Chapter 2

Role of Plan Evaluation Indices, Chronological Development and Dosimetrical Comparison

This chapter concentrated on the significance of plan evaluation, discusses the role of various plan evaluation indices and chronological development of various indices. Plan evaluation is a key component in treatment planning and radiation treatment process. Most of the time, we rely on the conventional method of plan evaluation such as slice by slice visual verification of prescription isodose line conforming to planning target volume (PTV) and dose volume histogram (DVH). Routinely, for each patient a number of treatment plans can be generated which differs from each other in terms of dose distribution. A best plan is selected and approved for treatment on the basis of merits of the plan. In earlier days this plan selection process was on the basis of subjective evaluation, which was purely dependent on evaluator skill and knowledge. But with the introduction of newer sophisticated treatment techniques (such as Intensity modulated Radiotherapy (IMRT), Image Guided Radiotherapy (IGRT), Stereotactic Surgery / Radiotherapy etc.), the plan evaluation process is become more complex and needs special care to get better clinical treatment outcome. To resolve the evaluator variability and increase the objectivity of plan evaluation process, RTOG in 1993 introduce Conformity index (CI) and Homogeneity Index (HI) to analyses DVH.(Shaw *et al.* 1993) Since the inception of these indices improvisation, modification and development is in progress.

1 Background

1.1 Conformity Index

Radiotherapy Oncology Group (RTOG) in 1993, introduced a tool to compare the quality of different treatment plans in terms of target coverage named as conformity index. It helps to assess degree of congruence between prescription isodose to planning target volume. Its major disadvantage was that it produced same value for plans having completely different dose distribution which means false perfect score (Shaw *et al.* 1993).

Van't Riet *et al* (1997) proposed a conformity index made of two terms, the first is measure of PTV coverage and second is the measure of how much normal tissue is irradiated. The product of these two terms is the conformation number (CN). In this formulation when there is perfect conformity, with the whole PTV receiving the prescription dose and no normal tissue irradiation, CN = 1, whereas a complete miss of the target yields CN = 0. This index does not yield any false perfect score. However, the product of the two measures leads to a loss of information, so that different plans, with vastly differing potential outcomes, can yield identical values of CN (Riet *et al.* 1997).

Tommy Knoos *et al.,* (1998) proposed Radiation conformity index (RCI) which is nothing but inverse of RTOG index. RCI, while containing useful information, also suffers from possibility of false perfect score. Dimos Baltas *et al.* (1998) reported a conformal index (COIN) to evaluate implant quality of brachytherapy treatment plan. It was the first attempt to subsume critical structure sparing in conformity index formula. Though COIN was introduced for evaluation of brachytherapy plans only but its application can be extended to evaluation of radiotherapy plans also. COIN subsumes target coverage, non-critical healthy tissue irradiation and irradiation of critical structures. COIN is a product of three components, first two components correspond to conformation number CN= C_1xC_2 investigated by Van't Riet's and third component takes care of various critical structures. There was a concern regarding

ISBN: 978-81-970666-3-4
Thesis DOI:10.21467/thesis.172

Series: AIJR Thesis

third component, in case when more than one treatment plan comparing; it is tough to decode degree of sparing of each critical structures estimated one by one, because this component provides only global information. However, it is possible to analyses each critical structure independently & assign priority to serial organ in which maximum dose is important against parallel organ.

Ian Paddick *et al.* (2000) proposed an index dedicated for stereotactic plans which is identical to index introduced by Van't Riet. In 2001, Nakamura *et al.* modified Paddik index by inversing the formulation named as New Conformity Index (NCI) and implemented in the evaluation of stereotactic plans created for gamma knife. This index possesses the same limitation of Paddick index. In 2003, Lomax and Scheib reported a conformity index which is a ratio of the volume of PTV receiving the prescription dose or more, to the volume enclosed by the prescription isodose line. This index can yield false perfect score when prescription isodose line can be totally included in the PTV, but part of PTV may not irradiated by the prescribed dose.

Q R Jackie Wu *et al.* (2003) investigated that existing conformity indices depend on target size and shape complexity Author proved that both volume and shape complexity can have significant effects on conformity values. To overcome this effect author proposed first time a distance based conformity measure, the Conformity distance index (CDI) which is independent of target shape and size. CDI measures the average distance between the prescription isodose surface and target contour surface in 3D space. In this study author simulated target by predefined shapes & surfaces because calculating distance between prescription isodose (PI) & PTV surfaces in 3D space is complex and time consuming. Since the author assumes that radiosurgery target contour surfaces are continuous, smooth & nearly spherical, so that approximation will be very close to true scenario. This is a major drawback associated with CDI and limits the use of it to radiosurgery plans only. In CDI approximation raised the question of accuracy and left with doubt of uncertainty. But author showed a new direction and unique concept in the development of conformity index.

Moyed Miften *et al.* (2004) presented target conformity index (TCI^{+}). Target conformity index consisted of two components; the target conformity index (TCI) for target and normal tissue sparing index (NTSI). Index was simple in formulation but involved complex and laborious evaluation. In his study author contemplates the TCI^{+} model as an alternative to TCP^{+} model for ranking of IMRT plans especially for treatment sites where clinical data available for TCP/NTCP models are inadequate. As we understand TCP^{+} model based on biological probability, whereas in this work TCI^{+} based on clinical judgment which can vary individual to individual. In this index penalty functions for target and organ at risk implemented. Various parameters used to calculate penalty function changes from site to site, hence need to calculate for every treatment site, penalty function mainly responsible to penalize over or under dose of target sub volumes. Penalty function for OAR quantifies dose volume violations for each critical structure using differential DVH. These penalty functions can be drawn from differential DVH only but there is problem because some TPS which have no facility of differential DVH e.g. Monaco. In his work, author tried to bridge gap between dosimetric and biological parameter with the help of TCI.

Chasing the same concept but on a different path J Menhel *et al.* (2006) conceptualized critical organ sparing index (COSI). Author in his work did not merged definitions of CI & COSI in a single formulation like COIN. Instead author established relationship between COSI & CN. This relationship was used to evaluate treatment plans using 2D graphical representation. As we know that COIN accounts only fractional volume of OAR receiving prescription doses & higher. Therefore, suffers from two drawbacks, first it combines the information of target coverage, normal tissue irradiation & critical

structure irradiation. Second issue is that COIN unable to calculate for each organ at its specific tolerance level [4]. COSI rid over the shortcomings of COIN. In COSI formulation specific attention has given to tolerance doses of OAR. The definition of COSI applies to single OAR and one can calculate COSI values for OAR which is in proximity of target. Both COSI & COIN follow same convention that index increased with increasing conformity and ranging between 0 &1. When there is a complete OAR sparing regardless of PTV coverage both indices yield a false perfect score. COSI addressed this shortcoming by facilitating a 2D graphical representation of COSI values versus conformity index defined by Lomax & Scheib in 2003. Author claimed that combination of CI_{Lomax}& COSI compensates both for the loss of information contained in the definition of COSI & $CI_{Lomax}$when each is calculated independently. It means when COSI=1, due to complete organ sparing but poor target coverage, this will be reflected in a low CI values. COSI & COIN both fail to evaluate treatment plans where different targets with different dose prescription assigned.

Lucullus Hing *et al.* (2007) reported plan quality index (PQI) which is a sum of three independent variables denoted by H, M & P. Modified healthy tissue conformity index (HTCI) denoted by "H'' specifically addressed plan evaluation in case of number of PTV with different dose prescription (SIB). This is modified version of HTCI proposed by Lomax & Sheib. To evaluate target coverage a merit function denoted by "M" introduced which takes care of PTV coverage and also monitors the hot, cold spots checks within PTV. Third variable is a normal tissue sparing denoted by "P" and it is a kind of penalty function which comes into play when any OAR in proximity of PTV breaches tolerance limit of respective OAR. An admiring thing about normal tissue sparing (P) is that it implements number of check point doses at which maximum tolerable normal tissue volume is defined. It is most useful in parallel kind of structure where different dose volume criteria are following. PQI provides detail information regarding plan quality. PQI evaluation also ranges between 0 & 1. So, for an ideal case, PQI=0.There is a little concern about PQI, as PQI has three independent variables hence there is a possibility that one plan may have a better M while another plan may have a better P. Therefore, ultimate decision depends solely on clinician experience.

Krzysztof Slosarek *et al.* (2008) conceptualized Radiation planning index (RPI) using C++ language computer program named as RPI win. It is personalized software which calculates CI by importing DVH parameters from treatment planning system. RPI incorporates both critical structure sparing and PTV conformity in number of target with different dose prescription. In RPI standard deviation (SD) of dose distribution within PTV calculated by assuming that whole volume of target is homogeneously covered with prescribed dose. From this we can infer that RPI indirectly accounts for homogeneity. Ideal value of RPI is one when SD is zero. In this work author did not compared results of RPI with published CI in literature. Only problem with this index is that it involved mathematical complexity.

Prabhakar R *et al.* (2011) developed plan normal tissue complication index (PNI) in Visual basic platform. A strange thing about this index is that it has employed TD5/5 & TD50/5 in its formulation which gives it a radiobiological touch. Author in his study applied combination of existing definitions of CI (RTOG & Lomax) with PNI for plan evaluation. Treatment plan DVH among the rival plans exported to developed program for calculating PNI and then based on PNI and CI value final treatment plan selected. As the critical structure involvement is judged by dose received to $1/3^{rd}$, $2/3^{rd}$& $3/3^{rd}$ volume of OAR, PNI satisfies for parallel structures but in case of serial structures there is a question of uncertainty. The proposed index is applicable to conventional fractionation schedule 1.8-2 Gy and this is a limitation of index that it is not suitable for SIB, SRS, SRT & SBRT treatment plans. The PNI evaluation criteria is ranging 0 to 3. If PNI reaches to 3 it means that all critical structures exceeded the

tolerance dose whereas minimum value shows best plan. Author evaluated PNI in four different sites head & neck, prostate, lung & upper abdominal cancers.

Fion W K Cheung *et al*. (2012) developed personalized CI_{DD} (dose distance based) for evaluating plan quality discerning power. Author emphasized on GTV coverage and cold spots within PTV while employing his developed CI_{DD}. According to author GTV must be covered by full prescribed dose and cold spots acceptable as away from GTV but can be within PTV. It is a two dimensional CI with dose and distance incorporated. CI_{DD} provided solution in case of different targets with different dose prescription treatment plan evaluation. Only concern with this index is that it cannot be implementing to post-operative patients where GTV don't exist hence formulation require modification. In this work author included patient specific spatial dose information which makes it unique if ignore mathematical complexity. One thing is contradictory as compare to other indices in plan evaluation criteria. In this case lower value of CI_{DD} results better plans. In his work author left with new finding that GTV is likely to have higher malignant cell density hence GTV under dose cannot accepted. CI_{DD} have been placed in group-A because CI_{DD} does not quantify the undesirable dose delivered to normal tissue and OAR. CI_{DD} does not produce false score and focused only target coverage.

Following the concept of Fion W K Cheung, J M Park *et al.* (2014) posted a new index using same concept of distance in different way. He assumed distance between the surfaces of the target volume (TV) and prescription isodose line (V_{RI}). It has overridden two drawbacks of W K Cheung proposed $CI_{DD.}$ First it included 3D information and secondly normal tissue irradiation adjacent to target. However, this index also left with short comings like no consideration of spatial dose information and not suitable for different targets with different dose prescription plans. Author outlines two CI, $CI_{distance}$ & $CI_{abs\_distance}$ with their respective standard deviation (SD). $CI_{distance}$ does not offer correct information about target coverage because it is an average value. Hence it was recommended to use $CI_{distance}$ with SD so that false perfect score will not appear. The values $CI_{distance}$& $CI_{abs\_distance}$ provides useful information when they are used in combination with their respective SD. It offers very simple criteria of plan evaluation, when distance between TV & V_{RI} is zero which means $CI_{distance}$& $CI_{abs_distance}$is zero there is a perfect match and complete normal tissue sparing. Author reported that $CI_{distance}$& $CI_{abs\_distance}$ cannot apply when the centroid located on the surface of TV as well as values $CI_{distance}$& $CI_{abs\_distance}$ was incapable to provide full information on target conformation unless not added values of SD. There is a possibility of geometric uncertainty which needs to be addressed while defining centroid in complex target structure, shape & size. The best thing about this index is it can distinguish the differences in 10% increase or decrease in V_{RI} occurs with respect to TV and cannot produce false perfect score which is a limitation of many CI as reported by author. This index includes in Group-A because of no OAR consideration.

Shahnawaz Ansari *et al.* (2018) presented Triple point conformity scale (CS3). Author in his work compared RTOG CI with his developed index. In the formulation author took ratio of sum of volume of 95%, 100% & 105 % prescription isodose line to thrice of target volume. Range of evaluation is in between 0.643 to 0.667 calculated for 10 head & neck IMRT plans. This index is evaluated under small sample size as well only for single site hence utility of this index need to be test for other sites also. This index somewhat tried to merged definitions of HI & CI into single index.

1.2 Homgeneity Index

Homogeneity index is influenced by many factors like target volume, location of target and prescribed dose and this is validated by various authors, still there are some factors need to be unveil. As we know

that different parts of the body possess varying degree of heterogeneity. Brain possess least heterogeneity in terms of density difference as compare to head & neck, thorax, abdomen and pelvis. Head and neck carry highest degree of density difference because of structures like oral cavity, nasal cavity, high density bone, high density teeth, tongue and sometimes dental implants which affects dose distribution significantly inside the target volume. It has been observed that treatment plans of brain cases presents more homogeneous dose distribution inside PTV except SRS/SRT treatment plans where dose heterogeneity is desirable as compare to other site treatment plans. Head and neck treatment plans especially SIB plans are found to have highest degree of heterogeneity or say poor value of HI if calculated individually for differential target volumes. One more useful finding is that HI index also get affected by proximity of OAR, extent of their overlapping with PTV and their respective tolerance doses. To identify presence of hot spots and cold spots which is a measure of underdose and overdose in PTV is a crucial step in plan evaluation. Ideally HI should take care of this but existing formulas of HI cannot satisfactorily express it and therefore slice by slice verification of dose distribution is always a primary choice of clinicians. Because many times presence of hot spot in GTV or CTV and cold spot adjacent to OAR but within PTV is acceptable while plan evaluation. It has been clinically accepted that presence of hot spot in GTV provides radiobiological advantage in terms of TCP [20, 21]. Existing formulas of HI cannot reveal location of multiple hot spot and cold spot within PTV and merely provides degree of heterogeneity. Let us discuss benefits and drawbacks of various definitions of HI.

Myonggeun Yoon *et al.* (2007) developed new homogeneity index named it sigma index (S-index). Sigma index is stranger than other homogeneity indices available in literature because first time it has utilized differential DVH information. In his study author reported that definitions of conventional and modified homogeneity indices can produce incorrect information. It means that HI values calculated for cumulative DVH of two different plans can be same even first plan is better than second plan in terms of homogeneity. According to author any HI based on the doses at only a limited number of points of the cumulative DVH may provide wrong information about dose homogeneity in PTV. We know that cumulative DVH is a plot of a given structure that receives at least a certain dose and it is easy to interpret. However, the differential DVH carry unique information regarding the extent of dose variation within a structure. Differential DVH is a plot of volume receiving a certain dose within a specified dose range. Using this unique property of differential DVH, sigma index provides better dose homogeneity effectively without producing false scoring. Sigma index was further tested by Pushpraj Pathak *et al* as compared to existing HI definitions. Manikandan P S *et al.* also evaluated sigma index in comparison with conventional and modified HI and found superiority of S-index over them. Results of sigma index look promising& convincing with a small problem is that many treatments planning system does not facilitate differential DVH like Monaco of Elekta Medical system.

Kataria T J *et al* (2012) verified and checked concordance level between values of HI obtained by various formulas of HI available in literature except sigma index [19]. Author showed strength of association between HI and prescribed dose, planning target volume & location of PTV in the patient body. Author concluded that the HI index has no direct correlation between the location and planning target volume but there is an indication of improved HI in plans of higher prescribed dose. Author did not discussed shortcomings of various formula used in her study. Azza Helal *et al.* (2015) also confirmed in his study that there is a strong correlation between HI and volume of target, prescribed dose.

Number of authors (Akpati *et al.* 2008; Ansari *et al.* 2018; Baltas *et al.* 1998; Cheung and Law 2012; Feuvret *et al.* 2006; Helal and Omar 2015; Leung *et al.* 2007; Leung, Chua, and Wu 1999; Lomax and

Scheib 2003; McNiven, Sharpe, and Purdie 2010; Menhel *et al.* 2006; Miften *et al.* 2004; Nakamura *et al.* 2001; Paddick 2000; Paddick and Lippitz 2006; Y. K. Park *et al.* 2014; J. M. Park *et al.* 2014; Petrova, Smickovska, and Lazarevska 2017; Piotrowski *et al.* 2009; Prabhakar 2010; Prabhakar and Rath 2011; Riet *et al.* 1997; Ślosarek *et al.* 2008; Tommasino, Nahum, and Cella 2017; Yaparpalvi *et al.* 2018; Yoon *et al.* 2007) defined CI with new ideas but most of them could not identifies many issues such as role of cold/hot spot in PTV, role of spatial dose information and different targets with different dose prescription etc. Some new indices were also defined to address the flaws of earlier indices, but mostly were personalized and created using special software such as MATLAB, C-language, and Visual basic etc. Hence their application is limited and cannot be generalized.

Second important parameter in plan evaluation is a Homogeneity index, which accounts for non-uniform dose distribution inside the PTV. Homogeneity index is influenced by many factors like target volume, location of target and prescribed dose and this is validated by various authors, still there are some factors need to be unveil.(Kataria *et al.* 2018)

Hence, there is a need to categories the available published conformity indices and homogeneity indices and find out the suitability of these indices in various clinical situations. In this present study an attempt has been made to classify the published plan evaluation indices and a dosimetrical suitability test between various indices was conducted.

2 Material and Methods

Multiple indices proposed in literature were categorized into two groups, Group-A and Group-B. Group-A contains those CI formulas which does not consider critical structure sparing while using them for evaluation but includes normal tissue and PTV coverage (Table-2.1). Group-B contains those CI formulas which consider PTV coverage, normal tissue and critical structure sparing simultaneously while using them for plan evaluation (Table-2.2). The intention behind forming two groups is to enhance clear understanding to reader regarding various CI definitions published in literature. Various HI formulas extracted from literature are presented in Table -2.3.

Table 2.1: *Group-A containing definitions of CI which do not take into account OAR sparing*

Author name	**year**	**Formulation**	**Parameter description**
dward Shaw	1993	$CI_{RTOG} = \frac{V_{RI}}{TV}$	$V_{RI} = volume\ of\ reference\ isodose\ line$ TV= target volume
Tommy Knoos	1998	$RCI = \frac{V_{PTV}}{Vi}$	V_{PTV} = Planning target volume Vi = treated volume or $V_{95\%}$ isodose line volume
Baltas	1998	$CN = \frac{TV_{RI}}{TV} \times \frac{TV_{RI}}{V_{RI}}$	TV_{RI}= volume of target covered by reference isodose line
Lomax and Scheib	2003	$CI_{LOMAX} = \frac{V_{T,PI}}{V_{PI}}$	$V_{T,PI}$= volume of PTV receiving prescription dose or more V_{PI} = volume enclosed by prescription isodose
Ian Paddick	2000	$CI_{PADDICK} = \frac{TV_{RI}^2}{TV \times V_{RI}}$	TV_{RI}= volume of target covered by reference isodose line $V_{RI} = volume\ of\ reference\ isodose\ line$
Jean L Nakamura	2001	$NCI = \frac{TV \times V_{RI}}{TV_{RI}^2}$	$V_{RI} = volume\ of\ reference\ isodose\ line$ TV_{RI}= volume of target covered by reference isodose line
Lcullus Hing	2007	$HTCI = \frac{TV_{RI}}{V_{RI}}$ $Modified\ HTCI = \frac{1}{r}\sum_{i=1}^{r}\left(\frac{TV_{RI,i}}{V_{RI,i}}\right)$	For more than one target $TV_{RI,i} = target\ volume\ covered\ by\ ith\ reference\ dose$ $V_{RI,i} = total\ isodose\ volume\ of\ the\ ith\ reference\ dose$
Q R Jackie Wu	2003	$CDI = \frac{NT_{PI} + (TV - TV_{PI})}{\frac{1}{2}(S_{PI} + S_{TV})}$ $where\ NT_{PI} = (PI - TV_{PI})$	S_{PI} and S_{TV} are the surfaces of prescription isodose and target volume NT_{PI} is a normal tissue volume receiving prescription dose or higher
J M Park	2014	$CI_{distance} = \frac{\sum_{i=1}^{N}\frac{D_D - D_T}{D_T}}{N} \times 100$ $CI_{abs\_distance} = \frac{\sum_{i=1}^{N}\frac{\lvert D_D - D_T\rvert}{D_T}}{N} \times 100$	$CI_{distance}$, D_D, D_T defined as the distance from the centroide to the points of intersection
Shehnawaj Ansari	2018	CS3 = (V_{95} + V_{100} + V_{105})/3V_T	V_{95}, $V_{100}$and$V_{105}$are the volume of 95,100 and 105 % isodose lines V_T is a volume of target

Table 2.2: *Group-B containing definitions of CI which take into account OAR sparing*

Author name	year	Formulation
Dimos Baltas	1998	$$COIN = CN \times \prod_{i=1}^{N_{CO}} [1 - \frac{V_{COref,i}}{V_{CO,i}}]$$ Where, CN is a confirmation number Ncs is a total number of critical structures Vcs,i is volume of ith critical structure Vcsref,i overlap volume of cs and reference isodose volume
Moyed M Miften	2004	$$TCI = P_{PTV}(\frac{PTV_{TD}}{PTV})$$ $$NTSI = P_{NTV}(1 - \frac{NTV_{TD}}{NTV})$$ Where, $$P_{PTV}(Vi, Di) = \begin{cases} e^{-\sigma c,i(Dmin-Di)} & for\ Vi > Vc, max\ and\ Di < Dmin \\ 1 & for\ Dmin \le Di \le Dmax \\ e^{-\sigma h,i(Di-Dmax)2} & for\ Vi > Vh, max\ and\ Di > Dmax \end{cases}$$ $$P_{NTV}(Vi, Di) = \begin{cases} 1 & for\ Di \le Dtol \\ e^{-\gamma_i(Di-Dtol)} & for\ Vi > Vmax\ and\ Di > Dtol \end{cases}$$ $$TCI^{+} = \prod_{i=1}^{Nt} TCI_i \prod_{J=1}^{Mnt} NTSI_j$$ P_{PTV} is a penalty function uses to penalize under/overdosage of target sub-volumes. P_{NTV} is a penalty function that depends on normal tissue subvolumes exceeding tolerance doses. PTV_{TD} is a PTV enclosed by therapeutic dose $NTV_{TD}$is a normal tissue volume received therapeutic dose
Krzysztof Slosarek	2008	$$RPI = \sqrt[n+m]{\prod_{i=1}^{m}\left(\prod_{j=1}^{n}\left[\left(1 - \frac{w_j \int_0^{D_{maxOAR}} V_{jOAR} dD_{OAR}}{\int_0^{D_{maxOAR}} V_{jOAR100\%}\ dD_{OAR}}\right)\left(\frac{\int_0^{D_{maxPTV}} V_{iPTV}\ dD_{PTV}}{\int_0^{D_{maxPTV}} V_{iPTV100\%} dD_{PTV}}\right)(1 - SD_{ev.p_i})\right]\right)}$$ Where, m is the number of PTV and n is the number of OAR Wj is importance factor to rank organs sensitivity to irradiation
J Menhel	2006	$$COSI = 1 - \frac{V_{OAR>TOLERANCE}}{TC_V}$$ Where, V_{OAR} is the fraction of volume of OAR receiving more than a pre-defined tolerance dose and TCv is the fractional volume of PTV covered by prescription isodose.
Lucullus Hing	2007	$$Modified\ HTCI\ (H) = \frac{1}{r}\sum_{i=1}^{r}\left(\frac{TV_{RI,i}}{V_{RI,i}}\right)$$ $$M = \frac{1}{r}\sum_{j=1}^{r}.\left[\frac{\sum_{i=1}^{p}\left(\frac{V_{T_jD_i}}{V_{T_jRD_i}}\right) + \sum_{i=1}^{q}\left(1 - \frac{V_{T_jD_i}}{V_{T_jAD_i}}\right)}{\sum_{i=1}^{p}\left(\frac{100}{V_{T_{j,RDI}}}\right) + q}\right]$$ $$P = \frac{1}{n} \times \sum_{j=1}^{n}\left\{\frac{1}{m} \times \sum_{i=1}^{m}\left[1 - \frac{V_{OjD_i}}{V_{OjAD_i}}\right]\right\}$$ $$PQI = \sqrt{[(1-H)^2 + (1-M)^2 + (1-P)^2]}$$
R Prabhakar	2011	$$PNI\ = f\ (n, j/3, TD)$$ $$PNI\ \left(n, \frac{j}{3}, TD\right) = \sum_{i=1}^{n}.\frac{\left(\sum_{i=1}^{3}.\left(\frac{D}{TD_{5/5}}\right)_{j/3}\right)_i}{n}$$ Where, n= critical structures j/3 = dose received by 1/3rd, 2/3rdand 3/3rd of the critical structure j= 1,2,3 TD = Tolerance dose and it can be $TD_{5/5}$ or $TD_{50/5}$

Table 2.3: *Various formulas of homogeneity indices available in literature.*

Sr.No.	Formulation	Parameter description
1	$HI_{RTOG} = \frac{I_{max}}{RI}$	Imax and RI are the maximum dose and reference dose to PTV
2	$HI = \frac{D_{max}}{D_{min}}$	$D_{max}$and D_{min} are the maximum and minimum dose in PTV
3	$HI = \frac{D_2 - D_{98}}{D_P} X100$	D2 and D98 are the doses to 2% and 98% volume of PTV Dp is a prescribed dose
4	$HI = \frac{D_5 - D_{95}}{D_p} \times 100$	D5, D95 are the doses to 5% and 95% volume of the PTV
5	$HI = \frac{D_{max}}{D_P}$	$D_{max}$and D_p are the maximum and prescribed dose to PTV
6	$HI = \frac{D_2 - D_{98}}{D_{50}} X100$	D2, D98 and D50 are the doses to 2%, 98% and 50% volume of PTV
7	$S - index = \sqrt{\sum_{i=1}^{n} . (D_i - D_{mean})^2 \frac{V_i}{V}}$	Vi is the i^{th} volume element receiving a dose of at least (Di) V is the total volume D_{mean} is a mean dose

Structure data set of twenty five patients were taken under consideration comprising five GBM cases of brain site , five carcinoma of larynx of head and neck site, five carcinoma of esophagus of thorax site, five carcinoma of lung of thorax and five carcinoma of cervix of pelvis site. For each patients two plans were created using VMAT technique in Eclipse treatment planning system version 11.3, Varian Medical system Inc., Palo Alto USA. Dose calculation grid size was set 3 mm for all planned cases. Dose volume optimizer (DVO) algorithm had been employed for optimization and Anisotropic Analytical Algorithm (AAA) for dose calculation. First type of plan (Plan- A) were generated considering all tissue objectives for targets and OARs whereas second type of plan (Plan-B) were generated considering only targets tissue objectives and excluding OARs tissue objectives during plan optimization. In Plan-B, we have removed all organs at risk from optimization process in order to search effect on various parameters of plan evaluation indices like conformity index and homogeneity index.

2.1 Plan comparison criteria

Plan comparison is performed between Plan-A and Plan-B in view of various formulas of CI. For target coverage, 95% of prescription dose must cover 100% of planning target volume. Different organ at risk receiving dose in Plan-A and Plan-B were also recorded in this study for comparison. Results obtained in this study cannot consider absolute because new plan created in this study can affected by various factors e.g optimization algorithm, normal tissue objective setting and planner's way of planning.

3 Result

It is observed that CI calculated by various formulas in two different scenario presented (table-2.4) less than 3% variation (Range: -1.07% to 2.3%). The percentage variation Organ at Risk (OAR) doses in two different plan were recorded in table 2.6,2.7,2.8,2.9& 2.10. It is observed that, when the OAR are situated in close proximity to the target, such as esophagus (table- 2.7) and cervix (Table-2.9) there is a marginal increase of OAR doses in Plan – B than Plan –A. Whereas, a significant decrease of OAR

doses in Plan – B than Plan –A was observed when the OARs situated at sufficiently farther from target, such as head and neck (table-2.6), brain (table-2.8) and lung (table-2.10). In esophagus cases, the variation was least for heart (5.1 %) and highest for right lung (8.9%) whereas in cervix cases, it was least for right femur (2.0 %) and highest for left femur (4.5 %). In head and neck cases the variation was least for right parotid (17.0 %) and highest for brainstem (51.2 %). Similarly in brain cases the variation was least in left optic nerve (9.4 %) and was highest for right optic nerve (23 %), whereas in lung cases it was least for heart (28%) and highest for contra lateral lung (31.6%).

Table 2.4: *CI belong to Group-A and target coverage evaluation in two different plans Plan-A and Plan-B*

	$CI_{RTOG} = \frac{V_{RI}}{TV}$		$RCI = \frac{V_{PTV}}{Vi}$		$CI_{LOMAX} = \frac{V_{T,PI}}{V_{PI}}$		$CI_{PADDICK} = \frac{TV_{RI}^2}{TV \times V_{RI}}$		$HTCI = \frac{TV_{RI}}{V_{RI}}$		Target Coverage in %	
patient site	PL-A	PL-B	PL-A	PL-B	PL-A	PL-B	PL-A	PL-B	PL-A	PL-B	PL-A	PL-B
HN	1.03	1.04	0.97	0.96	0.86	0.68	0.92	0.87	0.94	0.92	96.3	97.5
HN	1.02	1.04	0.98	0.96	0.87	0.74	0.95	0.92	0.96	0.94	95.6	96.8
HN	1.01	1.02	0.99	0.98	0.92	0.95	0.95	0.96	0.97	0.97	95.9	97.2
HN	1.16	1.17	0.86	0.86	0.94	0.96	0.86	0.86	0.86	0.86	96.0	97.1
HN	1.03	1.03	0.97	0.97	0.94	0.95	0.82	0.95	0.89	0.96	97.0	98.3
ESO	1.04	1.1	0.96	0.91	0.82	0.9	0.92	0.89	0.94	0.9	96.2	97.8
ESO	1.03	0.99	0.97	1.01	0.92	0.81	0.96	0.94	0.97	0.98	96.5	98.0
ESO	1.06	1.14	0.95	0.88	0.64	0.85	0.88	0.88	0.91	0.88	97.1	98.4
ESO	1.09	1.11	0.92	0.9	0.74	0.66	0.86	0.9	0.89	0.9	96.2	96.9
ESO	1.02	1.12	0.98	0.89	0.76	0.89	0.93	0.89	0.96	0.89	95.8	96.5
BRAIN	1.09	1.12	0.91	0.9	0.95	0.93	0.91	0.89	0.91	0.89	97.5	98.6
BRAIN	1.07	1.15	0.93	0.87	0.68	0.87	0.93	0.87	0.93	0.87	97.2	98.0
BRAIN	1.12	1.15	0.9	0.87	0.95	0.93	0.89	0.87	0.89	0.87	96.5	97.7
BRAIN	1.05	1.17	0.95	0.86	0.7	0.87	0.93	0.86	0.94	0.86	97.6	98.3
BRAIN	1.07	1.03	0.93	0.97	0.94	0.84	0.93	0.95	0.93	0.96	97.1	97.5
CERVIX	1.01	1.01	0.99	0.99	0.93	0.95	0.97	0.98	0.98	0.98	95.6	96.1
CERVIX	1.01	1.02	0.99	0.98	0.93	0.94	0.9	0.94	0.94	0.96	96.2	97.0
CERVIX	1.02	1.02	0.98	0.98	0.92	0.93	0.91	0.86	0.95	0.96	96.5	98.0
CERVIX	1.01	1.02	0.99	0.98	0.93	0.96	0.92	0.95	0.95	0.97	96.0	97.0
CERVIX	1.07	1.15	0.93	0.87	0.92	0.95	0.86	0.83	0.89	0.85	95.8	97.2
LUNG	1.03	1.03	0.97	0.97	0.85	0.87	0.91	0.92	0.94	0.91	95.6	97.0
LUNG	1.04	1.02	0.97	0.98	0.87	0.88	0.89	0.86	0.91	0.93	96.4	97.7
LUNG	1.03	1.03	0.97	0.97	0.87	0.89	0.83	0.84	0.9	0.87	96.7	98.1
LUNG	1.03	1.04	0.97	0.97	0.83	0.85	0.92	0.9	0.94	0.92	95.3	96.4
LUNG	1.04	1.04	0.96	0.96	0.88	0.89	0.84	0.83	0.9	0.89	95.8	97.3
MEAN	1.05	1.07	0.96	0.94	0.86	0.88	0.9	0.89	0.93	0.92	96.33	97.46
SD	0.04	0.06	0.03	0.05	0.09	0.08	0.04	0.04	0.03	0.04	0.63	0.67
%Variation		1.9		-2.0		2.3		-1.1		-1.07		1.17

SD= Standard Deviation

Target coverage is slightly improved in Plan-B (1.17%). This showed that by relaxing OAR won't help to improve conformity. CI evaluated in our study which belongs to group-A do not present true picture

of real situation. This may also depends on the optimization algorithm employed in commercial treatment planning system.

By following the same methodology of comparison (table-2.5), HI of two different scenarios were evaluated using seven formulas. Out of seven formulas four formulas with serial number 3, 4, 6 and 7 of table 2.3, showed marginal percentage variation -24.04%, -24.84%, -26.1% and -27.94% respectively. It is analysed that when OAR are removed from optimization, dose homogeneity improved which is specifically pointed by these four formulas. Sigma index found to be more efficient formula while evaluating HI of a treatment plan.

Table 2.5: *HI evaluation in two different plans Plan-A and Plan-B*

	$HI_{RTOG} = \frac{I_{max}}{RI}$		$HI = \frac{D_2 - D_{98}}{D_P} X100$		$HI = \frac{D_2 - D_{98}}{D_{50}} X100$		$HI = \frac{D_{max}}{D_P}$		$HI = \frac{D_5 - D_{95}}{D_p} \times 100$		$HI = \frac{D_{max}}{D_{min}}$		$S - index$	
Patient site	PL-A	PL-B	PL-A	PL-B	PL-A	PL-B	PL-A	PL-B	PL-A	PL-B	PL-A	PL-B	PL-A	PL-B
BRAIN	1.2	1.15	7.43	4.42	7.17	4.35	1.12	1.09	5.37	3.12	1.22	1.17	2.3	2.1
BRAIN	1.2	1.13	6.83	4.82	6.59	4.73	1.09	1.07	5.5	3.67	1.21	1.14	2.6	2.3
BRAIN	1.1	1.12	7.93	4.8	7.85	4.74	1.07	1.07	3.07	2.23	1.19	1.15	2.2	1.9
BRAIN	1.2	1.14	7.62	7.63	7.29	7.50	1.11	1.08	5.85	3.27	1.21	1.15	3.2	2.8
BRAIN	1.1	1.12	5.73	3.77	5.69	3.73	1.05	1.06	4.2	2.47	1.17	1.16	2.5	2.2
HN	1.2	1.18	12.4	11.6	12	11.5	1.13	1.12	10.1	8.14	1.35	1.32	3.4	3.1
HN	1.2	1.17	13.8	12.2	13.3	12	1.14	1.11	10.3	9.14	1.37	1.28	4.5	3.3
HN	1.2	1.16	12.3	10.8	11.8	10.8	1.13	1.1	11.2	7.2	1.31	1.24	4.3	3.2
HN	1.2	1.17	12.4	10.8	12	10.8	1.11	1.11	11.2	7.84	1.3	1.23	3.7	2.4
HN	1.2	1.17	13	9.76	12.5	9.68	1.14	1.11	11.5	7.62	1.35	1.28	2.7	1.9
ESO	1.2	1.22	14.6	13.6	14.3	13.2	1.17	1.16	10.4	9.93	1.37	1.27	6.3	4.2
ESO	1.2	1.16	11	6.22	10.6	6.18	1.13	1.1	8.31	7	1.26	1.18	5.5	3.5
ESO	1.2	1.14	12.2	7.33	12.1	7.25	1.09	1.08	9.16	5.62	1.24	1.17	4.3	3.1
ESO	1.2	1.1	12	4.38	11.8	4.36	1.1	1.04	9.4	3.49	1.2	1.09	3.9	2.8
ESO	1.2	1.14	11.6	5	11.5	4.96	1.13	1.08	8.6	4.71	1.34	1.21	4.4	3.3
CERVIX	1.2	1.14	5.64	5.12	5.37	4.9	1.09	1.09	4.3	3.96	1.2	1.18	2.4	1.8
CERVIX	1.2	1.14	9.48	7.4	9.41	7.21	1.09	1.08	7.32	5.48	1.25	1.3	2.8	2.2
CERVIX	1.2	1.16	10.8	9.38	10.6	9.05	1.12	1.1	7.34	7.8	1.36	1.23	2.1	1.7
CERVIX	1.2	1.15	6.12	4.74	5.9	4.55	1.1	1.09	4.66	3.7	1.29	1.18	2.5	1.9
CERVIX	1.1	1.12	7.32	6.48	7.05	6.31	1.08	1.06	5.36	4.7	1.25	1.22	2.4	1.6
LUNG	1.2	1.19	8.02	7.13	10.2	6.92	1.17	1.13	6.12	5.3	1.27	1.21	7.7	4.6
LUNG	1.2	1.13	8.33	6.08	7.92	6.22	1.09	1.08	6.4	4.55	1.26	1.25	6.1	3.9
LUNG	1.15	1.15	10	6.05	9.9	5.62	1.09	1.09	9.35	7.4	1.28	1.25	5.2	3.6
LUNG	1.2	1.14	8.25	7.12	8.23	7.01	1.17	1.08	8.18	5.97	1.36	1.22	6.5	4.1
LUNG	1.2	1.13	7.56	7.2	9.6	7.26	1.11	1.08	7.5	6.65	1.33	1.19	3.9	2.7
MEAN	1.2	1.15	9.69	7.36	9.62	7.23	1.11	1.09	7.63	5.638	1.278	1.211	3.9	2.81
SD	0.03	0.03	2.69	2.75	2.57	2.70	0.03	0.02	2.47	2.15	0.06	0.06	1.57	0.86
%variation	-4.2		-24.04		-24.84		-1.8		-26.1		-5.2		-27.94	

SD= Standard Deviation

Table 2.6: *OAR mean and maximum doses (BS=Brainstem, LP= Left Parotid, RP= Right Parotid)*

	Maximum Dose (cGy)		Maximum Dose (cGy)		Mean Dose (cGy)		Mean Dose (cGy)	
Patient site	Cord(PL-A)	Cord(PL-B)	BS(PL-A)	BS(PL-B)	LP(PL-A)	LP(PL-B)	RP(PL-A)	RP(PL-B)
Head neck	3474	4392	800	1349	2796	2899	2277	2551
Head neck	3890	4032	935	1275	2251	3161	3610	3960
Head neck	3650	4105	670	1072	2263	3015	2652	3523
Head neck	3562	3920	752	1120	2598	3456	2862	3106
Head neck	3488	3955	827	1211	2453	3087	2752	3422
mean	3612.8	4080.8	796.8	1205	2472.2	3123.6	2830.6	3312.4
% variation	12.9		51.2		26.4		17.0	

Table 2.7: *OAR mean and maximum doses (LL= left lung, RL= right lung)*

	Maximum Dose (cGy)		Mean Dose (cGy)		Mean Dose (cGy)		Mean Dose (cGy)	
Patient site	Cord(plan-A)	Cord(plan-B)	Heart(P-A)	Heart(P-B)	LL(PL-A)	LL(PL-B)	RL(PL-A)	RL(PL-B)
Oesophagus	3701	3736	935	973	1280	1448	1399	1526
Oesophagus	3853	4038	1344	1360	1425	1457	1486	1435
Oesophagus	3862	3960	2699	2926	1819	2078	1683	2036
Oesophagus	2977	3632	3115	3142	1842	1863	1893	1925
Oesophagus	3422	3786	2452	2678	1658	1786	1563	1820
mean	3563	3830.4	2109	2215.8	1604.8	1726.4	1604.8	1748.4
% variation	7.5		5.1		7.6		8.9	

Table 2.8: OAR mean and maximum doses (BS=Brainstem, OC= Optic chiasm, LON= left optic nerve, RON= right optic nerve)

	Maximum Dose (cGy)		Maximum Dose (cGy)		Maximum Dose (cGy)		Maximum Dose (cGy)	
Patient site	BS(P-A)	BS(P-B)	OC(P-A)	OC(P-B)	LON(P-A)	LON(P-B)	RON(P-A)	RON(P-B)
BRAIN	5551	6061	5355	6195	5330	6031	2733	4241
BRAIN	2689	3090	5362	6041	4298	4467	5396	6051
BRAIN	4745	5562	1563	2511	1181	1776	1138	2066
BRAIN	5381	5483	3692	2992	1933	1682	3227	3057
BRAIN	2616	2922	656	714	204	208	217	222
MEAN	4196.4	4623.6	3325.6	3690.6	2589.2	2832.8	2542.2	3127.4
% variation	10.2		10.1		9.4		23.0	

Table 2.9: *OAR mean and maximum doses (BS=Brainstem, LF= Left femur, RF= Right femur)*

	Mean Dose (cGy)		Mean Dose (cGy)		Mean Dose (cGy)		Mean Dose (cGy)	
Patient site	Bladder(P-A)	Bladder(P-A)	Rectum(P-A)	Rectum(P-B)	LF(P-A)	LF(P-B)	RF(P-A)	RF(P-B)
CERVIX	4507	4551	4836	4901	2009	2109	1956	1979
CERVIX	3978	3805	4600	4760	2123	2186	1950	2009
CERVIX	4071	4427	4721	5082	2110	2214	2306	2018
CERVIX	4381	4733	4662	4886	2495	2454	2440	2456
CERVIX	4078	4378	4700	4823	2148	2410	1949	2356
MEAN	4203	4378.8	4703.8	4890.4	2177	2274.6	2120.2	2163.6
% variation	4.2		3.96		4.48		2.04	

Table 2.10: *OAR mean and maximum doses (CL= Contra lateral Lung)*

	Maximum Dose (cGy)		Mean Dose (cGy)		Mean Dose (cGy)	
Patient site	Cord(PL-A)	Cord(PL-B)	Heart(PL-A)	Heart(PL-B)	CL(PL-A)	CL(PL-B)
LUNG	4252	4728	756	946	1167	1329
LUNG	4162	4653	400	600	1170	1704
LUNG	951	1000	1345	1434	530	566
LUNG	1330	1890	1330	1890	2306	3080
LUNG	323	464	323	464	1156	1653
MEAN	2203.6	2547	830.8	1066.8	1266	1666
% variation	15.6		28.4		31.6	

4 Discussion

Dose spillage both low and high outside PTV is a major concern during plan evaluation; surprisingly, neither definitions of CI available in literature addressed this issue. Two treatment plans one with dose spillage outside PTV and other without spillage cannot differentiated by existing formulas of CI hence forced to rely on visual slice by slice inspection of dose distribution of treatment plan. There is always a probability of hot spot and cold spots within target; they are unavoidable but where they created inside PTV is objectionable. Hot spot inside GTV increases TCP and cold spot inside PTV decreases TCP. Hot spot at the border of PTV margin but close to serial organ cannot be accepted where as cold spot at the border of PTV margin and adjacent to serial organ is acceptable.

Different targets with different dose prescriptions known as simultaneously integrated boost plans remained a major concern for almost all definitions of conformity index available in literature. Most of indices definitions provide satisfactory CI value for higher dose target but fail to satisfy other targets in SIB treatment plans. Only planning quality Index (PQI) developed by Lucullus Hing *et al.* addressed this issue satisfactorily. As we know that clinicians prefer to go for SIB plans over sequential plans because of its distinct clinical advantages and SIB plans are becoming routine practice for clinicians.

It has been observed that proximity of OAR to target perturbs plan outcome. When OAR has strict constrained and there is marginal dose variation between OAR and target then it is a possibility that either target coverage compromise or OAR sparing. It is a planner who has to set balance between them, it points out that proximity of OAR affects target coverage, conformity and dose distribution inside

target. Therefore, a definition of CI which does not take into account presence of OAR merely provides incomplete information of dose conformity to target.

As we know that different parts of the body possess varying degree of heterogeneity. Brain possesses least heterogeneity in terms of density difference as compare to head and neck, thorax, abdomen and pelvis. Head and neck carry highest degree of density difference because of structures like oral cavity, nasal cavity, high density bone, high density teeth, tongue and sometimes dental implants which affects dose distribution significantly inside the target volume. It has been observed that treatment plans of brain cases presents more homogeneous dose distribution inside PTV except SRS/SRT treatment plans where dose heterogeneity is desirable as compare to other treatment site plans. Head and neck treatment plans especially SIB (simultaneously integrated boost) plans are found to have highest degree of heterogeneity or say poor value of HI if calculated individually for differential target volumes. One more useful finding is that HI index also get affected by proximity of OAR, extent of their overlapping with PTV and their respective tolerance doses. To identify presence of hot spots and cold spots which is a measure of underdose and overdose in PTV is a crucial step in plan evaluation. Ideally HI should take care of this but existing formulas of HI cannot satisfactorily express it and therefore slice by slice verification of dose distribution is always a primary choice of clinicians. Because many times presence of hot spot in GTV or CTV and cold spot adjacent to OAR but within PTV is acceptable while plan evaluation. It has been clinically accepted that presence of hot spot in GTV provides radiobiological advantage in terms of TCP. Existing formulas of HI cannot reveal location of multiple hot spot and cold spot within PTV and merely provides degree of heterogeneity.

In the beginning gradient index (GI) was introduced for SRS/SRT treatment techniques only because, brain is such a sensitive area where sparing tiny volume of it make a marginal difference in treatment outcome.(Ayo *et al.* 2010; Leung *et al.* 1999; Menon *et al.* 2018; Paddick and Lippitz 2006) Definition of gradient index extended for SBRT plans also because for small volume target high dose gradient can be achieve easily resulting better CI. In case of larger volume targets GI shows poor value still it a good choice to consider while plan evaluation. As we understood that in SRS/SRT accept high degree of non-uniform dose distribution therefore HI have no major role while plan evaluation. Molecular imaging confirmed that all targets do not have homogeneous cell density hence concept of homogeneous dose distribution inside PTV is dissolving. New theory of biological target based planning is evolving and with advancement in the field of molecular imaging biological target based planning will be the right choice. Hence HI may be discontinuing using an effective or objective tool in plan evaluation instead GI is a good choice in addition with CI.

5 Conclusion

Conformity indices, which have assimilated presence of OAR in their formulation shows more reliability as a plan evaluation tool. Further innovations and research is required to define ideal, quantitative plan evaluation indices. Sigma index found to be more efficient formula while evaluating homogeneity of a treatment plan. Present study explain the importance of plan evaluation and the role various physical parameter based plan evaluation indices exist in literature. Multiple plan evaluation indices features, shortcomings and chronological development discussed. Because of complexity and time consuming nature of various plan evaluation indices their use is limited. Author have categorized according to their feature and investigated their suitability in general practice. Author shortlisted some formulas of conformity index, gradient index and homogeneity index based on experimental data for their routine application. Author discussed the limitations of physical parameter based indices and

recommended to use biological plan evaluation indices TCP and NTCP in complex treatment plans as a decision support system.

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