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Study Protocol to Quantify Breast-Chest Wall Motion in Free Breathing, Version 5.1

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ABSTRACT

Background: Four-dimensional computed tomography (4D-CT) acquires multiple CT images over time, allowing to visualize the respiratory motion of organs and tumors. In patients undergoing 4D-CT for stereotactic radiotherapy of intra-thoracic tumors, 4D-CT provides the opportunity to study the incidental movements of the breast during normal breathing. A study protocol to investigate breast respiratory motion is presented herein.

Methods: Patients with any primary cancer who underwent 4D-CT will be retrospectively selected from a radiotherapy treatment planning database. Study inclusion requires full lungs and breasts coverage in the 4D-CT images. Patients with advanced tumors are excluded. The protocol details breast locations of interest (upper, lower, inner, outer, central), specifies virtual breast tumor beds, and details how breast motion will be measured. Data will be analyzed to quantify the range of movements, to evaluate breast motion according to laterality and location, and to evaluate the correlation between movements of the breast and the intra-thoracic organs.

Results: Results should provide quantitative information on the extent of breast movements during free breathing, which could be valuable to plan for respiratory control during breast radiotherapy.

Conclusion: This study presents a protocol to investigate breast movements during normal breathing using 4D-CT. The findings will aid in planning respiratory control for breast radiotherapy.

INTRODUCTION

Randomized clinical trials have repeatedly shown improved tumor control when radiotherapy is given after surgery. [1,2] The impact on survival has however been modest, due to the risk of heart or lung toxicity counterbalancing the favorable effect of radiotherapy on tumor control. [3,4] Several techniques have been developed in order to improve the therapeutic ratio of radiotherapy, by reducing the risk of toxicity while maintaining the same anti-cancer effect. Among the techniques, intensity modulated radiotherapy (IMRT) has been shown to be effective. [5] Respiratory motion is a major concern in radiotherapy, and more so with IMRT. It can interfere with quality of radiation delivery by several mechanisms. Motion can cause artifacts during image acquisition, causing distortion of target volumes and incorrect positional and volumetric information. [6] Treatment fields have to be

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enlarged enough to take into account respiratory motion, increasing the risk of toxicity. During treatment, respiratory motion can affect the accuracy of the dose delivered. Many procedures have been considered in order to manage respiratory motion through the use of diverse techniques, including chest immobilization, Breath-hold, Tracking, and Gating. Drawbacks are the lengthening of treatment time, the impact on workload and the requirement for additional devices (spirometer, magnetic or infrared motion detection markers, cine-portal imaging). Efficient management of resources would require identifying when motion is, or is not, critical for breast radiotherapy.

The present study aims to retrospectively identify, among patients who underwent 4D-CT, the proportion of patients who had large breast/chest wall respiratory movements, and conversely to identify those who had little breast/chest wall movements.

The underlying hypothesis motivating the study protocol is that respiration is usually diaphragmatic, that chest wall movements would be minimal in the majority of patients in free breathing. The primary objective is to quantify the magnitude of breast movements during free breathing respiratory cycles. The secondary objectives of the study are:

- To identify whether patients present different types of respiratory patterns with regard to breast movements.
- To examine whether movements are different by laterality and by quadrant.
- To establish the degree of correlation or lack thereof between movements of intrathoracic organs and movements of breast.
- To evaluate the impact of breast motion on dose distribution.

A tertiary objective is to evaluate contour-segmentation workload.

METHODS

Study design

The study is retrospective, non-interventional, single center. Patients' data remain within the center. Measurements are anonymized by the investigators prior to analyses.

Patients' selection

Patients with any type of primary cancer who underwent 4D-CT imaging with CT images covering the entire lungs and breasts are retrospectively selected from the radiotherapy treatment planning database of our institution.

Inclusion criteria

- Availability of 4D-CT, regardless of primary disease site.
- Lungs and breasts are entirely scanned, with breasts fully visualized in all phases.

Exclusion criteria

- Prior thoracic radiotherapy
- Age<18 years old
- Locally advanced thoracic cancer. Thus, patients with disease extending to chest wall, ribs, muscles, with atelectasis, diaphragmatic paralysis, conditions affecting normal breathing, were excluded.

Number of patients

For the purpose of the present study, we define "minority" of patients as 25% or less of the patients' population, and "large motion" when the moving distances of the breast exceed 5 mm between any two phases of the respiratory cycle. Accordingly, the statistical hypothesis that we test is H0: 25% of the patients' population present large motion, versus H1: 15% or less of the population present large motion.
H0 is rejected at significance level of 0.05 and power of 0.80 with a study size of 107 cases.

Procedure summary

Location of the tumor

Each patient data set is used to generate 10 scenarios simulating a breast tumor bed located in upper inner quadrant, upper outer quadrant, lower outer quadrant, lower inner quadrant, and nipple areola complex separately in right and left breast.

Preliminary raw measurements

Record the maximum skin displacement between all respiratory phases: at the nipple's mean position, repeated for right and left side.

Using relative distances proportional to breast size, do the measurements: at two-thirds of upper breast size cranial to nipple, medially/laterally at two-thirds of medial/lateral breast size, and at two-thirds of lower breast size caudal to nipple, medially/laterally at two-thirds of medial/lateral breast size

1. Clinical target volumes (CTV) and organs at risk (OAR) contours are drawn on all respiratory phases.
2. The breast is drawn according to Offersen[7]. The breast contours are extended to include the skin. Later at planning, the breast will be cropped 5mm under the skin and at the chest wall's fascia muscularis in order to generate the breast-CTV.
3. Tumor beds are drawn using a sphere-brushing tool. A sphere of 4cm diameter (*) is created, centered relatively to the breast's centroid for upper/inner, lower/upper locations, centered on the nipple for the nipple areola complex, and cropped for parts extending outside the breast.

(*)_Simulated tumor bed_: tumor 15mm + (resection margin 5mm + expansion 7mm)x2 = 39mm, rounded to 40mm).

4. OARs are drawn as previously described in TomoBreast: heart, lungs, contralateral breast, esophagus, spinal cor
5. d, but not thyroid or brachial plexus.
6. Draw markers or skin fiduciaries if present.
7. Compound contours integrating all respiratory phases (ISV, integrated structure volume) are created for the breasts, heart, and lungs. The maximum thickness of the ISV's is measured on screen.
8. Record contouring times. Record breasts, OAR's and ISV's centroid coordinates.
9. Using the end of expiration phase, a treatment plan using tangential field in field IMRT is generated for right and left whole breast radiotherapy without boost (2 plans per patient), and a treatment plan is generated with boost (10 plans per patient), according to doses prescriptions and OAR constraints as previously described (TomoBreast trial). The treatment plan is done by dosimetrist/physicist blinded to the other respiratory phases.
10. The treatment fields as planned above are copied onto the other respiratory phases without correction. The doses are calculated using the same number of monitor units from the reference treatment plan. Compute the dose volume histograms (DVH).

Planning of data analyses

For the primary objective

Establish the frequency distributions of the maximum displacements of breast contours. Count the number/percentage of patients with max displacement <5mm. Test the significance of comparison with the predefined cutoff of 25% of patients.

For the secondary objectives

- Analyze the frequency distributions of the maximum displacements: identify whether these distributions indicate a homogeneous population or not.
- Do subgroup analysis of the displacements by laterality and by quadrant.
- Compute the correlations by respiratory phase between the CTVs and OARs.
- Compare the DVHs to evaluate the impact of respiratory movements on dose distribution.

DISCUSSION

The present study protocol covers in depth the methodology according to which the study is to be conducted, and – as literature supports – provides numerous practical benefits. [8-12] As the name "study protocol" implies, the article does not aim to describe a previously conducted original research, but to guide a study to be conducted in the future. We are aware that a study using retrospective data can be biased by the way the data are collected and the way they are analyzed. Hence, the protocol has been detailed in order to help the future interpretation of the data.

In the daily practice of breast cancer radiotherapy, many questions arise. Is respiratory motion important or not in the radiation treatment of breast cancer?

Is investment in motion control technology necessary or not for breast image-guided radiotherapy? If motion control is advised, should it be applied to all patients, or to only a subgroup? Do findings for whole breast radiotherapy apply or not to boost or partial breast irradiation? A study according to this study protocol is currently being conducted and its results are planned to be published separately.

Preliminary on-screen raw measurements of breast motion

Display the body contours of all respiratory phases.
Select on screen the following locations, under the respective labels (Table 1):

Table 1.

Location	Label Right Breast	Label Left Breast
At the tip of the nipple	CENR	CENL
Two-thirds of upper breast size cranial to nipple:		
Medially at two-thirds of medial breast size	UIQR	UIQL
Laterally at two-thirds of lateral breast size	UOQR	UOQL
Two-thirds of lower breast size caudal to nipple:		
Medially at two-thirds of medial breast size	LIQR	LIQL
Laterally at two-thirds of lateral breast size	LOQR	LOQL

At each of the above locations, measure the breast's surface displacement perpendicularly to its surface, do the measurement on the transverse and on the sagittal views.

1. Locate nipple. Center on nipple flush with breast contour. Draw sphere 4cm radius. In unilateral mastectomy, mirror the contralateral nipple on the same slice at the same distances ant-post and lateral

from the ribs, project perpendicularly onto the chest wall, set the intercept as virtual nipple.

2. Go up two-third-upper-breast from nipple slice. Center on crosshair. Move cursor 45 degrees inward and backward to the skin (i.e., get virtual projection of nipple). Measure medially at two-third-in and laterally at two-third-out.

3. Go down two-third-lower-breast from nipple slice. Do as in 2).

- Change absolute measurement levels to 4cm above and below nipple, instead of 6cm:
  "2. Preliminary raw measurements.
  Record the maximum skin displacement between all respiratory phases: at the nipple's mean position, ~~6cm~~ 4cm above the nipple, medially and laterally, ~~6cm~~ 4cm below the nipple, medially and laterally, repeated for right and left side."
  "2.1.1 Upper quadrants.
  Go to slice ~~6cm~~ 4cm cranial from nipple."
  "2.1.2 Lower quadrants.
  Go to slice ~~6cm~~ 4cm caudal from nipple."
- Added a paragraph for relative measurement levels:
  "2.4 Drawing subregions of Breast Right and Left using relative levels.
  The same procedure as using absolute levels, except instead of a fixed distance of 4 cm cranial and caudal to nipple, use relative levels: cranial to nipple two-thirds of the upper breast size, and caudal to nipple two-thirds of the lower breast size."

CONCLUSION

This study presents a protocol aimed at investigating the incidental movements of the breast during normal breathing using 4D-CT. By retrospectively selecting patients with full lungs and breast coverage in the 4D-CT images, the protocol intends to quantify the range of breast movements, assess breast motion based on literality and location, and explore the correlation between breast movements and intra-thoracic organs. The protocol will be useful in planning respiratory movements during free breathing.

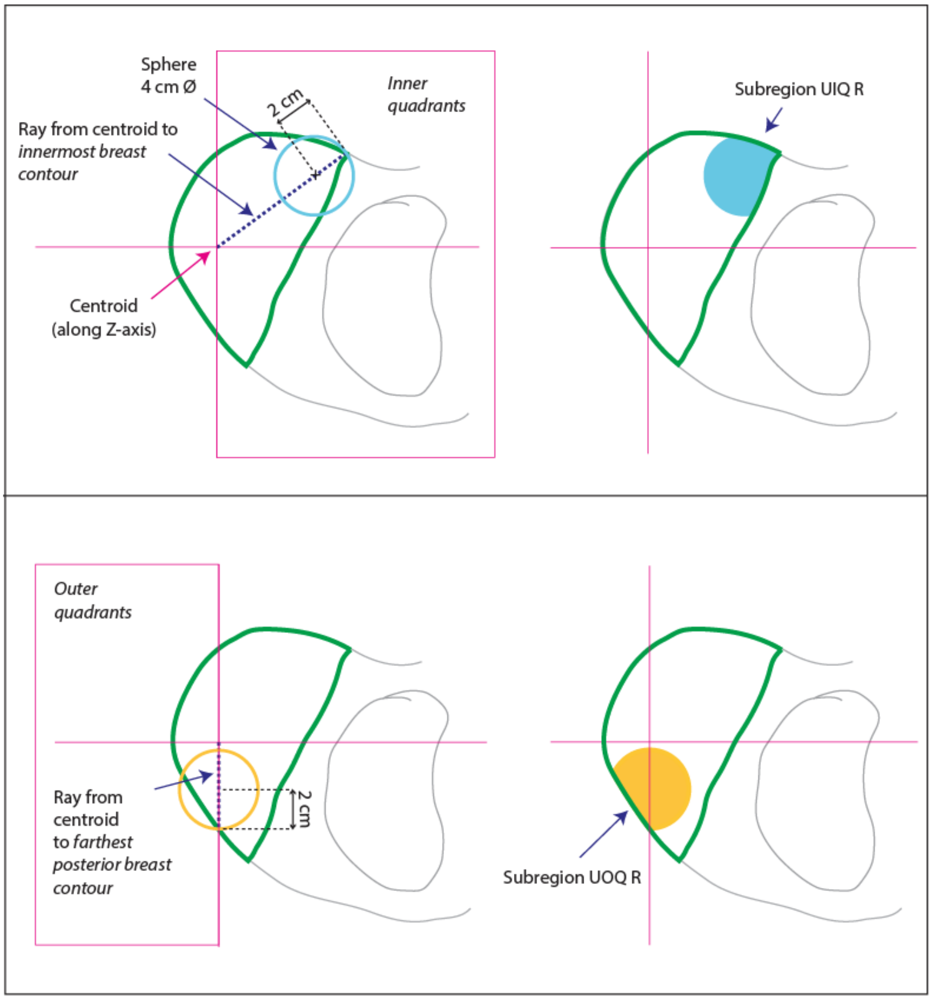

Figure 1. Drawing peripheral subregions, example UIQ R and UOQ R

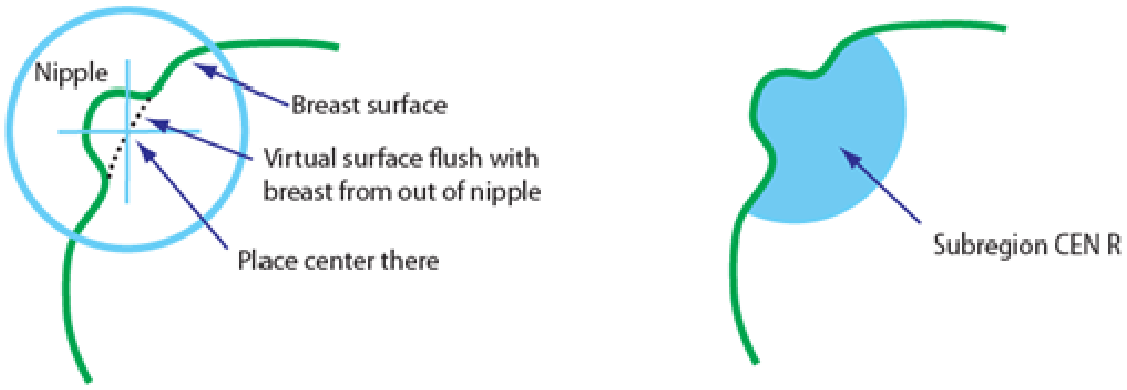

Figure 2. Drawing the central subregion of a breast, example CEN R

CONFLICT OF INTEREST

Vincent Vinh-Hung is section editor but did not interfere with the article's peer review.

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ETHICAL CONNSIDERATIONS

Ethics Committee Universitair ZIekenhuis Brussel approval 5 August 2015, ref 2015/247, B.U.N. 143201525186.

DATA AVAILABILITY

The data supporting the findings of this study are available on request from the corresponding author.

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