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Dosimetric Advantages of Irregular Surface Compensator Technique Using Flatten Filter Free (FFF) With Deep Inspiration Breath Hold (DIBH) For Whole Breast with Regional Nodes Irradiation

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Keywords:

Deep inspiration breath hold (DIBH); Whole breast irradiation; Irregular surface compensator (ISC); Flatten filter free (FFF)

1. Abstract

1.1. Purpose: Inclusion of internal mammary (IM) lymph nodes as a part of regional nodal breast irradiation has the potential to reduce local recurrence, distant recurrence, and improve survival in breast cancer patients. However, the increased risk of cardiac toxicity and lung injury associated with irradiation of the IM lymph nodes has drawn increased scrutiny. The use of deep inspiration breath holds (DIBH) to minimize this toxicity has increased significantly in recent years, especially for the treatment of left-sided breast cancer. This study evaluates dose delivery techniques for breast cancer patients with IM nodal involvement, including traditional tangential fields with field-in-field (FiF) modulation and flattened beam energy, and tangential fields with irregular surface compensator modulation (ISC) and flattening filter free beam energy (FFF). The effect of DIBH on organ at risk dose was also examined. Finally, treatment efficiency is a significant factor impacting the feasibility and accuracy of DIBH treatment, and was also evaluated in this study.

1.2. Methods: Twenty breast/chest wall patients, including 10 with left-sided and 10 with right-sided disease, were randomly selected. The breast target, IM nodes, ipsilateral lung and heart were contoured following the NSABP-B51/RTOG 1304 protocol. Each patient was planned using three different techniques: (1) Tangential beam arrangement with FiF modulation, flattened beam energy, and DIBH (2) Tangential beam arrangement with ISC modulation, FFF beam energy, and DIBH; (3) same as (2) but free-breathing (FB). FIF plans included open tangents and multi-leaf collimator-defined subfields, and utilized a monitor unit weighting of at least 70% for the open field and no more than 30% for sub-fields. ISC plans utilized an electronic compensator, a feature in the Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA, USA), which utilizes a sweeping multi-leaf collimator motion during delivery to improve dose homogeneity for irregular shapes. The prescription dose for all plans was 42.56 Gy delivered in 16 fractions. All plans were created using the Eclipse (Version 13.5) treatment planning system. Plans were compared and evaluated for target coverage, dose to Ipsilateral lung and heart, and treatment time. Dosimetric parameters examined included the breast target maximum dose (Dmax) and percentage of the breast target volume receiving 95% of the prescription dose (V95%). For the ipsilateral lung, the percentages of the volume receiving 20Gy,10Gy and 5Gy (V20Gy, V10Gy and V5Gy, respectively) were determined. Finally, for the heart, the mean dose (Dmean), and the dose to 10% of the heart volume (D10%) were evaluated. To assess the degree of OAR sparing offered by DIBH vs FB, the Dmean and V20Gy, V10Gy and V5Gy for both heart and ipsilateral lung were computed. Differences were assessed for statistical significance($p<0.05$) by use of Student's t-test.

1.3. Results: For the breast target volumes, both delivery techniques (FiF and ISC) exhibited similar coverage (V95%). However, ISC plans demonstrated improved dose homogeneity and a reduced maximum dose. ISC plans provided a slightly lower mean heart dose compared to FiF (1.0Gy vs. 2.1Gy, p=0.05). ISC plans also reduced the V20Gy of the ipsilateral lung (18%v.s.22%, p=0.03). The addition of DIBH offered significant OAR sparing compared to FB. Mean heart dose was significantly reduced for DIBH plans 3.39 Gy to 1.02 Gy (p=0.005). DIBH increased the volume of the ipsilateral lung by approximately 40% on average compared to FB. As a result, Dmean and V20Gy, V10Gy and V5Gy for the ipsilateral lung were significantly lower (p<0.0001) in the DIBH group. Finally, because of the dynamic MLC delivery of ISC and the ability to utilize FFF beam energies with this technique, beam-on time was reduced by 50% on average compared to FiF delivery with flattened beam energies.

1.4. Conclusions: Utilization of ISC to modulate breast tangents offers improved target dose homogeneity and OAR sparing, without sacrificing target coverage or skin flash compared to FiF modulation. ISC also offers the opportunity to use FFF beam energies, significantly improving treatment efficiency, allowing for a simpler application of DIBH to further reduce OAR dose. Reduced delivery time also helps to minimize patient motion associated with breath hold, improving delivery accuracy. ISC modulation for breast tangent fields is a suitable replacement for FIF, and when combined with DIBH and FFF provides an optimal combination of dosimetry and delivery efficiency for whole-breast irradiation with IM nodes.

2. Introduction

Whole breast radiotherapy (WBRT) is the standard therapy for early breast cancer following breast conservation surgery. WBRT reduces the risk of local recurrence and results in long-term survival similar to that obtained with mastectomy alone [1]. Inclusion of the internal mammary (IM) nodes in the target volume for WBRT (WB+IM RT) has been shown to improve disease-free and overall survival [2]. However, WB+IM RT increases dose to the heart up to three times [3]. A linear, no-threshold relationship between mean heart dose and major coronary events has previously been shown, with the risk of major coronary events increasing by 7.4% for every additional gray (Gy) delivered to the heart [4]. The most common cause of cardiac mortality is ischemic cardiac disease, believed to be the result of radiation exposure to the anterior heart, predominantly the left anterior descending artery. Higher doses of anthracyclines chemotherapy drugs combined with higher dose volumes of cardiac irradiation are associated with an increased risk of cardiac events [5]. In order to maximize the survival benefits of WB+IM RT, cardiac sparing techniques should be adopted.

Therefore, radiation therapy planning for WB+IM RT aims to protect organs at risk (OARs) and to deliver prescription dose uniformly throughout the target. Various advanced irradiation techniques such as intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) have been developed to reduce OAR dose in radiotherapy. However, their use is somewhat limited in WB+IM RT, and three-dimensional conformal radiation therapy (3DCRT) remains a standard planning technique. Although IMRT and VMAT can offer higher conformity and superior target coverage, these techniques are associated with increased low-dose exposure to OARs. Multiple studies have confirmed that IMRT and VMAT result in significantly larger low-dose volumes in surrounding normal tissues compared to 3DCRT [6]. This is a major concern when using IMRT or VMAT, since larger volumes of normal tissue exposed to lower doses may increase a radiation induced risk of secondary cancers [7]. In addition, IMRT and VMAT may not provide the necessary flash (field margin beyond the skin surface) to ensure appropriate target coverage and dosimetric robustness for whole-breast radiation. 3DCRT allows for the addition of flash and minimizes low dose exposure to the lungs, heart, and contralateral breast.

Practically, in three-3DCRT breast planning, and especially, WB+IM RT, the entrance and exit beams pass through or near the lung and heart. This is unavoidable due to the proximity of these OARs to the breast and nodal target volumes. these techniques A key method available for reducing the dose to these OARs is minimization of respiratory motion. This can be achieved using gating, breath tracking, or optimized free breathing methods. Currently, deep inspiration breath-hold (DIBH) is the most common method used, especially for treatment of left-sided breast cancer [8]. During both simulation and treatment delivery, the patient takes a deep breath and holds it in for some time to negate respiratory movement, expand the lung, and push the heart away from the chest wall. This increases the distance between the target and the heart, reducing the radiation dose delivered to the heart. Lung volume is also increased, improving volume-based dose statistics.

While the addition of DIBH can help to reduce OAR dose, WB+IM RT with 3DCRT is also complicated by irregularities in the chest wall tissue and varying thickness of lung tissue. These cause the resulting dose distribution in and around the target to be inhomogeneous, increasing hot spots and decreasing target coverage. OAR dose can also be increased, especially when high dose volumes approach the heart and lung. To address these challenges, techniques have been developed to maintain the benefits of 3DCRT, while allowing for a limited amount of dose modulation. A commonly used technique is the addition of field-in-field segments to the traditional parallel-opposed tangential fields for WBRT. However, reducing the volume receiving high doses (>107%) have been shown to result in a small increase in the tissue volume receiving < 95% prescribed dose [9]; this trade-off is considered a disadvantage of the FIF technique. In addition to FIF, the electronic compensation has been developed and reported to improve the dose conformity [10]. Electronic compensation is a relatively simple method of forward planning with a dynamic multi-leaf collimator (MLC) in order to improve dose distributions. Irregular surface compensator (ISC) is such an electronic compensation algorithm developed and implemented in the Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA, USA). The use of ISC in the presence of a curved compensation surface allows for more homogeneous dose distributions. The fluence distribution required to produce an isodose perpendicular to the central axis at a specified depth. The desired fluence is edited manually, allowing for the user to improve target dose homogeneity and reduce OAR dose as needed. As a result, this algorithm is useful in cases where the shape of the target volume is rounded, such as breast treatments.

Recently, modern linear accelerators have become capable of delivering both traditional flattened photon beams, as well as flattening filter-free (FFF) beams. These FFF beams have several advantages like increased dose rate, reduced the head scatter, less beam-on time and reduced out of field dose as compared to flattened beam [11]. However, the unmodulated beam profile is forward peaked compared to a traditional flattened beam. By pairing FFF beams with ISC for breast treatment, the user is able to take advantage of the properties of FFF, while maintaining the desired dose profile throughout the treatment volume.

Previous studies have demonstrated the superiority of ISC compared with the conventional tangential beams for the treatment for breast cancer [12]. However, none have examined the utilization ISC combined with DIBH and FFF as a potential replacement technique for traditional free-breathing FIF with flattened beam for WB+IM RT. This study dosimetrically evaluates and compares FiF delivery with flattened photon beam and ISC delivery with FFF beam for WB+IM RT. The addition of DIBH is also examined. Finally, treatment efficiency for these techniques is analyzed. Of note, this is also the first full dosimetric report of WB+IM RT for both breast sides, and is not limited to left-sided breast targets.

3. Materials and Methods

3.1. Patient Selection

20 invasive carcinoma of the breast cancer patients (10 left- and 10 right- side) who had an indication for whole breast radiotherapy, including the IM nodes, according to National Surgical Adjuvant Breast and Bowel Project (NSABP) B-51/ Radiation Therapy Oncology Group (RTOG) 1304 protocol [13] were selected. For this retrospective planning study, the patients were selected randomly, with no selection criterion used, other than treatment site, in order to differentiate the study group and to avoid selection bias. The median patients' age was 52 years (range 42–78).

3.2. Treatment Planning

All the patients were coached on the DIBH technique, which involved taking a deep breath, and holding it for a duration of 15s. and Using the respiratory gating for scanners (RGSC, Varian Medical Systems, Palo Alto, CA, USA) system for breath tracking, patients underwent computed tomography (CT) simulation (Somatom Confidence Pro RT; Siemens, Germany) under breath hold conditions. Breath tracker motion of 3mm or less was considered a successful hold. In addition to acquired breath hold scans, patients were also scanned free-breathing. A slice thickness of 3mm was used for both scan types. The breast clinical target volume (CTV), IM nodes and OARs (lungs, heart, liver, and spinal cord) were contoured on the CT scan for planning and then performed the deformation registration to propagate the contours to another CT dataset. Contours followed the guidelines outlined in the NSABP B-51/RTOG 1304 protocol. The planning target volume (PTV) was generated by expanding the CTV by 5 mm in all directions, except in the direction of the skin surface. PTV for evaluation of the dose distribution (Breast PTV_EVAL) was created by subtracting the chest wall and ribs from the PTV, and shrinking it by 3mm away from the skin surface. Deformable image registration was then performed in Velocity™ (Version3.1, Varian Medical System, Palo Alto, USA) to transform and copy all structure contours from the DIBH-CT to the FB-CT this study.

CT-based three-dimensional treatment planning was performed using the Eclipse™ planning system (Version 15.6, Varian Medical Systems, Palo Alto, CA, USA). Each patient was planned utilizing three different techniques: (1) FIF plan with flattened beam and DIBH (2) ISC with FFF beam and DIBH; (3) same as (2) but FB. The Acuros XB algorithm was used for dose calculation, and tissue heterogeneity correction was used in all the treatment plans. The prescribed dose was 42.56 Gy in 16 fractions. These three plans for each patient used the same isocenter, tangential beam angles, and dose normalization. For each plan, before either FIF or ISC modulation patterns were added, beam arrangement and field extent was determined by creating a 3D wide tangent plan with two parallel opposing tangential fields with beam angles and field borders chosen to encompass the entire Breast PTV_EVAL and IM nodal volumes. FIF or ISC modulation was then added to this beam arrangement.

The planning process for the addition of FIF modulation was as follows. First, the appropriate dose level to shield was determined by taking the dose at the maximum dose point (Dmax) and reducing it by 2-4%. This chosen dose level was then displayed as an isodose cloud in the in the beams eye view (BEV). One of the open tangential fields was then copied and designated the first subfield. The MLCs on this subfield were adjusted to shield the high dose cloud previously displayed in the BEV. Beam weighting between the open tangent and the subfield was then adjusted to try and minimize the appearance of the high dose cloud, thus minimizing the plan Dmax. If hot spot regions >105% of the prescribed dose remained, the process described above was repeated to create additional subfields, and achieve an optimal dose distribution. Finally, if there were observable cold regions within the target volumes receiving <95% of the prescribed dose, additional subfields were added with the MLCs set to fit the cold region in the BEV. The example of subfields of FIF was shown in (Figure 1).

The addition of ISC modulation was also started based on the original 3D wide tangential plan. The process for the addition of ISC modulation using the fluence editor was as follows. First, ISC was applied, and dose calculation was performed to generate the initial fluence map. On the fluence map, transmission factors values in hot spot regions (receiving >105% of the prescribed dose) were sampled using the transmission-measuring tool. The measured hot spot fluence transmission value was reduced by 3%, and this reduced value was entered into the manual fluence editing tool. The areas corresponding to hot spot regions were then painted on the fluence map, replacing the original transmission values with this reduced value. This process was performed for each field. The dose distribution was then recalculated with the new fluence pattern. If hot spot regions > 105% of the prescribed dose remained, the process described above was repeated to achieve an optimal dose distribution. Similarly, cold spot regions were modified by manually increasing the values of transmission factors on the fluence map. Transmission values were also modified to ensure sufficient flash. A typical initial fluence pattern is presented in (Figure 2).

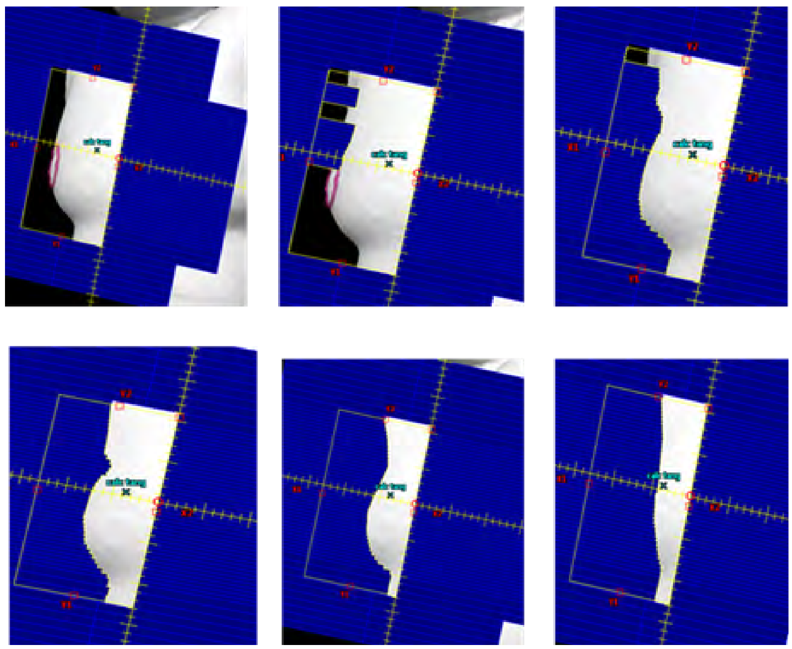

Figure 1: Example of primary and MLC-defined subfields for traditional field in field (FiF)

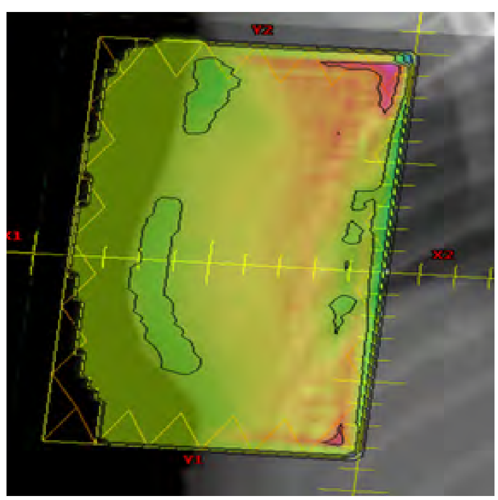

Figure 2: Example of editable fluence map for irregular surface compensator (ISC) modulation

3.3. Plan Evaluation and Delivery Time

The FIF and ISC treatment plans were compared objectively using dose-volume histogram (DVH) information for the breast PTV_EVAL and OARs. For the breast PTV_EVAL, the maximum dose (Dmax) and volume receiving at least 95% of the prescription dose (V95%) were calculated and compared. For the heart, the values of mean dose (Dmean) and the dose corresponding to 10% volume on the cumulative DVH (D10%) were evaluated. For the ipsilateral lung, the percent of the total volume receiving more than 5, 10, and 20 Gy (V5Gy, V10Gy, and V20Gy) were compared. Treatment efficiency was evaluated by looking at total monitor unit (MU) counts and calculated delivery time. Delivery time was calculated for each plan by dividing the total number of monitor units by the planned dose rate. The student's t-test paired two sample for means was used to compare each dosimetric parameter. The significance level was set at $p < 0.05$. Statistical analyses were performed using Microsoft Excel®.

4. Results

4.1. FIF v.s. ISC

The dosimetric results of the comparison between FiF and ISC modulation types for WB+IM RT can be found in (Table 1). ISC modulation slightly increased V95% and decreased Dmax for the breast PTV_EVAL compared with the FiF technique (p=0.05). For the ipsilateral lung, ISC demonstrated a significant decrease in V20Gy compared with the FIF technique (p=0.03). However, no significant difference was observed when V10Gy and V5Gy were compared. For the heart, the average Dmean of ISC plans was slightly reduced by 1.1Gy (p=0.05), but the difference in average D10% was not statistically significant (p=0.12). The average number of MU per fraction needed to deliver 2.66 Gy for the FiF and ISC techniques was 281±38 and 358±50 counts, respectively, demonstrating a significant difference (p= 0.01). Although The FIF plans required a significant increase in MU, the ability to use the FFF beam type with ISC, which has a 1400MU/min max dose rate, compared to 600MU/min for the flattened beam needed for FiF, resulted in a significant reduction in beam-on time for ISC compared to FiF (159±48 v.s. 325±50s, p=0.01).

Table 1: Comparison of dosimetric parameters and treatment efficiency of field-in-field (FiF) and irregular surface compensator (ISC) for whole breast + internal mammary node radiation therapy

	Breast PTV_EVAL		**Ipsilateral Lung**			**Heart**			
	V95%	**Dmax**	**V20Gy**	**V10Gy**	**V5Gy**	**D10% (cGy)**	**Dmean(cGy)**	**MU**	**Beam-on Time (sec)**
Irregular Surface Compensator (ISC)	95%±5%	105%±3%	18%±7%	25%±10%	1%±5%	375±110	103±36	358±25	159±48
Field-in-Field (FiF)	95%±4%	105%±4%	22%±9%	28%±15%	0%±9%	401±95	212±65	281±38	325±50
p-value	0.05	0.06	0.03	0.08	0.05	0.12	0.05	0.01	0.01

Abbreviations: PTV_EVAL = The volume of PTV reduced 5 mm below the skin surface and excluding the chest wall and ribs; MU = Monitor unit; D_{max} = Maximum dose; D_{mean} = Mean dose; $D_{10\%}$ = Dose to 10 % of organ volume; $V_{x\%}$ = Organ volume receiving x% of the prescription dose. V_{xGy} = Organ volume receiving xGy

4.2. FB v.s DIBH

An example of 2D isodose distributions in the transverse plan obtained from the same patient planned on FB and DIBH CT datasets are presented in (Figure 3). A DVH comparison for both techniques for the same patient is presented in (Figure 4). Dosimetric comparisons for the heart and ipsilateral lung are shown in (Table 2 and 3), respectively. Respiratory motion type (FB vs DIBH) did not have a significant effect on target coverage or maximum dose. However, for the heart, compared with FB, DIBH achieved a statistically significant reduction in the Dmean (3.4 Gy vs 1.0 Gy, p =0.005), V20Gy (5.4% vs 0.1 %, p =0.003), V10Gy (7.4% vs 0.3%, p =0.002), and V5Gy (9.1% vs 0.8%, p =0.003). For the ipsilateral lung, instituting DIBH conditions increased the lung volume by 40% on average compared to FB(p<0.001). This resulted in a significant reduction in Dmean on average (10.0 Gy vs 1.03 Gy), and a slight reduction in V20Gy (23.4% vs 17.3 %), V10Gy (28.7% vs 23.1%), and V5Gy (35.5% vs 31.4%). All reductions were statistically significant (p<0.001).

Table 2: Comparison of heart organ at risk dosimetric parameters for free breathing (FB) v.s. deep inspiration breath holds (DIBH) motion management techniques

	Volume (cm3)	**Dmean (cGy)**	**V5Gy (%)**	**V10Gy (%)**	**V20Gy (%)**
free breathing (FB)	705.5 ± 93.1	339.0 ± 226.5	9.1 ± 6.6	7.4 ± 6.7	5.4 ± 5.5
Deep inspiration breath hold (DIBH)	677.9 ± 78.1	102.5 ± 35.7	0.8 ± 0.6	0.3 ± 0.4	0.1 ± 0.1
p-value	0.11	0.005	0.003	0.002	0.003
△ (FB-DIBH) (% or cGy)	8.9 ± 1.2	236.5 ± 206.1	8.3 ± 6.4	8.3 ± 6.4	8.3 ± 6.4

Abbreviations: D_{mean} = Mean dose; $D_{10\%}$ = Dose to 10 % of organ volume; V_{xGy} = Organ volume receiving xGy

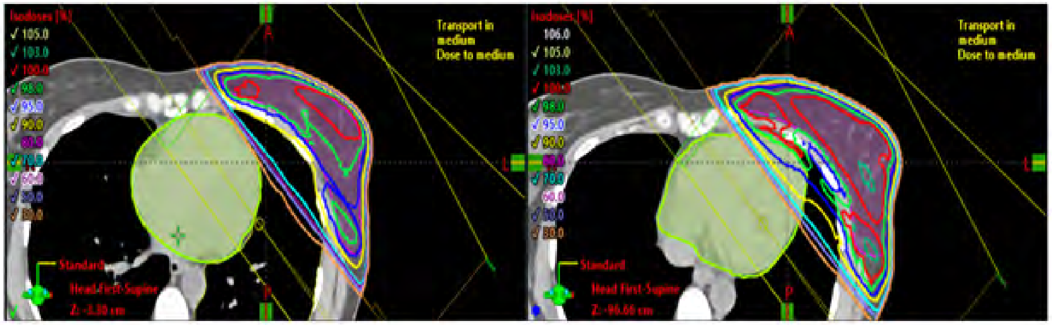

Figure 3: Example of transverse plane 2D isodose distribution for the same patient showing both deep inspiration breath holds (DIBH) (a) and free breathing (FB) (b) motion management. The prescription isodose line (42.56Gy) is show in red. The 95% of prescription isodose line (40.43Gy) is shown in blue. Volumes displayed are pink: PTV_EVAL, green: heart. The breast PTV_EVAL = the volume of the PTV reduced by 5 mm below the skin surface and subtracting the chest wall and ribs.

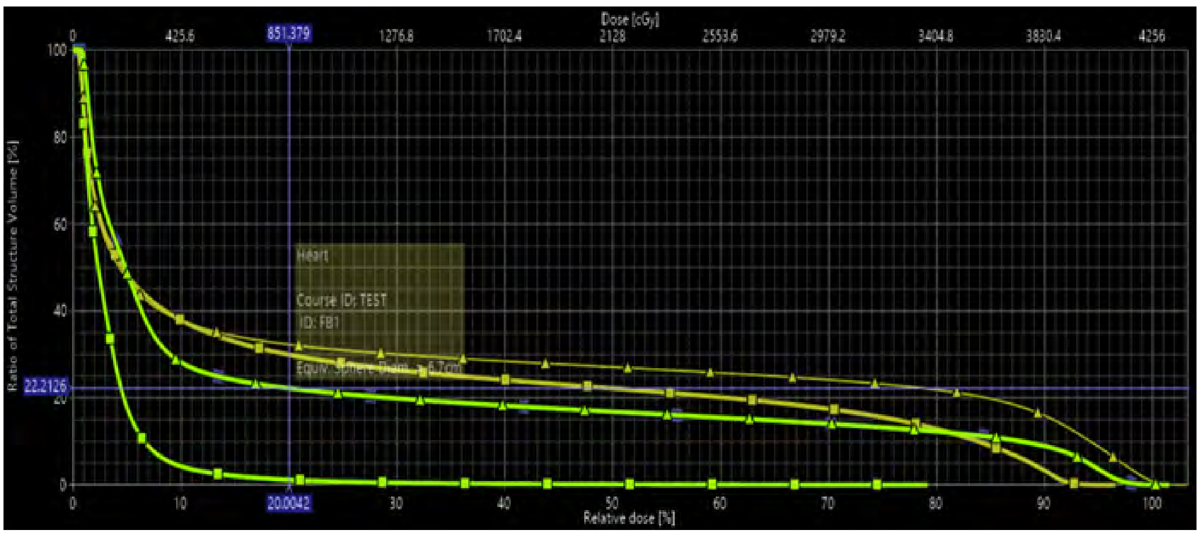

Figure 4: Example of organ at risk (OAR) dose-volume histogram comparison for free breathing (FB) vs. deep inspiration breath holds (DIBH) of one patient. Displayed lines are as follows, yellow : Ipsilateral lung; green: heart; ▲: FB; ■: DIBH.

Table 3: Comparison of ipsilateral lung dosimetric parameters for free breathing (FB) vs. deep inspiration breath hold (DIBH) motion management techniques

	Volume (cm3)	**Dmean (cGy)**	**V5Gy (%)**	**V10Gy (%)**	**V20Gy (%)**
Free Breath (FB)	1581.3 ± 407.9	1003.1 ± 354.5	35.5 ± 9.7	28.7 ± 9.2	23.4 ± 9.1
Deep inspiration breath hold (DIBH)	2172.0 ± 451.3	102.5 ± 35.7	31.4 ± 10.2	23.1 ± 8.6	17.3 ± 7.2
p-value			<0.001		
△ (FB-DIBH) (% or cGy)	39.6 ± 17.6	209.2 ± 102.6	4.1 ± 2.2	5.6 ± 2.6	6.1 ± 2.9

Abbreviations: D_{mean} = Mean dose; $D_{10\%}$ = Dose to 10 % of organ volume; V_{xGy} = Organ volume receiving xGy

5. Discussion

WB+IM RT is a commonly delivered treatment paradigm but presents challenges due to the dosimetric requirements to adequately treat the target volumes, and the proximity of the targets to sensitive OARs. Thorsen et al [2] discussed the treatment planning challenges involved in including the IM nodes in WBRT, driven by the location of the IM nodes, typically at deeper depths and adjacent to the lungs and/or heart. In recent years, dynamic radiotherapy techniques like IMRT and VMAT have been used to provide a more homogeneous and conformal dose distribution in radiotherapy treatment. These techniques allow delivery of a high dose to the target volume and an acceptably low dose to surrounding tissues. Various studies have compared static radiotherapy techniques like 3D-CRT with dynamic ones such as IMRT and VMAT [6-7,10]. Most of them showed that although IMRT and VMAT provide good homogeneity, conformity, and target coverage, they are characterized by much larger low-dose volumes in surrounding normal tissues compared to 3DCRT. A larger volume of normal tissue exposed to lower doses may increase the risk of radiation-induced secondary cancer. Since the breast cancer survival rate has improved over the years, it has become crucial to estimate the secondary cancer risk following radiation. In addition to concern about secondary malignancy, the intensely modulated fields of IMRT and VMAT may not provide the robust target coverage needed for WB+IM RT, due to the unstable nature of the breast surface. As a result, 3DCRT techniques remain common for WB+IM RT treatment.

The FiF technique for WB and WB+IM RT is a practical 3DCRT treatment planning method, which is widely used, and has become standard in recent years. ISC is less ubiquitous, and radiotherapy treatment planners at many institutions may be unfamiliar with the implementation of this technique. Our institution is unique in that ISC has been utilized extensively for many years for WB and WB+IM RT. Planning workflow standardization and national dosimetry protocols are critical to guarantee the quality of plans using the ISC modulation technique. Despite these challenges, ISC offers improvement in patient dose distributions for WB+IM RT. Although previous research has found ISC to be superior to tangents with physical wedge for WBRT without IM treatment [9] research comparing ISC and FiF for WB+IM RT is limited. Therefore, the present study aims to compare dosimetry between the ISC and FiF techniques following the national NSABP B-51/ RTOG 1304 protocol for WB+IM RT for both right and left-sided breast treatment. The comprehensive dosimetric data presented here for WB+IM RT with the ISC technique and FFF beam energy is also a valuable resource for planners hoping to gain experience with this planning technique.

The results of this study showed that the ISC technique is capable of improving target coverage and reducing dose heterogeneity and hotspots compared to FiF for WB+IM RT. This difference was shown to be greater for patients with larger target volumes. These results complement the findings of Sasaoka et al [9]. who investigated WB RT without IM. In general, it is thought that breasts of western women are much larger compared with Asian women. The mean volume of both the right and left breast targets in this study was approximately 1000cc. A larger breast volume is associated with increased high dose volumes (hot spots) for the same beam energy, and an increase in the required MU. Attempts to reduce hot spots by lowering target coverage may result in insufficient dose for effective treatment, increasing the likelihood of local recurrence. Maintaining target coverage is particularly important for patients with multifocal or lobular disease, for which cold spots in the PTV should be avoided. Furthermore, decreasing the volume and magnitude of hot spots could lead to a reduction in treatment toxicity. For this reason, ISC may be better suited to hypofractionated schedules compared to FiF where hotspots could increase the biological effect much more than the percent increase in physical dose. Schedules with 2.66 Gy per fraction have grown in popularity, having been shown to lead to the same clinical outcome as schedules with doses of 2 Gy per fraction [14], and might be favored by some radiation therapy departments to decrease waiting times or increase patient throughput. More than 40% of our WB+IM RT patients in our department are treated with this moderate hypofractionated schedule, and this schedule was used for this study. Due to its ability to decrease hot spots and maintain or increase target coverage compared to FiF, ISC was found to be the ideal 3DCRT technique, especially for patients with larger breasts. These benefits may be enhanced when treating multifocal or lobular disease, and/or when utilizing hypofractionated treatment regimens.

As noted previously, the reduction of heart dose has become a focus in breast radiotherapy due to the heart's apparent sensitivity to even low doses of radiation. The relative risk of major coronary event increases by 7.4% for every Gy of mean heart dose with no apparent threshold [4-5]. The most significant reduction in mean heart dose in this study was achieved by the addition of the DIBH motion management technique for left-sided breast cancer patients. Although ISC resulted in a slight decrease in mean heart dose compared to FiF, both techniques demonstrated relatively low (<3Gy) mean heart doses when paired with DIBH on average. For ISC plans generated on FB datasets, the heart Dmean increased from 1.0Gy (DIBH) to 3.4Gy (FB) on average. In addition, the heart volume receiving 5Gy-20Gy also increased by 5-9% when using a FB technique. Given the complex structure and physiology of the heart, there are radiobiological questions regarding which parameters are most harmful to the heart and cardiac vasculature—a large volume of the heart receiving a low radiation bath or a small volume of the heart receiving a higher dose. Hence, it is important to consider all dose parameters such as mean dose, V5Gy, V10Gy and V20Gy when assessing the risk of a future cardiac morbidity.

In addition to considerations of the heart dose, reduction in dose to the lung is also a challenge in WB+IM RT. It is known that increasing pulmonary dose is associated with a higher rate and severity of radiation-induced pneumonitis.

Studies [1-2] have noted grade 3 pneumonitis after radiotherapy for non-small cell lung cancer. In these studies, the incidence rate was 2%, 4% and 24% of lung volumes receiving V5Gy < 35%, V5Gy = 35–50%, and V5Gy > 50%, respectively. Although ISC did offer a reduction in ipsilateral V20Gy compared to FiF, a larger protective effect was seen with the addition of DIBH. DIBH demonstrated a statistically significant reduction in the percentage of lung volume receiving 5, 10, and 20Gy (V5Gy, V10Gy, V20 Gy). This reduction is predominantly due to expansion of the lung under DIBH conditions, increasing the total volume and decreasing the relative volume receiving each dose level. In addition, deep inspiration also decreases lung density, which may further contribute to lowering the amount of dose deposited in this tissue.

Although the MU required for treatment with ISC using FFF beam energies was found to be 27% more on average compared to FiF with flattened beam energies, the average beam-on time for ISC with FFF is 50% faster. This is due to the dynamic MLC motion of ISC, and the ability to utilize FFF beam energies, which boast dose rates significantly higher than traditional flattened beams (1200MU/min vs 600MU/min). FFF beam profiles are non-uniform, with a maximum dose at the center, decreasing towards the periphery. The linear accelerator is calibrated (1 cGy = 1MU) on the central axis of the beam under reference condition (10 × 10cm field sized at the depth of maximum dose. Therefore, delivery of dose away from central axis requires additional MU, and may result in higher dose on central axis. For this reason, the FiF technique, which depends on an open tangential field to delivery ~80% of its dose, requires a flattened beam profile, and cannot easily make use of FFF beam energies. In contrast, ISC, with its dynamic modulation can effectively correct for the non-uniformity of the FFF beam profile. The time-savings afforded by the use of FFF beam energies may be especially important for patients treated with DIBH. Patient comfort be increased by decreasing the amount of time required under breath hold conditions. In addition, it has been reported that displacement of the left anterior descending artery varied significantly under DIBH conditions, including during an individual treatment session8. This can significantly alter the dose received by the heart from breast RT. Faster treatment delivery achieved with ISC and FFF beams may reduce the probability of cardiac motion during treatment delivery.

Although the addition of both FiF and ISC modulation may require additional time and effort compared to the placement of unmodulated open tangential fields, for experienced planners, ISC planning times may be decreased by approximately 5–10 min compared with conventional FiF. This is because FiF requires additional steps to create the necessary subfields and manually adjust the weighting to achieve the desired dose distribution. The ISC fluence editor directly modulates the dose distribution and does not require manual subfield adjustment. Since both FiF and ISC field types are dynamically modulated by the multi-leaf collimator, patient-specific QA could be required depending on physicists' decision and departmental policies. Because the degree of modulation for these techniques is relatively low compared to IMRT or VMAT, it is possible that patient-specific QA could be simply performed by independently validating the machine MLC position using machine delivery logs.

6. Conclusion

This study provides a large-scale and comprehensive analysis of dosimetric parameters observed when comparing ISC with FFF beam energy vs. FiF with flattened beam energy, and DIBH vs. FB motion management techniques for right and left-sided WB+IM RT. The ISC modulation technique allows significant improvements in target dose distribution when compared with the FiF technique. OAR dose remained similar for both techniques, portending no difference in expected side effect profile. ISC also offers the ability to utilize FFF beam energies, reducing beam-on time and the potential for patient motion during treatment. The addition of DIBH motion management is relatively simple and can be incorporated into routine clinical practice without extensive additional work. DIBH was found to reduce unwanted dose exposure to hearts and lungs compared to FB. The ISC modulation technique for WB+IM RT, in conjunction with FFF beam energy and DIBH motion management allows for the benefits of 3DCRT, such as skin flash and reduced low dose exposure, offers improved target coverage and heterogeneity, better normal tissue sparing, and shorter treatment time compared to traditional FIF with flattened beam and FB conditions. The ISC modulation technique is a suitable replacement for FiF. Further enhanced by the addition of FFF beam energy and DIBH motion management, it is an optimal technique for WB+IM RT.

7. Disclosures

No financial support was provided for this study. All authors have no disclosures or conflicts of interest to declare.

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