

Original Article

Sustained improvement of quality of life for nasopharyngeal carcinoma treated by intensity modulated radiation therapy in long-term survivors

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Abstract: IMRT has achieved an excellent survival and less radiation-induced sequelae with improvement of QoL within 2 years compared to conventional radiotherapy for NPC. Whether IMRT could sustained decrease incidence of late sequelae and improve QoL further for long-term survivors remained unknown. 176 patients from Aug. 2002 to Jun. 2009 were retrospectively analyzed. Radiation-related toxicities were graded according to both the Acute and the Late Radiation Morbidity Scoring Criteria of the EORTC/RTOG; QoL was assessed by the EORTC QLQ-C30 and H&N35 questionnaires at 5 and 8 years. The 5-year overall survival rate was 68.2% with a median follow-up time of 86 months. The most common radiation-related acute and late toxicity was xerostomia, the incidence of Grade ≥ 1 xerostomia was 90.3%, 84.1%, 75.9% and 59.2%, respectively at acute, 6 months, 2 years and 5 years. Statistical analysis indicated a close relationship between 5 years with 6 months and 2 years for patients who had ≥ 3 xerostomia at acute phase ($r = 0.538$ for late xerostomia at 6 months with 5 years, $r = 0.732$ for 2 years with 5 years); Sustained amelioration of other sequelae was also observed; QoL questionnaires at 5 years showed a significant improvement of most items and got stable between 5 to 8 years. In conclusion: IMRT could sustain reduce late radiation sequelae and improve QoL for long-term survivors over time; Patients with severe acute xerostomia (\geq grade 3) would have a significant correlation of mitigatory xerostomia during the late follow-up time.

Keywords: Intensity modulated radiation therapy, nasopharyngeal carcinoma, acute toxicity, late toxicity, quality of life

Introduction

Nasopharyngeal carcinoma (NPC) is an endemic disease within specific regions in the world, it is rather common in the Southern Chinese (~25-30 per 100,000 persons per year), whereas among Caucasians from North American and other Western countries it is sporadic [1]; As the tumor is located in close proximity to base of the skull and important vital structures, the pivotal treatment modality of NPC is radiotherapy (RT) alone or combined with chemotherapy and surgery is generally not an initial option [2]. Over the past decades, Intensity-Modulated Radiation Therapy (IMRT) has been implemented for routine clinical use if resources permit. Many clinical studies had indicated that the technical and dosimetric superiority of IMRT over conventional RT and could translate

into clinical benefits, IMRT alone or combined with chemotherapy based on cisplatin and/or targeted drugs like cetuximab/nimotuzumab, with the local control rate exceeding 90% at 2-5 years [3].

Conventionally, the endpoints of medical care for cancer patients usually focus on the progression-free survival (PFS), local control rate etc. These endpoints are typically assessed from the physician's points of view and lack knowledge of patients' own experience of their treatment-related toxicities and quality of life (QoL); Perhaps no other group of cancer patients is QoL as important as in NPC patients that they may have obvious debilitating problems with swallowing, speech and hearing loss as well as psychological effects associated with loss of function and changes in body image in

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Table 1. Characteristics of 176 NPC patients

Characteristic	N	Percentage (%)
Age (years)		
Median	52	
Range	18-83	
Gender		
Female	58	33.0
Male	118	67.0
Histological differentiation		
WHO type I	6	3.4
WHO type II-III	168	95.5
Unclassified	2	1.1
T stage		
T1	26	14.8
T2a	39	22.2
T2b	38	21.6
T3	46	26.1
T4	27	15.3
N Stage		
N0	56	31.8
N1	60	34.1
N2	40	22.7
N3	20	11.4
Clinical Stage (2002 UICC)		
I	8	4.5
IIA	16	9.1
IIB	45	25.6
III	67	38.0
IVA	20	11.4
IVB	20	11.4
Doses to GTV		
< 70 Gy	5	2.8
≥ 70 Gy	171	97.2
Chemotherapy		
With	45	25.6
Without	131	74.4

long-term survivors [4]. It is well accepted that xerostomia is the most significant morbidity during and following radiotherapy due to major and minor salivary glands exposure to irradiation [5]. Two longitudinal studies indicated that patient-reported xerostomia decreased significantly, whereas QoL scores improved significantly over time during the first year after IMRT using European Organization of Research and Treatment of Cancer (EORTC) QLQ-C30 and H&N35 Questionnaires, which were well-validated and tested with excellent results [6-8].

Table 2. Distribution of T and N stages of 176 patients (%)

Stage	N0	N1	N2	N3	Total
T1	8	10	6	2	26
T2a	17	8	11	3	39
T2b	6	19	9	4	38
T3	16	16	10	4	46
T4	9	7	4	7	27
Total	56	60	40	20	176

In conventional RT-treated patients, the severity of the radiation-related symptoms was worse in patients with long-term follow-up and global QoL scores were significantly lower when compared to those at earlier periods in two studies [2, 9]. As irradiation to normal tissues could be significantly reduced, the influence of IMRT on late toxicities and QoL is an extremely important question to be answered. The current study represented the first attempt to evaluate the acute and late radiation related sequelae at 6 months, 2 years and 5 years, and the QoL scores for those long-term survivors treated with IMRT during Aug. 2002 to Jun. 2009 in our cancer center.

Patients and methods

Patients

This retrospective study was conducted at The First hospital of Wenzhou Medical College and informed consent was obtained from each participant. Inclusion criteria were as follows: (1) histologically confirmed NPC by pathology (2) no evidence of distant metastasis via chest CT scan, bone scintigraphy, and ultrasonography of the abdominal region (3) no previous malignancy or other concomitant malignant disease (4) no pregnancy or lactation, and (5) receiving radical IMRT at initial diagnosis. A total of 176 NPC patients were enrolled in this retrospective analysis. The demographic characteristics were summarized in **Table 1**, of which 118 were males and 58 were females, with a sex ratio of 2.0:1.0, median age was 52 years (range, 18-83 years). The histological types were according to WHO criteria for NPC. Magnetic resonance imaging (MRI) and contrast-enhanced computed tomography (CT) of the head and neck were applied to accurately evaluate the extent of the primary tumor and regional lymph nodes; all patients were staged

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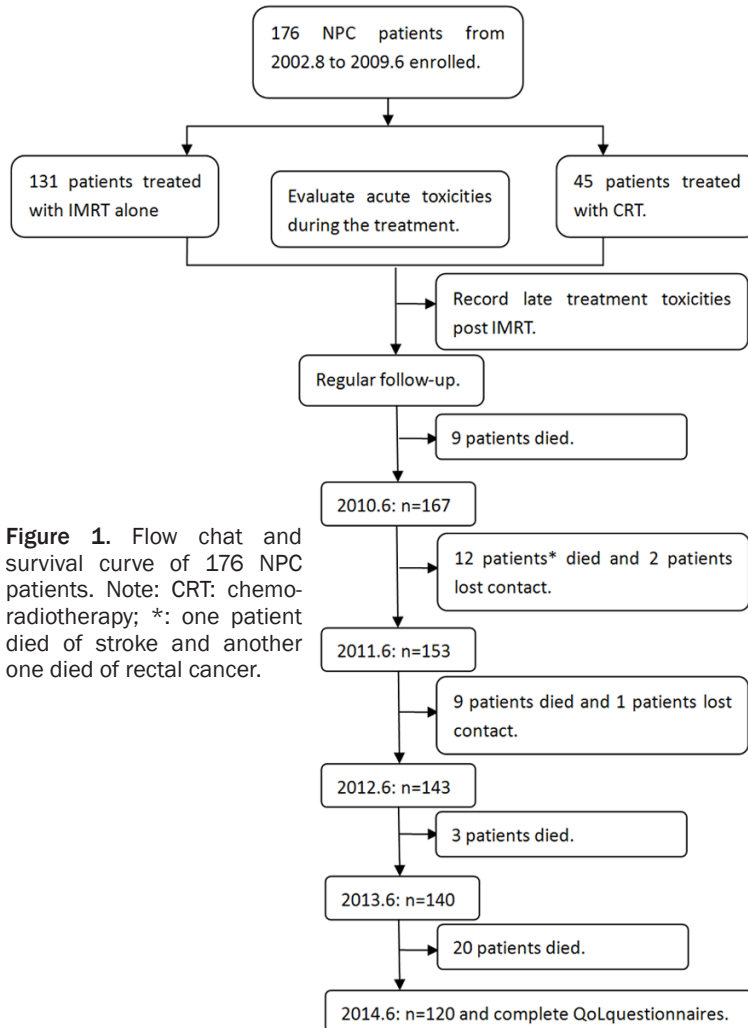
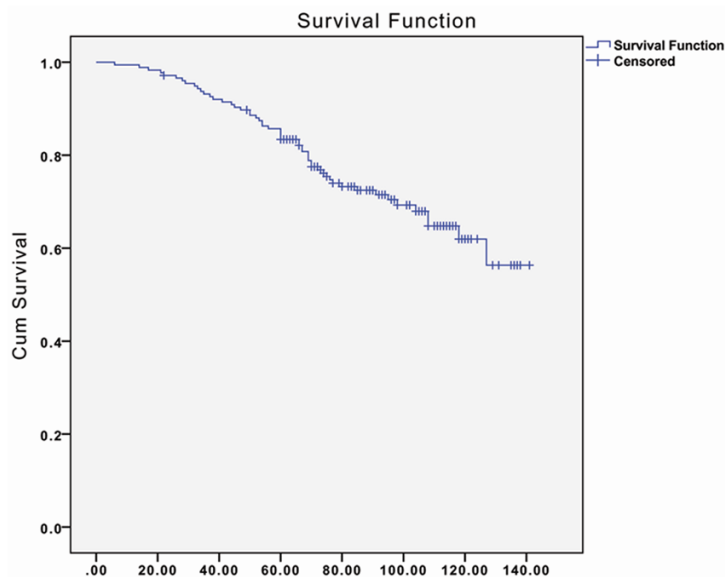


Figure 1. Flow chat and survival curve of 176 NPC patients. Note: CRT: chemoradiotherapy; *: one patient died of stroke and another one died of rectal cancer.



or restaged according to 2002 Union for International Cancer Control (UICC) staging sys-

tem. There were 8, 16, 45, 67, 20 and 20 patients with stage I, IIa, IIb, III, IVa and IVb respectively, detailed in **Table 2**.

Radiotherapy

The dose to GTV was 70 Gy with 28 fractions. The dose to CTV was 56 Gy with 28 fractions. The definition of GTV, CTV and dose-volume constraints of normal tissue in our institute was described previously [10-12].

Chemotherapy

A total of 45 patients (25.6%) with advanced UICC stages were treated with a combination of systemic chemotherapy as neoadjuvant/adjuvant concurrent sequence (1 patient with neoadjuvant, 10 with concurrent and 34 with adjuvant chemotherapy). The regimens used involved a combination of cisplatin (75 mg/m²/d on Days 1 and 22 or 25 mg/m²/d weekly) and/or paclitaxel (135 mg/m² on Day 1 and 22), administered intravenously.

QoL measurement

Chinese version of EORTC QLQ-C30 and H&N35 Questionnaires obtained from the QoL Unit (EORTC Data Center; Brussels, Belgium) were adopted [13-15]. Most items in these two questionnaires are scored on four-point Likert-type categorical scales ("not at all", "a little", "quite a bit", "very much"), We analyzed each item followed by the general principles of scoring according to the guideline: First, we estimated the average of the items that contribute to the scale and got the

raw scores (RS), and then used a linear transformation to standardized the RS and gained

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Table 3. Maximum acute and late toxicities for the enrolled NPC patients

Toxicity Type	Grade				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Acute toxicities, No. (%) (N = 176)					
Mucositis (radiation related)	42 (23.9)	82 (46.6)	46 (26.1)	6 (3.4)	-
Skin reaction (radiation related)	85 (48.3)	60 (34.1)	30 (17.0)	1 (0.6)	-
Xerostomia	17 (9.7)	36 (20.4)	80 (45.5)	40 (22.7)	3 (1.7)
Hearing loss	154 (87.5)	20 (11.4)	2 (1.1)	-	-
Late toxicities (6 months), No. (%) (N = 176)					
Xerostomia	28 (15.9)	78 (44.3)	64 (36.4)	5 (2.8)	1 (0.6)
Ear (deafness/otitis)	139 (78.9)	33 (18.8)	3 (1.7)	1 (0.6)	-
Skin and tissue fibrosis	168 (95.5)	6 (3.4)	2 (1.1)	-	-
Neuritis	173 (98.3)	3 (1.7)	-	-	-
Dysphagia	131 (74.4)	40 (22.7)	4 (2.3)	1 (0.6)	-
Late toxicities (2 years), No. (%) (N = 170)					
Xerostomia	41 (24.1)	80 (47.1)	43 (25.3)	6 (3.5)	-
Ear (deafness/otitis)	128 (75.3)	36 (21.2)	5 (2.9)	1 (0.6)	-
Skin and tissue fibrosis	165 (97.0)	3 (1.8)	2 (1.2)	-	-
Neuritis	167 (98.2)	2 (1.2)	1 (0.6)	-	-
Dysphagia	136 (80.0)	28 (16.5)	5 (2.9)	1 (0.6)	-
Late toxicities (5 years), No. (%) (N = 120)					
Xerostomia	49 (40.8)	67 (55.8)	4 (3.4)	-	-
Ear (deafness/otitis)	102 (85.0)	16 (13.3)	2 (1.7)	-	-
Skin and tissue fibrosis	114 (95.0)	6 (5.0)	-	-	-
Neuritis	116 (96.7)	3 (2.5)	1 (0.8)	-	-
Dysphagia	98 (81.7)	15 (12.5)	7 (5.8)	-	-

the standard score (SS), SS ranges from 0 to 100, a high score for a functional or global QoL scale represents a relatively high/healthy level of functioning or global QoL, whereas a high score for a symptom scale represents the presence of a symptom or problems.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS 16.0, Inc, Chicago, IL; for Windows; Microsoft, Redmond, WA) was used for statistical analysis. The survival function was analyzed using the Kaplan-Meier method and the correlations of xerostomia at different time points were examined with the Spearman rho non-parametric correlation coefficient (r). All tests were two-sided and significance was set at $P < 0.05$.

Results

Clinical outcomes

With a median follow-up time of 86 months (range, 6-141 months), the 5-year overall sur-

vival (OS) rate (taking into account all causes of deaths) was 68.2% shown in **Figure 1**.

Acute and late toxicities

All patients had a minimum follow-up of 6 months and were analyzed for acute and late toxicities, the incidence of radiation-related toxicities were listed in **Table 3**. The incidences of grade 1, 2 and 3 acute mucositis, skin reaction, xerostomia and hearing loss were 46.6% (82/176), 26.1% (46/176) and 3.4% (6/176); 34.1% (60/176), 17% (30/176) and 0.6% (1/176); 20.4% (36/176), 45.5% (80/176) and 22.7% (40/176); 11.4% (20/176) and 1.1% (2/176) respectively, and only 3 patients (1.7%) had grade 4 xerostomia; At 6 months after radiotherapy, the incidences of grade 1, 2 and 3 late xerostomia, ear (deafness/otitis), skin and tissue fibrosis, neuritis and dysphagia were 44.3% (78/176), 36.4% (64/176) and 2.8% (5/176); 18.8% (33/176), 1.7% (3/176) and 0.6% (1/176); 3.4% (6/176) and 1.1% (2/176); 1.7% (3/176); 22.7% (40/176), 2.3% (4/176) and 0.6% (1/176) respectively, and only 1 patient had grade 4 xerostomia; at 2 years after

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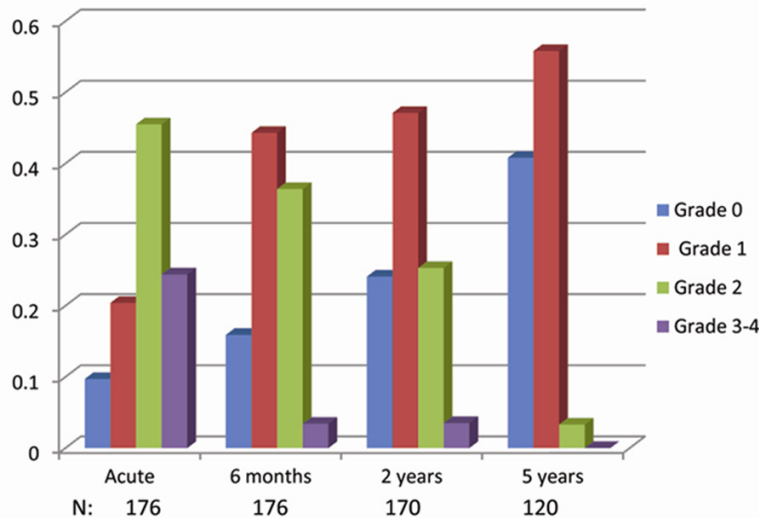


Figure 2. Incidence of xerostomia at different time points.

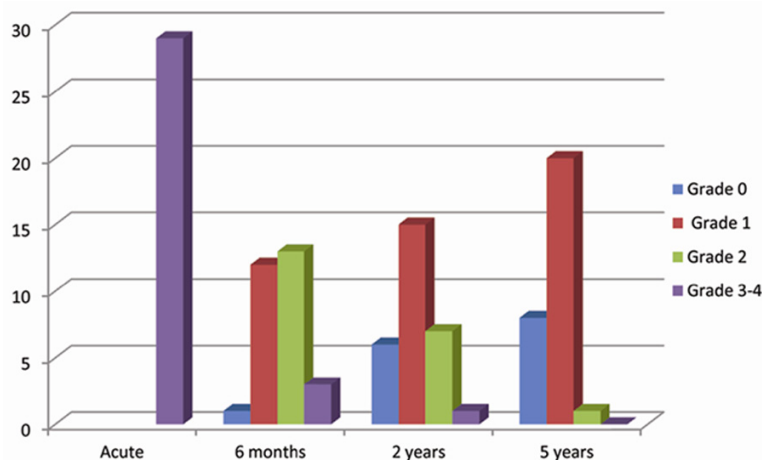


Figure 3. Subsequent consequences of patients who had grade ≥ 3 xerostomia at the acute phase (N = 29).

radiotherapy, except for 5 patients died of NPC and 1 patient lost contact, the incidences of grade 1, 2 and 3 late xerostomia, ear (deafness/otitis), skin and tissue fibrosis, neuritis and dysphagia were 47.1% (80/170), 25.3% (43/170) and 3.5% (6/170); 21.2% (36/170), 2.9% (5/170) and 0.6% (1/170); 1.8% (3/170) and 1.2% (2/170); 1.2% (2/170) and 0.6% (1/170); 16.5% (28/170), 2.9% (5/170) and 0.6% (1/170) respectively, none of these patients had grade 4 xerostomia; at 5 years after IMRT, 120 NPC patients survived and the incidences of grade 1, 2 and 3 late xerostomia, ear (deafness/otitis), skin and tissue fibrosis, neuritis and dysphagia were 55.8% (67/120)

and 3.4% (4/120); 13.3% (16/120) and 1.7% (2/120); 5% (6/120); 2.5% (3/120) and 0.8% (1/120); 12.5% (15/120) and 5.8% (7/120) respectively.

The most common radiation-related acute and late toxicity was xerostomia (**Figure 2**). Of 176 evaluable patients during IMRT, a total of 159 patients (90.3%) had Grade ≥ 1 xerostomia during treatment and 148 patients (84.1%) had Grade ≥ 1 xerostomia at 6 months after IMRT. Mucositis and Skin reaction ranked the second and third in the acute phase (134/176, 76.1% and 91/176, 51.7% respectively); at 6 months after RT, dysphagia and hearing problems (deafness/otitis) were the second and third severe problems for NPC patients and the same situation was also observed at 2 years and 5 years after IMRT. We also observed sustained decrease of late sequelae over time after IMRT.

Relationship of acute and late xerostomia

To further investigate the relationship of xerostomia in survival patients at different time points, we performed the statistical analysis using Spearman rho nonparametric test as shown in **Table 4**;

In our patient cohort at 2 years post irradiation (n = 170), both incidence of the acute and late at 6 months had a significant correlation with that in 2 years ($r = 0.325$, $P < 0.000$ and $r = 0.566$, $P < 0.000$ respectively); At 5 years after IMRT, the correlations of acute, 6 months, 2 years with 5 years xerostomia were 0.233, 0.354 and 0.409 respectively, all time points had a significant correlation; For patients with severe xerostomia (Grade 3-4), our subgroup analysis showed that there were significant associations of 6 months, 2 years with 5 years xerostomia (**Figure 3**), $r = 0.639$ for 6 months with 2 years, $r = 0.538$ for 6 months with 5

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Table 4. Correlation analysis for the acute and late xerostomia

Total:	2-year Xerostomia	P value
Acute Xerostomia (n = 170)	r = 0.325	P < 0.000
Late Xerostomia at 6 months	r = 0.566	P < 0.000
	5-year Xerostomia	
Acute Xerostomia (n = 120)	r = 0.233	P = 0.005
Late Xerostomia at 6 months	r = 0.354	P < 0.000
Late Xerostomia at 2 years	r = 0.409	P < 0.000
	2-year Xerostomia	
Subgroup Analysis (Grade 3-4 Xerostomia at Acute)		
Acute Xerostomia (n = 41)	r = -0.127	P = 0.214
Late Xerostomia at 6 months	r = 0.639	P < 0.000
	5-year Xerostomia	
Acute Xerostomia (n = 29)	r = 0.141	P = 0.233
Late Xerostomia at 6 months	r = 0.538	P = 0.001
Late Xerostomia at 2 years	r = 0.732	P < 0.000

years, $r = 0.732$ for 2 years with 5 years, the correlation coefficient (r) value indicating a close relationship between 2 years with 5 years xerostomia, but acute xerostomia was failed to reach significance with 2 years and 5 years xerostomia ($r = -0.127$, $P = 0.214$ and $r = 0.141$, $P = 0.233$, respectively).

QoL for long-term survivors

NPC patients who survived more than 5 years are considered as “clinical cured” and QoL has arisen as a very important issue for those long-term survivors. Based on this theory, we conducted the QoL survey with the questionnaires of EORTC QLQ-C30 and H&N35, the scores were shown in **Table 5**. At 5 years, the mean score for global QoL was 83.06. In our patient cohort, the highest symptom scores of EORTC QLQ-C30 were appetite loss (5.83), insomnia (5.56) and financial difficulties (5), and among the functional scales, physical functioning scored higher than other four functioning scales. In the H&N 35 module, dry mouth and sticky saliva ranked as the two worst symptoms, followed by weight loss/gain and less sexuality.

Up to Jun. 2014, 66 patients survived with more than 8 years, the mean score for global QoL was 82.2, indicating a relatively stable state between 5 to 8 years, same tendency was also observed for other QoL items, and dry mouth and sticky saliva were still the two worst symptoms in the H&N35 module (**Table 5**).

Discussion

To date, there is little controversy that IMRT has an excellent disease control and overall survival compared to conventional RT. Many studies had displayed that acute and late toxicities can be life-threatening or significantly erode the patient’s QoL and functional status in conventional radiotherapy. Hence, it remained as a crucial issue to manage those long-term NPC survivors in the IMRT era.

Most of past studies of QoL for NPC had discontinued follow-up and the accurate scores were within 2 years. Our results showed higher global QoL scores and most symptom scales of EORTC QLQ-C30 and H&N 35 were more mitigatory at 5 years, compared to the QoL scores at 2 years after IMRT from Pow et al. [16] and Fang et al. [17] and also indicated a stable state of QoL between 5 to 8 years. The parotid sparing strategies in the beginning phase of IMRT had obviously protected function due to low dose to parotid glands and the damage of low dose irradiation can be repaired more efficiently and time consuming and translate into QoL benefits for long-term survivors.

The most common radiation-related sequel after IMRT was xerostomia. We found the incidence of xerostomia during treatment could predict the experience of late xerostomia. The associations of xerostomia between acute/late and at 5 years were significant, particularly for patients had grade ≥ 3 xerostomia at acute phase of IMRT. The association of xerostomia

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Table 5. Calculated scores of EORTC QLQ-C30 and H&N35 scales for long-term survivors

Scales	5 year (n = 120)			8 year (n = 66)		
	Mean \pm SD	Median	Range	Mean \pm SD	Median	Range
QLQ-C30						
Global quality of life	83.06 \pm 11.38	83.33	16.67-100	82.58 \pm 9.99	83.33	50-100
Physical functioning	93.22 \pm 12.99	100	13.33-100	93.94 \pm 9.90	100	53.33-100
Role functioning	87.36 \pm 21.71	100	0-100	88.13 \pm 18.89	100	33.3-100
Emotional function	87.08 \pm 21.82	100	8.33-100	85.86 \pm 21.53	100	16.67-100
Cognitive function	88.19 \pm 19.97	100	0-100	87.10 \pm 18.20	100	50-100
Social function	88.19 \pm 18.86	100	0-100	88.89 \pm 16.62	100	33.33-100
Fatigue	4.43 \pm 9.80	0	0-66.67	4.36 \pm 8.24	0	0-33.33
Nausea/vomiting	0.69 \pm 4.53	0	0-33.33	0.51 \pm 4.10	0	0-33.33
Pain	0.69 \pm 3.98	0	0-33.33	0.76 \pm 4.56	0	0-33.33
Dyspnea	2.50 \pm 8.82	0	0-33.33	1.52 \pm 7.00	0	0-33.33
Insomnia	5.56 \pm 13.2	0	0-66.67	6.06 \pm 14.21	0	0-66.67
Appetite loss	5.83 \pm 15.97	0	0-66.67	6.06 \pm 14.21	0	0-66.67
Constipation	2.78 \pm 9.25	0	0-33.33	2.02 \pm 8.01	0	0-33.33
Diarrhea	1.94 \pm 7.85	0	0-33.33	2.53 \pm 8.89	0	0-33.33
Financial difficulties	5 \pm 12.71	0	0-66.67	6.57 \pm 13.36	0	0-33.33
QLQ-H&N35						
Pain	1.04 \pm 6.44	0	0-58.33	1.64 \pm 8.43	0	0-58.33
Swallowing	5.49 \pm 13.77	0	0-75	6.82 \pm 14.17	0	0-58.33
Senses problem	4.72 \pm 12.44	0	0-66.67	4.04 \pm 10.57	0	0-33.33
Speech problem	5.83 \pm 16.17	0	0-100	4.71 \pm 14.60	0	0-100
Trouble social eating	3.4 \pm 9.51	0	0-66.67	2.65 \pm 6.72	0	0-33.33
Trouble social contact	2.83 \pm 9.61	0	0-66.67	1.82 \pm 6.77	0	0-40
Less sexuality*	10 \pm 21.22	0	0-100	9.58 \pm 19.20	0	0-100
Teeth	2.22 \pm 8.35	0	0-33.33	2.53 \pm 8.89	0	0-33.33
Open mouth	5.28 \pm 12.96	0	0-66.67	4.55 \pm 11.53	0	0-33.33
Dry mouth	20.83 \pm 18.37	33.33	0-66.67	20.71 \pm 19.18	33.33	0-66.67
Sticky saliva	14.72 \pm 18.23	0	0-66.67	16.16 \pm 19.61	0	0-66.67
Coughing	6.11 \pm 14.32	0	0-66.67	5.56 \pm 13.82	0	0-66.67
Felt ill	7.22 \pm 21.25	0	0-100	7.07 \pm 20.68	0	0-100
Pain killers	0.83 \pm 9.13	0	0-100	0	0	0
Nutritional supplements	7.5 \pm 26.45	0	0-100	6.06 \pm 24.04	0	0-100
Feeding tube	0.83 \pm 9.13	0	0-100	0	0	0
Weight loss	12.5 \pm 33.21	0	0-100	15.15 \pm 36.13	0	0-100
Weight gain	11.67 \pm 32.24	0	0-100	10.61 \pm 31.03	0	0-100

Note: EORTC: European organization of research and treatment of cancer; *: n = 75 at 5 years and n = 40 at 8 years.

at 2 years with 5 years was more significant. The phenomenon suggested that take advantage of dosimetric superiority in treatment planning of IMRT as possible as we can. There were still half of NPC patients experienced late xerostomia although mild as grade 1, which could not be fully attributed by clinical and dosimetric factors. The inter-patient heterogeneity may account for the incidence of xerostomia. The polymorphisms of DNA repair gene such as

XRCC3 had been reported significantly associated with the risk of developing radiation-induced late xerostomia [18].

In contrast to conventional radiotherapy, the incidences of late radiation-related sequelae after IMRT were obviously decreased. Only less than 5% patients had grade 3 sequelae such as deafness, skin fibrosis and neuritis. No patients experienced grade 4 late sequelae that may

contribute to the improvement of QoL in long term-survivors.

Limitations of this study was that only 5.8% of patients in our study received concurrent chemotherapy, the acute toxicities would increase that may dilute the results with IMRT alone, we did not analyze this population.

In conclusion, IMRT significantly reduce late radiation sequelae and improve long-term QoL in NPC patients. Xerostomia remained negatively affect the QoL, patients with ≥ 3 acute xerostomia had a significant correlation of mild xerostomia during the late follow-up time.

Disclosure of conflict of interest

None.

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