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Original Article

Joint modeling of missing and mismeasured measurements for computing radiotherapy margins

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ABSTRACT

Purpose: Pelvic organs are naturally prone to positional and volumetric changes over time. These individual organ changes may result in variations in the clinical target volume (CTV) position and shape. Planning target volume (PTV) that encompasses the CTV with some margins to account for such uncertainties in patient positioning, organ motion, and beam geometry is universally accepted today in radiotherapy. Keeping this view in mind, the present study has been planned in order to determine the setup error (random and systematic) in patients of carcinoma cervix and rectum image-guided radiotherapy and to propose a population-based three-dimensional CTV to PTV margins in IGRT scenario.

Materials and methods: The mean margin displacements of 61 patients measured through different directions. The proposed method is used to estimate margins of displacement of specific CTV dosing. A further method is illustrated to simulate the dose received by the CTV. The margin distance compared with Van Herk model through consideration of systematic and random errors. Different site-wise displacements were measured and compared. The CTV performance dosimetry has been carried through proposed model and compared with the traditional margin for each of the datasets.

Results: The PTV margins obtained on lateral, longitudinal and vertical sides on Cervix site are 0.91, 1.93 and 0.96 [Van Hark's formula] and 0.84, 1.79 and 0.89 through proposed formula. It can be noted that in both the cases, the respective margin obtained through proposed method was lesser in comparison to that of Van Hark's method.

Conclusions: The presence of heterogeneity in patient's random error is natural. This random error is highly influential on radiotherapy margin widths of the patients. The Bayesian statistics are useful to deal with such a problem. In this article, a simple and well-defined model is adopted to deal with the patient's heterogeneity problem. It has been observed that the model accounted the variability in the margin estimation. The variation in margin can be extended from one cancer site to another cancer site.

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1. Introduction

The clinical target volume (CTV) is important to be considered during external beam radiotherapy. The margins are placed around the CTV to cover the daily movement in CTV position through repeated measurement. These margins are required to be large enough to avoid delivery of inadequate dose in CTV's position. However, larger amounts of margins can unnecessarily affect the healthy tissue to radiation and simultaneously increased toxicities. At various times, displacement arises between the assumed position of CTV during the planning and its actual position. This displacement can be divided into a systematic and random component.¹ The systematic part occurs due to the error during treatment planning and target delineation. The reason may be the use of a single delineated position of the tumor instead of a time-averaged CTV position. The random error occurs during the daily variation in tumor position due to organ movement relative to the reference markers used for beam alignment. The systematic error is defined as the standard deviation of the mean displacements of the CTV's across all patients. The standard deviation of the specific patient's CTV's displacements is defined as the random error.² The most widely adopted formula for calculating margins was introduced by Van Herk et al.²

The Van Herk margin formula is computationally simple and mathematically sophisticated. However, there are some mathematical assumptions about CTV displacements. It is assumed that mean displacements are normally distributed. Each patient's repeatedly measured fraction-to-fraction CTV displacements are assumed with the normal distribution, and there is no influential correlation in displacements between dimensions. It is also assumed that random error is constant for all patients.^{3–10} However, some patient's CTV displacements become larger than others. It can be solved through heterogeneity modeling.¹¹ The repeatedly measured data are prone to be affected with missing observations. In IG-IMRT era, Cone Beam Computer Tomography's (CBCT) are performed on the regular basis throughout the treatment verification. Ideally, we should take CBCT every day to verify our treatment plan and to execute our treatment which may not be feasible practically due to huge patient's burden and the shortage of time. This is a kind of compromise in our image verification part and optimum execution of treatment. With less number of CBCT's, we decide our random and systematic error, and finally calculate the Planning target volume (PTV) margin which may not be accurate. We are using Van Herk's formula to calculate the PTV margins which overlook missing or mismeasured observation for PTV calculation. For example, in Ca-cervix, we usually deliver a total dose of 50.4 Gy in 28 fractions over five and half weeks. Ideally, CBCT should be

performed in all those 28 days. If we consider CBCT for first three days and twice weekly for rest of the treatment, the total number of acquired CBCT's will be around 14. It is exactly half of the ideal required images to calculate the error and PTV margin. These attributes will highlight the new method of PTV calculation which will take missing and mismeasured observations into consideration that may further give the robust estimate of PTV margin. The presence of missing observation is inevitable in this type of study design. It is true that missing data are common in experiments with repeatedly measured observations. Three types of missing data are found in clinical data (i.e. missing completely at random (MCAR), missing at random (MAR), and non-ignorable missing (NIMR)).¹² It is often found that the variable is affected through missing measurement.¹³ The example of MAR is like, “Male participants are more likely to attend all the visits, but it does not have any reason about their gender to attend for visits more”. It is better to consider MAR when we do not have any idea about the reason of occurrence of missing data. In this work, the MAR is considered for simplicity. However, the presence of missing observations has been overlooked in earlier studies in PTV measurement. There has been virtually no literature at all for handling missing and mismeasured data simultaneously, that is, modeling the longitudinal process while patients are repeatedly measured, and then also jointly attempt the approach modeling for missing and mismeasured data.

In this study, we propose a model to handle missing and mismeasured variable. The variable is considered as “displacements”. Particularly displacement is separated with the random, systematic error and mismeasured error. This study is dedicated to evaluating the error in Ca-cervix and Ca-rectum patients undergoing radiotherapy. An optimum population-based CTV–PTV margin in carcinoma cervix and carcinoma rectum cancer patients will be obtained in patients undergoing conformal radiotherapy.

2. Methods

The mean margin displacements of 61 patients measured through four different directions (lateral, vertical, longitudinal and rotational) are detailed in Table 1. However, we concentrated on 3-dimensional displacement. The proposed method is used to estimate margins of displacement of specific CTV dosing. A further method is illustrated to simulate the dose received by the CTV. The margin distance is compared with Van Herk model through an assumption of systematic and random errors. Different site-wise displacements were measured and compared. The CTV performance dosimetry has been carried through proposed model and compared with the traditional margin for each of the datasets. The treatment planning with high geometrical accuracy can only deliver the

Table 1 – A summary of the patients cohorts used to mode day-to-day variation in CTV position.

Cohort	Treatment site	Number of patients	Averaged displacement			
			Lateral	Longitudinal	Vertical	Rotational
1	Cervix	44	0.47	0.65	0.27	0.14
2	Rectum	17	0.30	0.38	0.23	0.04

safe and optimum radio-therapeutic effect.¹⁴ The optimum radio therapy effect is dependent on the displacement between planned and executed treatment. This displacement is defined as “error”.

2.1. Measurement model

The measurement model is defined as

$$Y_{ij} = \mu_i(S_{ij}) + \text{Random Effect}_{ij} + \text{Measurement Error}_{ij} \quad (1)$$

where $\mu_i(S_{ij}) = x_{1i}^T(s)\beta_i$ is the mean displacement in any direction. The random effect can be mathematically defined by $w_{1i}(s) = d_{1i}^T(s)U_i$ and thereafter will be denoted as $w_{1i}(s)$.

The term, measurement error $_{ij} \sim N(0, \sigma^2)$, is a sequence of mutually independent measurement errors. The term $w_{1i}(s)$ is the true individual level 3-D displacement (through multiplication of three different directions displacement) after they have been adjusted for the overall mean trajectory and with other fixed effects. In ideal setting, it is expected that the displacement level for i th individual on j th time point should be zero i.e. $E(Y_{ij}) = 0$. The vector $x_{1i}(s)$ and β_1 show the time-varying explanatory variables and their corresponding regression coefficients, respectively. The term U_i is a vector of random effects corresponding to variable $d_{1i}(s)$ and is assumed to follow $N(0, \sigma^2)$. Now the $w_{1i}(s)$ is formed with

$$w_{1i}(s) = \gamma_1 U_{1i} + \gamma_2 U_{2i} + \gamma_3 (U_{1i} + U_{2i}) \quad (2)$$

The symbolic representation of random error, systematic error and independent frailty terms are γ_1 , γ_2 , and γ_3 , respectively. It is assumed that γ_1 and γ_2 follows $N(0, \sigma_1^2)$ and $N(0, \sigma_2^2)$ respectively. The notation γ_3 has been handled separately and considered in the section with “measurement error model” and thereafter merged with Eq. (2) to get the estimates of random error displacement. Our goal in this work is to obtain the posterior estimates of γ_1 , γ_2 , and γ_3 as an extension of Van Herk's formula that could accommodate the mis-measurement variation in PTV margin. Particularly, the term γ_1 and γ_2 were assigned to accommodate the random and systematic error through consideration of missing technique and γ_3 was adopted for mis-measurement.

Further Eq. (2) is defined as additive model by the following equations

$$U_{1i} = \alpha + \beta e_i + \varepsilon_i \quad (3)$$

$$U_{2i} = \varepsilon_i + \mu_i \quad (4)$$

$i = 1, 2, \dots, n$. The terms (U_{1i}, U_{2i}) are defined as observed random quantities. It is assumed that $(\varepsilon_i, \mu_i)'$, $i = 1, 2, \dots, n$ are i.i.d random vectors having mean $0 = (0, 0)'$ and covariance matrix $\text{diag}(\sigma_\varepsilon^2, \sigma_\mu^2)$. In this model the parameter $\theta = (\alpha, \beta, \sigma_\varepsilon^2, \sigma_\mu^2)$ is considered as structural parameters. Further, latent parameter is defined as $\varepsilon_i = (\varepsilon_{1i}, \dots, \varepsilon_{ni})'$. The inference is obtained through θ or function of θ such as β or $\sigma_\varepsilon^2/\sigma_\mu^2$ for the structural parameter. The parameters in Eq. (4) are

assumed to follow $\varepsilon_i \sim N_n(0, \sigma_\varepsilon^2 I_n)$, $\mu_i \sim N(0, \sigma_\mu^2 I_n)$ and $\varepsilon_i \perp \mu_i$, where $\varepsilon_i = (\varepsilon_{1i}, \dots, \varepsilon_{ni})'$, $\mu_i = (\mu_{1i}, \dots, \mu_{ni})'$. The term $\perp$ shows independence between random vectors. The likelihood function is defined as

$$\prod_{i=1}^n N \left[\begin{pmatrix} U_{2i} \\ U_{1i} \end{pmatrix} \begin{pmatrix} \alpha + \beta e_i \\ \varepsilon_i \end{pmatrix} \begin{pmatrix} \sigma_\varepsilon^2 & 0 \\ 0 & \sigma_\mu^2 \end{pmatrix} \right] \quad (5)$$

The large sample size provokes a number of unknown parameters for the measurement error model. It gives that normal functional measurement error model is not consistent for the structural parameters for different conditions. In this scenario Bayesian counterpart may play a crucial role to produce inference through assumption of prior distributions.

2.2. Marginal regression for longitudinal set-up

Let Y_{ij} be the univariate outcome for subject i at time j , X_{ij} be the vector of error-prone covariates and be Z_{ij} the vector of error-free covariates, where $i = 1, \dots, n$ and $j = 1, \dots, T$. We assume the intercept term, if any, of the model is included in Z_{ij} that denotes $Y_{ij} = (Y_{i1}, \dots, Y_{iT})'$, $X_{ij} = (X_{i1}, \dots, X_{iT})'$ and Z_{ij} similarly. Let $\mu_{ij} = E(Y_{ij}|X_{ij}, Z_{ij})$ and $v_{ij} = \text{Var}(Y_{ij}|X_{ij}, Z_{ij})$ be the conditional expectation and variance of Y_{ij} , respectively. In regression analysis, μ_{ij} is usually modeled via a generalized linear model $g(\mu_{ij}) = X'_{ij}\beta$ with g a specified link function, $\beta = (\beta_1, \dots, \beta_p)'$ a $p \times 1$ vector modeled via a generalized linear model $g(\mu_{ij}) = X'_{ij}\beta$ with g a specified link function, $\beta = (\beta_1, \dots, \beta_p)'$ a $p \times 1$ vector of regression parameters, and X_{ij} is a $p \times 1$ vector of known functions of (X_{ij}, Z_{ij}) being the working covariates in the model considered. For example, in the model with all the main and two-way interaction terms, and X_{ij} includes all individual elements of (X_{ij}, Z_{ij}) and all non-redundant pair wise cross products of the elements. The variance $v_{ij} = v(\mu_{ij}, \varphi)$ with v is a known function, and φ is a dispersion parameter of the products of the elements.

The variance $v_{ij} = v(\mu_{ij}, \varphi)$ with v a known function and φ a dispersion parameter that is known or to be estimated. The term X_{ij} , Y_{ij} and Z_{ij} are considered as i th time displacement at the direction of X , Y and Z , respectively and the representation of X , Y , and Z altered simultaneously for computation.

2.3. Measurement error mechanism

The measured covariates of mis-measured is defined as U_{ji} (i.e. $U_{1i} + U_{2i}$) and thereafter included in Eq. (2) to get the estimate of $w_{1i}(s)$. It is assumed that U_{ji} is related with unobserved directional displacement of X_{ji} , Y_{ji} and Z_{ji} through linear model as

$$U_{ji} = X_{ji} + \varepsilon_{ji}, \varepsilon_{ji} \sim N(0, \sigma_j^2) \quad (6)$$

$$U_{ji} = Y_{ji} + \varepsilon_{ji}, \varepsilon_{ji} \sim N(0, \sigma_j^2) \quad (7)$$

$$U_{ji} = Z_{ji} + \varepsilon_{ji}, \varepsilon_{ji} \sim N(0, \sigma_j^2) \quad (8)$$

The error term ε_{ji} is not dependent with X_i , Z_i , Y_i and ε_{jk} for $(ji) \neq (jk)$. It is assumed that the summation of error term ε_{ji} i.e.

$\sigma_j^2 (j = 1, \dots, T)$ is also applicable through repeatedly measured data.¹⁵ The term U_{ji} is considered as a dimension through multiplication of X , Y , and Z . Here, X , Y , and Z are considered as displacement in three different directions i.e. longitudinal, latitudinal and rotational.

2.4. Missing data mechanism

The indicator variable R_{ij} is considered to support the missing observations.^{23,24} Let the Y_{ij} is observed then $R_{ij} = 1$ otherwise $R_{ij} = 0$. Since the measurements are considered with three-dimensional scale. In this work, the displacement measurement with Y_{ij} dimension is considered as a response of interest. The displacement measurement with X_{ij} and Z_{ij} are considered as covariates with Y_{ij} . The full measurement of $(Y_{ij}, Z_{ij}, \text{ and } X_{ij})$ has been considered as missing when Y_{ij} is missing, even if some of the covariates are not missing. The missing data procedure is defined as

$$pr(R_{ij} = 1 | R_{ij}, Y_{ij}, X_{ij}) = pr(R_{ij} = 1 | \bar{R}_{ij}, \bar{Y}_{ij}, \bar{U}_{ij}, \bar{Z}_{ij}) \quad (9)$$

is adopted to show the history of.

The term $\bar{R}_{ij}$ is used to define the history of R_i till the time j , and further $\bar{R}_{ij}^0$ is the observed part of R_i up to time j . It is assumed that the missingness follows the MAR procedure. The above equation can be utilized to obtain the missing probability through the observed data. Let the part is assumed with

$$w_{1i}^*(s) = pr(R_{ij} = 1 | R_{ij}, Y_{ij}, X_{ij}) = pr(R_{ij} = 1 | \bar{R}_{ij}, \bar{Y}_{ij}, \bar{U}_{ij}, \bar{Z}_{ij}) \quad (10)$$

Here the term $w_{1i}^*(s)$ follows the binary regression with parameter. The estimation of $w_{1i}^*(s)$ can be obtained through maximizing the likelihood procedure as $\prod_i L_i(\alpha)$.

$$L_i(\alpha) = \prod_i w_{ij}^{*R_{ij}} (1 - w_{ij}^*)^{1-R_{ij}} \quad (11)$$

This provides with $\Sigma_i A_i(\alpha) = 0$ with $A_i(\alpha) = \left(\frac{\partial}{\partial \alpha}\right) \log L_i(\alpha)$. The notation $w_{1i}^*(s)$ is only considered to replace $w_{1i}(s)$ in Eq. (2) when there were missing data in any directional displacement.

3. Methodology and dose prescription

The positional and volumetric changes are natural to have occurred in pelvic organs during the study. There could be a difference between the pelvic anatomy at the time of radiotherapy planning and radiotherapy treatment. The organs like cervix, prostate and uterus can move due to variations in bladder and rectum filling. In this study, the CT images were obtained after immobilization with the vac lock on the CT machine GE Light Speed VFX (VARIAN) with 2.5 mm slice interval. The Eclipse treatment planning system (TPS) was used to transfer the data, and thereafter target volumes and normal structures at risk were contoured. The target volumes in Ca cervix and rectum were contoured according to

institutional protocols. The organ at risks (OAR) was also contoured according to RTOG guideline. A total dose of 50.4 Gy in 28 fractions was prescribed to PTV in both Ca cervix and Ca rectum. It was targeted that a total of >95% of PTV would receive 95% of the prescription dose and <1% PTV would not receive more than 115% of the prescription dose. It was also decided that at least 95% of CTV would also receive the 100% of the prescription dose.

Data of automatic image registration before each treatment for set up correction were collected. The mean margin displacements of 61 patients (44 Ca cervix and 17 Ca rectum) measured through four different directions (lateral, vertical, longitudinal and rotational) were noted. However, we concentrated on 3-dimensional displacement. The proposed method is used to estimate margins of displacement of specific CTV dosing. A further method is illustrated to simulate the dose received by the CTV. The margin distance is compared with Van Herk model through an assumption of systematic and random errors. Different site-wise displacements were measured and compared. The CTV performance dosimetry has been carried through proposed model and compared with the traditional margin for each of the datasets.

The treatment planning with high geometrical accuracy can only deliver the safe and optimum radio-therapeutic effect.¹⁴ The optimum radio therapy effect is dependent on the displacement between planned and executed treatment. This displacement is defined as “error”.

The Van Herk's formula was used to calculate the systematic and random setup errors with $2.5 + 0.7$. The systematic setup error was defined as the average set up an error for overall the treatment fractions, and the random errors are defined as the day-to-day difference in the set-up of the patient. It is assumed that the random error represents the day-to-day fluctuation in the set-up of the patients. It is assumed through the root square of SD of all the patients. The mean and standard deviation of systematic error were presented through and respectively. The mean of random error is assigned with σ . The distance between the 95% and 50% dose intensity points was defined as Penumbral width. The parameters are estimated through the Markov chain Monte Carlo (MCMC) methods.^{16,17} A sample of size of 20,000 was generated to provide posterior of the parameters.

4. Results and discussion

A random sample of 1000 individuals with three directions displacement data was generated from $N(0, 0.1)$ distributions. The number of visits for sampled individuals were randomly assigned through Poisson distribution with $\lambda = 4$. Thereafter, the number of complete measurements of 3 different directions were assigned through Poisson distribution with $\lambda = 2$ to represent the presence of missing observations. Both were selected with arbitrarily. It is assumed that the process will generate the mis-measured data through different directions. Thereafter the three methods discussed above were considered to generate the posterior estimates of 1, 2, and 3, respectively. The posterior estimates generated were considered to create the PTV margin on cervix and rectum site displacement. Table 2 shows the mean posterior estimates obtained for 1(2,2),

Table 2 – The posterior mean estimates of margin parameters.

Parameter	Posterior estimates mean	Posterior estimates standard error	Credible interval [2.5%, 97.5%]
γ_1	2.2	0.2	[2.16, 2.23]
γ_2	0.6	0.08	[0.54, 0.63]
γ_3	0.3	0.12	[0.25, 0.33]

Table 3 – The radiotherapy margin comparison observed through Van Herk's and proposed method.

Site	Side	Van Herk's margin	Proposed method's margin
Cervix	Lateral	0.91	0.84
	Longitudinal	1.93	1.79
	Vertical	0.96	0.89
Rectum	Lateral	1.08	0.94
	Longitudinal	1.99	1.73
	Vertical	0.92	0.81

2(0.6), and 3(0.3), respectively. The standard error and 95% credible interval with 1, 2, and 3 are (0.2, 0.08, 0.12) and [2.16, 2.23], [0.54, 0.63] and [0.25, 0.33], respectively. The PTV margins obtained on lateral, longitudinal and vertical sides on Cervix site are 0.91, 1.93 and 0.96 through Van Herk's formula and 0.84, 1.79 and 0.89 through proposed formula. In case of Rectum, the margins obtained on lateral, longitudinal and vertical sides are 1.08, 1.99 and 0.92 through Van Herk's formula and 0.94, 1.73 and 0.81 through proposed formula. It can be noted that in both the cases, the respective margin

obtained through proposed method was lesser in comparison to that of Van Herk's method.

The average displacement inlateral, longitudinal and vertical sides were (0.47, 0.65, 0.27) in Cervix and (0.30, 0.38, 0.23) in Rectum, respectively (Table 1). Figs. 1 and 2 reveal the visit-wise four-dimensional displacements in Cervix and Rectum. The comparative margins obtained through Van Herk's and proposed method are given in Table 3. The usual standard deviations used to van' Herks method also adopted to computed to calculate the ad joint part of 1 and 2. However, the weighted standard deviations of standard deviations were used to calculate the ad joint of 3. The comparative result shows that the margins in the entire three dimensions were less in comparison to Van Herk's proposed margin. Both the number of patients and number of site were considered with adequate sample size. The Bayesian inference via MCMC algorithms provides us to deal with computational complexity as compared to traditional statistical modeling approach. The model-based approach and debate on improving the handling of missing data techniques are well documented. Particularly, the model based approach through an application of mixed effect modeling through an assumption of MAR or MNAR are well adopted over the traditional approaches that are based on single data imputations like last observation carried forward (LOCF) and baseline observation carried forward (BOCF).^{18–21} The primary application of LOCF and BOCF is widely explored. In contrast, the improvements of other data retrieval strategies are based on final analysis of dataset consisting of patients with at least three types of follow-up: (I) patients with complete data; (II) patients who drop-out of the study at a certain time point and no further data are collected; (III) patients who drop-out but a certain amount of data are retrieved ethically. There is a gigantic literature on missing data methods for longitudinal studies. The majority is based on likelihood-based approaches and weighted estimating

Fig. 1 – PTV error deviation with spaghetti plot in rectum.

Fig. 2 – PTV error deviation with spaghetti plot in cervix

equations procedure. However, the parametric estimating procedure through NIMR data is difficult. It is required to specify the likelihood for the joint distribution of the data and missing data simultaneously. Broadly, three types of models namely shared-parameter, selection model and pattern mixture are useful.²² The limitation and advantages of selection modeling,^{29–31} pattern mixture modeling^{22,25–28} and shared parameter modeling^{29–31} are also well documented. It is assumed that all patients will be exposed to equal random error and the patient specific difference will only be addressed by systematic error. The patient specific heterogeneity has been explained by random error component into the model. It is confirmed that patients will be covered through a 95% dose increment.

5. Conclusions

The occurrence of heterogeneity in patient's random error is natural. This random error is highly influential on radiotherapy margin widths of the patients. The Bayesian statistics are useful to deal with such a problem. In this article, a simple and well-defined model is adopted to deal with the patients' heterogeneity problem. It has been observed that the model accounted the variability in the margin estimation. The variation in margin can be extended from one cancer site to another cancer site. The geometric distribution of CTV is dependent on the random error term. It is a measurement error term calculated between observed margins and the requirement to achieve clinical dosimetry location. This work is limited to 3-dimensional displacement instead of 4 dimensions to avoid the computational difficulties. It can be concluded that considering heterogeneity through random

errors during margin setting is important to be considered to allocate the optimum dose. Bayesian statistics are important to be considered to deal with heterogeneity effect.

Conflicts of interest

The authors have none to declare.

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