

Definitive-intent (chemo)radiotherapy for sinonasal undifferentiated carcinoma**Running title: Treatment of sinonasal undifferentiated carcinoma**

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Abstract

Objective: The current study aimed to investigate the value of definitive-intent (chemo)radiotherapy in treating sinonasal undifferentiated carcinoma (SNUC) in a single institution.

Methods: The medical records of twenty-one patients with SNUC treated with definitive-intent (chemo)radiotherapy between 2011 and 2021 in one single institution were retrospectively reviewed. We analyzed the treatment efficiency and long-term survivals.

Results: A total of twenty-one patients were included in this cohort, twelve patients presented with T4 stage at diagnosis, and six in T1/T2, three in T3 stage. Nine patients (42.9%, 9/21) showed cervical lymph node metastases. All the patients were scheduled to receive definitive (chemo)radiotherapy and five patients had been performed surgery for residual tumor after (chemo)radiotherapy. 66.7% (14/21) of patients had a complete response after the completion of treatment, 23.8% (5/21) of partial response, one of stable disease, and one of progressed disease. The 3-year overall survival (OS) of the entire group were 86.2%, and the 3-year progress free survival (PFS) were 66.3%, respectively. 52.4% of the patients (11/21) presented orbit invasion, compared with patients without orbit invasion, the patients who had orbit invasion were not found to have significantly poor 3-year OS (87.5% vs. 83.3%, $p=0.38$) and PFS (75.0% vs. 55.3%, $p=0.59$).

Conclusions: Definitive-intent (chemo)radiotherapy could be the preferred treatment for patients with advanced SNUC, and salvage surgery should be performed for the lesions showing stable disease, progressed disease, or residual tumor.

Key words: Definitive-intent, chemoradiotherapy, sinonasal undifferentiated carcinoma, orbit invasion.

Advance in knowledge: The value of definitive chemoradiotherapy in treating sinonasal undifferentiated carcinoma.

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16 carcinoma.
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19 20 21 22 **INTRODUCTION**

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24
25 Sinonasal undifferentiated carcinoma (SNUC) was first described in 1986 by Frierson and his colleagues
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28 ^[1], and it was believed to originate from the Schneiderian epithelium of the nose and paranasal sinuses.

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30 In addition, SNUC also might arise as a second malignancy following radiotherapy (RT) for
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32 nasopharyngeal carcinoma. Nevertheless, the SNUC was typically negative for Epstein-Barr virus, which
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34 could be distinguished from nasopharyngeal carcinoma. SNUC with neuroendocrine features shares a
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36 common site of origin with the other sinonasal neuroendocrine tumors, but its natural histories appear to
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38 be significantly different from esthesioneuroblastoma. Compared with esthesioneuroblastoma, SNUC
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40 has higher rates of local and distant failure. Therefore, combined-modality therapy is recommended for
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42 these patients ^[2].
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50 SNUC showed aggressive biologic behaviors that easily invaded the adjacent critical organs such
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52 as orbit, skull base, and brain, which might seriously increase the treatment difficulty. Xu *et al.* ^[3]
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54 demonstrated that 42.9% of patients had orbital involvement at the time of presentation. Lin *et al.* ^[4]
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56 retrospectively reviewed 19 patients with SNUC and revealed that 74% of cases were staged in T4b,
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1 including 47% of orbital invasion, 53% of dural invasion, and 21% of intraparenchymal brain
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3 involvement. More advanced disease predicted a worse prognosis in SNUC. Workman *et al.* [5] reported
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5 that 85% of SNUC presented with stage IV disease, which the 2-year and 5-year disease-specific survival
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7 were 66% and 46%, respectively. Another study evaluating the outcomes based on the SEER database
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9 indicated that median OS and DSS were 1.9 and 2.9 years, respectively, and OS at 2, 5, and 10 years
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11 were 43%, 30%, 25% [6].
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17 Given its low incidence, there was no consensus on the optimal management of the disease, so that
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19 the treatment decisions were based on small retrospective series. A combination of radical surgery,
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21 radiotherapy, and chemotherapy appeared to enhance the survival rate. Existing research recognized the
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23 critical role played by surgery; however, in patients who achieved a favorable response to induction
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25 chemotherapy, definitive (chemo)radiotherapy results in improved survival compared with those who
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27 undergo traditional surgery [7]. Although some recent studies have been carried out to discuss the
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29 predictive value of induction chemotherapy to radiation therapy, it is still not known whether definitive
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31 (chemo)radiotherapy could substitute the surgery followed by adjuvant treatment. In this study, we
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33 attempted to investigate the value of definitive-intent (chemo)radiotherapy in the treatment of SNUC and
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35 the possibility of definitive (chemo)radiotherapy as an eye-sparing therapy for those patients with orbital
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37 involvement.
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50 **MATERIALS AND METHODS**

51 **Patients**

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53 Twenty-four patients with primary SNUC treated at the XXX from November 2011 to March 2021 were
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55 retrospectively reviewed. Three patients underwent complete tumor resection followed by adjuvant
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1 chemoradiation, two of whom were lost to follow-up and were therefore excluded from the analysis. All
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3 the patients were diagnosed with pathological confirmation of SNUC and be previously untreated. None
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5 of the patients had the proof of distant metastasis at initial diagnosis. All the patients are over 18 years
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7 and were treated with curative intent. Data collection was conducted, including the patients' medical
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9 histories, baseline characteristics, image findings, treatment modalities, and follow-up visit information.
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11 The diagnosis of SNUC was made by two pathologists at our hospital, using morphologic features and
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13 immunohistochemical analysis in all cases. Patients underwent computed tomography (CT) and/or
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15 magnetic resonance imaging (MRI) of the head and neck prior to the initial treatment. The study and data
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17 accumulation were carried out with approval from the Research Ethics Committee of XXX, and informed
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19 consent for the research was obtained from the patients.
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31 Treatment and evaluation

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33 Radiation oncologists contoured the gross tumor volume (GTV) by planning CT scans using MRI,
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35 CT, PET/CT, and endoscopy images. The clinical tumor volume (CTV) was expanded around GTV plus
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37 a margin of 5 to 10mm, with further modification to encompass all tissue infiltrated initially by the tumor,
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39 operation fields, and adjacent vital organs. The dose constraints for organs at risk were as follows: spinal
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41 cord ≤ 45 Gy; optic nerve ≤ 62 Gy; optic chiasm ≤ 60 Gy; and brainstem ≤ 54 Gy. The planning target volume
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43 (PTV) was then generated using a uniform 0.3 cm expansion beyond the borders of the GTV and CTV.
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50 All radiation treatments were delivered using 3-dimensional conformal radiotherapy (3D-CRT),
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52 IMRT, or volumetric intensity-modulated arc therapy (VMAT). The average prescribed dose for the
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54 primary tumor was 64.5-71.3Gy of 2.0-2.25Gy/fractions (5 fractions per week). The average dose for
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56 lymph node was 64-70Gy of 2.0-2.2Gy/fractions, and the elective nodal irradiation of the neck was
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1 delivered with a dose of 50-60Gy.

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3 Induction chemotherapy (IC), concurrent chemotherapy (CCRT), and their combination were the main
4 chemotherapy modes. Induction chemotherapy was delivered for patients with stage II-IV or with
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6 cervical lymph node metastasis. The protocols of IC were mainly TPF (docetaxel + cisplatin + 5-FU)
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8 and TP (docetaxel + cisplatin), and PF (cisplatin + 5-FU) and GP (gemcitabine + cisplatin) were also
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10 commonly used. Cisplatin was administered as concurrent therapy at a dosage of 75mg/m² every three
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12 weeks, and nedaplatin was used as an alternative. Endoscopic endonasal resection was performed for
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14 patients who had residual tumors after three months of the completion of treatment.
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22 Both before treatment and three weeks after the IC, we evaluated the tumor response with MRI and
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24 CT scan of the head and neck, using the Response Evaluation Criteria in Solid Tumors Group criteria
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26 version 1.1. We also evaluated the tumor regression during the radiotherapy and within three months of
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28 the treatment. Treatment results were assessed by complete physical examination, MRI or CT scan of the
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30 head and neck, chest CT scan, and abdominal ultrasound scan three months after radiotherapy. Patients
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32 were then followed up every three months for the first two years, every six months for the next three
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34 years, and yearly thereafter.
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45 Statistical analysis

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47 Statistical analyses were performed using IBM SPSS version 26.0 (IBM, Armonk, NY, USA) and
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49 GraphPad VR Prism 8.0 (GraphPad Software Inc., La Jolla, CA, USA). Kaplan-Meier analysis was used
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51 to determine overall survival (OS) rate, progression-free survival (PFS) rate. Univariate analyses of
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53 factors concerning OS and PFS rates were performed. Categorical variables were compared using the
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55 chi-square test or Fisher's exact test. Two-tailed $p < 0.05$ was statistically significant for tests.
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RESULTS

Table 1 summarized the basic characteristics of all cases. Of the initial cohort of twenty-one patients, five were females, and sixteen were males. The mean age at diagnosis was 56.3 years old (range, 30-77y). According to the AJCC (American Joint Committee on Cancer) 2010 staging system, twelve patients presented with T4 at diagnosis, and six T1/T2, three T3. The most common primary subsite was the nasal cavity/ethmoid sinuses (95.2%, 20/21), and only one was the maxillary sinus. Eleven patients (52.4%, 11/21) had orbital invasion, including four grade I, two grade II, five grade III. Three patients complained of diplopia and the symptoms disappeared after treatment. Only one patient had unilateral moderate vision impairment at presentation and developed severe vision impairment during follow-up. Six patients had skull base involvement, and four lesions developed intracranial invasion. Facial skin involvement was found in two patients. Nine patients (42.9%, 9/21) showed cervical lymph node (LND) metastasis, including two cases of bilateral LND. Levels II (55.6%, 5/9) and VI_h (55.6%, 5/9) were the most common sites, followed by levels III (22.2%, 2/9), VIII (22.2%, 2/9), Ib (11.1%, 1/9). Further analysis showed that there was no correlation between the T stage and N status (p=0.66).

All the twenty-one patients were selected with definitive-intent (chemo)radiotherapy as the preferred treatment option. Five patients received surgery after (chemo)radiotherapy for significant residual tumors (Of all 5 patients with residual disease, 2 received ICT+CRT; 3 received IC+RT), and one case was suspended (chemo)radiotherapy due to tumor progression then underwent surgery. All five patients underwent transnasal endoscopic tumor resection. No patient performed elective neck node dissection in the initial treatment.

In total, 80.9% (17/21) of patients were delivered with chemoradiation, including sixteen cases of

1 IC combined CCRT and one case of concurrent chemotherapy. Among all the patients who accepted IC,
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3 fourteen patients presented an objective response to chemotherapy, and two patients showed stable
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5 disease. After careful evaluation, one patient refused chemotherapy, two elder cases and one patient with
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7 nephrectomy were not suitable for chemotherapy and were treated with radiotherapy (RT) alone. Typically,
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9 IC consisted of 2-3 cycles of docetaxel day 1 and cisplatin day 1 to day 3 at 75 mg/m² and continuous
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11 infusion fluorouracil at 600 to 750 mg/m² day 1 to day 5.
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17 There was one patient (4.8%, 1/21) who received 3-D conformal RT, one patient (4.8%, 1/21) with
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19 Volumetric Intensity Modulated Arc Therapy (VMAT), and nineteen patients (90.4%, 19/21) received
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21 intensity-modulated RT (IMRT) (Figure 1). Except for one T1N0M0 patient without receiving elective
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23 nodal irradiation (ENI), the remaining twenty patients received ENI. The average prescribed dose to the
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25 primary tumor was 67.7Gy (ranges from 64.5Gy to 71.3Gy). Among the five patients accepting surgery,
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27 one patient with apparent tumor regression after chemoradiotherapy (CRT) had negative pathological
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29 result, three cases with residual tumors were proved to be pathologically positive, one patient with
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31 progressed disease was found local recurrence at 22.7 months and died at 42.9 months. In general, after
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33 the completion of definitive-intent (chemo)radiotherapy, 66.7% (14/21) of patients had a complete
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35 response, 23.8% (5/21) of partial response, 4.8% (1/21) of stable disease, and 4.8% (1/21) of progressed
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37 disease, respectively (Figure 2). Strikingly, 52.4% of the patients (11/21) with orbit invasion accepted
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39 definitive-intent (chemo)radiotherapy, and all the lesions successfully underwent eye-sparing treatment.
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50 Four patients had intracranial tumor invasion; two received definitive (chemo)radiotherapy; two accepted
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52 surgeries after (chemo)radiotherapy, and one patient suspended radiotherapy for tumor progression and
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54 then accepted surgery.
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58 The median follow-up time was 30.1 months (ranges 7.9-99.3 months). At the time of analysis, 17
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1 patients were alive, and all the live patients had no evidence of disease. Four patients died, one presented
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3 local recurrence or local progression, one died of heart attack, other two died of other reasons. 9.5% of
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5 the patients (2/21) presented the regional control failure after definitive (chemo)radiotherapy; one
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7 recurred in level Ib and one in level IIa, and both patients accepted neck dissection after recurrence. No
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9 case was found distant metastasis.
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14 Table 2 provided the univariate analyses of variant factors in relation to survival. In general, the 3-
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16 overall survival (OS) of the entire group were 86.2%, and the 3-year progress free survival (PFS) were
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18 66.3, respectively. Compared with patients without orbit invasion, the patients who had orbit invasion
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20 were not found to have significantly poor 3-year OS (87.5% vs. 83.3%, $p=0.38$) and PFS (75.0% vs.
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22 55.3%, $p=0.59$). Therefore, the eye-sparing treatment did not sacrifice survival outcomes in patients with
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24 orbit involvement (Figure 3). There was also no significant difference in 3-year OS (57.1% vs. 85.7%,
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26 $p=0.21$) between N positive and N negative patients, while a significant difference in 3-year PFS (45.0%
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28 vs. 85.7%, $p=0.02$). In addition, no significant difference was found in regional failure for N positive
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30 patients and for N negative patients ($p=0.48$).
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39 Graded adverse events were evaluated using the National Cancer Institute Common Terminology
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41 Criteria for Adverse Events version 3.0. The treatment toxicities were generally mild, and no grade 3-4
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43 acute toxicities occurred. Radioactive sinusitis was the most common late adverse effect, and the degree
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45 of sinusitis appeared to be controlled by drug and decrease with time. Severe vision impairments were
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47 found in two patients, and no one was blindless. One patient complained of epiphora. One patient was
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49 proved of encephaledema. One patient developed restricted mouth opening seven months after the
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51 treatment.
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DISCUSSION

The incidence of histopathologic misdiagnosis among those rare sinonasal tumors such as SNUC, sarcoma, neuroendocrine carcinoma, and poorly differentiated carcinoma was reported to be 24%, which led to the reduced OS and disease-specific survival. So, an accurate diagnosis is vital for treatment selection and survival [8]. With the application of molecular pathology, the diagnosis of SNUC has become more restricted. Given the paucity of large clinical series, varied groups have differed significantly in the management of SNUC. Considering the high rate of systemic failure in patients with SNUC, combination therapy, including a combination of surgery, radiotherapy, and chemotherapy were recommended [2]. Although aggressive treatment, the prognosis of SNUC is poor, Chambers *et al.* [9] demonstrated the 5-year and 10-year survival of SNUC to be 34.9% and 31.3%, respectively, with a median survival of 22.1 months. Therefore, exploring the new treatment is essential to improve the survival of patients with SNUC. Khan *et al.*[10] reported that surgery followed by adjuvant chemoradiotherapy was associated with better survival than definitive (chemo)radiotherapy. However, in advanced-stage tumors, there was no difference in survival between the two treatment groups.

The present study was designed to determine the effect of definitive-intent (chemo)radiotherapy in the treatment of SNUC. In our study, 21 patients were scheduled to receive definitive (chemo)radiotherapy, and five of them accepted salvage surgery after the completion of (chemo)radiotherapy for residual tumors. The 3-year OS of the entire group were 86.2%, and the 3-year PFS were 66.3, respectively, which were better than those in literatures^[11,12]. Furthermore, most of the previous studies regarded surgery followed by CRT as the best treatment option for SNUC^[12,13]. Interestingly, increasing research began to realize the value of definitive (chemo)radiotherapy in the treatment of SNUC^[7,14,15].

1 Because of locally advanced diseases in most patients, radical open resection of the tumor might
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3 cause serve morbidity, and achieving a negative margin is highly challenging. Consequently,
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5 chemoradiotherapy takes advantage of both treatment and organ preservation. Recently, increasing
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7 evidence has shown that SNUCs were sensitive to chemotherapy. A large retrospective cohort study
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9 including 435 cases was performed by Kuo of Yale; his team found that surgery combined
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11 chemoradiotherapy was associated with significantly improved OS versus surgery followed by
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13 radiotherapy or radiotherapy alone, but not significantly different from chemoradiotherapy alone
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15 (p=0.364) ^[16]. Hitt *et al.* ^[17] demonstrated that 80% of SNUC had an overall response rate to
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17 chemotherapy. London ^[14] and his colleagues have assessed the potential role of induction chemotherapy
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19 in the treatment for SNUC and advocated induction chemotherapy followed by concurrent
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21 chemoradiation as routine management. Furthermore, several studies have identified some predictive
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23 biomarkers of induction chemotherapy response in cases with SNUC ^[18]. For patients who had a partial
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25 or complete response to induction chemotherapy, definitive (chemo)radiotherapy after induction
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27 chemotherapy had a better 5-year disease-specific survival rate than surgery followed by postoperative
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29 radiotherapy or chemoradiotherapy^[7].

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31 In this study, after the completion of definitive (chemo)radiotherapy, 66.7% of the patients (14/21)
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33 had a complete response, 23.8% (5/21) of partial response, one of tumor progression and one of stable
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35 disease. In general, 90.5% of the cases (19/21) showed an objective response to definitive
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37 (chemo)radiotherapy, and salvage surgery could be performed for those with residual tumor or poor
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39 (chemo)radiotherapy response. Even for the orbit invasion lesions, eye-sparing treatment based on
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41 definitive (chemo)radiotherapy successfully achieved comparable 3-year OS (83.3% vs. 87.5%, p=0.38)
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43 and PFS (55.3% vs. 75.0%, p=0.59) to those without orbit invasion.
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1 The 3-year OS and PFS were 86.2% and 66.3% in our study, and the yields were higher than
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4 Bonneau's that reviewing a multicenter showed that the 3-year OS and 3-year recurrence-free survival
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6 (RFS) rates were 62.4% and 47.8%, respectively [11]. In contrast, Christopherson *et al.* [19] reported that
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8 the prognosis of patients treated with definitive RT ± chemotherapy was less promising than those who
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10 received surgery and postoperative RT ± chemotherapy. But they failed to find a statistically significant
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12 difference in the local control rate for patients treated with surgery and RT versus patients treated with
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14 RT alone (p = 0.1799), therefore, the conclusion is less convinced. In addition, they did not investigate
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16 the value of combined radiotherapy and chemotherapy, but only emphasized the role of radiotherapy
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18 alone in the treatment of SNUC.
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25 Leirich *et al.* [20] reported that IC did not appear to provide additional OS benefit regardless of disease
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27 stage or timing before definitive treatment. Moreover, almost 30% of patients showed no response to
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29 induction chemotherapy, and these patients had poor survival. Therefore, monitoring the treatment
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31 response is imperative. Once the lesions showed stable disease (SD) or progressed (PD), surgery should
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33 be performed in advance. In addition, salvage surgery is also needed for patients having residual tumors
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35 after definitive radiotherapy and chemotherapy.
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42 Regarding radiation therapy, the dose of radiation is vital to achieving successful treatment or not.
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44 Al-Mamgani *et al.* found that local control was 75% in the group that received >60Gy versus 44% for
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46 the group that received ≤60Gy [21]. Ganez and his colleagues similarly concluded that improved OS was
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48 noted with IMRT and with doses ≥60Gy [22]. In this study, the average prescribed dose to the primary
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50 tumor is 67.7 Gy, and the complications caused by the radiation were endurable; even for those tumors
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52 that invaded the orbit and skull base, visual deterioration was found only in two patients, and no one was
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54 in blindless. Mayor's experience reported that the most common acute radiation toxicity was grade 1-2
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1 radiation dermatitis and mucositis, and the incidence of late toxicity and serious complications was
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3 reduced over time with the introduction IMRT [22]. Consistent with the Mayor's report, the toxicities in
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5 our study were well tolerated. Orbital exenteration was performed in 22.9% of patients with orbit
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7 invasion [4]. We successfully preserved all the orbits by definitive-intent (chemo)radiotherapy, and no
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9 patient developed blindness during follow-up. Radiation damage to optic nerves increases markedly
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11 when the total dose is more than 60Gy. A radiation-induced optic neuropathy incidence of approximately
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13 50% is obtained after an external radiation dose of 70Gy [23]. Therefore, it is vital to minimize the dose
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15 of optic nerves.
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22 Approximately 10-30% of SNUC patients had evidence of cervical lymph node (LND) metastases at
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24 the time of presentation, while distant metastases were an uncommon finding at initial presentation. Ann
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26 *et al.* reported 24.1% (27/112) of SNUC, and levels II-III were the most common involvement for
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28 nasal/ethmoid and levels I-III in non-nasal/non-ethmoid [24]. 42.9% of LND metastasis in this study,
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30 higher than that of previously reported rate, and levels II (5/9) and VIa (5/9) were the most common sites
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32 in patients had cervical LND involvement. It was similar to finding that there was no association in
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34 higher stage and size with higher nodal involvement rates[24]. Levels I-III remained the most significant
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36 risk for regional spread, and lymphoid metastasis predicted worse survival than those without LND
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38 metastasis. There were 9.5% of patients were proved to be a regional failure during the follow-up and no
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40 distant metastasis, which is lower than the previous study that 26.9% of patients demonstrating regional
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42 failure and 24.5% of distant failure at two years [25,26]. Both patients accepted neck dissection after
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44 recurrence.
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56 No significant difference was found in 3-year OS (57.1% vs. 85.7%, p=0.21) between N positive
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58 and N negative patients, while a significant difference in 3-year PFS (45.0% vs. 85.7%, p=0.02). which
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1 might benefit from the performance of ENI. Considering the high cervical LND involvement, ENI is
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3 performed in 95.2% of the cases except for one T1N0M0 case. The choice of ENI was recommended in
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6 cN0, especially for advanced tumors and elective neck treatment significantly reduced the risk of regional
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9 recurrence from 26.4% to 3.7% ^[27] , and the best locoregional control rate was achieved in patients
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12 undergoing neck dissection and chemoradiotherapy ^[28].

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14 The treatment toxicities were generally mild and tolerable, and no grade 3-4 acute toxicities occurred.
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17 Even though, there were eleven patients had orbit invasion at presentation, all the patients successfully
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20 underwent orbit preservation treatment, and only two patients were identified with severe vision
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23 impairment. One patient was proved of encephaledema, while no evidence of brain necrosis was found
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26 during follow-up. Restricted mouth opening occurred in one patient who underwent surgery, which
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29 caused trouble in eating and speaking. The tumor invaded the infratemporal fossa, and the double hit of
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32 surgery and irradiation might be the reason for restricted mouth opening, therefore, rehabilitation training
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35 on opening mouth is crucial for the patients ^[29,30].

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37 Our study had several limitations. Firstly, it was a retrospective study with a bias of case selection.
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40 Secondly, the small size of the samples might reduce the credibility of the results. Thirdly, the median
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43 follow-up time was only 31.6 months; we could not calculate the 5-year survival data accurately.
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47 **CONCLUSIONS**

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50 The purpose of the current study was to determine the value of definitive-intend (chemo)radiotherapy
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53 for patients with advanced SNUC. We affirmed that definitive (chemo)radiotherapy played an essential
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56 role in treatment and organ preservation. Notwithstanding these limitations, the study suggests that
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59 definitive (chemo)radiotherapy could be the preferred options for patients, and salvage could be
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1 performed for the lesions showing SD, PD, or residual tumor. Further research is required to establish
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3 the therapeutic efficiency of multimodality treatment.
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8 9 **ACKNOWLEDGEMENT**

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11 We sincerely thank all the patients and investigators involved in this study.
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BJR UNCORRECTED PROOFS

1 **FIGURE LEGENDS**

2
3 **Figure 1.** Axial (A) and coronal (B) views of the contouring. The red, green, and orange line presented
4 the GTV, CTV-high and CTV-low, respectively. Axial (C), coronal (D), and sagittal (F) views of the
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6 definitive intensity-modulated radiation therapy plan showed the prescribed PGTV of 68.2Gy to be
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8 delivered to the primary tumor. Dose-volume histogram (E) was presented.
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17 **Figure 2.** A 62-year-old male patient with sinonasal undifferentiated carcinoma. Axial T1- (A) and T2-
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19 weighted (B) MRI scans showed an iso-intense mass in the right nasal cavity (arrow). Axial (E), coronal
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21 (F), and sagittal (G) PET/CT scan demonstrated the mass with FDG avidity (arrow). Axial T1- (I) and
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23 T2-weighted (J) MRI, Axial (K) and coronal (L) post-contrast T1-weighted MRI scans showed the tumor
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25 regression after the completion of radiotherapy (arrow).
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33 **Figure 3.** Kaplan Meier curves showed (A) overall survival and (B) progression-free survival of the
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35 twenty-one patients. Comparison of (C) overall survival and (D) progression-free survival for cases with
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37 or without orbit invasion, there was no significant differences between the two groups.
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Figure 1

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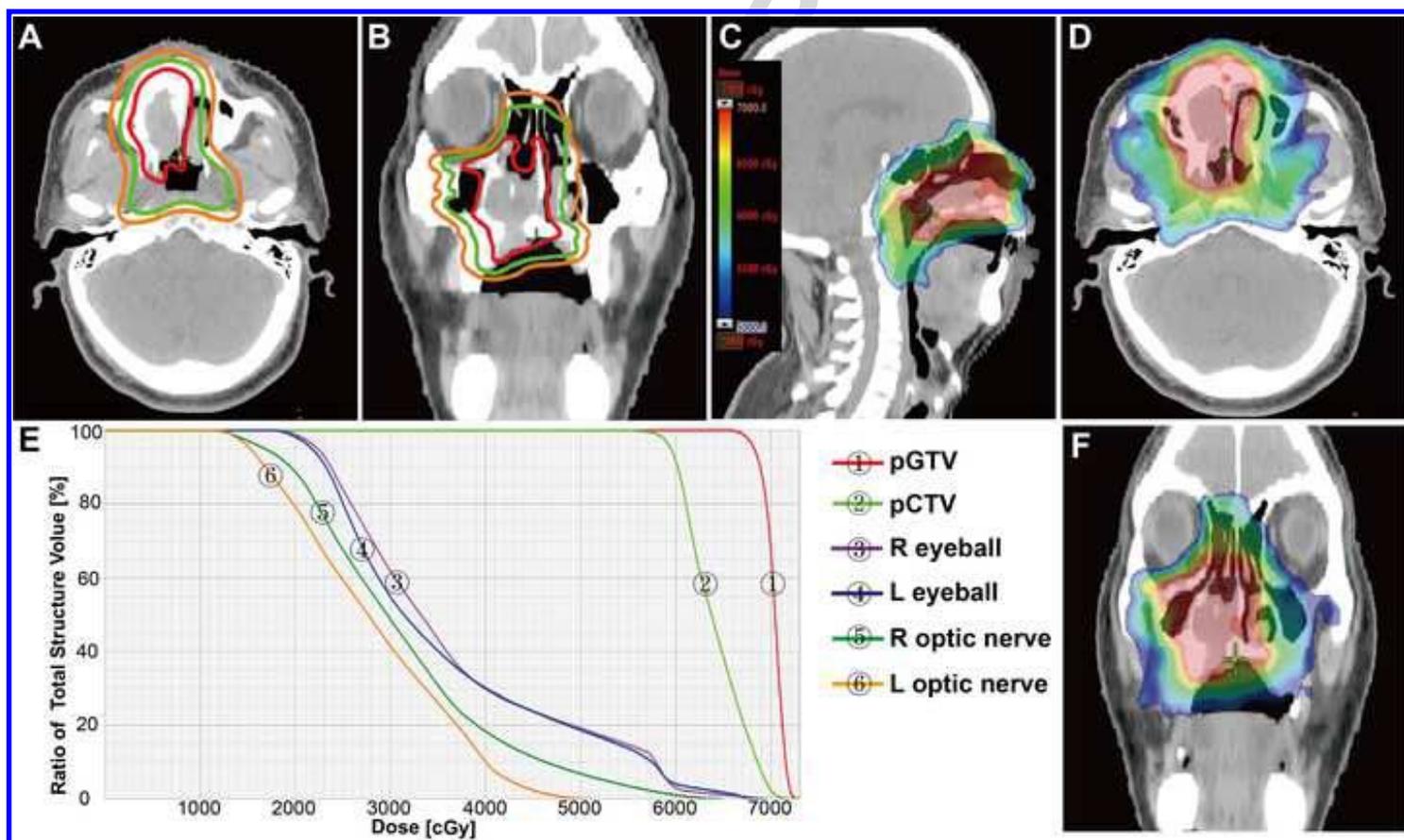


Figure 2

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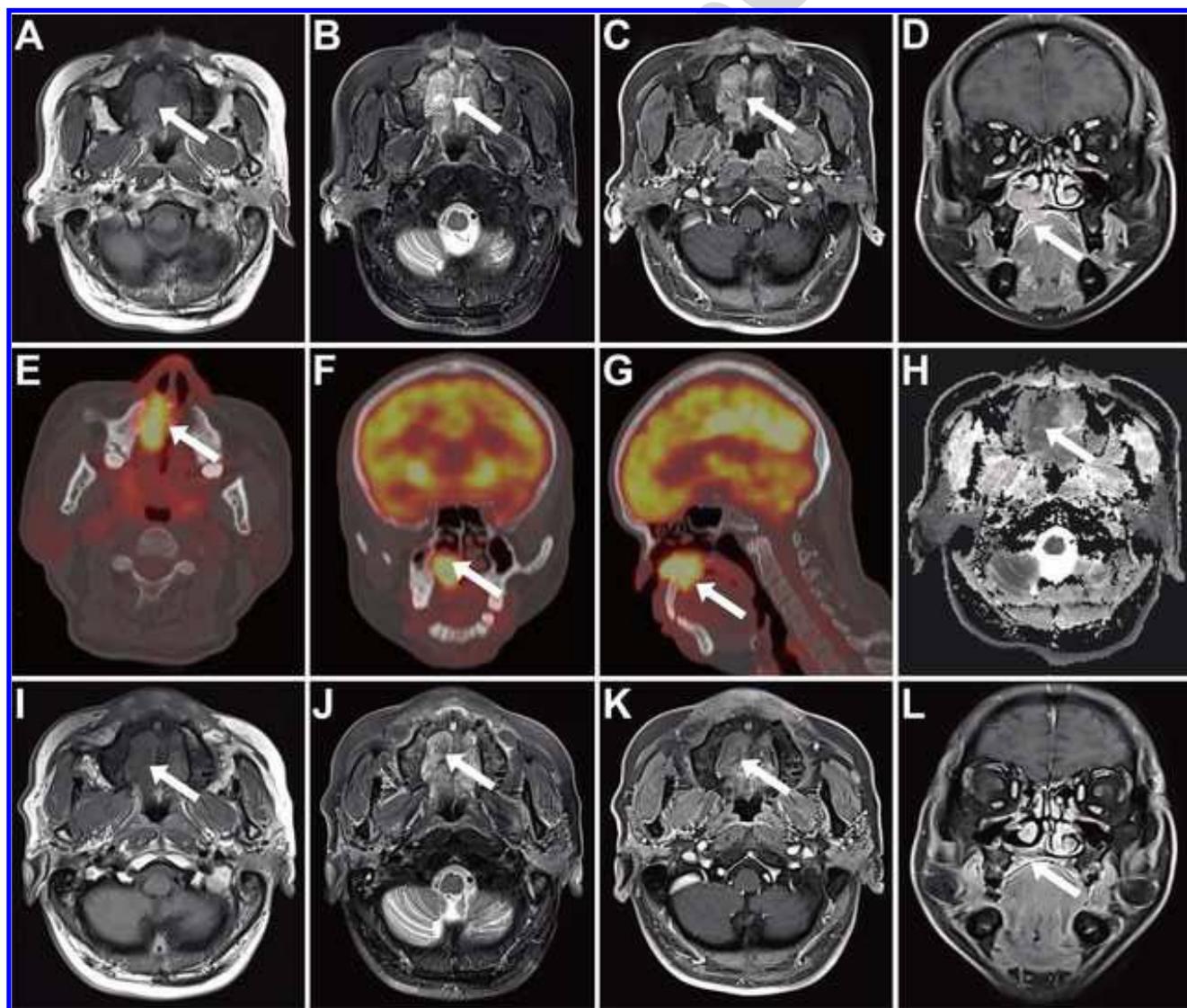
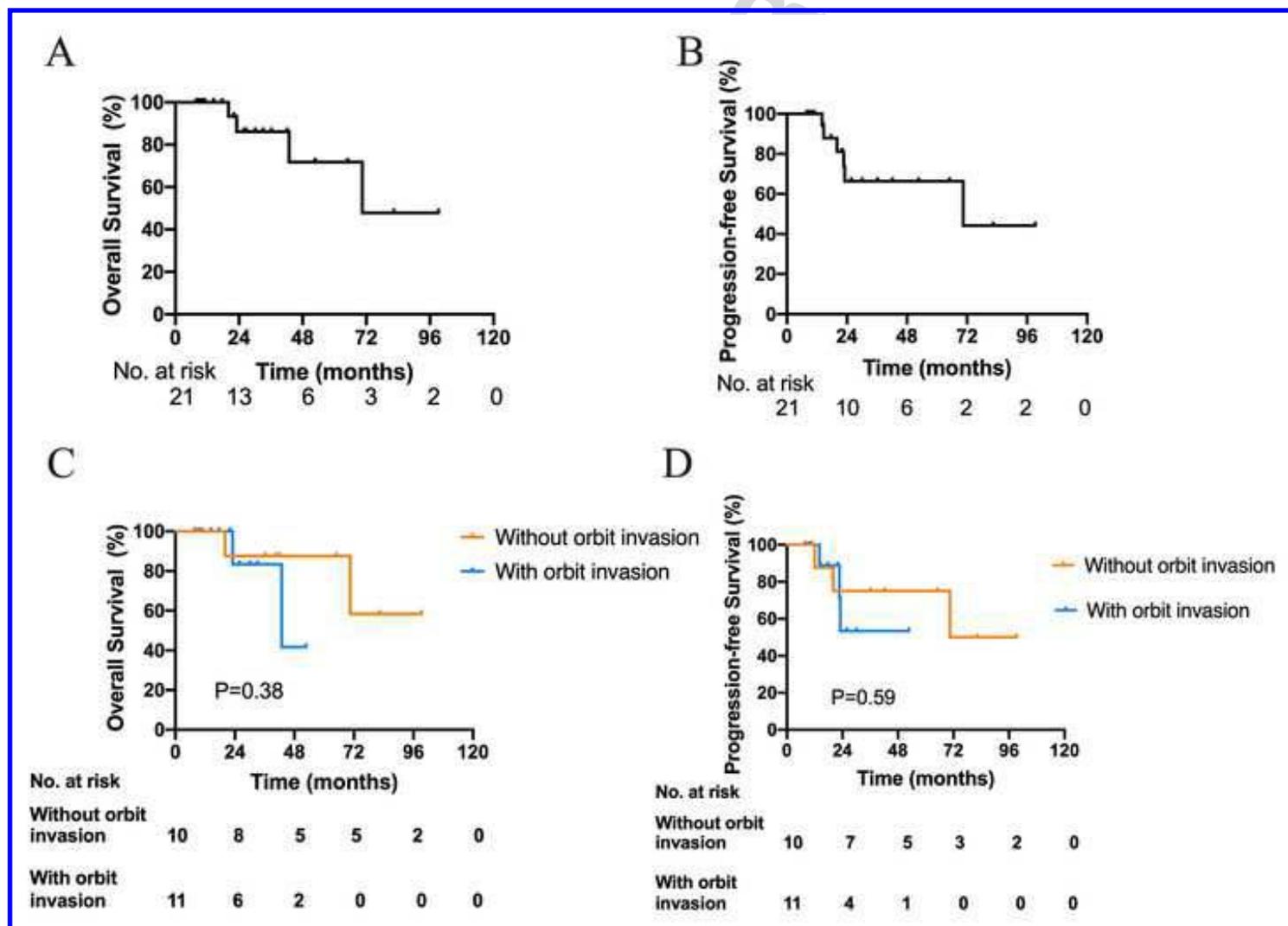


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Table 1. patients' basic characteristics

variables	No. of patients n=21 (%)
Age (y)	
<60	10 (47.6%)
≥60	11 (52.4%)
Gender	
Female	5 (23.8%)
Male	16 (76.2%)
T stage	
T1/2	6 (28.6%)
T3	3 (14.3%)
T4	12 (57.1%)
Lymph node	
Negative	12 (57.1%)
Positive	9 (42.9%)
Primary site	
Nasal cavity/ethmoid sinus	20 (95.2%)
Maxillary sinus	1 (4.8%)
Orbital invasion	
No	10 (47.6%)
Yes	11 (52.4%)
Skull base invasion	
No	15 (71.4%)
Yes	6 (28.6%)
Chemotherapy	
No	4 (9.1%)
Yes	17 (80.9%)
Surgery	
No	16 (76.2%)
Yes	5 (23.8%)
Irradiation technique	
3D-CRT	1 (4.8%)
IMRT	19 (90.4%)
VMAT	1 (4.8%)
ENI	
No	1 (4.8%)

Yes

20 (95.2%)

3D-CRT: three-dimensional conformal radiotherapy, IMRT: Intensity Modulated Radiation Therapy,
VMAT: volumetric-modulated arc radiation therapy, ENI: elective nodal irradiation

BJR UNCORRECTED PROOFS

Table 2. Univariate analyses of factors in relation to survival (n=21)

Variables	OS		PFS	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (years)				
<60	1(Reference)	0.17	1(Reference)	0.37
≥60	4.22(0.58-30.85)		2.11(0.43-10.47)	
Gender				
Female	1(Reference)	0.31	1(Reference)	0.31
Male	3.35 (0.16-68.64)		3.37 (0.32-35.32)	
T stage				
T1-3	1(Reference)	0.96	1(Reference)	0.44
T4	0.95 (0.14-6.76)		1.91 (0.39-9.47)	
Cervical lymph node				
Negative	1(Reference)	0.21	1(Reference)	0.02
Positive	0.26(0.04-1.89)		0.12(0.02-0.64)	
Orbital invasion				
No	1(Reference)	0.38	1(Reference)	0.59
Yes	2.17(0.26-17.89)		1.49(0.29-7.63)	
Skull base invasion				
No	1(Reference)	0.69	1(Reference)	0.89
Yes	0.62(0.08-4.94)		1.23(0.20-6.35)	