Mammary Chain Irradiation in Left-Sided Breast Cancer: Can We Reduce the Risk of Secondary Cancer and Ischaemic Heart Disease with Modern Intensity-Modulated Radiotherapy Techniques?

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Keywords

Internal mammary chain · Regional nodal irradiation · Breast cancer · Ischaemic heart disease · Secondary cancer

Abstract

Introduction: The aim of the present study was to estimate the impact of the addition of internal mammary chain (IMC) irradiation in node-positive left-sided breast cancer (BC) patients undergoing regional nodal irradiation (RNI) and comparatively evaluate excess relative and absolute risks of radiation-induced lung cancer/BC and ischaemic heart disease for intensity-modulated radiotherapy (IMRT) versus 3D conformal radiotherapy (3D-CRT). **Methods:** Four treatment plans were created (3D-CRT and IMRT +/- IMC) for each of the 10 evaluated patients, and estimates of excess relative risk (ERR) and 10-year excess absolute risk (EAR) were calculated for radiation-induced lung cancer/BC and coronary events using linear, linear-exponential and plateau models. **Results:** The addition of IMC irradiation to RNI significantly increased the dose exposure of the heart, lung and contralateral breast using both techniques, increasing ERR for secondary lung cancer (58 vs. 44%, $p = 0.002$), contralateral BC

(49 vs. 31%, $p = 0.002$) and ischaemic heart disease (41 vs. 27%, $p = 0.002$, IMRT plans). IMRT significantly reduced the mean cardiac dose and mean lung dose as compared to 3D-CRT, decreasing ERR for major coronary events (64% 3D-CRT vs. 41% IMRT, $p = 0.002$) and ERR for secondary lung cancer (75 vs. 58%, $p = 0.004$) in IMC irradiation, without a significant impact on secondary contralateral BC risks. **Conclusion:** Although IMC irradiation has been shown to increase survival rates in node-positive BC patients, it increased dose exposure of organs at risk in left-sided BC, resulting in significantly increased risks for secondary lung cancer/contralateral BC and ischaemic heart disease. In this setting, the adoption of IMRT seems advantageous when compared to 3D-CRT.

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Introduction

Currently, there is an ongoing debate about the role of internal mammary chain (IMC) irradiation in left-sided early breast cancer (BC) treatment [1, 2], as the additional morbidity caused by IMC irradiation contrasts with the actual advantage of this treatment in terms of overall sur-

Fig. 1. Representation of 3D-CRT versus IMRT treatment beams in IMC plan.

vival (OS), disease-free survival (DFS) and distant metastasis-free survival (DMFS). Randomised trials have reported a BC-specific survival benefit after regional nodal irradiation (RNI), especially when the IMC is treated, without an increase in cardiac morbidity and mortality [3–6]. As known from other studies, IMC irradiation can be associated with increased rates of cardiovascular disease and ischaemic heart disease, which remained increased for at least 20 years after treatment [7]. Due to the increased cardiovascular morbidity in left-sided BC radiotherapy, in the Danish Breast Cancer Cooperative Group Radiotherapy (DBCG)-IMN trial only patients with right-sided BC received internal mammary node radiotherapy, but organs-at-risk dose estimates were compared in right-sided versus left-sided BC patients. The study showed an absolute increase of 3% in OS when the IMC was added to RNI at a 7-year median follow-up. In fact, if a comparable gain is also assumed for left-sided patients, the benefits from IMC radiotherapy would outweigh the limitations of ischaemic heart morbidity [6]. Modern BC radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT) or volumetric-modulated arc radiotherapy (VMAT), are able to minimize the high-dose exposure of the heart in left-sided BC [8–13] but only at the cost of an increased low-dose exposure, when compared to 3D conformal radiotherapy (3D-CRT). This could potentially increase the risk for radiation-induced lung cancer and contralateral BC [12, 14]. The IMC represents a complex target volume due to its close proximity to the heart. In this special case, the application of IMRT or VMAT could improve target volume coverage and at the same time spare cardiac dose exposure. The aim of the present study was to evaluate the impact of the addition of IMC irradiation in women with node-positive left BC, candidates for adjuvant RNI. The study comparatively evaluates the excess relative and absolute risks of radiation-induced secondary lung cancer

and BC and ischaemic heart disease for different modern radiotherapy techniques (IMRT vs. 3D-CRT).

Materials and Methods

Patient Datasets and Treatment Planning

For this risk modelling study, 40 treatment plans were generated using computed tomography datasets of 10 women with node-positive left-sided BC. All patients were previously treated using external beam radiotherapy following breast-conserving surgery in clinical routine. After re-contouring, 4 different treatment plans were generated for each patient with a prescription dose (Dp) of 50 Gy in 25 fractions: for both techniques (3D-CRT and IMRT), 2 treatment plans were created, based on the inclusion of IMC. Target volume delineation was performed according to international guidelines [15–17]. Furthermore, the IMC target volume was contoured around the internal thoracic artery/vein with a 5-mm margin from the caudal limit of level IV to the first 3 intercostal spaces [17]. To avoid any inter-observer variability, 1 physician delineated all organs at risk and target volumes in all datasets. The 3D-CRT technique consisted of 4–7 opposing wedged fields with 6/15 MV photons. Gantry angles were chosen in order to provide full target coverage and minimize dose exposure to the contralateral breast, ipsilateral lung and heart. IMRT plans consisted of 7–9 beams with 6 MV photons for a Varian Trilogy Linac (®Varian Medical Systems, USA). Figure 1 shows the arrangement of the treatment beams for the 2 different techniques. In the present study, a respiratory gating/deep-inspiration breath hold (DIBH) technique was not included. Several studies have confirmed the substantial impact of DIBH on dosimetric endpoints, such as mean heart or ipsilateral lung dose in left-sided BC [14, 18, 19]. Nevertheless, even though in some countries DIBH is already routinely applied, it cannot be extensively used in most other countries. Therefore, the aim of the present study was to compare a 3D-CRT technique to IMRT – which is widely available. The authors are advocates of heart-sparing BC radiotherapy techniques and recommend to routinely use them. Therefore, the impact of an additionally applied respiratory gating will be evaluated in a further study.

All 3D-CRT and IMRT treatment plans were calculated using the AAA algorithm on an Eclipse® Treatment Planning System (Varian Medical Systems). Planning objectives during the forward (3D-CRT) and the inverse (IMRT) optimization process were full

Table 1. Ten-year baseline risk values used for EAR calculations

Age	Risk profile	Major coronary events ^a	Lung cancer ^b	Breast cancer ^c
40 years	Intermediate risk			0.8%
50 years	Intermediate risk High risk	0.5% 6.0%	0.3% 2.2%	
70 years	Intermediate risk High risk	2.8% 26.0%	3.7% 15.0%	

^a Baseline cardiac risks were calculated based on the standard Reynolds risk score algorithm [37] after subtracting the risk for stroke. “Intermediate-risk” profiles were estimated using the factors: systolic blood pressure, 125 mm Hg; total cholesterol, 208 mg/dL; high-density lipoprotein, 52 mg/dL; high-sensitivity C-reactive protein, 2.0 mg/L; non-smoker; with no family history of myocardial infarction before the age of 60 years. “High-risk” baseline risks were estimated using: systolic blood pressure, 135 mm Hg; total cholesterol, 235 mg/dL; high-density lipoprotein, 43 mg/dL; high-sensitivity C-reactive protein, 4.3 mg/L; smoker; with a family history of myocardial infarction before the age of 60 years. ^b Baseline risks for lung cancer were estimated using the risk prediction formula from Bach et al. [25]. Only smokers were taken into account: the “intermediate-risk” profile corresponds to a woman who had smoked 10 cigarettes per day but quit 5 years ago; “high-risk” corresponds to a current and continuing smoker with 30 cigarettes per day. In both cases, it was assumed that the woman started smoking at an age of 20 years. ^c Baseline risks for contralateral breast cancer were estimated with the Tyrer-Cuzick model [29], assuming a 40-year-old woman with a weight of 65 kg, height of 1.60 m, menarche at age 14 years, a child birth at age 30 years and no known genetic predisposition or positive family history for breast cancer.

target coverage, defined as the volume that received at least 95% of the prescription dose ($V_{95\%Dp} \geq 95\%$ planning target volume (PTV) and the dose received by 2% volumes of PTV ($D_{2\%PTV} \leq 107\%$ of the prescription dose (Dp) and adherence to dose constraints of organs at risk.

Referring to the QUANTEC recommendations for breast radiation therapy with conventional fractionation, we used the following dose constraints for the ipsilateral lung: $V_5 < 40\%$, $V_{20} \leq 15\%$, $V_{30} \leq 10\%$, mean lung dose (MLD) $\leq 8-9$ Gy. For the mean heart dose, we used constraints derived from the study of Taylor et al. [20], which reported a mean heart dose of 6–7.3 Gy for left-sided BC, accepting higher doses when IMC irradiation was added [6]. For the contralateral breast, we tried to minimize the dose as much as possible, while keeping the mean contralateral breast dose < 3 Gy.

Estimates of Excess Relative Risk and Excess Absolute Risk

Excess relative risk (ERR) and excess absolute risk (EAR) were calculated as described elsewhere [14]. The ERR was calculated as follows: $ERR = \delta \cdot OED_{linear}$. Regarding the heart, the organ equivalent dose (OED) OED_{linear} corresponded to the mean cardiac dose (MCD), and the linear risk coefficient $\delta_{Darby} = 0.074 \text{ Gy}^{-1}$, was taken from the dose-response relationship reported by Darby et al. [21], which relates to the risk of major coronary events (myocardial infarction, coronary revascularization, or death from ischaemic heart disease). For risk estimates of secondary lung cancer, OED_{linear} corresponded to the MLD and the parameter $\delta_{Grantzau}$ was derived from Grantzau et al. [22], who reported an ERR of 8.5% (95% CI 3.1–23.3%) per Gy of radiation-induced secondary lung cancer in 23,627 women following breast radiotherapy. Contralateral breast estimates were based on the OED_{linear} corresponding to the mean dose to the contralateral breast and the risk parameter $\delta_{Stovall} = 0.20 \text{ Gy}^{-1}$. This value was derived from BC patients treated before an age of 45 years [23].

The 10-year EAR was determined by multiplication of the ERR with the baseline risk: $EAR = ERR \cdot BaselineRisk$. The EAR was cal-

culated for 2 different ages of treatment (50 and 70 years) and for 2 different risk profiles (“intermediate-risk”/“high-risk”), respectively. For the definition of the risk profiles and baseline risk calculation (Table 1), we followed Brenner et al. [24] for major coronary events and the risk prediction formula from Bach et al. [25] for baseline risks of lung cancer. Regarding secondary contralateral BC, radiation-induced secondary BC is assumed to be mainly relevant for exposure at younger ages [26–28]. Therefore, an intermediate 10-year baseline risk was estimated for a woman aged 40 years using the Tyrer-Cuzick model [29].

Alternative Dose-Response Relationships

Studies on secondary cancer risk after low-dose radiation exposure, and in particular the study on atomic bomb survivors, typically observe higher relative risks as compared to studies on secondary cancer. This can be explained by a non-linear dose-response relationship. Therefore, Schneider et al. [30] have introduced the concept of OED. The OED is assumed to be proportional to the organ cancer risk but depends only on the dose distribution within the organ itself. Thus, the OED is suitable to compare the potential harm of different dose distributions within the same person. However, it should be noted that the coefficients $\delta_{Grantzau}$ and $\delta_{Stovall}$ do not apply for risk calculation with non-linear OEDs. Plausible functional forms of dose-response relationships were derived mechanistically and adjusted to the risks observed in atomic bomb survivors and patients with Hodgkin’s disease [31]. For comparison, we calculated OED using linear-exponential ($OED_{linear-exp}$) and plateau dose-response ($OED_{plateau}$) models as described elsewhere [15]. The organ-specific model parameters used for lung cancer where $\alpha = 0.022 \text{ Gy}^{-1}$ and $\beta = 0.056 \text{ Gy}^{-1}$, while for the contralateral breast the parameters $\alpha = 0.041 \text{ Gy}^{-1}$ and $\beta = 0.115 \text{ Gy}^{-1}$ were used.

Statistical Analysis

Statistical analyses were conducted using Matlab R2018b (MathWorks, USA). Wilcoxon signed-rank tests were used to es-

Fig. 2. Estimates of excess relative risk (ERR) for radiation-induced secondary lung and contralateral breast cancer and ischaemic heart disease for the different treatment modalities and target volumes (-/+IMC).

estimate statistical significance of differences between plans. All data were recorded with means and standard deviation, and p values <0.05 were considered statistically significant.

Results

Heart Exposure and Risk Estimation for Major Coronary Events

An overview of the OEDs of the different treatment modalities is tabulated in Table 2. The largest dose variations were seen for the MCD in 3D-CRT plans. The addition of the IMC to the target volume significantly increased the mean MCD using both treatment techniques, 3D-CRT and IMRT: in 3D-CRT plans, the MCD was 5.18 ± 2.26 Gy versus 8.68 ± 2.72 Gy (-/+IMC irradiation, $p = 0.002$); in IMRT plans, it was 3.59 ± 0.97 Gy versus 5.57 ± 1.58 Gy (-/+IMC, $p = 0.002$). As shown in Table 2, the lowest MCD was reached in IMRT plans without addition of the IMC. As compared to 3D-CRT, the use of IMRT significantly reduced the MCD in both cases, in RNI only ($p = 0.02$) and when the IMC was included in the target volume ($p = 0.002$). Regarding the volume of the heart receiving 5 Gy (V5Gy), the volume receiving at least 5 Gy was significantly larger when IMC was added to the target volume (3D-CRT: $15.79 \pm 7.38\%$ vs. $27.62 \pm 8.72\%$; -/+IMC irradiation, $p = 0.002$; in IMRT plans: $15.14 \pm 7.65\%$ vs. $31.05 \pm 13.20\%$; -/+IMC, $p = 0.002$). Nevertheless, there was no significant difference between IMC irradiation using 3D-CRT or IMRT ($p = 0.2$).

An overview of estimated ERR and 10-year EAR for ischaemic heart disease for the different treatment modalities and typical baseline risks is shown in Figures 2–4. The ERR for major coronary events was 38% in 3D-CRT

Table 2. MCD, V5Gy and the OED for different treatment modalities and OED calculation models (mean $\pm$ standard deviation)

Plan	Heart		Lung		Contralateral breast			
	MCD	V5Gy, %	OED _{lin}	OED _{lin-exp}	OED _{lin}	OED _{lin-exp}	OED _{plateau}	OED _{plateau}
3D-CRT RNI	5.18 (± 2.26)	15.79 (± 7.38)	6.02 (± 0.79)	3.29 (± 0.32)	1.10 (± 1.21)	0.82 (± 0.65)	0.79 (± 0.63)	0.79 (± 0.63)
3D-CRT RNI with IMC	8.68 (± 2.72)	27.62 (± 8.72)	8.81 (± 1.45)	4.22 (± 0.48)	2.11 (± 2.20)	1.18 (± 0.85)	1.15 (± 0.83)	1.15 (± 0.83)
IMRT RNI	3.59 (± 0.97)	15.14 (± 7.65)	5.17 (± 0.87)	3.82 (± 0.77)	1.55 (± 1.71)	1.30 (± 1.31)	1.24 (± 1.22)	1.24 (± 1.22)
IMRT RNI with IMC	5.57 (± 1.58)	31.05 (± 13.20)	6.78 (± 0.91)	4.54 (± 0.81)	2.47 (± 2.10)	1.78 (± 1.55)	1.67 (± 1.43)	1.67 (± 1.43)

MCD, mean cardiac dose; V5Gy, volume of the heart receiving 5 Gy; OED, organ equivalent dose; 3D-CRT, three-dimensional conformal radiotherapy; RNI, regional nodal irradiation; IMC, internal mammary chain irradiation; IMRT, intensity-modulated radiotherapy.

Fig. 3. Estimates of 10-year excess absolute risk (EAR) for radiation-induced secondary lung cancer and ischaemic heart disease for treatment age of 50 years. The Figure shows values for different treatment modalities, target volumes (-/+IMC) and 2 different baseline risks (see Table 1).

Fig. 4. Estimates of 10-year excess absolute risk (EAR) for radiation-induced secondary lung cancer and ischaemic heart disease for treatment age of 70 years. The Figure shows values for different treatment modalities, target volumes (-/+IMC) and 2 different baseline risks (see Table 1).

without IMC irradiation and 64% for 3D-CRT with IMC irradiation. When the IMRT technique was used, ERR was 27% and 41% without and with IMC, respectively. Therefore, the mean predicted risk increase through IMC irradiation was less pronounced in IMRT plans. Accordingly, also a higher 10-year EAR for major coronary

events was shown for 3D-CRT as compared to IMRT plans. Ten-year EAR calculations for major coronary events were strongly influenced by cardiac baseline risks (Table 1). Elderly patients (70 years) presenting with relevant cardiovascular disease risk factors ("high-risk"), had an absolute 10-year risk reduction of 3% for isch-

Fig. 5. 3D-CRT versus IMRT dosimetric comparison in non-IMC plans. Square: 3D-CRT plan; triangle: IMRT plan; red: PTV; blue: ipsilateral lung; green: heart; orange: contralateral breast.

aemic heart disease using an IMRT technique rather than 3D-CRT (–IMC). In case of IMC irradiation, the use of IMRT was associated with an overall 10-year cardiac EAR reduction of 6% compared to 3D-CRT. Nevertheless, even if using the IMRT technique, the estimated additional cardiac 10-year risk from irradiating the IMC was large (4%), thus compromising the benefit for patients with high cardiovascular risk (Fig. 4).

Lung Exposure and Risk Estimation for Secondary Lung Cancer

IMC irradiation also significantly increased the MLD in 3D-CRT and IMRT plans ($p = 0.002$, respectively; Table 2). The mean MLD value was 6.02 ± 0.79 Gy in 3D-CRT plans without IMC irradiation and 8.81 ± 1.45 Gy in 3D-CRT plans including the IMC. Regarding IMRT plans, the MLD was 5.17 ± 0.87 Gy (–IMC) and 6.78 ± 0.91 Gy (+IMC), respectively. However, dose volumes receiving more than 5 Gy were significantly higher using an IMRT technique as compared to 3D-CRT, irrespective of the inclusion of the IMC: $31 \pm 11\%$ versus $21 \pm 2\%$ without IMC ($p = 0.002$) and $35 \pm 12\%$ versus $25 \pm 3\%$ with IMC ($p = 0.03$). As a result, while IMRT significantly reduced MLD, the difference in non-linear OEDs was not statistically significant using the 3D-CRT technique.

Figure 2 shows the ERR for radiation-induced secondary lung cancer for each treatment modality estimated using the linear OED model. The ERR for secondary lung cancer was significantly influenced by IMC irradiation in both 3D-CRT and IMRT plans ($p = 0.002$). We estimated a reduction in the ERR for secondary lung cancer risk when using the IMRT technique in plans with RNI only (51 vs. 44%, $p = 0.04$) and when the IMC was added to RNI (75 vs. 58%, $p = 0.004$). Corresponding exemplary

10-year EAR calculations are depicted in Figures 3 and 4 for patients aged 50 or 70 years at treatment, respectively. However, it is important to note that the above-mentioned OED calculations have shown that the advantage of the IMRT technique may disappear when the dose-response relationship is not linear. Moreover, the applied baseline risk for lung cancer (Table 1) and the smoking status had the strongest impact on 10-year EAR estimation: intermediate-risk patients showed substantially lower 10-year EAR values for secondary lung cancer as compared to high-risk patients.

Exposure and Secondary Cancer Risk Estimation for the Contralateral Breast

Mean dose of the contralateral breast was 1.10 ± 1.21 Gy in 3D-CRT without IMC irradiation and 2.11 ± 2.20 Gy for 3D-CRT plans with IMC as compared to 1.55 ± 1.71 Gy for IMRT plans without IMC and 2.47 ± 2.10 Gy for IMRT plans with IMC, respectively (Table 2). The inclusion of the IMC in the target volume significantly increased the mean dose and non-linear OEDs of the contralateral breast in 3D-CRT and IMRT plans ($p = 0.002$, respectively). In this case, the use of an IMRT technique had no significant impact to reduce contralateral breast mean dose ($p > 0.5$).

We applied the linear model to estimate the ERR for radiation-induced contralateral BC for each treatment modality, as shown in Figure 2. The ERR for secondary BC was significantly increased by IMC irradiation in 3D-CRT and IMRT plans ($p = 0.002$) but, as stated before, there was no significant difference for the IMRT versus 3D-CRT technique: neither in –IMC plans (31 vs. 22%, $p = 0.56$), nor in +IMC plans (49 vs. 42%, $p = 1$).

Estimated intermediate-risk 10-year EARs at age 40 years were 0.35% in 3D-CRT –IMC and 0.67% +IMC ir-

Fig. 6. 3D-CRT versus IMRT dosimetric comparison in IMC plans. Square: 3D-CRT plan; triangle: IMRT plan; red: PTV; blue: ipsilateral lung; green: heart; orange: contralateral breast.

radiation, and 0.50% in IMRT –IMC and 0.79% +IMC irradiation. Figures 5 and 6 show 3D-CRT versus IMRT dosimetric comparison in non-IMC and IMC plans.

Discussion/Conclusion

The addition of RNI in node-positive BC or high-risk node-negative BC has recently shown to increase DMFS, which translates into better DFS [32] or even OS [31]. This has recently also been confirmed by the EBCTCG meta-analysis presented in San Antonio in 2018 (data not yet published). However, the debate about the IMC irradiation in left-sided BC treatment is still open for discussion, as the additional morbidity caused by IMC irradiation contrasts with its actual advantage. The BC-specific survival benefit after RNI including the IMC has been reported by several randomized trials. In 2015, Budach et al. [33] published a large meta-analysis of the 3 latest trials showing that additional regional radiotherapy, including the internal mammary and medial supraclavicular lymph nodes, in node-positive BC or high-risk node-negative BC, statistically significantly improved DFS, DMFS and OS in stage I–III BC. Later, the same group focused on the individual impact of the different axillary target volumes. The network meta-analysis showed that the improvement of cancer-specific survival through RNI is mainly achieved by inclusion of the IMC, deriving from a reduction in DMFS [34].

The clinical attention to radiation-induced heart damage and secondary cancer has recently increased. In view of the continuously increasing long-term survival rates of BC patients, one of the main goals in radiotherapy is the attempt to reduce radiation-induced morbidity. Especially in the context of multimodal treatment protocols, the

synergistic effects of radiotherapy and cardiotoxic anthracycline-based systemic therapy or targeted therapies (anti-Her2) are relevant [35, 36], as they are also associated with an increase in cardiomyopathy and heart failure [37, 38]. In this scenario, it seems reasonable to reduce the cardiac dose exposure by applying modern technological developments. Regarding radiation-induced cardiac morbidity, in 2013, Darby et al. [21] found a relative risk for major coronary events of 7.4% (95% CI 2.9–14.5) per every 1 Gy increase in MCD. As a result, new alternative treatment techniques, such as respiratory-gated radiotherapy using the DIBH technique or IMRT-VMAT techniques, have been introduced into clinical practice to reduce heart and lung exposure [18, 39, 40]. In a recent risk modelling study, Simonetto et al. [19] showed that heart-sparing techniques should be offered to all patients who have high cardiac risks at baseline, a high dose exposure of the heart, or a favourable tumour prognosis, regardless of their age at diagnosis. A large population-based study of 29,102 BC patients supports these findings [41]. In fact, elderly women with a history of cardiac disease had increased rates of coronary interventions and a survival reduction following breast radiotherapy. The present study showed a positive impact of the adoption of modern intensity-modulated radiation techniques when treating RNI including the IMC and is in line with other studies [42]. The use of IMRT resulted in an MCD reduction and consequently ERR and 10-year EAR reduction for ischaemic heart disease. An analysis of the 10-year EAR for major coronary events revealed that IMC irradiation significantly increased the risk for cardiovascular disease in 3D-CRT and IMRT plans as compared to RNI alone, but the mean predicted risk increase through IMC irradiation was less pronounced in IMRT plans. Nevertheless, even if using the IMRT technique, the estimated ad-

ditional cardiac risk from irradiating the IMC was large (up to 4%), thus compromising the benefit for patients with high cardiovascular risk (Fig. 4).

Similarly, the risk of radiation-induced secondary lung cancer in the current study was mainly influenced by the radiation technique (3D-CRT vs. IMRT). Many population-based studies have confirmed the risk of radiation-induced lung cancer [43–49], but comparative studies estimating radiation-induced lung carcinogenesis following different breast radiotherapy techniques are rare [14, 44]. Most of them compared a 3D-CRT approach with other modern techniques in the setting of breast radiotherapy only, without inclusion of RNI. In contrast to these reports, the present study evaluated the dosimetric impact of modern BC radiotherapy within the context of RNI and especially focused on the addition of the IMC region. As RNI and the IMC represent complex target volumes, the application of IMRT could spare dose exposure of organs at risk. Both scenarios (RNI +/- IMC) showed lower absolute risks for secondary lung cancer in IMRT plans. In this context, it has to be mentioned that the risk of radiation-induced lung cancer is highly influenced by the smoking status. Usually, non-smoking women undergoing radiotherapy have no higher risk for radiation-induced lung cancer [48]. It has been shown that ever-smoking was an independent risk factor for secondary lung cancer, while radiotherapy alone was not [49]. Taking into account all of the above-mentioned aspects, smoking cessation might have a higher impact on secondary lung cancer reduction than the influence of different radiotherapy techniques. In our study, the risk of radiation-induced contralateral secondary BC was similarly significantly influenced by IMC irradiation but not by the treatment technique itself. Other dosimetric studies showed the lowest mean contralateral breast dose using 3D conformal tangential and volumetric modulated arc techniques, whereas conventional IMRT techniques have resulted in an increase in contralateral breast dose up to 30% [50]. The present study showed no statistically significant difference in mean dose to the contralateral breast in IMRT plans as compared to 3D-CRT. Consequently, the 10-year predicted EAR for secondary contralateral BC was only significantly influenced by the addition of IMC irradiation. It is important to note that the actual risk of radiation-induced contralateral secondary BC might probably be lower than the predicted one [51].

The present study has some limitations due to the small sample size and the uncertainties of risk modelling. In fact, due to the small size of the study, the results may not be fully representative, as individual anatomy can have a significant impact on radiotherapy planning, although we excluded patients with unfavourable anatomy. In addition, a clear dose-response relationship for sec-

ondary lung and contralateral BC after BC radiotherapy has not yet been established, and we thus applied the OED concept for a relative comparison of different treatment methods with regard to a specific organ cancer risk. For BC, controversial evidence exists regarding the dependence on age at exposure. For example, in the atomic bomb survivors of Hiroshima and Nagasaki, the ERR was found to depend only slightly on exposure age after correcting for attained age [52, 53]. Furthermore, regarding cardiovascular disease risk prediction, the linear dose-response relationship has long been debated. Different biological radiation effects seem to be responsible for cardiovascular detriment at low doses and differ from those at high doses [54–56]. It has been suggested that a low-dose exposure to the left ventricle (volume receiving 5 Gy) might be a better predictor for acute coronary events than the mean heart dose [57]. We, therefore, added the V5Gy of the entire heart to give an estimate of low-dose exposure of the heart. Nevertheless, there was no significant difference between 3D-CRT and IMRT in IMC irradiation regarding the V5Gy of the heart.

In conclusion, IMC irradiation has been shown to increase survival rates in women with node-positive BC. Nevertheless, the addition of IMC to RNI in left-sided BC also increases heart, lung and contralateral breast dose exposure and can result in a significantly increased risk for secondary lung cancer and contralateral BC and ischaemic heart disease. The present study showed that the adoption of IMRT seems advantageous in this setting to mitigate cardiac toxicity and the risk of radiation-induced secondary cancers.

Statement of Ethics

Ethics committee approval was not required since this was not a clinical study performed on patients but a dosimetric simulation study. Informed consent was not required since the dosimetric simulation study was performed on anonymous patient data.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors received no specific funding for this work.

Author Contributions

V.F., F.A., C.S., S.C. and R.R. wrote the manuscript and tables and organized the study. S.N., G.S., A.D.S. and R.R. planned treatment of the patients. C.S. performed the statistical analysis. All authors read and approved the final manuscript.

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