Clinical Study

A Methodology for Implementing Deep Inspiration Breath Hold Radiotherapy for Patients with Left-sided Breast Cancer in a Radiation Oncology Department Using a Clinical Study

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Abstract

Introduction: Radiation oncology has seen increasing use of new techniques supported by modern technologies to improve the accuracy of treatment delivery. We utilized the methodology of a small-scale clinical trial to facilitate implementation of the Deep Inspiration Breath Hold technique (DIBH) for treating left-sided breast cancer.

Methods: We undertook a small-scale single arm clinical trial to assess and implement the DIBH technique in patients who underwent radiotherapy for left-sided breast cancer. Patients who had unfavorable cardiac anatomy with a Mean Cardiac Dose (MCD) > 2Gy on their Study-Compliant Free Breathing (SCFB) radiotherapy plan, subsequently underwent a Deep Inspiration Breath Hold (DIBH) planning CT. The DIBH plan was compared to the SCFB plan and if a > 30% reduction in MCD was demonstrated, the patient was treated using the DIBH technique.

Results: Ten of the 12 patients approached for study participation had unfavorable cardiac anatomy, and all demonstrated a $\geq 30\%$ reduction in MCD with DIBH in comparison to their respective SCFB plans. All 10 patients completed DIBH treatment successfully. There were statistically significant reductions in MCD ($p=0.002$) and mean dose to the Left Anterior Descending coronary artery (mLAD) ($p=0.002$). The median reduction in MCD was 2.41 Gy (95% CI, 1.85-3.92 Gy) and in mLAD was 15.11 Gy (95% CI, 11.32-22.38 Gy).

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There was a statistically significant increase in mean dose to the contra lateral breast ($p=0.037$) with a median increase of 0.16 Gy (95% CI, 0.03-0.40 Gy).

Conclusion: Through the small scale clinical study with a standardized intervention, predefined eligibility criteria and outcomes evaluation, DIBH radiotherapy was systematically implemented in our department for patients with left breast cancer and unfavorable cardiac anatomy. This same methodology can be adapted for effectively introducing other New Radiation Oncology Techniques and Technology (NROTAT) into a radiation oncology centre.

Introduction

Over the last two decades, new radiotherapy techniques and technologies have increasingly been incorporated into clinical practice in radiation oncology [1-4].

We introduced the Deep Inspiration Breath Hold (DIBH) radiotherapy technique for patients with left-sided breast cancer into our department in the context of a clinical study. The rationale is to study the complexity of the interaction between technique, technology and patients, so that its potential application to a larger cohort of patients and impact on the resources and workflow in a radiation oncology centre can be determined.

In patients undergoing radiotherapy for left-sided breast cancer using tangential beams, the incidental radiation doses to the heart have been shown to be associated with an increase in cardiac morbidity and mortality [5,6]. There are a range of techniques for reducing the heart dose, including cardiac shielding [7], prone or lateral decubitus patient positioning [8,9], non-tangential Intensity Modulated Radio Therapy (IMRT) [10], Partial Breast Irradiation (PBI) [11], and DIBH [12-14].

The DIBH technique has been shown to reduce the Mean Cardiac Dose (MCD), a widely studied surrogate measure of radiation dose to the heart and related cardiac morbidity and mortality [6] without compromising coverage of breast tissue as is the case with PBI and cardiac shielding [7,11]. Non-tangential IMRT may reduce peak dose to the heart but is associated with increased MCD [10]. Prone or lateral decubitus patient positioning has been criticized due to reliability and reproducibility of set-up [8,15].

The following criteria were selected to design the study in a way that would be clinically informative:

- Clear definition of the intervention
- Yield an estimate of the number of patients, who can benefit
- Yield an estimate of the benefit of the new radiotherapy technique and technology
- Provide an assessment of feasibility and safety

We aimed to determine the proportion of patients who might benefit from the DIBH technique, quantify the magnitude of benefit, and assess its feasibility and safety in comparison with non-DIBH radiotherapy using the framework of a clinical study utilizing a standardized technique and pre-defined eligibility criteria to enable its implementation. In addition, we aimed to adapt this framework in the

future to introduce new radiation oncology techniques and technologies into our department.

Methods

This prospective study was conducted at the Peter MacCallum Cancer Centre in Melbourne, Australia. The protocol was approved by the institutional ethics committee. All participants gave written informed consent. Twelve patients were screened from the breast clinic at our institute and 10 patients were deemed eligible.

Inclusion criteria were female's aged ≥ 18 years, ECOG performance status 0-2, diagnosis of left-sided breast cancer or DCIS, completed breast-conserving surgery or mastectomy, and no evidence of distant metastatic disease. Patients with severe pulmonary disease or who were unable to perform a deep inspiration breath hold for longer than 15 seconds were excluded.

All patients underwent an initial Study-Compliant Free-Breathing (SCFB) planning CT scan performed in the supine position, which is defined as a standard CT scan in treatment position with no alteration or intervention to a patient's breathing pattern. To determine eligibility, a SCFB radiotherapy plan was generated. The tangential fields were set clinically to include the entire ipsilateral breast or chest wall with a 1.5cm margin. No cardiac shielding was permitted on the SCFB plan. If the Mean Cardiac Dose (MCD) was ≥ 2 Gy on this plan, the patient was deemed to have unfavorable cardiac anatomy.

Eligible patients with MCD ≥ 2 Gy on their SCFB plan underwent a second supine planning CT scan acquired during Deep Inspiration Breath Hold (DIBH). This was felt to be a pragmatic dose threshold and was selected based on the QUANTEC analyses of normal tissue effects [16], which would ensure that the scan was only employed on patients that would benefit from the new technique and therefore limit extra dose. The Philips Medical Systems air bellows was employed for the DIBH scan, which utilized an elastic belt, positioned around the patient's abdomen, allowing the conversion of abdominal movements into a breathing trace. This allowed determination of the level of inspiration that the DIBH CT scan would be acquired. Coaching of the patient was utilized to ensure that the patient maintained a relaxed position and breathed in to a capacity that could be maintained and was diaphragmatic breathing rather than patient shift.

Contouring of all tumour volumes and the Left Anterior Descending coronary artery (LAD) were outlined by a single radiation oncologist in consultation with a radiologist. Cardiac tissue, right breast tissue and lung volume were also outlined.

A DIBH radiotherapy plan was generated and compared to the patient's SCFB plan. If a clinically meaningful reduction in MCD was achieved, i.e., $\geq 30\%$ reduction, the DIBH technique was adopted as the final treatment technique.

A Dose Volume Histogram (DVH) was used to determine the following measures on both the SCFB plan and DIBH plan: MCD; volume of heart receiving ≥ 25 Gy (V25); mean dose to the Left Anterior Descending coronary artery (LAD); mean dose to lungs; percentage of lungs receiving ≥ 20 Gy (V20); mean dose to Right Breast (mRtBreast); and target coverage defined as percentage of the dose evaluation volume falling within the 95% is Dose Volume (DEV95) [16].

Once finalized, the DIBH radiotherapy plan was delivered using the Varian® Real-time Position Management™ (RPM) system, which facilitated monitoring and real-time feedback of the patients' breathing cycle during treatment. Patients were offered visual real time

display during treatment in the form of fitted video eyewear, which displayed the RPM interface depicting the breathing trace moving inside or outside of the predetermined range. The trace included a threshold mark for the patient to gauge and control the amplitude of inspiration. This threshold was 30% below the patient's maximum deep inspiration. If a patient was unable to maintain their breath-hold within the threshold the system would terminate the treatment beam automatically and restart when it re-entered the range.

During treatment, portal images were acquired of both tangential fields for the first five fractions to assess intra-fraction variation. Medial tangential portal images were obtained for subsequent fractions to assess inter-fraction variation. The Maximum Perpendicular Lung Distance (MPLD) was measured and documented.

Statistical analysis: Analysis for this pilot study aims to test the feasibility of implementing deep inspiration breath hold radiotherapy for patients with left-sided breast cancer in a Radiation Oncology Department. A pragmatic sample size of 10 patients was identified and was considered feasible for recruitment within the proposed 12-months and facilitates rapid implementation of the technology into clinical practice.

Results

The proposed schema to test for the clinical introduction of DIBH is shown in figure 1, while a generic schema for the future introduction of any new technology is depicted in figure 2.

Figure 1: DIBH study specific schema.

Twelve eligible patients were recruited to participate in the study over a 10-month period. Ten patients were eligible to be registered to the study, with 2 patients excluded because their MCD on the SCFB plan was < 2 Gy. Table 1 demonstrates the plan evaluation and treatment for all patients.

Of the patients scanned for the DIBH technique all ten patients were treated using the DIBH plan as it demonstrated a $\geq 30\%$

Figure 2: The proposed scheme to introduce new technology and techniques into a Radiotherapy Department.

Variable	Count	% [95% CI]
mDIBH plan showed $\geq 30\%$ reduction in MCD compared to SCFB?		
No	0	0 [0 - 31]
Yes	10	100 [69 - 100]
Patient completed planned treatment?		
No	0	0 [0 - 31]
Yes	10	100 [69 - 100]
Breast Conservation Surgery		
No	3	30 [7 - 65]
Yes	7	70 [35 - 93]
Completed Treatment		
No	0	0 [0 - 31]
Yes	10	100 [69 - 100]
Dose		
42.5Gy in 16 fractions	5	50 [19 - 81]
50Gy in 25 fractions	5	50 [19 - 81]
Standard deviation (sd) of MDLP over treatment		
sd ≤ 2 mm	1	10 [0 - 45]
2 <sd ≤ 3 mm	4	40 [12 - 74]
3 <sd ≤ 4 mm	3	30 [7 - 65]
sd ≥ 4 mm	2	20 [3 - 56]

Table 1: Plan evaluation and treatment.

reduction in MCD compared to their SCFB plan (Figure 3).

The proposed method of radiotherapy planning and treatment was feasible, achieving 100% DIBH treatment completion rate, which represented 83.5% (10/12) of screened patients successfully completing

Figure 3: Comparison of MCD in gray for DIBH to SCFB techniques for each participant.

treatment with the new technique. One patient who had claustrophobia completed treatment successfully without the video eyewear.

The lowest MPLD standard deviation was 2.0mm and the highest was 4.5mm. 50% of the patients [95% CI (19 - 81)] had a standard deviation ≤ 3 mm, which was less than the 80% cut-off to consider the technique reproducible according to the protocol.

Table 2 shows the differences in various dosimetric parameters when using the DIBH technique compared to SCFB. The comparisons using DIBH and SCFB were statistically significant for most of the variables. mLung and V20 were not statistically significant, possibly due to the small sample size. DIBH had lower MCD, V25, mLAD, mLung and V20 but higher mRtBreast.

Dosimetry	median (95% CI)	p-value
MCD	-2.41 (-3.92 to -1.85)	0.002
V25	-4.25 (-7.60 to -2.24)	0.004
mLAD	-15.11 (-22.38 to -11.32)	0.002
mLung	-0.74 (-1.62 to 0.11)	0.064
V20	-1.96 (-3.72 to 0.13)	0.106
mRtBreast	0.16 (0.03 to 0.40)	0.037
Dev95	0.20 (-1.53 to 5.22)	0.695

Table 2: Difference in dosimetric parameters between mDIBH and SCFB. Parameters assessed: MCD (Mean Cardiac Dose); V25 (volume of heart receiving ≥ 25 Gy); mLAD (mean dose to the Left Anterior Descending coronary artery); mLung (mean dose to lungs); V20 (percentage of lungs receiving ≥ 20 Gy); mRtBreast (mean dose to Right Breast); Dev95 (breast target coverage defined as percentage of the Dose evaluation volume falling within the 95% isodose volume)

*Negative values imply that dose delivered in DIBH plan was lower than SCFB and positive values imply that dose delivered in DIBH plan was higher than SCFBplan.

Figures 3 and 4 graphically demonstrate for each individual patient the reduction in MCD and mLAD between the DIBH plan and the SCFB plan respectively.

There were statistically significant reductions in MCD ($p=0.002$) and mLAD ($p=0.002$). The median reduction in MCD was 2.41 Gy (95% CI [3.92 to 1.85]) and in mLAD was 15.11Gy (95% CI [22.38 to 11.32]). There was a statistically significant increase in mean dose to the contra lateral right breast ($p=0.037$) with a median increase of 0.16 Gy (95% CI [0.03 to 0.40]) but this difference may not be clinically relevant.

Discussion

The practice of radiation oncology is unique in the technology assessment environment because delivery of the therapy is

fundamentally based on maximizing the therapeutic window with specific dosimetric parameters and improving the accuracy of treatment delivery while minimizing dose to the surrounding tissue.

In the wake of an increasing number of technologies available, a radiation oncology department must be judicious when considering which technology to invest in, which subset of patients to target for the greatest benefit and how to implement it into clinical practice within a reasonable timeframe.

We implemented DIBH effectively into our department through the use of a clinical study. This methodology facilitated the rapid identification of a group of patients that would benefit an ability to measure the magnitude of the benefit, test the feasibility of the technology and use all of that information to incorporate the technique into our department's routine clinical practice. By using this methodology we were also able to transition to a working clinical protocol that had the scientific backing of an ethics approved clinical study.

Large randomized control trials comparing new and old technologies which measures endpoints such as toxicity, local control and overall survival are often impractical [17]. Recruitment could be difficult due to patients' or clinicians' bias for newer technology. Interdepartmental variations in treatment techniques and technologies would weaken pooled results. Study outcomes which often take many years to materialize are outpaced by rapid technological advances, and are at risk of becoming obsolete at the time of publication.

Figure 2 displays an adapted generalized methodology, which can be incorporated into any clinical protocol for the introduction of any new radiotherapy techniques and technologies.

It must be stressed that selecting common clinical problems and using clinical expertise to determine parameters that allow rapid accrual of eligible patients and subsequent testing of new radiotherapy techniques and technologies are key elements for this to occur. For example, selecting an eligibility criteria of a MCD of $> 2\text{Gy}$ which was a clinically relevant dose and was also low enough to allow for rapid patient accrual, together with a pragmatic sample size of 10 patients are both critical elements in the success of the methodology.

With specific reference to the DIBH study, our results indicate that all patients who receive left breast or chest wall radiotherapy that have heart dose $> 2\text{Gy}$ benefit from the technique. The DIBH plan showed $\geq 30\%$ reduction in MCD compared to SCFB in all patients. The average reduction was approximately 50% from 4.9 ± 2.2 to $2.2 \pm 1.2\text{Gy}$. Although the reproducibility as measured by the standard deviation of the MPLD ≤ 3 in 50% of the patients [95% CI (19 - 81)] had a standard

deviation $\leq 3\text{mm}$, which was less than the 80% cut-off to consider the technique reproducible, further clinical evaluation of the individual portal images revealed that the breast tissue was adequately covered and treated in each case.

The results of this study are comparable to other DIBH protocols published locally [18].

We acknowledge some caveats in implementing the DIBH technique across all departments. In particular, smaller departments may have issues pertaining to allocation of resources and staff training. In addition, resources used in this study including video eyewear and the Varian RPM system are costly to purchase and require a multi-disciplinary approach to implement safely. Cost analysis for this study was not performed or reported although new equipment was purchased. We are currently developing a multi-centre TROG trial to implement this solution at all centers and validate it using a range of technologies that are more widely and easily available.

However, even smaller departments may find the proposed technology implementation process useful as many departments employ new radiotherapy techniques and technologies without a scientific approach to assessing the magnitude of its benefit due to limited resources. Multiple authors have written on the challenges and costs of introducing new techniques and technologies and we propose well-devised studies in the future to answer the questions in a quantitative manner.

Conclusion

We successfully implemented a DIBH radiotherapy technique in our department for the treatment of left sided breast cancer under the framework of a small-scale clinical study; DIBH was demonstrated in our institution to be feasible. Using the scheme we also determined that approximately 80% of left sided breast cancer patients would benefit from DIBH with the technique conveying significant dosimetric benefit to all of these patients. DIBH is now in routine use in our institution. We have also developed a modified general methodology from our clinical study that we intend to use to guide the introduction of other new techniques and technology in our department.

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