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Model Parameters Estimating on Lyman–Kutcher–Burman Normal Tissue Complication Probability for Xerostomia on Head and Neck Cancer

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***Abstract*—**The purpose of this study is to derive parameters estimating for the Lyman–Kutcher–Burman (LKB) normal tissue complication probability (NTCP) model using analysis of scintigraphy assessments and quality of life (QoL) measurement questionnaires for the parotid gland (xerostomia). In total, 31 patients with head-and-neck (HN) cancer were enrolled. Salivary excretion factor (SEF) and EORTC QLQ-H&N35 questionnaires datasets are used for the NTCP modeling to describe the incidence of grade 4 xerostomia. Assuming that n= 1, NTCP fitted parameters are given as TD_{50}= 43.6 Gy, m= 0.18 in SEF analysis, and as TD_{50}= 44.1 Gy, m= 0.11 in QoL measurements, respectively. SEF and QoL datasets can validate the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) guidelines well, resulting in NPV's of 100% for the both datasets and suggests that the QUANTEC 25/20Gy gland-spared guidelines are suitable for clinical used for the HN cohort to effectively avoid xerostomia.

***Keywords*—**HN, NTCP, SEF, QoL, QUANTEC

I. Introduction

HEAD and neck (HN) cancer is a one of the leading causes of cancer mortality in Taiwan. Radiotherapy (RT) plays an important role in the treatment of HN cancer. Xerostomia is a common complication that occurs after RT for patients with HN cancer. Severe xerostomia is defined as long-term salivary function compared to the pre-RT baseline which based-on the Late Effects of Normal Tissues–Subjective, Objective, Management, Analytic (LENT-SOMA) criteria.

Whole-mouth salivary function has been shown to relate to quality of life (QoL) measurement questionnaires [1-2], and has been used in clinical oncology trials to compare different treatment strategies. In this prospective study, we longitudinally observed the parotid glands function by using salivary scintigraphy in patients receiving intensity modulated radiotherapy (IMRT).

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The normal tissue complication probability (NTCP) model proposed by Lyman will be used to determine the TD_{50} of parotid gland in local patients [3-4]. Moreover, patients-reported QoL questionnaire (QLQ-C30) and xerostomia-specific questionnaire (QLQ-H&N35) were given to patients before RT and periodically after therapy to assess their interrelationships with salivary function. NTCP fitted parameters are investigated for the local patients by the two datasets.

The Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC), a recent concerted effort in radiotherapy community, which reviewed and summarized normal tissue toxicity, and might suggest dose–volume treatment planning guidelines likely to be reduced the rates of side effects. QUANTEC guideline to limit the probability of severe xerostomia fit these criteria are: at least one parotid gland should receive ≤20Gy mean dose, or both parotid glands should receive ≤25Gy mean dose [5-6]. Therefore, we also perform a validation test of these QUANTEC guidelines against prospectively collected QoL datasets and salivary scintigraphic assessments in this study.

II. Methods and Materials

A. Study Population

A total numbers of 31 HN cancer patients who treated with IMRT at the Chiayi Chang Gung Memorial Hospital of the Chang Gung Medical Foundation, between May 2007 and Oct 2010 were used. The characteristics of patients are listed in Table I. Patients with successful salivary flow scintigraphy imaging and completion of QoL questionnaires before and at 1-year after treatment were analyzed. This study was approved by the institutional review board of the hospital (IRB-95-1430B).

B. Treatment Techniques

Patients were immobilized from head to shoulders using commercially available thermoplastic masks and/or an individually customized bite block. Computed tomography (CT) images (2.5-mm slice thickness) acquired from the top of the vertex to the level of the carina, containing 512×512 pixels in each slice, were used. Both parotid glands were delineated by a radiation oncologist. The dose distributions were calculated and separate dose–volume histograms (DVHs) were generated for both parotid glands, and enabled the analysis of each gland separately. IMRT treatment mode was used in a simultaneous integrated boost (SIB) treatment method [7].

IMRT was delivered by the computer-controlled auto-sequencing segmented or dynamic multileaf collimator of a linear accelerator (Varian Clinac 21 EX or Elekta Precise) aiming to spare parotid glands (predominantly contralateral side), while treating the primary targets and lymph node at risks. The prescribed doses were 67.4 to 70.8 Gy (mean dose 69.8 Gy) to the macroscopic tumor planning target volume (PTV1), 54.8 to 70.8 Gy (mean dose 62.0 Gy) to the resected tumor bed planning target volume (PTV2), and 46.8 Gy to the subclinical disease planning target volume (PTV3), at 1.8 to 2 Gy per fraction.

Based-on the RTOG 0514, 0615 and 0225, the planning objectives for PTVs were at a minimum dose >95% and, no more than 5% of any PTV1 received ≥110% of the prescribed dose. The structural constraints used were parotid gland mean dose ≤26 Gy or V_{30Gy}≤50%; oral cavity excluding PTV—mean dose must be ≤40 Gy. Parotid gland mean DVH values for all patients were calculated. All data were based on the mean DVHs obtained from Pinnacle$^{3®}$ with a bin size resolution of 0.01 Gy. The resolution of dose calculation was 2.5 mm for all IMRT plans.

C. Salivery Gland Scintigraphy

All patients received salivary scintigraphy. The patients had stimulated whole-mouth saliva collected before radiotherapy as well as various time intervals; for the purposes of this analysis, the 1-year follow-up time point (n = 31) was used. The study was performed after a 4 hours fasting. Patients then received intravenous injections of 10 mCi $_{99m}$Tc pertechnetate. The sequential images of 1 min/frame were acquired for 30 minutes over the left- and right-anterior views of the head and neck. The major salivary glands function was represented by the saliva excretion after sialogogue stimulation with acidic material. Salivary excretion factor (SEF) was quantified by determination of the maximal excretion activity per gland as a function of the maximal uptake. The parotid function was evaluated by salivary scintigraphy before, 1 year after radiotherapy, which measured the salivary excretion fraction (SEF) of the parotid gland. Salivary flow ≤45% compared with pre-RT was defined with complication of grade 4 xerostomia based-on the LENT-SOMA criteria [8] .

TABLE I
PATIENTS AND TUMOR CHARACTERISTICS

Characteristic	Value- *n*(%)
Age (y)	
Mean	53
Range	28-78
Gender (n)	
Female	1 (3.2
Male	30 (96.8)
Tumor site	
NPC	11 (35.5)
Oral cavity	14 (45.2)
Oropharynx	4 (12.9)
Larynx	1 (3.2)
Parotid	1 (3.2)
Stage (TNM staging system)	
T1	3 (9.7)
T2	12 (38.7)
T3	6 (19.4)
T4	7 (22.6)
Not applicable/Recurrent	3 (9.6)
N0	16 (51.7)
N1	5 (16.1)
N2	7 (22.6)
N3	0 (0.0)
Not applicable/Recurrent	3 (9.6)
Dose, Gy/# fractions	
	14 (45.2) 69.2/38
	1 (3.2) 54.8/30
	9 (29.1) 59.4/33
	4 (12.9) 57.6/32
	1 (3.2) 68.4/38
	1 (3.2) 70/35
	1 (3.2) 52.2/29
Surgery before RT	
Yes	16 (51.6)
No	15 (48.4)
Chemotherapy	
Yes	19 (61.3)
No	12 (38.7)
SEF recovery*	
Grade 4 xerostomia	10 (16.1)
No grade 4 xerostomia	52 (83.9)
QoL measurement*	
Grade 4 xerostomia	6 (19.4)
No grade 4 xerostomia	25 (80.6)

*SEF recovery and QoL measurement was at 1-year after RT.
Abbreviation: RT: radiotherapy; SEF: Salivary excretion factor; QoL: quality of life;

D. NTCP Modeling

The data were fit into the Lyman-Kutcher-Burman (LKB) NTCP model [3-4]. The model is to quantitatively assess the effects of both the radiation dose and the volume of the gland irradiated on the probability of radiation-induced changes in parotid gland function. Three parameters are presented in the sigmoid dose-response curve: n, m, and TD_{50}. The parameter n accounts for the volume effect of an organ, n is set to 1 in this study. The parameter m describes the slope of the dose–response curve. The TD_{50} is the dose resulting in a 50% probability of a complication for uniform irradiation of the whole partial volume. The model used is described as follows,

$$NTCP = \frac{1}{\sqrt{2}} \int_{-\infty}^{t} e^{-\frac{x^2}{2}} dx \quad (1)$$

$$t = \frac{D_{eff} - TD_{50}}{m \cdot TD_{50}} \quad (2)$$

$$D_{eff} = (\sum_i v_i D_i^{1/n})^n \quad (3)$$

Where D_{eff} is the equivalent uniform dose that, the original definition of the D_{eff} was derived on the basis of a mechanistic formulation using a linear-quadratic cell survival model, when n = 1, the D_{eff} reduces to an expression for mean organ dose.

E. QoL Evaluation

The traditional Chinese versions of the EORTC QLQ-H&N35 questionnaire was obtained from the Quality of Life Unit, EORTC Data Center in Brussels, Belgium [9-10].

And a prospective survey of QoL using the EORTC QLQ-H&N35 questionnaire was performed. The definition of grade 4 xerostomia was defined as moderate to severe xerostomia at 1-year after completion of radiotherapy. This pointed out the xerostomia induced by primarily radiation treatment itself. For the purposes of this analysis, the 1-year (n= 31) follow-up time point was used. All scales pertaining to the EORTC QLQ-H&N35 ranged from 0 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 problems [11-12].

F. Statistical analyses

The negative predictive value (NPV) is checked for the rate of correctly predicting the lack of xerostomia for the validation of QUANTEC constraints. Pearson's chi-square test was used to test the goodness of fit and test of association. The value higher than 0.05 criteria is said as statistical significance.

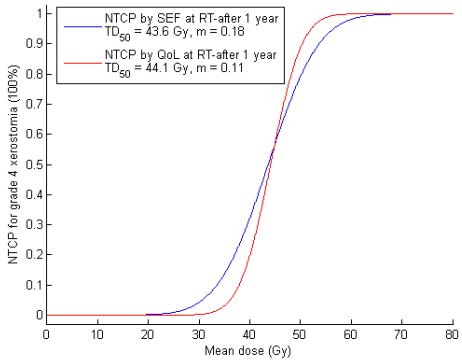

Fig. 1 The fitted incidence of grade 4 xerostomia, illustrated by normal tissue complication probability (NTCP) curves at 1-year after radiotherapy based-on the salivary excretion factor dataset (blue) (salivary flow ≤45% relative to pre-RT) and based-on the quality of life measurement as moderate to severe xerostomia (red) as a function of mean dose to spared parotid gland., respectively

III. Results

Figure 1 shows the fitted incidence of grade 4 xerostomia, illustrated by normal tissue complication probability (NTCP) curves at 1-year after radiotherapy based-on the salivary excretion factor dataset (blue) (salivary flow ≤45% relative to pre-RT) and based-on the quality of life measurement (as moderate to severe xerostomia (red)) as a function of mean dose to spared parotid gland., respectively.

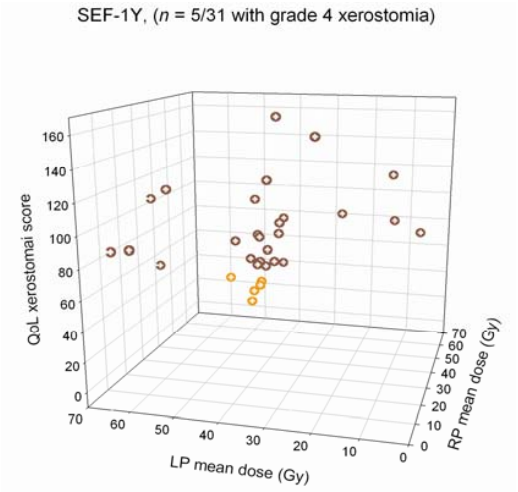

Fig. 2 Overall summary of the 25/20-Gy guidelines applied to head and neck cancer based-on the salivary excretion factor (SEF) data at 1-year after radiotherapy. As seen, the rate of xerostomia for plans meeting the QUANTEC guideline is none, resulting in NPV's of 100%. O: With grade 4 xerostomia; O: No grade 4 xerostomia;

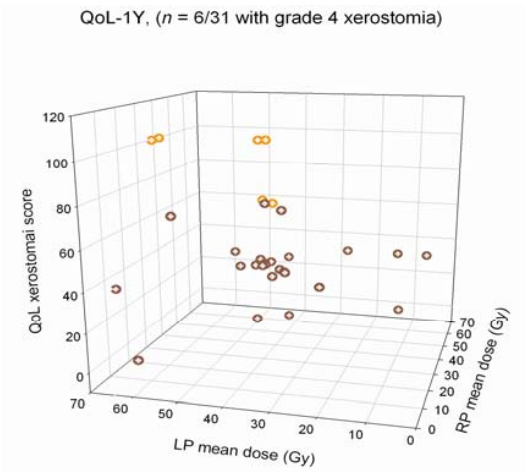

Fig. 3 Overall summary of the 25/20-Gy guidelines applied to head and neck cancer based-on the quality of life (QoL) data at 1-year after radiotherapy. As seen, the rate of xerostomia for plans meeting the QUANTEC guideline is none, also resulting in NPV's of 100%. O: With grade 4 xerostomia; O: No grade 4 xerostomia;

The local fitted parameters are given as $TD_{50} = 43.6$ Gy, and $m = 0.18$. The incidences of grade 4 xerostomia are ≈ 1% and ≈ 2% at 1-year for the recommendation of 20 Gy and 25 Gy respectively. For the observed data of QoL measurments, the fitted parameters are given as $TD_{50} = 44.1$ Gy, and $m = 0.11$.Figures 2 and 3 show the 20 Gy and 25 Gy guidelines applied to the SEF and QoL data respectively. As seen, the rate of xerostomia for plans meeting the QUANTEC guidelines are precisely, resulting in NPV's of 100% for the both SEF and QoL datasets.The *p*-value of Pearson's chi-square test was equal to 0.241, which corresponds to the variables having an association or relationship.

IV. Discussion

Figures and Tables For the LKB NTCP modeling, the local TD_{50} fitted parameters for 1-year after RT are given equal to 43.6 Gy for SEF analysis and 44.1 Gy for QoL assessments, respectively; they are higher than the report of Moiseenko et al. proposed, which is equal to 32.4 Gy. Whole-mouth salivary function has been shown to relate to QoL measurement questionnaires [1]. Deasy et. al. reported that a wide variation in the reported TD_{50} values (from 28.4 to 52 Gy) is unexplained but could result from several reasons, including differences in dose distributions, salivary measurement methods, segmentation, intragland sensitivity, and may differ from the living areas [5-6].

Xerostomia-specific questionnaires were found reliable and valid in measuring patient reported xerostomia [2]. In this study, Qol analyses were found valid in NTCP parameters modeling as SEF assessments. Pearson's chi-square test was used to test the association between two analysis methods. The *p*-value higher than the 0.05 criterion is said which corresponds to the variables having an association or relationship, imply SEF assessments and QoL analysis with similar result.

For IMRT planning goal, the mean dose to each parotid gland should be kept as low as possible, consistent with the desired clinical target volume coverage. Our study found that the incidence of grade 4 xerostomia is only ≈1% and ≈2% at 1-year for the QUANTEC recommendation of 20 Gy and 25 Gy respectively. Severe xerostomia can normally be avoided if at least one parotid gland has been spared to a mean dose ≤20 Gy or if both glands have been spared to a mean dose ≤25 Gy [6]. A lower parotid mean dose usually results in better function with respect to the effects on patient's QoL.

V. Conclusion

Our study provides agreements with such SEF analysis and QoL assessments for the NTCP parameters modeling and QUANTEC guidelines validation. Based on these results, we believe that the clinical use of the QUANTEC 25/20Gy spared-gland–mean-dose guideline is useful for the HN cohort.

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