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## Emerging Concepts in Sinonasal Tumor Research

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### Abstract

**Purpose of review:** Sinonasal malignancies are rare and understudied, often diagnosed at late stages, and may behave aggressively. This review explores investigative diagnostic, therapeutic, and scientific advances specific to sinonasal undifferentiated carcinoma (SNUC), intestinal-type adenocarcinoma (ITAC), and olfactory neuroblastoma (ONB).

**Recent findings:** A number of studies have recently contributed more robust knowledge of the genetic and molecular landscapes of SNUC, ITAC, and ONB. These analyses have identified SMARCB1 and IDH2 mutations in SNUC, potentially allowing for the tumor's subdivision. Recent studies have also defined a role for induction chemotherapy in SNUC. Somatic mutations for ITAC have been identified and may be potentially targetable with FDA approved therapies. Studies defining the tumor microenvironment for ITAC and ONB have introduced the possibility of immune checkpoint inhibition for these tumor types.

**Summary:** Studies reviewed here detail promising results of the most current and novel characterization of SNUC, ITAC, and ONB genetic and molecular landscapes, which have informed ongoing therapeutic discovery. With continued multi-institutional efforts, the field of sinonasal tumor research will achieve higher disease control and improved treatment outcomes for patients afflicted with these rare cancers.

### Keywords

Sinonasal malignancies; Sinonasal Undifferentiated Carcinoma; Intestinal-Type Adenocarcinoma; Olfactory Neuroblastoma

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## Introduction

Sinonasal malignancies comprise less than five percent of all head and neck tumors with a cumulative incidence of 0.5–1.0 per 100,000 individuals per year<sup>1,2</sup>. Although survival outcomes vary with tumor type, sinonasal malignancies may behave aggressively and are often diagnosed at late stages<sup>3</sup>. Treatment consists of endoscopic or open surgery, induction and/or definitive chemotherapy, and radiotherapy, with therapeutic decision-making hinging on tumor pathology, cancer stage, and implications for potential damage to anatomically adjacent neurovascular structures. Sinonasal squamous cell carcinoma (SNSCC) and adenocarcinoma, including intestinal-type adenocarcinoma (ITAC), represent the most common of the sinonasal tumor types<sup>4,5</sup>. Additional malignancies within the sinonasal tract include olfactory neuroblastoma (ONB), sinonasal undifferentiated carcinoma (SNUC), adenoid cystic carcinoma, and others<sup>2,6–8</sup>. Sinonasal tumors are rare and understudied<sup>3</sup>, but recent advancements have heralded improved genetic and molecular classification and the elucidation of potential targeted treatment strategies. The goal of this article is to explore these advances with a focus on SNUC, ITAC, and ONB.

### Sinonasal Undifferentiated Carcinoma

Sinonasal undifferentiated carcinoma is an uncommon and aggressive cancer defined by the World Health Organization as an undifferentiated tumor lacking glandular and squamous features, and to date has been effectively a diagnosis of exclusion<sup>9,10</sup>. SNUC comprises merely 3–5% of all sinonasal carcinomas<sup>9</sup>. Its incidence is low at 0.02 per 100,000 individuals<sup>11</sup>. SNUC has a male predominance of ~2–3:1 and typically presents in the fifth decade of life<sup>11,12</sup>. Although most cases originate within the ethmoid and maxillary sinuses<sup>13</sup>, patients often present with advanced, invasive disease that pervades dura in 50–74% of cases, and the orbit in 30–63% of cases<sup>14,15</sup>. The tumor has high metastatic potential with unfavorable outcomes<sup>9,13,15,16</sup>. Median survival is a bleak 22 months as reported by Surveillance, Epidemiology, End Results Program (SEER) database analysis of 318 cases<sup>11</sup>. While SNUC is known to arise from nasal and paranasal sinus epithelium, its immunohistologic profile remains largely uncharacterized<sup>17,18</sup>. Nevertheless, with the elucidation of genetic mutations such as SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1 (SMARCB1) and isocitrate dehydrogenase 2 (IDH2), this tumor's diagnosis is becoming more granular<sup>19,20</sup>.

**Genetic and molecular characterization of SNUC identified potential therapeutic targets**—Development of targeted therapy will come only with an improved understanding of the genetics and biologic behavior of this heterogenous carcinoma<sup>9</sup>; therefore, the establishment of the first human-derived SNUC cell lines by Takahashi et al. in 2012 proved a pivotal advance<sup>21</sup>. This group demonstrated that these SNUC cell lines express pan-keratin, cytokeratin 8, cytokeratin 19, and epithelial markers of E-cadherin and B-catenin, but lack mesenchymal markers including N-cadherin, vimentin, and alpha-SMA<sup>21</sup>. Twelve translocations spanning diverse chromosomes were also reported, further contributing to SNUC characterization<sup>21</sup>. Using the novel cell line, Takahashi et al. discovered the ERBB2 gene to be highly amplified, and thus, human epidermal growth factor receptor 2 to be overexpressed and phosphorylated within SNUC<sup>22</sup>. Subsequent

HER2 signaling pathway inhibition with FDA-approved dual small molecule EGFR/HER2 inhibitor, lapatinib<sup>23</sup>, stifled cell growth, suggesting HER2 as a potentially worthwhile molecular target<sup>22</sup>.

To differentiate SNUC histopathology from that of similar malignancies, including sinonasal neuroendocrine carcinoma (SNEC) and ONB, a 2018 study employed genome wide copy number profiling of tumor tissue<sup>24</sup>. SNUC tumors were defined by a cytokeratin positive (CK +) and neuroendocrine negative (Ne –) marker expression pattern and compared to samples previously diagnosed as SNUC by pathology alone. Of all tumors studied, 17 of 54 were reclassified, highlighting the diagnostic challenges in the correct diagnosis of this tumor<sup>24</sup>. Following this investigation, a 2019 study established seven genes that fully distinguished SNUC from SNSCC. Expression of the human chloride channel accessory-2 (CLCA2) gene, which encodes a calcium-activated chloride channel regulator protein with implications in p53 tumor suppression, was most markedly different between the two malignancies<sup>25</sup>. Gene ontologies corresponding to DNA repair and cell division were also upregulated in SNUC<sup>25</sup>. Furthermore, a 2019 MD Anderson study analyzed 13 treatment-naïve SNUC samples to ascertain prognostic markers for treatment response to induction chemotherapy (IC). Twenty-four genes distinguished responders from non-responders, particularly *IL20* and *FGF20*. Sixteen gene pairs were associated with IC positive response, encouraging future treatment decisions that cater towards differential characteristics of diverse SNUC tumors<sup>26</sup>.

Targeted sequencing in SNUC has allowed for the identification of mutations in IDH2, most of which occur within the protein's R140 and R172 arginine residues<sup>27,28</sup>. In 2017, IDH2 R172 mutations were reported within 55–80% of SNUC tumors<sup>27,28</sup>. This enzyme catalyzes  $\alpha$ -ketoglutarate formation, but when mutated, increases (R)-2-hydroxyglutarate (2-HG), an oncometabolite that disturbs cell differentiation via histone and DNA hypermethylation<sup>29,30</sup>. A 2019 study that examined the monoclonal antibody 11C8B1 to IDH2 R172S in SNUC concluded the antibody may be useful as a supplemental immunohistologic diagnostic marker<sup>31</sup>. A more recent 2020 evaluation of IDH2 mutation's specificity to SNUC reported that 11 of 36 (31%) SNUC samples contained IDH2 mutations, although IDH2 mutations also occurred in a minority of neuroendocrine carcinoma, high-grade non-intestinal-type adenocarcinoma, and poorly differentiated squamous cell carcinoma tumors<sup>32</sup>. The group noted that IDH2-mutant cases had a higher disease specific survival<sup>32</sup>, a finding corroborated by a 2021 study that highlights the influence IDH2 mutation status has on sinonasal tumor biology<sup>19</sup>. Similarly, Chitguppi et al. recently proposed a novel SNUC classification based on the expression of SMARCB1, a known tumor suppressor gene and core subunit of the SWI/SNF chromatin remodeling complex<sup>20</sup>. They noted that SMARCB1 deficiency portended a worse prognosis, with a 50% vs 0% 1-year mortality rate in the SMARCB1-deficient vs -retained group, respectively<sup>20</sup>. Thus, current research suggests that SNUC may in fact be comprised of multiple subtypes with unique behavioral patterns defined by the presence of genetic mutations, such as IDH2 and SMARCB1. Lastly, a 2020 study sought to characterize SNUC's immune-oncology gene expression. With next generation sequencing, PRAME (preferentially expressed antigen in melanoma), a testis-selective cancer antigen involved in rendering cancer cell qualities of stemness, invasion, and metastasis, was identified as the most upregulated gene in SNUC and may

serve as an important immunotherapeutic target<sup>6</sup>. Execution of the first whole genome or whole exome sequencing studies in SNUC will allow for continued granular subdivision of SNUC tumors and further precise therapeutic targets based on genomics.

**Recent advances in clinical treatment strategies**—Multiple studies have demonstrated the value of multimodal therapy for advanced sinonasal tumors, which may consist of radiotherapy, chemotherapy, and/or surgery, via an open craniofacial, endonasal, or combined approach<sup>9,12,17,26</sup>, in establishing higher disease control<sup>9,13,33</sup>. Given the aggressive nature of some sinonasal malignancies, induction chemotherapy (IC) is more commonly being incorporated prior to definitive therapy<sup>12,17,34–36</sup>. Proposed benefits of IC may include possible protection against distant metastasis and potential orbital preservation, although such notions continue to be investigated, most notably via a phase II IC, (NCT00707473), trial that is currently underway<sup>17,34,36–38</sup>. Response status to IC may also serve as a guide for likely efficacy of ensuing definitive chemoradiation<sup>12,15</sup>.

A landmark MD Anderson study by Amit et al. assessed the role of IC in guiding definitive therapy for SNUC in 2019<sup>17</sup>. Ninety-five treatment-naïve SNUC patients were treated with platinum-based IC regimen of cisplatin and etoposide<sup>17</sup>. In patients with a favorable IC response, improved survival was achieved with definitive chemotherapy and radiation (CRT), whereas in those without an IC response, surgery proved the preferred method for disease control<sup>17</sup>. 5-year disease specific survival in individuals with partial or complete IC response was 81% after treatment with CRT, whereas in individuals without IC response was 0% following CRT and 39% following surgery with chemoradiation<sup>17</sup>. This study's sample size contains the greatest number of untreated SNUC tumors to date, a significant feat considering the rarity of SNUC. It also represents a milestone in establishing therapeutic sequence guidelines for a thus far elusive cancer. Similarly, at The Ohio State University, a 2020 retrospective study of 21 SNUC cases by London et al. highlighted an institutional trend towards use of TPF (docetaxel, cisplatin, fluorouracil) IC in the treatment algorithm for treatment-naïve SNUC<sup>37</sup>.

Progress in understanding SNUC genetic and molecular composition, pathways relevant to carcinogenesis, and favorable treatment sequences is ongoing and flourishing. The continued development of potential genetic, molecular, and immunotherapeutic targets, as well as multi-institutional establishment of optimal treatment regimens is crucial to achieving sound control over this aggressive cancer, and thus, securing improved patient treatment outcomes.

### **Intestinal-Type Sinonasal Adenocarcinoma**

Intestinal-type sinonasal adenocarcinoma (ITAC) is a rare form of cancer arising in the epithelium of the paranasal sinuses and the nasal cavities. This cancer forms most often in the ethmoid sinuses (85%) and comprises 8–25% of all malignant sinonasal tumors<sup>39</sup>. Distant or lymph node metastasis is relatively uncommon while local recurrence and intracranial invasion account for the primary causes of mortality among these patients<sup>4,39,40</sup>. ITAC prevalence represents an important occupational health problem as the tumor's etiology is strongly related to wood dust exposure, making it a disease more commonly seen in carpenters and furniture makers. Individuals in professions with prolonged exposure

to wood dust have up to 500–900 times greater risk of developing ITAC compared to the wider community<sup>4</sup>. Contrarily, tobacco smoke exposure does not seem to play a major role in ITAC development<sup>4</sup>.

Five distinct histopathologic subtypes of ITAC have been described: colonic (40%), solid (20%), papillary (18%), and mucinous and mixed type (22% combined)<sup>39</sup>. Although it is known that papillary and colonic subtypes are associated with better clinical outcomes<sup>39</sup> while solid and mucinous subtypes possess more aggressive characteristics<sup>41</sup>, the events leading up to subtype differentiation remain a mystery.

**Potential mechanisms of tumorigenesis in ITAC**—Currently there is no established pathogenic mechanism or precursor lesion to explain the development of ITAC<sup>42</sup>. Wood dust, though not a direct mutagen, is thought to be an irritant to the nasal mucosa that precipitates prolonged inflammation to noxious stimuli, and thus, cell proliferation with long-term exposure<sup>39,42</sup>. An upregulation of inflammatory cytokine release of transcription factors, such as tumor necrosis factor and nuclear factor  $\kappa$ B, has been demonstrated in sinonasal cancer studies<sup>4,43,44</sup>. Other markers, such as increased COX2 expression, and TP53 G>A missense mutations possibly linked with the presence of reactive oxygen species, offer further evidence for prolonged inflammation as a potential player in ITAC tumorigenesis<sup>39,44,45</sup>. Another hypothesized mechanism to explain the origin of this sinonasal cancer is that of cancer stem cells (CSC) capable of differentiating into various cell types<sup>4</sup>. This model has also been suggested for other head and neck tumors and could provide a more intuitive explanation for ITAC's ability to form mixed histological types and recur as distinct tumor types post-resection<sup>1,4</sup>. However, to-date little research has investigated this possibility.

**Protein expression and genetic profiling of ITAC**—ITACs are named for their histomorphologic resemblance to adenocarcinoma of the intestinal tract, colorectal carcinoma (CRC)<sup>45</sup>. Indeed, one characteristic trait shared by all ITAC subtypes is that of intra- or extracellular mucin production<sup>39</sup>. However, recent studies have shown that although these tumors appear similar, ITAC and CRC likely arise from separate pathways. For instance, microsatellite instability (MSI) is an important process in the pathogenesis of CRC but unlikely to play an important role in that of sinonasal ITAC<sup>1,7</sup>. Additionally, while expression of anaplastic lymphoma kinase (ALK) protein was suspected in ITAC, as seen in lung adenocarcinoma, experiments using break-apart fluorescent in-situ hybridization and immunohistochemistry in 96 sinonasal adenocarcinoma samples offered no evidence of ALK protein expression<sup>46</sup>.

Other efforts have focused on linking detectable genomic markers and protein expression patterns with histologic or clinical outcomes<sup>41,45,47–49</sup>. Studies using direct sequencing, fluorescence in situ hybridization (FISH), multiplex ligation-dependent probe amplification (MLPA), and microarray comparative genomic hybridization (CGH) have indicated that ITACs possess ample genetic aberrations throughout the genome. However, the papillary subtype seems to consistently possess relatively few copy number alterations as compared to other subtypes<sup>47,50</sup>, and notably, is often associated with more favorable clinical outcomes<sup>39</sup>. Other genetic profiling investigations showed worse overall survival for tumors carrying

CGH losses at 4q32-ter and gains at 1q22, 6p22, and 3q29, or carrying MLPA losses of *TIMP2*<sup>47,48</sup>. With methylation-specific MLPA, Costales et al. demonstrated that ITAC carries a greater number of gene methylations than SNSCC, and, more specifically, that papillary and colonic ITAC subtypes possess more gene methylations than solid and mucinous ITAC subtypes, with a mean of 1.26 gene methylations per tumor versus 0.63, respectively<sup>5</sup>. This finding may suggest that gene methylation plays a larger, or at least distinct, role in the differential development of the less aggressive papillary and colonic tumors<sup>5</sup>. Using immunohistochemistry, positive p16 protein expression was found to be associated with shorter overall survival<sup>41</sup>, and with the same technique, an absence of annexin A2 expression was correlated with the aggressive mucinous subtype, and therefore, with decreased survival<sup>51</sup>. Direct sequencing of proto-oncogenes such as *EGFR*, *KRAS*, and *BRAF* have not proven as informative since few to no ITACs studied carried prognostic mutations in these genes<sup>49,52</sup>. Overall, such findings are helpful in characterizing ITAC genetic subgroups and have implications in future therapeutic decision making and personalized therapy development.

**Therapeutic advancements**—Standard treatment is surgical resection with post-operative radiotherapy<sup>4,40</sup>. However, resection with wide tumor-free margins may be challenging due to the close proximity to critical neurovascular structures<sup>4</sup>. The first immortal ITAC tumor cell line derived was established by Pérez-Escuredo et al. in 2010<sup>40</sup>. Multiple genetic alterations characteristic of ITAC were described within this cell line, validating its similarity to primary tumor samples<sup>40</sup>. An *in vitro* model such as this, which preserves the biological properties of the original cancer, has the potential to be a powerful tool for both functional studies and for the evaluation of novel therapeutic agents. In a study using next generation sequencing, Sánchez-Fernández et al. found one or more potentially actionable somatic mutations in 20 of 27 ITAC cases. Eight of these represent biomarkers for existing FDA-approved targeted therapies<sup>53</sup>. Other research looking at tumor infiltrating lymphocytes and PD-L1 expression optimistically describe that a subset of ITAC, especially papillary and colonic subtypes, may be candidates for immune checkpoint inhibition<sup>8,54</sup>.

### Olfactory Neuroblastoma

Olfactory neuroblastoma, or esthesioneuroblastoma, is a rare nasal cavity and anterior skull base malignancy first described in 1924<sup>55–57</sup>. ONB is thought to originate from olfactory neuro-epithelium in the upper nasal cavity at the region of the cribriform plate<sup>58,59</sup>. ONB incidence is low at 0.4 per million per year<sup>58</sup>. ONB progresses insidiously and has a 5-year survival rate of 80%<sup>60</sup>, although late local-regional recurrence is well-documented, for which long-term patient follow up is advisable<sup>58,61</sup>. Difficulty in identifying targeted therapies in ONB stems in part from a lack of precise oncogenic driver elucidation<sup>62</sup>.

**Investigation of the ONB genetic and molecular landscape**—A 2019 study by Classe et al. evaluated Ki67 proliferation index and tumor infiltrating lymphocytes (TILs) as prognostic alternates to the current Hyams grading system<sup>63,64</sup>. They demonstrated an association of both high Ki67 proliferation index and elevated intratumoral TILs with high grade ONB. Furthermore, a Ki67 PI greater than 25%, and a CD4/CD8 ratio of greater than two corresponded with poor survival, confirming Ki67 PI and TILs as advantageous

prognostic markers<sup>63</sup>. Although a broad variety of ONB cytogenetic and genomic alterations are reported in the literature, common findings include positive association of chromosome 11 deletion and chromosome 1p gain with poor ONB survival, and TP53 gene alterations that account for the tumor's most frequent mutations<sup>55,65–67</sup>. An important 2018 study further molecularly classified ONB into two etiologic groups: neural-like and basal-like<sup>62</sup>. Although, a third of this study's basal-like tumors were comprised of an IDH2 R172 mutant-enriched subgroup characterized by pervasive DNA hypermethylation,<sup>62</sup> prior studies have detected a low incidence of IDH2 mutation in ONB, ranging between 0–4%<sup>27,28,32,65</sup>. Finally, Cracolici et al. recently reported on uniform somatostatin receptor 2 (SSTR2) expression in ONB<sup>68</sup>. Following a finding of significantly greater SSTR2 staining in ONB than in histologically related neoplasms, they suggested SSTR2 likely represents a diagnostically important ONB marker<sup>68</sup>. Moreover, imaging and therapy based in a somatostatin analog have been applied to extensive or metastatic ONB<sup>69–72</sup>.

**Treatment targets in ONB**—Therapeutics directed towards the immune checkpoint pathway could be applicable for ONB. Programmed cell death ligand 1 (PD-L1), a transmembrane glycoprotein that interrelates with PD-1, contributes to tumor immune system evasion. A recent 2020 study showed PD-L1 expression in 40% of primary ONB and in 75% of cervical metastases derived from a primary PD-L1 negative ONB<sup>56</sup>. Greater PD-1+ and CD8+ lymphocyte presence was also identified within tumor and stroma of PD-L1+ tumors as compared to PD-L1- tumors; overall suggesting that PD-L1/PD-1 inhibition may improve ONB management<sup>56</sup>. ONB research has underscored the olfactory cancer's genetic and cytogenetic heterogeneity. Considering the rarity of ONB, a multi-institutional investigational approach to further genetic, epigenetic, and molecular stratification, and similarly, to therapeutic discovery, will facilitate a more comprehensive understanding of this malignancy for patients' benefit. In fact, a phase II immunotherapy trial specifically for recurrent or metastatic ONB, **Bintrafusp Alfa in Recurrent/Metastatic Olfactory Neuroblastoma (BARON)**, ([NCT05012098](#)), was recently approved at the National Institutes of Health<sup>73</sup>.

## Conclusion

Studies reviewed here detail promising results of the most current and novel characterization of SNUC, ITAC, and ONB genetic and molecular landscapes, which have informed ongoing therapeutic discovery. With continued multi-institutional efforts, the field of sinonasal tumor research will achieve higher disease control and improved treatment outcomes for patients afflicted with these rare cancers.

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### Conflicts of Interest

N. London receives research funding from Merck, holds stock in Navigen Pharmaceuticals, and was a consultant for Cooltech Inc., none of which are relevant to the present manuscript. All other authors declare no competing interests.

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**Key Bullet Points**

- Sinonasal tumors are rare and understudied, but recent advancements have enabled improved genetic and molecular classification with progress in targeted treatment development.
- The improved genetic characterization of SNUC tumors by the presence of SMARCB1 or IDH2 mutations, along with efforts to establish robust clinical therapeutic sequence guidelines, have contributed to a better understanding of the disease and its management.
- Work aimed at more granular characterization of ITAC genetic subgroups and discovery of somatic mutations targetable by FDA approved therapies is advancing the field of ITAC tumor research.
- Immune checkpoint inhibition may unveil an avenue of promising treatment options for sinonasal malignancies.