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Full Length Research Paper

Health-related quality of life outcome evaluation for intensity-modulated radiotherapy versus helical tomotherapy using EORTC QLQ-C30 and EORTC QLQ-HN35 core questionnaires for nasopharyngeal carcinomas

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This study compared the health-related quality of life (HRQoL) outcomes for patients with nasopharyngeal carcinoma (NPC) treated by step-and-shoot intensity-modulated radiotherapy (SaS-IMRT) versus helical tomotherapy (HT). Data from one-forty-two NPC patients consecutively treated at the same institute between March 2006 and December 2009 were collected and analysed. They received either SaS-IMRT (case number = 62) or HT (case number = 80) for their nasopharyngeal tumours and neck lymphatics. Health-related Quality of life was assessed by the European organization for research and treatment of cancer (EORTC) QLQ-C30 and the EORTC QLQ-H&N35 questionnaires at the time point of 6 months after RT. A two-tailed Wilcoxon matched pair signed-rank test was used to compare the mean scores between the two groups, and the linear regression model was applied for multivariate analysis. Patient characteristics were evenly distributed between the groups. Univariate analysis found that patients in the HT group had a significantly better HRQoL in the aspects of pain, swallowing, speech, social eating, teeth, sticky saliva, and feeling ill; and a marginal significance of fewer sensation changes in the HT group. Multivariate analysis further disclosed that patients with HT had significantly fewer complaints of swallowing, senses, and feeling ill. Compared with SaS-IMRT, HT may provide a significantly better HRQoL in the aspects of swallowing, senses, and feeling ill. This could be explained by the further reduction of treatment-related toxicity via well-designed HT.

Key words: Health-related quality of life, nasopharyngeal carcinoma, intensity-modulated radiotherapy, helical tomotherapy, EORTC.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a common malignancy in Taiwan and it was the tenth leading cancer among Taiwanese men in 2006, with an age-adjusted incidence rate of 8.25 per 100,000 males ('Taiwan Cancer

Registry', 2006). Radiotherapy (RT) plays an important role in the treatment of NPC. With the introduction of modern RT techniques and advances in chemotherapy, local control and survival rates have shown significant improvements. Recent data from the Memorial Sloan-Kettering Cancer Centre showed that 3-year local control and survival rates have improved to 91% and 83%, respectively (Wolden et al., 2006). However, as with other head and neck cancers, RT-induced acute and late toxicities can adversely compromise the treatment results. This is also of a significant public health and socioeconomic concern when we consider that most people develop NPC around 50 years of age ('Taiwan Cancer Registry', 2006).

Over the past decade, newly developed RT techniques have been focused on reducing treatment-related morbidity, as well as on tumour control. Intensity-modulated RT (IMRT), a more advanced form of conformal radiation, provides the special function of modulating the intensity of radiation within the target. Compared to the traditional forward-planning RT, it can spare more normal tissues and provide fewer doses to the organs at risk (OARs) without sacrificing tumour control (Fang et al., 2008; Teo et al., 2004). In contrast, the recently available Hi-Art helical tomotherapy (HT) (TomoTherapy, Madison, WI) is a specific design of RT with the fusion of a helical CT scanner and a linear accelerator. It is a type of IMRT with a focus on the accuracy of treatment target coverage, the sparing of normal organs, and dosimetry homogeneity (Fiorino et al., 2006). We have both a step-and-shoot IMRT (SaS-IMRT) and a HT modality available at our institute. We recently published an article regarding the dosimetric comparisons of these two methods for NPC patients, and showed that HT has some significant benefits in the dosimetry. For example, it could reduce the mean parotid gland dose from 29.7 to 21.3 Gy (Lee et al., 2008). We would like to evaluate whether or not the apparent dosimetric benefits of HT could translate into clinical outcome via the reduction of toxicities. To the best of our knowledge, there is no published literature comparing the toxicities induced by these two RT techniques for NPC. In this study, we analysed this issue by investigating the health-related quality of life (HRQoL) of our treated patients. The data pertaining to HRQoL were collected using the questionnaires of the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-H&N35 at one time point of 6 months after RT. We collected and compared the mean scores of these EORTC HRQoL scales at this time point for patients treated by SaS-IMRT and HT. A further statistical evaluation of the possible differences between these two techniques was performed by using univariate and multivariate analyses.

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MATERIALS AND METHODS

Patients

One hundred and forty-two consecutive patients with histology-confirmed NPC referred to our department for curative RT between March 2006 and December 2009 were enrolled in this study. They were treated either by IMRT (case number = 62, the median age was 46 (range, 24 to 69) years, with 42 males and 20 females) or HT (case number = 80, the median age was 48 (range, 23 to 78) years, with 66 males and 14 females). All participants were required to sign informed consent before participating in this study and completed the EORTC QLQ-C30 core questionnaire after radiotherapy. Eligibility criteria included 1) new diagnosis of NPC with pathological proof; 2) no previous or synchronous malignancy; 3) no distant metastasis at diagnosis with curative treatment intent; and 4) completion of a planned RT course. There were no age and gender restrictions. Pre-treatment evaluation included a complete history and physical examination, direct flexible fiberoptic nasopharyngoscopic examination, head and neck computed tomography (CT) and/or magnetic resonance imaging scans, and a chest X-ray. A bone scan and abdominal echogram were prescribed when clinically indicated. According to the sixth edition of the American Joint Committee on Cancer (AJCC) staging system, published in 2002, the distribution of clinical stages was as follows: stage I: 10 (7%), II: 40 (28%), III: 44 (31%), IV: 48 (34%). This study was approved by the appropriate institutional review boards (IRB) of Yuan's General Hospital.

RT techniques

The pre-planning preparations of SaS-IMRT and HT are the same. All patients were immobilized with a customized thermoplastic cast from head to shoulder, and then positron emission tomography (PET)/CT (Siemens Biograph LSO PET/CT) scans with 3 mm-thickness slices of the head and neck were performed. The image sets were transferred to and fused in the Philips Pinnacle$^{3®}$ (Version 7.4) (Philips, Fitchburg, WI) treatment planning system (TPS) and then delineation of the targets and OARs was performed. The gross tumour volume (GTV), including the macroscopic primary cancer and nodes greater than 1 cm in diameter or nodes with necrotic centres, was used for all plans. The clinical target volumes were as follows: clinical target volume-1 (CTV1) = GTV + 5 mm margin; Clinical target volume-2 (CTV_2) = CTV_1 + 5 mm margin plus areas at risk for microscopic involvement, including the primary cancer and neck levels with positive lymph nodes; and Clinical target volume-3 (CTV_3), which included the clinically negative low neck regions (Lee et al., 2002). Safety margins between the CTV and planning target volume (PTV) of 5 mm were used for CTV_1 and CTV_2 to account for patient setup errors and motion uncertainties, but in areas in which the GTV or the CTV was adjacent to critical normal structures (that is, the brainstem) the margin was reduced to 1 mm; no safety margin was used for the generation of Planning target volume-3 (PTV_3). The prescribed dose was set from 68.4 to 75.6 Gy with 1.8 Gy per fraction. The lower neck was usually excluded after a dose level of 54 Gy/30 fractions had been reached. The prescription dose was the isodose that encompasses at least 95% of the PTV_1, that is, $V_{100\%}$> 95%. No more than 20% of any PTV_1 received >110% of its prescribed dose. The spinal cord dose was restricted to 45 Gy or less. Clinical experience at our institution has demonstrated that more experienced planners produce superior dose distributions, so bias was minimized by the cross-planning of two equally experienced planners and by using dose

protocols approved by an oncologist specialized in nasopharyngeal carcinoma (in this study the same oncologist reviewed all plans).

SaS-IMRT

For the patients who received SaS-IMRT, the contours were transferred to Philips Pinnacle$^{3®}$ TPS for inverse treatment planning. A standard coplanar 7-field gantry arrangement was designed for all patients. The patients then received daily RT, five times per week, by the Elekta Precise^{TM} linear accelerator (Elekta Ltd, Crawley, UK) using SaS-IMRT technique.

Helical tomotherapy

For the patients who received HT, the contours were transferred to an HT planning system for inverse planning. In HT planning, three unique main parameters must be chosen by the operator: field width, pitch, and modulation factor (Mackie, 2006; van Vulpen et al., 2005). We have defined them briefly in a prior study (Lee et al., 2008). A 2.5 cm field width, a pitch of 0.3, and modulation factor of 2.5 were used in all HT plans in this study. The radiation beam was delivered by our HT machine with the same treatment schedule as SaS-IMRT.

Concurrent chemo-radiotherapy

Concurrent chemo-radiotherapy (CCRT) is routinely prescribed to patients with Stage III disease or above, and it is selectively given to younger patients with positive neck LN(s) or larger primary tumours. The radiosensitizing chemotherapy regimen is cisplatin and 5-FU.

HRQoL instruments

After treatment, the patients in both groups were checked weekly and followed regularly, and they were asked to fill out the questionnaires at the sixth month after treatment. We chose this time point because by then most patients have recovered from the treatment-related acute side effects and the items listed on the HRQoL questionnaire can reflect a patient's status, which may predict long-term or permanent toxicities. Fang et al. (2008) analysed the HRQoL of NPC patients and concluded that the potential advantage of HRQoL outcomes for some treatment methods might occur during the recovery phase of acute toxicity. The Taiwan Chinese versions of the EORTC QLQ-C30 and QLQ-H&N35 questionnaires were used. They were originally acquired from the Quality of Life Unit, EORTC Data Centre in Brussels, Belgium (Aaronson et al., 1993; Bjordal et al., 1999), and the EORTC QLQ-C30 is widely used in the field. It incorporates a broad range, with nine multi-item scales relevant to cancer patients. It has been translated into many languages and validated for many types of cancer, including head and neck cancer (Fang et al., 2008). It contains five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea/vomiting), a global HRQoL scale, and six other single-item scales (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). The QLQ-H&N35 is a module used specifically for assessing the HRQoL of patients with head and neck cancer. It embodies seven multiple-item scales that assess symptoms of head and neck: pain, swallowing ability, senses (taste/smell), speech, social eating, social contact, and sexuality. It also includes six single-item scales that assess the presence of symptomatic problems associated with teeth, mouth-opening, dry mouth, sticky saliva, coughing, and feeling ill. All scales incorporated in the EORTC QLQ-C30 and QLQ-H&N35 range from 0 to 100. A high score for a functional or global HRQoL scale represents a relatively high/healthy level of functioning or global HRQoL, whereas a high score for a symptom scale corresponds to the presence of symptom(s) or problem(s). For NPC, the Taiwan Chinese versions of the EORTC QLQ-C30 and the EORTC QLQ-H&N35 were found to have a moderate to high test-retest reliability, a high internal consistency in most scales, and they could show the expected differences between patients in active treatment and the follow-up group (Chie et al., 2003).

Statistical analysis

The EORTC QLQ scoring manual was used to calculate the mean scores(Fayers, 1999). Statistical tests of differences between our two patient groups were performed using a two-tailed Wilcoxon matched pair signed-rank test. Differences were considered statistically significant for p-values ≤ 0.05. To aid in the interpretation of the results, the "*clinical* significance" after comparing the scales between the two groups was also analysed. According to the reports by King et al.(1996) and Osoba et al. (1998), a difference of 10 points or more on a scale from zero to 100 should be interpreted as "clinically significant". Because more parotid gland sparing is one of the main aims of the treatment of NPC by the new RT techniques, we further analysed parotid gland associated toxicities, as well as the other items in the EORTC QLQ-HN35. We categorized the continuous variables (age, education years, annual family income, and radiation dose) into groups to determine whether or not there was any selection bias between these two different treatment methods (SaS-IMRT vs. HT). Subsequently, the linear regression method was used for multivariate analysis with the generation of un-standardized regression coefficients (β) and standard errors (SE). The statistical analysis was performed using the software SPSS for Windows (Version 12.0; SPSS Inc., Chicago, IL).

RESULTS

Tests for selection bias

Bias can exist in cases where patient characteristics are not evenly distributed between groups. This can mislead the interpretation of study results and should be tested for before further analysis. This was our main concern, because our patients were not randomized between the treatment methods. Therefore, we compared patient age, gender, education, annual income, clinical stage, histology, RT dose, chemotherapy or not, and comorbidity between the two groups. The comorbidity number was based on Charlson comorbidity index. We found no significant difference in any of these characteristics (Table 1, $p > 0.05$), and therefore assumed the subsequent analyses were valid.

Comparison of the EORTC QLQ-C30 QoL scales after different RT techniques

Table 2 illustrates the mean scores of the EORTC QLQ-C30 for NPC patients who received SaS-IMRT and HT. We found that patients in the HT group had higher mean scores in two out of the five functional domains than

Table 1. Patient characteristics. (n = 142).

Variables	SaS-IMRT (n = 62)	HT (n = 80)	p-values
Age, median (range) years	**46(24-69)**	**48(23-78)**	0.688
< 40	16(25.8%)	18(22.5%)	
40~ 59	42(67.7%)	52(65.0%)	
≧ 60	4(6.5%)	10(12.5%)	
Gender			0.171
Male	42(67.7%)	66(82.5%)	
Female	20(32.3%)	14(17.5%)	
Marital status			0.077
With spouse	32(51.6%)	60(75.0%)	
Without spouse	28(45.2%)	20(25.0%)	
Education years			0.065
<6	18(29.0%)	8(10.0%)	
6~12	22(35.5%)	28(35.0%)	
>12	20(32.3%)	44(55.0%)	
Annual family income (10^4 NTD)			0.110
<50	40(64.5%)	36(45.0%)	
50~100	18(29.0%)	22(27.5%)	
101~ 200	4(6.5%)	14(17.5%)	
> 200	0(0.0%)	8(10.0%)	
RT dose, median dose (Gy)	**69.9**	**71.55**	0.539
< 70.2	14(22.6%)	12(15.0%)	
≧ 70.2	48(77.4%)	68(85.0%)	
Chemotherapy			1.000
No	24(38.7%)	30(37.5%)	
Yes	38(61.3%)	50(62.5%)	
AJCC stage			0.104
I	8(12.9%)	2(2.5%)	
II	22(35.5%)	18(22.5%)	
III	12(19.4%)	32(40.0%)	
IV	20(32.3%)	28(35.0%)	
Comorbidity number			1.000
0	46(74.2%)	58(72.5%)	
≧1	16(25.8%)	22(27.5%)	

SaS-IMRT: step-and-shoot intensity-modulated radiotherapy; HT: helical tomotherapy; NTD: new Taiwan dollars (1 USD=33 NTD); AJCC: American Joint Committee on Cancer (AJCC 6th edition); Comorbidity number was based on Charlson comorbidity index.

patients in the SaS-IMRT group: this difference was statistically significant for both emotional functioning and cognitive functioning ($p < 0.05$). Furthermore, according to the criteria for clinical significance, patients in the HT

Table 2. Comparison of mean scores (standard deviation) of EORTC QLQ-C30 for NPC cancer patients—RT technique.

	SaS-IMRT	HT	
Scale	**Mean(SD)**	**Mean(SD)**	**p-values**
Global quality of life	64.2(19.6)	62.5(17.1)	0.690
Physical functioning	89.2(14.3)	92.2(9.3)	0.301
Role functioning	91.9(21.9)	92.9(12.5)	0.812
Emotional functioning	83.6(15.9)	90.4(11.7)	0.041[a]
Cognitive functioning	80.1(18.0)	92.5(11.9)	0.001[a]
Social functioning	83.9(19.5)	85.8(15.8)	0.641
Fatigue	28.3(24.7)	22.2(16.7)	0.219
Nausea/vomiting	6.5(11.9)	1.7(6.3)	0.033[a]
Pain	14.0(16.2)	12.1(13.1)	0.586
Dyspnea	9.7(15.4)	7.5(14.1)	0.537
Insomnia	26.9(26.4)	16.7(20.0)	0.068
Appetite loss	18.3(27.0)	9.2(16.9)	0.086
Constipation	14.0(18.8)	10.0(18.8)	0.380
Diarrhea	9.7(15.4)	3.3(10.1)	0.040[a]
Financial problems	26.9(33.8)	15.0(22.6)	0.081

NPC: nasopharyngeal carcinoma; RT: radiotherapy; SaS-IMRT: step-and-shoot intensity-modulated radiotherapy; HT: helical tomotherapy; SD: standard deviation; [a] $p < 0.05$.

group were also found to have better cognitive functioning (difference in mean scores ≧ 10 points). For the symptom scales, all of the mean scores for the eight symptoms (fatigue, nausea/vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea) for patients in the HT group were lower than for patients in the SaS-IMRT group, and a statistically significant difference was found for nausea/vomiting and diarrhoea, although the differences in these two symptoms between the two groups were not supported by the clinical interpretation (difference in mean scores < 10 points).

Comparison of EORTC QLQ-HN35 QoL scales after different RT techniques

We were more interested in knowing the HRQoL related to head and neck symptoms because it might be directly related to the RT technique for NPC. The QLQ-H&N35 is a module used for assessing the HRQoL of head and neck cancer patients. Table 3 lists the mean scores in the QLQ-H&N35 by RT technique. We found that the patients who had received HT had lower mean scores for all symptoms/complaints except for sexuality. Of these 13 head and neck symptoms, we noted that patients in the HT group had better HRQoL scores that were statistically significant for the items of pain, swallowing, speech, social eating, teeth, sticky saliva, coughing, and feeling ill ($p < 0.05$), and that they had better HRQoL scores that were marginally significant for the aspect of senses (taste/smell) ($p = 0.057$). Furthermore, when we used clinical interpretation to verify these symptoms, we found that the differences in swallowing, teeth, sticky saliva, and feeling ill were still significant (difference in mean scores < 10 points).

Comparison of QoL scales by stage in EORTC QLQ-C30 and EORTC QLQ-HN35

The symptoms that impact a patient's HRQoL may be related to the NPC itself, as well as to the treatment. We wanted to determine whether patients with more advanced disease had more symptoms. Table 4 demonstrates the mean scores of EORTC QLQ-C30 and EORTC QLQ-HN35 by AJCC stage. The only item that showed a statistically significant difference was diarrhoea. However, this difference did not show a consistent trend since it showed a fluctuation of mean score by stage.

Multivariate analysis of EORTC QLQ-HN35 QoL scales for the different RT techniques

To further investigate the association between the different RT techniques and the head and neck symptoms, we performed a multivariate analysis by using the linear regression model. Table 5 illustrates the significant parameter estimates after regression analysis for the EORTC QLQ-HN35. When we focused on the RT technique, statistically significant differences were found for the aspects of swallowing ($p < 0.01$), senses ($p < 0.05$), and feeling ill ($p < 0.05$). After correction for any confounding associations, this multivariate analysis found that patients who received HT had significantly less discomfort in these three aspects.

Table 3. Comparison of mean scores (standard deviation) of EORTC QLQ-HN35 for NPC cancer patients—RT technique.

	SaS-IMRT	HT	
Scale	**Mean(SD)**	**Mean(SD)**	***p*-values**
Pain	13.4(19.0)	4.6(9.8)	0.013[a]
Swallowing	19.6(23.0)	7.1(12.5)	0.004[a]
Senses (taste/smell)	18.3(25.3)	8.8(16.0)	0.057
Speech	16.5(24.8)	7.2(10.8)	0.038[a]
Social eating	16.1(20.3)	7.9(12.8)	0.041[a]
Social contact	9.9(18.1)	5.3(9.3)	0.174
Sexuality	12.9(24.2)	14.6(18.9)	0.744
Teeth	25.8(28.2)	11.7(23.3)	0.024[a]
Opening mouth	12.9(23.8)	8.3(16.5)	0.343
Dry mouth	38.7(27.3)	29.2(21.6)	0.105
Sticky saliva	30.1(29.0)	17.5(20.0)	0.034[a]
Coughing	21.5(23.6)	11.7(16.1)	0.041[a]
Feeling ill	31.2(27.1)	15.8(16.9)	0.005[a]

NPC: nasopharyngeal carcinoma; RT: radiotherapy; SaS-IMRT: step-and-shoot intensity-modulated radiotherapy; HT: helical tomotherapy; SD: standard deviation; [a] $p < 0.05$.

Multivariate analysis of EORTC QLQ-HN35 QoL scales by other predictors

For our patients, we were also interested in any other variables that might have had significant differences in predicting head and neck symptoms 6 months after RT. Table 5 shows the multivariate analysis of EORTC QLQ-HN35 QoL scales by other predictors. We found that male patients suffered more pain than female patients, but the opposite was shown for social contact. For the education level, the more highly educated patients tended to have fewer complaints about social eating and social contact. Patients with one or more comorbidities had less coughing. The higher RT dose had adverse impacts on social eating. Patients who had received concurrent chemoradiotherapy (CCRT) felt more discomfort regarding senses, teeth, and opening mouth.

DISCUSSION

In order to increase the cure rate of NPC, a decrease in treatment-related toxicity is also part of the goal for today's treatment planning. This poses a significant challenge in RT because many organs and tissues in the head and neck region are relatively sensitive to radiation, and an overdose to these structures may result in severe complications. In the traditional 2D-planning era, RT for head and neck cancers was usually delivered by bilateral, parallel opposed fields. The OARs in the pathways of radiation beams could receive almost the same dose as the tumour. For this reason, many NPC survivors suffered from xerostomia, hearing problems/otitis media, caries, and/or neck fibrosis. These complications significantly impacted the patients' HRQoL and compromised treatment outcome. Newly developed RT techniques focus on how to confine the RT dose to the tumour and administer lower doses to nearby normal organs. IMRT and HT are the products of today's developed techniques.

Studies have increasingly indicated that IMRT has both dosimetric and clinical superiority over conventional RT when applied in patients with NPC, not only in salivary function preservation, but also in tumour control and patient survival (Jen et al., 2005; Kwong et al., 2004; Lee et al., 2002, Sultanem et al., 2000; Wolden et al., 2006). Following the publication of these studies, IMRT and other three dimensional (3D) techniques have become the standard RT modality for NPC. There has been an interest in comparing the superiority of these modern techniques. Vergeer et al. (2009) compared IMRT and 3D conventional radiotherapy (3D-CRT) regarding patient-rated xerostomia and HRQoL in patients with head and neck squamous cell carcinoma and found that IMRT resulted in a significant reduction of patient- and observer-rated xerostomia, as well as in other head and neck symptoms. In our previous report, we observed that the HT plans significantly improved target coverage and spared normal organs compared to the SaS-IMRT plans for the aspect of dosimetry (Lee et al., 2008). Similar results have been published. Fiorino et al. (2007) compared simultaneous integrated boosts between HT and IMRT for NPC, and the results showed that HT improved the homogeneity of dose distribution within the PTV, together with a significantly greater sparing of OARs compared to 5-field IMRT using linear accelerators. Sheng et al.(2006) found out that HT provided improved dose homogeneity in the target and normal structures compared to SaS-IMRT in the treatment of oropharyngeal

Table 4. Comparison of mean scores (standard deviation) of EORTC QLQ-C30 and EORTC QLQ-HN35 for NPC cancer patients—AJCC stage.

	Stage I	Stage II	Stage III	Stage IV	
Scale	**Mean(SD)**	**Mean(SD)**	**Mean(SD)**	**Mean(SD)**	**p-values**
EORTC QLQ-C30					
Global quality of life	55.0(16.2)	65.0(19.8)	61.0(13.9)	65.6(20.6)	0.586
Physical functioning	94.7(8.7)	92.7(9.9)	88.2(12.7)	91.1(12.8)	0.549
Role functioning	100.0(0.0)	95.0(10.9)	92.4(12.3)	88.9(24.9)	0.490
Emotional functioning	78.3(13.9)	85.8(17.3)	87.9(11.1)	90.3(13.2)	0.342
Cognitive functioning	83.3(11.8)	85.0(14.2)	87.1(18.5)	89.6(16.2)	0.760
Social functioning	90.0(14.9)	81.7(20.9)	85.6(17.3)	86.1(15.3)	0.744
Fatigue	22.2(20.8)	22.8(18.5)	26.8(17.7)	25.5(25.3)	0.924
Nausea/Vomiting	6.7(9.1)	3.3(8.7)	2.3(7.8)	4.9(11.5)	0.716
Pain	10.0(14.9)	12.5(14.2)	13.6(14.2)	13.2(15.5)	0.965
Dyspnea	13.3(18.3)	6.7(13.7)	7.6(14.3)	9.7(15.5)	0.780
Insomnia	26.7(14.9)	21.7(24.8)	19.7(22.2)	20.8(25.7)	0.947
Appetite loss	6.7(14.9)	18.3(22.9)	9.1(18.3)	13.9(25.9)	0.524
Constipation	6.7(14.9)	13.3(16.8)	4.5(15.6)	18.1(21.9)	0.088
Diarrhea	13.3(18.3)	11.7(16.3)	1.5(7.1)	4.2(11.3)	0.033[a]
Financial problems	6.7(14.9)	21.7(24.8)	24.2(34.4)	18.1(27.8)	0.631
EORTC QLQ-HN35					
Pain	5.0(4.6)	12.9(17.6)	10.6(18.6)	3.5(8.1)	0.165
Swallowing	8.3(8.3)	11.7(17.8)	14.0(16.7)	12.8(23.2)	0.936
Senses (taste/smell)	3.3(7.5)	13.2(19.7)	15.9(22.1)	11.8(22.8)	0.674
Speech	6.7(9.9)	7.8(10.3)	13.6(22.5)	13.0(21.9)	0.681
Social eating	6.7(14.9)	15.8(19.1)	11.4(19)	9.0(13.0)	0.531
Social contact	4.0(6.0)	5.0(8.6)	9.4(18.8)	8.1(13.8)	0.716
Sexuality	13.3(18.3)	13.3(18.4)	15.2(19.2)	13.2(26.5)	0.990
Teeth	13.3(18.3)	15.0(22.9)	25.8(30.7)	13.9(25.9)	0.413
Opening mouth	0.0(0.0)	10.0(15.7)	13.6(24.5)	9.7(20.8)	0.589
Dry mouth	20.0(18.3)	33.3(24.2)	39.4(28.4)	30.6(21.8)	0.380
Sticky saliva	20.0(18.3)	21.7(19.6)	30.3(32.4)	18.1(21.9)	0.405
Coughing	20.0(18.3)	18.3(17.0)	16.7(24.7)	12.5(19.2)	0.759
Feeling ill	26.7(14.9)	18.3(20.2)	25.8(25.1)	22.2(25.4)	0.748

NPC: nasopharyngeal carcinoma; AJCC: American Joint Committee on Cancer (AJCC 6th edition); SD: standard deviation; [a] $p < 0.05$.

carcinoma. Van Vulpen et al. (2005) demonstrated that HT plans had a sharper dose gradient compared to the step-and-shoot plans for head and neck cancers. All concluded that HT is expected to be able to reduce the probability of parotid complications further, keeping similar target dose homogeneity. We were further interested in finding out whether or not the dosimetric superiority could translate into clinical benefits. This study was designed in response to this question. We compared SaS-IMRT vs. HT regarding HRQoL parameters for patients with NPC. Further analyses regarding patient survival and local control rates will be performed when we have a greater number of cases with sufficient follow-up times.

Xerostomia is a common late effect for NPC patients after RT. When the RT was performed in the 2D era, bilateral opposed fields allowed the radiation beam to traverse through the major salivary glands (especially the parotid glands), which often received a high radiation dose. Xerostomia affects a patient's speech, taste, deglutition and oral hygiene (Talmi et al., 2002). The RT-induced damage to the parotid gland is usually irreversible (Stephens et al., 1986). Therefore, permanent xerostomia with sticky saliva is a common complaint by NPC patients after RT. The severity can vary from an increased use of liquids with meals to a marked difficulty in swallowing. All side effects can significantly impact a patient's HRQoL. At the present, newly developed RT techniques are more sparing of the parotid glands, and we expect that patients will have fewer complaints

Table 5. Significant parameter estimates for regressions of EORTC QLQ-HN35.

Scale	Pain	Swallowing	Senses	Speech	Social eating	Social contact	Sexuality	Teeth	Opening mouth	Dry mouth	Sticky saliva	Coughing	Feeling ill
	R^2=0.29	R^2=0.22	R^2=0.29	R^2=0.25	R^2=0.30	R^2=0.26	R^2=0.15	R^2=0.26	R^2=0.17	R^2=0.20	R^2=0.19	R^2=0.20	R^2=0.25
Predictors	β(SE)	β(SE)	β(SE)	β(SE)	β(SE)	β(SE)	β(SE)	β(SE)	β(SE)	β(SE)	β(SE)	β(SE)	β(SE)
Age	…	…	…	…	…	…	…	…	…	…	…	…	…
Gender	-9.3(4.2)[a]	…	…	…	…	8.9(4.0)[a]	…	…	…	…	…	…	…
Education	…	…	…	…	-15.3(4.5)[†]	-7.8(3.9)[a]	…	…	…	…	…	…	…
Marital status	…	…	…	…	…	…	…	…	…	…	…	…	…
Annual family income	…	…	…	…	…	…	…	…	…	…	…	…	…
Comorbidity	…	…	…	…	…	…	…	…	…	…	…	-14.0(5.6)[a]	…
AJCC stage	…	…	…	…	…	…	…	…	…	…	…	…	…
RT-technique	…	-14.3(5.0)[†]	-10.8(5.3)[a]	…	…	…	…	…	…	…	…	…	-14.2(6.0)[a]
RT-dose	…	…	…	…	12.4(5.8)[a]	…	…	…	…	…	…	…	…
Chemotherapy	…	…	13.8(5.4)[a]	…	…	…	…	14.7(6.9)[*]	12.1(5.5)[a]	…	…	…	…

AJCC: American Joint Committee on Cancer (AJCC 6th edition); RT: radiotherapy; SE: standard error. β: un-standardized regression coefficient; Comorbidity number was based on Charlson comorbidity index. [a] $p < 0.05$; [†] $p < 0.01$.

regarding xerostomia or sticky saliva. Fang et al.(2007) found that NPC survivors who had received conformal RT had a lower probability of reporting a high level of xerostomia than survivors who had received conventional RT. Our experience with the HT technique showed that the mean parotid gland dose could be significantly reduced from 29.7 Gy as in SaS-IMRT to 21.3 Gy, and that the maximum parotid gland dose could be reduced from 68.7 Gy in SaS-IMRT to 66.4 Gy. Eisbruch et al. (2003) found that reducing the mean parotid gland dose to below 26 Gy causes less xerostomia. This study did not find a difference in xerostomia between the NPC patients treated with either SaS-IMRT or HT, but it did find that the patients who had received HT had a significantly lower probability of high levels of sticky saliva and swallowing difficulties and a marginally yet significantly lower probability of sensation changes by univariate analysis. Despite being the largest pair of salivary glands, the parotid glands only produce approximately 25% of the total saliva. The secretions produced by the parotid glands are serous in nature, and this may partially explain why there was a significant difference in sticky saliva and difficulties swallowing, but not in xerostomia. The difference in the sticky saliva sensation, however, was not significant after further analysis using the multivariate method. The linear regression model showed that the complaints of difficulty swallowing, senses (taste/smell), and feeling ill were significantly lower in patients who had received HT. Both the swallowing and taste are related to salivary gland function, so we can infer that the patients who had received HT had a better HRQoL regarding the symptoms related to xerostomia, although there was no difference in the xerostomia per se. The sense of “feeling ill” is such a non-specific term, but it may be expressed as feeling "something wrong”. In our analysis, we found that patients who had received HT had fewer complaints about this. We could thus infer that they felt more “healthy” compared to the patients who had received SaS-IMRT. This was easily concluded since almost all of the symptoms listed in Table 3 showed lower mean scores in the HT group, and “feeling ill” is a subjective

feeling that could be influenced by any of the symptoms.

Further discussion should be given to the other variables that resulted in significant differences in predicting the head and neck symptoms 6 months after RT. Male patients suffered more pain but fewer problems with social contact than female patients. Our results showed that patients with a higher education level had a better HRQoL, similar to the results of the RTOG study (Movsas et al., 2006). Normally, patients with a higher level of education undertake more social activities and tend to keep their usual activities as consistent as possible. It is reasonable that patients with a higher RT dose or CCRT would suffer more from treatment-related toxicities, so we expected to find that a greater number of these patients would complain of problems with social eating, senses, teeth, and opening mouth. The single inconsistency from our results was that patients with one or more comorbidities had less coughing. We expected patients with one or more comorbidities to have more complaints, including coughing. This unexpected result may have been due to the time delay for our questionnaires, which were administered 6 months after RT. Most of the patients were recovering from acute toxicities, and any residual treatment-related symptoms could have been be masked by the pre-existing symptoms of the comorbidity itself. Oozeer et al. (2008) found that patients with a moderate to severe comorbidity had a significantly worse HRQoL at the start and midpoint of RT, but not at the end of RT.

This study had limitations that should be addressed. First, we only chose one time point for the questionnaire and did not make a longitudinal assessment or have a baseline assessment. Such a design may decrease the probability of getting any statistically significant results. However, we still discovered some useful findings. A further limitation is that hearing is not covered by the HRQoL tools employed. We might have traded swallowing and taste side effects for the preservation of hearing function. According to our prior experience, there was no significant difference in the ear doses between the two methods (Lee et al., 2008). We aim to follow hearing outcomes for this patient population in the near future.

Conclusion

The comparison of HT with the SaS-IMRT technique revealed that HT has potential advantages for the HRQoL of patients regarding swallowing, senses (taste/smell), and feeling ill. A longer follow-up is warranted to assess whether or not the benefits can translate to a decrease in late toxicities without compromising local control or survival outcome.

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