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Author(s)	Tsang, RK; Kwong, DL; Ho, AC; To, VS; Ho, WK; Wei, WI
Citation	ORL: Journal for Oto-rhino-laryngology and Its Related Specialties, 2012, v. 74 n. 4, p. 228-233
Issued Date	2012
URL	http://hdl.handle.net/10722/163919
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Long term hearing results and otological complications of nasopharyngeal carcinoma patients: Comparison between treatment with conventional two-dimensional radiotherapy and intensity-modulated radiotherapy

Raymond K. TSANG FRCSE[1]

Dora L. KWONG FRCR[2]

Ambrose C. HO FRCSE[1]

Victor S. TO FRCSE[1]

Wai-Kuen HO FRCSE[1]

William I. WEI FRCS, FRCSE[1]

Division of Otorhinolaryngology – Head and Neck Surgery, Department of Surgery[1] and Department of Clinical Oncology[2], University of Hong Kong, Hong Kong SAR, China.

Short title: Audiological and otological complications after RT for NPC

Correspondence:

Dr. Raymond K. Tsang

Department of Surgery, University of Hong Kong

Queen Mary Hospital, 102 Pokfulam Road,

Hong Kong SAR.

E-mail: rkytsang@hku.hk

Fax: (852) 2819 3780

Tel: (852) 2255 4394

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Abstract

Objective: To assess the long-term audiological outcome and otological complications of nasopharyngeal carcinoma (NPC) patients who have received intensity-modulated radiotherapy (IMRT) versus conventional two-dimension radiotherapy (2DRT).

Study Design: Prospective study on the audiological outcome and otological complications 5-9 years after radiotherapy.

Methodology: Patients had pure tone audiogram before radiotherapy and 5 years after radiotherapy. Otological examination was performed 5 to 9 years after radiotherapy by otolaryngologist.

Results: There is significant deterioration of hearing threshold 5 years after radiotherapy but there is no statistical significant difference in the deterioration of hearing between IMRT and 2DRT. 6 patients in the 2DRT group and 1 patient in IMRT group had osteoradionecrosis of the external auditory canal (p=0.042).

Conclusion: There are fewer incidences of osteoradionecrosis of external auditory canal in patients treated with IMRT. There is no difference in bone conduction threshold in patients treated with IMRT or 2DRT.

Keywords: Nasopharyngeal carcinoma; intensity-modulated radiotherapy; sensorineural hearing loss; osteoradionecrosis.

Introduction

Nasopharyngeal carcinoma (NPC) is the commonest head and neck cancer in Southern China; it is the fifth commonest cancer in male in Hong Kong. Radiotherapy is the primary treatment modality of nasopharyngeal carcinoma. The technique of intensity-modulated radiotherapy (IMRT) further enhances the efficacy of radiotherapy for NPC and studies have shown that IMRT alone offers excellent locoregional control in early stage NPC[1-3]. When comparing with conventional two-dimensional radiotherapy (2DRT), there is less radiation to the adjacent structures like parotid glands and temporomandibular joints when IMRT is employed for treatment of early NPC[4]. Studies have shown that IMRT improves the quality of life of NPC patient after radiotherapy when compared to conventional 2D radiotherapy, especially in regard to preservation of salivary function[1, 5]. Radiation can damage the inner ear structures and neural pathways leading to hearing loss[6, 7]. Long term follow up studies have shown that NPC patients suffered from significant sensorineural hearing loss after radiotherapy treatment[8, 9]. The unique advantage of IMRT in offering adequate radiation dosage to the tumor while reducing the radiation dosage to the surrounding normal tissue may reduce the long term sensorineural hearing loss in NPC patients treated with radiotherapy. In this study we would like to compare the long term hearing results and otological complications in two groups of patients; one group treated with conventional 2DRT and the other group treated with IMRT. In order to avoid the confounding factor of ototoxicity from chemotherapy, no patients in the cohort received chemotherapy.

Materials and Methods

Patients

From January 2001 to March 2005, patients with UICC 2002 stage II nasopharyngeal carcinoma (T1N1, T2N0, T2N1 disease) were treated with radiotherapy alone with either 2DRT or IMRT. As IMRT was a novel treatment at that time, 2DRT was the standard of care. The choice of RT was based either in a trial setting or according to patient's preference or physician's decision. The pretreatment evaluation included a complete history and physical examination, nasopharyngoscopy, chest X-ray, complete blood count, liver and renal biochemistry. Patients were stage with contrast computer tomography (CT) scans to determine the eligibility to enter the study. None of the patients received neoadjuvant, concurrent or adjuvant chemotherapy, as our institution treatment protocol did not employ chemotherapy for stage II disease.

2DRT

2DRT were performed in 2 sequential phases. Phase I started with 2 large lateral opposing facio-cervical fields covering the nasopharynx and upper cervical lymph nodes and any parapharyngeal extension. 40Gy was given in 2Gy/fraction, 5 fractions per week in 4 weeks. After 40Gy, phase II treatment continued with 1 anterior facial and 2 lateral opposing fields to the nasopharynx to avoid the spinal cord to another 28Gy in same fractionation. The total dose to nasopharynx was 68Gy in 34 fractions. As the temporal bones were irradiated in both lateral fields during both phase I and phase II 2DRT, the dose to temporal bone is considered the same as the dose to nasopharynx, that is, about 68Gy. The lower neck was treated with a

separate anterior cervical field with midline shield to protect the spinal cord. The dose to the neck was 66Gy in 33 fractions.

IMRT

The nasopharynx and upper neck was treated with IMRT. IMRT was performed with Corvus system (MIMiC from NOMOS, Sewickley, USA). Treatment targets and organ at risks were localized on planning CT scan with patient in immobilization cast. The gross tumor volume included the tumor in nasopharynx and any tumor extension outside nasopharynx identified clinically or radiologically. The clinical target volume covered the gross tumor volume with margins to include any potential microscopic disease extension. The clinical target volume typically extended from the skull base to level II, III nodal regions on both sides. The planning target volume was clinical target volume with additional 3mm margin to account for potential set-up error in treatment. The dose to planning target volume to nasopharynx was 68-70Gy in 34 fractions, 5 daily fractions per week. The lower neck was treated with a matching anterior cervical field with midline shield to 66Gy in 33 fractions. The inner, middle and external ears on both sides were localized as organs at risk in IMRT planning and the doses to these structures were limited at 50Gy.

Audiological and otological assessments

All patients underwent otoscopic assessment by an otolaryngologist and pure tone audiogram (PTA) by an audiologist before the start of radiotherapy. Patients with otitis media with effusion were offered myringotomy and grommet insertion. A repeat PTA would be obtained if patient underwent grommet insertion and the post-

operative audiogram would be used for baseline assessment. The PTA included air conduction (AC) at frequency 256Hz, 512Hz, 1kHz, 4kHz and 8kHz and bone conduction (BC) at frequency 512Hz, 1kHz, 2kHz and 4kHz. Masking thresholds were obtained whenever it was appropriate. Patients had an audiogram performed 5 years after radiotherapy. As air conduction thresholds could be affected by middle ear pathologies, to measure the effect of radiation damage to inner ear, the bone conduction thresholds were used for statistical calculations. Similar to previous study by Ho, we calculated the pure tone average (PTAv), the average of thresholds at 512Hz, 1kHz, and 2kHz to reflect the threshold in speech range. The bone conduction threshold at 4kHz was chosen to represent high frequency threshold. Since the maximal output of the bone conductor of the audiometer is 65dB, it would not be possible to accurately measure the true threshold if the BC threshold was worse than 65dB. For ears with BC threshold worse than 65dB and no clinical or tympanometrical evidence of conductive hearing loss, the BC threshold would be assumed equivalent to the AC threshold.

Patients had otoscopic or microscopic examination of the ears by otolaryngologists in year 2010, 5 to 9 years after completion of radiotherapy. The presence of OME, eardrum perforation, grommet and osteoradionecrosis (ORN) of the external auditory canal were noted. Presence of exposed bone with bony sequestrum in the external auditory canal was use as the diagnostic hallmark of ORN of the external auditory canal[10]. Otitis media with effusion was confirmed with the presence of type B curve on tympanometry.

Statistical calculations

Individual ear would be used for statistical calculations. The serial change in hearing of individual ear after radiotherapy was determined by the paired t-test. For comparison between the changes in hearing of patients who received 2DRT versus IMRT, the change in the hearing threshold was calculated and the significance determined by t-test. Chi-square test and Fisher exact test were used for comparison of the occurrence of ORN, presence of grommets, OME and perforations between the two groups. A two tailed p value of less then 0.05 was considered significant. All statistical tests were calculated with SPSS 18.0 (Chicago, IL).

Results

Eighty-two patients (63 male and 19 female), 164 ears were recruited into the study, with each ear considered as an independent case. The age of patients ranged from 27 to 75 years old, with a median age of 46 years. There are 40 patients in the conventional 2DRT group and 42 patients in the IMRT group. There was no difference in the age, sex distribution and pre-treatment audiological threshold between the two groups of patients. The summary of the demographic data was shown in table 1. Eleven patients died within 5 years of completion of radiotherapy. Four patients developed local recurrence in the nasopharynx and were all salvaged with nasopharyngectomy via maxillary swing, the four patients are excluded from the study. One patient developed recurrence in the right parotid region and received a second dose of radiotherapy. One patient developed disseminated disease and

received cisplatin chemotherapy. Both patients were excluded from the study. Twelve patients were lost to follow up.

Audiological results

Complete audiological information at 5 years post-irradiation was available in 106 ears. 56 ears and 50 ears received IMRT and conventional radiotherapy respectively. There was no statistical difference in the age of the two groups of patients (p=0.38, t-test). Pre-irradiation hearing level and audiological information at 5-year follow-up was analysed. For the PTAv, the overall mean pre-irradiation BC level was 17.9dB (SD = 9.2dB) and the mean level at 5 year follow-up was 24.6 dB (SD = 16.6dB). Comparing with pre-irradiation hearing threshold, there was an average deterioration of hearing of 6.6dB (95% CI 4.4dB - 8.9dB) at 5 years after radiotherapy, which was statistically significant (paired t-test, $p<0.001$). At 4kHz, the overall mean pre-irradiation BC level was 26.4dB (SD = 17.1dB) and the mean BC level at 5 year follow-up was 41.4dB (SD = 26.0dB). The mean deterioration of hearing at 4kHz was 15.0dB (95% CI 2.0dB – 21.1dB), which was again significant (paired t-test, $p<0.001$). Table 2 shows the bone conduction thresholds of the whole cohort before and after radiotherapy.

The average deterioration in PTAv in the 2DRT group and IMRT group are 7.0dB and 6.2dB respectively, and this is not statistically significant (p=0.74, t-test). The average deterioration in hearing at 4kHz in the 2DRT and IMRT group are 13.8dB and 16.2dB respectively and this is statistically not significant (p=0.57, t-test). Table 3 summarized the hearing results of the two groups of patients. The average

difference in the change in hearing between the two groups of patients is less than 5dB and clinically this small difference is not significant.

Otological complications

Ninety-four ears (47 patients), 52 ears in the IMRT group and 42 ears in the 2DRT group were available for otological assessment. In the IMRT group, 1 out of 52 ears (1.9%) had osteoradionecrosis while in the conventional radiotherapy group, 6 in 42 ears (14.3%) had osteoradionecrosis. The difference in the occurrence of osteoradionecrosis between the two groups was significant. (Fisher's exact test, p = 0.042). Otitis media with effusion was present in 14 ears (26.9%) in the IMRT group and 3 ears (7.1%) in the conventional radiotherapy group. The difference between the two groups was significant (p=0.016, Fisher's exact test). One ear in the IMRT group had a grommet present and one ear in the 2DRT group had a grommet present during otological assessment. One ear in the IMRT had a chronic perforation of the tympanic membrane and one ear in the 2DRT group had a chronic perforation of the tympanic membrane. Table 4 summarized the otological findings.

In summary, from our present cohort, there is statistical significant deterioration in the bone conduction threshold in the speech frequency and in the high tone in the whole cohort five years after radiotherapy treatment for NPC. We are unable to demonstrate any difference in the deterioration of bone conduction threshold between patients treated with IMRT or 2DRT. Patients who received 2DRT have a higher incidence of developing osteoradionecrosis of the external auditory canal comparing with patients who received IMRT. On the contrary, patients who

received IMRT have a higher incidence of otitis media with effusion than patients who received 2DRT.

Discussion

Radiation therapy has been known to damage the auditory apparatus and hearing. Previous study in our institute has demonstrated the presence of long term hearing loss after radiotherapy for nasopharyngeal carcinoma[8]. The presence study confirmed this finding. The deterioration in hearing could not be attributed to aging alone. Robinson and Sutton had calculated that the expected age-related threshold shift in 5 years should be in the range of 2.6 to 4.6 dB for 4kHz and 1.3 to 1.4dB for PTAv. The present study showed that the average change in hearing thresholds 5 years after radiotherapy are 15.2dB at 4kHz and 7.3dB for PTAv. The present study also demonstrated that there is more significant damage to the high frequency hearing than speech frequency after radiotherapy. Moreover, many studies on hearing deterioration after radiotherapy for NPC included patients in more advanced stage and had received chemotherapy. Chemotherapy, especially cisplatin is cytotoxic. Chemotherapy will be a confounding variable in many of the studies. In the current cohort, none of the patients had received chemotherapy. There could be other confounding factors affecting hearing in the patients in the five years after radiotherapy like diabetes, noise exposure and genetic factors. We are unable to control these factors in contribution to hearing loss and these confounding variables may be a factor contributing in the negative findings in the difference in hearing between the two groups.

Intensity-modulated radiotherapy offers the radiotherapist the advantage of sparing the adjacent organs high dose radiation and should improve the quality of life of patients after radiotherapy. The improvement of quality of life after radiotherapy for NPC has been demonstrated in the aspect of preservation of salivary function[1, 5]. In order to achieve the preservation of salivary function, the contralateral parotid gland has been deliberately excluded from the high dose zone during radiotherapy planning. On the other hand, the petrous temporal bone, cochlear and Eustachian tube were considered as at risk organs and limited to a maximum of 50Gy radiation. Therefore, the cochlear may well receive a radiation dose that will cause damage to hearing and this can explain the similar deterioration in hearing between the IMRT group and 2DRT group. Chen et al.[11] demonstrated that radiation dose over 48Gy to the cochlear would significantly increased the risk of sensorineural hearing loss; though in his study, patients also received ototoxic chemotherapy. In another cohort of patients with head and neck cancer treated with IMRT, Zuur et al. demonstrated a that the dose to the coochlear, pretreatment hearing loss, green eyed patients and older age all were risk factors for post treatment hearing loss, though the authors did not present maximum safe dose for the cochlear for hearing preservation[12]. In our current cohort, the patients in the IMRT group would receive a dose of 50Gy to the cochlear while the 2DRT group would receive up to 68Gy. As both groups of patients in the current study received more than 48Gy of radiation to the cochlear, this can explain the fact that there is no difference in the hearing loss between both groups.

Osteoradionecrosis of the external auditory canal and tympanic ring is a serious complication of radiotherapy. The condition affects the quality of life the patients. Osteoradionecrosis was due the endarteritis and subsequent avascular necrosis of the bone, first described by Ewing[13]. Ramsden et al.[14] divided

temporal bone osteoradionecrosis into the localize form and diffuse form. Both forms of temporal bone ORN would include the tympanic ring, where the blood supply was precarious, with the diffuse form involving parts of the temporal bone in addition to the tympanic ring. Osteoradionecrosis is a difficult condition to manage. Patient would present with recurrent otorrhea that require frequent aural toileting and treatment of infection. Osteoradionecrosis of the temporal bone can also lead to serious complications including facial nerve palsy and cerebrospinal fluid otorrhea. In severe cases, surgical intervention including radical debridement of the necrotic bone and flap reconstruction may be required[15]. Moreover, patients with ORN of the temporal bone frequently suffer from chronic discharging ears, making the use of conventional hearing aids difficult. Recently there is a report of use of bone-anchored hearing aid to circumvent the problem of discharging ears in hearing rehabilitation of this group of patients[16].

The present study showed that there is much less incidence of ORN of the temporal bone in patients who have received IMRT when comparing to patients who have received conventional 2DRT. In conventional 2DRT, the radiation to the nasopharynx is delivered by a lateral opposing field. The lateral opposing fields will include the tympanic ring and petrous temporal bone and both structures would receive high dose of radiation. In IMRT, the radiation is delivered from several beams from different angles to the nasopharynx. The tympanic ring, which is situated further away from the nasopharynx and clinical tumor volume (CTV), would receive a lesser dose of radiation than conventional 2DRT. This may explain the observed reduction of ORN in patients who received IMRT. In a similar study, Hsin et al. also demonstrated that patients treated with IMRT suffered from less otological complications but similar incidence of sensorineural hearing loss[17].

We cannot find a plausible explanation of increased incidence of otitis media with effusion in patients who received IMRT. The results from Hsin et al. study showed similar incidence of otitis media with effusion in patients receiving conventional 2DRT or IMRT[17]. Further research will be required to look in to the effect of IMRT on the Eustachian tube functions of NPC patients.

In conclusion, there is significant reduction in the incidence of osteoradionecrosis of the external auditory canal in patients who had received IMRT but there is no clinical and statistical difference in the long-term bone conduction hearing thresholds in nasopharyngeal carcinoma patients who had received IMRT or 2DRT. IMRT can reduce the long-term otological complications of nasopharyngeal carcinoma patients.

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