

# Potential Risks of Radiation-Induced Breast Cancer with Different Accelerated Partial Breast Irradiation Techniques



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## Purpose

There is increasing current interest in treating early stage breast cancer with accelerated partial breast irradiation (APBI). One of the major rationales of APBI is to minimize the long-term risk of a radiation-induced second cancer. The purpose of this study was to determine if different external beam APBI techniques produce significantly different predicted risks of radiation-induced breast and lung cancers, both ipsilateral and contralateral.

## Materials/Methods

An anthropomorphic whole-body phantom (Figure 1) was used, with realistic breasts based on a CT scans of a female in a supine position. Point dose measurements using MOSFET detectors within the ipsilateral left breast, the contralateral right breast, the right and left lung were used to validate calculated organ dose distributions for six different external-beam APBI techniques. APBI techniques compared were 1) a tangential technique (T) using a 30° enhanced dynamic wedged pair; 2) a two field multi-segment static (field in field) forward planning IMRT technique (FF); 3) a two field dynamic multi-leaf collimator forward planning intensity modulated radiation therapy (IMRT) technique (2FDMLC); 4) a four-field dynamic multi-leaf collimator forward planning intensity modulated radiation therapy technique (4FDMLC); 5) a three-dimensional conformal radiation therapy technique (3D-CRT) using four non-coplanar fields, as outlined in the RTOG-0413 protocol; 6) a dynamic multi-leaf collimator inverse planning IMRT technique (IDMLC) using the same four non-coplanar fields as the 3D conformal technique.

Breast and lung cancer risks were calculated from calculated dose-volume histograms (Figure 2) using a recent validated mechanistic model (PNAS 102, 13040-5, 2005) which incorporates pre-malignant stem cell initiation, inactivation and, crucially, proliferative repopulation. Proliferation of pre-malignant cells during post-irradiation repopulation explains why cancer risks do not decrease sharply at high radiation doses, as is now clear from recent epidemiological data.

Figure 1  
Anthropomorphic Whole-Body Phantom

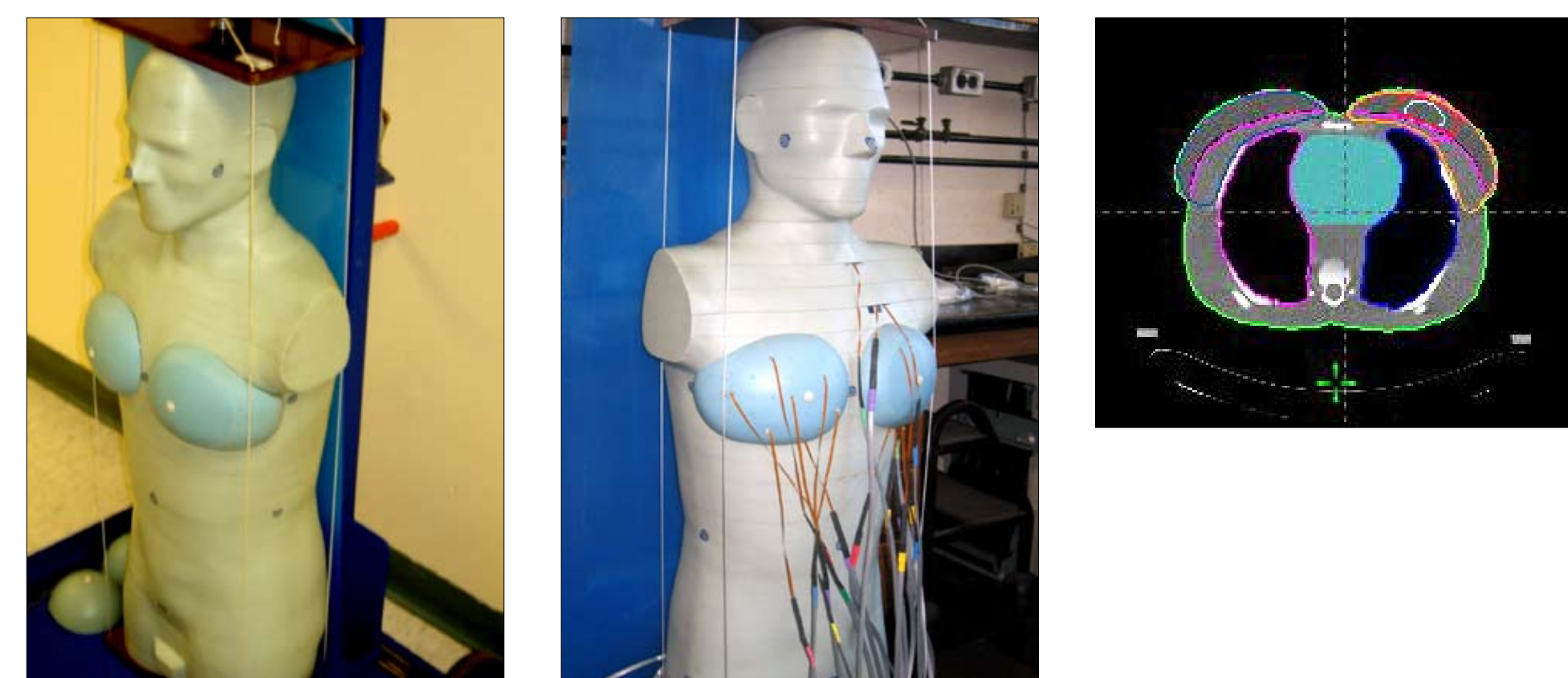
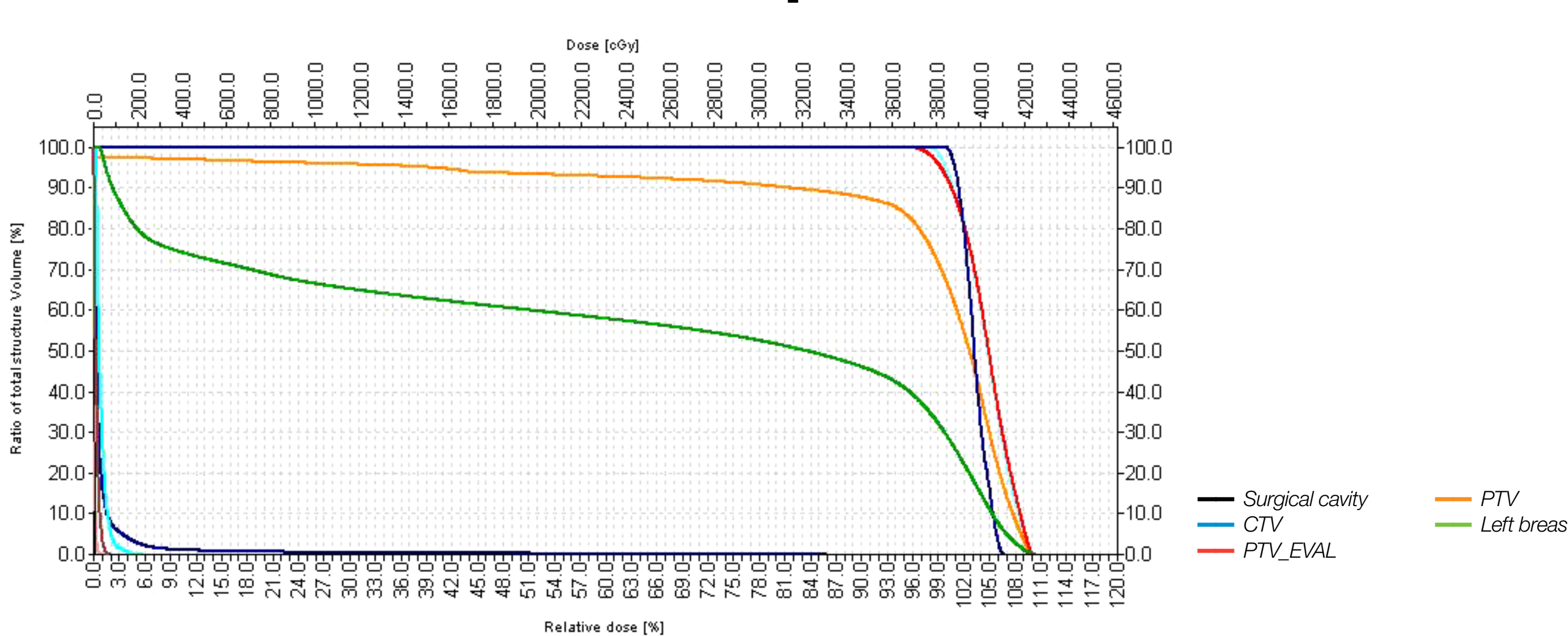


Figure 2  
Dose-Volume Histogram for APBI 3D-CRT Technique



## Results

Table 1 illustrates the similarity in volume of tissue in the anthropomorphic phantom CT volumes used in the 6 APBI treatment techniques and CT volumes used in the NSABP-39/RTOG 0413 credentialing process. The CTV was defined as a uniform expansion of the excision cavity volume by 15 mm, limited by 5 mm from the skin surface and by the posterior breast tissue extent. The PTV was defined as a uniform 10 mm expansion of the CTV. The PTV\_EVAL was defined to exclude part of the outside of the ipsilateral breast and the first 5 mm of tissue under the skin, and excluded the PTV expansion beyond the posterior extent of the breast tissue (chest wall, pectoralis muscles and lung).

Table 2 compares the NSABP-B39/RTOG 0413 dose limitations for normal structures with the six different APBI techniques. Dose limitations of uninvolved normal breast tissue could not be met for T and FF APBI techniques, and for contralateral breast tissue in T, FF, 2FDMLC and 4FDMLC, with maximum prescribed contralateral breast dose being highest in the T and FF APBI techniques and close to contralateral dose limitations in the 2FDMLC and 4FDMLC APBI techniques. Although 90% of the prescribed dose covered 90% of the PTV\_EVAL in all 6 APBI techniques, IDMLC provided the lowest coverage to the PTV\_EVAL (93% vs. 99%).

Tables 3, 4, 5, 6 shows preliminary estimates of the absolute lifetime second cancer risk associated with the radiation exposure (ipsilateral breast, contralateral breast, ipsilateral lung, contralateral lung) for women treated at ages 40-70 with the six different APBI techniques. Each APBI technique delivered 10 fractions of 3.85 Gy/fraction for a total APBI dose of 38.5 Gy. The estimated risks decreased with increasing age, quite rapidly for the breast (more than a factor of 10 between ages at exposure 40 to 70), and quite slowly for the lung (less than a factor of 2 between ages at exposure 40 to 70). Despite the fact that the doses to the lung were far less than those to the breast, the absolute cancer risks were quite similar for breast vs. lung, for a woman treated at, say, age 60.

The six treatment protocols resulted in quite different predicted second cancer risks for all the sites studied. This effect was particularly marked for the ipsilateral lung, which represents the largest predicted risk for women exposed over age 60; here, the different plans resulted in predicted ipsilateral lung cancer risks which varied by more than a factor of 10.

Among the six APBI techniques studied, IDMLC followed by 3D-CRT gave the lowest estimate lifetime cancer risks, reflecting lower mean doses to both breasts and both lungs.

## Conclusions

Different APBI techniques in breast conserving therapy result in quite different dose distributions and mean doses to the ipsilateral and contralateral breast and lung, and thus quite different predicted risks of radiation-induced second breast cancer and lung cancer. 3D-CRT and, particularly, IDMLC result in much lower doses and risks than other techniques. This is particularly important for radiation-induced ipsilateral lung cancer, where, for example, the estimated lifetime risk for a 60 year old woman can be reduced from 2.3% to 0.24% by using an appropriate technique.

While the benefits of breast irradiation in breast conserving therapy certainly outweigh the risks of developing subsequent radiation induced cancers, the excellent long-term survival rate for women undergoing breast conserving therapy suggests that it is imperative that second-cancer risks be reduced as much as possible. Consideration should be given to breast treatment planning techniques that decrease the radiation exposure to the contralateral breast and lung and, particularly, the uninvolved ipsilateral breast and the ipsilateral lung. These considerations hold for all women treated with radiation therapy for breast cancer, not only those treated at a young age, with a positive family history, and/or BRCA1/2 mutation carriers.

Table 1  
Comparison of the Phantom CT Volumes and CT Volumes used in the NSABP B-39/RTOG 0413 Credentialing Process

Organ	Phantom Volumes (cm <sup>3</sup> )	PBI Volumes used for Credentialing (cm <sup>3</sup> )
Left Breast	653.46	653.32
Right Breast	648.11	466.93
Tumor Bed/Cavity	3.96	3.94
CTV	48.93	48.35
PTV	169.24	168.01
PTV_EVAL	86.84	86.53

Table 2  
Comparison of NSABP B-39/RTOG 0413 Dose Limitations for Normal Tissue Structures with Different APBI Techniques

Normal Tissue	NSABP B-39/RTOG 0413 Dose Limitations for Normal Tissue Structures	Tangential Using 30 Degree Enhanced Dynamic Wedged Pair (T)	2 Field Multi-Segment Static (Field in Field) Forward Planning IMRT (FF)	2 Field Dynamic Multi-Leaf Collimator Forward Planning IMRT (2FDMLC)	4 Field Dynamic Multi-Leaf Collimator Forward Planning IMRT (4FDMLC)	3D-CRT Using 4 Non-Coplanar Fields (3D-CRT)	(3D-CRT) Multi-Leaf Collimator Inverse Planning IMRT (IDMLC)
Uninvolved Normal Breast	< 60% of the whole breast should receive > 50% of the prescribed dose  And < 35% of the whole breast should receive the prescribed dose	75.11% V 50% D	75.14% V 50% D	59.44% V 50% D	57.52% V 50% D	60.23% V 50% D	45.62% V 50% D
Contralateral Breast	< 3% of the prescribed dose to any point	Max 34.8% Mean 0.9%	Max 30.8% Mean 0.8%	Max 8.4% Mean 0.5%	Max 4.2% Mean 0.4%	Max 1.9%	Max 1.5%
Ipsilateral Lung	< 15% of the lung can receive 5% of the prescribed dose	9.53% V 5% D	8.94% V 5% D	6.46% V 5% D	6.78% V 5% D	3% V 5% D	1.29% V 5% D
Contralateral Lung	< 15% can receive 5% of the prescribed dose	Max 2.1%	Max 1.9%	Max 1.1%	Max 1.1%	Max 0.9%	Max 0.7%
Heart (Left-sided lesions)	5% of the prescribed dose (V5) should be less than the 40%	9.38% V 5% D	8.2% V 5% D	2.83% V 5% D	2.68% V 5% D	0.05% V 5% D	Max 4.4%
Thyroid	Maximum point the dose of 3% of prescribed dose	0.2%	0.2%	0.1%	0.1%	0.1%	0.1%
PTV_EVAL	90% of the prescribed dose covers ≥ 90% of the PTV_EVAL And maximum dose does not exceed 120% of prescribed dose	99.99% V 90.0% D	99.89% V 90.0% D	99.92% V 90.0% D	99.75% V 90.0% D	99.98% V 90.0% D	92.9% V 90.0% D

Table 3  
Estimated Lifetime Ipsilateral (Left) Breast Cancer Risks for Woman Treated with Different APBI Techniques at Age 40-70, Based on Calculated DVHs

APBI Technique	Mean Dose (cGy)	Lifetime Cancer Incidence Risk (%) Age 40	Lifetime Cancer Incidence Risk (%) Age 50	Lifetime Cancer Incidence Risk (%) Age 60	Lifetime Cancer Incidence Risk (%) Age 70
Tangential Using 30 Degree Enhanced Dynamic Wedged Pair (T)	2903	9.1	4.5	2.0	0.78
2 Field Multi-Segment Static (Field in Field) Forward Planning IMRT (FF)	2846	9.1	4.5	2.0	0.77
2 Field Dynamic Multi-Leaf Collimator Forward Planning IMRT (2FDMLC)	2338	7.4	3.7	1.6	0.64
4 Field Dynamic Multi-Leaf Collimator Forward Planning IMRT (4FDMLC)	2294	7.4	3.7	1.6	0.64
3D-CRT Using 4 Non-Coplanar Fields (3D-CRT)	2379	7.4	3.7	1.6	0.64
Dynamic Multi-Leaf Collimator Inverse Planning IMRT (IDMLC)	1758	5.8	2.9	1.3	0.50

Table 4  
Estimated Lifetime Contralateral (Right) Breast Cancer Risks for Woman Treated with Different APBI Techniques at Age 40-70, Based on Calculated DVHs

APBI Technique	Mean Dose (cGy)	Lifetime Cancer Incidence Risk (%) Age 40	Lifetime Cancer Incidence Risk (%) Age 50	Lifetime Cancer Incidence Risk (%) Age 60	Lifetime Cancer Incidence Risk (%) Age 70
Tangential Using 30 Degree Enhanced Dynamic Wedged Pair (T)	33.8	0.22	0.11	0.049	0.019
2 Field Multi-Segment Static (Field in Field) Forward Planning IMRT (FF)	32.7	0.22	0.11	0.049	0.019
2 Field Dynamic Multi-Leaf Collimator Forward Planning IMRT (2FDMLC)	18.0	0.12	0.062	0.027	0.010
4 Field Dynamic Multi-Leaf Collimator Forward Planning IMRT (4FDMLC)	17.1	0.12	0.059	0.026	0.010
3D-CRT Using 4 Non-Coplanar Fields (3D-CRT)	14.4	0.10	0.051	0.022	0.008
Dynamic Multi-Leaf Collimator Inverse Planning IMRT (IDMLC)	9.8	0.067	0.033	0.015	0.006

Table 5  
Estimated Lifetime Ipsilateral (Left) Lung Cancer Risks for Woman Treated with Different APBI Techniques at Age 40-70, Based on Calculated DVHs

APBI Technique	Mean Dose (cGy)	Lifetime Cancer Incidence Risk (%) Age 40	Lifetime Cancer Incidence Risk (%) Age 50	Lifetime Cancer Incidence Risk (%) Age 60	Lifetime Cancer Incidence Risk (%) Age 70
Tangential Using 30 Degree Enhanced Dynamic Wedged Pair (T)	230.2	2.7	2.6	2.3	1.7
2 Field Multi-Segment Static (Field in Field) Forward Planning IMRT (FF)	222.1	2.7	2.6	2.3	1.7
2 Field Dynamic Multi-Leaf Collimator Forward Planning IMRT (2FDMLC)	79.3	0.95	0.91	0.80	0.59
4 Field Dynamic Multi-Leaf Collimator Forward Planning IMRT (4FDMLC)	78.3	0.94	0.90	0.79	0.58
3D-CRT Using 4 Non-Coplanar Fields (3D-CRT)	40.5	0.48	0.46	0.40	0.29
Dynamic Multi-Leaf Collimator Inverse Planning IMRT (IDMLC)	23.0	0.28	0.27	2.4	1.8

Table 6  
Estimated Lifetime Contralateral (Right) Lung Cancer Risks for Woman Treated with Different APBI Techniques at Age 40-70, Based on Calculated DVHs

APBI Technique	Mean Dose (cGy)	Lifetime Cancer Incidence Risk (%) Age 40	Lifetime Cancer Incidence Risk (%) Age 50	Lifetime Cancer Incidence Risk (%) Age 60	Lifetime Cancer Incidence Risk (%) Age 70
Tangential Using 30 Degree Enhanced Dynamic Wedged Pair (T)	11.1	0.13	0.12	0.10	0.07
2 Field Multi-Segment Static (Field in Field) Forward Planning IMRT (FF)	10.7	0.13	0.12	0.10	0.07
2 Field Dynamic Multi-Leaf Collimator Forward Planning IMRT (2FDMLC)	6.4	0.076	0.073	0.064	0.047
4 Field Dynamic Multi-Leaf Collimator Forward Planning IMRT (4FDMLC)	6.2	0.074	0.071	0.062	0.045
3D-CRT Using 4 Non-Coplanar Fields (3D-CRT)	5.4	0.065	0.062	0.054	0.039
Dynamic Multi-Leaf Collimator Inverse Planning IMRT (IDMLC)	3.3	0.039	0.037	0.032	0.023

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