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CLINICAL REVIEW

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Contemporary treatment and outcome of sinonasal undifferentiated carcinoma: A meta-analysis

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Abstract

Induction chemotherapy (IC) recently gained importance for treatment of sinonasal undifferentiated carcinoma (SNUC). We analyzed our SNUC cases and performed a meta-analysis with focus on survival-rates stratified by treatment. SNUC cases at our institution were retrospectively evaluated. A systematic literature review was conducted to analyze treatment and outcome of SNUC. To calculate 5-year and 2-year overall survival (OS), individual patient data (IPD) were analyzed using Kaplan–Meier estimators and Cox proportional hazard regression to identify associations between types of therapy and survival. A random effects model for pooled estimates of 5-year survival was applied to studies without IPD data. Five-year OS of our SNUC cases ($n = 9$) was 44.4%. The IPD analysis ($n = 192$) showed a significantly better 5-year OS for patients who received induction chemotherapy (72.6% vs. 44.5%). The pooled 5-year OS of 13 studies identified in the literature search was 43.8%. IC should be considered in every patient diagnosed with SNUC.

KEYWORDS

chemotherapy, induction chemotherapy, sinonasal cancer, sinonasal undifferentiated carcinoma (SNUC)

1 | INTRODUCTION

Sinonasal undifferentiated carcinoma (SNUC), which was first described by Frierson and colleagues in 1986, is an extremely aggressive neoplasm deriving from the Schneiderian epithelium.[1] It is histologically characterized by its specific architecture and the lack of squamous or glandular differentiation.[2] SNUC can occur in patients within the age range of 20–80 years with an average age of 50–59 years at diagnosis. It is more common in male than in female patients (3:1 male-to-female ratio).[3] As SNUC presents with unspecific and often only mild sinonasal symptoms, many patients are diagnosed with advanced stage disease.[4] Overall, the prognosis of the disease is poor due to an often locally already advanced disease with orbital or skull base infiltration, high recurrence rates, and distant metastases.[5] Because of the lack of randomized controlled trials, therapy regimens are based on small case series. However, therapy recommendations have been changing in the past several years. Whereas in former times surgery in combination with radiation therapy (RT) was considered to be an important component in the therapy of SNUC,[6–9] more recent findings suggested treatment with induction chemotherapy (IC) would improve outcome of patients with SNUC. In 2019 Amit et al. published an analysis of 95 patients receiving IC with curative intent. The applied IC regime was cisplatin with etoposide. Three weeks after IC the patients' response to IC was assessed by nasal endoscopy and imaging (CT, MRI, or PET-CT). Patients with complete or partial response underwent definitive chemoradiation (CRT), patients with less than partial response received surgical resection of their tumor. The 5-year overall survival (OS) probability was 66% for patients treated with IC followed by CRT, and 43% for patients treated with IC followed by surgery.[10] These results are supported by London and colleagues who treated their patients with 3 cycles IC (docetaxel, cisplatin, and fluoruracil) followed by concurrent CRT since 2016.[11] De Bonnecaze and colleagues discovered an improved recurrence-free survival in patients treated with IC.[12] However, in an analysis of Lehrich and colleagues IC was not associated with improved OS.[13] The recent changes in therapy and remaining uncertainties because of heterogeneous recommendations make a thorough review of available literature on SNUC and a meta-analysis of survival-rates stratified by treatment necessary. Moreover, we present the cases which were treated at the Department of Otorhinolaryngology of the University Hospital Augsburg in the past 10 years.

2 | METHODS

To analyze our own SNUC cases, we retrospectively searched our patient management system (ORBIS) for the period from January 1, 2012 to December 31, 2021 with the relevant ICD-10 diagnosis codes C30.0 (Malignant neoplasm of nasal cavity), C31.0 (Malignant neoplasm: maxillary sinus), C31.1 (Malignant neoplasm: maxillary sinus), C31.2 (Malignant neoplasm: frontal sinus), C31.3 (Malignant neoplasm: sphenoid sinus), C31.8 (Malignant neoplasm: overlapping lesion of accessory sinuses), or C31.9 (Malignant neoplasm: accessory sinus, unspecified). Results were filtered for patients with a diagnosis of SNUC by reviewing medical records. In the pathology department, the histological sections of the patients were re-examined to confirm the diagnosis according to the WHO diagnostic criteria.[14] Histological features of SNUC are nests, sheets, and cords of medium-sized polygonal cells, no evidence of glandular or squamous differentiation, pleomorphic and hyperchromatic nuclei with large and prominent nucleoli, as well as mitotic figures and necrosis (Figures S1 and S2, Supporting Information). A subset of SNUC, which have the IDH2 mutation, have been reported and appear to have a better prognosis.[15] Each confirmed case was then analyzed in detail and, if necessary, the patients, their relatives or family doctors were called to obtain information on the patients' current health status.

For the meta-analyses, a PubMed/MEDLINE search was performed according to PRISMA guidelines.[16] Two independent reviewers searched for "sinonasal undifferentiated carcinoma" and "sinonasal undifferentiated carcinoma OR SNUC" from 2000 to 2022, with English or German abstracts available. The aim was to find articles analyzing the treatment and outcome of patients with SNUC. Excluded were records on pediatric patients ($n = 3$), overviews, abstracts, and reviews ($n = 20$), and records focusing on specific factors other than therapy, such as histological features, surgical approach, or lymph node involvement ($n = 10$). In addition, we excluded 22 case reports that did not provide detailed information on therapy, follow-up, or outcome. We also excluded case reports with a follow-up of less than 6 months ($n = 4$) and case reports of patients treated with palliative intent or best supportive care ($n = 2$). For the meta-analysis, papers were analyzed according to the most frequent variable related to outcome, which was the 5-year OS rate. Therefore, a further five papers had to be excluded due to missing data on 5-year OS or missing data on treatment for SNUC. Among the remaining 13 papers, three and two papers, respectively, used the same database for data collection. To avoid duplicate data, we only included one paper using the respective database. For the analysis of individual patient data, in order to obtain as homogeneous a cohort as possible, we excluded pediatric cases ($n = 3$), cases with a follow-up of less than 6 months ($n = 34$), cases with metastases ($n = 7$), cases describing treatment for recurrence ($n = 1$), and cases with palliative treatment ($n = 9$). In addition, there were two cases with conflicting data that were also excluded. The inclusion and exclusion criteria are summarized in a flow chart in Figure 1.

2.1 | Statistical analysis

Individual cases were described with descriptive statistics, where information was available. Two-year and 5-year OS with 95% confidence intervals was calculated using Kaplan–Meier estimators for each therapy combination and for each therapy separately. Cox proportional hazard regressions were performed to identify associations between types of therapy and survival. In the meta-analysis, heterogeneity between studies was calculated by

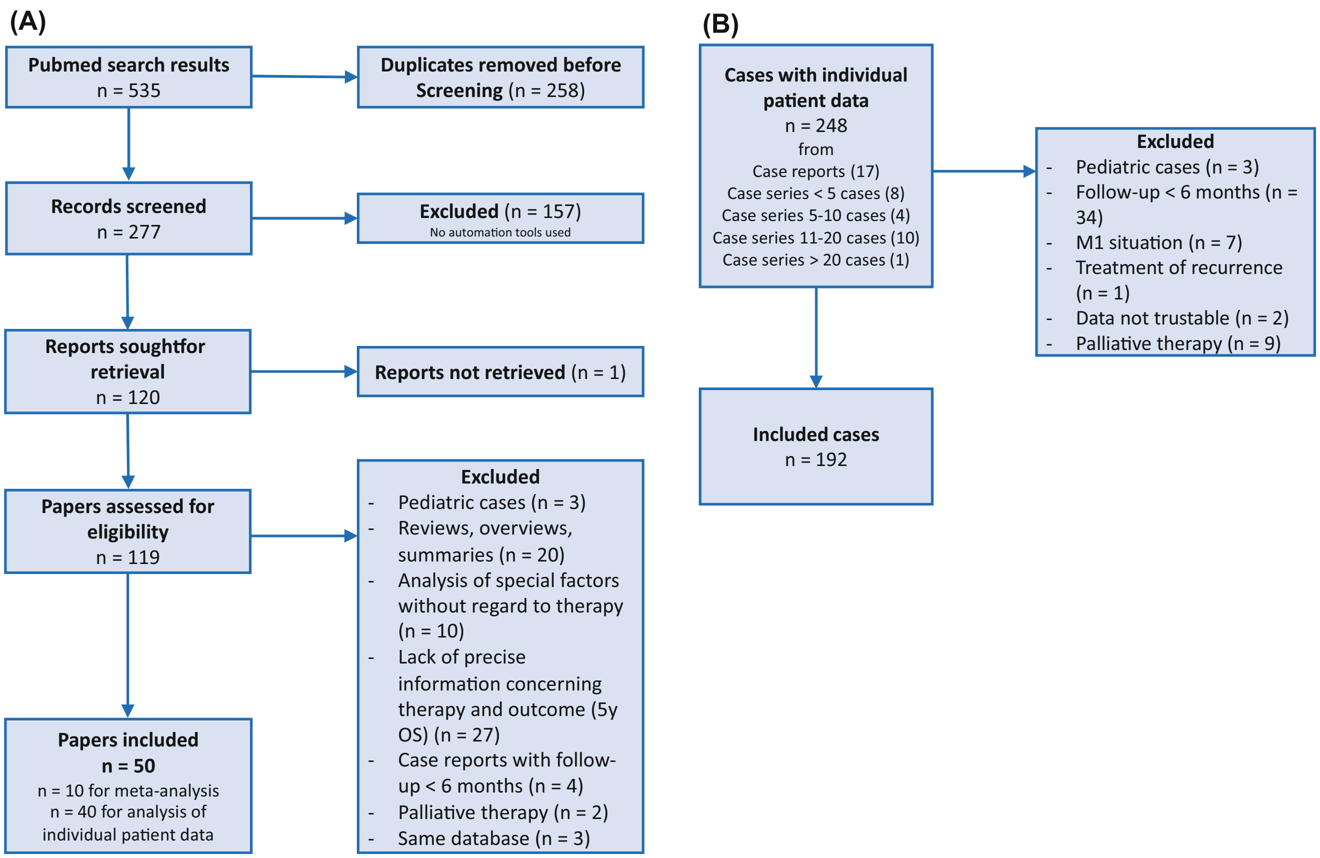

FIGURE 1 (A) PRISMA diagram for literature search. (B) Flow diagram displaying in- and exclusion criteria for individual patient data cases. [Color figure can be viewed at wileyonlinelibrary.com]

I^2 statistics. Due to a high heterogeneity between the studies, we applied a random effects model for pooled estimates of 5-year survival. A p-value <0.05 was considered statistically significant. Statistical analyses were performed with R (version 4.2.1.).

3 | RESULTS

3.1 | Treatment and outcomes of SNUC in our facility

In our facility, we found nine cases treated with a diagnosis of SNUC between 2012 and 2021. All cases are summarized in Table S1. Seven of the nine patients underwent surgical resection and one was treated with primary CRT. One patient refused any therapy and died 3 months after initial diagnosis. The patient who received CRT developed metastases in the bones and brain and died 16 months after diagnosis.

Concerning our surgical approach, we performed lateral rhinotomy in two cases with low tumor stage (T1), in both cases R0 resection was achieved. Two cases (T3) received total endoscopic resection, both R0 (one after follow-up resection). In two cases surgery was performed in cooperation with the department of neurosurgery. In one of these cases R0 resection was achieved, in the other case intraoperative findings showed tumor extension behind the optical chiasma, which made an R0 resection impossible. This patient received adjuvant radiation and a brachytherapy boost. In one the tumor was debulked for symptom control due to its extension. As expected there were positive margins and the patient received and adjuvant chemoradiation.

Three of the five patients who received R0 resection underwent adjuvant chemoradiotherapy (two patients) or RT (one patient), and two did not receive adjuvant therapy. Four of these five patients are still alive.

One patient developed a local recurrence which was surgically removed with orbital exenteration, one patient had lymph node recurrence, which was treated with neck dissection. Patients with distant metastasis were treated with individual concepts depending on the site and the extent of the metastases.

In summary, we followed a surgical approach with adjuvant RT or CRT whenever possible. Regardless of resection status, five of the seven patients are still alive after surgical treatment. Two of them without signs of disease, in one case the status is unknown, and two patients have distant metastases. In two cases, no adjuvant therapy was performed after surgical treatment. One of these patients is alive without signs of disease, and one has developed a metastasis. The two patients who died after surgical treatment had a high stage of disease with infiltration of the orbit and brain.

Since end of 2022 we had another two SNUC cases at our institution which were both initially treated with IC. Both responded well to the induction treatment and are thus currently undergoing definitive CRT.

3.2 | Results from the literature research

The literature search yielded 535 results. After exclusion of duplicates ($n = 258$), 277 records were screened. After excluding a further 157 records, 120 were searched for retrieval. A total of 50 papers were included, including 40 case reports and case series with individual patient data on SNUC cases and 10 studies with more general data on the distribution of treatment in cohorts and 5-year OS as outcome. The 40 papers considered for individual patient data analysis consisted of 17 case reports, 8 case series with less than 5 patients, 4 case series with 5–10 patients, 10 case series with 11–20 patients, and 1 case series with more than 20 cases. In one case series, 11 cases were analyzed, of which only one was a SNUC, so only this case was included in the analysis. In total, the 40 papers provided 248 cases. After exclusion a total of 192 cases were included in the analysis (Figure 1).

3.3 | Analysis of the individual patient data

We included 192 cases in the analysis of individual patient data. The baseline data are summarized in Table S2. The median age of the patients for whom corresponding data were available ($n = 163$) was 51 years. Gender was reported in 128 cases. 74.6% of these cases were male, 25.4% were female. Tumor stage data were available for 123 cases. Of these, 2 were T1 (1.6%), 5 were T2 (4.1%), 10 were T3 (8.1%), and 106 were T4 (86.2%). Lymph node involvement was stated in 132 cases. Twenty-five of these cases had positive lymph nodes (18.9%) and 107 were N0 (81.1%). The age and sex distribution, tumor stage, and lymph node involvement were consistent with the literature.[4,17,18] Regarding therapy, 30 cases received IC before definitive RT or CRT, 29 cases were treated with primary CRT or RT, 86 cases were treated with surgery followed by adjuvant CRT or RT, 10 cases were treated with surgery alone, and 37 cases received neoadjuvant therapy before surgery alone or surgery followed by adjuvant CRT or RT. Neoadjuvant therapy included different treatments before surgery, that is, IC, neoadjuvant RT or neoadjuvant CRT (we combined these treatment modalities into the group "neoadjuvant therapy + surgery (+CRT)" to avoid too many small treatment groups). The terms "induction chemotherapy" and "neoadjuvant chemotherapy" often overlap. Correctly speaking, IC refers to chemotherapy before a definitive radiotherapy, and neoadjuvant chemotherapy refers to chemotherapy before a surgical treatment.[19]

The 5-year OS of all 192 cases was 50.5% (95% CI 42.1%–60.7%) (Figure 2A). In a further analysis we

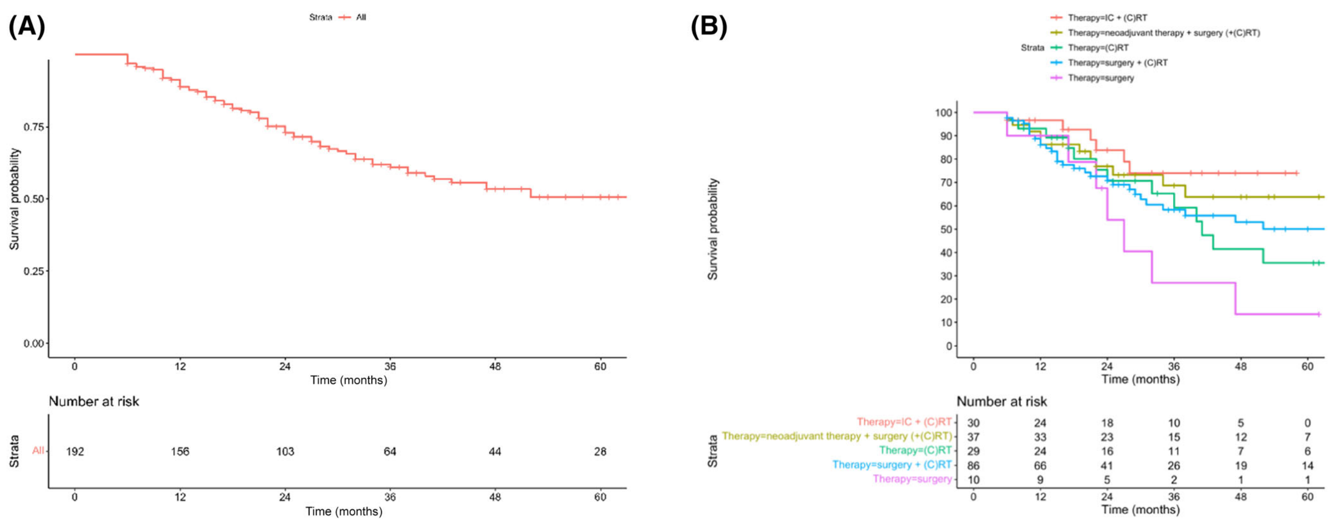

FIGURE 2 (A) Kaplan–Meier curve of all 192 case, 5-year OS 50.5%. (B) Kaplan–Meier curve comparing different treatment groups. [Color figure can be viewed at wileyonlinelibrary.com]

compared 5-year OS of patients with advanced stage disease versus low-stage disease. Advanced stage was defined by the following criteria: T3 or T4, Kadish C, lymph node involvement (N+), and orbital or skull base infiltration (if not T stage was documented), respectively. Low stage was T1 or T2, Kadish A and B, N0, and no orbital or skull base infiltration, respectively. Ten patients could not be assigned to one of these groups due to missing data. Five-year OS between advanced and low stage did not differ significantly. It was 47.7% (95% CI 38.5%–59.1%) for patients with advanced stage, and 52.2% (95% CI 32.5%–83.9%) for patients with low stage (HR = 1.05, 95% CI 0.50–2.21, $p = 0.89$) (Figure S3).

Figure 2B shows a comparison between the different treatment groups. The 2-year OS was 83.8% (95% CI 70.4%–99.9%) for IC + (C)RT, 76.9% (95% CI 63.9%–92.4%) for neoadjuvant therapy + surgery (+(C)RT), 70.8% (95% CI 60.9%–82.4%) for surgery + (C)RT, 70.6% (95% CI 54.3%–92.0%) for primary (C)RT, and 54.0% (95% CI 28.8%–100%) for surgery alone. The 5-year OS was 63.7% (95% CI 48.0%–84.6%) for neoadjuvant therapy + surgery (+(C)RT), 50.1% (95% CI 37.9%–66.2%) for surgery + (C)RT, 35.6% (95% CI 19.1%–66.2%) for primary (C)RT, and 13.5% (95% CI 2.2%–82.5%) for surgery. The 5-year OS for IC + (C)RT was not available as all patients had either died or dropped out of follow-up within 5 years. In the Cox proportional hazard regression, surgery had a significantly higher risk of death than IC + (C)RT (HR = 3.96, $p = 0.014$). The difference between IC + (C)RT and the other treatment groups was not significant.

In addition, we analyzed the influence of a specific treatment method on OS. The comparison between all cases treated with IC (before surgery or (C)RT) and those without IC showed a significantly better 5-year OS for the cases treated with IC (HR = 0.42, 95% CI 0.21–0.85, $p = 0.016$), as shown in Figure 3A. Patients treated with neoadjuvant therapy before surgery had better 5-year overall survival than patients without neoadjuvant therapy, although not significantly (HR = 0.62, 95% CI 0.36–1.07, $p = 0.084$; Figure 3B). Surgical treatment had no effect on OS (HR = 1.20, 95% CI 0.70–2.04, $p = 0.508$). We also found no benefit for cases with trimodal therapy compared with those without (HR = 0.98, 95% CI 0.61–1.59, $p = 0.948$). As only 13 patients were treated with one modality, a comparison between bi- or trimodal therapy and monomodal therapy was not meaningful. Table 1 gives an overview of the 2-year and 5-year OS of the different treatment groups and the influence of the specific treatment modalities.

3.4 | Meta-analysis

We included 10 papers with information on treatment strategy and 5-year OS of SNUC cases in the meta-analysis. A random effects model was used to calculate the pooled 5-year OS, which was 47.5% (Figure 4). However, the studies were very heterogeneous ($I^2 = 78\%$).

In seven studies, the maximum number of cases was $n = 40$.[6,7,20–24] These studies are summarized in Table 2. The 5-year OS in these studies ranged from 32%[20] to 81.8%.[21] In terms of tumor stage and age, all studies were quite similar. Concerning tumor stage, the studies comprise nearly exclusively high-stage tumor patients. The study of Amit and colleagues analyzed a cohort of 95 patients who were all treated with IC. The 5-year OS was 56%.[10] The two studies with the highest weights in

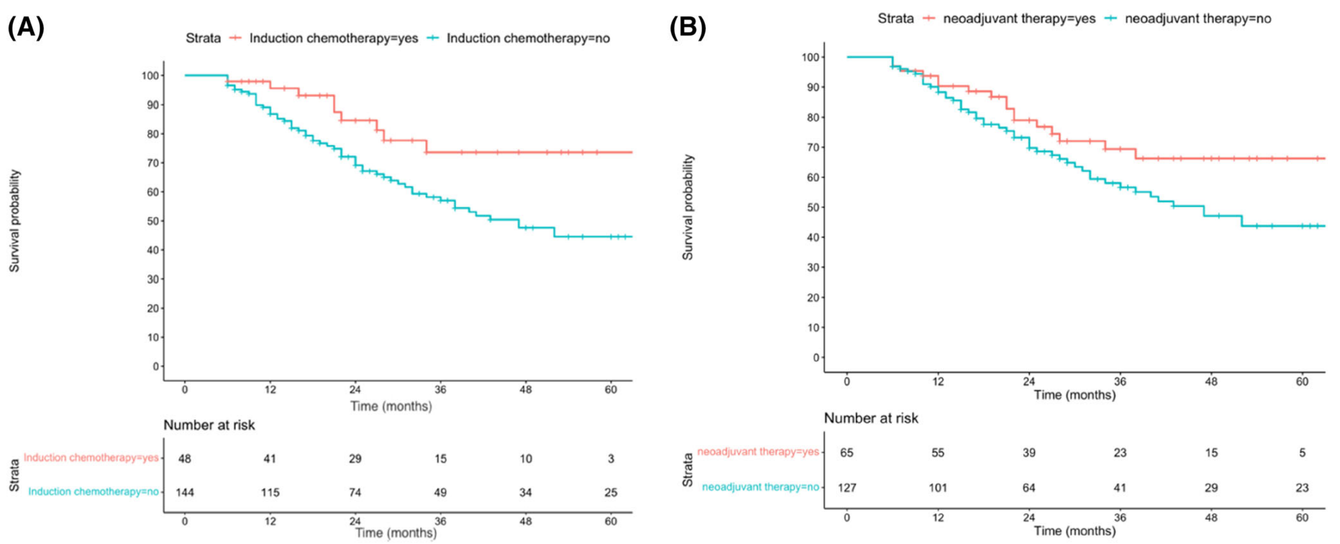

FIGURE 3 (A) Kaplan–Meier curves comparing induction chemotherapy versus no induction chemotherapy. (B) Kaplan–Meier curves comparing neoadjuvant therapy versus no neoadjuvant therapy. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Two-year and 5-year overall survival of different treatment groups and impact of specific treatment modalities.

	24 months		60 months		Cox proportional hazard regression		
	2-year OS	**95% CI**	**5-year OS**	**95% CI**	**HR**	**95% CI**	***p*-value**
Total	73.0%	66.4%–80.3%	50.5%	42.1%–60.7%			
Therapy							
IC + (C)RT	83.8%	70.4%–99.9%	Not available		Reference		
Neoadj. therapy + surgery (+(C)RT)	76.9%	63.9%–92.4%	63.7%	48.0%–84.6%	1.42	0.53–3.81	0.482
(C)RT	70.6%	54.3%–92.0%	35.6%	19.1%–66.2%	2.28	0.86–6.00	0.096
OP + (C)RT	70.8%	60.9%–82.4%	50.1%	37.9%–66.2%	1.98	0.82–4.77	0.126
Surgery	54.0%	28.8%–100%	13.5%	2.2%–82.5%	3.96	1.33–11.80	0.014
Neoadjuvant therapy							
Yes	79.0%	69.0%–90.4%	66.2%	53.9%–81.5%	0.62	0.36–1.07	0.084
No	69.8%	61.4%–79.3%	43.7%	33.9%–56.5%	Reference		
IC							
Yes	84.6%	73.9%–96.9%	73.6%	59.8%–90.7%	0.42	0.21–0.85	0.016
No	69.1%	61.3%–78.0%	44.5%	35.3%–56.2%	Reference		
Surgery							
Yes	71.2%	63.3%–80.2%	50.5%	40.8%–62.6%	1.20	0.70–2.04	0.508
No	77.2%	66.1%–90.2%	49.4%	34.0%–71.9%	Reference		
Trimodality							
Yes	70.5%	60.8%–81.8%	56.2%	44.8%–70.6%	0.98	0.61–1.59	0.948
No	75.0%	66.4%–84.8%	45.3%	33.8%–60.7%	Reference		

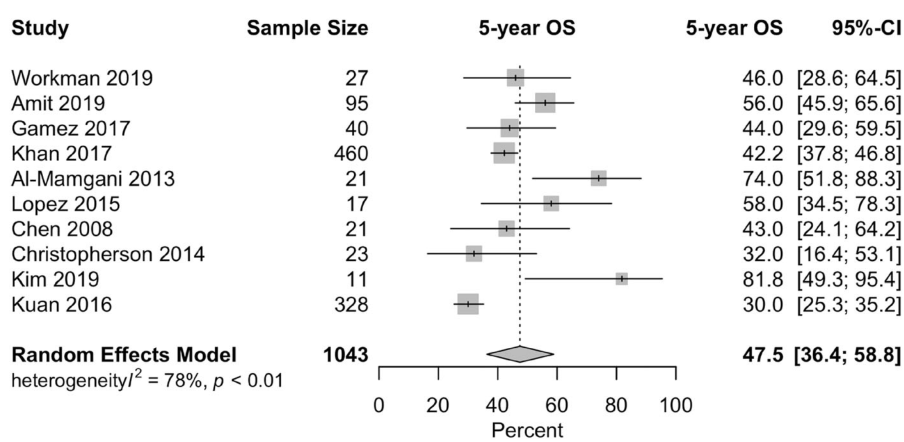

FIGURE 4 Random effects model for 5-year overall survival.

our random effects model were by Kuan and colleagues[9] and Khan and colleagues.[25] Kuan et al. analyzed information on 328 cases from 1973 to 2011. The 5-year OS in this cohort was 30%. Khan and colleagues analyzed the largest cohort of 460 patients. The 5-year OS was 42.2%.

4 | DISCUSSION

With an incidence of only 0.2 per 100 000, SNUC is a very rare disease[8] and no clear treatment recommendations have been developed in the years since it was first described in 1986. In this article, we present our institution's cases from the last 10 years, as well as a meta-analysis with individual patient data and an analysis of available studies regarding the treatment of SNUC and the 5-year OS. At our institution, we mostly followed a surgical approach with adjuvant CRT. After analyzing the current literature on changes in therapy for SNUC, we have treated two patients with IC since 2022. Both responded well and are currently on definitive CRT. In the analysis of 192 cases from case reports and case series, we demonstrated significantly better 5-year OS for patients treated with IC, regardless of subsequent

TABLE 2 Studies with case numbers ≤40.

	Cases	Age	Lymph node involvement	T3/T4	Stage III/IV	Median follow-up (months)	IC	Surgery	5 year OS
Chen et al.[22]	21	47 (median)	2 (10%)	21 (100%)	N/A	36	0	19 (90%)	43%
Al-Mamgani et al.[7]	21	52 (median)	2 (10%)	21 (100%)	N/A	54	7 (33%)	14 (67%)	74%
Christopherson et al.[20]	23	56.5 (median)	N/A	N/A	23 (100%)	36	4 (17%)	15 (65%)	32%
Lopez et al.[6]	17	53 (median)	2 (12%)	17 (100%)	N/A	39	3 (18%)	14 (82%)	58%
Gamez et al.[23]	40	56,7 (median)	3 (7.5%)	37 (92.5%)	N/A	83	8 (20%)	33 (83%)	44%
Kim et al.[21]	11	59 (mean)	N/A	N/A	10 (91%)	N/A	0	3 (27%)	82%
Workman et al.[24]	27	55.6 (mean)	9 (33%)	N/A	26 (96%)	N/A	5 (19%)	23 (85%)	46%

Abbreviation: N/A, not available.

treatment, compared with patients who did not receive IC. The distribution of important variables such as age, sex, tumor stage, and lymph node involvement among the 192 cases is consistent with the known characteristics of SNUC, making the cohort homogeneous and the results reliable. Our meta-analysis of the 10 different studies yielded a pooled 5-year OS of 47.5%, which is lower than the 5-year OS in the 192 cases (5-year OS of 50.5%). However, the studies included in the random effects model were very heterogeneous ($I^2 = 78\%$). Different aspects were highlighted, and the treatment groups used for comparison and analysis of outcomes by treatment were often different in the studies: Kim and colleagues[21] studied 11 cases of which all achieved disease-free status after initial treatment. This and the low case number could contribute to their high 5-year OS rate of 81.8%. The 5-year OS calculated in the study of Al-Mamgani et al.[7] was 74%. They used IC as therapy in at least 33% of their cases. The most used therapeutic approach in the studies with rather low case numbers (Table 2) was surgery. Apart from Al-Mamgani and colleagues, IC was used in at least 20% of the study cases. These studies all had worse 5-year OS than the study of Al-Mamgani et al. This raises the question if the use of IC contributes to the better 5-year OS, which would be in line with our results from the individual patient data analysis. However, none of the studies in Table 2 investigated the impact of IC itself on OS or compared IC-based treatment groups with other treatment groups. There are different factors which could also contribute to a worse 5-year OS in the studies which rather concentrated on surgical therapy. Workman and colleagues for example had positive lymph nodes in 33% of their cohort and discovered a significant association between neck disease at presentation and increased mortality. In our individual patient data analysis lymph node was less likely (18.9% of 132 cases with data on lymph node involvement). Occult lymph node metastases and the role of elective neck treatment is another interesting, yet controversial question in the treatment of sinonasal carcinomas. As pointed out, the described studies are very heterogeneous, which makes it difficult to draw generally applicable conclusions. A larger cohort (95 patients) was analyzed by Amit and colleagues. All patients were treated with IC. Depending on the response to IC, they divided their cohort into two further treatment groups. Patients who responded well to IC (according to radiological assessment) received definitive CRT, and patients who did not respond well underwent surgery. The 5-year OS of the entire cohort was 56%. For patients who received CRT after IC, the 5-year OS was 66%, and for patients who had surgery after IC, the 5-year OS was 43%.[10] In our individual patient data analysis, the 5-year OS for patients treated with IC was 73.6%. The studies of Kuan and colleagues and Khan and colleagues analyzed 328 and 460 cases, respectively, using databases. In the study of Kuan and colleagues, the 5-year OS was 30.0%. Nearly half of all patients (42.7%) received unimodal therapy, which may contribute to the low 5-year OS. Information on chemotherapy and metastatic disease was not available. They found an improvement in OS in patients who received RT and surgery. In our individual patient data analysis, cases with combination therapies consisting of surgery, chemotherapy and/or radiation had a better 5-year OS than patients receiving only surgery, or only CRT (Table 1). The 5-year OS of patients treated with trimodal therapy was 56.2% compared to 45.3% for patients not treated with trimodal therapy, albeit not significant, which underlines the importance of a multimodal treatment approach. The 5-year OS in the study of Khan and colleagues was 42.2%. They compared patients treated with surgery followed by CRT ($n = 169$) with patients treated with definitive CRT and discovered a significantly better 5-year OS for patients with surgery followed by

CRT (55.8% vs. 42.6%, $p = 0.0071$). This is in line with our results. There was also—not surprisingly—a significant difference in 5-year OS for patients with metastases (18.6%) and patients without metastases (45.6%). Although these two studies have a higher number of cases, they do not provide evidence for the role of IC in the treatment of SNUC. Furthermore, the databases used in these studies do not provide all relevant treatment data, especially on chemotherapy. This is why in our opinion, the summary of individual cases is therefore a detailed and feasible approach to obtain an overview of the results of the different therapeutic approaches of the last 20 years. We found a significant advantage for patients treated with IC compared to patients treated without IC. These results are in line with data from Amit and colleagues in 2019, as pointed out above. Based on these results, London and colleagues analyzed their SNUC cases from 2010 to 2018. Since 2016, they have used IC followed by CRT as the standard treatment for SNUC. Patients treated with this approach responded well and showed no signs of disease at a mean follow-up of 16.8 months.[11] This contrasted with the findings of Lehrich and colleagues in 2020, who compared 70 patients treated with IC (before definitive RT, surgery followed by RT, or surgery only) with 370 patients treated with other therapy (the specific treatment was not stated) and found no survival benefit for patients treated with IC. Information on response to IC is not available.[13] In 2014, de Bonnecaze et al. analyzed a cohort of 54 patients and discovered that IC as a treatment modality significantly improved recurrence-free survival, even though IC had no impact on OS.[12] In 2019 Orlandi et al. analyzed a cohort of 69 patients with locally advanced sinonasal malignancies, of which 26 had SNUC. All were treated with IC followed by surgery and adjuvant C(R)T or followed by definitive CRT. Sixty-four percent developed recurrent or metastatic disease. Treatment for recurrence was salvage surgery, palliative chemotherapy, re-irradiation, and best supportive care. OS since relapse for patients treated with salvage surgery in case of recurrence was 29.5 and 4.6 months for patients receiving first-line palliative chemotherapy. Interestingly, response to IC in the curative setting was also associated with longer survival after recurrence.[26]

Recently, the role of IC has been investigated in other types of sinonasal carcinoma, which is particularly important as organ preservation by down staging for patients with late stage sinonasal carcinoma.[27,28] IC reduces the occurrence of distant metastases[29] and allows an immediate start of therapy, as it does not need as much complex planning as surgery or radiation therapy do (preparing patients for anesthesia, capacity for surgery, planning CT, dental restorations). Therefore, IC seems a reasonable treatment option for such aggressive entities as SNUC.[30] Furthermore, response to IC predicts a higher effectiveness of the definitive radiation therapy (chemoselection). Thus, selection of patients according to their response to IC is possible.[31] For the future, it would be of interest to predict response to IC in order to optimize treatment success with IC and to identify patients who might not benefit from IC. Takahashi and colleagues recently addressed this issue and identified biomarker predictive for response to IC.[32]

In 2012, Reiersen and colleagues published a meta-analysis that included all articles published since SNUC was first described in 1986 to compare different treatment methods. They analyzed 167 patients. Forty-six of them were treated with surgery and adjuvant RT. The remaining patients were treated with RT alone, chemotherapy alone, RT and chemotherapy, surgery alone, surgery and chemotherapy, surgery with RT and chemotherapy, or no treatment. It was shown that the survival rate of patients who had surgery was 3.1 times higher (odds ratio [OR] = 3.1, 95% CI 1.63–5.89) compared with patients who did not have surgery. In the comparison between surgery alone and surgery with RT and/or chemotherapy, the survival of patients who received surgery and RT and/or chemotherapy was 2.6 times higher. This led the authors to conclude that surgery with adjuvant RT and/or chemotherapy is the best treatment option for SNUC.[33] In 2017, Morand et al. published another meta-analysis in which they investigated the relationship between treatment modalities and survival.[34] They compared the treatment groups "palliative," "RT," "RT + chemotherapy," "surgery," "RT + surgery," and "RT + chemotherapy + surgery" and found that patients treated with radiotherapy and surgery had the best outcome. However, they did not address IC or the therapy sequence. They discovered an impaired survival of patients treated with single modality compared to patients treated with double or triple modality. They found, however, no significant difference between double and triple modality, which is consistent with our results: We found no advantage for patients treated with triple modality compared to patients who did not receive triple modality. Patients who were not treated with triple modality mostly underwent double modality treatment, as only 10 of 192 patients received a single modality therapy, which was surgery, in our analysis. These 10 patients had a significantly higher risk of death compared with the patients treated with IC + (C)RT, indicating a worse outcome for patients treated with one modality only. This is, again, consistent with the results of Morand and colleagues, who showed a higher risk of death for patients treated with single modality compared to patients treated with double or triple modality, as already mentioned above. In a 2019 literature review by Abdelmeguid and colleagues, IC was described as a factor that could improve outcome by reducing tumor size, allowing for complete tumor resection with clear margins and therefore as a promising part in the treatment of SNUC.[18]

As described above, IC gained in importance in the available literature and research about SNUC over the past years. But to our knowledge, there has been no meta-analysis with individual patient data analyzing the impact of IC, so far. Our results underline the importance of IC in the treatment algorithm of SNUC. The role of surgery has changed. As initial treatment it is less commonly used as it was before. However, it still plays an important role for patients who do not respond to IC, as they have a worse prognosis.[10] Of special importance are cases which initially present with a resectable disease. Having progressive disease under induction chemotherapy means losing the chance of R0-resection for these patients. Despite the recent promising results with IC, this must be discussed clearly with every individual treated for SNUC. It applies above all for patients with low-stage disease, which are underrepresented in our meta-analysis as well as in most cited studies (Tables S2 and 2). This selection bias as well as a certain publication bias following the "trend" of IC must be considered when interpreting our results and the results on IC in general.[35] Adequate staging and the ability to correctly assess the possibility of R0 resection remains crucial in terms of individual, patient-centered therapy of SNUC. The results of older studies emphasizing the benefit of surgery, as described above, should still be considered.

The present analysis has several limitations. For our literature search we used PubMed/MEDLINE only. This might have led to missed records published in a journal not listed in these databases; however, PubMed is the largest database concerning medical research and presumably the most relevant studies have been identified. All included studies were retrospective analyses, and a lack of data documentation was transmitted to our study. Furthermore, case reports were included which might cause a selection bias as these usually report very outstanding, specific cases. By excluding patients with metastases, recurrences, or palliative treatment, we were able to obtain a homogenous cohort. We focused on the treatment regime only and did not take into account other factors like lymph node involvement. However, there are potential confounders in treatment approaches, both surgical and radiotherapeutic. Different centers across the world might have different strategies in radiotherapy planning and extent of surgical resection. Furthermore, as SNUC is very rare, the chosen treatment regimens might often by based either on individual experience of the treating team or on individual patient factors. In order to reduce this selection bias and to make different treatments more comparable prospective randomized trials are necessary.

5 | CONCLUSION

The present analysis showed a significant better 5-year survival rate for patients treated with IC over the past 20 years and therefore supports the trend towards IC in recent years. Thus, IC should be considered in every SNUC patient. For further investigation, prospective studies are needed which focus on consistent variables and outcome in order to draw a comprehensive conclusion. Due to the low incidence of SNUC, studies must be comparable if certain statements want to be proven or rejected. In the future, feasible and affordable tests are needed to predict the response to IC in order to offer every patient the best, most suitable therapy.

AUTHOR CONTRIBUTIONS

Conceptualization: Manuela Burggraf and Johannes Döscher. *Data curation*: Manuela Burggraf, Noran Elawany, and Johannes Döscher. *Formal analysis*: Manuela Burggraf, Stephan Schiele, and Johannes Döscher. *Investigation*: Manuela Burggraf and Johannes Döscher. *Methodology*: Manuela Burggraf and Johannes Döscher. *Resources*: Francisco José Farfán López, Noran Elawany, and Stefan Schiele. *Software*: Manuela Burggraf. *Supervision*: Johannes Döscher, Rubens Thölken, and Johannes Zenk. *Visualization*: Manuela Burggraf and Johannes Döscher. *Writing – original draft*: Manuela Burggraf and Stephan Schiele. *Writing – review & editing*: Rubens Thölken, Francisco José Farfán López, Noran Elawany, Johannes Döscher, and Johannes Zenk. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee of Ludwig Maximilian University (LMU) of Munich (22-0963). Patient consent was waived due to retrospective character and a large percentage of the patients being deceased or lost to follow-up at the time of data collection.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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