



American Head and Neck Society - Journal Club

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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 (Ivan El-Sayed, Chair and Ian Witterick, Vice-Chair)

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Dear Colleagues,

The AHNS Skull Base Surgery Section is pleased to present the April issue of the AHNS Journal Club. Our goal for the Skull Base Surgery Section Journal Club issues is to provide insight into contemporary treatment of skull base tumors with themed issues. This second issue will address recent publications on treatment of sinonasal undifferentiated carcinoma (SNUC).

SNUC is a rare malignancy that was originally identified in 1986 by Frierson et al. as a distinct malignancy apart from other small blue cell tumors due to unique immunohistochemical staining patterns.¹ Since that time, there have been many large single-institution studies published to determine the best course of treatment for this aggressive malignancy with poor overall survival.²⁻⁴ SNUC is extremely rare (representing 4% of sinonasal malignancies and 0.0064% of all cancers), so population-based studies and database studies remain important in understanding its incidence, presentation, natural history, and outcomes based on treatment types.^{5,6}

To date, there is still no consensus on the optimal treatment. Most patients have advanced disease with involvement of the brain or orbit on initial presentation. There is a similar lack of consensus on appropriate treatment of the neck in SNUC. A recent systematic review suggests that dual modality treatment and elective treatment are warranted given the currently available data and treatment failure rates.^{6,7} In light of the poor overall prognosis, Amit et al. assess which patients would most benefit from nonsurgical treatment vs. surgery using response to induction chemotherapy as a guide and found improved 5-year disease-specific survival and decreased distant failures for those responding to induction chemotherapy who underwent definitive concurrent chemoradiotherapy.⁴ Finally, genetic markers for SNUC have been found that may have relevance to treatment outcomes including sensitivity for platinum-based chemotherapy and as potential targets for molecular therapies.^{8,9}

We believe this issue will help shine light on current knowledge gaps and new areas requiring future study in the treatment of SNUC. Comments are welcome and can be sent to meghan.turner@hsc.wvu.edu. Please also feel free to send suggestions about themes for our next issue.

Sincerely,

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Induction Chemotherapy Response as a Guide for Treatment Optimization in Sinonasal Undifferentiated Carcinoma

Moran Amit, Ahmed S Abdelmeguid, Teemaranawich Watcherporn, Hideaki Takahashi, Samantha Tam, Diana Bell, Renata Ferrarotto, Bonnie Glisson, Michael E Kupferman, Dianna B Roberts, Shirley Y Su, Shaan M Raza, Franco DeMonte, Ehab Y Hanna

*From the **Clinical Oncology**. February 2020.*

Purpose: Multimodal therapy is a well-established approach for the treatment of sinonasal undifferentiated carcinoma (SNUC); however, the optimal sequence of the various treatments modalities is yet to be determined. This study aimed to assess the role of induction chemotherapy (IC) in guiding definitive therapy in patients with SNUC.

Methods: Ninety-five previously untreated patients diagnosed with SNUC and treated between 2001 and 2018 at The University of Texas MD Anderson Cancer Center were included in the analysis. Patients were treated with curative intent and received IC before definitive locoregional therapy. The primary end point was disease-specific survival (DSS). Secondary end points included overall and disease-free survival, disease recurrence, and organ preservation.

Results: A total of 95 treatment-naive patients were included in the analysis. For the entire cohort, the 5-years DSS probability was 59% (95% CI, 53% to 66%). In patients who had partial or complete response to IC, the 5-year DSS probabilities were 81% (95% CI, 69% to 88%) after treatment with definitive concurrent chemoradiotherapy (CRT) after IC and 54% (95% CI, 44% to 61%) after definitive surgery and postoperative radiotherapy or CRT after IC (log-rank $P = .001$). In patients who did not experience at least a partial response to IC, the 5-year DSS probabilities were 0% (95% CI, 0% to 4%) in patients who were treated with concurrent CRT after IC and 39% (95% CI, 30% to 46%) in patients who were treated with surgery plus radiotherapy or CRT (adjusted hazard ratio of 5.68 [95% CI, 2.89 to 9.36]).

Conclusion: In patients who achieve a favorable response to IC, definitive CRT results in improved survival compared with those who undergo definitive surgery. In patients who do not achieve a favorable response to IC, surgery when feasible seems to provide a better chance of disease control and improved survival.

Summary Statements:

- The study is the one of two single-institution studies providing five-year DSS for previously untreated SNUC is 59% for both surgical and nonsurgical therapy.
- The 5-year DSS following IC with response for definitive concurrent CRT is 81% vs. 54% in those undergoing surgery with adjuvant treatment in the treatment of SNUC.
- In SNUC patients who fail to respond to IC have a 5-year DSS of 0% if pursuing nonsurgical therapy and 39% with surgery and adjuvant radiotherapy or chemoradiotherapy.
- IC may help select patients which patients with SNUC would benefit from definitive CRT over surgery with adjuvant therapy. Those without response to induction chemotherapy benefit from surgery, when feasible, followed by adjuvant treatment



Strengths:

- This is the largest, single-institution study examining outcomes for SNUC, a rare cancer with poor 5-year-OS and is one of two providing 5-year disease-specific survival outcomes.
- This study examines treatment failures in nonsurgical (66%) and surgical groups (34%) and demonstrated that distant failures occurred three times as often in those treated with surgery after at least a partial response to IC as compared to those treated with concurrent chemoradiotherapy.
- This is the only study examining the use of induction chemotherapy as a means to select patients who are likely to fail nonsurgical therapy and might spare some patients surgical treatment and its morbidity in a disease with poor overall and disease-specific survival.

Weaknesses:

- The results of this study are not necessarily translatable to other centers given the selection bias, patient population differences in patients willing and healthy enough to undergo IC and/or surgery for SNUC.
- Adverse events occurred in 60% of patients receiving induction chemotherapy with 62 patients (64%) completing at least two cycles of IC and 33 patients completing only one cycle (range, one to five cycles; median, three cycles). Most patients were partial responders, (61%). The complete response rate was only 6%.
- The surgical approaches in this study were variable (open craniofacial resection, endoscopic anterior craniofacial resection, and endoscopic-assistance with open craniofacial resection) with 61% positive margins rate, which cannot be understood by approach and the effect of positive margins on outcomes in surgical patients was not studied.

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Outcome by treatment modality in sinonasal undifferentiated carcinoma (SNUC): A case-series, systematic review and meta-analysis

Grégoire B Morand, Nanina Anderegg, Domenic Vital, Kristian Ikenberg, Gerhard F Huber, Michael B Soyka, Matthias Egger, David Holzmann

From the *Clinical Oncology*. February 2020.

Purpose: Sinonasal undifferentiated carcinoma (SNUC) is an aggressive malignancy. As the tumor is very rare, current treatment recommendations are based on institutional case reports and series. The authors hence supplemented their own institutional series with a systematic review and meta-analysis to investigate how treatment modalities are associated with survival.

Methods: The authors' literature review included searches of Ovid, Medline, Ovid Embase, Web of Science, Biosis, Scopus and the Cochrane Library database libraries. They combined this with their own institutional series and extracted aggregate and individual patient data for statistical analysis. To study the association between treatment modalities and survival, They used random-effects meta-regression for the aggregate-and cox mixed-effects models.

Results: 379 citations were found; 29 case series could be included in the final analysis, including a total number of 390 single patients (34.6% female). Median age at diagnosis was 52 years. 80.9% of patients presented with a T4 tumor and 16.0% with nodal metastasis at diagnosis. In individual patient data (IPD) meta-analysis, single modality (surgery alone or radiation alone) treatment was associated with reduced survival compared to double modality (surgery & radiation or chemoradiation) treatment (adjusted Hazard Ratio [aHR] 2.97, 95% Confidence Interval [1.41-6.27]) and compared to triple modality (surgery & radiation & chemotherapy) treatment (aHR 2.80 95%-CI 1.29-6.05 for triple vs. single modality). Triple modality treatment was not superior to double modality treatment. (aHR 1.06, 95%-CI 0.59-1.92).

Conclusion: Double and triple modality treatment are associated with improved survival over single modality but there is no evidence that triple modality is superior to double modality treatment.

Summary Statements:

- Large meta-analyses of a rare and aggressive skull base malignancy with an overall 5 year survival rate of 36.4%
- Multimodal treatment had consistently better treatment outcomes across all stages on multivariate analyses (whether chemoradiation or surgery with adjuvant radiation) over single modality treatment being almost 3 times more likely to die. No appreciable benefit was found with triple modality treatment
- 16% of patients exhibited regional disease at presentation with over a quarter of patients failing regionally at 2 years
- 8.1% of patients possess distant disease (lung, bone, liver) at presentation but equally almost a quarter progress to distant disease in 2 years



Strengths:

- Large meta-analyses of almost 400 patients
- Individual patient data was available for two thirds of the studies reviewed
- Both individual and aggregate data highlighted the importance of regional disease

Weaknesses:

- Significant clinical and methodological heterogeneity (not quantified in the paper) limits interpretation of the data particularly with respect to individual patient factors and treatment specifics.

Elective neck treatment in sinonasal undifferentiated carcinoma: Systematic review and meta-analysis

Muhammad Faisal, Rudolf Seemann, Claudia Lill, Sasan Hamzavi, Arno Wutzl, Boban M Erovic, Stefan Janik

*From the **Surgical Pathology**. April 2017.*

Purpose: Sinonasal undifferentiated carcinomas (SNUCs), being an aggressive malignancy with dismal survival outcome, have given limited consideration regarding management of regional failures. A total of 12 studies, published between 1999 and 2019, met inclusion criteria. We performed a meta-analysis assessing regional (neck) relapse after elective neck treatment compared to observation in clinically node negative (N0) necks. Clinical data of 255 patients were used for meta-analysis. Among them, 83.4% of patients presented with T4 tumors and 14.1% had positive neck nodes. Elective neck treatment was applied in 49.5% of analyzed patients. Regional relapses occurred in 3.7% of patients who have undergone elective neck treatment compared to 26.4% in patients who had not. Elective neck treatment significantly reduced the risk of regional recurrence (odds ratio 0.20; 95% confidence interval 0.08-0.49; $P = .0004$). The meta-analysis indicates that elective neck treatment could significantly reduce the risk of regional failures in patients with SNUCs.

Summary Statements:

- This meta-analysis published in 2019 includes 12 single-institution studies (2 case series and 10 cohort studies) published between 2008 and 2018 and included data on 255 patients with sufficient data for analysis. In this series 49.5% had upfront elective treatment of the neck. Follow-up in the studies ranged from 14-82 months.
- The incidence of pathologically positive nodes was 14.1% for those undergoing elective neck dissection.
- Elective neck treatment was associated with a regional relapse rate of 3.7%, while those patients who were observed had a regional relapse rate of 26.4%, favoring upfront treatment of the neck in patients with SNUC (odds ratio 0.20; 95% confidence interval 0.08-0.49; $P = .0004$).

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Strengths:

- This study presents the best data thus far on the incidence nodal metastasis on presentation (14.1%) in a large cohort of patients with adequate follow-up from single institution studies.
- This study validates the use of elective neck treatment and provides parameters by which the clinician might advise patients to undergo elective treatment.
- This data also suggests that dual and/or trimodality therapy improves the LRC for SNUC.

Weaknesses:

- The authors do not clearly state whether nodal positivity was based on pathologic staging, radiographic staging, or both. The incidence of nodal metastasis is assumed to be the incidence of occult positive metastasis found in neck dissection specimens performed electively.
- This study did not perform subgroup analysis to examine regional relapse based on the type of elective neck treatment (surgery vs. elective neck irradiation vs. surgery with adjuvant neck irradiation).
- For elective neck treatment, there is no mention of the extent of treatment (levels of neck dissection, radiation dosing to the neck, or differences between extent of neck treatment (uni-, dual or tri-modality)), so the reader cannot determine if LRC rates in the neck are improved with single, dual or tri-modality treatment or whether or not surgery or nonsurgical therapy is more effective.

Intensive treatment and survival outcomes in NUT midline carcinoma of the head and neck

Nicole G Chau, Shelley Hurwitz, Chelsey M Mitchell, Alexandra Aserlind, Noam Grunfeld, Leah Kaplan, Peter Hsi, Daniel E Bauer, Christopher S Lathan I, Carlos Rodriguez-Galindo, Roy B Tishler, Robert I Haddad, Stephen E Sallan, James E Bradner, Christopher A French

*From the **Cancer**. December 2016.*

Background: NUT midline carcinoma is a rare and aggressive genetically characterized subtype of squamous cell carcinoma frequently arising from the head and neck. The characteristics and optimal management of head and neck NUT midline carcinoma (HNNMC) are unclear.

Methods: A retrospective review of all known cases of HNNMC in the International NUT Midline Carcinoma Registry as of December 31, 2014, was performed. Forty-eight consecutive patients were treated from 1993 to 2014, and clinicopathologic variables and outcomes for 40 patients were available for analyses; they composed the largest HNNMC cohort studied to date. Overall survival (OS) and progression-free survival (PFS) according to patient characteristics and treatment were analyzed.

Results: This study identified a 5-fold increase in the diagnosis of HNNMC from 2011 to 2014. The median age was 21.9 years (range, 0.1-81.7 years); the male and female proportions were 40% and 60%, respectively; and 86% had bromodomain containing 4-nuclear protein in testis (BRD4-NUT) fusion. The initial treatment was initial surgery with or without adjuvant

chemoradiation or adjuvant radiation (56%), initial radiation with or without chemotherapy (15%), or initial chemotherapy with or without surgery or radiation (28%). The median PFS was 6.6 months (range, 4.7-8.4 months). The median OS was 9.7 months (range, 6.6-15.6 months). The 2-year PFS rate was 26% (95% confidence interval [CI], 13%-40%). The 2-year OS rate was 30% (95% CI, 16%-46%). Initial surgery with or without postoperative chemoradiation or radiation ($P = .04$) and complete resection with negative margins ($P = .01$) were significant predictors of improved OS even after adjustments for age, tumor size, and neck lymphadenopathy. Initial radiation or chemotherapy and the NUT translocation type were not associated with outcomes.

Conclusions: HNNMC portends a poor prognosis. Aggressive initial surgical resection with or without postoperative chemoradiation or radiation is associated with significantly enhanced survival. Chemotherapy or radiation alone is often inadequate.

Summary Statements

- NUT midline carcinoma (NMC) is a rare and aggressive genetically defined subtype of carcinoma characterized by chromosomal rearrangement of the nuclear protein in testis (NUT) gene (also known as NUTM1 or Chr15orf55). It is characterized by somatic t(15:19) translocation that positions NUT in frame with bromodomain containing 4 (BRD4), which is a ubiquitously expressed transcriptional coactivator. Approximately 30% of NMCs lack BRD4 rearrangement and are termed NUT variants
- NMCs are poorly differentiated tumors that display variable degrees of squamous differentiation. The diagnosis is made by the demonstration of NUT rearrangement by molecular analysis, including reverse transcriptase–polymerase chain reaction, fluorescence in situ hybridization, and cytogenetic analysis.
- The prognosis is poor. Patients have rapidly growing tumors with frequent metastasis. More than 80% of patients will die within 1 year of their diagnosis despite intensive treatment.
- Early diagnosis allows for aggressive initial surgical resection with negative resection margins, which is with or without postoperative chemoradiation or radiation is associated with significantly enhanced survival.
- Chemotherapy, radiotherapy, and targeted therapy alone does not result in sustained control of tumor.

Strengths:

- This cohort from the International NUT Midline Carcinoma Registry is the largest published to date to examine outcomes for NMC, which is an under-recognized, rare tumor. It is also one of the few publications to focus on NMC of the head and neck.
- It offers detailed analysis of survival by site, disease, and treatment modality.
- Surgical resection, complete resection and negative margins were significantly associated with improved PFS and OS.
- The sequencing of the initial treatment strategy was statistically significantly associated with survival. Patients who initially underwent surgery with or without subsequent

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- radiation-based therapy had better 2-year OS (50%) than those who had initial chemotherapy (2-year OS of 18%) or radiotherapy (2-year OS of 0%).
- Thus, this publication gives important information on optimal treatment of NMC of the head and neck.

Weaknesses:

- Retrospective analysis and small cohort over two decades from 1993 to 2014.
- Heterogenous population of adult and pediatric patients.

SMARCB1 (INI-1)-deficient Sinonasal Carcinoma: A Series of 39 Cases Expanding the Morphologic and Clinicopathologic Spectrum of a Recently Described Entity

Abbas Agaimy, Arndt Hartmann, Cristina R Antonescu, Simion I Chiosea, Samir K El-Mofty, Helene Geddert, Heinrich Iro, James S Lewis Jr, Bruno Märkl, Stacey E Mills, Marc-Oliver Riener, Thomas Robertson, Ann Sandison, Sabine Semrau, Roderick H W Simpson, Edward Stelow, William H Westra, Justin A Bishop

*From the **Head and Neck**. May 2020.*

Purpose: Sinonasal Undifferentiated Carcinomas are rare, locally aggressive tumors with significant risk of both locoregional and distant failure despite multimodal treatment. The advance of molecular biology techniques has allowed for a more precise tumor classification based on recurring biological and genetic alterations. Consequently, the group of tumors defined previously as SNUCs has been diminishing as new specific entities are identified. In 2014, Agaimy et al and Bishop et al independently described a variant of sinonasal carcinoma characterized by loss of nuclear SMARCB1 expression (SMARCB1 Deficient Sinonasal Carcinoma). To more fully characterize the nature of this tumor type including its complete morphologic spectrum, its clinical behavior and its biology, the authors updated their previously reported experience and prospectively collected new cases from both their own practices as well as from multiple other institutions.

Methods: Cases were retrieved from the routine surgical pathology files at a number of contributing hospitals and directed to the consultation files of the Institute of Pathology, University Hospital of Erlangen, Germany and the Pathology Department at The Johns Hopkins University. Eleven cases were reported in the original descriptions of the entity but follow-up was updated, additional immunohistochemistry was performed, and missing molecular studies were completed

Results: The group analyzed 39 SMARCB1-deficient sinonasal carcinomas collected from multiple medical centers (28 previously unpublished cases). The tumors affected 23 males and 16 females with an age range of 19 to 89 years (median, 52). All patients presented with locally advanced disease (T3, n=5; T4, n=27) involving the sinuses (mainly ethmoid) with variable involvement of the nasal cavity. Thirty patients received surgery and/or radiochemotherapy with curative intent. At last follow-up, 56% of patients died of disease 0 to 102 months after diagnosis

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(median, 15), 2 were alive with disease, and 1 died of an unrelated cause. Only 9 patients (30%) were alive without disease at last follow-up (range, 11-115 months; median, 26). The original diagnosis of retrospectively identified cases was most often sinonasal undifferentiated carcinoma (n=14) and non-keratinizing/basaloid squamous cell carcinoma (n=5). Histologically, most tumors displayed either a predominantly basaloid (61%) or plasmacytoid/ rhabdoid morphology (36%).

Conclusion: SMARCB1-deficient sinonasal carcinoma represents an emerging poorly differentiated/undifferentiated sinonasal carcinoma that 1) cannot be better classified as another specific tumor type, 2) has consistent histopathological findings (albeit with some variability) with varying proportions of plasmacytoid/ rhabdoid cells, and 3) demonstrates an aggressive clinical course. This entity should be considered in any difficult-to-classify sinonasal carcinoma, as correct diagnosis will be mandatory for optimizing therapy and for further delineation of this likely underdiagnosed disease.

Summary Statements:

- SMARCB1-deficient sinonasal carcinoma is a recently appreciated subtype of aggressive sinonasal carcinoma previously commonly misdiagnosed as either SNUC, neuroendocrine carcinomas or even adenocarcinomas
- This group has previously established that SMARCB1 loss is not a feature seen in any other sinonasal cancer of epithelial or glandular origin
- With just over 100 cases reported in the literature, this multi-institutional series is still the largest recorded
- As per definition, all tumors on immunohistochemical testing showed complete loss of nuclear SMARCB1 (INI1) expression with retained strong reactivity in the background inflammatory, stromal and/or epithelial cells
- Two distinct histological appearances emerged with 59% taking on a basaloid or 'blue cell' appearance (notably none demonstrated over squamous differentiation), and 36% appearing as a more eosinophilic or 'pink cell' tumor with nests and sheets of predominantly plasmacytoid/rhabdoid cells

Strengths:

- Excellent review of the differential pathological features of SMARCB1 deficient tumors in contrast to other high grade sinonasal carcinomas

Weaknesses:

- While the series demonstrated clearly the pathological features and nuances of disease, it fails to really characterize the clinical behavior of the disease and its response to treatment beyond its obviously aggressive overall course citing a 54% mortality rate the majority within 2 years of diagnosis