Gross tumor volume determines toxicity and quality of life for patients with nasopharyngeal carcinoma treated by concurrent chemoradiotherapy with simultaneously integrated boost technique

Tai-Lin Huang

Chang Gung Memorial Hospital Kaohsiung Branch

Hui-Ching Chuang

Chang Gung Memorial Hospital Kaohsiung Branch

Chun-Chieh Huang

Chang Gung Memorial Hospital Kaohsiung Branch

Chih-Yen Chien

Chang Gung Memorial Hospital Kaohsiung Branch

Shau-Hsuan Li

Chang Gung Memorial Hospital Kaohsiung Branch

Wen-Ling Tsai

Cheng Shiu University

Tsair-Fwu Lee

National Kaohsiung University of Science and Technology

FU-MIN FANG (✉ ard3779@gmail.com)

Chang Gung Memorial Hospital Kaohsiung Branch <https://orcid.org/0000-0003-0165-771X>

Research

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Abstract

Background: To evaluate the impact of gross tumor volume (GTV) on toxicities and quality of life (QoL) for patients with nasopharyngeal carcinoma (NPC) treated by concurrent chemoradiotherapy with simultaneously integrated boost technique (chemo-SIB-IMRT).

Methods: A total of 278 NPC patients with stage II-IVb treated by chemo-SIB-IMRT were enrolled. Toxicities were evaluated according to CTCAE version 4.03. QoL outcomes (n=219) were measured by using the EORTC QLQ-C30 and HN35 questionnaires at the time point of 12 months after chemo-SIB-IMRT.

Results: A higher GTV was observed to be significantly associated with a higher mean or maximal dose in most organs at risk, together with more severe acute (mucositis, dermatitis, weight loss, and use of analgesic) and late toxicities (xerostomia, neck fibrosis, and radiation neuropathy). A linear regression model revealed that a higher GTV was significantly associated with a decline in role functioning and an increment in taste/smell, speech, social eating, opening mouth, dry mouth, and sticky saliva.

Conclusion: GTV is the determining factor of some acute and late toxicities and QoL scales for NPC patients treated by chemo-SIB-IMRT.

Background

Concurrent chemoradiotherapy (CCRT) has become the standard treatment strategy for patients with locally advanced nasopharyngeal carcinoma (NPC), since the first report of significant survival gain in the intergroup-0099 study [1]. Radiotherapy (RT) techniques for the treatment of nasopharyngeal carcinoma (NPC) have evolved from conventional 2D-RT and 3D conformal RT to intensity-modulated RT (IMRT) in the recent decades. IMRT has become the most commonly employed technique of RT in radical treatment for NPC nowadays. IMRT may be applied in the conventional fractionation scheme as sequential-IMRT, or in a newer fractionation scheme, known as simultaneous integrated boost (SIB-IMRT), which offers the opportunity to treat different targets simultaneously at different dose levels. SIB-IMRT, compared to sequential IMRT, has the advantages of providing a higher dose per fraction to the treatment target and a shorter overall treatment time, and has become the standard fractionation strategy in treating NPC [2-5].

Diseases with a larger tumor burden afford a favorable environment for the proliferation of hypoxic cells and G0 cells and, thus, result in lower radiosensitivity and require larger RT doses to produce a radical cure [6]. Gross tumor volume (GTV) is linearly correlated with tumor burden and is the most direct indicator of tumor burden. Accurate measurement of tumor volume was difficult under conventional 2D-RT but has now become easily available with the advent of SIB-IMRT. Growing studies have reported the influence of GTV on locoregional control and survival for NPC patients [6-8]. However, as far as we know, the impact of GTV on toxicities and quality of life (QoL) for NPC patients has scarcely been studied. In the current study, we evaluated the correlation of GTV with the dosimetric outcome of the organs at risk (OARs) in a cohort of NPC patients treated by concurrent chemoradiotherapy with SIB-IMRT (chemo-SIB-IMRT) and further explored the association of GTV with acute/late toxicities and patients' QoL one year after treatment.

Materials And Methods

Patient characteristics

The eligibility criteria for the patients in this study included if they had a new diagnosis of non-distant metastasis NPC, and were treated by chemo-SIB-IMRT with or without adjuvant chemotherapy in the institute between Jan. 2012 and Dec. 2017. Table 1 lists the socio-demographic and clinical related variables of the 278 patients meeting the inclusion criteria. The median age was 52 (range: 15-87) years. The histology was type II in 98.6% of cases according to the 1991 WHO classification. The comorbidity status was recorded on the Charlson comorbidity index and 44.6% of the patients had one comorbidity at least. The clinical stage was recorded according to American Joint Cancer Committee (AJCC) 7th edition, with the distribution of stage II: 32.4%, stage III: 29.8%, and stage: IVa-b: 37.8%, respectively.

Treatment methods

The details of the SIB-IMRT technique for NPC in the institute have been reported previously [9, 10]. All patients underwent computed tomography (CT)-planned simulation and received the continuous treatment course with one fraction per day and 5 fractions per week. Computerized optimization was used with fusion of MRI with treatment planning CT images, when possible, to accurately delineate the GTV, which included the primary disease and nodes greater than 1 cm in diameter or nodes with necrotic centers. The values of GTV in the study were calculated from the treatment planning system. Three different dose levels of clinical target volumes (CTVs) were created. The high dose level of CTV (CTV-H) was defined as the GTV with an isotropic extension of 5 mm. The middle dose level of CTV (CTV-M) covered the CTV-H plus the areas at risk for microscopic involvement, including the entire nasopharynx, parapharyngeal space, skull base, retropharyngeal lymph nodes, and bilateral upper neck nodes. The low dose level of CTV (CTV-L) included the CTV-M plus bilateral lower neck nodes. To account for organ motion/daily treatment set-up uncertainties, a planning target volume (PTV) was added with additional margin of 3 to 5 mm to each of the CTVs. The prescribed dose and fractionation for PTV-H, PTV-M, and PTV-L were 6996 cGy, 5940 cGy, and 5280 cGy in 33 fractions, respectively. The delineations of the OARs and constrains of the dosage applied to OARs were under the framework of Radiation Therapy Oncology Group (RTOG) 0225 protocol [11].

The planning system Pinnacle³ (version 9.2, Philips) was used. SIB-IMRT was delivered by step-and-shoot (n=153) or dual arc technique (n=125). The step-and-shoot technique was designed basically using seven fixed coplanar gantry beams in most cases, but one or two more beams from non-coplanar directions would be added for those cases with a tumor located near the brain stem or eyeballs, which necessitated a better dose coverage. A collapsed-cone convolution algorithm was used for dose calculations, with a dose grid resolution of 4 mm. The minimum segment area was set to 5 cm², and minimum segment MU was 5 MUs. A direct machine parameter optimization module was adopted for plan optimization. The dual arc technique consisted of dual coplanar arcs of 360° and was simultaneously optimized to be delivered with opposite rotation (clockwise and counter-clockwise). There was a total of 182 control points, with a collimator angle of 10-15°. Continuous gantry motion, dose-rate variation and the motion of multi-leaf

collimators (MLC) were approximated by optimizing individual beams at 2-4° gantry angle increments. The collapsed cone convolution algorithm was used for dose calculations and the SmartArc module was adopted for dose optimization. For both techniques, the beam delivery was generated with 6-MV photons by the Linac machines equipped with dynamic MLC. All treatment plans were evaluated to ensure that 95% of all the PTVs received the prescription dose. The dose volume histograms of PTVs and OARs were quantitatively assessed and the isodose curves on axial CT slices were qualitatively inspected for each plan.

The regimen of concurrent chemotherapy was weekly cisplatin 30 mg/m² administered during SIB-IMRT courses. Adjuvant chemotherapy with cisplatin 70-80 mg/m² on day 1 and 5-fluorouracil 700-800 mg/m²/d on days 1-4 were administered every 3-4 weeks was given for 2-4 cycles to those patients (n=138) with advanced nodal status or persistent elevation of plasma EBV-DNA titer after SIB-IMRT.

Toxicity assessment

The severity of acute toxicities (mucositis, dermatitis, weight loss, use of analgesic, and presence of tube feeding) and late toxicities (xerostomia, dysphagia, otitis media, neck fibrosis, and neuropathy) were retrospectively collected from the medical charts. Acute toxicities were considered peak grade during the period of chemo-SIB-IMRT. The grade of late toxicities was considered as the maximal grade that persisted or occurred during the period from three months after chemo-SIB-IMRT to the date of the last visit. The objective assessment of pain severity was regarded as the strongest analgesic used, which was graded according to the WHO analgesic ladder (0: no analgesic use 1: use of non-narcotic analgesics, 2: use of weak narcotics, 3: use of strong narcotics). The toxicities were graded mainly based on the criteria of Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v.4.03).

QoL assessment

The QoL outcomes were periodically assessed by the Taiwan Chinese versions of EORTC QLQ-C30 and HN35 questionnaires at the following time points: before RT, during RT (about 40 Gy), at 3 months and 12 months after RT, and then annually thereafter in the institute. Data measured at the time point of 12 months after chemo-SIB-IMRT was used for analysis in the study. The questionnaires have been tested in Taiwanese NPC patients and excellent reliability and validity were obtained [12]. The EORTC QLQ-C30 is a widely used questionnaire, incorporating a range of QoL issues relevant to a broad range of cancer patients. It contains five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea/vomiting), a global QoL scale, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) [13]. The HN35 is a module used for assessing the QoL for head-and-neck cancer patients. It incorporates seven multiple-item scales that assess the symptoms of pain in the head and neck, swallowing ability, senses (taste /smell), speech, social eating, social contact, and sexuality. Also included are six single-item scales, which survey the presence of symptomatic problems associated with teeth, mouth-opening, dry mouth, sticky saliva, coughing, and feeling ill [14]. All scales pertaining to the EORTC QLQ-C30 and HN35 range from zero to 100. A high score for a functional or global QoL scale represents a relatively high/healthy level of functioning or global

quality of life, whereas a high score for a symptom scale represents the presence of a symptom or problem(s).

Follow-up

Patients were regularly followed up until death or their last appointment. They were scheduled to visit the clinics at 3 months, and 4- to 6-month intervals in the first two, and third to fifth years, respectively. The median follow-up months were 36.6 months (range, 2 to 83.6 months). Physical and nasopharyngoscopic examinations were routinely performed on every visit. Head and neck MRI scans were performed within 2 months after RT and then annually or when there were clinical indications.

Statistical analysis

The mean scores of QoL scales were calculated according to the EORTC QLQ scoring manual. To deal with the missing data, the missing items were assumed to have values equal to the average of those items that were present for the respondent, if at least half of the items from the scale had been answered (i.e., mean imputation). The Pearson correlation was used to assess the correlation between GTV and the dosimetric values of OARs and the scores of QoL. The Chi-square test was used to assess the associations between category variables. A binary logistic regression model was used to perform the multivariate analysis to evaluate the prognostic factors associated with the outcome of acute and late toxicity, and a linear regression model (backward) was used to explore the prognosticators associated with the scores of the scales of QoL. The cumulative incidence of the occurrence of late toxicity was estimated by using the Kaplan-Meier method. Microsoft SPSS-20.0 was used for data processing, with a p -value <0.05 from the two-sided test regarded to be statistically significant.

Results

GTV and dosimetry of OARs

The mean (SD), median and range of GTV in the study cohort were 84.6 (69.4) ml, 63 ml, and 2-372 ml, respectively. GTV was observed to be significantly and positively correlated with the mean and/or maximal dose of OARs concerned, as revealed in Table 2, including the brain stem, eyeballs, optic nerves, parotid glands, oral cavity, larynx, posterior pharyngeal wall, and cervical esophagus ($p<0.05$, correlation coefficients: 0.227-0.481). The mean dose of parotids was observed to be correlated with GTV with the highest correlation coefficients (right parotid: 0.481, left parotid: 0.472).

GTV and acute toxicity

Almost every patient experienced some degree of acute toxicities, including mucositis, dermatitis, weight loss, or use of analgesic during the treatment period. As shown in Table 3, the distributions of acute toxicities with grade 2 or more were 214 (76.9%) for mucositis, 259 (57.2%) for dermatitis, 78 (28.0%) for weight loss, and 206 (74.1%) for the use of analgesic, respectively. Tube feeding by nasogastric tube or through gastrostomy was observed in 30 patients (10.8%). Entering all the socio-demographic and clinical

variables simultaneously with each of the five dependent variables of acute toxicities at a time into the binary logistic regression models, we found that GTV was significantly associated with four acute toxicities (mucositis, dermatitis, weight loss, and use of analgesic). Compared with the counterpart, those with GTV>63ml (median value) had a higher probability of acute toxicities, with a difference of 2.6-fold (95% CI: 1.3–5.1) in mucositis $\geq$ grade 2, 7.2-fold (95% CI: 3.8–13.6) in dermatitis $\geq$ grade 2, 1.7-fold (95% CI: 1.1–3.1) in weight loss $\geq$ grade 2, and 4.3-fold (95% CI: 1.6–12.1) in use of analgesic $\geq$ grade 2 (Table 4). In contrast, those with T3-4 classification were observed to have a higher probability of mucositis $\geq$ grade 2, with a difference of 3.0-fold (95% CI: 1.1–8.3) compared with those with T1-2; those with N2-3 classification were observed to have a higher probability of dermatitis $\geq$ grade 2, with a difference of 2.0-fold (95% CI: 1.0–3.8) compared with those with N0-1.

GTV and late toxicity

Xerostomia, dysphagia, otitis media, and neck fibrosis were the common late toxicities concerned. The distributions of the four late toxicities with grade 2 or more were 78 (28.4%) for xerostomia, 53 (19.0%) for dysphagia, 82 (29.5%) for otitis media, and 9 (3.2%) for neck fibrosis. In addition, radiation neuropathy was also observed in 15 (5.4%) patients, including temporal lobe necrosis in 10 (3.6%) patients, and cranial nerve palsy in five (1.8%) patients (four hypoglossal nerve palsy and one optic neuropathy). All radiation neuropathy was mild and did not interfere in the activities of patients' daily life (grade 1). The 5-year cumulative incidence of developing at least one of the five late toxicities with grade 3 or more was 7.8%. Entering all the socio-demographic and clinical variables simultaneously with each of the five dependent variables of late toxicities at a time into the binary logistic regression models, we found that GTV was significantly associated with three late toxicities (xerostomia, neck fibrosis, and radiation neuropathy). Compared with the counterpart, those with GTV>63ml had a higher probability of late toxicities, with a difference of 2.2-fold (95% CI: 1.2–4.1) in xerostomia $\geq$ grade 2, 2.4-fold (95% CI: 1.2–4.3) in neck fibrosis $\geq$ grade 1, and 8.9-fold (95% CI: 2.1–16.6) in radiation neuropathy $\geq$ grade 1 (Table 5). In contrast, those with age>52 years (median value) were observed to have a higher probability of xerostomia $\geq$ grade 2, with a difference of 1.8-fold (95% CI: 1.1–3.8) compared with those with age $\leq$ 52 years; those with N2-3 classification were observed to have a higher probability of neck fibrosis $\geq$ grade 1, with a difference of 1.5-fold (95% CI: 1.0–3.0) compared with those with N0-1; and those with T3-4 classification were observed to have a higher probability of radiation neuropathy $\geq$ grade 1, with a difference of 1.9-fold (95% CI: 1.0–4.0) compared with those with T1-2.

GTV and QoL

The mean scores of each QoL scale for those (n=218) who completed the QoL questionnaires at the time point of 12 months after chemo-SIB-IMRT are shown in Table 6. GTV was observed to be significantly negatively correlated with role functioning (p=0.007, correlation coefficients: -0.232) and positively correlated with symptom scales, including dyspnea, constipation, sense (taste/smell), speech, social eating, opening mouth, dry mouth, and sticky saliva (p<0.05, correlation coefficients: 0.176-0.369). Adjusting the socio-demographic and clinical variables into a linear regression model, we observed a 10 ml increase of GTV was statistically significantly associated with a 6.3% (95% CI, 1.7% to 10.9%) decline in the score of

role functioning, and a 5.7% (95% CI, 0.8% to 5.7%) increment in dyspnea, 7.4% (95% CI, 0.2% to 14.7%) increment in constipation, 15.2% (95% CI, 8.5% to 21.8%) increment in sense (taste/smell), 10.0% (95% CI, 5.3% to 14.7%) increment in speech, 8.3% (95% CI, 3.1% to 13.5%) increment in social eating, 9.6% (95% CI, 2.5% to 16.8%) increment in opening mouth, 12.5% (95% CI, 4.2% to 20.9%) increment in dry mouth, and 17.8% (95% CI, 9.6% to 26.0%) increment in sticky saliva, respectively (Table 7).

Discussion

The dosimetry of OARs is usually tumor site and volume dependent. It has been reported that the tumor site is a prognostic factor for morbidities and QoL for patients after receiving head and neck irradiation by conventional 2D-RT [15]. Unlike other head and neck cancer, NPC usually presents with high propensity of tumor infiltration into the skull base and bilateral neck lymph nodes; thus, elective irradiation with large fields from the level of the skull base to the infra-clavicular nodal area is mandatory, even in patients with an early clinical stage. Using SIB-IMRT composed of three fixed dose levels, with a higher dose per fraction to GTV and two lower doses to cover the uniform subclinical or elective anatomic sites, we observed the major differences of dose-volume received by OARs in NPC patients depending on the GTV. GTV was observed to be significantly and positively correlated with the mean and/or maximal dose in most OARs concerned. Furthermore, as far as we know from the literature, this is the first report to show GTV to be the determining variable for acute/late toxicity and QoL of NPC patients treated by SIB-IMRT combined with chemotherapy.

The location and size of the primary tumor, lymph node staging, tumor laterality, treatment techniques, and anatomical changes during treatment have all been shown to be significant factors in terms of the actual dose received by OARs [16]. Mucositis is common for NPC patients receiving chemo-RT. The problems associated with mucositis include oral pain, odynophagia, impaired taste, and weight loss. Mucositis was known to have a dose-effect relation with RT; however, the ability of clinical or dosimetric parameters in predicting severe mucositis was still controversial, using IMRT technique [17, 18]. In the study of Li et al [19], weight loss and V30Gy predict severe oral mucositis in NPC patients treated by concurrent chemo-IMRT. In contrast, the mean dose in the oral cavity was found to impact the duration of oral mucositis by Orlandi et al [20]. In treating NPC, the oral cavity was usually outside the CTV fields, but its mean dose still ranges 35-42 Gy using the IMRT or VMAT technique [21-23]. Without using the detailed dosimetric analysis for oral mucositis in current study, we observed GTV positively correlated with the mean dose in the oral cavity and was predictive of mucositis and its related problems, e.g. weight loss and analgesia used.

Xerostomia remains one of the most common late toxicities for NPC patients treated by chemo-SIB-IMRT. The severity of xerostomia is largely dependent on the dose/volume in the salivary gland in the radiation field [24, 25]. The incidence of grade 2 or greater xerostomia in our cohort was 28.4%, which was higher than that reported in the literature [11, 21]. The parotid mean dose was around 30 Gy in the study, which is compatible with other reports [26, 27]. We observed the mean dose in the parotids most significantly correlated with GTV. This is mainly due to the major overlap of the PTV with the deep lobes of the parotids. An overzealous effort in sparing the parotids can result in the under-dosing of part of the GTV which is at risk for local recurrence, especially in those with parapharyngeal space invasion or upper neck lymph node

enlargement. Growing reports have demonstrated there is no direct dose-effect relationship between the parotid dose and xerostomia for NPC patients [28, 29]. The reasons might be that the parotid dose revealed in the pre-treatment plan was different from the actual dose received because of the positional change of the gland during the treatment process and the mean dose of parotid in most NPC patients beyond the dose constraints recommended from the QUANTEC guideline [30, 31]. In contrast, GTV was observed to be predictive of xerostomia in our study. In this scenario, the other major salivary glands, the submandibular glands, were taken into consideration because they were usually exposed to high-dose irradiation if large nodes existed at level II.

Progressive neck fibrosis, which might compromise neck movement and increases the risk of vasculopathy of the carotid artery or neuropathy, was common in NPC patients treated by conventional 2D-RT but has been markedly reduced by IMRT.³² The incidence of symptomatic neck fibrosis and cranial neuropathy was 3.2% and 1.8%, respectively, in our series, which is compatible with other reports [33, 34]. However, our patients with larger GTV beneath the sternocleidomastoid muscle still had a significantly higher risk of suffering from progressive neck fibrosis.

The determinants of radiation neuropathy in previous reports included T classification, total RT dose, fraction size, overall treatment time, receiving chemotherapy, and GTV. In these studies, the patients analyzed underwent heterogeneous RT techniques, varying from conventional 2D-RT, 3D conformal RT, to IMRT [34-36]. In contrast, with a consistent technique of SIB-IMRT in our series, we observed the pre-treatment variable of advanced T classification and larger GTV were significantly associated with the occurrence of radiation neuropathy.

Socio-demographic variables and RT techniques were observed to be the determinants of post-treatment QoL outcome for NPC patients in the literature [15, 37, 38]. Most of the reports were in cohorts either treated by conventional 2D-RT or a mixture of different RT techniques. Huguenin et al. observed that head and neck cancer patients with large target volumes (e.g. NPC) treated by 2D-RT suffered from more QoL problems, including dry mouth, sticky saliva, trismus, problems with teeth, and trouble eating, than those with small target volumes (e.g. glottis ca) [15]. They also observed that these symptoms did not have a high impact on global QoL or functional scales on the QLQ-C30 core questionnaire. In the current study, we also observed NPC patients with a large GTV had more symptom problems, including dyspnea, constipation, taste/smell, speech, social eating, opening mouth, dry mouth, and sticky saliva. Meanwhile, global QoL and most functional scales (except for role functioning) were not observed to be significantly correlated with GTV in our study.

There are growing reports supporting the therapeutic benefits in dosimetry, tumor control and QoL for NPC patients if re-planning could be conducted either for patients with GTV reduction or the geometric change of OARs during the treatment course of SIB-IMRT [39, 40]. Using SIB-IMRT techniques, the major benefit of re-planning, especially for those without significant body shape change, is to reduce the GTV during the treatment course, which might potentially reduce the dose to the OARs. In the study by Yang et al. [39], the authors reported NPC patients treated by SIB-IMRT would have better QoL in global QoL, role and social

functioning and some symptom scales if re-planning was done. We believe our study could echo the need for re-planning, especially for those with GTV reduction during the course of SIB-IMRT in NPC patients.

It should be noted that there are some limitations in the study. First, as mentioned above, geometric changes of GTV and OARs during treatment were not determined and the actual dose received might have varied from the dose shown on the pre-treatment plans. Second, it was difficult to determine whether the toxicities measured were the result of RT, chemotherapy or both, or the result of the existing cancer.

In conclusion, for NPC patients treated by chemo-SIB-IMRT, we observed GTV was significantly associated with mean or maximal dose in most OARs concerned, and patients with higher GTV presented with more severe acute and late toxicities and more symptomatic problems as measured by QoL scales.

List Of Abbreviations

GTV: gross tumor volume; QoL: quality of life; NPC: nasopharyngeal carcinoma; chemo-SIB-IMRT: concurrent chemoradiotherapy with simultaneously integrated boost technique; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30 and HN35 module: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Head and Neck 35-questions; CCRT: concurrent chemoradiotherapy; RT: radiotherapy; 2D-RT: two-dimensional radiotherapy; IMRT: intensity-modulated radiotherapy; OARs: organs at risk; GTV: gross tumor volume; CTV: clinical target volume; PTV: planning target volume; RTOG: Radiation Therapy Oncology Group; MLCs: multi-leaf collimators.

Declarations

Ethics approval and consent to participate: This study obtained ethics approval from the Institutional review board/ Ethics committee (No. 201700085B0) of Kaohsiung Chang Gung Memorial Hospital.

Consent for publication: not applicable

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Competing interests: The authors declare that they have no competing interests.

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Author's contributions: TLH collected and interpreted the data, and was the major contributor in writing the manuscript. FMF conceived of the study and its design, supervised its conduct, carried out target delineation, and helped draft the manuscript.

WLT and TFL assisted statistical analyses and interpretations of the data. HCC, CCH, CYC, and SHL participated in recruitment of subjects and assisted in drafting of the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Patient characteristics

Table 1. Patient characteristics

SIB-IMRT: simultaneously integrated boost intensity modulated radiotherapy; AJCC: American Joint Cancer Committee (AJCC) 7th edition

Table 2. Correlations of gross tumor volume with the dosimetric values of the organs at risk (n=278)

	N	%	
Age, median (range) years	52	(15-87)	
Gender			
Male	198	71.2	
Female	80	28.8	SD: standard deviation
Education years			
≤12	68	24.5	
>12	210	75.5	Table 3. Frequency of acute and late toxicities (n=278)
Marital status			*Graded according to the CTCAE Version 4.03.
Without spouse	75	27.0	
With spouse	203	73.0	‡ Based on WHO analgesic ladder: 0: no analgesic use; 1:
Smoking history			use of non-narcotic analgesics; 2: use of weak narcotics; 3:
No	156	56.1	use of strong narcotics.
Yes	122	43.9	
Body mass index, median (range) Kg/m ²	24.9	(14.0-42.8)	
Charlson comorbidity index			\$Tube feeding: 0: no tube feeding; 1: feeding with
0	154	55.4	nasogastric tube or through gastrostomy.
≥1	124	44.6	
WHO histology			
Type 1	4	1.4	
Type IIA	125	45.0	
Type IIB	149	53.6	Table 4. Logistic regression model of variables associated
Gross tumor volume, median (range) ml	63	(2-372)	with variables of acute toxicities (n=278)
AJCC stage			
II	90	32.4	
III	83	29.8	Graded according to the CTCAE Version 4.03; Analgesic use
IVa-b	105	37.8	was based on WHO analgesic ladder: 0: no analgesic use, 1:
T classification			use of non-narcotic analgesics, 2: use of weak narcotics, 3:
T1-T2	171	61.5	use of strong narcotics; Tube feeding: 0: no tube feeding; 1:
T3-T4	107	38.5	feeding with nasogastric tube or through gastrostomy.
N classification			
N0-N1	136	48.9	
N2-N3	142	51.1	
SIB-IMRT			
Step-and-shoot	153	55.0	
Dual arc	125	45.0	Table 5. Logistic regression model of variables associated
Chemotherapy			with variables of late toxicities (n=278)
Concurrent	243	87.4	
Adjuvant	138	49.6	Graded according to the CTCAE Version 4.03

Variables	Mean (SD)	Correlation coefficient	P value	
Brain stem, maximum	5094 (418)	0.295	<0.001	Table 6. Correlation of gross tumor volume with the mean scores of quality of life measured at one year after treatment (n=219)
Spinal cord, maximum	4059 (241)	0.115	0.058	
Right eyeball, mean	827 (333)	0.241	<0.001	
Left eyeball, mean	825 (265)	0.275	<0.001	
Right optic nerve, maximum	5212 (1512)	0.274	<0.001	
Left optic nerve, maximum	5002 (1448)	0.289	<0.001	
Right parotid, mean	3013 (479)	0.481	<0.001	
Left parotid, mean	3026 (474)	0.472	<0.001	
Oral cavity, mean	3735 (450)	0.256	<0.001	
Larynx, mean	3850 (473)	0.304	<0.001	
Posterior pharyngeal wall	3547 (376)	0.278	<0.001	
Cervical esophagus, mean	3248 (475)	0.258	<0.001	

	Grade 0	N (%)	Grade 1	N (%)	Grade 2	N (%)	Grade 3	N (%)	Grade 4	N (%)
Acute toxicity										
Mucositis*	0	(0)	64	(23)	175	(62.9)	39	(14.0)	0	(0)
Dermatitis*	0	(0)	118	(42.8)	147	(52.9)	12	(4.3)	0	(0)
Weight loss*	74	(26.6)	124	(45.3)	74	(26.6)	4	(1.4)	0	(0)
Analgesic use‡	8	(2.9)	64	(23.0)	136	(48.9)	70	(25.2)	-	
Tube feeding§	248	(89.2)	30	(10.8)	-		-		-	
Late toxicity*										
Xerostomia	73	(26.3)	126	(45.8)	79	(28.4)	0	(0)	0	(0)
Dysphagia	136	(48.9)	89	(32.0)	51	(18.3)	2	(0.7)	0	(0)
Otitis media	111	(39.9)	85	(30.6)	81	(29.1)	1	(0.4)	0	(0)
Neck fibrosis	195	(70.1)	74	(26.6)	7	(2.5)	2	(0.7)	0	(0)
Radiation neuropathy										
Temporal lobe necrosis	268	(96.4)	10	(3.6)	0	(0)	0	(0)	0	(0)
Cranial nerve palsy	273	(98.2)	5	(1.8)	0	(0)	0	(0)	0	(0)

	Mucositis $\geq$ Grade 2		Dermatitis $\geq$ Grade 2		Weight loss $\geq$ Grade 2		Analgesic use $\geq$ Grade 2		Tube feeding $\geq$ Grade 1	
	OR (CI)	p	OR (CI)	p	OR (CI)	p	OR (CI)	p	OR (CI)	p
Socio-demographic variable										
Age: ≤ 52 v 52 years	0.8 (0.4-1.5)	0.49	1.2 (0.7-2.3)	0.49	0.7 (0.4-1.3)	0.26	1.1 (0.6-2.2)	0.71	1.3 (0.5-3.1)	0.60
Gender: female v male	1.2 (0.6-2.4)	0.66	0.9 (0.5-1.8)	0.84	0.7 (0.4-1.4)	0.40	0.8 (0.4-1.6)	0.57	1.5 (0.5-4.5)	0.51
Education years: ≤ 12 v >12	0.9 (0.4-1.9)	0.83	1.8 (0.9-3.6)	0.10	1.2 (0.60-2.3)	0.66	0.6 (0.3-1.2)	0.17	1.6 (0.6-4.3)	0.40
Smoking: no v yes	0.9 (0.4-1.8)	0.14	0.8 (0.4-1.6)	0.61	1.0 (0.6-1.9)	0.92	1.3 (0.6-2.5)	0.52	2.0 (0.8-4.9)	0.14
Body mass index: ≤ 24.9 v >24.9	1.6 (0.8-2.9)	0.44	1.2 (0.7-2.1)	0.55	1.1 (0.6-1.9)	0.70	1.8 (0.9-3.3)	0.08	1.2 (0.5-2.7)	0.63
Clinical variable										
Charlson comorbidity index :0 v ≥ 1	1.3 (0.7-2.4)	0.44	1.0 (0.6-1.9)	0.90	1.0 (0.5-1.7)	0.90	0.9 (0.5-1.7)	0.82	0.6 (0.3-1.4)	0.27
AJCC stage: stage II v III- IV	0.4 (0.1-1.7)	0.23	0.9 (0.3-2.8)	0.80	1.0 (0.3-3.1)	0.99	0.3 (0.1-1.1)	0.07	1.0 (0.2-5.0)	0.96
T classification : T1-2 v T3-4	3.0 (1.1-8.3)	0.03	0.5 (0.2-1.2)	0.15	1.8 (0.8-3.7)	0.13	2.0 (0.7-5.8)	0.18	2.9 (0.9-9.0)	0.09
N classification : N0-1 v N2-3	1.9 (0.6-6.1)	0.25	2.0 (1.0-3.8)	0.04	1.0 (0.4-2.2)	0.93	1.5 (0.6-4.8)	0.14	1.2 (0.4-3.6)	0.78
Gross tumor volume : ≤ 63 v >63 ml	2.6 (1.3-5.1)	0.005	7.2 (3.8-13.6)	0.001	1.7 (1.1-3.1)	0.02	4.3 (1.6-12.1)	0.01	1.2 (0.8-2.3)	0.10
RT technique: step-and-shoot v Dual arc	0.7 (0.4-1.2)	0.19	0.6 (0.3-1.0)	0.06	0.8 (0.5-1.4)	0.47	0.6 (0.3-1.1)	0.09	1.5 (0.7-3.3)	0.35
Adjuvant chemotherapy: no v yes	0.9 (0.4-1.9)	0.80	1.8 (0.8-3.5)	0.10	1.3 (0.6-2.5)	0.50	1.8 (0.9-3.7)	0.08	0.8 (0.3-2.2)	0.71

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30-questions; EORTC QLQ-H&N35: European Organization for Research and Treatment of Cancer Quality of Life Head and Neck module; SD: standard deviation

Table 7. Linear regression models of variables associated with scales of quality of life (n=219)

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30-

	Xerostomia $\geq$ Grade 2		Dysphagia $\geq$ Grade 2		Otitis media $\geq$ Grade 2		Neck fibrosis $\geq$ Grade 1		Radiation neuropathy $\geq$ Grade 1	
	OR (CI)	p	OR (CI)	p	OR (CI)	p	OR (CI)	p	OR (CI)	p
Socio-demographic variable										
Age: $\leq$ 52 v 52 years	1.8 (1.1-3.8)	0.02	1.6 (0.8-3.2)	0.22	0.9 (0.5-1.7)	0.79	0.9 (0.5-1.7)	0.85	1.1 (0.3-4.3)	0.88
Gender: female v male	0.8 (0.4-1.5)	0.42	1.0 (0.4-2.1)	0.94	0.6 (0.2-1.6)	0.11	1.2 (0.6-2.4)	0.54	2.0 (0.3-1.6)	0.45
Education years: $\leq$ 12 v >12	1.2 (0.6-2.5)	0.53	0.4 (0.1-1.1)	0.07	0.8 (0.4-1.6)	0.53	0.7 (0.4-1.3)	0.28	1.2 (0.2-6.2)	0.83
Smoking: no v yes	1.0 (0.5-1.8)	0.92	1.0 (0.5-1.9)	0.93	0.8 (0.3-1.7)	0.64	1.1 (0.6-1.8)	0.84	1.1 (0.3-4.4)	0.86
Body mass index: $\leq$ 24.9 v >24.9	1.4 (0.8-2.5)	0.21	1.9 (0.9-3.6)	0.61	0.9 (0.5-1.6)	0.73	1.2 (0.7-2.0)	0.62	2.5 (0.7-8.5)	0.15
Clinical variable										
Charlson comorbidity index :0 v $\geq$ 1	1.2 (0.7-2.2)	0.51	1.7 (0.8-3.4)	0.11	1.2 (0.7-2.2)	0.49	1.5 (0.5-4.5)	0.48	1.2 (0.3-4.3)	0.78
AJCC stage: stage II v III- IV	2.9 (1.0-8.8)	0.06	1.6 (0.4-5.9)	0.49	2.0 (0.6-6.1)	0.22	0.7 (0.3-1.5)	0.39	1.1 (0.4-5.1)	0.77
T classification : T1-2 v T3-4	0.6 (0.3-1.3)	0.19	0.6 (0.2-1.5)	0.24	1.0 (0.5-2.2)	0.96	1.1 (0.4-2.6)	0.89	1.9 (1.0-4.0)	0.03
N classification : N0-1 v N2-3	0.6 (0.2-1.4)	0.24	0.4 (0.1-1.2)	0.10	1.0 (0.4-2.5)	0.99	1.5 (1.0-3.0)	0.03	0.3 (0.6-1.3)	0.98
Gross tumor volume : $\leq$ 63 v >63 ml	2.2 (1.2-4.1)	0.01	1.7 (0.9-3.6)	0.12	2.1 (0.9-3.1)	0.07	2.4 (1.2-4.3)	0.02	8.9 (2.1-16.6)	0.008
RT technique: step-and-shoot v Dual arc	0.9 (0.5-1.8)	0.66	0.4 (0.2-1.2)	0.21	0.8 (0.5-2.1)	0.10	0.8 (0.4-1.5)	0.47	0.3 (0.1-1.2)	0.11
Adjuvant chemotherapy: no v yes	0.8 (0.4-1.6)	0.57	0.7 (0.4-1.6)	0.51	1.1 (0.5-2.1)	0.86	1.4 (0.7-2.8)	0.30	1.1 (0.5-2.7)	0.20

questions; EORTC QLQ-H&N35: European Organization for Research and Treatment of Cancer Quality of Life Head and Neck module; GTV: gross tumor volume

Variables	Mean (SD)	Correlation coefficient	<i>P</i> value
EORTC QLQ-C30			
Global quality of life	67.1 (18.0)	-0.062	0.485
Physical functioning	91.6 (9.8)	-0.066	0.453
Role functioning	93.7 (13.2)	-0.232	0.007
Emotional functioning	86.6 (13.9)	0.029	0.744
Cognitive functioning	85.1 (14.5)	-0.065	0.456
Social functioning	84.2 (18.3)	-0.074	0.399
Fatigue	22.2 (16.9)	-0.001	0.990
Nausea/Vomiting	4.4 (10.4)	0.137	0.116
Pain	12.4 (16.5)	0.030	0.734
Dyspnea	6.8 (14.1)	0.172	0.053
Insomnia	22.3 (23.5)	-0.093	0.289
Appetite loss	11.4 (20.6)	0.123	0.164
Constipation	14.4 (20.7)	0.160	0.058
Diarrhea	6.7 (13.4)	0.025	0.082
Financial problems	17.3 (23.1)	0.121	0.168
EORTC QLQ-HN35			
Pain	9.1 (11.9)	0.092	0.295
Swallowing	14.2 (14.5)	0.136	0.120
Senses (taste/smell)	18.4 (20.0)	0.369	<0.001
Speech	10.7 (14.0)	0.345	<0.001
Social eating	11.0 (15.0)	0.287	0.001
Social contact	5.3 (9.8)	0.117	0.181
Sexuality	21.7 (25.3)	0.053	0.555
Teeth	26.5 (23.6)	0.067	0.448
Opening mouth	13.9 (20.6)	0.229	0.009
Dry mouth	43.7 (24.1)	0.253	0.003
Sticky saliva	31.8 (23.8)	0.356	<0.001
Coughing	21.0 (22.6)	0.087	0.324
Feeling ill	17.5 (21.2)	0.126	0.150

Quality of life	Variables	β	95% CI	<i>P</i> value
EORTC QLQ-C30				
Role functioning	GTV	-0.063	-0.109--0.017	0.007
EORTC QLQ-HN35				
Senses (taste/smell)	GTV	0.152	0.085-0.218	<0.001
Speech	GTV	0.100	0.053-0.147	<0.001
Social eating	GTV	0.083	0.031-0.135	0.002
	T stage (T3-4 v T1-2)	5.528	0.314-10.743	0.038
	Age	0.240	0.041-0.439	0.018
Opening mouth	GTV	0.096	0.025-0.168	0.009
Dry mouth	GTV	0.125	0.042-0.209	0.003
Sticky saliva	GTV	0.178	0.096-0.260	<0.001