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AHNS Skull Base Surgery Section Edition

This Issue of the AHNS Journal Club has been compiled and reviewed by members of the
AHNS Skull Base Surgery Section:
(Shirley Su, Chair MD, Marilene Wang MD, Vice-Chair)

Dear Colleagues,

This Journal Club Edition is from the AHNS Skull Base Surgery Section and is on the topic of sinonasal adenocarcinoma. Articles put forth represent some of the most complete data on the subject and we hope the readership finds them interesting. We begin with two population-based studies from the National Cancer Database. We follow this up with a bi-institutional case-control study to provide insight into the surgical management of this rare disease. We finish we with a molecular study demonstrating association of tp53 mutation and occupational exposure to wood dust.

We hope you find this journal club enlightening and enjoyable.

Best,
Meghan Turner, MD, FACS
Hari Jeyarajan, MD
Ian Witterick, MD

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Population-Based Analysis on The Effect of Nodal and Distant Metastases in Sinonasal Adenocarcinoma

Cynthia M Chweya, Christopher M Low, Jamie J Van Gompel, Kathryn M Van Abel, Janalee K Stokken, Garret Choby

From the **Head Neck.** *September 2020.*

Background: Minimal information has been reported on the effect of distant and nodal metastases at the time of diagnosis on survival in patients with sinonasal adenocarcinoma (SNAC).

Methods: The Surveillance, Epidemiology, and End Results database was utilized to compare overall survival (OS) and disease-specific survival (DSS). Results: Of the 325 patients with SNAC identified, 5-year and 10-year OS for all included patients was 64% and 58%, respectively. On multivariate analysis, the presence of distant metastases ($P < .0001$), maxillary and frontal sinus primary tumors ($P = .0042$, $P = .0006$), and increasing age ($P = .007$) were risk factors for worsened DSS. The presence of regional spread to multiple cervical nodal basins (OS RR 3.26, $P = .002$; DSS RR 2.51, $P = .013$) and a single nodal basin (DSS RR 2.19, $P = .046$) was associated with worsened survival compared to no regional spread.

Conclusion: Survival in SNAC was significantly worsened with increasing age, tumor site of origin, and distant metastatic disease.

Summary Statement
- This represents the largest study to date from the US (325 patients) and includes patients across the United States which eliminates selection bias and institutional biases in treatment.
- Provides excellent long-term follow-up and reports overall and disease-specific survival at 5- and 10 years.
- The authors report the novel finding of worsened disease specific survival with regional disease and distant disease, which highlights the need for metastatic workup at initial presentation.

Strengths
- SEER does not include data on surgical margins, so survival analysis is limited in this regard.
- SEER does not include data on grade, which has been shown to significantly impact survival (low-grade vs. high-grade) in this particular histopathology.
- Distant metastases at diagnosis having a worsened disease-specific survival is somewhat self-evident, though the call to do a distant workup on presentation may still be needed as regional metastasis is rare.

Weaknesses

- Expected limitations of a simulated model rather than real-world data (estimated rates of HPV infection, OPC conversion, treatment costs, and fewer risk-factor variables available).
- Only non-surgical treatment costs were included in the model.
- Cost of increasing HPV vaccination rates (i.e. public health campaigns) was not included.

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Survival in Low-Grade and High-Grade Sinonasal Adenocarcinoma: A National Cancer Database Analysis

Aryan Shay, Ashwin Ganti, Anish Raman, Hannah N Kuhar, Samuel R Auger, Michael Eggerstedt, Tirth Patel, Edward C Kuan, Pete S Batra, Bobby A Tajudeen

Background: Sinonasal adenocarcinoma (SNAC) is a rare malignancy arising from mucus-secreting glandular tissue. Limited large-scale studies are available due to its rarity. We evaluated SNAC in the National Cancer Database (NCDB), a source that affords multi-institutional, population studies of rare cancers and their outcomes.

Methods: The NCDB was queried for adenocarcinoma in the sinonasal tract.

Results:
A total of 553 patients were identified. The cohort was composed of 59.3% males. The nasal cavity was the most common primary site, representing 44.1% of cases. About 5.7% of patients presented with nodal disease, while 3.3% had distant metastases. About 40.6% of cases presented with stage IV disease. About 73.5% of patients underwent surgery, 54.2% received radiation therapy, and 27.7% had chemotherapy. Median OS was 71.7 months, while OS at 1, 2, and 5 years was 82, 73.0, and 52%, respectively. On multivariate analysis, advanced age (hazard ratio [HR]: 1.04; 95% confidence interval [CI]: 1.02-1.05), Charlson-Deyo score of 1 (HR: 1.99; 95% CI: 1.20-3.30), advanced tumor grade (HR: 2.73; 95% CI: 1.39-5.34), and advanced tumor stage (HR: 2.71; 95% CI: 1.33-5.50) were associated with worse OS, whereas surgery (HR: 0.34; 95% CI: 0.20-0.60) and radiation therapy (HR: 0.55; 95% CI: 0.33-0.91), but not chemotherapy (HR: 1.16; 95% CI: 0.66-2.05), predicted improved OS.

Conclusions: SNAC is a rare malignancy with a 5-year survival approximating 50%. Surgery and radiation therapy, but not chemotherapy, are associated with improved survival, and likely play a critical role in the interdisciplinary management of SNAC.

Strengths:
Large database study allowing for study of rare disease.
This study is able to evaluate survival based on treatment type with surgery demonstrating best over survival (HR 0.34; 95%CI:0.20-0.60), which is not possible in single-institution studies with treatment paradigm biases.

Weaknesses:
Limited survival analysis to overall survival, which is a sometimes poor assessment given that comorbidities and death from other causes muddles assessment of cancer-related treatment outcomes.

Treatment Strategies for Primary Early-Stage Sinonasal Adenocarcinoma: A Retrospective Bi-Institutional Case-Control Study

Mario Turri-Zanoni, Paolo Battaglia, Alessia Lambertoni, Marta Giovannardi, Alberto Schreiber, Luca Volpi, Andrea Bolzoni-Villaret, Davide Lombardi, Maurizio Bignami, Francesca Magnoli, Carla Facco, Paolo Antognoni, Piero Nicolai, Paolo Castelnuovo

Objective: To investigate different treatment strategies for primary early-stage (pT1-T2) sinonasal adenocarcinomas.

Methods: : Retrospective case-control study. From 2000 to 2011, 61 cases were radically resected using an endoscopic endonasal approach. Surgery as a single treatment modality was adopted for 33 patients (study group) while it was followed by postoperative radiotherapy (poRT) in 28 patients (control group).

Results: Median follow-up was 61 and 67 months for the study and control group respectively. Patients were stratified according to the pT classification and no statistically significant differences were found in terms of Overall (OS) and Recurrence-free (RFS) survival. When analyzing the high-grade tumors (47 cases), statistically significant differences were observed between the control and study groups both in terms of OS ($90.5\% \pm 6.5\%$ versus $57.6\% \pm 15.4\%$, $P = 0.03$) and RFS ($92.3\% \pm 7.39\%$ versus $80.2\% \pm 8.88\%$, $P = 0.05$). Using multivariate analysis, OS was independently determined by poRT (Hazard Ratio = 0.16; $P = 0.03$) thus confirming its protective role for high-grade adenocarcinomas.
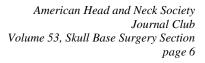
Conclusions: Our preliminary results suggest that endoscopic endonasal surgery could be used as a single treatment modality for primary early-stage low-grade sinonasal adenocarcinoma, resected with negative margins. Surgery followed by poRT offers the best treatment strategy not only for advanced-stage lesions but also for high-grade adenocarcinomas, regardless of the stage of disease at presentation.

Strengths:
- Case-control design allows for the highest level of evidence in many rare diseases.
- Bi-institutional design limits the selection bias as well as bias derived from having a single surgeon experience.
- Demonstration of the success of surgical resection with negative margins.
- Allows decent understanding of the impact of postoperative radiation on survival.

Weakness:
- Relatively small sample size of 61 patients with 31 in each group.
- May have limited generalizability outside of these institutions whose senior surgeons are extremely skilled at endoscopic resection.

Mutations in TP53 tumor suppressor gene in wood dust-related sinonasal cancer

Background: The causal role of work-related exposure to wood dust in the development of sinonasal cancer has long been established by numerous epidemiologic studies. To study molecular changes in these tumors, we analyzed TP53 gene mutations in 358 sinonasal cancer cases with or without occupational exposure to wood dust, using capillary electrophoresis single-strand conformation polymorphism analysis and direct sequencing. A significant association between wood-dust exposure and adenocarcinoma histology was observed [adjusted odds ratio (OR) 12.6, 95% confidence interval (CI), 5.0-31.6]. TP53 mutations occurred in all histologies, with an overall frequency of 77%. TP53 mutation positive status was most common in adenocarcinoma (OR 2.0, 95% CI, 1.1-3.7; compared with squamous cell carcinoma), and mutation positivity showed an overall, nonsignificant association with wood-dust exposure (OR 1.6, 95% CI, 0.8-3.1). Risk of TP53 mutation was significantly increased in association with duration (> or =24 years, OR 5.1, 95% CI, 1.5-17.1), average level (>2 mg/m(3); OR 3.6, 95% CI, 1.2-10.8) and cumulative level (> or =30 mg/m(3) x years; OR 3.5, 95% CI, 1.2-10.7) of wood-dust exposure; adjustment for formaldehyde affected the ORs only slightly. Smoking did not influence the occurrence of TP53 mutation; however, it was associated with multiple mutations (p = 0.03). As far as we are aware, this is the first study to demonstrate a high prevalence of TP53 mutation-positive cases in a large collection of sinonasal cancers with data on occupational exposure. Our results indicate that mutational mechanisms, particularly TP53 mutations, are associated with work-related exposure to wood dust in sinonasal cancer.

Strengths:
- Multi-institutional study from three different cancer registries and as such, it is the largest study to date examining mutational burden of tp53 in sinonasal adenocarcinoma.
- The authors demonstrate a dose-dependent and duration of exposure-related relationship to tp53 mutations in those patients with wood dust exposure.

Weaknesses:
- Not a proven actionable target, however, tp53 has been a marker for response to chemotherapy and immunotherapy in "head and neck cancer" as well as "adenocarcinoma of the lung."
- Study patients are only from European countries. These same mutational burdens may not translate to other patient non-European populations.