



Quality of life outcome among nasopharyngeal carcinoma survivors in Kuala Lumpur

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Background: We assessed the quality of life (QoL) of nasopharyngeal carcinoma (NPC) survivors who had completed treatment at least more than 1 year earlier in Kuala Lumpur, Malaysia and we analysed factors influencing QoL.

Methods: We conducted a cross-sectional study in Universiti Kebangsaan Malaysia Medical Centre (UKMMC) from January 2017 to January 2018 where all patients who completed curative treatment for NPC, fulfilling the inclusion criteria were consecutively sampled (Level 3). The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) (version 3.0) and EORTC Head and Neck Module were used to assess the QoL and the prevalence of radiotherapy (RT) induced complications were calculated. Linear correlation was used to analyse the factors influencing QoL.

Results: Sixty-four patients were recruited with a mean age of 56.78 years [25, 82]; 79.7% of patients underwent concurrent chemoradiotherapy. The mean global QoL score was 76.43 (95% CI: 71.57 to 81.29). At a significance level of $\alpha=0.05$, factors influencing the QoL identified were dyspnoea ($P<0.001$), fatigue ($P<0.05$), appetite loss ($P<0.001$), loss of sexuality ($P<0.001$), pain ($P<0.001$), trouble with social eating ($P<0.001$), sticky saliva ($P<0.001$), swallowing ($P<0.001$), speech ($P<0.05$), senses ($P<0.001$), teeth ($P<0.05$) problems and chemoradiation ($P<0.05$). Loss of sexuality showed a moderate negative linear correlation with mean global QoL score ($r=-0.508$). The main RT induced complications documented were xerostomia and hearing loss with prevalence of 96% and 31% each.

Conclusions: The global QoL score among NPC survivors in Kuala Lumpur was good. Prevalence of xerostomia and hearing loss were high in NPC survivors, emphasizing the importance of continued combined oral and otological management post treatment.

Keywords: Quality of life (QoL); nasopharyngeal neoplasms; radiation effects

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Introduction

Nasopharyngeal carcinoma (NPC) is a malignant tumour that arises from the epithelial lining of the nasopharynx. In recent studies, the reported incidence of NPC world-wide was 129,000 with mortality reported to be over 72,000 in 2018 (1). The primary modality of treatment for NPC is radiotherapy (RT) as it has been shown to be very sensitive to radiation. Recent advancement in technology of radiation from two dimensional (2D) then three dimensional (3D) to intensity-modulated RT (IMRT) has resulted in a greater local and regional control with reduced toxicity rate (2,3). For loco regionally advanced NPC the treatment of choice is cisplatin-based concurrent chemotherapy and radiation therapy (CCRT) (3). Due to close proximity to vital organs like the brain, ears, eyes, major salivary gland and the cervical spine, the patient may develop complication following radiation which will in turn reduce quality of life (QoL). It can be further divided into early complications which develop during the course of RT or shortly after completing RT (about 2–3 weeks) and late effects that manifest months to years after completing RT. It includes xerostomia, osteoradionecrosis, soft tissue fibrosis, carotid artery injury, trismus, dysphagia, and ototoxicity to name a few (4).

The World Health Organisation defines QoL as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns. It is a broad-ranging concept which describes the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment in a complex way. It is now even more important to understand the QoL of patient post-treatment as NPC patients have a high 5-year survival rate. Therefore, they will have to face problems with swallowing, speech, and hearing, as well as psychological effects associated with loss of function and change in body image for the remainder of their lifetime (5). This was the first study to document the health related QoL outcome among NPC survivors in Kuala Lumpur, Malaysia. The primary objective of the study was to describe the QoL outcomes in NPC survivors, one year after completion of curative treatment. Additionally, we would like to explore factors that influenced the QoL and examine the late complications present in these patients. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/anpc-20-14>).

Methods

A cross-sectional study was conducted in Universiti Kebangsaan Malaysia Medical Centre (UKMMC), a tertiary centre in Kuala Lumpur, Malaysia from January 2017 to January 2018. The study population was all patients who completed curative treatment more than 1 year earlier, fulfilling the inclusion and exclusion criteria and undergoes follow-up at our centre. The patients were sourced from the otolaryngology, oral maxillofacial and oncology clinics as well as the institutional oncological treatment registry. The sampling method was universal consecutive patients within the study period. All patients provided written informed consent and the study was approved by the institutional ethical review board for human research of National University of Malaysia within which the study was undertaken (IRB code of approval: FF 2017-179). The conduct of the study conformed to the provisions of in accordance with the Helsinki Declaration (as revised in 2013).

The inclusion criteria included all adults (18 years and above) and consented NPC patients who completed curative treatment at least one year prior to sampling. We included patients with available, complete medical records. Exclusion criteria were patients less than 18 years old, patients who refused to participate and in availability of medical records.

The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (version 3.0) (QLQ-C30) and EORTC Head and Neck Module (QLQ-H&N35) was used to assess the QoL of NPC survivors (6). The QLQ-C30 is a thirty-item questionnaire which includes twenty-eight items scored 1–4, and two items scored 1–7. It composed of both multi-item scales and single-item measures. These included five functional scales, three symptom scales, a global health status scale, and six single items. The QLQ-H&N35 consisted of thirty items scored 1–4, and five items scored no or yes. The questionnaire incorporates seven multi-item scales that assess pain, swallowing, senses (taste and smell), speech, social eating, social contact, and sexuality. There are also eleven single items. All of the scales and single-item measured range in scores from 0 to 100. A high score for a functional scale represents a high level of functioning; a high score for the global health status represents a high QoL. Conversely, a high score for a symptom scale represents a high level of symptomatology or problems. The questionnaires were given to the patients and all were self-administered in their preferred languages either English, Malay and Mandarin. Potential factors

Table 1 Demographic characteristic of the study population

Characteristic	Subtype	Value
Age (years)	Mean \pm SD	56.78 \pm 12.19
	Median [range]	56.50 [25–82]
Years since last treatment (years)	Mean \pm SD	7.80 \pm 7.24
	Median [range]	6.00 [1–32]
Gender	Female	23 (35.9%)
	Male	41 (64.1%)
Ethnicity	Malay	17 (26.6%)
	Chinese	46 (71.9%)
	Indian	1 (1.6%)
Highest education level	No education	2 (3.1%)
	Primary	21 (32.8%)
	Secondary	29 (45.3%)
	Tertiary	12 (18.8%)
Marital status	Single	3 (4.7%)
	Married	61 (95.3%)
Treatment received	Chemoradiotherapy	51 (79.7%)
	Radiotherapy	13 (20.3%)

that may affect the QoL within the study population like gender, education level and type of treatment received were examined. The multi-ethnic study population and diverse spiritual backgrounds may have caused cultural differences in the way the patients perceive certain questions related to sexuality which was not further examined in this study. The RT induced complications were obtained from patient interview, clinical examination and investigation, then presented as percentages.

Statistical analysis

Statistical analysis was performed using IBM Statistical Package for the Social Sciences software (SPSS®) version 22. Means with standard deviations and 95% confidence interval are used to describe the QoL of the NPC survivors. Pearson correlation coefficient was used to describe relationship between continuous variables influencing QoL and *t*-test was used to compare QoL scores between gender, education level and type of treatment received. The significance level was set at 0.05.

Results

Sixty-nine NPC survivors were identified from the otolaryngology, oral maxillofacial and oncology clinics as well as the institutional oncological treatment registry. Five patients (7.2%) were excluded due to young age less than 18 years old. The remaining 64 patients (92.8%) fulfilled the inclusion and exclusion criteria and were recruited for the study. The mean age was 56.78 years with the youngest being 25 years old and the oldest was 82 years old (*Table 1*); 41 patients were male (64.1%) and 23 were female (35.9%). The majority of our patients were Chinese, 46 patients (71.9%) followed by Malay, 17 patients (26.6%) and Indian, 1 patient (1.6%). The mean follow-up duration was 7.8 years with the least being 1 year and the longest being 32 years since the year of initial diagnosis; 51 of our follow up patients underwent concurrent chemoradiotherapy which accounted for 79.7% and 13 (20.3%) of them underwent RT alone as their modality of treatment; 61 patients (95.3%) were married and 3 (4.7%) were single. The proportion of patients with no, primary, secondary and tertiary educations were 3.1%, 32.8%, 45.3%, and 18.8% respectively (*Table 1*).

Table 2 Functional scale analysis

Variable	Mean (SD)	Range	95% CI	Correlation coefficient (r)
Global health status/QoL	76.43 (19.45)	0–100	71.57–81.29	1.000
Functional scale				
Physical functioning	90.91 (10.71)	60–100	88.24–93.59	0.435**
Role functioning	91.93 (20.79)	0–100	86.74–97.12	0.253*
Emotional functioning	83.46 (17.09)	33.33–100	79.19–87.73	0.391**
Cognitive functioning	82.55 (18.65)	16.67–100	77.89–87.21	0.265*
Social functioning	91.67 (18.31)	0–100	87.09–96.24	0.158

*, correlation is significant at the 0.05 level (2-tailed). **, correlation is significant at the 0.01 level (2-tailed).

Table 3 General symptom scale analysis

Variable	Mean (SD)	Range	95% CI	Correlation coefficient (r)
Global health status/QoL	76.43 (19.45)	0–100	71.57–81.29	1.000
Symptom scale				
Fatigue	17.36 (19.38)	0–66.67	12.52–22.20	–0.313*
Nausea	1.82 (10.76)	0–83.33	0–4.51	–0.234
Pain	7.55 (15.12)	0–66.67	3.77–11.33	–0.307
Dyspnoea	3.65 (12.05)	0–66.67	0.64–6.66	–0.361**
Insomnia	30.73 (39.08)	0–100	20.97–40.49	–0.285
Appetite loss	7.81 (18.54)	0–100	3.18–12.44	–0.325**
Constipation	9.9 (24.26)	0–100	3.84–15.95	–0.199
Diarrhoea	4.69 (13.1)	0–66.67	1.41–7.96	–0.027
Financial difficulties	26.56 (32.08)	0–100	18.55–34.58	0.016

*, correlation is significant at the 0.05 level (2-tailed). **, correlation is significant at the 0.01 level (2-tailed).

The mean global health status QoL score of our patients was 76.43 (95% CI: 71.57 to 81.29) as shown in *Tables 2* and *3*. In the specific functional scale of physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning, the patients scored highly at 90.91, 91.93, 83.46, 82.55 and 91.67 respectively indicating good functional level (*Table 2*). Out of these five categories, two categories significantly correlated with the mean global QoL scores. Physical and emotional functioning scores correlated with the global QoL with a P value of less than 0.01. This shows that a high physical and emotional function score will result in a better QoL. The general symptom scale analysis showed a high score for symptoms such as insomnia, financial difficulties, and fatigue (*Table 3*). Dyspnoea ($r=-0.361$), fatigue ($r=-0.313$) and appetite

loss ($r=-0.325$) showed statistically significant negative correlation with global QoL. A significant moderate negative correlation was observed between these three general symptoms with global QoL with a P value of less than 0.01.

The specific head and neck symptom scale analysis showed that the main symptoms suffered by the patients were difficulty in opening mouth, sticky saliva and dry mouth (*Table 4*). Among the many symptoms which contributed to poor QoL scores, the highest correlation was observed in the loss of sexuality ($r=-0.508$). It was followed by pain ($r=-0.435$), trouble with social eating ($r=-0.411$), sticky saliva ($r=-0.329$), swallowing ($r=-0.324$), senses problem ($r=-0.346$) and also teeth problem ($r=-0.303$).

There was no significant difference between the global

Table 4 Specific head and neck symptom scale analysis

Variable	Mean (SD)	Range	95% CI	Correlation coefficient (r)
Global health status/QoL	76.43 (19.45)	0–100	71.57–81.29	1.000
Head & neck cancer				
Pain	11.37 (13.39)	0–50	8.03–14.72	–0.435**
Swallowing	4.95 (11.47)	0–50	2.08–7.81	–0.324**
Senses problem	5.21 (13.89)	0–83.33	1.74–8.68	–0.346**
Speech problems	15.8 (16.78)	0–77.78	11.61–19.99	–0.305*
Trouble with social eating	10.55 (15.16)	0–83.33	6.76–14.33	–0.411**
Trouble with social contact	14.9 (14.92)	0–73.33	11.17–18.62	0.053
Less sexuality	11.72 (15.34)	0–50	7.89–15.55	–0.508**
Teeth	9.37 (17.28)	0–66.67	5.06–13.69	–0.303*
Opening mouth	20.31 (24.93)	0–100	14.09–26.54	–0.216
Dry mouth	14.58 (25.11)	0–100	8.31–20.86	–0.188
Sticky saliva	16.67 (24.49)	0–100	10.55–22.78	–0.329**
Coughing	1.04 (8.33)	0–66.67	0–3.12	–0.173
Felt ill	4.69 (13.1)	0–66.67	1.41–7.96	–0.027
Painkillers	4.17 (12.6)	0–66.67	1.02–7.31	–0.115
Nutritional supplements	6.77 (14.76)	0–66.67	3.08–10.46	–0.050
Feeding tubes	2.08 (8.13)	0–33.33	0.05–4.11	–0.159
Weight loss	4.69 (13.1)	0–66.67	1.41–7.96	–0.044
Weight gain	4.69 (15.56)	0–66.67	0.80–8.58	–0.066

*, correlation is significant at the 0.05 level (2-tailed). **, correlation is significant at the 0.01 level (2-tailed).

QoL scores between male and female with scores of 76.42 versus 76.45 as shown in *Table 5*. We have further grouped the education levels into low and high education level where the low education level includes patient with no formal education and primary school and the high education includes those who completed secondary and tertiary level of education. The QoL of the patients with low education was better than patients with high education with a QoL score of 80.07 compared to 74.39. Comparison of QoL scores between patients who underwent chemoradiotherapy and RT alone showed a better QoL score for RT alone with a score of 83.97 versus 74.51 and this was statistically significant with a P value of 0.048.

Sixty-three patients, reported to still suffer from xerostomia as their main complication. It accounted for 96.88% of our study population. It was followed by otological complications which included middle ear

effusion, chronic otitis media and also hearing loss. The otological complications accounted for 31.25% of our study population. Other long-term complication includes cranial nerve palsy—6.25%, posterior choanae stenosis—4.69%, osteoradionecrosis—3.13% with both carotid artery stenosis and also panhypopituitarism accounting for 1.56% each.

Discussion

The recent advances in radiation oncology have resulted in a greater survival in patients with nasopharyngeal carcinoma. In nasopharyngeal carcinoma (NPC) particularly the evolution of RT from 2D to 3D and to currently IMRT has resulted in better of QoL based on previous studies (3). A previous study conducted in Peninsula Malaysia showed a good 5-year overall survival of 81.8% for stage I, 77.9% for stage II, 47.4% for stage III and 25.9% for stage IV (7).

Table 5 Factors affecting global QoL scores

Factor	Global health status/QoL (mean/SD)	P value
Gender		
Female	76.45 [22]	0.996
Male	76.42 (18.15)	
Highest education level		
No education	75 (11.78)	0.696
Primary	80.56 (22.72)	
Secondary	73.85 (19.38)	
Tertiary	75.69 (14.42)	
Highest education level		
Low education (no education& primary education)	80.07 (21.87)	0.265
High education (secondary education & tertiary education)	74.39 (17.91)	
Treatment received		
Chemoradiotherapy	74.51 (20.44)	0.048*
Radiotherapy	83.97 (12.94)	

*, significant at the 0.05 level (2-tailed).

Thus, it is important to understand the factors that affect the QoL in NPC survivors in Malaysia. With the knowledge that we have, we as physicians can help future patients prepare for the challenges ahead after they have survived the disease. The key findings of this study were global QoL scores of 76.43 with concurrent chemoradiotherapy, education level and symptoms related to xerostomia and loss of sexuality affecting the QoL.

In the present study, the global QoL score was 76.43 (95% CI: 71.57 to 81.29) with a mean survival duration of 7.80 years. We believe that the global QoL score in our study population was good compared to the highest possible QoL of 100. Another study by Hong *et al.* using the same EORTC QLQ version 3.0, reported a global QoL score of 74.21 among NPC survivors in Fujian, China, a result very similar to ours (8). On the other hand, Chiou *et al.* reported a higher global QoL score among their NPC survivors in Taiwan at 83.4 (9). In comparison to these developed countries, our country is considered a developing nation. We postulate that the slightly higher scores observed by these authors were contributed by more advanced radiation technologies available in their countries.

Xerostomia is still one of the major complications in patients who received RT in head and neck cancer especially in NPC where the radiation field is wide. Previously

published studies have confirmed that this side effect can persist even after years of completion of RT. In the present study, prevalence of xerostomia was highest (96.8%) among our study population. The prevalence of this complication was higher compared to another study conducted in another tertiary centre in Malaysia which reported that only 66.7% of their patient suffered from xerostomia. In this study, the data were retrospectively collected from the patients' medical records; hence it may be underrepresented (7). Wang *et al.* in their study reported that 85.9% of their patient had xerostomia as their long-term complication even with IMRT as their modality of treatment (2). Conversely, Hong *et al.* reported a prevalence of only 17.59% while Tsai *et al.* showed 75% had xerostomia of grade 1 to 3 (8,10). The lower prevalence of xerostomia seen in some of the studies may be attributed to the use of IMRT, sparing of at least one of the parotid gland to a mean dose of 20 Gy or under reporting by physicians (11,12).

Many specific head and neck symptoms studied in the present study are directly related to xerostomia as a long term complication. Symptoms like sticky saliva, swallowing, speech and teeth problems as well as appetite loss and trouble with social eating are attributable to xerostomia. Therefore, it is not surprising to see significant negative correlation between these symptoms and mean global QoL. A study

by Hong *et al.* similarly concluded that mouth dryness was a significant factor affecting QoL in NPC survivors using multiple linear regression analysis ($P < 0.001$) (8). Many studies are still being undertaken to reduce the prevalence of xerostomia in patients receiving RT. Apart from using IMRT as a primary modality of treatment and limiting the dose to the major salivary glands (11), emphasize should be given in promoting better oral health as well as saliva substitute to better manage this important sequel. Active participation of oral health dental specialists in combined care of NPC survivors can potentially improve the QoL outcomes in the future.

Otological complications rank the second highest late complication that was reported in this study. Among the otological complications recorded were hearing loss, middle ear effusion and also chronic otitis media. Tsai *et al.* in their study of 242 NPC survivors reported that 50.4% of their patient had some form of hearing loss (10). In a systematic review on QoL outcomes among elderly with hearing impairment by Ciorba *et al.*, several instruments have been used including Hearing Handicap Inventory for the Elderly (HHIE); Hearing Handicap Inventory for Adults (HHIA) and International Outcomes Inventory-Hearing Aids (IOI-HA). Reduced hearing has been shown to cause difficulty in social interaction, potentially giving rise to frustration, loneliness and dependence on other people which in turn gravely affects the QoL (13). The authors believe that the instrument used in the present study, EORTC QLQ version 3.0 questionnaire has limited utilisation in measuring the impact of the otological complications to QoL outcomes.

Moving forward, IMRT is coined to be the treatment of choice for NPC as many studies have reported this treatment modality to reduce the prevalence of late complications of RT. Compared to conventional RT, IMRT provides superior conformity of the radiation dose to the tumor and greater sparing of adjacent organs such as parotid and temporo-mandibular joints (14). In addition, Zheng *et al.* concluded in their study that IMRT exhibited advantages for reducing most late toxicities of NPC patients with long-term survival (15). However, there are still some conflicting reports that showed IMRT might not have a much better outcome than conventional RT. Fang *et al.* refuted by stating that the advantage from 3D conformal RT to IMRT in QoL was ambiguous and small in their series but it does show a marked improvement in reducing xerostomia (5). In a large long-term study by Kiang *et al.*, patients who were more than 10 years post-IMRT was shown to have worst cognitive and NPC-specified QoL when compared with

patient who were between 2.5 to 6 years post-IMRT (14). Few possibilities were postulated of why the patient had a poorer cognitive result. One possibility is long-term irradiation damage to the temporal lobe resulting in short-term memory loss. Secondly, radiation-induced changes to the carotid artery leading to reduced perfusion to the brain causing cognitive impairment. McDowell *et al.* reported that after receiving IMRT, survivors of NPC still experience many physical symptoms like hearing toxicity that persist many years after treatment (16). Depression, anxiety, and fatigue remain common in long-term survivors and are highly correlated with QoL even in patients receiving IMRT (16). Therefore, combined oral, otologic and audiological care is still relevant in the follow up of NPC survivors despite the recent advancements in radiation oncology.

The present study showed that the QoL of patients receiving RT alone was significantly better compared to CCRT. This can be explained as radiation toxicity is likely to be potentiated by the addition of concurrent and/or adjuvant chemotherapy (14). Bentzen *et al.* found similar results that chemoradiotherapy has increased the late toxicity effects in their patients (17). Our results showed a trend towards the lower educated patients to have a higher QoL score 80.07 comparatively to the higher educated patients at 74.39. We postulate that patients with higher education would have already achieved a stable social status and good lifestyle prior to treatment. However, after they have been diagnosed and treated with NPC, many were unable to sustain the lifestyle they previously had. This is further consolidated as our patients rated high financial difficulties as a factor affecting their QoL.

Late radiation toxicities manifesting in poor QoL outcomes are findings not peculiar to nasopharyngeal carcinoma. In the head and neck region, oropharyngeal cancer is also predominantly treated using concurrent chemoradiation protocols given in wide fields similar to nasopharyngeal cancer. Findings of a recent meta-analysis by Høxbroe Michaelsen *et al.* using the same questionnaire concurred with our findings, where clinically important deteriorations in xerostomia, dysphagia and chewing were also seen among 644 oropharyngeal carcinoma patients following treatment (18).

Immunotherapy has emerged as a potential treatment option in NPC. EBV-specific cytotoxic T cell or vaccination has been proposed in the recent literature. This is because Epstein Barr virus has been found to be present in undifferentiated cancer especially in NPC (19). A pre-

clinical study which studied the effect of LMP1 vaccine on tumor metastasis in mice has shown promising results. The vaccination was able to suppress LMP1-expressing tumor growth and metastasis *in vivo* compared with the control (20). Even though it may still be in the experimental stage, it will potentially pave a way to prevent NPC in endemic regions of the world, improving current treatment outcomes.

There are few limitations to our study. Firstly, questionnaires used in this study did not explore the effect of hearing loss to patients' QoL, albeit hearing loss being a common long term complication documented. Future studies could improve by utilizing QoL questionnaires with specific focus to xerostomia and hearing loss. Secondly, loss of sexuality was found to have a moderate negative linear correlation with mean global QoL score. This study was not able to explain this with regards to the toxicity effects of the treatment received by the patient. The authors postulate that the prevalent anxiety and depression among our study population may have caused loss of sexuality. Although another study by Wu *et al.* concluded 14% prevalence of depression among head and neck cancer survivors at 6 months (21), a conclusive association could not be established within the present study as we did not use the anxiety and depression scale as one of our study instruments.

The present study utilised a validated research questionnaire self-administered in various languages to suit the multi-ethnic study population. The global QoL scores can be generalized to the present state of NPC survivors in Malaysia, since the demographic characteristics of the study population is reflective of studies published in other urban parts of Malaysia (7). Certain confounding factors such as education and financial status may need to be considered before generalising the study findings to other rural parts of the country.

Conclusions

The global QoL in our patients was comparable with other studies. The prevalence of xerostomia and hearing loss were high in NPC survivors, emphasizing the importance of continued combined oral and otological management post treatment.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki 2013. The study was approved by institutional ethics board of National University of Malaysia (IRB code of approval: FF 2017-179) and informed consent was taken from all the patients.

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