Estimation of Second Cancer Risk after IORT, APBI, m-IMRT and VMAT using NCRP Report 116 for Breast Cancer

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Abstract— Second cancer risk after breast conserving radiation therapy has severe late effects. Intraoperative radiotherapy (IORT), accelerated partial breast irradiation (APBI) and external beam radiotherapy techniques (EBRT) such as multibeam IMRT step & shoot IMRT (m-IMRT) and Volumetric Modulated Arc Therapy (VMAT) are increasingly used for the treatment of breast cancer. In this study, we compare the second cancer risk using NCRP report 116 for doses to internal organs after IORT, APBI and EBRT techniques (m-IMRT & VMAT) for breast cancer. Computer tomography scans of an anthropomorphic phantom were acquired with an INTRABEAM IORT applicator (diameter 4 cm) in the outer quadrant of the breast and transferred via DICOM to the treatment planning systems. An INTRABEAM source (50 kV) was defined with the tip of the drift tube at the center of the spherical applicator. A dose of 20 Gy at 0 mm depth from the applicator surface was prescribed for IORT and 34 Gy (5 d × 2 × 3.4 Gy) at 10 mm depth for APBI. For EBRT (m-IMRT & VMAT) a total dose of 50 Gy in 2 Gy fractions was planned. The mean and maximal doses, ipsilateral breast DVH and volumes receiving more than 0.1 Gy and 4 Gy of organs at risk (OAR) were calculated and compared. The life time risk for secondary cancers was estimated according to NCRP report 116. External beam radiotherapy techniques (m-IMRT and VMAT) yielded the largest doses to contralateral breast, ipsilateral lung, contralateral lung, heart and spine. IORT delivered the lowest maximal doses to contralateral breast (< 0.3 Gy), ipsilateral (1.8 Gy) and contralateral lung (< 0.3 Gy), heart (1 Gy) and spine (< 0.3 Gy). Maximal doses for APBI were 2-5 times higher than for IORT. Using NCRP report 116, the estimated risk for secondary cancer in the respective OAR is considerably lower after IORT and/or APBI as compared to EBRT techniques (m-IMRT & VMAT). For m-IMRT second cancer risks for contralateral breast (30%) and ipsilateral lung (15%) is higher than for VMAT. The calculations for maximal doses, mean doses and volumes of OAR suggest that second cancer risk after IORT and APBI is considerably lower than for m-IMRT and VMAT for contralateral breast, ipsilateral lung and contralateral lung.

Index Terms— Second cancer risk, Computed Tomography, Intraoperative radiotherapy (IORT), Volumetric Modulated Arc Therapy (VMAT), Intensity Modulated Radiation Therapy (IMRT), Organ at Risk (OAR), Breast cancer.

1 INTRODUCTION

Breast cancer is a worldwide problem, accounting for 10.4% of all cancer incidences among women and second most common cause of cancer-related death. Over the past 30 years, substantial improvements have been made in the outcomes for patients with early stage breast cancer. In the United States and Europe, the most common treatment is breast conserving surgery followed by adjuvant radiotherapy [1], [2], [3]. Breast-conserving surgery (BCS) followed by external-beam whole-breast radiotherapy (EBRT) has become the standard of care in early breast cancer. Adjuvant EBRT after BCS significantly reduces the risk for in-breast tumor recurrence (IBTR) and improves overall survival over BCS alone [1], [4], [5]. As patients diagnosed with breast cancer are more likely to survive longer, it is essential to prevent treatment induced fatalities. The main types of radiation therapy induced fatalities that have been widely reported are cardiomyopathy and secondary cancers [6]. Though their occurrence is also influenced by lifestyle and/or a predisposing genetic condition [7], [8], it is primarily related to the amount of dose deposited in specific organs [8], [9].

There is clear evidence for the association between radiation exposure and cancer, especially from epidemiological studies of survivors of the atomic bombings in Japan [10], [11]. Secondary cancer risks (SCRs) after radiotherapy have been reviewed by international organizations, e.g. the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), the International Commission on Radiological Protection (ICRP), the National Council on Radiation Protection and Measurement (NCRP), and the American Associa-

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tion of Physicists in Medicine (AAPM). Secondary tumors occur in organs that are closest to radiation fields. Organs located far from the tumor volume (out-of-field organs) are assumed to receive low doses of radiation and, therefore, are frequently ignored in treatment planning, even though it is well known that small radiation doses to these organs can induce secondary cancers as well [9], [12].

Radiation therapy has changed significantly in the last decades, for instance radiation type, application of treatment, treatment duration and 3D dose distributions. For early stage breast cancer, multiple techniques have been developed such as accelerated partial breast irradiation (APBI) [13], intensity modulated radiotherapy [14], volumetric modulated arc therapy (VMAT) [15], permanent breast seed implant (PBSI) [16], intraoperative radiotherapy (IORT) using 50 kV X-rays [13], or intraoperative radiotherapy with electrons (ELIOT) [17], and 3D conformal radiotherapy as partial breast irradiation [18]. IORT with low-energy X-rays is an innovative technique that can be used during breast-conserving surgery as a sole treatment for low risk patients or as a tumor bed boost followed by external beam radiotherapy (EBRT) [19]. Regardless of advances in breast radiotherapy, treatment techniques should continue to focus on reducing the dose to critical structures (lung, and heart) as minimal as possible to reduce the risk of cardiac and pulmonary complications and secondary malignancy.

The purpose of this study is to evaluate the doses, associated differences in volume-dependent radiation exposure to organs and second cancer risk using NCRP report 116 after IORT, APBI and EBRTtechniques (m-IMRT & VMAT).

2 MATERIALS AND METHODS

CT scans were acquired of the phantom with Intrabeam applicator (4 cm diameter) (Carl Zeiss Surgical, Oberkochen, Germany) in the breast as shown in Fig. 1a. All images were transferred via DICOM to the treatment planning system (Nucletron Plato Brachytherapy planning system, version 14.2.6, Veenendaal, The Netherlands). Organs at risk were defined and contoured accurately.
A spherical Intrabeam applicator of 4 cm in diameter was used for isodose distribution of IORT and APBI. The intrabeam source of 50 kV was defined and placed at the center of the spherical applicator. By using the CT images of the breast phantom, only one source-dwell position was planned in the catheter to deliver a dose of 20 Gy at 0 mm from applicator surface for IORT as used in TARGIT trial [13], [20] and 34 Gy in 10 fractions (5 d × 2 × 3.4 Gy) at 10 mm depth from the applicator surface for APBI [13] (Figs. 1a & 1b. The isodose lines of 1%, 5%, 10%, 50% and 100% were selected by using the dose preferences option in Plato for IORT and APBI as shown in Figs. 1a & 1b. The 3D dose distribution was then calculated and stored for evaluation purposes.

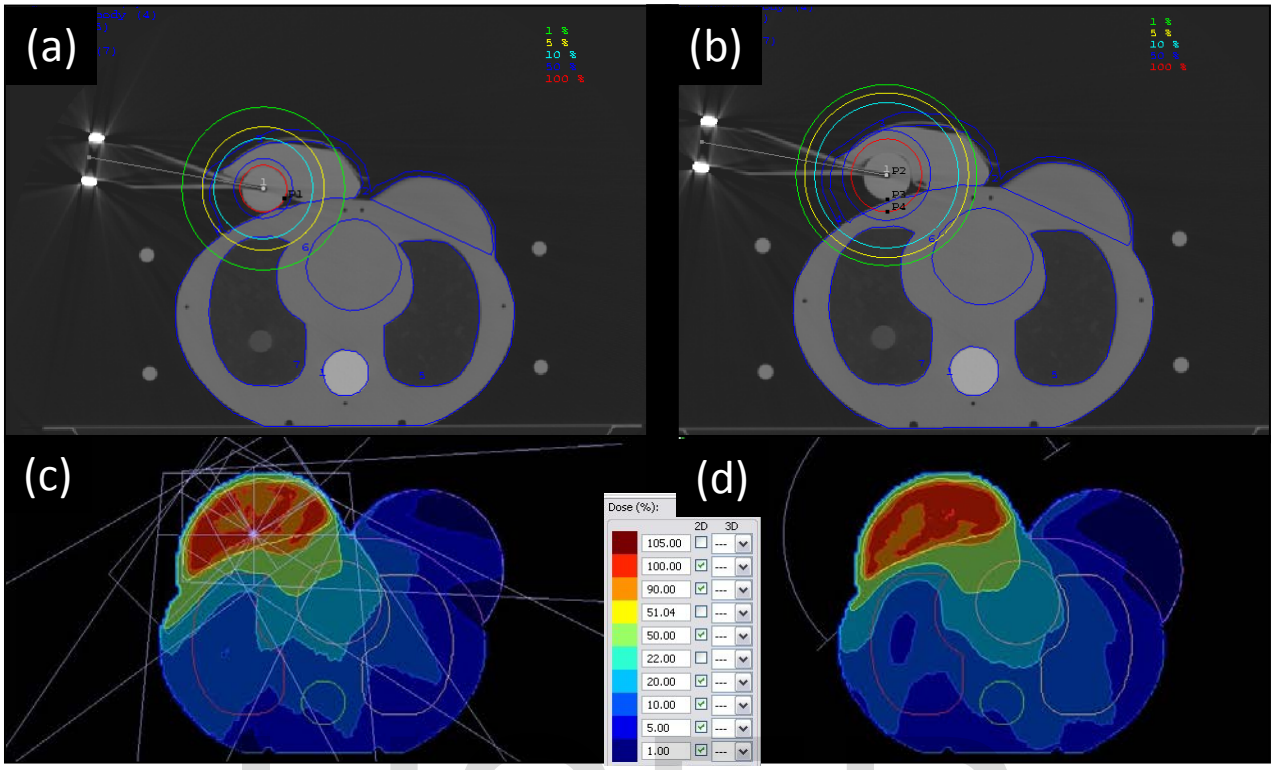

Fig. 1. Planning CT of an anthropomorphic phantom with an Intrabeam applicator in the upper outer quadrant of breast showing calculated isodoses (1%-100%). (a) IORT (20 Gy at 0 mm, 50 kV). (b) APBI (34 Gy at 10 mm, 50 kV). (c) m-IMRT(50 Gy, 6 MV) (d) VMAT (50 Gy, 6 MV).

For multibeam step & shoot IMRT (m-IMRT) and VMAT [15], all planning CT images were transferred via DICOM to Monaco (version 3.0, Elekta, CMS software, St. Louis, USA) for the 3D dose calculation. The OARs were contoured in Monaco plan software in the same way as for IORT and APBI in the Plato brachytherapy planning software. For multibeam (6-7 beams) step and shoot intensity modulated technique (m-IMRT), the gantry angles were individually chosen for each case to facilitate both optimal target coverage and mainly minimizing both inlet and exit dose to the contralateral breast. The VMAT plan had slightly more than half an arc (~200°), equivalent to the start and end angles of the m-IMRT plan. Dose calculations were done for a 6 MV ElektaSynergy linear accelerator up to a planning target volume (PTV) dose of 50 Gy in 25 fractions. All plans were optimized and evaluated for optimal target coverage, conformality, homogeneity and dose limits of OARs (as low as possible, without compromising target coverage or conformality). We selected the isodose lines of 1%, 5%, 10%, 50%, 90% and 100% for m-IMRT & VMAT as shown in the Figs. 1c & 1d.

Ipsilateral breast dose volume histogram (DVH) was calculated as shown in Fig. 2 after the calculation of dose distribution for all four techniques (IORT vs. APBI vs. m-IMRT vs. VMAT). The mean and maximum doses and volumes receiving more than 0.1 Gy and 4 Gy of the OARs were calculated and compared. Some values such as 0.1 Gy to 0.3 Gy for IORT and 0.1 Gy to 0.5 Gy for APBI were extrapolated by option polynomial with the standard Software Excel™ (Microsoft Corporation, Redmond, Seattle, USA), because in Plato brachytherapy system it was not possible to calculate values for lower doses and also volumes according to these doses.

The lifetime probabilities of developing fatal secondary malignancies were calculated per Sv absorbed in breast and lung using the National Council on Radiation Protection and Measurements (NCRP) report 116 (Table Seven Part Two page 32) [21], according to similar studies by Pignol et al. [22] and Aziz et al. [13].

3 Results

Isodose distributions for these four breast radiotherapy techniques are shown in Fig. 1. There are

large differences in the dose distributions and especially in the low doses regions delivered to the OARs. OARs received higher doses by m-IMRT, VMAT and APBI compared to IORT.

DVHs provide dose volume information for the organs contoured in the treatment planning system. Fig 2 provides the comparison and the dose volume contribution of DVHs of ipsilateral breast by IORT, APBI, m-IMRT and VMAT. Most of the volume of the ipsilateral breast receives almost 100% dose by m-IMRT and VMAT. In comparison, a considerable dose reduction to large volumes is seen in the ipsilateral breast by the partial breast irradiation techniques IORT and APBI. However, due to the steep dose gradient and the prescription to 10 mm tissue depth, APBI delivers the highest maximal dose to the ipsilateral breast.

In Table 1 the mean and maximal doses for the risk estimation of stochastic and deterministic normal tissue effects to selected organs during IORT, APBI, VMAT and m-IMRT are shown. Mean and maximal doses in the OARs delivered by IORT were consistently lower as compared to APBI, VMAT and m-IMRT. The maximal dose to the heart is larger during EBRT techniques than after APBI and considerably smaller using IORT. Multibeam step & shoot IMRT radiotherapy yields the largest maximal dose in the ipsilateral lung (26.3 Gy) and contralateral breast (16.4 Gy). Higher maximal dose is seen for contralateral lung (12 Gy) and spine (9.2 Gy) by VMAT in comparison to other techniques. Due to very low mean doses in the spine, contralateral lung and contralateral breast after IORT and APBI with less than 1.5% of the prescribed dose, it was not possible to calculate exact values for these OARs with the Plato brachytherapy system.

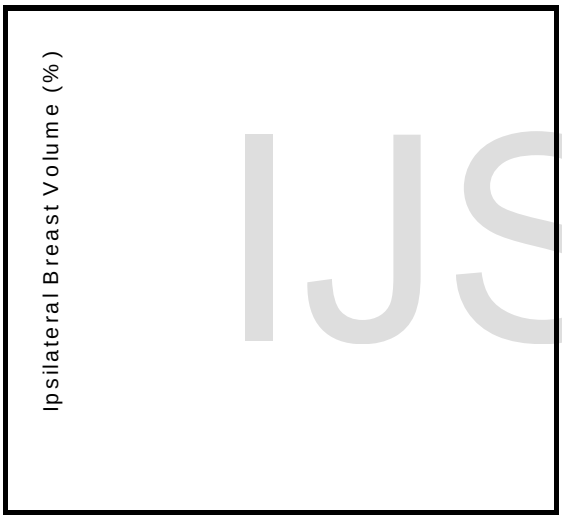

Fig. 2. Cumulative DVH for ipsilateral breast for IORT, APBI, m-IMRT and VMAT.

To evaluate the associated differences in volume-dependent radiation exposure to OARs for second cancer risk, in table 2 the doses for corresponding volumes of OARs receiving more than 0.1 Gy and 4 Gy from the different breast radiotherapy protocols are presented. The ipsilateral breast showed a smaller volume for doses higher than 0.1 Gy and 4 Gy after IORT than in the case of APBI, VMAT and m-IMRT. There was a larger volume with doses > 4 Gy within the ipsilateral lung for EBRT techniques (m-IMRT & VMAT) than after APBI, while this dose was not reached by IORT at all. For EBRT techniques, almost the total volume for spine, contralateral lung and contralateral breast received doses of > 0.1 Gy while these organs show negligible volumes for doses receiving more than 0.1 Gy by IORT and APBI. With the m-IMRT & VMAT techniques, most of volume of the contralateral breast, contralateral lung and spine received doses > 4 Gy. There is no volume for heart, spine and contralateral lung receiving doses higher than 4 Gy from these radiotherapy protocols (IORT & APBI).

Using the NCRP report 116, table 3 gives the estimation of secondary cancer risk from these breast radiotherapy techniques. Secondary cancer risk calculated from maximal doses where mean doses were not available but clearly then this is a conservative estimation of the risk. Higher risks were

shown by m-IMRT for contralateral breast (0.68%) and ipsilateral lung (4.1%). In the case of ipsilateral lung, secondary cancer risk (0.02%) is considerably less for IORT as compared to APBI, VMAT and m-IMRT. Higher risk was seen by VMAT for contralateral lung (15%) than m-IMRT. The secondary cancer risk for contralateral breast (< 0.06%) calculated from maximal dose for IORT is lower than for APBI and m-IMRT.

4 Discussion

Various studies have been established for the treatment of selected early-stage breast cancer patients. The goal of the radiotherapy techniques is always to deliver the maximum dose to target. Multibeam IMRT and VMAT show large variations in doses in comparison to APBI and IORT. There is seen difference in volume-dependent radiation exposure to organs from these breast radiotherapy techniques as shown in the treatment planning Fig. 1. In the case of external beam radiotherapy techniques such as VMAT and m-IMRT [15], the dose is prescribed to a conventional PTV margin whereas IORT and APBI deliver a high dose to parts of the breast, i.e.
the tissue around the tumor cavity up to a depth of 1-2 cm, within a short overall treatment time as shown in Fig. 1. In TARGIT approach [20], IORT using a low-energy X-ray device (Intrabeam), the dose is not prescribed to a defined depth. The highest dose is at the applicator surface and it decreases with increasing distance from the applicator. This steep dose fall-off results in very low doses to surrounding organs (Fig. 1a). Reports about local tumor control, acute and long-term side effects have been published with follow-up times up to ten years. There are no clinical analyses about second cancer induction using radiotherapy techniques (IORT vs. APBI vs. m-IMRT vs. VMAT) due to the limited time span of clinical availability. To estimate the long term risks of breast radiotherapy including secondary cancer, we performed dosimetric comparisons of breast radiotherapy techniques (IORT vs. APBI vs. m-IMRT vs. VMAT) using NCRP report 116.

TABLE 1

MAXIMAL AND MEAN DOSES FOR OARS FOR IORT (20 GY AT 0 MM DEPTH), APBI (34 GY AT 10 MM DEPTH) FROM APPLICATOR SURFACE AND EXTERNAL BEAM RADIOTHERAPY TECHNIQUES (M-IMRT AND VMAT) WITH PRESCRIBED DOSE OF 50 GY.

Dose to Organs	IORT		APBI		Multibeam IMRT		VMAT	
	Mean dose (Gy)	Max dose (Gy)	Mean dose (Gy)	Max dose (Gy)	Mean dose (Gy)	Max dose (Gy)	Mean dose (Gy)	Max dose (Gy)
Ipsilateral Breast	2.2	20	10.4	102	48.7	55.9	48.8	54.8
Contralateral breast	…….	< 0.3	……..	< 0.56	3.4	16.4	2.4	14.5
Ipsilateral Lung	0.03	1.8	0.13	7.4	4.9	26.3	4.1	20.8
Contralateral lung	……	< 0.3	……..	< 0.56	3.5	10.8	4.0	12
Heart	0.01	1	0.06	3.8	14.3	35.7	13.9	33.5
Spine	…….	< 0.3	……..	< 0.56	3.8	8.7	4.0	9.2

It is reported that high-dose radiation increases the risk of second malignancy after breast or chest-wall irradiation and data from the Surveillance Epidemiology and End Results (SEER) databases support this [23]. A study by M.P. Little distinguished the difference between A-bomb survivors and patients treated by radiotherapy to the role of cell killing at high doses greater than 2 Gy [24]. Hall et al. showed that the risk increases linearly with proportionality to the dose between low doses and moderated doses (from 0.1 Gy to 3 Gy) [7], [25]. Secondary malignancies are mainly observed in tissues having absorbed doses above 2 Gy (fractionated irradiation) and their incidence increases with dose [25]. We therefore chose volumes receiving more than 0.1 Gy (threshold) and 4 Gy (relevant dose) for comparison in our analysis.
The calculated doses to the OAR in our study are considerably lower for IORT as compared to APBI and external beam radiotherapy techniques (m-

IMRT and VMAT) and therefore the estimated risk for secondary cancer should be considerably lower. A study by Lettmaier et al. concluded that maximum doses received by different volumes of the heart, the lungs and the skin, dose values for all OARs are consistently lower for partial breast irradiation using brachytherapy than those for whole breast irradiation with EBRT [26]. Intensity-modulated radiotherapy has been developed to improve the homogeneity of the dose distribution within the target volume, but, in contrast to 3D radiotherapy, is generally associated with a larger volume of healthy tissue being irradiated to low doses. This is due to an increase in the number of beams used with this technique and the number of monitor units, resulting in radiation leakage, and an increase in the total body exposure. These two factors could lead to an increase in the risk of second cancers [7], [25]. Rotational IMRT techniques or isotropic multi-field IMRT may be associated with a dose bath, i.e. a large volume receiving low doses [7], [25]. In our results as discussed in Table 2, VMAT and m-IMRT are associated with larger volume at low doses.

Another important point for comparative risk estimation is that low energy X-rays have an increased relative biological effectiveness (RBE). In our earlier study, the maximal doses to OARs are 3 – 20 times lower after IORT as compared to EBRT [13]. In our results, we calculated maximal doses to OARs 2.5-40 times lower for IORT than EBRT techniques (m-IMRT & VMAT) whereas by using the intrabeam source of 50 kV at 10 mm depth maximal doses for APBI were 2-5 times higher than IORT. RBE values of 1.3 up to 3 have been reported for Intrabeam [27], [28] which would still result in lower maximal biological doses for IORT and APBI as compared to EBRT techniques (m-IMRT & VMAT).

TABLE 2

VOLUMES OF ORGANS RECEIVING DOSES GREATER THAN 0.1 GY AND 4 GY FOR IORT, APBI AND EXTERNAL BEAM RADIOTHERAPY TECHNIQUES (M-IMRT AND VMAT)

	IORT		APBI		m-IMRT		VMAT	
	%Vol>0.1 Gy	%Vol>4 Gy	%Vol>0.1 Gy	%Vol>4 Gy	%Vol>0.1 Gy	%Vol>4 Gy	%Vol>0.1 Gy	%Vol>4 Gy
Ipsilateral Breast	84.5	18.1	88.2	54.4	100	100	100	100
Contralateral breast	<1	0	<1	0	100	30.7	100	10.2
Ipsilateral Lung	4.5	0	5.0	1.3	97.8	56.8	94.1	56.1
Contralateral lung	<1	0	<1	0	98	49.0	98.2	61.7
Heart	1.8	0	4.2	0	99.5	96.2	99.3	96
Spine	<1	0	<1	0	98.2	57.1	98.3	64.2

TABLE 3

THE PROBABILITY PER SIEVERT WAS TAKEN FOR ESTIMATION OF LIFE TIME SECONDARY CANCERS USING NATIONAL COUNCIL ON RADIATION PROTECTION AND MEASUREMENTS (NCRP) REPORT 116 FOR IORT, APBI AND EXTERNAL BEAM RADIOTHERAPY TECHNIQUES (M-IMRT AND VMAT). MEAN ORGAN DOSES WERE USED FOR THE CALCULATION OF SECONDARY CANCER RISK (*MAXIMAL DOSES WERE USED WHERE MEAN DOSES WERE NOT AVAILABLE). NOTE THAT RBE EFFECTS WERE NOT TAKEN INTO ACCOUNT (SEE DISCUSSION).

Organs	Probability (%/Sv)	IORT	APBI	Multibeam IMRT	VMAT
Contralateral Breast	0.20	< 0.06%*	< 0.11%*	0.68%	0.48%
Ipsilateral lung	0.85	0.02%	0.11%	4.1%	3.48%
Contralateral lung	0.85	< 0.25%*	< 0.47%*	2.9%	3.4%

Lifetime breast cancer induction risk for a breast exposed to 1 Gy is approximately 5% if irradiated at the age of < 35 years, < 3% at the age of 35–45 years, and much less at an older age [12]. For a phantom case study [22] the incremental risk of secondary cancer was calculated for the tangential whole breast technique with wedge compensators based on National Council on Radiation Protection and Measurements (NCRP) report 116 [21] as 0.34% which is likely to be undetectable compared to the observed frequency of contralateral breast cancer of about 7% at 10 years and 10% at 15 years [29], [30]. In our phantom based study, the secondary cancer risk for contralateral breast (< 0.06%) calculated from maximal dose for IORT is lower than for APBI and m-IMRT. The causes of contralateral breast cancer amongst breast cancer patients given radiotherapy are less obvious. A large study by Kirova et al. did not show an increased risk of contralateral breast cancer for those receiving radiotherapy [31]. Obedian et al. did not find a significant difference in the occurrence of contralateral breast cancer at 15 years in a retrospective series of 2,416 patients treated with breast conserving surgery and adjuvant radiotherapy or mastectomy without radiotherapy [30].

The calculated risk for lung cancer after EBRT in a phantom study was 0.49% [22]. This value is slightly higher but of the same order of magnitude as the 0.30% increased risk for adjuvant radiotherapy found by Zablotska and coworkers on a cohort of 260,000 patients included in the Surveillance Epidemiology and End Results (SEER) database [32]. The calculated value for secondary cancer risk of ipsilateral lung (0.02%) is considerably less for IORT as compared to APBI, VMAT and m-IMRT. Higher risk is seen by VMAT for contralateral lung (15%) than m-IMRT as calculated in Table 3. For the particular case of lung irradiation during the treatment for breast cancer, Inskip et al. have concluded that for an average dose of 10 Gy the risk for radiation-induced secondary cancer is around 0.9% which represents about a twofold increase of risk of pulmonary neoplasia among 10-year survivors of breast cancer [33].

Radiation induced late heart disease has been observed in patients who received therapeutic doses of about ≥35 Gy to partial volumes of the heart [34]. Recent studies based on atomic bomb survivors also suggest a relationship between cardiac mortality and low radiation doses in the range of ≤4 Gy [10], [35]. In clinical case series no clear evidence of late cardiac mortality after breast radiotherapy was found [36] but in a recent critical view published by Schultz-Hector suggests that acute single doses of 1-2 Gy to the heart increased the risk of developing ischemic heart disease significantly [37]. Considering this, it is of interest to notice that m-IMRT and VMAT deliver a higher maximal dose to parts of the heart as compared to IORT and APBI.

5 Conclusion

This is to our knowledge the first report using IORT, APBI, m-IMRT and VMAT about the estimation of second cancer risk using NCRP report 116 for breast cancer. In comparison with m-IMRT and VMAT, the calculated mean and maximal doses for OAR are lower for IORT and APBI. This would suggest that the risk of secondary cancer induction after IORT and APBI is lower than after APBI and EBRT. These risk differences should be considered when selecting the optimal therapy for the breast cancer patient.

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