.5)	
Crosses midline	15 (27.3)	26 (76.5)	7.37 (2.71-19.99)
Unknown	6 (10.9)	0	
Distance from midline, mean (SD), cm	0.46 (0.40)	0.16 (0.24)	0.05 (0.00-4.69)
Clinical T stage			
T0	14 (25.5)	4 (11.8)	NA
T1-T2	34 (61.8)	17 (50.0)	1.75 (0.50-6.14)
T3-T4	7 (12.7)	13 (38.2)	6.50 (1.54-27.49)
Pathologic T stage			
T1-T2	45 (81.8)	21 (61.8)	2.79 (1.05-7.38)
T3-T4	10 (18.2)	13 (38.2)	
LVI			
No	36 (65.5)	14 (41.2)	
Yes	18 (32.7)	20 (58.8)	2.86 (1.18-6.94)
Unknown	1 (1.8)	0	
PNI			
No	50 (90.9)	29 (85.3)	
Yes	4 (7.3)	5 (14.7)	2.16 (0.54-8.67)
Unknown	1 (1.8)	0	
Clinical N stage in ipsilateral neck			
cN0	4 (7.3)	1 (2.9)	2.59 (0.28-24.18)
cN1+	51 (92.7)	33 (97.1)	
No. of positive nodes, mean (SD)	2 (2)	4 (5)	1.23 (1.02-1.48)
Largest node, mean (SD), cm	3.53 (1.52)	3.99 (1.38)	1.25 (0.92-1.70)
ECS			
Absent	22 (40.0)	7 (20.6)	
Present	29 (52.7)	26 (76.5)	2.82 (1.04-7.67)
Unknown	4 (7.3)	1 (2.9)	

Abbreviations: ECS, extracapsular lymph node spread; LVI, lymphovascular invasion; NA, not available; OR, odds ratio; PNI, perineural invasion.

[a] Unless otherwise indicated, data a expressed as number (percentage) of patients.

[b] Refers to patients who on analysis of pathologic findings had no evidence of disease in contralatera neck nodes.

[c] Refers to patients who on analysis of pathologic findings had at least 1 node with evidence of disease in the contralateral neck.

- Risk factors for contralateral nodal disease on univariate analysis include crossing midline, higher clinical and pathologic T stage, lymphovascular invasion, higher number of involved ipsilateral nodes and extracapsular spread. Multivariate analysis demonstrates significance only for tumors that crossed midline.
- No patients with pathologic negative contralateral neck status had a regional recurrence. Six patients (5.3%) with unilateral neck dissection had a contralateral nodal recurrence compared with 1 patient (1.1%) with bilateral neck dissection (P=.11).

Strengths

- Largest investigation of contralateral occult nodal metastases in patients with HPV related BOT OPSCC who underwent elective contralateral neck dissection.
- Median followup of 30 month

Weaknesses

- Despite it being the largest investigation into this patient population, still a low N and also a retrospective review. Few institutions perform bilateral neck dissection for occult contralateral disease and appears, over the course of the 16 year time period, there was a change in practice patterns at this institution from elective contralateral neck radiotherapy to neck dissection.

- Incidence of contralateral nodal disease may be underestimated, because this study included only patients undergoing up front surgery to the contralateral neck. The pathologic nodal status of patients treated with contralateral neck elective radiotherapy is unknown to date but also nearly impossible to ascertain.

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