J Breast Cancer. 2022 Oct;25(5):349-365
https://doi.org/10.4048/jbc.2022.25.e37
pISSN 1738-6756·eISSN 2092-9900

Journal of Breast Cancer JBC

Review Article

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Intensity Modulated Radiotherapy and Volumetric Modulated Arc Therapy in the Treatment of Breast Cancer: An Updated Review

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OPEN ACCESS

Received: Mar 12, 2022
Revised: Jul 16, 2022
Accepted: Jul 24, 2022
Published online: Aug 24, 2022

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ABSTRACT

Radiation therapy (RT) plays a critical role in breast cancer treatment. In the modern technological era, innovations and progress in breast RT and delivery techniques have greatly improved the clinical outcomes. Intensity-modulated RT (IMRT) is a modern RT technology that permits the modulation of RT beams, ensuring a more uniform dose distribution through the target tissue and better avoidance of underlying critical structures. Recently, several studies have been published on breast IMRT. However, the interpretation of these results can be challenging because of the wide diversity of patients and treatment. The purpose of this study was to review these studies, focusing on the impact of IMRT on reducing toxicity and increasing convenience, as well as addressing concerns regarding breast IMRT.

Keywords: Breast Neoplasms; Radiotherapy; Radiotherapy, Intensity-Modulated

INTRODUCTION

In the treatment of breast cancer, randomized trials have demonstrated a significant benefit in ipsilateral breast tumor control following whole breast radiation therapy (RT), which has led to an increase in survival rates when compared with surgery alone [1]. Studies have further assessed the impact of comprehensive regional nodal RT with whole breast or chest wall RT in women with either node-positive disease or high-risk node-negative disease, and have indicated a significant benefit in regional control and survival [2,3]. The benefits of RT in breast cancer treatment are well established; however, there is a struggle for previous trials to keep up with the rapid development of technology for imaging and treatment delivery. For instance, in the early days of breast RT, technology specific to 3-dimensional (3D) imaging of the body did not exist. Instead, RT was delivered using 2D imaging produced by kilovoltage radiation and surface anatomy. This allowed the bony anatomy to be rendered but failed to show the organs at risk (OARs) as well as targets in the soft tissue. Therefore, it was only possible to approximate the tumor bed, internal mammary lymph nodes (IMNs), and axillary lymph nodes. During this time, it was not possible to ensure target coverage or predict the volume of critical organs exposed to harmful radiation, because the path of the

Funding

This study was supported by a faculty research grant of Yonsei University College of Medicine (6-2021-0233) and a grant from the National Research Foundation of Korea (NRF) funded by the Republic of Korea (MSIT) (No. 2019R1C1C1009359).

Conflict of Interest

The authors declare that they have no competing interests.

Author Contributions

Conceptualization: Chang JS, Kim K; Data curation: Chang JS, Kim K; Funding acquisition: Chang JS; Investigation: Chang JS, Chang JH, Kim N, Kim K; Methodology: Chang JS; Project administration: Kim K; Supervision: Kim YB, Shin KH; Visualization: Chang JS; Writing - original draft: Chang JS, Chang JH, Kim N, Kim YB, Shin KH, Kim K; Writing - review & editing: Chang JS, Chang JH, Kim N, Kim YB, Shin KH, Kim K.

radiation beam was only verified through kilovoltage imaging. In the past century, RT has advanced through expanded knowledge of oncological disease processes, applied physics, and technological developments. Although computed tomography (CT) imaging was first developed in 1972, it was not available to radiation oncology departments for treatment planning until the 1990s [4]. Currently, CT treatment planning is the standard of care and is of critical importance for calculating 3D dose distribution and achieving a balance between tumor control and critical OARs protection [5,6].

3D CONFORMAL RADIATION THERAPY IN BREAST CANCER

In 3D-conformal radiation therapy (CRT), although it might be difficult to distinguish between historical 2D plans and modern 3D plans, 3D plans differ by performing optimizations based on the dose to the target areas and OARs [7]. In a common beam path, parallel opposed photon tangent fields are used to treat the chest wall, breast, IMNs, and/or low axilla [8]. If the high axilla and supraclavicular nodes were irradiated, the anterior photon field that treated these regions was matched to the parallel opposed photon tangents. If the IMNs were irradiated, physicians modulated the field size of the photon tangents or added high-energy electrons in lieu of photons to include the IMNs, thus resulting in substantial exposure of the lungs and heart. Materials that absorb radiation can be placed in the path of the beam, and smaller fields can be inserted within a larger field to adjust the dose homogeneity, particularly in the tangent fields.

IMRT IN BREAST CANCER

Intensity-modulated radiation therapy (IMRT) was introduced as an advanced RT technique, and uses dynamic multileaf collimators [9]. IMRT differs from conventional treatment modalities—2D or 3D-CRT—because of its ability to modulate the intensity of radiation directed at specific regions. IMRT planning should be developed according to 3D target volumes that have been contoured on CT images, rather than on surface anatomy, skin incisions, and/or 2D images of underlying bony anatomy and critical OARs (e.g., the heart and lungs) [10]. The process of contouring anatomically individualized targets with standardized OARs requires a high level of expertise and a large amount of time [11]. Additionally, physicians must work with physicists and dosimetrists to determine the optimal parameters to adequately cover the target areas and minimize the radiation dose to OARs. Given that the dose reduction to normal tissues achieved by advanced techniques can be translated into reduced toxicity, dose constraints for potential OARs, which are continually changing because of the evolving knowledge on the dose–volume parameters attributed to known toxicities [12-14], can be used to limit the toxicity risk alongside modern delivery techniques.

Breast IMRT can be classified into two types according to the optimization algorithms for segment weight definition [15]: 1) forward IMRT, which is a simplified version of IMRT wherein only a few segments are manually optimized and is also known as the "field-in-field (FIF)" technique, and 2) inverse IMRT, which is more complex and uses a cost-function reduction algorithm (a process of tradeoffs between target coverage and normal organ sparing) that allows for a more homogeneous dose distribution while sparing the normal tissue from excess radiation dose exposure. However, by considering inverse treatment

planning as an essential component of IMRT, forward IMRT or FIF is often placed in the same classification as traditional "forward" planned 3D-CRT in modern perspectives [16].

When using 3D-CRT, the physician and dosimetrist team select the beam angles and evaluate the dose distribution to optimize the target coverage and predefined OAR constraints. However, using IMRT, 1) the target coverage and OAR constraint goals are entered into the treatment planning system and 2) the number of beams and their angles are selected. The system then generates a plan to conform the radiation dose to the target and avoid the exposure of healthy tissue by varying the beam intensities and shapes throughout the treatment. A complete planning optimization procedure involves repeated optimization iterations under appropriate constraints (**Figure 1**).

Volumetric modulated arc therapy (VMAT) is a form of IMRT that achieves high-dose conformity, but in a shorter time period [17]. Unlike standard IMRT, which relies on multiple independent beam angles, VMAT continuously administers radiation in an arc, while the gantry rotates. Several parameters can be modulated during this delivery (e.g., the field shape

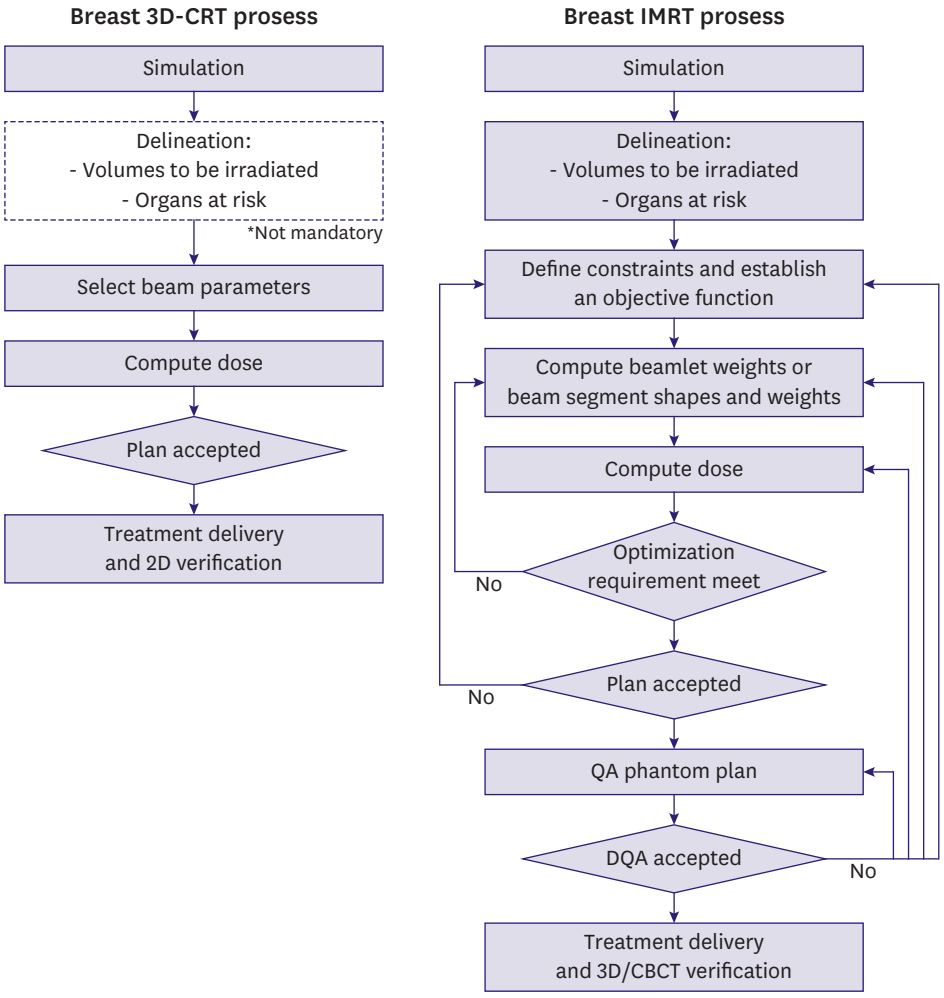

Figure 1. Workflow diagram of the 3D-CRT and IMRT procedures for breast cancer treatment.
3D = 3-dimensional; CRT = conformal radiation therapy; IMRT = intensity-modulated radiotherapy; CBCT = cone-beam computed tomography; QA = quality assurance; DQA = delivery quality assurance.

https://doi.org/10.4048/jbc.2022.25.e37

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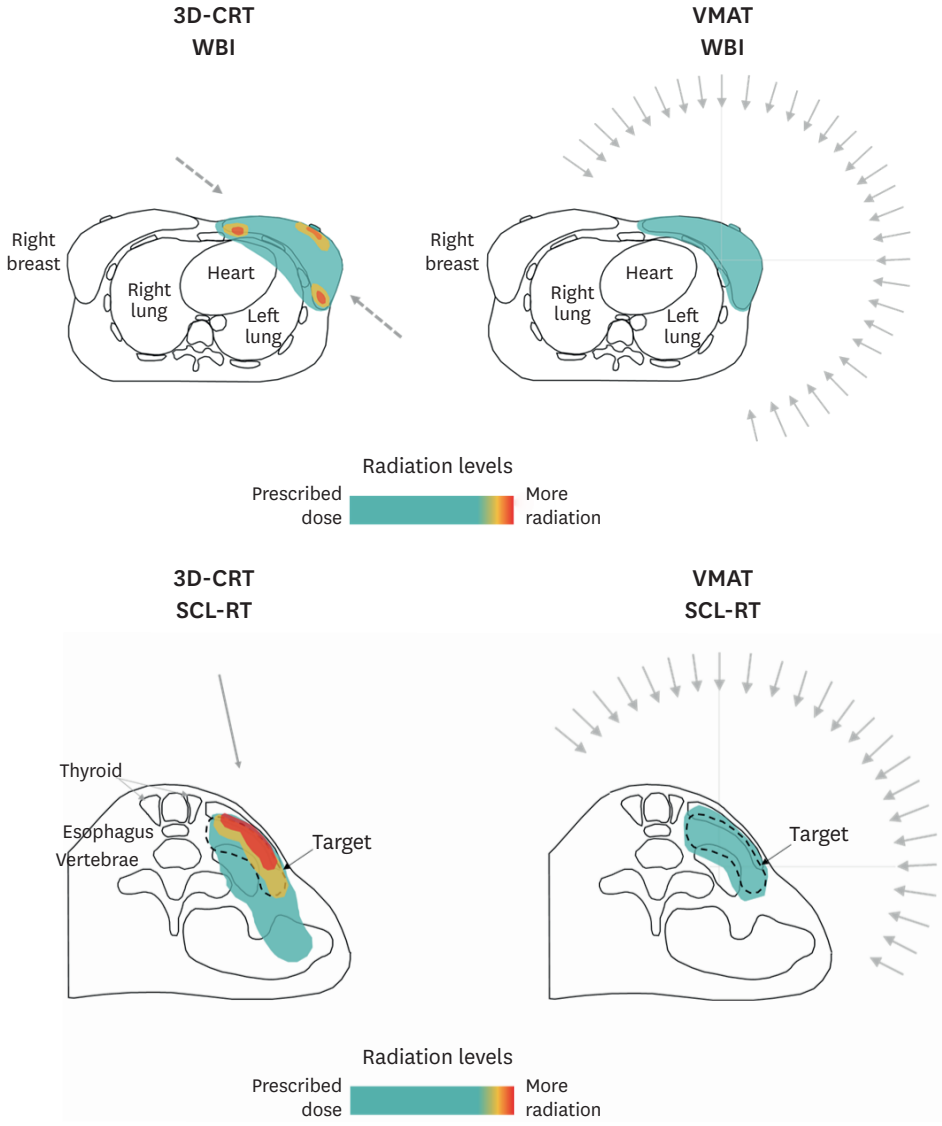

Figure 2. Schematic illustration of the dose distribution of 3D-CRT and VMAT on axial CT images at the level of breast (upper) and lower neck (lower).
3D = 3-dimensional; CRT = conformal radiation therapy; VMAT = volumetric modulated arc therapy; CT = computed tomography; WBI, whole breast irradiation; SCL, supraclavicular; RT, radiotherapy.

and orientation, dose rate, and rate of gantry rotation). Numerous planning studies have demonstrated improved dose distribution and better conformity and homogeneity index in IMRT or VMAT when compared with 3D-CRT (**Figure 2**) [18,19].

IMRT was first performed in Korea in 2001. A decade later, in 2011, IMRT treatment for certain sites of cancer, including the head and neck, brain, prostate, spine, and re-irradiation cases, was partially covered by national health insurance. Since July 2015, this coverage has been extended to include nearly all cancer types. A study investigating recent trends in IMRT reported an 18-fold increase in the use of IMRT for breast cancer in Korea, from 1,921 patients in 2011 to 34,759 in 2018 [20].

https://doi.org/10.4048/jbc.2022.25.e37

Owing to improvements in radiation techniques over the past decade, it is now possible for breast RT to be delivered with adequate dose coverage, while maintaining reduced toxicity. Many studies have recently been published on breast RT using IMRT; however, interpretation of these results can be difficult because of the wide diversity of patients and treatments involved. This article summarizes the studies of breast IMRT in narrative review form with clinically relevant outcomes in either a randomized (**Table 1**) [21-28] or non-randomized design (**Table 2**) [29-34].

OLD FORWARD-IMRT TRIALS IN THE EARLY 2000S

In breast cancer treatment, the first randomized trial that investigated the utility of an advanced technique was the Royal Marsden/UK breast study published in 2007 [21]. A total of 306 patients were randomized to receive either a 2D wedge plan (2D-RT) or the FIF technique

Table 1. Summary of the randomized controlled trials on the role of IMRT for adjuvant radiation therapy in breast cancer

Name	Trial group	Number	Control (Gy/fraction)	Intervention (Gy/fraction)	Local relapse of control vs. IMRT (%)	Remark	Primary or global NTEs		Secondary or specific NTEs	
							NTE being measured	NTE of control vs. IMRT (%)	NTE being measured	NTE of control vs. IMRT (%)
RMH/GOC trial [21]	2D vs. FIF	306	50 Gy/25fx	50 Gy/25fx	NA		Cosmesis	OR 0.48 favoring FIF @ 5yr (p 0.001)	Breast pain, breast discomfort, breast thickening, etc.	p = NS
Canadian trial [22]	2D vs. FIF	358	50 Gy/25fx	50 Gy/25fx	NA		Acute skin reaction	36.7% vs. 27.1% (p = 0.06) for Gr 3–4 acute skin reaction	Moist desquamation	47.8% vs. 31.2% (p = 0.002)
Cambridge Breast IMRT trial [23]	2D vs. FIF	814	40 Gy/15fx	40 Gy/15fx	2.56% vs. 1.35% @ 5yr (p = 0.36)	LRR	Cosmesis	OR 0.65 favoring FIF @ 5yr (p = 0.038)	Induration, telangiectasia, breast edema	OR 0.57 favoring FIF @ 5yr (p = 0.031) for telangiectasia
KROG 15-03 [24]	3D-CRT vs. IMRT-SIB	693	59.4 Gy/33fx (sequential boost)	57.4 Gy/28fx (SIB)	99.4% vs. 98.5% @ 3yr (p = 0.523)	LRRFS	Radiation dermatitis	37.1% vs. 27.8% (p = 0.009) for Gr 2+ acute dermatitis		
IMRT-MC2 [25]	3D-CRT vs. IMRT-SIB	502	66.4 Gy/36fx (sequential boost)	64.4 Gy/28 fx (SIB)	99.6% vs. 99.6% @ 2yr (p = 0.487)	LC	Cosmesis	OR 0.961 @ 2yr (p = 0.797)		
UK IMPORT-HIGH [26]	3D-CRT vs. IMRT-SIB	2,617	46 Gy/23fx (sequential boost)	48 Gy/15fx (SIB) or 53 Gy/15fx (SIB)	1.9% vs. 2.0% (48 Gy/15fx) vs. 3.2% (53 Gy/15fx) @ 5yr (p = NS)	IBTR	Any AE in breast	2.8% vs. 2.0% (48 Gy/15fx) vs. 2.8% (53 Gy/15fx) @ 5yr by clinician (p = 0.011 for 48 Gy vs. 53 Gy) for moderate/marked AE	Breast induration	6% vs. 5% (48 Gy/15fx) vs. 9% (53 Gy/15fx) @ 5yr by clinician (p = 0.006 for 48 Gy vs. 53 Gy) for moderate/marked induration
ARO 2013-15/HYPOSIB [27]	3D-CRT vs. IMRT-SIB	2,324	60.4–66.4 Gy/33–36fx (sequential boost) or 58.8–63 Gy/28fx (conventional SIB) or 52.56–58.56 Gy/21–24fx (hypofractionated SIB)	48 Gy/16fx (hypofractionated SIB)	NA		Radiation dermatitis	23.9% vs. 13.8% @ 6 weeks (p = NA) for Gr 2+ radiation dermatitis		
APBI-IMRT-Florence [28]	3D-CRT-WBI vs. IMRT-APBI	520	60 Gy/30fx (sequential boost)	30 Gy/5fx	2.5% vs. 3.7% @ 10yr (p = 0.40)	IBTR	Cosmesis	0% vs. 1.9% by physician (p = 0.0001) for fair/poor cosmesis	Acute and late period AE	37.7% vs. 2.0% (p = 0.0001) for Gr 2+ acute AE 2.7% vs. 0% (p = 0.015) for Gr 2+ late AE

2D = 2-dimensional radiation therapy; 3D-CRT = 3-dimensional-conformal radiation therapy; AE = adverse events; APBI = accelerated partial breast irradiation; FIF = field-in-field; IBTR = ipsilateral breast tumor recurrence; IMRT = intensity-modulated radiation therapy; LC = local control; LRR = loco-regional recurrence; LRRFS = loco-regional recurrence-free survival; NA = not assessed; NTE = normal tissue effects; NS = not significant; OR = odds ratio; SIB = simultaneous integrated boost; WBI = whole breast irradiation.

https://doi.org/10.4048/jbc.2022.25.e37

Table 2. Summary of the non-randomized studies on the role of IMRT for adjuvant radiation therapy in breast cancer

Name	Trial group	Number	Control (Gy/fraction)	Intervention (Gy/fraction)	Local relapse of control vs. IMRT (%)	Remark	Primary or global NTEs		Secondary or specific NTEs	
							NTE being measured	NTE of control vs. IMRT (%)	NTE being measured	NTE of control vs. IMRT (%)
McDonald et al. [29] (2008)	2D vs. FIF	245	45–50 Gy/25fx	45–50 Gy/25fx	90% vs. 95% @ 7yr (p = 0.36)	Freedom from IBTR	Skin toxicity	52% vs. 39% (p = 0.047) for Gr 2+ dermatitis		
Lee et al. [30] (2015)	FIF vs. IMRT-SIB	126	60–64 Gy/30–32fx (sequential boost)	60.2 Gy/28fx	NA		Skin toxicity	18.3% vs. 4.5% (p = 0.048) for Gr 2+ dermatitis		
Yang et al. [31] (2016)	2D vs. IMRT	234	50 Gy/25fx	45 Gy/25fx	96.7% vs. 97.6% @ 8yr (p = 0.393)	LRFFS	Skin toxicity	56.5% vs. 40.8% (p = 0.017) for Gr 2+ dermatitis	Moist desquamation	21.4% vs. 10.7% (p = 0.029)
Chen et al. [32] (2020)	3D-CRT vs. IMRT	308	50 Gy/25 fx or 42.56 Gy/16fx	50 Gy/25 fx or 42.56 Gy/16fx	NA		Skin toxicity	HR 0.27 favoring IMRT (p < 0.001)	Lung injury	HR 0.49 favoring IMRT (p = 0.01)
Kim et al. [33] (2021)	3D-CRT (CF) vs. 3D-CRT (HF) vs. IMRT	5,749	50.4 Gy/28fx or 40.05 Gy/15fx	40.05 Gy/15fx	2.8% (3D-CF) vs. 2.6% (3D-HF) vs. 2.4% (IMRT) @ 5yr (p = NS)	LRR	Acute/ subacute toxicity	OR 0.11 favoring IMRT compared with 3D-CF (p < 0.001) for Gr 2+ toxicities OR 0.45 favoring IMRT compared with 3D-HF (p = 0.010) for Gr 2+ toxicities	Late toxicity	OR 0.58 favoring IMRT compared with 3D-CF (p < 0.001) for any toxicities OR 0.79 favoring IMRT compared with 3D-HF (p = 0.084) for any toxicities
Jagsi et al. [34] (2022)	3D-CRT vs. FIF vs. IMRT	5,167	NA	NA	NA		Acute toxicity	OR 0.64 favoring IMRT-CF compared with 3D-CF (p = 0.0158) for any toxicity OR 0.41 favoring IMRT-HF compared with 3D-HF (p = 0.0007) for any toxicity	Radiation dermatitis toxicity-related treatment break	0.7% in 3D-HF vs. 0.2% in FIF-HF vs. 0% in IMRT-HF (p = 0.026) for Gr3+ dermatitis 5.0% in 3D-CF vs. 2.1% in FIF-CF vs. 3.6% in IMRT-CF (p = 0.003) for treatment break

2D = 2-dimensional radiation therapy; 3D-CRT = 3-dimensional-conformal radiation therapy; CF = conventional fractionation; FIF = field-in-field; HF = hypofractionation; HR = hazard ratio; IBTR = ipsilateral breast tumor recurrence; IMRT = intensity-modulated radiation therapy; LRR = loco-regional recurrence; LRRFS = loco-regional recurrence-free survival; NA = not assessed; NTE = normal tissue effects; NS = not significant; OR = odds ratio; SIB = simultaneous integrated boost; WBI = whole breast irradiation.

using step-and-shoot multileaf collimators or a physical 3D compensator (although the authors used the term "IMRT arm," we used the term "FIF" to distinguish forward IMRT from the modern concept of IMRT in this article). According to the analysis of the 5-year photographs, changes in appearance were 1.7-times higher in the 2D-RT arm than in the FIF arm. The incidence of palpable induration was lower in the FIF group.

The second randomized trial was a Canadian/Sunnybrook breast study first published in 2008 [22]. A total of 331 patients were randomized to receive either 2D wedge-based RT or FIF. This study found that the rate of moist desquamation, which is significantly associated with pain and reduced health-related quality of life, was reduced from 47.8% with standard wedge RT to 31.2% with FIF (p = 0.002).

The third randomized trial was a 2-year-long Cambridge study published in 2013 [23]. A total of 1,145 patients were randomized to receive either tangential techniques or FIF. Unlike the 2 aforementioned trials, which used a 2 Gy daily fraction (50 Gy), this trial used moderate hypofractionation (40 Gy in 15 fractions with a 2.67 Gy daily fraction). The development of telangiectasia was 1.7 times more common in the control group. In a subgroup analysis of patients with good surgical cosmesis, patients with FIF were less likely to experience moderate or poor cosmesis than those in the control group. Given that hypofractionated (HF)-whole breast irradiation (WBI) is the preferred dose-fractionation scheme for the

https://doi.org/10.4048/jbc.2022.25.e37

majority of early breast cancer patients [35], unplanned dose inhomogeneities (so called "hotspots") in breast tissue could be penalized more severely in a larger fraction size. Therefore, dose–volume restrictions and dose conformity within the breast may be more important with HF-WBI.

In these earlier studies, the forward IMRT, "simple" IMRT, or FIF technique was used, which aimed to reduce a higher-dose area than the prescription dose within the breast, but was unable to substantially reduce doses to the OARs, such as the lung and heart. The avoidance of a high-dose area within the breast contributed to a reduction in the incidence of moist desquamation, as demonstrated in a randomized trial conducted by Pignol et al. [22]. Long-term follow-up data from this trial showed that late subcutaneous fibrosis and telangiectasia were correlated with moist desquamation, which was reduced by FIF [36]. In addition, the Cambridge breast trial demonstrated that FIF improved overall cosmesis and reduced skin telangiectasia [23].

INVERSE IMRT STUDIES IN THE MODERN ERA

Whole breast irradiation using IMRT

A recent trial conducted in Korea suggested that inverse-planned IMRT is likely to further reduce acute toxicity when compared with 3D-CRT [24]. In the Korean Radiation Oncology Group (KROG) 15-03 trial, 693 women with pT1-2N0M0 early breast cancer were randomly assigned to undergo either IMRT or 3D-CRT. The conformity index was significantly higher in the IMRT arm than in the 3D-CRT arm ($p < 0.001$), and the incidence of grade 2 or higher dermatitis was significantly lower in the IMRT arm than in the 3D-CRT arm (27.8% vs. 37%, $p = 0.009$). Furthermore, Jagsi et al. [34] reported the results of a comparative effectiveness analysis of 3D-CRT versus IMRT in a prospective multicenter cohort of patients with breast cancer receiving WBI without nodal irradiation. They separately analyzed acute toxicity in patients treated with conventionally fractionated (CF) or HF-WBI. Multivariate analysis showed that the odds ratio (OR) for acute toxicity after inverse-planned IMRT versus 3D-CRT was 0.64 with CF-WBI and 0.41 with HF-WBI.

Kim et al. reported a large-volume single-center experience of breast RT using various combinations of fractionation and techniques in 4,209 women [33]. They observed that grade 2+ acute/subacute toxicities were the highest in the 3D-CRT group (15.0%, 2.6%, and 1.6% in CF-3D, HF-3D, and HF-VMAT, respectively; $p < 0.001$), and the use of HF-VMAT significantly reduced grade 2+ acute/subacute toxicities when compared to CF-3D (OR, 0.11) and HF-3D (OR, 0.45).

Partial breast irradiation using IMRT

Breast conservation with WBI in the treatment of early-stage breast cancer has been a pivotal achievement in modern cancer history. Following this achievement, extensive clinical research has been conducted, focusing on reducing the burden of care imposed by 5–7 weeks of daily radiation delivery after lumpectomy. Partial breast irradiation, which targets the breast tissue around the surgical cavity, was one of the earliest alternatives studied [37]. Accelerated partial breast irradiation (APBI) using IMRT is well established as one of the effective approaches for RT in early-stage breast cancer patients (**Figure 3**) [38].

With increasing interest in the de-escalation of breast RT, APBI is gradually being employed among select low-risk patients. The criteria for patient selection have been suggested by

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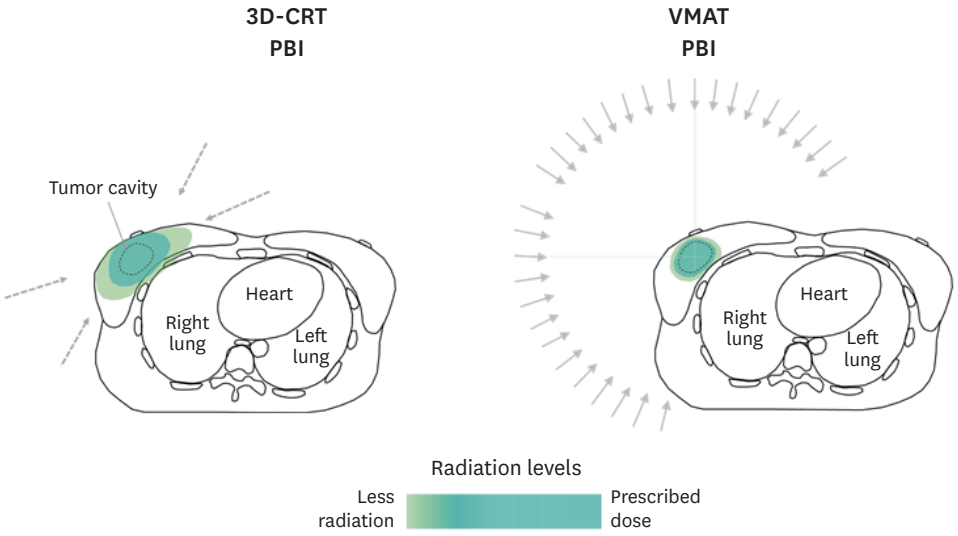

Figure 3. Schematic illustration of the dose distribution of 3D-CRT and VMAT-based PBI.
3D = 3-dimensional; CRT = conformal radiation therapy; VMAT = volumetric modulated arc therapy; PBI = partial breast irradiations.

several oncology societies, including the American Society for Radiation Oncology (ASTRO), Groupe Européen de Curiethérapie, European Society for Radiotherapy & Oncology (GEC-ESTRO), and American Brachytherapy Society (ABS), although minor differences are observed among these standards [39,40]. There are also various APBI techniques, including external beam RT, applicator brachytherapy, interstitial brachytherapy, and intraoperative RT [41]. According to the ABS, the strongest evidence for APBI supports interstitial brachytherapy and IMRT [42]. While interstitial brachytherapy-based APBI requires specific expertise, is more demanding, and is mainly performed at specialized centers, external beam-based APBI can be applied in all radiation oncology departments. Unlike intraoperative RT, brachytherapy and external beam-based APBI may be delivered following recovery from surgery and after receiving the final pathological results.

It is important to understand that adverse events and cosmetic outcomes are highly influenced by the irradiated volume, ratio with non-target ipsilateral breast volume, RT technique, and adopted schedule [43]. As the irradiated volume (V50%, the non-target ipsilateral breast volume of the dose receiving 50% of the prescription dose) increases, adverse events and cosmetic outcomes worsen [44]. In a previous prospective KROG 08-04 trial evaluating 3D-CRT-based APBI in Korean breast cancer patients, the median V50% of the ipsilateral breast was 42%, and the dose constraint of V50% < 50% was not achieved in 10% of patients [45]. The authors concluded that APBI using 3D-CRT is not feasible in Korean women.

APBI using IMRT was compared with WBI in a phase 3 randomized trial in Italy [28]. A total of 520 patients were randomized to receive APBI-IMRT (30 Gy in 5 fractions, every other day for 2 weeks) and WBI (50 Gy in 25 fractions), followed by a sequential boost. The 10-year ipsilateral breast tumor recurrence rate did not differ between the two arms. The mean V50% of the uninvolved breast volume was 32% in the APBI-IMRT arm, and less acute and late toxicities, as well as improved cosmetic outcomes, were observed in the APBI-IMRT arm.

In a retrospective study by Lee et al. [46], similar feasibility was achieved by IMRT in 104 Korean women. The median ipsilateral breast V50% was 35.8%, despite the smaller breast

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volumes. The change in skin thickness appeared to be limited to the tumor bed after APBI-IMRT, in contrast to the diffuse skin thickening observed after HF-WBI. Another Korean study reported the initial experience of APBI-IMRT in 37 patients using magnetic resonance imaging-guided adaptive RT, which enables the adaptation of seroma changes during the course of RT [47].

Concomitant boost technique using IMRT

Boost irradiation, which refers to an extra dose of radiation that surrounds the tumor bed, is intended to decrease the local recurrence rates. Two randomized trials that investigated the impact of tumor bed boost after breast conserving surgery implied that boost results in a lower rate of local recurrences and, subsequently, a lower rate of mastectomies [48,49]. If a boost is administered, 10–16 Gy in 2 Gy fraction over 1–2 weeks is typically delivered after the completion of WBI. An additional advantage of the IMRT technique is its ability to provide differential dose distributions, which allows for simultaneous integrated boost (SIB) delivery (**Figure 4**). SIB delivers an additional dose to the high-risk area while simultaneously delivering the conventional dose to the standard or low-risk area at the same time [50]. Using the IMRT technique, a tumor bed boost can be delivered simultaneously with WBI, which can reduce patient visits. There are a number of prospective trials evaluating tumor bed boost delivered as SIB using IMRT technique (IMRT-SIB) in breast cancer.

The IMRT-MC2 trial is a phase 3, randomized, non-inferiority trial comparing IMRT-SIB (whole breast 50.4 Gy in 28 fractions, SIB 64.4 Gy in 28 fractions) with 3D-CRT followed by sequential boost (whole breast 50.4 Gy in 28 fractions, boost 16 Gy in 8 fractions) [25]. A total of 502 patients were enrolled, and there were no significant differences in cosmesis, local control, or overall survival between the two treatment schedules at a median follow-up of 5.1 years. The overall treatment times were 1 to 1.6 weeks shorter in the IMRT-SIB arm than

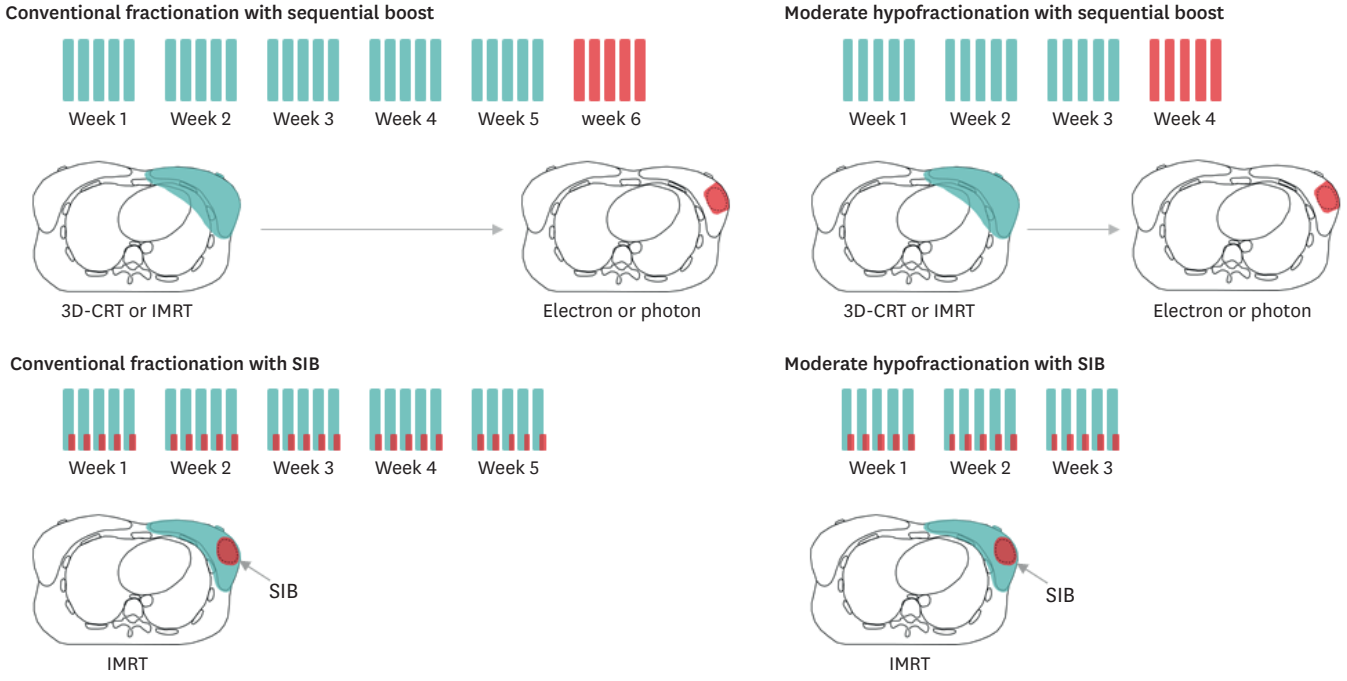

Figure 4. Schematic illustration of breast sequential and SIB either in conventional fractionation or moderate hypofractionation schedules.
3D = 3-dimensional; CRT = conformal radiation therapy; IMRT = intensity-modulated radiation therapy; SIB = simultaneous integrated boost.

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in the 3D-CRT arm, which most likely improves patient convenience. Breast pain and arm symptoms were more favorable in the IMRT-SIB arm than in the 3D-CRT arm. KROG 15-03 trial compared IMRT-SIB (whole breast 50.4 Gy in 28 fractions, SIB 57.4 Gy in 28 fractions) versus 3D-CRT followed by sequential boost (whole breast 50.4 Gy in 28 fractions, boost 9 Gy in 5 fractions) [24]. IMRT with the SIB method not only reduced grade 2+ radiation dermatitis but also reduced treatment times (from 33 fractions to 28 fractions), with a similar loco-regional failure-free survival approaching 99%.

In 2017, international guidelines adopted HF-WBI as the preferred dose fractionation scheme for a majority of patients with early breast cancer [35]. The IMPORT-HIGH trial is a phase 3 randomized trial to test dose-escalated SIB compared with sequential boost using moderately HF-WBI in high-risk early breast cancer. The dose-fractionation schedule of the control arm was 40 Gy in 15 fractions to the whole breast, followed by a sequential boost (16 Gy in 8 fractions) [51]. The dose levels of the experimental arms were as follows:36 Gy/15fx to the low-risk breast, 40 Gy/15fx to the index quadrant, and 48 Gy/15fx to the tumor bed in arm 1; the same doses to the low-risk breast and index quadrant as in arm 1, but dose escalated to the tumor bed (53 Gy/15fx) in arm 2. A total of 2,617 patients were accrued, and the 5-year moderate/marked adverse events were broadly similar between each test group and control group, but with a higher risk of breast induration and distortion in the 53 Gy/15fx arm [26]. This study concluded that IMRT with SIB (48 Gy/15fx) is a safe treatment with fewer patient visits.

Currently, 2 ongoing randomized trials (HYPOSIB and RTOG 1005) are evaluating SIB versus sequential boost in women receiving HF-WBI. In 2020, the preliminary safety data of the HYPOSIB randomized phase 3 trial, which recruited 2,324 patients from 88 centers in Germany and Austria, was presented [27]. An SIB of 48 Gy in 15 fractions was administered using IMRT in the IMRT-SIB arm, and acute skin reactions were less pronounced and completed before the peak skin reaction occurred in the IMRT-SIB arm than in the control arm.

Regional nodal irradiation using IMRT

A study published in 2013 by Darby et al. showed a linear no-threshold relationship between mean heart dose (MHD) and the incidence of heart disease after breast RT, finding a 7.4% relative risk of ischemic heart disease for every 1-Gy increment in MHD [52]. Chung et al. [53] confirmed these findings in a Korean population, independently corroborating this linear no-threshold model for MHD, regardless of the risk factors for coronary events. Left-sided breast cancer and the inclusion of IMNs in the treatment volume are well-known risk factors for increased MHD in RT planning. Therefore, breast RT planning should focus on achieving optimal coverage of targets and minimizing radiation to OARs, considering 1) the expected long-term survival in early breast cancer and 2) the impact of regional node irradiation (especially IMN and supraclavicular) on survival among patients with node-positive and high-risk node-negative breast cancer, as demonstrated in the MA.20 and EORTC 22922 trials [54].

IMRT, especially VMAT, has been suggested as a heart-sparing technique (**Figure 5**) [55]. However, MHD, a parameter associated with an increased risk of ischemic heart disease, is often higher with IMRT than 3D-CRT if cardiac sparing is not prioritized in the IMRT planning process. A prospective study conducted by Memorial Sloan-Kettering Cancer Center reports that an MHD of 13.2 Gy (range, 8.6–20 Gy) was achieved among left-sided breast cancer patients receiving multibeam IMRT [56]. The cardiac-sparing capability of IMRT can be synergized with a controlled breathing technique, such as deep inspiration breath-hold (DIBH) or continuous positive airway pressure (CPAP) [19,57]. A small, randomized trial tested the

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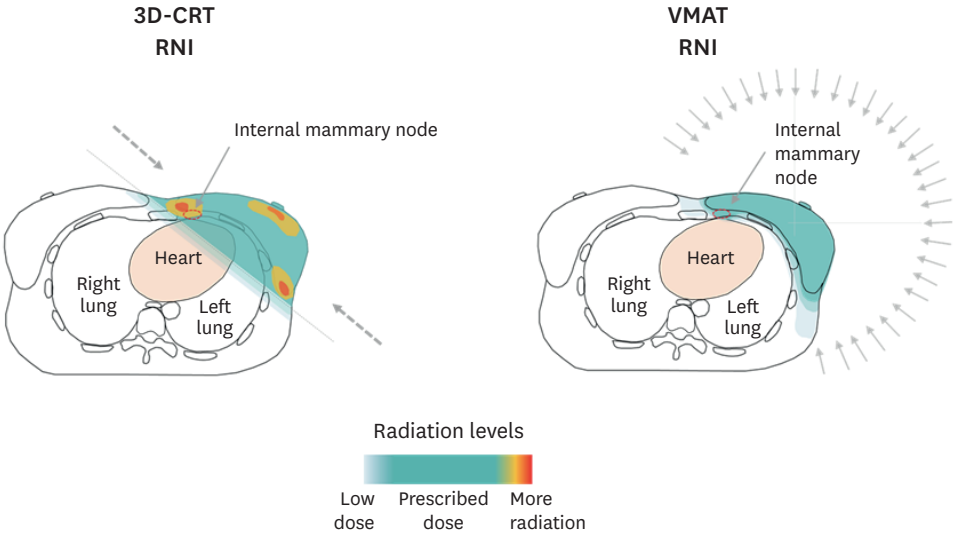

Figure 5. Schematic illustration of the dose distribution of 3D-CRT and VMAT in RNI with internal mammary nodal irradiation.
3D = 3-dimensional; CRT = conformal radiation therapy; VMAT = volumetric modulated arc therapy; RNI = regional nodal irradiation.

benefit of IMRT with DIBH compared to 3D-CRT in left-sided, node-positive patients receiving nodal irradiation including IMNs [57]. Mean doses to the heart, left ventricle, and left anterior descending coronary artery were significantly lower, and the left ventricular ejection fraction at 1-year was higher in the IMRT-DIBH group, although perfusion defects on single-photon emission computed tomography did not differ between the 2 groups. Another dosimetric study demonstrated that MHD could be reduced by 50% with the use of DIBH or CPAP, and the use of VMAT could further lower MHD by approximately 40% [19].

Based on the same principle, VMAT has the potential to reduce radiation exposure to the lungs if lung sparing is prioritized in the RT planning process. Kim et al. [33] analyzed 5,749 patients treated with 3D-CRT or VMAT at a single institution. Late toxicities, including radiation pneumonitis, lymphedema, hypothyroidism, cardiotoxicity, and secondary contralateral breast cancer, were also evaluated. There was no significant difference in any late toxicity except radiation pneumonitis, which favors VMAT over 3D-CRT. As emerging late toxicities are highlighted, delineation and constraints to more OARs, such as the thyroid [12], esophagus [12], and axillary-lateral thoracic juncture [14], would improve the quality of IMRT in breast RT. Because an unintended increased radiation dose to the reconstructed breast is associated with an increased risk of reconstruction complications, including capsular contracture, VMAT may mitigate radiation-related complications by improving dose homogeneity in the reconstructed breast (**Figure 6**) [58,59]. Recent target volume guidelines can further reduce the dose to the heart while maintaining target volume coverage in breast reconstruction with subpectoral implant placement [60].

ISSUES RELATED TO IMRT IN BREAST CANCER

There are concerns regarding secondary malignancies as a late toxicity of RT. Compared with 3D-CRT, IMRT for breast cancer increases the low-dose area outside the target volume,

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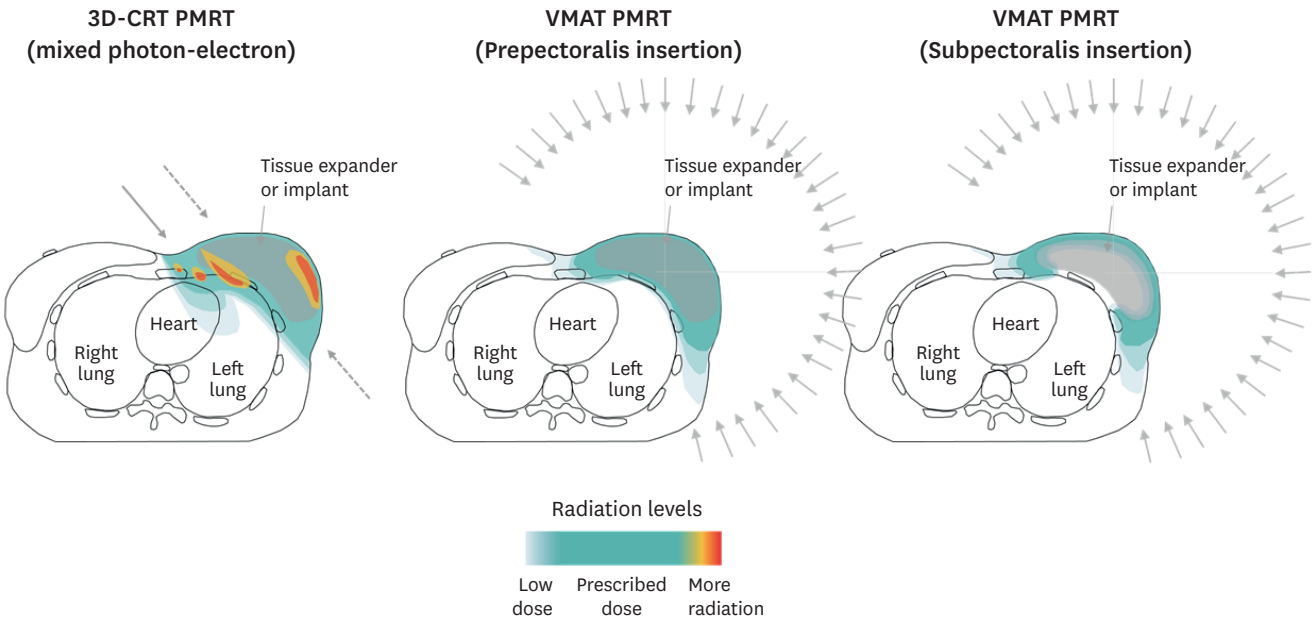

Figure 6. Schematic illustration of the dose distribution of 3D-CRT and VMAT in PMRT after implant-based immediate breast reconstruction.
3D = 3-dimensional; CRT = conformal radiation therapy; VMAT = volumetric modulated arc therapy; PMRT = post-mastectomy radiation therapy.

which potentially increases the risk of secondary malignancy, including contralateral breast cancer. A recent dosimetric study by Ko et al. [19] showed that although VMAT increased the radiation dose to the contralateral breast relative to 3D-CRT, the difference in the mean dose between these techniques was approximately 1 Gy. Another dosimetric study by Ranger et al. showed that there is no significant difference in mean contralateral breast dose between VMAT and 3D-CRT (1.7 Gy vs. 1.2 Gy, respectively) [55]. In real-world data using the National Cancer Database, the second cancer diagnosis was similar after 3D-CRT and IMRT at a median follow-up of 5.1 years after the completion of RT [61]. There was no difference in second cancer risk between 3D-CRT and IMRT when the analysis was confined to primary breast cancer alone. A recent study that evaluated the long-term risk of secondary malignancy with > 10 years of follow-up in childhood cancer patients who were treated with IMRT showed that many secondary malignancies develop in the high-dose region after IMRT [62].

As IMRT becomes more sophisticated, its implementation introduces several issues related to quality control. Considering that errors in RT treatment may have dire consequences for patients, quality management is an integral component of preventing deviations from the intended track. Quality control includes all facility activities during simulation, contouring, planning, and treatment. According to TG-100 by the American Association of Physicists in Medicine, a program needs to ensure that the following components are in place [63]: 1) adequate resources—physicians, dosimetrists, medical physics, therapists, equipment, and administrative support—to perform the breast IMRT procedure; 2) quality training for the staff and established standardized procedures (e.g., contouring of clinical target volume and OARs and planning considerations); 3) a program focused on maintaining equipment and software; and 4) clear and effective lines of communication. Above all, inter-physician variations in contouring and planning present the greatest challenges for standardization and increased quality control. Currently, the KROG 21-01 study is underway to improve the quality of breast IMRT in Korea [64].

https://doi.org/10.4048/jbc.2022.25.e37

CONCLUSION

With the modernization of RT, 3D treatment planning has been incorporated into practice, along with the use of CT simulation. Further innovations in technology include the improvement of standard linear accelerators that allow for the avoidance of healthy tissue using multileaf collimators, ability to obtain 3D images in real-time using cone beam CT, improvements in cardiac sparing techniques (e.g., respiratory motion management including DIBH), and advances in treatment planning and delivery (e.g., IMRT). Altogether, these innovations have enabled great progress in relation to dose fractionation and targets in breast RT. In the years to come, breast RT is expected to evolve further, allowing for even shorter regimens, reduced toxicities and patient visits, incorporation of tumor genetics or biomarkers, new opportunities for patients with metastatic breast cancer, and further increases in the therapeutic ratio of techniques.

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