

Sinus mucosa status in patients with nasopharyngeal carcinoma treated with intensity-modulated radiotherapy: A 5-year follow-up

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ABSTRACT: *Background.* Sinus mucosa abnormalities on image studies, which is the major diagnostic measure for sinusitis, were investigated in patients with nasopharyngeal carcinoma (NPC) after intensity-modulated radiotherapy (IMRT).

Methods. A retrospective review of the MRIs for patients with NPC was conducted. Sinus mucosa abnormalities were staged by the Lund–Mackay system.

Results. A total of 94 patients were enrolled in this study. The rate and severity of sinus abnormalities were highest on the third postradiotherapy month ($p < .005$, t test). There was no significant increase in the incidence of abnormalities on the fifth postradiotherapy year (t test). The

anterior ethmoid and maxillary sinuses were the most affected sinuses before and after radiotherapy ($p < .005$, chi-square test).

Conclusion. Our data showed that the anterior ethmoid and maxillary sinuses were the most vulnerable sinuses for therapeutic toxicity after IMRT in patients with NPC. In the long run, however, the application of IMRT does not significantly increase the incidence of sinus toxicities.

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KEY WORDS: nasopharyngeal carcinoma, intensity-modulated radiotherapy, rhinosinusitis, complication, MRI

INTRODUCTION

Nasopharyngeal carcinoma (NPC) remains endemic in specific regions of the world and is a distinct entity of head and neck cancers because of its pathogenesis and treatment, which is comprised primarily of external beam radiation therapy to the nasopharynx and potential regions of spread.¹ The treatment, however, often produces undesirable complications because of the therapeutic toxicity to the nearby radiation dose-limiting organs, including the brain stem, spinal cord, pituitary-hypothalamic axis, temporal lobe, temporal bone, and parotid glands. Although paranasal sinuses are generally not considered to be radiosensitive tissues, according to the related literature regarding tolerance doses for organs in the head and neck region,² the epithelial lining is often irreversibly damaged by the irradiation.^{3,4} In a single institutional study of irradiated patients with NPC, rhinosinusitis was found to be one of the most common treatment complications.⁵ Other studies using image study to evaluate the paranasal sinus in patients with NPC also demonstrated an increased incidence of sinus mucosa disease after conventional radiotherapy.^{6,7}

To decrease radiation-induced toxicities, 3D planning schemes have been utilized since the 1990s, including 3D

conformal radiotherapy and intensity-modulated radiotherapy (IMRT).⁸ Prior study demonstrated that IMRT is distinctly superior in escalation of dose coverage to target and reduction of radiation to adjacent tissues because it further improves the dose differential between the tumor and the dose-limiting organs.⁹ Clinical observational studies accordingly showed that IMRT-treated patients with NPC have less therapeutic side effects and better a quality of life than those treated by conventional radiotherapy while maintaining satisfactory local control of the disease.^{10–12} Moreover, these advantages of IMRT for the patients with head and neck cancers have recently been demonstrated by a multicenter randomized controlled trial.¹³ Although various radiation-induced complications can be reduced by modern techniques, morbidities pertaining to the paranasal sinus after IMRT in patients with NPC is relatively underreported in the related literature.

CT and MRI scans are considered to be the most reliable tools for examining the paranasal sinus and are the tests of choice to confirm the diagnosis of sinusitis and to quantify inflammation of the sinuses.^{14,15} In addition, the Lund–Mackay staging system for sinusitis has been shown to exhibit the most direct linear correlation between nasal symptom severity and findings on the image studies.¹⁶ Thus, this study aimed to determine the status of sinus mucosa by using the Lund–Mackay staging system on serial MRI studies in patients with NPC after IMRT and to evaluate the potential factors associated with this complication.

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PATIENTS AND METHODS

Patients

A retrospective review of histologically proven patients with NPC who underwent entire an IMRT course between January 2003 and September 2008 was conducted at the Chung Shan Medical University Hospital. The institutional review board approved the study for a review of each patient's clinical chart with the extraction of demographic and clinical data. All patients were staged by a standard protocol comprised of a physical examination, nasopharyngoscopy, MRI of the nasopharynx and neck region, chest radiograph, abdominal sonography, and whole body bone scan. The American Joint Committee on Cancer (AJCC) 2002 staging classification was used for disease staging. Patients with evidence of distant metastasis were excluded from the study. Patients were also excluded if pretreatment or scheduled post-RT MRIs were lacking, and those who failed to be followed up for at least 5 years.

Protocol of MRI

Pretreatment and follow-up MRIs of the nasopharynx and neck region were performed in all patients as followed. MRI evaluation was conducted with a field strength of 1.5 Tesla units, using a standard circular polarized head coil. A spin-echo technique was used. The basic contrast was T1 and T2, and all patients underwent examination before and after gadolinium-diethylenetriamine penta-acetic acid injection. Images were acquired in the sagittal, axial, and coronal planes. Section thickness was 5 mm with 2.5-mm intersection gap in the axial plane and 4 mm with a 1-mm gap in the sagittal and coronal planes. A minimum display matrix size should be 256*256 pixels. Acceleration of measurement times can be achieved by application of fast gradient-echo sequences and with turbo spin echo sequences.

Radiotherapy protocol

All the patients received IMRT as primary curative treatment. Cisplatin-based chemotherapy was administered concurrently with radiotherapy except for those with a stage I disease. The radiation was delivered to these patients via 7 fixed-gantry angles with a linear accelerator. The IMRT plans were prepared using the Helio inverse planning system. The following 3 volumes were measured.

Gross tumor volume. The gross tumor volume (GTV) was defined as the volume of the gross visible nasopharyngeal tumor or entire nasopharyngeal mucosa for those with a T1 tumor stage. The GTV for positive lymph node(s) was defined as the volume of gross visible metastatic lymph node(s).

Clinical tumor volume. Clinical tumor volume (CTV) was the GTV plus a margin, including the skull base, inferior portion of the sphenoid sinus, entire nasopharynx, retropharyngeal nodes, pterygopalatine fossae, posterior nasal cavity, maxillary sinuses, and parapharyngeal space. Bilateral cervical lymphatic areas included levels II, III, IV, and V, and the supraclavicular fossa.

Planning target volume. Planning target volume was the CTV plus 3 mm margins. The goal was to deliver a minimum dose of 70 Gy to the GTV and 55 to 60 Gy to the CTV, with the respective fraction sizes of 2.12 and 1.7 to 1.8 Gy. Dose constraints for organs at risk were listed as follows: brainstem, Dmax <60 Gy; spinal cord, Dmax <50 Gy; optic chiasm, Dmax <50 Gy; and parotid glands, Dmean <30 Gy.

Post-treatment follow-up

All irradiated patients underwent a structured interview for clinical manifestations, nasopharyngoscopy for detection of local recurrence, and examinations of the neck every 2 months the first 2 years after radiotherapy and every 3 to 4 months thereafter. A follow-up MRI of the nasopharynx and neck region was performed 3 months after completion of radiotherapy and then yearly or when clinically indicated. Chest radiograph, abdominal sonography, and whole body bone scan were conducted on an annual basis for evaluation of distant metastasis. Patients with evidence of local recurrence or distant metastasis at follow-up were excluded from the study.

Evaluation of paranasal sinuses

Traditionally, severity of rhinosinusitis is graded using the Lund–Mackay staging system, which designates a score to the ostiomeatal complex and each sinus group (maxillary, anterior ethmoid, posterior ethmoid, sphenoid, and frontal sinuses) according to CT scan findings.¹⁷ The sinuses are scored between 0 and 2 (0, no abnormality; 1, partial opacification; 2, total opacification). The scores of the individual sinus in each side can be summed to a total score, which is considered to represent the severity of rhinosinusitis. However, MRI possesses the advantage of excellent tissue contrast and is superior in evaluating the extent of the tumor,¹⁸ the current study uses this imaging modality to follow up head and neck structures. Therefore, the status of the sinus mucosa was flexibly assessed by documenting mucosal changes on the MRI, and the scores of the individual sinus were obtained before radiotherapy, and 3 months, 1 year, 3 years, and 5 years after treatment. Because ostiomeatal complex could not be clearly evaluated on MRI, scoring of this entity was omitted. All sections of MRI images, including axial, coronal, and sagittal, were read in order to interpret all paranasal sinuses accurately. Of note, we did not score the maxillary sinus retention cyst as positive findings under the Lund–Mackay staging system because prior study showed the condition does not reflect obstructive pathology and is not associated with potentially obstructive anatomic sinus variations.¹⁹ Moreover, we analyzed the score of the individual sinus instead of adding the scores for ipsilateral sinuses together, thus, the sequential status of the individual sinus can be investigated separately.

Statistical methods

The means and SDs for continuous variables and the relative frequencies for the nominal variables were calculated. The differences of the occurrence of sinus abnormality at successive time periods were analyzed by *t* test. The comparisons of abnormalities between different sinuses

TABLE 1. Patients, tumor, and treatment characteristics.

Characteristic	No. of patients (%)*
Sex	
Male	67 (71.3)
Female	27 (28.7)
Tumor classification	
T1	28 (29.8)
T2	45 (47.9)
T3	14 (14.9)
T4	7 (7.4)
Nodal classification	
N0	24 (25.5)
N1	32 (34.0)
N2	24 (25.5)
N3	14 (14.9)
Stage group (AJCC 2002)	
I	10 (10.6)
II	37 (39.4)
III	26 (27.7)
IV	21 (22.3)
Treatments	
Radiotherapy alone	10 (10.6)
Concurrent chemoradiation	84 (89.4)

Abbreviation: AJCC, American Joint Committee on Cancer.

*Amounts may not add to 100% because of rounding.

were analyzed by the chi-square test. Because these analyses were conducted in multiple-comparison procedures, a more conservative significance level ($p < .005$) was used in order to reduce false positives. Factors that may associate with the occurrence of postirradiation sinus abnormality, such as patient's sex and age, T classification, and radiation dose, were analyzed by logistic regression with a forward selection algorithm. A coefficient with a p value of $< .05$ was considered to be statistically significant.

RESULTS

Patient demographics

A total of 94 patients were enrolled in the retrospective review. There were 67 men and 27 women, with a mean age when the disease was diagnosed at 42.7 years (range, 20–74 years). According to the AJCC 2002 staging classification, there were 28 patients (29.8%) in T1, 45 patients (47.9%) in T2, 14 patients (14.9%) in T3, and 7 patients (7.4%) in T4 lesions. For the N classification, 24 (25.5%) were in N0, 32 (34.0%) in N1, 24 (25.5%) in N2, and 14 (14.9%) in N3. For TNM staging group, 10 patients (10.6%) were in stage I, 37 (39.4%) in stage II, 26 (27.7%) in stage III, and 21 (22.3%) in stage IV, respectively. The overall radiation dose applied to the nasopharynx was 73.9 ± 2.5 Gy (ranged from 68.0 Gy to 81.0 Gy). All patients were followed up for 5 years or more and without evidence of local recurrence or distant metastasis. The patient, tumor, and treatment characteristics are summarized in Table 1.

Abnormal rates of sinus mucosa before and after intensity-modulated radiation therapy

Both sides of the paranasal sinus in each patient were analyzed independently and hence there were 188 sinus sets (each set containing maxillary, anterior/posterior

ethmoid, sphenoid, and frontal sinuses) for these 94 patients. The Lund–Mackay staging scores for individual sinuses on the MRI were obtained before radiotherapy, 3 months, 1 year, 3 years, and 5 years after treatment. The occurrence rates of abnormal sinus mucosa (score = 1 or more) before radiotherapy were 49 (26.1%), 55 (29.3%), 22 (11.7%), 23 (12.2%), and 4 (2.1%) for the maxillary, anterior ethmoid, posterior ethmoid, sphenoid, and frontal sinuses, respectively. Of note, mucocele was found in 10 maxillary sinuses before radiotherapy, and thus the pretreatment abnormal rate of the maxillary sinus would be 31.4% if mucocele was taken into consideration when designating the score.

The incidences of abnormal sinus mucosa in the maxillary, anterior ethmoid, posterior ethmoid, sphenoid, and frontal sinuses before radiotherapy, 3 months, 1 year, 3 years, and 5 years after treatment are summarized in Table 2. The sinuses could be generally classified to high-risk (maxillary and anterior ethmoid sinuses), moderate-risk (posterior ethmoid and sphenoid sinuses), and low-risk (frontal sinus) groups according to a similar vulnerability to treatment toxicity. Chronologically, the abnormal rates of sinus mucosa were highest on the third postradiotherapy month for all sinuses except the frontal sinus. In the long run, there was no significant increase in the incidence of mucosal abnormalities on the fifth postradiotherapy year comparing to pretreatment time for all paranasal sinuses ($p > .05$, chi-square test).

Chronological changes of severity of sinus mucosa abnormality before and after intensity-modulated radiation therapy

To assess the severity of sinus mucosal abnormality at different times, the mean value of the Lund–Mackay staging score for each sinus was plotted against pretreatment and different follow-up periods. The scores of the maxillary, anterior ethmoid, posterior ethmoid, sphenoid, and frontal sinuses before radiotherapy, 3 months, 1 year, 3 years, and 5 years after treatment are shown in Figure 1. For maxillary, anterior, and posterior sinuses, a significant increase in the score was noticed on the third postradiotherapy month comparing to pretreatment ($p < .0001$, t test). Afterward, a dropping trend of the Lund–Mackay staging score was found from the third month to fifth year after radiotherapy. For sphenoid and frontal sinuses, there was no remarkable change in the mean value of score on the pretreatment and different postradiotherapy times. Of note, on the fifth postradiotherapy year, there was no significant change in the Lund–Mackay staging scores of all sinuses ($p > .05$, t test) when comparing to pretreatment time.

Effect of radiotherapy on preexisting abnormal paranasal sinus

Preexisting mucosal abnormalities before the radiotherapy were noticed in 49 maxillary sinuses, 55 anterior ethmoid sinuses, 22 posterior ethmoid sinuses, 23 sphenoid sinuses, and 4 frontal sinuses (Table 2). Considering different possible trends of postradiotherapy abnormalities in sinuses with or without preexisting disease, we also plotted the mean value of the Lund–Mackay staging score for

TABLE 2. Incidences of mucosal abnormalities in 188 side sinuses.

	High-risk group		Moderate-risk group		Low-risk group Frontal
	Maxillary	Anterior ethmoid	Posterior ethmoid	Sphenoid	
Pre-RT	49 (26.1%)	55 (29.3%)	22 (11.7%)	23 (12.2%)	4 (2.1%)
3 mo post-RT	96 (51.1%)*	112 (59.6%)*	49 (26.1%)*	33 (17.6%)	6 (3.2%)
1 y post-RT	86 (45.7%)*	107 (56.9%)*	35 (18.6%)	24 (12.8%)	5 (2.7%)
3 y post-RT	77 (41.0%)*	98 (52.1%)*	41 (21.8%)	31 (16.5%)	8 (4.3%)
5 y post-RT	60 (31.9%)	78 (41.5%)	32 (17.0%)	33 (17.6%)	5 (2.7%)

Abbreviation: RT, radiotherapy.

* $p < .005$, when compared chronologically to pre-RT data.

patients with pretreatment abnormal sinuses against different time periods (see Figure 2). The analysis for the frontal sinus with preexisting abnormalities, however, was not carried out because of its low incidence. Unlike the abovementioned rising-then-dropping pattern, there was no remarkable increase in the score for sinuses with preexisting abnormality on the third postradiotherapy month. Moreover, there was even a significant decrease of score for the posterior ethmoid and sphenoid sinuses after conclusion of irradiation ($p < .05$, t test).

The mean value of the Lund–Mackay staging score for patients without pretreatment abnormal sinus mucosa was also plotted against various time periods, which showed a regular rising-then-dropping pattern (see Figure 3).

Factors associated with long-term status of sinus mucosa after intensity-modulated radiation therapy

In addition to preexisting sinus abnormality, factors which may be associated with the integrity of sinus mucosa of irradiated patients with NPC were also investigated. Parameters such as patient's sex (0.02; -0.18 to 0.21 ; $p = .865$), age (-0.04 ; -0.25 to 0.16 ; $p = .680$), and radiation dose (-0.03 ; -0.23 to 0.18 ; $p = .797$) were not associated with the occurrence of postirradiation sinus mucosal abnormality in the fifth postradiotherapy year (logistic regression). The T classification of primary tumor, however, was associated with the occurrence of postirradiation sinus mucosal abnormality in the fifth

postradiotherapy year (0.91; 0.11 – 1.72 ; $p = .03$; logistic regression).

DISCUSSION

Treatment toxicities are common in patients with NPC because exposure to non-target organs during the irradiation of the skull base and neck areas is unavoidable. Several recording systems have been developed to describe various toxicities after radiotherapy, including the Common Terminology Criteria for Adverse Events (version 3.0) and SOMA scale.²⁰ Although clinical observation and prior studies find that treatment toxicities of the paranasal sinus are common in NPC survivors after conventional radiotherapy,^{3,5–7} the abovementioned systems include limited or even no sinonasal complications in their recording inventory. More information regarding these toxicities is needed to provide better health care for irradiated patients with NPC and to help refinement of modern radiotherapy.

The current study, which used MRI to investigate the paranasal sinuses in IMRT-treated patients with NPC, showed an approximately 2-fold incidence of sinus mucosal abnormality in the acute stage (third postradiotherapy month) for maxillary, anterior, and posterior ethmoid sinuses (Table 2). Increases of the Lund–Mackay staging scores in the acute stage for these sinuses were also remarkable (see Figure 1). The acute mucosal changes, however, decreased steadily during the follow-up period. In the long run (fifth postradiotherapy year), IMRT did not significantly increase the incidences of mucosal

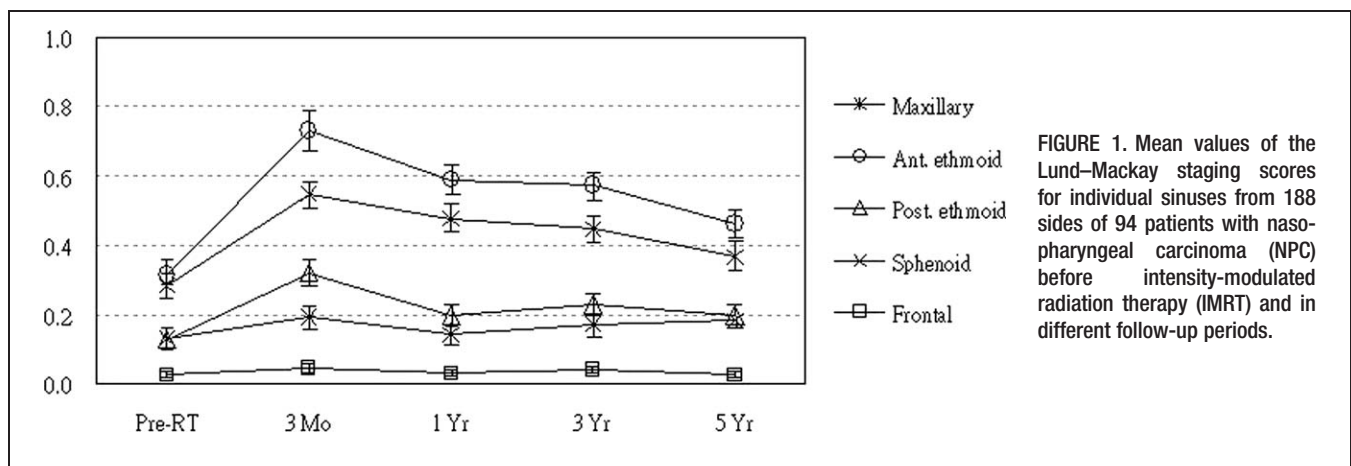
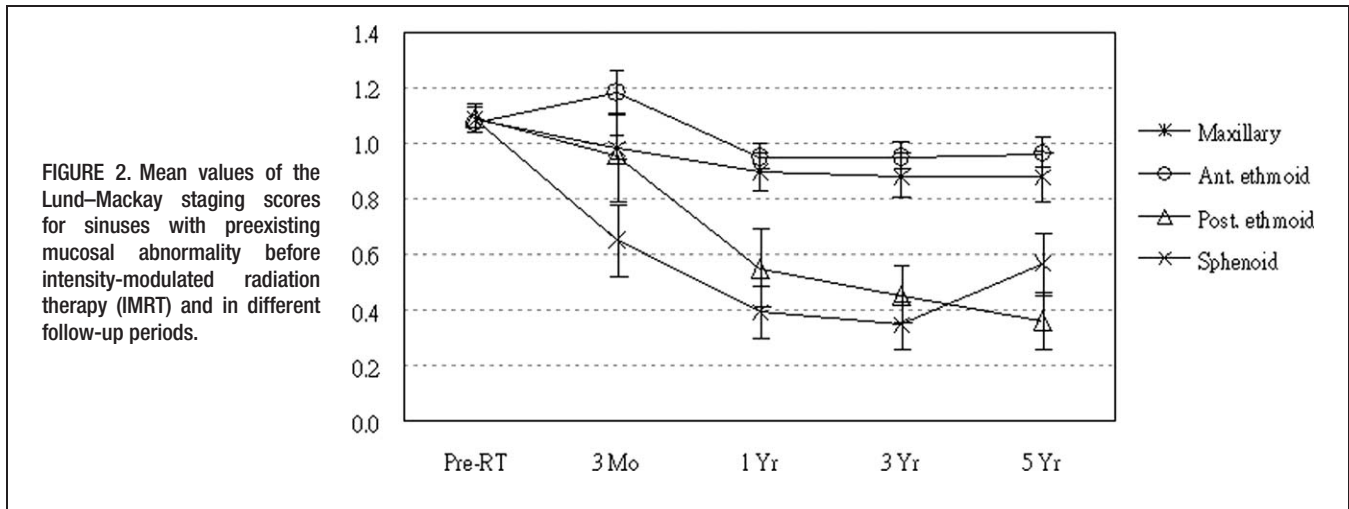


FIGURE 1. Mean values of the Lund–Mackay staging scores for individual sinuses from 188 sides of 94 patients with nasopharyngeal carcinoma (NPC) before intensity-modulated radiation therapy (IMRT) and in different follow-up periods.

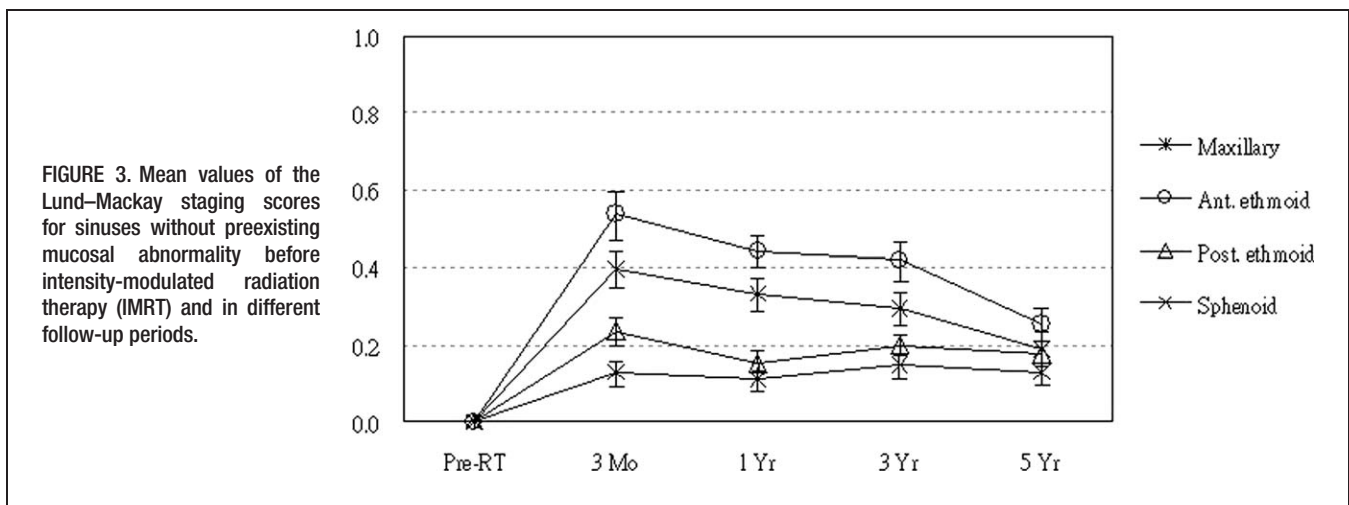


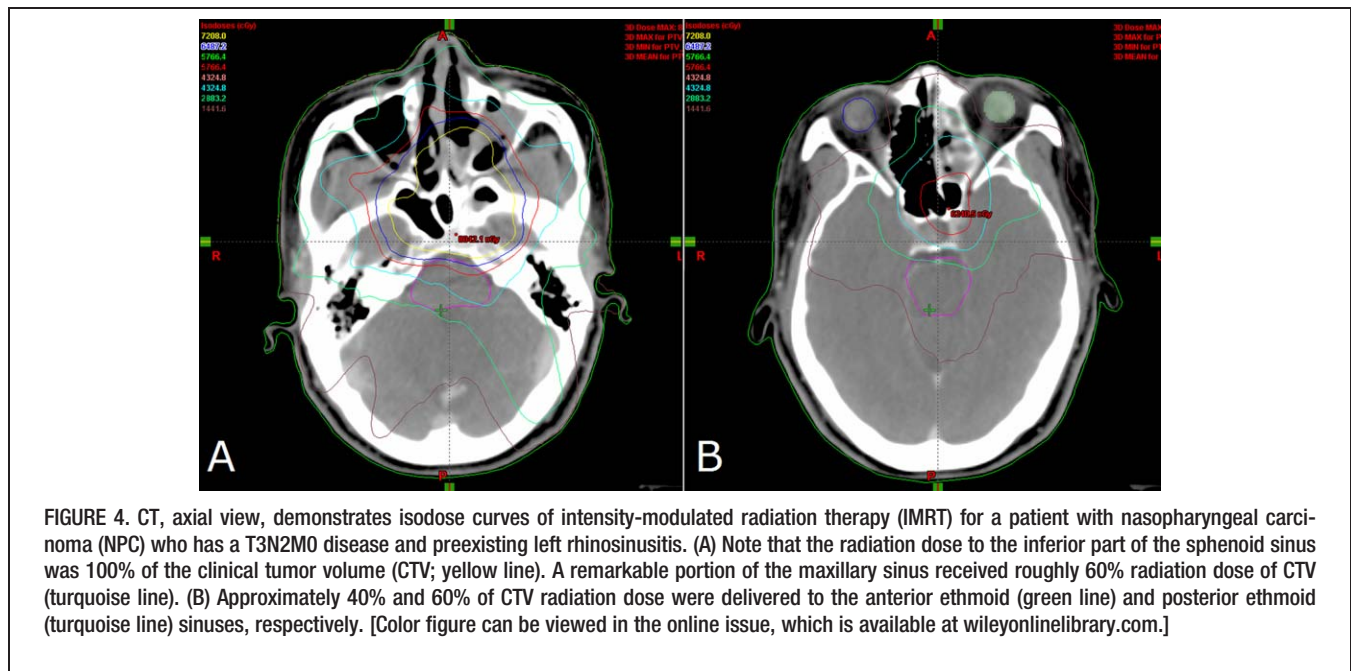
abnormality for all paranasal sinuses. These data suggested that the practice of modern radiotherapy exerts little late toxicities to the sinus.

As to the different sinus groups, previous studies discovered that the maxillary sinus is the most common area of treatment toxicities after conventional radiotherapy.^{3,6,21} Our data demonstrate that both the maxillary and anterior ethmoid sinuses are the most vulnerable ones after IMRT for NPC, although radiation dose over the anterior ethmoid sinus is not as high as other sinuses except the frontal sinus (see Figure 4). Moreover, although most of the mucosa in the sphenoid sinus receive full dose of irradiation because of their proximity to the primary tumor (see Figure 5), there is no significant increase in the rate or severity of mucosa changes any time after radiotherapy when comparing to pretreatment (Table 2 and Figure 1). These observations imply that radiation dose is not the major factor involved in the pathogenesis of postirradiation sinus abnormalities. It is likely that these radiation-induced changes also share the common etiology of regular rhinosinusitis, which suggests that a wealth of bony and mucosal structures in a relatively narrow space of the ostiomeatal complex is vulnerable to obstruction and hence important in the generation

of rhinosinusitis.²² On the other hand, although the sphenoid sinus is very close to the nasopharynx and received nearly the full dose of irradiation, there is no increase in the Lund-Mackay staging score after radiotherapy and the incidence of mucosal abnormalities does not rise. These findings suggest that sphenoid sinus, whose ostium is not as complex or narrow as ostiomeatal complex, is rather resistant to radiation insults. Therefore, deliberate reduction of irradiation dose to the sphenoid sinus appears not needed, whereas an additional decrease of irradiation dose to the anterior ethmoid sinus and ostiomeatal complex might be beneficial in preventing postradiotherapy sinus toxicities because of their vulnerability to the treatment. Accordingly, the basal lamina should be identified as an important landmark and serve as a reference boundary for dose constraints in planning IMRT for patients with NPC. Further studies with modification of radiation delivery to the paranasal sinuses, however, are needed to confirm this notion.

Analysis of treatment effects on the paranasal sinuses with preexisting abnormalities was also carried out and, unlike the rising-and-dropping pattern previously described, there was no remarkable increase of the Lund-Mackay staging scores after radiotherapy. Moreover, there



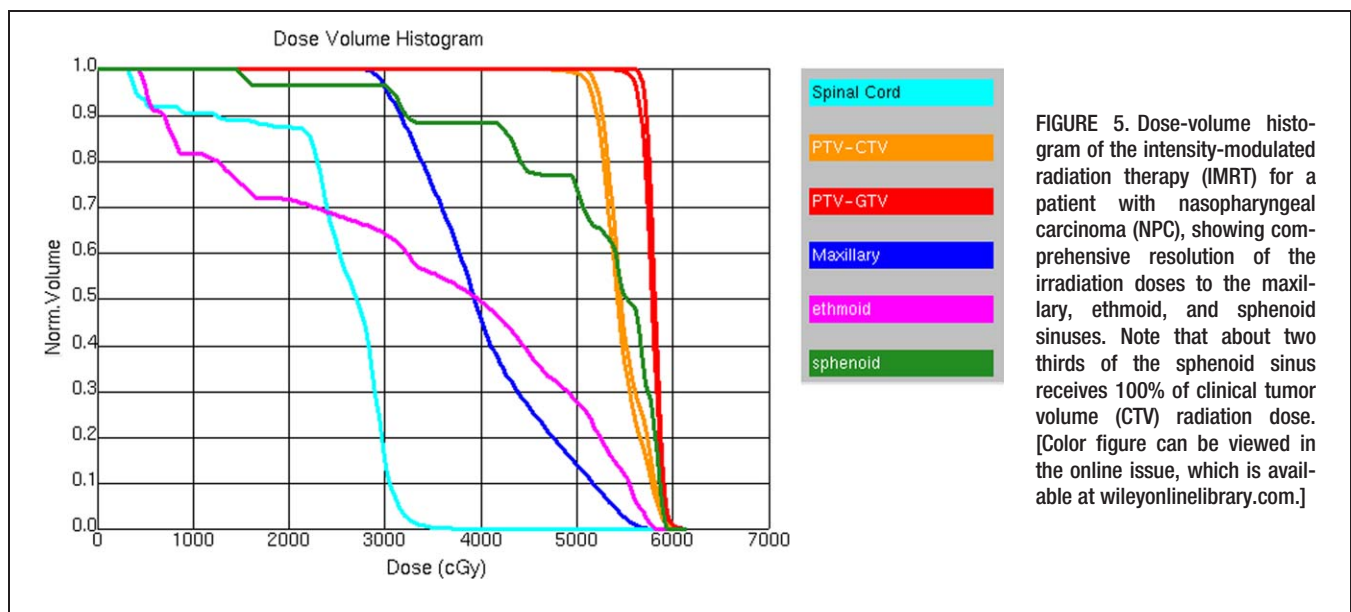


was a significant decrease of the scores on the third post-radiotherapy month for both post ethmoid and sphenoid sinuses with preexisting mucosal abnormalities. The data suggested that many, if not all, of these sinuses with preexisting mucosal problems may be directly or indirectly associated with NPC, and the treatment of NPC can improve the condition of sinus mucosa. A recent study demonstrated a higher incidence of sinus abnormalities in patients with NPC, and the authors proposed that these patients might be prone to sinonasal infections because of compromised local immunity.²³

Traditionally, CT scan of the paranasal sinus is considered the gold standard test in the diagnosis of sinonasal disease.¹⁵ Because of the following reasons, our study did not use CT scan for the evaluation of the paranasal sinus. First, the Lund–Mackay staging of the sinus diseases by MRI is closely correlated to corresponding staging based

on CT, and MRI does not significantly overstage or overclassify patients with sinus disease.²⁴ Second, a notable study by Brenner and Hall²⁵ indicated that there is convincing evidence for the direct link between CT scans and an increased risk of cancer. Taken together, use of additional sinus CT in these patients with NPC who already had an MRI was unnecessary, costly, and even harmful.

Unlike the study by Huang et al,²³ the current study did not include maxillary sinus retention cysts as positive findings under the Lund–Mackay system. A recent study by Wittkopf et al²⁶ discovered that maxillary sinus retention cysts contribute almost half of the total score within the asymptomatic individual. Our data found 10 maxillary sinuses having retention cysts before the treatment, roughly 5% of all maxillary sinuses and 17% of maxillary sinuses with abnormal Lund–Mackay staging score.



Bhattacharyya¹⁹ suggested that a maxillary sinus retention cyst does not reflect obstructive pathology and is not associated with potentially obstructive anatomic sinus variations. Our study showed that 9 of these 10 maxillary sinuses exhibiting no postirradiation sinus abnormality in the long run, a finding compatible with Bhattacharyya's study.

To the best of our knowledge, the current study is the first to describe the long-term toxicities of the paranasal sinuses in patients with NPC treated by IMRT. There are, however, some limitations to our study that are worth highlighting. First, although sinus image studies are considered gold standard for diagnosing sinus diseases, the association between image findings with clinical symptoms remains uncertain.^{27,28} Interpretation of our data regarding the relationship between mucosal abnormalities and rhinosinusitis needs further elucidation. Second, the number of patients enrolled in the study is limited because we adopted stringent inclusion criteria, which excluded patients losing to regular follow-up or missing scheduled image studies. This sample size is relatively small for a multiple-group study design and may limit more informative analysis of our data. Furthermore, nearly 90% of the study patients underwent concurrent chemotherapy, whose impact on the integrity of sinus mucosa is not clear at the present time.

CONCLUSION

IMRT is currently the mainstay of treatment for NPC. Our data showed that, with this therapeutic modality, the anterior ethmoid sinus and maxillary sinus were the most vulnerable sinuses having mucosal abnormalities after treatment, especially at the acute stage. Sphenoid sinus, on the other hand, appeared resistant to the occurrence of radiotherapy toxicity. Reduction of irradiation dose to the ostiomeatal complex region, therefore, might be beneficial in preventing post-radiotherapy sinus toxicities. In the long run, however, the application of IMRT does not significantly increase the incidence of sinus toxicities in patients with NPC.

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