Retrospective Dosimetric Analysis of Occurrence of Radiation Pneumonitis

by

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Medical Physics Program of
Duke Kunshan and Duke University

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Timothy Turkington

Thesis submitted in partial fulfillment of
the requirements for the degree of Master of Science
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ABSTRACT

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Abstract

Purpose: To retrospectively evaluate the impact of dosimetric parameters in treatment planning and dose discrepancies from patient inter-fractional motion on the high radiation pneumonitis (RP) occurrence rate in breast cancer patients receiving radiotherapy at First People's Hospital of Kunshan associated with Duke Kunshan University Medical Physics Graduate Program.

Method: Dose-volume parameters were extracted from breast cancer patients' treatment plans and were compared with corresponding experience-based thresholds associated with RP, including total dose, mean lung dose (MLD), percent of lung volume that receives a dose of 5 Gy or higher (V5), 13 Gy or higher (V13), 20 Gy or higher (V20), and 30 Gy or higher (V30).[2, 8-12] In addition, an in-house dose calculation system based on MATLAB and Varian Eclipse treatment planning system (TPS) was used to obtain actual dose distributions based on planning computed tomography (CT) scans, cone-beam computed tomography (CBCT) scans and couch shifts. The calculated actual dose was analyzed and compared to the original planning dose to evaluate inter-fractional motion induced dose discrepancies and their impacts on the occurrence of RP.

Result: For patients diagnosed with RP, the median MLD is 15.38 Gy and the median V20 is 25.6%, which are higher than corresponding constraints 14 Gy and 24% respectively. Other dose-volume parameters were also much higher than their

corresponding constraints for preventing RP. The inter-fractional patient motion induced discrepancies between planning and actual dose-volume parameters. For Patient 1, V20 increases from 23.93% to 28.33% due to the motion, which exceeds the V20 constraint of 24%. V30 increases to 17.99%, which is very close to the V30 constraint of 18%. For Patient 2, V10 increases from 32.00% to 35.43% and V13 increases from 29.86% to 32.99% due to the motion, both becoming to exceed the constraints. For Patient 3, MLD, V10, V13, V20 and V30 all decrease, where MLD and V20 decrease to the values lower than constraints.

Summary: Dose-volume parameters in breast cancer treatment plans at First People's Hospital of Kunshan were reviewed. Existing results show that the dose-volume parameters related to RP were higher than internationally recommended constraints, which contributes to the high RP incidence. In addition, an automated MATLAB-based actual dose calculation system was developed and used to analyze the dose discrepancies between planning and actual dose distributions. Inter-fractional patient motions were found to cause discrepancies between the original planning dose and the actual dose.

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1. Introduction

1.1 Radiation Pneumonitis

Radiation pneumonitis (RP) is a common dose-limiting toxicity following irradiation in lung regions. In radiotherapy, the therapeutic dose of radiotherapy is usually set under certain constraints in order to prevent the occurrence of RP. Therefore, RP limits the treatment dose, called dose-limiting, and substantially affects the therapeutic ratio of radiotherapy. As a type of radiation-induced lung injury (RILI), RP might lead to chronic complications in lung and even become life-threatening.[1,2,3] Therefore, for patients receiving thoracic irradiation for lung cancer, breast cancer, or esophageal cancer, it is important to constrain the development of RP in order to benefit local tumor control and improve patients' life.

The time for the occurrence of RP is usually several weeks to months after radiotherapy. Most studies have reported that the onset time is within the first 8 months.[2] Therefore, the complete post-radiotherapy follow-up procedures are required to evaluate the development of RP.

Various grading systems have been available for evaluating the severity of RP, including National Cancer Institute (NCI)'s Common Terminology Criteria for Adverse Events (CTCAE)[4], Radiation Therapy Oncology Group (RTOG), European Organization for Research and Treatment of Cancer (EORTC)[5] and Southwest Oncology Group (SWOG)[6]. Typically, there are 5 grades in these systems for grading RP. The severity of

RP increases from Grade 1 to 5. Grade 1 corresponds to asymptomatic or mild symptoms, while Grade 4 and Grade 5 represent life threatening symptoms and even death.

1.2 RP Risk Factors

The risk factors of the occurrence of RP mainly comprise two aspects: factors related to patients and factors related to treatments.

1.2.1 Factors Related to Patients

Factors related to patients include patients' age, sex, smoking history, and chronic pulmonary diseases. According to a comprehensive meta-analysis of risk factors for the occurrence of RP, older age and pulmonary comorbidity are significant risk factors, where $p < 0.0001$ and $p = 0.007$ respectively.[7]

1.2.2 Factors Related to Treatment

Treatment-related factors include radiotherapy, chemotherapy, immunotherapy, and surgery. In this study, dosimetric parameters in radiotherapy are mainly discussed.

1.2.2.1 Radiotherapy

The treatment-related factors include 1) radiotherapy fractionation (i.e., conventional fractionation vs. hypofractionation), 2) techniques of irradiation (i.e., intensity-modulated radiation therapy (IMRT) vs. three-dimensional conformal radiation therapy (3DCRT), radiation modality (i.e., photons vs. protons) have been found associated with development of RP.[8]

Currently the dose-volume constraints for preventing RP are widely used in clinical radiotherapy treatments and will be mainly discussed in this study. Various volume dose-based parameters have been observed to be associated with the occurrence of RP, including total dose prescribed, mean lung dose (MLD), percent of lung volume receiving a dose of 5 Gy or more (V5), 13 Gy or more (V13), 20 Gy or more (V20), 25 Gy or more (V25), and 30 Gy or more (V30).[2, 8-12] The most commonly used parameters are V20 and MLD. Recommendations have been made to constrain V20 lower than 30-35% and MLD lower than 20-23 Gy in order to limit the risk of RP lower than 20%.[8] Other parameters, such as V5, V13, V25, V30, were also able to predict RP.[13] However, these parameters tend to be collinear internally, which means that one parameter will change as another parameter changes.[8]

1.2.2.2 Chemotherapy

1. Concurrent chemotherapy vs. sequential chemotherapy.

According to a systematic analysis based on 1607 patients in 2012, sequential chemotherapy was found to associate with a higher risk of developing RP than concurrent chemotherapy.[7] The reason behind this finding is still not clear.

2. Types of chemotherapy medicines

A meta-analysis based on more than 70 published articles in 2013 found that the high risk of RP existed in patients > 65 years old receiving carboplatin / paclitaxel.[13]

Some chemotherapy medicines have been found to correlate with the high risk of developing RILI, such as bleomycin and taxanes.[14]

1.2.2.3 Surgery

A retrospective study on 147 lung cancer patients and a subsequent meta-analysis have reported that there were no statistically significant correlations between the extent of resection surgery and development of RP.[7,15] However, this finding is challenged by another study about concurrent chemotherapy and radiotherapy followed by resection.[16] It is reported that patients receiving chemotherapy with subsequent lobectomy have a higher survival rate than patients receiving only chemotherapy.

1.2.2.4 Immunotherapy

According to a recent comprehensive meta-analysis, patients receiving immunotherapy have the incidence of 2.7% for grade 3 RP and 0.8% for RP grade ≥ 4.[17] However, since radiotherapy has an effect on immune response, it is unclear whether the effect of immunotherapy on developing RP is synergistic with radiotherapy.[8]

1.3 Radiation Therapy for Breast Cancer

Radiation therapy has been proven to be an effective and essential treatment for breast cancer. Several radiotherapy techniques have been developed and widely used for breast cancer treatment, such as 3D-CRT and IMRT. [18]

1.3.1 Comparison between 3D-CRT and IMRT

Though 3D-CRT with tangential fields has long been used for treating breast cancer, it has limitations in providing conformal dose distribution and steep dose gradient and might bring excessive dose to normal tissues.[19] In contrast, IMRT performs better in target coverage and dose homogeneity and has a lower toxicity to normal tissues by modulating the intensity of the beams in multiple beamlets.[20] However, IMRT could increase the low-dose exposure of organs at risk (OAR) because it usually adopts more fields and monitor units (MU) in treatments.[19]

1.3.2 Fractionation in Radiotherapy

In radiation therapy, the process of splitting the therapeutic dose into multiple small daily doses called fractions is defined as fractionation. Fractionating radiation treatments is widely accepted for conventional radiotherapy to improve the overall patient outcome.[21] The underlying biological effects that affect the response of tumors and normal tissues to fractionated radiation dose can be summarized as "4 Rs": repair, reassortment (redistribution), repopulation, and reoxygenation.[22]

1.3.2.1 Repair

Exposures to small doses can accumulate direct DNA damage that cannot be repaired by cells.[39] Meanwhile, small doses of radiation allow normal tissues' sublethal damage repair. Both tumor cells and normal cells can repair sublethal damages following radiation exposure, but tumor cells repair slower than normal cells.[23, 24]

Therefore, being exposed to the fractionated dose, both tumor cells and normal cells can be damaged by the fractionated dose, but tumor cells repair slower than normal cells, which leads to the decreased number of tumor cells while preserving normal cells.[23]

1.3.2.2 Reassortment

Human cells in different cell cycles have different radiosensitivities. These cell cycles include mitosis, G_1, S, G_2, and G_0 phases. Mitosis phase and late G_2 phase are the most radiosensitive cell phases.[23] When cells are exposed to the single total radiation dose, most of cells have a high probability of being in the radioresistant phases and are difficult to kill. On the other hand, cells might develop to more radiosensitive phases when the dose are delivered in multiple times. Thus, fractionation benefits the treatment outcome since the probability that cells are exposed to radiation during a radiosensitive phase increases.[23]

1.3.2.3 Repopulation

Both tumor cells and normal cells continue to proliferate while being exposed to radiation.[22] Radiotherapy schemes should be well arranged to keep a balance between allowing normal tissues to repopulate and limiting tumoral proliferation.

1.3.2.4 Reoxygenation

Hypoxic-necrotic regions will occur in the tumor tissues when the tumor tissue's vascularity becomes unable to supply enough oxygen due to the continuous proliferation of tumor cells and increased tumor volume.[22] Hypoxic cells are more

resistant to radiation compared to well-oxygenated cells. With fractionated dose delivery, well-oxygenated cells die and hypoxic cells can gradually obtain more oxygen and become radiosensitive, which benefits the therapeutic outcome.

In sum, dividing the total dose into multiple fractions can increase the damage to tumors through redistribution and reoxygenation. At the same time, it can also spare normal tissues through normal cells' repair of sublethal damage during inter-fractional periods and repopulation of surviving cells. Thus, fractionation is widely adopted in modern radiation therapy.

1.3.3 Patient Positioning and Inter-fractional Patient Motion

One of the important requirements of modern radiotherapy is to provide precise dose distributions that cover tumors and spare surrounding normal tissues. During the radiotherapy workflow, however, inter-fractional patient motion, referring to the patient motion between treatment fractions, results from patient positioning variations between fractions. Inter-fractional patient motion might cause the inaccuracy of radiation delivery and thus comprise local tumor control and induce toxicities to normal tissues.[25] For patients receiving radiotherapy for breast cancer, the inter-fractional motion might cause unnecessary dose to lung and thus lead to radiation induced lung injuries like RP. Therefore, the accurate positioning of the patient is crucial for radiotherapy, especially for highly conformal radiotherapy techniques like IMRT.

Various reliable techniques for guiding and monitoring patient positioning are widely used today, including electronic portal imaging devices (EPID) and CBCT. CBCT imaging can provide good volumetric CT images with good contrast and spatial resolutions. However, it will cause extra imaging dose to patients.[26] For breast cancer radiotherapy using IMRT technique, compared to EPID, kilovoltage cone beam computed tomography (kV-CBCT) can provide the information of both bones and soft tissues, clearly visualize the tumor and OARs, and reduce random deviations. With these capabilities, utilization of kV-CBCT benefits the accuracy of treatment delivery and thus improves the tumor control.[27-29]

To achieve accurate patient positioning, the treatment couch is shifted following CBCT scans in order to correct inter-fractional patient motion measured by CBCT.[30,31] However, only using the pre-treatment couch shifts cannot fully correct the motion. For example, patients might experience rotations, which cannot be corrected by couch shifts alone since the couch in our institution can only move straightly in 6 directions: right / left, up / down, and in / out. By studying the planning CT scans, daily pre-treatment CBCT scans and online couch shifts records, we found that there were still discrepancies between actual positions and planning positions for breast cancer treatments.

1.3.4 Immobilization in Radiotherapy

Similar to the pre-treatment patient positioning, patient immobilization during the treatment is also crucial to the accuracy of radiotherapy. Various immobilization

devices are widely used in radiotherapy in order to reduce patient motion during the treatment and ensure the setup can be reproducible from day to day.[32] Immobilization devices for different body parts include head frames, thermoplastic masks, polyurethane foam systems, vacuum cushion systems, breast boards and so on.

For breast setup and immobilization, breast boards are commonly used. Breast boards can provide rigid support for patients and allow technologists to easily immobilize patients in a comfortable and reproducible way. There are two types of setup techniques for breast setup: supine technique and prone technique. The supine technique has the advantages of easy setting up and better patient comfort. However, for patients with large breasts, supine technique is difficult to perform and might bring the loss of skin sparing effect. In contrast, prone technique is suitable for this case and can provide a more homogenous dose distribution. However, it has a lower accuracy than supine positioning and is difficult for patient setup.[33] At First People's Hospital of Kunshan, the supine technique with a breast board is used for positioning and immobilization of breast cancer patients.

1.4 Research Motivation and Purpose

It was found that the patients receiving radiotherapy for breast cancer and esophageal cancer at First People's Hospital of Kunshan associated with Duke Kunshan University Medical Physics Graduate Program had a high rate of developing RP. The chemotherapy and surgery were found widely used in both patients with RP and

patients without RP. All the patients received radiotherapy via the same linear accelerator (LINAC) with photons of the same energy. Other factors such as fractionation, techniques used were also found similar in both patients with RP and patients without RP. We hypothesized the potential defects in treatment plans or the inter-fractional motion might contribute to the high RP risk. The purpose of this study is to retrospectively evaluate the impact of unconstrained dosimetric parameters in treatment planning and dose discrepancies resulting from patient inter-fractional motion on the high RP incidence in breast cancer patients receiving radiotherapy in our institution.

2. Materials and Methods

2.1 Patients and Treatments

2.1.1 Patient Characteristics

With the institutional review board (IRB) approval, 42 breast cancer patients and 45 esophageal cancer patients receiving radiotherapy (RT) in 2019 at First People's Hospital of Kunshan were retrospectively reviewed, 9 and 7 were diagnosed with RP respectively. Among 42 breast cancer patients, 9 patients with RP were assigned as Group 1 while 9 randomly selected patients without RP were assigned as Group 2. The basic characteristics of patient population are listed in Table 1.

Table 1: Basic Characteristics of Patients

	RP (Group 1, n=9)	No RP (Group 2, n=9)	Total (n=18)
Age at diagnosis (years)			
Median(range)	45 (32-75)	46 (32-64)	45 (32-75)
≤60	5 (56%)	8 (89%)	13 (72%)
>60	4 (44%)	1 (11%)	5 (28%)
Sex			
Male	0 (0%)	0 (0%)	0 (0%)
Female	9 (100%)	9 (100%)	18 (100%)
Chemotherapy			

Yes	6 (67%)	8 (89%)	14 (78%)
No	3 (33%)	1 (11%)	4 (22%)
Surgery			
Yes	9 (100%)	9 (100%)	18 (100%)
No	0 (0%)	0 (0%)	0 (0%)

2.1.2 Treatment Characteristics

2.1.2.1 Chemotherapy and surgery

All breast cancer patients reviewed received pre-radiotherapy surgery. Among patients from Group 1 and Group 2, there were respectively 6 and 8 patients receiving chemotherapy. The surgery techniques, chemotherapy techniques, and chemotherapy medicines are not considered in this study.

2.1.2.1 Radiotherapy

Among total 18 patients, 16 patients received multiple-field IMRT radiotherapy through the same LINAC Varian Clinac iX with 6 MV photons (Varian Medical System, Palo Alto, CA). Two patients without RP received multiple-field 3D-CRT through the same LINAC with 6 MV photons. Treatment planning is achieved on Varian Eclipse Treatment Planning System (TPS). Analytic anisotropic algorithm (AAA) with heterogeneity correction on Eclipse was used for volume dose calculation in treatment planning.

Commissioning and annual quality assurance (QA) of TPS and LINAC is well performed by the official service from Varian Medical Systems Beijing Co. Ltd. Pre-treatment IMRT dose verification is performed in three methods: 1) point absolute dose measurement based on solid water phantoms; 2) field-by-field dose measurement in planes with fixed gantry positions utilizing PTW OCTAVIUS Ⅰ QA System with Detector 729 (PTW, Freiburg, Germany); 3) LINAC beam output calculation with different gantry positions utilizing 3D patient dose QA software Compass (IBA, Louvain-la-Neuve, Belgium).

Planning CT scans were performed through a 64-slice CT scanner in helical mode (GE Lightspeed VCT 64; GE Healthcare, USA). The CT parameters used were 5 mm slice thickness, 120 kVp, 23 mAs exposure, 233 mA tube current, with body filter, and with the standard convolution kernel.

Because of kV-CBCT's ability to provide information of both bones and soft tissue and visualization of tumors, before each treatment fraction, kV-CBCT scans were performed for patient setup utilizing Varian On Board Imager (OBI) mounted on the LINAC. CBCT mode is low-dose thorax and acquisition mode is half fan. Patient orientation is head first supine (HFS). Other CBCT imaging parameters include diameter of 45 cm for PA-axis and 45 cm for LR-axis, reconstruction volume of 384 * 384, reconstruction diameter of 450 mm, slice thickness of 2.5 mm, peak kilovoltage of 110

kVp, X-ray tube current of 20 mA, and exposure of 270 mAs. CBCT imaging isocenter is at the center of the CBCT scan image.

Following CBCT scanning, the matching and translational position correction is achieved by pre-treatment couch shifts from reference setup position in 6 directions: right / left, up / down, and in / out.

The beast board with supine positioning method is used for positioning and immobilization of breast cancer patients. The breath control techniques are not adopted.

2.2 Evaluation of Dosimetric Factors

Dosimetric factors of treatment plans are extracted and recorded from dose volume histograms (DVH) on Eclipse TPS, including total dose, MLD, V5, V10, V13, V20, and V30. For both Group 1 patients and Group 2 patients, the mean and median values of these parameters are calculated respectively.

The number of patients from each group with the dose-volume parameters exceeding certain experienced-based thresholds for preventing RP are counted and the corresponding percentage is calculated. The dose-volume constraints used in this study are listed in Table 2.

Table 2: Constraints for Dose-Volume Parameters

Parameters	Constraint values
Total dose, Gy	60 Gy
MLD, Gy	14 Gy

V5, %	40%
V10, %	35%
V13, %	32%
V20, %	24%
V30, %	18%

2.3 Evaluation of Inter-fractional Patient Motion

2.3.1 Obtaining Actual Dose Distributions

With the aim of obtaining the dosimetric consequences of inter-fractional patient motion, an automated actual dose calculation system based on MATLAB and Eclipse is developed. For each patient, rigid image registration (RIR) of planning CT images to daily CBCT images were performed on Eclipse. The results of RIR were qualitatively assessed and were considered as accepted in clinical practice. Patients' entire treatment planning data and transformation matrices of RIR were exported from Eclipse to MATLAB. The planning CT images are processed on MATLAB incorporating the transformation matrix and couch shift records. The processed CTs are able to provide the actual positions of each fraction and to be used for dose calculation. After that, processed CTs are imported into TPS and the dose is calculated by utilizing processed CTs and original plans. This newly calculated dose distribution is the actual dose

distribution and will be compared with the original dose. The whole workflow is illustrated in Figure 1.

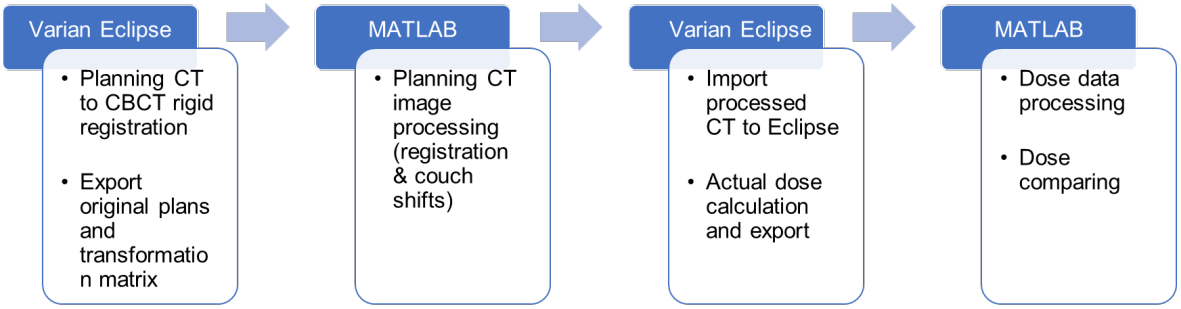

Figure 1: Workflow for Obtaining Actual Dose Distribution

2.3.2 Comparison between Planning Dose and Actual Dose

During the calculation of actual dose, each fraction has its own patient positions shown by processed CT. Thus, it is difficult to evaluate the overall actual dose distribution in the same planning CT image on Eclipse. The actual dose files are exported to and processed on MATLAB in order to gain the overall dose distribution shown on the original CT, which can be compared to original planning dose distributions later. The dose discrepancies are calculated based on the difference between original dose and actual dose. For each patient, the mean, median, standard deviation, minimum, and maximum of dose difference in lung and are calculated respectively.

3. Results

3.1 Dosimetric Parameters Evaluation

RP was found to usually develop in the region of lung that receives a relatively high dose during radiotherapy, which is demonstrated in Figure 2.

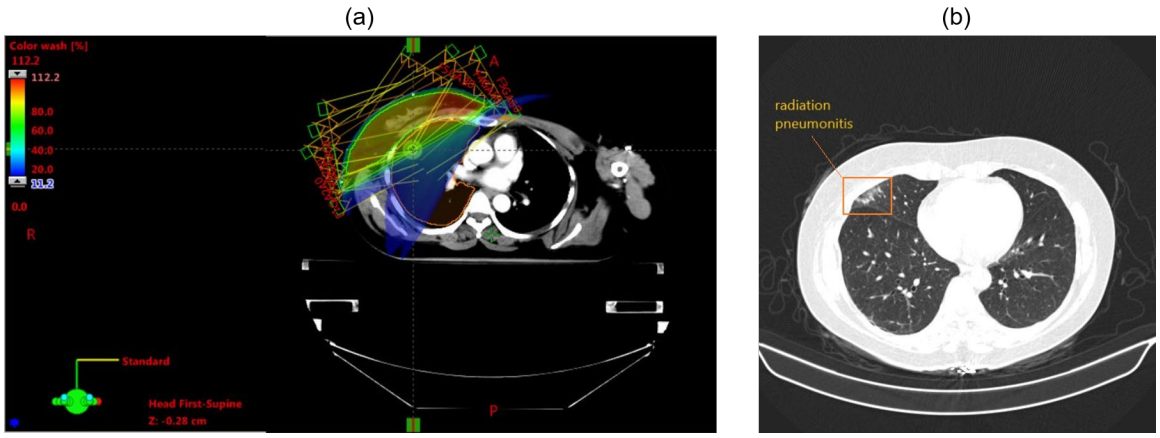

Figure 2: Demonstration of Development of RP: (a) Sample Treatment Plan of a Patient with RP; (b) Location of RP in the same patient

3.1.1 Dose-Volume Parameters

Detailed radiotherapy characteristics and dosimetric parameters of patients with and without RP are summarized in Table 3.

Table 3: Radiotherapy Characteristics and Dosimetric Parameters of Patients

Group	Patient ID	Radiotherapy technique	Ipsilateral lung volume (cm3)	Total dose prescribed (Gy)	Number of fractions	Dose per fraction (Gy)	Mean Lung Dose (Gy)	V5 (%)	V10 (%)	V13 (%)	V20 (%)	V30 (%)
RP - Group 1	1	6F-IMRT	872.8	61.60	28	2.20	16.52	86.3	62.8	49.6	23.9	15.3
	2	4F-IMRT	1539.1	50.00	25	2.00	12.70	40.6	32.0	29.9	27.0	23.6
	3	6F-IMRT	888.0	61.60	28	2.20	15.07	79.1	45.5	36.6	25.6	17.7
	4	6F-IMRT	1320.7	60.20	28	2.15	15.38	86.8	52.8	42.5	25.5	14.4
	5	5F-IMRT	1343.9	60.20	28	2.15	17.25	98.2	54.2	36.6	26.1	19.7
	6	6F-IMRT	1158.6	60.20	28	2.15	16.83	80.6	65.7	46.7	24.7	16.5
	7	6F-IMRT	1337.0	50.00	25	2.00	15.22	80.3	49.4	40.8	26.1	15.3
	8	6F-IMRT	1097.2	50.00	25	2.00	18.14	95.2	73.9	56.8	29.1	16.7
	9	6F-IMRT	1279.0	60.20	28	2.15	15.36	88.8	48.9	36.2	23.3	16.6
No RP - Group 2	10	6F-IMRT	855.5	50.00	25	2.00	16.69	92.1	63.8	45.4	24.9	16.6
	11	6F-IMRT	1418.3	60.20	28	2.15	17.61	91.7	66.0	50.7	27.7	18.6
	12	6F-IMRT	799.8	60.20	28	2.15	15.46	87.0	54.9	41.9	22.6	13.5
	13	6F-IMRT	1439.9	50.00	25	2.00	17.52	96.7	71.5	54.9	27.2	16.0
	14	6F-IMRT	806.4	50.00	25	2.00	36.40	93.1	68.1	52.2	29.8	19.2
	15	6F-IMRT	1236.3	60.20	28	2.15	17.80	99.9	71.0	54.8	27.8	17.2
	16	4F-CRT	1031.9	50.40	28	1.80	21.10	31.4	23.4	21.6	19.3	17.0
	17	5F-IMRT	685.9	50.00	25	2.00	30.30	71.8	45.0	38.4	27.9	18.7
	18	4F-CRT	1138.8	50.00	25	2.00	29.30	47.5	34.5	31.3	27.0	23.3

For both Group 1 patients (with RP) and Group 2 patients (without RP), mean and median dose-volume parameters are recorded in Table 4.

Table 4: Mean and Median Dose-Volume Parameters of Patients with and without RP

Parameters	RP (Group 1, n=9) mean (median)	No RP (Group 2, n=9) mean (median)
Total dose, Gy	57.11 (60.20)	53.44 (50.00)
MLD, Gy	15.83 (15.38)	22.47 (17.80)
V5, %	81.8 (86.3)	79.0 (91.7)
V10, %	53.9 (52.8)	55.4 (63.8)
V13, %	41.7 (40.8)	43.5 (45.4)

V20, %	25.7 (25.6)	26.0 (27.2)
V30, %	17.3 (16.6)	17.8 (17.2)

3.1.2 Counting of Patients with Parameters Exceeding Constraints

For each dosimtric parameter, there is an experience-based constraint for preventing the development of RP. The number of patients with parameters exceeding constraints are counted.

Table 5: Counts of Patients with Dosimetric Parameters Exceeding Constraints

Number n	RP (Group 1, n=9) number (percentage)	No RP (Group 2, n=9) number (percentage)
n (total dose > 60 Gy)	6 (67 %)	3 (33%)
n (MLD > 14 Gy)	8 (89%)	9 (100%)
n (V5 > 40%)	9 (100%)	8 (89%)
n (V10 > 35%)	8 (89%)	7 (78%)
n (V13 > 32%)	8 (89%)	7 (78%)
n (V20 > 24%)	7 (78%)	7 (78%)
n (V30 > 18%)	2 (22%)	4 (44%)

3.2 Discrepancies between Planning Dose and Actual Dose

Up to date, the actual dose of three patients in Group 1 have been calculated and compared to the original dose. The results are demonstrated in Figure 3 to 5.

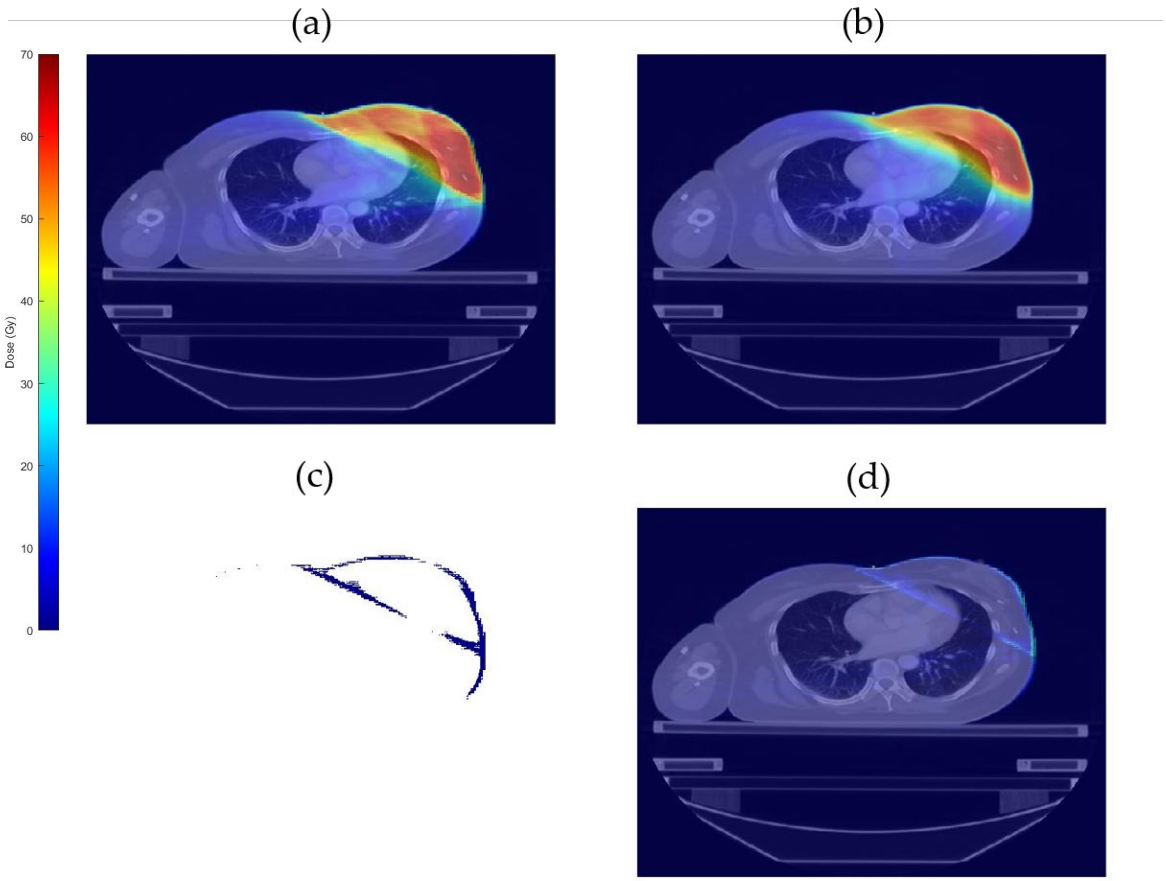

Figure 3: Dose Distributions and Differences on a CT Slice of Patient 1 in Group 1: (a) Original Planning Dose Distribution; (b) Actual Dose Distribution (c) Dose Differences Shown on White Background (d) Dose Differences Shown on Original Planning CT

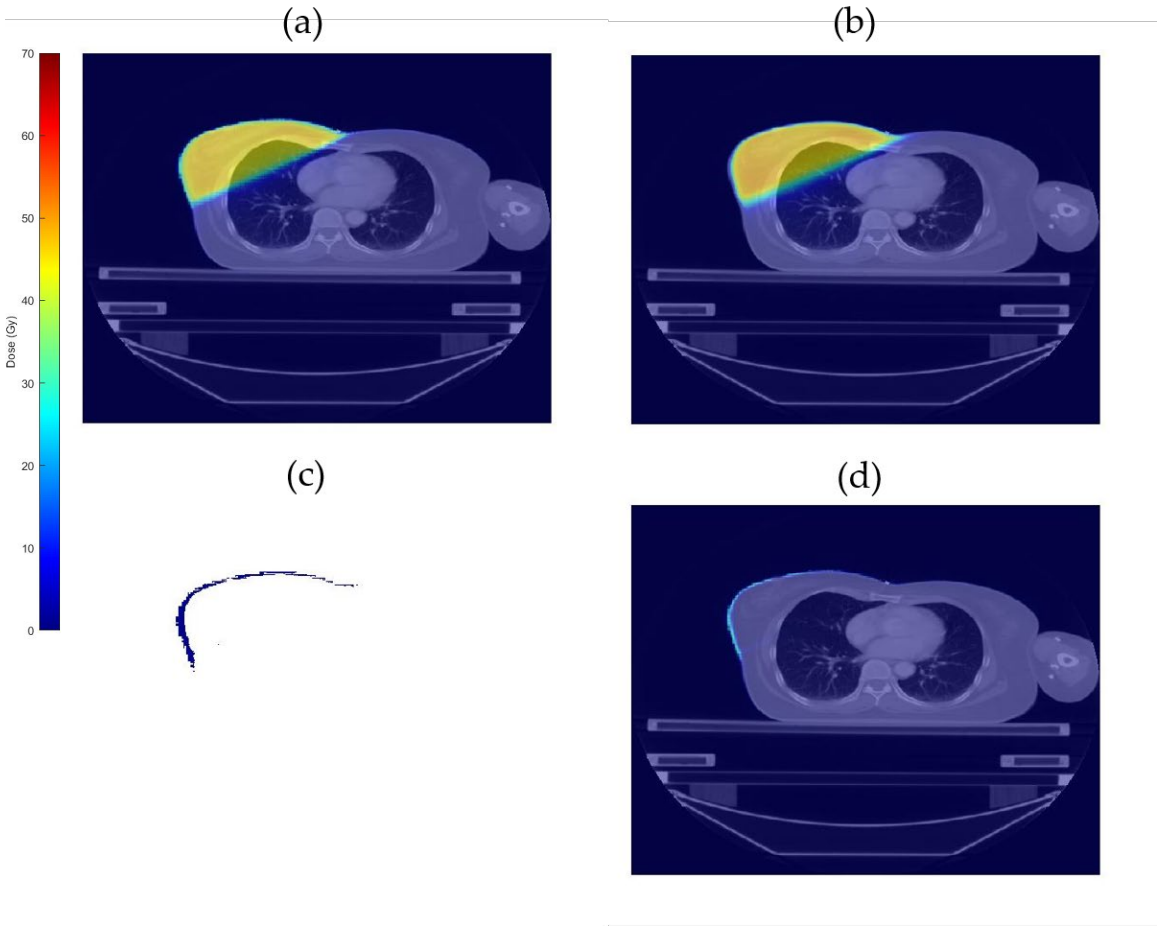

Figure 4: Dose Distributions and Differences on a CT Slice of Patient 2 in Group 1: (a) Original Planning Dose Distribution; (b) Actual Dose Distribution (c) Dose Differences Shown on White Background (d) Dose Differences Shown on Original Planning CT

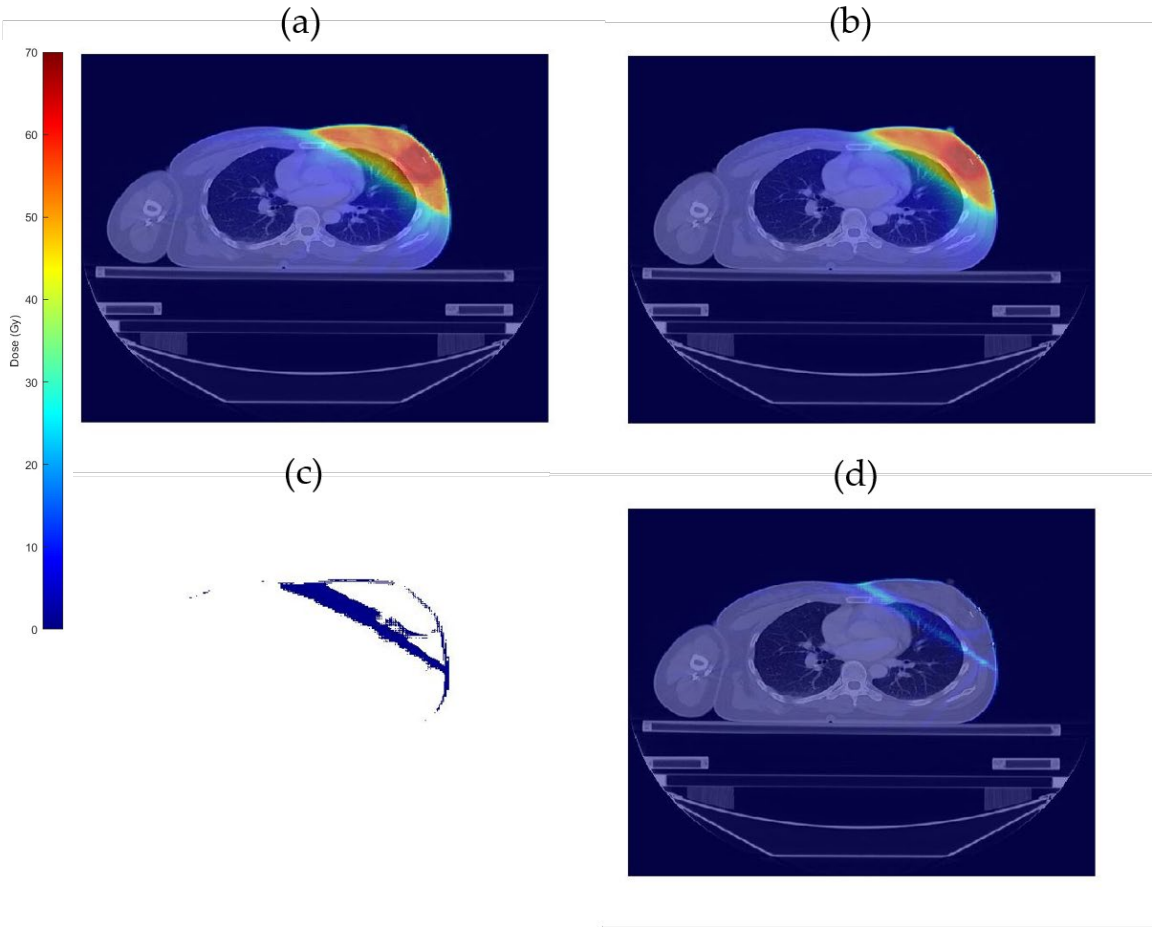

Figure 5: Dose Distributions and Differences on a CT Slice of Patient 3 in Group 1: (a) Original Planning Dose Distribution; (b) Actual Dose Distribution (c) Dose Differences Shown on White Background (d) Dose Differences Shown on Original Planning CT

For each patient reviewed, the statistics of dose differences in lung are summarized in Table 6.

Table 6: Statistics of Dose Difference in Lung

Dose Difference (planning – actual)	Patient 1	Patient 2	Patient 3
Mean, Gy	-0.71	-1.01	2.46
Median, Gy	-0.26	-0.17	0.47
Standard Deviation, Gy	2.53	2.63	4.57
Minimum, Gy	-16.72	-28.87	-4.43
Maximum, Gy	9.68	29.18	23.79

Table 7: Planning and Actual Dose-Volume Parameters in Lung

Parameters	Patient1		Patient2		Patient3	
	Planning	Actual	Planning	Actual	Planning	Actual
MLD, Gy	16.52	17.23	12.70	13.71	15.07	12.61
V5, %	86.28	86.25	40.63	43.16	79.11	80.59
V10, %	62.81	59.97	32.00	35.43	45.47	44.01
V13, %	49.56	47.70	29.86	32.99	36.63	32.92
V20, %	23.93	28.33	26.97	29.04	25.57	19.06
V30, %	15.29	17.99	23.65	24.20	17.69	8.73

4. Discussion

4.1 Results Discussion

4.1.1 Dose-Volume Parameters Related to RP

A meta-analysis based on 74 articles has summarized various experience-based dosimetric thresholds for preventing development of RP. It was reported that total dose ≥ 60 Gy leads to a high incidence of all grades of RP. MLD ≥ 14 Gy, V5 > 40%, V10 > 35%, V13 > 32%, V20 > 24% and V30 > 18% are correlated to a higher RP risk (grade ≥ 2).[9,12] In this study, these thresholds are used for evaluating the occurrence of RP.

4.1.1.1 Group 1 - Patients with RP

For patients developing RP, the median total dose and median MLD are higher than respective threshold values. There are 6 patients with total dose ≥ 60 Gy and 8 patients with MLD ≥ 14 Gy. All the mean and median values of V5, V10, V13, and V20 are much higher than corresponding threshold values.

Most patients with RP have the over-threshold values of total dose, MLD, V5, V10, V13, and V20. In contrast, there are only 2 patients having V30 > 18 %. From V5 to V30, the number of patients with over-threshold parameters shows a decreasing trend, which might mean that the lung volume receiving a lower dose is more effective in predicting the development of RP.

4.1.1.2 Group 2 - Patients without RP

In this group, except the total dose and V30 are lower than corresponding constraints, all other dose-volume parameters exceed constraints. This observation suggests that dose-volume parameters are not the only determining factors of the occurrence of RP. Other unconsidered factors also influence the evaluation results, such as chemotherapy and patients' physical state.

As the same as Group 1 patients, with the increasing dose-volume parameter (i.e., from V5 to V30), the number of patients with over-threshold parameters decreases, especially near V30. Though the internal relationships have been found between these parameters, they are not strictly colinear according to the observation.

4.1.1.3 Comparison between Group 1 and Group 2

Patients in both Group 1 and Group 2 have the over-threshold mean and median values of MLD, V5, V10, V13, and V20. Compared to patients with RP, patients without RP usually have a lower prescribed total dose. Based on the existing data, it indicates that the dose-volume parameters exceeding constraints are correlated with the development of RP. However, they alone cannot determine the development of RP. The occurrence of RP is a complex process involving various factors. The treatment planning in this institution should be improved by constraining the dosimetric parameters related to RP in order to prevent the occurrence of RP.

4.1.2 Inter-fractional Motion Induced Dose Difference

For three patients reviewed, the average dose difference in lung between original planning dose and actual dose are -0.71 Gy, -1.01 Gy, and 2.46 Gy. The mean absolute value of the difference is 1.40 Gy and the median absolute value of difference is 0.30 Gy, which are relatively small compared to the total dose received. However, the absolute maximum difference could reach 29.18 Gy, which might result from the uncertainties in dose calculation in the margins of the lung.

For evaluating the development of RP, the dose values alone are not enough. Volumes and doses need to be incorporated and considered concurrently. The discrepancies between original planning dose-volume parameters and actual dose-volume parameters are summarized in Table 8.

Table 8: Discrepancies between Actual and Planning Dose-Volume Parameters

Parameters	Patient1		Patient2		Patient3	
	Difference (planning – actual)	Percentage Change	Difference (planning – actual)	Percentage Change	Difference (planning – actual)	Percentage Change
MLD, Gy	-0.71	-4.33%	-1.01	-7.94%	2.46	16.32%
V5, %	0.03	0.03%	-2.53	-6.22%	-1.49	-1.88%
V10, %	2.84	4.52 %	-3.43	-10.71%	1.47	3.23%
V13, %	1.86	3.76%	-3.13	-10.48%	3.71	10.12%

V20, %	-4.40	-18.38%	-2.06	-7.65%	6.50	25.43%
V30, %	-2.70	-17.66%	-0.56	-2.35%	8.96	50.64%

The absolute difference of MLD ranges from 0.71 Gy to 2.46 Gy, which is relatively high especially when MLD is near the constraint value. While the MLDs of Patient 1 and Patient 2 increases for about 1 Gy, the MLD of Patient 3 even decreases from 15.07 Gy to 12.61 Gy that is lower than the constraint MLD of 14 Gy.

The absolute differences of V5, V10 and V13 of three patients reviewed range from 0.03 % to 3.71 %, which are relatively low compared to the high original values. However, these changes are worthy of consideration when the parameter is near the constraints. For example, V5, V10, V13 of Patient 2 are initially below thresholds but increase to the values higher than thresholds, which might contribute to the development of RP.

The changes of V20 and V30 are relatively large compared to the lower original values. The percentage change of V20 and V30 could reach 25.43% and 50.64% respectively in Patient 3. While V20 and V30 of Patient 1 increase to exceed the constraints, they decrease to be lower than the constraints in Patient 3. These changes near the thresholds might influence the occurrence of RP.

It is worth noting that the dose-volume parameters in Patient 3 decrease due to the motion, which seems to help prevent from developing RP. However, it is because of

the deficiencies of over-constraint parameters in treatment planning in this institution. In normal cases, the dose-volume parameters are well constrained to prevent RP and the motion induced changes will compromise the local tumor control and the normal tissue sparing.

In sum, the unconstrained dose-volume parameters in treatment planning are related to the high incidence of RP. The uncorrected inter-fractional motion leads to the dose discrepancies. However, due to the complexity of RP developing and limited data size, it cannot be concluded that the motion leads to occurrence of RP in our institution.

4.2 Other Factors Affecting Evaluation of Developing RP

Apart from dosimetric parameters in radiotherapy, there are other factors we need to consider for evaluating occurrence of RP systematically.

4.2.1 Patient Characteristics

As mentioned above, 9 of 42 breast cancer patients were diagnosed with RP by post-treatment follow-up several months later. However, some patients did not complete three times of follow-up. Thus, Group 2 data might have uncertainties since some patients did not develop RP for the first time of follow-up but might develop RP later without being diagnosed.

4.2.2 Patient Related Factors

There are some patient-related factors associated with RP that have not been considered in our study, including smoking history, older age, and chronic obstructive

pulmonary disease (COPD). These factors may also affect our study and results of evaluation. There are some patients reviewed with older age, which could be evaluated. However, the number of patients was insufficient to study this effect.

4.2.3 Chemotherapy

The chemotherapy types and chemotherapy medicines are also significant risk factors of RP. In 18 breast cancer patients reviewed, there are 14 patients with chemotherapy and 4 patients without chemotherapy. The interesting point is that there are 3 patients with RP did not receive chemotherapy while only 1 patient without RP did not receive chemotherapy. Due to the limitation of data size and time, in this particular case, considering chemotherapy factors is not possible and thus might affect our evaluation.

4.2.4 CBCT Dose to Lung

Utilization of CBCT has significantly improved the accuracy of radiotherapy and is used routinely in modern image-guided radiation therapy (IGRT). The typical breast cancer treatments in our institution consist of 20 to 28 fractions and the CBCT scans were performed in each fraction for all patients. Previous studies based on Monte Carlo methods have pointed out that the dose of Varian OBI system to chest is about 2-9 cGy per fraction.[34] Using 23 as the average number of fractions in patients reviewed, the total dose from CBCT to tumor and normal tissues is estimated to 46 cGy to 207 cGy. The highest value 2.07 Gy could be comparative to the dose of one fraction. However, the

CBCT dose is not integrated into the treatment planning in our institution, which means the dose delivered to patients is higher than planned dose and might contribute to the development of RP.

Integrating megavoltage (MV) CBCT dose into the treatment plans is easy to achieve since the imaging system utilizes the therapeutic beam. However, in this case of utilizing kV-CBCT, considering imaging dose requires further data collection and modeling work, which cannot be achieved yet. The CBCT imaging dose can be decreased by reducing frame numbers or changing current-time settings with the cost of the decreased image quality.[30]

4.2.5 Tumor Shrinkage

During the treatment course based on the initial planning CT, there might exist tumor shrinkage, which might bring higher dose to OARs and increase potential toxicities, especially when there are typically 20 to 28 fractions in the cases reviewed. Therefore, replanning is encouraged to adjust the plan during fractions in order to consider the changing tumor and normal tissue anatomy. Replanning is expected to spare more normal tissues and help reduce the risk of RP.

4.3 Errors Affecting Evaluation of Patient Motion

4.3.1 Accuracy of Rigid Image Registration

In order to obtain the correct patient position shown on CT images, rigid registration of CT to CBCT was performed. In practice, the qualitative verification of

rigid registration was achieved by using split screen and checkerboard displays, and image overlay displays. It is guided that for the case of 1 mm plane resolution and 2-3 mm slice thickness, the overall accuracy should be lower than 2 mm.[35]

The registration process will bring uncertainties compared to the position shown on original CBCT. However, patient-specific quantitative verification of registration is usually difficult to perform due to the limited time and uncertainties of the ground truth.[35] The result of RIR in this study is assessed in quality and is considered acceptable, which will have relatively small impact on evaluation of set-up variations.

4.3.2 Rigid Image Registration vs. Deformable Image Registration

Rigid image registration (RIR) has been widely used in radiotherapy for a long time. RIR works well when there are no anatomic changes. However, inaccuracies will be brought when applying RIR for patients with weight loss, tumor shrinkage, or soft-tissue displacement. In contrast, deformable image registration (DIR) has much more degrees of freedom (DOF) and can manage/correct these changes by mapping the corresponding volume elements in two images.[36]

Several studies based on qualitative evaluation have shown that DIR performs better accuracy compared to RIR in the case of lung cancer.[37, 38] In our practice of registration, the priority is given to the lung region in registration and the results of RIR were found to be acceptable.

4.3.3 Uncertainties in Image Processing and Dose Calculation

During the CT image processing, rotation and translation of CT images might bring in errors. Though transformation of the images might cause some margins of images need to be interpolated using linear interpolation, these areas are very small and locate at the edges of images, which will cause little difference when calculating dose distributions using the processed CT images. The quality of processed CT images is reviewed and is considered acceptable. However, an experiment needs to be done to validate the accuracy of the developed actual dose calculation system. It can be achieved by comparing the measured dose in the phantom after translation and rotation with the calculated dose in the phantom using processed phantom CT data in our system.

5. Conclusion

We reviewed dose-volume parameters in breast cancer treatment plans in our institution. Besides, an automated MATLAB-based actual dose calculation system was developed and used to analyze the dose discrepancies between planning and actual dose distributions due to inter-fractional patient motion.

Existing results showed that there exist deficiencies in treatment planning for breast cancer in our institution. The dosimetric factors related to RP are significantly higher than internationally recommended constraints, which contributes to the high RP rate. The treatment planning needs urgently to be improved to avoid unnecessary irradiation in normal lung tissue for breast cancer patients in order to prevent the development of RP.

In addition, the inter-fractional patient motion is not totally corrected by pre-treatment CBCT scans and couch shifts, which lead to the discrepancies between planning and actual dose-volume parameters. Advanced motion control techniques and treatment replanning are encouraged to be used to assure the accuracy of the treatment.

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