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醫學研究所

碩士學位論文

鼻咽癌患者放射治療後鼻竇變化之觀察

The Paranasal Sinuses Change in Post-irradiation Patients with Nasopharyngeal Carcinoma

指 導 教 授 ：高大成　副教授

研 究 生：梁凱莉

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中文摘要

背景：鼻咽癌是台灣第二常見的頭頸癌。放射治療是目前對鼻咽癌治療的主要方式。放射治療後的患者常產生鼻及鼻竇炎的併發症，臨床上醫師常建議病患以鼻腔沖洗來緩解症狀。但至今關於鼻腔沖洗對放射治療後引發之鼻及鼻竇炎的療效尚無報告。本研究的目的在希望瞭解放射治療引起的鼻及鼻竇炎之發生率及病程進展。同時嘗試研究鼻腔沖洗對放射治療引起的鼻及鼻竇炎的治療效果。

材料與方法：首先進行回溯性的觀察，以瞭解電腦斷層診斷之鼻及鼻竇炎在放射治療後鼻咽癌患者的發生率。收案自 2002 年 1 月至 2004 年 6 月間在本院診斷為鼻咽癌且接受全程放射治療的患者，觀察其放射治療後一年內的電腦斷層鼻竇變化。自 2004 年 10 月至 2006 年 5 月間開始收案在本院新診斷鼻咽癌的患者，排除未接受完整放射治療、沒有治療後追蹤及追蹤期間診斷有局部復發者。將收案患者隨機分為接受鼻沖洗或沒有接受鼻沖洗兩組，接受鼻腔沖洗者於放射治療開始即接受每日鼻腔沖洗至治療後第 6 個月，在放射治療開始前、放射治療第 4 週、放射治療完成以及放射治療後的 1 個月、2 個月、3 個月、6 個月和 12 個月患者接受鼻內視鏡檢查和鼻及鼻竇炎問卷訪視。

結果：回溯性的觀察 50 名患者在一年內連續的鼻竇電腦斷層變化，發現在放射治療後電腦斷層的評分即爬升，但在 6 個月時已漸下降，至治療後 12 個月時電腦斷層分數仍略高於治療前，但已接近治療前。後續進行的前瞻性研究共收案 107 名患者。接受鼻腔沖洗的患者在接受沖洗期內的鼻內視鏡及鼻及鼻竇炎症狀

分數較低，兩組在沖洗治療期間的內視鏡及問卷呈有意義的差別(p=0.0001 及 0.0012)。若就各觀察點而言，在放射治療後的 2 個月及 3 個月兩組的內視鏡或問卷分數達最明顯的差異。但無論患者是否接受鼻沖洗，治療後 12 個月時患者的平均症狀及內視鏡檢查都減緩至接近治療前。

結論：本研究的結果發現鼻及鼻竇炎是鼻咽癌患者放射治療後常見的併發症。以目前的放射治療技術，多數患者的鼻及鼻竇炎症狀在治療後 6 個月漸趨緩解。而鼻腔沖洗有助於減少患者在治療初期的鼻腔不適。

關鍵字：併發症、鼻咽癌、鼻腔沖洗、放射治療、鼻及鼻竇炎

Abstract

Background: Nasopharyngeal carcinoma (NPC) is the second common head and neck cancer in Taiwan. Radiotherapy (RT) is the standard treatment for NPC. RT-induced rhinosinusitis is a common side effect in post-irradiated NPC patients. Nasal irrigation is frequently recommended for treatment of post-RT rhinosinusitis. To our knowledge, there was no study related to this subject till now. The purpose of this study was to find the RT effect on the paranasal sinuses in patients with NPC, including the incidence and the timing course. And we try to evaluate the efficacy of nasal irrigation for RT-induced rhinosinusitis.

Materials and Methods: A retrospective study was preformed first for estimate the incidence of IMRT-induced rhinosinusitis in our institute and the timing course of sinus mucosal change in the first post-treatment year. Patients who received full course RT for NPC and had 4 times CT scans at baseline, post RT 3months, 6 months and 12 months in our hospital were retrospectively recruited from January 2002 to June 2004. From October 2004 to May 2006, patients with NPC were consecutively recruited. Patients who did not complete RT, who had residual or recurrent nasopharyngeal tumor during the study period, and who lost to follow-up after RT were excluded. All patients were randomly allocated to irrigation or non-irrigation groups. Patients in irrigation group received daily nasal irrigation till 6 months after

RT. The endoscopy and questionnaire scores were recorded at baseline (the week before radiotherapy), at 4th week of RT, at the week RT completed and at post-RT 1, 2, and 3, 6 and 12months.

Results: Fifty patients with NPC were enrolled for the retrospective study. The CT scores rose after RT and gradually decreased at post-RT 6 months. The CT scores at post-RT 12 months remained slightly higher than the baseline. It seemed the RT effect on paranasal sinuses had acute and late phases. The prospective study designed under this hypothesis enrolled 107 patients with NPC: When patients were grouped as irrigation or non-irrigation, patients in the irrigation group had lowered endoscopic and questionnaire scores than patients in non-irrigation group. Significant differences between two groups were observed when including all follow-up points till post-RT 6 months both in endoscopic and questionnaire scores (p=0.0001 and 0.0012, respectively). The between-group differences were most obvious at post-RT 2 and 3 months. However, the mean endoscopic and questionnaire scores decreased to near the baseline level at post-RT 12 months, both in irrigation and non-irrigation groups.

Conclusions: The results of this study confirmed that rhinosinusitis was a common RT side effect in patients with NPC. With the advances of radiotherapy technique, most IMRT-induced rhinosinusitis improved after 6 months. Nasal irrigation was proved as a safe and effective management for relief the acute post-RT nasal

symptoms.

Keywords: complication, nasopharyngeal carcinoma, nasal irrigation, radiotherapy, rhinosinusitis

Chapter 1 **Introduction**

1.1 Background

Nasopharyngeal carcinoma (NPC) is a squamous-cell carcinoma arising from the epithelium of the nasopharynx. Nasopharyngeal carcinoma is rare in western countries and its incidence is less than one per 100,000 population.[1] However, NPC occurs much frequent in southern China, especially at the Guangdong province. Hong Kong and Taiwan, which geographically located near the province of Guangdong, are also with high incidence of NPC. The reported incidence of NPC among men and women in Hong Kong is 20–30 per 100 000 and 15–20 per 100 000, respectively.[2] In Taiwan, the crude annual incidence was 7.9 per 100,000 males and 3.3 per 100,000 female. The ratio between male to female was 2.4:1.[3]

The possible etiology of NPC includes genetic, ethnic and environmental factors. Familial clustering of cases of NPC indicates the potential role for genetic factors.[4-6] The consumption of salted fish is associated with increased risk.[7-9] The Epstein-Barr virus (EBV) has been implicated as an important causative agent in NPC. The EBV is consistently found in tumor cells of NPC. The serum EBV DNA in patients of NPC showed a strong correlation with disease stage and prognosis.[10,11]

The histological classification of NPC proposed by WHO included 3 types and subdivided into two groups, according to their relationship to EBV and disease

patterns (table 1.1).[12] Patients with keratinising squamous cell carcinomas (WHO type I) have a reduced EBV titer, whereas those with non-keratinising carcinomas (WHO type II or type III) have raised titers. The histology distribution of NPC in southern Chinese and Taiwan were different from western countries, with a much higher incidence of undifferentiated carcinoma. The distribution of type I, II and III NPC in southern Chinese was 2%, 3%, and 95%, respectively.[13] Patients with undifferentiated carcinomas have a higher local control rate and higher distance metastasis rate than those with differentiated carcinomas.

Table 1.1 Histological classification of nasopharyngeal carcinoma

Keratinising squamous-cell carcinoma	WHO type I
Non-keratinising carcinoma	
1. differentiated non-keratinising carcinoma	WHO type II
2. undifferentiated carcinoma	WHO type III

Radiotherapy (RT) is the standard treatment for NPC. In conventional radiotherapy, 50 Gy is given to regions at risk for harboring subclinical disease and 65-75 Gy is given to the primary tumor and the involved neck nodes. Patients with early stage NPC (stage I and stage II) generally have good treatment outcomes. For

patients with advanced NPC (i.e., T3, T4 or node-positive diseases), RT alone is not adequate. NPC is also a chemosensitive tumor, especially with cisplatin-based regimens. A combination of chemotherapy with RT is the optimal way to treat high-risk patients. Phase III trials have showed increased local control and survival benefit with concurrent chemoradiation.[14-17] But the drug of choice, the timing, dosage and duration of chemotherapy remain controversial.

The main principles of radiotherapy are the delivery of a tumoricidal dose to the primary site and suspected lymphatic spread region with well recognition of normal tissue tolerance. Radiotherapy results in some undesirable toxicity, including acute and late complications. Acute effects develop during a standard 6- or 7- weeks course of radiation therapy and the late effects develop weeks, months, or years after the end of treatment. The acute RT reactions result from the injury of rapidly renewing normal tissue. And the late reactions result from cell loss in nonregenerating or slowly renewing normal tissues.[18] The brain stem, spinal cord, pituitary gland, orbit, paranasal sinuses, nasal cavities, parotid glands oral cavity, inner and middle ears all located closely surround the nasopharynx. These are all inevitably injured by RT. Survivors of NPC usually have impaired quality of life. The possible radiation sequelae are xerostomia, trismus, rhinosinusitis, otitis media, cranial nerves palsies, dysphagia, hearing loss or temporal lobe necrosis etc.[19-24]

With the advances in computing and engineering techniques, newer techniques of radiotherapy as 3D treatment planning and intensity-modulated radiotherapy (IMRT) had replaced the conventional radiotherapy with the advantage of more precision of aiming the radiation beam at irregular tumors. The IMRT techniques improve the differential between the tumor and the dose–limiting organs, therefore decrease toxicity for surrounding critical organs with improved loco-regional control.[25,26] In recent years, its use has spread rapidly in both academic and community radiation oncology facilities but its outcomes and follow-up reports are still limited. IMRT in the head and neck is more feasible than in other sites because organ motion is practically absent.[25,27,28] Some research had reported the IMRT had reduced the severity of xerostomia after treatment in patients with head and neck tumor.[29,30]

Fang et al analyzed the quality of life (QOL) of patients who received conventional RT or IMRT showed patients who received IMRT had better quality of life.[31] The authors analyzed the QOL of NPC patients with the European Organization for the Research and Treatment of Cancer Core QOL questionnaire (EORTC QOL-C30) and the Head and Neck QOL questionnaire (EORTC QOL-HN35). However, these two questionnaires were not specific to some common sequelae of NPC survivors as otitis media, rhinosinusitis temporal lobe necrosis or deafness.

These undetected factors also contributed to the patients' QOL.

Most studies about NPC were related to the treatment outcomes. Only few reported the post-RT complications. An article published in 2005 by Wei et al[2] did a rigorous review of researches about NPC. However, only a short paragraph in this article discussed the radiation side effects because of lacking of associated reports. The authors stated that cutting down the complications of treatment should be one of the main objectives of future clinical trials.

1.2. Purpose

NPC was the second common head and neck tumor in Taiwan. Its incidence was just lower to the oral cavity cancer. The reported newly diagnosed NPC was 1,004 for male and 379 for female per year. And it remained the 14th leading cause of cancer death in recent three years.

About one hundred patients with NPC received treatment in our hospital per year. In our experience, xerostomia, dermatitis, otitis media and rhinosinusitis were the most common acute sequelae after RT. Radiotherapy for treatment of NPC usually includes the nasopharyngeal tumor and involved lymph node plus a margin of potential microscopic spread. The posterior third of nasal cavity and maxillary sinuses, and inferior sphenoid sinuses were included in the RT field. However, few published reports related to RT-induced rhinosinusitis. The IMRT has become a standard tool in treatment of head and neck tumors since mid 1990. Reduce the radiation injury is expected with the popularity of IMRT. However, the incidence of IMRT related rhinosinusitis were unknown.

The survivors of NPC have impaired health-related quality of life. But most studies related to NPC were developing novel treatment approach to raise tumor control. The RT-induced complications draw little interest from researchers. Both the incidence and the timing course of possible complications were not clear yet. And

lacking of studies tried to develop methods to avoid complications.

The purpose of this study was to find the IMRT-effect on the paranasal sinuses in patients with NPC, including the incidence and the timing course. And we try to evaluate the efficacy of nasal irrigation, a common treatment option for RT-induced rhinosinusitis.

Chapter 2 Materials and Methods

2.1. Study Subjects

This study was undertaken after approval by the Institutional Review Board of Taichung Veterans General Hospital, Taiwan. Patients with NPC who underwent IMRT were enrolled in this study. All patients had pathological examination of the nasopharyngeal masses with histological confirmations of NPC. Patients who did not complete RT, who had residual or recurrent nasopharyngeal tumor during the study period, and who lost to follow-up after RT were excluded.

The tumor staging of these patients was according to the AJCC staging manual, 5th edition, 1997.[32] A standard treatment protocol for NPC had been put forth in our hospital: For patients with stage I NPC, they received radiotherapy alone. For patients with stage II.NPC, they received concurrent chemoradiotherapy. Two cycles of concurrent chemotherapy with cisplatin 20 mg/m^2/d plus 5-fluorouracil 400mg/m^2/d by 96-hour continuous infusion during the weeks 1 and 5 of RT.[14] Patients with stage III and IV NPC received neoadjuvant chemotherapy and radiotherapy. The neoadjuvant chemotherapy consists of cisplatin 60 mg /m^2, alternating with 5-fluorouracil 2500 mg/m^2 plus leucovorin 250 mg/m^2 by a weekly schedule for a total of 10 weeks. Local IMRT was delivered within one week after neoajuvent chemotherapy.[33] All patients received IMRT for primary tumor and bilateral upper

neck, and conventional RT for bilateral lower necks. The regular RT dose was 70Gy with 35 fractions (200 cGy per fraction) and adjusted individually. The full course RT usually took 7 weeks.

2.2. Study design

Evaluation the paranasal sinuses can be made by several methods including imaging, nasal endoscopy and questionnaire assessments. Among them, the nasal endoscopy, computed tomography (CT) and questionnaire assessment were most popular.

The nasal endoscopy was usually performed as a routine examination for patients with nasal complaint. Both rigid and flexible nasal endoscopy can assess the nasal cavity, nasopharynx and sinus osteia with good visualization. The most popular staging system of nasal endoscopy was the Lund endoscopic staging system[34] (table 2.1). The Lund endoscopic staging system recorded the endoscopic findings including edema, discharge, polyp, crusting, and scarring. All were graded from zero (normal) to two (severely diseased).If the nasal polyps were limited to the middle meatus, the grade was one. If the nasal polyps extended beyond the middle meatus, the grade was two.

The CT scans provide information of the extent of sinus mucosal diseases and the anatomic variants. And there were several international staging systems available. The Lund-Mackay staging system[34] (table 2.2) was the most popular one. Each sinus was graded as 0 to 2. The scores ranged from 0 (normal) to 24 (severely diseased). The osteomeatal complex was graded as 0 if it was not occluded and graded as 2 if it

was occluded. A CT scan was demonstrated with the Lund radiologic scores in Fig 2.1.

The questionnaire used in this study was the validated Chinese version Lund symptom score that included 6 common sinonasal symptoms: nasal blockage, rhinorrhea, sneezing, headache, facial pain and olfactory change.[34] All symptoms were graded from zero (the mildest) to ten (the most severe).

Table 2.1 The Lund endoscopic scoring system

Characteristic	Left	Right
Polyp	0,1,or 2	
Edema		
Discharge		
Scarring		
Crusting		
Total points		

Scoring for polyps: 0= no polyps; 1= polyps in middle meatus only; 2= polyps beyond middle meatus.

Scoring for edema, scarring and crusting: 0=absent, 1=mild, 2=severe. Scoring for discharge: 0= absent; 1= clear; thin discharge; 2= thick, purulent discharge.

Table 2.2 The Lund-Mackay radiologic grading of sinus systems

Sinus system	Left	Right
Maxillary	0,1 or 2	
Anterior ethmoidal		
Posterior ethmoidal		
Sphenoidal		
Frontal		
Osteomeatal complex	0 or 2	
Total points for each side		

Scoring for sinus systems: 0=no abnormalities; 1= partial opacification; 2= total opacification.

Scoring for the osteomeatal complex: 0= not occluded; 2= occluded

Fig 2.1 The CT scans of patient with post-RT rhinosinusitis (the Lund radiologic score of each sinus was demonstrated)

2.2.1 A retrospective study

A retrospective study was preformed first for estimate the CT-diagnostic incidence of IMRT-induced rhinosinusitis in our institute and the timing course of sinus mucosal change within the first post-treatment year.

Patients who received full course RT for treatment of NPC and had pre- and post-RT CT scans (post RT 3 months, 6 months and 12 months) in our hospital were retrospectively recruit from January 2002 to June 2004.The exclusion criteria was proven recurrent disease in the nasopharynx or sinuses within the first post-RT year. In our institute, patients received MRI for tumor staging. Then they received CT before RT for delineation of the targets. After treatment, patients received CT scans for follow-up locoregional tumor control at 3 months and 12 months post-RT. Some patients also received CT scans at 6 months post-RT for suspected submucoal recurrence. The CT scans of the eligible patients at baseline and at post-RT 3 months; 6 months and 12 months were evaluated and scored with the Lund-Mackay staging system.

The findings of the retrospective study could be taken as hypothesis generating and further confirmation was made by a prospective study.

2.2.2 A prospective study

From October 2004 to May 2006, patients with NPC who received full course IMRT were consecutively recruited. Patients who were lost to follow-up or who had local recurrence in post-RT 12 months were excluded. All patients were randomly allocated to irrigation or non-irrigation groups. Patients in irrigation group received daily nasal irrigation since RT began. The irrigation device was a pulsatile nasal irrigator (Yun-Wang Industrial CO LTD, Tainan, Taiwan, Fig 2.1) designed by Dr Grossan.[35] The irrigation solution was buffered normal saline prepared by mixing 500ml boiled water with manufactured powder (containing 3 gm non-iodized salt and 1.5 gm baking soda). The patients in the irrigation group performed irrigation with 500ml warm saline once a day (250 ml for each nostril) till 6 months after RT.

The questionnaire scores and nasal endoscopy scores were recorded at baseline (the week before radiotherapy), at 4th week of RT, at the week RT completed and at post-RT 1, 2, and 3, 6 and 12months. The post-RT 12 months follow-up provided further information of the disease course. Patients also received CT scans for follow-up the tumor local control (at baseline, post-RT 3 and 12 months).

Physicians were allowed to prescribe a course (10-14 days) of empirical antibiotic for patients who had acute exacerbation of nasal symptoms and had purulence in nasal cavities. For patients suffered with chronic nasal obstruction or rhinorrhea, they were

allowed to use nasal steroid.

2.3 statistic methods

The data were analyzed by intention-to-treat analysis and using the SPSS statistical system 15.0 version (SPSS, Chicago, IL). The paired T test was used to compare the endoscopic and questionnaire scores between irrigation and non-irrigation groups at baseline and each follow-up point. The analysis of variance with repeated measures test was used to compare the endoscopic and questionnaire scores between two groups including 7 follow-up points during trial period (baseline to post-RT 6 months). Pearson coefficients were used to analyze the correlation between CT, endoscopic and questionnaire scores. P values <.05 was considered statistically significant.

Fig2.2 The pulsatile irrigator used in this study

Chapter3. Results

3.1. The retrospective study

A total of 50 patients with NPC were enrolled for retrospective study. There were 7 females and 43 males, with a mean age of 44.9 (17-69) years old. Among them, 16 patients (32%) were with T1 stage NPC, 5 (10%) were with T2a NPC, 4 (8%) were with T2b, 15 (30%) were with T3 NPC and 10 (20%) were with T4 NPC.

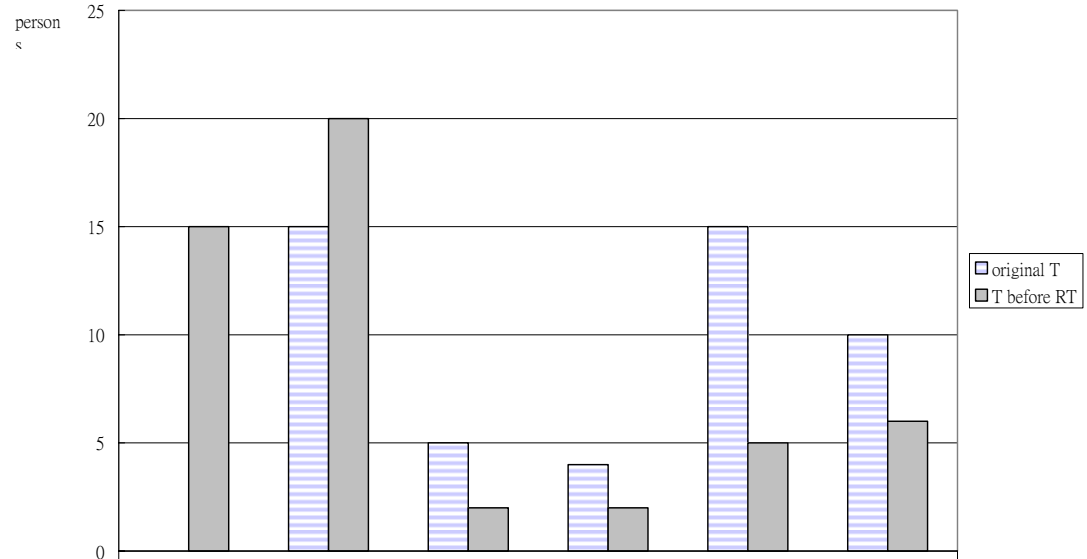
Twenty patients (40%) received concurrent chemo-radiotherapy, and 30 (60%) received neoajuvent CT pulse RT. The tumor volume shrunk a lot after 10 courses CT in patients who received neoajuvent CT. The original T stages and the T stage before RT were shown in Fig 3.1. Most patients were with invisible or T1-2 nasopharyngeal tumor when RT started.

The Lund CT scores at baseline, post-RT 3 months, 6 months and 12 months were shown in Fig 3.2. We found the CT scores rose after RT and gradually decreased at post-RT 6 months. The CT scores at post-RT 12 months remained higher than the baseline. It seemed the RT effect on paranasal sinuses presented with acute and late phases.

Based on these findings, we tried to test the following hypothesis with a prospective study: the RT effects on paranasal sinuses present with acute and chronic phases, and the acute effect resolve within one year. We also tried to test that the nasal

irrigation, an empirical treatment for radiation rhinosinusitis, was effective for relief the acute radiation side-effect.

Fig 3.1 The original and T stage before radiotherapy of patients (n=50).



	invisible	I	II a	II b	III	IV
original T	0	15	5	4	15	10
T before RT	15	20	2	2	5	6

Fig 3.2 the mean CT scores of patients with NPC (N=50), data presented as mean ± SE

3.2 The prospective study

3.2.1 Descriptive statistics

A total of 107 patients were recruited. A written informed consent was obtained from each patient. There were 23 females and 84 males. The mean age was 47.7 (17-81) years old. Among the eligible patients, 63 patients were in the non-irrigation group and 44 patients were in the irrigation group.

Among the eligible patients, 7 patients (6.5%) received IMRT alone, 43 patients (40.2%) received concurrent chemo-radiotherapy, and 57 patients (53.3%) received neoajuvent chemotherapy pulse radiotherapy. The median dose of IMRT for primary tumor and upper neck were 70cGy (ranged from 5600 to 7680). The T stage and the T stage before RT (the neoajuvent CT reduced the tumor volume) was shown in fig 3.3.

The endoscopic and questionnaire assessment were performed at the baseline (one week before radiotherapy), the 4th week of RT, at the week RT completed, 1,2,3,6 and 12 month after RT. The endoscopic and questionnaire scores of 107 patients were listed in table 3.4 and shown in fig 3.4. Patients' nasal symptoms gradually rose after RT and achieved peak at 2 months after RT. Their symptoms then slowly reduced. Their mean symptom scores were close to the baseline level at post-RT 12 months.

There were 106 patients received follow-up CT scans at 3 months after RT and

89 patients received CT scans at 12 months after RT. The incidence of CT diagnosed rhinosinusitis (CT scores >=1) was 47.2% (50/106) at post RT 3 months and 34.8% (31/89) at post-RT 12 month.

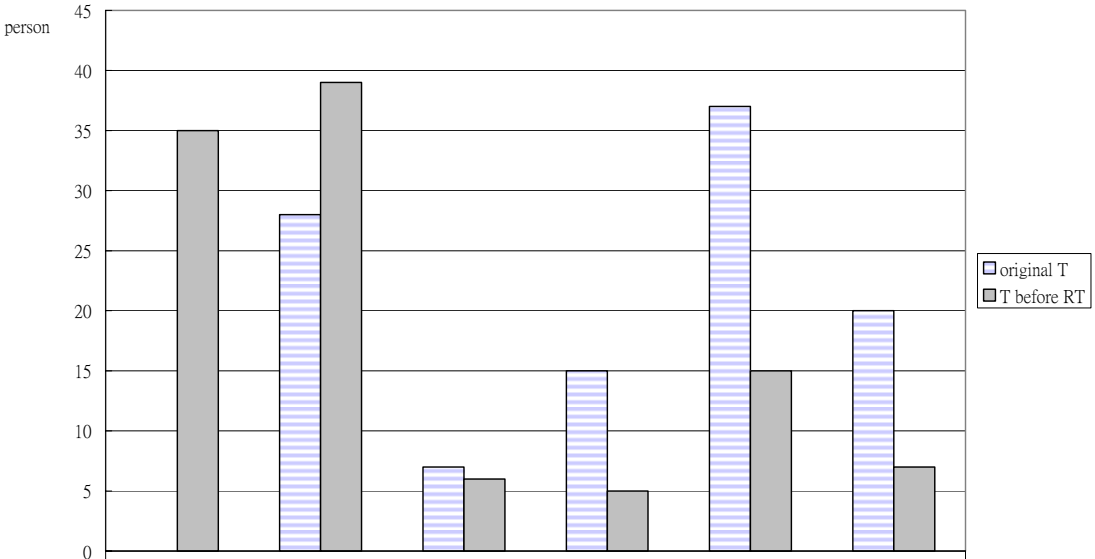
3.2.2 Referral statistics

When patients were grouped as irrigation or non-irrigation groups, their characteristics, endoscopic and questionnaire scores were listed in Table 3.5. Patients in the irrigation group had lowered endoscopic and questionnaire score than patients in non-irrigation group. Significant differences between two groups were observed when including all follow-up in post-RT 6 months both in endoscopic and questionnaire scores (p=0.0001 and 0.0012, respectively). And the between-group differences were most obvious at post-RT 2 months (in endoscopic and questionnaire scores, p=0.021 and 0.001, respectively) and 3 months (in questionnaire scores, p= 0.028).

3.2.3 The correlation between CT, endoscopic and questionnaire scores

The CT scans, endoscopy and questionnaire assessment were performed within one week in 142 times patients' follow-up. We found the both the endoscopic and questionnaire correlated to the CT scores well (both p=0.000). And the endoscopic scores significantly correlated to the questionnaire scores (p=0.000).

Fig 3.3 The original and T stage before radiotherapy of patients (n=107).



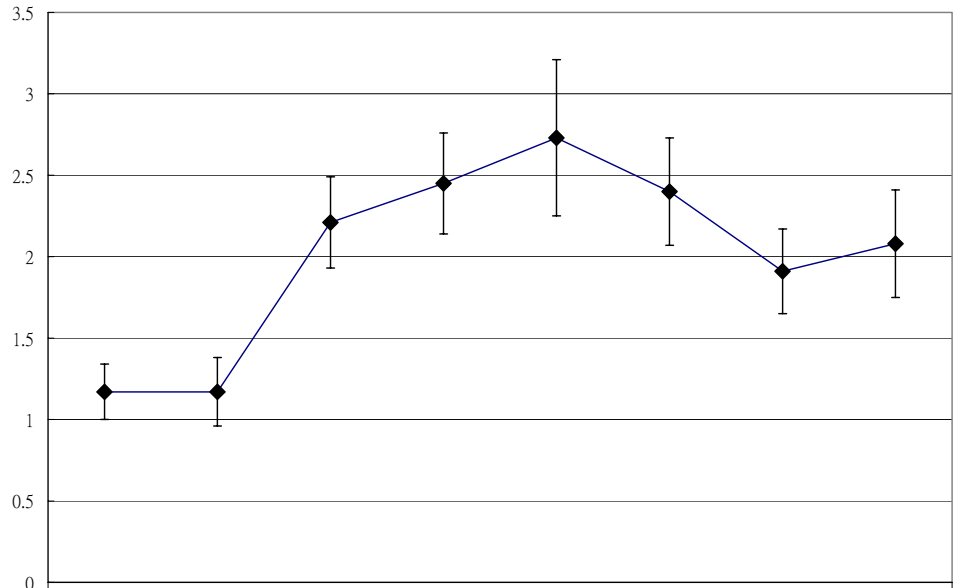
	invisible	I	II a	II b	III	IV
original T	0	28	7	15	37	20
T before RT	35	39	6	5	15	7

Table3.1 The endoscopic and questionnaire scores of patients in prospective study, data presented as mean ± SE

	Endoscopic score	Questionnaire score
Baseline	1.17 ± 0.17 (n=106)	7.92 ± 0.83 (n=107)
Week 4 of RT	1.17 ± 0.21 (n=68)	9.23 ± 0.89 (n=65)
RT completed	2.21 ± 0.28 (n=70)	11.01 ± 1.10 (n=71)
1 month after RT	2.45 ± 0.31 (n=78)	10.53 ± 0.95 (n=78)
2 months after RT	2.73 ± 0.48 (n=75)	10.11 ± 0.97 (n=75)
3 months after RT	2.40 ± 0.33 (n=77)	9.48 ± 0.93 (n=77)
6 months after RT	1.91 ± 0.26 (n=75)	8.42 ± 0.90 (n=74)
12 months after RT	2.08 ± 0.33 (n=62)	7.32 ± 0.88 (n=63)

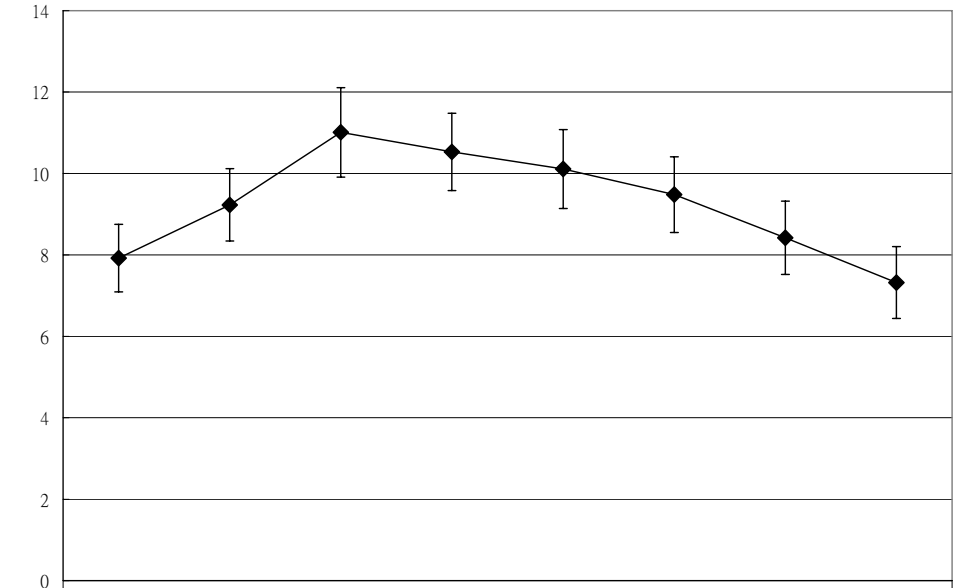
Fig 3.4 The mean endoscopic (a) and questionnaire scores (b) of patients (n=107)

(a)



	baseline	during RT	RT completed	1 mo	2 mo	3 mo	6 mo	12 mo
mean endoscopic score	1.17	1.17	2.21	2.45	2.73	2.4	1.91	2.08

(b)



	baseline	during RT	RT completed	1 mo	2 mo	3 mo	6 mo	12 mo
mean questionnaire score	7.92	9.23	11.01	10.53	10.11	9.48	8.42	7.32

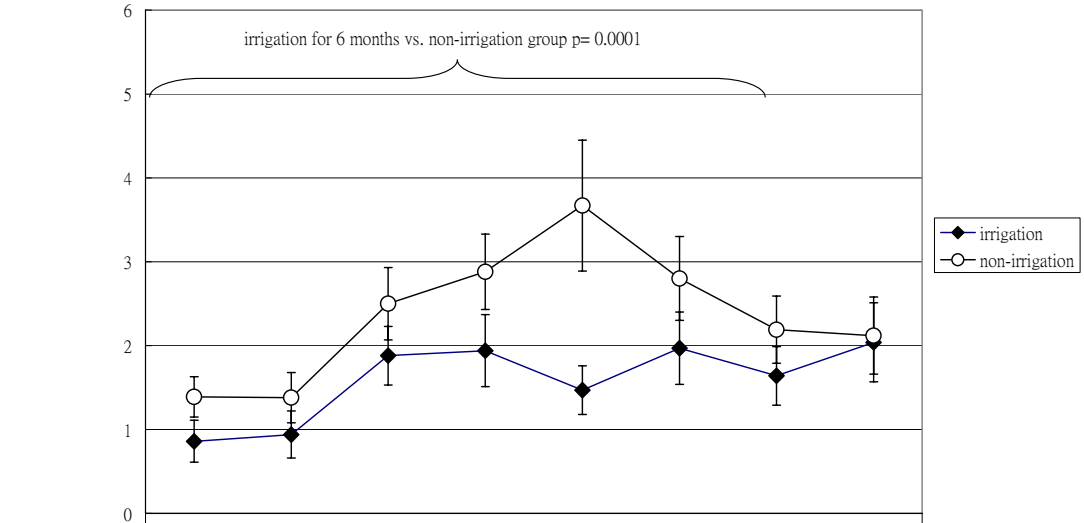
Table 3.2 The characteristics of irrigation and non-irrigation groups

	Non-irrigation group	Irrigation group	*P* values
Age (years)	49.13 ± 1.81 (n=63)	45.61 ± 1.68 (n=44)	0.252 [a]
Sex (F/M)	14/93	9/35	1.000 [b]
Endoscopic scores			
Baseline	1.39 ± 0.24 (n=62)	0.86 ± 0.25 (n=44)	0.139 [a]
Week 4 of RT	1.38 ± 0.30 (n=34)	0.94 ± 0.28 (n=32)	0.288 [a]
RT completed	2.50 ± 0.43 (n=38)	1.88 ± 0.35 (n=32)	0.271 [a]
1 month after RT	2.88 ± 0.45 (n=42)	1.94 ± 0.43 (n=36)	0.138 [a]
2 months after RT	3.67 ± 0.78 (n=43)	1.47 ± 0.29 (n=32)	0.021 [a*]
3 months after RT	2.80 ± 0.50 (n=40)	1.97 ± 0.43 (n=37)	0.215 [a]
6 months after RT	2.19 ± 0.40 (n=36)	1.64 ± 0.35 (n=39)	0.298 [a]
12 months after RT	2.12 ± 0.46 (n=34)	2.04 ± 0.47 (n=28)	0.902 [a]
Questionnaire scores			
Baseline	8.71 ±1.08 (n=63)	6.77 ± 1.28 (n=44)	0.250 [a]
Week 4 of RT	8.73 ±1.22 (n=33)	9.75 ±1.32 (n=32)	0.571 [a]
RT completed	11.00 ±1.45 (n=39)	11.03 ±1.70 (n=32)	0.989 [a]
1 month after RT	11.52 ± 1.26 (n=42)	9.36 ± 1.42 (n=36)	0.257 [a]
2 months after RT	12.74 ± 1.41 (n=43)	6.56 ± 0.96 (n=32)	0.001 [a*]
3 months after RT	11.43 ± 1.29 (n=40)	7.38 ± 1.26 (n=37)	0.028 [a*]
6 months after RT	9.97± 1.31 (n=35)	7.03 ± 1.21 (n=39)	0.103 [a]
12 months after RT	7.38 ± 1.18 (n=34)	7.24 ± 1.35 (n=29)	0.937 [a]

Data presented as mean ± standard error; [a] independent T test; [b] Chi-square test; [c] analysis of variance with repeated measures; * $p < 0.05$

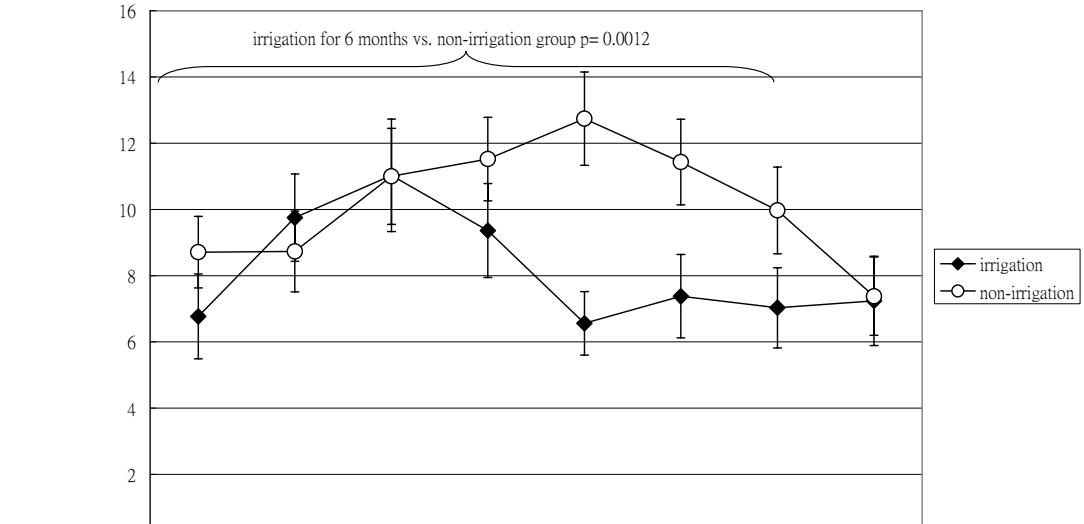
Fig 3.5 The mean endoscopic (a) and questionnaire scores (b) of patients in irrigation group and non-irrigation group

(a)



	baseline	during RT	RT completed	1 mo	2 mo	3 mo	6 mo	12 mo
irrigation	0.86	0.94	1.88	1.94	1.47	1.97	1.64	2.04
non-irrigation	1.39	1.38	2.5	2.88	3.67	2.8	2.19	2.12

(b)



	baseline	during RT	RT completed	1 mo	2 mo	3 mo	6 mo	12 mo
irrigation	6.77	9.75	11.03	9.36	6.56	7.38	7.03	7.24
non-irrigation	8.71	8.73	11	11.52	12.74	11.43	9.97	7.38

Chapter4. Discussions

In cancer treatment, the therapeutic effectiveness has to be balanced with side-effect to normal tissue. This becomes even more important in the treatment of patients with early disease. Published data on acute and late RT effects on normal tissue is still lacking. The effects of RT for NPC patients on the paranasal sinuses were demonstrated in only a few studies.

Chang et al[36] analyzed the computed topographies of 69 patients with NPC and found the CT studies revealed 58.8% of the post-RT scans had mucosal disease of sinuses. And it remained a high prevalence until the 4-year follow-up. In their results, only 24 patients had two post-RT follow-up scans and 14 of them had the 4-year follow-up CT scans. It is difficult to know the time course of sinus mucosal change after RT from this study. In another recently published study, Huang et al[37] evaluate the magnetic resonance images in post-RT NPC patients. They found that the incidence and severity of sinus mucosal disease was found to be highest at post-RT 3 months and decreased gradually with time. Their results were very similar to ours. However, MRI is usually not the best choice in evaluation of sinus mucosa although it is superior in evaluation of tumor status. CT scan was most recommended for diagnosis of chronic rhinosinusitis according to the 2003 Rhinosinusitis Task Force Report.[38]

Kamel et al[39] comprised 32 cases of NPC and analyzed their nasal endoscopy, CT and saccharidne test before and after radiotherapy. The saccharine test was used to measure the mucociliary clearance of the nasal epithelium. They found that the mucociliary clearance deteriorates for up to 6 months and then stabilized and persisted. The total endoscopic appearance score was highest after 2-6 weeks. Both findings suggest acute vs. late radiation effect on the paranasal sinuses. To our knowledge, Kamel's study was the only prospective study about RT-induced rhinosinusitis.

A computed tomographic study conducted by Porter et al[40] in Hong Kong compared the CT findings between control and patients with pre-irradiated NPC. They found higher prevalence of major sinus mucosal abnormalities in patients with pre-irradiated NPC. The possible reasons were tumor blockage the nasal airway and necrotic tumor surface resulted in secondary infection. These two factors both correlated to the tumor size. The larger the tumor size, the more it interferes the sinus clearance. Another study also published by Porter et al[41] stated that some cases of preexisting sinus disease showed improvement after tumor shrinkage. Because most of our patients were with advance T stage, we adjusted this confounding factor by starting the observation after neo-adjuvant CT. Most tumors shrunk to invisible or T1-2 when neoajuvent chemotherapy completed.[33]

Among the published report of RT-induced rhinosinusitis, all were retrospective

in nature except the Kamel's report. And none of them mentioned the effect of RT on patients' nasal symptoms. Besides, those cross-sectional studies cannot provide information of the timing course of disease either.

The believed reason of the post-irradiated rhinosinusitis is the impairment of mucociliary function by radiation damage. Stringer et al[42] found the saccharin test demonstrated the mucociliary clearance rates were markedly reduced after irradiation in 9 adult patients. Surico et al[43] also observed the same findings in 20 children who had treated with radiotherapy of the head and neck region.

Severe morphological change in the mucociliary system after RT had been observed both in animal and human morphological pathology. In an animal study of irradiation nasal mucosal pathology, the ciliary activity of rabbit nasal mucosa decreased immediately after RT and gradually up to 6 weeks after RT. Goblet cell hyper-secretion, cytoplasmic vacuolation and sloughing of ciliated cells was observed for up to 3 weeks then epithelial metaplasia started [44] Lou et al[45] enrolled 10 patients with irradiated NPC who received endoscopic choanoplasty and had their nasal mucosa examined under light and electron microscopy. The average interval since RT of these 10 patients was 5.9 years. The pathologic findings demonstrated in this study were epithelial metaplasia, deposition of collagen fibers on the lamina, reduced cytoplasmic volume of the epithelial cells, intercellular and intracellular voaucolation,

epithelial cells sloughing, ciliary loss and ciliary dysmorphism.. The possible radiation effect on respiratory mucosa were listed in table 4.1.

The treatment of RT-induced rhinosinusitis remained uncertain. Endoscopic sinus surgery has been performed for excision of the synechia bands, drainage and ventilation of sinuses, and correction of choanal stenosis. Some reports improvement of nasal symptoms in these patients but the risk of poor wound healing and bleeding need to be concerned.[46,47] Without the knowledge of time sequence of RT-induced rhinosinusitis, we have no idea when is the best timing of surgical intervention. If it is a self-limited disease, surgery should be delayed till the mucosal change is irreversible.

Nasal irrigation was the most popular treatment for the RT-induced rhinosinusitis. The mechanisms of nasal irrigation are physical cleaning, enhancement of mucociliary function, and removal of local inflammatory mediators. Nasal irrigations are used for various sinonasal conditions including allergic rhinitis, acute or chronic rhinosinusitis, and post-operative care in nasal surgery cases or RT-induced rhinosinusitis.[48,49] Different devices and solutions are available for nasal irrigation. The delivery systems include positive-pressure, negative-pressure, and nebulizers. Previous studies reported that positive-pressure irrigation provided better penetration into sinuses than other delivery systems.[50,51] Various solutions have been used for

nasal irrigation and the normal saline is the most popular and physiologic one.[52]

Because the pathophysiology of RT-induced rhinosinusitis is the impairment of mucociliary function, nasal irrigation is a good choice of treatment. Nasal irrigation provides physical cleaning and enhancement of mucociliary function. Many studies have proved nasal irrigation is a safe, well-tolerated, inexpensive, effective therapy for patients with chronic sinonasal symptoms.[49,53] Patients can long-term use at home with minimal training, therefore they can self management of their nasal symptoms and reduce the use of medical resources.

In our results, the IMRT-induced rhinosinusitis had a self-limited property. Most patients reduced their nasal symptoms within one year. Patients who received nasal irrigation had less nasal complaints compared with those who did not received nasal irrigation. Most nasal symptoms subsided within one year both in irrigation and non-irrigation group.

There were some limitations in our study. First at all, our questionnaire was a symptom visual analog scale without measurement of quality of life. Now a validated Chinese version rhinosinusitis specific quality of life questionnaire (Rhinosinusitis Outcome measures 31 items) has been available in our institute and can be used for QOL evaluation. Second, a sub-group of patients did suffer from long-term rhinosinusitis after RT. Further study is necessary for understanding the risk factors of

prolonged RT-induced rhinosinusitis.

Table 4.1 the radiation effect on respiratory mucosa

Acute effect
Pathological: vacuolation of ciliated cells, expansion of intercellular spaces, hyperreactivity of secretion, stromal edema
Clinical: hyperemia, macerated mucosa, discharge
Delayed effect
Pathological: reduction of cytoplasmic mass, variable degrees of ciliary loss ,widened intercellular spaces
Clinical: crusting, scarring, adhesions, atrophic mucosa

Chapter 5 Conclusions

The results of this study confirmed that chronic rhinosinusitis was a common complication of radiotherapy in patients with NPC. With the advances of radiotherapy technique, the IMRT-induced rhinosinusitis improved after 6 months follow-up. Nasal irrigation was proved as a safe and effective management for relief of the acute post-RT nasal symptoms.

However, prolonged RT-induced rhinosinusitis remained a bothersome problem in small group of patients. Further investigation needs to identify patients with risk of prolonged RT-induced rhinosinusitis. Therefore nasal irrigation or medical treatment can be advised to these patients in early post-RT period for prevention disease progression.

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