

## ORIGINAL ARTICLE

# Flourescein Angiogram and Fundusoscopic Features of Radiation Induced Retinopathy: A Descriptive Value of Retinopathy Severity in Patients with Nasopharyngeal Carcinoma

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## ABSTRAK

Retinopati akibat dari radiasi (RR) ialah komplikasi yang sering berlaku kepada pesakit Nasopharyngeal Carcinoma (NPC). Kajian ini bertujuan untuk menentukan kaitan RR dengan dos radiasi yang diterima oleh pesakit NPC melalui pemeriksaan mata dan fundus fluorescein angiogram (FFA). Suatu kajian rentas lintang telah dilakukan melibatkan pesakit NPC yang telah menerima rawatan radiasi di Klinik Onkologi, Universiti Kebangsaan Malaysia Medical Centre (UKMMC). Sebanyak 82 mata dari 42 pesakit telah diperiksa dan prevalence RR didapati sebanyak 35.4%. Keterukan RR berkait rapat dengan dos radiasi kepada retina (Nilai Spearman correlation = 0.48,  $p < 0.001$ ). Antara ciri-ciri RR yang dilihat melalui pemeriksaan FFA ialah salur darah telangiectatic (26.2%) dan capillary non-perfusion (14.3%). Retinal neovascularization dilihat berlaku kepada 10.7% dari mata yang diperiksa. Keterukan penglihatan didapati berkait rapat dengan keterukan RR dengan 26% daripada mata tersebut mempunyai penglihatan 6/18 atau lebih teruk. Lebih dari satu pertiga pesakit mendapat RR, dengan maculopathy radiasi sebagai penyebab yang paling kerap dilihat sebagai penyebab kehilangan penglihatan yang signifikan. FFA ialah alat yang sangat berguna untuk mengesan tanda-tanda awal RR dan maculopathy.

**Kata kunci:** karsinoma nasopharyng, retinopati radiasi, angiogram fluorescein fundus

## ABSTRACT

Radiation retinopathy (RR) is a known complication after radiotherapy for Nasopharyngeal Carcinoma (NPC). This study aims to relate the relationship of

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RR and radiation dose in patients with NPC through assessment with clinical funduscopy and fundus fluorescein angiogram (FFA). A cross sectional study was conducted on patients with NPC who had completed radiotherapy treatment in the Oncology Clinic, Universiti Kebangsaan Malaysia Medical Centre (UKMMC). Eighty two eyes of 42 patients were examined and the prevalence of RR was found to be 35.4%. The severity of RR is strongly associated with the dose of radiation to the retina (Spearman correlation value=0.48;  $p < 0.001$ ). The common features of RR assessed by FFA were telangiectatic vessels (26.2%) and capillary non-perfusion (14.3%). Retinal neovascularization occurred in 10.7% of eyes. The level of visual deterioration correlated with the severity of RR with 26% of eyes experiencing a visual acuity of 6/18 or worse. More than one third of patients developed RR, with radiation maculopathy being the commonest cause for significant visual loss. FFA is a useful tool in detecting early signs of radiation retinopathy and maculopathy.

Keywords: nasopharyngeal carcinoma, fluorescein fundus angiography, retinopathy, radiotherapy

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## INTRODUCTION

Nasopharyngeal carcinoma (NPC) is the most radiosensitive head and neck cancer in which radiation therapy is the primary treatment modality. The incidence rate ranges between 10 and 50 per 100 000 (Ho 1978). Radiation doses between 40-70 Gy is typically delivered to adequately treat the entire tumor without damaging local structures such as the parotid gland and optic nerve (Puri et al. 2005). In a recent cohort of over 2500 patients with NPC, the control rate with these doses of radiation alone at 5 years was 85%. Although the rate increases with higher doses, greater local side effects such as radiation optic neuropathy is commonly seen (Lee et al. 2005).

Radiation-induced retinopathy (RR) is a delayed progressive retinopathy thought to be due to selective destruction of capillary endothelial cells leading to vascular occlusion, capillaries atrophy and subsequent

ischemia (Noble & Kupersmith 1984). The onset varies from 1 month to 15 years, though noticeable clinical signs usually appear within 3 years of treatment (Parsons 2004). The overall incidence of RR in patients with NPC varies with the dose of radiation (Takeda et al. 1999) with reported incidences as high as 56% with doses greater than 50 Gy and as low as 16% with lower doses (Rosenblatt et al. 2003). The dose response curve of radiation-related ophthalmopathy is sigmoidal with the risk of RR increasing steeply above 45 Gy and complete blindness reported with doses as low as 60 Gy (Parsons et al. 1983). RR is rarely seen below 30 Gy and rare cases of profound visual loss at these lower doses was found to be due to ischaemic maculopathy (Hempel & Hinkelbein 1993).

Other factors for worse RR include radiation fraction size, area irradiated, concomitant chemotherapy, pre-existing vascular disorders like diabetes

mellitus and increasing age (Brown et al. 1982).

The aim of the present study was to determine the prevalence of RR in patients with NPC who have completed radiotherapy in a tertiary hospital in Malaysia and to identify if a relationship exists in our population that mirrors that of published series, between the dose and occurrence of RR.

## **MATERIALS AND METHODS**

A total of 42 NPC patients who had been exposed to fractionated external-beam irradiation between 2000 and 2004 in the Oncology Department, Universiti Kebangsaan Malaysia Medical Centre (UKMMC) were identified and considered for the study following informed consent. Ethical approval was obtained from the UKMMC Ethical Committee prior to study initiation (study code: FF-019-2006).

Patients were excluded if they had any of the following conditions i.e. significant media opacity obscuring adequate fundus view such as cataract, patients with known allergy to fluorescein dye, eyes with tumour invasion at the time of examination and patients who did not consent for fluorescent angiogram. Patients with diabetes mellitus (DM) were not excluded.

The principal investigator (NMD) examined the patients which included assessment of visual acuity, slit lamp examination particularly looking for the presence of rubeosis iridis, corneal and lens clarity, tonometry and dilated fundus examination. Coloured fundus photographs were taken before the

patient was subjected to a Fundus Fluorescein Angiography (FFA). The FFA and fundus photos were graded by a secondary investigator (KHS) who was blinded to the patient's clinical details.

The radiation dose was estimated from the simulation and portal films and done in collaboration with the doctors and physicist from the Department of Radiotherapy and Oncology, UKMMC. When the globe lay at the border of the treatment field, the dose was estimated to be 50% of the total dose delivered. If the globe lay within the treatment field, the dose was estimated according to the graph obtained from a computerized plan. When the globe was shielded, the dose received by the retina was estimated to be between 2 to 5% of the total dose delivered.

The severity of RR by clinical fundoscopy was graded into normal, non-proliferative or proliferative retinopathy, depending on the presence or absence of RR and retinal neovascularization. The severity of RR by FFA was graded as normal, mild, moderate, severe, and proliferative RR based on the criteria adopted from the Branch Retinal Vein Occlusion Study (Branch Vein Occlusion Study Group 1986) (Figure 1-4). Absence of any angiographic changes was graded as normal, mild RR was defined with the presence of changes such as telangiectatic vessels, microaneurysms and cotton wool spots, without areas of capillary non-perfusion, moderate RR was defined when there is less than 5 disc diameter (DD) of area of capillary non-perfusion, severe RR was when there was greater than 5 DD of capillary non-perfusion and proliferative RR was

defined as presence of leaking new vessels.

Data was analyzed using SPSS version 12.0. Chi Square test was used to determine any association between qualitative variables. ANOVA was used to compare the means of more than variables. The data on patients with DM was only used when assessing the association between concurrent medical illnesses and severity of radiation retinopathy. Results were given as mean and standard deviation.

## RESULTS

A total of 82 eyes from 42 patients were included in the study. There was a slight male preponderance with 24 (57.1%) males and 18 (42.9%) females with a male to female ratio of 1.3:1. The mean age was  $50.3 \pm 12.1$  years, and ranged from 20 to 72 years. There were 26 Chinese patients (61.9%), 15 Malay patients (35.7%) and only one (2.4%) Indian patient, reflecting the acknowledged increased risk of NPC amongst the different ethnic groups.

Among non-diabetics, the prevalence of eyes with RR as assessed by FFA was 29.6% (21 eyes out of 71 eyes) with 18.3% (13 eyes) had mild RR, 4.2% (3 eyes) had moderate and 7% (5 eyes) had proliferative RR. The prevalence of clinically detectable RR by fundus photos was lower at 18.3% (13 eyes), with 16.9% (12 eyes) having non-proliferative RR and 1.4% (1 eye) with proliferative RR (Figure 5 and 6). When diabetic patients were included, the prevalence of RR was slightly higher (35.4% [29 of 82 eyes] with FFA and 25.6% [21 of 82 eyes] with clinical grading).

The proportion of eyes with more severe RR was significantly associated with higher doses of radiation,  $p < 0.0001$  (Figure 7). Half of all eyes receiving radiation doses less than 26 Gy had no evidence of RR by FFA, and increased levels of moderate and proliferative RR were seen in those receiving doses greater than 26Gy.

Three eyes in the study were totally blind with no perception of light (NPL) from radiation induced optic neuropathy. Twenty six percent of eyes experienced visual acuity of 6/18 or worse. When comparing mean visual acuity in Logmar to the severity of RR, worst RR is significantly associated with poorer visual acuity ( $p=0.003$ ).

The commonest clinical feature seen in the studied eyes by clinical fundoscopy examination was hard exudation (14.3%) (Table 1). In contrast, the commonest manifestation seen on FFA was telangiectatic vessel (26.2%) (Table 2).

Macular oedema was more common than macular ischaemia (13.3% vs 4.9%). All eyes with macula ischaemia received radiation dose of more than 36 Gy. The mean radiation dose was higher in the ischaemic group (42Gy) compared to the oedema group (28Gy), although statistically insignificant ( $p = 0.076$ ) (Figure 8).

## DISCUSSION

RR is a potentially blinding condition which results from radiation delivered to the periorbital tissues for radiosensitive tumors like NPC. It is characterized by typical changes affecting the vasculature in the metabolically highly



Figure 1: Mild radiation retinopathy (Red arrows indicate areas of telangiectatic vessels and microaneurysm)

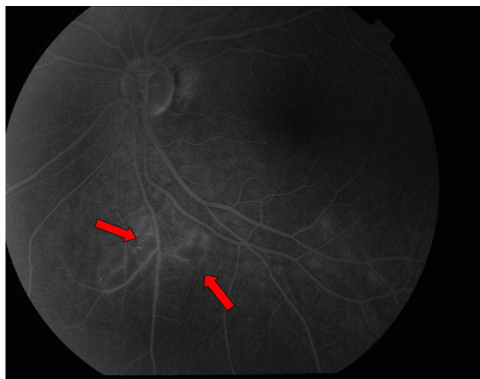


Figure 2: Moderate radiation retinopathy (Red arrows indicate areas of capillary non-perfusion the size of less than 5 disc diameter)

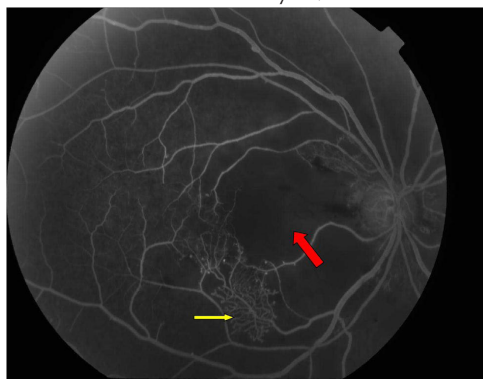


Figure 3: Severe radiation retinopathy (Red arrow indicates areas of capillary non-perfusion the size of which is bigger than 5 disc diameter Yellow arrow indicates neovascularization.

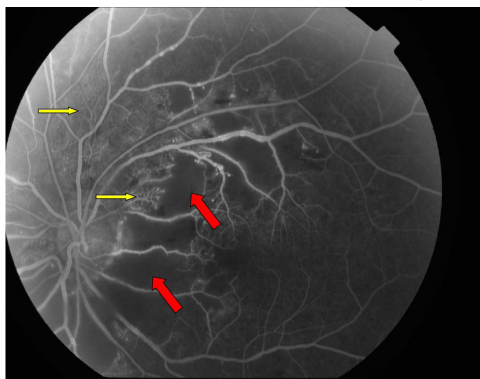


Figure 4: Proliferative radiation retinopathy (Red arrows denote area of capillary non-perfusion and yellow arrows indicated florid neovascularization)

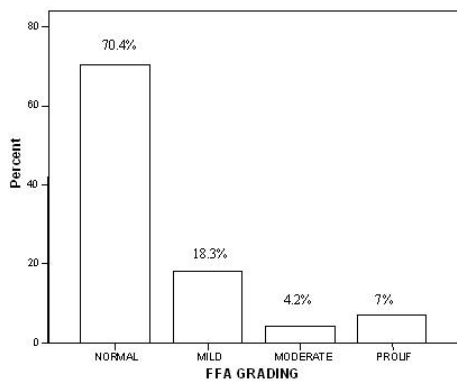


Figure 5: Percentage of radiation retinopathy and the breakdown in severity as graded by Fundus Fluorecein Angiogram.

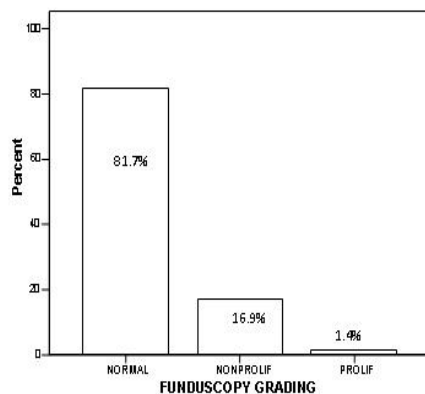


Figure 6: Percentage of eyes with radiation retinopathy as detected by funduscopy

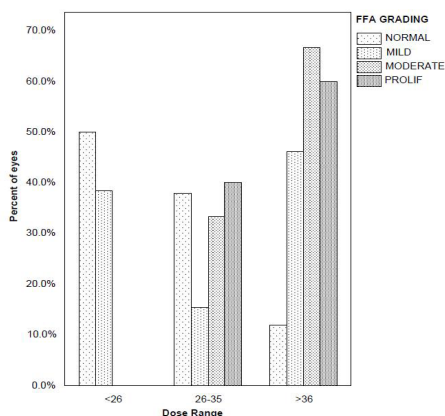


Figure 7: Relationship between dose to the retina and severity of radiation retinopathy.

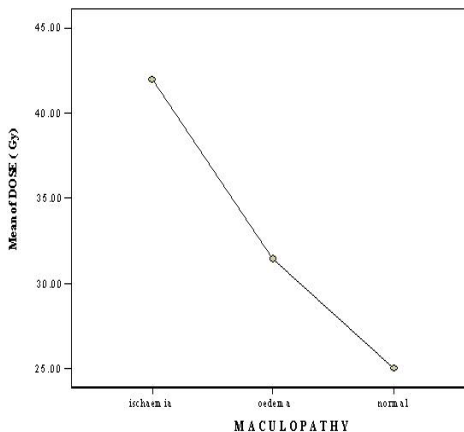


Figure 8: Association between mean radiation dose and maculopathy.

Table 1: Clinical manifestation as seen by clinical fundus examination.

Clinical feature	No. of eyes (%)
Cotton wool spots	6 (7.1)
Telangiectatic vessels	3 (3.6)
Microaneurysm	10 (11.9)
Hard exudates	12 (14.3)
Neovascularization	1 (1.2)
Total	22 (38.1)

Table 2: Clinical manifestations as detected by fundus fluorescein angiogram.

Clinical feature	No. of eyes (%)
Telangiectatic vessels	22 (26.2)
Capillary non perfusion	12 (14.3)
Neovascularization	9 (10.7)
Microaneurysm	13 (15.3)
Total	56 (66.5)

active macula, papillomacular and optic nerve area. Previous studies of RR have singled out the strongest risk factor to be the irradiated dose reaching these sensitive structures (Takeda et al. 1999; Rosenblatt et al. 2003). The present study attempted to identify the prevalence and clinical features of RR by using FFA in the local population.

The population of patient studied was largely Chinese concurring with previous studies on NPC (Chan et al. 2002). RR was present in about a third of our cases when FFA was used as the tool of detection. This is comparatively higher than previously reported studies where FFA was not used as the tool of detection (Takeda et al. 1999;

Rosenblatt et al. 2003).

The dominant risk factor for RR in the present study was the dose of radiation to the retina. RR occurred in eyes which has received radiation doses of as low as 3.5 Gy. Other studies reported significant risk factors which included the fraction size of radiation, increasing age and concomitant chemotherapy (Brown et al. 1982).

In the present study, the calculation of retinal dose is estimated from simulation and portal films which were 2 dimensional. Estimation of the distance of the posterior border of the globe to the radiation field border is important for the calculation of the retinal radiation dose. Three dimensional planning was not available to allow greater accuracy of dose estimation.

The irradiated dose to the retina varies as the retina is a curved planar structure that lines the part of the globe and hence different areas of the retina would receive different amount of radiation. The technique of parallel-opposed radiation is practiced at UKMMC and hence the temporal retina receives less radiation compared to the nasal retina. However, in this study we found that most changes occurred around the macula. This reflects the hypothesis that the areas most affected by RR are metabolically the most active, in this case, the macula.

Clinically detectable RR was present in 25.6% of eyes as compared to 35.4% when FFA was used. This implies that if there are no changes on clinical funduscopy, FFA may detect RR undetectable clinically such as areas of capillary non-perfusion. This would be helpful in identifying the

cause of visual loss in cases where there are no detectable clinical signs. In most eyes with RR, vision was not compromised, as the pathological changes did not significantly involve the fovea or optic nerve. However, these patients may still develop proliferative RR because of extensive areas of peripheral capillary non-perfusion, which spares the fovea and hence maintains good vision. In the present study, the commonest feature of RR is telangiectatic vessels within the temporal vascular arcades. These telangiectatic vessels are considered to be the hallmark of radiation damage.

The second commonest feature was capillary non-perfusion, which usually affects the retinal area inferior to the inferior arcades. Because the sphenoid sinus, posterior ethmoid sinuses and posterior half of the orbit is included in the standard radiotherapy field, some part of retina may be radiated especially with clinical involvement of these structures by the tumour.

Patients who have retinopathy alone without maculopathy are usually asymptomatic unless they have other complications such as optic neuropathy. Other causes of poor vision in our study was advanced proliferative retinopathy which may still cause poor vision despite treatment with laser argon peripheral retinal photocoagulation because of ischaemic maculopathy. Macula oedema was found to be more common than macula ischaemia in our study. The eyes with ischaemic maculopathy had received a mean radiation dose of 42 Gy. Eyes with macular oedema on the other hand received lower radiation dose (mean 28

$\pm 17.00$  Gy) whereas eyes without RR received a mean radiation dose of  $24.2 \pm 16.4$  Gy. As the vessels supplying the macula area are largely end arteries ending at the fovea avascular zone, these vessels appear to be susceptible to radiation related endarteritis obliterans (Noble & Kupersmith 1984).

The results of this study carries the implication that when detected early, the treatment of RR may be more effective and brings about better visual outcome rather than late detection. To date, the treatment of proliferative RR and radiation maculopathy is limited to several modalities, such as oral Pentoxifylline (Gupta et al. 2001), pan retinal photocoagulation (Kinyoun et al. 1996) and intravitreal agents such as triamcinolone acetonide and anti-vascular endothelial growth factor (anti-VEGF). These agents may be more effective if RR is detected earlier.

The study may be flawed by the problems associated with a retrospective population such as incomplete data collection. Furthermore, there was a large sampling bias as many patients declined to participate in this study and therefore it is possible that only those with eye symptoms will agree to participate. Many patients were also excluded because of incomplete data as to whether there was tumour extension intracranially or to the anterior nose or sinuses. Tumors with these extensive extensions require a larger treatment field that inevitably results in a higher dose to the retina.

A prospective observational study on newly diagnosed NPC in which FFA is performed before and serially after radiation would more accurately detail

the natural history of the development of RR and the aggravating factors for the development of RR.

Our recommendation is that patients who have had radiation therapy for NPC should have an ocular examination one year after the treatment and based on the clinical findings, be followed –up with yearly assessment if no clinical findings are noted. Should clinical findings be noted then an FFA is suggested, as the existence of neovascularisation may not be symptomatic and only identifiable by FFA.

## CONCLUSION

In summary, about one third of the studied eyes showed features of RR. The dose of the radiation to the retina is strongly associated with the occurrence of radiation retinopathy. Worst vision is associated with more severe RR. However, as the initial visual acuity of these patients were not documented, the exact contribution of visual loss from RR is difficult to estimate.

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