A retrospective review of non-intestinal-Type adenocarcinoma of nasal cavity and paranasal sinus.

Jinmei Li (✉ 1079612915@qq.com)

Southern Medical University Nanfang Hospital <https://orcid.org/0000-0001-5631-5819>

Bei Chen

Southern Medical University Nanfang Hospital <https://orcid.org/0000-0003-2553-3279>

Baofeng Li

PLA General Hospital of Southern Theatre Command: People's Liberation Army General Hospital of Southern Theatre Command

Jin Xu

Southern Medical University Nanfang Hospital

Feng Ye

Southern Medical University Nanfang Hospital

Yuting Xu

Southern Medical University Nanfang Hospital

Shuhua Wu

Southern Medical University Nanfang Hospital

Shuqiong Cheng

Southern Medical University Nanfang Hospital

Yinghao Lu

Southern Medical University Nanfang Hospital

Jian Guan

Southern Medical University Nanfang Hospital

Research Article

Keywords: Non-Intestinal-Type adenocarcinoma, surgery, radiotherapy, overall survival, Prognostic factors

Posted Date: April 19th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-419897/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: Adenocarcinomas of the nasal cavity and paranasal sinus, which includes non-intestinal adenocarcinoma of nasal cavity and paranasal sinuses (n-ITAC), are rare and heterogeneous. The diagnosis of n-ITAC is commonly achieved by exclusion, and several entities of considerable biological diversity are included. The literature on n-ITAC is rarely reported. It is reported in the literature that the prognosis of most sinonasal adenocarcinomas still remains poor. We hope that the analysis can provide recommendations for the treatment of n-ITAC.

Objective: To analyze the clinical characteristics, outcomes, prognostic factors and the best treatment of n-ITAC.

Methods: We located the time on the PACS system of Southern Hospital of Southern Medical University from February 1995 to February 2020. We searched the keyword " n-ITAC " and selected pathology. A total of 16 patients were searched, of which 2 were undiagnosed and 1 lost follow-up. Finally, we analyzed a total of 13 n-ITAC patients.

Results: The follow-up time was 34.6 months in average. The 1-year overall survival (OS) rate of G1 tumors was 100%, and the 3-year OS rate was 71.4%. The 1-and 3-year OS rates of G3 tumors were 50% and 16.7%, respectively. It was significantly associated with OS ($p=0.03$). Pathological grade is an independent prognostic factor. The OS of the surgery group was significantly better than that of the non-surgery group (1-year OS was 90.9% vs 0%, 3-year OS was 54.5% vs 0% $P < 0.001$). Surgery is an indispensable means of treatment and benefit. Patients with certain risk factors were given radical radiotherapy. The radiation dose for cases without surgery or with positive surgical margin was 66-70Gy/33F, and the dose for cases with negative margin was 60Gy/28F.

Conclusions: N-ITAC is a rare disease, and high-grade tumors have a poor prognosis. Surgery is still the main treatment for n-ITAC. Patients with no surgery, high-grade tumors and/or positive surgical margins should be given radical radiotherapy, and preventive radiotherapy in the drainage area of the lymph node at the same time. If the margins are negative, the radiation dose can be appropriately reduced. Whether combined with chemotherapy and targeted therapy needs further study.

Introduction

Malignant tumors of the sinonasal tract are relatively rare, accounting for 3% of all head and neck malignancies. Adenocarcinomas of various types account for 10–20% of all primary malignant tumors of the nasal cavity and paranasal sinuses [1]. According to the 4th edition of the WHO classification, these tumors can be distinguished into salivary and non salivary type [2], and the latter further divided into intestinal (ITAC) and non-intestinal type (non-ITAC) [3]. The latter is further subdivided into high-grade and low-grade lesions. Management of SNAC follows a rather standardized and internationally accepted paradigm, which consists of histological diagnosis, radiological staging, radical surgery, and adjuvant radiation therapy [4]. The literature focusing on n-ITAC is inadequate. Most published series of articles,

including homogeneous and relatively large series, are focused on ITAC, describing treatments, outcomes, and prognostic factors [5]. Regarding n-ITAC studies, most studies include all adenocarcinoma subtypes [6] or focus on low-grade tumors [7] or histological features [8].

Due to the lack of specific symptoms, diagnosis is usually made when the tumor has spread widely and invaded surrounding tissues (T_3 and T_4 diseases) [9]. The choice of treatment is to use open or endoscopic techniques for complete surgical resection when possible, and to perform adjuvant radiotherapy when the disease progresses to an advanced stage to enhance local control. Due to the limited risk of local metastasis (7%), the degree of standardization of systemic therapy is low, and elective neck dissection is not routinely performed [9, 10]. Overall, the prognosis of most sinus adenocarcinomas is still poor, mainly because the high risk of local recurrences which are often unresectable and re-irradiation is not possible because the procedure is often performed as part of the treatment at the first presentation of the tumor [9, 10]. Therefore, there is a great need to develop good treatment methods based on the research of rare tumors. In this retrospective study, we analyzed 13 consecutive patients with n-ITAC diagnosed in Nanfang Hospital of Southern Medical University from February 1995 to February 2020. The aim of this study was to report the clinical characteristics, outcomes, prognostic factors and the best treatment strategy of this particular group of patients.

Materials And Methods

Patients

We searched 16 patients but reviewed the medical records of 13 n-ITAC patients admitted to Nanfang Hospital of Southern Medical University in Guangzhou, Guangdong, China from February 1995 to February 2020. Epidemiologic and clinical data, surgical and histologic reports, preoperative and postoperative radiologic imaging, data on adjuvant therapy, and follow-up data were reviewed. The specific process is shown in Fig. 1.

The extent of the neoplasm was assessed preoperatively by clinical, endoscopic, and radiologic examinations, in particular, with multiplanar computed tomography (CT) and contrast enhanced magnetic resonance imaging. After imaging evaluation, endoscopic biopsies were performed under local anesthesia or pathological biopsies were obtained under general anesthesia. In cases of histologic analysis performed at an outside institution, the pathologic slides were reviewed at our institutions. The presence of local or distant metastasis was evaluated by bone scan, CT scan and neck ultrasound. All patients in the series were retrospectively staged using clinical, radiologic, and histopathologic evaluations according to the 8th edition of the American Joint Commission on Cancer (AJCC) TNM staging criteria in 2017.

Follow-up and statistical analysis

Follow-up duration was calculated from the date of diagnosis of n-ITAC to the date of last follow-up. The cutoff time was the date of the last contact of these patients or the date of last follow-up. The following

variables were analyzed with respect to survival: (1) patient factors: age, sex, smoking or not; (2) n-ITAC tumor factors: TNM stage and tumor site; (3) n-ITAC pathologic factors: grade and status of surgical margins; and (4) treatment of n-ITAC: surgery, radiotherapy, chemotherapy, or a combination of these strategies. Overall survival (OS) was calculated from the date of n-ITAC diagnosis to the date of either death or the last follow-up. OS rates were estimated using the Kaplan-Meier method and compared using the log-rank test. All statistical analyses were performed by using SPSS version 25.0 software (SPSS Inc., Chicago, IL, USA). P values less than 0.05 were considered statistically significant.

Results

Characteristics of patients with n-ITAC

The clinicopathologic characteristics of all 13 patients who were diagnosed with n-ITAC are listed in Table 1. Of patients, 11 were men (84.62%) and 2 were women (15.38%), resulting in a slight male predominance with a male-to-female ratio of 5.5. The mean age was 50 years (range, 33 ~ 72 years). No clear evidence of occupational predisposing factors was found; 6 patients were unemployed, 3 were staff, 1 was professional and technical, and 3 were unknown. Nasal obstruction and nosebleed were the most frequent symptoms, reported in 10 of 13 patients (76.9%), and a small number of them were accompanied by blurred vision, headache, loss of smell, tears, eye and facial swelling. Whereas cervical mass was observed in 1 (7.7%). Being found by microscope or naked eye was reported in 2(15.4%) of 13 patients. 10 (76.9%) arose n-ITAC only in the nasal cavity, and 1 (7.7%) in the nasal cavity and ethmoid sinus. 2 patients (15.4%) had lesions both in nasal cavity and maxillary sinus. Eleven of the 13 patients (84.6%) underwent surgery for n-ITAC; of the 11 patients, 6(54.5%) who underwent resection had negative margin and 5(45.5%) had positive margin. The tumors were staged according to the 8th edition of the American Joint Commission on Cancer (AJCC) TNM classification in 2017, as follows: 3 patients with $T_1 \sim T_2$ (23.1%), and 10 patients with $T_3 \sim T_4$ (76.9%). Regarding the grade of differentiation, 7 tumors were at a low grade (53.8%), and 6 were at a high grade (46.2%).

The pathology of n-ITAC

The pathology and immunohistochemistry of non-intestinal adenocarcinoma is shown in Fig. 2. Figure 2A represents a low-grade tumor. The cells are uniformly arranged in compact acinar, back-to-back, confluent glands, cystic space and papillary. They maintain a tall columnar to cuboidal arrangement without much layering. The cytoplasm is usually abundant, but the appearance is variable-basophilic, granular, mucous, eosinophilic, and cytolytic. The nuclear atypical is mild to moderate, with few mitosis. Figure 2B shows a high-grade tumor, showing significant nuclear polymorphism, nucleolar and mitotic activity. The signet ring cells and necrosis can often be seen.

Treatment of patients with n-ITAC

Of the 13 patients, 1 (7.7%) did not receive any treatment. 1 (7.7%) only received radiotherapy and chemotherapy. 11 (84.6%) people underwent surgery, of which 4 (36.4%) only underwent surgery, 3

(27.3%) who had surgery and received radiotherapy, 4(36.4%) had surgery, radiotherapy and chemotherapy (Fig. 3). Most of our patients undergo surgery, and the surgical method is basically endoscopic endonasal resection (EER). Of the 11 patients who underwent surgery, 6 (54.5%) achieved gross negative margins and 5(45.5%) had gross or microscopic positive margins. 6 patients were treated with intensity modulated radiotherapy(IMRT) in our hospital (Table 3). The radiation dose of primary focus and metastatic lymph node for cases without surgery or with positive surgical margin was 66-70Gy/33F, and the dose of cervical lymphatic drainage was 54-64Gy/30-33F in patients with negative margin, the tumor bed was irradiated for 60Gy/28F, and the lymphatic drainage area of the neck was irradiated for 50Gy/28F. The chemotherapy regimen was platinum 80mg/ square meters, once every 3 weeks. Only one patient received targeted therapy with cetuximab.

Prognostic factors for OS of patients with n-ITAC

The univariate analysis results showed that grade and treatment type of n-ITAC tumor were independent prognostic factors for OS (Table 2). The 1- and 3-year OS rates were 100% and 71.4% for patients with G1 and were 26.1% and 13.0% for patients with G3 ($P = 0.03$; Fig. 6A). In order to analyze the impact of surgery on the survival of patients, we divided the patients into surgical ($n = 11$) and non-surgical ($n = 2$) groups. The median follow-up time in the surgical group was 39 months. 10 patients are still alive, and the longest follow-up period is 98 months. 1 patient died and the OS was 15 months. The median follow-up time in the non-surgical group was 5 months. Both patients died, and the OS was 2 months and 8 months respectively. The 1-year OS rate and 3-year OS rate of the surgical group were 90.9% and 54.5%, while the non-operative group were both 0.0% ($P \leq 0.001$; Fig. 5A). In order to further analyze the effect of surgery combined with radiotherapy, the patients were divided into simple operation group and operation combined radiotherapy group. The 1- and 3-year OS rates for those not receiving radiation were 100% and 75%, and receiving radiation were 85.7% and 42.9% ($P = 0.414$; Fig. 5C). Using the average values as cutoff points, patient age was not a significant prognostic factor for OS. Moreover, the univariate analysis results showed that sex, smoking, TMN stage, margin status were also not significantly associated with OS (Fig. 4,5,6).

A multivariate analysis was performed comparing OS between sexes (male vs. female), T classification ($T_1 \sim T_2$ vs $T_3 \sim T_4$), N classification (N_0 vs $N_1 \sim N_2$), grading (G1 vs. G3), and surgery (yes vs no). Results of the Cox proportional hazards analysis are reported in Table 4.

Discussion

This retrospective study reports the clinical characteristics, outcomes, prognostic factors and the best treatment of a uniform cohort of 13 patients with sinonasal n-ITAC. To the best of our knowledge, there are few reports focusing on n-ITAC in the literature.

N-ITAC is a rare malignant tumor, defined as an adenocarcinoma without the histopathological features of sinus ITAC or salivary adenocarcinoma [11]. In the past 15 years, only 13 patients have been

diagnosed in our hospital, perhaps because it is a diagnosis of exclusion and a rare tumor. Although it is reported in the literature that n-ITAC mainly develops in the maxillary sinus, in our study, the most representative site of origin is the nasal cavity (12, 92.3%). There are reports in the literature that the etiology of ITAC is related to wood and leather dust [14], but no occupational or environmental factors are related to the development of n-ITAC. Moreover, our research has no clear evidence related to career incentives. According to the literature, the median age is around 50 years old, and the male prevalence is very high. In our study, men are also dominant, with a male-female ratio of 5.5, which may be related to smoking, but we do not have enough evidence to explain it ($P = 0.399$; Fig. 4D).

As far as we know, there are not many large-scale studies on ITAC and n-ITAC in the literature. Choussy et al. [15] considered 418 patients and reported that their 5-year OS rate was 64%. Bhayani et al. [16] considered 66 patients, 31 of whom had n-ITAC, and reported a 5-year OS rate of 65.9%. Orvidas et al. [17] considered 24 patients, 58% of whom had n-ITAC, and reported a 5-year OS rate of 58%. The research of Chen [6], Bignami [19] and others is the only research that independently analyzes n-ITAC. In the study of Bignami et al. [19], 5-year OS and DSS were 95.2%. The 1-year overall survival rate of the patients in our study was 76.9%, and the 3-year overall survival rate was 46.2%. We did not count the 5-year overall survival rate because the average follow-up time was shorter, only 34.6 months, but we have one patient with the longest follow-up which has been 98 months and is still alive. However, it is reported in the literature that the clinical outcome of patients with sinonasal carcinomas remains poor [9, 10, 18]. Therefore, we need a longer follow-up to further prove it. High-grade tumors have an aggressive course and are usually associated with a poor prognosis, with a 3-year survival rate of 20% [7, 12, 13]. Orvidas et al. [17] reported that patients with high-grade tumors are 5.4 times more likely to die from any cause than those with low-grade tumors ($P = 0.04$). In contrast, Choussy et al. [15] reported that there was no statistically significant difference in survival rates between low-grade and high-grade tumors. However, in our study the 1-year and 3-year OS rates of patients with low-grade tumors were 100% and 71.4%, respectively, but only 26.1% and 13.0% of patients with high-grade tumors ($P = 0.03$; Fig. 6A), which is statistically significant, indicating that high-grade tumors are an independent adverse factor affecting the prognosis of patients. From the chart, we can see that there is a trend in the survival curve of clinical stage (Fig. 6B) and T stage (Fig. 6C), which may be factors affecting the prognosis of patients. P value is not statistically significant and we think it is related to the number of cases.

According to reports in the literature, the main method of treatment is radical surgical resection with or without adjuvant radiotherapy. Endoscopic rhinoplasty has recently been promoted as the preferred surgical treatment for ITAC with correct planning and indications [20], with encouraging results and the advantage of reducing the incidence. Surgical therapy continues to be a mainstay for curative treatment. Some people argue that surgery alone is sufficient in patients with early tumors [16, 22, 23]. Bignami [19] et al. proposed that endoscopic transnasal approach is the preferred surgical method, and surgery combined with postoperative radiotherapy is the main treatment. [21] Some advocated that postoperative radiotherapy should be performed in all cases, regardless of stage or grade. Most cancers of the nasal cavity and paranasal sinuses present at later stages, often leading to the use of multimodality treatment [24–27]. Blanch et al. [28] proposed that no survival benefit from the addition of radiotherapy to surgery

for early-stage lesions. Conversely, for distant disease, radiation alone offered improved survival over no treatment at all, but also improved relative survival when added to surgery as a combination therapy. We found that the relative survival rate of patients with local diseases who received radiotherapy decreased. This finding is possibly due to bias in patient selection, since many patients who were treated with radiation were with high-grade and/or positive surgical margin tumors and therefore were treated with palliative therapy. Many patients have so large primary tumors (T3 and T4 diseases) at diagnosis that the surgical margin cannot be guaranteed to be negative. If there is no radiotherapy after surgery, the survival prognosis of patients may be even worse, so we think that apparent improvements were observed in patients with regional and/or distant disease. Despite separating patients by extent of disease, case-by-case differences certainly may result in the selection of one modality over another, and this certainly represents 1 of the limitations of this and other studies. The standard of care for the majority of these lesions continues to be surgery or surgery followed by adjuvant radiotherapy, with the use of radiation as a single modality offering questionable benefit. It has been reported in the literature [15, 29–31] that for ITAC and non-ITAC, the dosage is 30 fractions of 2 Gy, for a total of 60 Gy, with an extra boost of 6 Gy in case of presumed involved margins, delivered by intensity-modulated RT (IMRT) which combines a comparable or even better local tumor control and survival with a reduced treatment-related toxicity. In the above literature, the two types of adenocarcinoma were studied together, and three-dimensional and conformal radiation therapy were the main methods. The prognosis of non-intestinal type is poor, so our radiotherapy dose is slightly higher than that reported in the literature, and we all use intensity modulated radiotherapy (IMRT), which has the advantage of increasing the target dose without significantly increasing side effects [32–34]. There are many OAR in non-intestinal adenocarcinoma of head and neck, so we recommend intensity modulated radiotherapy (IMRT) with a dose of no less than 66 Gy. As for whether radiotherapy should be used to prevent cervical lymph node drainage, our patients were irradiated, because suspicious lymph nodes were often seen on images, and there were no obvious complications such as cervical lymphedema and fibrosis after radiotherapy. However, whether to prevent irradiation in the drainage area of cervical lymph nodes needs to be further studied.

Study has shown that sinus adenocarcinoma often exhibits EGFR overexpression, and mutations that determine the constitutive activation of the downstream signaling cascade of EGFR are rare, indicating that these tumors may be good candidates for anti-EGFR therapy [35]. Only one of our patients was tested for EGFR, which showed (++), and was given cetuximab targeted therapy. Since only 1 patient received targeted therapy, no clear recommendations could be given. We suggest that such patients can be tested for EGFR in the future, and if it is positive, it can be combined with targeted therapy to observe whether it can improve the survival benefits of patients. Since our patients seldom have combined chemotherapy, it is not clear whether systemic chemotherapy is beneficial or not.

Conclusion

ITAC is a rare type of tumor. High grade is an independent poor prognostic factor. Surgery is the optimal treatment, and negative surgical margins are the ultimate goal of benefiting patients. Patients with no

surgery, high-grade tumors and/or positive surgical margins should be given radical radiotherapy, and preventive radiotherapy in the drainage area of the lymph node at the same time. If the margins are negative, the radiation dose can be appropriately reduced. Whether combined with chemotherapy and targeted therapy needs further study.

Declarations

Author contributions: All authors contributed to the study conception and design. Jinmei Li: writing manuscript, collecting and analyzing data. Baofeng Li and Bei Chen: analyzing data, critically revised the final manuscript. Jin Xu: writing manuscript and searching for related literature. Feng Ye, Yuting Xu, Shuhua Wu, Shuqiong Cheng, Yinghao Lu, Jian Guan: searching for related literature. All authors read and approved the final manuscript and agree with its submission to the Journal of Neuro-Oncology.

Ethics and consent to participate: All include patients gave their oral informed consent. The study was approved by Medical Ethics Committee of Nanfang Hospital, Southern Medical University. We will keep patient information confidential.

Data availability: Available upon request.

References

1. Barnes L (1986) Intestinal-type adenocarcinoma of the nasal cavity and paranasal sinuses. *Am J Surg Pathol* 10:192–202. <https://doi.org/10.1097/00000478-198603000-00006>
2. Leivo I (2016) Sinonasal adenocarcinoma: update on classification, immunophenotype and molecular features. *Head Neck Pathol* 10:68–74. <https://doi.org/10.1007/s12105-016-0694-9>
3. El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ (2017) WHO Classification of Head and Neck Tumours. International Agency for Research on Cancer, Lyon
4. Rampinelli V, Ferrari M, Nicolai P (2018) Intestinal-type adenocarcinoma of the sinonasal tract: an update. *Curr Opin Otolaryngol Head Neck Surg* 26:115–121. <https://doi.org/10.1097/moo.0000000000000445>
5. Fiaux-Camous D, Chevret S, Oker N, TurriZanoni M, Lombardi D, Choussy O et al (2017) Prognostic value of the seventh AJCC/UICC TNM classification of intestinal-type ethmoid adenocarcinoma: systematic review and risk prediction model. *Head Neck* 39:668–678. <https://doi.org/10.1002/hed.24663>
6. Chen MM, Roman SA, Sosa JA, Judson BL (2015) Predictors of survival in sinonasal adenocarcinoma. *J Neurol Surg B Skull Base* 76:208–213. <https://doi.org/10.1055/s-0034-1543995>
7. Stelow EB, Jo VY, Mills SE, Carlson DL (2011) A histologic and immunohistochemical study describing the diversity of tumors classified as sinonasal high-grade nonintestinal adenocarcinomas. *Am J Surg Pathol* 35:971–980. <https://doi.org/10.1097/pas.0b013e31821cbd72>

8. Choi HR, Sturgis EM, Rashid A, DeMonte F, Luna MA, Batsakis JG et al (2003) Sinonasal adenocarcinoma: evidence for histogenetic divergence of the enteric and nonenteric phenotypes. *Hum Pathol* 34:1101–1107. <https://doi.org/10.1053/j.humpath.2003.08.024>
9. Castelnovo P, Turri-Zanoni M, Battaglia P, Antognoni P, Bossi P, Locatelli D (2016) Sinonasal malignancies of anterior skull base. Histology-driven treatment strategies. *Otolaryngol Clin North Am* 49:183–200. <https://doi.org/10.1016/j.otc.2015.09.012>
10. Robin TP, Jones BL, Gordon OM, Phan A, Abbott D, McDermott JD, Goddard JA, Raben D, Lanning RM, Karam SD (2017) A comprehensive comparative analysis of treatment modalities for sinonasal malignancies. *Cancer* 123:3040–3049. <https://doi.org/10.1002/cncr.30686>
11. Barnes L, Eveson JW, Reichart P, Sidransky D (eds) (2005) *Pathology and Genetics of Head and Neck Tumours*, 3rd edn. IARC Press, Lyon. <https://ovidsp.dc2.ovid.com/ovid-a/ovidweb.cgi?T=JS&PAGE=fulltext&D=ovft&AN=00003524-200685020-00001&NEWS=N&CSC=Y&CHANNEL=PubMed>
12. Heffner DK, Hyams VJ, Hauck KW, Lingeman C (1982) Low-grade adenocarcinoma of the nasal cavity and paranasal sinuses. *Cancer* 50:312–322. [https://doi.org/10.1002/1097-0142\(19820715\)50:2%3C312::aid-cncr2820500225%3E3.0.co;2-z](https://doi.org/10.1002/1097-0142(19820715)50:2%3C312::aid-cncr2820500225%3E3.0.co;2-z)
13. Knecht PP, Ah-See KW, vd Velden LA, Kerrebijn J (2001) Adenocarcinoma of the ethmoidal sinus complex: surgical debulking and topical fluorouracil may be the optimal treatment. *Arch Otolaryngol Head Neck Surg* 127:141–146. <https://doi.org/10.1001/archotol.127.2.141>
14. Bonzini M, Battaglia P, Parassoni D, Casa M, Facchinetti N, Turri-Zanoni M et al (2013) Prevalence of occupational hazards in patients with different types of epithelial sinonasal cancers. *Rhinology* 51:31–36. <https://doi.org/10.4193/rhino11.228>
15. Choussy O, Ferron C, Vedrine PO, Toussaint B, Liétin B, Marandas P et al (2008) Adenocarcinoma of ethmoid: a GETTEC retrospective multicenter study of 418 cases. *Laryngoscope* 118:437–443. <https://doi.org/10.1097/mlg.0b013e31815b48e3>
16. Bhayani MK, Yilmaz T, Sweeney A, Calzada G, Roberts DB, Levine NB et al (2014) Sinonasal adenocarcinoma: a 16-year experience at a single institution. *Head Neck* 36:1490–1496. <https://doi.org/10.1002/hed.23485>
17. Orvidas LJ, Lewis JE, Weaver AL, Bagniewski SM, Olsen KD (2005) Adenocarcinoma of the nose and paranasal sinuses: a retrospective study of diagnosis, histologic characteristics, and outcomes in 24 patients. *Head Neck* 27:370–375. <https://doi.org/10.1002/hed.20168>
18. Turner JH, Reh DD (2012) Incidence and survival in patients with sinonasal cancer: a historical analysis of population-based data. *Head Neck* 34:877–885. <https://doi.org/10.1002/hed.21830>
19. Bignami M, Lepera D, Volpi L, Lambertoni A, Arosio A, Pistochini A, Nicolai P, Castelnovo P. Sinonasal Nonintestinal-Type Adenocarcinoma: A Retrospective Review of 22 Patients. *World Neurosurg.* 2018;120:e962-e969. <https://doi.org/10.1016/j.wneu.2018.08.201>
20. Nicolai P, Schreiber A, Bolzoni Villaret A, Lombardi D, Morassi L, Raffetti E et al (2016) Intestinal type adenocarcinoma of the ethmoid: outcomes of a treatment regimen based on endoscopic surgery

- with or without radiotherapy. *Head Neck* 38(Suppl 1):E996–E1003.
<https://doi.org/10.1002/hed.24144>
21. Bogaerts S, Vander Poorten V, Nuyts S, Van den Bogaert W, Jorissen M (2008) Results of endoscopic resection followed by radiotherapy for primarily diagnosed adenocarcinomas of the paranasal sinuses. *Head Neck* 30:728–736. <https://doi.org/10.1002/hed.20771>
 22. Nicolai P, Castelnovo P, Lombardi D, Battaglia P, Bignami M, Pianta L et al (2007) Role of endoscopic surgery in the management of selected malignant epithelial neoplasms of the naso-ethmoidal complex. *Head Neck* 29:1075–1082. <https://doi.org/10.1002/hed.20636>
 23. Lund VJ, Chisholm EJ, Takes RP, Suárez C, Mendenhall WM, Rinaldo A et al (2012) Evidence for treatment strategies in sinonasal adenocarcinoma. *Head Neck* 34:1168–1178.
<https://doi.org/10.1002/hed.21770>
 24. Jakobsen MH, Larsen SK, Kirkegaard J, Hansen HS (1997) Cancer of the nasal cavity and paranasal sinuses. Prognosis and outcome of treatment. *Acta Oncol* 36:27–31.
<https://doi.org/10.3109/02841869709100727>
 25. Sakata K, Aoki Y, Karasawa K et al (1993) Analysis of the results of combined therapy for maxillary carcinoma. *Cancer* 71:2715–2722. [https://doi.org/10.1002/1097-0142\(19930501\)71:9%3C2715::aid-cnrcr2820710905%3E3.0.co;2-0](https://doi.org/10.1002/1097-0142(19930501)71:9%3C2715::aid-cnrcr2820710905%3E3.0.co;2-0)
 26. Harbo G, Grau C, Bundgaard T et al (1997) Cancer of the nasal cavity and paranasal sinuses. A clinico-pathological study of 277 patients. *Acta Oncol* 36:45–50.
<https://doi.org/10.3109/02841869709100731>
 27. Parsons JT, Mendenhall WM, Mancuso AA, Cassisi NJ, Million RR (1988) Malignant tumors of the nasal cavity and ethmoid and sphenoid sinuses. *Int J Radiat Oncol Biol Phys* 14:11–22.
[https://doi.org/10.1016/0360-3016\(88\)90044-2](https://doi.org/10.1016/0360-3016(88)90044-2)
 28. Blanch JL, Ruiz AM, Alos L, Traserra-Coderch J, Bernal-Sprekelsen M (2004) Treatment of 125 sinonasal tumors: prognostic factors, outcome, and follow-up. *Otolaryngol Head Neck Surg* 131:973–976. <https://doi.org/10.1016/j.otohns.2004.08.001>
 29. Choussy O, Ferron C, Vedrine PO, Toussaint B, Lietin B, Marandas P, Babin E, De RD, Reyt E, Cosmidis A, Makeieff M, Dehesdin D (2010) Role of radiotherapy in the treatment of nasoethmoidal adenocarcinoma. *Arch Otolaryngol Head Neck Surg* 136:143–146.
<https://doi.org/10.1001/archoto.2009.212>
 30. Van Gerven L, Jorissen M, Nuyts S, Hermans R, Vander Poorten V (2011) Long-term follow-up of 44 patients with adenocarcinoma of the nasal cavity and sinuses primarily treated with endoscopic resection followed by radiotherapy. *Head Neck* 33:898–904. <https://doi.org/10.1002/hed.21556>
 31. Cantu G, Solero CL, Mariani L, Salvatori P, Mattavelli F, Pizzi N, Riggio E (1999) Anterior craniofacial resection for malignant ethmoid tumors – a series of 91 patients. *Head Neck* 21(199905):185–191.
[https://doi.org/10.1002/\(sici\)1097-0347\(21:3%3C185:aid-hed1%3E3.0.co;2-8](https://doi.org/10.1002/(sici)1097-0347(21:3%3C185:aid-hed1%3E3.0.co;2-8)
 32. Dirix P, Vanstraelen B, Jorissen M, Vander Poorten V, Nuyts S (2010) Intensity-modulated radiotherapy for sinonasal cancer: improved outcome compared to conventional radiotherapy. *Int J*

33. Duprez F, Madani I, Morbee L, Bonte K, Deron P, Domjan V, Boterberg T, De GW, De Neve W (2012) IMRT for sinonasal tumors minimizes severe late ocular toxicity and preserves disease control and survival. *Int J Radiat Oncol Biol Phys* 83:252–259. <https://doi.org/10.1016/j.ijrobp.2011.06.1977>
34. Bhayani MK, Yilmaz T, Sweeney A, Calzada G, Roberts DB, Levine NB, DeMonte F, Hanna EY, Kupferman ME (2014) Sinonasal adenocarcinoma: a 16-year experience at a single institution. *Head Neck* 36:1490–1496.35. <https://doi.org/10.1002/hed.23485>
35. Franchi A, Innocenti DR, Palomba A, Miligi L, Paiar F, Franzese C, Santucci M. Low Prevalence of K-RAS, EGF-R and BRAF Mutations in Sinonasal Adenocarcinomas. Implications for Anti-EGFR Treatments. *Pathol Oncol Res.* 2014 Jul;203(3). <https://doi.org/10.1007/s12253-013-9730-1>

Tables

Table 1 The clinicopathologic characteristics of patients with n-ITAC.

Gender		No. of patients(%)
Male		11 (84.62)
female		2 (15.38)
Age (y)		
mean/range		50/33-72
Clinical symptoms and signs		
Nasal congestion	Nosebleed	10 (76.9)
Mass in the neck		1 (7.7)
Mass founded by microscopic or eyes		2 (15.4)
Primary site ^a		
Nasal cavity		12
Ethmoid sinus		1
Maxillary sinus		2
T classification		
T ₁ ~T ₂		3 (23.1)
T ₃ ~T ₄		10 (76.9)
N classification		
N ₀		8 (61.5)
N ₁ ~N ₂		5 (38.5)
TNM classification		
I~II		2 (15.4)
III~IV		11 (84.6)
Margin status ^b		
Positive		5 (45.5)
negative		6 (54.5)
Grade		
G1		7 (53.8)
G3		6 (46.2)

a: 1 of 13 patients had lesions in both the nasal cavity and the ethmoid sinus.

2 of 13 patients had lesions in both the nasal cavity and the maxillary sinus.

b: Only 11 of 13 patients underwent surgery.

Table 2 Association of overall survival with the characteristics of patients with n-ITAC.

Characteristic	Survival rate(%)		P
	1-year	3-year	
Sex			
Male	72.7	36.4	0.427
Female	100	100	
Age(years)			
≤50	85.7	57.1	0.399
>50	66.7	33.3	
Smoking			
Yes	66.7	33.3	0.399
No	85.7	57.1	
Surgery			
Yes	90.9	54.5	0.001
No	0	0	
Margin status			
Positive	80	60	0.221
negative	100	50	
Grade			
G1	100	71.4	0.030
G3	50	16.7	
T classification			
T ₁ ~T ₂	100	100	0.303
T ₃ ~T ₄	70	30	
N classification			
N ₀	87.5	50	0.903
N ₁ ~N ₂	60	40	
TNM stage			
I~ II	100	100	0.427
III~IV	72.7	36.4	

Table 3 The radiation dose of patients with n-ITAC.

Grade	Margin status	radiation dose
G1	negative	PTV _p : 60Gy/28F PTV1 : 50Gy/28F
G3	negative	PTV _p : 60Gy/28F PTV1 : 50Gy/28F
G3	NA	PTV _p : 70Gy/33F
G3	Positive (R1)	PTV _p : 70Gy/33F PTV _{nd.} : 70Gy/33F PTV1 : 64Gy/33F PTV2 : 59Gy/33F
G3	Positive (R2)	PTV _p : 70Gy/33F PTV _{nd.L.} : 70Gy/33F PTV1 : 60Gy/30F PTV2 : 54Gy/30F
G3	Positive (R2)	PTV _{nx} : 70Gy/33F PTV _{nd..} : 66Gy/33F PTV1 : 63Gy/33F

Table 4 Multivariate Analysis of Overall Survival.

Variable	Hazard Ratio	P Value
Sex, male vs female	2.03	0.96
T ₁ ~T ₂ vs T ₃ ~T ₄	0.35	0.93
N ₀ vs N ₁ ~N ₂	12.63	0.49
Grade	256.64	0.54
Surgery, yes vs no	0.00	0.62

Tumor staging according to the 8th edition of the American Joint Commission on Cancer (AJCC) TNM staging criteria in 2017.

Figures

Figure 1

The flowchart summarizes the process of screening, recording, and follow-up.

A

B

(A) Low-grade tumors;

(B) High-grade tumors

Figure 2

The pathology of n-ITAC.

Figure 3

Treatment and survival outcome of 13 patients with n-ITAC.

Figure 4

(A)overall survival (B)overall survival depending on age (C)overall survival depending on sex (D)overall survival depending on smoking.

Figure 5

(A)overall survival depending on surgery (B)overall survival depending on surgical margin (C)overall survival depending on treatment. R:radiotherapy; S:surgery; Combine:radiotherapy and surgery; SA:surgery alone; SR:surgery+radiotherapy

Figure 6

(A)overall survival depending on grade (B)overall survival depending on clinical stage (C)overall survival depending on T stage (D)overall survival depending on N stage.