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Technical note

A new formalism of Dose Surface Histograms for robust modeling of skin toxicity in radiation therapy

Giuseppe Palma*, Laura Cella

Institute of Biostructures and Bioimaging, Italian National Research Council, Napoli, Italy

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ABSTRACT

Purpose: To present a new formalism for a robust computation of Dose-Surface Histograms (DSHs) to be exploited in the analysis of surface effects in radiation induced toxicity phenomena.
Methods: A new formal recipe for the DSH extraction is described. It is based on the computation of the Dose-Volume Histogram (DVH) on a 3D structure in the limit of vanishing thickness to approach the two-dimensional organ manifold. The theory is customized for the application to skin description.
Results: The derived formalism resulted in a redefinition of the generalized equivalent uniform dose (gEUD) and, accordingly, in an extension of the scope of the classical Lyman-Kutcher-Burman (LKB) Normal Tissue Complication Probability (NTCP) to a DSH-based toxicity modeling.
Conclusions: Our approach properly fits the intrinsic 3D nature of the DSH computation issue, and guarantees the rotational invariance and the robustness of the results. The proposed formalism can be easily implemented in treatment planning systems for dose optimization and potentially paves the way to a consistent analysis of radiation-induced morbidity endpoints related to surface effects in hollow organs.

1. Introduction

In modern radiation therapy (RT), technological advances have increased user control over healthy tissues dose distributions. In this framework, mathematical models of radiobiological effects potentially play an essential role and Normal Tissue Complication Probability (NTCP) modeling may help to identify the optimal plan that minimizes radiation-induced side effects for individual patients [1–3].

Modeling of NTCP has been performed with different techniques for many organs and end-points [4,2,5–7]. Lyman-Kutcher-Burman (LKB) approach [8–10] to NTCP modeling, in particular, is the most well-known and traditionally accepted method for predicting toxicity after radiation treatment.

However, the LKB formalism was not commonly adopted for evaluating the toxicity effect of dose to the skin [11]. Skin toxicity is, nonetheless, a crucial issue in breast cancer irradiation impacting patients' quality of life. All the available NTCP models for breast fibrosis are based on the dose-volume histogram (DVH) from the breast volume [12–15] or are based on DVH from a pseudo-skin structure defined as a layer of 5 mm inward from the body contour [16,17]. Similarly, NTCP models for radiation induced alopecia have been developed in brain cancer patiens from DVH of the scalp, defined as the body contour cropped by 3–6 mm [18,19].

A different approach could directly consider the surface phenomena connected to the actual organ at risk, *i.e.* the skin. In this regard, the concept of dose-surface histogram (DSH) is not new in radiation toxicity mathematical modeling, having been introduced in the mid of '90s [20] as a slice-by-slice 1D linear interpolation scheme of the dose. Since then, the computation power of clinical workstation has largely grown, thus allowing for a more robust and positioning-invariant approach.

Aim of this paper is to lay the theoretical groundwork for a novel DSH computation scheme in order to afford a robust LKB modeling of radiation induced skin toxicity. First, the formal definition of DVH is presented to allow the introduction of the new scheme for DSH calculation. Then, the formalism is applied to refashion the generalized equivalent uniform dose (gEUD) for the LKB modeling of toxicities related to the skin or, more generally, to any type of hollow organs. The proposed pipeline may be straightforwardly implemented in clinical treatment planning (TP) systems for dose plan optimization.

2. Methods

In the following, a formal definition of classical DVH concept is given (§2.1), before applying it to the new proposed version of DSH (§2.2).

* Corresponding author.
E-mail address: giuseppe.palma@ibb.cnr.it (G. Palma).

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2.1. Dose-Volume Histograms

For a given RT plan dose distribution $D(\vec{r})$, the absolute cumulative DVH is a function expressed in the Iverson formalism by

$$\mathrm{DVH}(x) = \int_{\Omega} d\vec{r}\,[D(\vec{r}) > x], \tag{1}$$

where Ω represents the organ at issue.

From Eq. (1) it is possible to derive several DVH variations, namely: the relative cumulative DVH

$$\mathrm{rDVH}(x) = \frac{1}{\lambda(\Omega)}\mathrm{DVH}(x) \tag{2}$$

($\lambda(\Omega)$ being the Lebesgue measure of Ω); the absolute differential DVH

$$\mathrm{dDVH}(x) = -\frac{d}{dx}\mathrm{DVH}(x); \tag{3}$$

and the relative differential DVH

$$\mathrm{rdDVH}(x) = \frac{1}{\lambda(\Omega)}\mathrm{dDVH}(x). \tag{4}$$

2.2. Dose-Surface Histograms

In order to understand the effects of surface irradiation, such as the irradiation in thin skin layers, it is necessary to evaluate dose-surface effects on a given Structure. Accordingly, DSHs can be extracted from the Structure (for skin application, the Structure is intended to be the patient body – hereafter, Body) potentially close to the tumor (target) region as representative of the irradiation in surface layers.

A formal definition of the concept of DSH can be given by considering the relative complement in the Structure of its 3D erosion defined by a spherical structuring element of radius r:

$$\Omega_{\mathrm{shell},r} = \Omega_{\mathrm{structure}} \setminus (\Omega_{\mathrm{structure}} \ominus B_r[0]), \tag{5}$$

where $B_r[0]$ is the ball of radius r centered at the origin.

On such shell, each version of DVH can be computed according to Eqs. (1)–(4). Relative DSHs can be directly obtained as

$$\mathrm{rDSH}(x) = \lim_{r\to 0} \mathrm{rDVH}_{\Omega_{\mathrm{shell},r}}(x) \tag{6}$$

and

$$\mathrm{rdDSH}(x) = \lim_{r\to 0} \mathrm{rdDVH}_{\Omega_{\mathrm{shell},r}}(x), \tag{7}$$

while absolute DSHs are given by

$$\mathrm{DSH}(x) = \lim_{r\to 0} \frac{\mathrm{DVH}_{\Omega_{\mathrm{shell},r}}(x)}{r} \tag{8}$$

and

$$\mathrm{dDSH}(x) = \lim_{r\to 0} \frac{\mathrm{dDVH}_{\Omega_{\mathrm{shell},r}}(x)}{r}. \tag{9}$$

For practical purposes, the starting point to evaluate individual patient dose distribution is the patient TP-CT scan on which the RT plan is calculated. This object is standardized in a DICOM (Digital Imaging and COmmunications in Medicine) RT object (including CT scan, dose map and contoured organ structures), and is defined voxelwise on a finite element grid. Therefore the use of a finite value of r in Eqs. (6)–(9) is preferred instead of passing to the limit as $r \to 0$. The choice of r actually depends on the surface layer to be considered for toxicity analysis and should never fall below the CT voxel sizes.

For instance, if the purpose is skin toxicity prediction, the shell of interest is represented by the skin ($\Omega_{\mathrm{shell},r} = \Omega_{\mathrm{skin},r}$), the Structure from where it is derived is the Body, and r is the order of magnitude of mean skin thickness ($\simeq 3$ mm). In this respect, TP-CTs scans necessarily include the support of the dose, but almost never are required to be total body scans; therefore, quite a large amount of arbitrariness is associated with the axial extent of the Body CT coverage and with the definition of $\Omega_{\mathrm{skin},r}$ resulting from Eq. (5). This problem has no relevance in the domain of absolute DSHs, but introduces a severe normalization bias in the definition of relative DSHs. As such, a fair workaround is found by applying Eqs. (6)–(9) on a robust $\bar{\Omega}_{\mathrm{skin},r}$:

$$\bar{\Omega}_{\mathrm{skin},r} = \Omega_{\mathrm{skin},r} \cap \Xi, \tag{10}$$

where Ξ can be defined on anatomical

$$\Xi = \Omega_{\mathrm{organ}} \oplus B_d[0] \tag{11}$$

(with d bigger than the average distance from the epidermis of an organ like the breast or, even, of a structure like the brain) or dosimetric bases

$$\Xi = L^{+}_{D_0}(D) \tag{12}$$

(the superlevel set of $D(\vec{r})$ defined by a very low dose threshold D_0 that delimits the skin area belonging to the target region).

3. Results

In this section we show how the theory presented in §2 can be integrated into the definition of a DSH-based gEUD (§3.1) and of an LKB model recast for surface morbidity effects (§3.2). In the spirit of providing the reader with a useful guide, we also summarize in §3.3 the relevant mathematical results concerning the estimation NTCP parameters and their confidence intervals.

3.1. Re-definition of gEUD

The gEUD is a key point to bridge the gap between the infinitely many degrees of freedom of $D(\vec{r})$ and the single value estimating the probability of radio-toxicity on a normal tissue. Conceptually, it is defined as the uniform dose that yields the same radiobiological effect of a given $D(\vec{r})$.

A phenomenological model (functional) for gEUD on a given organ Ω has been proposed in [21] as

$$\mathrm{gEUD}[D] = \frac{\|D_\Omega\|_{1/n}}{\lambda(\Omega)} = \left(\int_0^\infty \mathrm{rdDVH}(x)x^{1/n}dx\right)^n, \tag{13}$$

where D_Ω: $\Omega \to \mathbb{R}^+$ is defined such that $D_\Omega(\vec{r}) = D(\vec{r})$, and n is a parameter describing the volume effect of the considered tissue. Defining $a = n^{-1}$, for $a \geq 1$ gEUD turns out to be the average in the Lebesgue space $L^a(\Omega)$. Therefore, small values of n ($0 < n \ll 1$) indicate a pronounced sensitivity to the highest doses ($\mathrm{gEUD} = D_{\max}$, as $n \to 0^+$), even if delivered on a small region, whereas values closer to 1 indicate that the response is due to a near arithmetic average of effects across the organ ($\mathrm{gEUD} = D_{\mathrm{mean}}$, for $n = 1$).

For skin or hollow organs, Eq. (13) can be proficiently recast as

$$\mathrm{gEUD}[D] = \left(\int_0^\infty \mathrm{rdDSH}(x)x^{1/n}dx\right)^n. \tag{14}$$

3.2. The DSH-based LKB model

The concept of gEUD reduces the estimate of the NTCP to the definition of a proper monotonically increasing function NTCP(gEUD). In this respect, the LKB model provides one of the most robust NTCP:

$$\mathrm{NTCP}_{\mathrm{LKB}}[D] = \sqrt{\frac{1}{2\pi}}\int_{-\infty}^{t} e^{-x^2/2}dx, \tag{15}$$

where

$$t = \frac{\mathrm{gEUD}[D] - TD_{50}}{m \cdot TD_{50}}. \tag{16}$$

The NTCP can be estimated according to gEUD derived for a DSH, as given by Eq. (14). The model contains three parameters:

- the tolerance dose TD_{50} is the uniform dose given to the entire organ surface that results in 50% complication probability;
- m is a measure of the slope of the model sigmoid curve;
- n implicitly accounts for the surface effect through the gEUD definition.

3.3. Maximum likelihood fitting and confidence intervals

Providing an LKB model for a given endpoint after irradiation of an organ, thus, corresponds to the customization of a triplet $\theta_{LKB} = (TD_{50}, m, n)$ that could best fit the properties of a training group of N patients followed for that endpoint after irradiation of the specified organ.

The inference on a list of parameters θ that rules the probability mass function (PMF) of the observed stochastic process $\mathbf{y} = \{y_i | 1 \leqslant i \leqslant N\}$ can be made by means of the likelihood function $L(\theta)$. It is a random variable defined as

$$L(\theta) = \prod_{i=1}^{N} p(y_i|\theta), \tag{17}$$

where, in the context of NTCP modeling, the PMF of the binary outcomes $\{y_i \in \{0, 1\}\}$ is given by

$$p(y_i|\theta) = |y_i - 1 + \mathrm{NTCP}_\theta[D_i]|. \tag{18}$$

The maximum likelihood (ML) estimate of the parameters θ are the values θ_{LKB} that globally maximize $L(\theta)$ or, equivalently, its logarithm (the log-likelihood function – LLH):

$$\mathrm{LLH}(\theta) = \sum_i \log |y_i - 1 + \mathrm{NTCP}_\theta[D_i]|. \tag{19}$$

The LLH function can be numerically maximized by one of the many robust minimization algorithms (see, for instance, the `MINUIT` engine), obtaining

$$\theta_{LKB} = \max_\theta \mathrm{LLH}(\theta). \tag{20}$$

As long as $N \gg 1$, the Wilks' theorem for nested models proves useful to provide the confidence intervals for each θ_j (or, more generally, the confidence region for a subset $\theta_0 = (\theta_1, ..., \theta_M)$ of the parameters θ) at a given confidence level $P = 1 - \alpha$. It states that, in the large sample limit, the profile likelihood ratio

$$\Lambda(\theta_0) = \frac{L[\theta_0, \hat{\xi}(\theta_0)]}{L(\theta_{LKB})} \tag{21}$$

(where the parameters $\xi = \theta \backslash \theta_0$ are fitted to $\hat{\xi}(\theta_0) = \max_\xi L(\theta_0, \xi)$) satisfies

$$-2\log\Lambda(\theta_0) \sim \chi^2(M). \tag{22}$$

Therefore, the P-level confidence region for an arbitrary set of parameters θ_0 of the LKB model is defined by

$$\log\Lambda(\theta_0) \geqslant -\frac{1}{2} F^{-1}_{\chi^2}(P, M), \tag{23}$$

where $F^{-1}_{\chi^2}(\cdot, M)$ is the $\chi^2(M)$ quantile function.

4. Discussion

The DSH has been proposed as an additional synthetic dosimetric tool besides the standard DVH [20] and has been applied in several radiation induced toxicity analyses [22–26]. Furthermore, the implementation of DSH is provided in open source software such as CERR (Computational Environment for Radiotherapy Research) [27] and HART (Histogram Analysis in Radiation Therapy) [28]. It is noteworthy that the recipe for DSH calculation we proposed here, in Eqs. (6)–(9), is conceptually different from the purely 2D interpolation schemes adopted in the above literature. Indeed, it is based on a well established concept such as the DVH, which is computed on a 3D structure in the limit of vanishing thickness to approach the two-dimensional organ manifold. The fully 3D approach we presented correctly fits the intrinsic 3D nature of the problem, thus overcoming the limitation of previous schemes based on the choice of a preferred direction (usually perpendicular to the CT slice planes) and ensuring a rotational invariance of the obtained DSH. This should guarantee an improved robustness of the results, with particular regard to the contributions coming form regions in which the surface of the organ Ω gets locally coplanar to some of the acquired CT slices. An example of this critical circumstance is given by the inframammary skin fold, where radiation induced skin damage can be typically observed. An even more striking example can be found in radiation induced hair loss from cranial irradiation, in which large portions of the scalp involve very few upper CT slices and show rapidly evolving axial level sets.

Moreover, the availability of an additional degree of freedom, represented by the choice of a finite r in Eqs. (6)–(9), allows for properly localizing the doses relevant for the specific toxicity endpoint under evaluation (*e.g.* 3 mm for dermatitis or 4.5 mm for hair loss).

Of note, the same mathematical morphology formalism used for the definition of $\Omega_{skin,r}$ can be exploited to compute and apply DSH for the toxicity modeling of inner organ layer (*e.g.* for the study of dermis as opposed to epidermis), by easily computing DSH on differently eroded Ω_i sets (in order to exclude the external layers).

The methodology described here in its full mathematical details was previously applied on some cohorts of breast or brain cancer patients treated with RT and assessed for skin toxicity [29,30]. A further confirmation of the reliability of the proposed approach is thus given by the soundness of the obtained θ_{LKB} parameters.

In particular, as for the breast toxicity, the tolerance dose $TD_{50} = 39$ Gy is in good agreement with the described epidermis basal cell loss at radiation dose level of 20–25 Gy and with a maximum depletion of basal cells at 50 Gy [31]. The estimated value of $n = 0.38$ is consistent with a reasonable surface effect for the skin also reported in preclinical studies in which the intensity of the skin reaction depended on the size of the irradiation field [32]. In addition, the above model was also applied in a comparative study on breast cancer patients [33] to predict skin toxicity from different RT techniques. Interestingly, the skin NTCP for photon plans resulted in agreement with the frequency of observed toxicity events reported in clinical studies.

Similarly, the study of radiation induced alopecia in patients treated for brain tumors using the DSH of the scalp highlighted that the relative surface receiving at least 20 Gy is highly predictive for late alopecia [30].

5. Conclusions

The DSH represents a natural tool for describing radiation-induced morbidity for hollow organs and it is not a new concept in the RT field.

In this paper we formally defined a new way for robust DSH computation and, accordingly, provided a re-definition of gEUD that could allows for a DSH-based LKB NTCP for the description of surface toxicity phenomena.

We believe that this formalism – easily implementable within commercial TP systems – might improve the knowledge on toxicity endpoints that are supposed to be related to surface effects.

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