RESEARCH ARTICLE

Treatment Outcome for Nasopharyngeal Carcinoma in University Malaya Medical Centre from 2004-2008

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Abstract

Background: Nasopharyngeal carcinoma (NPC) is the commonest radiocurable cancer in Malaysia. This study aimed to determine the treatment outcomes and late effects of radiotherapy for NPC patients treated in University Malaya Medical Centre (UMMC). Materials and Methods: All newly diagnosed patients with NPC referred for treatment to the Oncology unit at UMMC from 2004-2008 were retrospectively analyzed. Treatment outcomes were 5 years overall survival (OS), disease free survival (DFS), cause-specific survival (CSS), loco-regional control (LRC) and radiotherapy-related late effects. The Kaplan-Meier method was used for survival analysis and differences in survival according to AJCC stage was compared using the log-rank test. Results: A total of 176 patients with newly diagnosed NPC were treated in UMMC during this period. Late presentation was common, with 33.5% presenting with T3-4 disease, 84.7% with N1-3 disease and 75.6% with AJCC stage 3-4 disease. Radical RT was given to 162 patients with 22.7% having RT alone and 69.3% having CCRT. The stipulated OTT was 7 weeks and 72.2% managed to complete their RT within this time period. Neoadjuvant chemotherapy was given to 14.8% while adjuvant chemotherapy was administered to 16.5%. The 5 years OS was 51.6% with a median follow up of 58 months. The 5 years OS according to stage were 81.8% for stage I, 77.9% for stage II, 47.4% for stage III and 25.9% for stage IV. The 5 years overall CSS, DFS and LRC were 54.4%, 48.4% and 70.6%, respectively. RT related late effects were documented in 80.2%. The commonest was xerostomia (66.7%). Other documented late effects were hearing deficit (17.3%), visual deficit (3.1%), neck stiffness (3.1%) , dysphagia (3.4%), cranial nerve palsy (2.5%), pneumonitis (0.6%) and hypothyroidism (1.2%). Conclusions: The 5 years OS and LRC in this study are low compared to the latest studies especially those utilizing IMRT. Implementation of IMRT for NPC treatment should be strongly encouraged.

Keywords: Nasopharyngeal carcinoma - outcome - radiotherapy

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Introduction

Nasopharyngeal carcinoma (NPC) is a major disease in the South-East Asia region and ranks fifth in incidence rate in Peninsular Malaysia for the year 2006 (National Cancer Registry, 2006). Thus far, the only available published data regarding treatment outcome in Malaysia was from a study on 285 patients treated from 2001-2005 at Penang General Hospital where the 5 years overall survival (OS) was only 33.3% (Phua et al., 2011). Reported 5 year OS rates worldwide ranged from 32% to 62% based on more than 9500 patients with all stages of NPC but these were results from older series (Shu-Chen, 1980; Hsu et al., 1982; Al-Sarraf et al., 1990; Lee et al., 1992; 1993; Qin et al., 1998; Wang et al., 1998; Ali et al., 1999; Lin et al., 1999, Terence et al., 2003). The University of California-San Francisco reported a study involving 67 patients who underwent Intensity-Modulated Radiotherapy (IMRT) treatment for NPC (70% stage III and IV) and showed a 4 years OS of 88% (Lee et al., 2002). In China, at the Cancer Hospital of Fujian Medical University 326 patients (81% stage III and IV) were treated with IMRT, a 90% 3 years OS was reported (Lin et al., 2009). The Xijing Hospital in Northwest China also reported a pilot study where 138 NPC patients (82% stage III and IV) were treated with IMRT and the 3 years OS rate was 83.1% (Wang et al., 2012). Advances in radiotherapy (RT) techniques including the widespread usage of 3 dimensional conformal radiotherapy (3DCRT) and IMRT in the last 2 decades have contributed to improved outcome. In addition, giving RT concurrent with chemotherapy has been shown to improve OS over that of RT alone. Two meta-analyses involving more than 2500 patients from ten randomized trials reported an absolute survival benefit of 4-6% at 5 years and this benefit was most pronounced with concurrent chemo-irradiation (Langendijk et al., 2004; Baujat et al., 2006). As there is still a paucity of treatment outcome data for NPC in Malaysia, we aim to look at the results of the patients treated in our institution.

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Materials and Methods

This study retrospectively analyzed all newly diagnosed patients with NPC referred for treatment to the Oncology unit at University Malaya Medical Centre (UMMC) from 2004-2008. Patients of any age and stage of disease with histologically proven diagnosis were accepted for analysis. Patients with no histological confirmation of NPC, those with recurrence or patients who were already treated prior to referral to UMMC were excluded. Information collected included patient demographics, clinical stage based on TNM and AJCC staging for NPC, treatment received including any neo-adjuvant, concurrent or adjuvant chemotherapy and the treatment outcome. Treatment outcome determined were 5 years OS, 5 years disease free survival (DFS), 5 years cause-specific survival (CSS), 5 years loco-regional control (LRC), median overall survival for patients with stage IVC distant metastatic disease and radiotherapy-related late effects. Patients lost to follow-up were contacted via phone to determine their current status and if any of these patients were not contactable, their current survival status was determined by contacting the National Registration Department. Statistical analysis was performed using the SPSS v.18 software. Kaplan-Meier and log rank analysis was used to determine survival outcomes, which was stratified according to AJCC stage.

Radiotherapy (RT) technique

Radical RT was given using 3DCRT. Immobilization was done with a tailored beam directional shell in a comfortable neck position and patients were scanned using Philips Brilliance wide bore 16-slice CT simulator (Philips Healthcare, MA, USA) using 3 mm slice thickness from the vertex to below the clavicles. CT data were imported to the Eclipse treatment planning system version 8.9 (Varian Medical Systems, CA, USA) for contouring of targets and organs at risk (OAR) as well as for treatment planning. The prescribed dose ranged from 66-70Gy. Verification of isocentre was performed by checking orthogonal fields using the Aquity conventional simulator (Varian Medical Systems, CA, USA. Portal imaging was carried out using radiographic film during the first three fractions of the treatment and whenever necessary. Acceptable overall treatment time (OTT) was set at 7 weeks. Treatment was delivered once daily, 5 fractions per week using the Varian Clinac 2100C linear accelerator.

Results

Between 1st January 2004 and 31st December 2008, 176 patients with newly diagnosed NPC were treated in UMMC. The clinicopathological features of this patient cohort is summarized in Table 1. The majority of patients were in the 51-69 years age group (50.5%) with a mean age of 51.5 years and range of 21-79 years. Males accounted for 69.9%. The Chinese was the predominant race presenting with this disease (81.3%). WHO type III was the major histology subtype (70.5%) and there was no documented case of WHO type I disease in this cohort. Late presentation was commonly observed here with 33.5% presenting with T3-4 disease, 84.7% with N1-3 disease and 75.6% with AJCC stage 3-4 disease. Radical RT was given to 162 patients with 22.7% having RT alone and 69.3% having CCRT. The stipulated OTT was 7 weeks and 72.2% managed to complete their RT within this time period. Neoadjuvant chemotherapy prior to RT was given to 14.8% of the patients while adjuvant chemotherapy was administered to 16.5% of the patients.

The 5 years OS rate for the 176 patients was 51.6%

Table 1. Table 1.Clinicopathological Features and Outcome of 176 NPC Patients

	Item	No. of patients	%
Age (years)	<50	75	42.6
	51-69	89	50.5
	≥70	12	6.9
Gender	Male	123	69.9
	Female	53	30.1
Race	Malay	24	13.6
	Chinese	143	81.3
	Indian	2	1.1
	Others	7	4
Performance status	0	72	40.9
	1	89	50.6
	2	10	5.7
	3	5	2.8
Co-morbidities	Yes	44	25
	No	132	75
Tumour Stage	T1	57	32.4
	T2	60	34.1
	T3	24	13.6
	T4	35	19.9
Nodal Stage	N0	27	15.3
	N1	34	19.3
	N2	81	46
	N3	34	19.3
Presence of metastasis	Yes	13	7.4
	No	163	92.6
AJCC stage	I	11	6.3
	II	32	18.2
	III	70	39.8
	IV	63	35.8
WHO type	1	0	0
	2	52	29.5
	3	124	70.5
Radiotherapy	EBRT alone	40	22.7
	CCRT with Cisplatin	122	69.3
	Others	14	8
Overall Treatment	Within 7 weeks	117	72.2
Time (OTT)	>7 weeks	45	27.8
Neoadjuvant	Yes	26	14.8
Chemotherapy	No	150	85.2
Adjuvant	Yes	29	16.5
Chemotherapy	No	147	83.5
Late effects	Yes	130	80.3
	No	32	19.7
Types of late effects	Xerostomia	108	66.7
	Hearing deficit	28	17.3
	Visual deficit	5	3.1
	Neck stiffness	5	3.1
	Dysphagia	6	3.4
	Cranial nerve palsy	4	2.5
	Pneumonitis	1	0.6
	Hypothyroidism	2	1.2
Recurrence	Yes	87	53.4
	No	76	46.6
Site of recurrence	Local	26	16
	Regional	7	4.3
	Locoregional	9	5.5
	Distant	45	27.6

with a median follow up of 58 months. The 5 years OS according to stage were 81.8% for stage I, 77.9% for stage II, 47.4% for stage III and 25.9% for stage IV (Figure 1). There were 96 deaths in this cohort as of March 2013 and most of the deaths were due to NPC (88 deaths, 91.7%). Other causes of death were sepsis (3), cardiac failure (1), lymphoma (1), motor vehicle accident (1), old age (1) and unknown cause(1). The 5 years overall CSS rate was higher at 54.4%. The 5 years CSS according to stage were 81.8% for stage I, 84% for stage II, 53.1% for stage III and 35.6% for stage IV.

For the 163 patients without distant metastasis at presentation (stage I-IVB), the overall 5 years DFS rate was 48.4% with a median follow up of 45 months. The 5 years DFS according to stage were 70% for stage 1, 65.3% for stage II, 47.4% for stage III and 35.1% for stage IVA-B (Figure 2). The overall 5 years LRC rate was 70.6%. The 5 years LRC according to stage were 70% for stage I, 73.5% for stage II, 73.5% for stage III and 66.6% for stage IVA-B. This group of patients had a higher rate of recurrence at a distant site than locoregional recurrence. The pattern of recurrence is presented in Table 1. There were 87 recurrences (53.4%) out of the 163 patients without distant metastatic disease. The commonest pattern was distant metastasis (27.6%) followed by local recurrence (16.0%). For stage IVA-B disease, 43.1% (22/51) developed distant metastasis while 27.5% (14/51)developed locoregional disease. Stage III had 30% (21/70) developing distant metastasis with 22.8% (16/70) recurring locoregionally. These figures dropped to 9.4% (3/32) developing distant metastasis and 25% (8/32) having locoregional recurrences for stage II disease. None of the stage I patients developed distant metastasis while 30% (3/10) developed local recurrence. For the 13 patients who presented with distant metastasis (stage IVC), the median survival was 12 months with a range of 2-36 months.

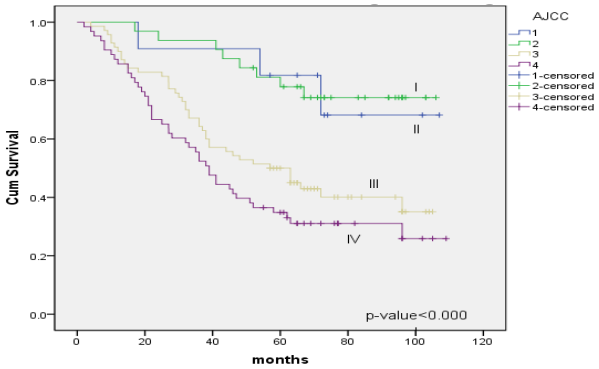

Figure 1. Overall Survival According to AJCC Stage

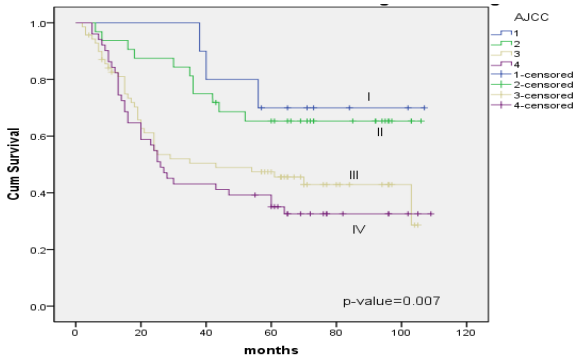

Figure 2. Disease Free Survival According to AJCC Stage

Radiotherapy related late side effects were documented in 80.2% of the patients treated radically with radiation therapy. The commonest late effect was xerostomia occuring in 66.7% of the patients. Other documented late effects were decreased hearing (17.3%), visual deficit (3.1%), neck stiffness (3.1%), dysphagia (3.4%), cranial nerve palsy (2.5%), pneumonitis (0.6%) and hypothyroidism (1.2%).

Discussion

The main result of this series shows a marked improvement of the 5 years OS of 51.6% compared to the 33.3% reported in the previous Malaysian study (Phua et al., 2011). It is unlikely to be due to late presentation as this study had 75.6% of its patients with stage III-IV disease compared to 79.3% in the earlier study. However, concurrent chemo-irradiation which can lead to higher survival was used more frequently in this study (69.3% versus 51.9%). Although the results appear to be in the upper range of the 5 years OS reported in the older series, it still lags behind the latest reported results using IMRT treatment which had comparable rates of advanced stage patients (Lee at al., 2002; Lin et al., 2009; Wang et al., 2012). These findings could be due to a number of factors. The first may be the radiation technique itself as patients in this study were treated with 3DCRT with no patients receiving IMRT. IMRT is rapidly gaining widespread acceptance amongst radiation oncologists and has been touted as the new standard RT treatment for NPC by the EHNS-ESMO-ESTRO clinical practice guideline (Chan et al., 2012). The usage of IMRT for NPC in this country remains sparse. The only published data available regarding its use comes from a study based in Penang General Hospital on NPC patients who underwent radical IMRT treatment from June 2011 to February 2012 (Phua et al., 2012). Another cause for concern is the effect of prolonged OTT. Only 72.2% of patients completed their RT within 7 weeks. Interruptions in RT causing a prolonged treatment time have been reported to be detrimental for local control and survival in NPC (Vikram et al., 1985; Cox et al., 1992; Luo et al., 1994; Kwong et al., 1997). The number of patients having neo-adjuvant or adjuvant chemotherapy was low in this study at 14.8% and 16.5% respectively but meta-analyses (Langendijk et al., 2004; Baujat et al., 2006) have shown no survival benefit, therefore it is arguable whether this played a contributory role.

Recurrence occurred in 53.4% of the 163 patients who presented initially without distant metastatic disease. The major clinical problem was with distant metastasis accounting for more than half of the recurrences. Loco-regional recurrences occurred in 20.3% of patients with an overall 5 years LRC rate of 70%. In fact, the 5 years LRC for stage IVA-B was at 66.6% showing that locally advanced disease can be treated effectively with chemo-irradiation. For the time being, there is no known effective adjuvant treatment that has been shown to improve

survival (Langendijk et al., 2004; Baujat et al., 2006). However, the field of oncology is moving rapidly and there are many targeted therapy in the pipeline that may eventually prove to be successful in improving survival for NPC. For example, the approach of adding EGFR-targeted therapy to conventional treatment approaches is being actively pursued in loco-regionally advanced NPC.

Late effects of radical RT occurred in 80.3% of patients though we are mindful that this is probably an underestimation as data were collected retrospectively. Xerostomia was the commonest late effect affecting 66.7% of patients. The parotids contribute 60-70% of the total salivary gland secretion (Kam et al., 2003). With the advent of IMRT, better sparing of the parotids can be obtained and has been shown to have lower rates of xerostomia compared to 2DRT and 3DCRT (Chao et al., 2001; Kam et al., 2007). Hearing deficit was also present in 17.3% of patients. The cochlea lies in close proximity to the clivus and the upper parapharygngeal space, both of which are part of the clinical target volume during RT. If clinicians were to compromise on clinical target volume coverage to reduce the dose to the cochlea, there is a risk of higher rates of local recurrence. IMRT in this instance is an area still under investigation, especially since the cochlea is increasingly being appreciated as a critical organ at risk. The other recorded late effects were below 5%, which is the generally accepted rate of RT late complications when RT is given in the curative setting.

The 5 years OS and LRC rates in this study are low compared to the latest studies especially those utilizing IMRT. IMRT is no longer considered a high-end treatment but is increasingly being considered the RT technique of choice especially for NPC. The mean age of our patient population was 51.5 years which represents a relatively young, productive section of society and any improvement which can be achieved in local control, survival and quality of life will be highly meaningful. Therefore, every effort must be taken to ensure that NPC patients can be treated with the best available RT technique in this country, not least because NPC remains the commonest cancer which can be treated effectively with RT.

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