Visual Functions in Locally Advanced Nasopharyngeal Carcinoma Patients after External Beam Radiation

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Abstract

Purpose: To evaluate the effects of radiation to the anterior visual pathway in locally advanced nasopharyngeal carcinoma (NPC) patients after low energy photon external beam radiation.

Design: A cross-sectional, observational case series.

Methods: Fifty- one patients treated with the same radiotherapy were assessed in visual acuity (VA), color vision, visual field (VF), and contrast sensitivity. The patients with post radiation interval of ≤ 3 years were defined as group 1, of > 3 years as group 2, and healthy volunteers as control group 3. The visual functions were analyzed between the three groups.

Results: One patient in group 1 developed radiation-induced optic neuropathy (RION) with decreased VA, color vision defect, decreased contrast sensitivity, and VF defect. No RION was detected in group 2. There was no statistical significance in color vision defect ($P = 0.303$) or mean contrast sensitivity ($P = 0.235$) between the three groups. There was statistical significance in mean contrast sensitivity value ($P = 0.044$) between the irradiated and non-irradiated group.

Conclusions: This study reported the acceptable incidence of RION in 1.96% of locally advanced NPC patients after external beam radiotherapy. Significant decrease in contrast sensitivity was the subclinical anterior visual pathway abnormality, observed among the irradiated group. Monitoring subjective and objective visual changes is helpful for irradiated patients in detecting and assessing treatment for minimizing long term devastating results on the visual conditions.

Keywords: Radiation induced optic neuropathy; Locally advanced nasopharyngeal carcinoma; External beam radiotherapy

Introduction

Nasopharyngeal carcinoma (NPC) is one of the most common cancers in northern Thailand. High numbers of disease-free and overall survival rates, even in the locally advanced stages, have been observed among cancer patients, treated primarily with radiation therapy (RT). The basic principle of this treatment is to deliver a curative dose of RT to the tumor, while minimizing the dose to surrounding structures, especially critical normal organs such as the spinal cord, brainstem, and visual apparatus. In locally advanced NPC, the anterior visual pathways are usually within the radiation field due to their proximity to the base of skull, cavernous sinus, or orbital apex region. While a total dose of 60-70 Gy is required to control a local tumor, the doses of this range may be intolerable and may cause injuries to the anterior visual pathway, thus producing radiation-induced optic neuropathy (RION) [1]. Types of radiation delivery have been reported as contributing factors to RION [2-4]. Several other studies have also reported the relationship between RION and the following factors: dose response, volume response, techniques of radiation, dose fractionation, and quantity of radiation [5-9]. One purpose of this study was to evaluate the visual functions in locally advanced NPC patients, treated with low energy photon external beam radiation therapy (EBRT). The other purpose was to confirm the association of RT and RION as well as to identify which visual function change could potentially be used as an indicator for early detection of RION.

Patients and Methods

There were 598 patients reported with NPC in the cancer registry

at the Faculty of Medicine, Chiang Mai University. A retrospective chart review at the Division of Therapeutic Radiology and Oncology, conducted from January 2002 to December 2007, had identified a number of patients diagnosed with locally advanced NPC staging at T3 or T4 according to the American Joint Committee on Cancer (AJCC) 1992, or T2b and later in accordance with the AJCC 1997. These patients were treated completely following the same radiation protocol.

For each patient, radiotherapy was given with a 6-MV linear accelerator by 2-dimensional techniques, whereby a two-lateral opposing field technique was used to cover the tumor. Defined on the basis of anatomical structures, the primary radiation field margins were the 2-cm peripheries around the CT-detected primary site, and inferiorly down to the thyroid notch to include the lymph nodes. Eyes, brain and brain stem were shielded from the beginning. Once 40 Gy had been delivered, the spinal cord was then shielded. After that the primary tumor was boosted with an additional 30 Gy using

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6 MV photons. The posterior upper neck was treated with 10-12 MeV electrons via lateral beam to avoid overexposure of the spinal cord. The brain stem and the eyes were also shielded during the boost phase. A matching anterior low neck field with a midline block of 50 Gy was used to irradiate the supraclavicular lymph nodes. Radiotherapy was delivered in 5 equal fractions per week, with 2 Gy per day.

Included in this study were 51 patients, who showed no evidence of recurrent disease (locoregional or distant), and had no previous history of hypertension, diabetes mellitus, or other ophthalmic diseases that could lead to prior impairment of visual functions. These patients were divided into 2 groups according to their follow-up intervals, i.e. the duration between the first day of radiation therapy and the day of ophthalmologic examination. Group 1 patients included those with shorter than 3 years follow-up intervals and group 2 included all the remainders. Healthy volunteer subjects were recruited as control group 3.

This study was approved by the research ethics committee of the Faculty of Medicine, Chiang Mai University, Thailand. After giving written informed consents, all the patients and the healthy subjects underwent complete ophthalmic examinations conducted between January 2009 and July 2009 by one ophthalmologist and one optometrist using the same processes, the examinations included the following:

- Best corrected visual acuity (BCVA) by a Snellen acuity chart;
- Anterior segment and fundus evaluation;
- Intraocular pressure measurement using a Goldmann applanation tonometer;
- Visual field (VF) testing by an automatic Humphrey Field Analyser, model 750 (Carl Zeiss Meditec, Dublin, CA, USA) with The Swedish Interactive Threshold Algorithm (SITA) standard 30-2, white on white program (1 absolute scotoma or 3 consecutive relative scotomas defined as visual field defects);
- Color vision testing by Ishihara plates (the corrected reading value of less than 8 was defined as color vision defect); and
- Contrast sensitivity testing by a Pelli Robson chart.

Statistical analysis

Visual parameters were compared among the groups by adopting the Mann-Whitney U test for continuous variables and chi-square test for categorical variables. All analyses were conducted using SPSS

software (SPSS, Inc, Chicago, Illinois, USA). *P* values of ≤ 0.05 were considered statistically significant.

Results

Table 1 summarizes the demographic data of the patients and the healthy subjects as well as their visual functions. Group 1 enrolled 29 patients (58 eyes). Eighteen males and eleven females, with ages ranged from 11 to 72 years old, made up this group. The mean age was 46.7 and the median age was 47.0 years. The follow-up times were between 8 months and 35 months, with mean and median of 19.6 and 17.0 months respectively. Constituting 3.4%, one patient showed evidence of RION development (in both eyes) with visual acuity (VA) of equal to or less than 6/60, color vision defect, and cecentral absolute scotoma visual field defect. Another patient showed color vision defect in one eye. The contrast sensitivity value for this group ranged from 1.35 to 1.95 in log unit, with mean and median of 1.60 and 1.54 respectively.

Group 2 enrolled 22 patients (44 eyes). With ages ranged from 17 to 65 years old, seventeen were male and five were female. The mean age and the median age were 46.5 and 48.0 years respectively. The follow-up times were between 37 and 72 months, with mean value of 49.4 and median value of 48.0 months. None of these patients was diagnosed as RION and none of them had developed visual field defect. Two patients had VA of less than 6/60 in both eyes, and one patient had color vision defect in one eye. These represent 4.5% in poor VA incidences and 2.2% in color vision defect incidences. The range, mean, and median contrast sensitivity values for this group were 1.50-1.95, 1.57, and 1.52 respectively.

Group 3 enrolled nine male and 22 female healthy subjects (62 eyes). The age range, mean age, and median age were 24-59, 35.5, and 39.0 years respectively. All of these subjects had VA of equal to or better than 6/12. None showed color vision defect or visual field defect. The contrast sensitivity range for this group 3 was 1.65-1.95, with mean of 1.79 and median of 1.80.

While there was no statistical significance in color vision defect ($P = 0.303$) or mean contrast sensitivity ($P = 0.235$) among the three groups, there was statistical significance in mean contrast sensitivity value ($P = 0.044$) between the irradiated and non-irradiated group.

Discussion

Normal ocular tissue has a spectrum of radiation tolerance. The lacrimal system, lens, eyelashes, retina, and anterior visual pathway are ophthalmic radiosensitive structures. The optic nerve has a higher risk for RION compared to other cranial nerves, due to its myelination by oligodendrocytes, which are radiosensitive. RION has been reported as an uncommon post-radiation visual abnormality [9-11]. The interval between irradiation and the development of visual function impairment ranged from 3 months to over 8 years [1,9]. Early onset of RION has been thought to come from acute inflammation, [11] and late onset from endothelial cell damage, fibrinoid necrosis and ischemic injuries of the tissue [12]. Most cases occurred within 3 years, with peak incidences at 1 to 1.5 years[13,14] The maximum dose of visual apparatus tolerance was reported, with a tendency to reduce complications at a dose of less than 50-60 Gy and fraction sizes of less than 2 Gy [15-17]. In patients with pituitary tumors, a lower tolerance dose of optic nerve has been reported and RION can occur after a considerable latency period (5 months - 10 years) [18]. The patients in this study received an RT dose range of 66-70 Gy, with a fraction size of 2 Gy per day which was higher than the tolerance dose of 50 - 65 Gy of optic nerve and chiasm. One patient in this study, after treated with

	Group 1	Group 2	Group 3
Patients (n)	29	22	31
Eyes (n)	58	44	62
Sex (n)			
Male	18	17	9
Female	11	5	22
Age (yr)			
Median	47	48	39
Range	11-72	17-65	24-59
Eyes with visual acuity $\leq 6/60$ (%)	2/58 (3.4)	2/44 (4.5)	0
Eyes with color vision defect (%)	3/58 (5.1)	1/44 (2.2)	0
Eyes with visual field defect (%)	2/58 (3.4)	0/22 (0)	0
Contrast Sensitivity (log unit)			
Mean	1.60	1.57	1.79
Range	(1.35-1.95)	(1.50-1.95)	(1.65-1.95)

Table 1: Demographic data of the patients in 3 groups.

low energy photon external beam radiation, developed post-radiation bilateral RION after 22 months. This 2% occurrence suggested an acceptable RION incidence. Various pathologic vascular conditions such as diabetes mellitus or hypertension have been attributed as risk factors for RION [5,19,20]. However, this study reported an incidence of RION in patients with no influence from vascular compromised conditions. Esassolak et al. concluded that radiation-induced injury to the anterior visual pathways could result in an increase in VEP latency and a decrease in VEP amplitude and contrast sensitivity in locally advanced nasopharyngeal carcinoma patients who treated with high dose radiotherapy [21]. Change in subjective visual functions, such as visual field and contrast sensitivity, should be regarded as an indication of subclinical damage to the anterior visual pathway. In most community-based hospitals, this visual change could be monitored so that each involved NPC patient can be forewarned. This study showed a statistically significant decrease in contrast sensitivity among the irradiated groups when compared with the normal group. However, no statistically significant difference of visual field was observed among the three groups.

The therapeutic options for RION, including corticosteroid, anticoagulant or hyperbaric oxygen, showed variable visual outcomes with little benefit [11]. Anti-vascular endothelial growth factor (VEGF), the drug reported in past studies, has been used recently through intravitreal injection in early RION and has shown improvement in the visual acuity [22]. Careful monitoring of both subjective and objective clinical visual function is crucial in detecting immediate visual pathway injuries, which will allow for an early intervening attempt to recover or stabilize the vision after treatment.

The limitations of this study were the retrospective nature, small number of patients, and one time point evaluation of visual functions.

Conclusion

This study indicated an acceptable RION incidence of 1.96% among locally advanced NPC patients, treated with a fraction size of 2 Gy external beam radiation. Significant decrease in contrast sensitivity was the subclinical anterior visual pathway abnormality, observed among the irradiated group. The changes in this visual function could be monitored regularly in most community-based hospitals. Visual examination program should be offered to all NPC patients as an integral part of the radiotherapy protocol. Early detection of functional visual impairment and immediate subsequent treatment are effective strategies for minimizing long term devastating results on the visual conditions.

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