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FULL PAPER

Secondary cancer risk after whole-breast radiation therapy: field-in-field versus intensity modulated radiation therapy versus volumetric modulated arc therapy

[1]EMEL HACIISLAMOGLU, Ph.D, [2]YUNUS CINAR, M.Sc, [3]FATIH GURCAN, Ph.D, [1]EMINE CANYILMAZ, MD, [4]GORKEM GUNGOR, M.Sc and [4]ADNAN YONEY, MD

[1]Department of Radiation Oncology, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey
[2]Department of Radiation Oncology, Recep Tayyip Erdogan University Faculty of Medicine, Rize, Turkey
[3]Department of Computer Engineering, Karadeniz Technical University Faculty of Engineering, Trabzon, Turkey
[4]Department of Radiation Oncology, Acibadem University, Istanbul, Turkey

Address correspondence to: Dr. Emel Haciislamoglu
E-mail: *emel.haciislamoglu@ktu.edu.tr*

Objective: In this study, we used the concept of organ-equivalent dose (OED) to evaluate the excess absolute risk (EAR) for secondary cancer in various organs after radiation treatment for breast cancer.
Methods: Using CT data set of 12 patients, we generated three different whole-breast radiation treatment plans using 50 Gy in 2 Gy fractions: three-dimensional conformal radiotherapy with a field-in-field (FinF) technique, intensity modulated radiation therapy (IMRT), and volumetric modulated arc therapy (VMAT). The OEDs were calculated from differential dose–volume histograms on the basis of the "linear–exponential," "plateau," and "full mechanistic" dose–response models. Secondary cancer risks of the contralateral breast (CB), contralateral lung (CL), and ipsilateral lung (IL) were estimated and compared.
Results: The lowest EARs for the CB, CL, and IL were achieved with FinF, which reduced the EARs by 77%, 88%, and 56% relative to those with IMRT, and by 77%, 84%, and 58% relative to those with VMAT, respectively. The secondary cancer risk for FinF was significantly lower than those of IMRT and VMAT. OED-based secondary cancer risks for CB and IL were similar when IMRT and VMAT were used, but the risk for CL was statistically lower when VMAT was used.
Conclusion: The overall estimation of EAR indicated that the radiation-induced cancer risk of breast radiation therapy was lower with FinF than with IMRT and VMAT. Therefore, when secondary cancer risk is a major concern, FinF is considered to be the preferred treatment option in irradiation of whole-breast.
Advances in knowledge: Secondary malignancy estimation after breast radiotherapy is becoming an important subject for comparative treatment planning.When secondary cancer risk a major concern, FinF technique is considered the preferred treatment option in whole breast patients.

INTRODUCTION

Presently, breast cancer is frequently diagnosed at an early stage and has an excellent prognosis. Surveillance, Epidemiology, and End Results data show that 60% of the patients are diagnosed at a localized stage, without extension to the regional nodes, and the 5 year cancer-specific survival for those patients is 98.9%.[1] Evolving early-stage breast cancer treatment strategies have improved the survival of patients who undergo breast conservation surgery. After surgery, patients generally receive radiotherapy (RT) of the whole breast.[2] This strategy allows improving local control and overall survival in early-stage patients with breast cancer.[3] However, it has been shown that the risk of developing a secondary cancer is increased after RT for females <40 years old.[4]

In three-dimensional conformal radiotherapy (3D-CRT) for breast cancer, the tangential technique is commonly used. Tangential field techniques, such as hard-wedge, dynamic-wedge, and field-in-field (FinF) techniques, are generally used for whole-breast irradiation to improve dose uniformity to the tumor.[5–8] Introducing new irradiation techniques may result in differences in the amount of dose to the whole body and, thus, in differences in the risk

Table 1. Parameters for second malignancy risk calculation

		"Full Mechanistic" Model		"Linear-exponential" Model	"Plateau" Model
Site	**EAR_0**	**ά(Gy^{-1})**	**R**	**ά(Gy^{-1})**	**ά(Gy^{-1})**
Female breast	8.2	0.044	0.15	0.041	0.115
Lung	8.0	0.042	0.83	0.022	0.056

EAR, excess absolute risk; Gy = Gray.

of radiation-induced secondary cancer.[9,10] Many studies have compared the existing treatment method, 3D-CRT, with more advanced methods, such as intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT).[11–13] An advantage of IMRT and VMAT over the 3D-CRT technique is they reduce the dose to surrounding normal tissues. However, a concern about the IMRT and VMAT treatments is the volume that receives a low dose can be significantly higher than that in the conventional technique because the former methods have greater scattering and monitor units.[14,15] This might increase the risk for secondary malignancies, which is a very important issue regarding the life expectancy of patients with breast cancer.

The excess absolute risk (EAR) of developing a secondary cancer after exposure to radiation can be estimated from differential dose–volume histograms (dDVHs) based on biological models that are fitted to data of atomic bomb survivors and Hodgkin patients treated with RT.[16–20] The aim of this study was to calculate and compare solid secondary cancer risks among three treatment modalities (FinF, IMRT, and VMAT) for breast cancer by using the concept of organ-equivalent dose (OED) for the linear–exponential, plateau, and full mechanistic dose–response models.

METHODS AND MATERIALS

Patients and treatment techniques

CT scans that were used previously for whole-breast RT planning for 12 patients with left-sided breast cancer who had undergone breast-conserving surgery and needed adjuvant RT without nodal irradiation were selected at random. The CT scans were acquired on a CT-simulator according to Karadeniz Technical University, Department of Radiation Oncology standard protocol in 5 mm slices, with the patient in the supine position and ipsilateral arm abduction above the head.

Auto contouring of the body and both lungs was used. The clinical target volume (CTV) included the whole breast. Image delineation of the CTV and organs at risk [OARs; heart, contralateral breast (CB), contralateral lung (CL), and ipsilateral lung (IL)] was performed by using the treatment planning system (Eclipse, v. 10; Varian Medical Systems, Palo Alto, CA).

In total, three treatment plans were created for each patient by using the three different treatment techniques: FinF, IMRT, and VMAT (each with 6 MV photons). The FinF technique was used for 3D-CRT because it generates lower scattered radiation than those in the hard- and dynamic-wedge techniques. The FinF plan consisted of two parallel opposed tangential beams. Gantry angles were chosen for best target coverage while completely avoiding the CB and minimizing the exposure to the IL. With subfields created by a multileaf collimator for dose compensation. Nine fields were placed at equal intervals and two partial-arcs arrangements were used for IMRT and VMAT.

The prescription dose was set to 50 Gy in 25 fractions, and the plan was normalized as the dose covering 95% of the CTV. All plans were optimized and evaluated for optimal target coverage, conformality, homogeneity, and dose limits of OARs. Dose constraints for IL volumes receiving 20 Gy (V_{20}) and 10 Gy doses (V_{10}) were set to <20% and<40% of the lung volume, respectively. Doses to the other organs were kept as low as possible without compromising target coverage or conformality.

Calculation of secondary malignancy risk estimates

Schneider's concept of OED was used to compare and estimate the risk of radiation-induced secondary malignancies from whole-breast RT.[16,19,21] According to the OED concept, two different RT plans that result in the same risk of secondary malignancy have the same OED. Therefore, the OED of one plan relative to another gives the relative risk of secondary malignancy for those two techniques. The OEDs for CB, CL, and IL were calculated on the basis of the dDVHs for the linear–exponential, plateau, and full mechanistic dose–response models[16,22] according to

$$OED_{linear-exp} = \frac{1}{V_T} \sum_i V_{Di} D_i e^{-D_i}$$

$$OED_{plateau} = \frac{1}{V_T} \sum_i V_{Di} \frac{1-e^{-D_i}}{}$$

$$OED_{mechanistic} = \frac{1}{V_T} \sum_i V_{Di} \frac{e^{-D_i}}{R} \left(1 - 2R + R^2 e^{D_i} - (1-R)^2 e^{-\frac{R}{1-R} D_i}\right)$$

where V_T is the total organ volume and the sum is taken over all bins of the DVH and V_{Di} is a volume of the organ that is exposed to dose D_i. For the full mechanistic model, the organ specific parameters ά = 0.044 Gy^{-1}, R = 0.15 for a female breast and ά = 0.042 Gy^{-1}, R = 0.83 for lungs have been derived from a combined fit to the data of atomic bomb survivors and data of Hodgkin patients treated with single doses of 2 up to 40 Gy assuming an α/β value of 3 Gy.[19] Similarly, α'=0.041 Gy^{-1} for the linear-exponential model and α'=0.115 Gy^{-1} for the plateau model for female breast, and α'=0.022 Gy^{-1} for the linear-exponential model and α'=0.056 Gy^{-1} for the plateau model for lungs. Table 1 shows the parameters used for OED calculations.

The risk of developing a solid secondary cancer after RT is usually represented by EAR. The EAR describes the absolute difference in cancer rates of persons exposed to a dose d and those not exposed to a dose beyond the natural dose exposition per 10,000 person-years (PYs).[19]

The EAR can be calculated by using the concept of OED according to

$$EAR = EAR_0\ OED$$

where EAR_0 is the initial slope, which is the slope of the dose–response curve at a low dose. All population-related parameters, such as attained age (a), age at exposure (e), and sex (s), are included in EAR_0 (e,s,a).

For this study, EAR values were calculated at an age at exposure of 30 years and an attained age of 70 years and reported per 10,000 PYs per Gy. In the calculation of the EAR, the difference between the baseline risks of developing cancer without exposition to radiation for Japanese and Western populations has been accounted for, leading to values of EAR_0(30,f,70)=8.2 (CI95: 6.1–11) for female breast and EAR_0(30,s,70)=8.0 (CI95: 5.5–11) for lung (sex averaged). Since for lungs EAR_0 does not vary significantly with sex according to Preston et al,[23] it was considered appropriate to use the sex averaged value for the calculation of the EAR for lungs in this study. EAR_0 values for a Western population and for different sites are taken from Schneider et al.[19] (Table 1).

Statistical analysis

Statistical analysis was performed using SPSS software (v. 18.0). Quantitative data were expressed as mean ± standard deviation. Multiple groups of means were compared with one way analysis of variance (ANOVA), after testing for equality of variance. Homogeneity of variance was assessed using Levene's test. Post-hoc test was used for situations where there were significant differences between groups.

RESULTS

The mean doses (D_{mean}) from DVHs and mean OED values for 12 patients generated using the three treatment modalities are presented in Table 2, which shows that the OEDs were the lowest with the FinF plans. The OEDs in the CL for VMAT were lower than those for the IMRT plans. In contrast, the VMAT plans resulted in higher OEDs in the IL than those of the IMRT plans.

Similarly, compared with IMRT and VMAT, the FinF technique had the lowest EARs for all three organs. Table 3 shows the EARs as calculated by the linear–exponential, plateau, and full mechanistic models for the CB, CL, and IL for the investigated breast RT techniques.

For the FinF technique, the average EARs for the CB, CL, and IL according to the mean values of the models used for calculation were 4.4 per 10,000 PYs, 3.5 per 10,000 PYs, and 28.5 per 10,000 PYs, respectively. The lowest EARs for the CB, CL, and IL were achieved with FinF, which reduced the EAR by 77%, 88%, and 56%, respectively, relative to that of IMRT and by 77%, 84%, and 58% relative to those of the VMAT, respectively.

The secondary cancer risk after the FinF technique was statistically lower than those for IMRT and VMAT. The OED-based secondary cancer risks for CB and IL were similar when IMRT and VMAT were used, but the risk for the CL was statistically lower when VMAT was used (Table 4).

Figure 1 gives a graphical illustration of the D_{mean}, OED, and EAR for all treatment techniques, which shows that the calculated OEDs were equal to or lower than the mean doses in the FinF, IMRT, and VMAT plans for CB, CL, and IL. The differences between the OEDs and mean doses were higher for the IL in all techniques.

An illustrative DVH comparison for CTV, heart, IL, CL and CB for a representative patient is shown in Figure 2. For IMRT and VMAT techniques, the 90% isodose curve (45 Gy) fits best to the concave shape of the CTV compared to the FinF plan. The IMRT and VMAT plans achieved similar sparing of critical organs.

Figure 3 shows the isodose distribution for the FinF, IMRT, and VMAT plans in axial plane for a representative patient. The

Table 2. Mean dose and OED for contralateral breast, contralateral lung and ipsilateral lung.

Plan	Contralateral breast				Contralateral lung				Ipsilateral lung			
	Mean dose (Gy)	$OED_{lin-exp}$ (Gy)	OED_{plat} (Gy)	OED_{mech} (Gy)	Mean dose (Gy)	$OED_{lin-exp}$ (Gy)	OED_{plat} (Gy)	OED_{mech} (Gy)	Mean dose (Gy)	$OED_{lin-exp}$ (Gy)	OED_{plat} (Gy)	OED_{mech} (Gy)
FinF	0.54 ± 0.10	0.54 ± 0.09	0.53 ± 0.09	0.54 ± 0.09	0.44 ± 0.10	0.44 ± 0.08	0.44 ± 0.08	0.44 ± 0.08	7.24 ± 2.59	3.61 ± 1.00	3.54 ± 0.99	3.54 ± 1.00
IMRT	2.80 ± 0.58	2.44 ± 0.44	2.33 ± 0.40	2.42 ± 0.43	4.11 ± 0.77	3.64 ± 0.61	3.54 ± 0.58	3.40 ± 0.55	12.58 ± 1.75	8.38 ± 0.99	7.99 ± 0.93	7.71 ± 0.89
VMAT	2.82 ± 0.33	2.42 ± 0.24	2.30 ± 0.21	2.39 ± 0.23	3.10 ± 0.53	2.85 ± 0.46	2.80 ± 0.44	2.70 ± 0.41	12.71 ± 1.37	8.99 ± 0.75	8.52 ± 0.69	8.16 ± 0.67

D_{mean} = mean dose; FinF = field-in-field; Gy = Gray; IMRT = intensity modulated radiation therapy; lin-exp = linear–exponential; mech = full mechanistic; OED = organ-equivalent dose; plat = plateau; VMAT = volumetric modulated arc therapy.

Table 3. EAR for contralateral breast, contralateral lung and ipsilateral lung.

Plan	Contralateral breast			Contralateral lung			Ipsilateral lung		
	$EAR_{lin\text{-}exp}$	EAR_{plat}	EAR_{mech}	$EAR_{lin\text{-}exp}$	EAR_{plat}	EAR_{mech}	$EAR_{lin\text{-}exp}$	EAR_{plat}	EAR_{mech}
FinF	4.4 ± 0.74	4.4 ± 0.73	4.4 ± 0.74	3.5 ± 0.63	3.5 ± 0.63	3.5 ± 0.63	28.9 ± 8.05	28.3 ± 7.91	28.3 ± 8.04
IMRT	20.0 ± 3.65	19.1 ± 3.32	19.9 ± 3.56	29.1 ± 4.88	28.3 ± 4.65	27.2 ± 4.40	67.1 ± 7.95	63.9 ± 7.41	61.7 ± 7.12
VMAT	19.8 ± 1.95	18.8 ± 1.76	19.6 ± 1.93	22.8 ± 3.66	22.4 ± 3.53	21.6 ± 3.32	71.9 ± 6.00	68.1 ± 5.51	65.2 ± 5.36

EAR = excess absolute risk;FinF = field-in-field; IMRT = intensity modulated radiation therapy; lin-exp = linear-exponential; mech = full mechanistic; plat = plateau; VMAT = volumetric modulated arc therapy.

color-wash thresholds were set to 3, 5 and 45 Gy, respectively. The received maximum dose of heart in FinF was higher compared with IMRT and VMAT. Both IMRT and VMAT achieved a better protection on heart. However, the volumes of the healthy tissue outside of CTV irradiated by a low dose (3 and 5 Gy) were higher for IMRT and VMAT.

The doses of heart according to three different plans are summarized in Table 5. IMRT and VMAT had the low heart maximum and V_{30} doses but resulted in higher heart V_5 and V_{10} doses compared to the FinF plan.

DISCUSSION

In the treatment of breast cancer, RT has an important role, and the 3D-CRT, IMRT, and VMAT techniques have all been applied for this purpose. The 3D-CRT techniques with tangential fields, such as hard-wedge, dynamic-wedge, and FinF techniques, are generally used for whole-breast radiation to improve dose uniformity to the tumor.[5,6,8] In recent years, IMRT and VMAT have been used increasingly to give more conformal dose distribution in breast cancer treatment. The basic principle of intensity modulated techniques involves irradiation from a number of different directions with beams of nonuniform energy fluences, which have been optimized to deliver a high dose to the target volume and an acceptably low dose to the surrounding normal structures. Many dosimetric studies have compared the existing treatment method, 3D-CRT, with more advanced methods, such as IMRT and VMAT.[12,24,25] Most of these studies have shown that IMRT and VMAT offer excellent results in terms of target coverage, conformity, and homogeneity. However, low-dose volumes in the contralateral organs and normal tissues were greater with IMRT or VMAT than with 3D-CRT. A larger volume of normal tissue exposed to lower radiation doses might increase radiation-induced carcinogenesis.[26,27]

Secondary malignancies are late complications arising after RT. The risks for developing a solid secondary cancer after RT of breast cancer is becoming more important because of improved long-term survival rates. Different dose–response models have been developed to predict the EAR of secondary cancer after RT based on DVHs of the treatment plans. The parameters used in the calculation of EAR involve large errors. To keep the uncertainties at a minimum, we opted to use the OED values for evaluation of the risk of secondary cancer when comparing different radiation techniques. It is known that for doses <2 Gy, the dose–response is linear.[26] However, for higher doses and inhomogeneous dose distributions, the dose–response is no longer linear,[16,26] and other dose–response functions are required. Previous studies have demonstrated that for inhomogeneous dose distributions >2 Gy, the full mechanistic, plateau, and linear-exponential models represent a better description of the dose–response function than that of the linear model.[17,19] For therapeutic doses >2 Gy, we calculated OEDs on the basis of the "linear–exponential," "plateau," and "full mechanistic" dose–response models because cell killing and sterilization of already mutated cells may become more important at higher doses.A few studies have published comparisons of secondary cancer risks for different techniques

Table 4. Estimated *p*-values for compared treatment modalities in terms of EAR

	Contralateral breast			**Contralateral lung**			**Ipsilateral lung**		
	EAR-exp	EAR-plat	EAR-mech	EAR-exp	EAR-plat	EAR-mech	EAR-exp	EAR-plat	EAR-mech
FinF *vs* IMRT	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
FinF *vs* VMAT	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
IMRT *vs* VMAT	0.997	0.993	0.994	**0.005**	**0.006**	**0.007**	0.259	0.320	0.423

EAR = excess absolute risk;FinF = field-in-field; IMRT = intensity modulated radiation therapy; lin-exp = linear–exponential; mech = full mechanistic; plat = plateau; VMAT = volumetric modulated arc therapy.

in breast RT.[28–31] Two of these studies have reported the secondary cancer risks after 3D-CRT, IMRT, and VMAT for breast cancer.[28,29] Abo-Madyan et al[29] compared tangential 3D-CRT, tangential IMRT, multibeam IMRT, and VMAT for whole-breast treatment of left-sided breast cancer. They estimated an increased EAR in the CB and lungs for IMRT and VMAT relative to that of 3D-CRT and tangential IMRT using the linear, linear–exponential, and plateau dose–response models. Lee et al[28] performed measurements in an anthropomorphic phantom to compare dose exposition of the CB and IL in whole-breast RT and also found an increased secondary cancer risk for IMRT and VMAT relative to that for 3D-CRT. Combining the results of these studies shows that the risk of secondary cancer induction is higher for both IMRT and VMAT than for 3D-CRT. This finding is attributed to increased out-of-field leakage radiation due to the higher number of fields and monitor units used in the IMRT and VMAT plans. Similarly, in our study, comparison of the three treatment planning techniques showed a significant reduction in EAR of the CB, CL and IL for FinF relative to those for IMRT and VMAT in all dose–response models. The lowest EARs for the CB, CL, and IL were achieved with FinF, which reduced the EAR by 56 to 88% relative to those of IMRT and VMAT. Comparing the results for the different risk models in this study showed that the differences between the linear–exponential, plateau, and full mechanistic dose–response relationships were small, except for the IL, which was because the higher doses occur in the IL. As only the IL contains pixels with high doses, there is a large difference among the models.

The results of this study also showed that the VMAT, as compared with the IMRT, resulted in higher OEDs in the IL because of the higher volume of irradiation. This tendency is similar to the tendency shown in the results of Lee et al.[28] Even though the VMAT plans resulted in higher OEDs in the IL, there was no significant difference in the EAR value of the IL among the two techniques. OED-based secondary cancer risks for CB and IL were similar when IMRT and VMAT were used; however, the risk for the CL was significantly lower when VMAT was used. Based on this analysis, it would be safe to say that the shift from IMRT to VMAT techniques poses no increased secondary cancer risks for the CB and IL but does for the CL; however, the

Figure 1. Mean dose (D_{mean}), OED, and EAR of the contralateral breast, contralateral lung, and ipsilateral lung. The OED and EAR were calculated on the basis of the DVHs of the (a) contralateral breast, (b) contralateral lung, and (c) ipsilateral lung for all techniques. Calculations of the OED and EAR were performed by using the linear–exponential (dark blue), plateau (blue), and full mechanistic (light blue) dose–response models. The mean values per 10,000 person-years per Gy averaged over all 12 patients are shown. DVH, dose–volume histogram; EAR, excess absolute risk; IMRT, intensity modulated radiationtherapy; OED, organ-equivalent dose; VMAT, volumetric modulated arc therapy.

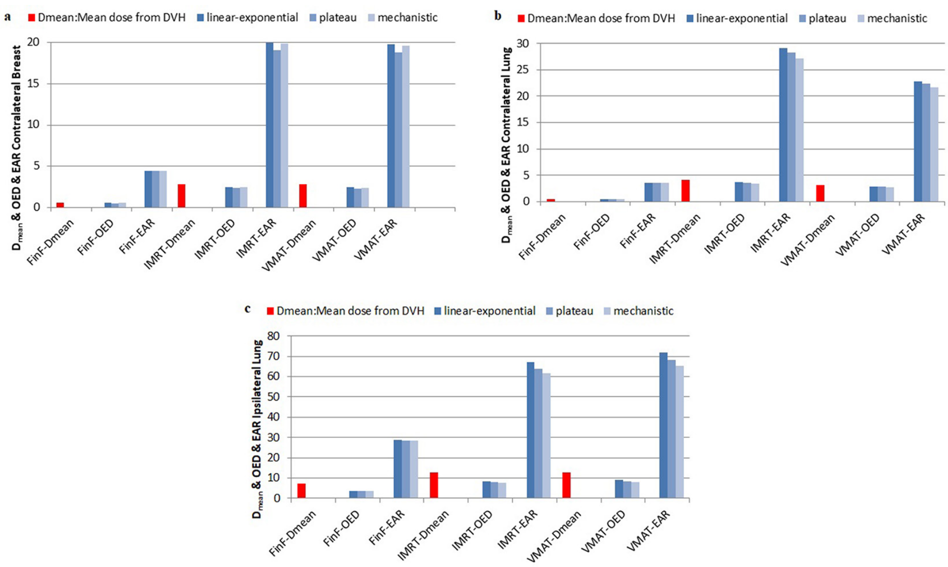
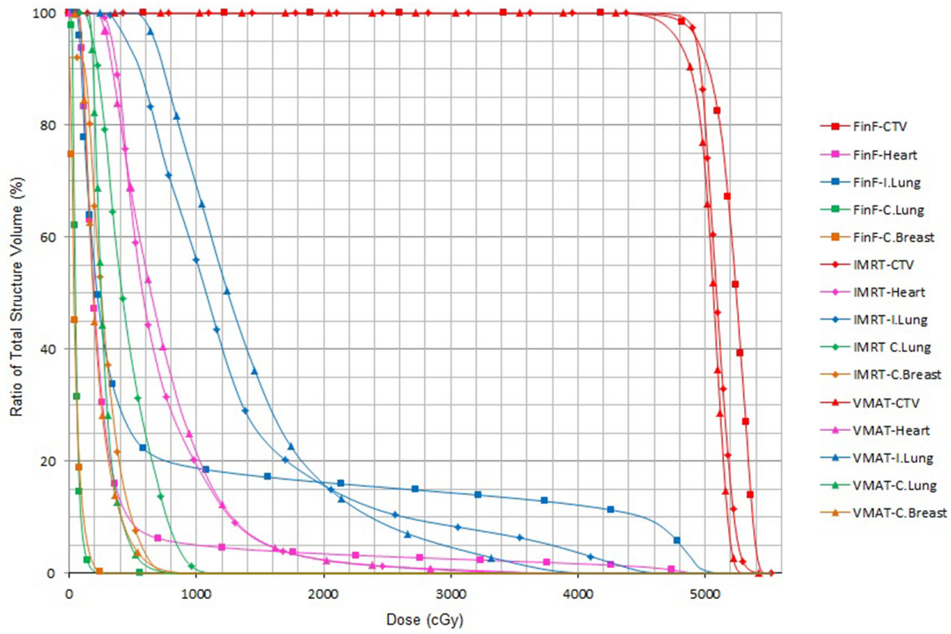


Figure 2. Dose-volume histogram comparison of a representative patient for FinF, IMRT and VMAT. Red line, CTV; Magenta line, heart; Blue line, IL; Green line, CL; Orange line, CB. CB,contralateral breast; CL, contralateral lung; CTV, clinical target volume; FinF, field-in-field; IL, ipsilateral lung; IMRT, intensity modulated radiationtherapy; VMAT, volumetric modulated arc therapy.



use of the IMRT or VMAT techniques instead of the FinF technique increases this risk. The risk of developing cancer in the CB after RT appears to be common among pre-menopausal females (<40 to 45 years) when exposed to RT.[32] The results of this study are especially important for younger patients (<45 years) who are at greater risk for RT-induced secondary malignancies. Although intensity modulated techniques may be less safe for younger patients in terms of secondary cancer risk, they should still be considered to be a valid treatment option for young patients with left-sided cancer when considering the risk of late cardiac complications. There are several published studies on the various techniques to decrease heart irradiation in females treated for left-sided breast cancer.[33–35] These techniques include breath holding techniques, prone positioning or multi beam IMRT.

Figure 3. The isodose distribution for the three plans in axial plane for a representative patient. Color-wash thresholds were set to to 3, 5 and 45 Gy, respectively. (a) FinF; (b) IMRT; and (c) VMAT; Gy (Gray). FinF, field-in-field; IMRT, intensity modulated radiationtherapy; VMAT, volumetric modulated arc therapy.

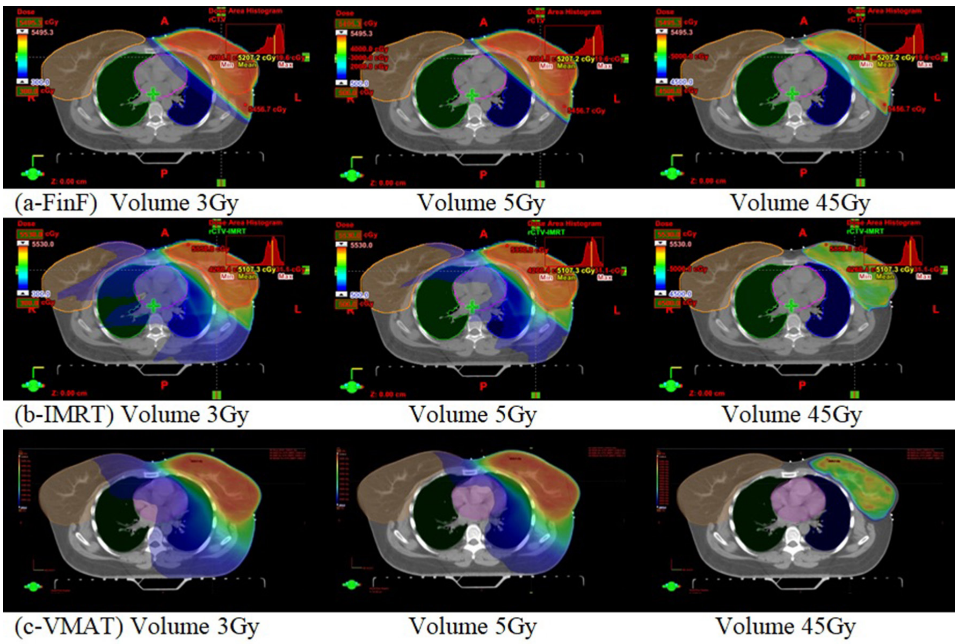


Table 5. Comparision of heart dose-volume metrics as a function of plan modality ($\overline{X}$±sd)

Heart (Metric)	FinF	IMRT	VMAT	*p*-value
D_{max} (Gy)	45.25 ± 11.86	37.55 ± 8.13	35.42 ± 8.02	**<0.001**
D_{mean} (Gy)	4.41 ± 2.20	8.40 ± 2.54	9.26 ± 2.16	**<0.001**
V_5 (%)	9.4 ± 5.28	62.8 ± 19.22	68.4 ± 17.56	**<0.001**
V_{10} (%)	7.5 ± 5.41	22.8 ± 10.26	28.1 ± 10.20	**<0.001**
V_{20} (%)	6.0 ± 4.80	7.1 ± 5.98	8.0 ± 5.52	**<0.001**
V_{30} (%)	5.2 ± 4.28	2.2 ± 1.60	2.1 ± 2.35	**<0.001**

D_{max} = maximum dose; D_{mean} = mean dose;FinF = field-in-field; Gy = Gray; IMRT = intensity modulated radiation therapy; VMAT = volumetric modulated arc therapy; V_x = volume (%) receiving x dose (Gy) or higher.

This study has shown that specifically with respect to the heart doses, IMRT and VMAT decrease the heart volumes receiving maximum and V_{30} doses compared with the FinF. However, FinF technique was superior in terms of minimizing the dose to normal tissues and contralateral organs.

CONCLUSIONS

Comparison of the three treatment planning techniques showed a significant reduction in the EARs of the CB, CL, and IL for FinF relative to those for IMRT and VMAT in all dose–response models. Until now, there have been no clinical analyses reporting on secondary cancer induction after IMRT techniques because of the limited time span. Additional theoretical and clinical studies are needed to determine the correlations between treatment techniques and secondary cancer risk. Once sufficient data are collected, treatment plans in the future may be evaluated on the basis of not only conventional factors from a DVH but also on the secondary cancer risk assessments.

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