



Anatomy-based prediction method for determining ipsilateral lung doses in postoperative breast radiation therapy assisted by diagnostic computed tomography images

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ABSTRACT

Background: This study aimed to investigate whether ipsilateral lung doses (ILDs) could be predicted by anatomical indexes measured using diagnostic computed tomography (CT) prior to the planning stage of breast radiation therapy (RT).

Materials and methods: The thoracic diameters and the length of lines drawn manually were measured on diagnostic CT images. The parameters of interest were the skin maximum lung distance (sMLD), central lung distance (CLD), Haller index (HI), and body mass index (BMI). Lung dose-volume histograms were created with conformal planning, and the lung volumes receiving 5–40 Gy (V5–V40) were calculated. Linear regression models were used to investigate the correlations between the anatomical indexes and dose differences and to estimate the slope and 95% confidence intervals (CIs).

Results: A total of 160 patients who had undergone three-dimensional conformal RT after breast-conserving surgery were included. Univariable analysis revealed that the sMLD ($p < 0.001$), CLD ($p < 0.001$), HI ($p = 0.002$), and BMI ($p < 0.001$) were significantly correlated with the V20. However, multivariable analysis revealed that only the sMLD (slope: 0.147, $p = 0.001$, 95% CI: 0.162–0.306) and CLD (0.157, $p = 0.005$, 0.048–0.266) were strongly correlated with the V20. The p-value for the sMLD was the lowest among the p-values for all indexes, thereby indicating that the sMLD had the best predictive power for ILD.

Conclusions: sMLD and CLD are anatomical markers that can be used to predict ILD in whole breast RT. An sMLD > 20.5 mm or a CLD > 24.3 mm positively correlated with a high ILD.

Key words: breast cancer; radiation therapy

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Introduction

Whole breast radiation therapy (RT) after a breast-conserving surgery is a standard practice in breast cancer treatment. Studies have shown that RT can reduce the rates of local recurrence and mortality [1, 2]. Among the various RT modal-

ities, three-dimensional conformal RT (3D-CRT) is widely used because it provides a good coverage. However, because the radiation field encompassing the breast also includes the lungs, the ipsilateral lung is at risk. Radiation-induced lung disease (RILD) is a potential adverse effect of RT and follows a dose-dependent evolution that is consis-

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tent with the superposition of early (pneumonitis) and late (fibrosis) components [3, 4]. The incidence of RILD in patients with breast cancer is 1–3% [5, 6].

Routine clinical-practice attempts for minimizing the lung radiation dose during breast RT planning are a popular concept. Previous studies have concluded that the mean ipsilateral lung dose (ILD; Dmean) and the percentage volume of the ipsilateral lung exposed to radiation doses of 20 Gy and above (V20) are the predictive dose-volume parameters for RILD [7, 8]. Recently, the use of advanced modes of high-precision RT [such as intensity-modulated RT (IMRT), tomotherapy, and volumetric modulated arc therapy (VMAT)], has become increasingly common in daily clinical practice; compared to conventional 3D-CRT, these modes allow excellent dose homogeneity within the target [9]. However, there is an ongoing debate on whether IMRT exposes the surrounding organs to low-dose radiation [10]. Schubert et al. revealed that although all modalities provided adequate coverage of the target breast, helical tomotherapy exposed large volumes of normal tissue to increased amounts of low-dose radiation [11]. In 2013, the American Society for Radiation Oncology discouraged the routine use of IMRT in whole breast RT [12]. Therefore, 3D-CRT remains the first choice of RT for patients with breast cancer.

Most institutions face a shortage of manpower when dealing with a large number of patients with breast cancer [13, 14]. At our institution, 3D-CRT is administered for early-stage breast cancer, and the ILD and V20 are limited to ≤ 10 Gy (Dmean) and $\leq 25\%$, respectively. We have adopted alternative treatment techniques (such as IMRT or VMAT) only for patients in whom the ILD could not be limited as described above. Generally, the lung dose parameters are determined after hours of simulation computed tomography (CT-sim). However, IMRT/VMAT simulation usually requires more time than 3D-CRT simulation, because we use extra immobilization devices (such as vacuum fixation cushions) to maintain the body position during the simulation. If indexes capable of identifying patients with ILDs that could potentially increase are available, we could perform CT-sim for IMRT/VMAT at the beginning of the treatment.

The aim of this study was to investigate whether there is a correlation between simple anatomical indexes measured on diagnostic CT images and the ILD prior to all RT planning procedures. Such a correlation would help in choosing the appropriate RT technique and informing the patients about the risk of ipsilateral lung radiation exposure, thus saving both time and health resources.

Materials and methods

Patients

This single-center retrospective study analyzed the dosimetric data from patients with breast cancer. The inclusion criteria for this study were as follows: 1) patients aged ≥ 18 years with a histological diagnosis of breast cancer, 2) patients who underwent preoperative diagnostic CT, and 3) patients with stage 0–IIB disease according to the Union for International Cancer Control TNM Classification of Malignant Tumors (8th edition), and 3) treatment with 3D-CRT between October 2018 and September 2020. The exclusion criteria were as follows: 1) total mastectomy before breast surgery, 2) surgical correction of chest deformities before breast surgery.

An ethics approval for this study was obtained from the institutional review board of the Shizuoka General Hospital on December 17, 2020 (application number: 2020063). An opt-out consent approach was used in this retrospective study.

Anatomical indexes

The anatomical indexes were measured using diagnostic preoperative CT. The CT scan was acquired using a 320-row CT scanner (Aquilion One, Canon Medical Systems Co., Tokyo, Japan) with a slice thickness of 3 mm. All patients were scanned in a supine position with their arms raised above their heads. The indexes were analyzed using correlation analysis to quantify the relationship between the dose difference and the dependent variables [such as the skin maximum lung distance (sMLD), central lung distance (CLD), and Haller Index (HI)].

For each patient, the slice including the affected-side nipple was selected for performing the measurements. The following artificial lines were drawn to determine the anatomical features. The first was a line connecting the middle point of the posterior

edge of the sternum and the anterior central point of the vertebral body (i.e., the A line); this line was extended to the anterior thoracic skin and was defined as the anterior–posterior axis. The next was a new line that was drawn perpendicular to the A line through the anterior border of the vertebral body while avoiding the osteophytes (i.e., the B line). The B line was also extended to the edge of the skin. A new line was drawn to connect the point of the front edge of the skin and the side edge of the chest wall skin (i.e., the C line). Another perpendicular line was drawn from the C line to the edge of the chest wall, and the maximum length of this line was defined as the sMLD (Fig. 1).

The CLD was measured as the perpendicular distance from the posterior border of the radiation field to the anterior chest wall along the central axis on digitally reconstructed radiography (Fig. 2A) [15]. The HI was used to exclude chest wall deformities. The formula used was as follows (Fig. 3) [16]:

$$HI = (\text{maximum transverse diameter of the thorax}) / (\text{distance between the posterior surface of the sternum and the anterior border of the vertebral body at the point of maximum depression})$$

An $HI \geq 3.3$ was considered to indicate a deformation [17].

The body mass index (BMI) was defined as the body weight divided by the square of the body height. BMI is not a standard anatomical index; however, obesity always affects breast RT. Therefore, we included BMI as a potential predictive factor. The BMI also differs according to the race and ethnicity; the commonly accepted normal range of BMI is 18.5–25 kg/m² [18].

Radiation therapy and dosimetric analysis

The patients were randomly assigned to two experienced radiation oncologists. All target volumes and organs at risk in this study were contoured in accordance with the guidelines of the European Society for Radiotherapy and Oncology for target volume delineation for elective RT for early-stage breast cancer [19, 20]. The prescribed total dose for all patients was 50 Gy in 25 fractions to the whole breast, with or without a 10–16 Gy (2.0 Gy/fraction) boost to the tumor bed. The planned target volume was expanded from the clinical tar-

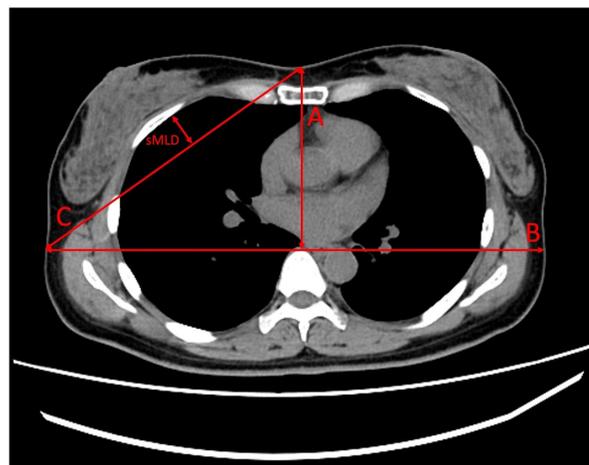


Figure 1. Measurement of the skin maximum lung distance (sMLD). The landmark slice included the nipple on the affected side. A line connecting the middle point of the posterior edge of the sternum and the anterior central point of the vertebral body is drawn to yield the anterior–posterior axis; it is extended to the anterior thoracic skin (A line). The B line is drawn perpendicular to the A line through the anterior border of the vertebral body. The B line is also extended to the edge of the skin, while avoiding the osteophytes. The C line is drawn connecting the points on the anterior and lateral edges of the chest wall skin. After drawing a perpendicular line from the C line to the edge of the chest wall, the maximum length of this line is defined as the sMLD

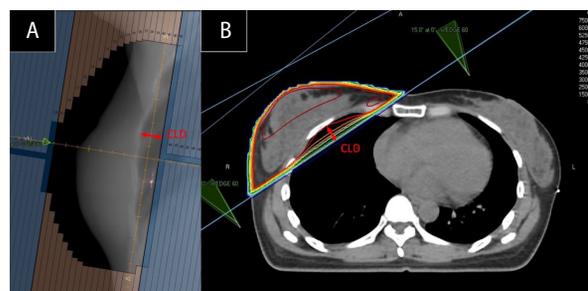


Figure 2. Measurement of the central lung distance (CLD). The CLD is measured as the perpendicular distance from the posterior border of the radiation field to the anterior chest wall. The length is measured at the central axis of the tangential field in a digitally reconstructed radiograph (A) or it is measured as the maximum distance on a simulation computed tomography image (B). (B) also shows a typical isodose distribution

get volume to encompass the entire breast tissue (Fig. 2B). The treatment plan in this study was generated using the RayStation Version 6.2 treatment planning system (RaySearch Laboratories AB, Stockholm, Sweden). The surrounding critical healthy structures, such as the lungs, were auto-

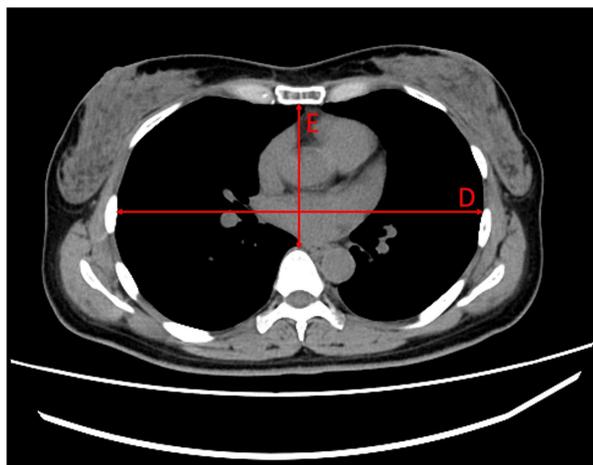


Figure 3. Measurement of the Haller index (HI). The HI is the ratio of the shortest distance between the transverse diameter of the chest and the sternum (D) to the distance between the vertebrae (E). $HI = D/E$

matically delineated and checked by the same two radiation oncologists. Please note that 3D-CRT techniques were used to generate treatment plans using 6 MV photon beams or a combination of 6 and 10 MV photon beams, with a wedge pair irradiating the entire breast. The “field-in-field” technique was used to improve the dose homogeneity. As per the plan, 95% of the prescribed dose would cover all of the ipsilateral breast tissues. The otherwise high-dose regions would receive 107–110% of the prescribed dose. The ILD was limited to $D_{mean} \leq 10$ Gy, while the V20 was limited to $\leq 25\%$.

The clinical treatment plans were used to collect the dosimetric data. The V5, V10, V20, V30, and V40 were determined from the cumulative dose-volume histograms (DVH).

Statistical analysis

The data were analyzed using IBM SPSS Statistics for Macintosh, Version 22.0 (IBM Corp., Armonk, NY, USA). The descriptive data was represented as mean, median, standard deviation (SD) or percentage. All the dosimetric parameters were evaluated for normal distribution. Univariable and multivariable linear regression models were used to investigate the correlations between anatomical indexes and the dose differences and slope; 95% confidence intervals and the p-values were also calculated. Statistical significance was set at $p < 0.05$. The Radiation Therapy Oncology Group

(RTOG) guidelines state that when administering RT to the residual breast tissue alone, the ideal V20 of the ILD should not exceed 15% [21]. We also believed that $V20 < 15\%$ was a good surrogate marker for ILD. Thus, we generated the receiver operating characteristic (ROC) curves of the significant parameters to determine their optimal cut-off values using the Youden’s index.

Results

Table 1 shows characteristics of the 160 patients who met the eligibility criteria. The median age of the patients was 58 years (range, 26–78 years). Right and left breast cancers were observed in 81 (50.6%) and 79 (49.4%) patients, respectively. In this study, the median BMI was 22.9 kg/m^2 (range, 15.6–34.3 kg/m^2). Most patients had early-stage cancers, with Tis, T1, T2, and T3 stages accounting for 22.5%, 50.6%, 23.7%, and 1.9% of the cases, respectively. Most of the tumors were located in the upper outer quadrant, and the most common histological type was invasive ductal carcinoma. The median values of sMLD, CLD, and HI were 21.8 mm (range, 1.4–38.7 mm), 19.7 mm (range, 6.0–34.8 mm), and 2.7 mm (range, 1.5–4.2 mm), respectively. The mean \pm SD values of the ILD and of V5, V10, V20, V30, and V40 are presented in Table 1.

Univariable analysis revealed that the BMI, HI, CLD, and sMLD were significantly correlated with the V20 ($p = < 0.001$, 0.002, < 0.001 and < 0.001 , respectively). However, multivariable analysis revealed that the CLD ($p = 0.005$) and sMLD ($p = 0.001$) were strongly correlated with V20. The p-value of the sMLD was 0.001; this was the lowest among the p-values for all indexes, indicating that the sMLD had the strongest predictive power for V20 (Tab. 2).

The ROC curves revealed that the predictive cut-off values of sMLD and CLD for ILD were 20.5 mm and 24.3 mm, respectively (Fig. 4).

Discussion

RT after a breast-conserving surgery or mastectomy can undoubtedly reduce the risk of local-regional breast cancer recurrence and improve the overall survival [22]. To ensure that RT is effective as well as safe, the radiation dose must be adequate for the tumor and should not be toxic

Table 1. Patient characteristics

Basic characteristics	(%)
Age [years] [median (range)]	58 (26–78)
Laterality	
Right	81 (50.6)
Left	79 (49.4)
BMI [median (range)]	22.9 (15.6–34.3)
T-Stage	
pT0	2 (1.3)
pTis	36 (22.5)
pT1	81 (50.6)
pT2	38 (23.7)
pT3	3 (1.9)
N-Stage	
pN0	136 (85.0)
pN1mi	6 (3.8)
pN1a	18 (11.3)
Location of the tumor	
Upper outer quadrant	73 (45.6)
Upper inner quadrant	32 (20.0)
Lower outer quadrant	10 (6.3)
Lower inner quadrant	8 (5.0)
Center portion	7 (4.4)
Mixed	30 (18.7)
Histology	
DCIS	38 (23.7)
IDC	79 (49.4)
ILC	17 (10.6)
Others	26 (16.3)
Chest wall index [median (range)]	
sMLD [mm]	21.8 (1.4–38.7)
CLD [mm]	19.7 (6.0–34.8)
HI	2.7 (1.5–4.2)
Radiation dose parameters	
Prescription dose [cGy]	5000–6000
Mean ipsilateral lung dose [cGy] [mean ± SD]	602.4 ± 166.8
V5 (%) [mean ± SD]	22.1 ± 4.9
V10 (%) [mean ± SD]	15.1 ± 4.2
V20 (%) [mean ± SD]	10.7 ± 3.7
V30 (%) [mean ± SD]	8.4 ± 3.4
V40 (%) [mean ± SD]	5.5 ± 2.9

BMI — body mass index; DCIS — ductal carcinoma *in situ*; IDC — invasive ductal carcinoma; ILC — invasive lobular carcinoma; sMLD — skin maximum lung distance; CLD — central lung distance; HI — Haller index; SD — standard deviation

to the surrounding healthy organs. Traditionally, breast RT was planned using two-dimensional data

of the central axis of the treatment field.²³ Recently, CT-sim has been used, which enables an accurate determination of the target volume; it has reduced the secondary cancer risk in patients receiving RT for breast cancer [24]. Furthermore, a CT-based treatment plan enables a better understanding of the RT dose distribution. More recently, the IMRT and VMAT have been applied clinically. Previous studies have reported that 1–3% of the patients receiving RT for breast cancer develop RILD [5, 6]. Although the incidence of RILD is not high, younger patients with breast cancer reportedly experience severe pre-RT emotional distress regarding the RT itself or the associated adverse events [25]. Rades et al. suggested psychological support before the start of a radiotherapy course [26]. Therefore, an RILD prediction tool can allow physicians to either take the necessary steps for reassuring such patients that the side effect rates are low or switch to a high-precision RT technique.

The most common methods for predicting RILD are comparisons of the ILD [27]. Dosimetric parameters derived from DVHs have been studied for many years, and it is widely known that the V20 of the lung is a predictor of RILD in patients with lung cancer [28]. In recent years, emphasis has been placed on reducing the dose to V5 or V10 [29]. Gokula et al. conducted a meta-analysis of 10 studies and found that the Dmean and V20 were the strongest dose-volume parameters associated with RILD [30]. The authors also suggested that the lung V20 and Dmean should be maintained at < 24% and < 15 Gy, respectively, to minimize the risk of RILD if possible. The RTOG published clinical practical guidelines stating that the ideal V20 of the ILD should not exceed 15% [21]. V20 is reportedly a more accurate and clinically useful surrogate marker; our findings revealed that a cut-off sMLD value > 20.5 mm could predict a V20 > 15%. Our findings also revealed that a CLD > 24.3 mm could predict a V20 > 15%, which is consistent with previous findings [31]. However, the CLD requires CT-sim for measurement. Therefore, sMLD, which is measured on pre-operative diagnostic CT images, is a more useful tool; multivariable analysis indicated that it had the strongest predictive power for V20.

The novelty of this study is the use of simple anatomical indexes measured on diagnostic CT images to predict the ILD. Several previous studies have

Table 2. Results of the univariable and multivariable regression analyses of V20

Variable	Univariable analysis			Multivariable analysis		
	Slope (β)	95% CI	p-value	Slope (β)	95% CI	p-value
BMI	-0.405	-0.569– -0.240	< 0.001	-0.179	-0.376–0.018	0.075
HI	1.864	0.714–3.014	0.002	0.916	-0.251–2.084	0.123
CLD	0.247	0.137–0.347	< 0.001	0.157	0.048–0.266	0.005
sMLD	0.234	0.162–0.306	< 0.001	0.147	0.162–0.306	0.001

V20 — the percentage of lung dose; CI — confidence interval; BMI — body mass index; HI — Haller index; CLD — central lung distance; sMLD — skin maximum lung distance; #Bold type indicates statistical significance

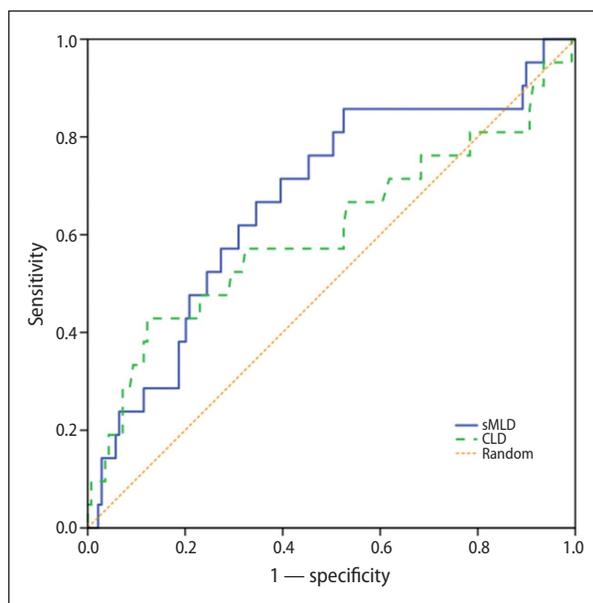


Figure 4. Receiver operating characteristic (ROC) curve analysis of the optimal cutoff values of the skin maximum lung distance (sMLD) and the central lung distance (CLD) for predicting the ipsilateral lung dose. The areas under the curves for the sMLD and CLD are 0.672 and 0.606, respectively

proposed models for predicting ILD by incorporating various geometric factors. However, these models were based on traditional two-dimensional data or on post-planning results [15, 32]. Kaymak and Özseven attempted to evaluate the correlation between anatomical features and the ILD, and concluded that the anatomical index could predict the lung doses [33]. However, they also measured the parameters on CT-sim images; thus, all analyzed models had an innate disadvantage in that they could not be assessed until CT-sim was performed. Usually, the accuracy of IMRT delivery grows increasingly dependent on set-up errors and breathing motions. This is not an issue when standard 3D-CRT is used for isolated breast treat-

ment, as the generous field design allows the target to remain in the field despite an inter- or intra-fraction motion [34]. At our institution, we only use vacuum fixation cushions for patients who undergo IMRT/VMAT to ensure positioning accuracy. The deep-inspirational breath-hold method was used for decreasing the chest wall motion during 3D-CRT in patients with left-sided breast cancer and during IMRT/VMAT in patients with breast cancer of either laterality. In some cases, the lung dose may be too large to deliver in patients with right-sided breast cancer who may have already completed the radiation plan on a primary CT-sim set for 3D-CRT. In such cases, the patients are then forced to undergo a re-simulation for IMRT/VMAT. This poses an unnecessary burden on the patients, who are required to return for a second CT-sim session. Thus, post-CT-sim-based assessment tools delay treatment initiation and increase the demand for medical resources. Our method allows clinical practitioners to predict the lung dose before CT-sim. This is particularly advantageous to patients residing far away from the hospitals. To the best of our knowledge, this is the first study to demonstrate the usefulness of sMLD for predicting the ILD via diagnostic CT before the planning stage by targeting the residual breast tissue in patients with breast cancer. By predicting the ILD, it is possible to choose more appropriate RT techniques, such as IMRT.

It is worth mentioning why we performed skin-to-skin measurement. The breast position differs slightly according to the therapeutic position, especially in obese patients. Usually, patients are simulated in a supine or prone position on an inclined breast board. When the breasts are large and the patients are in a supine position, the breasts may sag on both sides. Because we have to irradiate the entire residual breast tissue in RT,

considering the bony structures only is insufficient; the skin and subcutaneous fat also have to be considered. Thus, our method is potentially the first to evaluate these structures when predicting the lung irradiation dose. Some researchers have suggested that patients with large breasts should be irradiated in a prone position [35]. However, we do not recommend it, because it is an uncomfortable position and might result in potential movement during the procedure, which may, in turn, increase setup uncertainties [36].

Our study has several limitations. First, the sample size was small. Second, owing to the retrospective nature of the study, a selection bias was unavoidable. Finally, the respiration control method used was not considered in these models. Nevertheless, our study highlights the utility of the sMLD as a potential anatomical surrogate marker for determining the treatment choice before the planning stage.

Conclusion

Our findings revealed that the sMLD and CLD are anatomical markers that can be used to predict ILD in whole breast RT. An sMLD > 20.5 mm or a CLD > 24.3 mm positively correlated with a high ILD. We recommend using the sMLD (measured on diagnostic CT images) for predicting ILD prior to whole breast RT.

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Conflict of interest

The authors declare that there is no conflict of interests regarding this article.

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Conference presentation

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