# Re-classification of historic cases of Sinonasal Undifferentiated Carcinoma using contemporary diagnostic understanding – a 24-year experience

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## Introduction

Sinonasal undifferentiated carcinoma (SNUC) is a rare and aggressive malignancy of the nasal and paranasal sinus epithelium, characterized by its rapid progression and poor prognosis. Due to its rarity, understanding the molecular and histopathological characteristics of SNUC remains challenging[1,2]. The sinonasal tract can give rise to a spectrum of morphologically similar poorly-differentiated tumours, making their diagnosis challenging.

SNUC has been a term given to a spectrum of epithelial malignancies arising in sinonasal tract without glandular or squamous features and not otherwise classifiable. Recent advances in genomic profiling have led to the recognition of several molecularly distinct entities that were previously included in the SNUC spectrum and therefore likely under-recognised. These include NUT carcinoma, SMARCB1 (INI1)-deficient carcinoma, SMARCA4-deficient sinonasal carcinoma. With the increasing availability of more specific immunohistochemical stains and increasing use of molecular techniques[1-4], it has become possible to reliably re-classify these under-recognised entities.

This has important implications for management and prognosis, given the continuing development of molecularly-targeted therapies.
Modern understanding of newly described neoplasms (e.g. NUT midline carcinoma) and more recently understood subsets of SNUC (e.g. SMARCB1 deficient sinonasal carcinoma) would suggest that cases previously labelled as SNUC may in fact have an alternative diagnosis based on current pathology criteria[3].

The aim of this study was to determine the proportion of historic SNUC cases which would be given an alternate diagnosis based upon current diagnostic methods and understanding, and to determine if patients with alternative diagnoses were found to have different outcomes.

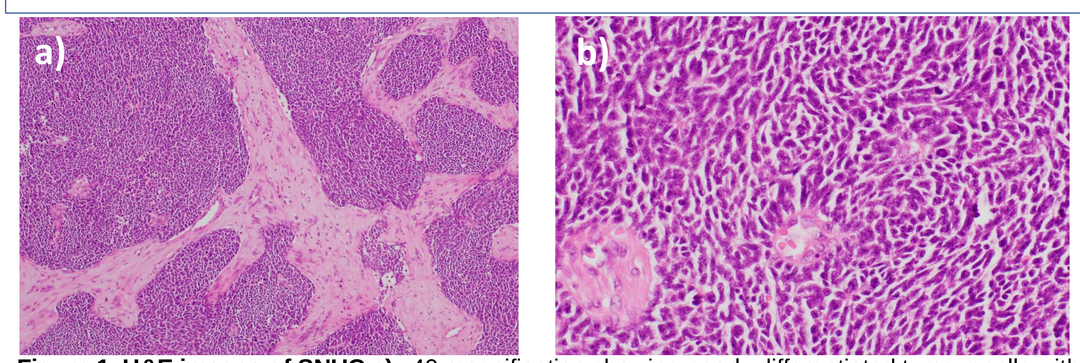


**Figure 1. H&E images of SNUC a)** x40 magnification showing poorly differentiated tumour cells with minimal cytoplasm, ovoid hyperchromatic nuclei and mitotic activity
**b)** x10 magnification of SNUC showing infiltrative coalescing nests and sheets of tumour cells

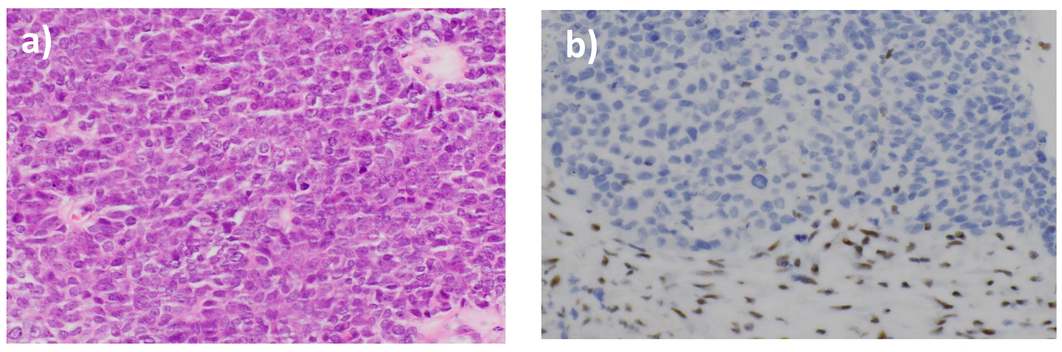


**Figure 2. Histopathology/IHC of INI-deficient sinonasal carcinoma, a)** H&E images x40 magnification showing tumour cells with high nuclear to cytoplasmic ratio, indistinct cytoplasm, vesicular chromatin and mitotic activity **b)** 40x magnification, loss of INI1 immunostaining in tumour cell, with retained staining in stromal cells (below)

## Methods and Materials

Study design – Retrospective cohort study
Patient cohort – Patients diagnosed with and treated for SNUC
Setting – Sydney, NSW (Royal Prince Alfred Hospital, St Vincent's Hospital Network)

Histopathological review of the cases and additional INI1, SMARCA4 and NUT immunohistochemistry was performed on archived formalin fixed paraffin embedded tissue. Molecular profiling using RNA next-generation sequencing was performed on cases without a specific histological diagnosis after further immunohistochemical analysis (e.g. NUT, INI1-, SMARCA4-deficient carcinoma). Tumour profiling to detect sequence alterations and abnormal gene fusions was undertaken using the Ion Torrent™ Oncomine Childhood Cancer Research Assay (Thermo Fisher) according to the manufacturer's protocol. This tool analyses 203 unique genes, with comprehensive mutation coverage and includes an RNA panel for 97 fusion drivers. Pathology data were correlated with patients' presentation, treatment course and clinical outcomes.

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## Results

Clinical database search yielded a total of 21 patients with a history of sinonasal undifferentiated carcinoma treated at Royal Prince Alfred Hospital (n=14),and St. Vincent's Hospital Sydney (n=7), between 2000 and 2024.

There were 20 cases which had adequate tissue for immunohistochemistry.
2/20 cases showed loss of INI1 on IHC.
In total, there were 11/21 patients who met inclusion criteria for Next Generation Sequencing, In the 11 cases sequenced, no single nucleotide variants, insertion/deletions, copy number variations or known fusion transcripts were identified.
These results are graphically displayed in Figure 3 below.

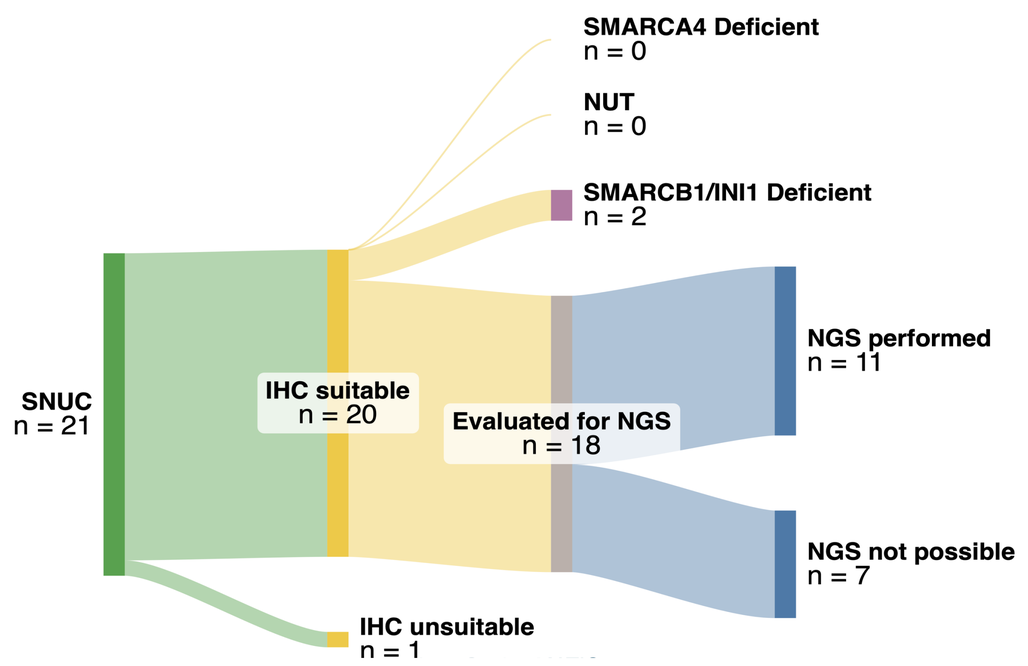


**Figure 3. Flowchart showing sequential re-evaluation process of existing SNUC tissue samples**
**Abbreviations: SNUC = Sinonasal Undifferentiated Carcinoma; IHC = Immunohistochemistry; NGS = Next Generation Sequencing**

**Table 1. Differences in survival between patients with reclassified sinonasal tumours**

| New classification | Number | Mean survival (months) |
|---|---|---|
| Remains as SNUC | 19 | 72.9 +/- 67.37 |
| SMARCB1/INI1 deficient | 2 | 29.0 +/- 13.1 * |

***Unequal variances T-Test P < 0.05**

## Discussion

This study demonstrates the utility of modern diagnostic tools in refining historical SNUC diagnoses based upon a contemporary understanding of the pathology. In total,10% of cases able to be analysed were identified to be SMARCB1(INI1) deficient carcinomas, and these were found to have a significantly poorer survival in our study, which is consistent with previous studies[2]. These findings demonstrate that a proportion of cases previously labelled as SNUC have distinct molecular subsets, and these are demonstrated to have significant clinical implications.

No pathogenic molecular aberrations (single nucleotide variants, insertion/deletions, copy number variations or known fusion transcripts) were identified in this study, and this was possibly due to prolonged Formalin-Fixed Paraffin-Embedded tissue storage times decreasing tissue quality. NGS nevertheless offers an additional layer of diagnostic precision by identifying genetic aberrations or unique molecular markers. Integrating NGS results with histopathological and immunohistochemical findings could further stratify these rare sinonasal malignancies, allowing further understanding and perhaps enabling tailored therapeutic approaches.

This study demonstrates the utility of revisiting archived cases using advanced methodologies to better understand evolving rare diagnoses. Retrospective analyses refine diagnostic accuracy, reveal biological diversity within SNUC, and inform treatment strategies. Ongoing research and translating these findings into clinical practice may ultimately benefit patients with rare and aggressive sinonasal malignancies if alternate treatment modalities are found to be more effective.

## Conclusions

This study highlights the value of retrospective analysis in rare cancers such as SNUC, allowing a greater understanding to be gained by applying contemporary knowledge and diagnostic methods.

## Contact

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## References

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