RESEARCH ARTICLE

Intensity-Modulated Radiotherapy for Nasopharyngeal Carcinoma: Penang General Hospital Experience

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Abstract

Purpose: To study the overall treatment time (OTT) and acute toxicity of intensity-modulated radiotherapy (IMRT) treatment for nasopharyngeal carcinoma (NPC). Methods: This retrospective study covered all NPC patients who underwent radical IMRT treatment at the Penang General Hospital from June 2011 to February 2012. Patients of any age and stage of disease with histologically proven diagnosis were included. Information was collected on patient demographics, clinical stage, treatment received, including any neoadjuvant and/or concurrent chemotherapy, acute toxity and completion of IMRT within the OTT. Results: A total of 26 NPC patients were treated with IMRT during the study period; 88.5% had stage III/IV disease. 45.2% received neo-adjuvant chemotherapy while 50.0% were given concurrent chemo-irradiation. All patients completed the treatment and 92.3% within the 7 weeks OTT. Xerostomia was present in all patients with 92.3% having grade 2. Severe grade III/IV acute toxicity occurred in 73.1% of patients, the commonest of which was oral mucositis (57.6%). This was followed by dysphagia which occurred in 53.8%, skin reactions in 42.3% and weight loss in 19.2%. However, haematological toxicity was mild with only one patient having leucopaenia. Conclusion: IMRT treatment for NPC is feasible in our center. More importantly, it can be delivered within the 7 weeks OTT in the majority of patients. Severe grade 3/4 toxicity is very common (73.1%) and thus maximal nutritional and analgesic support is required throughout the treatment.

Keywords: Nasopharyngeal carcinoma - intensity-modulated radiotherapy - overall treatment time - acute toxicity

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Introduction

Nasopharyngeal carcinoma (NPC) is the fifth commonest malignancy in Peninsular Malaysia with an incidence rate of 8.5 and 2.6 per 100,000 populations for males and females respectively according to the latest available incidence report by the National Cancer Registry for Peninsular Malaysia in 2006 (National Cancer Registry, 2006). The 5 years overall survival (OS) reported in Penang General Hospital, Malaysia for a cohort of 285 patients treated between 2000-2005 was only 33.3% (Phua et al., 2011). This result was relatively poor compared to the overall worldwide 5 years survival rate which ranged from 32% to 62% involving more than 9500 patients with all stages of NPC (Shu-Chen, 1980; Hsu et al., 1982; Al-Sarraf et al., 1990; Lee et al., 1992; Lee et al., 1993; Qin et al., 1998; Wang et al., 1998; Ali et al., 1999; Lin et al., 1999, Terence et al., 2003). The results published for later studies were even better with the advent of new radiotherapy techniques including intensity-modulated radiotherapy (IMRT). The University of California-San Francisco reported a study involving 67 patients who underwent IMRT for NPC showed a 4 years OS of 88% (Lee et al., 2002). In this study 70% of the patients had stage III or IV disease compared to 79.3% in the Penang General Hospital study. In yet another study using IMRT in the Cancer Hospital of Fujian Medical University involving 326 patients of which 80.5% had stage III or IV disease, a 90% 3 years OS was reported (Lin et al., 2009). The Xijing Hospital, Northwest China also reported a pilot study where 138 NPC patients were treated with IMRT with 81.9% of the patients having stage III or IV disease. The 3 years OS rate was 83.1% (Wang et al., 2012). Early results from the Pamela Youde Nethersole Eastern Hospital, Hongkong utilizing IMRT reported a 2 years OS of 92.0% in a study with 193 patients of which 93% had stage III or IV disease (Ng et al., 2011). Meanwhile, the University of Hongkong, Queen Mary Hospital published its early result for 50 patients with stage III or IV NPC who were treated with IMRT which showed an encouraging 2 years OS of 92.1% (Kwong et al., 2006). Radiotherapy (RT) is the only curative treatment option in the management of NPC. However, RT for NPC is fraud with danger as the nasopharynx is surrounded by many radiosensitive structures such as the spinal cord, brainstem, temporal lobes, optic chiasm,

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optic nerves, retina, lenses, middle and inner ears and the parotid glands. NPC has a propensity to spread along all directions often making the RT target volume large and irregular. This is especially so in stages III and IV disease where complicated target volumes which lie very close to critical organs like the spinal cord and brainstem making it impossible to be treated with adequate high dose with conventional 2D or 3D conformal RT. However, IMRT has been shown to be able to deliver high dose to the target areas despite these obstacles (Cheng et al., 2001 Waldron et al., 2003). Therefore, it is of utmost importance that IMRT treatment be implemented in our country as the standard of care as soon as possible in view of the late presentation of many of our NPC patients. Besides the Penang General Hospital study that showed 79.3% of patients having stage III or IV disease, another study in University Hospital, Kuala Lumpur revealed an even higher proportion at 94% (Prasad and Pua, 2000). The latest available data in Malaysia based on NPC patients treated in six major tertiary referral centers from July 2007 to February 2008 still showed 75% of patients presented with stage III or IV diseases (Pua et al., 2008).

The successful implementation of IMRT for NPC treatment must be accompanied by acceptable toxicities and even more importantly compliance with overall treatment time (OTT). Interruptions in RT causing prolonged treatment time have been reported to be detrimental for local control and survival in multiple tumour sites including NPC and head and neck cancers (Vikram et al., 1985; Cox et al., 1992; Zelefsky et al., 1992; Luo et al., 1994; Van den Bogaert et al., 1995; Kwong et al., 1997). For a radical RT course for NPC, the usual acceptable OTT is completion of the entire course within 7 weeks. The main reasons for prolonged OTT include severe acute toxicities requiring treatment delay, holidays, machine interruptions and patient non-compliance. Public holidays and machine interruptions can be dealt with by careful planning and if unavoidable, additional treatment can be given on the weekends or treating twice a day with at least 6-8 hours apart to ensure OTT stays within 7 weeks. Patient compliance can be improved with adequate education about the need to stay within the OTT right from the outset of treatment and assurance that side effects can be dealt with effectively. The addition of chemotherapy concurrently with RT can improve overall survival and local control but this must not be done at the expense of increasing overall treatment time. The addition of chemotherapy to RT for the treatment of NPC has been conclusively shown to be beneficial for locally advanced NPC. Two meta-analyses involving more than 2500 patients and ten randomized trials reported an absolute survival benefit of 4-6% at 5 years and this benefit was most pronounced with concurrent chemoirradiation (Langendijk et al., 2004; Baujat et al., 2006). However, this can only be achieved with increased toxicities. As such it is of utmost importance that the usage of chemotherapy does not lead to increase in OTT which will then defeat the purpose of adding chemotherapy into the treatment regimen. We must be cognizant to the fact that the definitive treatment for NPC is RT and not chemotherapy. Ensuring that patients can get through RT including when using the IMRT technique in the stipulated OTT is of paramount importance. This is especially so when chemotherapy is given concurrently and it is foreseeable that patients need maximal dietary and analgesic support during this grueling treatment period.

We are not aware of any published data on IMRT treatment for NPC in Malaysia as of this time. The aim of this study is to establish the feasibility of high dose IMRT treatment for NPC in Malaysia with regards to acute toxicities and also compliance within the stipulated OTT.

Materials and Methods

This study retrospectively analysed all NPC patients who underwent radical IMRT treatment under the Penang General Hospital from June 2011 to February 2012. Patients of any age and stage of disease with histologically proven diagnosis who underwent radical IMRT were included in this study. Information collected included patient demographics, clinical stage based on the TNM and AJCC staging for NPC, treatment received including any neoadjuvant and/or concurrent chemotherapy, acute toxities and completion of IMRT within OTT. Acute toxicities were based on the Radiation Therapy Oncology Group (RTOG) acute radiation morbity scoring criteria and toxicities collected included xerostomia, skin reaction, dysphagia, mucositis, weight loss, haemoglobin level, white blood count and platelet level. Acceptable OTT was completion of IMRT within 7 weeks.

Patients were immobilized with a tailored beam directional shell in a comfortable neck position. Intravenous contrast-enhanced CT using 3mm slice from the vertex to below the clavicles was performed using the CT simulator. CT data were imported to the Oncentra treatment planning system. Targets and organs at risk (OAR) were localized on the CT images. The gross tumour volume (GTV70) included all known gross disease in the primary area and the neck area determined from CT, MRI clinical information and endoscopic examination. Enlarged neck nodes included any lymph nodes >1cm or nodes with a necrotic center. The clinical target volume (CTV70) to account for microscopic spread was obtained by giving a margin of 1cm circumferentially around the GTV. A second clinical target volume (CTV59.4) which is bigger than the CTV70 was delineated to account for all potential routes of spread for the primary and the nodal regions. These included the entire nasopharynx, parapharyngeal space, pterygopalatine fossa, posterior third of the nasal cavity and maxillary sinuses, inferior sphenoid sinus, posterior ethmoid sinus, base of skull (including the foramen ovale and rotundum bilaterally) and anterior half of the clivus. The cavernous sinus was also included for high risk patients. As for the nodal region, the CTV59.4 included the nodes in the junctional, parapharyngeal, retropharyngeal, submandibular regions, level II, III, IV, V nodes and supraclavicular fossa bilaterally. Subsequently, separate planning target volume (PTV) were obtained by providing a margin of 0.5 cm around the CTV to account for variabilities of treatment set up and internal organ movement resulting in PTV70 and PTV59.4. Margins were reduced to as low

as 1 mm for target volumes in close proximity to critical OAR for example the brainstem. The treating radiation oncologist modified these final PTVs accordingly based on the surrounding critical OARs. The contoured OARs included the spinal cord, brainstem, optic chiasm, optic nerves, eyes, lenses,cochleas, parotid glands, oral cavity, larynx, mandible, temporomandibular joints and brachial plexus.

Inverse planning for IMRT was performed using the CMS XiO version 4.60. The prescribed doses were 70 Gy to the PTV70 in 33 fractions at 2.12 Gy per fraction and 59.4 Gy in 33 fractions to the PTV59.4 at 1.8 Gy per fraction. With regards to the OARs, the critical organs were the spinal cord and brainstem. Maximal allowable dose to any part of the spinal cord was 45 Gy and for the brainstem it was 54 Gy without any compromise. The optic nerves and eyes were kept below 50 Gy while the optic chiasm was kept below 54 Gy. If the doses of any of these optic apparatus were exceeded due to extensive disease informed consent for blindness was obtained from the patient prior to plan approval. The maximal allowable dose for the brachial plexus was 66 Gy unless there was gross disease in its vicinity. DVH was generated for all the target volumes and OARs. For evaluation of the dose volume histogram (DVH), the treating oncologist used the following guideline for acceptability of a plan: 95% of any PTV70 was at or above 70 Gy and 99% of PTV70 was at or above 65.1 Gy. In addition, no more than 20% of the PTV70 was at or above 77 Gy and no more than 5% of the PTV70 was at or above 80 Gy. Plans fulfilling the criteria for PTV70 needed to be within the dose constraints for OARs as outlined above. Quality assurance for finalized plan was done using the MapCHECK tool for point dose and fluence testing. Verificaton of isocentre was subsequently done by checking orthogonal fields using the SimViewNT Siemens Simulator. IMRT was delivered via seven fixed angles with an Elekta Precise Linear Accelerator. Portal imaging was done weekly using the Elekta iview electronic portal imaging version 3.4. Acceptable OTT was set at 7 weeks. Treatment was delivered once daily, 5 fractions per week, over 6 weeks and 3 days. All targets were treated simultaneously.

Results

Between June 2011 and February 2012, 26 patients with NPC were treated with radical high dose IMRT. The clinic-pathological features of these 26 patients are presented in Table 1. The patients' age ranged from 35 to 72 years with a median age of 54. 80% of the patients were males and the majority was of Chinese descent (69%). This majority of patients in this cohort also had locally advanced disease with 88.5% having either stage III or IV disease. Most patients did not have any co-morbidity. The 6 patients who had co-morbidity had either ischaemic heart disease, hypertension, diabetes, osteoarthritis, chronic hepatitis or end stage renal failure on regular haemodialysis. All the patients were relatively fit with 50% having performance status ECOG 0 and 50% having ECOG 1.

Neoadjuvant chemotherapy was given to 12 patients

Table 1. Clinico-Pathological Features of 26 Patients

Items	No. of patients	%
Age	Up to 50 years 11	42.3
	51 – 69 years 13	50
	70 years and above	2
7.7		
Gender	Female 5	19.2
	Male 21	80.8
Race	Malay 6	23.1
	Chinese 18	69.2
	Indigenous 2	7.7
Performance status	0 13	50
	1 13	50
Presence of co-morbid disease	Yes 6	23.1
	No 20	76.9
Tumour Stage	TI 7	26.9
	T2 8	30.8
	T3 4	15.4
	T4 7	26.9
Nodal Stage	N0 2	7.7
	N1 2	7.7
	N2 14	53.8
	N3 8	30.8
AJCC stage	I 2	7.7
	II 1	3.8
	III 10	38.5
	IV 13	50
Neo-chemotherapy	Yes 12	46.2
	No 14	53.8
Concurrent chemoradiotherapy	Yes 13	50
	No 13	50

(46.2%) prior to definitive IMRT. These patients were given 3 cycles of 5-Fluorouracil 750mg/m^2 D1-5 and cisplatin 75mg/m^2 D1 only on a 3 weekly basis. 50% of patients received concurrent chemoirradiation during IMRT treatment with weekly cisplatin 30mg/m^2. OTT ranged from 44 days to 65 days with a mean of 47.6 days. 24 patients (92.3%) managed to complete the IMRT within the stipulated 7 weeks period. One patient completed the IMRT within 59 days. She was 62 years old and received neoadjuvant chemotherapy prior to definitive IMRT alone for stage 4a disease. The delay in OTT was due to severe skin reaction and mucositis (grade 4). On review 6 weeks post IMRT, the skin reaction and mucositis has healed. The other patient completed IMRT only after 65 days. However, the delay was not due to acute toxicities but due to patient non-compliance. Despite numerous counseling sessions, the patient remained non-compliant and eventually completed the treatment in 9.3 weeks as an outpatient.

The results of the acute toxicities are presented on Table 2. 19 patients (73.1%) suffered from at least one grade 3 or 4 acute toxicitiy. Xerostomia was present in all patients and 92.3% had grade 2 xerostomia (moderate to complete dryness/thick, sticky saliva/ markedly altered taste). Skin reaction was also present for all patients with 10 patients (38.5%) having grade 3 skin reaction (confluent, moist desquamation other than skin folds, pitting oedema). One patient had grade 4 skin reaction (ulceration, haemorrhage, necrosis). This patient required delay in the IMRT treatment which was completed only after 8.4 weeks. On review after 6 weeks post IMRT,

the skin reaction had healed. More than half (53.8%) of the patients suffered from severe grade 3 dysphagia (severe dysphagia or odynophagia with dehydration or weight loss > 15% from pretreatment baseline requiring nasogastric feeding tube, IV fluids or hyperalimentation). Grade 3 mucositis (confluent fibrinous mucositis/may include severe pain requiring narcotic) was present in 14 patients (53.8%) and 1 patient had grade 4 mucositis (ulceration, haemorrhage or necrosis). This was the same patient with grade 4 skin reaction and on review at 6 weeks post IMRT the mucositis had healed. Weight loss was present in 25 out of the 26 patients. However severe grade 3 weight loss (anorexia with >15% weight loss from pretreatment baseline or requiring nasogastric tube or parenteral support) was present in only 5 patients (19.2%). Haematological toxicities during IMRT was mild with only one patient having grade 3 leucopaenia which recovered in the subsequent week.

Table 2. Early Side Effects of Radical IMRT Treatment of Study Cohort

Items		No. of patients	%
Xerostomia	Grade 0	0	0
	Grade 1	2	7.7
	Grade 2	24	92.3
	Grade 3	0	0
	Grade 4	0	0
Skin reaction	Grade 0	0	0
	Grade 1	4	15.4
	Grade 2	11	42.3
	Grade 3	10	38.5
	Grade 4	1	3.8
Dysphagia	Grade 0	2	7.7
	Grade 1	2	7.7
	Grade 2	8	30.8
	Grade 3	14	53.8
	Grade 4	0	0
Mucositis	Grade 0	0	0
	Grade 1	2	7.7
	Grade 2	9	34.6
	Grade 3	14	53.8
	Grade 4	1	3.8
Weight Loss	Grade 0	1	3.8
	Grade 1	6	23.1
	Grade 2	14	53.8
	Grade 3	5	19.2
	Grade 4	0	0
Full Blood Count	Grade 0	16	61.5
	Grade 1	8	30.8
	Grade 2	2	7.7
	Grade 3	0	0
	Grade 4	0	0
White Count	Grade 0	18	69.2
	Grade 1	5	19.2
	Grade 2	2	7.7
	Grade 3	1	3.8
	Grade 4	0	0
Platelet	Grade 0	26	100
	Grade 1	0	0
	Grade 2	0	0
	Grade 3	0	0
	Grade 4	0	0
Completed IMRT within 7 weeks	Yes	24	92.3
	No	2	7.7

Discussion

The main result of this study showed all 26 patients managed to complete the IMRT treatment, albeit with 92.3% managing to complete it within the stipulated 7 weeks OTT. Unfortunately this rate has seldom been reported in published IMRT studies thus far. One report that did state this rate was a Hong Kong study involving 50 patients that showed a similar rate of 92% completing the IMRT treatment without requiring a treatment break (Kwong et al., 2006).Our completion rate within the stipulated OTT is very encouraging in view of the importance of completion of radical RT within the 7 weeks time frame as studies have estimated a loss of approximately 1.4% local control for every day of delay beyond the OTT. This will translate to a loss of 10-12% of local control with a delay of one week during treatment (Maciejewski et al., 1983; Vikram et al., 1985; Maciejewski et al., 1989; Barton et al., 1992; Fowler et al., 1992). This effect is most likely due to proliferation of surviving clonogenic tumour cells between dose fractions and it is most prominent between the 3rd and 7th week of conventional RT of head and neck cancers. An average of 0.5-0.7 Gy are lost per day by repopulation of clonogenic cancer cells (Slevin et al., 1992; Trott, 2009). Unfortunately, once there is a treatment delay beyond the 7 weeks OTT, there is no effective way to maintain local control rate as increasing the total dose delivered will lead to unacceptable increase in risk of radiation late effects. This is especially so in the treatment of NPC as the nasopharynx is flanked by multiple critical structures. As such, all effort should be concentrated on completing the treatment within the stipulated OTT. Any unplanned interruptions from machine breakdown or public holidays should be compensated by treating over the weekends or additional fractions given during the same treatment day with an inter-fraction interval of at least 6 hours to avoid increasing the OTT. Each member of the multidisciplinary cancer management team including the patient and their family members must be kept well aware of the rationale and importance of treatment interruptions (Bese et al., 2007). This was well illustrated in one patient in our study who lacked compliance despite multiple sessions of counseling regarding the importance of continuing treatment without gaps. More focus should be given towards patient education even before treatment has started and mental preparation for this grueling treatment must be accompanied by assurance that acute toxicities can be managed effectively with full nutritional and analgesic support.

The second important finding was that 73.1% of patients suffered from either grade 3 or 4 acute toxicity. This rate was similar to the rate reported by a Hong Kong study involving 193 NPC patients treated with IMRT where severe acute toxicity occurred in 69.4% of the patients including 3 treatment related deaths (grade 5 toxicity) related to pneumonia and fulminant sepsis (Ng et al., 2011). Another IMRT study in Hong Kong with 50 patients had 78% of their patients having severe acute toxicity with one treatment related death (Kwong et al.,

2006). However, IMRT studies on NPC patients in China reported a lower rate of severe acute toxicities ranging from 17.5-40.6% (Lin et al., 2009; Han et al., 2010; Wang et al., 2012).

Severe skin reaction was present in 42.3% of patients. Available data from other IMRT studies including those from China reported a rate of between 4.5-5.1% for severe skin reaction (Lin et al., 2009; Han et al., 2010; Lu et al., 2010; Wang et al., 2012). However, data from Hong Kong reported a higher rate ranging from 13-46% (Kwong et al., 2006; Ng et al., 2011). Although the rate of skin reaction was high in our study, however all patients had complete resolution of this reaction 6 weeks post IMRT. It is also important to note that 84.6% of our patients had N2-3 disease and skin sparing effect by ensuring a larger margin from the target volumes to the skin might have compromised nodal disease control. Many of these cases were treated with a margin as little as 2 mm from the skin to avoid underdosing the nodal disease. In fact a few patients were treated with bolus applied to the BDS to increase the dose to larger nodal disease situated very close to the skin. Grade 3 dysphagia occurred in 53.8% of our study population and all these patients required intensive dietary support and/or nasogastric tube feeding. However, Hu and colleagues (2010) in China reported a rate of only 9.1% while the study in Hong Kong involving 193 patients reported a rate of 15% (Ng et al., 2011). Unfortunately, this complication was not specifically reported in the other studies. The commonest severe acute toxicity in our patient population was oral mucositis which occurred in 57.6% of patients. This rate was similar to the studies in Hong Kong on IMRT for NPC. Recent IMRT studies in Hong Kong had rates between 65-78% (Kwong et al., 2006; Ng et al., 2011). However, the studies in China reported lower rates ranging from 3.2-29.5% ((Lin et al., 2009; Han et al., 2010; Lu et al., 2010; Wang et al., 2012). Regardless, it is clear that maximal dietary support, and in many cases nasogastric tube feeding will be required, for the successful implementation of IMRT treatment for NPC more so if we wish to complete the treatment within the stipulated OTT.

In conclusion, IMRT treatment for NPC is feasible in our center. More importantly, it can be delivered within the 7 weeks OTT in the majority of our patients. Severe grade 3/4 toxicity is very common (73.1%) and thus maximal nutritional and analgesic support is required throughout the treatment. Effort must be made to institute this effective treatment modality widely in our country and data regarding its OTT, acute and late toxicities, local control and survival rates must be diligently collected to guide future treatment for NPC.

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