

HEAD AND NECK

Comparisons of quality of life for patients with nasopharyngeal carcinoma after treatment with different RT technologies

Confronto della qualità della vita nei pazienti con carcinoma rinofaringeo dopo trattamento con differenti metodiche di RT

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SUMMARY

The objectives of this study were determine the quality of life (QoL) for patients with nasopharyngeal carcinoma (NPC) after treatment with different advanced technologies in radiotherapy (RT). A total of 150 patients with NPC were consecutively treated using curative RT in the Department of Radiation Oncology at Tri-service General Hospital in Taiwan. Data were collected prospectively from medical records and questionnaires. We used the Short-Form-36 (SF36) health survey questionnaire to evaluate general QoL, and a modified EORTC QLQ-H&N35 questionnaire to evaluate the correlation of xerostomia with QoL. The selection of RT methodology among two-dimensional radiotherapy (2D-RT), three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) was a significant factor for predicting difficulty of speech ($P = 0.003$), difficulty in chewing ($P = 0.012$), swallowing ability ($P = 0.004$), dry throat sensation during meals ($P = 0.006$) and the frequency of drinking water to maintain a moist mouth ($P = 0.01$). Our data suggest that the intensity-modulated radiotherapy technique plays a significant role in improving the QoL of NPC patients in our study.

KEY WORDS: Nasopharyngeal Carcinoma • Intensity-Modulated Radiotherapy

RIASSUNTO

Obiettivo del nostro studio è stato determinare la qualità della vita (QoL) dei pazienti con carcinoma del rinofaringe (NPC) dopo trattamento con differenti metodiche avanzate di radioterapia (RT). Presso il Dipartimento di Radioterapia Oncologica del Tri-service General Hospital di Taiwan sono stati trattati con RT un totale di 150 pazienti affetti da carcinoma del rinofaringe. I dati sono stati raccolti prospettivamente utilizzando il questionario "Short-Form-36 (SF36) health survey" per valutare la qualità della vita generale e il questionario EORTC QLQ-H&N35 modificato per valutare la correlazione tra xerostomia e qualità della vita. La diversa metodologia radioterapica utilizzata, scelta fra: RT bidimensionale (2D-RT), radioterapia tridimensionale conforme (3D-CRT) e radioterapia ad intensità modulata (IMRT), è stato un importante fattore predittivo della difficoltà a parlare ($P = 0,003$), difficoltà a masticare ($P = 0,012$), capacità di deglutire ($P = 0,004$), sensazione di gola asciutta durante i pasti ($P = 0,006$) e la frequenza con cui è necessario bere per mantenere la bocca umida ($P = 0,01$). I nostri dati dimostrano che la radioterapia ad intensità modulate gioca un ruolo significativo sull'incremento della qualità della vita dei pazienti trattati per carcinoma rinofaringeo.

PAROLE CHIAVE: Carcinoma nasofaringeo • Radioterapia di intensità modulata

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Introduction

Nasopharyngeal carcinoma (NPC) is common in the southern regions of China, particularly in Guangdong, and accounts for 18% of all cancers in China. However, the incidence of NPC is < 1 case per 100,000 individuals in the United States and most other nations. NPC arises

from the mucosal epithelium of the nasopharynx, is most often found within the lateral nasopharyngeal recess or fossa of Rosenmüller and is associated with infection with Epstein-Barr virus.

There are multiple factors which contribute to QoL, including emotional, social and psychological issues¹. QoL is very important for patients with head and neck cancer

(HNC), and difficulty in swallowing, hearing loss, speech impediments and psychological effects are major problems for these patients.

NPC is prevalent in Taiwan, and is usually found in younger patients with no prior history of smoking or alcohol abuse. Radiotherapy alone, or administered concurrent with chemotherapy, offers a high possibility for cure in NPC patients, even when the tumour is at an advanced stage². For this reason, QoL for NPC patients is a very important issue. Understanding the effects of various treatments on NPC survivors is important for the following reasons: (1) physicians can better identify specific functional impairments related to certain types of treatment; (2) the predicted QoL for NPC patients may help healthcare planners to evaluate what types of services a patient is likely to need; (3) understanding the QoL for NPC patients treated with different methods may help in the development of novel therapeutic strategies. Several different instruments are used to evaluate the QoL for HNC patients, and in this study we used the Short-Form-36 (SF36) health survey questionnaire. We also used a modified EORTC QLQ-H&N35 questionnaire to evaluate the correlation of xerostomia with QoL, and scores on all scales reflect modified QLQ-H&N35 scores ranging from 0 to 10. This study analysed the QoL for NPC patients experiencing disease-free survival, and examined the benefits of utilizing different new RT treatments at our hospital during different time periods.

Materials and methods

A total of 150 newly diagnosed NPC patients were consecutively treated by curative RT in the Department of Radiation Oncology at Tri-service General Hospital in Taiwan. Data were collected prospectively from medical records and questionnaires. Disease-free status was confirmed by results of clinical examinations, including nasopharyngoscopy and magnetic resonance imaging (MRI) studies. Questionnaires were not completed for 14 of the 150 patients, and therefore, 136 patients were included in this analysis. The research was approved by the authors' institutional review board, and was performed in accordance with the Helsinki agreement.

RT techniques

2D-RT

Briefly, 2D-RT was administered in 2 phases with a 6-MV photon beam at 2~1.8 Gy per fraction, once daily (5 fractions per week). In the first phase, lateral opposed fields were used to irradiate the gross tumour in the nasopharynx and regional neck lymphatic drainage area, and one lower anterior cervical field with a central larynx block or half-block was used to irradiate the anatomical structures at risk, until 45 Gy of the maximum dose tolerated by the spinal cord had been administered. In the second phase,

irradiation of the residual gross tumour and bilateral retropharyngeal space via bilateral opposing photon beams off the spinal cord was boosted. The total doses of radiation delivered were at least 70 Gy for primary T1-2 tumours, 72-74 Gy for T3-4 tumours and 70 Gy for enlarged lymph nodes with mixed photon and electron beam boost.

3D-CRT

The total doses and dose per fraction when using 3D-CRT for NPC radiotherapy followed guidelines for 2D-RT. The gross tumour volume (GTV) included the gross nasopharyngeal tumour plus the enlarged node. Clinical targeted volume (CTV) was defined as GTV \pm 0.5 cm and nasopharyngeal adjacent anatomic structures, and bilateral neck lymphatic vessels, including level V and supraclavicular nodes. The maximum dose delivered to the brain stem, bilateral temporal lobes and spinal cord was < 50 Gy, while the optic chiasm and optic nerve received < 40 Gy. The bilateral parotid glands were defined as critical organs and spared as much as possible. A wedge or compensator was used as needed. Treatment simulation was conducted with computed tomography, and treatment planning was done using PLATO software. Based on extension of the individual tumour, 5 to 6 co-planar beams positioned from different directions were used for irradiation. The 90-95% isodose curve was usually applied to cover the planned target volume (PTV).

IMRT

For treatment with IMRT, the patient sat in the supine position with the head and neck immobilized using a thermoplastic mould. The CTV included the entire nasopharynx, sphenoid sinus, posterior ethmoid sinus, base of the skull, 1/3~1/2 of the posterior nasal cavity, pterygoid fossa, lateral pharyngeal walls, retropharyngeal space and bilateral neck. We also used the PLATO treatment planning system with an inverse planning module to perform inverse planning and dose optimisation. At least 7 co-planar beams originating from different directions were used for irradiation. The constraints applied for organs at risk³ and dose calculation included critical organs as previously defined for 3D-CRT^{4,5}. The bilateral parotid glands were defined as critical organs with mean dose < 26 Gy. The doses were delivered using a linear accelerator (LINAC) equipped with multi-leaf collimators (MLC).

Chemotherapy

A total of 123 patients were treated with at least 2-3 cycles of concurrent chemoradiation followed by adjuvant chemotherapy. The chemotherapy regimens using a platinum-based agent (e.g. cisplatin or carboplatin) and 5-fluorouracil (5-FU) were administered intravenously. Tri-weekly cisplatin 80-100 mg/m² was administered concurrently with irradiation. 5-FU 250 mg/m² on D1-D4 were administered with tri-weekly cisplatin in a clinical T4 lesion.

QoL instruments

We used the Taiwan Chinese version of the Short-Form-36 (SF36) health survey questionnaire to evaluate the general QoL of patients, and a modified EORTC QLQ-H&N35 questionnaire to evaluate the correlation of xerostomia with QoL. Scores on all scales pertained to a modified QLQ-H&N35 score ranging from 0 to 10. The SF36 used single-item scales to survey the presence of symptomatic problems associated with social function, working ability, self-care, health condition, mood and easily feeling ill. In our study, we only focused on the eight items related to symptomatic problems associated with speech difficulty, chewing difficulty, swallowing ability, dry throat sensations before and during meals, insomnia and drinking water to maintain a moist mouth in EORTC QLQ-H&N35. When assessing the results of tests, a high score represented a relatively healthy function or good quality of life.

Statistical analyses

Data from questionnaires completed by 136 patients was prospectively collected and included in this analysis. SPSS10.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. General information concerning patient's age, gender, performance status, education level and clinical stage was treated as an independent variable factor. Dependent variable factors included SF36 and QLQ-H&N35 questionnaires with multiple-item scales that surveyed the presence of symptomatic problems. A generalised estimating equation (G.E.E.), the multivariate of variance (MANOVA) test and Pearson's correlation analysis were used to analyse correlations between the factors assessed and QoL scales.

Results

To avoid selection bias, we compared demographic characteristics (including age and gender) between NPC survivors with characteristics of other patients treated during the same time period, as found in the cancer registry database in the department. Finally, 136 newly diagnosed NPC patients consecutively treated by curative RT were included in this study. Characteristics of patients, gender, age, history of chemotherapy, clinical stage and drugs used for dry mouth disorder are listed in Table I. No statistically significant differences were found between groups, except for the group being treated with chemotherapy.

NPC survivors treated with RT usually have the associated problem of a dry mouth. The symptoms of this are manifested by the patient's teeth, mouth opening ability, dry mouth (xerostomia), sticky saliva, coughing and sense of feeling ill. We compared the 3 RT technologies for their association with dry mouth problems by using EORTC QLQ-H&N35, and the results are shown in Table II. Only insomnia and the presence of a dry throat without a meal failed to show a statistically significant difference. Changes for the other associated dry mouth problems were all statistically significant. All 3 technological advances in RT, including 2D-RT, 3D-CRT and IMRT were significant factors for predicting a patient's difficulty to speak ($P = 0.003$), difficulty to chew ($P = 0.012$), swallowing ability ($P = 0.004$), dry throat sensation during a meal ($P = 0.006$) and need to drink water to maintain a moist mouth ($P = 0.01$). According to this analysis, patients undergoing IMRT presented better QoL in xerostomia than 2D-RT and 3D-CRT.

A patient's perception of their individual health is also an important issue for NPC survivors. Therefore, we compared the 3 RT technologies for their association with

Table I. Patient characteristics (n = 136).

		2DRT	3DCRT	IMRT	p-value
Patient number		30	30	76	
Gender	Male	23	25	58	0.722
	Female	7	5	18	
Age (years)	Mean±SD	54.2±14.8	45.7±12.4	46.3±21.1	0.011
Follow-up (months)	Median	137	62	16	< 0.001
	Mean±SD	158.1±81.4	62.4±11.9	19.9±15.6	
Clinical stage	I	4	2	7	0.243
	II (IIA/IIB)	4 (1/3)	8 (0/8)	28 (2/26)	
	III	14	12	20	
	IV (IVA/IVB)	8 (5/3)	8 (7/1)	21 (14/7)	
Chemotherapy	Yes	5	27	68	< 0.001
	No	25	3	8	
Drug used for dry mouth	Yes	5	7	6	0.088
	No	25	23	70	

SD: standard deviation; RT: radiotherapy; 2DRT: two-dimensional RT; 3DCRT: three-dimensional conformal RT; IMRT: intensity-modulated RT

Table II. Results of Modified EORTC QLQ-H&N35 for NPC survivors.

	2DRT Mean±SD	3DCRT Mean±SD	IMRT Mean±SD	p-value
Difficulty in speech	4.80±3.61	3.30±2.78	2.30±2.70	0.003
Difficulty in chewing	5.13±3.81	3.43±2.99	2.75±3.03	0.012
Swallowing ability	6.36±3.39	5.50±3.82	3.86±3.66	0.004
Dry throat sensation during meal	5.03±3.66	4.36±3.16	2.89±2.74	0.006
Drinking water to keep moist mouth	6.03±3.32	4.90±3.25	3.86±3.24	0.01
Insomnia	3.70±3.50	3.26±3.14	2.93±3.17	0.58
Drinking water assessment by swallow	6.13±3.43	3.53±3.52	3.64±3.42	< 0.001
Dry throat without meal	4.08±3.48	3.66±2.94	3.43±2.92	0.165

NPC: nasopharyngeal carcinoma; H&N35: Head and Neck Module; SD: standard deviation; RT: radiotherapy; 2DRT: two-dimensional RT; 3DCRT: three-dimensional conformal RT; IMRT: intensity-modulated RT

Table III. Results of SF36 for NPC survivors.

		2DRT	3DRT	IMRT	p-value
Compared healthy condition before therapy	Better	23.3%	53.4%	38.1%	0.163
	No different	46.7%	36.7%	31.6%	
	Worse	30.0%	10.0%	30.3%	
Social function	No effect	73.3%	80.0%	93.4%	0.001
	Mild	23.4%	6.7%	6.6%	
	Sever	3.3%	13.3%	0%	
Affected working ability	Yes	60.0%	53.3%	30.3%	0.007
	No	40.0%	46.7%	69.7%	
Self-care	No effect	43.3%	60.0%	80.3%	0.005
	Mild	50%	33.3%	15.8%	
	Sever	6.7%	6.7%	3.9%	
Duration of depressive mood	Always	6.7%	0%	0%	0.006
	Mostly	3.3%	0%	0%	
	Often	6.7%	10.0%	3.9%	
	Sometime	33.3%	6.7%	18.4%	
	Less happen	23.3%	53.3%	59.2%	
	Never	26.7%	30.0%	18.4%	
Feeling easily-ill	No feel	23.3%	20.0%	26.3%	0.01
	Mild	26.6%	43.3%	59.2%	
	Sever	50.0%	36.7%	14.5%	

NPC: nasopharyngeal carcinoma; SF36: Short-Form-36 health survey; RT: radiotherapy; 2DRT: two-dimensional RT; 3DCRT: three-dimensional conformal RT; IMRT: intensity-modulated RT.

problems of social function, working ability, self-care, health condition, mood and easily feeling ill. We used SF36 to compare the three RT technologies for their association with an individual's perception of their health, and the results are shown in Table III. Patients treated with the three different RT technologies showed no significant differences in their statements of health at one month and one year after treatment. However, the use of different RT technologies significantly affected a patient's social function ($P = 0.001$), working ability ($P = 0.007$), self-care ($P = 0.005$), duration of a depressive mood ($P = 0.006$) and chance of easily feeling ill ($P = 0.01$). It showed that patients in the IMRT group presented better global QoL than either 2D-RT or 3D-CRT.

Discussion

In our study, the use of advanced RT techniques tended to improve QoL, but the improvements resulting from the transition from 2D-RT to 3D-CRT were not significant for most scales, and thus detailed data were not presented. When IMRT was used, the patient's swallowing ($P = 0.004$), social eating ($P = 0.006$) and mouth opening ability ($P=0.012$) were greatly improved, and switching from 2D-RT to IMRT produced significant increases in QoL.

Due to significant difference in age, chemotherapy and follow-up months in the three groups, this might have caused bias in our study. Previous studies have usually used 2D-RT, 3D-CRT, or IMRT for the treatment of NPC.

These RT technologies provide clearer radiological visualization of the tumour and the special relationships of organs, and therefore attenuate the risk to organs^{5,6}. 2D-RT, 3D-CRT and IMRT are simply different ways of trying to deliver radiotherapy in a highly conformal way to treat the cancer and avoid normal tissues. In some instances, the cancer is located very close to a number of normal organs, and the plans of 3D-CRT and IMRT look very similar. However, in our study, IMRT in sparing radiation dose to parotid gland approaches was clearly superior. 2D-RT was too difficult to limit the radiation dose to the parotid glands in plain film. In addition, 3D-CRT and IMRT provide a therapeutic benefit by their ability to escalate the dose of radiation given to a target tumour tissue, while reducing toxicity to normal tissues⁷. Finally, 3D-CRT or IMRT can be administered to HNC patients in a manner that preserves salivary function, and to some extent improve a patient's QoL⁸. Fang et al.² reported that patients treated with more advanced RT techniques had better QoL outcomes, and that following IMRT treatment, improvements were noticed for head- and neck-related symptoms of social eating, mouth opening, quality of teeth and swallowing.

Some studies have reported that IMRT produced a significant reduction of xerostomia and other head and neck symptoms in HNC patients compared to treatment with standard 3D-CRT⁸. These results suggest that the significant advantage of using IMRT over 3D-CRT is closely related to the anatomic site of the tumour. Additionally, tumour extensions in these cases may have existed in close proximity to dose-limiting organs.

Symptoms related to xerostomia are the most common complications found in HNC patients treated with RT. We found that IMRT had a minimal effect in producing xerostomia, because when using this new technique, we especially focused on sparing the parotid glands. However, we also observed that reducing the mean dose to parotid glands to ≤ 26 Gy was usually difficult to achieve in NPC patients⁸. Further study is required to define the mean dose to the parotid glands for optimisation of QoL.

Some reports have shown that when comparing QoL measurements obtained from NPC patients treated with IMRT or 2D-RT, IMRT significantly attenuated salivary flow^{9,10}, and other studies have revealed that dysphagia induced by radiation is also an important symptom for QoL measurements¹¹. A retrospective randomised trial of 425 HNC patients showed significant association between toxicities produced by therapy and patient-reported QoL, and also found that xerostomia and RTOG measurements of swallowing ability also greatly affected general dimensions of QoL¹¹.

It should be noted that the Short-Form-36 (SF36) and modified EORTC QLQ-H&N35 still have some limitations regarding their ability to measure QoL for NPC patients, because radiation neuropathy, hypopituitarism,

otitis media deafness and the symptoms from temporal lobe necrosis are not the focus of questions regarding late sequelae in NPC survivors. In addition, pre-treatment QoL data was not available for our study, and the QoL questionnaire was completed because patients had survived for three years. However, our investigation enabled patients to alter their life goals, develop plans to adapt to treatment-related sequelae and review their satisfaction with life.

In conclusion, different RT techniques were observed to have different roles in improving QoL for NPC patients. The usage of questionnaires investigated subjective opinions of patients. The intensity-modulated radiotherapy technique played a significant role for improving the QoL of NPC patients in our study. Additional studies should be conducted to further explore the effects of using various irradiated doses in salivary gland and muscles used for speech, chewing and swallowing on QoL scores as related to swallowing ability.

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