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Review

Plan evaluation indices: A journey of evolution

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ABSTRACT

Aim: A systemic review and analysis of evolution journey of indices, such as conformity index (CI), homogeneity index (HI) and gradient index (GI), described in the literature.
Background: Modern radiotherapy techniques like VMAT, SRS and SBRT produce highly conformal plans and provide better critical structure and normal tissue sparing. These treatment techniques can generate a number of competitive plans for the same patients with different dose distributions. Therefore, indices like CI, HI and GI serve as complementary tools in addition to visual slice by slice isodose verification while plan evaluation. Reliability and accuracy of these indices have been tested in the past and found shortcomings and benefits when compared to one another.
Material and methods: Potentially relevant studies published after 1993 were identified through a pubmed and web of science search using words "conformity index", "Homogeneity index", "Gradient index"," Stereotactic radiosurgery"," stereotactic Body radiotherapy" "complexity metrics" and "plan evaluation index". Combinations of words "plan evaluation index conformity index" were also searched as were bibliographies of downloaded papers.
Results and conclusions: Mathematical definitions of plan evaluation indices modified with time. CI definitions presented by various authors tested at their own and could not be generalized. Those mathematical definitions of CI which take into account OAR sparing grant more confidence in plan evaluation. Gradient index emerged as a significant plan evaluation index in addition to CI whereas homogeneity index losing its credibility. Biological index base plan evaluation is becoming popular and may replace or alter the role of dosimetrical indices.

1. Introduction

The ultimate objective of modern radiotherapy is to deliver maximum therapeutic dose with great conformity to the target volume homogeneously while minimizing the dose to surrounding normal tissue and critical organs. Till date, clinicians have relied on the conventional method of slice by slice visual verification of prescription isodose line conforming to planning target volume (PTV) and dose volume histogram (DVH). It often happens that for the same patient a number of treatment plans can be generated with almost the same dose distribution. This kind of situation is usually confusing for clinicians as they do not know on what basis they should approve the treatment plan. This urges to have a tool that can integrate this data in a simpler way to quantitatively assess the quality of treatment plans. Conformity index, homogeneity index and gradient index are such tools for treatment plan analysis.

In 2006, Feuvret et al.[1] surveyed a number of conformity indices (CI) developed by various authors and carried out critical analysis. Although it might not be an exhaustive review of all conformity indices considered in the review article. Author missed some definitions of CI which were published till 2006 and could not become part of his review article. Author did not consider issues like the role of cold spot & hot spot in PTV, role of spatial dose information and different targets with different dose prescription, etc. in plan evaluation criteria using CI. In this article we have incorporated the Feuvert et al. study and further extrapolated. We have included missed CI definitions as well as new definitions developed during the period from 2006 to 2018. A number of authors have developed CI with new ideas which we will investigate one by one. Most of the new indices developed were personalized & created using MATLAB, C-language, and Visual basic etc. hence their application is limited to them and could not be generalized. This study fragmented mul-

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Table 1
Category-1 containing mathematical formulas of CI which do not take into account OAR sparing.

Author name	Year	Formulation	Parameter description
Shaw et al.[2]	1993	$CI_{RTOG} = \frac{V_{RI}}{TV}$	VRI = volume of reference isodose line TV = target volume
Van't Riet et al.[9]	1997	$CN = \frac{TV_{RI}}{TV} \times \frac{TV_{RI}}{V_{RI}}$	TV_{RI} = volume of target covered by reference isodose line
Quast et al.[10]	1998	$RCI = \frac{V_{PTV}}{Vi}$	V_{PTV} = planning target volume Vi = treated volume or $V_{95\%}$ isodose line volume
Paddick et al.[3]	2000	$CI_{PADDICK} = \frac{TV_{RI}^2}{TV \times V_{RI}}$ $CI_{PADDICK} = \frac{0.9773}{CI_{RTOG}}$	TV_{RI} = volume of target covered by reference isodose line V_{RI} = volume of reference isodose line
Nakamura et al.[12]	2001	$NCI = \frac{TV \times V_{RI}}{TV_{RI}^2}$	V_{RI} = volume of reference isodose line
Lomax and Scheib[13]	2003	$CI_{LOMAX} = \frac{V_{T,PI}}{V_{PI}}$	TV_{RI} = volume of target covered by reference isodose line $V_{T,PI}$ = volume of PTV receiving prescription dose or more V_{PI} = volume enclosed by prescription isodose
Jackie Wu et al.[14]	2003	$CDI = \frac{NT_{PI} + (TV - TV_{PI})}{\frac{1}{2}(S_{PI} + S_{TV})}$ where $NT_{PI} = (PI - TV_{PI})$	S_{PI} & S_{TV} are the surfaces of prescription isodose and target volume NT_{PI} is a normal tissue volume receiving prescription dose or higher
Leung et al.[17]	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
Cheung and Law al.[21]	2014	$CI_{distance} = \frac{\sum_{i=1}^{N}\frac{D_D - D_T}{D_T}}{\sum_{i=1}^{N}\frac{\lvert D_D - D_T\rvert}{D_T}} \times 100$ $CI_{abs\_distance} = \frac{i=1}{N} \times 100$	$CI_{distance}$, D_D, D_T defined as the distance from the centroide to the points of intersection
Park et al.[22]	2018	$CS3 = (V_{95} + V_{100} + V_{105})/3V_T$	V_{95}, V_{100} & V_{105} are the volume of 95,100 & 105 % isodose lines V_T is a volume of target

tiple indices proposed in literature in two categories, category-1 & category-2. Category-1 contains those CI formulas which do not consider critical structure sparing while using them for evaluation but includes normal tissue & PTV coverage as presented in Table 1. Category-2 contains those CI formulas which consider PTV coverage, normal tissue and critical structure sparing simultaneously while using them for plan evaluation as presented in Table 2. The intention behind forming two categories is to enhance effective understanding by the reader regarding various CI definitions published in literature. Second important parameter in plan evaluation is the Homogeneity Index (HI). HI which accounts for non-uniform dose distribution inside the PTV did not receive as much attention as that obtained by CI. It is basically a ratio of maximum dose to minimum dose in target volume.[2]

Recently stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) became common practice in most clinics. In SRS dose in the order of 10–50 Gy to small targets having typical volumes ranging from 1 to 35 cm^3 is delivered in a single fraction; therefore, SRS requires high positional and dose delivery accuracy. Third parameter in plan evaluation gradient index (GI) is a measure of steep dose gradient outside the target volume; therefore; the gradient index plays a significant role in addition to the conformity index.[3,4] The dose fall off outside target volume is very important in SRS as a measure of plan quality, especially a predictor of complications. Gradient indices have been proposed to compare treatment plans of equal conformity.[5] The Stereotactic Body Radiotherapy (SBRT) is an extracranial hypofractional treatment modality, especially introduced for early non small cell lung cancer. With time, SBRT has proved its efficacy and begun to be used in practice in pancreas and liver tumors. Potential advantages of SBRT includes higher biological effective dose. RTOG 0915 recommended gradient index, $R_{50\%}$, HD_{loc} and $D_{2\,cm}$ indices in addition to the conformity and homogeneity index for SBRT plan evaluation.[6] Homogeneity index may not be of high priority in stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) plans as heterogeneity is desirable. In this study, we have comprehensively analyzed and tried to understand how the evolution of planning evaluation indices occurred since 1993 to June 2019. This article is intended to motivate researchers to discover more sophisticated tools for plan evaluation.

2. Materials and methods

Potentially relevant studies published after 1993 were identified through a pubmed and web of science search using words "conformity index", "Homogeneity index", "Gradient index"," Stereotactic radiosurgery"," stereotactic Body radiotherapy" "complexity metrics" and "plan evaluation index". Combinations of words ''plan evaluation index conformity index" were also searched. Bibliographies of downloaded papers were also searched. The search includes studies indexed until Feb 2019 and was limited to articles in English. Records were further filtered on the basis of repetition of concept and excluded from the study.

2.1. Conformity index

In 1993, the Radiation Therapy Oncology Group (RTOG) introduced a tool to compare the quality of different treatment plans in terms of target coverage named the conformity index and described it in the International Commission on Radiation Units and Measurements (ICRU) report 62.[2,7] ICRU report 83 recommended the use of CI in routine practice as it helps to asses the degree of congruence between prescription isodose and planning target volume.[8] It was a simple index with a disadvantage of producing false perfect score in case of the same volume of target and prescription isodose line.

In 1997, Van't Riet et al. projected a conformity index made of two terms; the first is a measure of PTV coverage and the other is a measure of how much normal tissue is irradiated as shown in Fig. 1.[9] The product of these two terms is the Conformation Number (CN). In this formulation, when there is a perfect conformity, with

Table 2
Category-2 containing mathematical formulas of CI which take into account OAR sparing.

Author name	Year	Formulation & parameter description
Baltas et al.[11]	1998	$COIN = CN \times \prod_{i=1}^{N_{CS}} [1 - \frac{V_{CSref,i}}{V_{CS,i}}]$ 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 critical structure & reference isodose volume
Miften et al.[15]	2004	$TCI = P_{PTV}(\frac{PTV_{TD}}{PTV})$ $NTSI = P_{NTV}(1 - \frac{NTV_{TD}}{NTV})$ Where, $P_{PTV}(Vi, Di) = \begin{cases} e^{-\sigma c,i(Dmin-Di)} for Vi > Vc, \text{maxandDi} < Dmin \\ 1\, for Dmin \le Di \le Dmax \\ e^{-\sigma h,i(Di-Dmax)2} for Vi > Vh, \text{maxandDi} > Dmax \end{cases}$ $P_{NTV}(Vi, Di) = \begin{cases} 1\, for Di \le Dtol \\ e^{-\gamma_i(Di-Dtol)} for Vi > Vmax and Di > Dtol \end{cases}$ $TCI^{+} = \prod_{i=1}^{Nt} TCI_i \prod_{J=1}^{Mnt} NTSI_j$ 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
Menhel et al.[16]	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.
Leung et al.[17]	2007	$\text{Modified HTCI}(H) = \frac{1}{r}\sum_{i=1}^{r}\left(\frac{TV_{RI,i}}{V_{RI,i}}\right)$ $M = \frac{1}{r}\sum_{j=1}^{r}\left[\frac{\sum_{i=1}^{p}\left(\frac{V_{T_jD_i}}{V_{T_jRD_i}}\right) + \sum_{i=1}^{q}\left(1 - \frac{V_{T_jD_i}}{V_{T_jAD_i}}\right)}{\sum_{i=1}^{p}\left(\frac{100}{V_{T_{j,RDI}}}\right) + q}\right]$ $P = \frac{1}{n} \times \sum_{j=1}^{n}\left\{\frac{1}{m} \times \sum_{i=1}^{m}\left[1 - \frac{V_{OjD_i}}{V_{OjAD_i}}\right]\right\}$ $PQI = \sqrt{\left[(1-H)^2 + (1-M)^2 + (1-P)^2\right]}$ Where, PQI = plan quality index comprising H, M & P
Ślosarek et al.[18]	2008	$RPI = \sqrt[n+m]{\prod_{i=1}^{m}\left(\prod_{j=1}^{n}\left[\left(1 - \frac{w_j\int_0^{D_{maxOAR}} V_{jOAR}\, dD_{OAR}}{\int_0^{D_{maxOAR}} V_{jOAR100\%}\, dD_{OAR}}\right)\left(\frac{\int_0^{D_{maxPTV}} V_{iPTV}\, dD_{PTV}}{\int_0^{D_{maxPTV}} V_{iPTV100\%}\, dD_{PTV}}\right)\left(1 - SD_{ev.p_i}\right)\right]\right)}$ Where, m is the number of PTV & n is the number of OAR Wj is importance factor to rank organs sensitivity to irradiation
Piotrowski et al.[19]	2009	**TCCI(CS;ES)** : $CS = \prod_{i=1}^{n} CS_n$ $ES = \frac{1}{n}\sum_{i=1}^{n} ES_i + \sum_{j=1}^{k} RI_j$ $CSi = \frac{V_{PTV,n}}{V_{PTV,tot}}$ $CSi = 1 - (\frac{V_{AC,n} - V_{PTV,n}}{V_{PTV,tot}})$ $CSi = 1 - \left(\frac{V_{PTV,n}}{V_{PTV,tot}}\right)$ $EI = \frac{V_{Body,n} - V_{PTV,n}}{V_{PTV,tot}}$ $ESi = \frac{EI_n - AE_n}{EI_n}$ Where **CS** is the coverage score describing quality of the PTV coverage by more than one Isodose line& **ES** is the excess score describing quality of the excess doses in healthy tissues by more than one isodose line $V_{PTV,n}$ = PTV volume covered by the specified isodose V_{PTV} = total volume of the PTV n = number of specifications included in the physician's intent $V_{AC,n}$ = theoretical volume of the PTV specified by the physician (AC — acceptance criteria) $V_{Body,n}$ = the volumes of body covered by n-specified isodose levels EIn = the observed excess index for n-selected isodose levels AEn = the acceptable value of excess index for n-selected isodose levels RIj = risk index calculated for PRVj.

Table 2 (*Continued*)

Author name	Year	Formulation & parameter description
Piotrowski et al.[19]	2011	$\mathrm{PNI}\left(n, \frac{j}{3}, TD\right) = \sum_{i=1}^{n} \frac{\left(\sum_{i=1}^{3}\left(\frac{D}{TD_{5/5}}\right)\right)_{j/3}^{i}}{n}$ $\mathrm{PNI} = f(n, j/3, TD)$ Where, n = critical structures j/3 = dose received by 1/3rd, 2/3rd & 3/3rd of the critical structure j = 1,2,3 TD = Tolerance dose and it can be $TD_{5/5}$ or $TD_{50/5}$

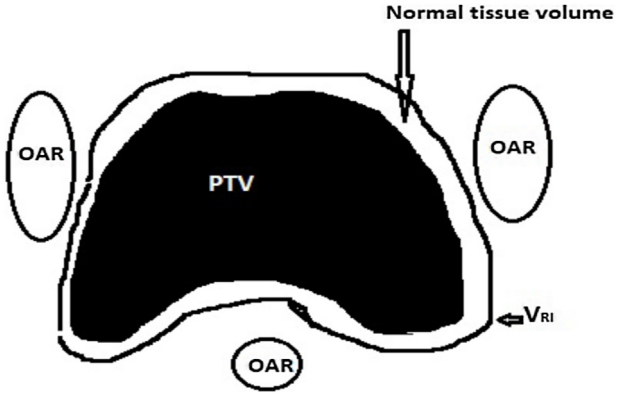

Fig. 1. Showing conformity to PTV by prescription isodose level.

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. A simple diagram showing.

In 1998, Quast et al. proposed a Radiation Conformity Index (RCI) which is nothing but an inverse of RTOG index.[10] RCI, while containing useful information, also suffers from possibility of false perfect score. Baltas et al. reported a Conformal Index (COIN) to evaluate implant quality of brachytherapy treatment plan.[11] It was the first attempt to subsume critical structure sparing in a conformity index formula. Although COIN was introduced for evaluation of brachytherapy plans only, its application also extended to evaluation of external beam radiotherapy plans. 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 the Conformation Number $CN = C_1 x C_2$ investigated by Van't Riet et al. and the third component takes care of various critical structures. There was a concern regarding the third component, in case when more than one treatment plan was compared; it is tough to decode the degree of sparing of each critical structures estimated one by one, because this component provides only global information. However, it is possible to analyze each critical structure independently & assign priority to a serial organ in which maximum dose is important against a parallel organ.

In 2000, Paddick et al. proposed an index designed for stereotactic radiosurgery plans which is identical to the index introduced by Van't Riet et al.[3,9]

In 2001, Nakamura et al. modified Paddik's index by inversing the formulation named New Conformity Index (NCI) and implemented the evaluation of stereotactic radiosurgery plans created for gamma knife.[12] This index has the same limitation as Paddik's 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.[13] This index can yield a false perfect score when prescription isodose line can be totally included in the PTV, but part of PTV may not be irradiated by the prescribed dose.

In 2003, Jackie Wu reported that the existing conformity indices depended on target size and shape complexity. Author proved that both volume and shape complexity can have significant effects on conformity values.[14] To overcome this effect, the author investigated first time a distance based conformity measure, the Conformity Distance Index (CDI) which is independent of the target shape and size. CDI measures the average distance between the prescription isodose surface and target contour surface in 3D space. In this study, the author simulated the target by predefined shapes & surfaces because calculating the 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, that approximation will be very close to a true scenario. This is a major drawback associated with CDI that limits the use of it to radiosurgery plans only. The CDI approximation raised the question of accuracy and the doubt of uncertainty. But the author showed a new direction and unique concept in the development of conformity indices.

In 2004, Miften et al. presented the Target Conformity Index (TCI^+). Target Conformity Index consisted of two components; the target conformity index (TCI) for target and normal tissue sparing index (NTSI).[15] Index was simple in formulation but involved complex and laborious evaluation. In his study, the author contemplates the TCI^+ model as an alternative to the Tumor Control Probability ($TCP^{+)}$ model for the ranking of IMRT plans, especially for treatment sites where clinical data available for TCP/NTCP models are inadequate. As we understand TCP^+ model is based on biological probability, whereas in this work TCI^+ was based on clinical judgment which can vary from 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 the need to calculate every treatment site, penalty function mainly responsible for penalizing over- or underdose 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 a problem because some TPS have no facility of differential DVH e.g. Monaco. In his work, the author tried to bridge the gap between dosimetric and biological parameter with the help of TCI.

In 2006, chasing the same concept but on a different path Menhel et al. conceptualized the Critical Organ Sparing index (COSI).[16] The author in his work did not merge definitions of CI & COSI in a single formulation like COIN. Instead, he established a relationship between COSI & Conformation Number (CN). This relationship was used to evaluate treatment plans using 2D graphical representation. As we know that COIN accounts only for fractional volume of OAR receiving prescription doses & higher. Therefore, it suffers from two drawbacks, first it combines the information of target coverage, normal tissue irradiation & critical structure irradiation.

Second issue is that COIN is unable to calculate for each organ at its specific tolerance level. COSI got rid of the shortcomings of COIN. In COSI formulation specific attention was 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 the target. Both COSI & COIN follow the same convention that the index increases 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 the conformity index defined by Lomax and Scheib in 2003. Author claimed that the 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 that 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 for different targets with different dose prescription assigned.

In 2007, Leung et al. reported the Plan Quality Index (PQI) which is a sum of three independent variables denoted by H, M & P.[17] Modified Healthy Tissue Conformity Index (HTCI) denoted by "H" specifically addressed plan evaluation in the case of a number of PTVs with different dose prescription (SIB). This is a modified version of HTCI proposed by Lomax and Sheib to evaluate target coverage, a merit function denoted by "M" was 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 organ at risk (OAR) in proximity of PTV breaches the tolerance limit of a respective OAR. An great thing about normal tissue sparing (P) is that it implements a 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's experience.

In 2008, Ślosarek et al. conceptualized Radiation Planning Index (RPI) using C++ language computer program named RPI win.[18] It is a personalized software which calculates CI by importing DVH parameters from the treatment planning system. RPI incorporates both critical structure sparing and PTV conformity in a number of targets with different dose prescription. In RPI standard deviation (SD) of dose distribution within PTV is calculated by assuming that the whole volume of the 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 the author did not compare results of RPI with CI published in literature. The only problem with this index is that it involved mathematical complexity.

In 2009, Piotrowski et al. offered an interesting definition of CI named the Two Component Conformity Index (TCCI) which allows to compare treatment plans generated in two different planning stations of two different radiotherapy equipment Tomotherapy and Linear accelerator.[19] The good thing about TCCI is that it provided freedom to evaluate plans for more than one isodose levels in PTV and healthy tissues not specified as PRV. Authors claimed that existing CI definitions having one value describes two effects; therefore, TCCI definition is more promising. A computer program was created for calculating TCCI which takes DVH file in the ASCII format of different plans as an input, hence there is no need for manual calculations. The first component. Coverage Score (CS). Describes the quality of the PTV coverage by more than one isodose levels and score ranging between 0–1. The second component, Excess Score (ES), describes the quality of the excess doses in healthy tissues by more than one isodose including PRV influence. In addition, there is a Risk Index (RI) for OAR, it ranges between 0–1. Value of 1 indicates that the observed parameters are higher than the acceptable criteria and 0 indicates that the observed parameters are lower than the acceptable criteria. The good thing about TCCI formula is that it allows flexibility in choosing more than one isodose levels (95%, 90%, 85% etc.) as per wish of the user. This index acts as a combo package considering many aspects of the treatment plan. The only shortcoming which we observed is that TCCI definition is not tested for SIB treatment plans.

In 2011, Prabhakar developed the Plan normal Tissue Complication Index (PNI) in a Visual Basic platform.[20] 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 the combination of existing definitions of CI (RTOG & Lomax) with PNI for plan evaluation. Treatment plan DVH among the rival plans is exported to a developed program for calculating PNI and then, based on PNI and CI value, the final treatment plan is selected. As the critical structure involvement is judged by dose received to 1/3rd, 2/3rd & 3/3rd volume of OAR, PNI is satisfactory for parallel structures but in the 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 the index that it is not suitable for simultaneously integrated boost (SIB), stereotactic radiosurgery (SRS) & stereotactic body radiotherapy (SBRT) treatment plans. The PNI evaluation criteria are ranging between 0–3. If PNI reaches 3, it means that all critical structures exceeded the tolerance dose whereas minimum value shows the best plan. Author evaluated PNI in four different sites the head & neck, prostate, lung & upper abdominal cancers.

In 2012, Cheung et al. developed personalized CI_{DD} (dose distance based) for evaluating plan quality discerning power.[21] Author focused on GTV coverage and cold spots within PTV while employing his developed CI_{DD}. According to the author, GTV must be covered by a fully prescribed dose and cold spots are acceptable away from GTV but can be within PTV. It is a two dimensional CI with dose and distance incorporated. CI_{DD} provided solution in the case of different targets with different dose prescription treatment plan evaluation. The only concern with this index is that it cannot be implemented to post-operative patients where GTV do not exist; hence, the formulation require modification. In this work the author included patient specific spatial dose information which makes it unique if mathematical complexity is ignored. One thing is contradictory as compared to other indices in plan evaluation criteria. In this case, lower value of CI_{DD} results in better plans. In his work the author came up with a new finding that GTV is likely to have a higher malignant cell density, hence GTV underdose cannot be accepted. CI_{DD} has been placed in category-1, 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 on target coverage.

In 2014, following the concept of Fion W.K. Cheung et al., Park et al. posted a new index using the same concept of distance in a different way.[22] They assumed the distance between the surfaces of the target volume (TV) and prescription isodose line (V_{RI}). It overrode 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 had some shortcomings, like no consideration of spatial dose information and was unsuitable 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 a false perfect score will

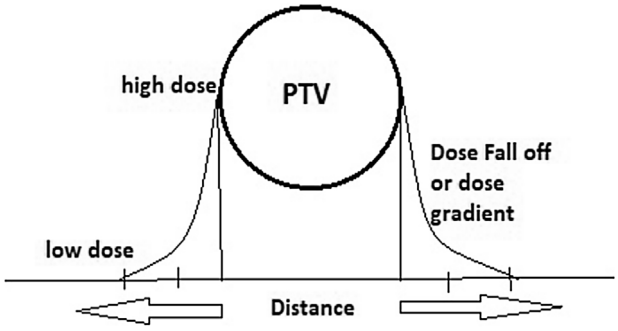

Fig. 2. Showing dose gradient outside PTV.

not appear. The values $CI_{distance}$ & $CI_{abs.distance}$ provide useful information when they are used in combination with their respective SD. It offers very simple criteria of plan evaluation, when the 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 $CI_{distance}$ & $CI_{abs.distance}$ were incapable of providing full information on target conformation unless the values of SD were added. There is a possibility of geometric uncertainty which needs to be addressed while defining the centroid in a complex target structure, shape & size. The best thing about this index is it can distinguish the differences if a 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 the author. This index belongs to Category-1 because OAR is given no consideration.

In 2018, Ansari et al. presented Triple Point Conformity Scale (CS3). Author in his work compared RTOG CI with his developed index.[23] In the formulation, the author took the ratio of the sum of volume of 95%, 100% & 105% prescription isodose line to thrice the size of the 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 as only for a single site; hence, the utility of this index needs to be tested for other sites also. This index tried in a way to merge definitions of HI & CI into a single index. Various mathematical definitions of CI discussed above are shown in the below Tables 1 and 2.

2.2. Gradient index

In 1999, Leung et al. postulated Equivalent Fall Off Distance (EFOD) to compare stereotactic radiosurgery plans.[24] This study formed the basis for considering dose gradient outside the target volume. Dose gradient is shown in Fig. 2.

In 2003, Clinic et al. were the first to coin the term gradient index that can measure the dose falloff outside the target volume.[25] It is called Conformity Gradient Index (CGI) containing two components as shown in Table 2. The conformity gradient index relies on an effective radius of the target which can be easily calculated by the treatment planning system. A 3 mm fall off is allowed from prescription isodose volume to half of the prescription isodose volume. Shaw's conformity index was a part of CGI which is known to produce false perfect scores.[9]

In 2006, Paddick and Lippitz proposed a simple formula of gradient index to complement the conformity index.[4] GI was used to compare treatment plans of equal conformity. Gradient index could become an effective tool to compare different methods of radiosurgery, for example treatment plans performed on different models of linear accelerator (accelerator with micro MLC), gamma knife, cyber knife, tomotherapy and proton therapy.

In 2010, Mayo et al. evaluated dosimetric indices for conformality, homogeneity, and dose gradient and compared them with published results for other frameless, intracranial SRT techniques, including Cyber-Knife, Tomotherapy, and static-beam IMRT.[26] Mathematical definition of GI is shown below in Table 3.

2.3. 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 that need to be unveiled.[27–30] As we know, different parts of the body have a varying degree of heterogeneity. Brain has least heterogeneity in terms of density difference as compared to the head & neck, thorax, abdomen and pelvis. Head and neck carry highest the degree of density difference because of structures like the oral cavity, nasal cavity, high density bone, high density teeth, tongue and sometimes dental implants which affect dose distribution significantly inside the target volume. It has been observed that treatment plans of brain cases present more homogeneous dose distribution inside PTV, except SRS/SRT treatment plans where dose heterogeneity is desirable as compared to other site treatment plans. Head and neck treatment plans, especially simultaneously integrated boost (SIB) plans, are found to have the highest degree of heterogeneity or say poor value of HI if calculated individually for differential target volumes.[31] One more useful finding is that the HI index also gets affected by proximity of OAR, extent of overlapping with PTV and respective tolerance doses. To identify the 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 the presence of hot spot in GTV or CTV and cold spot adjacent to OAR but within PTV is acceptable while evaluating the plan. It has been clinically accepted that the presence of hot spot in GTV provides radiobiological advantage in terms of TCP.[32] Existing formulas of HI cannot reveal the location of multiple hot spots and cold spots within PTV and merely provides the degree of heterogeneity. Let us discuss benefits and drawbacks of various definitions of HI.

In 2007, Yoon et al. introduced a new homogeneity index and called it the Sigma Index (S-index).[33] Sigma index is stronger than other homogeneity indices available in literature because for the first time it has utilized differential DVH information. In their study the authors 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 the same even if the first plan is better than the other in terms of homogeneity. According to the authors, any HI based on 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, the Sigma Index provides better dose homogeneity effectively without producing false scoring. Sigma Index was further tested by Pushpraj Pathak et al. as compared to the existing HI definitions. Manikandan et al. also evaluated the Sigma Index in comparison with conventional and modified HI and found superiority of S-index over them.[34] Results of the Sigma Index look promising & convincing with a small problem that many treatment planning systems do not facilitate differential DVH, like Monaco of Elekta Medical system.

Table 3
Mathematical formulation of gradient index published in literature.

Author name	Year	Formulation
Ansari et al.[23]	1999	EFOD=($\sqrt[3]{TVR1}$- $\sqrt[3]{TVR2}$)xR Where, TVR = TV/V_{RI} EFOF = Equivalent fall off distance TVR1 and TVR2 is a target volume ratios for dose values under consideration R is the equivalent radius of the target volume
Leung et al.[24]	2003	CGI = (CGIc + CGIg)/2 CGIc = (TV/PIV) × 100% CGIg = 100−{100[($R_{eff,50\%Rx}$−$R_{eff,Rx}$)−3 mm]} Where, CGI = conformity gradient index, suffix g & c means gradient and conformity $R_{eff,50\%Rx}$ = effective radius of isodose that is 50% of prescription isodose $R_{eff,Rx}$ = effective radius of prescription isodose line
Paddick and Lippitz[4]	2006	GI or R50% = Volume of 50% isodose line/volume of Prescription isodose line Where, GI = Gradient index
Mayo et al.[25]	2010	GI = 50%/[($R_{eff,50\%Rx}$-$R_{eff,Rx}$) Where, Reff, 50%Rx = $\sqrt[3]{\frac{3V_{50\%Rx}}{4\pi}}$ Reff, Rx = $\sqrt[3]{\frac{3V_{Rx}}{4\pi}}$ $V_{RX\ AND}$ $V_{50\%RX}$ are the volume of prescription isodose and 50% prescription isodose curves.

Table 4
Mathematical formulas of homogeneity indices published in literature.

Author	Formulation	Parameter description
RTOG[2]	$HI_{RTOG} = \frac{I_{max}}{RI}$	Imax & RI are the maximum dose & reference dose to PTV
RTOG[2]	$HI = \frac{D_5}{D_{95}}$	D5, D95 are the doses to 5% & 95% volume of the PTV
ICRU-62 [7]	$HI = \frac{D_{max}}{D_{min}}$	D_{max} & D_{min} are the maximum & minimum dose in PTV
ICRU-83[8]	$HI = \frac{D_2-D_{98}}{D_p}$ X100	D2 & D98 are the doses to 2% & 98% volume of PTV Dp is a prescribed dose
ICRU-83[8]	$HI = \frac{D_5-D_{95}}{D_p} \times 100$	D5, D95 are the doses to 5% & 95% volume of the PTV
ICRU-62[7]	$HI = \frac{D_{max}}{D_p}$	D_{max} & D_p are the maximum & prescribed dose to PTV
ICRU-83[8]	$HI = \frac{D_2-D_{98}}{D_{50}} \times 100$	D2, D98 & D50 are the doses to 2%, 98% & 50% volume of PTV
Tomé and Fowler[32]	$S-index = \sqrt{\sum (D_i - D_{mean})^2 \frac{V_i}{V}}$	Vi is the ith volume element receiving a dose of at least (Di) V is the total volume D_{mean} is a mean dose

In 2012, Kataria et al. verified and checked the concordance level between values of HI obtained by various formulas of HI available in literature except sigma index.[29] The authors showed the strength of association between HI and prescribed dose, planning target volume & location of PTV in the patient body. The authors 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. They did not discuss shortcomings of various formulas used in their study. In 2015, Helal and Omar also confirmed in their study that there is a strong correlation between HI, volume of target and prescribed dose.[28] Mathematical definitions of HI are shown in Table 4.

3. Discussion

Hot spot (volume receiving dose greater than 107% of prescribed dose) & cold spots (volume receiving dose less than 95% of prescribed dose) can appear anywhere within or outside the target and are unavoidable. Location and volume of hot spots and cold spots in PTV are 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 a serial organ cannot be accepted whereas cold spot at the border of PTV margin and adjacent to a serial organ is acceptable.[32] Different targets with different dose prescriptions known as simultaneously integrated boost plans remained a major concern for almost all definitions of a conformity index available in literature. Most of the index 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 Leung et al. addressed this subject satisfactorily.[17] As we know, clinicians prefer to go for SIB plans over sequential plans because of their 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 constraints and there is a marginal dose variation between OAR and the target. Then it is possible that either target coverage or OAR sparing is compromised. 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 the target. Therefore, a definition of CI which does not take into account the presence of OAR provides incomplete and unreliable information of dose conformity to the target. Dose spillage both low and high outside PTV is a major concern during plan evaluation; unfortunately, neither definition of CI available in literature addressed this subject. Two treatment plans, one with dose spillage outside PTV and the other without spillage, cannot be differentiated by existing formulas of CI; hence, they need to rely on visual slice by slice inspection of dose distribution of treatment plan.

In 2000, Sanchez-Nieto et al. were the first to introduce in-house developed dose volume histogram analysis software for biological tissue response based plan evaluation.[35] This software (BIOPLAN) was able to predict tumor control probability (TCP) and normal tissue complication probability (NTCP) of irradiated tissue based on radiobiological models by feeding DVH parameters of any treatment plan. This software was not intended to rank the number of treatment plans depending upon the plan evaluation criteria. It has raised questions: DVH of which treatment plan should be

chosen as an input, what should be the criteria of ranking a good plan?

Akpati et al. presented the Unified Dosimetric Index (UDI) that computes dose coverage, conformity, homogeneity and dose gradient simultaneously.[36] They evaluated UDI for stereotactic radiosurgery treatment plans. This was the first initiative to come up with a single index for plan evaluation. Indices included in UDI had same common criteria of plan evaluation, ranging between 0 and 1. Zero value indicates a poor plan and one value indicates the best plan. UDI faced the same limitation which is inherently associated with the indices used in its formulation. UDI is unable to rank treatment plans with different targets or different prescription nor doses it give them any critical structure consideration during evaluation.

Extending the concept of UDI, Pyakuryal et al. in 2010 developed a computational tool known as Histogram Analysis in Radiation Therapy (HART) which comprised most of definitions of CI and HI existing in literature till 2010 into a single index.[37] They have been given flexibility in their developed tool to use any formula of CI and HI according to the wish of the end user. The authors opened a way for radiobiological model based on an evaluation plan by considering the sensitivity of TCP and NTCP calculation for small changes in DVH shape points that require an accurate and efficient method of computing DVH parameters. This computational tool incorporated spatial dose information of dose distribution achieved in treatment plans. Universal Plan Index (UPI) which included indices should have common criteria of evaluation, ranging between 0 and 1. Hence, it faces the same limitations as indices used by UPI. Zhao et al. in 2010 also developed a software tool called "SABER" for radiotherapy plan evaluation. The authors assumed that both spatial and biological information is necessary for true optimization of the treatment plan for predicting clinical outcome. This software incorporates both spatial and biological information into the treatment planning process. The application of multiple methods for the incorporation of biological and spatial information has demonstrated that the order of application of biological models can change the order of plan ranking.[38]

In the beginning, the Gradient Index (GI) was introduced for stereotactic radiosurgery (SRS) treatment techniques as a sharp dose gradient is mandatory requirement. Definition of gradient index extended for SBRT treatment of extracranial small lesions hypofractionated plans. Because of a small volume target, high dose gradient can be achieved easily resulting in better CI.[39] In the case of a larger volume targets, GI shows a poor value but still it is a good choice to consider for plan evaluation. As we understood, in SRS/SRT a high degree of non-uniform dose distribution is accepted, therefore HI does not have a significant contribution during plan evaluation.

New complexity metrics seek attention for comparing competitive treatment plans keeping in view the advancement in treatment techniques. Advances in technology carry additional sources of variability which affects treatment plans having similar dose distributions which may differ greatly in their complexity. Plan complexity can lead to treatment delivery errors. Plan complexity may also affect dosimetry and dose calculations.[40–42] The uncertainty factors such as gap error and dose error for various gap widths associated with multi leaf collimator (MLC fields) may compromise PTV coverage and higher dose to OAR. The VMAT technique is intrinsically very complex in nature; therefore, with respect to existing plan evaluation indices, complexity metric cannot be overlooked.[43]

With the advancement in biological imaging (PET, MRI), it is now possible to identify a region of solid volume and porous volume which means heterogeneity. This heterogeneity can be targeted by dose boosting, the so called dose painting by numbers (DPBN).[44] Homogeneity index (HI) which is commonly used in routine practice for plan evaluation needs to be modified for dose painting based planning, since such indices are formulated based on paradigm of uniform dose distributions.[45] Molecular imaging confirmed that all tumor targets do not have homogeneous cell density; hence, the 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.

Recently, radiobiological model based plan evaluation becomes very popular and it is a need of hour. RB model based plan evaluation is the present and future of modern radiotherapy. Day by day clinical data is generating to validate existing radiobiological models. In literature, a number of authors developed personalized software/programs using different radiological models for plan evaluation. Most radiobiological models have certain limitations and their applications should be cautiously performed.[46] RB model based plan evaluation software requires DVH of the most optimized plan as an input to bring out outcome in terms of TCP and NTCP. Therefore, physical or dosimetric plan evaluation indices do not lose their importance, instead there is a need to develop most accurate plan evaluation indices.

4. Conclusions

Out of many mathematical definitions of CI discussed in this article, few have been developed and tested by authors at their personalized level, hence their applications are limited. Definitions of CI which have assimilated the presence of organ at risk (OAR) in their formulation present a more reliable tool in addition to slice by slice visual inspection of dose distribution in the target. The only problem is that information is in pieces and scattered. There is a need to create a robust dosimetric tool like CI by taking into account all new parameters suggested by various authors. The scope of new planning evaluation indices is wide and demanding. It will be wrong to say that a future treatment plan evaluation will be based purely on biological indices because dosimetrical indices like CI & GI will remain an integral part of plan evaluation. Application of the homogeneity Index (HI) as a plan evaluation tool is under shadow of doubt and its application is solely end user dependent.

Conflict of interest

None declare.

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