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Realistic Respiratory Motion and its Impact on Partial Breast Intensity Modulated Radiotherapy Treatment Planning

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Realistic Respiratory Motion and its Impact on
Partial Breast Intensity Modulated Radiotherapy Treatment Planning

by

Sarah Quirk

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES
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Abstract

Respiratory motion degrades plan quality in partial breast intensity modulated radiation therapy resulting in the requirement for some patients to have respiratory management during treatment. In this thesis we identify which patients require respiratory management through the evaluation of patient-specific anatomy and extent of respiratory motion. The first step in this work was to realistically model respiratory motion for this patient population. We first examined an extensive patient database of external respiratory motion, then also conducted a volunteer study of healthy females in order to better represent the breast cancer population. For both of these populations peak-to-peak amplitude, period, and end exhale were found to quantify the extent of motion. Inter- and intra-fraction variability were quantified, as well as baseline drift for both populations. In order to extend the simplified sinusoidal models typically found in the literature, a shape analysis was completed employing Akaike's Information Criterion to evaluate candidate models. A four-parameter sigmoid fit was found to be optimal. With this fit we found an improvement on $\sin^2(x)$ for 98% of patient exhale and 70% of inhale traces and better than $\sin(x)$ for 100% of both inhale and exhale traces. This respiratory extent of motion, variability, and shape analysis were combined to build a realistic respiratory trace generator (RTG). This provides a method of generating custom respiratory data that can be used for initial implementation and testing of new technologies.

The knowledge gained from the respiratory modelling part of this project was implemented in determining the impact of respiratory motion on partial breast intensity modulated radiation therapy. The volunteer population data was used with the entire database of partial breast intensity modulated radiation therapy plans from the RAPID clinical trial to determine which patient anatomies were more susceptible to the effects of respiratory motion. We examined two patient selection metrics found in the literature, ipsilateral breast volume

(IBV) and PTV-to-IBV ratio, as well as proposing our own metric: DEV-to-PTV ratio. We found that the DEV-to-PTV ratio is a better patient selection metric to predict which patient plans will experience more extensive dose degradation due to respiratory motion and patient anatomy. This metric is also independent of the IBV definition. Current inconsistencies in breast contouring protocols render breast volume and PTV-to-breast volume ratios subject to intra-observer and intra-study variability for quantifying patient suitability for partial breast radiotherapy. We recommend respiratory management for patients with a DEV-to-PTV ratio of less than 55% as these plans experienced a larger degradation in plan quality. For patients with DEV-to-PTV ratio of greater than 55%, population-based respiratory motion has little impact on plan quality. However, there will be a maximum amplitude of motion that will cause these plans to degrade to unacceptable levels of plan quality. We examined ten patients with DEV-to-PTV ratios of greater than 55% and escalated the amplitude of respiratory motion from 2 - 20 mm. We found that dose homogeneity, namely hotspot and homogeneity index, were the limiting factor in plan quality and not target coverage. We recommend respiratory management for patients with respiratory amplitude greater than 10 mm. Due to the propensity of hotspots and regions of inhomogeneity to become exacerbated with respiratory motion, we recommend caution during the planning process. Our results show that if the plan does not meet planning criteria, or if it only barely meets planning criteria, respiratory management should be considered.

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List of Symbols, Abbreviations and Nomenclature

Symbol	Definition
U of C	University of Calgary
TNM	Tumour-Node-Metastasis
NSABP	The National Surgical Adjuvant Breast Project
EBCTCG	Early Breast Cancer Trialists Collaborative Group
3DCRT	Three-dimensional conformal radiotherapy
4DCT	Four-dimensional computed tomography
ICRU	International Commission on Radiation Units and Measurement
GTV	Gross Tumour Volume
CTV	Clinical Target Volume
PTV	Planning Target Volume
IMRT	Intensity Modulated Radiation Therapy
OAR	Organs at Risk
RTOG	Radiation Therapy Oncology Group
EDW	Enhanced Dynamic Wedges
PW	Physical wedges
CBD	Contralateral Breast Dose
DVH	Dose Volume Histogram
VX	Percent volume receiving at least X% of the prescribed dose
DX	The minimum dose to X% of the volume
MU	Monitor unit
SEER	Surveillance, Epidemiology and End Results
EBCTCG	Early Breast Cancer Trialists Cooperative Group

QUANTEC	Quantitative Analysis of Normal Tissue Effects in the Clinic
BCS	Breast conserving surgery
PBI	Partial Breast Irradiation
PET	Positron emission tomography
MRI	Magnetic resonance imaging
CT	Computed tomography
SD	Standard Deviation
RPM	Real-time Position Management
AP	Anterior-posterior
SI	Superior-Inferior
LR	Left-Right
ANOVA	Analysis of variance
CV	Coefficient of variation
RTG	Respiratory Trace Generator
PDF	Probability Density Function
AIC	Akaike's Information Criterion
RAPID	Randomized Trial of Accelerated Partial Breast Irradiation
ABC	Active Breathing Control
DEV	Dose Evaluation Volume
IBV	Ipsilateral breast volume
AAA	Analytical Anisotropic Algorithm
CTV _{su}	CTV plus 5 mm for set up uncertainties
HI	Homogeneity index
UI	Uniformity index
EUD	Equivalent Uniform Dose

Chapter 1

Introduction

Breast cancer is the most common nondermatologic malignancy and is the second leading cause of cancer related death for women. In 2012, there were an estimated 22,700 new cases of breast cancer and 5,100 estimated deaths in Canada [1]. Early stage breast cancer is often treated with breast conserving surgery and radiotherapy. Although radiotherapy is planned on a static CT image, when it is actually delivered the breast is moving with respiration. The object of this thesis is to examine the impact of respiratory motion on breast cancer radiotherapy.

The first chapter will outline the current standard of care in the treatment of breast cancer including progress made in both surgery and radiotherapy to spare healthy breast tissue and improve patient quality of life and cosmesis. It will discuss the possible side effects of radiotherapy for breast cancer including secondary malignancies and toxicities. This chapter concludes with the radiobiological support for using hypofractionation for breast cancer treatment and the phase three trials investigating external beam partial breast irradiation for select, low risk patients. The second chapter details respiratory motion, how it is described in the literature and the common ways of accounting for it in the medical physics literature. That chapter will explore the impact of respiratory motion on whole breast radiotherapy treatment planning and current methods employed to manage respiratory motion during treatment. The preliminary investigations of the impact of respiratory motion for partial breast will be outlined. These two chapters motivate the current thesis objective to develop a realistic respiratory model and use it to determine the impact of respiratory motion on partial breast radiotherapy treatment planning, specifically for intensity modulated radiotherapy.

1.1 Breast Cancer Staging

Breast cancer is most prevalent in women ages 50 - 69, but can affect women of any age (Table 1.1) with almost 20% of breast cancer cases diagnosed in women under the age of 50. The prognosis and treatment options for breast cancer depend mainly on staging, but can also depend on histologic grade, hormone receptor status, co-morbidities, menopausal status, and age [2]. Breast cancer staging is based on the tumour-node-metastasis (TNM) staging system [3]. In the TNM staging system, the primary tumour (T) is described by T0-T4 depending on the clinical measurement and pathologic extent. T0 indicates no evidence of primary tumour; T1, a tumour of 2 cm or less; T2, a tumour between 2 and 5 cm; T3, a tumour greater than 5 cm; and T4, any tumour extended into the chest wall or skin. The primary tumour can also be classified as carcinoma *in situ* (Tis), either lobular or ductal. Lobular carcinoma *in situ* is abnormal tissue in the lobules of the breast; it does not progress to invasive breast cancer but may increase the risk of developing invasive breast cancer and women found to have lobular carcinoma *in situ* are recommended rigorous surveillance. Ductal carcinoma *in situ* can progress to breast cancer so it is treated with standard therapy for early stage breast cancer. These T-classifications also have sub-categories to help define the extent of disease. The regional lymph nodes (N) are described by N0-N3 depending on the presence of clinically or pathologically positive nodes. The designation of N0 indicates no regional lymph node involvement, N1mi is the designation for micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm); N1 and N2 are designated for one or more involved ipsilateral axillary nodes (movable and fixed, respectively) or ipsilateral internal mammary nodes (N2b); and N3 designates involvement of ipsilateral infraclavicular lymphnodes, ipsilateral internal mammary nodes, or supraclavicular lymph nodes. The distant metastasis (M) are classified as M0 (no metastases) or M1 (one or more metastases). [3, 4]

The TNM system is utilized to classify the stage at diagnosis. Stage 0 is classified as *in*

Table 1.1: Estimated new cases and deaths for breast cancer in Canada, 2012 [1]

Ages	Cases (%)	Deaths (%)
<30	0.5	0.1
30-49	18.3	9.8
50-69	51.1	39.6
≥ 70	30.0	51.0
All ages		
Total	22,700	5,100

situ (TisN0M0); stage I (T1N0M0) and stage II (T0-T2N1M0 and T3N0M0) are classified as early invasive; stage III (T3N1M0,T4N0M0,T0-T4N2M0,T0-T4N3M0) is locally advanced; and stage IV (any T/any N/M1) is metastatic [3]. Table 1.2 details the five-year survival by stage at diagnosis and clearly shows that early breast cancer has very good prognosis. The remainder of this thesis will focus on “early stage” (stage I & II) breast cancer, specifically patients with node negative breast cancer.

Table 1.2: Breast cancer 5-year survival rates by stage from the United State’s National Cancer Data Base, and are based on diagnoses in 2001 and 2002 [5].

Stage	Classification	5-year Survival Rate
0	<i>In situ</i>	93%
I	Early invasive	88%
II		74 - 81%
III	Locally advanced	41 - 67%
IV	Metastatic	15%

Due to long survival time for early stage breast cancer patients, clinical treatment quality is assessed not only by overall survival and local control, but also by post-therapy breast cosmesis and quality of life, secondary cancers, and damage to surrounding normal tissues. The current standard of care for early stage breast cancer is a combination of surgery and radiation therapy. Adjuvant! is an online tool that may be used to glean more patient

specific outcomes; it can be found at www.adjuvantonline.com [6].

1.2 Treatment Options for Early Stage Breast Cancer

1.2.1 Surgery

Surgical resection has always played an important role in breast cancer treatment. In the early 1900s, surgery involved not only the breast and surrounding tissue but could also include amputation of adjacent limbs and prophylactic oophorectomy [7]. Until the 1970s, the Halsted radical mastectomy, including the removal of the involved breast, chestwall muscles, and axillia, was the standard of care for all stages of breast cancer [7]. In 1971, after dissatisfaction with treatment options and results, The National Surgical Adjuvant Breast Project (NSABP) B-04 started accruing patients to a randomized controlled clinical trial to determine outcome differences between three treatment arms: radical mastectomy, total (“simple”) mastectomy without axillary dissection but with regional irradiation, and total mastectomy with axillary dissection only if nodes were subsequently positive [8, 9]. Of the 1,665 women on the trial, one-third were designated to each treatment arm [9]. The twenty-five year results from this trial showed no statistically significant differences among the three groups of women, conclusively showing no advantage to radical mastectomy with respect to disease-free survival, relapse-free survival, distant disease-free survival or overall survival [9].

Following the start of the B-04 mastectomy trial, two other trials commenced to determine if even less invasive surgical techniques could be equivalently effective to radical mastectomy. Breast conserving surgery, often called lumpectomy, involves only resecting cancerous tissue and enough of the normal tissue to ensure clear margins. In 1973, the Milan Cancer Institute started accruing women with early stage breast cancer (< 2 cm) to their randomized trial comparing radical mastectomy versus breast conserving surgery plus radiotherapy [10]. The trial accrued 701 women between 1973 and 1980 and found after 20

years follow up that there was no difference in overall survival between the two groups. In 1976, a second trial by NSABP (B0-6) randomized women to three treatment arms: total mastectomy, lumpectomy alone, or lumpectomy plus whole breast irradiation [11]. Between 1976 and 1984, 1,851 women were accrued and after 20-year follow up there was a statistically significant difference in local recurrence in the ipsilateral breast between lumpectomy plus radiotherapy at 14.3% compared to those treated with lumpectomy alone at 39.2% ($p < 0.001$). Although local recurrence was significantly reduced with radiotherapy, there were no significant differences observed among the three groups with respect to disease-free survival, distant disease-free survival, or overall survival. Both the Milan trial and NSABP B-06 concluded that breast conserving surgery followed by whole breast irradiation was equivalent to mastectomy. A meta-analysis was performed by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) of 7,300 patients treated with breast conserving surgery randomized to treatment with and without radiotherapy. This analysis showed a significant difference in 5-year local recurrence rate of 7% with and 26% without radiotherapy [12]. A statistically significant decrease in the 15-year mortality was also observed: 30.5% with versus 35.9% without radiotherapy [12].

Based on the results of these clinical trials, the current standard of care for patients with early stage breast cancer is breast conserving surgery (lumpectomy) followed by whole breast radiotherapy. The trend toward breast conserving surgery over mastectomy has improved the quality of life for breast cancer survivors. Along with surgery, radiotherapy practice for breast cancer treatment has also progressed over the past 30 years. Researchers are investigating possible improvements including partial breast irradiation, intensity modulated radiotherapy, and respiratory management techniques such as breath hold and active breathing control.

1.2.2 Radiation Therapy

Radiotherapy for breast cancer reduces local recurrence after breast conserving surgery [10, 11, 12]. In the 1970-1990s, breast radiotherapy was planned using a 2-dimensional approach,

consisting of a pair of parallel-opposed tangent fields planned on a single axial contour through the centre of the breast [13, 14, 15]. Various wedge angles and field weights were employed to compensate for the rounded shape of the breast in order to meet planning criteria. Wedges are specifically used to decrease hot spots that occur near the posterior field border and nipple.

In 2D planning, the dose distribution in the transverse plane is usually taken to represent the dosimetry of the entire breast; however, many investigators found dose heterogeneity superior and inferior (posterior border and nipple) to the reference plane with hot spots that exceed 125% [16, 17]. In order to improve dose homogeneity, breast radiotherapy is now most often planned with three-dimensional conformal radiotherapy (3DCRT). A typical whole breast treatment is planned using an entire 3D CT dataset. Similar to the 2D approach, tangential parallel-opposed fields are employed; however, with the 3D dataset the entire volume of breast is optimized for dose homogeneity.

Breast volume is typically defined by palpating the breast tissue and using anatomical land marks. Breast borders are: the chest wall as the posterior field border, mid-axillary line or palpable breast as the lateral border, the suprasternal notch as the superior border, the mid-line of the chest as the medial border and inframammary crease (plus 2 cm) as the inferior border [18], although exact border definitions vary between institutions and physicians (Table 1.3). Breast volumes are not typically contoured using contouring guidelines employed by most other tumour sites. Further details are provided in Table 1.3.

The International Commission on Radiation Units and Measurement (ICRU) has published two reports ICRU 50 (1993) and an update, ICRU 62 (1999) that detail the margin definitions required to deliver conformal therapy and decrease the risk of missing tumour cells [19, 20]. Three volumes are described that assist in providing adequate target coverage: GTV, CTV, PTV (Figure 1.1). The GTV is the Gross Tumour Volume encompassing the palpable or visible extent of the tumour; in breast the tumour is excised before radiotherapy

so the GTV is the surgical cavity or seroma, but often no GTV volume is strictly defined for whole breast radiotherapy. The CTV is the Clinical Target Volume which is an expansion of (a margin around) the GTV designed to encompass sub-clinical spread. This is the volume that must be treated adequately in order to ensure the elimination of all tumour cells. For whole breast radiotherapy, the CTV includes the entire breast volume with the borders (Table 1.3) located by palpation, inspection, and anatomical landmarks [21], and should incorporate CT apparent glandular breast tissue and lumpectomy cavity [18]. The PTV is the Planning Target Volume that is a geometric expansion designed to encompass uncertainties from both set-up (set up margin) and organ motion (internal margin). In whole breast radiotherapy sometimes the PTV is cut back from skin and chest wall or excludes pectoralis muscles, chestwall muscles and ribs [18]; when this occurs it is no longer a true PTV but rather an evaluation structure. In breast radiotherapy uncertainties in the anterior direction are accounted for by adding “flash” to the plan. Flash is a planning technique that involves opening the anterior jaws by 2 cm after the treatment plan is optimized.

Radiotherapy treatment plans are designed to meet predefined treatment planning criteria such as hotspot (usually a maximum of 107% of the prescription dose to 2 cm³), mean dose, minimum dose (to 1 cm³ volume or point dose) and doses to organs at risk (heart, thyroid, ipsilateral and contralateral lungs, and contralateral breast) to ensure plan quality.

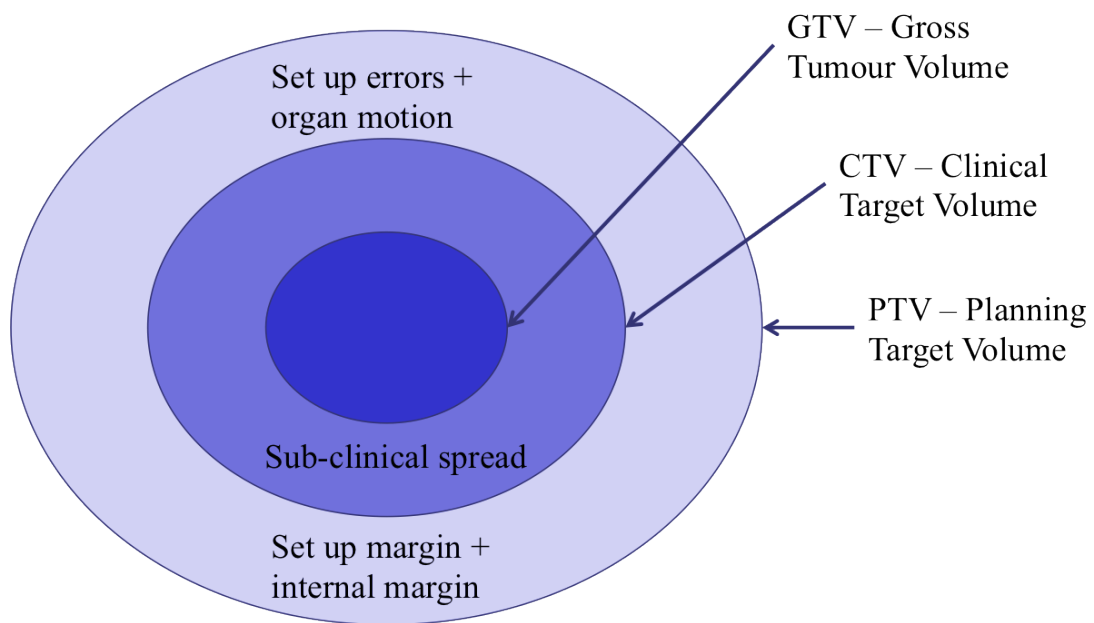


Figure 1.1: GTV, CTV, and PTV volumes defined to provide adequate target coverage [19, 20].

Table 1.3: Target volume definition for whole breast IMRT

Study	Cranial	Caudal	Anterior	Posterior	Lateral	Medial	CTV	PTV
RTOG Breast Atlas [18]	CR+2nd rib insertion	CR+loss of CT apparent breast tissue	skin	Exclude pectoralis, chest wall muscles+ribs	CR+mid axillary line exclude Lat dorsi m	Sternal - rib junction		
DEGRO practical guidelines [22]							WB (gland+ chestwall)	Margin 1 - 1.5 cm added to CTV
Cambridge Breast IMRT trial (R Ph 3) [23]	1 cm below suprasternal notch	1 cm below palpable breast	5 mm from skin excluded	Lung-chestwall interface	1 cm posterior to palpable breast	Midline		
Royal Marsden Hospital Trial (R Ph 3)[13]	Sternal notch	1 cm below inframammary fold	Extended 2 cm beyond anterior skin		Reduced if volume included > 2 cm lung or cardiac apex	Reduced if volume included > 2 cm lung or cardiac apex	WB to deep fascia, not including muscle, rib cage, or skin	WB inspection + palpation
IMRT-MC2 (R Ph 3) [24]							DEGRO guidelines	CTV+10 mm under skin
Off-trial (Netherlands) [25]	15 mm beyond palpable breast	15 mm beyond palpable breast			20 - 30 mm dorsally from lateral palpable breast	Mid-sternal marker	10 mm margin	5 mm margin
Off-trial (Atlanta, GA) [26]	2 cm beyond palpable breast	2 cm beyond palpable breast			Along mid-axillary line	Midline of sternum		
Planning Study (Melbourne) [27]	Inferior edge of clavicular head	Inframammary fold	5 mm from external skin excluded	Junction of breast tissue and pectorial fascia	All apparent breast tissue	Ipsilateral sternal edge		7 mm for respiratory motion & set up
Planning Study (Omaha, NE) [28]			5 mm retracted from skin				All radio-graphically visualized breast tissue	7 mm for respiratory motion & set up

CR - Clinical reference
WB - Whole breast
DEGRO - German Society of Radiation Oncology
R Ph3 - Randomized phase three trial

Although whole breast 3DCRT remains the standard of care across most of Canada, many international centres (and a few Canadian centres) are moving toward a more uniform approach with intensity modulated radiotherapy (IMRT) [29]. The main benefit of IMRT is increased dose homogeneity achieved by reducing hotspots. Improved dose homogeneity has been shown to reduce acute tissue toxicity [30], and results in improved cosmetic outcome [31]. IMRT also provides better coverage of the medial breast tissue, and possible reduction of high dose regions in organs at risk (OARs) [32]. There are many different methods to deliver IMRT for breast including inverse planned, electronic compensators, tangential beam IMRT, multi-field IMRT, forward planned IMRT, hybrid approaches, and step and shoot IMRT [15, 33]. IMRT plans are assessed with the same metrics as for 3DCRT; however, for IMRT plans the dose is prescribed to the entire volume of the breast, whereas for 3DCRT plans dose is most often prescribed at a reference point. Newer methodologies continue to strive for therapeutic advancements; but, there are risks associated with all radiotherapy techniques including toxicities to normal tissues, secondary malignancies, and diminished cosmetic outcome. The next sections discuss these risks.

1.3 Induced Secondary Malignancies

The linear no-threshold model assumes that at low doses there is a linear dose-response relationship between exposure to ionizing radiation and the development of cancer [34, 35]. The assumption in the model is that low-dose radiation carcinogenesis is caused by double strand DNA breaks by a single electron track where dose is directionally proportional to the number of tracks and the probability of secondary cancer induction is proportional to dose [34, 35]. The risk of secondary malignancies is present for all radiotherapy treatments. The risk of developing subsequent breast cancers, most often in the contralateral breast, account for almost 40% of new malignancies after the initial breast cancer [36]. Curtis *et al.* (2006) found that the risk of developing new breast cancer was increased 67% over the

expected risk for the general population during the first 10-years of follow up [36]. For breast cancer patients that receive radiotherapy, the risk of developing subsequent breast cancer is marginally higher than breast cancer patients that do not receive radiotherapy with studies reporting between 18% excess risk [12] and no overall risk [37]. Breast cancer patients also have an increased risk of esophagus, lung, bone, soft tissue, ovarian and uterine corpus cancers [36, 38]. Breast irradiation has only a small increased risk (4%) for subsequent colon cancer and no excess risk of rectal cancer [36, 39].

Radiation-induced lung cancer can pose a risk for women following radiotherapy for breast cancer, with the greatest risk occurring among 20-year survivors [36]. The risk of lung cancer is greater in the ipsilateral lung due to a higher received dose [12, 36]. Based on a study by Inskip *et al.* (1994) of almost 9000 women with breast cancer surviving at least 10 years and treated with radiotherapy between 1935 and 1971, it is estimated that an average lung dose of 10 Gy would induce 9 lung cancers in 10,000 women after 10 years [40]. By the early 1990s technical improvements in breast cancer radiotherapy resulted in less extensive dose and volume exposure of the lungs and a much lower risk of secondary lung cancer [40].

1.4 Dose to Organs at Risk

1.4.1 Contralateral Breast

The Netherlands Cancer Institute conducted a study between 1970 and 1986 to study the late effects of radiation therapy in breast cancer patients (stage I to IIIA) in a cohort of over 7,000 women [41]. The median follow up was 13.8 years and 503 contralateral breast cancers were observed with a median time of 7.7 (range 1.0 - 27.3) years. For high-energy photons, the average dose to the contralateral breast was 0.6 - 1.1 Gy for outer quadrant lesions and 1.6 - 2.9 Gy for inner quadrant lesions, depending on treatment technique [41]. Many studies have shown that young women (< 45) and positive family history have an increased risk of contralateral breast cancer [38, 41]. The Netherlands study found that women younger than

35 had an increased risk of developing contralateral breast cancer (hazard ratio = 1.78) compared to women over 45 (hazard ratio = 1.09) [41]. Younger women have more time to develop contralateral breast cancer following radiation therapy. Family history was also a major contributing factor, when patients had three or more relatives with breast cancer, the increased risk of contralateral breast cancer increased 2.4 times compared to those in the cohort with no relatives with breast cancer [41]. Stovall *et al.* (2008), showed in a study of over 2000 women with asynchronous bilateral breast cancer (708) and with unilateral breast cancer (1,399) that women younger than 40 years of age who received more than 1.0 Gy to the contralateral breast had 2.5 times greater risk of contralateral breast cancer than unexposed [42]. The same study showed no excess risk was observed in women irradiated when they were older than 40 [42].

Breast radiotherapy treatments rely on several methods to account for the rounded contour of the breast. The two most common are physical and enhanced dynamic wedges (EDW). Physical wedges (PW) are made of metal placed external to the linac head in the path of the beam with all radiation reaching the patient passing through the PW. EDWs use the translation of the primary collimating jaw of the linac to create a wedge field, most of the dose comes from the open component of the field and very little is transmitted through the jaw. With the EDW, the jaw is located inside the linac head which significantly reduces the scatter off the attenuating material compared to the physical wedge which causes an increased scatter dose to the contralateral breast [43, 44, 45]. Physical wedges are in the field for the entire beam, the transmission through the wedge results in electrons and scattered photons. There have been many studies that show the dose to the contralateral breast is decreased with the EDW compared to the physical wedge [46, 43, 47]. Weides *et al.* (1995) measured contralateral breast dose (CBD) in an anthropomorphic phantom, and found that physical wedge results in CBD of 2 - 6% of the prescription dose and the EDW in a CBD of 1 - 5%, with an average of 2.5% [43]. Saur *et al.* (2009) performed a phantom study

comparing the mean CBD between physical and EDW plans and found the mean CBD is reduced by 19 - 35% when an enhanced dynamic wedge is used instead of a physical wedge (depending on medial field: 0.49 Gy (PW) to 0.32 Gy (EDW) or lateral field: 0.70 Gy (PW) to 0.57 Gy (EDW), for a prescription dose of 50 Gy) [47].

While IMRT is more conformal and provides superior dose homogeneity than 3DCRT, it often requires more monitor units to deliver the prescribed dose. Increasing the number of monitor units increases the leakage in the linac head that the patient experiences and subsequently may increase the dose to the contralateral breast. There are many studies that compare the CBD between physical wedges and various IMRT methodologies. Fong *et al.* found that contralateral breast dose depended strongly on which of the 4 IMRT planning types were compared to the standard, physical wedged tangents. The standard wedge technique had a mean contralateral breast dose (CBD) of 2.3 Gy, the coplanar multi-field IMRT had a mean CBD of 6.1 Gy, electronic compensator IMRT had a mean CBD of 2.4 Gy, tangential IMRT had a mean dose of 1.8 Gy, and non-coplanar multifield IMRT had a mean CBD of 1.4 Gy. This study does not give a comparison value for enhanced dynamic wedge plans [33]. Zhang *et al.* (2011) compared physical and 3DCRT wedge treatments to direct machine parameter optimization IMRT in a treatment planning study and found that the V3 (% volume receiving 3% or more of the prescribed dose) for the contralateral breast was 3.3 ± 3.7 %, 2.4 ± 3.1 %, and 12.9 ± 12.6 % for physical, EDW, and IMRT respectively [48]. Both of these studies [33, 48] were treatment planning studies, and did not involve direct patient or phantom measurements.

Bhatnagar *et al.* (2006) measured the surface dose to the contralateral breast of 65 patients treated with IMRT using thermoluminescent dosimeters on the patient's skin. Their study found that the dose to the contralateral breast increased with breast volume [49].

Overall, physical wedges result in larger dose to the contralateral breast than enhanced dynamic wedges. As discussed above, some studies report lower CBD with IMRT and some

report higher compared to PW and EDW techniques. Comparison between studies is not straightforward because of the multitude of beam arrangements, planning types, and MU used.

1.4.2 Heart

Cardiac toxicity is a late effect from breast radiation therapy. It can manifest as a range of effects including pericarditis (inflammation of the pericardium), pancarditis (inflammation of the entire heart), valvular disease, or congestive heart failure, but is primarily seen as an increase in ischaemic heart disease (reduced blood supply to the heart) [50]. Historically, radiation induced cardiac toxicity was a major component in breast cancer radiation induced morbidity and mortality [51, 52]. Breast cancer radiation treatment with older techniques such as orthovoltage and cobalt delivered a significant dose to the heart [53, 54].

A recent, somewhat controversial, case-controlled study by Darby *et al.* (2013) [55] investigated 2,168 women in Sweden and Denmark treated with radiotherapy from 1958 to 2001 who were younger than 75 at diagnosis. This study retrospectively chose 963 women who received radiotherapy for breast cancer and had major coronary events and matched them with 1205 controls based on the following criteria: country of residence, age at time of diagnosis, and year of diagnosis. To calculate dose to the heart, radiographic charts (diagram or photo of treatment fields) in 2D were reconstructed on a CT of a woman with typical anatomy. The assumption of typical anatomy and the reconstruction of radiotherapy planning from 2D to 3D introduce uncertainty to the results.

For the women with coronary events, 44% occurred less than 10 years after diagnosis, 33% between 10 and 19 years after diagnosis and 23% after 20 years or more [55]. Women with left-sided breast cancer had higher rates of major coronary events than those with right sided breast cancer ($p = 0.002$) [55]. The mean dose to the heart ranged from 0.03 to 28 Gy, with a average dose for all women of 4.9 Gy. The relative risk of a major coronary event increased linearly with the mean heart dose at 7.4% per Gy with no threshold [55].

The absolute risk of cardiac morbidity is higher for women with existing heart risk factors before radiotherapy. Darby *et al.* (2013) [55] gives the very clear example comparing the risk of 3 Gy mean dose to the heart for a woman with no cardiac risk factors and a woman with one or more risk factors. For the woman without preexisting cardiac risk factors, the risk of death from ischemic heart disease before the age of 80 increases from 1.9% to 2.4%. For the woman with existing cardiac risk factors, the risk of death from increases from 3.4% to 4.1%. The findings from this study allow for estimates of absolute risk of radiation-related ischemic heart disease following radiation therapy [55]. This retrospective case controlled study is not as powerful as other data presented below based on prospective studies.

One indicator of radiation-induced cardiac mortality is evaluating the prevalence between left versus right tumour laterality. A review examining heart dose in breast radiotherapy from the 1950s - 1990s found the mean dose to the heart for left-sided treatment ranged between 0.9 and 14 Gy and between 0.4 and 6 Gy for right-sided [54] with the largest doses from orthovoltage. Studies from the 1960s and 1970s showed increased mortality in patients that received radiotherapy, especially for left-sided involvement [56]. A UK study was performed with the SEER (Surveillance, Epidemiology and End Results) public-use data on over half a million women diagnosed with breast cancer between 1973 - 2008. For women irradiated between 1973 - 1982, the cardiac mortality ratios between left and right sided treatments were 1.19 (1.03 - 1.38, $p < 0.0001$) during the first decade after treatment, 1.35 (1.05 - 1.73, $p < 0.0001$) during 10 - 14 years; 1.64 (1.26 - 2.14, $p < 0.0001$) after 15 - 19 years; and 1.90 (1.52 - 2.37, $p < 0.0001$) for 20 or more years [57]. Cardiac mortality in the first decade post-treatment has decreased between the 1970s and the 1990s cohorts with little evidence of any radiation-related mortality for heart disease for women diagnosed between 1983 - 1992; although follow-up is incomplete. [57, 58].

Cuzick *et al.* found in their 1994 study investigating the 10-year mortality rate, that there was no longer a statistically significant difference between women receiving breast ra-

diatherapy and those not. This implies that cardiac toxicity results were strongly influenced by techniques used in early trials [59]. In general, mean heart doses for left-side treatments have decreased by almost half since the 1970s [60]. Cardiac dose has decreased mainly due to advances in technology used to deliver radiation therapy including using 3DCT dataset to monitor the contoured heart and its relationship to the treatment fields [56].

Volume constraints from the Early Breast Cancer Trialists' Cooperative Group (EBCTCG) suggest that even though specific dose-volume parameters are not clearly known, doses greater than 5 Gy are significantly associated with increased risk of heart mortality [56]. The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) study recommends minimizing the irradiated heart volume to the greatest extent possible without compromising target coverage. The QUANTEC study also suggests using conformal blocking and breath-hold if necessary to limit dose to the heart during breast radiotherapy. A conservative estimate predicts that $V_{25Gy} < 10\%$ (in 2 Gy fractions) will be associated with $< 1\%$ probability of cardiac mortality approximately 15 years after radiation therapy [50].

1.4.3 Lung

Lung toxicity may manifest as pneumonitis (the inflammation of the lung tissue), or pulmonary fibrosis (the scarring of lung tissue) [51, 52]. These two effects are experienced in different time frames: pneumonitis is as an early effect, occurring up to 8 months after radiotherapy and pulmonary fibrosis is a late effect, occurring later than 6 months following treatment [61, 62]. These effects can progress independently or simultaneously [51, 52]. The volume of lung irradiated is a determining factor in the development of both pneumonitis and fibrosis. Concurrent chemotherapy, smoking habits, age and performance status may also impact these late effects; however, results are inconclusive [51, 52, 63, 64, 65, 66, 67]. Pneumonitis occurs in approximately 1 - 5% of patients with breast only treatments and the total reported rate of radiation lung injury varies between 1 - 60 % of patients [67, 68, 69].

Lung dose has been correlated to radiation induced lung damage [62, 67]. Although the

exact dose to cause pneumonitis is not known, 20 Gy is the approximate value that has been correlated in many studies as a significant dose [67, 68]. Goldman *et al.* (2010) studied 88 women receiving local regional radiation therapy for breast cancer and minimized the dose to the ipsilateral lung to $V_{20} < 30\%$. They found that the use of this dose-volume constraint significantly reduced moderate to severe radiological changes observed on chest x-rays, and that symptomatic pneumonitis was rare [70, 71].

The QUANTEC analysis found a variety of dose levels predictive of radiation pneumonitis which suggests that there is no single sharp threshold determining risk [71]. The QANTEC study also suggests that dose constraints of V20 less than or equal to 30 - 35% should be used to limit the risk of radiation pneumonitis [71].

1.4.4 Skin

Skin reactions are a common toxicity associated with breast irradiation. Symptoms include skin reddening, dry or moist desquamation (skin flaking), depigmentation (lightening) or hyperpigmentation (darkening of skin) [72], erythema (skin reddening), and telengectesia (dilated blood vessels near skin surface) [73]. The RTOG radiation morbidity scoring criteria for skin reaction grades 0 - 4 are listed in Table 1.4 for both acute and late morbidities [74]. Mild to moderate acute symptoms are common during treatment. A study by Sharp *et al.* (2011), showed that the majority of patients (93%) had acute radiation skin reactions, although most were mild [75, 76]. About one-third of breast cancer patients receiving radiotherapy develop significant acute skin toxicity [77]. These reactions are painful and can limit the patient's ability to continue treatment [76]. Pignol *et al.* (2008) conducted a double blind, multicentre, randomized clinical trial of 358 patients and found that breast IMRT significantly reduced the occurrence of moist desquamation when compared to a standard wedge technique [30]. This study also found that moist desquamation was correlated with increased pain and decreased quality of life. Severe acute skin injury is rare and mainly occurs in patients with extra sensitive skin or radiation sensitivity [65].

Telangiectasia is a late skin toxicity that increases progressively with longer follow-up times. Bentzen *et al.* (1990) found that almost 5 years are required to observe 90% of ultimate damage and 15 years to observe a full grade 3 injury [78]. Lilla *et al.* (2007) found that 131/416 patients experienced telangiectasia after a median follow up time of 51 months [79]. Skin reactions have been correlated to irradiated dose and volume, radiation therapy treatment technique, surgery type, as well as patient factors such as smoking status and high body mass index [76, 80].

Table 1.4: RTOG skin scoring criteria for both acute and late morbidities [74].

RTOG Acute Skin Radiation Morbidity scoring criteria	
Grade	Morbidity
Grade 0	No change from baseline
Grade 1	Follicular, faint, or dull erythema/epilation/dry desquamation
Grade 2	Tender or bright erythema, patchy moist desquamation/moderate edema
Grade 3	Confluent, moist desquamation, other than skin folds, pitting edema
Grade 4	Ulceration, hemorrhage, necrosis
RTOG Late Skin and Subcutaneous Radiation Morbidity scoring criteria.	
Grade	Morbidity
Skin	
Grade 0	None
Grade 1	Slight atrophy; pigmentation change; some hair loss
Grade 2	Patch atrophy, moderate telangiectasia and total hair loss
Grade 3	Marked atrophy, gross telangiectasia
Grade 4	Ulceration
Subcutaneous	
grade 1	Slight fibrosis
grade 2	Moderate, asymptomatic fibrosis
grade 3	Severe fibrosis and loss of subcutaneous tissue
grade 4	Necrosis

1.4.5 Cosmesis

Cosmesis is an important clinical outcome in breast cancer treatment and skin toxicities can be a critical contributing factor. In a study by Sutherland *et al.* (1989), cosmesis ranked very important compared with 27 other items concerned with general health or quality of life after

treatment [81]. The overall cosmetic outcome is scored on a four point scale from excellent to poor, often by evaluating photographs of the treated breast compared to the untreated breast, by both patients and physicians. Table 1.5 outlines the cosmetic scoring system and includes the effects of the biopsy procedure, localized skin changes, and overall symmetry between the treated and untreated breast [82, 83]. The change in nipple position relative to the suprasternal notch has been investigated as a means to track cosmetic changes either manually [84] or with an automated computer program [85]. In a systematic review, Munshi *et al.* (2009), identified 10 different methodologies to assessing cosmesis and concluded that there is no ideal method of assessment [14]. Overall a system must be able to judge both quantitative (nipple displacement) and qualitative changes (severe telangiectasia or skin necrosis) [84]. Arenas *et al.* (2006), provided a summary of 40 studies that assessed cosmesis and found cosmesis was assessed, on average, as good to excellent by 70 ± 11 % of patients/physicians (range from 55% to 97%) [86].

Table 1.5: Cosmetic scoring system [82].

Localized fibrosis and skin change at the matchline between adjacent radiation fields	
0	None
1	Slight
2	Moderate
3	Severe
Assessment of cosmetic result of the biopsy procedure	
0	Scar unapparent
1	Scar apparent
2	Major tissue loss
Overall cosmetic score	
1 - Excellent	Treated breast nearly identical to untreated breast
2 - Good	Treated breast slightly different than untreated
3 - Fair	Treated breast clearly different from untreated but Not seriously distorted clear deformation of breast contour, Nipple displacement or skin changes
4 - Poor	Treated breast seriously distorted Severe retraction or fibrosis, severe teleangiectasia

Fibrosis is the predominant skin toxicity contributing to unfavourable cosmetic outcome,

causing breast retraction, contour distortion, hardening, change in shape and decrease in breast volume [73, 51]. Similar to lung fibrosis, it is a late effect that occurs 6 - 18 months after radiation therapy and may get worse with time. Lilla *et al.* (2007) assessed late complications in breast radiotherapy for 416 patients and found after a median follow up of 51 months, 6.7% of patients experienced fibrosis [79]. The same study found that increasing age was a risk factor for fibrosis.

An early reaction that impacts cosmesis is breast oedema caused by the disruption of lymphatic drainage; however, this usually resolves over the first 18 - 36 months [14, 73]. Significant breast oedema is seldom observed in the absence of axillary surgery and is directly related to extent of resection of lymph nodes [73]. Three years after treatment only 10 - 20% of patients continue to have mild oedema [73].

Factors affecting cosmesis include dose homogeneity, breast size, extent of surgical excision and fractionation scheme [87]. It is clear from the literature that large breasts are more difficult to treat with conventional RT methods [88, 89]. Women with large breasts are more likely to have significant dose heterogeneity with standard treatment [90, 91]. The difficulty with larger breasts is that the large separation results in hot spots which can lead to acute skin reactions and poorer cosmetic results [92]. There is no consensus as to what qualifies as a 'large' or 'small' breast in definitive terms. Dundas *et al.* concluded after performing their own analysis of breast size from 50 women and comparing their data to published data that women with cup size $\geq D$ or bra circumference size ≥ 40 inches should be categorized as 'large breasted' [93]. Breast size can also be categorized by chest wall separation [94].

Moody *et al.* (1994) conducted a prospective study of 559 patients to assess late changes in breast appearance after BCS and radiation therapy and found that late changes were highly dependent on breast size. Moderate or severe late changes were observed in only 6% of small breasted patients compared to 22% with medium breast size and 39% with large breast size and a significant correlation was found between breast size and dose inhomogeneity which

accounts for the observed differences [89]. However, this study did not clearly define what constituted a large, medium, or small breast. Gray *et al.* (1991) concluded that, although inferior cosmetic results are seen in larger breasted patients, the magnitude of the difference should not exclude these women from breast conserving therapy [95].

Several studies have looked at the differences in cosmetic evaluation between patients and physicians [96, 86, 97, 83]. Cosmetic satisfaction depends on patient age and weight [96, 86], tumour location [98], and tumour size [97]. Key criteria that influence physician's long-term assessment of cosmetic outcome are breast retraction, telangiectasia, and breast oedema [83]. Warner *et al.* (1998) reported that patients gave a lower cosmetic score when responding to the questionnaire than when giving verbal response in the clinical setting [99]. Studies have also shown that physicians are often more critical of cosmetic outcome than patients [86, 100].

IMRT has been investigated to improve dose homogeneity in the breast and therefore cosmetic outcome. Vicini *et al.* (2002) evaluated 95 patients receiving breast conserving surgery and step and shoot, multileaf collimator IMRT whole breast irradiation. After one year post radiotherapy, 99% of patients were rated as good or excellent with no reports of telangiectasia, significant fibrosis, or persistent breast pain [31]. A study by Hoarsolia *et al.* (2007) of 172 patients showed a reduction in acute grade 2 or worse dermatitis, oedema, and hyperpigmentation in those patients treated with IMRT compared to wedged 3DCRT [101]. In women with breast volume larger than 1600 cm³, acute and chronic oedema and hyperpigmentation were statistically significantly reduced with IMRT.

In an effort to improve cosmesis and quality of life for breast cancer patients, partial breast irradiation is currently under investigation as a possibility for early stage breast cancer. Studies have shown that 44 - 86% of local recurrences occur close to the tumour bed [102, 103]. Partial breast irradiation (PBI) involves treating only the lumpectomy cavity plus adequate margins instead of the entire breast. Treating a smaller volume spares normal

breast tissue. There are currently a wide variety of treatment options for PBI including external beam radiation therapy (3DCRT and IMRT), multicatheter interstitial brachytherapy [104], balloon catheter brachytherapy [105], and intra-operative radiation therapy [106]. There are many comprehensive reviews on different methodologies of PBI [107, 108]. For the remainder of this thesis only external beam PBI will be discussed. The following sections will discuss breast radiobiology, the various fractionation schemes studied for whole breast irradiation that take advantage of this, and external beam partial breast trials and preliminary outcomes. External beam PBI will be discussed in more detail in Section 1.6.

1.5 Radiobiology: Breast

Based on the linear quadratic model used in radiobiology to describe the cell survival curve, the α/β ratio describes the point at which the linear and quadratic components of cell killing are equal. The α/β ratio is typically used to describe if a tissue is late (for example spinal cord) or early (for example skin and most tumours) responding. For the linear quadratic model, early responding tissues tend to have a larger α/β ratio than late responding tissues. The α/β ratio for breast cancer was initially assumed to be similar to the classic model ratio for early responding tumour cells, approximately 10 Gy [109]. Recent studies based on outcome data from randomized clinical trials of early stage breast cancer were used by Qi *et al.* to determine an average and range of α/β ratios that may more appropriately describe the radiobiological behaviour of breast cancer [110]. Qi *et al.* (2011) examined 10 different randomized studies [11, 111, 112, 113, 114, 115, 116, 117, 118] which used different fractionation schemes to treat breast cancer, including three studies that used no radiation. Disease-free survival was calculated based on the generalized linear quadratic survival model and Poisson statistics from the data in these studies. In the Qi study, an average breast cancer α/β from the ten studies was found to be 2.88 Gy with a range of 0.75 - 5.01 Gy [110]. Based on this analysis breast cancer most likely has a lower α/β ratio than commonly

thought.

A low tumour α/β ratio infers that hypofractionation for breast cancer radiotherapy could be advantageous. In Canada, there is a growing trend of delivering 42.5 Gy in 16 fractions (delivered in three and a half weeks) compared to the standard 50 Gy in 25 fractions (delivered in five weeks) [11]. This is largely based on the multi-institutional randomized controlled Canadian trial by Whelan *et al.* (2010) that showed equivalency between the two regimes [111, 119]. The trial compared the two fractionation schemes for 1,234 patients with the primary outcome of local recurrence, and secondary outcomes of cosmesis and toxicity. At 10 years, no statistically significant differences were found between the two fractionation schemes for local recurrence (the probability of survival was 84.4% in the control group as compared with 84.6% in the hypofractionated group with a 95% confidence interval (CI) of the absolute difference: -4.3 to 4.0), cosmesis (an excellent or good cosmetic outcome was reported for 71.3% in the control group and 69.8% in the hypofractionated group, with a 95% CI of the absolute difference of -6.9 to 9.8), or toxicity (no late skin effects in 70.5% of control group and 66.8% of hypofractionated group with 95% CI of the absolute difference: -4.9 to 12.1) [119].

The UK has conducted three randomized controlled trials: Royal Marsden Hospital (RMH) and the Gloucestershire Oncology Centre (GOC) [112] and two by the Standardization of Breast Radiotherapy (START) group - trials A and B [115, 116]. The RMH/GOC trial accrued 1410 patients between 1986 and 1998 and compared the standard 50 Gy in 25 fractions to two experimental fraction schemes: 39 Gy in 13 fractions and 42.9 Gy in 13 fractions. All fractionation schemes were delivered in five weeks. The START Trial A accrued 2236 patients between 1998 and 2002 and compared the standard fractionation to 41.6 Gy or 39 Gy in 13 fractions over five weeks and was designed to be able to combine its data with the RMH/GOC trial [115]. The START Trial B accrued 2215 patients between 1999 and 2001 and compared the standard 50 Gy in 25 fractions over five weeks to 40 Gy

in 15 fractions in three weeks [116]. The RMH/GOC trial has released ten year results and the START trials A and B have released five year results.

The RMH/GOC trial found the risk of ipsilateral tumour relapse after 10 years was 12.1% (95% CI 8.8 - 15.5) in the 50 Gy group, 14.8% (11.2 - 18.3) in the 39 Gy group, and 9.6% (6.7 - 12.6) in the 42.9 Gy group; the probability of local recurrence between the two hypofractionated groups was statistically significant. The START Trial A found that rates of disease-free survival, overall survival, and distant relapse were similar between fractionation schemes with no clinically significant disadvantage of either hypofractionated schemes. The START Trial B concluded that the hypofractionated course of radiotherapy was equivalent in terms of local regional tumour control and rates of late normal tissue effects at five years [116].

The Radiation Therapy Oncology Group (RTOG) recently started a phase three trial (RTOG 1005) comparing the control arm of standard fractionation 50 Gy in 25 fractions (42.7 Gy in 16 fractions allowable) followed by a sequential boost (12 Gy in 6 fractions or 14 Gy in 7 fractions) to an experimental hypofractionated whole breast 40Gy in 15 fractions with a concurrent boost of 48 Gy in 15 fractions [120]. The trial allows seven different delivery methods, including 3DCRT, IMRT, and electrons. This trial primary objective is to test non-inferiority of the hypofractionated whole breast irradiation plus concurrent boost to the standard scheme. Secondary goals include comparison of breast-related toxicity and cosmesis, risk of late cardiac toxicity, and treatment costs [120].

The results of these four trials give strong evidence that hypofractionated schemes give equivalent local control, cosmesis, and normal tissue effects when compared to the current five week standard for patients with similar disease and demographic characteristics. The success of these trials encouraged the investigation of hypofractionation schemes for whole breast boost and external beam partial breast radiotherapy.

1.6 Partial Breast Irradiation

External beam partial breast irradiation is currently under investigation as a possibility for early stage breast cancer to improve cosmesis and quality of life for breast cancer patients. Studies have shown that 44 - 86% of local recurrences occur close to tumour bed [102, 103]. External beam partial breast irradiation as noted above involves treating the surgical cavity plus an adequate margin to account for daily set up errors (interfraction) and respiratory motion (intrafraction). The surgical cavity is defined using a combination of one or more of the following: position of surgical clips, pre-operative imaging, ultrasound of the seroma, PET positive tissue, MRI, and CT based planning [121]. Table 1.6 summarizes the expansions of the lumpectomy cavity. In general, there is a total 15 - 30 mm total expansion, including variations in skin limitations and the chestwall/lung interface.

Partial breast irradiation also has the added advantage of being delivered in a reduced number of fractions, lowering the overall treatment time. This is important because although the evidence is convincing that radiotherapy decreases local recurrence, it is believed that 15 - 30% of patients who undergo lumpectomy do not receive radiation therapy (North America) [122]. Under-utilization of radiation therapy for breast conserving treatment is often associated with the 6 - 7 week commitment involved in a typical radiation treatment. Other factors may include distance and convenience of the radiation facility for non-urban patients, lack of transportation, lack of social support, poor ambulatory status, cost, patient age, fear of radiation and physician bias [122, 123, 124]. Accelerated fractionation schemes decrease the total time required for radiation treatment and aim to increase the number of patients receiving radiation therapy. Fractionation schemes investigated include 38.5 Gy in 10 fractions, delivered twice a day (with a fraction separation of at least 6 hours) [125, 126, 127]; 40 Gy in 10 fractions, delivered twice a day (separated by 6 hours) [128]; and 30 Gy in five fractions [129].

Starting in the late 1990s and early 2000s, there have been several non-randomized,

prospective partial breast irradiation phase I and II trials for external beam radiation therapy. Table 1.7 details accrual numbers, length of follow-up, overall cosmetic results, grade 3 or worse toxicities, and ipsilateral breast tumour recurrence. The initial results for these studies were positive with a generally a high percentage of patients reporting good to excellent cosmesis, low numbers reporting grade 3 or higher toxicities, and very few ipsilateral breast recurrences. The positive outcome of these preliminary studies set the ground work for a number of multi-institutional, prospective, randomized, controlled Phase 3 trials set to determine if external beam accelerated partial breast irradiation is equivalent to the standard of care.

Table 1.8 details the six trials underway with target accrual, primary end point, and secondary endpoints. Only the smaller, Italian trial investigating PBI IMRT has reported results on 259 of their target 520 patients. They found acute toxicities extremely low, only 5% and 0.8% for grade 1 and 2 skin toxicities. The follow-up has not been long enough to allow results on late toxicity, cosmesis, or clinical outcomes [129]. The remaining trials have not yet released results, and five-year overall survival results will not be available until 2017. The primary endpoint for all trials is to determine if the ipsilateral rate of recurrence for partial breast irradiation is equivalent to that of whole breast irradiation. All of the trials have secondary endpoints as well, including overall survival and distant disease-free survival. Most trials also have secondary end points aimed at investigating quality of life, cosmesis, and economic impact of the truncated radiation schedules. The trials will provide long-term efficacy and safety results on APBI, and also patient selection [130].

Table 1.6: Volume definition for Partial Breast Irradiation

Study	CTV	PTV	Total
Phase 3 Randomized Controlled Trials			
RAPID [125]	cavity + 10 mm 5 mm from skin exclude chest wall, pectoralis muscles	CTV + 10 mm	20 mm
RTOG 0413 [126]	cavity + 15 mm	CTV + 10 mm 5 mm from skin exclude chest wall, pectoralis muscles	25 mm
IRMA [127]	cavity + 15 mm	CTV + 5 mm	20 mm
SHARE [128, 131]	tumour bed	CTV + 15-20 mm 5 mm from skin exclude chest wall, pectoralis muscles	15-20 mm
IMPORT LOW [132]	cavity + 15 mm	CTV + 10	25 mm
Italy [129]	cavity + 10 mm 3 mm from skin and lung-chestwall interface	CTV + 10 mm 3 mm from skin extends ≤ 4 mm inside ipsilateral lung	20 mm
Phase 1 & 2 Prospective Trials			
RTOG 0319 [133]	cavity + 10-15 mm 5 mm from skin and lung-chestwall interface	CTV + 10 mm	20-25 mm
Canadian Multi-institutional [134]	seroma + 10-15 mm	CTV + 10 mm 5 mm from skin excluding chestwall	20-25 mm
William Beaumont Hospital [135, 72]	cavity + 15 mm 5 mm from skin and lung-chestwall interface	CTV + 5 mm (motion) + 5 mm (set up)	25 mm
Denver, CO [136]	cavity + 10 mm	CTV + 10 mm 2-5 mm from skin	20 mm
Littleton, CO [137]	cavity + 10 mm 5 mm from skin and lung-chestwall interface	CTV + 10 mm 5 mm from skin	20 mm
University of Michigan [138, 139]	cavity + 10 mm	CTV + 5 mm 5 mm from skin	15 mm
Tuffs [140]	tumour bed + 15 mm	CTV + 10 mm 5 mm from skin excluding chest wall	25 mm
NYU [141, 142]	surgical cavity	CTV + 15-20 mm (+ 7 mm for beam penumbra)	22-27 mm

Table 1.7: Phase I/II non-randomized prospective partial breast irradiation studies

Trial/ Institution	N	Accrual years	follow-up (months)	Cosmetic result (good/excellent)	Grade 3 or worse	IBTR
RTOG 0319 [133, 143]	52	2003 - 2004	64	82% at 1 year 64% at 3 years	5.8%	3
William Beaumont Hospital [72]	91	2005 - 2007	50	88%	4%	0
Harvard [144] Ph+E, Ph, Pr	98 (60,19,19)	2003 - 2005	71	97% (patients) 95% (physician)		3,0,2
NYU [142] Prone	98		64	89%	2%	
Canadian Multi- institutional [134]	127	2005 - 2006	37	82%	1%	1
Tuffs [140]	60	2004 - 2007	15	81.7%	8.3%	0
U of M [139] IMRT ABC	34	2004 - 2007	30	78%	8.8%	0

IBTR - ipsilateral breast tumour recurrence; Ph+E, Ph, Pr - Photons + electrons, photons alone, protons
Prone - refers to prone setup and treatment for this study
IMRT ABC - this study uses IMRT with active breathing control

Table 1.8: Phase III randomized controlled external beam partial breast irradiation trials

Trial	Study Design	Primary End Point	Secondary End Points
RAPID/OCO [125] Start: Jan 2006 End: July 2021 Canada	Control: WBI Experiment: 3DCRT APBI N = 2128	Ipsilateral recurrence	Adverse cosmetic outcome Disease free survival Event free survival Overall survival Radiation toxicity Quality of life cost effectiveness
RTOG 0413/ NSABP B-39 [126] Start: 2005 USA	control: WBI experiment: 3DCRT APBI experiment: Brachy N = 4300	Ipsilateral recurrence	Overall survival Recurrence-free survival Distant disease-free survival Cosmetic results Fatigue Perceived convenience of care Acute and late toxicity
IRMA [127] Start: April 2007 End: Dec 2017 Italy	control: WBI experiment: 3DCRT APBI N = 3302	Ipsilateral recurrence	Overall survival Recurrence-free survival Distant disease-free survival Cosmetic results Acute and late toxic effects Economic and organizational impact of treatment and resulting quality of life
SHARE [128] start oct 2010 end oct 2023 France	control: WBI+boost experiment: Hypo-WBI experiment: 3DCRT APBI N = 2796	Ipsilateral recurrence (rate of)	recurrence-free survival nodal regional recurrence free survival distant recurrence free survival disease specific survival overall survival rate and type of acute and late toxicities comparison of cosmetic results quality of life and satisfaction medico-economic
IMPORT LOW [132] Start: Oct 2006 UK	control: WBI (IMRT) experiment: reduced WBI+ PBI (IMRT) experiment: PBI (IMRT) N = 1935	Ipsilateral recurrence	Location of tumour relapse Contralateral primary breast cancer or other primary tumours Regional and distant metastases Late adverse effects in normal tissue (photo-assess, physician, patient self assess) Quality of life Cost-effectiveness
Italian IMRT [129] Start: September 2005 End: September 2008	control: WBI experiment: APBI IMRT N = 520		

There are still many unanswered questions with partial breast studies including:

- What is the most appropriate fraction scheme?
- What is the most appropriate treatment setup verification?
- What impact does respiratory motion have?
- Should patient selection be used to choose the patients that will best respond to this treatment?

This thesis will be addressing the last two questions. The next chapter will give a detailed relevant literature review on respiratory motion, its known impact on whole breast treatments and limited initial investigation in external beam partial breast irradiation. The subsequent chapters will detail our research papers that systematically address this issue.

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Chapter 2

Respiratory Motion

Respiratory motion affects radiotherapy treatment in the thoracic and abdominal regions. This chapter reviews respiratory motion and methods to account for it during radiotherapy treatment planning. Both the respiratory and medical physics literature are reviewed for measurement, sources, and modelling of respiratory motion. The impact of respiratory motion on whole breast radiotherapy is reviewed, as well as current motion management techniques. The preliminary studies investigating the extent of motion during partial breast radiation therapy are explored.

2.1 Respiratory Characteristics and Measurements

Trends in respiratory patterns have been studied extensively in the respiratory physiology field. Studies dating back to the 19th century have examined differences in respiratory motion within the population and tried to quantify the causes: age, sex, activity status, disease, etc. In respiratory science, data may be collected passively, using observation of chest motion, or actively, using devices such as pulmonary plethysmograph (device for measuring the volume of lungs and lung capacity) and spirometer (device for measuring the volume of air inhaled or exhaled). Although some studies suggest that active measuring devices may introduce error into measured values [1], a 1985 study by Perez *et al.* found that respiratory variables remained approximately the same regardless of instruments employed [2]. The literature reviewed in this chapter is exclusively for patients in supine resting conditions as these are most similar to radiotherapy conditions.

Many studies have observed that respiratory motion is highly diverse between individuals in the population. In the 1800s two large studies were conducted: one by Quetelet, with

300 subjects; and another by Hutchinson with 1,714 subjects [3]. These studies showed a wide range in period of the human breathing cycle ranging from 6 to 31 breaths per minute (1.9 - 10 s/breath). Priban *et al.* (1963) found that the difference in breathing patterns and measurements between individuals is highly significant; however, participants were found to have similar breathing characteristics measured on different occasions [4]. Tobin *et al.* did an extensive (130 subjects) two-part study on healthy [5] and diseased subjects [6]. In normal breathing, it was found that the mean values of breathing patterns, such as respiratory frequency, were not affected by age but that older subjects exhibited more irregular breathing [5]. The population displayed a wide variation in the relative abdominal and thoracic contributions to respiratory motion. Overall, there was a predominance to abdominal breathing but some subjects had predominantly rib cage movements [5]. In diseased patients, the respiratory rate was found to be increased in smokers, patients with COPD, restrictive lung disease and pulmonary hypertension compared to healthy subjects. Even asymptomatic smokers had major differences in breathing pattern [6].

Painter *et al.* (1992) studied subjects under three different stimuli conditions: graded hypercapnia (too much carbon dioxide in the blood causing a reflex to increase access to oxygen by increasing breathing), hypoxia with graded hypercapnia, and exercise [3]. These three conditions were analyzed using mean flow patterns by calculating the average shape of the respiratory cycle by first normalizing inhale and exhale durations to the mean phase duration and then superimposing the flow patterns of all breaths, summing and averaging for each stimulus. It was found that the inhale and exhale durations and the tidal volumes were independent of the stimulus [3].

In a more recent study by Benchetrit (2000), the differences in breathing pattern were examined further by breaking the breathing cycle into inhale and exhale durations. Many combinations were found, but the overall constraint was that the inhale time is less than the exhale time [1]. This work also discussed the existence of breathing patterns based on the

large body of respiratory literature, with many studies reporting reproducibility of a single subject’s respiratory pattern when measured on consecutive days. Benchetrit also observed that the same subjects would reproduce regular or irregular breathing patterns under the same conditions on different days [1]. No differences in size, weight, body surface area, sex, or smoking habits were found to attribute to differences in flow profiles [1].

2.2 Modelling Respiratory Motion

This respiratory literature gives a basis of how important the differences between human respiratory patterns are and illustrates that any model of respiratory motion must be able to incorporate this variation. The medical physics literature takes a more quantitative approach to account for and predict the impact of respiratory motion on the delivery of radiotherapy. Two common methods of modelling respiratory motion are using sinusoidal patterns or individual patient respiratory traces.

Lujan *et al.* (1999) modelled respiratory motion as $\sin^{2n}(x)$, one of the most frequently cited respiratory models in medical physics literature [7]. The complete model is $z(t) = z_0 - b \cos^{2n}(\pi t/\tau - \phi)$ where z_0 is the position of exhale, b is the extent of motion, $(z_0 - b)$ is the position of inhale, τ is the breathing cycle period, n is the shape parameter and ϕ is the starting phase of the breathing cycle. This work was based on modelling liver motion, however, it is commonly cited for all treatment sites that experience respiratory motion.

George *et al.* (2005) examined the accuracy of the Lujan’s model and determined which value of n was most appropriate for lung cancer patients. Correlation coefficients were found to be similar for $\cos^1(x)$, $\cos^2(x)$, and $\cos^4(x)$. For simplicity $\cos^1(x)$ was used for the remaining analyses comparing this sinusoidal model with bimodal and normal distributions. Probability distribution functions (PDFs) were developed for all three models (sinusoidal, bimodal, and normal) and 331 patient respiratory traces, and George *et al.* found that both of the non-sinusoidal models had higher correlation coefficients with the individual patient

PDFs and population PDFs than the sinusoidal model [8].

The benefit of using a sinusoidal-type model is that it can be easily evaluated mathematically and inputted into function generators, motors for phantom studies, and simulation studies. The downfall of any sinusoidal model is that it assumes that parameters do not change between and within breathing cycles for individual patients or among the entire population. This does not allow for any variation to be introduced into the situations that the respiratory model is used to test. Sinusoidal models are also symmetric and, as shown in the respiratory literature, the exhale portion of a respiratory cycle is generally longer than the inhale portion, creating a natural asymmetry. This is also seen in the previously discussed study: the symmetry of a sinusoidal pdf with two equal peaks does not fit respiratory data well [8].

One way of introducing a limited amount of variation is by using single patient traces. This methodology introduces intra-fraction variability; however, it still lacks variation across the population. There are various methods of data acquisition used to acquire patient respiratory traces and these can be divided into two main categories: external surrogates and internal measurements. Two common external surrogate systems are the Real-time Position Management system (RPM, Varian Medical Systems, Palo Alto, California) and the pneumatic bellows (Philips Medical Systems, Andover, Massachusetts). The RPM system uses a small, plastic box with two to six reflective markers placed on the patients abdomen or thorax and an infrared camera mounted in the treatment room [9]. The markers on the box are tracked simultaneously to calibrate the extent of motion. Clinically, the marker box is placed between the xiphoid process and umbilicus, optimizing for position of largest respiratory amplitude; however, it can also be placed in the upper thorax region to measure that extent of motion. The RPM system can be used to monitor and record external respiratory motion. The bellows system consists of a deformable belt placed around the abdomen that changes tension with the expanding and contracting of the abdomen and produces a

respiratory signal.

Another common method for assessing respiratory motion is four-dimensional computed tomography (4DCT) which uses an external surrogate respiratory signal to retrospectively bin the images of a CT dataset by respiratory phase. A 4D image is reconstructed with the respiratory-binned CT dataset to provide the extent of tumour motion during a breathing cycle. In breast radiotherapy, 4DCT is often used in planning studies to compare treatment plans developed on free-breathing CTs, 4DCT, and breath hold CTs [10, 11, 12].

The external motion is not necessarily correlated with the internal tumour sites, this is especially an issue for lung, liver, and abdominal tumours. To effectively use external surrogates for internal targets, a correlation model with tumour location is required and for these cases internal motion real-time tracking may be necessary. One such system is Cyberknife (Accuray, California) which uses continuous tracking of an external surrogate and x-ray imaging to create a correlation model and then during treatment uses occasional x-ray imaging to update the correlation model. This available Cyberknife data is an extremely valuable resource for motion researchers. However, even it is not a direct measurement of continuous internal tumour motion, but is instead an estimate based on external surrogates, combined with intermittent orthogonal x-ray imaging. The resulting tumour trajectories are subject to jumps that occur when the correlation model changes. Another tracking during treatment prototype is the Real-Time Tumour Tracking (RTRT, Mitsubishi Electronics Co., Ltd., Tokyo) system that uses fluoroscopy with two orthogonal units and requires continuous imaging [13]. Fiducial markers can be used to assist in real-time tumour localization. Cone-beam CT is an imaging modality available at the treatment unit that provides a static image used for patient setup, but the individual projection images can be used to reconstruct the tumour trajectory. The algorithm developed to reconstruct this tumour position during respiration could be used to provide respiratory information at the treatment unit during patient setup [14, 15] (Appendix A).

External surrogates are adequate for breast treatment because the breast is essentially an external organ that can be assumed to move in a rigid, non-deformable manner comparable to the external surrogate motion [16]. The following sections will review the literature investigating the impact of respiratory motion on whole breast radiotherapy.

2.3 Respiratory Motion in Breast Radiotherapy

2.3.1 Whole Breast

Phantom Studies

The impact of respiratory motion on breast cancer radiation therapy has been explored in two types of studies: planning and phantom. Both methods provide different information, but have thus far employed limited or simplified respiratory motion and, often, small sample sizes. To date, the phantom studies have used anthropomorphic polystyrene breast phantoms with either film [17, 18] or ion chamber dose measurements [19]. These studies all simulated respiratory motion as simple sinusoidal motion with ranges of amplitudes (0.4 to 3 cm) and period (4 to 13 s). A range of plan complexities has been explored with these phantom studies including physical and enhanced dynamic wedge plans [18], and IMRT plans [17, 19, 18].

Thilmann *et al.* (2006) delivered step and shoot segmented IMRT plans to a moving phantom with amplitudes of 4 and 10 mm and period of 5 and 10 s. The phantom that they used was a solid polystyrene phantom with 10 mm slice thickness. The maximum deviation was found for the large amplitude and short period. Liu *et al.* (2007) [17] also investigated step and shoot IMRT plans with a similar phantom design and amplitudes of 5, 10, and 20 mm and a period of 4 s. Liu *et al.* (2007) and Thilmann *et al.* (2006) both concluded that the dosimetric impact of motion was minimal (always within $\pm 5\%$) for breast delivery [17, 19].

Sidhu *et al.* (2006) investigated motion with an amplitude of 20 mm and periods of 3 and 8 seconds. Sidhu *et al.* (2006) found that, on average, respiratory motion decreases

the dose to the breast planning target area for all plan types studied (physical wedge plans, enhanced dynamic wedged plans, and step and shoot IMRT) [18]. Menon *et al.* (2011) completed a phantom study that quantified the changes in delivered dose due to respiratory motion for four different planning types: 2D conventional and three IMRT (forward-planned, surface-compensated, and hybrid IMRT); and four respiratory conditions: breath-hold, deep breathing (2 cm), quiet breathing (1 cm), and an extreme exhale target displacement. They found that dose differences were increased with plan complexity and plan inhomogeneity increased with increasing amplitude [20].

Treatment Planning Studies

Treatment planning studies have also been used to determine the impact of respiratory motion on breast radiotherapy. One of the first studies, by George *et al.* (2003) [21], investigated seven patients and eight different plans with varying motion amplitudes and set up error. Only a single patient respiratory trace for all seven plans was examined; it was scaled for shallow, deep, and normal breathing. The patients were planned with dynamic IMRT. In this study, to incorporate the respiratory motion, the IMRT leaf sequence file was superimposed on the breathing trace. While no statistically significant differences were found, PTV dose heterogeneity was found to increase with respiratory motion [21]. Other studies have investigated respiratory motion by planning on a free-breathing CT and then exporting the plan to breath hold CT [10, 22], select phases of 4DCT [23], and all phases of 4DCT [11, 24].

Cao *et al.* investigated eight patients, each with three CT images: free-breathing, end exhale, and end inhale. The free-breathing image was used to develop both conventional wedged, step-and-shoot IMRT, and dynamic IMRT plans and then applied to the breath-hold plans to encompass the extent of motion. They found that the conventional and step-and-shoot plans did not change under respiration, but that the dynamic IMRT plan had an average difference in CTV coverage of 10% between free-breathing and end inhale CTs.

They recommended whole breast IMRT not be used for respiratory amplitudes greater than 6 mm [10].

Frazier *et al.* (2004) used a similar technique to Cao *et al.* by obtaining three CT imaging datasets, however, used active breathing control during the breath-hold scans. Standard wedge and step-and-shoot IMRT plans were investigated for differences in dose delivered to the breast under the three conditions. Frazier *et al.* (2004) reported non-statistically significant difference on average for the 10 patients studied, but differences in V95% were shown to be up to 8% in some patients [22].

Richter *et al.* (2004) investigated the impact of respiratory motion for ten patient plans developed for both wedged and segment-based tangential beam arrangements. For each patient a regular CT and a 4DCT were obtained and datasets were registered. Cine mode EPID images were acquired and the resulting motion trajectories were determined. Differences between the two planning techniques were minimal. The mean amplitude of respiratory motion for this patient cohort was found to be 1.8 mm (0.9 mm). Degradation in target coverage (V90) was observed for both treatment techniques by, on average, 3% (segmented technique) and 4.2% (wedge technique). A small, but significant decrease in dose homogeneity was observed, quantified with a homogeneity index (D90/D05). The homogeneity index decreased significantly more in the wedged plans than the segmented. The authors concluded that although differences were observed between static and respiratory incorporated, the impact was minimal [24].

Qi *et al.* employed 4DCT data to construct 3DCRT plans for 18 patients at 0 (inhale), 20 (reference), and 50% (exhale) phase. PTV coverage was found to vary by 1-7% with the lowest coverage occurring at end exhale, and largest extents of motion [23]. Qi *et al.* also used equivalent uniform dose (EUD) to quantify the changes due to respiratory motion and found that the PTV EUD higher at end inhale. This study attributed differences in PTV coverage to differences in lung volume change, with the largest decrease in PTV coverage

(7%) observed for the patient with the largest lung volume change (approximately 20%).

Yue *et al.* (2007) simulated breast treatment based on a 4DCT datasets for 12 patients. The dose distribution was generated for each phase of the 4DCT based on the same beam parameters as the 3DCRT plan. Yue *et al.* showed differences in target coverage with averages of -5.4%, -3.1%, -13.4%, -5.1%, and -3.2% for D95, D90, V100, V95, and V90, respectively [11]. Yue *et al.* also showed significant changes in minimum dose to the target, and small changes to the maximum dose regions [11]. The authors concluded that respiratory motion may degrade target coverage and the degree of degradation may increase with increasing respiratory motion.

2.3.2 Partial Breast

The overview of the whole breast literature makes it clear that the dosimetric impact of respiratory motion on whole breast radiotherapy is small, but measurable. Dose homogeneity in the breast has been shown to decrease with organ motion due to respiration [20, 21]. The dosimetric impact of respiratory motion in partial breast external beam radiotherapy remains largely unanswered. Respiratory motion can affect partial breast planning by both loss of homogeneity (as with whole breast) and also with loss of coverage. There have been studies that estimate the extent of motion for partial breast patients, and have used this to geometrically estimate safe margins to account for respiratory motion, but no studies have explicitly investigated the dosimetric effect of respiratory motion on partial breast treatment planning.

A recent study by Kim *et al.* (2012) [25] summarized 19 PBI motion studies. The range of average motion spans from 0.8 mm to 8.5 mm over the 19 studies with five studies reporting average respiratory motion less than 2 mm, ten reporting motion between 2 - 4 mm, and four studies reporting motions larger than 5 mm [25]. The reported studies used many different methods of measuring respiratory motion, including fiducial tracking, 4DCT, fluoroscopy, surface imaging, and electromagnetic tracking. Most studies reported motion

primarily in the anterior-posterior (AP) and superior-inferior (SI) directions, often with the AP direction two to four times larger than the SI direction [25]. Kim *et al.* conclude that disagreement in the literature of amplitude ranges makes it difficult to conclude what level of respiratory motion is considered normal and that individual assessment of motion for partial breast patients may be beneficial.

In order to adequately account for respiratory motion a uniform, three dimensional expansion from the CTV to the PTV is employed; this expansion encompasses uncertainties due to both set up errors and organ motion. These can be separated and evaluated separately. A set up margin of 5 mm is standard and was retrospectively analyzed for its validity by Baglan *et al.* (2003) using electronic portal imaging and rib motion as a surrogate for CTV motion. An average standard deviation in rib position was 1.8 (1.1 - 3.0) mm and the 5 mm margin was concluded to be more than enough [26]. Cox *et al.* (2007) found that for every 5 mm increase in the margin from CTV-to-PTV there was a 6 - 7% absolute increase in the amount of normal tissue irradiated. They advise using the smallest necessary PTV consistent with local control [27].

Typically, in partial breast external beam radiotherapy, a 5 mm margin is also allocated to account for respiratory motion. This is largely based on a study by Baglan *et al.* (2003) of 16 patients with a mean motion of 6 mm (range 3 - 9 mm) and where a conservative margin of 5 mm was suggested [26]. This is a geometric margin designed to encompass almost twice the value of the mean motion. If the target volume is in its mid-cycle respiratory position a symmetric, systematic margin of 5 mm encompasses a 10 mm motion. Kim *et al.* (2012) suggested that since motion has often been reported as less than 4 mm, on a geometric basis the margin for external beam PBI could be reduced to 2 mm. Reducing or minimizing margins in partial breast radiotherapy is important because the aim of partial breast radiotherapy is to decrease dose to normal breast tissue and other organs at risk.

As noted, the above describes a geometric margin, which is added based on the geometric

concept that the breast moves by a certain amount and thus must be directly covered by a margin. There are two other strategies that can be employed for defining the necessary margin expansion: statistical and dosimetric. Dosimetric margins are derived by determining the impact on dosimetric plan quality parameters (such as dose coverage) and are often smaller than geometric margins. Statistical margins are based only on statistical data and are determined through statistical constructs such as the central limit theorem and gaussian distributions. In practice a combination of dosimetric and statistical margins can be derived based on specific assumptions, including: gaussian distribution of uncertainties, spherical symmetry, lack of inhomogeneities, and perfectly conformal dose distributions.

A hybrid statistical-dosimetric methodology is described by van Herk [28] that assumes the impact of treatment preparation (systematic) errors and execution (random) variations are completely separable. Systematic errors are uncertainties introduced in the treatment preparation stage, and are perpetuated throughout the entire treatment. Examples of systematic uncertainties include organ motion during the CT scan (resulting in a planning image that is not representative of the mean position of the target volume) or contouring uncertainties. Random errors are uncertainties that vary from day-to-day, such as patient set-up and breathing motion. Random errors result in a blurring of the dose distribution, whereas systematic errors cause the dose distribution to shift relative to the CTV. Under these assumptions, van Herk derived a simplified margin formula based on the standard deviation (SD) of random (σ) and systematic (Σ) errors: $m_{ptv} = \alpha\Sigma + \beta\sigma - \beta\sigma_p$, where σ_p is the standard deviation of the penumbra width, and α and β are determined based on the population and dose objectives. The most commonly used of these recipes is for the objective of 90% of the patient population receiving a minimum dose to the CTV of 95% of the prescription dose. For $\sigma_p = 3.2$ mm, the CTV-to-PTV margin formula becomes: $m_{ptv} = 2.5\Sigma + 0.7\sigma'$, where σ' is the SD from all execution errors excluding the penumbra. This formula was derived based on geometrical and beam characteristic assumptions valid

for prostate cancer; however it may not be applicable to other treatment sites and should be applied with caution [28].

There is no clear best or most appropriate way to add margins to account for organ motion and setup errors. The standard for PBI is to allow 5 mm for each, totalling 10 mm added to the CTV. Many studies conclude that reducing margins would be ideal if it could be shown to be dosimetrically valid; however, this remains an open question for external beam partial breast radiotherapy and breast boosts. Strategies for minimizing the effect of respiratory motion with motion management will be discussed below.

2.4 Respiratory Management in Breast Radiotherapy

There are many different strategies for minimizing the impact of respiratory motion in whole and partial breast (PBI) radiotherapy. In partial breast radiation therapy, adding adequate margin expansion to the CTV is the most basic and universally applied strategy. In an effort to reduce dose to normal tissue and spare organs at risk other methods are used, including: respiratory gating [29], respiratory coaching, deep inspiration breath hold [12], active breathing control (ABC) [30], and real-time tumour tracking system (RTRT) [31]. The following section will present a sample of the literature of each technique used in partial or whole breast radiotherapy. In respiratory gating, free-breathing or breath-hold, often the duty cycle (the ratio of beam-on time to treatment delivery time) is used to quantify treatment efficiency. Respiratory motion management in other thoracic and abdominal radiotherapy sites is beyond the scope of this thesis.

Deep inspiration breath hold (DIBH) is becoming more widely used, especially for left-sided breast cancers, in order to spare both the lung and the heart. DIBH can be passive with the patient voluntarily holding their breath, or active with active breathing control (ABC). Upon a deep inspiration the chest wall moves anteriorly and the heart moves superiorly, causing an increased distance between the target volume of the breast and the heart. This

anatomic advantage removes the heart from a potentially high dose region at the posterior of the breast. DIBH also spares lung tissue due to a decrease of lung density during inspiration which reduces the amount of healthy tissue irradiated. Chopra *et al.* (2006) showed that after respiratory training for five patients a mean increase was observed in breath hold time (31 to 44 seconds) and in tidal volume (560 to 1600 cm³) [32].

DIBH can be monitored with external surrogate tracking, such as the Real-time Position Management system (RPM, Varian Medical Systems, Palo Alto, USA). The treatment is gated manually for DIBH or automatically at a preset phase or amplitude position during free-breathing. In order to increase reproducibility of breath hold, active methods such as active breathing control can be used. This method employs an apparatus that controls the patient airflow by regulating the volume of air entering the patient's lungs before each breath hold, and temporarily blocking airflow during treatment.

Korreman *et al.* (2005) [12] examined the dosimetric differences between planning on 17 patients for five different respiratory conditions: free-breathing, free-breathing end inhale gating, free-breathing end exhale gating, end inhale breath hold (DIBH), and end exhale breath hold. After developing whole breast 3DCRT plans for each respiratory condition, it was found that both DIBH and free-breathing inhale gating had better sparing of lung and heart (and specifically, left anterior descending coronary artery) than free-breathing or exhale gating/breath hold [12].

Giraud *et al.* (2012) [30] conducted a prospective, nonrandomized, multicentre analysis of respiratory gated whole breast irradiation and 3D conformal radiotherapy. They included 233 patients in the study with 79 treated with respiratory gating. Respiratory gating was performed with ABC or with RPM monitored DIBH. The study aimed to verify that the gating devices used were reliable and reproducible, and also investigated toxicity, dosimetry, local control, recurrence-free and overall survival. The RPM system was only used in 8% of treatments and the remaining used an ABC device. The total lung volume was significantly

larger for DIBH than conventional treatment; this lead to a reduction in maximum and mean lung doses, and the lung volume receiving 25% of the prescription dose (V25). Maximum and mean dose to the heart was also significantly reduced with DIBH. No significant differences in overall survival, specific survival, or disease-free interval were observed between the two groups, nor between the different gating/breath hold techniques after a median of 28 months follow-up. [30]

Lewin *et al.* (2011) [29] employed respiratory gating in a study of 36 early stage breast cancer patients receiving PBI using IMRT. Phase-based prospective gating was used for both simulation and treatment encompassing the end exhale portion of the respiratory cycle (30 - 40% duty cycle). Coaching was used to encourage patients to breathe more reproducibly aiming to achieve 10 breaths per minute. After a median follow up of approximately 45 months local control was 97% (one ipsilateral breast recurrence), grade 3 toxicities were observed in only 3% of patients, and cosmesis was rated as good or excellent by 94% of patients and 97% of physicians. This study is an example of how respiratory management may be employed in PBI.

These respiratory management options are available to minimize the dosimetric impact of respiratory motion and limit dose to heart and lungs. Each option adds to the time and resources required for each stage of treatment. It is important to determine which patients would most benefit from respiratory management with these techniques. PBI inherently spares more normal breast tissue and potentially heart and lung than whole breast because only a portion is being treated.

The AAPM TG76 report emphasizes that the use of respiratory management increases medical supervision and treatment times. The workload of physicists, physicians, and therapists is increased during simulation, planning and treatment. Depending on the respiratory management technique, training sessions with the patient before treatment may be necessary and often the physicist is required to attend at least the first treatment with respiratory

management. The quality assurance workload may also be increased. Often machine time is limited and the extra time on specific units for respiratory managed treatments may cause lower throughput of patients [33].

2.5 Thesis overview

This thesis aims to answer some of the outstanding questions about external beam partial breast irradiation and respiratory motion. Specifically it will address the questions of which patients need respiratory management during external beam partial breast intensity modulated radiotherapy.

In order to answer this question first we needed a respiratory motion that would be representative of the breast cancer population. We had an extensive patient dataset from our clinical repository of external respiratory motion, but it included data from mostly lung, liver, and abdominal patients which may not be representative of the breast cancer population that is often younger and with a healthier lung capacity. We completed a volunteer respiratory motion measurement study to fill this gap. Chapter 3 will detail the analysis and statistics of the volunteer and patient respiratory databases that were used as the basis of respiratory modelling. This study provides a database of parameters to use when testing implementation of techniques that rely on external surrogates. It also provides a useful comparison between patients with mainly liver, lung, and abdominal cancer and a volunteer population that could more accurately represent breast cancer patients.

Chapter 4 provides the details of a realistic respiratory trace generator (RTG) based on these volunteer and patient databases and the respiratory modelling involved in its development. We developed this tool to fill a hole in the literature providing accessible realistic respiratory motion for preliminary testing and implementation of pre-clinical technology. Where sinusoidal models and single patient traces are used in implementation and testing, our RTG provides an alternative allowing for customization of shape and extent of motion,

but more importantly allows for testing with variable motion. It is possible to select individual patient traces for testing, but the RTG ensures the traces used will cover the spectrum of clinical variability and allows users to isolate the impact of different patterns of motion and variability. Instead of sorting through hundreds of patient traces looking for the exact situation that is desired for testing, the RTG allows the user to define the respiratory signal characteristics. This is especially relevant when testing the more extreme respiratory situations such as high variability and large baseline drifts.

Chapter 5 and 6 use the knowledge gained through the realistic respiratory studies and apply that to external beam partial breast irradiation. Chapter 5 examines the anatomy specific characteristics associated with plan quality degradation due to respiratory motion that may be more susceptible to effects of respiratory motion, based on our volunteer population respiratory data. We propose a new metric that may assist in excluding patient plans that are most negatively impacted by respiratory motion and set a patient cut-off based on this metric. This chapter also gives treatment planning guidelines that aim to minimize the effect respiratory motion in the treatment planning stage of radiotherapy. Chapter 6 uses the set of patients from Chapter 5 that are not affected significantly by respiratory motion on a population basis and applies amplitude escalation to determine at what point the majority of patients fail to meet the necessary minimal plan quality criteria and would require respiratory management. Chapter 7 is overall conclusions and future work.

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Chapter 3

Population Statistics

General Introduction

Work presented in this chapter is an analysis of patient and volunteer external respiratory motion. This is the necessary first step in modelling how the breast moves with respiration. The work presented in this chapter has been published in a peer reviewed journal, *Journal of Applied Clinical Medical Physics* [1]. I was the first author on this work, and the contributing authors were Dr. Nathan Becker and Dr. Wendy Smith. This work was completed under the supervision of Dr. Wendy Smith. Dr. Nathan Becker assisted with data collection and analysis, specifically the peak-finding algorithm used in this analysis. I prepared the initial draft of this manuscript and all authors contributed to the review of the results and preparation of the final manuscript.

External respiratory motion analysis and statistics for patients and volunteers

Sarah Quirk, Nathan Becker, and Wendy Smith

Abstract

We analyzed a large patient and volunteer study of external respiratory motion in order to develop a population database of respiratory information. We analyzed 120 lung, liver, and abdominal patients and 25 volunteers without lung disease to determine the extent of motion using the Varian Real-Time Position Management system. The volunteer respiratory motion was measured for both abdominal and thoracic placement of the RPM box. Evaluation of a subset of 55 patients demonstrates inter- and intrafraction variation over treatment. We also calculated baseline drift and duty cycle for patients and volunteers. The mean peak-to-peak amplitude (SD) for the patients was 1.0 (0.5) cm, and for the volunteers it was abdomen 0.8 (0.3) cm and thoracic 0.2 (0.2) cm. The mean period (SD) was 3.6 (1.0) s, 4.2 (1.1) s, and 4.1 (0.8) s, and the mean end exhale position (SD) was 60% (6), 58% (7), and 56% (7) for patient, volunteer abdomen, and volunteer thoracic, respectively. Baseline drift was greater than 0.5 cm for 40% of patients. We found statistically significant differences between the patient and volunteer groups. Peak-to-peak amplitude was significantly larger for patients than the volunteer abdominal measurement and the volunteer abdominal measurement is significantly larger than the volunteer thoracic measurement. The patient group also exhibited significantly larger baseline drift than the volunteer group. We also found that peak-to-peak amplitude was the most variable parameter for both intra- and interfraction motion. This database compilation can be used as a resource for expected motion when using external surrogates in radiotherapy applications.

3.1 Introduction

Patient respiratory data is easily and readily accessible through external surrogates, which are frequently used to monitor respiratory motion. External chest wall and abdominal surrogate motion are used clinically for 4D CT [2, 3], to gate images for patient setup, respiratory gated treatments, and for motion tracking [4, 5, 6, 7].

Common external surrogate systems include Real-time Position Management and pneumatic bellows. The RPM system employs an infrared camera and small plastic box with reflective markers placed on the patient thorax or abdomen to monitor and record external motion. The bellows system consists of a deformable belt placed around the abdomen that expands and contracts with respiratory motion. The changing tension in the belt is measured to produce the respiratory signal. Both these surrogates are commercially available and currently used clinically. Ideally, internal tumour motion can be tracked with real time x-ray imaging, but this is at the cost of increased radiation dose to patients. External surrogates can complement x-ray based imaging techniques as a means to reduce the required frequency of imaging interventions.

Although external surrogates are widely used in radiotherapy applications, the extent of this motion is not well-described in the literature. There have been a few small sample sized studies that have investigated respiratory motion parameters for external respiratory surrogates [8, 9, 10]. In order to fully describe this respiratory motion, a large population study is needed. To complete the picture of respiratory motion, not only do the basic extent of motion parameters, such as peak-to-peak amplitude, period, and end exhale phase need be described, but also the variability of respiratory motion including inter- and intrafraction motion.

While gating is traditionally used with lung, liver, and abdominal patients, it is increasingly applied to breast cancer treatments [11]. There is limited respiratory data specific to this population. The breast cancer patient population may have different respiratory quali-

ties based on potentially better lung function, the fact that patients are often younger, and almost exclusively female. The inclusion of the healthy volunteer study provides a different population group from the commonly studied lung cancer patient population. Lung cancer patients often have compromised lung function and the general characteristics of their breathing patterns will not necessarily be representative of all populations [12]. It has been suggested that women may breathe more with their thorax than men [13]. The thoracic respiratory motion will be more important for breast cancer patients than abdominal motion that is more commonly studied. Motion of the thorax can crucially impact the heart dose in left-sided breast cancer patients [14]. Dose homogeneity in the breast has been shown to decrease with organ motion due to respiration [15, 16]. In the specific case of breast cancer patients, the external surrogate motion should be directly related to tumour motion; however, this is not necessarily the case for other tumour locations.

With this in mind, we have analyzed a large patient database and compiled a volunteer study of respiratory motion in order to develop a population database of respiratory information. Extent of motion information including peak-to-peak amplitude, period, and end exhale positions, are necessary for understanding the typical ranges to expect during radiation therapy treatment. Fluctuations of parameters during typical treatment times and between treatments days are studied in order to understand the expected intra- and interfraction variations. Baseline drift and duty cycle are also examined. Duty cycle is a critical part of any gating program and should be optimized for efficiency and efficacy of treatment. We have also determined the amplitude/phase correspondence for the external surrogates across typical phase bins used in 4D imaging. This analysis has implications for gated radiotherapy where imaging is phase-based and treatment is often amplitude-based. These analyses will be valuable for both treatment planning and commissioning of external surrogates.

3.2 Materials and Methods

We obtained respiratory data from the Real-Time Position Management System (RPM, Varian Medical Systems, Palo Alto, CA). The two main components of the RPM system are a marker block and a tracking camera [17]. The camera is a charge coupled device (CCD) with an infrared (IR) emitter and was installed on the ceiling of the treatment rooms and on the foot of the bed in the simulation room. Two reflective circular markers on the plastic cuboid block are tracked simultaneously to measure the calibrated vertical motion. We used this RPM set up to study two different populations: patients and volunteers. The RPM patient database consists of traces from lung, chest, and abdominal patients (Table 3.1). The data were acquired with RPM block placed between the xiphoid process and the umbilicus at the position of largest respiratory motion. There are over 1000 patient traces from 120 individual patients.

Table 3.1: Patient characteristics.

	Patients	Volunteers
Mean age (range)	68.6 (4 – 92) years	35 (22 – 65)
Male/female	57/63	5/25
Lung/Chest/Other ^a	80/33/7	N/A
R/L vs C	45/53 vs. 15	N/A

^aOther includes liver, abdominal, Hodgkins, seminoma (blood vessels), and spine.

The volunteer study consisted of 30 (25 female and 5 male) healthy participants without lung cancer. We recorded RPM data at two respiratory positions: the abdomen, similar to the clinical setup and the thorax on the sternum at the nipple line, which provides an estimate of breast motion. These two placements allow for comparison between abdominal and thoracic respiratory motion. For five of the female volunteers, we also rotated the RPM camera, block placement, and volunteer couch position 90 degrees to assess the superior – inferior (SI) component of the motion. Each patient and volunteer breathing trace consists of up to six minutes of respiratory data. For complete population data without weighting bias,

we analyzed the single longest trace for each patient. We excluded null data traces where the IR signal was blocked or data were incorrectly recorded. We also excluded datasets with a large number of breath holds that were not representative of normal breathing, and any datasets with less than one minute of respiratory data.

The University of Calgary’s Conjoint Faculties Research Ethics Board approved these studies.

3.2.1 Population statistics

From the RPM data, we found the peak-to-peak amplitude, period, and end exhale phase for each subject. End exhale is the phase of the local minima for an individual breathing cycle. Analysis of variance (ANOVA) was conducted for amplitude, period, and end exhale phase for the three groups: patient abdominal, volunteer abdominal, and volunteer thoracic. Two-tailed t-tests determined which parameters were statistically different, with a 5% significance level. We performed all analyses in MATLAB (The MathWorks, Natick, MA).

Baseline drift is defined as the change in the vertical position of the local minima (end exhale) of the respiratory cycle [3] and was calculated for each trace, as shown in Figure 3.1. Dependency of baseline drift on tumour location was examined by comparing both the absolute and percent baseline drift between right/left and centrally located tumours. Duty cycle is an important measure of treatment efficiency in gated radiotherapy. It is defined as the ratio of beam-on time to treatment delivery time. In this study, we calculated duty cycle for amplitude-based gating for gating windows of 10% – 60% [18].

In order to investigate amplitude variation across common phase bins used for applications such as 4D CT, we examined the spread of amplitude points at typical phase windows. Each patient trace was separated into phase-binned cycles (phase 1 – 101) and then these were split into phase bins of 1 – 11, 11 – 21, ... , 91 – 101. Box and whisker plots of each bin are used to display the variation across each bin.

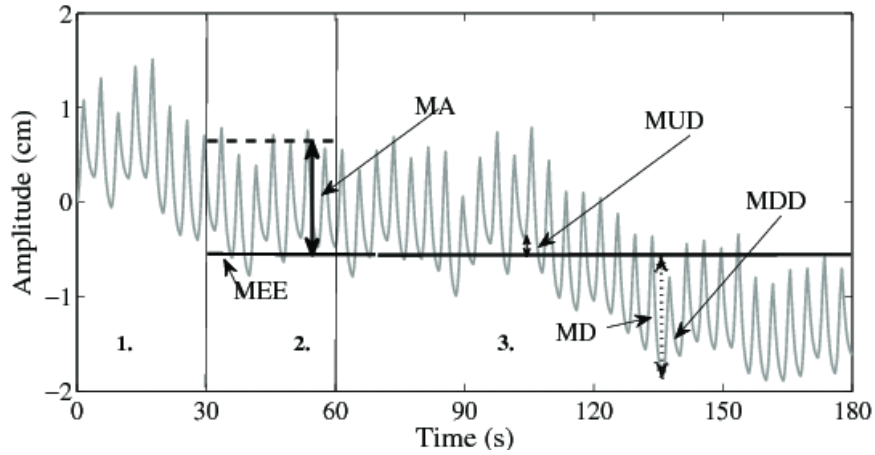


Figure 3.1: The first 30 seconds of data (a) are discarded to allow subjects to relax into restful breathing and to exclude any set up changes such as couch shifts and patient adjustments; (b) for the next 30 – 60 s, the mean location of end exhale (MEE) and cycle amplitude (MA) were found; the maximum upward (MUD) (c) and downward drift (MDD) were calculated from MEE and the maximum drift (MD) and percent drift determined

3.2.2 Patient statistics over time

To investigate inter- and intrafraction motion, we examined patient respiratory traces from three different treatment days, each spaced at least one week and up to two weeks apart. Fifty-five of 120 patients matched these criteria. We evaluated the inter- and intrafraction variability for period, peak-to-peak amplitude, and end exhale phase. The interfraction variation was defined as the standard deviation (SD) of all data over the three days of treatment, and the intrafraction variation as the SD from each treatment day. We evaluated the mean change over time by averaging the three daily intrafraction measurements. The coefficient of variation ($CV = SD/\text{mean} \times 100\%$) provides a standardized comparison between the three parameters: period, peak-to-peak amplitude, and end exhale phase. The correlation coefficient was calculated between the CV of peak-to-peak amplitude, period, and end exhale phase to determine if variability of one parameter had a definitive impact on another. Baseline drift was also analyzed over time for two subsets of the population: 50 patients over three different treatment days and 10 patients over five days.

3.3 Results

3.3.1 Population statistics

The population mean and standard deviation of the peak-to-peak amplitude, period, and end exhale phase are shown in Table 3.2, and the histograms comparing these measurements for patients, volunteer abdominal, and volunteer thoracic are shown in Figures 3.2(a), 3.2(b), and 3.2(c). Peak-to-peak amplitude, period, and end exhale all have similar, approximately normal, distributions. Only the female volunteers were included in the analysis, because for the males in our study, the motion of the RPM box placed on the thorax was not reliably detectable (<0.5 mm). For the volunteer study, the superior-inferior (SI) motion of a small subset of the volunteers was analyzed. The mean peak-to-peak amplitude of these five volunteers was 0.1 cm (range of 0 – 0.2 cm), the mean period was 3.6 s (2.6 – 4.8 s), and the mean end exhale phase was 56.7% (52.9% – 61.3%). The SI motion was smaller in each volunteer than the corresponding measurement of either the thoracic or abdominal motions in the anterior-posterior direction.

Table 3.2: Mean, median, and standard deviation (SD) of peak-to-peak amplitude, period, and end exhale phase for patients and volunteers, both abdominal and thoracic placement.

		Patient Abdomen	Volunteer Abdomen	Volunteer Thoracic
Amplitude (cm)	Mean	1.0	0.8	0.2
	Median	0.9	0.8	0.2
	SD	0.5	0.3	0.2
Period (s)	Mean	3.6	4.2	4.1
	Median	3.5	4.0	4.1
	SD	1.0	1.1	0.8
End exhale (%)	Mean	59.5	57.7	56.1
	Median	59.0	58.0	56.0
	SD	6.3	6.9	6.8

The differences between the abdominal motion of the volunteers and patients, and the

thoracic and abdominal motion of the volunteers were tested for statistical significance. The period was not statistically different between these groups. Patients had significantly greater abdominal peak-to-peak amplitude of motion ($p = 0.04$) than volunteers. The volunteers thoracic motion was significantly smaller than their abdominal motion ($p = 0.01$). Statistically, the end exhale phase for patients occurred later in the breathing cycle than for volunteers ($p < 0.001$). A systematic phase difference in volunteers thoracic and abdominal end exhale phase was observed, with the abdominal end exhale position at a later phase than the thoracic position ($p < 0.001$).

The amplitude/phase correspondence across typical imaging phase bins was analyzed. Figure 3.3(a) shows box and whisker plots for each of the phase bins for the amplitudes of all patients. The box portion of the plot represents the 25th and 75th quartiles and the central line the 50th quartile (median). The whisker portion is the 95% spread of the data. It can be seen in this plot that the spread of the exhale bins is smaller than the inhale bins, which is consistent with findings showing end exhale as the more stable position. The last two graphs in Figure 3.3 show the variation found from single patients. Figure 3.3(b) shows the patient with the minimal standard deviation of amplitude in each bin, while Figure 3.3(c) shows the patient with maximal variation. Figure 3.3(c) represents a patient that falls beyond the 95% of the data shown in Figure 3.3(a).

Figure 3.4 shows the baseline drift for patient and volunteer abdominal measurements. The shapes of the curves are very similar; however, patient baseline drift is larger than that of the volunteers ($p = 0.008$). The absolute baseline drift was measured up to 2 cm in the patient group and 0.3 cm in the volunteer group. Over 40% of patients show baseline drifts of 30% of the amplitude, while 10% of patients show percent baseline drifts greater than 60% of the amplitude. The absolute baseline was greater than 0.5 cm for 40% of patients. The percent baseline drift of the volunteers is much smaller. Only 10% of volunteers have a baseline drift of 30% and less than 5% have a baseline drift greater than 60%.

A subanalysis compared the correlation of baseline drift to tumour position for the chest/lung cancer patients between centrally and right/left located tumours. We found no statistically significant differences between either absolute baseline drift (central: 19 ± 16 mm and right/left: 32 ± 31 mm) or percent baseline drift (central: $20.9\% \pm 24.5\%$ and right/left: $50.2\% \pm 80.0\%$). Baseline drift is hypothesized to be associated with stress [3] and the nonstatistically significant difference between central and peripheral tumours is consistent with this hypothesis, as the stress levels of the patients would not necessarily be different across those two groups.

The duty cycles for both the volunteers (abdominal) and the patients are shown in Figure 3.5 and the results are similar. The duty cycle spread is greater in the patient population. For the volunteers, the outliers represent the same two volunteers: one at the upper bound and one at the lower.

3.3.2 Patient statistics over time

We calculated both inter- and intrafraction variability for a subset of 55 patients. Table 3.3 gives the mean, standard deviation, and coefficient of variation (CV) for inter- and intrafraction motion. The CV allows for comparison between the three parameters and indicates that end exhale is more stable between and within fractions than amplitude or period. The CV is larger for interfraction motion than intrafraction motion. Figure 3.6 shows that the variability of one parameter is not correlated with the variability of the others with correlation coefficients of 0.10 (end exhale and period), 0.08 (amplitude and period), and 0.12 (end exhale and amplitude). Figures 3.7(a) and 3.7(b) show the baseline drift for the 50 patients over three days and the 10 patients over five days. Baseline drift is found to fluctuate over time, with no clear increasing or decreasing trends.

Table 3.3: Intra- and interfraction variability of peak-to-peak amplitude, period, and end exhale for 55 patients.

Intrafraction Motion			
	Amplitude (cm)	Period (s)	End Exhale (%)
Mean	0.9	3.6	60.3
SD	0.2	0.4	2.3
CV (%)	22.5	10.2	3.8
Interfraction Motion			
Mean	0.9	3.6	60.3
SD	0.3	0.9	4.9
CV (%)	37.0	24.3	8.1

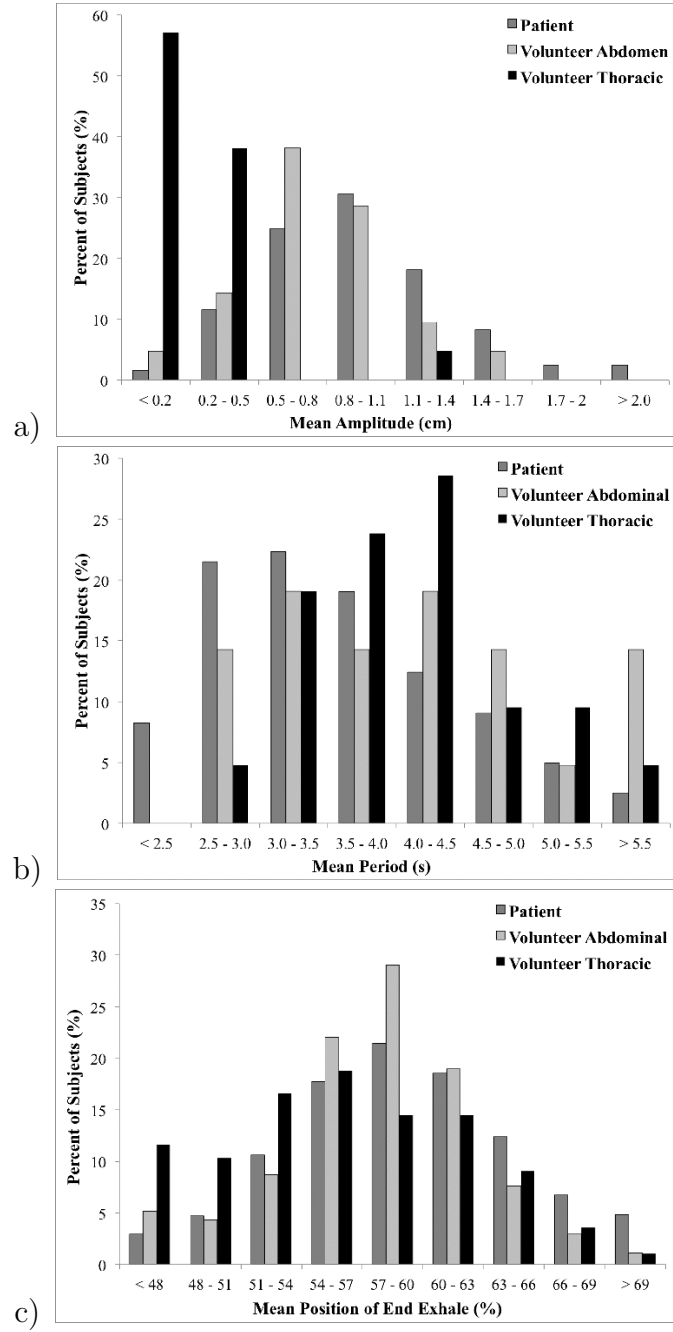


Figure 3.2: Histograms of a) peak-to-peak amplitude (cm), b) period (s), and c) end exhale phase (%) are shown for patients (dark grey), volunteers abdominal measurement (light grey), and volunteer thoracic measurement (black)

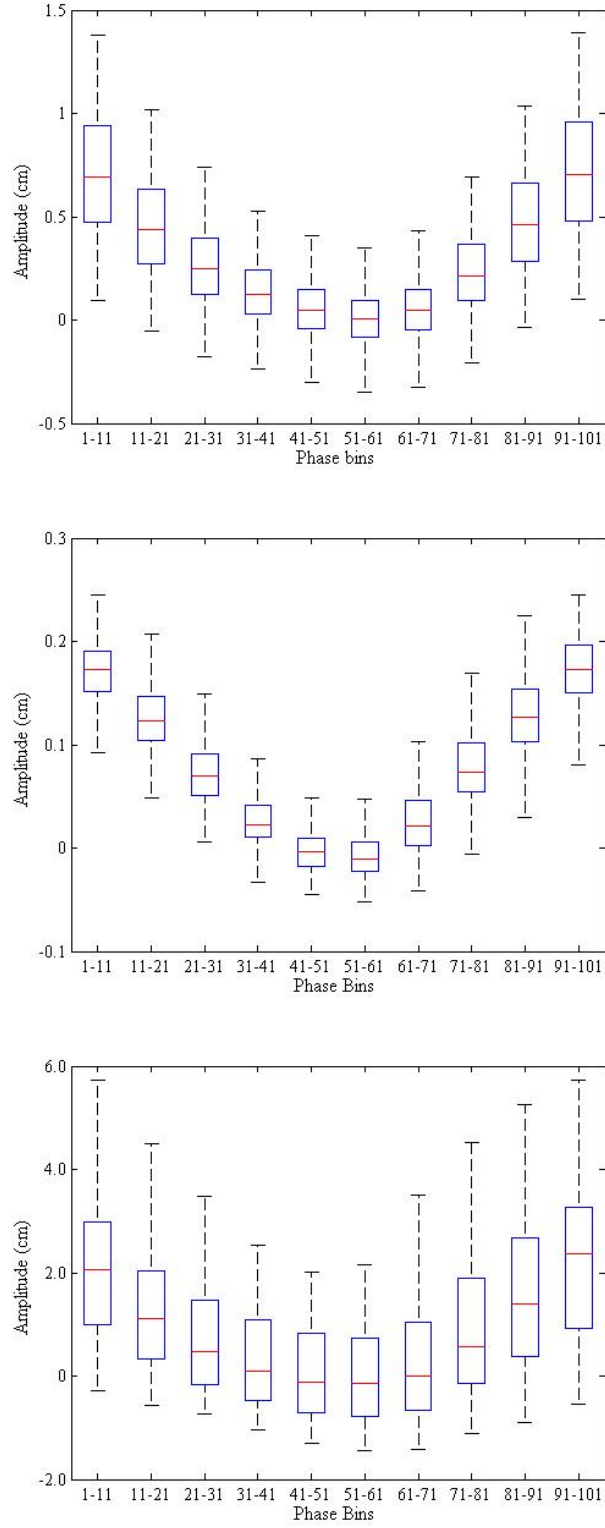


Figure 3.3: The amplitude/phase correspondence is shown for all patients (top), as well as the patient with the minimal variation (middle) and the maximal variation (bottom).

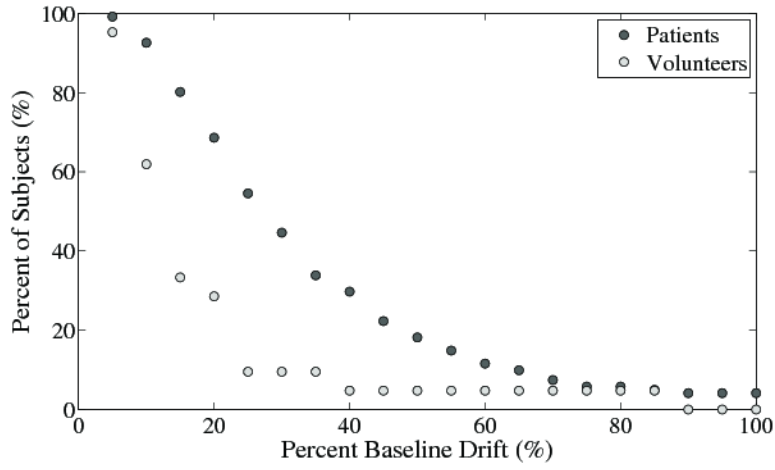


Figure 3.4: Cumulative plot of percent baseline drift of patients (black circles) and volunteers (light grey circles) is shown. The percent baseline is calculated as shown in Figure 3.1.

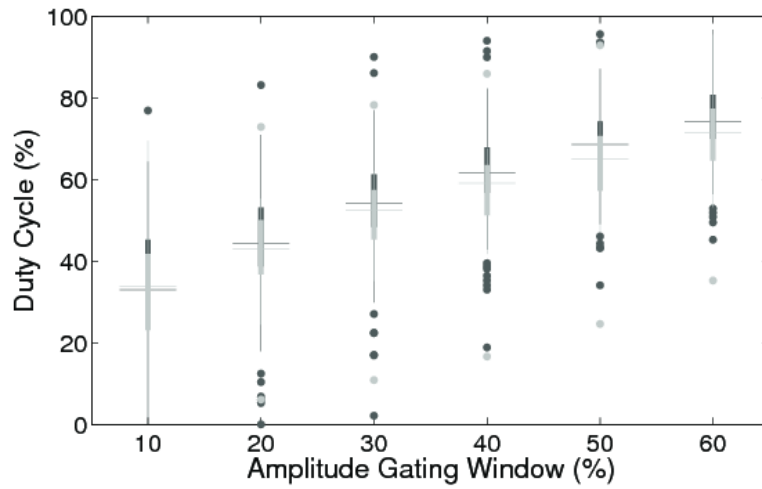


Figure 3.5: Duty cycle of patients (dark grey) and volunteers (light grey).

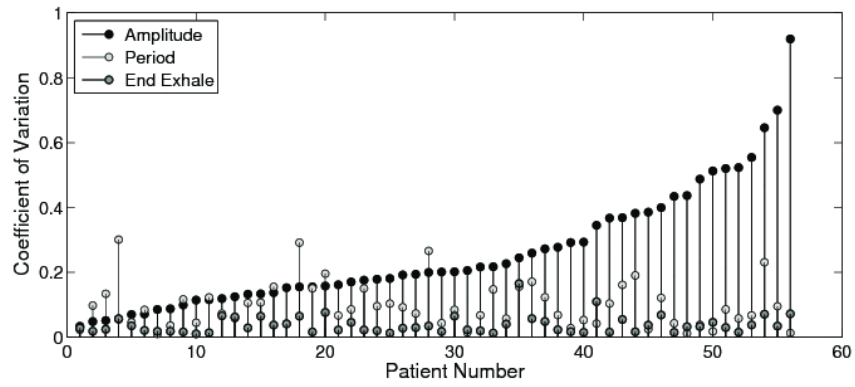


Figure 3.6: Interfraction coefficient of variation is shown for amplitude (black), period (light grey), and end exhale (dark grey). The data are presented in order of increasing amplitude variability. For the coefficient of variation, the standard deviation was calculated from three different treatment days, each a week apart. There is no correlation between the coefficient of variation for amplitude, period, and end exhale.

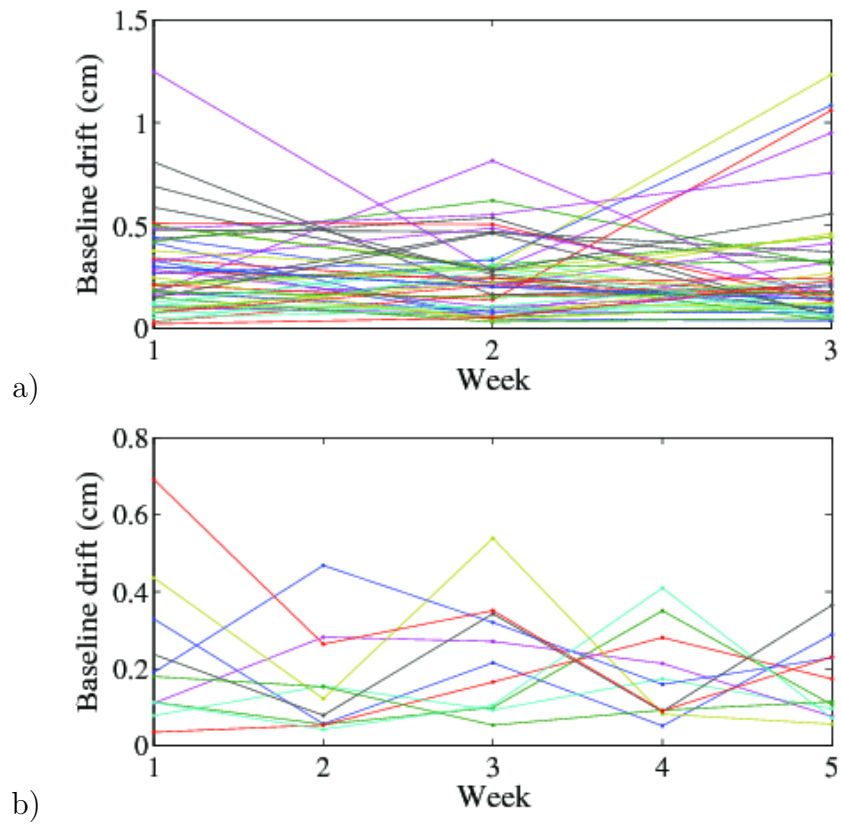


Figure 3.7: Baseline drift for: (a) 55 patients with three measurements each a week apart, and (b) 10 patients, five measurements each a week apart. There is no obvious trend of increasing or decreasing baseline drift over the course of treatment.

3.4 Discussion

Our study examines the external motion of the chest wall and not internal tumour motion. This data is one-dimensional and therefore cannot account for hysteresis, but should portray similar characteristics to the internal motion. External surrogates are beneficial because the data are easily accessible; however, caution must be taken to verify the internal-external correlation prior to clinical applications. Our measurements and analysis provide accumulation respiratory motion data that can be consulted for typical ranges of motion and variability.

Respiratory motion measures, including peak-to-peak amplitude and period, have been explored in the literature for external surrogates with smaller patient numbers [8, 9, 10, 19]. Our results for mean (SD) for amplitude, 1.0 (0.5) cm, and period, 3.7 (1.0) s, fall into the range of motion found for external motion range of amplitudes of 3 mm to 3 cm [9, 10] and a range of period of 4.8 (1.2) s [19].

Only one paper, to the best of our knowledge, shows a comparison between lung cancer patients and volunteers. Cai *et al.* [20] investigated internal lung motion in seven healthy volunteers and five lung cancer patients. The differences between the two groups were not explicitly examined and analysis of the two groups were not combined. Using the data provided in their manuscript, we calculated the mean amplitude of 0.90 ± 0.29 cm and 0.90 ± 0.30 cm for volunteers and patients, respectively. Although, their analysis was performed on an internal dataset, the relationship between the magnitude volunteer and patient respiratory motion is consistent with our results of 0.8 ± 0.2 cm and 1.0 ± 0.5 cm for volunteers and patients.

The use of an external surrogate is potentially closer to reality for the early stage breast patient population because the trajectory of the tumour will be more true to the trajectory of the external surrogate. Our volunteer group represents this population in such characteristics as age, lung function, and activity level ranges. The thoracic position of respiratory motion measured for the volunteers is potentially representative of breast motion, but does

not account for the difference in stress levels that a breast cancer patient may experience compared to a volunteer. Chopra *et al.* [21] found, for a study of five breast cancer patients, the maximum thoracic amplitude during normal breathing to be approximately 0.2 cm and during deep breathing to be up to 0.5 cm. This result is consistent with the amplitude of 0.3 ± 0.2 cm from our volunteers.

Our results show that the end exhale position of both the volunteers and patients was close to 60% phase. For more than 95% of subjects, the majority of the respiratory cycle is spent in exhale. This indicates the asymmetry between time spent in exhale and inhale during the respiratory cycle. The assumption that end exhale occurs at 50% phase [22, 23] is often used, but this simplification ignores the asymmetric quality of respiratory motion. Lujan *et al.* [24] explored the impact of asymmetry of motion for 10 liver patients by showing that the effective volume change of the uninvolved liver can vary between -5% and 10% for an asymmetric motion with 70% end exhale phase, while smaller variations are seen when the motion is more symmetric. Lujan and colleagues concluded that there was a small dosimetric impact on conventional radiation therapy, but a greater impact could be seen for highly conformal treatments such as IMRT.

The end exhale phase differed with statistical significance between all three groups. Between patients and volunteers abdominal measurement the average difference is small ($<1\%$) so there is little clinical significance in this finding. In the volunteer group, a statistically significant difference in end exhale phase was found between abdominal and thoracic breathing (2%). The difference between thoracic and abdominal phase for volunteers could suggest a phase shift between internal/external correlation. Again this average difference is quite small, so the clinical impact is minimal. The maximal difference of one volunteer was over 12% and could have a clinical significance if the thoracic motion was used as a surrogate for abdominal motion.

The results for interfraction motion show significant changes in amplitude and period be-

tween treatment fractions. Amplitude had the largest interfraction variation with a standard deviation of 5 mm. Korreman *et al.* [25] looked at interfraction variability for 17 patients and found similar results with 1.6 to 8.1 mm standard deviations over the entire course of treatment for external respiratory amplitude. We found that on average, the interfraction variability was larger than the intrafraction variability. This is consistent with results for end exhale phase by Juhler-Nottrup *et al.*[26] that showed the interfraction variation was significantly larger than the intrafraction variation.

Lujan *et al.* [24] looked at the clinical impact of intrafraction variability of amplitude and found that small changes (<3 mm) in amplitude may not result in clinically significant changes, but larger variations (>5 mm) can lead to significant changes. Our average intrafraction standard deviation is 3 mm, with 12/55 patients having standard deviation greater than 5 mm. This indicates approximately 20% of our patients may see clinically significant changes due to their intrafraction variability.

Baseline drift requires monitoring during both gated and non-gated treatments because of the potential for a geometric miss. It is important during commissioning to ensure that proper systems are in place to handle baseline drifts. When drift occurs during respiratory gating, the treatment is stopped and the gating window is readjusted, increasing uncertainty in the treatment and overall delivery time [27]. We found a statistically significant difference in baseline drift between patients and volunteers. This indicates that baseline drift could be correlated to lung function and, if this is the case, patients with poor lung function should be closely monitored if using gating or other complex radiotherapy methods with small internal target volume (ITV) margins. The difference in baseline drift between the two populations could also be due to disparity of stress/relaxation levels between patients with the stress of cancer treatment and volunteers participating in a lower stress study. Rietzel *et al.* [3] explored the cause of baseline drift and found that an important cause could be relaxation of the patient during the procedure or changes between abdominal and thoracic breathing,

while also concluding that the influence on internal motion is unclear. Baseline drift has been demonstrated in internal tumour motion studies [28, 29] and significant shifts are found in some patients [6, 29]. A definitive correlation between external and internal drift is not available and must be investigated on a patient-by-patient basis [12, 29].

We calculated duty cycle for the patients and volunteers from the position of end exhale for simulated amplitude-based gating. Most clinical gating studies use a 25% – 50% duty cycle [22]. We found that this corresponded to a median amplitude gating window of 10% – 30% for both patients and volunteers. On average, this gating window is very small, approximately 1 – 3 mm of external motion, requiring external surrogate monitoring with submillimeter accuracy.

3.5 Conclusions

We analyzed external chest wall respiratory motion for 120 patient and 25 volunteer traces to determine mean values for peak-to-peak amplitude, period, and end exhale phase. Statistically and potentially clinically significant differences were found for both peak-to-peak amplitude between the patient and volunteer abdominal measurements (1.0 ± 0.5 cm vs. 0.8 ± 0.3 cm), and between the volunteer abdominal and thoracic measurements (0.8 ± 0.3 cm vs. 0.2 ± 0.2 cm). As well, inter- and intrafraction variability was evaluated for 55 patients and it was found that variability between fractions was larger than variability within a fraction, and that amplitude was more variable than period and end exhale phase for both inter- and intra fraction measurements. No time pattern to the variability could be discerned. This study provides a database of parameters to use when testing implementation of techniques that rely on external surrogates. It also provides a useful comparison between patients with mainly liver, lung, and abdominal cancer and a volunteer population that could more accurately represent breast cancer patients.

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General Conclusions

This paper provides a respiratory database of parameters to use when testing implementation of techniques that rely on external surrogates. It also provides a useful comparison between patients with mainly liver, lung, and abdominal cancer and a volunteer population that could more accurately represent breast cancer patients. This dataset is used in the remaining work to develop a realistic respiratory trace generator and apply respiratory effects to partial breast treatment planning.

Chapter 4

Realistic Respiratory Trace Generator

General Introduction

Work presented in this chapter describes the development of a realistic respiratory trace generator based on the analysis of patient and volunteer externally measured respiratory data. The shape of the respiratory cycle was modelled to incorporate asymmetry between inhale and exhale components of the respiratory cycle. This work is published in a peer reviewed journal, *Medical Physics* [1]. I was first author on this work and contributing authors were Dr. Nathan Becker and Dr. Wendy Smith. Dr. Nathan Becker assisted with performing measurements and interpreting the results, under the supervision of Dr. Smith. I prepared the initial draft of this manuscript, and all authors have been a part of reviewing the final manuscript.

External respiratory motion: Shape analysis and custom realistic respiratory generation

Sarah Quirk, Nathan Becker, and Wendy Smith

Abstract

Background and purpose: The authors developed a realistic respiratory trace generating (RTG) tool for use with phantom and simulation studies.

Methods and materials: The authors analyzed the extent of abdominal wall motion from a real-time position management system database comprised of 125 lung, liver, and abdominal patients to determine the shape and extent of motion. Using Akaike's Information Criterion (AIC), the authors compared different model types to find the optimal realistic model of respiratory motion.

Results: The authors compared a family of sigmoid curves and determined a four parameter sigmoid fit was optimal for over 98% patient inhale and exhale traces. This fit was also better than $\sin^2(x)$ for 98% of patient exhale and 70% of patient inhale traces and better than $\sin(x)$ for 100% of both patient inhale and exhale traces. This analysis also shows that $\sin^2(x)$ is better than $\sin(x)$ for over 95% of patient inhale and exhale traces. With results from shape and extent of motion analysis, we developed a realistic respiratory trace generating (RTG) software tool. The software can be run in two modes: population and user defined. In population mode, the RTG draws entirely from the population data including inter- and intra fraction amplitude and period variability and baseline drift. In user-defined mode, the user customizes the respiratory parameters by inputting the peak-to-peak amplitude, period, end exhale position, as well as controls variability in these parameters and baseline drift.

Conclusion: This work provides a method of generating custom respiratory data that can be used for initial implementation and testing of new technologies.

4.1 Introduction

Respiratory management systems require extensive testing before implementation. Prospective systems should be tested on breathing patterns that are representative of the patient population, in terms of breathing regularity, shape of the breathing pattern, amplitude and period variability and baseline drift, in order to analyze how they will perform for a variety of patients. Even retrospective systems, such as retrospectively gated 4DCT imaging and Cone-Beam Motion Estimation [2] must accurately bin motion, and this cannot be fully examined without considering the full range of patient breathing patterns.

Previous work commissioning respiratory motion management tools has generally been limited to two models of respiratory motion: a idealized, regular motion such as $\sin(x)$ or $\sin^2(x)$ or single or limited patient respiratory data [3, 4]. The first simplification does not allow for the asymmetry, variability or pattern variation commonly observed in the clinic. Such simple, repetitive motion will only accurately model a small portion of patients; as most patients exhibit variability and irregularity far beyond that model [5]. Other studies test motion management techniques using single or limited patient respiratory data, [4] does introduce motion variability specific to that patient. However, this limited patient data does not necessarily include the variability in amplitude, period, or baseline drifts seen in the general patient population.

In this paper we develop a realistic, population-based respiratory model that will allow motion management analyses to be extended from a basic sinusoid to determine the true impact of respiratory motion on radiation treatment. This model is used to create a Respiratory Trace Generator (RTG) available on the internet

(<http://www.ucalgary.ca/rop/Research/Respiratory>). The RTG can be used to produce patient traces based on population data, as well as traces with varying degrees of amplitude and period variability and baseline drift. Simulation and phantom studies can be fully tested using the range of variability from completely repetitive, to extremely irregular. The RTG

also allows single parameters (such as peak-to-peak amplitude, period, and baseline drift) of variability to be customized while holding the other parameters constant. This may provide an important step in clinical testing of new techniques and modalities.

4.2 Materials and methods

We acquired respiratory data from the real-time position management system (RPM Version 1.4, Varian Medical Systems, Palo Alto, California) [6]. The RPM database consists of more than 1000 patient breathing traces from lung, liver, and abdominal patients (120 individual patients) of the anterior-posterior motion. To investigate inter- and intra-fraction motion, we examined patient respiratory traces from three different days, each spaced at least one week and up to two weeks apart, during both simulation and treatment. 55 of 120 patients matched these criteria.

4.2.1 Shape evaluation

For each patient the local maxima and minima of each cycle was found and individual cycles separated, as described by Suh *et al.* [7]. Each cycle was resampled and labeled phase 1-101 using spline interpolation and then normalized. False peaks were excluded by limiting peak separation to at least 0.4 s [7]. An average patient trace was found (Fig. 4.1) and inhale and exhale portions of the respiratory cycle were divided at end exhale to model each portion independently.

Based on visual initial inspection, the sigmoidal family of curves was investigated (Table 4.1). The meaning of the parameters (Table 4.1) are as follows: a is the lower asymptote value, b is the upper asymptote value, $1/c$ is the width or steepness in slope parameter, d is the point of inflection and f is a horizontal shift.

A method to distinguish between the models is necessary to determine the analytical equations that best model the motion data. Goodness-of-fit parameters are insufficient as

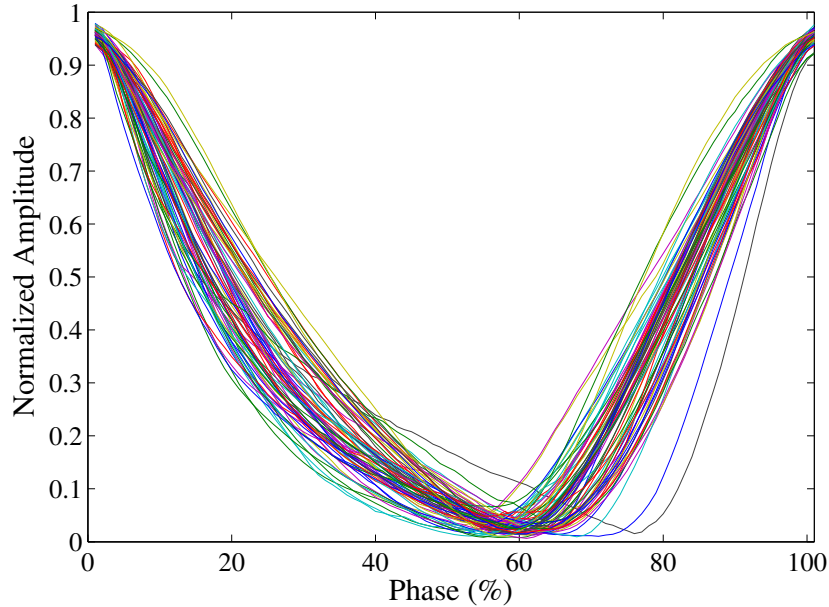


Figure 4.1: Average traces from 75 patients give an example of the shape range in the population.

the sole tool to determine the most appropriate model because increasing the number of parameters in a model will always improve the goodness-of-fit measure, as small fluctuations in the data are better described. A model with many parameters may not be ‘better’ since it can be computationally intensive and may lack physical meaning. In general, a less complicated model for the same level of accuracy is preferable [8].

We chose Akaike’s Information Criterion (AIC) to evaluate candidate models because it can test non-nested models. For discussion on the choice of AIC over other information theory techniques, such as Bayesian information criterion, we refer the reader to existing in-depth comparisons [9]. The *AIC* incorporates both the goodness-of-fit and the number of parameters to discriminate between models, a complete formalism of AIC is described in Burnham *et al.* 2002 [9]. We used MATLAB (Mathworks, Natick, Massachusetts) for all analyses.

The relative difference between *AIC* for two different models (A and B), $\Delta AIC_{A,B}$,

Table 4.1: Sigmoidal models used in *AIC* analysis.

Inhale Models		Exhale Models	
In ₅	$\mathbf{y} = \mathbf{a} + \frac{(\mathbf{b}-\mathbf{a})}{1+\mathbf{f} \cdot \exp(-\mathbf{c} \cdot (\mathbf{x}-\mathbf{d}))}$	Ex ₅	$\mathbf{y} = \mathbf{a} + \frac{(\mathbf{b}-\mathbf{a})}{1+\mathbf{f} \cdot \exp(\mathbf{c} \cdot (\mathbf{x}-\mathbf{d}))}$
In ₄	$\mathbf{y} = \mathbf{a} + \frac{(\mathbf{b}-\mathbf{a})}{1+\exp(-\mathbf{c} \cdot (\mathbf{x}-\mathbf{d}))}$	Ex ₄	$\mathbf{y} = \mathbf{a} + \frac{(\mathbf{b}-\mathbf{a})}{1+\exp(\mathbf{c} \cdot (\mathbf{x}-\mathbf{d}))}$
In ₃	$\mathbf{y} = \frac{\mathbf{b}}{1+\exp(-\mathbf{c} \cdot (\mathbf{x}-\mathbf{d}))}$	Ex ₃	$\mathbf{y} = \frac{\mathbf{b}}{1+\exp(\mathbf{c} \cdot (\mathbf{x}-\mathbf{d}))}$
In ₂	$\mathbf{y} = \frac{1}{1+\exp(-\mathbf{c} \cdot (\mathbf{x}-\mathbf{d}))}$	Ex ₂	$\mathbf{y} = \frac{1}{1+\exp(\mathbf{c} \cdot (\mathbf{x}-\mathbf{d}))}$

is calculated (equation 4.1) such that the ratio of the goodness-of-fit parameters, sum-of-squares deviations (sum of the square of the vertical distances of the measurement and the fitted curve), for the two models, SS_A and SS_B , is weighted against the increasing number of parameters. The sum-of-squares is taken over the average trace for each patient. K_A and K_B are the number of parameters plus one for each model and N is the number of data points. The multiplication of 2 in front of the number of parameters term is part of the AIC formalism, Akaike used this parameter as the asymptotic bias correction. This term varies with different information theory criterion and has been discussed in the literature by Burnham *et al.* [9].

$$\Delta AIC_{A,B} = N \cdot \ln \left(\frac{SS_A}{SS_B} \right) + 2 \cdot (K_A - K_B) \quad (4.1)$$

As an example, if model A is more complex than model B , and the $\Delta AIC_{A,B}$ is greater than zero, the change in the sum of squares error is not as large as expected with the increased number of parameters and the simpler model, B , is preferred. If $\Delta AIC_{A,B}$ is negative, the extra parameters are justified and model A is preferred.

4.3 Results

4.3.1 Model evaluation

The AIC analysis for both inhale and exhale shows that the most complicated, five parameter sigmoidal fit, does not increase the quality of the fit enough to justify an extra parameter. The four parameter fit (Ex_4 and In_4) is favoured over the five parameter fit for 100% of inhale traces and 98% of exhale traces and also favoured for 99% of inhale and 83% of exhale traces over the three parameter fit. The results of this analysis conclude that the four parameter sigmoid fit is the most robust for both inhale and exhale traces. We tested our four parameter sigmoid fit against two common sinusoidal fits used to describe respiratory motion, $A * \sin(B * x + C)$ and $A * \sin^2(B * x + C)$ (Figs. 4.2 a and 4.2 b). The four parameter sigmoid (Ex_4 and In_4) fits better than $\sin^2(x)$ in 98% of exhale and 70% of inhale and better than $\sin(x)$ for 100% of both inhale and exhale. This analysis also shows that $\sin^2(x)$ is better than $\sin(x)$ for over 95% of both inhale and exhale.

From the four parameter sigmoidal fit a distribution of coefficients was compiled to be used as an input for the RTG (Fig. 4.3). Extent of motion parameters were also analyzed to determine distributions (not shown) for amplitude, period, and end exhale positions. Baseline drift information from the population study was also incorporated in the RTG. Baseline drift is defined as the change in the vertical position of the local minima (end exhale) of the respiratory cycle [10].

4.4 Respiratory trace generator (RTG)

We developed a software tool that allows the user to generate either population-based or customized respiratory traces for their respiratory application (<http://www.ucalgary.ca/rop/Research/Respiratory>). This tool randomly selects a correlated set of shape parameters from the parameter sigmoidal shape shown by our analysis

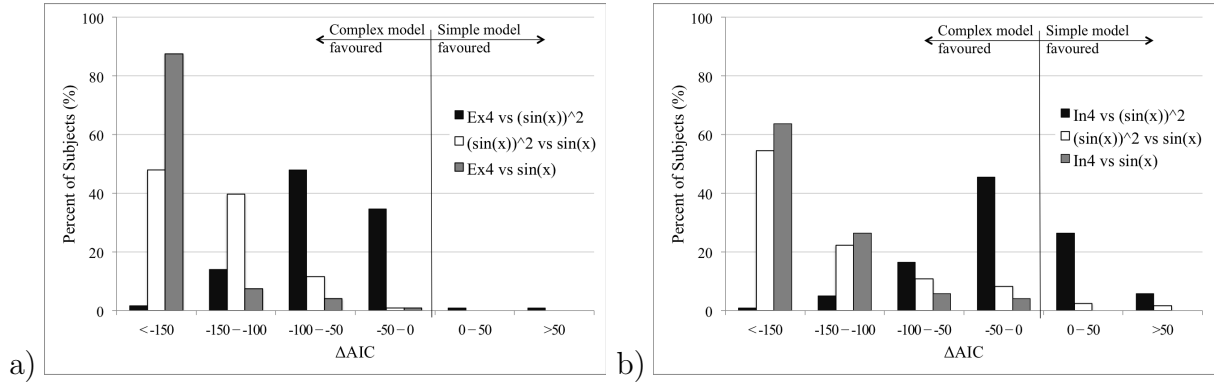


Figure 4.2: In plots *a* and *b*, ΔAIC for $\sin(x)$, $\sin^2(x)$, and In_4 and Ex_4 . It can be seen, from the largely negative ΔAIC values, that the sigmoid fit (Ex_4 and In_4) is favoured over sine squared for 100% and 70% of patients for exhale and inhale, respectively. Sine squared is favoured over sine for over 95% of patients for both inhale and exhale traces. In all plots the more complex model is the first of the two listed in the legend.

to best represent the population motion. Once the shape is chosen, a peak-to-peak amplitude, period and end exhale phase are chosen from the distributions found in the population study. The variability is introduced by selecting a standard deviation from the distribution of standard deviations in the population for each parameter (peak to peak amplitude, period, and end exhale phase). These distributions of standard deviations for each parameter are approximately normal. Then a random fraction of that standard deviation is added or subtracted to the mean, previously selected, for each segment of *e-i* or *i-e* for peak to peak amplitude, period, and end exhale phase. The RTG can be run in two different modes: population based and user defined. Examples of generated traces are shown in Fig. 4.4.

Population defined mode:

- Draws entirely from the population data, representative of typical patient motion
- Maximum variability based on population outliers
- Can generate one trace per patient, or multiple (representative of inter-fraction)
- Can generate one patient or multiple (population variability)

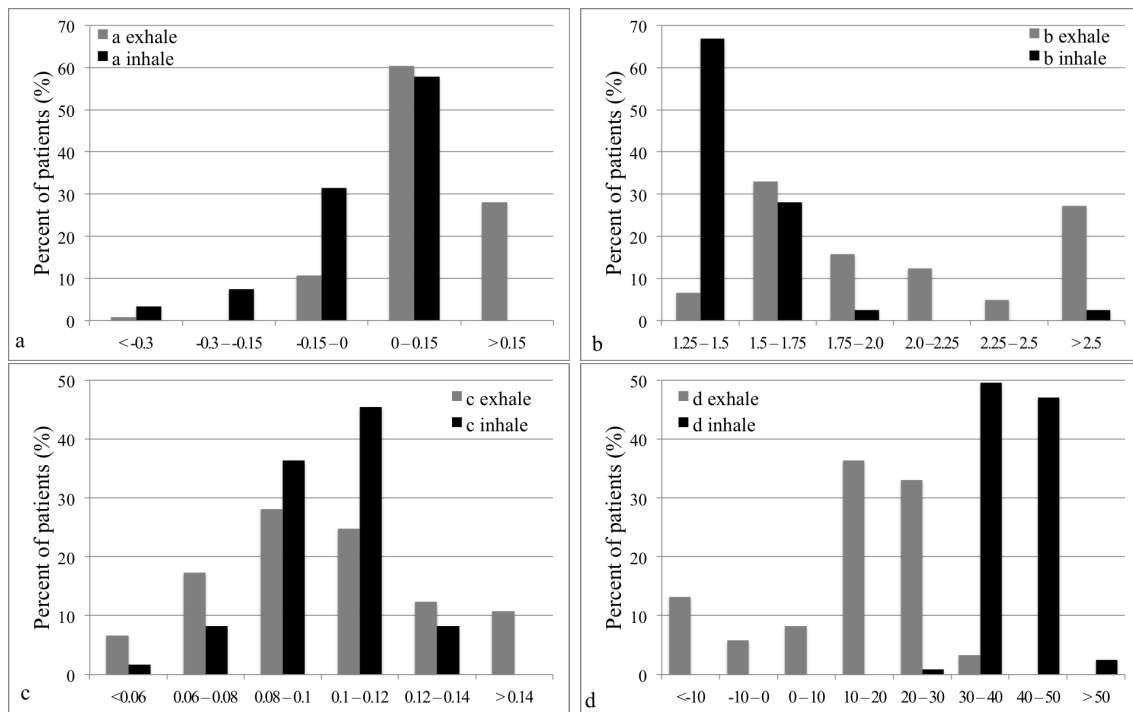


Figure 4.3: Histograms of the four parameter sigmoid fit coefficients for inhale (black) ($y = a + \frac{(b-a)}{1+\exp(-c \cdot (x-d))}$) and exhale (grey) ($y = a + \frac{(b-a)}{1+\exp(c \cdot (x-d))}$).

- Can vary length of trace
- Can vary sampling frequency

User defined mode:

- User controls variability of respiratory motion
- Can choose input values of peak-to-peak amplitude, period, and end exhale position
- Can vary peak-to-peak amplitude, period, and baseline drift (manually with sliders)
- Maximum variability up to 10x population SD
- Can vary all parameters listed in population mode

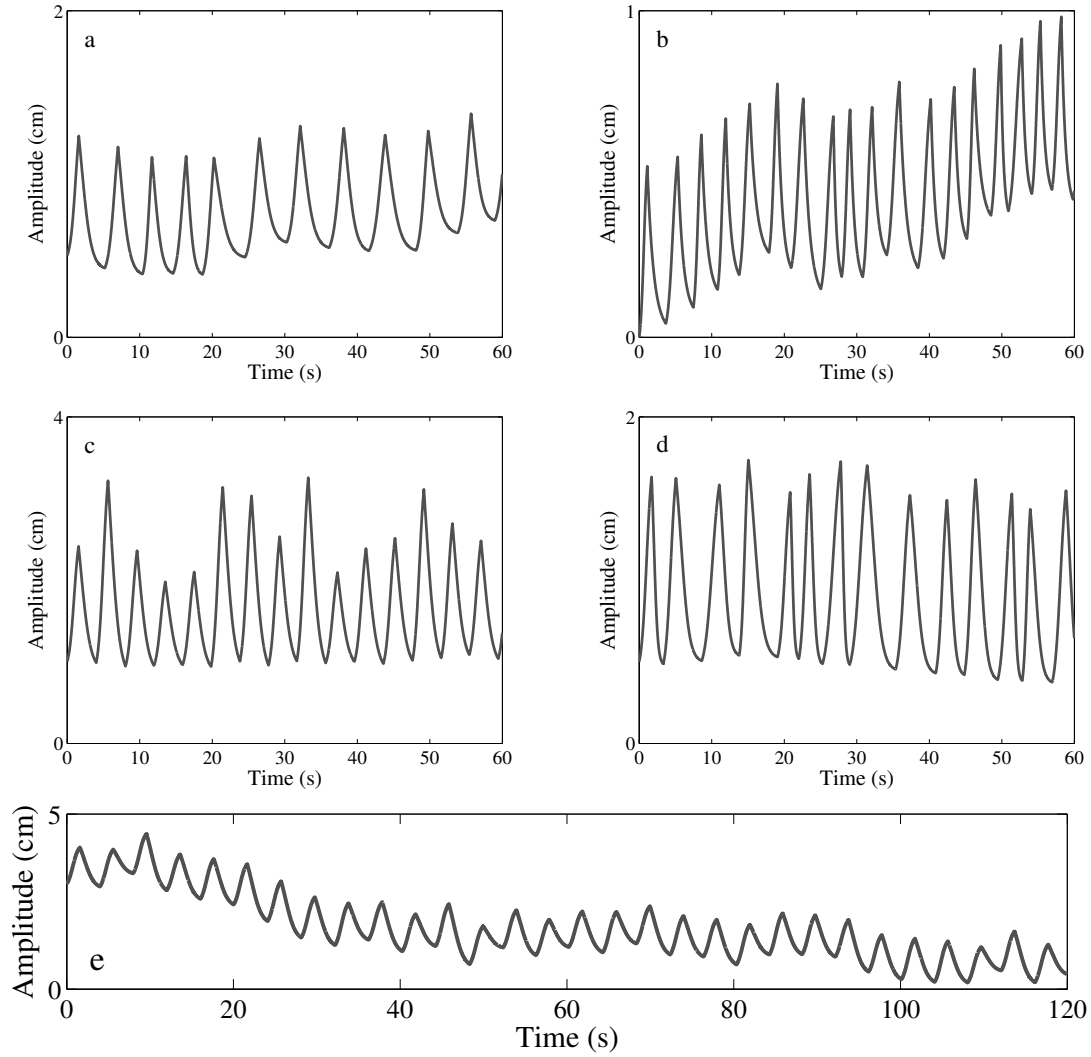


Figure 4.4: Plots *a* and *b* are examples of respiratory data generated with the RTG run in population mode. They were consecutively generated and show the typical respiratory variation over one minute. Plots *c*, *d*, and *e* are examples of respiratory data generated with the RTG run in user defined mode. Plot *c* shows highly variable amplitude, plot *d* shows variable period, and plot *e* is shows large baseline drift.

4.5 Discussion

Respiratory motion has historically been estimated either as a simple sinusoidal motion, $\sin(x)$ or $\sin^{2n}(x)$ [3, 11], or estimated with individual breathing traces [4]. Both of these motions are simple to implement for phantom studies. Our study shows that neither is sufficient to model the majority of patients. Lujan’s model provides a good first order approximation for the motion, the authors of this study suggest a more complex method is required to model more complex motion [3]. Our RTG trace generator can be utilized for many applications, including both phantom and simulation studies. Historically sinusoidal patterns have been most often used for phantom studies, because it is simple to implement. However, programmable motors are readily available and can be customized for more complex motions than simple repetitive motions. The RTG could be employed for any applications where variability in respiratory motion is a concern, including respiratory gating, real-time tracking, image guided radiation therapy, 4DCT studies, or any new modalities.

The ability to change variability is useful throughout the different stages of testing and implementation. Early in the testing process of algorithms or simulations, a more reproducible motion may be useful to provide initial proof of concept. As an algorithm or simulation study is developed, more realistic motion with clinically representative variability can be implemented (population mode). In the final stages of testing, it is imperative to determine under what conditions the algorithm or simulation will break down, the extremes of motion, including large variations in amplitude, period and baseline drifts.

Our study models the external motion of the chest wall, and not internal tumour motion. This data is one dimensional, and therefore cannot account for hysteresis, but should portray similar characteristics to the internal motion. External surrogates are beneficial because they are easily accessible, however, caution must be taken to verify the internal-external correlation prior to clinical applications. Given a true internal motion dataset, this analysis could be easily extended to supply realistic, three dimensional internal tumour trajectories

that include hysteresis. Where sinusoidal models and single patient traces are used in implementation and testing, our RTG provides an alternative allowing for customization of shape and extent of motion, but more importantly allows for testing with variable motion. It is possible to select individual patient traces for testing, but the RTG ensures the traces used will cover the spectrum of clinical variability and allows users to isolate the impact of different patterns of motion and variability. Instead of sorting through hundreds of patient traces looking for the exact situation that is desired for testing, the RTG allows the user to define the respiratory signal characteristics. This is especially relevant when testing the more extreme respiratory situations such as high variability and large baseline drifts.

4.6 Conclusion

We have shown that the sinusoidal models are insufficient to model respiratory motion for the majority of patients. The work shown here provides a method of generating realistic respiratory data that can be used for implementation and testing purposes for new modalities and technologies before patient testing is initiated. The RTG allows the user to customize respiratory traces to meet their algorithm, simulation testing, and phantom study needs.

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General Conclusions

The respiratory trace generator developed here provides a method for generating custom respiratory data that can be used in implementation and testing of new technologies prior to patient testing. It gives a method to generate traces with a controllable amount of variability that allows testing of a wide range of respiratory conditions. In Chapter 6, we use it to generate respiratory traces with realistic shape, but minimal variability, in order to limit the confounding variables.

Chapter 5

Partial Breast Irradiation and Respiratory Motion: Patient specific anatomical characteristics, a new metric, and population based respiratory motion

General Introduction

This chapter assumes the population data acquired from the volunteer study to be representative of respiratory motion of breast cancer patients. We examine the anatomy specific characteristics that may be more susceptible to effects of respiratory motion, based on our volunteer population respiratory data. We propose a new metric that may assist in excluding patients whose plan quality is degraded by respiratory motion and set a patient cut-off selection based on this metric. This manuscript is prepared for submission. I am the first author of this paper, and contributing authors were Leigh Conroy and Dr. Wendy Smith. Dr. Wendy Smith supervised this work and provided assistance in all facets of preparation. Dr. Theresa Trotter and Dr. Tien Phan provided a clinical consultation on this work. Leigh Conroy helped develop the patient plans for this study and assisted with data throughput. All authors participated in the editing of the manuscript.

Rigid Body Assumptions

The results of the next two papers depend on the assumption that the breast moves rigidly under respiratory motion. This is likely not strictly true for all patients. Here, we discuss the assumptions that others have used in the literature, and data that presents both sides of this debate. A few groups do employ a deformable dose calculation scheme for limited data, unfortunately no comparison is made to determine how different that analysis is from using

a rigid body assumption. Several groups conclude that the breast moves as a rigid body, but other methods are still used in the literature.

In a recent study, Yue *et al.* (2007) [1] investigated 21 partial breast cancer patients for the magnitude of respiratory motion. Each patient had 4-6 gold fiducial markers sutured to the walls of the surgical cavity covering the superior, inferior, medial, lateral and posterior extent. The extent of motion was evaluated using fluoroscopic images and software to track the lateral, vertical, and longitudinal directions of the motion. The study found that all fiducial markers moved very similarly with respiration, even in patients with irregular breathing motion. Yue *et al.* concluded that the breast most likely moved rigidly with respiratory motion with little deformation [1].

Price *et al.* [2] conducted a study of 13 breast cancer patients using high-frequency dense surface point imaging with the aim of determining if breast motion was uniform across the target site. They determined that the motion period is uniform across the surface of the breast and the main body of the breast moves uniformly and to a greater extent than the lateral and medial edges of the breast. This work also investigated the difference in large and small patient motion and inter-fractional differences. They found amplitude ranges similar between both cohorts and relatively low inter-fraction variability, leading the authors to conclude that if the dose distribution is robust to respiratory motion during one fraction it is likely to continue to be so for the duration of treatment [2].

Qi *et al.* [3] retrospectively analyzed 18 patients with 3DCRT plans created with 4DCT data at 0 (end inhale), 20 (reference), and 50% (exhale) phase to simulate the effects of breathing. Motion of the “centroid” position of the lumpectomy cavity and total breast volume, as well as the ipsilateral lung, heart, and other surround tissues was quantified. A difference in the range of maximum centroid movement was found between the lumpectomy volume (0.3 to 5.5 mm) and the ipsilateral breast volume (1.1 to 3.9 mm), however, the authors concluded that the average centroid movement was similar between the breast

lumpectomy volume and entire ipsilateral breast volume.

In an early study by Yue *et al.* (2007) [4], a partial deformation method was used for respiratory motion by allowing contours between different 4DCT phases to be translated, rotated, and not moved uniformly at each slice. The authors did not report on how many patients or slices required the rotations as well as translations [4]. A study by the same group by Ding *et al.* [5] used a deformable in-house software to calculate dose based on a 4DCT dataset of breast motion of six patients. They investigated the impact of respiratory motion on beam-on timing during respiratory gating. Unfortunately neither of these studies compared the use of the deformable model to that of rigid translations. Although using 4DCT data has the possibility of including deformable motion of the breast, it too has inherent limitations in that analysis is often limited to a small number of phases and choosing 50% as the end exhale phase may not be maximum extent of motion which is often closer to 60% phase. No changes in breathing pattern overtime were included.

All truly independent, deformable breast models found in the literature are MRI or ultrasound based for the purpose of interventional situations [6]. It is currently not feasible to use this type of model in a study such as the one that we will present. Numerous breast radiotherapy studies have used the assumption that the breast volume moves rigidly (include a list of references), including George *et al.* who state that the motion of the external surrogate in breast radiotherapy has a direct correlation to the target [7, 8, 9, 10, 11?]. Based on these studies and the limitations of acquiring a truly deformable breast model, we concluded that the assumption of rigidity does not detract from the validity of our results and therefore we have used this assumption in the following two papers.

Population Respiratory Motion Assumptions

Our studies may be limited because the respiratory population data is based on a limited number of healthy volunteers. In general, we feel that this population is closer in respiratory characteristics to breast cancer patients than the lung, liver, and abdominal patients investi-

gated in chapters 3 and 4. Our volunteer age range is similar to that of the early stage breast cancer population (20 - 65), but most likely includes a larger proportion of younger women. The volunteer study was designed such that it was open to women of all ages; however, the demographic that was willing to participate tended to be younger. However, our volunteers are not under stress during the time of taking their respiratory trace, unlike real radiation treatment conditions. Stress during radiotherapy can cause baseline drift which may mean breast cancer patients may exhibit larger baseline drift than volunteers. The motion magnitudes found in our volunteer study are consistent with those found in the literature [12]. For the patient population, all patients that had respiratory trace of longer than one minute, no sections of null data, and no breath-holds were used for evaluation.

Patient Data Assumptions

The number of patient specific anatomies included was limited by the number of available patient dataset that were treated in the experimental arm of the original RAPID trial. For the population-based respiratory motion study we used all 36 available patient datasets that had completed treatment. If the patient was listed on the experimental arm, but there was not an existing PBI 3DCRT plan for them we did not use their CT dataset. We had no way of knowing why the patient did not continue in the course of radiotherapy and whether or not that may be a factor in our study for which we could not control. Practically speaking, we also relied on the existing beam arrangements so that we would know that the plans were deliverable and not limited by patient mobility or machine clearance issues. We chose only to analyze ten representative anatomies for the amplitude escalation study (Chapter 6) as that was adequate to accurately determine the trends. There is the possibility that we have missed outliers by only investigating a small number of patients.

All studies have limitations in some form, we feel that the work presented here is valid within our assumptions and realize that if clinical practice was to be drastically changed more extensive analysis may need to be performed.

Accounting for respiratory motion in partial breast intensity modulated radiotherapy during treatment planning: patient specific anatomical characteristics, a new metric, and population based respiratory motion

Sarah Quirk, Leigh Conroy, and Wendy Smith

Abstract

Purpose: External beam partial breast intensity modulated radiotherapy (PBI IMRT) is conformal and may experience coverage degradation and increased dosimetric inhomogeneity in the presence of respiratory motion. We can identify which patients may need respiratory management through patient specific geometry.

Materials & Methods: Thirty-six patients datasets were planned with inverse optimized PBI IMRT. Population respiratory data, representative of breast patients, were used to create a probability density function that was convolved with the static plan fluences and the dose was recalculated to determine the delivered dose. We investigate two planning strategies to determine how to minimize the impact of respiratory motion at the planning stage. We explore which anatomical characteristics indicate a clinically significant degradation in delivered plan quality due to respiration. To quantify the difference between static and respiratory plan quality, the mean dose shift of the entire target DVH, the dose shift at 95% of the volume (D95) and the dose shift at the hotspot to 2 cm³ of the DEV volume are compared. Taking advantage of rigorous contouring of the seroma volume compared to the ipsilateral breast volume, we propose the metric DEV-to-PTV ratio as a delineating characteristic for determining which patient plans will be more degraded by respiratory motion.

Results: Planning with extended coverage of the PTV and using flash for anterior targets can minimize the effect of respiratory motion. We found that patients with severe contour changes may have increased dose degradation. Patients plans with DEV-to-PTV ratios of

less than 55% are more susceptible to degradation due to respiratory motion.

Conclusions: For patients with a DEV-to-PTV ratio less than 55% we recommend either not using PBI IMRT or employing motion management. DEV-to-PTV ratios of less than 55% are seen in anatomies that are very close to inhomogeneities (air and lung) which exacerbate the dosimetric effect of respiratory motion. If the ipsilateral breast size is smaller than 900 - 1000 cm³ it is unlikely that the DEV-to-PTV ratio will meet this criteria.

5.1 Introduction

External beam partial breast irradiation (PBI) is an increasingly popular method of delivering radiation therapy to early stage breast cancer patients in conjunction with breast conserving surgery. In general, for whole breast irradiation, large breasted patients have more hotspots (poorer dose homogeneity) which is correlated with poorer cosmetic outcomes. External beam partial breast irradiation is motivated by the desire to decrease the amount of normal tissue irradiated which decreases toxicities and hotspots potentially improving cosmesis.

Typically, the PBI treatment plan is developed on a static image, usually of a free-breathing patient CT, but the treatment is delivered to a continuously breathing patient. The delivered treatment plan may experience reduction in both target coverage and dose homogeneity due to this respiratory motion. Loss of coverage means that part of the target could be missed leading to increased recurrence. Decreasing dose homogeneity can result in poorer cosmetic outcomes due to hotspots or increased probability of recurrence due to coldspots in the target volume. One might reasonably expect that the extent of degradation depends on patient anatomy such as seroma location and breast size and shape; therefore some patients will be more affected by respiratory motion than others. It is crucial to identify those patients for whom PBI is an appropriate treatment option.

Both ipsilateral breast volume (IBV) and the ratio of planning target volume (PTV)

to breast volume have been proposed as metrics by which to select those patients most appropriate to receive PBI treatment [13, 14, 15, 16]. One selection characteristic that is often used is ensuring the PTV-to-IBV ratio is less than 25-35%. However, large variability in breast volume contouring makes these metrics hard to compare across individuals, institutions, and studies. For PBI IMRT and 3DCRT studies published to date, the range of breast volume was 190 - 3500 cm³ with the PTV-to-IBV ratio ranged from 6 to 99% [13, 14, 15, 17, 18, 19, 20, 21, 22, 23, 24, 25]. The dose evaluation volume (DEV) is defined as the PTV trimmed back at the lung-chestwall and skin-air interfaces (by 3 - 7 mm). We suggest that the DEV-to-PTV ratio is a better patient selection metric to predict which patient plans will experience more extensive dose degradation due to respiratory motion and patient anatomy. The DEV-to-PTV ratio gives information about both the breast volume and the location of the seroma.

We examine how respiratory motion dosimetrically changes the static external beam PBI IMRT treatment plans, as well as how to predict which patient plans are most affected by respiratory motion. We investigate two planning strategies to assess the planning target coverage necessary to adequately account for respiratory motion.

5.2 Methods

5.2.1 IMRT PBI plans

Thirty-six early stage breast cancer patients treated with the RAPID (3D conformal Radiation therapy for Accelerated Partial breast IrraDiation (RAPID) trial by the Ontario Clinical Oncology Group) trial protocol at our institution were used as our patient dataset. All patients had ipsilateral and contralateral breasts, ipsilateral and contralateral lungs, heart, thyroid, and target volumes contoured by treating physicians during the trial and met rigorous review standards. CT patient data was acquired under free-breathing conditions. We used these patient plans to create partial breast dynamic intensity modulated radiotherapy

(IMRT) plans that met the planning guidelines used in the RAPID trial (Table 5.1) [26]. Three to five beam angles were chosen based on the existing 3DCRT PBI plans for each patient to ensure the plans were deliverable. For some patients, an additional anterior oblique field was necessary to achieve target coverage. For the RAPID study, patients were selected to ensure that the DEV was always less than 35% of the total ipsilateral breast volume and that the seroma was visible on CT and available to be contoured. Minor deviations ($<3\%$) on organ at risk constraints were allowed to achieve total DEV coverage.

The University of Calgary’s Conjoint Faculties Research Ethics Board approved both the RAPID study and the specific use of this data in the current analysis.

Table 5.1: RAPID study dose constraint/criteria [26]

Contour	Volume	Dose
DEV	100%	95%
DEV	Max Dose to 2 cm ³	107%
Ipsilateral Lung	10%	$<30\%$
	20%	$<10\%$
Ipsilateral Breast	25% (up to 35%)	$<95\%$
	50% (up to 60%)	$<50\%$
Contralateral Breast	Max Dose	$<3\%$
Thyroid	Max Dose	$<3\%$
Heart:		
Right Breast	5%	5%
Left Breast	5%	10%

Figure 5.1a details the distribution of patient breast volume, binned by cup size as defined by Offerman *et al.* (2011) [27]. From the skew of this histogram it is clear that the majority of the patients had a cup size of D or larger. Figure 5.1b shows the distribution of DEV-to-PTV ratio which is approximately normally distributed with a mean (standard deviation) of 67% (15%). Figure 5.1c shows that breast volume and DEV-to-PTV ratio are correlated (Pearson correlation coefficient of 0.71) which indicates at larger breast volumes, the DEV-to-PTV ratio tends to be closer to 100%. We hypothesize that the ratio of DEV-to-PTV can be used in conjunction with breast size as an inclusive/exclusive criteria for selecting patients for partial breast IMRT.

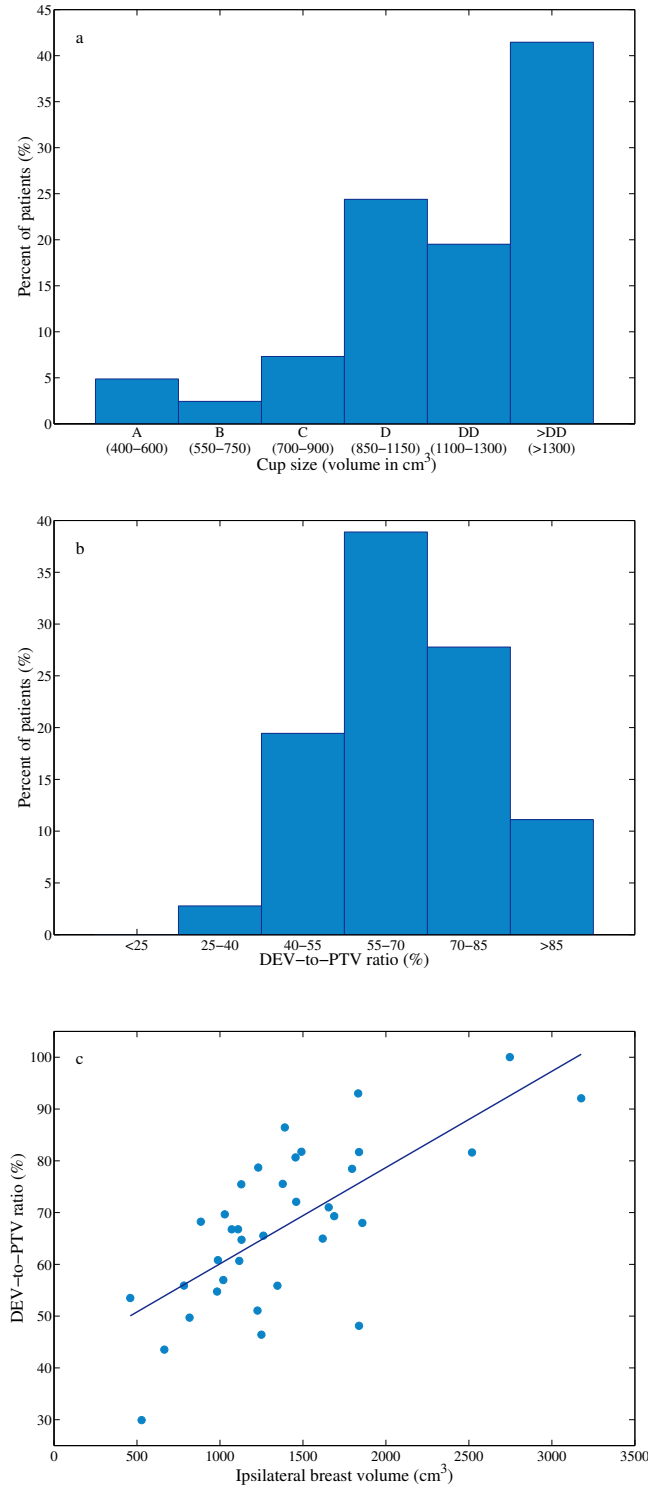


Figure 5.1: The breast size and volume metrics for our 36 patients. a) Ipsilateral breast volume binned by cup size as defined by Offerman *et al.* (2011) [27], b) DEV-to-PTV ratio histogram, and c) correlation plot of ipsilateral breast size and DEV-to-PTV ratio. The Pearson correlation coefficient is 0.71. When the ipsilateral breast volume increases the DEV-to-PTV ratio tends to increase.

We applied two planning strategies for this study: Planning Strategy A and Planning Strategy B (Figure 5.2). Both of these strategies meet the dose constraints listed in Table 5.1, but employed different optimization volumes to achieve them. Both planning strategies used the planning volume DEV plus 1 mm (DEVimrt) as an optimization structure/volume. In order to minimize dose to the uninvolved breast tissue, a planning structure IpsiBreast – PTV was created by using the Boolean subtraction operation with the ipsilateral breast volume and the PTV volume and constrained to receive not more than the prescription dose. Optimization constraints to organs at risk were added as necessary to meet dose volume criteria. Inverse planned optimization with Eclipse (Varian Medical Systems, Palo Alto, Ca) treatment planning software (8.9.08), calculated with Analytical Anisotropic Algorithm (AAA) using the heterogeneity correction was used to determine the fluence maps to achieve optimal target coverage while minimizing dose to organs at risk. Plans were reviewed under the guidance of a radiation oncologist and small deviations to organ at risk criteria ($< 3\%$) were allowed in order to achieve appropriate target coverage.

Planning Strategy A

- Optimize to DEV
- Only DEV coverage considered
- DEVimrt used as the optimization volume

Planning Strategy B

- Optimize to PTV (DEVimrt also employed as an additional optimization volume)
- PTVcbfs (PTV cut back from skin by 5 mm) used as the optimization volume
- PTVcbfs mitigates hotspots at nipple, while allowing more posterior coverage
- Flash (2 cm) added after optimization with Eclipse’s flash tool

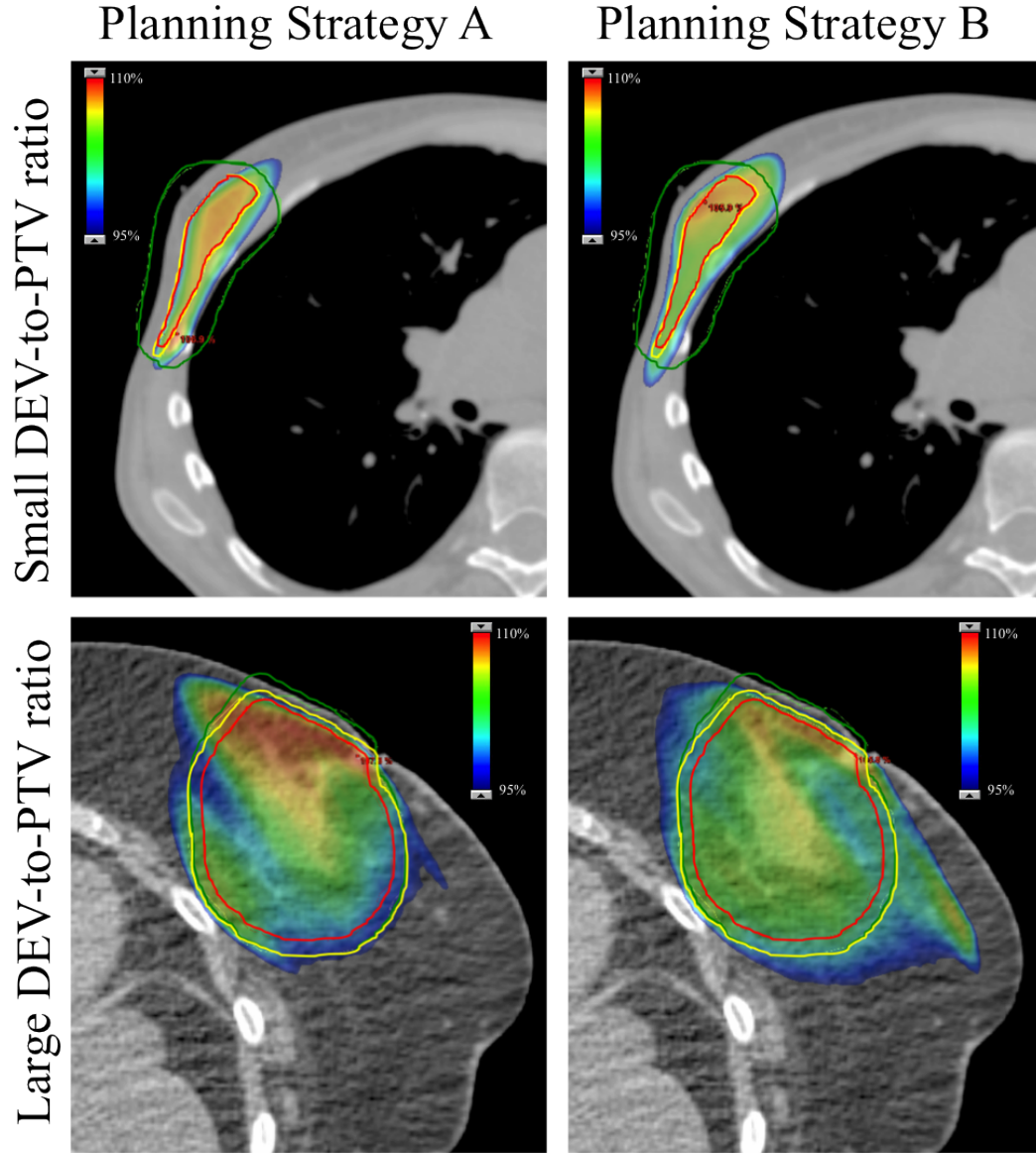


Figure 5.2: Top: Small DEV-to-PTV ratio plan with planning strategy A and B; DEV-to-PTV is 30%, IBV 530 cm³, and PTV-to-IBV is 20%. Bottom: Large DEV-to-PTV ratio plan with planning strategy A and B; DEV-to-PTV is 92%, IBV 3200 cm³, and PTV-to-IBV is 8%. The contours shown are the PTV (green), the DEV (yellow), and the CTVsu (red). For small DEV-to-PTV ratio plans using Planning Strategy B increases posterior coverage and flash increases anterior coverage. For large DEV-to-PTV there are less differences in coverage between the two planning strategies. Planning Strategy B typically provides more uniform coverage, but at the cost of covering a larger volume.

5.2.2 Fluence Convolution

External respiratory motion, analyzed in a previous study by Quirk *et al.* (2013) [28], of 21 healthy volunteers was employed to construct a population probability density function (PDF) of breast motion (Figure 5.3). The data was measured in the anterior-posterior (AP) direction and scaled by half for the superior-inferior (SI) direction.

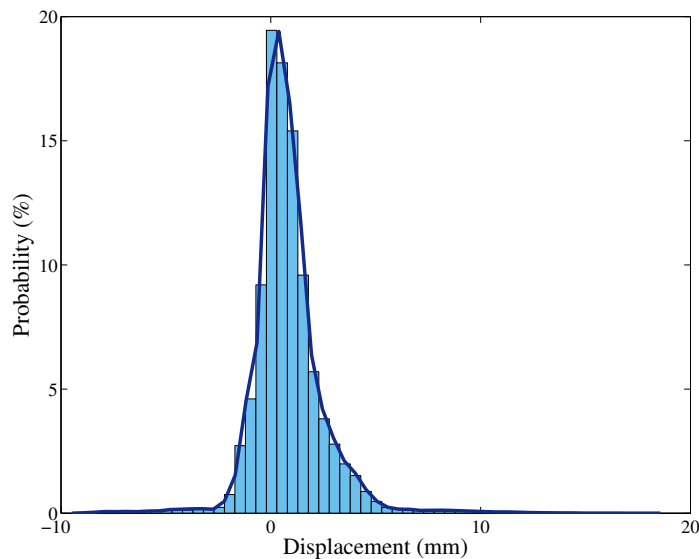


Figure 5.3: The population respiratory PDF is shown for the AP direction; a similar PDF was used for the SI direction with half the amplitude.

We used the fluence-convolution methodology described by Beckham *et al.* (2002) [29] to explicitly incorporate the motion introduced by respiration into the treatment planning process [29, 30]. The planned fluences were extracted from existing patient plans, and convolved with respiratory population PDFs (Figure 5.3) to simulate the delivered fluence under realistic respiratory conditions. We then used these delivered fluences to calculate delivered dose and assess the plan quality. All doses (static and delivered) were calculated using Varian Eclipse AAA (8.9.08). The resultant dose models rigid anatomy translations with respiration for realistic population respiratory data.

5.2.3 Evaluation

To evaluate only the respiratory component of planning, we created an evaluation structure, CTVsu, an expansion of the CTV by 5 mm for set up uncertainties [21]. The CTVsu volume accounts for setup errors only and allows us to test whether the 5 mm allowed for respiratory motion is adequate. Comparison of dose volume histogram (DVH) curves for DEV and CTVsu between respiratory and static conditions was the main factor used to evaluate plan quality. Five patient datasets were planned with Planning Strategy A and B and a further 31 patient datasets (plus the five planned with A) were planned with Planning Strategy B. The impact of the DEV-to-PTV ratio and breast size was evaluated by comparing static and respiratory DVH curves for the DEV. Those planned with Planning Strategy B were evaluated for the difference between static and respiratory target DVH curves with the mean dose shift of the entire DVH, the dose shift at 95% of the volume (D95) and the dose shift at the hotspot to 2 cm³ of the DEV volume. The DVH curves for organs at risk (OARs) were examined, specifically the dose-volume planning criteria listed in Table 5.1, but only minor deviations (<3 %) were found.

In order to identify which patient plans are most changed by incorporating respiratory motion, we evaluate the correlation of the mean DVH shift, shift at D95 and hotspot with three patient-anatomy based metrics: Ipsilateral breast volume (IBV), PTV-to-IBV ratio, and DEV-to-PTV ratio. The Pearson correlation coefficient was calculated for each comparison. Further analysis of the mean shift examines the statistical significance of the chosen stratification point between IBV and DEV-to-PTV ratio using the student t-test.

5.3 Results

5.3.1 Planning Strategies A versus B

DEV-to-PTV ratio $> 55\%$

Figure 5.4 shows the DVH curves for both planning strategies for the example patient in Figure 5.2 with the larger DEV-to-PTV ratio. Figure 5.4a shows the change due to respiratory motion in the DVH using Planning Strategy A and Figure 5.4b shows the change due to respiratory motion in the DVH using Planning Strategy B. For both planning strategies the difference between static and respiratory incorporated plans is minimal. These results were typical for larger DEV-to-PTV ratio anatomies.

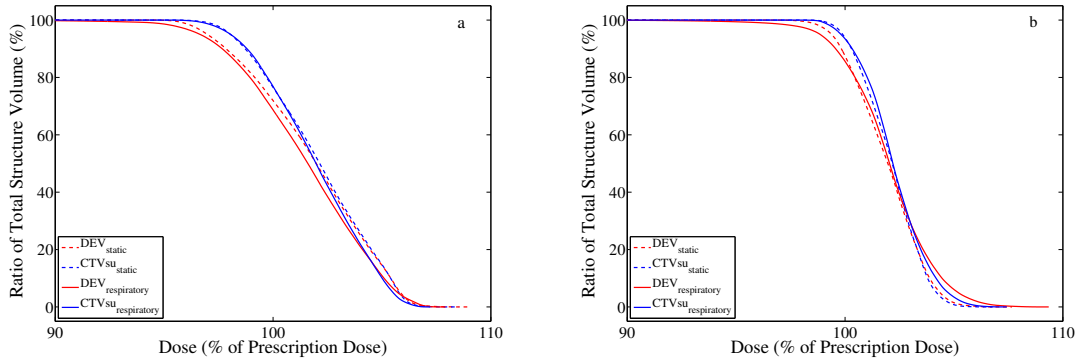


Figure 5.4: Typical large DEV-to-PTV ratio DVHs. a) Planning Strategy A, b) Planning Strategy B. The DVH curves from static plans are dashed and DVH curves with respiratory motion incorporated are solid.

DEV-to-PTV ratio $\lesssim 55\%$

The DVH curves for both planning strategies for the example patient in Figure 5.2 with the smaller DEV-to-PTV ratio are shown in Figure 5.5. The difference in DVH curves between planning methods for smaller DEV-to-PTV ratio plans can be quite significant. Planning strategy A (Figure 5.5a) experiences coverage degradation and the hotspot increases when respiratory motion is introduced. For planning strategy B (Figure 5.5b) the DVH curves experience a minimal reduction in coverage, but the entire curve is shifted hotter. These results were typical for smaller DEV-to-PTV ratio anatomies.

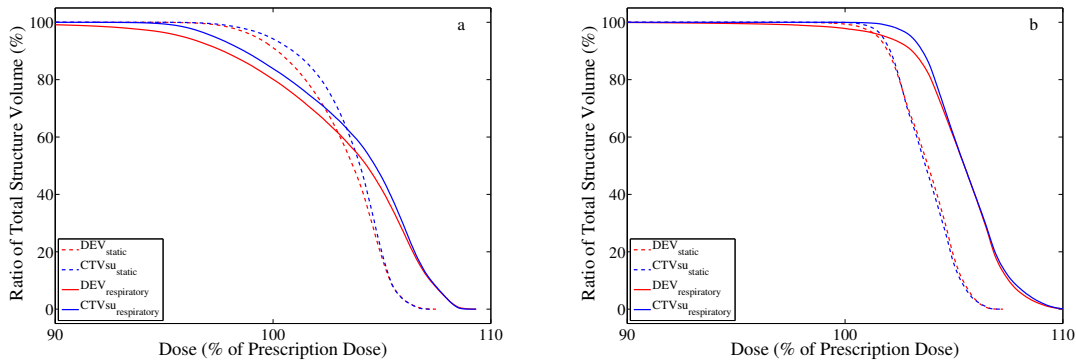


Figure 5.5: Typical small DEV-to-PTV ratio DVHs. a) Planning Strategy A, b) Planning Strategy B. The DVH curves from static plans are dashed and DVH curves with respiratory motion incorporated are solid.

There are typically two changes in DVH due to respiratory motion: degradation of the shoulder region (ie reduced dose homogeneity in the target) or the whole DVH shifts hotter. The above examples demonstrate that for some patients, often with larger DEV-to-PTV ratios, respiratory motion has little impact beyond blurring the shoulder of the DVH curve. For other patients, with smaller DEV-to-PTV ratios, the impact may be clinically significant. Based on this qualitative analysis we recommend using Planning Strategy B for all patients and aim to include better coverage of the original PTV structure than strictly necessary to meet the DEV criteria. Although the differences between planning strategy A and B are

minimal, by employing planning strategy B coverage of anterior or posterior targets close to inhomogeneities are better improved. For the remaining 31 patients, Planning Strategy B alone was used to identify the patients for whom respiratory motion may be more significant. Flash and the larger optimization volume were used to achieve target coverage.

Irregular Contours

Patients with severe contour changes may also exhibit dose degradation and inhomogeneity with respiratory motion. Figure 5.6 shows an example of a patient whose static plan has a 1 cm³ cold spot of 95.4% (within RAPID planning criteria) but when respiratory motion is incorporated there is a resulting large low dose area and a 1 cm³ cold spot of 93.4 %. This is an example of patient specific anatomy that should engender caution when considering PBI IMRT as a treatment option as dosimetry may be more impacted by respiratory motion than expected. For such patients, if PBI IMRT is deemed appropriate, greater initial minimum coverage or respiratory management may be necessary.

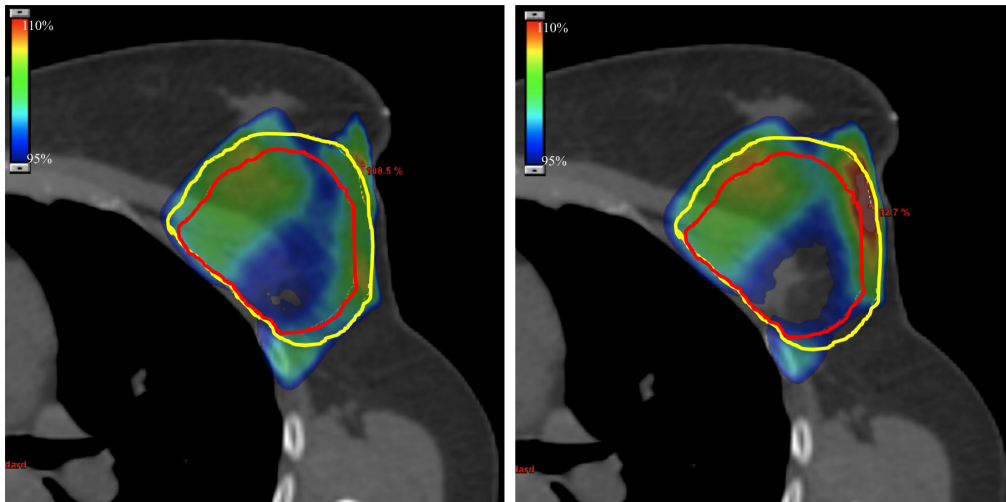


Figure 5.6: Severe contour change: In the static IMRT plan there is a point cold spot of 94.9% near the center of the CTVsu. When respiratory motion is incorporated the cold volume becomes significant with point doses measuring as low as 91.8% and 1 cm³ cold spot reduced from 95.4% to 93.4%. Lateral beams are severely impacted by contour change.

5.3.2 Identifying appropriate patients for PBI IMRT

The above analysis establishes that some patient anatomies alter plan quality more when respiratory motion is incorporated than others. In order to identify which patients are more affected, we aim to establish a patient-based metric that can easily be employed to stratify patients. Using Planning Strategy B for all 36 patients, we calculated our proposed metric DEV-to-PTV ratio, as well as ipsilateral breast volume (IBV) and PTV-to-IBV ratio.

The DEV-to-PTV ratio plotted against three dose evaluation metrics is shown in Figure 5.7. The DEV-to-PTV ratio had a stronger correlation to mean DVH shift, D95, and hotspot shift (-0.44, -0.34, -0.27) than either ipsilateral breast volume (-0.10, -0.02, -0.11) (not shown) or PTV-to-IBV ratio (-0.01, -0.05, 0.10) (not shown). The mean shift between the static and respiratory DVH curves decreased as the DEV-to-PTV ratio approaches 100% (DEV = PTV volume).

Figure 5.8 shows the mean shift plotted against DEV-to-PTV ratio, ipsilateral breast volume, and PTV-to-IBV ratio. The DEV-to-PTV ratio provides a stratifying location at approximately 55% (Figure 5.8a). This can be used as a guide to determine an allowable mean shift of 1%. Figure 5.8b and c show that a mean shift of 1% can be adequately well delineated by ipsilateral breast volume with a possible cutoff range of 900 - 1000 cm³. The PTV-to-IBV ratio provides no clear delineating point. Each cutoff excludes a few outliers that could be included, and include a few outliers that should be excluded.

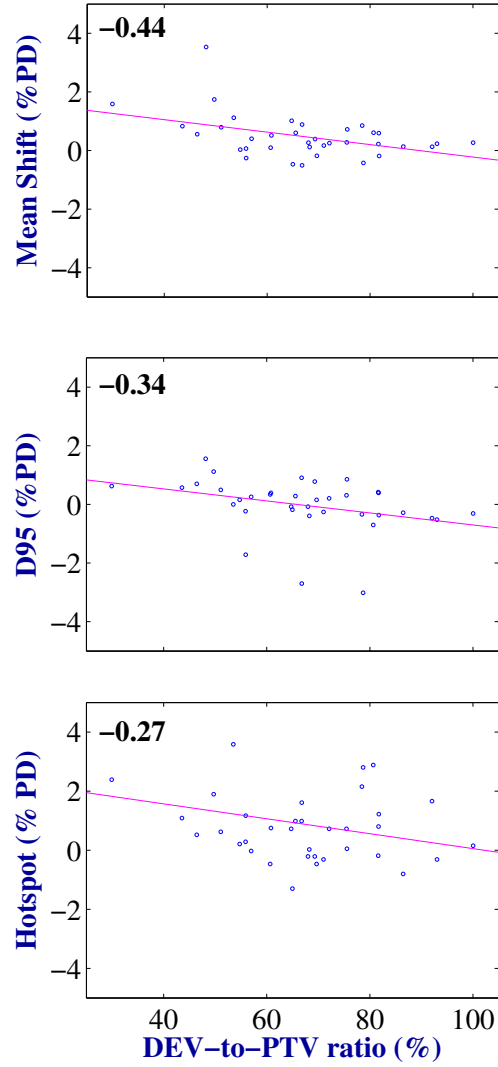


Figure 5.7: The three metrics evaluated to determine the difference between DVH curves under static and respiratory conditions. The plots show the the percent change (static minus respiratory) in prescription dose (PD) for hotspot, D95, and mean shift. The Pearson correlation coefficients are shown on each plot. The mean shift has the highest correlation, although none are very strong due to the scatter in the data.

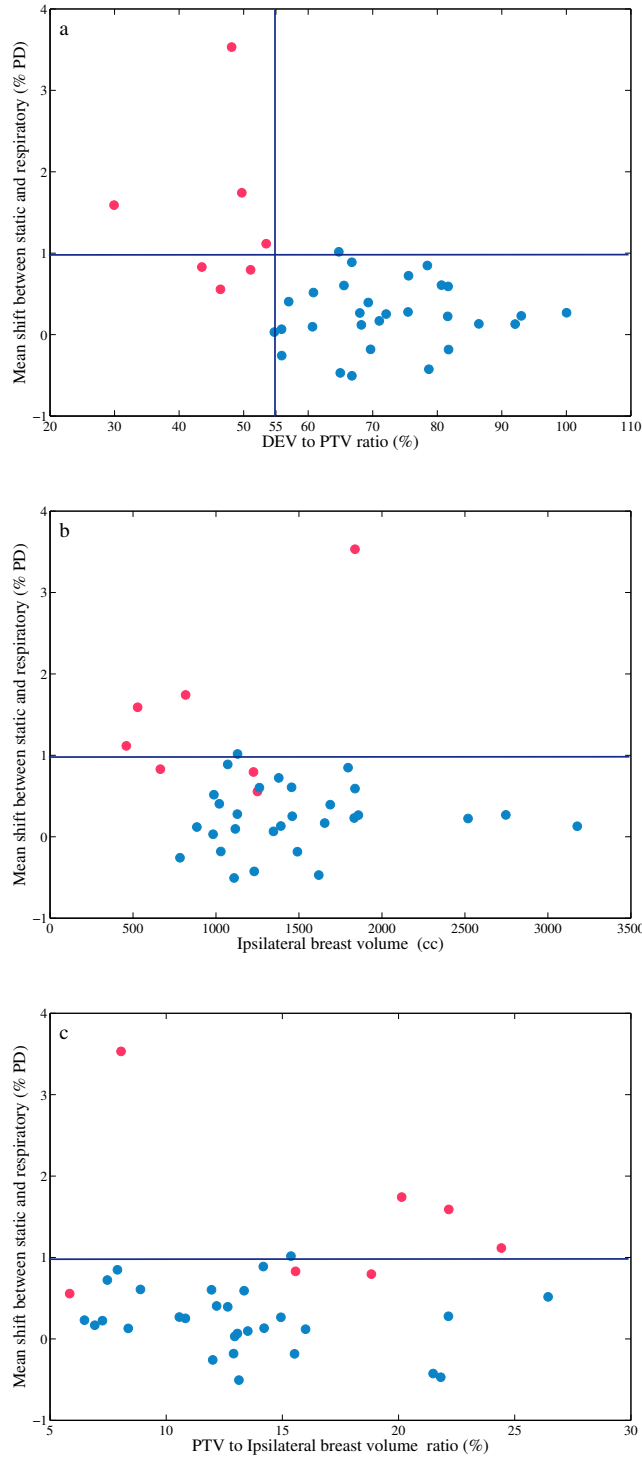


Figure 5.8: The mean shift between the DVH curves under static and respiratory conditions are plotted against a) DEV-to-PTV ratio, b) ipsilateral breast volume, c) PTV-to-IBV ratio. a) Indicates the proposed cutoff of 55% DEV-to-PTV ratio and the same points in red are plotted in b) and c). The DEV-to-PTV ratio and ipsilateral breast size could both provide delineating capabilities while PTV-to-IBVolume does not.

The candidate delineating metrics of DEV-to-PTV ratio and IBV are further tested in Figure 5.9 with two sets of boxplots and student t-tests. The patient data is separated between those with a mean shift greater than 1% and those less. A boxplot of ipsilateral breast volume and DEV-to-PTV ratio separated data shows that the difference is more strongly delineated with DEV-to-PTV ratio. When a two tail t-test is performed, the DEV-to-PTV ratio split is statically significant ($p = 0.002$) and ipsilateral breast volume is not statistically significant ($p = 0.07$).

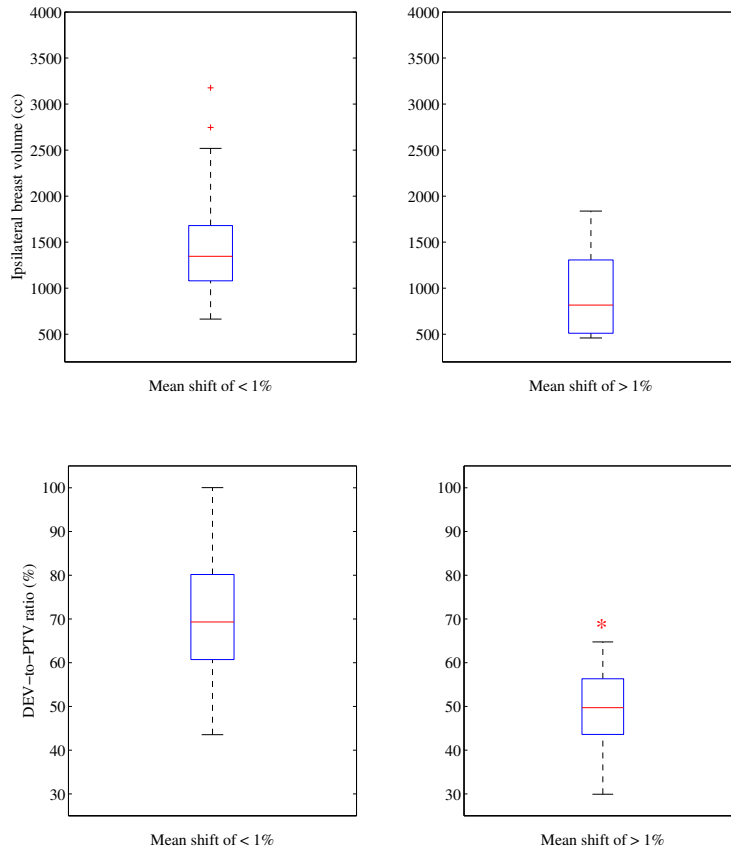


Figure 5.9: Two sets of boxplots of comparing the ipsilateral breast volume (top) and DEV-to-PTV ratio (bottom) of two subsets of patients when the mean DVH shift is split above and below 1%. The split by DEV-to-PTV is statistically significant (* on plot) between the two groups ($p = 0.002$). The crosses indicate the data outliers. The split by ipsilateral breast volume is not ($p = 0.07$).

5.4 Discussion

In this study we have assumed that the breast motion under respiration is rigid and undergoes little deformation [1]. The use of external surrogate data in this study is appropriate as the breast motion is well approximated by the external marker. The limitation of our population PDF is that it is based on relatively few healthy volunteers whose breathing was recorded under conditions much less stressful than receiving radiotherapy. We have ignored interplay effects that may occur between the moving of the MLC leaves during IMRT delivery and respiratory motion. Many studies, including those by George *et al.* (2003) [7] and Bortfeld *et al.* (2004) [31] have shown this is minimal compared to the blurring of the dose distribution that results from respiratory motion. Fluence-convolution methodology assumes a multi-fraction treatment delivery [29]. Studies evaluating convolution methods have shown that greater than ten fractions is an adequate number to employ this convolution methodology without directly compensating for biological or interplay effects [32, 33].

Yue *et al.* (2007) [4] investigated the dosimetric impact of respiratory motion for 3DCRT PBI in four patients. Their study incorporated respiratory motion based on the cumulative dose computed from all phases of the 4DCT images. Yue *et al.* (2007) [4] found that respiratory motion had the greatest effect on the minimum dose with changes to D_{min} between static CT and 4DCT ranging from -15.2% to 11.7% and with larger reductions in coverage observed for larger respiratory amplitudes (up to 23 mm). The small patient numbers limits the significance of this study since we see from our study that patient anatomy has a significant contribution on respiratory dosimetric impact.

Our results are not likely to be directly extended to 3DCRT PBI as dose distributions are not as conformal as those rendered with IMRT. Our results suggest planning with flash in 3DCRT when the target volume is anterior. The effect of respiratory motion on 3DCRT plans is likely to be similar to that observed in whole breast studies: small, but measurable [7, 34].

In other PBI studies, various volumes and ratios have been described as potential metrics for stratifying patients to choose those most likely to benefit from PBI with best cosmetic results and lowest toxicity. Table 5.2 lists volumes and ratios found in 13 different studies from the literature. This sampling of the literature demonstrates a variety of metrics are used to quantify patient volume characteristics, and that patient populations and contouring definitions are quite diverse. This is particularly evident in ipsilateral breast volume and seroma volume. For example, our seroma to ipsilateral breast ratio is an order of magnitude lower than Oliver *et al.* (2007) [13]. This could be due to patient selection for the RAPID trial which had the fairly strict criteria that DEV/IBV was always less than 35%, causing patients with smaller seromas and larger breast volumes to be accrued. Oliver *et al.* (2007) [13] state their mean DEV-to-IBV ratio as 50%; however, their IBV definition could result in a substantially smaller breast volume contoured than that in the RAPID patient dataset. They defined the ipsilateral breast as the volume that lies within the radio-opaque breast wire and as deep as the anterior chest wall muscles. In the RAPID patient dataset, the ipsilateral breast was defined similar to the RTOG Breast Atlas [35] with a more generous definition of breast tissue. The mean ipsilateral breast volume in our patient dataset was 1436.8 cm³, but Oliver *et al.* (2007) [13] had a patient dataset mean volume that was only 795 cm³. The ipsilateral breast volume and PTV-to-IBV ratio in Chen *et al.* (2010) [14] were more comparable to ours, having defined the breast volume with the palpable borders of breast tissue by the treating physician [14]. In order to properly compare volumes between studies, consistent definitions of contour volumes need to be used and it is better to use contour volumes that are more robust to inter-observer variation. Current inconsistencies in breast definition render breast volume and PTV-to-breast volume ratios subject to intra-observer and intra-study variability for quantifying patient suitability for partial breast radiotherapy.

The DEV-to-PTV ratio may be used to exclude those patients who will experience a degradation in plan quality with motion. Contouring guidelines have been developed espe-

cially to ensure consistency in contouring the seroma volume between studies [36, 37, 38]. With increased consistency in seroma volume delineation, the DEV-to-PTV ratio could represent a more consistent selection criteria. This ratio incorporates breast size, seroma size, and seroma position into a single number. The DEV-to-PTV ratio correlates to breast volume (0.71) and weakly to PTV-to-IBV (-0.36). Intuitively, most observers would agree that a partial breast evaluation volume which is severely trimmed back from the skin, chest wall or both, is suboptimal for plan quality. We recommend either not using PBI when the DEV-to-PTV ratio is less than 55%, or using motion management techniques for this group of patients to avoid plans that become overall hotter with respiratory motion. We further recommend planning to the PTV, including flash and posterior coverage where appropriate, particularly when the DEV is severely cut back from the PTV.

Although the dose prescription is to the dose evaluation volume, we have shown that, especially for patients with smaller DEV-to-PTV ratios, it is advantageous to plan with extended posterior coverage and flash. The ASTRO guidelines recommend that $\geq 90\%$ of the prescription dose cover $\geq 90\%$ of the DEV [39] with a maximum dose of $\leq 120\%$. We observed that coverage can be degraded and that the ASTRO planning target coverage guideline may be insufficient, specifically if coverage is only to the DEV. Although Planning Strategy B, with increased coverage and decreased degradation of plan quality with respiratory motion, did have the trend of causing plans with DEV-to-PTV ratio less than 50 - 60% to have the potential of becoming overall hotter by 1 - 2%. This is likely due to the target volume being enclosed closely between two low density inhomogeneities (air anteriorly and lung posteriorly). We recommend either excluding these patients from PBI IMRT or employing respiratory management techniques.

Table 5.2: Average (range) volumes of ipsilateral breast (IB), seroma, CTV, PTV, DEV (dose evaluation volume), and respective ratios.

Volumes (cm ³)						
Study	IB	Seroma	CTV	PTV	DEV	Ratios (%)
Current series 36 patients, IMRT	1297.5 (460-3177)	11.2 (1-38)		176.6 (73-353)	119.6 (34-290)	S/IB, PTV/IB, DEV/IB 0.9, 15.0, 9.4 (0.1-4), (6-30), (3-17)
Oliver <i>et al.</i> [13] 15 patients, IMRT	795.1 (256-1767)	69.2 (11-135)				S/IB, CTV/IB, DEV/IB 9.9, 32.7, 56.5 (3-26), (13-63), (28-99)
Livi <i>et al.</i> (2010) [17] 259 patients, IMRT				44 (20-110)	123 (55-277)	PTV/IB 21 (10-38)
Lewin <i>et al.</i> (2012) [18] 36 patients, IMRT		20.9 (2-87)	71.4 (19-231)			
Jagsi <i>et al.</i> (2010) [19] 34 patients		40.3 (10-102)		185.8 (60-382)		
Rusthoven <i>et al.</i> (2008) [20] 63 patients, IMRT		20.6	86.6	187.5		PTV/IB 24 (7-58) (7-58)
Moon <i>et al.</i> (2009) [15] 30 patients, 3DCRT, IMRT, Tomo, proton	588.5 (214-1712)			83.8 (39-238)		PTV/IB 17.9 (9-30)
Baglan <i>et al.</i> (2003) [21] 16 patients, 3DCRT		12* (5 - 65)				CTV/IB, PTV/IB (6-13), (12-23)
Leonard <i>et al.</i> (2007) [22] 55 patients, IMRT						PTV/IB 22 (2-58)
Formenti <i>et al.</i> (2004) [23] 47 patients, 3DCRT (prone)	1102 (258-3468)	52 (7-379)		228 (57-1118)		CTV/IB, PTV/IB, CTV/PTV 5, 22, 20 (1-22), (10-44), (6-46)
Vicini <i>et al.</i> (2003) [24] 31 patients, 3DCRT		22 22 (3-70)	118 (28-231)	250 (82-482)		PTV/IB 17 (11-22)
Kozak <i>et al.</i> (2006) [25] 16 patients, 3DCRT	990 (190-2700)	50 (6-238)		200 (54-567)		

5.5 Conclusions

Some patient PBI IMRT plans can be significantly impacted by respiratory motion and the extent of coverage used in planning can influence the magnitude of this effect. We recommend always planning to the PTV and using flash to ensure adequate coverage of the DEV under respiratory conditions. We have proposed using the DEV-to-PTV ratio as a robust method for patient selection because it is less changed by inconsistencies in defining breast volumes and implicitly includes information about breast size and seroma location. For patients with a DEV-to-PTV ratio less than 55% we recommend either not using PBI IMRT or employing motion management. In most situations, if the breast size is smaller than approximately 900 - 1000 cm³ it is unlikely that the DEV-to-PTV ratio will meet this criteria.

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General Conclusions

We propose a metric, DEV-to-PTV ratio, that should be robust to contouring differences observed across studies. We recommend that in the treatment planning stage of partial breast irradiation, plans can be made more robust to respiratory motion by planning with extended posterior coverage and adding flash for anterior targets. Based on population respiratory motion, for patients with DEV-to-PTV greater than fifty-five percent, the impact on treatment planning was minimal. In the next chapter we further investigate the impact of respiratory motion by increasing the respiratory amplitude to determine at what amplitude respiratory management is advisable for this set of patients (DEV-to-PTV ratio greater than 55%).

Chapter 6

Partial Breast Irradiation and Respiratory Motion: An Amplitude Escalation Study

General Introduction

For the patients deemed in the previous study to have anatomical characteristics that led to treatment plans that were robust to population-based respiratory motion, we determine at what amplitude these patients would require respiratory management. A range of respiratory amplitudes (2 - 20 mm) were used for a trace generated with minimal variation using the respiratory trace generator described in Chapter 4. This manuscript is prepared for submission. I am the first author of this paper, and contributing authors were Leigh Conroy and Wendy Smith. Dr. Wendy Smith supervised this project and contributed expertise and scientific guidance. Leigh Conroy helped develop the patient plans and assisted with through-putting the large volume of data. I prepared the manuscript and Wendy and Leigh assisted with revisions and improvements.

When is respiratory management necessary for partial breast intensity modulated radiotherapy ?

Sarah Quirk, Leigh Conroy, and Wendy Smith

Abstract

Purpose: The impact of typical amplitude of respiratory motion is often minimal for partial breast irradiation, but there is a point at which the amplitude will be large enough to degrade plan quality. We determine at what amplitude respiratory management may be required.

Methods & Materials: Ten patients were planned with inverse optimized, dynamic partial breast intensity modulated radiotherapy. Respiratory traces with peak-to-peak amplitudes of 2-20 mm were used to create probability density functions that were convolved with the static plan fluences to generate delivered planned fluences and the prescribed dose was recalculated to determine the delivered dose. The CTVsu (CTV plus 5 mm for set up) was used as the evaluation volume in order to isolate the effects of respiratory motion. Evaluation metrics included target coverage (100% of the target volume receiving 95% of the dose), ipsilateral breast hotspot (dose to 1 and 2 cm³) and CTVsu cold spot (1 cm³) to CTVsu, minor and major deviations to dose constraints for organs at risk; homogeneity and uniformity indices; equivalent uniform dose; and mean dose shift of the CTVsu DVH.

Results: Hotspot to the ipsilateral breast was the key criteria in delineating an amplitude cut-off. Even at 2 and 5 mm motion amplitude, 2/10 plans had hotspots larger than 107% and at 10 mm 5/10 the plans had a hotspot greater than 107%. At 15 mm amplitude, 5/10 plans failed to meet minimum target coverage, and at 20 mm no plans met minimum coverage. Coverage was not an issue at less than 10 mm; the limiting factor was dose homogeneity.

Conclusions: We recommend that if respiratory amplitude is greater than 10 mm, respiratory management or alternative radiotherapy should be considered due a significant increase in the hotspot in the ipsilateral breast and a decrease in dose homogeneity.

6.1 Introduction

Partial breast irradiation (PBI) is actively being investigated in controlled randomized, multi-institutional trials as an effective way to minimize the dose to normal breast tissue, decrease toxicity, and improve cosmetic outcome in early stage, low risk breast cancer patients. In external beam partial breast intensity modulated radiotherapy (PBI IMRT), respiratory motion can impact both coverage and dose homogeneity. Respiratory motion may be a greater detriment to accurate and effective partial breast radiotherapy than for whole breast irradiation.

Some PBI IMRT studies employ respiratory management techniques such as respiratory gating [1, 2], deep inspiration breath hold with or without active breathing control [3], and prone delivery [4] to minimize the impact of respiratory motion. Other studies, including the Italian phase III trial by Livi *et al.* (2010) [5], implement PBI IMRT relying on adequate margins to account for respiratory motion [5, 6].

Previous work [7] demonstrated that patient PBI IMRT plans with a DEV-to-PTV ratio of greater than 55% are minimally impacted by respiratory motion in a population based study. Even in this set of patients, there will be a respiratory amplitude that will affect plan quality. It is necessary to identify at what amplitude respiratory motion will significantly impact dose homogeneity and target coverage. In the current study we investigate five peak-to-peak amplitudes: 2, 5, 10, 15, and 20 mm. By escalating the amplitude of respiratory motion we can determine at what point it would be advisable to use respiratory management for delivery of partial breast IMRT or avoid the use of PBI IMRT in this set of patients.

6.2 Methods

Datasets from ten patients enrolled in the RAPID (Randomized Trial of Accelerated Partial Breast Irradiation) trial were used to create PBI IMRT plans for this study. For the existing patient dataset, all relevant volumes were contoured by the primary radiation oncologist,

including: seroma, ipsilateral breast and lung, contralateral breast and lung, heart, and thyroid. The seroma was expanded by 10 mm to create the CTV (clinical target volume), then another 10 mm were added to expand to the PTV (planning target volume). The 10 mm margin accounts for set up uncertainties (5 mm) and respiratory motion (5 mm). The Dose Evaluation Volume (DEV) is the volume used for plan quality evaluation and comprises of the PTV cut back by 5 mm from the skin and lung-chestwall interface. We chose ten patient datasets with a DEV-to-PTV ratio greater than 55% (range: 57 - 100%) selected consecutively from the existing database.

These patient plans were used to create partial breast intensity modulated radiotherapy (IMRT) plans that met the planning guidelines used in the RAPID trial (Table 6.1) [8]. The target coverage criteria for these plans is 100% of the DEV covered by 95% of the prescription dose. Three to five non co-planar beam angles were chosen based on the previously planned 3DCRT PBI plans for each patient in order to ensure that all plans were deliverable. An additional anterior oblique field was added for some patients to achieve optimal target coverage. For the IMRT optimization we created three planning volumes to achieve adequate coverage and minimize the dose to normal breast tissue: the PTV cut back from skin by 5 mm (PTVcbfs), the DEV expanded by 1 mm (DEVimrt), and the ipsilateral breast volume minus the PTV to minimize dose to normal breast tissue (PTV-ipsibreast). Beam weighting for optimal target coverage and minimal dose to organs at risk was achieved using inverse planning optimization with Eclipse (Varian Medical Systems, Palo Alto, Ca) treatment planning software (8.9.08) using the AAA algorithm with heterogeneity correction. Small deviations to organs at risk criteria ($< 3\%$) were allowed in order to achieve target coverage. After optimization, 2 cm of flash was added to plans with anterior target volumes. Target coverage criteria were strictly met and plans were reviewed under the guidance of a radiation oncologist.

The University of Calgary's Conjoint Faculties Research Ethics Board approved these

studies.

Table 6.1: RAPID study dose constraints [8]

Contour	Volume	Dose
DEV	100%	95%
DEV	Max Dose to 2 cm ³	107%
Ipsilateral Lung	10%	<30%
	20%	<10%
Ipsilateral Breast	25% (up to 35%)	<95%
	50% (up to 60%)	<50%
Contralateral Breast	Max Dose	<3%
Thyroid	Max Dose	<3%
Heart:		
Right Breast	5%	5%
Left Breast	5%	10%

6.2.1 Fluence Convolution

The respiratory trace generator (RTG) described by Quirk *et al.* (2012) [9] was used to generate a respiratory trace with realistic shape. The peak-to-peak amplitude was scaled to 2 mm, 5 mm, 10 mm, 15 mm, and 20 mm. We used traces with minimal variation to ensure that analysis was not confounded by other respiratory characteristics. Figure 6.1 shows the traces used and probability density functions (PDFs) for all five respiratory amplitudes. The trace was measured in the anterior-posterior (AP) direction and scaled by half for the superior-inferior (SI) direction.

We used the fluence-convolution methodology described by Beckham *et al.* (2002) [10] and Chetty *et al.* (2003) [11] to explicitly incorporate respiratory motion in treatment planning. The planned fluences were extracted from existing patient plans, and convolved with respiratory population probability density functions (Figure 6.1b) to simulate the delivered fluence under realistic conditions. We then imported these delivered fluences into the treatment planning system (Eclipse) and re-calculated a delivered dose incorporating respiratory

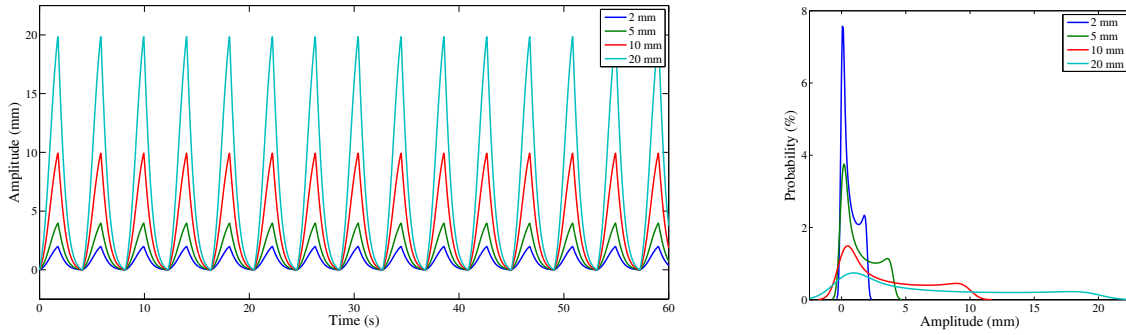


Figure 6.1: a) Respiratory traces and b) PDFs for four different peak-to-peak amplitudes: 2, 5, 10, and 20 mm (15 not shown).

motion to assess the plan quality. The resulting dose models rigid anatomy translations due to the simulate respiratory motion.

6.2.2 Evaluation

For this study, minor deviations in doses to organs at risk are defined as $<3\%$ and major deviations as $>3\%$. Failure to meet dose homogeneity or target coverage criteria is considered a major deviation. We evaluated major and minor deviations at all respiratory amplitudes. The structure CTVsu is defined as the CTV plus 5 mm margin for setup uncertainties but does not include the 5 mm added for respiratory motion. By not including the 5 mm in our evaluation we are dosimetrically testing the robustness of the respiratory margin. If it is adequate there should be no degradation in coverage when respiratory motion is introduced.

Target coverage and dose homogeneity were evaluated by examining the hotspot, cold spot, and target coverage of the CTVsu. The cold spot was defined as the minimum dose to 1 cm^3 of the CTVsu volume; as was deemed clinically relevant by the consulting radiation oncologist. The hotspot to the ipsilateral breast was evaluated at both 1 and 2 cm^3 volumes. The 2 cm^3 is used for treatment planning and 1 cm^3 as a comparable volume to the cold spot. Target coverage was defined as the percentage of the CTVsu volume receiving 95% of the dose (V95%).

In addition to target coverage and dose constraints to organs at risk, we also use four metrics to assess plan quality (Table 6.2): homogeneity index (HI) [12], uniformity index (UI) [13, 14], equivalent uniform dose (EUD) [15, 16, 17], and the mean shift (DVH_{shift}) between the static CTVsu DVH curve and each respiratory motion incorporated CTVsu DVH curve. The HI uses the difference between the maximum (dose to 2% of the volume) and minimum doses (dose to 98% of the volume) normalized to the prescription dose to evaluate the homogeneity of the target. A larger HI indicates a less homogeneous dose distribution in the target volume [12]. The uniformity index compares the dose to 95% of the target volume (D_{95}) to the maximum dose (to a volume of 4 cm³) with a higher UI indicating a more uniform dose distribution [13, 14]. EUD is the uniform dose that would lead to the same probability of a radiobiological effect as the original inhomogeneous dose distribution [17]. For this analysis a biological parameter of $a = -7.2$ has been used for the calculation of EUD.

We use a library of 28 RAPID patient plans on static breast images to calculate and means and standard deviations and to set a baseline of comparison for UI, HI, and EUD. We define a major deviation for the plan quality metrics as the mean index value plus/minus two standard deviations. The mean (standard deviation) for HI was 7.0 (1.4), UI was 0.94 (0.01), and EUD was 39.0 (0.6). A larger HI indicates a less homogeneous dose distribution, so the baseline for HI is the static mean plus two standard deviations; a smaller UI indicates a less uniform dose distribution, so the baseline for UI is the static mean minus two standard deviations. We defined a major deviation of the DVH_{shift} as $\pm 1\%$ based on previous analysis [7]. Both EUD and DVH_{shift} were evaluated in the positive and negative directions from the mean for changes.

Table 6.2: Quality metrics used to evaluate static and respiratory plans

Metric	Description
Dose constraints to target	
$V95_{CTVsu}$	% of target volume (CTVsu) receiving 95% of PD dose
D_{max2IB}	Max dose (1 & 2 cm ³) Ipsi breast
$D_{max2CTVsu}$	Max dose (1 & 2 cm ³) target (CTVsu)
D_{max2IB}	Max dose (2 cm ³) Ipsi breast
$D_{max2DEV}$ & $D_{max2CTVsu}$	Max dose (2 cm ³) target (DEV & CTVsu)
$CS_{CTVsu}(1 \text{ \& } 2 \text{ cm}^3)$	Min dose (1 & 2 cm ³) target (DEV & CTVsu)
Organs at risk - Contralateral breast, ipsilateral and contralateral lung, heart, thyroid	
Minor deviation	between 0-3%
Major deviation	> 3%
Plan quality	
Homogeneity index (HI) [12]	$(D_2 - D_{98})/D_{PD} \times 100$
Uniformity index (UI) [13, 14]	D_{95}/D_4
EUD	$EUD = (\frac{1}{N} \sum_{i=1}^N D_i^a)^{\frac{1}{a}}$ N is the number of voxels in the structure a is the normal tissue or tumour specific parameter, -7.2 for breast [18] D_i is the dose to the i th voxel
DVH_{shift} of CTVsu	Mean dose shift between the static and respiratory DVHs
CS is cold spot, EUD is equivalent uniform dose, PD is prescription dose	

6.3 Results

Table 6.3 details the mean ($\pm$ standard deviation) of the evaluation criteria with each amplitude (2 - 20 mm). At 2 and 5 mm there were few major deviations to target coverage and homogeneity. There were no major deviations in CTVsu coverage until the amplitude was increased to 20 mm at which point 4/10 plans failed to meet the coverage criteria. The hotspot (1 cm³) in the ipsilateral breast (Figure 6.2a) increases above 107% of the prescribed dose for 2/10 plans at 2 and 5 mm. At 10 mm and greater, half of the plans (5/10) had a hotspot of 1 cm³ greater than 107%. The 2 cm³ hotspot to the ipsilateral breast had no major deviations at 2 mm and for greater than 2 mm was the same as the 1 cm³ hotspot. A similar trend was observed for the hotspot to the CTVsu (data not shown), with only 1 major deviation at 5 mm and 2 at 10 mm, and 5/10 plans with major deviations for both 15 and 20 mm. The cold spot (1 cm³) in the CTVsu (Figure 6.2b) decreased below the required 95% coverage at 15 mm for 5/10 plans, and at 20 mm no patients/plans met this target coverage requirement.

We also evaluated equivalent uniform dose, homogeneity and uniformity indices, and mean dose shift. Both the homogeneity (Figure 6.3a) and uniformity indices (Figure 6.3b) were degraded at higher respiratory amplitudes. The larger the HI, the less homogeneous the dose distribution and the lower the UI, the less uniform the dose distribution. A major deviation for each was defined as two standard deviations from the mean value from 36 static patient plans. For the HI, there was 1/10 plan with a major deviation at 5 mm, 3/10 at 10 and 15 mm and 8/10 plans at 20 mm. For the UI, there was 1/10 plan with a major deviation at 10 mm, 2/10 at 15 mm, and 7/10 plans at 20 mm. The shifts between the static and respiratory CTVsu DVH curve at each increasing amplitude were calculated and the mean difference calculated (Figure 6.3c). The only major deviations in DVH_{shift} were are observed at 20 mm for 3/10 patients/plans. The EUD (data not shown) did not change significantly with respiratory motion.

Overall, the organs at risk were not significantly affected by the inclusion of respiratory motion in the treatment plan. Small variations were observed in the ipsilateral lung and contralateral breast. At the planning stage it was often necessary to accept a 3% deviation in the second ipsilateral lung dose constraint (20% volume receiving $< 10\%$ of dose) in order to meet target coverage constraints. Three of the ten plans had minor deviations under static conditions, this increased to four minor deviations at 2 - 20 mm and at 20 mm there was an additional major deviation ($> 3\%$). The contralateral breast had a minor deviation for one plan under static conditions and 1 - 2 minor deviations for 2 - 10 mm. At 15 and 20 mm the minor deviation increased to a major deviation. There were no major or minor deviations for thyroid, contralateral lung, and right sided heart. For left-sided heart, 1/2 patients had major deviations at 15 and 20 mm. This data are only included for comparison, because 2 left-sided patients is too small a sample size for any significance and the heart does not necessarily moved rigidly with the chest wall.

The target coverage, ipsilateral breast hotspot, and CTVsu cold spot are the most im-

portant criteria in determining the appropriate cutoff for maximum allowable respiratory amplitude. Table 6.3 shows clearly that the limiting factor is the hotspot to the ipsilateral breast, as both the cold spot and coverage are affected at amplitude of 15 mm or greater. Two of ten patients experience hotspots greater than 107% at 2 and 5 mm, but this dramatically increases to 5/10 patients at 10 mm. The homogeneity and uniformity indices also show the trend of only one major deviation at 5 mm, while 3 and 1 major deviations, respectively, at 10 mm. Doses to organs at risk add little decision making evidence with only one major deviation at 15 and 20 mm for contralateral breast and at 20 mm for ipsilateral lung. Based on this analysis we recommend employing respiratory management or not using PBI IMRT for patients with respiratory amplitude greater or equal to 10 mm. Particular caution may be warranted in treatment planning for the allowable hotspot in PBI IMRT as it often increases with respiratory motion.

Table 6.3: Mean and standard deviation for plan quality metrics; major deviations in blue, minor deviations in green; the number of deviations increases with opacity.

	Static	2 mm	5 mm	10 mm	15 mm	20 mm
Target Coverage – CTVsu						
V95 _{CTVsu}	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	99.9 ± 0.1	98.6 ± 1.8	94.7 ± 3.4 4 major
HS _{IB} (1 cm ³)	105.7 ± 0.8	106.1 ± 1.0 2 major	106.2 ± 1.5 2 major	106.8 ± 1.9 5 major	107.1 ± 2.0 5 major	107.0 ± 1.9 5 major
HS _{IB} (2 cm ³)	105.3 ± 0.7	105.7 ± 0.9	105.8 ± 1.3 2 major	106.2 ± 1.7 2 major	106.5 ± 1.8 5 major	106.5 ± 1.8 5 major
CS _{CTVsu} (1 cm ³)	97.7 ± 1.4	97.6 ± 1.2	97.7 ± 1.3	97.4 ± 1.7	95.7 ± 2.4 5 major	90.7 ± 3.4 10 major
Plan quality indices – CTVsu						
HI _{CTVsu}	6.9 ± 1.4	7.4 ± 1.6	7.4 ± 1.9 1 major	8.0 ± 2.6 3 major	9.5 ± 3.0 3 major	13.7 ± 3.4 8 major
UI _{CTVsu}	0.94 ± 0.01	0.94 ± 0.01	0.94 ± 0.01	0.94 ± 0.02 1 major	0.93 ± 0.02 2 major	0.91 ± 0.02 7 major
Shift _{CTVsu}		0.3 ± 0.1	0.4 ± 0.2	0.5 ± 0.2	0.7 ± 0.1	0.8 ± 0.2 3 major
Organs at risk - Dose Limits						
Ipsi lung 1	11.6 ± 9.8	12.1 ± 10.1 1 minor	12.0 ± 9.9	12.2 ± 10.0	12.5 ± 10.3	13.0 ± 10.6 1 minor
Ipsi lung 2		6.0 ± 4.7 3 minor	6.2 ± 4.8 4 minor	6.1 ± 4.8 4 minor	6.1 ± 4.8 4 minor	6.2 ± 4.8 4 minor
Contra breast	2.1 ± 0.6 1 minor	2.1 ± 0.6 1 minor	2.2 ± 0.8 2 minor	2.4 ± 1.2 1 minor	2.6 ± 1.6 1 major	2.8 ± 1.9 1 major

V95 is the volume receiving 95% of the prescribed dose

HS_{IB} is the hotspot to the ipsilateral breast volume

CS_{CTVsu} is the coldspot to the CTVsu

HI_{CTVsu} is the homogeneity index of the CTVsu

UI_{CTVsu} is the uniformity index of the CTVsu

Shift_{CTVsu} is the mean shift of the CTVsu DVH curve

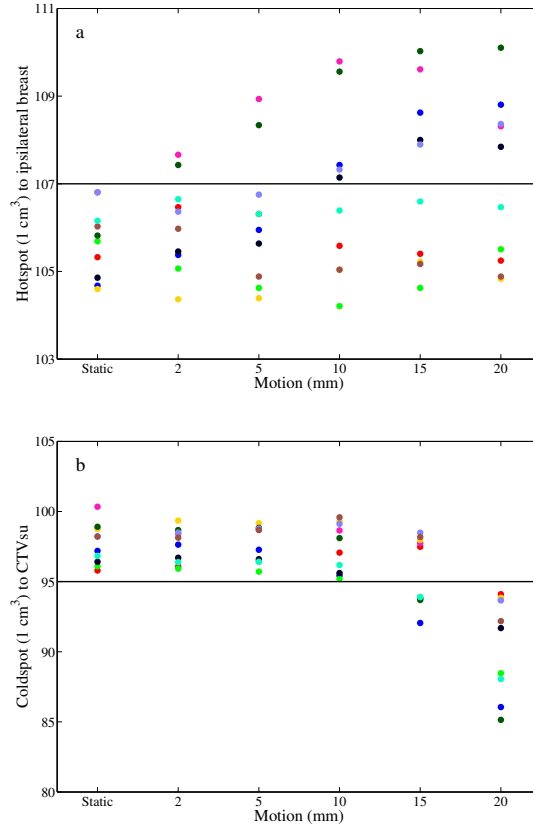


Figure 6.2: a) Hotspot (1 cm³) to ipsilateral breast where the solid black line is 107% of the prescribed dose and any points above that line do not meet the dose homogeneity criteria. There were two deviations at 2 and 5 mm and five deviations at 10 - 20 mm. b) Cold spot (1 cm³) to the CTVsu where the solid black line is 95% of the prescribed dose as the minimum required dose to the entire volume. Any points below 95% fail to meet target coverage criteria. The different coloured points are different patients. There were no deviations in coverage until 15 mm and no plan met coverage criteria at 20 mm.

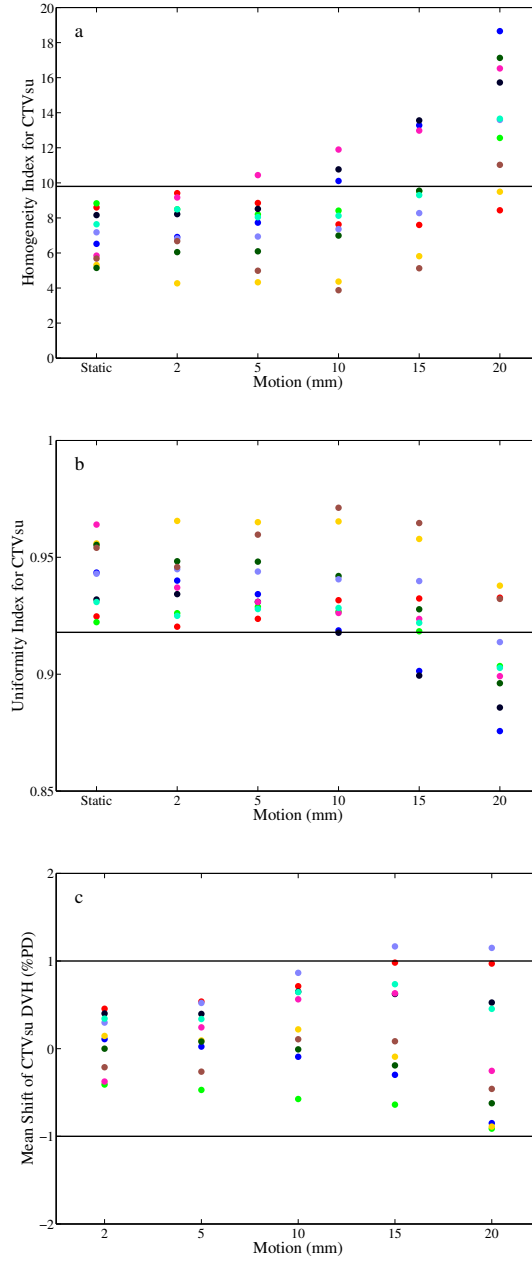


Figure 6.3: a) The homogeneity index of CTVsu with the horizontal black line the threshold above which is a major deviation. b) The uniformity index for CTVsu with the black horizontal line below which is a major deviation. c) mean dose shift for the CTVsu DVH curve. The black horizontal lines indicate $\pm 1\%$ in prescription dose as the constraint of an acceptable deviation. The different coloured points are different patients.

6.4 Discussion

In partial breast irradiation literature, the mean peak-to-peak amplitude of respiratory motion ranges over an order of magnitude. Kim *et al.* (2012) [19] reported from 19 external beam partial breast irradiation studies mean respiratory motions ranging from 0.8 mm to 8.5 mm [19, 20, 21] and the maximum motion for a single patient up to 11 mm. Whole breast studies have employed motions up to 2.5 cm to investigate the impact of respiratory motion on treatment planning and delivery [22]. Of the 19 studies investigated by Kim *et al.* (2012) [19], five studies reported motion less than 2 mm, ten studies reported motion between 2 and 4 mm and four studies reported motion greater than 5 mm. In a previous study of healthy volunteers by Quirk *et al.* (2013) [23], more than 95% of volunteers had a mean peak-to-peak amplitude of less than 5 mm, with only one volunteer having an amplitude greater than 10 mm. Choosing a respiratory motion cutoff of 10 mm above which it is necessary to employ respiratory management or not use PBI IMRT should only impact a small portion of the patient population ($< 5\%$).

We have used the motion of the chestwall to be representative of the motion of the breast and surrounding organs, and to model rigid anatomy translations. This is an appropriate assumption for the breast, as it can be assumed to translate rigidly and deform little during respiration [24]. It is also likely sufficient as a first order approximation for ipsilateral lung dose, as the lung moves with the chestwall; however, the lung does deform with respiration and change volume. The heart is not attached to the chestwall and does not move rigidly with breast motion. The doses for heart are shown only as a comparison, and not a decision making value. We have also assumed the interplay effects that occur between the MLC leaf motion during IMRT delivery and respiratory motion are minimal compared to the blurring of the dose distribution from respiratory motion and are likely to average out over a typical course of treatment [22, 25].

There are a number of trials investigating PBI IMRT for equivalent disease control and

potentially improved cosmesis compared to standard whole breast treatment in early stage breast cancer. A wide range of respiratory management approaches are used. The Italian phase III trial implements PBI IMRT relying on adequate margins to account for respiratory motion without any additional respiratory management strategies [5]. In contrast, Lewin *et al.* (2012) [1] employ respiratory gating for the delivery of PBI IMRT in their study. Both studies report favourable cosmetic results and low toxicity after three to four years follow-up [5, 1]. The guideline we are presenting here may help select those patients who will benefit most from respiratory management.

The results of our study may also be applicable to simultaneous or consecutive boost if an adequate number of fractions are used for the boost. The RTOG1005 study is investigating the use of boosts in early stage breast cancer comparing two treatment arms: standard fractionation whole breast radiotherapy (50 Gy in 25 fractions or 42.7 Gy in 16 fractions) followed by a sequential boost (12 Gy in 6 fractions or 14 Gy in 7 fractions) and a hypofractionated whole breast radiotherapy (40 Gy in 15 fractions) with a concurrent daily boost (48 Gy in 15 fractions) [26]. The analysis presented here could potentially provide guidance for when respiratory management may be necessary or when an IMRT boost may not be appropriate if the respiratory amplitude of these patients is greater than 10 mm.

Typically, in external beam partial breast radiotherapy the CTV-to-PTV expansion is 10 mm: 5 mm for respiratory motion and 5 mm for setup errors [27]. These margins were based on typical ranges of respiratory motion (3 - 9 mm) and set up errors (1 - 5 mm) and are designed to encompass all motion. We have used a dosimetric approach to assess the validity of the respiratory margin and found that evaluating only a lack of coverage is not enough to determine the degradation of a treatment plan. We found that the limiting factor was not coverage of the CTV_{su}, but that the hotspot in the ipsilateral breast increased beyond acceptable. By using flash and generous posterior coverage during planning, loss of coverage due to respiratory motion is minimized [7].

6.5 Conclusions

In this analysis of the effect of escalating respiratory amplitude on partial breast intensity modulated radiotherapy we have demonstrated that at amplitudes greater than 10 mm respiratory management or an alternative radiotherapy technique may be warranted. The dose increase of the hotspot guided this decision, as well as significant decrease in coverage at larger motions (> 15 mm). Plan quality metrics such as homogeneity and uniformity index showed a loss of homogeneity and uniformity at larger respiratory amplitudes. The approach we detailed here is a dosimetric validation of the respiratory margin used for most external beam partial breast radiotherapy. We showed that loss of coverage alone is not sufficient to determine whether margins are adequate and deterioration of plan quality with the inclusion of respiratory motion should also be considered. Due to the propensity of hotspots and regions of inhomogeneity to become exacerbated with respiratory motion we recommend caution is taken during the planning process and that if the plan does not meet planning criteria, or if it only barely meets planning criteria that respiratory management should be considered.

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General Conclusions

From this analysis we determined that if respiratory amplitude is greater than 10 mm, respiratory management is advisable. From our volunteer study, and consistent with data in the literature, we know that this should be less than 5 % of the population. We also found that loss of coverage was not the limiting factor in reduction of plan quality due to respiratory motion, but degradation of dose homogeneity, namely hotspots.

Chapter 7

Conclusions and Future work

7.1 Conclusions

In this thesis we presented an extensive respiratory study of both healthy and patient populations and used that data to create a realistic respiratory trace generating (RTG) tool. This tool provides a method to extend respiratory testing beyond the simplified approach of sinusoidal models or single patient traces. The RTG allows for customization of respiratory traces including shape, extent of motion, and variability in order to determine the precise impact of respiratory motion on a specific technology or simulated study. This is especially relevant when testing the more extreme respiratory situations such as high variability and large baseline drifts.

We took the knowledge gained through the respiratory studies, the healthy population data, and the trace generating capabilities, and applied it to the specific case of external beam partial breast intensity modulated radiotherapy (PBI IMRT). The main goal was to determine which patients should either be excluded from receiving PBI IMRT, or require respiratory management, based on the effects of respiratory motion on delivered dosimetry. We approached this by first determining what anatomy specific characteristics lead to plan degradation when respiratory motion is introduced, and then by simulating an increasing respiratory peak-to-peak amplitude determined an upper limit on the respiratory extent of motion beyond which dosimetric impact was unacceptable.

We investigated two planning strategies, with the aim of minimizing the impact of respiratory motion during treatment planning, to avoid the use of potentially costly respiratory management. We found that by planning to include increased posterior coverage of the target and adding flash to anterior targets, respiratory motion had a minimal effect for the

majority of patients. We proposed the metric DEV-to-PTV ratio as a means to determine which patients should be excluded from external beam PBI due to detrimental effects of respiratory motion on plan quality. This metric has two advantages: 1) the seroma volume, from which margins are geometrically expanded, has consistent standards that are met during the contouring stage compared to contouring of the ipsilateral breast volume that is largely determined clinically and varies significantly between centres; 2) the DEV-to-PTV ratio inherently gives information about breast size and location of target volume. The DEV-to-PTV is lower when the DEV is cut back from the inhomogeneities of lung/chestwall and air/skin. Smaller breast volumes often result in target volumes close to both inhomogeneities, resulting in DEV-to-PTV ratios that may be as low as 50%. Patients with DEV-to-PTV ratios of less than 55% were found to significantly degrade in coverage when planning was done without flash and posterior coverage.

By incorporating increasing peak-to-peak amplitude respiratory traces, we investigated the effects of respiratory motion further with a set of ten patients, with DEV-to-PTV ratios greater than 55%. This study was designed to determine dosimetrically if the 5 mm margin, typically added geometrically to account for respiratory motion, was adequate. We found that the limiting factor in plan quality was not target coverage, but degradation of dose homogeneity, namely, hotspots. The homogeneity and uniformity indices used to quantify plan quality also degraded with increased motion. Decreased target coverage was only observed at 15 and 20 mm motions, with half of the plans at 15 and all of the plans at 20 mm failing to meet minimum coverage standards. We recommend either using respiratory management if patients have an average respiratory motion with an amplitude greater than 10 mm (or choosing a different treatment technique). Due to the propensity of hotspots and regions of inhomogeneity to become exacerbated with respiratory motion, we recommend caution during the planning process and that if the plan does not meet planning criteria, or if it only barely meets planning criteria that respiratory management should be considered.

The results of our study are for the specific case of partial breast intensity modulated radiotherapy; however, the trends we observe are similar to those shown for previously for whole breast. Namely the increase in dose heterogeneity, as seen in many studies, is a limiting factor. Many studies also correlate increased degradation with increased respiratory motion amplitude of their patient populations studied.

Many whole breast studies found that coverage was degraded in the presence of respiratory motion, as described in detail in section 2.3. Richter *et al.* (2009) [1] observed target coverage degradation on average 3% for segmented IMRT and 4.2% for wedged tangents. Qi *et al.* (2010) [2] found PTV coverage varied by 1 - 7% and Yue *et al.* (2007) [3] found target coverage decreased by as much as 13.4% for V100 and 3 - 5% for D95, D90, V95, and V90. Frazier *et al.* (2004) [4] found differences in V95 of up to 8% in some patients. Cao *et al.* (2009) [5] found CTV coverage degradation was in general less than 10%, but up to 18% in one patient.

The range of target coverage degradation in the literature was between 1 - 18% depending on the methodology used. Some of these studies examined the change in CTV coverage, while others used PTV. We looked at CTV_{su} coverage. As well, we simulated the effect of respiratory motion in a realistic way accounting for all phases of motion while several of the previous studies exaggerated the motion by simply combining inhale and exhale, assuming the target spent half of the time at each. Finally, the whole breast studies cited here may not explicitly add a margin to account for respiratory motion. We did not find coverage to be the limiting factor in our studies. Using the population respiratory PDF on the partial breast IMRT plans examined in this work, the maximum decrease in D95 was 3%.

Dose homogeneity was also found as a contributing factor to plan quality degradation by a number of studies in whole breast radiotherapy. George *et al.* (2003) [6] found that dose heterogeneity increased with increasing respiratory motion. Richter *et al.* (2009) [1] used the homogeneity index to quantify dose homogeneity and found decreases of 1 - 2% with

respiration. In experimental studies, Sidhu *et al.* (2006) [7] found that plans, in general, became cooler, decreasing the dose to the breast by 15 - 22% depending on the technique used. Menon *et al.* (2011) [8] found that respiratory motion had more of an impact for IMRT plans than the conventional plans which is attributed to the increase modulation of the fluence. Dose inhomogeneity was found to increase with increasing motion amplitude. In experimental studies by Liu *et al.* (2007) [9] and Thilmann *et al.* (2006) [10] the difference in dose between moving and static deliveries was on the order of $\pm 5\%$ which matches in magnitude what we found in our simulation studies. In our study, the average DVH shift was 0.5% and the homogeneity index decreased by 13%.

The trend of dose homogeneity degradation with increasing motion is consistent with our results, as we found that this was the limiting factor instead of coverage. Our study was designed to encompass all phases of motion and as such is more sensitive to changes in dose homogeneity instead of simply coverage. Although most of the above studies concluded that the degradation in plan quality was negligible, they did not directly compare the results to planning criteria. In our studies we saw that even small changes due to respiratory motion can result in failures to meet planning criteria. We recommend that respiratory management be implemented if patients have a respiratory motion of greater than 10 mm or unacceptable dose heterogeneity may limit plan quality.

The only other study we found that made a recommendation on allowable respiratory amplitude specific to breast treatment (aside from the general guidance of AAPM Task Group report 76) was a study by Cao *et al.* This study concluded that a maximum amplitude of motion of 6 mm should be used for whole breast beamlet IMRT based on the degradation of CTV coverage at V100% between the free-breathing CT and the end inhale. Degradation was found to be in general less than 10% but up to 18%. This cut off is even more conservative than our proposed 10 mm respiratory limit. Their analysis was performed on the extreme end inhale and exhale phases only. The vast majority of our healthy volunteers had respiratory

motion less than both 6 and 10 mm, which is consistent with ranges in the literature, so it is likely that neither a 6 or 10 mm cut off exclude many patients.

The insensitivity to respiratory motion found in many of the planning (and phantom) studies may attributed to the step-and-shoot IMRT delivery technique where often large proportion of dose is delivered with open tangents resulting in fairly uniform dose distributions and the same conclusions may not be valid with dynamic MLC IMRT as seen in our study with an increase in dose heterogeneity. From the review of the literature, IMRT is the most susceptible to changes due to respiratory motion [8], 3DCRT is moderately affected and step-and-shoot segment IMRT [1] may be the least susceptible.

7.2 Future Work

If a true internal/external correlated dataset was available, the respiratory modelling project could be extended and the analysis methodology followed to model the shape and variability characteristics and develop an internal/external respiratory trace generator that could serve for testing and implementation

Extending PBI IMRT to include a similar analysis with 3DCRT is warranted as a large majority of clinics, especially in Canada, treat PBI and boosts primarily with 3DCRT. The expected impact of respiratory motion on 3DCRT is less than that of IMRT due to decreased conformality. Degradation in coverage will likely be minimal, but the potential for decreasing homogeneity with increasing hotspots exists.

Another extension of this analysis is to determine prospectively what margin is necessary to account for respiratory motion, or to combine with set up errors to find a complete margin. What we have shown here is the validity of the 5 mm margin for respiratory motion. The limiting factor of our results was not coverage, but degradation of plan homogeneity. Examining margins for partial breast is not as straight forward as simply uniformly expanding from seroma to PTV because these volumes are trimmed, sometimes severely, from the

inhomogeneities of lung/chestwall and skin/air. Careful attention to confounding variables defining the margin expansions and potential patient selection would be necessary to achieve meaningful results in this sort of study. Another approach might be to investigate margins in 1D or 2D to remove a layer of complexity by assessing dose profiles instead of dose volumes.

A fully deformable model of patient anatomy could be developed in order to estimate the impact of respiratory motion on surrounding normal tissue. Our assumption of rigid translations is valid for the breast itself, but for rigorous analysis of organs at risk a more complex geometry is necessary. This may be of particular use for the heart as it tends to move in the superior-inferior direction, while the breast and chestwall move in the anterior-posterior direction. The heart may also rotate and deform.

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Using cone-beam CT projection images to estimate the average and complete trajectory of a fiducial marker moving with respiration

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Abstract

Stereotactic body radiotherapy of lung cancer often makes use of a static cone-beam CT (CBCT) image to localize a tumor that moves during the respiratory cycle. In this work, we developed an algorithm to estimate the average and complete trajectory of an implanted fiducial marker from the raw CBCT projection data. After labeling the CBCT projection images based on the breathing phase of the fiducial marker, the average trajectory was determined by backprojecting the fiducial position from images of similar phase. To approximate the complete trajectory, a 3D fiducial position is estimated from its position in each CBCT project image as the point on the source-image ray closest to the average position at the same phase. The algorithm was tested with computer simulations as well as phantom experiments using a gold seed implanted in a programmable phantom capable of variable motion. Simulation testing was done on 120 realistic breathing patterns, half of which contained hysteresis. The average trajectory was reconstructed with an average root mean square (rms) error of less than 0.1 mm in all three directions, and a maximum error of 0.5 mm. The complete trajectory reconstruction had a mean rms error of less than 0.2 mm, with a maximum error of 4.07 mm. The phantom study was conducted using five different respiratory patterns with the amplitudes of 1.3 and 2.6 cm programmed into the motion phantom. These complete trajectories were reconstructed with an average rms error of 0.4 mm. There is motion information present in the raw CBCT dataset that can be exploited with the use of an implanted fiducial marker to sub-millimeter accuracy. This algorithm could ultimately supply the internal motion of a lung tumor at the treatment unit from the same dataset currently used for patient setup.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

Image guidance is important in radiotherapy today, as prescribed doses escalate and treatments become increasingly conformal. For stereotactic body radiotherapy (SBRT) of lung cancer, it is particularly important to know the respiratory motion of a tumor prior to treatment (Belderbos and Sonke, 2009). This motion is patient dependent (Stevens *et al* 2001), can vary in amplitude from less than a millimeter to several centimeters (Mori *et al* 2007, Maxim *et al* 2007) and is subject to inter- and intra-fraction variability (Seppenwoolde *et al* 2002, Ruan *et al* 2008). These variations make it a challenge to properly select treatment margins to provide adequate dose to the target, while preserving the maximum possible amount of healthy normal tissue. The uncertainty associated with respiratory-induced tumor motion can be reduced if it is measured and monitored at all stages of treatment.

Currently, respiratory motion is estimated with four-dimensional computed tomography (4DCT) (Keall *et al* 2004, Vedam *et al* 2003). This modality is indispensable during treatment planning, but has limitations for use in monitoring the day-to-day changes of motion during treatment. Image analysis and acquisition for 4DCT can be time and resource intensive, and the assessment of motion by contouring can vary between users (van Dam *et al* 2010). It produces an aggregate tumor motion from 15 to 20 different breathing cycles, which causes imaging artifacts if the motion changes from one breathing cycle to the next. 4DCT fails to provide information on the breathing cycle variability, including changes in the amplitude and shape of the motion. Because of these limitations, the increase in imaging dose for daily 4DCT motion estimation is difficult to justify.

Alternative methods to monitor tumor motion at the treatment unit have been introduced. One commercial system, Cyberknife[®] (Accuray[®], Sunnyvale, California), is able to track tumor motion in real time using a combination of internal and external markers (Brown *et al* 2007). Another prototype tracking system called real time tumor-tracking radiotherapy (Mitsubishi Electronics, Co., Tokyo, Japan) uses two orthogonal fluoroscopy units to track the tumor in real time (Seppenwoolde *et al* 2002), but requires continuous imaging, increasing dose to the patient. These specialized systems are either research equipment, or commercial systems with a high cost of implementation. Costs can be reduced by using equipment already available on modern linear accelerators, such as an on-board kilovoltage imager or an electronic portal imaging device for use with a megavoltage photon beam. Linear accelerators have been modified to allow simultaneous use of these orthogonal imaging devices and thus can track the 3D position of a fiducial marker in real time (Wiersma *et al* 2008). Another modality, cone-beam CT (CBCT), also makes use of the on-board imager and is used for the daily setup of lung patients prior to SBRT (Bissonnette *et al* 2009). Respiratory motion during acquisition degrades this 3D image, and the motion is difficult to quantify. However, motion information can be extracted from the raw projection images that are discarded after reconstruction. These images can be viewed in a 2D ‘cine’ mode with projected planning volumes, to determine if the tumor motion is moving within the planned treatment boundaries (Reitz *et al* 2008).

Instead of tracking the tumor directly, others have used an implanted fiducial marker near the tumor to aid in extracting such motion information (Marchant *et al* 2008, Poulsen *et al* 2008). Since CBCT is already used for daily imaging, motion information can be extracted without extra imaging dose or cost for new hardware. We propose a method to estimate the average and complete trajectory of a fiducial marker as it moves with respiration from the projection images. This could be used wherever CBCT is available, during simulation and at the treatment unit, to measure and verify the internal motion during patient setup at each fraction.

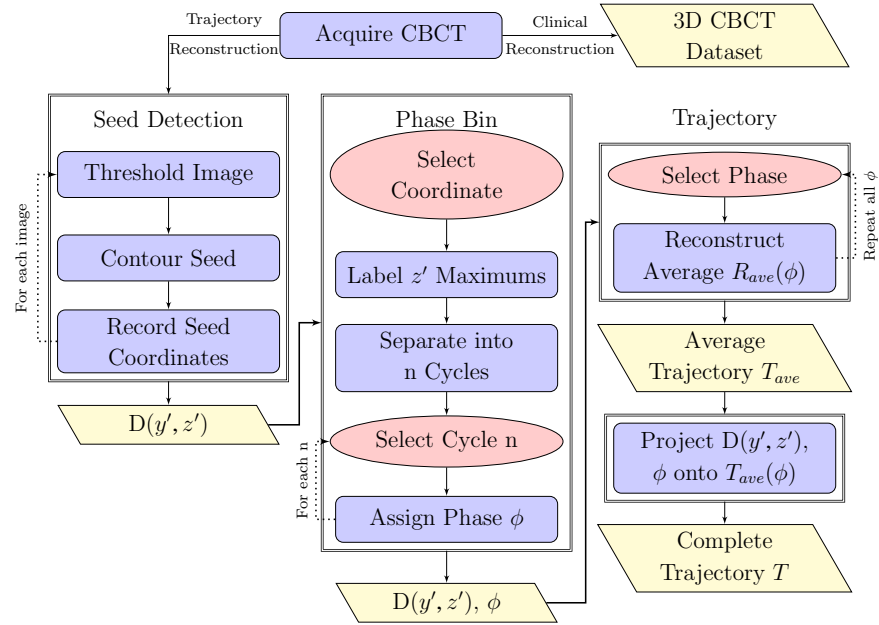


Figure 1. This flowchart outlines the steps in the motion trajectory reconstruction. These include fiducial marker location, phase interpolation, average trajectory reconstruction and complete trajectory estimation. $D(y', z')$ corresponds to the detector coordinates of the fiducial marker, ϕ represents the phase of motion, $R_{ave}(\phi)$ is the 3D coordinate at a given phase, $T_{ave}(\phi)$ is the average trajectory and T is the complete trajectory.

2. Methods

2.1. Reconstruction overview

The CBCT data are acquired as the imager, a kV source and detector, rotates in a 360° arc while capturing over 600 two-dimensional (2D) projection images. Normally, these images are reconstructed to produce a 3D volumetric image used to align the treatment beam to the daily position of the tumor (Purdie *et al* 2007). If a fiducial marker is implanted in or near the tumor, we can estimate its position by backprojecting from a pair of images acquired at different angles (Amols and Rosen, 1981). In the case of respiratory motion, the seed moves between images but is confined to a small region (less than a few centimeters), so motion can be retrieved by taking advantage of the repetitive, cyclical nature of respiratory motion.

The motion reconstruction algorithm we developed can be separated into four stages. The first stage of the algorithm analyzed the CBCT projection data to identify the fiducial marker coordinates in each projection image. In the second stage, each of the CBCT projection images (and corresponding fiducial coordinates) are assigned a phase angle according to the superior–inferior motion of the fiducial. The fiducial’s coordinates at regularly sampled values of the breath phase are then estimated using linear interpolation. In the third stage, an average position was found for each phase value, and an average trajectory estimated. The final stage uses this average to estimate a 3D coordinate for each projection image, which resulted in a complete trajectory reconstruction. A flowchart outlining these steps is shown in figure 1.

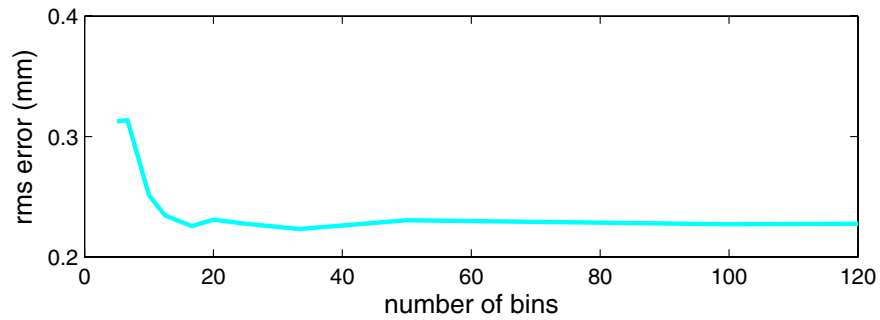


Figure 2. The rms error decreases to a flat region as the number of phase samples increases. The number of phase samples used in this study lies in this plateau region.

2.2. Seed detection and phase binning

After CBCT acquisition, the projection images were converted to a raw image format (software courtesy of Varian Medical Systems™, Palo Alto, California). Using MATLAB® (The Mathworks™, Natick, Massachusetts) we developed an automated thresholding program to find the location of the fiducial marker in each image. The marker was outlined for visual verification, and the image coordinates of the marker $D(y', z')$ recorded for each projection image along with the imager angle (θ). As the marker does not move far in successive CBCT projection images, performance was improved by limiting the search space to a small area centered around the previous seed location.

The images are then tagged with a value indicating the breathing phase, based on the motion in the superior–inferior (SI) direction which corresponds to the z' direction on the imaging panel. This method required an SI component to the motion of at least 2 mm to differentiate motion from noise. This will work in most cases, since the primary motion of lung tumours is often in the SI direction (Seppenwoolde *et al* 2002). If there is no significant SI motion, an alternate method of labeling phase, such as an external marker (for example RPM), may be necessary.

Peaks in the SI motion versus time plot were automatically detected, verified visually and labeled as zero phase. In order to account for ‘false peaks’ from shallow breaths, automatic breathing filters were applied that mandated peak-to-peak distance be at least 0.8 s (Suh *et al* 2008). Each image is then assigned a phase value corresponding to its acquisition time between the zero phase points. Marker positions were then determined at regularly sampled intervals of phase using linear interpolation. We simulated reconstructions for five different patients to determine how the number samples per phase affected the reconstruction result. Figure 2 shows that the mean rms error of the reconstruction decreased as we increased the number of interpolation points. We chose 100 phase samples which gave a low rms error and a reasonable reconstruction time of about 10 s.

2.3. Average trajectory reconstruction

The average trajectory was estimated by taking advantage of the repetitive nature of the respiratory motion. For regular breathing, images at the same phase sample corresponded to times when the marker occupied nearly the same 3D position, which was found using a backprojection method. For each image, we found the 3D coordinates of the source (S), as well as the projected marker on the detector (D). In the imager’s rotating frame of reference,

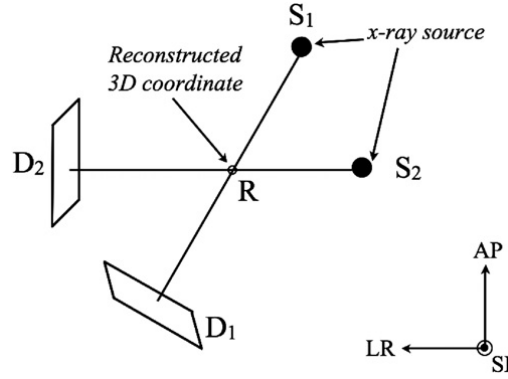


Figure 3. The seed coordinates are located in each 2D image. Lines are drawn from the x-ray source to these seed coordinates. The intersection of the rays is the 3D coordinate of the fiducial marker.

the source and detector were at fixed distances (s and d , respectively) from the rotation axis, and the seed's projection on the imaging panel was at coordinates $D(y', z')$. This frame was rotated with respect to the stationary room coordinate frame about the z -axis as denoted by the imager angle (θ). In the rotating frame of reference, the source position (S') was

$$S' = (s, 0, 0) \quad (1)$$

and the projection of the seed in the detector (D') was

$$D' = (-d, y', z'). \quad (2)$$

To convert to room coordinates, we used the transformation matrix shown in equation (3):

$$M = \begin{bmatrix} \cos(\theta) & \sin(\theta) & 0 \\ -\sin(\theta) & \cos(\theta) & 0 \\ 0 & 0 & 1 \end{bmatrix}. \quad (3)$$

The resulting positions of S and D in the room's reference frame were found by solving equations (4) and (5):

$$S = S' * M \quad (4)$$

$$D = D' * M. \quad (5)$$

Once we found the room coordinates of S and D , the backprojected ray connecting these points was parametrized by q (equation (6)):

$$X = S - q * (S - D). \quad (6)$$

Normally the backprojection method determines a 3D coordinate using two images. As demonstrated in figure 3, if a line from the source (S) to detector (D) is defined for each image, the intersection point occurs when these two lines are equal (equation (7)):

$$S_1 - q_1 * (S_1 - D_1) = S_2 - q_2 * (S_2 - D_2). \quad (7)$$

If the marker moves between the images, an intersection point may not exist. In this case, we found the point that was closest to both lines as an estimate of the intersection. If the points P_1 and P_2 are on the lines $S_1 - D_1$ and $S_2 - D_2$, respectively, a line connecting these points will have the shortest distance when

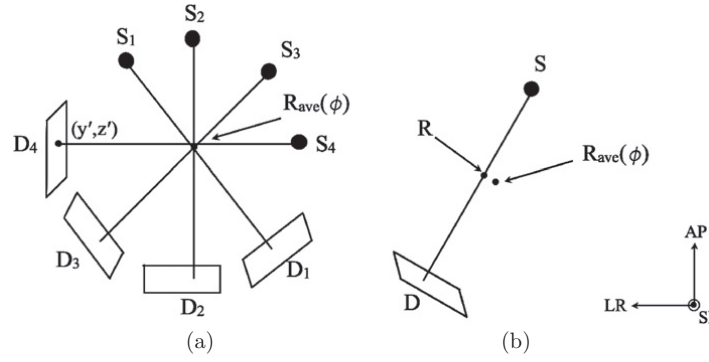


Figure 4. (a) The average intersection of the backprojected rays from a given phase represents the average 3D coordinate for the marker at that phase. (b) The 3D coordinate for each image (R) is estimated as the point along the backprojection ray closest to the average trajectory ($R_{ave}(\phi)$).

$$(P_1 - P_2) \cdot (S_1 - D_1) = 0 \quad (8)$$

$$(P_1 - P_2) \cdot (S_2 - D_2) = 0. \quad (9)$$

The point closest to the lines $S_1 - D_1$ and $S_2 - D_2$ is half-way between the points P_1 and P_2 (equation (10)):

$$R = \frac{P_1 + P_2}{2}. \quad (10)$$

Instead of using only two images for reconstruction, an estimate of the 3D coordinate for each phase value was found by backprojecting all marker image positions with that phase value. The intersection of all pairs of backprojection rays was found using the method described. These points were averaged to estimate the average 3D coordinate for each phase value ($R_{ave}(\phi)$), as shown in figure 4(a). This was repeated for every value of phase from 0 to 99% resulting in the complete average trajectory (T_{ave}).

2.4. Complete trajectory reconstruction

The final step of the algorithm estimated a complete 3D trajectory using the reconstructed average trajectory as a starting point. For each 2D projection image, the true position of the fiducial marker lay along the S–D line, but the position along the ray was not resolved. However, figure 4(b) shows how we estimated the 3D position by choosing the point along the ray that was closest to the average trajectory. For each image, we knew the 3D coordinates of S and D , the phase of motion (ϕ) and the average position for that phase ($R_{ave}(\phi)$). We also knew that the true position (R) of the seed lay somewhere along the source to detector line, as given by equation (11):

$$R = S + q \cdot (S - D). \quad (11)$$

To find R , such that the distance to $R_{ave}(\phi)$ is minimized, we solved equation (12):

$$(R - R_{ave}(\phi)) \cdot (S - D) = 0. \quad (12)$$

By repeating this for all images, we estimated a 3D coordinate for every image in the CBCT projection dataset, thus estimating the entire trajectory (T) of the fiducial marker during the CBCT.

2.5. Simulation testing

We developed a method to simulate CBCT imaging of a moving fiducial marker in MATLAB. The intent of the simulation study was to demonstrate the proof of concept that reconstruction is possible with high accuracy using the proposed algorithm. Starting with any input trajectory, the 3D room coordinates of the fiducial marker were projected onto the virtual imaging panel. These imaging coordinates represented the raw CBCT projection data required for reconstruction. Imaging of the true motion was simulated using clinically relevant parameters (360° rotation, 1 rpm, 10 fps), which resulted in 600 projection images.

The input motion patterns were created using clinical traces from the real time position management (RPM) System[®] (Varian Medical Systems[™], Palo Alto, California). Each 1D breathing trace was used for the SI motion. The AP and LR motions were scaled versions of the SI motion ranging from 0.5 to 1.5 times (AP) and 0.2 to 0.4 times (LR) the size. This allowed for the AP motion to be larger than the SI motion in 1/3 of the simulation studies. One minute segments of RPM data from 60 different patients were used to these build 3D trajectories. An additional 60 datasets were built with hysteresis by setting the LR and AP motion out of phase from the SI motion by up to 1 s. CBCT datasets were simulated from these motion data, and both the average and complete trajectories were reconstructed and compared to the true motions.

2.6. Experimental validation

The next step was to experimentally test the algorithm at the treatment unit in order to show that the reconstruction was clinically feasible. Five different 1D RPM traces were entered into a BrainLAB phantom (BrainLAB[®] AG, Heimstetten, Germany) capable of 1D programmable motion. The traces and phantom positioning were chosen to represent a wide range of motions, including regular breathing, variable shape and amplitude, baseline drift and dominant off-axis motion.

In the first experiment, the phantom was directed along the couch in the SI direction, with an average range of 2.6 cm. For the second, the phantom was again aligned along the couch in the SI direction with the same amplitude, and then the couch was rotated by 5° to give a small LR component to the motion. In the last three cases, the motion amplitude was 1.3 cm, with one end of the phantom raised by 3° to give AP motion. The third case simulated large off-axis motion by rotating the phantom 75° from the z -axis. The final two experiments were with the phantom rotated by 15° from the z -axis, with variable motion, as well as a slight baseline drift. In all cases, the motion of the phantom was measured using a digital encoder (Model PED-127-2, US Digital, Vancouver, Washington). We acquired a CBCT of each motion using a Varian Trilogy[®] (Varian, Palo Alto, California), and the complete trajectory was reconstructed and compared to the true motion of the marker measured by the digital encoder.

3. Results

3.1. Simulation testing

The 3D trajectories used for the simulation study had an average range of 5.0 mm with a standard deviation of 2.6 mm in the SI direction. In the LR and AP directions, the average (standard deviation) range was 3.8 mm (1.3 mm) and 1.8 mm (0.1 mm), respectively. The hysteresis added to the LR and AP motions were randomly selected between 0 and 1 s out

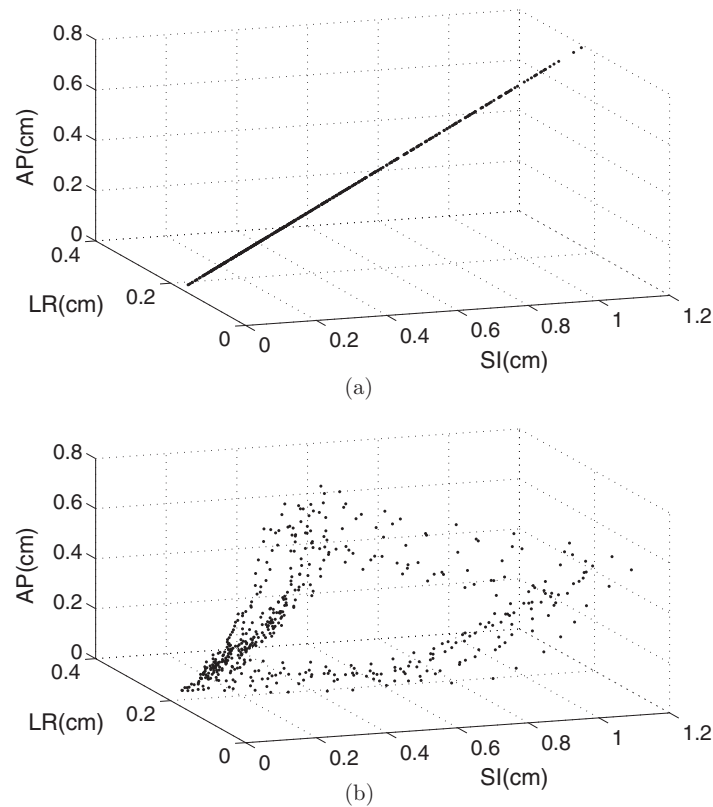


Figure 5. (a) A 3D view of a normal trajectory without hysteresis. (b) The same trajectory with hysteresis added.

Table 1. Simulation study: the average trajectory reconstruction for normal traces, and for those with hysteresis added. The mean rms error for all trajectories, the worst case mean rms error for one trajectory and maximum error for a single reconstructed point are shown.

	LR (mm)	AP (mm)	SI (mm)
Average trajectory—normal traces (60 patients)			
Mean rms error	0.08	0.09	0.01
Worst case mean rms for one trajectory	0.23	0.36	0.03
Maximum error in any point	0.39	0.52	0.10
Average trajectory—hysteresis (60 patients)			
Mean rms error	0.08	0.09	0.01
Worst case mean rms for one trajectory	0.21	0.33	0.04
Maximum error in any point	0.46	0.44	0.13

of phase. Figure 5 shows a sample breathing trace with (figure 5(a)) and without hysteresis (figure 5(b)).

The first step in reconstruction was to find the average trajectory of the marker during the CBCT. Table 1 compares the reconstructed average to the true average trajectory, and shows the mean rms error for all trajectories, the worst case mean rms error for one trajectory and the worst case rms error for a single reconstructed point.

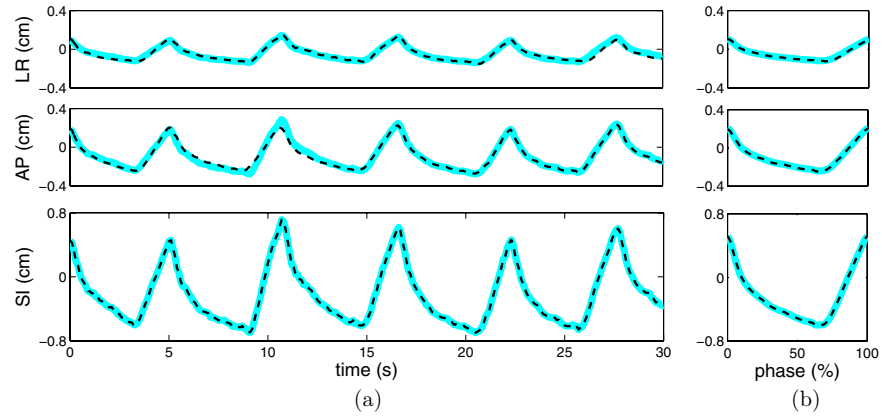


Figure 6. A typical (a) complete trajectory, and (b) average trajectory obtained from the simulation study. The reconstructed trajectory is shown with the dashed line while the true trajectory is the solid line, for the LR (top), AP (middle) and SI (bottom) directions.

Table 2. Simulation study: the complete trajectory estimation for normal traces, and for those with hysteresis added from the simulation study. The mean rms error for all trajectories, the worst case mean rms error for one trajectory and maximum error for a single reconstructed point are shown.

	LR (mm)	AP (mm)	SI (mm)
Complete trajectory—normal traces (60 patients)			
Mean rms error	0.16	0.22	0.01
Worst case mean rms for one trajectory	0.35	0.51	0.02
Maximum error in any point	2.19	3.93	0.11
Complete trajectory—hysteresis (60 patients)			
Mean rms error	0.17	0.23	0.01
Worst case mean rms for one trajectory	0.35	0.51	0.02
Maximum error in any point	2.86	4.07	0.15

After the average trajectory was reconstructed, we estimated the complete trajectory of the marker for each simulated CBCT. The mean rms error, the worst case rms error and the maximum error in any point between the true and reconstructed trajectories are shown in table 2. As expected, with hysteresis added, there is little change in the reconstruction accuracy. A typical average (figure 6(b)) and complete trajectory (figure 6(a)) reconstruction for all three directions is shown. Figures 7 and 8 show additional reconstructions of irregular motion and a small baseline drift, respectively.

3.2. Experimental validation

Using real CBCT data of the motion phantom, the algorithm was able to reconstruct the complete trajectory of the fiducial marker with an rms error of less than 0.4 mm. Table 3 gives the average rms errors for both trajectory reconstructions, as well as the maximum error in any point. Figure 9 shows the reconstruction of variable motion.

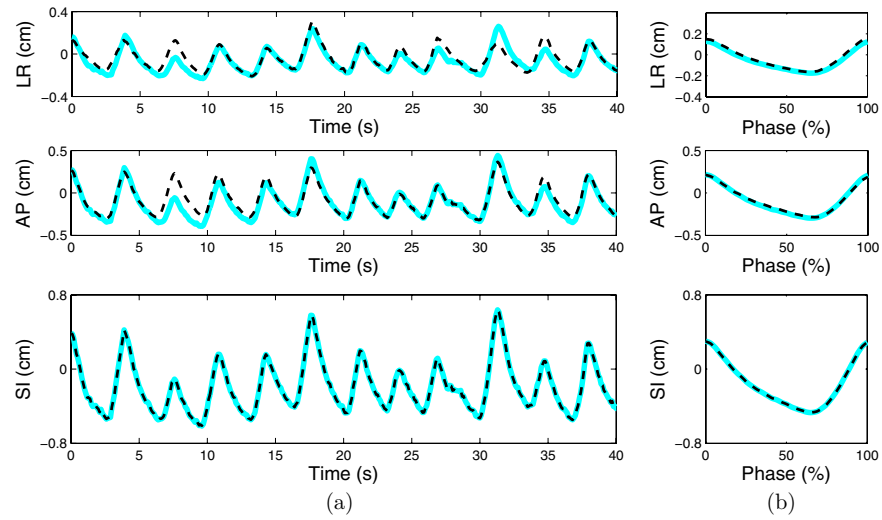


Figure 7. An irregular motion (a) complete trajectory, and (b) average trajectory obtained from the simulation study. The reconstructed trajectory is shown with the dashed line while the true trajectory is the solid line, for the LR (top), AP (middle) and SI (bottom) directions.

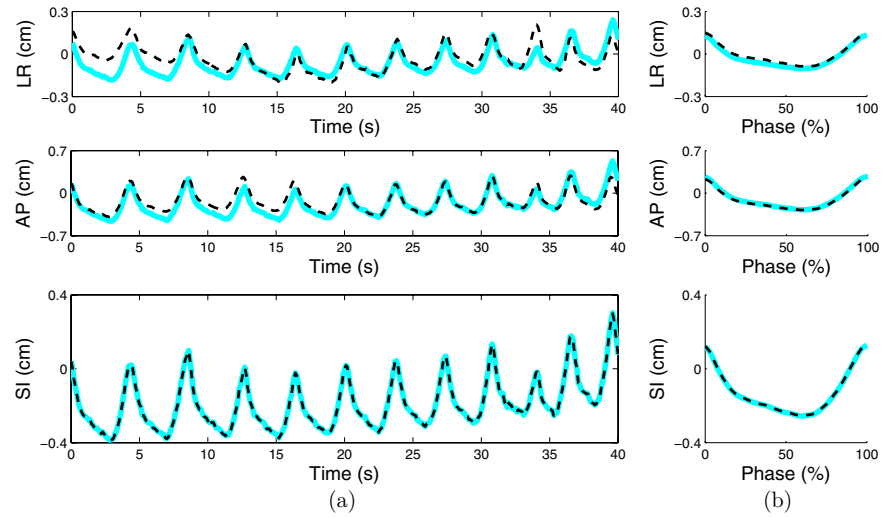


Figure 8. A motion with baseline drift (a) complete trajectory, and (b) average trajectory obtained from the simulation study. The reconstructed trajectory is shown with the dashed line while the true trajectory is the solid line, for the LR (top), AP (middle) and SI (bottom) directions. Initially, the algorithm overestimates the SI and LR motion, but as the baseline increases, the estimation underestimates these motions.

4. Discussion

The algorithm we developed extracts motion information from the raw projection data of a CBCT scan. During simulation testing, we were able to reconstruct the complete trajectory with a mean rms error of 0.2 mm in the AP and LR directions, and only 0.01 mm in the SI direction. The reconstruction algorithm is most accurate in the SI direction, as this axis

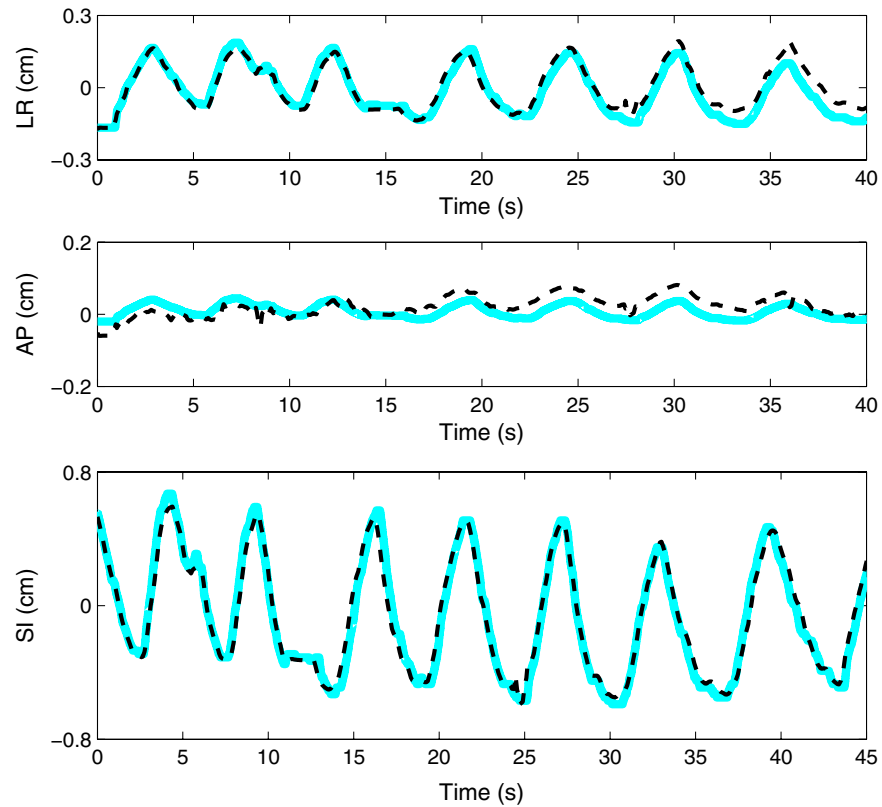


Figure 9. A comparison of the reconstructed motion (dashed line) and the true motion (solid line) as measured by the digital encoder, using real CBCT images.

is perpendicular to the rotation of the imager. Due to the monoscopic nature of the CBCT projection data, the reconstruction accuracy is reduced in the AP and LR directions when the imager is parallel to that direction, and increases as the imager becomes perpendicular.

There has been limited research into extracting motion information from CBCT projection data. Reitz *et al* (2008) viewed these images in a 2D ‘cine’ mode with projected planning volumes, to determine if the tumor motion stays within the planned treatment boundaries. They found that by post-processing the MV-CBCT images, they could verify the tumor motion for medium to large tumors in the upper lobe. Due to the limited soft-tissue contrast, the visibility of small tumors was greatly dependent on tumor location and imaging angle.

Marchant *et al* (2008) solved this problem using fiducial markers implanted near the tumor. These markers were easily identified on the projection data, and allowed for the quantitative measurements of the average position of the fiducial marker to within 1 mm, as well as the range of motion in three dimensions. They used the entire CBCT dataset for estimating the SI motion, however, only a 20° arc of images was used to estimate the LR and AP motions, when the imager was perpendicular to that direction. This resulted in a motion estimation from only one or two breathing cycles, making it more susceptible to errors if the patient breathed irregularly for one of these cycles.

Poulsen *et al* (2008) managed to overcome this difficulty by using the entire CBCT dataset for estimation of all three motion directions. They used a maximum likelihood estimation (MLE) based on the projection data to determine the mean position and standard deviation of

Table 3. Phantom study: experimental results from the phantom study show the mean rms error for the complete trajectory reconstruction and the maximum error for a single point.

	LR (mm)	AP (mm)	SI (mm)
Experimental trace 1 (3 cm range—SI direction)			
Complete trajectory: mean rms	0.04	0.06	0.25
Maximum error in any point	0.30	0.25	1.53
Experimental trace 2 (3 cm range—5° couch rotation)			
Complete trajectory: mean rms	0.34	0.28	0.32
Maximum error in any point	0.59	0.67	1.36
Experimental trace 3 (1.2 cm range—variable motion)			
Complete trajectory: mean rms	0.60	0.29	0.61
Maximum error in any point	2.11	1.42	2.97
Experimental trace 4 (1.2 cm range—baseline drift)			
Complete trajectory: mean rms	0.43	0.28	0.51
Maximum error in any point	1.90	2.97	7.96
Experimental trace 5 (1.2 cm range—large AP motion)			
Complete trajectory: mean rms	0.51	1.35	0.45
Maximum error in any point	1.93	10.6	1.37

the marker. Using this approach, simulations of the algorithm estimated the mean position with an average rms error of 0.05 mm, and a maximum error of 0.76 mm.

The main advance presented in our method is resampling the projection data based on phase, which allows us to reconstruct each phase as if the marker were stationary. We then can construct an ‘average’ motion over a breath cycle rather than just specify an average position over the entire cycle. The average trajectory contains the information about the mean position and extent of motion, and provides additional 4D information about how the marker moves in 3D space as time progresses. The average trajectory itself is a useful step, as it may be more informative to watch how the average tumor trajectory changes over treatment, rather than specific breathing cycles.

Another breakthrough first published by Poulsen *et al* (2008) was the ability to estimate the complete trajectory of the fiducial marker. By projecting each CBCT projection image through the MLE of the position, they estimated a 3D coordinate for each image, and thus the complete trajectory. Our algorithm again extends this approach by using the average trajectory as a starting point, rather than the average position data. This allows for each marker image position at a given phase value to be compared with the most likely position of the marker at that phase, potentially providing better estimated 4D trajectory information. Our results show that even after adding hysteresis to the fiducial marker trajectory, we are still able to reconstruct the average and complete trajectory without a decrease in accuracy.

The variability in the breathing cycle is the factor that has the greatest effect on the reconstruction accuracy. This algorithm phase samples the images to take advantage of the repetitive nature of breathing motion, and suffers when this is not the case. Even though phase sampling is still possible when the breathing is variable from cycle to cycle, or there is a drift in the baseline of the motion, it does not group together images in which the fiducial marker is at the same 3D position. In the future, using amplitude labeling, or perhaps a combination of binning techniques, may help to overcome this obstacle. Also, future work will investigate and quantify how breathing variations affect the accuracy of this reconstruction method.

There are many potential implementations of this algorithm in the clinic. The AAPM's task group 76 (Keall *et al* 2006) stressed the importance of research involving internal motion imaging at the treatment unit. In its current state, we see this algorithm used to monitor the internal motion of a tumor over the course of treatment. CBCT data are already available from patient setup, and if a fiducial marker is implanted, it is just a matter of accessing the data and running the reconstruction. This process is fast (seconds); however, the image processing can take several minutes to run. In order to have access to these data immediately at the treatment unit, we would need faster image processing to find the image coordinates of the marker, which others have developed (Cho *et al* 2009, Liu *et al* 2008). With the data available at the treatment unit, the internal motion of the tumor could be correlated with external surrogates, such as markers on the patients' chest, to be used with respiratory gating. This technology is currently limited in use, but may be trusted more if the internal/external correlation was measured on a daily basis.

5. Conclusion

We have demonstrated a new method for determining the trajectory of an implanted fiducial marker using CBCT projection images. This method can be used for clinically relevant motion, producing an average trajectory, and a complete trajectory estimation of the marker during the entire CBCT scan. It makes use of CBCT that is already available from the setup CBCT. These tools were validated with computer simulations, as well as an experimental phantom study. This work can be implemented to verify the internal target motion of lung tumor patients on a daily basis with no extra imaging dose when CBCT is used for patient setup.

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