Dosimetric Study of Hybrid Intensity Modulated Radiation Therapy Treatment Plan with Flattened Filter Free Photon Beam for Carcinoma of Breast: Treatment Planning Study

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OBJECTIVE
This study assesses the use of the flattening filter free (FFF) photon beam in hybrid treatment planning for breast carcinoma and the various dosimetric indices of planning target volume (PTV) and organs at risk (OARs).

METHODS
We selected 15 female breast cancer patients treated with Field-in-Field technique to a dose of 40 Gy/15 fractions. Retrospectively, hybrid intensity-modulated radiation therapy (IMRT) plans with FF, and FFF photon beams were created. To make the hybrid IMRT plan, a planning weightage of 60% (3DCRT): 40% (IMRT) was applied. The dose-volume histograms (DVH) were assessed for various dosimetric indicators for PTV and OARs.

RESULTS
A UDI scoring of 1.090±0.023 and 1.078±0.024 was observed between 6FF_Hybrid and 6FFF_Hybrid treatment plans with p<0.05. ID for I/L lung was 6387±1658.51 (Gy-L) and 6347.056±1643.41 (Gy-L) in 6FF_Hybrid and 6FFF_Hybrid IMRT plan (p=0.05), respectively. ID value to heart was 2272.52±1086.63 (Gy-L) and 2212.40±1059.49 (Gy-L) in 6FF_Hybrid and 6FFF_Hybrid IMRT plans (p>0.05), respectively. The beam on time (BOT) values of 0.882±0.08 (6FF_Hybrid) and 0.5436±0.07 (6FFF_Hybrid) were reported.

CONCLUSION
Hybrid IMRT planning with an FFF photon beam offers comparable target coverage, conformality, and homogeneity with greater OAR sparing and faster treatment time.

Keywords: Ca-breast; flattened filter free; hybrid plan; intensity-modulated radiation therapy; radiotherapy.

INTRODUCTION
The most common cancer in women and the main cause of cancer death in women is breast cancer.[1] In several randomized clinical trials, it has been shown that adding chest wall and regional lymph node irradiation after modified radical mastectomy improves disease-free survival (DFS) and overall survival (OS) in breast cancer patients with positive axillary lymph nodes.[2–4] Since 1990, the death rate from breast
cancer has decreased in industrialized nations due to better detection methods and a combination of radiation, chemotherapy, and surgery.[5,6] Radiotherapy (RT) is a crucial adjuvant therapy for patients undergoing breast-conserving surgery or with a high risk of recurrence after a modified radical mastectomy. Numerous radiation theories and mechanisms have evolved throughout time. Tangential opposing fields with hard wedge filters are used in static three-dimensional radiotherapy in conventional radiation therapy (3D-CRT). To give more uniform and conformal dose distributions for the target volume (PTV), two modern dynamic irradiation techniques, volumetric modulated arc therapy (VMAT) and intensity-modulated radiation therapy (IMRT) have been developed.[7–9] IMRT has outperformed three-dimensional conformal radiation therapy in several locations, including the head and neck, central nervous system, lung, and prostate (3D-CRT). Using multileaf collimators, IMRT regulates fluence and breaks a beam into tiny beamlets to provide the best radiation to the target while preserving vital organs. In the event of chest wall radiation, the lungs and heart remain the two most important vital organs.

With high accuracy, IMRT concentrates radiation on the breast tumor and modifies the radiation beams’ intensities, sparing the surrounding healthy tissue. With IMRT, each radiation dosage may be precisely adapted to the breast tumor's geometrical form.[10] On the other hand, because of increased low-dose exposure and more monitor units (MU), dynamic radiation techniques may promote the development of secondary tumors. [11] To maximize the advantages of static and dynamic radiation treatments, Mayo et al.[12] suggested a composite technique combining 3DCRT and IMRT, dubbed hybrid IMRT (H-IMRT). Traditional open fields and IMRT fields computed through inverse treatment planning are combined in a hybrid IMRT. Our previous research demonstrated that the hybrid IMRT plan provided equivalent target coverage and minimal dosage to neighboring OARs.[13] The enhanced dosimetric potential of flattening filter free (FFF) beams has been the subject of several articles.[14,15] Reports on the impact of the FFF beam on breast radiation may be found in many articles.[16–18] Published results [13,19–21] show that 3DCRT is a good base-dose plan for breast RT ideas that use a flat beam of photons.

The current research uses the 3DCRT with the FF photon beam as the base plan and incorporates the FFF photon beam into the hybrid IMRT treatment plan. This research aims to evaluate the hybrid IMRT treatment plan using FF and FFF photon beams. In addition, a novel idea known as the Unified Dosimetry Index (UDI) was put forth by Akpati et al.[22] The UDI, used to rank the designs, was used to assess the plans using different dosimetric indices. Full uniform dose coverage, flawless target fit, and a gradual fall-off dosage beyond the target are all characteristics of a great plan.[23–25] The four dosimetric indicators, coverage index (C), conformity index (CI), homogeneity index (HI), and gradient index (GI), as well as the UDI rating, are all taken into account. It was recommended to have the lowest possible UDI score.

**MATERIALS AND METHODS**

**Patient Simulation and Target Delineation**

Fifteen female patients with infiltrating ductal carcinoma of the left breast were chosen for this study. Their primary diagnosis was left breast cancer with lymph nodes in the supraclavicular and axillary regions (SCL). All patients were treated for 15 fractions with a Field-in-Field (FiF) treatment plan with a daily dose of 2.67 Gy.

All patients were immobilized in the head first supine position and scanned in a Siemens CT Scanner with a 3 mm slice thickness. A Carbon Fiber breast board was used to immobilize the patients, and their left arms were lifted above their heads to keep them out of the treatment field. After the planning CT was finished, digital imaging and communication in medicine (DICOM) pictures were uploaded to the Eclipse treatment planning system (version 16.1, Varian Medical Systems, USA). The body outlines the ipsilateral lung (IL), contralateral lung, contralateral breast, heart, spinal cord, and planning target volume (PTV), as well as the gross tumor volume (GTV), clinical tumor volume (CTV), and PTV, were developed. The GTV, or GTV, is the total lumpectomy cavity that can be detected using surgical clips implanted after surgery. The CTV, PTV, and organs at risk (OARs) were created using the RT0G protocol. The CTV was defined by a three-dimensional uniform 1.5 cm margin expanded in all directions surrounding the GTV. However, it had to fit within 5 mm of the external contour and up against the main muscle.

**Treatment Planning**

Eclipse treatment planning system (TPS) V16.1 (Varian Medical Systems, USA) was used to generate the hybrid plan for vital beam linear accelerator (LINAC) equipped with 120 micro leaf controllers (MLC). For each patient, hybrid IMRT plan with 6MV FF photon beam (hybrid-FF) and FFF photon beam (hybrid-FFF) were created. Both the Hybrid plans are optimized by
keeping the 3DCRT treatment plan as a base. Please put the photograph of all the plans described in this paper. The 3DCRT plan had two coplanar open tangential fields that passed via an isocenters axially at the lung-PTV interface and craniocaudally at the center of the PTV (photograph, please). With collimator angles of 0°, the gantry angles were calculated based on the PTV curvature, heart, and IL involvement. These tangential fields were extended 2.5 cm outside the body to account for the breast setup mistake. The analytical anisotropic algorithm (AAA) was used for volume dose calculation using a 2.5 mm dose grid matrix. All 3DCRT plans were normalized to deliver prescription doses to PTV mean. Two 3D-CRT and 2 IMRT beams are combined in hybrid IMRT planning. Plans for hybrid IMRT were created in two steps. Two tangent open beams of 6 MV photon beam is used to conform the breast PTV make up step one. With a 60% beam weightage, doses were computed for the tangent fields. The 3DCRT plan was used as the base plan while optimizing an IMRT treatment plan with 6 MV Photon beam with a similar beam angle. The fluence was computed for the IMRT field. Step 2 involved copying the 3DCRT beam to the IMRT plan and calculating the final dose along with 2 open tangent field calculated in step 1. A hybrid plan consists of 3DCRT and IMRT plan in a 60:40 ratio. All plans were normalized to achieve mean PTV doses equal to prescribed dose. Similar methodology was involved in the development of hybrid IMRT plan with FFF photon beam. Hybrid-6FF and hybrid 6FFF treatment plan is developed with 6 MV FF and 6MV FFF photon beam, respectively. Hybrid 6FFF treatment plan consists of 3DCRT plan with 6MV FF photon beam and IMRT plan with 6MV FFF photon beam. Photon optimizer (PO) was used for inverse treatment plan optimization. A leaf motion calculator was used to convert the fluences into dynamic MLC sequences, and final dose computation was performed with the AAA algorithm. During inverse optimization, dose constraints listed in Table 1 were utilized. Both hybrid IMRT plan uses the same optimization parameter and dose penalty.

**Planning Evaluation Indices**

The treatment plans can be evaluated qualitatively by performing a visual slice-by-slice examination using isodose line distribution. A qualitative assessment is required for treatment plans containing hot and cold areas. Dose volume histograms (DVH) were all included in the quantitative analysis. To assess the dose to various structures in various schemes, DVH was developed. The dose-volume parameters D98% (minimum dose received by 98% of PTV volume) and D2% (maximum dose received by 2% of PTV volume) were analyzed for PTV as per the International Commission on Radiation Units and Measurements (ICRU) report 83. [26] DVHs were used to calculate various dosimetric indices doses for PTV and OARs and to compute the integral doses for the OARs.

**Statistical Tools and Analysis**

The statistical analysis was conducted using IBM Corporation's Statistical Software Package for the Social Sciences (SPSS) version 17.0. To find the mean and median, descriptive analysis was used. To compare the Hybrid FF plan to the Hybrid FFF plan IMRT, a paired t-test was used. For statistical significance, p=0.05 was used. 100% of the PTV receiving the prescribed dose is referred to as dose coverage. It is a metric that indicates how effectively the prescribed dose covers the PTV. It is acceptable to have a plan that covers 92% of the required dose. [27]
Coverage index (C) = \( \frac{PTV_{PI}}{PTV} \)

Where \( PTV_{PI} \) is the PTV getting the prescribed isodose (PI), as stated in ICRU Report No. 62.[28] RTOG recommended the CI in 1993. The relationship between the volumes of the reference dosage and the target dose is displayed.

Conformity index (CI) = \( \frac{V_{IR}}{TV} \)

Where \( V_{IR} \) is the reference dose volume, and TV is the total target volume.

To assess the level of conformity, CI value ranges have been defined. The ideal CI value is 1, according to the theory. The treatment is deemed to comply with the treatment plan if the CI is between 1 and 2. RTOG proposed guidelines for routinely evaluating plans on several factors and HI in 1993. The dosimetric analysis of the treatment plan served as the foundation for developing the HI concept.[29]

Homogeneity Index (HI) = \( \frac{I_{max}}{RI} \)

\( I_{max} \) is the target’s maximal isodose, and RI is the reference isodose.

If HI value is \( 0<HI \leq 2 \): No Violation,
\( 2<HI \leq 2.5 \): A minor violation,
\( HI \geq 2.5 \): Major violation.

The dose GI can compare plans that are similar in conformance but have distinct dose gradients. The ratio of the volume receiving the PI line to the volume receiving half of the recommended isodose line is known as the dose GI.[25]

\[ D_{50\%} = \frac{D_{50\%}}{D_{100\%}} \]

Where \( D_{100\%} \): Volume of the prescribed dose.
\( D_{50\%} \): Volume of half the prescribed dose.

All four parameters stated above are included in the UDI. It is an effective tool for determining the best treatment plan strategy. The CI, HI, GI, and C are the ideal parameter to evaluate treatment plan quality. Changes can influence UDI’s value in any of the four components. A UDI value near 1 is preferable, while a greater UDI value is not considered.

\[ UDI = CN \times CI \times HI \times GI \]

RESULTS

Table 2 summarizes the patient’s characteristics. The patient’s age ranged from 31 to 65 years, with a mean of \( 50 \pm 10.56 \) years. The average PTV volume was 313.15 cc with a standard deviation of 105.81 cc. The PTV volume ranged from 109.1 cc to 530.9 cc. Right, and left lung volumes were 827.19±153.50 cc and 945.91±143.39 cc, respectively. The heart and contralateral (C/L) breast volumes were 502.67±133.91 cc and 790.07±310.68 cc, respectively.
Table 3 illustrates the dosimetric parameter for the planning target volume (PTV) in the intensity modulated radiation therapy (IMRT) plan for 6X_FF (Flattened Filter) & 6X_FFF (Flattened Filter Free)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Treatment plans</th>
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<tbody>
<tr>
<td></td>
<td>6FF_Hybrid (Mean±SD)</td>
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<tr>
<td>Coverage index (C)</td>
<td>0.950±0.007</td>
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<tr>
<td>Conformity index (CI)</td>
<td>0.970±0.010</td>
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<tr>
<td>Homogeneity index (HI)</td>
<td>1.125±0.026</td>
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<tr>
<td>Gradient index (GI)</td>
<td>0.566±0.034</td>
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<tr>
<td>Unique dosimetric index (UDI)</td>
<td>0.586±0.033</td>
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<tr>
<td></td>
<td>6FFF_Hybrid (Mean±SD)</td>
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<tr>
<td>Coverage index (C)</td>
<td>0.945±0.013</td>
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<tr>
<td>Conformity index (CI)</td>
<td>0.963±0.021</td>
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<tr>
<td>Homogeneity index (HI)</td>
<td>1.134±0.025</td>
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<tr>
<td>Gradient index (GI)</td>
<td>0.540±0.037</td>
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<tr>
<td>Unique dosimetric index (UDI)</td>
<td>0.557±0.041</td>
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Table 4 illustrates the dosimetric indices for the Organs at Risk (OARs)

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<th>Variables</th>
<th>Treatment plans</th>
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<tr>
<td></td>
<td>6FF_Hybrid (Mean±SD)</td>
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<tr>
<td>Lungs V5Gy (%)</td>
<td>27.51±5.02</td>
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<td>Lungs V10Gy (%)</td>
<td>21.51±4.59</td>
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<tr>
<td>Lungs V20Gy (%)</td>
<td>17.23±3.54</td>
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<tr>
<td>Lungs mean (Gy)</td>
<td>7.72±1.31</td>
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<tr>
<td>Heart V20Gy (%)</td>
<td>8.06±3.69</td>
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<tr>
<td>Heart V10Gy (%)</td>
<td>10.24±4.10</td>
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<tr>
<td>Heart mean (Gy)</td>
<td>4.29±1.40</td>
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<tr>
<td>C\L breast (Max)</td>
<td>5.81±6.8</td>
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<tr>
<td>C\L (D5%)</td>
<td>0.64±0.33</td>
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<tr>
<td></td>
<td>6FFF_Hybrid (Mean±SD)</td>
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<tr>
<td>Lungs V5Gy (%)</td>
<td>27.39±5.21</td>
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<tr>
<td>Lungs V10Gy (%)</td>
<td>21.32±4.27</td>
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<tr>
<td>Lungs V20Gy (%)</td>
<td>17.09±3.51</td>
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<tr>
<td>Lungs mean (Gy)</td>
<td>7.67±1.35</td>
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<tr>
<td>Heart V20Gy (%)</td>
<td>7.89±3.59</td>
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<tr>
<td>Heart V10Gy (%)</td>
<td>10.05±4.08</td>
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<tr>
<td>Heart mean (Gy)</td>
<td>4.18±1.41</td>
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<tr>
<td>C\L (D5%)</td>
<td>0.63±0.35</td>
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Table 5 shows the Comparison of ID, MU and BOT between 6FF_Hybrid and 6FFF_Hybrid IMRT Plan.

<table>
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<tr>
<th>Variables</th>
<th>Treatment plans</th>
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<tr>
<td></td>
<td>6FF_Hybrid (Mean±SD)</td>
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<tr>
<td>ID (Gy-L)</td>
<td>2272.52± 1086.63</td>
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<tr>
<td>Heart</td>
<td>6387 ± 1658.51</td>
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<tr>
<td>C/L Lung</td>
<td>101.61 ± 27.07</td>
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<tr>
<td>Number of MUs</td>
<td>529.14 ± 50.46</td>
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<tr>
<td>BOT (min)</td>
<td>0.882 ± 0.08</td>
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<tr>
<td></td>
<td>6FFF_Hybrid (Mean±SD)</td>
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<tr>
<td>ID (Gy-L)</td>
<td>2212.40 ± 1059.49</td>
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<tr>
<td>Heart</td>
<td>6347.056 ± 1643.41</td>
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<tr>
<td>C/L Lung</td>
<td>117.27 ± 30.81</td>
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<tr>
<td>Number of MUs</td>
<td>761.07 ± 102.51</td>
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<tr>
<td>BOT (min)</td>
<td>0.5436 ± 0.07</td>
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Table 3 shows the different treatment plan quality index comparisons for 6FF_Hybrid and 6FFF_Hybrid treatment plans. The coverage index for the 6FF_Hybrid plan was 0.945±0.013, and for the 6FF_Hybrid treatment was 0.950±0.007 with p>0.05. PTV in the 6FF hybrid plan had a conformity index of 0.970±0.010, whereas the 6FFF Hybrid had a conformity index of 0.963±0.021 with p>0.05. The hybrid IMRT treatment with 6FF and 6FFF photon beams had HI values of 1.125±0.026 and 1.134±0.025, respectively. In the 6FF_Hybrid and 6FFF_Hybrid treatment plans, an insignificant GI value of 1.050±0.020 and 1.042±0.017 was found (p>0.05). A UDI scoring of 1.090±0.023 and 1.078±0.024 was observed between 6FF_Hybrid and 6FFF_Hybrid treatment plans with p>0.05.

Table 4 illustrates the different volumetric doses to the OARs for the 6FF-Hybrid and 6FFF_Hybrid IMRT plans. V5Gy and V10Gy of the IL were smaller in the 6FF_Hybrid
IMRT plan compared to the 6FF_Hybrid IMRT plan (p>0.05). V20Gy of IL received a lesser dose in 6FF_Hybrid than 6FFF_Hybrid IMRT plan (p>0.05). The mean dose of the IL was less in the 6FF_Hybrid IMRT plan than in the 6FFF_Hybrid IMRT plan (p>0.05). V20Gy and V10Gy of the heart were reported with smaller radiation doses in the 6FF_Hybrid IMRT plan compared to the 6FFF_Hybrid IMRT treatment plan (p>0.05). Significantly, the 6FFF_Hybrid IMRT plan delivers lower doses of radiation in comparison to the 6FF_Hybrid IMRT plan. The Dmax of the contralateral breast significantly received reduced doses of radiation on the 6FFF_hybrid plan concerning the 6FF_Hybrid plan. D5% of contralateral breasts receives an insignificantly lesser dose in 6FFF_Hybrid IMRT compared to 6FF_Hybrid plan.

**Integral Doses**

Table 5 shows the comparison of integral dose (ID), monitor unit (MU), and beam on time (BOT) between the 6FF_Hybrid IMRT and 6FFF_Hybrid IMRT. ID for I/L lung was 6387±1658.51 (Gy·L) and 6347.056±1643.41 (Gy·L) in 6FF_Hybrid and 6FFF_Hybrid IMRT plan (p<0.05), respectively. I/p breast was reported with ID of 117.27±30.819 (Gy·L) and 101.61±27.07 (Gy·L) in 6FF_Hybrid and 6FFF_Hybrid IMRT plan (p<0.05). ID value to heart was 2272.52±1086.63 (Gy·L) and 2212.40±1059.49 (Gy·L) in 6FF_Hybrid and 6FFF_Hybrid IMRT plans (p<0.05), respectively. The number of MUs for the 6FF_Hybrid and 6FFF_Hybrid IMRT plans was 529.14, 50.46 and 761.07 102.51, respectively, with a significant difference of p<0.05.

The BOT in the 6FF_Hybrid IMRT plan was much lower than in the 6FF_Hybrid IMRT plan. 6FF_Hybrid and 6FFF_Hybrid IMRT plans have BOT values of 0.882±0.08 and 0.5436±0.07, respectively (p<0.05).

**DISCUSSION**

A limited study is available for a Hybrid treatment plan compared with IMRT, 3DCRT and VMAT. Numerous studies have compared the IMRT treatment with the FFF photon beam and FF photon beam for the different treatment sites. They have concluded that no significant dose difference was observed between the IMRT treatment plan with FF and FFF photon beam. Figure 1 shows the color dose wash of 95% isodose of prescribed dose for 6FFF and 6FF Hybrid IMRT plan.

Figure 2a shows the CI, C, and HI comparison between the FF and FFF Hybrid plans. Similar results were also observed in our study of Hybrid treatment plans with and without the flattening filter. No significant dose difference was found for PTV target coverage (C, CI, and HI between 6FF_Hybrid IMRT and 6FFF_Hybrid IMRT treatment plan. Figure 2b compares GI and UDI between the FF and FFF Hybrid plans. Higher dose fall is one of the main characteristics of the FFF photon beam, but here in our study, the GI value for a hybrid plan using the FFF photon beam does show how significant the dif-
The difference is from that of the FF hybrid plan. Comparing the UDI score, the FFF hybrid plan has a lesser score than the FF hybrid plan. One of the dominating factors in calculating UDI was the GI value.

The fundamental goal of the hybrid technique is to preserve the heart, I/L, C/L lung, and C/L breast to avoid radiation-induced secondary cancers and long-term consequences (such as heart failure and lung pneumonia).

Figure 3 illustrates the volume of the left lung receiving various doses in the 6FF_hybrid and 6FFF_Hybrid treatment plan. Radiation pneumonitis, which
subsequently develops into irradiated lung fibrosis, can affect patient’s right after irradiation. Clinically severe pneumonitis should be uncommon in breast cancer patients if the $V_{20\text{Gy}}$ of the IL is $<30\%$. $V_{20\text{Gy}}$ was the lowest in both types of Hybrid plans and achieved the lowest value in the FFF hybrid plan. $V_{5\text{Gy}}$ and $V_{10\text{Gy}}$ were well below their threshold value, and FFF hybrid attains the lowest volume compared to the FF Hybrid plan.

Another important OARs while treating the ca-breast with radiation therapy is the heart. The Figure 4 shows the comparison of mean dose, $V_{20\text{Gy}}$ and $V_{10\text{Gy}}$ received by heart between 6FF_hybrid and 6FFF_Hybrid treatment plan. Evidence from various research indicates that for every additional 1 Gy given to the heart’s normal exposure, the incidence of major coronary accidents rises by 7.4%.[32] The average $D_{\text{mean}}$ to heart was 2.6% lower in the FFF Hybrid plan than in the FF hybrid. Our study achieved the mean dose to heart well below the planning threshold in both planning schemes.

$D_{\text{ID}}$ is the absorbed dose within the specific organ. The distribution of the ID doses for the heart and

![Heart Dose Comparison](image1)

**Fig. 4.** The comparison of heart doses between the 6FF_Hybrid and 6FFF_Hybrid Treatment plans.

FF: Flattened Filter; FFF: Flattened Filter Free; Gy: Gray.

![Integral Doses for Left Lung and Heart](image2)

**Fig. 5.** The integral dose comparison between 6FF_Hybrid and 6FFF_Hybrid treatment plans for the heart and left lung.

FF: Flattened Filter; FFF: Flattened Filter Free; ID: Integral dose; Gy: Gray; L: Liter.
lungs for the 6FF_ and 6FFF_Hybrid IMRT Treatment Plans is shown in Figure 5. It is typically reported that the ID of IMRT increases as the number of small aperture and monitor units increases. 6FFF_Hybrid plan has more MU than the 6FF_Hybrid plan, but the ID for the heart and left lung was less in the 6FFF_Hybrid plan than the 6FF_Hybrid plan. This could be because of the less scattered dose in the FFF photon beam. Saroj et al.[15] reported similar results. 70% reduction in scattered dose for IMRT planning with FFF photon beam is reported by Cashmore et al.[33]. Another advantageous aspect of the FFF photon beam is the availability of a higher dose rate. IMRT plan with FFF photon beam has more MU than FF IMRT plan. Our finding is consistent with the literature. We have seen a 44% increase in the number of MUs with the 6FFF_Hybrid IMRT plan as opposed to the 6FF_Hybrid IMRT plan. FFF photon beam with a high dose rate will help deliver the higher MU in a shorter time. A 62% reduction is observed in BOT for the 6FFF_Hybrid plan compared to 6FF_hybrid Plan. Lower BOT will help reduce patients’ couch time during treatment.

**CONCLUSION**

The scope of the hybrid treatment plan was expanded with additional benefits by including the FFF photon beam. The FFF photon beam hybrid technique still provides a desirable and acceptable treatment plan. A hybrid IMRT treatment plan with FFF photon beam characteristics spares the OARs better than a hybrid IMRT plan with an FF photon beam, giving patients a higher standard of living. Finally, our study concludes that using an FFF photon beam in a Hybrid IMRT plan for the ca-breast patient will be beneficial due to better OARs sparing, less scattered dose, and faster treatment delivery.

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**Conflict of Interest:** All authors declared no conflict of interest.

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**REFERENCES**


