Clinical characteristics and prognostic factors of sinonasal undifferentiated carcinoma: a multicenter study

Guillaume de Bonnecaze, MD, MSc[1], Benjamin Verillaud, MD, PhD[2], Leonor Chaltiel, PhD[3], Sylvestre Fierens, MD[4], Mark Chapelier, MD[1], Cécile Rumeau, MD, MSc[5], Olivier Malard, MD, PhD[6], Marie Gavid, MD, MSC[7], Xavier Dufour, MD, PhD[8], Christian Righini, MD, PhD[9], Emmanuelle Uro-coste, MD, PhD[10], Michel Rives, MD[11], Christine Bach, MD[12], Bertrand Baujat, MD, PhD[13], François Janot, MD, PhD[14], Ludovic de Gabory, MD, PhD[4] and Sebastien Vergez, MD, PhD[1]

Background: **Sinonasal undifferentiated carcinoma (SNUC) is a very rare entity with a poor prognosis. Due to the lack of studies on the subject, evidence is lacking concerning its management.**

Methods: **A multicenter collaborative study was conducted to assess treatment strategy, oncological outcome, and prognostic factors.**

Results: **Definitive analyses focused on 54 patients with a majority of advanced stage; the 3-year overall survival (OS) and 3-year recurrence-free survival (RFS) rates were, respectively, 62.4% and 47.8%. During the follow-up, 18 patients (33.3%) died, 10 (18.5%) developed metastases, 7 had lymph-node involvement (13%), and 12 (22.2%) showed recurrence or local progression. In univariate analyses, treatment modalities associated with improved RFS were induction chemotherapy ($p = 0.02$) and intensity-modulated radiotherapy ($p = 0.007$). In the multivariate analyses, only induction chemotherapy ($p = 0.047$, hazard ratio [HR] = 0.39) was significantly associated with improved RFS.**

Conclusion: **Multimodal therapies including induction chemotherapy and intensity-modulated radiotherapy may improve the prognosis of SNUC; surgery might improve local control. Further multicenter studies are required.**

Key Words:
sinus cancer; sinonasal undifferentiated carcinoma; multicenter study; induction chemotherapy; multimodal approach

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Sinonasal undifferentiated carcinoma (SNUC) is characterized by low-level tumor differentiation and can be difficult to distinguish from other tumors of the sinonasal tract. The cancer is characterized by rapid progression, advanced locoregional disease, and a poor prognosis. Since

[1]*Department of Otorhinolaryngology–Head and Neck Surgery, University Hospital Rangueil-Larrey, Toulouse, France;* [2]*Department of Otorhinolaryngology–Head and Neck Surgery, University Hospital Lariboisière, Paris, France;* [3]*Biostatistics Department, L'Institut Universitaire du Cancer de Toulouse-Oncopole (IUCT-Oncopole), Cancer Institute, Toulouse, France;* [4]*Department of Otorhinolaryngology–Head and Neck Surgery, University Hospital Pellegrin, Bordeaux, France;* [5]*Department of Otorhinolaryngology–Head and Neck Surgery, University Hospital of Nancy, Nancy, France;* [6]*Department of Otorhinolaryngology–Head and Neck Surgery, University Hospital Nantes, Nantes, France;* [7]*Department of Otorhinolaryngology–Head and Neck Surgery, University Hospital Saint-Etienne, Saint-Priest-en-Jarez, France;* [8]*Department of Otorhinolaryngology–Head and Neck Surgery, University Hospital Poitiers, Poitiers, France;* [9]*Department of Otorhinolaryngology–Head and Neck Surgery, University Hospital Grenoble, Grenoble, France;* [10]*Department of Pathology, IUCT-Oncopôle, Cancer Institute, Toulouse, France;* [11]*Radiation Oncology Department, IUCT-Oncopôle, Cancer Institute, Toulouse, France;* [12]*Department of Otorhinolaryngology–Head and Neck Surgery, Hopital Foch, Suresnes, France;* [13]*Department of Otorhinolaryngology–Head and Neck Surgery, Tenon Hospital, Paris-Est University, Paris, France;* [14]*Department of Otorhinolaryngology–Head and Neck Surgery, Institut Gustave Roussy, Villejuif, France*

Correspondence to: Guillaume de Bonnecaze, MSc, PhD, Otorhinolaryngology, Head and Neck Surgery Department, University Hospital Toulouse, Rangueil-Larrey Hospital, 24 Chemin de Pouvourville, 31059, Toulouse, France; e-mail: debonnecaze.g@chu-toulouse.fr

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Frierson et al.[1] initially described SNUC in 1986, several case studies and small case series have explored the outcomes of the disease. SNUC is both rare and aggressive; information on optimal treatment is thus limited. Furthermore, misdiagnosis is common, being more so in the past. A recent meta-analysis found only 167 documented cases of SNUC since 1986.[2] In 2016, Kuan et al.,[3] using the Surveillance, Epidemiology, and End Results (SEER) database, presented interesting data on SNUC prognostic factors and treatment outcomes. In univariate analysis, both surgery and radiation therapy were associated with improved overall survival (OS) and disease-free survival (DFS); multivariate analysis showed that this was also the case for patients with lower Kadish scores undergoing radiation therapy. However, several issues remain, including the optimal order of treatments, the role of surgical resection, and the preferred radiation treatment. Also, few prognostic factors have been defined. Here, we analyzed the outcomes of SNUC patients referred to the French Rare Head-and-Neck Cancer Expert Network (REFCOR). The REFCOR is a multidisciplinary group composed of ear, nose, and throat surgeons, oncologists, radiotherapists, neuroradiologists, and pathologists drawn from 42 tertiary French referral centers. REFCOR maintains a database of accurately identified rare head-and-neck cancers of the larynx, salivary glands, and sinonasal cavities.

The principal objective of this study was to describe the oncological outcomes of a cohort of SNUC patients followed in 13 French centers since January 2007. Our secondary objective was to identify prognostic factors of DFS.

Patients and methods

Ethical considerations

Our study adhered to all ethical considerations of the Declaration of Helsinki. Informed consent was obtained from all participants. The institutional review boards of the French Rhinological Society and REFCOR approved the study.

Study design/inclusion criteria

This was a retrospective study using prospectively collected data of patients treated with curative intent. SNUC patients logged in the REFCOR database between January 2007 and June 2014 were selected. Data harvesting, to ensure patient anonymity, was performed in each hospital, either by individual physicians or clinical research technicians or associates.

The database contains information on demographics, staging, extent of disease, treatment strategies, and survival. Only first-course treatments were included in analysis; these included all treatments recorded in plans that were in fact instituted prior to disease progression or recurrence.

Exclusion criteria

Patients were excluded if they were lost to follow-up or if their treatment status was unknown (missing data). We also excluded patients lacking 2 pathology reviews performed by at least 1 expert pathologist (a REFCOR member). Patients receiving palliative treatment only were also excluded.

Statistical analyses

Categorical variables are expressed as frequencies with percentages, and continuous variables as medians with ranges. Survival times were calculated from the dates of diagnosis. OS and recurrence-free survival (RFS) were assessed using the Kaplan-Meier method, with 95% confidence intervals (CIs). The first-event definitions included metastasis, node involvement, recurrence or local progression, death during the RFS period, and death within the OS period. Patients who were recurrence-free or alive at the time of last follow-up were censored. Univariate analyses were performed using the log-rank test to evaluate categorical variables. Cox proportional hazards model was used for multivariate analyses; we derived hazard ratios (HRs) with 95% CIs. Factors significant on univariate analyses ($p < 0.05$) were then subjected to multivariate analyses. Following Concato et al.,[4] when performing multivariate analysis, we included 1 variable per 10 events (recurrences), focusing on clinically relevant parameters. Comorbidity was classified using the World Health Organization (WHO) system; 0 = no comorbidity; 1 = cardiovascular disease, dementia, chronic pulmonary disease, rheumatological disease, a peptic ulcer, mild liver disease, or diabetes; and 2 = diabetes with chronic complications, hemiplegia or paraplegia, renal disease, moderate or severe liver disease, or acquired immune deficiency syndrome (AIDS). Patients were classified by tumor stage (T-stage: T1, T2, T3, T4a, T4b, and TX); node stage (N-stage: N0, N1, N2, N3, and NX); and metastasis stage (M-stage: M0, M1, and MX) according to the seventh edition of the American Joint Committee on Cancer staging[5] and the modified Kadish staging system.[6]

Results

Clinical characteristics and treatment modalities

The REFCOR database contained reports on 73 patients with primary diagnoses of SNUC. Five patients were excluded because of erroneous diagnoses: 1 had nuclear protein in testis (NUT) midline carcinoma, 2 had Epstein-Barr virus (EBV)-associated nasopharyngeal carcinomas with sinonasal extensions, and 2 had non-carcinomatous tumors. Seven patients were excluded because of missing data and 7 received only palliative care. Our final, definitive statistical analyses focused on 54 patients. Patient characteristics are shown in Table 1. The mean patient age was 54 years (range: 27 to 81 years), and males predominated (male/female ratio = 1.6). The median follow-up time was 43 months (95% CI, 29 to 48 months). Tobacco smoking was recorded in 34% of cases, and alcohol abuse in 15%. Only 5 patients exhibited immunodeficiencies; 3 had type 2 diabetes without complications and 1 had mild

TABLE 1. Demographic characteristics of patients with sinonasal undifferentiated carcinoma (n = 54)

Characteristic	Value
Age	
Mean (years)	54
Range (years)	27–81
≤55 years, n (%)	30 (55.6)
>55 years, n (%)	24 (44.4)
Gender, n (%)	
Male	33 (61.1)
Female	21 (38.9)
Tobacco smoker, n (%)	
Yes	29 (65.9)
No	15 (34.1)
Missing data	10
Alcohol abuse, n (%)	
Yes	8 (14.8)
No	46 (85.2)
Immunodeficiency, n (%)	
Yes	5 (9.3)
No	49 (90.7)
WHO score, n (%)	
0	32 (84.2)
1	4 (13.2)
2	1 (2.6)
Missing data	17
Primary site, n (%)	
Ethmoid sinus (n = 49)	43 (87.8)
Maxillary sinus (n = 49)	7 (14.3)
Frontal sinus (n = 49)	2 (4.1)
Sphenoid sinus (n = 49)	1 (2)
Other site (inferior turbinate)	1
Missing data	4
AJCC T, n (%)	
T1	1 (1.9)
T2	3 (5.8)
T3	9 (17.3)
T4	39 (75)
Missing data	2
AJCC N, n (%)	
N0	40 (76.9)
N+	12 (23.1)
Missing data	2
Modified Kadish stage, n (%)	
A	2 (3.9)
B	10 (19.6)
C	30 (58.8)
D	12 (17.6)
Treatment modalities, n (%)	
Surgery + RT	6 (11.1)
CT + RT	29 (53.7)
Surgery + RT + CT	14 (25.9)
Other	5 (9.3)
Induction chemotherapy, n (%)	
Yes	26 (55.3)
No	21 (44.7)
Missing data	7
Radiotherapy (n = 50), n (%)	
IMRT	31 (63.3)
Conventional	18 (36.7)
Missing data	1
Surgery, n (%)	23 (42.6)
Endoscopic approach	10
External approach	13
Margins, n (%)[b]	
R0	14
R1	5
R2	3
Missing data	1

AJCC = American Joint Committee on Cancer; AJCC N = lymph nodes affected; AJCC T = tumor size; CT = chemotherapy; IMRT = intensity-modulated radiation therapy; R0/1/2 = resection margin score; RT = radiation therapy; WHO = World Health Organization.

liver disease attributable to hepatitis B infection. All such patients had a WHO classification of 1. The final patient, who had diabetes with chronic complications and AIDS, had a WHO classification of 2. All patients were treated with curative intent. Thirteen patients had early-stage disease (stage I to III) and 39 had late-stage tumors (stage IV). The 2 most commonly used treatment modalities were

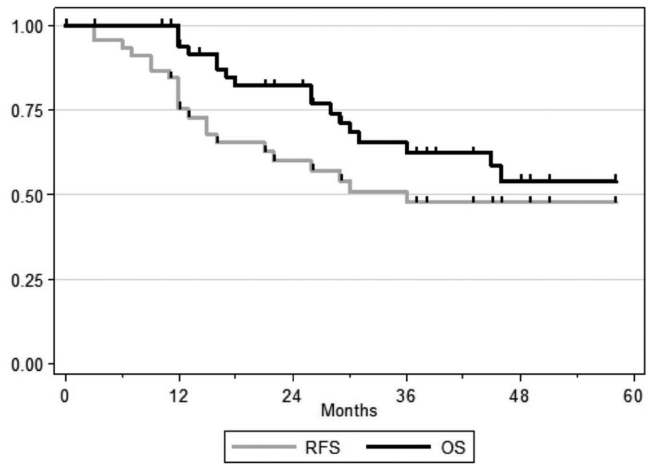

FIGURE 1. Kaplan-Meier estimates of overall and recurrence-free survival of 54 patients with sinonasal undifferentiated carcinoma. OS = overall survival; RFS = recurrence-free survival.

surgery with adjuvant chemoradiotherapy, and chemoradiotherapy alone. In total, patients underwent surgical resection: 13 via an open approach (4 patients of stage T3 and 9 of stage T4) and 10 via an endoscopic approach (1 patient of stage T1, 2 patients of stage T2, 3 patients of stage T3, and 4 patients of stage T4a). Tumor-free margins were obtained in 14 patients; dura mater invasion most commonly accounted for positive margins.

In total, 45 patients underwent chemotherapy (83%); 26 had induction chemotherapy followed by surgery with or without concurrent chemoradiotherapy, 12 had concurrent chemoradiotherapy and 7 had surgery followed by adjuvant chemoradiotherapy. The choice of the chemotherapy agent was at the discretion of the treating medical oncologist, and differed among centers: the most frequent form of induction chemotherapy was cisplatin + fluorouracil (5FU) + docetaxel and the main adjuvant therapy was cisplatin + etoposide. Medication dosages were sometimes varied for patients with poor WHO scores.

In total, 50 patients (94%) received radiotherapy: 18 had conventional radiotherapy, and 31 had intensity-modulated radiation therapy (IMRT). The mean radiation dose was 70 Gy (range, 56 to 72 Gy). Only 3 patients underwent neck dissection but 23 underwent neck irradiation.

During follow-up, 18 patients (33.3%) died, 10 (18.5%) developed metastases, 7 exhibited lymph-node involvement (13%), and 12 (22.2%) developed recurrence or local progression. The 3-year OS and 3-year RFS rates were, respectively, 62.4% (95% CI, 45.0% to 75.6%) and 47.8% (95% CI, 31.3% to 62.5%) (Fig. 1).

Prognostic factors

Table 2 summarizes the prognostic factors included in univariate analyses. We included factors prognostic of both RFS and OS. In univariate analyses, T-stage, N-stage, Kadish stage, free margin status, orbital invasion, and skull-base involvement were not associated with RFS. No factor correlated with OS in univariate analysis.

Impact of treatment modalities

On univariate analyses, the treatment modalities associated with improved RFS were induction chemotherapy ($p = 0.02$; Fig. 2) and IMRT ($p = 0.007$; Fig. 3). Other treatments (even those that created free margins) did not significantly improve survival. OS tended to improve, albeit not significantly, when multiple modalities were used. In multivariate analyses, only induction chemotherapy (HR = 0.39; 95% CI, 0.15 to 0.99; $p = 0.047$) was significantly associated with RFS (Table 3). Kaplan-Meier curves for M0 patients receiving different treatment modalities are shown in Figure 4. On pairwise log-rank comparisons, concurrent chemoradiotherapy was associated with improved RFS compared to surgery plus radiation therapy or radiation therapy alone ($p = 0.01$).

Discussion

SNUC is a recently discovered and extremely rare malignancy; thus, no clear management guidelines exist. The general consensus is that aggressive multimodal therapy is appropriate, but this conclusion is limited by the small sample sizes of published studies. Thus, to explore such questions, larger population studies, such as those employing the REFCOR database, are helpful. In our present study tumor extent appeared to have no influence on survival; this is very different to what is observed in other sinonasal malignancies. Thus, we suggest that SNUC is aggressive even though the tumor may be relatively small and patients with low tumor-node-metastasis (TNM)-stage tumors are probably under-treated, often not receiving induction chemotherapy or multimodal therapy. Factors prognostic of SNUC remain unknown. Al-Mamgani et al.[7] reported contradictory findings from univariate analyses. They found that a 2-modality rather than 3-modality approach to treatment was appropriate. The presence of dural or orbital invasion, and the lack of surgical treatment, were significantly correlated with poor local control. The U.S. National Cancer Database indicates that significant prognostic factors may include age, health insurance status, T-stage, N-stage, and treatment modality.[8] In contrast, our results are in agreement with those of Reiersen et al.,[2] who explored the significance of tumor stage in SNUC patients using traditional Kadish staging (A, B, and C only); no survival difference was evident between patients of different stages. This is in contrast to the situation with other neuroendocrine tumors of the sinonasal tract, such as esthesioneuroblastoma, for which stage is an independent predictor of survival.[9,10] Clinical classification seems to be of limited utility when employed to predict SNUC prognoses. Molecular studies are required and few such studies have been performed to date. In 2014, Gray et al.[11] analyzed human papillomavirus status in 14 SNUC patients

TABLE 2. Univariate analyses of predictors and treatment modalities for recurrence-free survival of 54 patients with sinonasal undifferentiated carcinoma*

Parameters	Patients with ≥1 event (death, metastasis or recurrence)	Patients with recurrence-free survival (24 months)	two-years recurrence-free survival (%)[a]	*p*
Age				0.84
≤55 years	12	30	63.5	
>55 years	9	24	54.7	
Gender				0.29
Female	6	21	63.9	
Male	15	33	57.1	
WHO score				0.1
0	12	32	66.5	
>0	4	6	20.0	
AJCC T				0.43
T1/2/3	6	13	45.5	
T4	14	39	66.9	
AJCC N				0.12
N−	17	40	57.5	
N+	3	12	72.7	
Surgery				0.19
No	11	31	67.99	
Yes	10	23	48.12	
Margins				0.61
R0	6	14	43.64	
R1/2	4	8	57.14	
Radiotherapy				**0.006**
IMRT	9	31	73.78	
Conventional	11	18	39.68	
Chemotherapy				**0.03**
No	3	9	25.00	
Yes	18	45	63.38	
Induction chemotherapy				**0.02**
No	10	21	40.00	
Yes	8	26	73.17	
Skull base involvement				0.26
No	12	25	44.06	
Yes	9	22	75.48	
Orbital invasion				0.82
No	8	21	60.19	
Yes	13	26	58.91	

(Continued)

TABLE 2. Continued

Parameters	Patients with ≥1 event (death, metastasis or recurrence)	Patients with recurrence-free survival (24 months)	two-years recurrence-free survival (%)[a]	*p*
Treatment modalities				**0.01**
RT + CT	10	29	70.61	
Surgery + RT + CT	7	14	54.42	
Other	4	11	20.00	

*Bold values are significant.
[a]Percentages are _____.
[b]R0, no cancer cells seen microscopically at the resection margin; R1, cancer cells present microscopically at the resection margin (microscopic positive margin); and R2, gross examination by the naked eye shows tumor tissue present at the resection margin (macroscopic positive margin).
AJCC = American Joint Committee on Cancer; AJCC N = lymph nodes affected; AJCC T = tumor size; CT = chemotherapy; IMRT = intensity-modulated radiation therapy; R0/1/2 = resection margin score; RT = radiation therapy; WHO = World Health Organization.

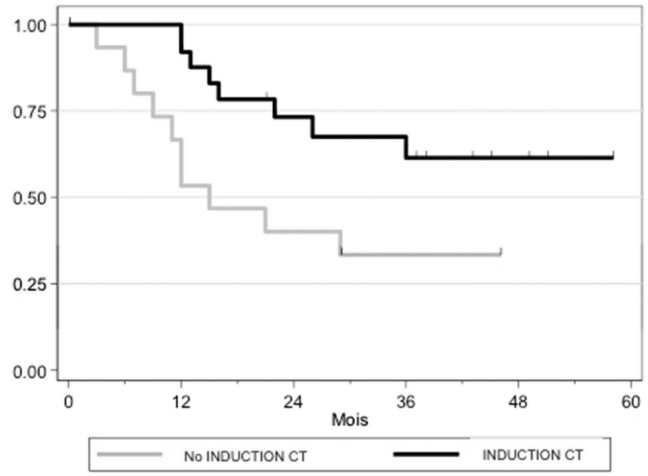

FIGURE 2. Kaplan-Meier curves of RFS of patients treated or not by induction chemotherapy. CT = chemotherapy; Mois = months; RFS = recurrence-free survival.

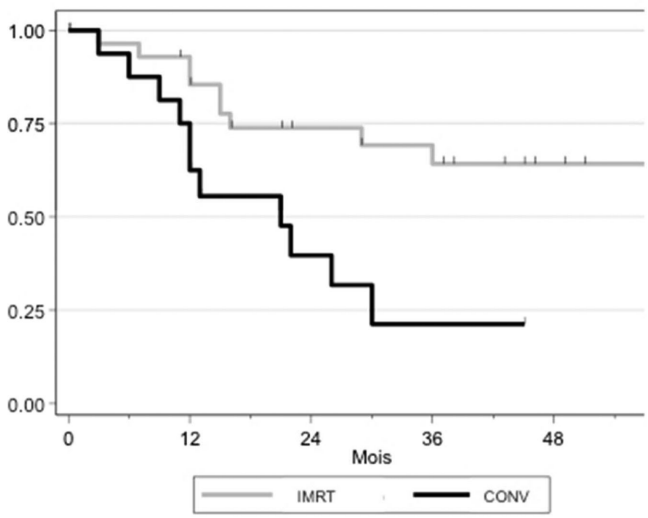

FIGURE 3. Kaplan-Meier curves of RFS of patients treated or not by IMRT. CONV = conventional radiotherapy; IMRT = intensity-modulated radiation therapy; Mois = months; RFS = recurrence-free survival.

treated in their institution. Eleven patients were positive for cytoplasmic p16 and exhibited significantly better OS than others.[11] An early case series of SNUC patients found that more than one-half did not survive for >5 years[12–15]; the published survival rates range from 20% to 63%.[16–19] However, our oncological results are encouraging; the 3-year OS and RFS were 62.4% and 47.8%, respectively, implying that SNUC prognosis remains poor but may be improved by application of multimodal treatments (radiation therapy, induction chemotherapy, and perhaps surgical resection affording free margins).

Regarding treatment modalities, we found that RFS improved significantly in patients who received chemotherapy, especially induction chemotherapy. We also highlight the current interest in IMRT, which should improve future outcomes. These 2 findings are novel; earlier large retrospective studies did not reach these conclusions. On multivariate analysis, Kuo et al.[8] found that outcomes after induction and adjuvant chemotherapy did not differ significantly.

SNUC treatment may exhibit a dose-response relationship: IMRT may allow the radiotherapy dose to be increased (further improving RFS), and the same probably applies to chemotherapy. Thus, dose-response relationships may be important in the context of SNUC.[20] The use of induction chemotherapy in an attempt to downstage the disease could be considered to improve local control, RFS, and OS. In addition, this would avoid any unnecessary delay in starting radiotherapy, especially in patients requiring immediate attention. Prior work showed that adjuvant therapy improved survival. The addition of radiation and/or chemotherapy improved survival but, statistically, no significant difference was apparent when either one or both treatments was applied to stage-C patients. However, it is possible that the relatively low numbers of patients examined in previous studies rendered it impossible to discern any difference.[2]

Our results show that the role of surgery in SNUC patients remains unclear. We found that patients who underwent surgery experienced more recurrence and mortality compared to those who received only concurrent

TABLE 3. Multivariate Cox regression analyses (n = 45)*

Characteristic	Overall survival		Recurrence-free survival	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Conventional RT	1.62 (0.58–4.51)	0.36	2.49 (0.96–6.43)	0.06
Induction CT	0.57 (0.20–1.61)	0.29	0.39 (0.15–0.99)	**0.047**

*Bold values are significant.
CI = confidence interval; CT = chemotherapy; HR = hazard ratio; RT = radiation therapy.

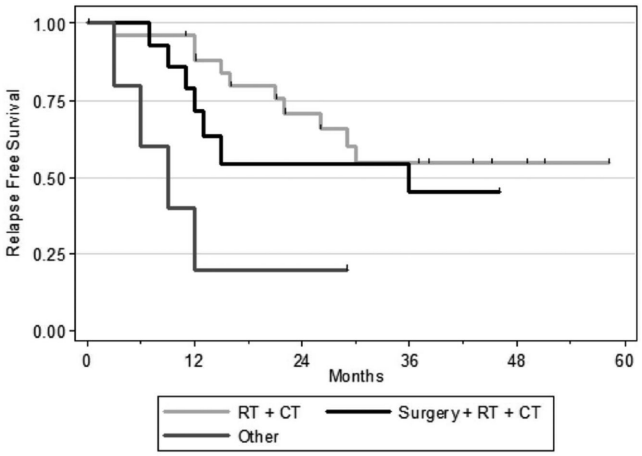

FIGURE 4. Kaplan-Meier curves for sinonasal undifferentiated carcinoma based on treatment modality. (n = 54). CT = chemotherapy; RT = radiation therapy.

chemoradiotherapy. We advance 2 possible explanations for this: first, most patients were diagnosed with late-stage tumors; and second, some centers could not perform endoscopic or endoscopically assisted resection, instead opting for alternative treatments such as concurrent chemoradiotherapy. A few authors have suggested that surgery aids local control.[7] In 2002, Jeng et al.[21] studied 36 patients, of whom 47% underwent tumor resection. These patients exhibited better prognoses than the nonsurgical group. Musy et al.[16] reported a trend toward improved survival in patients who underwent surgery, but this was not significant ($p = 0.076$). The cited authors also found residual tumors in 70% of surgical specimens after primary chemoradiation, suggesting that surgery should be an essential component of multimodal therapy. In terms of surgical margins, we found that the prognosis of patients with free margins was not significantly better than that of the other patients. However, we emphasize that patients with clear margins received substantially less adjuvant therapy (especially chemotherapy) than those with cancerous margins, and were thus probably undertreated. Finally, we consider that the evidence does not support the idea that chemoradiotherapy should be used as primary treatment, especially in those with early-stage (T1 to T3) disease.

The strengths of our study included long-term follow-up and analysis of certain comorbidities and treatment methods. The REFCOR database contains not only data indicating whether patients should undergo surgery, but also indications for the appropriate type of surgery (eg, the extent of resection, open vs endoscopic surgery, neck management) and/or the need for radiation (eg, timing, number of treatments). The database provides information on chemotherapy/radiation therapy regimens (eg, dose, type, number of cycles, sequences, chemotherapeutic agents), cause-specific survival, and locoregional failure rates. Unfortunately, the number of patients in each group was too low to allow statistical analysis; more patients should be included in future studies. However, it is unlikely that REFCOR case reports are inaccurate. As firm diagnostic criteria for SNUC were first reported only in 1986, we emphasize that expert histological review is essential before clinical data are analyzed to eliminate certain initial diagnoses. Some SNUCs may be initially misdiagnosed as NUT midline carcinoma, human papillomavirus (HPV)-associated or Epstein-Barr virus (EBV)-associated carcinoma, integrase interactor 1 (INI1)-deficient carcinoma, or Ewing sarcoma (a primitive neuroectodermal tumor expressing cytokeratin). The required immunohistochemical and in situ hybridization tools are not available in all pathology departments; some differences between our results and those of previous studies may be explained by the previous absence of any expert histological review.[3,22]

The limitations of our study were attributable to the rarity of SNUC; our patient numbers were low, prohibiting certain analyses (eg, by treatment modality sequencing or type of chemotherapy). Furthermore, only a few patients were followed for 5 years and ethical issues render it difficult to perform randomized studies investigating optimal treatment.

Conclusion

SNUC is a rare but aggressive sinonasal malignancy and multimodal therapies may improve prognosis. Induction chemotherapy and IMRT seem to predict improved DFS; however, any role for surgical resection remains unclear and surgery should be discussed on a case-by-case basis by surgeons and oncologists.

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