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Research Article

Retrospective Analysis of Treatment Results for Nasopharyngeal Carcinoma in Philippine Oncology Centre Corporation from 2002–2009

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Abstract: **Objective:** This study aimed to determine the treatment outcomes and late effects of radiotherapy for NPC patients treated in Philippine Oncology Centre Corporation (POCC). **Materials and Methods:** The patients with NPC referred for treatment at POCC from 2002–2009 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 106 patients with newly diagnosed NPC were treated in POCC during this period. Late presentation was common, with 19.8% presenting with T3–4 disease, 88.7% with N1–3 disease and 73.5% with AJCC stage 3–4 disease. Radical RT was given to 96 patients with 23.6% having RT alone and 67.4% having CCRT. The stipulated OTT was 7 weeks and 72% managed to complete their RT within this time period. Neoadjuvant chemotherapy was given to 13.5% while adjuvant chemotherapy was administered to 17%. The 5 years OS was 51.5% with a median follow up of 56 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 70.9%, respectively. RT related late effects were documented in 71.7%. The commonest was xerostomia (66.7%). Other documented late effects were hearing deficit (18.2%), visual deficit (4.2%), neck stiffness (4.2%), dysphagia (2.3%), cranial nerve palsy (2.4%), pneumonitis (0.9%) and hypothyroidism (1.3%). **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.

Introduction

Nasopharyngeal carcinoma (NPC) is a major disease in the South-East Asia region. NPC incidence in the Philippines was 1.2 per 100,000 (age-standardized rate) according to GLOBOCAN 2008[1]. Thus far, the available published data regarding treatment outcome in Philippines was rare[2]. In other areas, however, the report concerning treatment outcome was relatively more[3–8]. 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

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OS of 88%[9]. 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[10]. 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 84.2%[11]. 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[12–13]. As there is still a paucity of treatment outcome data for NPC in Philippines, we aim to look at the results of the patients treated in our institution.

Materials and Methords

This study retrospectively analyzed the patients with NPC referred for treatment to the Oncology unit at Philippine Oncology Centre Corporation (POCC) 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 POCC 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 66–70 Gy. 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 1 January 2002 and 31 December 2009, 106 patients with newly diagnosed NPC were treated in POCC. 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 56.5 years and range of 21–79 years. Males accounted for 63.2%. The Chinese was the predominant race presenting with this disease (68.9%). WHO type Ⅲ was the major histology subtype (69%) and there was no documented case of WHO type I disease in this cohort. Late presentation was commonly observed here with 19.8% presenting with T3–4 disease, 88.7% with N1–3 disease and 73.5% with AJCC stage 3–4 disease. Radical RT was given to 96 patients with 23.6% having RT alone and 67.4% having CCRT. The stipulated OTT was 7 weeks and 72% managed to complete their RT within this time period. Neoadjuvant chemotherapy prior to RT was given to 13.5% of the patients while adjuvant chemotherapy was administered to 17% of the patients.

The 5 years OS rate for the 106 patients was 51.5% with a median follow up of 54 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 86 deaths in this cohort as of May 2013 and most of the deaths were due to NPC (80 deaths, 93%). Other causes of death were sepsis (2), cardiac failure (2), lymphoma (1) and motor vehicle accident (1). The 5 years overall CSS rate was higher at 54.3%. The 5 years CSS according to stage were 81.8% for stage Ⅰ, 84% for stage Ⅱ, 54.2% 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 47.4% with a median follow up of 46 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 69.9%. The 5 years LRC according to stage were 71% for stage Ⅰ, 72.5% for stage

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Table 1 Clinicopathological Features and Outcome of 106 NPC Patients

	Item	No. of patients	%		Item	No. of patients	%
Age (years)	<50	38	35.8	WHO type	1	0	0
	51-69	62	58.5		2	33	31
	≥70	6	5.7		3	73	69
Gender	Male	67	63.2	Radiotherapy	EBRT alone	25	23.6
	Femal	39	39.8		CCRT with Cisplain	71	67.4
Race	Philippine	22	20.8		Others	10	9
	Chinese	73	68.9	Overall Treatment Time (OTT)	Within 7 weeks	76	72
	Indian	2	1.8		>7 weeks	30	28
	Others	9	8.5	Neoadjuvant Chemotherapy	Yes	14	13.5
Performance status	0	44	41.5		No	92	86.5
	1	51	48.1	Adjuvant Chemotherapy	Yes	18	17
	2	8	7.5		No	88	83
	3	3	2.9	Late effects	Yes	84	79.7
Co-morbidities	Yes	26	25		No	22	20.3
	No	80	75	Types of late effects	Xerostomia	71	66.7
Tumour Stage	T1	37	34.9		Hearing deficit	19	18.2
	T2	48	45.3		Visual deficit	4	4.2
	T3	9	8.5		Neck stiffness	4	4.2
	T4	12	11.3		Dysphagia	2	2.3
Nodal Stage	N0	12	11.3		Cranial nerve palsy	3	2.4
	N1	22	20.8		Pneumonitis	1	0.7
	N2	51	48.1		Hypothyroidism	2	1.3
	N3	21	19.8	Recurrence	Yes	56	52.6
Presence of metastasis	Yes	9	8.5		No	50	47.4
	No	97	91.5	Site of recurrence	Local	16	15
AJCC stage	I	8	7.2		Regional	6	5.2
	II	20	19.3		Locoregional	5	4.6
	III	41	38.7		Distant	28	26.5
	IV	37	34.8				

Ⅱ, 74.5% for stage Ⅲ and 67.6% 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 (52.3%) 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 Ⅳ A-B disease, 44.2% (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.

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Radiotherapy related late side effects were documented in 71.7% 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 (18.2%), visual deficit (4.2%), neck stiffness (4.2%), dysphagia (2.3%), cranial nerve palsy (2.4%), pneumonitis (0.9%) and hypothyroidism (1.3%).

Discussion

The main result of this series shows a marked improvement of the 5 years OS of 51.5% compared to the 33.3% reported in the previous Philippine study[2]. It is unlikely to be due to late presentation as this study had 73.5% 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 (67.4% 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[6, 7, 9]. 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[14]. 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 Makati Medical Center on NPC patients who underwent radical IMRT treatment from June 2011 to February 2012[2]. Another cause for concern is the effect of prolonged OTT. Only 72% 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[15–18]. The number of patients having neo-adjuvant or adjuvant chemotherapy was low in this study at 13.5% and 17% respectively but meta-analyses[18] have shown no survival benefit, therefore it is arguable whether this played a contributory role.

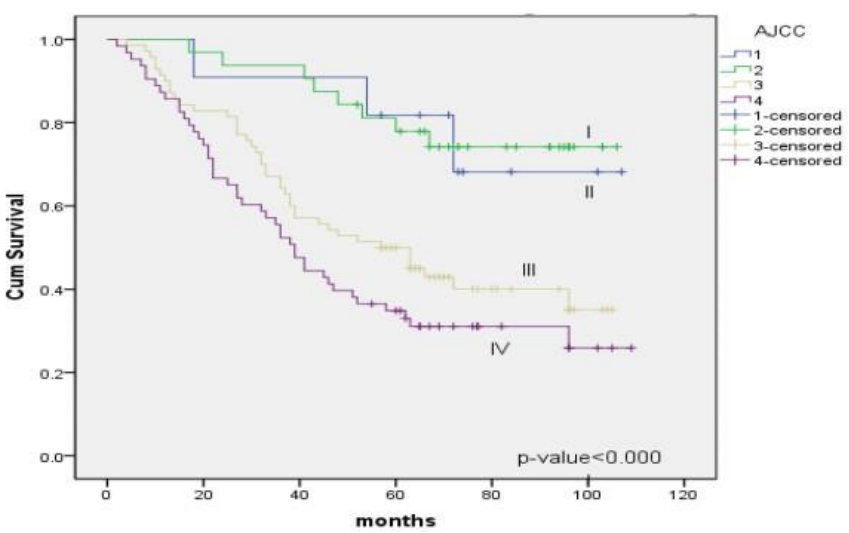

Figure 1. Overall Survival According to AJCC Stage.

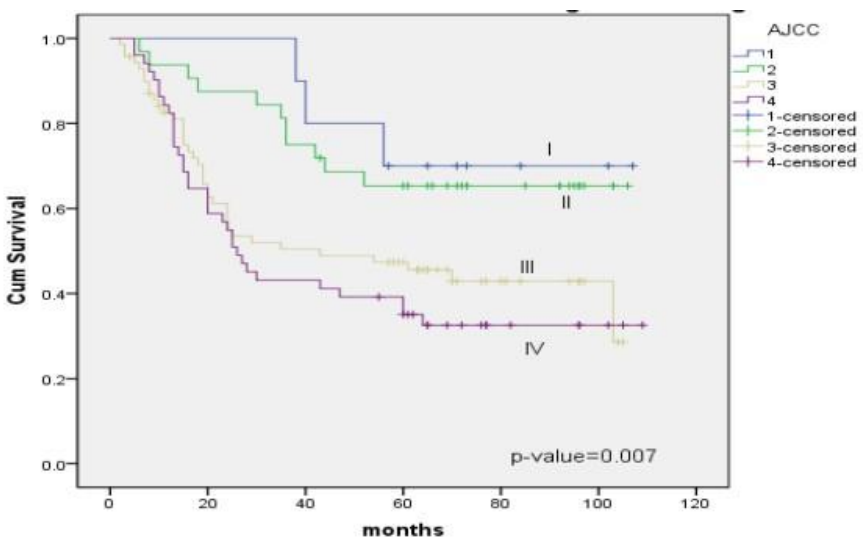

Figure 2. Disease Free Survival According to AJCC Stage.

Recurrence occurred in 52.3% 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 Ⅳ A-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[20]. 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[21]. 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[22–23]. Hearing deficit was also present in 18.2% 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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