Chapter 4

Problem Based Application of Developed Program for TCP & NTCP Estimation

This chapter discussed the applications of radiobiological (RB) models in different clinical scenarios for estimating TCP and NTCP. This chapter focuses on the scope of spinal cord tolerance dose revision in intensity modulated SIB treatment plans of locally advanced H&N cancer. In this chapter author tried to demonstrate that how tolerance dose limit for spinal cord (late responding tissue) is overestimated during plan evaluation. This demonstration performed based on both dosimetric as well as biological parameters.

1 Background

The spinal cord is an integral part of central nervous system; it is responsible for the communication between brain and the rest of the body. The human spinal cord consists of 31 segments which include 8 cervical, 12 thoracic, 5 lumbers, 5 sacral and 1 coccygeal. It is studied that, cervical spinal cord is more radiosensitive as compared to lumbar or thoracic part.(Bijl *et al.* 2005) In radiotherapy, radiation induced myelopathy (RM) is a severe complication which observed rarely. Timothy *et al* in his experimental study of the radiation dose response on human spinal cord found that there is risk of 0.03% of cervical myelopathy at 45 Gy, and at 50 Gy the incidence of myelopathy is approximately 0.2%.(Schultheiss 2008) As per QUANTEC report the risk for myelopathy for irradiation of full cord cross section at maximum dose of 50 Gy, 60 Gy and 69 Gy is 0.2%, 6% and 50% respectively.(Marks *et al.* 2010) This article describes the myths and facts in radiation oncology community regarding spinal cord dose constraints. An attempt has been made to demonstrate the possibility to revise or increase the spinal cord tolerance dose in the treatment of Head & Neck cancers using modern day radiotherapy techniques and fractionation regimen from dosimetrical and radiobiological point of view. This article also analyses the possible benefits or detriments achieved towards treatment goal in revising the spinal cord tolerance dose.

1.1 Myths

In most of the clinical scenario it is observed that, the dose received by spinal cord is the limiting factor for prescribing higher dose to aggressive tumors. Clinicians always adhere to strict constraint of maximum tolerance dose to spinal cord which should be less than 45 Gy. It is often happen that, the target coverage has to compromise with lack of adequate radiation dose or sacrifice the adjacent organ at risks (OARs) at the cost to limit spinal cord tolerance dose.

1.2 Facts

In contrast to the myths a number of publications and dose constraint recommendations suggested that spinal cord can tolerate higher maximum dose than our myth allows.(DYNES and SMEDAL 1960) (Nieder *et al.* 2006) (Nieder *et al.* 2005) Limiting the spinal cord tolerance dose constraint at lower values sometimes cost the possible treatment benefits. When the prescribed dose to tumor is delivered by conventional technique like Three Dimensional Conformal Radiotherapy (3DCRT), the normal tissue or OARs irradiated with fairly uniform dose of same prescribed fraction size. In case of modern techniques like Intensity Modulation Radiotherapy (IMRT), the volume of normal tissue is exposed to

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lower dose as compared to prescribed dose to PTV and the dose delivered at fraction sizes ranging from nearly zero to the prescribed fraction size**.**(Marks *et al.* 2010) For example, consider a case in which prescription doses for gross tumor volume (GTV), high risk planning target volume (PTV), intermediate risk PTV and low risk PTV are 70 Gy, 61 Gy and 54 Gy in 35 fractions with 5 fractions per week respectively. A simultaneously integrated boost (SIB) plan with volumetric modulated arc therapy (VMAT) technique is generated in which the spinal cord tolerance dose is distributed throughout the course then one can assume tolerance maximum dose of spinal cord as 52.50 Gy ($d_{\text{Spinal Cord}}$ = 1.50 Gy, α/β = 1.5 Gy^{-1}, EQD_2 = 45 Gy) and PRV spinal cord as 56.35 Gy ($d_{\text{PRV Spinal Cord}}$ = 1.61 Gy, α/β = 1.5 $Gy^{-1,}$ EQD_2 = 50 Gy) as described in table 4.1. So, the "Window of Opportunity" is about 7.50 Gy for spinal cord and 6.35 Gy for PRV spinal cord. In this article, the value of α/β taken as 1.5 Gy^{-1} from the meta-analysis study and suitable references.(van Leeuwen *et al.* 2018)

Table 4.1: *Biological Dose calculation of spinal cord and PRV spinal cord considering the given example*

OAR	**Spinal cord (Current Considerations)**	**Spinal Cord (Tolerable Considerations)**	**PRV spinal cord (Current Considerations)**	**PRV spinal cord (Tolerable Considerations)**
Dose per fraction (Gy)	1.28	1.5	1.43	1.61
Number of fractions	35	35	35	35
α/β (Gy)	1.5	1.5	1.5	1.5
EQD2 (Gy)	35.83	45	41.8	50
BED	83.60	105	97.6	116.8
Physical Dose (Gy)	45	52.5	50	56.35

1.3 Scope of revision

The extent of required prescribed dose to PTV is restricted by the tolerance dose of normal tissue and OAR surrounding the target. In conventional technique, parallel opposed shrinking field technique is used to treat H&N cancers, where in the first phase for the most of the cases, the field includes the spinal cord and target receives the maximum total dose of 40 Gy to 44 Gy (as per prescription) with 2 Gy per fractional dose. The spinal cord receiving dose between 40- 45 Gy with 2 Gy per fractional dose over 23 fractions as shown in figure-3A. Spinal Cord is spared completely in following boost phases because of off cord treatment. Sometimes, the adequate dose delivery is not possible in order to spare the spinal cord which ultimately decreases tumor control probability. But with the advent of intensity modulation treatment technique the situation is quite different. The optimized radiation beam enters from multiple directions and can effectively spare the critical organs within the tolerance dose and also minimizes dose to normal healthy tissue. In SIB regimen the OARs tolerance dose is equally distributed throughout the treatment (Figure-3B).

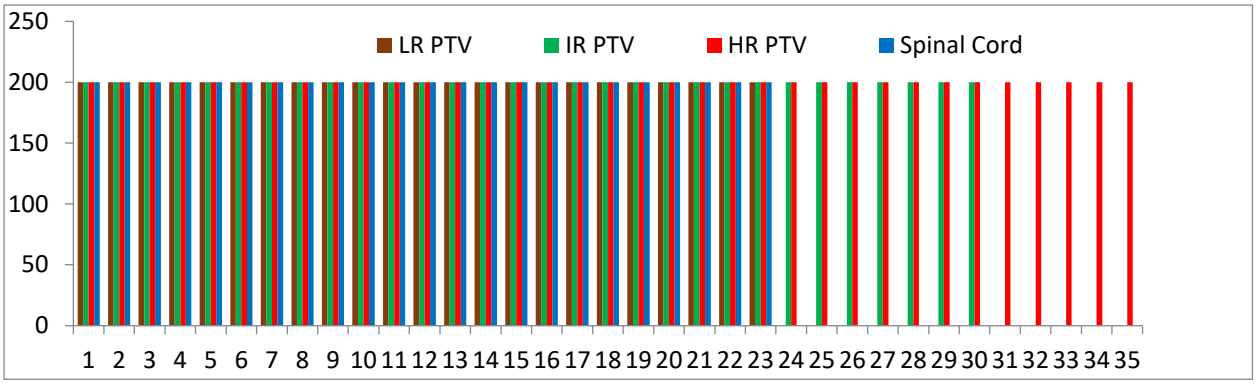

Figure 3A: *Conventional technique with conventional fractionation which means low risk (LR), intermediate risk (IR) & high risk (HR) volume receiving dose with equal dose per fraction (spinal cord receiving dose ~ 200cGy/ fraction over 23 fractions)*

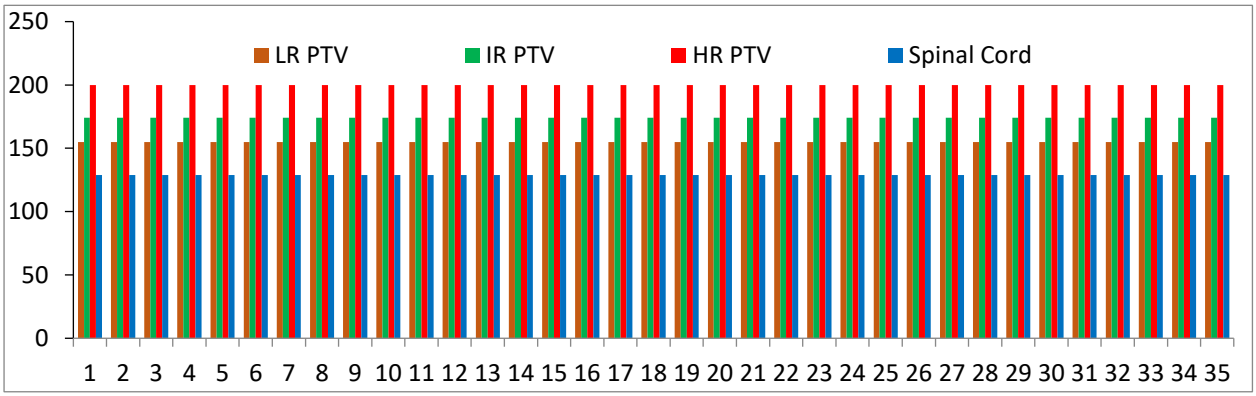

Figure 3B: *Intensity modulated radiotherapy with SIB fractionation means different PTV receiving differential dose per fraction for low risk (LR), intermediate risk (IR) & high risk (HR) volume (spinal cord receiving dose ~ 128cGy/ fraction over 35 fractions)*

In both the presented cases (Figure-3A and 3B), physician prescribed the spinal cord tolerance dose to be the same i.e. maximum dose of 45 Gy. In SIB treatment plan, the spinal cord may receive maximum physical dose of 45 Gy, with much lesser spinal cord dose per fraction than 2 Gy per fraction. When the spinal cord dose distributed throughout the course of treatment, one may plan the treatment, equating radio biologically, considering higher spinal cord tolerance dose with lower spinal cord dose per fraction and higher fraction numbers. While evaluating the dose to spinal cord on dose volume histogram (DVH), one very important parameter to be considered is usually the point dose (within 0.1 cc and up to 1 cc volume). This is because spinal cord is a serial organ and having higher sensitivity to small volume, which may cause radiation induced myelopathy (RM).(Dörr 2009) (Kirkpatrick, van der Kogel, and Schultheiss 2010) Modern radiotherapy technique (IMRT & VMAT) provides facility of differential dose fractionation therefore we have a safe option to increase the tolerance dose of spinal cord as compared to conventional technique, we may exploit this “window of opportunity” in two ways (Boisselier *et al.* 2016). In the first option, one can escalate the PTV dose (increase in dose/ fraction and total target dose keeping the same fraction number) still reaching up to increased tolerance dose of spinal cord. Whereas in the second option, without changing dose fractionation regimen, one may improve the plan quality i.e. better sparing of other OARs, improve target volume coverage and better logistic benefits in terms of Monitor Unit (MU) and treatment time reduction.

2 Material and Methods

A total of 12 patients CT data sets along with approved structure set of H&N cancer used for treatment planning in Eclipse version 11.3 (Varian Medical system Pvt. ltd) treatment planning system. AAA algorithm was employed for dose calculations of all treatment plans. Three independent volumetric modulated arc (VMAT) simultaneous integrated boost (SIB) plans were generated for all the 12 patients. The first plan was generated considering spinal cord tissue constraint of maximum dose 45 Gy (EQD2=35.9 Gy) and PRV spinal cord maximum dose 50 Gy (EQD2=41.9 Gy) named as SPC (with spinal cord constraint 45 Gy) and second plan was generated considering spinal cord tissue constraint of maximum dose 52.50 Gy (EQD2=45 Gy) and PRV spinal cord maximum dose 56.35 Gy (EQD2=50 Gy) named as SPR (with spinal cord relax constraint 52.5 Gy) during volumetric arc intensity modulation optimization. The rest of the tissue objectives were kept the same in both plans during optimization. The third plan was generated by increasing the dose per fraction for target volumes, reaching up to spinal cord tissue constraint of maximum dose 52.50 Gy and PRV spinal cord maximum dose 56.35 Gy named as SPDE (with target dose escalation and spinal cord constraint 52.5 Gy). The flow chart of the planning process as shown in figure 3C. The figure 3.1 represents DVH comparing SPC and SPDE plans. The figure 3.2 represents DVH comparing SPC and SPR plans.

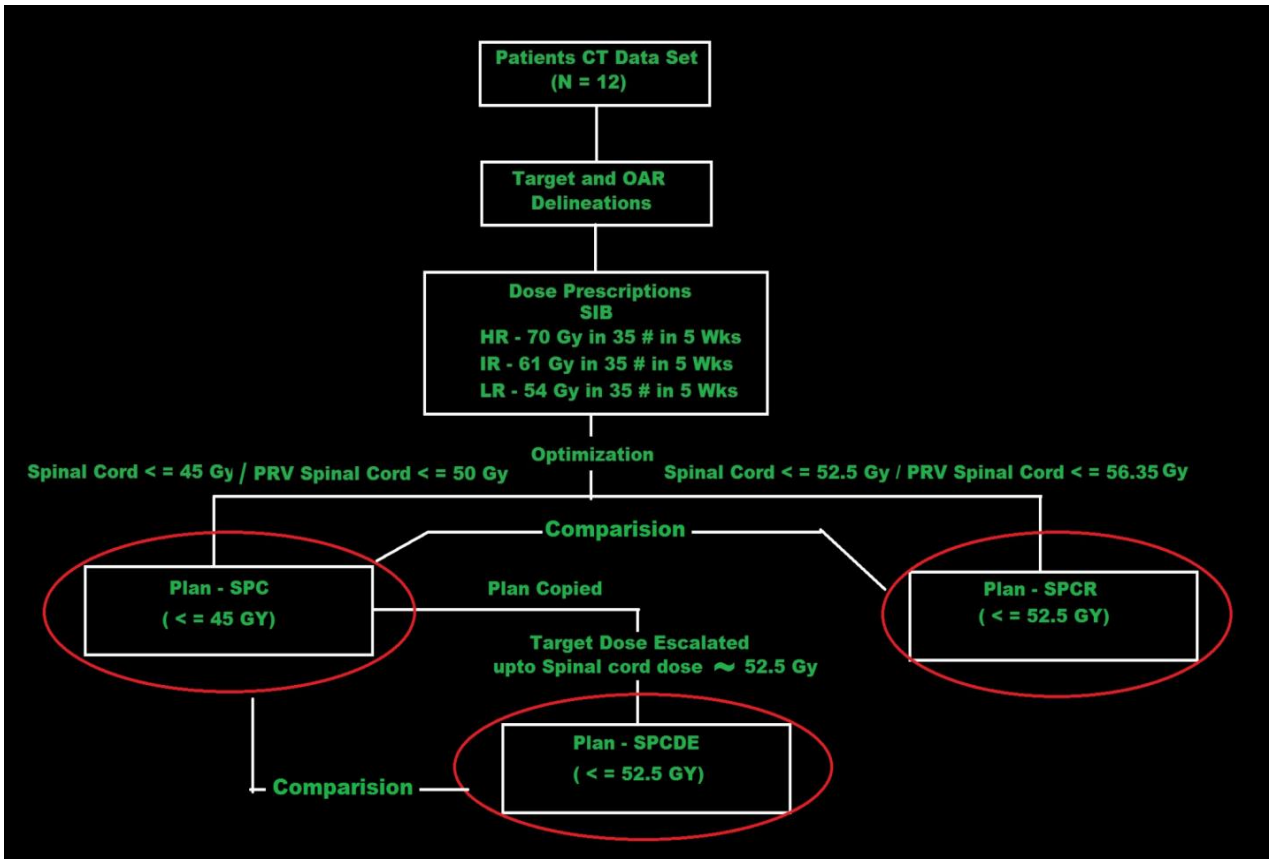

Figure 3C: *Flow chart of the study methodology*

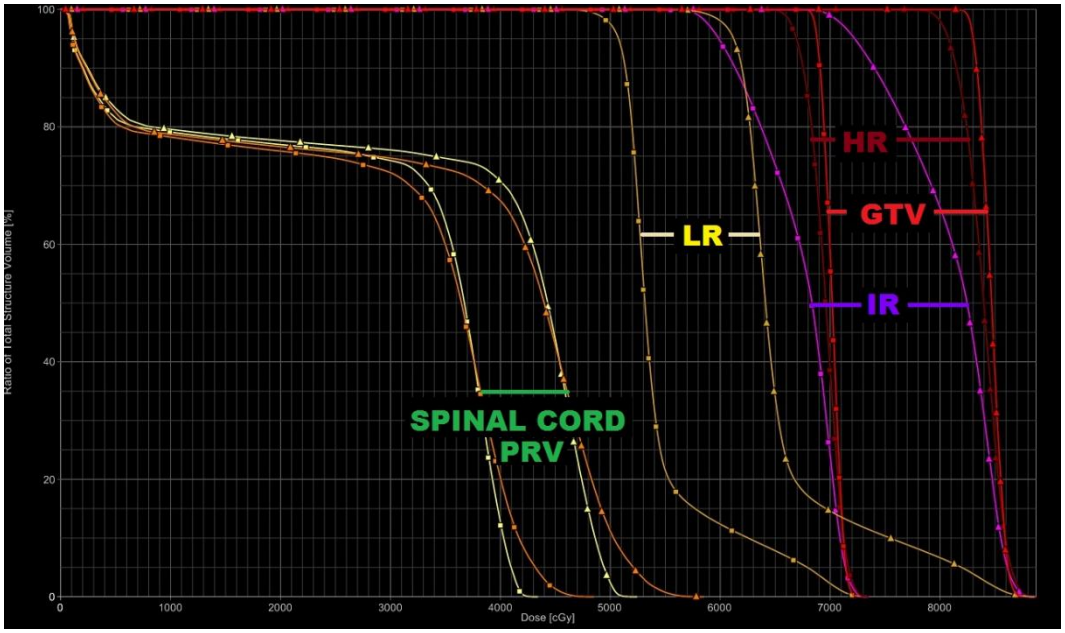

Figure 3.1: *Considering the Increased Spinal Cord tolerance dose (green DVH separation), effective physical dose escalation for all targets (yellow, purple, dark red and red DVH separation) was observed. The* ▬■▬ *symbol represents SPC plan DVH lines and* ▬▲▬ *symbol represents SPDE plan DVH lines.*

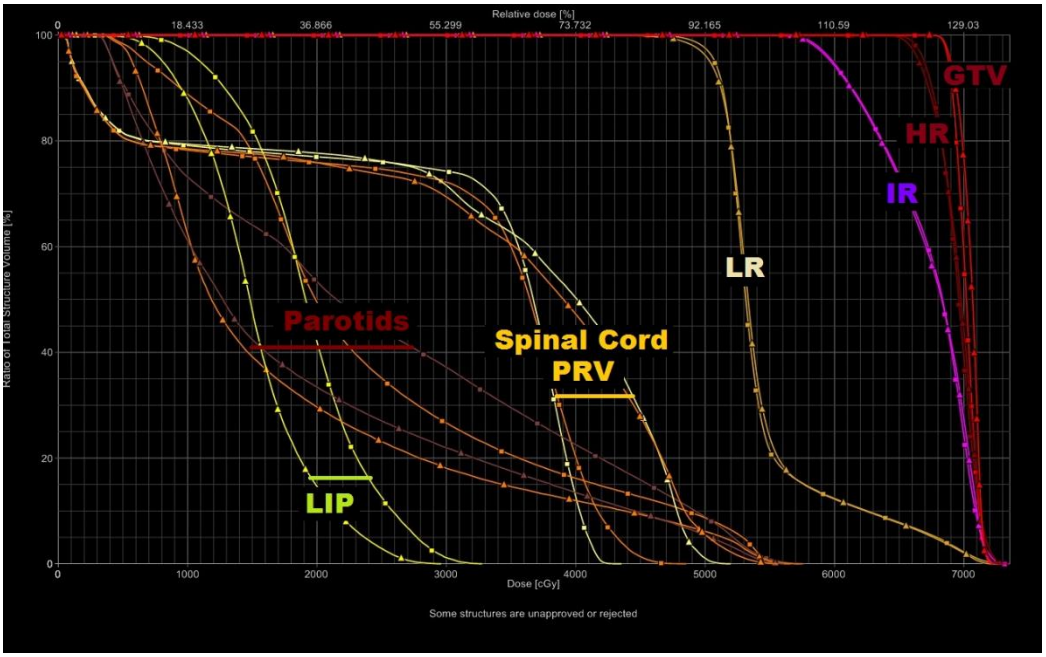

Figure 3.2: *Considering the Increased Spinal Cord tolerance dose (yellow DVH separation), effective dose reduction for anterior OAR (lip: highlighter green DVH separation) and lateral OAR (parotids: dark red DVH separation) were observed without compromising target coverage. The* ▬■▬ *symbol represents SPC plan DVH lines and* ▬▲▬ *symbol represents SPR plan DVH lines.*

Indigenously developed software in MATLAB (Version 2016b) environment based on radiobiological models was used to calculate Equivalent Uniform Dose (EUD), Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP). The software calculated EUD, TCP and NTCP for three different plans of 12 patients by two different radiobiological models Niemierko EUD model and Lyman-Kutcher-Burmen (LKB) model. Both models took into account fractionation effect while evaluating TCP and NTCP. LKB model is widely used phenomenological model and validated

QUANTEC dose constraints in various clinical studies.(Adamus-Górka *et al.* 2011) (Semenenko and Li 2008) (Oinam *et al.* 2011)

3 Results

3.1 Possibilities of dose escalation

Dose received by 95% volume ($D_{95\%}$) for LR PTV, IR PTV and HR PTV were compared between SPC and SPDE plans, whereas for GTV, the dose received by 100% volume ($D_{100\%}$) values were compared. A sufficient dose escalation is observed for all the target volumes. In this study an average physical dose escalation of 18.2%, 18.3%, 18.3% and 18.4% for LR PTV, IR PTV, HR PTV and GTV target volumes were observed respective (Table-4.2).

Table 4.2: *Physical dose escalation*

Target Volume	Average Physical dose Escalation (%)	Average biological dose Escalation (%)
LR PTV	18.2	21.0
IR PTV	18.3	21.4
HR PTV	18.3	21.7
GTV	18.4	21.9

Biological effective dose (BED_{10}) is calculated for all the target volumes by taking α/β ratio as 10 Gy. BED_{10} calculated for LR PTV, IR PTV and HR PTV using $D_{95\%}$ dose values, whereas for GTV $D_{100\%}$ dose values considered. An average BED_{10} values escalation of 21.0%, 21.4%, 21.7% and 21.9% were observed for LR PTV, IR PTV, HR PTV and GTV target volumes respectively (Table-4.2).
Mean median and range of all calculated radiobiological parameters comparison between SPC and SPDE plans are provided in the Tables-4.3 and 4.4.

Table 4.3: *Calculated Radiobiological parameters of SPC plans*

Radiobiological Parameter	Mean	Median	Range
PTV_EUD in Gy	69.84	69.7	67.47 - 71.37
EUD_TCP in %	71.71	71.39	62.12 - 77.34
POISSONS_TCP in %	71.73	71.68	63.10 - 77.93
EUD based NTCP_CORD in %	0.0017	0.001	0.001 - 0.009
LKB_NTCP_CORD in %	1.86	1.8	1.05 - 3.65
EUD_PAROTID in Gy	33.77	40.78	16.55 - 47.20
EUD_NTCP_PAROTID in %	56.42	90.5	0.59 - 95.89
LKB_NTCP_PAROTID in %	22.93	24.26	9.54 - 39.43

Table 4.4: *Calculated Radiobiological parameters of SPDE plans*

Radiobiological Parameter	Mean	Median	Range
PTV_EUD in Gy	85.00	85.33	81.74 - 87.26
EUD_TCP in %	96.75	97.07	94.43 - 97.79
POISSONS_TCP in %	96.94	97.11	94.42 - 98.12
EUD based NTCP_CORD in %	0.026	0.02	0.009 - 0.092
LKB_NTCP_CORD in %	6.65	6.27	5.35 - 10.45
EUD_PAROTID in Gy	41.22	49.14	19.39 - 59.83
EUD_NTCP_PAROTID in %	62.27	97.59	2.07 - 99.42
LKB_NTCP_PAROTID in %	35.41	46.05	12.36 - 61.11

An increase in average EUD for PTV of 21.7%, EUD based TCP for PTV of 34.9%, Poisson_TCP of 35.14% were observed while the spinal cord average NTCP values calculated using Niemerko EUD and LKB model were under acceptable limits i.e. 0.03% and 6.65% respectively. The parotid average NTCP values were 62.3% and 35.4% observed in dose escalated plan.

3.2 Possibilities of achieving planning gain

The plan parameters were compared between SPC and SPR plan. Negligible variations in $D_{95\%}$ values were observed. Average $D_{95\%}$ increase of 0.1% for LR PTV, 1.0% decrease for IR PTV and 1.2% decrease for HR PTV in SPR plan were observed. Whereas average $D_{100\%}$ values, an increase of 0.1% for GTV was observed in SPR plan.

The lateral and anterior OARs shows sufficient dose reduction in SPR plans. The average dose reduction of 16.9%, 15.1% and 23.1% were observed in SPR plans for right, left parotids and lip respectively. An average reduction of 6.9% MU is also observed in SPR plans.

From comparison in Table-4.1 and Table-4.3, it can be observed that EUD and TCP values were comparable between SPC and SPR plan. A decrease of 38.5% and 17.0% were observed in average NTCP values calculated using EUD and LKB models respectively. The spinal cord average NTCP values calculated using EUD and LKB model were 0.03% and 6.84%.

4 Discussion

In this article, myths, facts and scope of revision of spinal cord tolerance dose in intensity modulated SIB treatment of H&N were discussed. As per radiobiological calculation, it was observed that with modern radiotherapy techniques, clinicians may have the liberty to relax the spinal cord tolerance dose constraint (increase of the tolerance dose). This consideration of increment in tolerance dose constraint is considered as “Window of Opportunity” as this opportunity is utilized to generate treatment plans with high therapeutic yield, which may increase the chance of tumor control and improvement in other planning goals (target coverage, homogeneity, conformity, OARs sparing and logistical benefits). The possibilities of target dose escalation was assessed and it was found that a sufficient dose escalation is possible if we relax the spinal cord tolerance dose up to 52.50 Gy (EQD_2=45 Gy) in case of intensity modulated SIB treatment plan (Table 4.5).

Table 4.5: *Achieving planning gain in physical dose*

Description	**Average Percentages**	**Increase** ↑ /Decrease ↓
HR PTV D_{95}	1.2 %	↑
IR PTV D_{95}	1.0 %	↑
LR PTV D_{95}	0.1 %	↓
Right Parotid	16.9 %	↓
Left Parotid	15.1 %	↓
Lip	23.1%	↓
MUs	6.9 %	↓

Using the Window of opportunity, the possibilities of improving plan qualities were also explored. In terms of target coverage and homogeneity, no significant merits or demerits were observed. The planning objectives were kept constant for both SPC and SPR group of plans, which leads to the similarities in achieving the target coverage and homogeneity. But the increase in spinal cord tolerance dose constraint during treatment plan optimization resulting better sparing of anterior and lateral OARs such as parotids and lips. In the relaxed situation (SPR plans) the planning system have the liberty to throw higher MUs from posterior direction as compare to treatment plan with tighter constraint (SPC plans), which leads to better sparing of anterior and lateral OARs. In addition, the total MUs and total treatment time reduction were also observed in relaxed situation (SPR plans). By relaxing the spinal cord tolerance dose limit facilitates the lesser efforts of MLCs (leaf movements, speeds) in achieving the planning objectives than tighter constrained objective. Because of relaxed optimization process MLC complexities decreases which directly reflect in lesser MUs to fulfill the planning objectives for SPR plans against SPC plans.

Martel *et al* suggested that spinal cord continues to receive dose even after shrinking treatment fields or off cord treatment for delivering the total prescribed dose (Martel *et al.* 1998). It is not clearly explained in literature that what actually true dose spinal cord received at the end of treatment. Some studies found that the maximum doses received by the spinal cord ranges from 49 to 56 Gy for the total prescription dose of 70 Gy.(DYNES and SMEDAL 1960) (Sarica *et al.* 2012) RTOG 0631 recommended that the spinal cord should be contoured starting from 5-6 mm above the superior extent of the target volume to 5-6 mm below the inferior extent of the target volume for right assessment of dose-volume effect. The spinal cord should be drawn on every slice of simulation CT.(Road 1818) The motive behind contouring extra slices of spinal cord is to include scatter dose contribution. This enhances accuracy in dose calculation and true dose estimation of spinal cord.

As we have discussed that dose per fraction effect in modern techniques is less than the actual prescribed dose per fraction effect in conventional techniques and additional support of radiobiological model based TCP/NTCP prediction can boost sufficient confidence in physicians to opt for dose escalation in order to improve therapeutic gain. This study primarily concentrated on spinal cord tolerance dose because there are enough evidences published in literature which showed that at 45 Gy, the (extrapolated) probability of myelopathy is 0.03%; and at 50 Gy it is 0.2% (Schultheiss 2008). The risk for myelopathy for irradiation of full cord cross section at maximum dose of 50 Gy, 60 Gy and 69 Gy is 0.2%, 6% and 50% respectively (Marks *et al.* 2010).

Radiobiological model based predictions are highly dependent on which type of models are incorporated while estimating normal tissue complication probability (NTCP). Because of volume effect is different in serial structure and parallel structure, sensitivity of estimated NTCP based on radiobiological model also differs. As in our demonstration we considered Neimierko EUD based NTCP and LKB based NTCP models which provide satisfactory NTCP prediction but author would like to recommend relative seriality model as a better predictor for serial structure NTCP and encouraged to search for most suitable NTCP models for serial structure NTCP estimation. There is risk associated with NTCP models while applying them like variation and sensitivity of biological input parameters of the models, as the RB models are only as good as the reliable and large data available. NTCP model based predictions are based on dose volume histogram (DVH) and it is observed that DVH is not the ideal representations of actual 3D dose distribution. The prime concern is that DVH discard all organ specific spatial dose information which means it assumes all regions of anatomical structure are of equal functional importance (Marks *et al.* 2010). New developments have also been focused on moving away from OAR-based dose-response modeling, and shifting towards voxel-based analyses correlating risk of toxicity with three-dimensional dose maps. It is also noteworthy that radiobiological parameters of RB models derived based on clinical experience gained due to the conventional fractionation schemes (1.8-2 Gy per fraction) as well as by conventional techniques (3DCRT) in which dose distribution is nearly homogeneous against modern techniques where there is high degree of dose heterogeneity (Yorke and Ellen 2001). Therefore, application of these radiobiological models for estimation of NTCP for treatment plans based on modern techniques presents some doubts and should be considered while evaluation (Palma *et al.* 2019). It is recommended to readers that RB models should be clinically validated at their institutional level before accepting it completely.

5 Conclusion

The present dosimetrical and radiobiological analysis lends support to the possibility of spinal cord tolerance dose revision for the intensity modulated SIB treatment regimen of H&N cancers. This revision allows sufficient target dose escalation or planning benefits, which effectively increase the probabilities of achieving treatment goal without any further increment in normal tissue complications. This study encourages the clinical trials to establish the hypothesis or assumptions. This chapter concentrated on application of developed program for estimation of TCP and NTCP. In this chapter NTCP calculated for spinal cord by Gay Niemierko EUD and LKB models. It is demonstrated that how tolerance dose of spinal cord is underestimated during plan evaluation based on physical parameters (maximum dose to spinal cord should be less than 45Gy). This part of study differentiated that tolerance dose of spinal cord for conventional technique and modern technique cannot be considered same because in modern technique dose per fraction received by OAR is less than actual dose per fraction which is not accounted by physical dose based evaluation. Author calculated NTCP for spinal with both RB models EUD & LKB. It observed that those patients received maximum dose more than 45Gy have NTCP values less than 1% and 3% by EUD and LKB model respectively which is in accordance with actual scenario.

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