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

JINMEI LI[1*], BAOFENG LI[2*], JIN XU[1*], HUIMIN WANG[1], QINGZU GAO[3], FENG YE[1], YUTING XU[1], SHUHUA WU[1], SHUQIONG CHENG[1], YINGHAO LU[1], JIAN GUAN[1] and BEI CHEN[1]

[1]Department of Radiation Oncology, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong 510515; [2]Department of Orthopaedics, General Hospital of Southern Theater Command of PLA, The First School of Clinical Medicine, Southern Medical University, Guangzhou, Guangdong 510010; [3]Department of Pathology, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong 510515, P.R. China

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Abstract. Non-intestinal adenocarcinoma of nasal cavity and paranasal sinuses (n-ITAC) is a heterogeneous tumor, which has rarely been reported in previous studies. Most high-grade n-ITAC has poor prognosis and there is a lack of classic therapeutic strategy. The present study examined using the PACS system of Nanfang Hospital of Southern Medical University between January 2000 and June 2020. It searched the keyword 'n-ITAC' and selected pathology. A total of 15 consecutive patients were searched. Finally, the present study analyzed a total of 12 n-ITAC patients. The follow-up time was 47 months on average. For low-grade (G1) tumors, 1 and 3-year overall survival (OS) rate were 100 and 85.7% respectively, while for high-grade (G3) tumors, 1 and 3-year OS rates were 80.0 and 20.0% respectively. Pathological grade may be an adverse prognostic factor (P=0.077). The OS of the surgery group was significantly superior to that of the non-surgery group (3-year OS was 63.6 vs. 0%, P=0.0009). Surgery is an indispensable means of treatment. The OS of patients with positive incisal margin was lower compared with that of patients with negative margin (P=0.186), suggesting that complete resection may be one of the prognostic factors. Patients with high risk factors received radiotherapy. The radiation dose was 66-70 Gy/33F for patients with positive margin or non-operation and was 60 Gy/28F for those with negative margin. Most of the patients received prophylactic irradiation of cervical area. Therefore, the prognosis of pathological high-grade n-ITAC is poor. Surgery is the most effective and an indispensable treatment for n-ITAC. For patients with high risk factors, surgery combined with radiotherapy may be a reasonable treatment. With regard to the cover range of radiotherapy, the primary tumor combined with lymph node drainage area is often used in Nanfang Hospital of Southern Medical University and the total dose of radiotherapy can be reduced if the surgical margin is negative.

Correspondence to: Dr Bei Chen, Department of Radiation Oncology, Nanfang Hospital, Southern Medical University, 1838 North Guangzhou Avenue, Guangzhou, Guangdong 510515, P.R. China
E-mail: beichentg7@163.com

*Contributed equally

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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 types (2) and the latter further divided into intestinal (ITAC) and non-intestinal type (n-ITAC) (3). n-ITAC is further subdivided into high-grade (G3) and low-grade (G1) lesions. G3 tumors have an aggressive course and are usually associated with a poor prognosis, with a 3-year survival rate of 20% (4-6). Patients with G3 tumors are 5.4 times more likely to succumb than those with low-grade tumors (P=0.039) (7). Moreover, 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) (8), which makes the treatment more difficult. At present, the options include open or endoscopic techniques for complete surgical resection, radical or adjuvant radiotherapy, chemotherapy and targeted therapy. However, 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 (9). Regarding n-ITAC studies, most studies include all adenocarcinoma subtypes (10) or focus on low-grade tumors (4) or histological features (11), but lack suggestions for classic treatment. Therefore, the present study analyzed 12 consecutive patients with n-ITAC diagnosed in Nanfang Hospital, Southern Medical University during the last 20 years. The aim of the present study was to explore the clinical characteristics, outcomes, prognostic factors and the best treatment strategy for this particular tumor.

Materials and methods

Patients. The present study was approved by the Ethics Committee of Nanfang Hospital of Southern Medical University (Guangzhou, China; approval no. NFEC-2022-448). A total of 15 patients with n-ITAC were examined using the PACS imaging system of Nanfang Hospital; the patients were admitted to Nanfang Hospital of Southern Medical University between January 2000 and June 2020. Finally, the images and medical records of 12 patients (excluding one with two primary tumors, one without pathological diagnosis and one without treatment) were obtained and reviewed. Of the patients, 10 were men (83.33%) and two were women (16.67%), resulting in a male-to-female ratio of 5.0. The mean age of the patients was 48 years (range, 33-65 years). 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 by clinical, endoscopic and radiologic examinations, in particular with multiplanar computed tomography (CT) and contrast enhanced magnetic resonance imaging. Endoscopic biopsies were performed under local anesthesia or pathological biopsies were obtained under general anesthesia. In cases of biopsies performed at an outside institution, the pathologic slides were reviewed at the Nanfang Hospital, Southern Medical University. Distant metastasis was evaluated by bone scan, CT scan and 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 (12).

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 following variables were analyzed with respect to survival: i) patient factors: Age, sex and smoking history; ii) tumor factors: TNM stage and tumor site; iii) pathologic factors: Grade (G1/G3) and status of surgical margins; and iv) treatment: Surgery, radiotherapy, chemotherapy, targeted therapy or a combination of these strategies. Overall survival (OS) was calculated from the date of n-ITAC diagnosis to the date of either mortality 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 using SPSS version 25.0 software (IBM Corp.). $P<0.05$ was considered to indicate a statistically significant difference.

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

Clinicopathologic characteristic	No. of patients (%)
Sex	
Male	10 (83.33)
Female	2 (16.67)
Age (years)	
Mean/Range	48/33-65
Smoking	
Yes	5 (41.67)
No	7 (58.33)
Clinical symptoms and signs	
Nasal congestion, Nosebleed	10 (83.33)
Mass founded by microscopic or macroscopically	2 (16.67)
Affected site[a]	
Nasal cavity	11
Ethmoid sinus	1
Maxillary sinus	2
T classification	
T_1-T_3	6 (50.0)
T_4	6 (50.0)
N classification	
N_0-N_1	8 (66.67)
N_2	4 (33.33)
TNM classification	
I-III	4 (33.33)
IV	8 (66.67)
Type of surgery[b]	
Endoscopic surgery	11 (100)
Open surgery	0 (0)
Margin status[b]	
Positive	5 (45.5)
Negative	6 (54.5)
Grade	
G1	7 (58.33)
G3	5 (41.67)

[a]1 of 12 patients had lesions in both the nasal cavity and the ethmoid sinus. 2 of 12 patients had lesions in both the nasal cavity and the maxillary sinus. [b]Only 11 of 12 patients underwent surgery. n-ITAC, non-intestinal adenocarcinoma of nasal cavity and paranasal sinuses.

Results

Characteristics of patients with n-ITAC. The clinicopathologic characteristics of all 12 patients who were diagnosed with n-ITAC are listed in Table I. Of the patients who were included in the present study, 10 were men (83.33%) and two were women (16.67%), resulting in a slight male predominance with a male-to-female ratio of 5.0. The mean age was 48 years (range, 33-65 years). No clear evidence of occupational predisposing factors was found; five patients were unemployed, three were office clerks, one was professional and technical, and three patients' occupations were unknown. Nasal obstruction and nosebleed were the most frequent symptoms, reported in 10 of 12 patients (83.33%) and a small number of them were accompanied by blurred vision, headache, loss of smell, tears, eye and facial swelling. Mass being found by microscope or macroscopically was reported in two (16.67%) of 12 patients. Of the patients, 9 (75.0%) exhibited n-ITAC only in the nasal cavity and one (8.3%) in the nasal cavity and ethmoid sinus. A total of two patients (16.7%) had

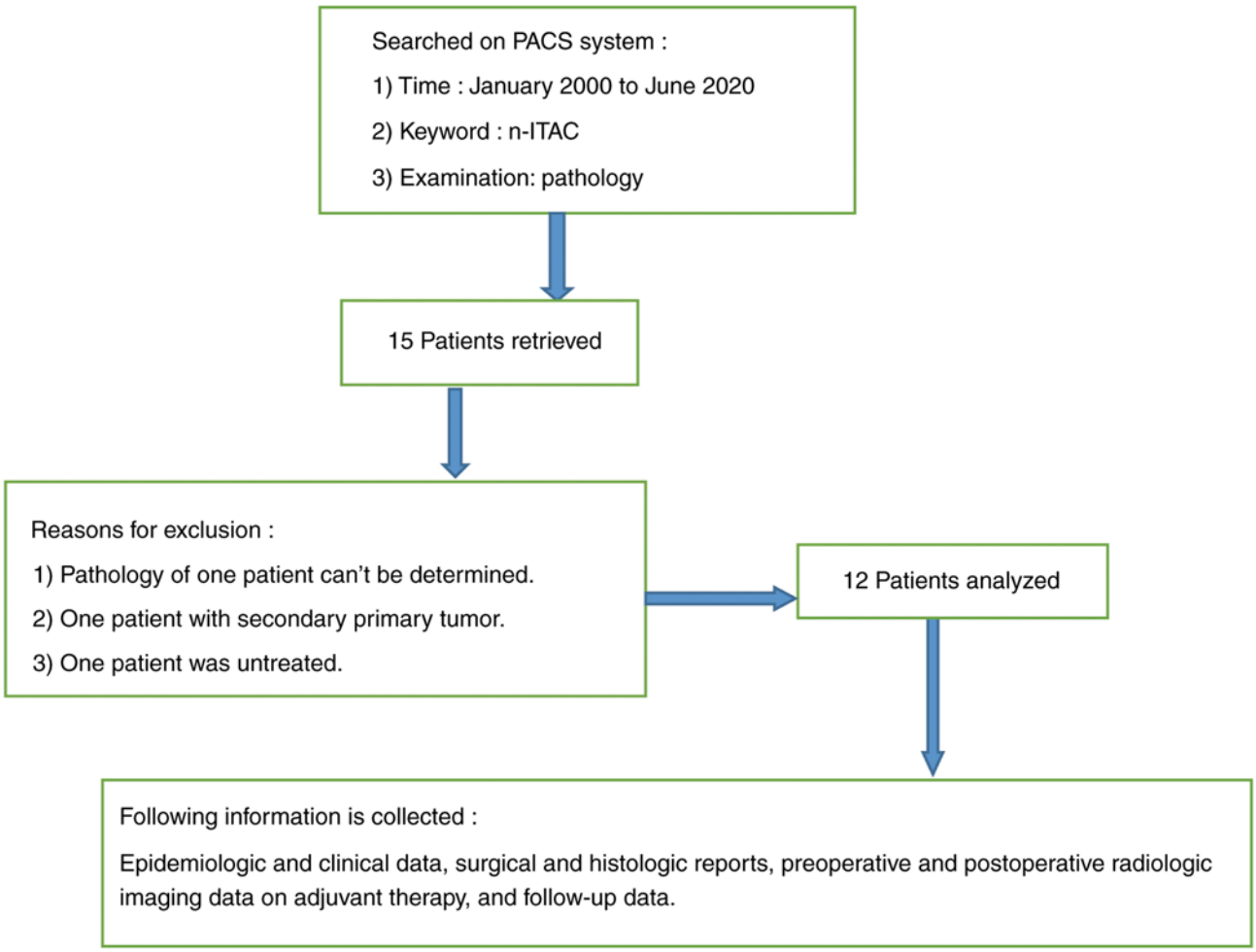

Figure 1. Flowchart summarizing the process of screening, recording and follow-up. n-ITAC, non-intestinal adenocarcinoma of nasal cavity and paranasal sinuses.

lesions in both the nasal cavity and maxillary sinus. Of the 11 patients (91.7%) who underwent surgery for n-ITAC, six (54.5%) who underwent resection had negative margin and five (45.5%) had positive margin. The tumors were staged according to the 8th edition of the AJCC TNM classification in 2017, as follows: Six patients with T_1-T_3 (50.0%) and 6 patients with T_4 (50.0%). Regarding the grade of differentiation, seven tumors were at a low grade (58.33%) and 5 were at a high grade (41.67%).

Pathology of n-ITAC. The pathology of non-intestinal adenocarcinoma came from our patients, including HE staining and immunohistochemistry, as shown in Fig. 2. Fig. 2A represents a low-grade tumor HE staining. 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 little mitosis. Fig. 2C shows a high-grade tumor HE staining, showing significant nuclear polymorphism, nucleolar and mitotic activity. The signet ring cells and necrosis can often be seen. Fig. 2B and D show immunohistochemical results of low-grade and high-grade tumors, respectively.

Treatment of patients with n-ITAC. Of the 12 patients, one patient (8.3%) received concurrent chemo-radiotherapy (platinum 80 mg/m^2, q3w) without surgery. The other 11 (91.7%) were treated surgically. The surgical method was basically endoscopic endonasal resection (EER). Of these 11, six (54.5%) achieved gross negative margins (R0) and five (45.5%) had gross or microscopic positive margins (R+) (Fig. 3).

Adjuvant treatment included radiation, chemotherapy and targeted therapy. A total of eight patients (66.7%) underwent radiation, including five with G3 tumors (one T_3 and four T_4) and three with G1 tumors (one T_1, one T_3 and one T_4). The technique was intensity-modulated radiotherapy (IMRT; Table II). Besides the primary tumor site, most patients also received prophylactic irradiation of the cervical area. The radiation dose for cases without surgery or with positive margin was relatively high: 66-70 Gy/33F for primary tumor and 54-64 Gy/30-33F for prophylactic cervical levels; while for patients with negative margin, the tumor bed was irradiated for 60 Gy/28F and the cervical prophylactic dose was 50 Gy/28F. A total of five patients received concurrent chemotherapy (platinum 80 mg/m^2, q3w). Only one patient received targeted therapy with cetuximab.

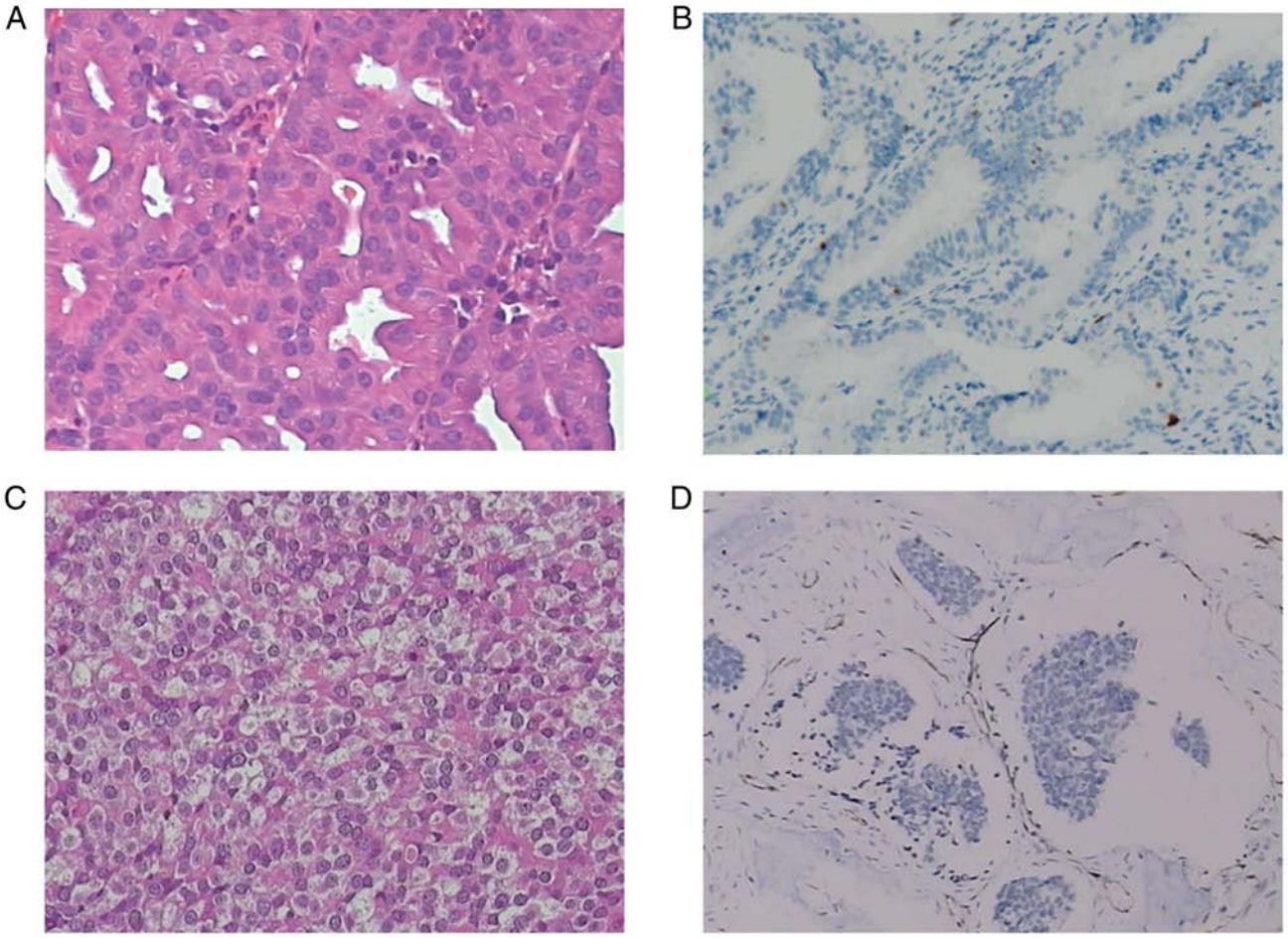

Figure 2. Pathology of n-ITAC. (A) HE staining of low-grade tumors (magnification, x400). (B) Immunohistochemistry of low-grade tumors (magnification, x200). (C) HE staining of high-grade tumors (magnification, x400). (D) Immunohistochemistry of high-grade tumors (magnification, x200). n-ITAC, non-intestinal adenocarcinoma of nasal cavity and paranasal sinuses; HE, hematoxylin and eosin.

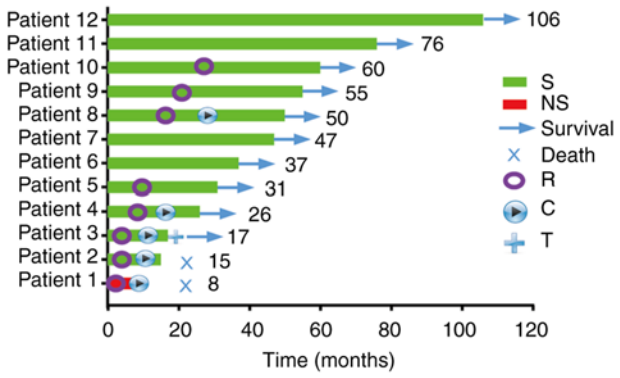

Figure 3. Treatment and survival outcome of 12 patients with n-ITAC. The time shown is the patient's survival or follow-up time. n-ITAC, non-intestinal adenocarcinoma of nasal cavity and paranasal sinuses; S, surgery; NS, no surgery; R, radiotherapy; C, chemotherapy; T, targeted therapy.

Prognostic factors for OS of patients with n-ITAC. Mean follow-up time was 47 months (range, 17-106 months) and no patients were lost to follow-up. At the time of the analysis, 10 of 12 patients (83.3%) were alive with no evidence of disease (NED) and 2 patients (16.7%) succumbed to the disease. One patient (8.3%) treated with radiotherapy and chemotherapy and whose tumor was stage T_4, grade G3, succumbed to the disease after 8 months. One patient (8.3%) treated with surgery, radiotherapy and chemotherapy, whose tumor was T_4, grade G3, and positive surgical margins (R2) succumbed to the disease after 15 months. Of the five patients with positive incisal margin, four patients received radiotherapy and the median OS was 50 months.

The univariate analysis results showed that grade and treatment type of n-ITAC tumor were prognostic factors for OS (Table III). The 1- and 3-year OS rates were 100 and 85.7% for patients with G1 and were 80.0 and 20.0% for patients with G3 (P=0.077; Fig. 4A). In order to analyze the impact of surgery on the survival of patients, the present study divided the patients into surgical (n=11) and non-surgical (n=1) groups. The median follow-up time in the surgical group was 47 months. Of the patients, 10 are still alive and the longest follow-up period is 106 months. One patient succumbed to the disease with an OS of 15 months. The only patient in the non-surgical group succumbed to the disease and their OS was 8 months. The 1-year OS rate and 3-year OS rate of the surgical group were 100 and 63.6%, while the non-operative group were both 0.0% (P=0.0009; 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 with radiotherapy group. The 1- and 3-year OS rates for those not receiving radiation

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

Grade	Margin status	Purpose of radiation	Radiation dose
G1	Negative	Adjuvant	PTV_p: 60 Gy/28F PTV1: 50 Gy/28F
G3	Negative	Adjuvant	PTV_p: 60 Gy/28F PTV1: 50 Gy/28F
G3	NA	Radical	PTV_p: 70 Gy/33F
G3	Positive (R1)	Adjuvant	PTV_p: 70 Gy/33F PTV_{nd}: 70 Gy/33F PTV1: 64 Gy/33F PTV2: 59 Gy/33F
G3	Positive (R2)	Adjuvant	PTV_p: 70 Gy/33F $PTV_{nd.L}$: 70 Gy/33F PTV1: 60 Gy/30F PTV2: 54 Gy/30F
G3	Positive (R2)	Adjuvant	PTV_p: 70 Gy/33F PTV_{nd}: 66 Gy/33F PTV1: 63 Gy/33F

n-ITAC, non-intestinal adenocarcinoma of nasal cavity and paranasal sinuses; PTV_p, planned target volume of primary lesion; PTV_{nd}, planned target volume of lymph nodes; PTV1, planned target volume of high-risk prevention area; PTV2, planned target volume of low-risk prevention area; $PTV_{nd.L}$, planned target volume of the left lymph node.

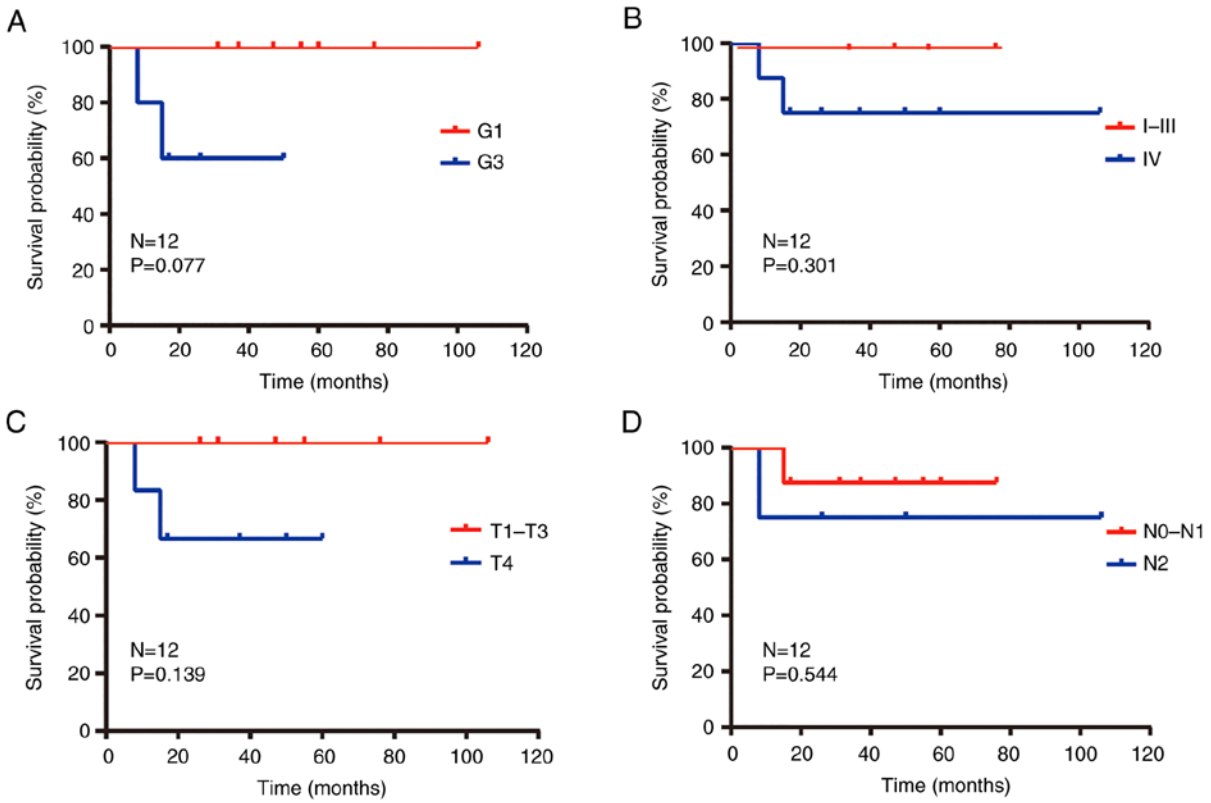

Figure 4. Prognostic factors of overall survival. (A) Overall survival depending on grade. (B) Overall survival depending on clinical stage. (C) Overall survival depending on t stage. (D) Overall survival depending on n stage.

were both 100% and for those receiving radiation were 100 and 42.9% (P=0.449; 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 (Figs. 4-6).

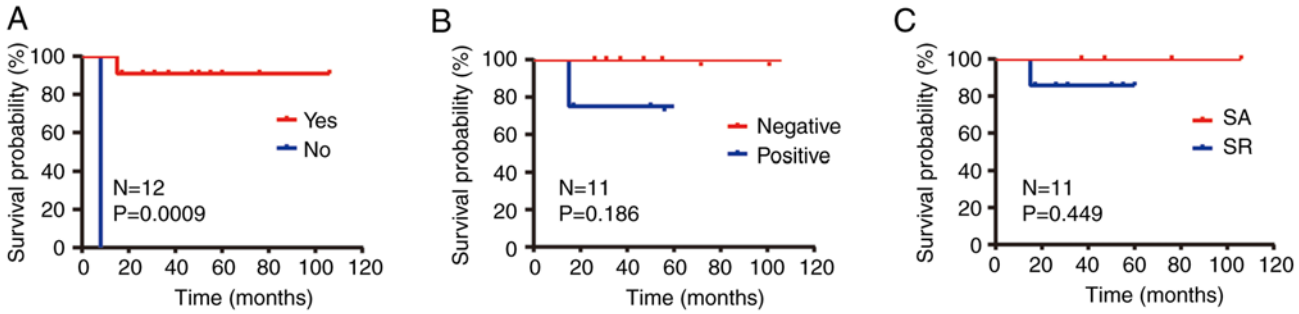

Figure 5. Prognostic factors of overall survival. (A) Overall survival depending on surgery. (B) Overall survival depending on surgical margin. (C) Overall survival depending on treatment. SA, surgery alone; SR, surgery + radiotherapy.

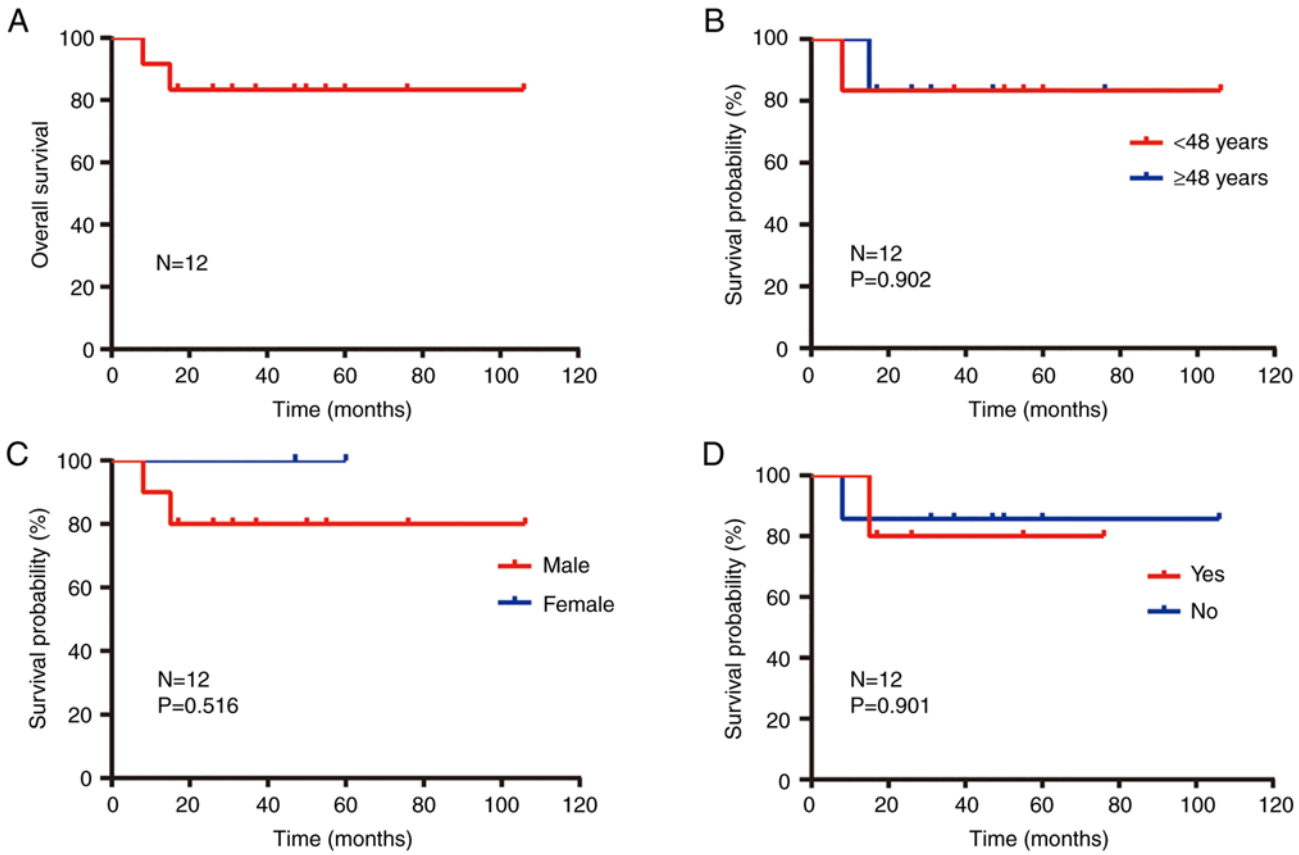

Figure 6. Prognostic factors of overall survival. (A) Overall survival. (B) Overall survival depending on age; (C) Overall survival depending on sex. (D) Overall survival depending on smoking.

Discussion

This retrospective study discussed the clinical characteristics, outcomes, prognostic factors and treatments of a uniform cohort of 12 patients with sinonasal n-ITAC. To the best of the authors' knowledge, there are few reports focusing on n-ITAC treatments and prognosis.

n-ITAC is a rare malignant tumor, defined as an adenocarcinoma without the histopathological features of sinus ITAC or salivary adenocarcinoma (13). In the past 20 years, only 14 patients have been diagnosed in Nanfang Hospital, Southern Medical University and 12 patients were analyzed in the present study. Although it was previously reported that n-ITAC develops mainly in the maxillary sinus, in the present study, the most representative site of origin was the nasal cavity (11, 91.67%). According to the literature (14), the median age was ~60 years old and the female prevalence was very high. In the present study, there was male predominance, with a male-female ratio of 5.0, which may be related to smoking, but there was not have enough evidence to explain it (P=0.901; Fig. 6D).

There has not been any large-scale study on n-ITAC due to its low incidence. Choussy *et al* (15) considered 418 patients of ITAC or n-ITAC and reported a 5-year OS rate of 64%. Bhayani *et al* (16) considered 66 patients, of whom 31 had n-ITAC and reported a total 5-year OS rate of 65.9%. Orvidas *et al* (7) considered 24 patients (58% with n-ITAC) and reported a 5-year OS rate of 58%, but there are no survival

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

Characteristic	Survival rate (%)		P-value
	1-year	3-year	
Sex			
Male	90.0	50.0	0.516
Female	100.0	100.0	
Age (years)			
<48	83.3	83.3	0.902
≥48	100.0	33.3	
Smoking			
Yes	100.0	40.0	0.901
No	85.7	71.4	
Surgery			
Yes	100.0	63.6	0.0009
No	0	0	
Margin status			
Positive	100.0	50	0.186
Negative	100.0	71.4	
Grade			
G1	100.0	85.7	0.077
G3	80.0	20.0	
T classification			
T_1-T_3	100.0	66.7	0.139
T_4	83.3	50.0	
N classification			
N_0-N_1	100.0	62.5	0.544
N_2	75.0	50.0	
TNM classification			
I-III	100.0	75.0	0.301
IV	87.5	50.0	

data for n-ITAC in their study. To the best of the authors' knowledge, the researches of Chen *et al* (10), Bignami *et al* (14) were the only two researches that focused only on n-ITAC. In the study of Chen *et al* (10), the 5-year disease specific survival for the nonintestinal type was 71.2%. In the study of Bignami *et al* (14), 5-year OS was 95.2%. The median follow-up time of the present study was 47 months and 1 and 3-year OS rate were 76.9 and 46.2% respectively. The poor prognosis of our patients was mainly due to the fact that most of the tumors were of high T stage (T_3-T_4). It is reported in the literature that the clinical outcome of patients with sinonasal carcinomas remains poor (8,17,18). The high-grade tumors of nonintestinal sinonasal adenocarcinomas have an aggressive course and are usually associated with a poor prognosis, with a 3-year survival rate of merely 20% (4-6). Orvidas *et al* (7) reported that patients with high-grade tumors are 5.4 times more likely to succumb to any cause than those with low-grade tumors (P=0.039). By 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 the present study the 1 and 3-year OS rates of patients with low-grade tumors were 100 and 85.7%, respectively, significantly higher than those of patients with high-grade tumors (80.0 and 20.0%; P=0.077; Fig. 4A). It was therefore indicated that high pathological grade may be an adverse prognostic factor. The pathological grade is related to the prognosis, but there was no statistical significance in multivariate analysis, which may be due to the small number of cases. In Bignami *et al* (14), the 5-year OS was 100% for pT_1, pT_2 and pT_3 and 83.3±1.52% for pT_{4a} and pT_{4b} (P=0.037). However, there is no significant relationship between N stage and prognosis, which may be due to the fact that there are lower probability of lymph node metastasis and a small number of cases in the disease. In the present study, there was a trend in the survival curve of clinical stage (Fig. 4B) and T stage (Fig. 4C), which may be factors affecting the prognosis of patients. P-value was not statistically significant and may be related to the number of cases.

The main therapeutic strategy for n-ITAC is radical surgery with or without adjuvant radiotherapy. Endoscopic rhinoplasty has recently been promoted as the preferred surgical treatment for ITAC with correct planning and indications (19), with encouraging results and the advantage of reducing the incidence. Surgical therapy continues to be a mainstay for curative treatment. The main controversial point is whether to add adjuvant therapy after surgery at present. Some individuals argue that surgery alone is sufficient in patients with early tumors (16,20,21). However, Bignami *et al* (14) proposed that endoscopic transnasal approach is the preferred surgical method and surgery combined with postoperative radiotherapy is the main treatment in cases of high-stage (T_3 and T_4) and high-grade tumors (22). Some advocate that postoperative radiotherapy should be performed in all cases, regardless of stage or pathological grade, as most cancers of the nasal cavity and paranasal sinuses present at later stages, often leading to the use of multimodality treatment (23-26). Blanch *et al* (27) proposed that there was no survival benefit from the addition of radiotherapy to surgery for early-stage lesions. In the present study, the OS of the surgery alone group was slightly higher compared with that of the surgery plus radiotherapy group (P=0.449). It is known that the indications of RT are high-grade tumor, positive surgical margin, high T stage and positive lymph node (14,22). Therefore, the patients in the combined radiotherapy group had more risk factors than the patients with operation alone, resulting in a significant bias in the baseline between the two groups. Unfortunately, no randomly controlled data were available and this certainly is a common limitation of the present and other studies. Prospective studies may be needed in the future to verify the value of radiotherapy. The above results only suggested that surgery combined with radiotherapy is also an alternative treatment mode for patients with high risk factors.

On the mode of radiotherapy, it has been reported in the literature (15,28-30) that for ITAC and n-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 positive margins. In the present study, the radiation dose for cases without surgery or with positive margin was relatively higher: 66-70 Gy/33F for primary

tumor and 54-64 Gy/30-33F for prophylactic cervical levels; while for patients with negative margin, the dose for tumor bed was 60 Gy/28F and the cervical prophylactic dose was 50 Gy/28F. The dose in the present study was higher because it only focused on n-ITAC, which was more aggressive than ITAC. On the technology of radiotherapy, it was delivered by IMRT or three-dimensional radiotherapy, the former provided a local control and survival as well as a reduced toxicity. In previous studies (16,31,32), three-dimensional and conformal radiation therapy were the main technology, while in the present study, all patients received IMRT, which has the advantage of increasing the target dose without significantly increasing side effects. With regard to the scope of exposure, the main controversial point is whether prophylactic cervical lymph node irradiation should be performed. The patients in the present study all received prophylactic cervical irradiation, as suspicious lymph nodes were often seen on images. Besides, the results of the present study showed no obvious complications such as cervical lymphedema and fibrosis after radiotherapy.

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 (33). Only one of the patients in the present study was tested for EGFR, which showed (++) and the patient was given cetuximab targeted therapy. Since only one patient received targeted therapy, no clear recommendations could be given. Since cetuximab has been validated to be an extremely effective agent in HNSCC and is included in the guidelines, it was hypothesized that targeted therapy such as cetuximab might be an effective candidate for treatment of n-TIAC. Since only a few of the patients in the present study received chemotherapy, it is not clear whether systemic chemotherapy was beneficial or not.

The limitations of the present study are as follows: First, the study was a retrospective analysis and the selection of patients was biased. Patients received both surgery and radiotherapy had more potential risk factors at the baseline. Second, because of the low incidence of n-ITAC, the number of cases was relatively small. Third, longer follow-up time is needed to further verify its conclusions.

n-ITAC is a rare type of tumor. Pathological high grade may be a 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.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JL, BL, JX, HW, QG, FY, YX, SW, SC, YL, JG and BC contributed to the study conception and design. JL wrote the manuscript and collected and analyzed data. BL and BC analyzed data and critically revised the final manuscript. JX wrote the manuscript and searched for related literature. HW, QG, FY, YX, SW, SC, YL and JG searched for related literature. All authors read and approved the final manuscript. JL and BC confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Nanfang Hospital of Southern Medical University (approval no. NFEC-2022-448). Due to the retrospective nature of the study, the committee agreed to exempt patients from informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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