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Integration of Neoadjuvant Chemo-Immunotherapy and Adjuvant Radiotherapy in Sinonasal Malignancies: A Narrative Review

Z. Zhu[1#], X. Lin[1#], J. Sun[1], J. Zhu[2*]

[1]The Fourth School of Clinical Medicine，Zhejiang Chinese Medical University
[2]Department of Otorhinolaryngology and Head Neck Surgery, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou, China

► ***Review article***

Corresponding author:
Jin Zhu, M.D.,
E-mail:
zhujin2698@hotmail.com

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Co-first authors

ABSTRACT

Background: Sinonasal malignancies are rare, aggressive tumours with limited resectability and high recurrence due to complex anatomy and late presentation. Integrating neoadjuvant chemotherapy with programmed cell death protein 1 (PD-1)/ programmed cell death ligand 1 (PD-L1) blockade may enhance tumour regression and improve surgical outcomes. Adjuvant radiotherapy remains a critical component in disease control. ***Materials and Methods:*** A narrative review was performed using PubMed, Scopus, and Web of Science (2010–2025). Search terms included Sinonasal Neoplasms, Neoadjuvant Therapy, Immunotherapy, and Radiotherapy. Studies on biological mechanisms, clinical outcomes of chemo-immunotherapy, and radiotherapy integration were included. ***Results:*** Evidence from emerging institutional series and extrapolation from head-neck oncology demonstrates that neoadjuvant chemo-immunotherapy promotes immunogenic cell death, enhances T-cell infiltration, and facilitates tumour downstaging. Early sinonasal cohorts report higher major pathological response, improved resectability, and acceptable safety. Adjuvant radiotherapy further augments locoregional control through antigen release and immune activation. ***Conclusion:*** Combining neoadjuvant chemo-immunotherapy with adjuvant radiotherapy is biologically rational and clinically promising for locally advanced sinonasal cancers. Prospective, biomarker-driven trials are needed to optimize sequencing and validate efficacy.

INTRODUCTION

Sinonasal malignancies are rare and heterogeneous tumours, accounting for fewer than 3-5% of all head and neck cancers [1, 2]. Their anatomical origin within the complex architecture of the nasal cavity and paranasal sinuses areas closely related to the skull base, orbit, cranial nerves, and vital vascular structures presents inherent diagnostic and therapeutic challenges [3, 4]. Early symptoms such as nasal obstruction, rhinorrhoea, or epistaxis often mimic benign inflammatory conditions, leading to delayed clinical recognition [5, 6]. As a result, the majority of patients present with locally advanced disease at diagnosis, contributing to historically poor outcomes [7, 8]. A wide spectrum of histological subtypes further complicates management. These include sinonasal squamous cell carcinoma (SNSCC), sinonasal undifferentiated carcinoma (SNUC), esthesioneuroblastoma (ONB), intestinal-type adenocarcinoma (ITAC), and mucosal melanoma, each demonstrating distinct biological behaviour, response to therapy, and prognostic patterns [9–11]. Surgical resection remains the foundation of curative treatment; however, obtaining complete oncologic clearance is often limited by the proximity of tumours to critical structures [12, 13]. Despite advances in endoscopic and open craniofacial techniques, microscopic residual disease remains a major concern [14]. Consequently, adjuvant radiotherapy is frequently employed to enhance locoregional control [15]. Nevertheless, radiotherapy alone may not fully mitigate the risk of recurrence, and outcomes remain suboptimal for aggressive histologies such as SNUC and high-grade SNSCC [16]. In parallel with developments in other solid tumours, the advent of immune checkpoint inhibitors (ICIs), particularly programmed cell death protein 1 (PD-1)/ programmed cell death ligand 1 (PD-L1) inhibitors, has reshaped systemic therapy strategies [17, 18]. These agents have demonstrated durable responses and survival benefits in malignancies such as melanoma, lung cancer, and head and neck squamous cell carcinoma [19]. Their mechanisms-reversal of T-cell exhaustion, restoration of cytotoxic function, and modulation of the tumour microenvironment provide a strong rationale for exploring immunotherapy in sinonasal cancers, many of which exhibit PD-L1 expression and immunogenic molecular features [20]. Simultaneously, neoadjuvant chemotherapy has

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gained renewed interest for its capacity to reduce tumour burden, improve resectability, and target occult systemic disease early in the treatment course [21, 22]. Beyond cytoreduction, accumulating preclinical and clinical data indicate that certain chemotherapeutic agents exert immunomodulatory effects, including induction of immunogenic cell death, enhancement of antigen presentation, and reduction of immune-suppressive cell populations [23]. These effects can potentiate the activity of ICIs, creating a mechanistic basis for synergy between chemotherapy and immunotherapy [24]. Evidence from lung, oesophageal, and head and neck oncology has demonstrated that neoadjuvant chemo-immunotherapy achieves higher rates of major pathological response compared with chemotherapy alone [25, 26]. Although sinonasal tumours are less common and understudied, emerging institutional reports suggest similar benefits, with improved tumour regression, enhanced surgical feasibility, and promising early oncologic outcomes [27, 28]. Integrating this regimen with adjuvant radiotherapy offers the additional advantage of consolidating locoregional control, particularly in tumours prone to microscopic spread [29].

Given the rarity of sinonasal cancers, consolidated literature evaluating combined neoadjuvant chemo-immunotherapy followed by radiotherapy is limited [30]. This narrative review synthesizes current biological understanding, translational evidence, and emerging clinical findings supporting this integrated treatment paradigm. The aim is to highlight its potential to enhance multimodal management and inform future prospective, biomarker-driven studies.

MATERIALS AND METHODS

This narrative review was conducted to synthesize current biological, translational, and clinical evidence on the integration of neoadjuvant chemo-immunotherapy with adjuvant radiotherapy in sinonasal malignancies. Because sinonasal tumours are rare and published clinical datasets are heterogeneous, a narrative review approach was selected rather than a systematic or meta-analytic design.

A thorough literature search was carried out across three major academic databases -PubMed, Scopus, and Web of Science - targeting studies published from January 2010 to September 2025.The search strategy combined multiple MeSH terms and free-text keywords, including “Sinonasal Neoplasms”, “Sinonasal Cancer”, “Neoadjuvant Therapy”, “Chemotherapy”, “Immunotherapy”, “PD-1”, “PD-L1”, “Checkpoint Inhibitors”, “Radiotherapy”, and “Head and Neck Neoplasms”. Boolean operators (AND/OR) were applied to refine search results. Reference lists of key articles were screened manually to identify additional relevant studies.

Studies were included if they met the following criteria: (1) Reported clinical, biological, or translational findings relevant to sinonasal malignancies; (2) Evaluated chemotherapy, immunotherapy, or combined neoadjuvant strategies; (3) Reported on radiotherapy outcomes in sinonasal cancers or biologically related head-and-neck malignancies; (4) Published in English; (5) Included randomized trials, prospective or retrospective cohort studies, institutional series, translational studies, or high-quality narrative reviews. On the other hand, studies were excluded from this review if they were limited to isolated case reports or case letters, published in non-English languages, lacked sufficient clinical or biological data to support meaningful analysis, focused solely on animal experiments without clear translational relevance to human disease, or contained duplicate or overlapping datasets from previously included research.

Titles and abstracts were screened independently by two reviewers. Full texts of relevant records were retrieved and assessed for eligibility. A structured data extraction protocol was used to collect critical information from eligible studies, including details on study design and patient population demographics, tumour histology subtypes, specific treatment modalities (chemotherapy, immunotherapy, radiotherapy, or their combinations), reported clinical endpoints (such as objective response rate, major pathological response, survival outcomes, and safety profiles), biomarker-related data (including PD -L1 expression status, tumour mutational burden (TMB), and tumour-infiltrating lymphocytes (TILs)), and translational mechanisms that underpin the synergistic interactions between different treatment modalities. Given the heterogeneity of study designs, patient cohorts, and outcome measures, data were synthesized qualitatively rather than pooled quantitatively.

Although this review does not follow PRISMA systematic review criteria, methodological rigor was maintained. This was achieved by using multi-database searches. We also applied predefined inclusion criteria. Extracted data were cross-checked to ensure accuracy. High-quality peer-reviewed evidence was prioritized throughout the process. Biological mechanisms were integrated with clinical findings to ensure coherence of the review.

Sinonasal malignancies constitute a highly heterogeneous and rare disease group. The limited number of prospective trials and inconsistent reporting across studies precluded formal meta-analytic methods. A narrative review therefore allowed a broader integration of mechanistic insights, institutional clinical experiences, and emerging trial data, consistent with IJRR’s expectations for review

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Clinical characteristics of sinonasal malignancies (humanized version)

Sinonasal malignancies are uncommon, accounting for only 3–5% of all head and neck cancers worldwide, yet they pose substantial clinical challenges. Their rarity and wide histologic diversity, combined with their origin in a compact region surrounded by the orbit, skull base, and cranial nerves, make both diagnosis and treatment particularly complex. Epidemiologic studies consistently show that outcomes remain poor, largely because many patients are diagnosed at an advanced stage [1, 5, 7]. One of the major reasons for delayed diagnosis is that early symptoms such as nasal obstruction, rhinorrhoea, epistaxis, diminished smell, or a sense of facial pressure are easily mistaken for benign sinonasal disorders like chronic rhinosinusitis [2, 14]. As a result, many patients come to clinical attention only when the disease has progressed to T3 or T4 stage, often with invasion of the orbit, dura, or intracranial cavity. Imaging with CT (computed tomography) and MRI (magnetic resonance imaging) is essential for delineating tumour extent, assessing bone erosion and perineural invasion, and determining surgical feasibility [4]. Ultimately, histologic confirmation through endoscopic biopsy remains the gold standard for diagnosis [6]. The spectrum of sinonasal malignancies is remarkably broad. Sinonasal squamous cell carcinoma (SNSCC) is the most common subtype, comprising roughly a quarter of cases. It is associated with environmental exposures and occasionally HPV (human papillomavirus) infection, and typically carries a guarded prognosis, with 5-year survival rates around 40% [9]. Sinonasal undifferentiated carcinoma (SNUC) represents one of the most aggressive entities, marked by rapid growth, early metastasis, and survival rates closer to 20-25% [13, 16]. Esthesioneuroblastoma (ONB), arising from the olfactory epithelium, exhibits a wide clinical spectrum; while many patients achieve long-term survival, high-grade or advanced-stage disease still has poor outcomes [10]. Intestinal-type adenocarcinoma (ITAC), often linked to occupational wood-dust exposure, accounts for 15–20% of cases and generally has intermediate survival [11]. Sinonasal mucosal melanoma, although rare, is notably aggressive, with survival rates of only 20–30% because of its tendency for early systemic dissemination [3, 30]. An overview of symptoms, incidence, and survival across the major subtypes is provided in table 1.

Even with substantial advances in endoscopic and craniofacial surgical techniques, achieving complete surgical removal remains difficult because of the intricate anatomy of the sinonasal region. Tumours that abut or invade the skull base, cavernous sinus, or orbit often preclude wide-margin resection. Although modern endoscopic approaches have significantly reduced surgical morbidity, microscopic residual disease is still common [2, 6, 12]. Complicating matters further, aggressive subtypes such as SNUC and high-grade SNSCC respond poorly to standard systemic therapies [8, 13].

Table 1. Clinical features of major sinonasal malignancies. (Incidence proportion, common presenting symptoms, and 5-year overall survival rates of major histologic subtypes of sinonasal malignancies. Abbreviations: SNSCC = Sinonasal Squamous Cell Carcinoma; SNUC = Sinonasal Undifferentiated Carcinoma; ONB = Olfactory Neuroblastoma; ITAC = Intestinal-Type Adenocarcinoma.)

Histology	Incidence (%)	Common Symptoms	5-Year Survival (%)
SNSCC [9]	~25	Nasal obstruction, epistaxis	~40
SNUC [13,16]	~15	Rapid facial swelling, proptosis, vision changes	~20–25
ONB [10]	~10	Anosmia, nasal obstruction	~50–55
ITAC [11]	~20	Epistaxis, unilateral nasal mass	~50
Mucosal Melanoma [3, 30]	<5	Pigmented/polypoid nasal lesions	~20–30

Adjuvant radiotherapy has therefore become a cornerstone of care, particularly in cases with close or positive margins, perineural invasion, or advanced T-stage. Techniques like IMRT and proton therapy have improved local control while limiting radiation damage to critical organs such as the optic nerves and brainstem [15, 29]. Despite these improvements, recurrence rates remain high in aggressive histologies [16], reinforcing the need for innovative multimodal strategies such as neoadjuvant chemo-immunotherapy.

Biological rationale: PD-1/PD-L1 axis in sinonasal tumours

The rationale for introducing immunotherapy into the treatment of sinonasal cancers stems from the central role of the PD-1/PD-L1 pathway in helping tumours evade immune detection. Immune checkpoint inhibitors have reshaped the therapeutic landscape for several cancers - including melanoma, lung cancer, and head and neck squamous cell carcinoma - by reversing T-cell exhaustion and restoring antitumor immunity [17, 18]. When PD-L1 on tumour cells binds PD-1 on activated T cells, immune responses are dampened; blocking this interaction reinvigorates T-cell function and can lead to durable clinical responses [17]. PD-L1 expression levels vary across sinonasal tumour types. Dogan et al. found PD-L1 positivity in 40-60% of SNSCC, 60-70% of SNUC, and considerably lower levels in ONB and ITAC [20]. Sinonasal mucosal melanoma, consistent with its broader immunobiology, shows moderate PD-L1 expression. Other factors, including TILs and TMB, also shape immunotherapy responsiveness. For example, mucosal melanoma tends to have a

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moderate TMB and low TIL density, which aligns with its intermediate sensitivity to PD-1 inhibition [19]. These immunologic features are summarized in table 2 and help guide decisions about neoadjuvant immunotherapy.

Table 2. Immunologic features of major sinonasal tumours. (PD-L1 expression (CPS >1 positivity rate), TIL density, and expected clinical response to ICI across major sinonasal tumor types. Abbreviations: PD-L1 = Programmed Death-Ligand 1; CPS = Combined Positive Score; TIL = Tumor-Infiltrating Lymphocyte; ICI = Immune Checkpoint Inhibitors; SNSCC = Sinonasal Squamous Cell Carcinoma; SNUC = Sinonasal Undifferentiated Carcinoma; ONB = Olfactory Neuroblastoma; ITAC = Intestinal-Type Adenocarcinoma.)

Tumour Type	PD-L1 CPS >1 (%)	TIL Density	Expected Response to ICI
SNSCC [20]	40–60	Moderate	Moderate
SNUC [20]	60–70	Low	Exploratory/variable
ONB [20]	20–30	Variable	Limited
ITAC [20]	15–25	Low	Poor
Mucosal Melanoma [19]	35–55	Low	Moderate

Immunomodulatory effects of chemotherapy

Modern understanding of chemotherapy emphasizes not only its cytotoxic effects but also its ability to modify the immune environment in ways that enhance immunotherapy. A key mechanism is immunogenic cell death (ICD). As tumour cells undergo ICD, they release DAMPs such as ATP, calreticulin, and HMGB1, which stimulate dendritic cells and improve antigen presentation [23]. Chemotherapy also increases MHC-I expression on tumour cells, improving their visibility to cytotoxic T cells [24].

Another important effect is the remodelling of the tumour microenvironment. Chemotherapy can deplete immunosuppressive cell populations including regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) while recruiting and activating CD8+ T cells and NK cells [23, 24]. These changes collectively create a tumour environment more responsive to immune checkpoint blockade.

Synergistic potential of neoadjuvant chemo-immunotherapy

The combination of chemotherapy with PD-1 inhibitors has shown clear synergistic effects across several cancer types. In the pivotal CheckMate 816 trial, adding nivolumab to chemotherapy markedly improved major and complete pathological response rates in resectable NSCLC (non-small cell lung cancer) [25]. Similar improvements have been reported in oesophageal cancer [26], and accumulating data in head and neck oncology point toward enhanced resectability and disease control with chemo-immunotherapy [22]. Although sinonasal cancers are rarer and therefore less extensively studied, emerging evidence suggests comparable benefits. Patel *et al.* demonstrated improved downstaging and surgical outcomes in advanced sinonasal tumours following neoadjuvant therapy [27], while Abiri *et al*. more recently noted substantial tumour regression and favourable toxicity with chemo-immunotherapy [28]. A summary of the most relevant studies is provided in table 3.

Table 3. Selected Neoadjuvant Chemo-Immunotherapy Trials Relevant to Sinonasal Cancer. The key clinical trials of chemo-immunotherapy applied in head and neck oncology and related malignant tumors, including the respective treatment regimens and major pathological or clinical outcomes. Abbreviations: NSCLC = Non-Small Cell Lung Cancer; HNSCC = Head and Neck Squamous Cell Carcinoma; pCR = Pathological Complete Response; MPR = Major Pathological Response; SNUC = Sinonasal Undifferentiated Carcinoma.

Study / Trial	Cancer Type	Regimen	Key Outcomes / Pathologic Response
CheckMate 816 [25]	NSCLC	Nivolumab + platinum-based chemo	pCR: 24%, improved MPR and surgical outcomes
KEYNOTE-689 [22]	HNSCC	Pembrolizumab + chemotherapy (ongoing)	Early reports suggest improved MPR
Nivolumab + Chemo (Kato *et al.*) [26]	Esophageal cancer	Nivolumab + chemo	Improved disease-free survival
Institutional SNUC Pilot [28]	SNUC	Cisplatin + taxane + PD-L1 inhibitor	MPR ~35%
Hanna *et al.* / Patel *et al.* [22, 27]	HNSCC / sinonasal	Neoadjuvant chemo-immunotherapy	Improved tumour regression and resectability

Clinical evidence in sinonasal tumours

Because sinonasal cancers are uncommon, large prospective trials are scarce. However, retrospective studies and institutional experiences increasingly support neoadjuvant chemo-immunotherapy. Amit *et al*. demonstrated that neoadjuvant chemotherapy improved both resectability and survival outcomes in advanced disease [21]. Early incorporation of PD-1 blockade appears to further enhance these benefits:

- **SNSCC:** responses rise from ~45% (chemotherapy alone) to ~65%
- **SNUC:** responses improve from ~35% to ~55%
- **ONB and ITAC:** moderate but meaningful tumour reduction
- **Mucosal melanoma:** responses nearly double

Abiri *et al*. (2023) also observed significant tumour necrosis and downstaging with the combination approach [28]. These results are summarized in table 4.

Predictive biomarkers

A growing set of biomarkers is being used to refine patient selection for immunotherapy-based treatment:

- **PD-L1 CPS:** correlates strongly with responsiveness to PD-1 inhibitors [20]
- **TMB:** moderate in mucosal melanoma, supporting ICI activity [19]
- **TIL density:** a key predictor of immune

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responsiveness

- **MSI-H/dMMR:** rare in sinonasal cancers but a powerful predictor when present
- **Emerging biomarkers:** include ctDNA trends, immune gene-expression profiles, and neoantigen load.

Together, these markers support personalized, biomarker-guided treatment approaches.

Table 4. Clinical outcomes of neoadjuvant chemo-immunotherapy in sinonasal tumours. Comparison of the clinical response rates of major sinonasal tumor subtypes to neoadjuvant chemotherapy alone and neoadjuvant chemo-immunotherapy, with supplementary clinical notes on treatment benefits. Abbreviations: SNSCC = Sinonasal Squamous Cell Carcinoma; SNUC = Sinonasal Undifferentiated Carcinoma; ONB = Olfactory Neuroblastoma; ITAC = Intestinal-Type Adenocarcinoma.

Tumour Type	Response With Chemotherapy Alone (%)	Response With Chemo-Immunotherapy (%)	Clinical Notes
SNSCC [21, 28]	~45	~65	Better downstaging and resectability
SNUC [21, 28]	~35	~55	Significant tumour shrinkage in aggressive disease
ONB [21, 28]	~30	~45	Moderate improvement; histology-dependent
ITAC [21, 28]	~30–35	~40–50	Improved surgical access, modest response gain
Mucosal Melanoma [21, 28]	~15–20	~30–40	Responses nearly double

Surgical considerations following neoadjuvant chemo-immunotherapy

Neoadjuvant chemo-immunotherapy can significantly influence intraoperative planning and surgical technique. Tumour shrinkage often improves resectability, but treatment-induced fibrosis, necrosis, and vascular changes may complicate dissection. Updated MRI and CT scans are therefore essential for accurate preoperative restaging.

Frozen sections may be more challenging to interpret due to extensive therapy-related necrosis. Reconstruction also requires careful planning, especially when free flaps are being considered, as vascular changes may affect flap viability. Although immune checkpoint inhibitors have been associated with delayed wound healing in some cases, such issues are generally manageable with coordinated perioperative care [22].

Role of adjuvant radiotherapy

Adjuvant radiotherapy remains central to sinonasal cancer treatment due to the high likelihood of microscopic residual disease and local recurrence. Contemporary approaches such as IMRT (Intensity-Modulated Radiotherapy) and proton therapy allow for highly conformal dose distributions that spare the optic apparatus, brainstem, and other delicate structures [15, 29].

When administered after chemo-immunotherapy, radiotherapy may have augmented effects because of increased antigen release and immune activation - raising the possibility of synergistic or even abscopal responses. Improved locoregional control has been documented in difficult-to-treat subtypes such as SNUC and high-grade SNSCC when radiotherapy is included [16]. A comparative overview of these strategies is provided in table 5.

Table 5. Radiotherapy approaches and immune modulation in sinonasal cancer. Outlines of the common radiotherapy modalities used in sinonasal cancer treatment, their key advantages, interaction with the antitumor immune response, and associated clinical effects on local disease control and treatment-related toxicity. Abbreviations: IMRT = Intensity-Modulated Radiotherapy; SIB = Simultaneous Integrated Boost; RT = Radiotherapy.

Radiotherapy Modality	Advantages	Interaction With Immune Response	Clinical Impact
IMRT (Intensity-Modulated Radiotherapy) [15, 16, 29]	Conformal dose shaping; optic and brainstem sparing	May enhance antigen release and T-cell recruitment	Improves local control with reduced toxicity
Proton Therapy [16, 29]	Superior normal-tissue sparing, ideal for skull base	Potentially greater synergy due to precise targeting	Lower late toxicity; useful for younger patients
Post-Chemo-Immunotherapy RT [16]	Consolidates response; targets microscopic disease	May trigger abscopal or systemic immune effects	Particularly beneficial in SNUC & high-grade SNSCC
Adjuvant RT for Positive Margins [15, 16]	Reduces local recurrence	Enhances immune activation in residual tissue	Standard of care in most resected cases
Boost Techniques (SIB, brachytherapy) [16, 29]	Higher dose to tumor bed	Could intensify immunogenic effects	Useful for residual disease zones

Ongoing trials and future directions

The future of sinonasal cancer therapy is increasingly oriented toward biomarker-driven and immunologically informed treatment strategies. Several trial designs currently underway or in development include:

- PD-L1– and TMB-stratified enrolment
- Basket trials enrolling tumours with shared molecular or immune features
- Combination checkpoint inhibition (e.g., LAG-3, TIGIT, OX40, CD137)
- Personalized neoantigen vaccine approaches, especially for mucosal melanoma
- Oncolytic viral therapies integrated with ICIs or radiotherapy

These strategies aim to refine patient selection, improve pathological response rates, and enhance long-term outcomes in this challenging group of cancers.

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DISCUSSION

The integration of neoadjuvant chemo-immunotherapy followed by adjuvant radiotherapy represents a promising evolution in the management of sinonasal malignancies, a disease group historically defined by late diagnosis, complex anatomy, and high recurrence rates [31, 32]. Contemporary population analyses highlight that survival has improved only modestly over the past decades, underscoring the need for therapeutic innovation [33, 34]. Despite advances in surgical and radiation techniques, achieving durable locoregional control remains challenging because many patients present with advanced disease and biologically aggressive histologies [35,36]. The difficulty in achieving negative surgical margins, especially in tumours abutting the skull base or orbit, has long been recognized as a key limitation of surgery alone [37]. While multimodal treatment has improved outcomes, recurrence patterns suggest a persistent risk of microscopic residual disease and systemic spread in high-grade tumours [38]. Neoadjuvant chemotherapy has historically been employed to facilitate resectability, but its impact on long-term outcomes has been inconsistent. However, the addition of immunotherapy has shifted this paradigm. Chemotherapy not only reduces tumour volume but also enhances immunogenicity by promoting antigen release and dendritic-cell priming, thereby potentiating checkpoint blockade responses [39, 40]. Emerging studies from head and neck oncology demonstrate that neoadjuvant immune checkpoint inhibition can reshape the tumour microenvironment, increasing effector T-cell infiltration and reducing suppressive populations such as MDSCs and regulatory T cells [41]. These changes appear to translate into improved pathological responses and more favourable surgical outcomes. Early clinical experiences with chemo-immunotherapy in sinonasal cancers, though limited, echo these findings. Improved resectability and higher major pathological response rates have been observed, particularly in SNSCC and SNUC, where standard systemic therapy historically performs poorly [42, 43]. Radiotherapy continues to serve as a cornerstone of sinonasal cancer management, especially for tumours with close or positive margins, perineural invasion, or skull-base involvement. Modern conformal techniques including IMRT and proton therapy provide superior target coverage while protecting adjacent critical structures [44, 45]. The biological interplay between radiation and immunotherapy may offer an additional advantage; radiation can enhance antigen release, promote T-cell infiltration, and in some cases trigger systemic immune activation known as the abscopal effect [46]. Early data from head and neck cancers suggest that combining radiation with checkpoint blockade may provide additive or synergistic benefits, a concept highly relevant for sinonasal tumours [47].

As multimodal strategies evolve, biomarker-driven patient selection will play an increasingly critical role. Although PD-L1 expression provides useful guidance, it does not fully capture the immunologic heterogeneity of sinonasal cancers. Comprehensive markers such as tumour mutational burden, immune-gene signatures, and ctDNA kinetics may serve as more precise predictors of response [48, 49]. For instance, Liu *et al*. (2022) identified a 12-chemokine gene signature in colorectal cancer liver metastases (CRC-LM) that correlated with enhanced immunogram scores, highlighting the potential of immune-gene signatures to reflect tumour immunogenicity and guide precision immunotherapy [50]. The integration of these biomarkers into ongoing and future clinical trials will be essential to developing individualized therapeutic strategies. The current evidence strongly suggests that neoadjuvant chemo-immunotherapy followed by adjuvant radiotherapy may improve outcomes by increasing resectability, augmenting systemic control, and strengthening locoregional disease management.

Nonetheless, several limitations of this study should be acknowledged. This narrative review has several limitations. First, as a narrative rather than a systematic review or meta-analysis, literature selection and synthesis did not follow a formal systematic-review framework, and potential selection bias cannot be excluded. Second, evidence on integrating neoadjuvant chemo-immunotherapy and adjuvant radiotherapy for sinonasal malignancies remains limited and heterogeneous. Available studies vary considerably in patient populations, histological subtypes, treatment regimens, radiotherapy strategies, follow-up periods, and outcome measures,

limiting direct comparisons. Moreover, much of the evidence derives from retrospective studies, small institutional series, and other non-randomized studies, while high-level evidence still remainsscarce [51, 52]. Variations in treatment and follow-up protocols contribute to outcome heterogeneity, while prospective randomized evidence remains limited. Therefore, findings require cautious interpretation. Multicentre studies using standardized treatment and outcome-assessment protocols are needed to confirm effectiveness and long-term benefits of multimodal strategies.

In summary, combining chemotherapy, immunotherapy, and advanced radiotherapy represents a biologically rational and clinically promising approach for treating sinonasal malignancies. As more robust evidence emerges, this multimodal framework may redefine standard care for these rare and challenging tumours.

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CONCLUSION

Sinonasal malignancies are among the most challenging head and neck cancers due to complex anatomy, biological diversity and late presentation. Despite advances in endoscopic surgery and precision radiotherapy, outcomes for aggressive subtypes (SNUC, high-grade SNSCC, mucosal melanoma) remain suboptimal, necessitating novel therapies beyond conventional modalities. Insights into tumour immunobiology (notably the PD-1/PD-L1 axis) support neoadjuvant chemotherapy combined with immune checkpoint inhibitors: chemotherapy reduces tumour burden and enhances immunogenicity to remodel the tumour microenvironment, while immunotherapy reverses T-cell exhaustion and sustains antitumor immunity. Early small-cohort data show this combination improves tumour regression, major pathological response rates and resectability, especially in therapy -resistant subtypes. Adjuvant radiotherapy is essential for addressing microscopic residual disease, and combining it with prior immunotherapy may amplify antitumor effects via enhanced antigen release, T-cell recruitment and potential systemic immune activation. In summary, neoadjuvant chemo-immunotherapy followed by adjuvant radiotherapy is a promising multimodal strategy for select sinonasal malignancies, with the potential to improve locoregional control and systemic disease management. Future research should focus on multicentre collaboration, biomarker-driven patient selection and optimized treatment sequencing to redefine the standard of care for these rare, aggressive tumours.

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