Chapter 6

Clinical Validation of Radiobiological (RB) Models

1 Background

As Radiobiological (RB) models started to appear in 1980s for their use, since then number of RB models published in literature, as discussed in literature review section.

1.1 DVH versus RB models based plan evaluation

DVH based plan evaluation indices provides binary outcome which means that an effect takes place if a DVH of particular OAR passes above a certain point in dose volume curve, and does not occur when it passes below dose volume curve. This sets a threshold kind of criteria for assessing complication risk which is nothing but a rough approximation of actual biological endpoint. Whereas, RB model based evaluation in terms of TCP and NTCP provides continuous estimates of complication probabilities. In case when two or more dose volume points are used to evaluate a dose distribution in a particular organ at risk, it may happen that the dose distribution passes the evaluation test for some points and fails for others. This kind of scenario demands physicist and radiation oncologist to look for different dose volume criteria. EUD and TCP/NTCP are the biological indices used for biologically based treatment plan evaluation (Allen Li *et al.* 2012). Biological indices can be useful in such scenarios because it can prioritize different dose volume criteria and merge them into a single unambiguous estimate of biological outcome (toxicity). There are some RB models available in literature which can directly consider tissue specific radiosensitivity as a function of dose per fraction (Brodin *et al.* 2018). If these models properly calibrated using clinical approved data for a range of fraction sizes, can be used to predict outcomes of different fractionation regimens. Whereas dose volume plan indices are only applicable to a single fraction size for which their accuracy and efficacy has been tested. If the conventional fractionation regimen is changed, dose volume based prescription and dose constraints need to be modified based on individual clinical experience as well as isoeffect dose calculations.

1.2 Clinical validation

Validity means close to truth. Clinical validation is a process in which user has to verify and perform validation either prospectively or retrospectively on selected patient data at a single institution level or multi-institutional level before incorporating the output of models under study (Lee and Fang 2013). There are two alternatives available to implement radiobiological (RB) models for plan evaluation. First option is to cautiously use biological parameter published in literature. In literature, published data available for many tumor sites and different organs. However, this approach associated with risks if published parameters are applied injudiciously without following the same practices that were used to generate the original data. If demographic characteristics of the patient population under study substantially differs from the original patient cohort used to derive published parameter estimates, special precaution is required. While using literature based biological parameters for plan evaluation, it has to be carefully verified that they are associated with the correct endpoints, fractionation regimens and organ volume definitions.

The second option is to use self-designed model for parameters estimation, based on their own experience by calibrating selected models under study against observed clinical outcomes (complications). This approach has the potential to come out with most reliable data directly reflecting

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the true practice adopted in an institution. Furthermore, it is possible to refine initial parameter used as more follow-up data become available.

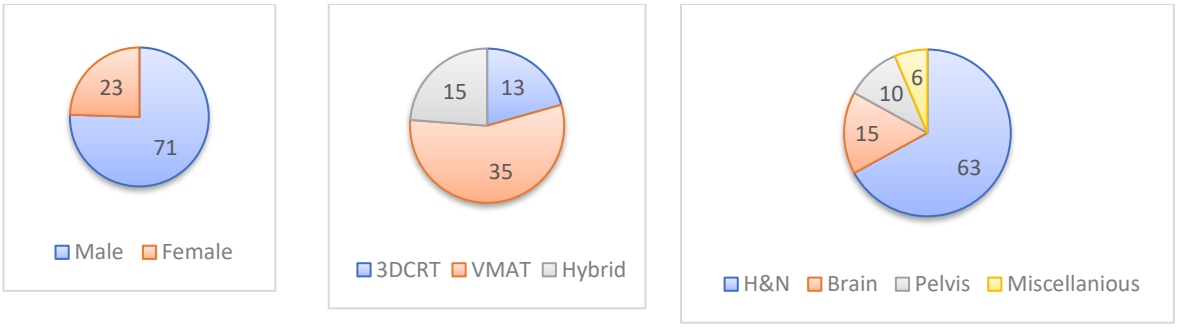
Present thesis work adopted first option, by using published parameters based on critical analysis while evaluating complications. It is because model parameters based on cumulative experience at different centres can be more accurate for population based estimation of normal tissue complication probability rather than derived from single institutional data. Aim of present study is to evaluate the clinical application of radiobiological (RB) models for the estimation of the incidence of radiation induced complications in a relatively large group of cancer patients. And to do validation of RB models outcome based on patient rated quality of life (QoL) instruments specifically designed for organ specific toxicity.

2 Material And Methods

In present thesis work, patients treated with radiotherapy in the Department of Radiotherapy and Radiation Medicine, IMS, BHU from March 2019 to April 2022 were enrolled. Institute ethical committee (IEC) approved the study. Histologically proven cancer patients of head and neck, Breast, lung, cervix, prostate and brain sites, treated with curative intent were included in the study. Patients with palliative treatment and re-irradiation or recurrences were excluded from the study. Patient characteristics is shown in table 6.1. As the study contains highest number of patients of H&N site, the characteristics of H&N cancer is shown in table 6.2. In this study patients treated with different techniques included 3D CRT, VMAT and hybrid as shown in figure 5.1. Hybrid is a combination of 3D CRT & VMAT technique in which either phase 1 is treated with VMAT or phase 2 is treated with VMAT.

Table 6.1: *Characteristics of the patients under study*

Total number of patients	**94**
Head & Neck site	63 patients
Brain	15 patients
Pelvis	10 patients
Miscellaneous	6 patients
Pelvis site	
Prostate	03
Cervix	05
Gall bladder	02
Brain site	
GBM	06
CSI (Medulloblastoma)	06
Craniopharyngioma	02
Meningioma	01
Miscellaneous	
Oesophagus	02
Breast	03
Stomach	01



a) b) c)

Figure 5.1: *Pie chart showing a) population of male & female b) Types of techniques c) various sites of treatment*

Table 6.2: *Characteristics of the Head & Neck patients only*

Tumor site (H&N)	Number of cases	CCRT	26
Larynx	17	RT alone	37
Tongue	14		
Buccal mucosa	09	Died	6
Alveolus	05	Recurrence	02
Nasopharynx	02	Loss of follow up	02
Oropharynnx	03	Defaulted	02
Hard palate	03		
Soft palate	01	No of the effective patient for follow up	51 patients
Supraglottis	02		
Pyriform fossa	01		
Parotid	01		
Pyriform sinuses	01		
Maxilla	01		
Gengiva	02		
Tonsilar	01		
Post-Operative cases	**12**		

2.1 Radiotherapy (RT) technique

2.1.1 Patient immobilization: RT is a localised treatment therefore requires patient immobilization. It is the first step in radiotherapy where we prepare thermoplastic cast or Vac-Lock for each patient intended to immobilize during radiation dose delivery. After immobilization preparation patient has to go under computed tomography (CT) scan. After imaging all CT images transferred to treatment planning system (TPS).

2.1.2 Imaging and segmentation: TPS is a place where contouring, dose prescription, planning and treatment scheduling performed. The CT 3D images transverse, sagittal and coronal are required for contouring. Contouring is a process where Radiation Oncologist delineate tumour and various tumor surrounding structures depends upon the site. After contouring, the CT structure set is utilized for planning by predefined technique decided by radiation oncologist.

2.1.3 Treatment planning: Treatment planning system embedded with dose calculation algorithm based on electron density therefore requires CT data for planning. There are various techniques to create

plan for patient such as 3D CRT, IMRT and VMAT. After patient specific plan is done, it has approved by radiation oncologist. The approved plan schedule for treatment delivery on machine.

All 94 study patients of various sites as mentioned in table 6.1 followed the above steps for treatment. Treatment planning system named as eclipse version 11.3 supplied by Varian Medical Systems Pvt. Ltd., USA used for planning and dose calculations of all patients' treatment plans. Dose delivery of all planned patient took place on Medical Linear accelerator (Model: Unique Performance) having 6 MV (Mega Voltage) energy. The criteria set for planning objectives is based on Radiation Therapy Oncology Group (RTOG) recommendations. According to RTOG, At least 95% planning target volume (PTV) should be covered by minimum 95% of prescribed dose with no more than 5% of any PTV(in case of multiple PTVs) should receive dose ≥110% of the prescribed dose. The dose constraints for surrounding structures for various sites is followed from QUANTEC guidelines.

The dosimetrical plan evaluation for each patient of the study performed. It is based on dose volume histogram (DVH) in addition with slice by slice visual dose verification. The various physical parameters (mean dose, max dose and mean dose) and plan evaluation indices (Conformity index, homogeneity index) were applied to get best plan among the competing plans. After following these steps of plan evaluation, treatment plan is approved. The DVH files of various organs at risk structures and PTV were extracted from treatment planning system using a bin size of 0.1 Gy and the dose calculation resolution set 2.5 mm for all treatment plans. The DVH files in .txt format from approved treatment plan work as an input for the radiobiological model based program (discussed in detail in chapter II) for estimating normal tissue complication probability (NTCP).

2.2 Toxicity grading in organ at risk (OAR)

This study focused on the complications (toxicities) observed in salivary glands, oral cavity, larynx, spinal cord, brainstem, optic nerve, optic chiasm, eye, lens, lung, heart, bladder and rectum. The toxicity grading is based on Common Terminology Criteria for Adverse Events (CTCAE) and Radiotherapy Oncology group (RTOG) guidelines. CTCAE developed by National Cancer Institute and widely accepted in oncology community for adverse events grading. As per CTCAE and RTOG, grade1, 2 and 3 represents mild, moderate and severe symptoms whereas grade 4 and 5 represents life threatening and death adverse events respectively. In present study there was no grade 5 toxicity observed in all 94 patients.

2.2.1 Salivary Glands:

During head and neck RT, in most of the cases it is unavoidable to spare the OARs like parotid, submandibular, and minor salivary glands from irradiation. Radiation exposure induces salivary dysfunction which means reduction in salivary flow and affects patient's quality of life. The amount of reduction in saliva flow is directly related to amount of dose received by the parotid gland. Sensitivity of the salivary glands are more to radiation: saliva flows reduced significantly after irradiation of 10 to 15 Gy after beginning of RT (Jellema *et al.* 2005). Long term survivors after RT of head and neck patients faces moderate to severe degree of xerostomia. Xerostomia leads to additional problems to patient like dental hygiene, oral infections, sleep disturbances, oral pain and difficulty in swallowing and chewing (Lee *et al.* 2014). Parotid gland produces largely 60 to 70% of total saliva. Rest saliva production (unstimulated) balanced by submandibular, sublingual and minor salivary glands. Recovery of parotid gland function usually takes place at 6 months and one year after RT. Recovery keeps going on after RT. Parotid gland complication considered when stimulated saliva flow rate becomes <25% as compare to pre-RT flow rate (Patrik Brodin *et al.* 2018). Xerostomia can be assesses by many ways

such as scintigraphy, MRI sialography of ductal flow and patient reported QoL instruments. Parotid gland endpoint defined in CTCAE and RTOG guidelines. Many studies reported xerostomia based on scintigraphy technique in which patient has to provide stimulated saliva sample before starting of RT and after certain predefined interval of RT (Lee *et al.* 2012). This is a costly test and generally in India like country most of the patients cannot afford. The alternative way to record xerostomia is to get filled patient reported QoL questionnaire as per the standard instruments e.g. EORTC and the Late Effects Normal Tissue-Subjective, Objective, Management, Analytic (LENT-SOMA).(Pavy *et al.* 1995; Rubin *et al.* 1995) The patient-reported outcomes/QOL instruments like EORTC used xerostomia-specific questionnaire forms after predefined interval after RT.

There is less probability of severe xerostomia (Grade II and higher) if at least one parotid gland receive a mean dose less than 20 Gy or if both the glands received a mean dose less than 25 Gy(ref).(Beetz, Schilstra, Burlage, *et al.* 2012) It is reported in some studies that sparing at least one parotid gland and sparing at least one submandibular gland appears to reduce xerostomia risk and increases salivary function (stimulated and unstimulated).(Beetz, Schilstra, Burlage, *et al.* 2012; Beetz, Schilstra, Van Luijk, *et al.* 2012) If the mean dose to submandibular gland restricted by <35 Gy it might reduce the probability of xerostomia symptoms. In some studies V30<30% (means volume receiving 30 Gy dose less than 30 % of total volume have less probability of severe xerostomia (Grade II and higher) .(Beetz, Schilstra, Van Luijk, *et al.* 2012; Brodin *et al.* 2018; Deasy *et al.* 2010; Kager *et al.* 2015)

2.2.2 LARYNX

Laryngeal edema due to inflammation and lymphatic disruption is the side effect commonly observed in head and neck patients of RT. Aspiration pneumonia associated with dysphagia after intensive chemo- RT has recently been appreciated (Trott *et al.* 2012).

In order to minimize the risks of laryngeal edema and vocal dysfunction, it is recommended that the volume receiving 50 Gy should be less than 27 % of total volume of larynx Gy ($V50Gy \leq 27\%$) and the mean laryngeal dose should be restricted less than 44 Gy (Mittal and Eisbruch 2011).

By reducing the volume of the pharyngeal constrictors muscles (PCM) and larynx receiving dose more than or equal to 50 to 60 Gy is associated with reduced aspiration or dysphagia.

In some studies aspiration was observed when the mean dose to PCM exceeded 60 Gy and the dose–volume threshold was V40Gy=90%, V50Gy=80%, V60Gy=70%, and V65Gy>50% respectively (Mittal and Eisbruch 2011).

Swallowing process involves movement of several muscles especially pharyngeal constrictor muscles voluntary and involuntary. Because of this complex process contouring larynx structure always poses uncertainty. This result dose volume parameters have major impact on assessment of associated toxicity. CTCAE is the most commonly used observer-rated dysphagia grading tool and there are other multiple patient reported QoL instruments like RTOG/EORTC and the subjective Objective Management Analytic (SOMA) scoring scales available, these instruments have been developed to assess quality of life (QOL) in patients with head and neck cancer. These QoL questionnaire forms specifically includes questions about swallowing dysfunction.

2.2.3 ORAL CAVITY

Oral mucositis is chemo-RT induced symptomatic and regimen limiting toxicity frequently observed. It is found that the oral mucositis is one of the prime reason of treatment interruptions, reduction in chemo dose, and use of feeding tube for patients. There are many risk factors associated with oral mucositis (OM) bad oral hygiene, smoking habit, below average nutritional status, body mass index and renal function. The toxicity onset period for mucositis is 4-8 weeks post radiotherapy.

2.2.4 SPINAL CORD

Spinal cord is a serial organ and myelopathy is the radiation induced late toxicity which may appear after a latent period of 6 to 12 months. The cervical cord is more sensitive than thoracic and lumber. Size of fraction and total dose is the deciding factor for radiation induced myelopathy. Several studies in literature presented that a dose of 50 Gy in 2 Gy per fraction have 0% probability of myelopathy and 60 Gy can be safely delivered if fraction size is less than 2 Gy. (Kirkpatrick et al 2010) Short length of spinal cord can easily tolerate a dose of 60 Gy in dose range of 1.8 to 2 Gy per fraction size. There is no solid evidence that volume effect plays important role in the incidence of myelitis in patients treated with standard fractionation regimen (Dynes *et al.* 1960). In literature, the model parameters for biological models of spinal cord are limited in human studies. Most studies are on rats, mice and chimpanzees. Therefore most commonly practice guideline is that a dose of 50 Gy with BED of 100 Gy is associated with less than 1% probability of myelopathy. It is observed that addition of surgery and chemotherapy decreases the spinal cord tolerance dose. The detail discussion of spinal cord is mentioned in chapter III.

2.2.5 BLADDER

It is found that less than 10% of patients treated with radiotherapy in cervix, prostate and bladder cancer faces severe bladder complication.(Marks *et al.* 1995) The bladder complication can also occur as a consequence of other co-morbidities such as infection and incontinence besides radiation induced injury. Acute effects of bladder during radiotherapy mostly disappears within 2 to 3 months. But long term toxicity or late effects remain exists and affect patient quality of life. Late effects are increased frequency of urination, urgency, reduced flow and contracture. Scoring of bladder toxicity is complex, there are subjective and analytical scoring systems available like LENT-SOMA and CTCAE. It is reported in many studies that patient reported toxicities are more reliable than physician observation based reporting in bladder.

Challenges in volume definition: The bladder is highly movable organ and its volume keeps on changing and depends on amount water filling. Literature data showed that in locally advanced cancer treated with external beam therapy (EBRT) alone with bladder receiving dose >60Gy reported high incidence of late bladder toxicity.(Marks *et al.* 1995) Therefore combination of EBRT and brachytherapy is preferably used. Recommended dose volume constraints: According to RTOG (0415), bladder constraint definitions are 80Gy dose should not receive more than 15% of total volume, 25% of volume should not receive more than 75Gy, 35% of volume should not receive more than 70Gy, 50% of volume should not receive more than 65Gy.(Viswanathan *et al.* 2010)

2.2.6 RECTUM

Radiation proctitis which means excessive rectum bleeding and mucosal discharge, ulceration and fistula are the late toxicity associated with rectum irradiation (Strigari *et al.* 2009). Rectum is a serial structure because its functional subunits aligned in a serial form. Rectal endpoints defined as rectal bleeding, fecal incontinence (unwilling loss of stool), increase in stool frequency (more than 4-5 times per day) and rectal pain according to CTCAE. Rectum is a movable organ and its location cannot be same at the time of treatment as compared to position of rectum during planning CT scan. This inter or intra-fraction variation is because of intestinal gas, rectal filling and bladder filling. Present study considered grade 2 or higher toxicity as an endpoint. Grade 2 toxicity common symptoms are bowel

movement more than 5 times in a day and excessive rectal bleeding. If rectum receive dose ≥60Gy, it leads to late rectal toxicity.(Dale, Olsen, and FossÅ 1999)

Dose volume constraints: based on conventional fractionation, the dose constraints for rectum are V50<50%, V60<35%, V65<25%, V70<20% and V75<15% of total volume of rectum.(Michalski *et al.* 2010; Schaake *et al.* 2016) In multiple studies reported that minimizing V70 & V75 volumes below the recommended dose constraint 20% and 15% without compromising the PTV coverage can result in low probability of grade 2 toxicity.

2.3 Patient reported Quality of Life (QoL) evaluation

To assess patient quality of life post RT and to gauge effect of radiation on normal tissues and organ at risk involved during radiotherapy, a standard QoL scoring system is required which widely accepted in practice. European organization for research and treatment of cancer (EORTC) is one of the instrument commonly accepted for scoring the toxicity grading based on set of questions prepared for site specific diseases. These patient rated quality of life (QoL) instruments as shown in table 6.3 specifically designed for organ specific toxicity. These QoL instrument consist of set of disease specific questionnaire forms and can be obtain on request from EORTC.(Cox, Stetz, and Pajak 1995; Og 2007; Rubin *et al.* 1995)

Author has approached EORTC via email and requested various questionnaire forms in Hindi and English language for H&N site, lung, heart, bladder and rectum. Author received following forms for toxicity assessment (grading) with scoring manual.

Table: 6.3: *Quality of life questionnaire references*

EORTC QLQ- H&N35, QLQ-C30	For assessing xerostomia associated with parotid gland
EORTC QLQ- OH35	For assessing oral health to grade mucositis
EORTC QLQ- BLM30	For assessing radiation induced damage to bladder
EORTC QLQ- LC13	For assessing radiation induced lung damage (pneumonitis)
EORTC QLQ- PRT20	For assessing radiation induced rectum injury (Proctitis)

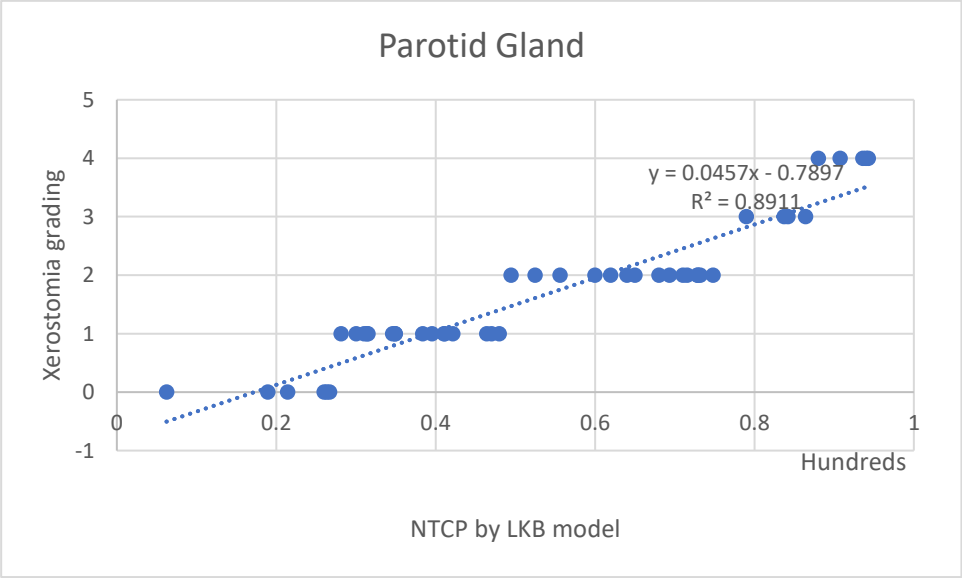
Two QLQ received in both Hindi and English and three in English language only. Author converted there QLQ into Hindi language as study is taking place in Uttar Pradesh and Hindi is a local language. For larynx associated toxicity dysphagia author referred Baylor All Saints Medical Centres questionnaire QLQ form and converted into Hindi Language. Author modified the language of some questions mentioned in questionnaire forms wherever it is required. This is because in the beginning many patients were facing to perceive the logic behind the question and unable to answer. To obtain a score from EORTC QLQ, scale ranged from 0-100 is used. A high score for a functional quality of life scale represents a relatively healthy level of functioning, whereas a high score for a symptoms scale represents the presence of a symptom or problem associated with the organ. All patients under study completed the questionnaire forms during OPD visits. Those patients could not come regularly because of Covid 19 pandemic restrictions, a telephonic communication established and questions were asked by the resident doctors. QLQ forms for assessing dysphagia and mucositis not filled for patients diagnosed with larynx cancer and cancer of tongue and mouth.

3 Result

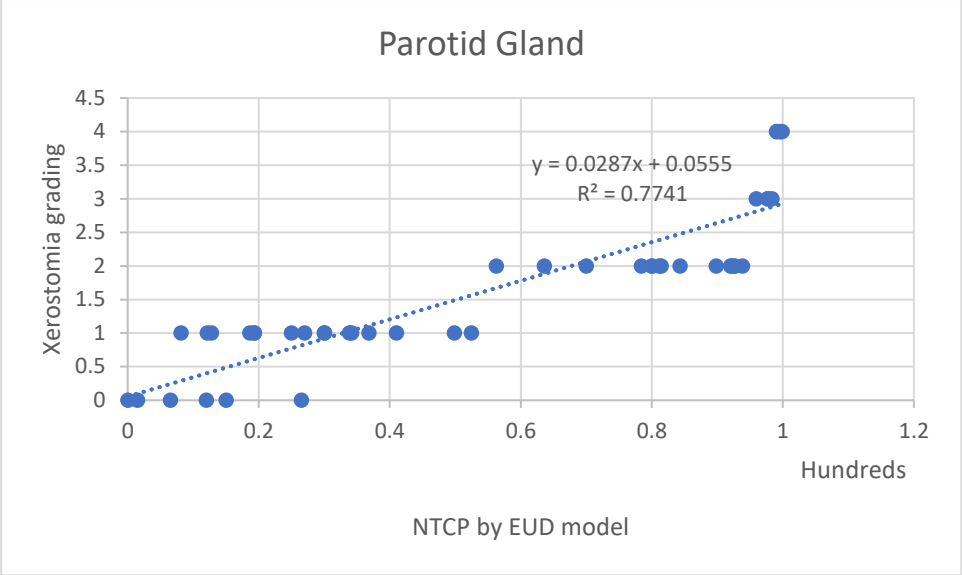
3.1 Correlation analysis

The demographic and tumor characteristics of the study population are listed in table 6.1. The NTCP values derived from the DVH of each OAR of 94 patients from in house developed program named as RBMODV1. The severity of xerostomia was found to correlate with derived normal tissue complication probability for parotid gland, with a correlative strength of 0.89 [figure 5.2 (a)] and 0.77 [figure 5.2 (b)] for LKB model and Gay & Niemierko EUD model (R^2, Pearson correlation coefficient value). Similarly, there is strong correlation observed for larynx and oral cavity with correlation coefficient values are 0.91[figure5.3 (a)] and 0.92 [figure 5.4 (a)] for LKB model. For EUD model values are 0.92 [figure 5.3 (b)] and 0.93 [figure 5.3 (b)] respectively.

The dashed line shows the best fit of the severity of grading with the derived NTCP values based on the available data of 51 patients of H&N site. By LKB model, the line of best fit equations were measured at y=0.0457x-0.789 for xerostomia [figure 5.2 (a)], and y=0.0361x-0.321 for mucositis [figure 5.3 (a)] and y=0.0287x-0.055 for dysphagia (figure 5.4). By EUD model, the line of best fit equations were measured at y=0.0457x-0.789 for xerostomia [figure 5.2 (b)], and y=0.0385x-0.1024 for mucositis [figure 5.3 (b)], and y=0.0365x-0.0294 for dysphagia [figure 5.4 (b)]. In these equations y represents the severity of complication grading and x is the derived NTCP by LKB model as well as EUD model. There is no correlation study performed for the rest OARs because of low number of patients and no incidence of complications (spinal cord, brainstem, optic chiasm, eye, lung and heart) were observed.

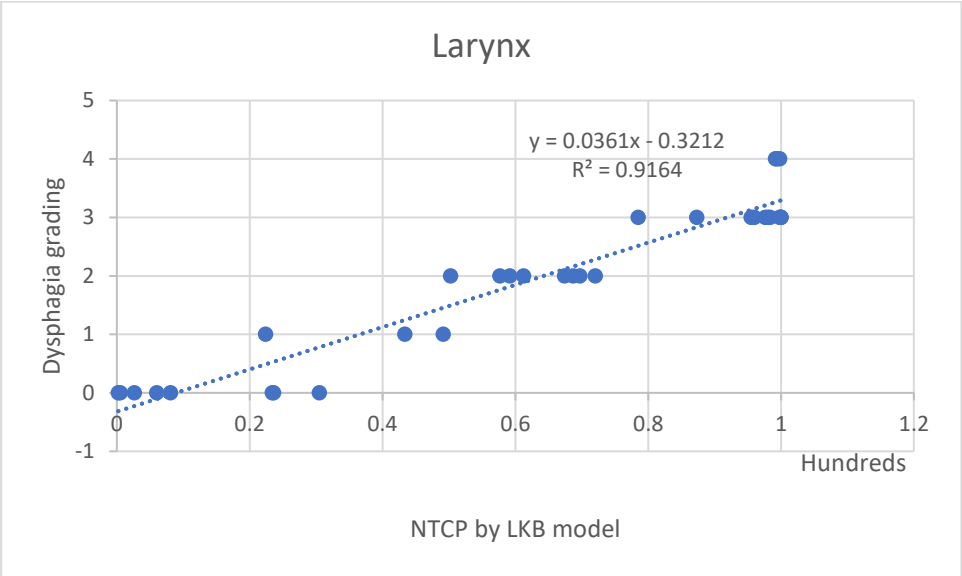


a) Correlation between the severity of xerostomia with the LKB model

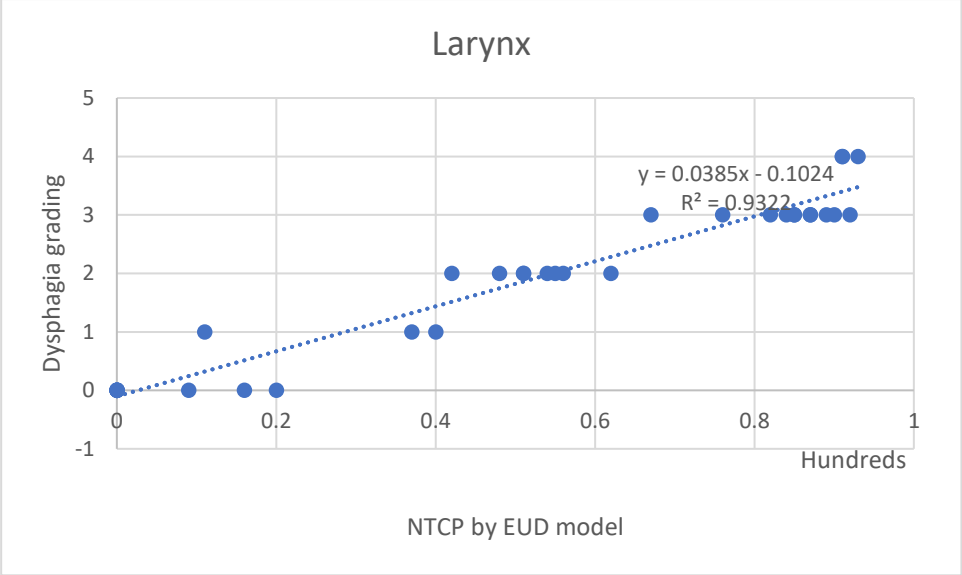


b) Correlation between the severity of xerostomia with the EUD model

Figure 5.2: *Correlation between the severity of (a) xerostomia with the LKB model and b) Xerostomia with Gay & Niemierko EUD model of bilateral parotid glands for TD50 = 31.4 Gy.*

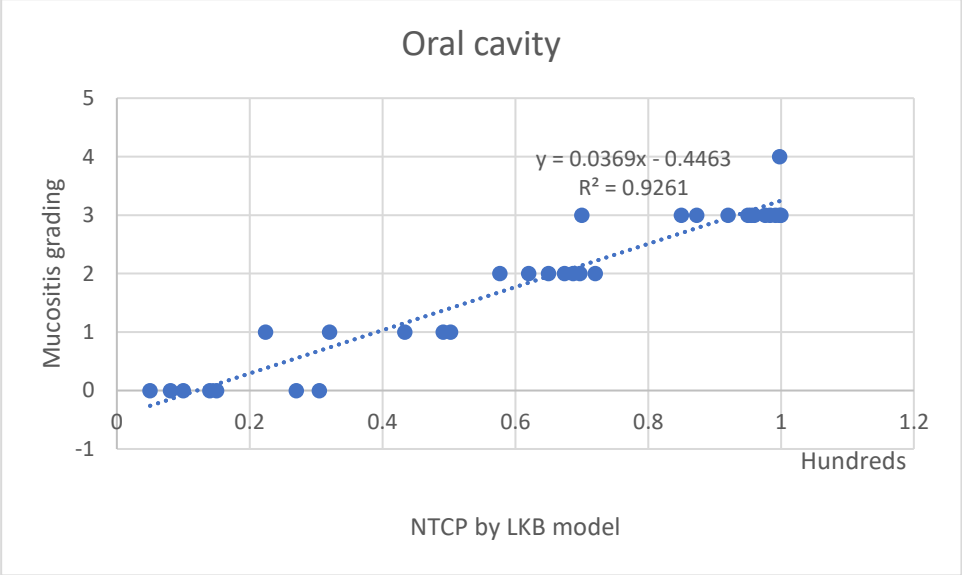


a) Correlation between the severity of dysphagia with the LKB model

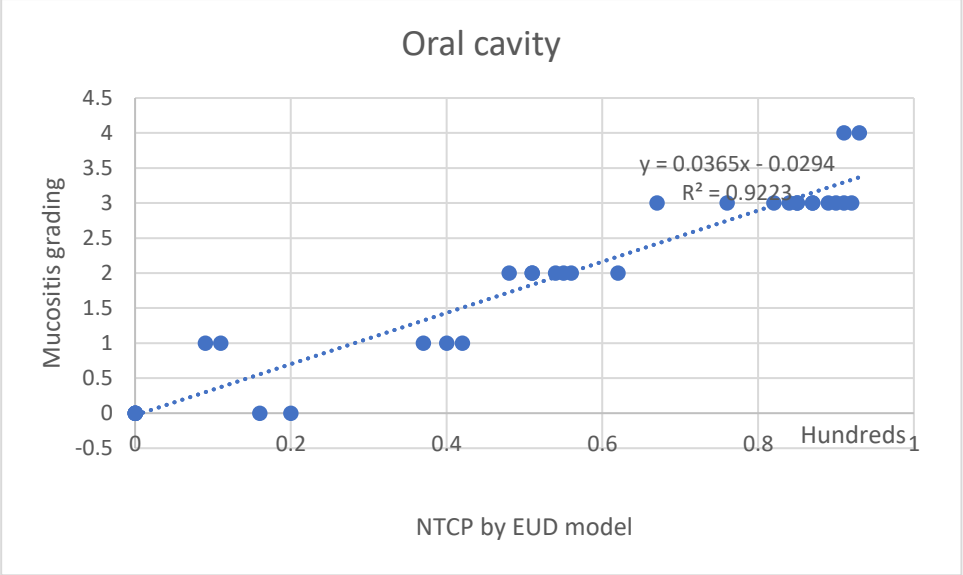


b) Correlation between the severity of dysphagia with the EUD model

Figure 5.3: *Correlation between the severity of (a) dysphagia with the LKB model and b) dysphagia with Gay & Niemierko EUD model of bilateral parotid glands for TD50 = 46.3 Gy.*



a) Correlation between the severity of mucositis with the LKB model



b) Correlation between the severity of mucositis with the EUD model

Figure 5.4: *Correlation between the severity of (a) mucositis with the LKB model and b) mucositis with Gay & Niemierko EUD model of bilateral parotid glands for TD50 = 55.9 Gy.*

3.2 Curve fitting and parameter estimation

In this section, fitting of patient data based on patient reported quality of life (QoL) and calculated NTCP by LKB model performed as well as LKB model parameter is derived from fitted dose response curve. All patient DVH files for each OAR collected from treatment planning system and converted into readable form of MATLAB. Then NTCP is calculated by LKB and Gay & Niemierko EUD model. The NTCP values obtained from MATLAB and patient data from QoL questionnaire processed in SPSS software. Based on scoring manual curve is plotted for H&N site. The curve fitting could possible for OARs of H&N site only because of sufficient number of patients (Parotid gland (N=51), Oral cavity (N=36), and Larynx (N=34)). In case of bladder, rectum, heart and lung there were not sufficient number suitable for statistical analysis. In case of OARs like spinal cord, brainstem, optic chiasm, cochlea, and kidney no incidence of endpoint occurred in all patients of the study therefore curve fitting was not feasible. Out of 94 patients 2 patients faced cataract because of higher dose received by the lens (more than 15Gy).

Assuming n=1 (parallel structure), the m and TD50 parameter estimated by fitting the data to the LKB NTCP model. 95% confidence intervals for parameter estimates were obtained by the profile likelihood method.

Figure 5.5 shows the observed quality of life (QoL) data and fitted dose response curves for LKB model for the incidence of xerostomia at 1 year after completion of RT. The Local fitted parameters are TD 50 = 34.1 Gy (CI: 33.6-41.4 Gy) and m=0.11 (CI: 0.09-0.14Gy). Dashed lines shows the 95% confidence interval for the model fit to QoL dataset (solid line). The squares represents the average probability for group of patients in bin 6 Gy width.

Figure 5.6 shows the observed QoL data and fitted dose response curves for LKB model for the incidence of oral mucositis at 6-8 weeks after completion of RT. The Local fitted parameters are TD 50 = 48.5 Gy (CI: 44.4-50.2Gy) and m=0.18 (CI: 0.15-0.20 Gy). Dashed lines shows the 95% confidence interval for the model fit to QoL dataset (solid line). The squares represents the average probability for group of patients in bin 5 Gy width.

Figure 5.7 shows the observed QoL data and fitted dose response curves for LKB model for the incidence of dysphagia at 1 year after completion of RT. The Local fitted parameters are TD 50 = 43.6 Gy (CI: 42.5-45.8 Gy) and m=0.16 (CI: 0.15-0.20 Gy). Dashed lines shows the 95% confidence interval for the model fit to QoL dataset (solid line). The squares represents the average probability for group of patients in bin 4 Gy width.

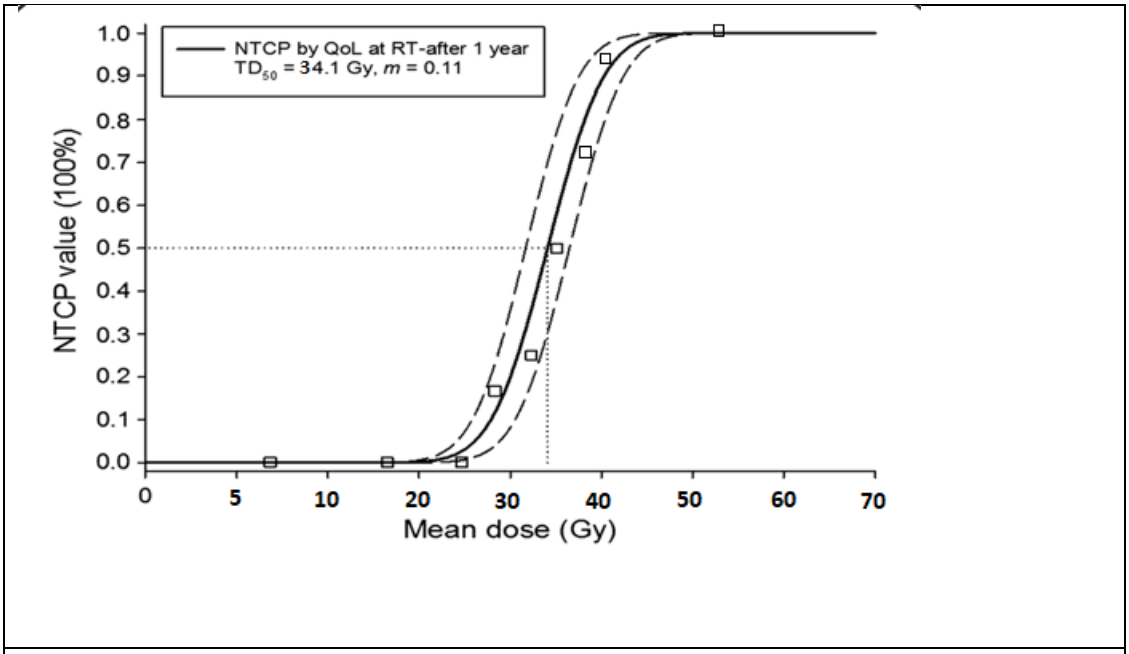


Figure 5.5: *shows the observed QoL data and fitted dose response curves for LKB model for the incidence of xerostomia at 1 year after completion of RT. The squares represented the average probability for group of patients in bin 6 Gy width.*

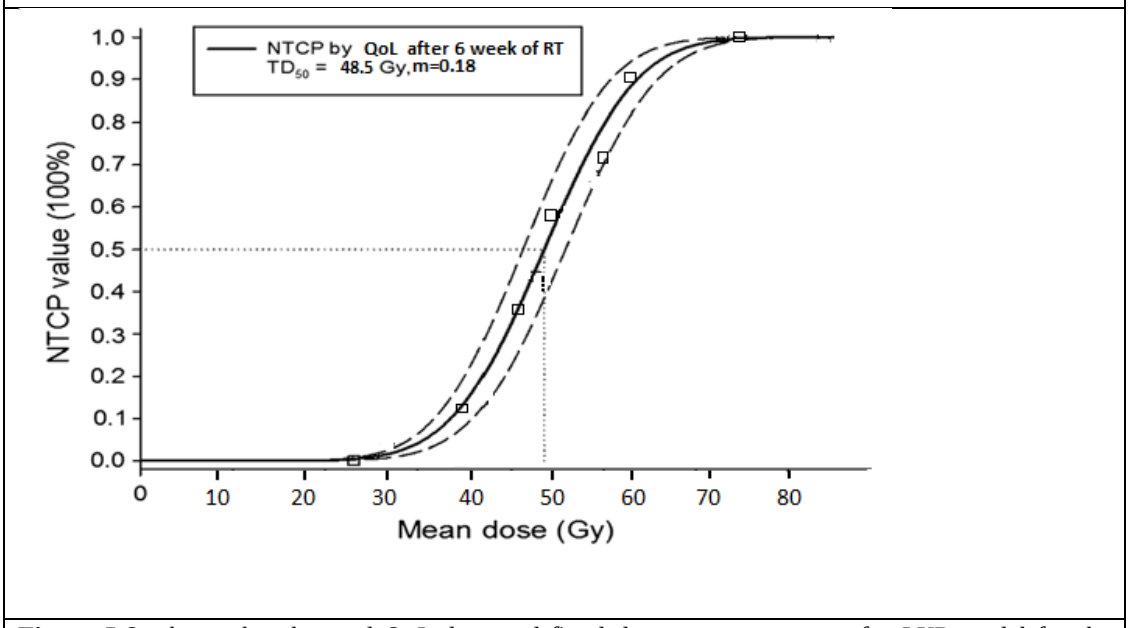


Figure 5.6: *shows the observed QoL data and fitted dose response curves for LKB model for the incidence of oral mucositis at 6-8 weeks after completion of RT. The squares represented the average probability for group of patients in bin 5 Gy width.*

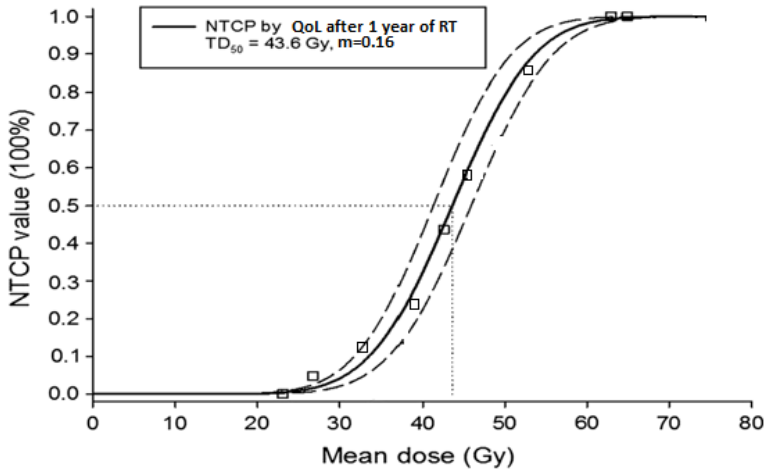
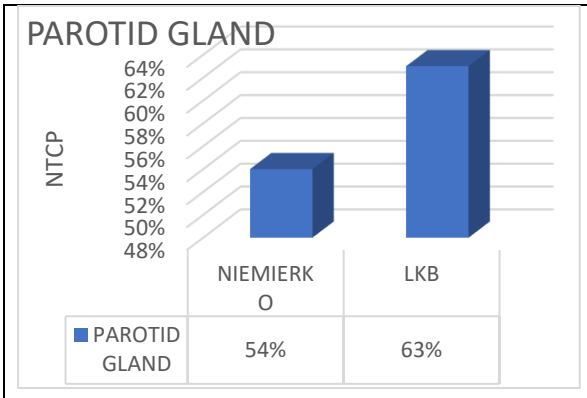


Figure 5.7: *shows the observed QoL data and fitted dose response curves for LKB model for the incidence of dysphagia after 1 year completion of RT. The squares represented the average probability for group of patients in bin 4 Gy width.*

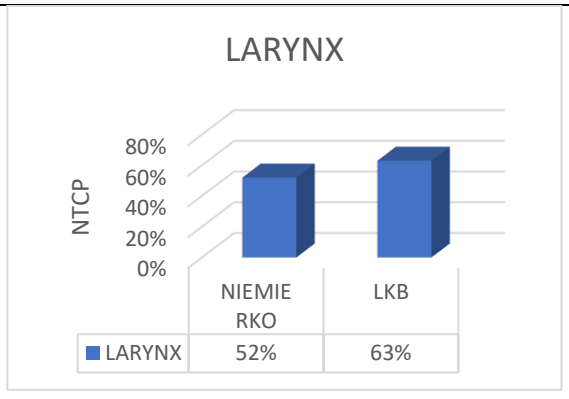
3.3 RB model accuracy calculation

Figure 5.8 (a),(b)(c) showing mean values of calculated NTCP for OARs (parotid gland larynx & oral cavity) by LKB and Gay & Niemierko EUD models. The difference in mean values are 9%, 11% & 12% for parotid gland, larynx and oral cavity respectively. This showed that EUD model estimated NTCP is less than estimated NTCP of LKB model.

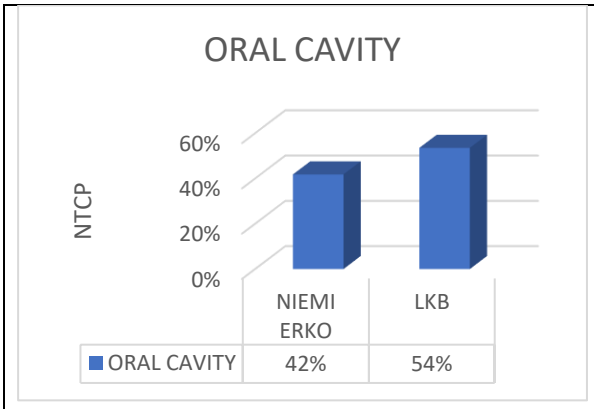
Figure 5.8 (d),(e)(f) showing mean values of calculated NTCP for spinal cord, bladder and rectum by LKB Gay & Niemierko EUD models. The difference in mean values are 3%, 9% & 13% for spinal cord, bladder and rectum respectively. The NTCP calculations for different OARs by both models indicating that calculation accuracy differs from each other. This differences are because of different approach of RB models for NTCP estimation.



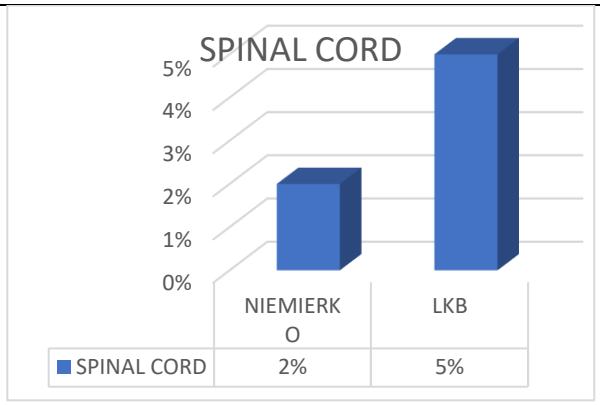
a) NTCP forparotid gland



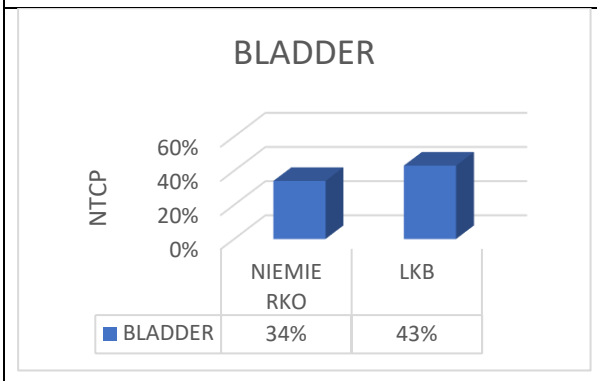
b) NTCP for larynx



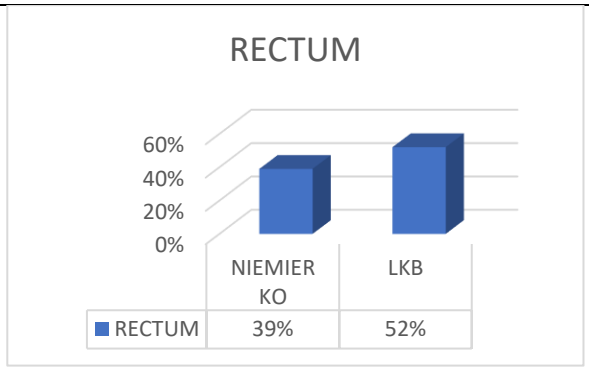
c) NTCP for oral cavity



d) NTCP for spinal cord



e) NTCP for bladder



f) NTCP for rectum

Figure 5.8: *Graphs showing mean differences between calculated NTCP by two different models a) Parotid gland b) Larynx c) oral cavity d) Spinal cord e) Bladder f) Rectum.*

Assumptions:

In present study, selection of appropriate toxicity grading to correlate with calculated NTCP plays significance role in order to verify accuracy of prediction power of models under study. It is assumed that NTCP more than 50% should represent presence biological endpoint associated with respective organ at risk. NTCP less than 50% should represent no biological endpoint occurred in the OAR. In OAR, grade I toxicity is a moderate in nature and recover with time post RT treatment and this has no adverse effects on patient daily activities. Grade II toxicity enters into severe category and it directly affect patients day to day life activities which directly affect patients quality of life. In this study dose response curves were drawn assuming grade II as a biological endpoint definition based on predicted NTCP by LKB and EUD model.

The RB model accuracy calculation performed by the following mathematical formula.

Accuracy=100% - Error rate

Error rate= [(Complication based on calculation – Actual observed complication)/Actual observed complication] x100

Note: Number of patients faced Grade-II and higher complication based on model based NTCP calculation (NTCP≥50%) whereas Actual observed complication based on patient reported QoL questionnaire.

For OARs like brainstem, spinal cord, heart and lung no adverse complications observed in patients under study till date.

Two patients of cranio-spinal irradiation (CSI) out of six patients under study complaint of Cataract and redness in eye.

Table 6.2 shows the calculated NTCP accuracy of different organs of patients under study.

Table 6.3: *Calculated accuracy for different OARs by LKB & EUD model.*

OAR	EUD model			LKB model		
	Calculated NTCP	Observed NTCP	Accuracy (%)	Calculated NTCP	Observed NTCP	Accuracy (%)
Parotid Gland	15	17	88.23	18	17	94.11
Larynx	19	22	86.36	24	22	90.90
Oral Cavity	17	20	85.00	22	20	90.00
Spinal cord	0	0	-	0	0	-
Brainstem	0	0	-	0	0	-
Bladder	2	3	66.66	3	3	100
Rectum	3	4	75.00	5	4	75.00
Eye lens	2	2	100	2	2	100
Eye	2	2	100	2	2	100
Lung	0	0	-	0	0	-
Heart	0	0	-	0	0	-
Optic chiasm	0	0	-	0	0	-
Optic nerve	0	0	-	0	0	-

4 Discussion

It was aimed to validate prediction power of LKB and Niemierko EUD model for various organs of different sites. In the 94 patients, we found maximum cases enrolled in H&N site (N=63) and there were less number of patients of other sites. Therefore present thesis more concentrated on the RB modelling of OARs of head & neck site (parotid gland, larynx, oral cavity, spinal cord and brainstem). Table 6.3 showed that both Gay& Niemierko EUD model and LKB model can predict xerostomia, dysphagia and mucositis with acceptable accuracy. But the predictive power of LKB model is superior to the EUD model. The accuracy of NTCP estimation for rest of OARs cannot be guaranteed because of less number of patients under study.

The primary goal of study was to validate recommended dose constraints of QUANTEC guidelines for various OAR under study.(Bentzen *et al.* 2010) In our analysis it is observed that in patients those receiving parotid dose V30Gy<50% of organ volume have no xerostomia even though their mean dose is in the range of 28-33 Gy. But in case of patients failing to achieve this criteria have resulting in xerostomia of grade2 and higher which is reflected in the predicted NTCP by LKB model. This result contradicts the QUANTEC recommended dose constraint, when at least one parotid gland is spared to a mean dose ≤20 Gy or when both glands have been spared to a mean dose ≤25 Gy. In larynx and oral cavity the predicted NTCP by LKB model followed the recommended dose constraints of QUANTEC. Laryngeal edema during course of Radiotherapy in Head & Neck cancer is one of the common side effect and it occurs due to inflammation and lymphatic disruption. In most of the disease larynx and pharynx is always a part of PTV hence prone to receive significant part of prescribed radiation dose. To minimize the risks of laryngeal edema, it is recommended that the larynx should receive the mean dose be =44 Gy and V50Gy be =27%.(Mittal and Eisbruch 2011) In our analysis, it is observed that estimated NTCP by LKB model is in line with the QUANTEC recommended dose constraint.

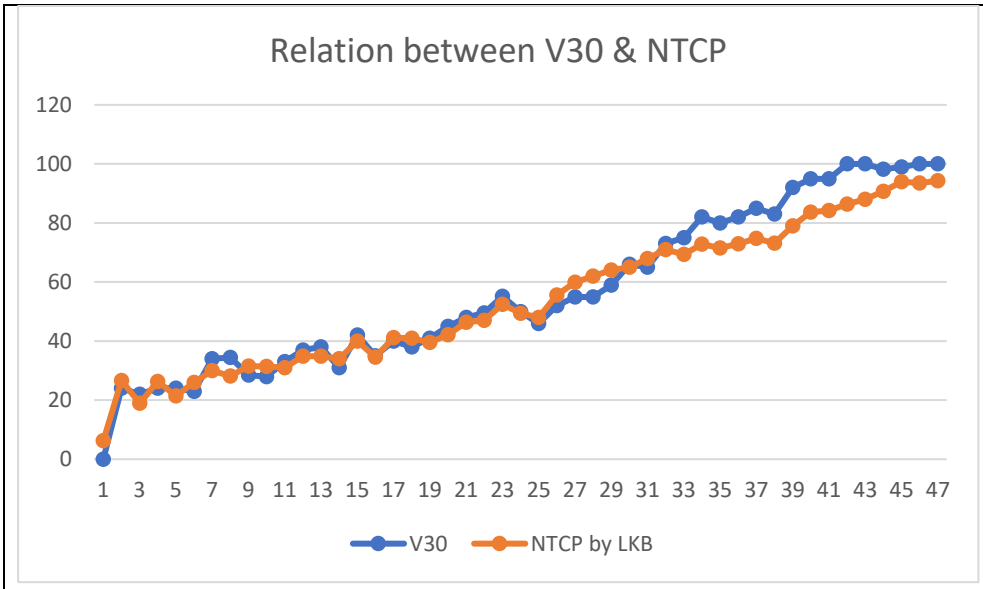


Figure 5.9: *Graph indicating relation between V30 and calculated NTCP by LKB model*

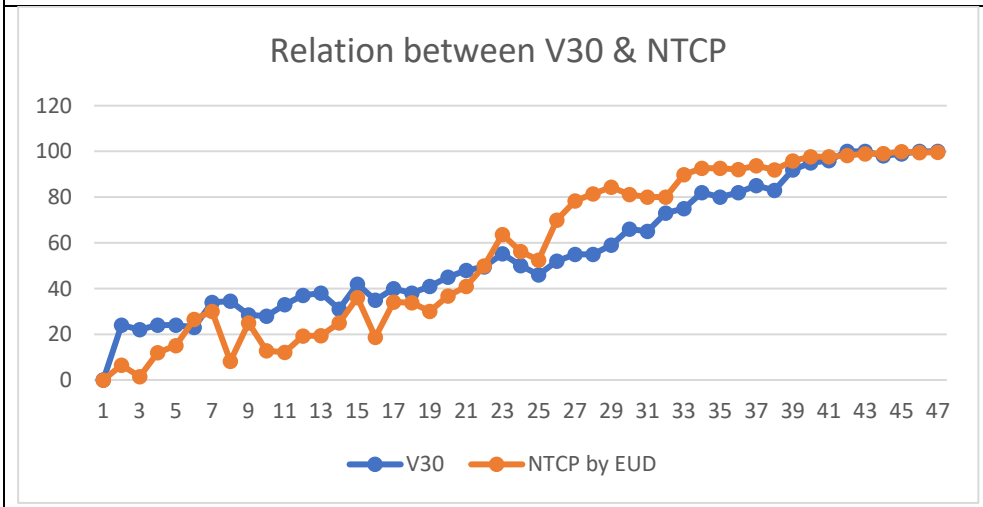


Figure 6.0: *Graph indicating relation between V30 and calculated NTCP by EUD model*

From above figure 5.9 & 6.0, for a parotid gland it is noted that there is some sort of linear relationship exist between physical dose descriptor V30 (volume of organ receiving 30 Gy dose) and calculated NTCP by Gay & Niemierko EUD model and LKB model. It is found that those patients satisfied the criteria of V30≤50%, not observed the grade 2 and higher toxicity (xerostomia). This is indicating that a correlation can be established between dose volume parameter and estimated NTCP by biological models.

One of the limitations of the present study include the low number of patients with incidence of toxicities related to spinal cord, brainstem, bladder, rectum, heart, lung, optic chiasm, eye and lens organs. Therefore, it is not recommended to blindly follow the predictions made by RB models under study. Author is continuing to collect follow up data from more patients to strengthen the outcome of RB models. The other reason that can affect the prediction power of RB model is the observer to observer organ delineation of various structures of interest. Although in our department, all consultants follow the Charlotte consensus guidelines for OAR delineation aiming to reduce interobserver variability (Brouwer *et al.* 2015). Grade selection of the biological endpoint associated with respective OAR is another potential limitation of the present study. This is because there is no direct relation established between toxicity grading and value of NTCP obtained from any RB model in application. Assuming lower grade of toxicity as an endpoint results in overestimation of NTCP by the model in application and vice a versa. Therefore, author used the physical parameters (e.g.V30≤50% criteria for parotid gland) as a surrogate with RB model predicted NTCP for obtaining accuracy in outcome

In conventional era, there was a direct relationship between the prescribed dose and the expected outcome and toxicity in normal tissue and OAR because both tumor and OAR received uniform dose. Hence it was quite easy to evaluate treatment plans. In modern radiotherapy, when intensity modulation technique started to implement, it becomes challenging to assess the outcome and toxicity. This is due to the fact that modern technique dose delivery methods led to non-uniform dose distribution in organs. This breaks the direct relation between prescribed dose and associated toxicity. Hence, plan evaluation based on physical dose descriptors and biological models facing various challenges. These challenges are, role of multiple dose volume physical parameters (V20, V30 etc.) and selection of appropriate endpoint for grading toxicities.

5 Conclusion

Present study conclude that Indian patients of head and neck cancers treated with radiotherapy have better tolerance for OAR (parotid gland and oral cavity) with respect to recommended dose constraint. The patients enrolled in the study is single institutional based and treated in government hospital. Mostly patients treated in our institute belonged to low socio-economic status and cannot afford good diet. Even though patient reported higher tolerance of associated toxicity which is contradictory with the patients of western and European countries those have better socio-economic status. This difference can be possible with multiple reasons such as error in reporting toxicity, physiology of Indian patients, inherent tolerance capacity and single institutional study. Therefore, it is encourage to have a multi-institutional trials in covering different parts of the country. This is the first study based on Indian patients and presenting different picture of toxicity assessment in Indian patients. In present chapter clinical validation of RB models (Gay & Niemierko and LKB) performed in Indian population. Validation of estimated TCP is not feasible and excluded from validation process. RB model based NTCP outcome is not regularly applied in routine practice of plan evaluation. This may be due to several reasons such as uncertainty in model parameters, complexity in use creates lack of confidence on biological model

application and limited validation studies. The prime intention of this work is to motivate the use of RB model based plan evaluation in routine practice. This study validated biological model that most commonly used in community (LKB model) having sufficient availability of biological parameters data in literature. Validation of RB model in patients of Indian demographic is the unique feature of the study. This study also estimated biological parameter for LKB model considering Indian patient's physiology and biochemistry which differs from western and European population.

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