Damage of nasal mucociliary movement after intensity-modulated radiation therapy of nasopharyngeal carcinoma

Gen-Di Yin¹, Guan-Xia Xiong¹, Chong Zhao²,³, Yuan-Yuan Chen²,³

¹ Otorhinolaryngology Hospital, the First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong 510080, P. R. China; ² State Key Laboratory of Oncology in South China, Guangzhou, Guangdong 510060, P. R. China; ³ Department of Radiation Oncology, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong 510060, P. R. China

Abstract Background and Objective: Radiation usually results in paranasal sinusitis in patients with nasopharyngeal carcinoma (NPC), which influences patients' quality of life. This study aimed to determine the relationships between dose distribution in the nasal cavity and nasal mucous injury in patients with NPC treated by intensity-modulated radiation therapy (IMRT), and to find the tolerable radiation dose for the nasal mucous. Methods: Sixty-six patients with NPC treated by IMRT between October 2006 and November 2008 were enrolled. The radiation dose in the nasal cavity was determined by the computer with the IMRT work platform. Mucociliary transport rate (MTR) was detected by modified saccharine test before IMRT, at the end of IMRT, and at 3, 6, and 12 months after IMRT. Results: The data were available for 129 cavities. The cavities receiving a mean dose below or equal to 37 Gy showed substantial preservation of nasal mucus after IMRT. The MTR decreased to (62.82 ± 38.59)%, (56.78 ± 37.79)%, (64.05 ± 39.37)%, and (71.13 ± 39.55)% of pre-IMRT value at 4 time points after IMRT, with significant differences among the data (P < 0.05). In contrast, when the cavities received a mean dose higher than 37 Gy, no significant differences in MTR among the time points were observed. At 3 months after IMRT, the MTR was the lowest (38.27% of pre-RT value). Conclusions: A mean radiation dose of ≤37 Gy for the nasal cavity is an optimal dose to protect the nasal cavity function.

Key words: Nasal mucosa, soft tissue injuries, radiotherapy, conformal, dose-response relationship, radiation

Nasopharyngeal carcinoma (NPC) has an incidence of 11.76 to 20.88 per 100 000 people in Guangdong¹. Although radiotherapy-based comprehensive treatment has increased the 5-year survival rate to 80%–90% in patients with early NPC², conventional radical radiotherapy for NPC usually covers the posterior 1/3 to 1/2 part of the nasal cavity, middle and posterior ethmoid sinuses, and whole sphenoid sinus, resulting in nasal tissue damage commonly and causing various nasal complications, such as nasal congestion, purulent nasal discharge, and epistaxis³. The degree of radiotherapy-caused nasal mucosa damage is closely related to clinical stage, basic disease, and individual factors. Among these factors, radiation dose is the most crucial one. The relationship between radiation dose and the organ damage in radiation field and subsequent clinical symptoms are of concern. Although it is agreed that larger radiation dose will cause more serious damage, the relationship between damage and dose has not been elucidated. The main reason is that the ⁶⁰Co and linear accelerator were commonly used in radiotherapy in the past, and the doses to the posterior nasal cavity had little variety, often about 70 Gy, hence, there was no clinical basis for studying the dose-effect relationship between radiation damage and radiation. However, over the past 20 years, with the development of three-dimensional conformal radiotherapy and other new radiotherapy techniques³, the radiation doses to the nasal cavity and normal tissue or organs surrounding the lesions are expected to decrease⁴, which provides a suitable platform for the study of dose-effect relationship of radiation and damage. Related
research reports promote understanding of the prevention
and treatment of post-radiation complications to a new
degree[7]. Theoretically, it is believed that the influences of
different rays on the nasal mucociliary system are certainly
not the same, and greater dose leads to greater damage.
But it is not clear whether this dose-damage relationship is
a simply rising slant or other underlying law. The dose-effect
relationship that a higher dose leads to a greater damage is
only obtained from the past simple animal model. Human
nasal mucociliary system has its specificity, and its
irradiation reaction, tolerance, recovery degree, and other
rules response to different radiation doses are different from
other animals too. In fact, our clinical observations show
that after intensity-modulated radiation therapy (IMRT),
some patients have obvious nasal complications, whereas
some patients have only mild or no nasal complications.
IMRT-caused post-treatment variety makes it necessary and
possible to study the relationship of different doses and
damage to the nasal mucosa. As we know, the nasal cavity
mainly has self-clearance, temperature and humidity control,
sense of smell, resonance, and other functions, among
which self-clearance function has a significant role in normal
cleaning and defensiveness of the nasal cavity. Impairment
of self-clearance often causes failed clearance of viruses,
bacteria, fungi, and other harmful substances in the nasal
cavity, resulting in sinusitis, nasal stones, and other
illnesses. Mucociliary transport function directly affects the
self-clearance function of the nasal cavity.

We designed a prospective cohort study using modified
saccharin test with high credibility to detect the nasal
mucociliary transport function in patients with NPC treated
by IMRT, and analyzed the change characteristics of nasal
mucociliary transport function before and after IMRT and its
relationship with radiation dose to preliminarily investigate
the tolerance dose of nasal mucociliary system.

Materials and Methods

General information

The patients with NPC treated by IMRT between
October 2006 and May 2009 in Sun Yat-sen University
Cancer Center were enrolled. The enrollment criteria included:
patients with NPC treated by IMRT; 25 to 45 years old; no
tumor invasion in the nasal cavity; no history of chronic
rhinitis, sinusitis, severe nasal septal deviation, allergic
rhinitis, and other nasal diseases; no upper respiratory tract
and systemic acute inflammation 1 week before the test; no
medication in the nasal cavity 1 week before the test; no
previous head and neck radiotherapy for other diseases; no
long-term exposure history of dust and other irritants in work
environment. All patients signed informed consent.

A total of 66 patients, 46 men and 20 women, were
enrolled. Their age ranged from 25 to 44 years, with a
median of 37.5 years. Of the 66 patients, 61 had poorly
differentiated squamous cell carcinoma, 2 had moderately
differentiated squamous cell carcinoma, 1 had
undifferentiated squamous cell carcinoma, and 2 had
vesicular nucleus cell carcinoma. According to the 1992
Fuzhou staging system, 9 had stage I disease, 14 stage II,
32 stage III, and 11 stage IV. Forty-three patients were
 treated with cisplatin (DDP) plus 5-fluorouracil (5-FU) or
with DDP alone as induction, concurrent, or adjuvant
chemotherapy. One patient had a history of trauma in the
right nasal cavity and physical examination showed an
obvious scar on the right inferior turbinate. Therefore, this
right nasal cavity was excluded from the study. Two patients
had severe deviated septum reaching the inferior turbinate,
and had these nasal cavities excluded. A total of 129 nasal
cavities were included in our analyses.

Determination of mean radiation dose to the
nasal cavity

The radiotherapy plans were designed according to the
tolerance doses of tissues and organs[8]. In all patients, the
mean radiation doses to sensitive organs near the lesions
were less than the tolerance doses of corresponding
organisms. Among 132 sides of parotid glands, only 28
(21.2%) received doses exceeding the tolerance dose. For
other organs, a few (1–4) cases received doses exceeding
the tolerance dose, accounting for less than 5% of the total
(Table 1).

On the IMRT work platform, the radiotherapy plans
were retrieved, and the nasal cavity was delineated at every
level, using the junction of bone and mucosa as the
boundary of delineation area. The radiation doses to the 129
nasal cavities ranged from 23.14 to 56.38 Gy, with a mean
of (36.46 ± 11.23) Gy, given by 30 fractions. The mean
radiation dose to the nasal cavity was automatic calculated
by computer.

Modified saccharin test

Before and at the end of radiotherapy, all included
nasal cavities were examined by modified saccharin test.
Patients were in sitting up position with quiet nasal
breathing. Saccharin crystal particles with diameters of
about 2.5 mm × 0.5 mm were selected (Guangzhou
Tianguan Food Additive Co., Ltd, lot number: 20060802). A
grain of saccharin stained by methylene blue was placed on
the surface of inside mucosa 1.0 cm behind the inferior
turbinate by a gun-shaped forceps, then timing started at
this time. Patients were asked to swallow every 20 s. The
The study found that when the dose was larger than a certain dose, the MTR ratio (the ratio of post-IMRT MTR to pre-IMRT MTR) changed significantly, then maintained at a low level. The dose at this level was considered as the threshold dose. To determine the threshold dose of saccharin tests at different phrases more objectively, a segmented regression model ([9]) (Formula 1) taking radiation dose as the independent variable was used to describe the mean MTR ratio. Setting m as the threshold dose, independent variables were divided into low dose (\( \leq m \)) group and high-dose (\( > m \)) group. Data in low dose group were put into the equation 1 and data in high dose group were put into the equation 2 to determine the equation coefficient.

\[
\text{Ln}Y = \begin{cases} 
  a_1 + b_1 X_i, & (X_i \leq m) \\
  a_2 + b_2 X_i, & (X_i > m)
\end{cases}
\] (Formula 1)

By analyzing the scatter diagram, the possible value of m was estimated and the independent variables determined by m values were iteratively put into the equation. When the equation had the maximal determination coefficient R^2, m was determined as the threshold dose value.

Other statistical methods included f-test, ANOVA, and multiple linear regression analysis.

### Results

#### The threshold dose

The MTR ratio (%MTR) could reflect the impact of rays on MTR, therefore, %MTR was selected as a main observation indicator. The relationship between %MTR and radiation doses at different time are demonstrated in a scatter diagram (Figure 1).

At the end of radiotherapy, and at 3 and 12 months after radiotherapy, the threshold dose was 37 Gy. At 6 months after radiotherapy, the threshold dose was 39 Gy. To facilitate descriptions, the data of %MTR were divided into high and low dose groups according to threshold dose.

#### The comparison of %MTR between high and low dose groups in 1-year observation

In the low dose group, at the end of radiotherapy, and at 3, 6, 12 months after radiotherapy, the %MTR were (62.82 ±
38.59), (56.78 ± 37.79), (64.05 ± 39.37), and (71.13 ± 39.55), respectively, with significant differences among them (P < 0.05). The damage of the nasal mucosa did not stop after the end of radiotherapy. During the 1-year observation, the %MTR was the minimum at 3 months after radiotherapy, then increased over time.

In high dose group, the %MTR kept at a low level; at the end of radiotherapy, at 3, 6, 12 months after radiotherapy, the %MTR were (15.41 ± 7.21), (15.76 ± 7.28), (16.57 ± 7.62), and (14.84 ± 7.55) respectively, with no significant difference among them (P > 0.05).

The change of nasal MTR in 1-year observation

Before radiotherapy, the mean MTR was (8.24 ± 3.27) mm/min. At the end of radiotherapy, the mean MTR significantly decreased to only 40.59% of pre-IMRT value. During 1-year observation, the MTR was the minimum at 3 months after radiotherapy (only 38.27% of pre-IMRT value), and gradually increased after then, indicating gradual recovery of the nasal mucociliary function. The MTR increased to 48.90% of pre-IMRT value at 12 months after radiotherapy.

Multivariate analysis of factors affecting %MTR

The radiation dose to the nasal cavity, gender, age, stage, chemotherapy, and the time after radiotherapy were considered as independent variables, and %MTR was considered as a dependent variable to establish a multiple linear regression model. The result showed that only the radiation dose to the nasal cavity was the independent factor affecting %MTR (P < 0.05) (Table 2).

Discussion

Due to the limitation of current radiotherapy techniques, to ensure adequate radiation dose to lesions, it is inevitable for some sensitive organs close to lesions receiving dose greater than the tolerance dose. Kwong et al. analyzed the data of 33 patients with early stage NPC treated with IMRT in Hong Kong Queen Mary Hospital. They found that the mean dose to the parotid glands was 38.8 Gy, higher than the tolerance dose. Among our patients, 28 had the parotid gland receiving a mean dose [(31.56 ± 8.67) Gy] higher than the tolerance dose, only a few had other organs receiving a mean dose higher more than the tolerance dose (Table 1). The NPC target delineation for our patients was based on the principle in the reference. The radiotherapy plan was reasonable.

In this study, we observed the changes of nasal MTR before and after radiotherapy to preliminarily explore the relationship between radiation dose and the nasal mucociliary system damage and the tolerance dose of the nasal mucociliary system. Previous studies showed that the determination of the tolerance dose of sensitive tissues or organs near the lesions and the outcomes after radiotherapy is important in making comprehensive radiotherapy plan to control the radiation doses to sensitive tissues or organs in reasonable ranges. According to the tolerance dose of parotid gland reported by Eisbruch et al., we propose to
limit the volume dose to two-thirds of the parotid within 32 Gy in all patients with head and neck cancer treated with radiotherapy\(^8\). However, at present, the radiation-damage of the nasal mucociliary system has not been studied by using a similar thinking.

The threshold doses to the nasal mucus at different stages were calculated with a segmented regression model. At the end of radiotherapy, and at 3, 6, 12 months after radiotherapy, the threshold doses to the nasal mucus were 37, 37, 39, and 37 Gy. The above findings and the changes of the indicators after radiotherapy indicated that a dose less than 37 Gy to the nasal cavity caused less damage to the transfer function of the nasal mucociliary system. During the observation period, the nasal MTR recovered gradually. Therefore, we propose that the tolerance dose of the nasal mucus is 37 Gy.

Our results suggested that nasal mucosa damage did not stop since the end of radiotherapy, and the damage of nasal mucociliary transfer function at 3 months after radiotherapy was more severe than that at the end of radiotherapy. Through histological study, Wang et al.\(^13\) showed that the middle ear mucosa damage caused by radiation continued to aggravate after the cessation of radiotherapy, and the collapse and deficiency of the mucosa epithelial cilia at 3 months after radiotherapy was more obvious than that at 1 month before radiotherapy. This continuous damage may be mainly related to the delayed effect of radiation, which means radiation damage effect continues after radiotherapy\(^14\). In a clinical study on 32 patients treated with conventional radiotherapy, Kamel et al.\(^15\) also observed a continuous decrease of the nasal MTR, which became stable and persistent at 6 months after radiotherapy.

Nasal complications can be reduced by applying clinical interventions for the nasal cavity during and after radiotherapy. We observed that the nasal mucosa damage aggravated continuously from the beginning of radiotherapy to 3 months after radiotherapy, which was the developing period of nasal cavity complications. From 3 months to 1 year after radiotherapy, the function of the nasal mucociliary system recovered gradually, but did not yet return to normal. During this period, nasal mucosa congestion, nasal discharge, crusting, nasal bleeding could still be observed by using front nose scope or nasal endoscope. Therefore, we suggest that in 1 year after radiotherapy some methods such as nasal irrigation can be used to reduce the edema, secretions, and other situations caused by nasal mucosa dysfunction, and the period from the beginning to time 3 months after radiotherapy is a critical period to prevent nasal complications. Timely and effective clinical intervention is important in preventing nasal cavity complications and improving the quality of life of patients.

In this study, the multiple regression analysis of the relationship between the nasal MTR and the radiation dose to the nasal cavity, gender, age, stage, chemotherapy, and the time after radiotherapy showed that only the radiation dose to the nasal cavity was the independent factor affecting the nasal MTR. Therefore, the determination of the tolerance dose to the nasal mucociliary system is important in protecting the nasal mucociliary system during radiotherapy. With the development of radiation techniques, the in-depth understanding of radiation-caused complications, and patients’ improved requirements for quality of life, investigators will pay more attention to control the local radiation dose to the nasal cavity technically and improve the understanding of the nasal mucociliary system protection. Our preliminary research shows that, while ensuring the radiation dose to NPC lesions, controlling the radiation dose to the nasal cavity within 37 Gy via advanced radiotherapy technique can protect the transfer function of the nasal mucociliary system reasonably. How to improve the data such as changes of the nasal cavity morphology and quality of life related to nasal cavity, and explore the tolerance dose to the nasal mucosa should be further studied.

### References


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