EVALUATION OF OPTIC NERVE HEAD AND MACULA PARAMETERS PRE-AND POST EXTERNAL BEAM RADIOTHERAPY IN PATIENT WITH HEAD AND NECK TUMOR

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DISCLAIMER

I hereby certify that the work in this dissertation is my own except for the quotation and summaries which have been duly acknowledged.

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ABSTRAK

Latar Belakang:

Kanser di sekitar kepala dan leher merupakan kanser yang kesepuluh biasa dijumpai di seluruh dunia. Ia mempunyai kadar kematian dan kadar mobiditi yang tinggi. Disebabkan lokasi cancer tersebut, pembedahan adalah sukar dan ia selalunya memerlukan radioterapi dan chemoterapi untuk mengawal kanser tersebut. Dengan itu, radiotherapi merupakan therapi yang utama dalam penyakit kanser kepala dan leher. Walaupun dengan adanya laser radiotherapi berteknologi baru, protokol radioterapi yang terkini dan alat pelindung diri, kerosakan akibat radiotherapy kepada tisu-tisu yang normal di sekitar kancer tersebut adalah tidak dapat dielakan. Kerosakan akibat radiasi kepada saraf optik dan makula mata merupakan komplikasi yang diketahui selama ini. Fungsi dan struktur anatomi makula dan saraf optik akan terjejas dan ia boleh mendatangkan kerosakan penglihatan yang kekal. Dengan sedemikian, pengesanan awal keatas perubahan pada makula dan sarak optic akibat daripada radiasi adalah penting supaya rawatan awal boleh dibagi untuk mengelakan kerosakan penglihatan. Mesin OCT (optical coherence tomography) adalah sejenis mesin yang mampu menganalisis struktur makula dan saraf optik dengan senang dan teliti. Jadi, matlamat kita adalah menganalisis ketebalan makula dan struktur saraf optik sebelum dan enam bulan selepas radioterapi untuk pesakit yang mempunyai kanser kapala dan leher.

Objektif:

Matlamat kajian kita adalah menganalisis min ketebalan makula dan struktur kepala saraf optik parameter sebelum dan enam bulan selepas radioterapi untuk pesakit yang menghidapi kanser kepala dan leher.

Kaedah Kajian:

Ini merupakan sebuah kajian rentas. Tiga puluh pesakit yang dipastikan menghidapi penyakit kanser kepala dan leher melalui ujian histologi direkrut diantara masa bulan Desember 2016 sehingga bulan Ogos 2017. Pemeriksaan mata termasuk ketebalan makula dan kepala saraf parameter (cakera keluasan kepala saraf, keluasan rim kepala saraf, isipadu cawan kepala saraf, nisbah cawan dan cakera kepala saraf, ketebalan lapisan saraf sekitar kepala saraf) dipungut dan dianalisiskan dengan menggunakan Spectral Domain-Cirrus optical coherence tomography mesin. Enam bulan selepas menjalani radioterapi, penilaian yang serupa dijalankan sekali lagi. Keputusan dianalisis dengan menggunakan kaedah descriptive analysis, paired t-test dan multivariate ANCOVA dalam perisian SPSS.

Keputusan:

Analysis menunjukkan bahawa makula menjadi nipis di kumpulan selepas radioterapi, walaupun keputusannya adalah tidak signifikasi. Tiada perubahan yang ketara didapati dalam parameter struktur kepala saraf optik. Ketebalan saraf (RNFL) sekitar kepala saraf optik terutamanya kuadran bawah didapati tebal di kumpulan selepas radioterapi dimana keputusannya adalah signifikasi.

Kesimpulan:

Dalam kajian ini kita mendapati bahawa makula adalah lebih nipis dan ketebalan lapisan saraf sekitar kepala saraf mata adalah lebih tebal di kumpulan enam bulan selepas radioterapi. Tetapi, perubahan yang dikesan adalah kecil. Kita mendapati bahawa adalah tidak wajar dan terlalu awal untuk membuat kesimpulan berdasarkan keputusan pada masa kini. Dengan demikian, kajian yang lebih teliti, lebih banyak

peserta dan melanjutkan tempoh permerhatian adalah diperlukan sebelum kita membuat kesimpulan yang muktamat.

ABSTRACT

Background:

Head and neck cancers is one of the tenth most common cancer worldwide with high mortality and morbidity rate. Due to its location, surgical clearance is often difficult and require radiotherapy and chemotherapy to achieve locoregional control. Therefore, radiotherapy is considered the mainstay treatment in head and neck cancers. Despite advancement of laser beam, radiation protocol and protective equipment, radiation damage to surrounding normal tissue is inevitable. Radiation optic neuropathy and retinopathy are known ocular complication following radiotherapy. Early detection and prompt early treatment might prevent debilitating visual loss. Optical coherence tomography of macula and optic nerve head parameters will be able to provide an objective measurement and evaluation of above areas.

Objectives:

Our objective of this study is to compare mean macular thickness and optic nerve head parameters pre-and six-month post external beam radiotherapy in patient with head and neck tumours.

Methods:

A cross sectional study involving 30 patients histologically diagnosed head and neck cancers. Patient who fulfilled inclusion and exclusion criteria were recruited from a single centre in Malaysia. Recruitment was carried out between December 2016 and August 2017. Evaluation of optic nerve head parameters and macular thickness were conducted using Spectral Domain-Cirrus optical coherence tomography. Optic nerve head parameters, retinal nerve fibre layer (RNFL) thickness and macular thickness were evaluated prior to radiotherapy. A repeat procedure was conducted six months

post external beam irradiation. Assuming both eye received similar radiation exposure, right eye ONH parameters and macular thickness are analysed and discussed in this study. Descriptive analysis, paired t-test and multivariate ANCOVA method is performed in this study using SPSS.

Result:

Macular is thinner in post radiotherapy, but without statistically significant. There were no changes in mean optic nerve head parameters between pre-and post radiotherapy period. Mean RNFL thickness showed thickening in the post radiotherapy period. Temporal and inferior quadrant of RNFL showed thickening in post radiotherapy period, in which inferior quadrant showed statistically significant result.

Conclusion:

There was thinning of macular thickness and thickening of optic nerve head RNFL in six-month post radiotherapy. But the changes were small and it is too early to justify the parameters. Further researches, larger studies and longer follow up period need to be conducted before we can further draw the conclusion of other parameters related to early exposure to radiation.

Chapter 1

Introduction

1.1 EPIDEMIOLOGY OF HEAD AND NECK TUMOURS

Head and neck tumours are tumours found situated at the aero digestive tract (which include oral cavity, nasopharynx, oropharynx, hypopharynx and larynx), paranasal sinuses and salivary glands. Cancer of the mouth and oropharynx ranked tenth most common cancer worldwide and cancer induced mortality ranking seventh in the world (Mathers, 2008). World Health Organization (WHO) documented estimated of 600 000 new cases of head and neck cancers every year, commonest site being the oral cavity, followed by larynx and pharynx (Marur and Forastiere, 2008). These cancers are largely seen in Indian subcontinent, Australia, France, Brazil and Southern Africa (Marur and Forastiere, 2008; Mignogna *et al.*, 2004).

Nasopharyngeal carcinoma (NPC) is the commonest tumour in the nasopharynx, with specific demographic pattern and racial distribution. NPC has a predilection toward the Chinese population, having the highest incidence rate in the central region of Guangdong Province in Southern China and Hong Kong (Mignogna *et al.*, 2004). Malaysia has been categorized with intermediate occurrence rate with age standardized incidence rate for Malaysian males are 6.5 per 100 000 persons per year (Mimi and Yuan, 2002). In general head and neck cancers affect the older population, in which 98% of patients are diagnosed over 40 years of age (Mathers, 2008). However, NPC was also reported to affect younger population aged 15 to 35 (Mimi and Yuan, 2002). About 90% of head and neck cancers derived from squamous cell carcinoma, other histological types are malignant melanoma, lymphoma, adenocarcinoma, anaplastic and rhabdomyosarcoma (Grégoire *et al.*, 2010; Lund and Howard, 1990; Mathers, 2008; Mimi and Yuan, 2002).

Tobacco and alcohol are two main risk factors related to development of head and neck cancers. Recently there is a rise in human papilloma virus (HPV) related oropharynx

cancer due to changing of sexual practices (Chaturvedi *et al.*, 2011; Crozier and Sumer, 2010; Mehanna *et al.*, 2010). Head and neck cancers are generally locally invasive tumour with regional lymph nodes metastasis. Early diagnosis and staging is crucial and associate with favourable outcome (Lo and Lu, 2010). However, due to its location, its presentation often subtle and disease tend to progress into relatively advanced stage before patient presented to clinician (Lo and Lu, 2010).

Staging of the cancer is important to classify the extend, strategize optimum therapy and predict the tumour outcome (O'Sullivan and Yu, 2010). NPC staging is adopted from American Joint Committee on Cancer (AJCC) Staging and End Result Reporting/International Union for International Cancer Control (UICC), in which the extend of main tumours, lymph node involvement and spread to distant site are taken into consideration (Grégoire *et al.*, 2010; Wei and Sham, 2005).

Table 1: AJCC staging system for NPC.

AJCC stage	Stage grouping	Stage description*
0	Tis N0 M0	The tumor is only in the top layer of cells lining the inside of the nasopharynx, and has not grown any deeper (Tis). The cancer has not spread to nearby lymph nodes (N0) or to distant parts of the body (M0).
I	T1 N0 M0	The tumor is in the nasopharynx. It might also have grown into the oropharynx (the part of the throat in the back of the mouth) and/or nasal cavity but no farther (T1) The cancer has not spread to nearby lymph nodes (N0) or to distant parts of the body (M0).

II	T1 (or T0) N1 M0	The tumor is in the nasopharynx. It might also have grown into the oropharynx (the part of the throat behind the mouth) and/or nasal cavity but no farther (T1). OR no tumor is seen in the nasopharynx, but cancer is found in lymph nodes in the neck and is Epstein-Barr virus (EBV) positive, which makes it very likely to be NPC (T0). The cancer has spread to 1 or more lymph nodes on one side of the neck, or it has spread to lymph nodes behind the throat. In either case, no lymph node is larger than 6 cm across (N1). The cancer has not spread to distant parts of the body (M0).
	OR	
	T2 N0 or N1 M0	The tumor has grown into the tissues of the left or right sides of the upper part of the throat (but not into bone) (T2). The cancer has not spread to nearby lymph nodes (N0). OR it has spread to 1 or more lymph nodes on one side of the neck, or it has spread to lymph nodes behind the throat. In either case, no lymph node is larger than 6 cm across (N1). The cancer has not spread to distant parts of the body (M0).
III	T1 (or T0) N2 M0	The tumor is in the nasopharynx. It might also have grown into the oropharynx (the part of the throat behind the mouth) and/or nasal cavity but no farther (T1). OR no tumor is seen in the nasopharynx, but cancer is found in lymph nodes in the neck and is Epstein-Barr virus (EBV) positive, which makes it very likely to be NPC (T0). The cancer has spread to lymph nodes on both sides of the neck, none of which is larger than 6 cm across (N2). The cancer has not spread to distant parts of the body (M0).
	OR	

	T2 N2 M0	The tumor has grown into the tissues of the left or right sides of the upper part of the throat (but not into bone) (T2). The cancer has spread to lymph nodes on both sides of the neck, none of which is larger than 6 cm across (N2). The cancer has not spread to distant parts of the body (M0).
	OR	
	T3 N0 to N2 M0	The tumor has grown into the sinuses and/or the bones nearby (T3). The cancer might or might not have spread to nearby lymph nodes in the neck or behind the throat, but none are larger than 6 cm across (N0 to N2). The cancer has not spread to distant parts of the body (M0).
IVA	T4 N0 to N2 M0	The tumor has grown into the skull and/or cranial nerves, the hypopharynx (lower part of the throat), the main salivary gland, or the eye or its nearby tissues (T4). The cancer might or might not have spread to nearby lymph nodes in the neck or behind the throat, but none are larger than 6 cm across (N0 to N2). The cancer has not spread to distant parts of the body (M0).
	OR	
	Any T N3 M0	The tumor might or might not have grown into structures outside the nasopharynx (any T). The cancer has spread to lymph nodes that are either larger than 6 cm across, or located in the shoulder area just above the collarbone (N3). The cancer has not spread to distant parts of the body (M0).

IVB	Any T Any N M1	The tumor might or might not have grown into structures outside the nasopharynx (any T). The cancer might or might not have spread to nearby lymph nodes (any N). The cancer has spread to distant parts of the body (M1).

1.2 RADIOTHERAPY TREATMENT IN HEAD AND NECK TUMOURS

Ionizing radiation has a direct effect on the tumour cells by damaging the DNA and cellular molecules. It also produces free radicals that kill the tumour cells indirectly. This result in functional deficiency of microvascular structure and depopulation of the tumour (Baskar *et al.*, 2014). Most squamous cell type head and neck cancers are radiosensitive. At early stage of the disease (stage I-II), either conservative surgery or radiotherapy give loco-regional control of the tumour (Argiris *et al.*, 2008; Grégoire *et al.*, 2010). In NPC, radiotherapy play an important role following surgical clearance of nasopharynx as the surgical clearance often incomplete owning to limited accessibility in nasopharynx (Wei and Sham, 2005). As for locally advanced stage III and IV tumours, chemoradiotherapy following surgical clearance is advocated and it has been proven to improve survivability (Adelstein *et al.*, 2003; Grégoire *et al.*, 2010; Wei and Sham, 2005).

Radiotherapy is a mainstay of treatment in squamous cell type head and neck cancers. Conventional fractionated radiotherapy is typically given in daily fractions of 2.0 Gy, 5 days a week, up to a total of 70 Gy over 7 weeks. Patients undergoing irradiation to the head and neck are immobilized in a beam direction shell made of plastic placed onto patient's face. This is to ensure accuracy and reproducibility of the treatment set

up, and radiation side effect to surrounding normal tissue is minimized (Sanderson and Ironside, 2002). Despite of such high dose fraction, conventional radiotherapy does not yield satisfactory loco-regional control especially in locally advanced cancers. About one third of locally advanced head and neck cancer that undergo conventional radiotherapy has poor prognosis, risk of recurrence and 5-years survival rate of 30% (Bourhis *et al.*, 2006; Wendt *et al.*, 1998). Therefore hyperfractionated and accelerated fractionation radiotherapy are more preferred nowadays and they are proven to be able to gain more loco-regional control, improve overall survival and reduce cancer related mortality (Argiris *et al.*, 2008; Bourhis *et al.*, 2006).

1.3 COMPLICATION OF RADIOTHERAPY TO HEAD AND NECK

With recent advancement of laser beam, various radiation protocol and radiation protective shields, radiation injury mainly limit to the field of radiation. As for head and neck radiotherapy, injury to adjacent structures includes oral cavity, neck and brain are relatively common and difficult to treat (Vissink *et al.*, 2003).

Oral mucosa is commonest site developing radiotherapy side effect due to its high cellular turnover, diverse and complex microflora (Sciubba and Goldenberg, 2006). Example of acute complications are mucositis, infection, sialadenitis, xerostomia, taste dysfunction and sinusitis. Chronic complication such as dry mouth, mucosal atrophy, dental caries, chronic infection, taste dysfunction, soft tissue necrosis, trismus, dry eye, retinopathy, cataract, optic neuropathy and vocal cord palsy (Epstein *et al.*, 1999; Parsons *et al.*, 1983; Sciubba and Goldenberg, 2006; Vissink *et al.*, 2003).

The commonest site of radiation injury to brain tissue is located at the temporal lobe which can lead to learning and memories disability (Welzel *et al.*, 2008). Long term

follow up of patient underwent radiotherapy has been demonstrated to be at risk of developing radiation induced cranial nerve palsy, with incidence occurrence ranging from 3.9% to 30.9% (Janssen *et al.*, 2015; Lee and Borruat, 2011).

1.3.1 RADIATION INDUCED OPTIC NEUROPATHY

Radiation induced optic neuropathy is a known complication of radiation effect on visual pathway. Although it is rare with reported incidence rate of 0.001% (Wang *et al.*, 2016), once develop can result in profound, irreversible visual loss (Delanian *et al.*, 2012; Parsons *et al.*, 1994; Yousef and Finger, 2012). Common site of injury includes chiasm and retrobulbar optic nerve (Lee and Borruat, 2011). Onset of radiation induced optic neuropathy varies from 3 months to 9 years, with mean onset between 10-20 months following exposure to radiotherapy (Parsons *et al.*, 1994; Yousef and Finger, 2012).

It is typically presented as acute, painless, progressive unilateral visual loss with visual acuity at 20/200 or worst even to no perception of light. Often, visual field defect accompanies visual loss, which include altitudinal, central scotoma, bitemporal hemianopia or junctional syndrome (Archer *et al.*, 1991; Delanian *et al.*, 2012; Parsons *et al.*, 1994; Yousef and Finger, 2012). Clinical appearance of the optic disc is often normal, perhaps posterior optic neuropathy is commoner than anterior (Indaram *et al.*, 2015; Kumre *et al.*, 2015).

Anterior radiation optic neuropathy can exhibit features like optic disc oedema, hyperaemia, cotton wool spots and haemorrhages. Few case reported that optic nerve functions and parameters may be abnormal months prior to the loss of vision and clinical signs (Danesh-Meyer, 2008; Delanian *et al.*, 2012; Yousef and Finger, 2012).

In acute radiation optic neuropathy, there is increase in papillary thickness and decrease in optic cup depth by optical coherence tomography examination (Yousef and Finger, 2012).

1.3.2 RADIATION INDUCED RETINOPATHY AND MACULOPATHY

Radiation maculopathy, retinopathy and chorioretinopathy are also documented as potential sight threatening complication post radiotherapy treatment. In fact, radiation maculopathy is the most common irreversible irradiation related visual loss (Elmassri, 1986; Finger *et al.*, 2010; Zamber and Kinyoun, 1992). Pathology of radiation retinopathy resemble diabetic retinopathy, with presence of vaso-occlusive features and microvascular damage leading to retinal non-perfusion, neovascularization and macular oedema (Sutter and Gillies, 2003). It has following clinical presentation such as microaneurysm, retinal haemorrhages, nerve fibre layer infarct, retina oedema, macular oedema, cotton wool spots, vitreous haemorrhages, telangiectasia, fibrovascular proliferation and tractional retinal detachment (Elmassri, 1986; Zamber and Kinyoun, 1992). Breaching of inner blood retinal barrier could also be responsible to the development of radiation maculopathy, in which intravitreal triamcinolone has showed beneficial result possible by restoring the blood retinal barrier (Sutter and Gillies, 2003). A study showed decreased in the retinal nerve fibre layer thickness, inner plexiform layer, ganglion cell layer and outer nuclear layer of macula in patient with radiation maculopathy. Inner nuclear layer and outer plexiform layer did not show any significant changes in thickness (Yousef and Finger, 2012).

1.4 RADIOTHERAPY IN HOSPITAL UNIVERSITI SAINS MALAYSIA

Department of Nuclear Medicine, Radiotherapy and Oncology in Hospital Universiti Sains Malaysia was established since 1995 to provide cancer treatment and nuclear medicine service to the East Coast of Peninsular Malaysia. Machine PRIMUS, manufactured by SIEMEN is used to deliver conventional ionizing proton beam (x-ray) radiation, delivered via external beam irradiation to most of the head and neck cancers. All treatment is individualized. Patient will undergo a lengthy simulation procedure and customized shielding mould will be made prior to radiotherapy. Regime practiced for head and neck carcinoma is a total of 70 Gy given in divided fraction for 35 times, over a course of 7 weeks.

1.5 RATIONAL OF THE STUDY

Radiation related optic neuropathy and maculopathy always lead to poor visual outcome. Currently available treatment regime for radiation optic neuropathy and retinopathy are corticosteroids, anticoagulant and hyperbaric oxygen (Danesh-Meyer, 2008; Guy and Schatz, 1986). However, treatment outcome is often poor. Radiation related optic neuropathy and maculopathy often present at 10 to 20 months, with average 18 months after treatment; but the onset of disease may range from 3 months to 9 years (Danesh-Meyer, 2008; Miller, 2004). The aim of the study is to detect any optic nerve head parameters and macular thickness derangement as early as six months following external beam irradiation for head and neck cancer patients. Those parameters, if proven significant, can be used as early predictor of radiation optic neuropathy and maculopathy. Assessment of optic disc and macular parameters using optical coherence tomography (OCT) able to provide objective measurement before and six months after external beam irradiation.

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