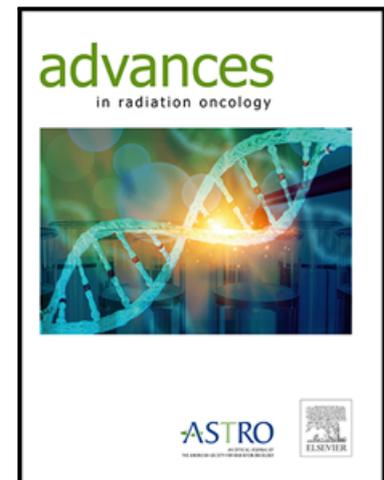


## Journal Pre-proof

Outcomes of Breast Cancer Patients Treated with or without Internal Mammary Irradiation: A Single-center, Retrospective Propensity Score-matched Study

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PII: S2452-1094(22)00178-6  
DOI: <https://doi.org/10.1016/j.adro.2022.101072>  
Reference: ADRO 101072



To appear in: *Advances in Radiation Oncology*

Received date: 21 December 2021  
Accepted date: 6 September 2022

Please cite this article as: Tanun Jitwatcharakomol M.D. , Jiraporn Setakoranukul M.D. , Suthinee Ithimakin M.D. , Rungroj Krittayaphong M.D. , Kullathorn Thephamongkhon M.D. , Outcomes of Breast Cancer Patients Treated with or without Internal Mammary Irradiation: A Single-center, Retrospective Propensity Score-matched Study, *Advances in Radiation Oncology* (2022), doi: <https://doi.org/10.1016/j.adro.2022.101072>

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**Outcomes of Breast Cancer Patients Treated with or without Internal Mammary Irradiation: A Single-center, Retrospective Propensity Score-matched Study**

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**Short Title :** Internal Mammary Irradiation in Lymph Node Positive Breast Cancer

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**Abstract**

**Background:** Internal mammary lymph node radiotherapy (IMN-RT) has unclear benefits. Historical data were based on only conventional (two-dimensional) radiation techniques. In this three-dimensional radiation therapy era, we compared the distant metastasis-free survival (DMFS) rates of patients receiving IMN-RT with those who did not include coverage of the IMN (non-IMN-RT).

**Objective:** This study aimed to determine the relationship between IMN-RT and distant metastasis control in patients with lymph node-positive breast cancer.

**Methods:** This was a single-center retrospective cohort study. Patients were divided into 2 groups: IMN-RT and non-IMN-RT. The criterion of the IMN-RT group was that 80% of the prescribed dose covered 98% of the CTV<sub>IMN</sub>. The primary outcome was 4-year DMFS, and

the secondary outcomes were 4-year overall survival, 4-year disease-free survival, and cardiac toxicity.

**Results:** From January 2012 to December 2018, 570 patients were evaluated (IMN-RT, 143 patients; non-IMN-RT, 427 patients). Propensity score matching decreased the number of patients in each group to 139. The median follow-up was 4.3 years. The 4-year DMFS rates were as follows: IMN-RT, 79.1% (95% CI, 70.1–85.6) and non-IMN-RT, 82.8% (95% CI, 74.2–88.7;  $P = 0.43$ ). The groups' 4-year overall survival and disease-free survival rates did not differ. The 4-year overall survival rates were 84.3% (95% CI, 76.4–89.8) for IMN-RT and 88.1% (95% CI, 81.0–92.7;  $P = 0.39$ ) for non-IMN-RT. The 4-year disease-free survival rates were 77.1% (95% CI, 68.1–83.8) for IMN-RT and 82.1% (95% CI, 73.6–88.1;  $P = 0.29$ ) for non-IMN-RT. There was no significant difference in cardiac toxicity (IMN-RT, 1.4%; non-IMN-RT, 1.4%;  $P = 1.0$ ).

**Interpretation:** In the modern radiation technique era with real-world data, we could not find a benefit of internal mammary irradiation.

## Introduction

Breast cancer is the most common malignancy in women and is increasing in incidence. Nevertheless, the optimal treatment is still controversial, especially concerning radiation use. Regional lymph nodes (supraclavicular, axillary, and internal mammary)<sup>[1-3]</sup> are frequently included in the radiation volume. However, internal mammary lymph node irradiation has not yet shown clear benefits.

The internal mammary lymph nodes are of concern because they are hypothesized to be a core area for micrometastases<sup>[4]</sup>, increasing the risk of distant metastases in the future. However, irradiation of the internal mammary lymph nodes inevitably increases the dose to the lung and heart. Data from Darby *et al.*<sup>[5]</sup> found a 7.4% increase in relative cardiovascular risk for every 1 Gy of heart dose. Therefore, the benefit of internal mammary lymph node irradiation must be proven.

In a landmark, large-scale trial, the Danish Breast Cancer Cooperative Group—Internal Mammary Lymph Node<sup>[6]</sup> investigated the impact of internal mammary lymph node irradiation. The research compared the outcomes of 2 groups: 3089 patients with early-stage, lymph node-positive breast cancer (1) who received internal mammary lymph node irradiation (right-sided disease) and (2) nonirradiated patients (left-sided disease). The median follow-up time was 14.8 years. The results showed that the patients who received internal mammary irradiation had a better 15-year overall survival, a lower breast cancer-specific mortality, and a lower distant recurrence rate.

Another landmark trial showed inconsistent results. The French Internal Mammary Lymph Node Study<sup>[7]</sup> investigated 1334 patients with positive axillary nodes or central/medial tumors with or without positive axillary nodes. The median follow-up time was 11.3 years. The

results did not show statistical significance for the 10-year overall survival or disease-free survival of patients receiving internal mammary irradiation and nonirradiated patients.

The results of the two landmark trials created controversy about the use of internal mammary irradiation. However, both trials were carried out in the conventional (two-dimensional) radiation therapy era. Since then, radiation techniques have advanced substantially. Three-dimensional conformal radiation therapy (3D-CRT) is now widely available. These sophisticated techniques allow the irradiation area to be well defined and evaluated.

The recently published KROG 08-06 trial<sup>[8]</sup>, which used an advanced radiation technique, investigated 735 patients with histologically confirmed node-positive breast cancer. The median follow-up time was 8.4 years. There was no significant difference in the 7-year disease-free survival of patients receiving internal mammary irradiation and nonirradiated patients.

Because there have been few investigations on internal mammary irradiation in the 3D-CRT era, the available data are limited. The present study compared the 4-year DMFS, overall survival, disease-free survival, and cardiac toxicity of patients receiving IMN-RT via the 3D-CRT technique with the results of patients who did not have internal mammary lymph node coverage.

## **Methods and materials**

### ***Study population***

Eligible patients were newly diagnosed female patients who had pathologically confirmed breast cancer between 2012 and 2018; underwent mastectomy or conservative breast surgery with biopsy or dissection of the axillary lymph nodes; had pathologically

confirmed positive lymph nodes; had complete staging, including evaluations of the bones, liver, and lungs; and received postoperative 3D-CRT with CT-based simulation. Exclusion criteria were metastatic disease (stage M1, according to the Eighth Edition of the AJCC Cancer Staging Manual); neoadjuvant chemotherapy; bilateral breast cancer; preexisting internal mammary lymph nodes in pre-radiation imaging; multiple primary cancer; and progressive disease before radiation.

Patients were observed with a clinical examination at 3- to 4-month intervals for 2 to 3 years and biannually after that. Mammogram plus ultrasound was performed annually. If symptoms suspicious for recurrence occurred, additional tests were investigated.

### ***Study design***

The study was designed as a single-center, retrospective cohort at Siriraj hospital, Thailand. Before starting the research, its protocol was approved by the Siriraj Ethical Review Board. The internal mammary lymph nodes (CTV<sub>IMN</sub>) between the first and third intercostal space and the heart were retrospectively re-delineated in all patients using the Radiation Therapy Oncology Group guidelines<sup>[9, 10]</sup>. This approach allowed the doses to be calculated. The patients were arranged into 2 groups: an internal mammary irradiation group (IMN-RT) and an absence of internal mammary irradiation group (non-IMN-RT). The criterion for the IMN-RT group was 80% of the prescribed dose covered 98% of the CTV<sub>IMN</sub> (V<sub>80% of prescribed dose</sub> 98%). The primary outcome was 4-year DMFS, and the secondary outcomes were 4-year overall survival, 4-year disease-free survival, and cardiac toxicity<sup>[9]</sup>. Subgroups were divided based on N stage (N1mi/1, N2, N3), intrinsic subtypes (***luminal A/B***: ER/PR positive, HER2-negative; ***HER2-positive***: ER/PR negative, HER2-positive; ***triple-negative***: ER/PR/HER2-negative), and location (outer, center, inner) to analyze the 4-year DMFS rate of each subgroup.

### ***Statistical analysis***

Propensity scores were calculated to balance confounders using R version 4.0.3. Based on historical data<sup>[11]</sup>, the variables placed in our model were age, laterality(left, right), T stage, N stage, grade, in-breast location(inner, central, outer), luminal status, and menstruation status. We matched the patients using MatchIt version 4.1.0 with a caliper of 0.26. With a caliper used to stabilize the model and better match the results, a few patients from the IMN-RT group dropped at this point. Data were extracted from R software and analyzed using Stata 16.1.

The characteristics of the patients and their treatments were compared. Categorical data were evaluated using Fisher's exact test, and continuous data were analyzed with a t-test. The final analysis of DMFS, overall survival, and disease-free survival was performed on the matched population. We used the Kaplan–Meier method and log-rank tests to compare study groups, while Fisher's exact test was used for cardiac toxicity<sup>[12]</sup>.

Subgroups based on N stage (N1mi/1, N2, N3), intrinsic subtypes (luminal A/B, HER2-positive, triple-negative), and in-breast locations (outer, center, inner) were performed to analyze DMFS. We used the Kaplan–Meier method and log-rank tests to compare groups in each subgroup.

### **Results**

From January 2012 to December 2018, a total of 1808 newly diagnosed patients with breast cancer received surgery and postoperative radiation with 3D-CRT. After excluding ineligible patients, 570 remained (*Figure 1*).

We reviewed all the contours and treatment plans before allocating the patients into 2 groups, according to the IMN-RT criteria. Eventually, 143 IMN-RT patients and 427 non-IMN-RT patients were available for the analyses.

Comparisons were made of the baseline characteristics of the whole population and the baseline characteristics after using the matching propensity scores (*Tables 1 and 2*). The mean age of the IMN-RT group was 55.1 years, while that of the non-IMN-RT group was 53.1 years. Most of the IMN-RT group had an inner location (38.3%), whereas most patients in the non-IMN-RT group had an outer location (67.9%). The most common T stage of both groups was T2 (IMN-RT, 64.3%; non-IMN-RT, 60.2%). The N stages of the IMN-RT group were mainly N2 and N3 (60.2%), but the non-IMN-RT group mainly had N1 and N2 (84.0%). Most of the patients had luminal A/B subtypes. The irradiated IMN volumes were 99.7% for the IMN-RT group and 53.2% for the non-IMN-RT group. All patients underwent 3D-CRT, DIBH was used in a low percentage due to lack of tools and experience at that point of time. Most patients received adequate systemic treatment.

The median follow-up was 4.3 years for the entire population.

Propensity score matching was required because the IMN and non-IMN groups had markedly different distributions of their baseline variables. Even though the number of patients decreased to 139 per group, the variables were balanced (*Tables 1 and 2*).

After matching the propensity scores, the data were analyzed (*Figure 2*). IMN irradiation demonstrated no benefit for DMFS. The 4-year DMFS was 79.1% (95% CI, 70.1–85.6) for the IMN-RT group and 82.8% (95% CI, 74.2–88.7) for the non-IMN-RT group ( $P = 0.43$ ).

There were no differences between the groups' overall survival and disease-free survival rates. For the IMN-RT group, the 4-year overall survival was 84.3% (95% CI, 76.4–89.8), while for the non-IMN-RT group, it was 88.1% (95% CI, 81.0–92.7;  $P = 0.39$ ). The 4-year disease-free survival was 77.1% (95% CI, 68.1–83.8) for the IMN-RT group and 82.1% (95% CI, 73.6–88.1) for the non-IMN-RT group ( $P = 0.29$ ). There was no significant

difference in cardiac toxicity (*Table 3*): 1.4% for the IMN-RT group and 1.4% for the non-IMN-RT group ( $P = 1.0$ ).

Subgroup analyses were performed on propensity score-matched populations. The subgroups included for analysis were N stage (N1mi/1, N2, N3), intrinsic subtype (luminal A/B, HER2-positive, triple-negative), and in-breast location (outer, center, inner). IMN-RT did not significantly improve the 4-year DMFS in any subgroup (*Supplement : Figure 1*).

Multivariable analysis for DMFS of the whole population ( $n = 570$ ) was also performed to identify the effect of each variable (*Supplement : Table 2*). The highest impact was observed for the N3 stage (HR 5.1, 95% CI, 2.8–9.3).

## Discussion

This study demonstrated no significant advantages for IMN-irradiated patients regarding their DMFS, overall survival, or disease-free survival.

According to a recently published, Orit Kaidar-Person and colleagues<sup>[13]</sup> found that radiation techniques did impact the oncologic outcomes of the patients. They compared radiation techniques used in EORTC22922/10925 trial between standard technique vs standard-modified technique vs individualized technique. The absolute improvements of oncological outcomes in terms of disease-free survival, overall survival and breast cancer specific mortality with internal mammary and medial supraclavicular lymph node (IM-MS) RT compared to no IM-MS RT were 6.8%, 4.9% and 5.8% for the individualized technique, vs 1.6%, 2.9% and 4.3% for modified standard and 1.4%, 1.1% and 3% for standard technique, respectively. These findings suggest that the use of more individualised RT techniques is associated with higher rates of oncological improvements.

The 3D-CRT technique is considered one of the individualized techniques. CT-based simulation helps physicians contour IMNs well and evaluate IMN radiation doses, neither of which historical trials could do. This technique can also evaluate heart and lung doses. If the mean heart dose exceeds the accepted tolerance level, physicians can perform the more advanced technique, deep inspiratory breath-hold (DIBH), to decrease the mean heart dose. Nevertheless, this study could not demonstrate a benefit of IMN-RT.

There are three possible reasons for the results. First, the proportion of distant metastasis events was much lower than expected<sup>[14, 15]</sup>. We observed only 13.86% for the whole population. The reason might be improvements in systemic treatments (such as chemotherapy or targeted therapy such as trastuzumab), which are now widely used. The effect of the low proportion of events is a lack of power to determine the benefits of IMN radiation.

Second, this study had a relatively short follow-up period, with a median follow-up of only 4.3 years. This duration contrasts markedly with the periods of the previously mentioned landmark trials, which had a follow-up of at least a decade. A longer follow-up could have increased the differences between our 2 study groups.

Third, the non-IMN-RT group received an incidental dose. When evaluated with the 80% prescribed dose, the mean IMN volume across all non-IMN-RT patients was 53.2%. The level of 53.2% may have interfered with our interpretations when comparing the IMN-irradiated and non-IMN-irradiated groups. This is because 80% of the prescribed dose might be sufficient to eradicate micrometastases in the internal mammary lymph nodes.

The results of this study are consistent with the French Internal Mammary Lymph Node Study (French-IMN) and a recent randomized controlled trial in Korea (KROG-0806).

The French-IMN study was conducted in the 2D era. It investigated 1334 patients with positive axillary nodes or central/medial tumors with or without positive axillary nodes. The results did not show significance in the 10-year overall survival (IMN-RT, 62.6%; non-IMN-RT, 59.3%;  $P = 0.8$ ). Pre-stratified subgroups, which were based on tumor location, histopathology nodal status, and adjuvant chemotherapy, also failed to demonstrate a benefit of IMN-RT.

KROG-0806 was conducted in the 3D era. It randomly assigned 735 patients with histologically confirmed node-positive breast cancer to IMN-RT and non-IMN-RT groups. The 2 groups' 7-year disease-free survival rates did not significantly differ (IMN-RT, 85.3%; non-IMN-RT, 81.9%;  $P = 0.22$ ).

The only large-scale landmark trial that established a benefit of IMN-RT was the Danish Breast Cancer Cooperative Group—Internal Mammary Lymph Node (DBCG-IMN). It enrolled 3089 patients with early-stage lymph node-positive breast cancer. The research found that patients who received internal mammary irradiation had a better 15-year overall survival, a reduced breast cancer-specific mortality, and a lower distant recurrence rate. The corresponding 15-year overall survival rates were 60.1% and 55.4%. The adjusted hazard ratio (HR) for death was 0.86 (95% CI, 0.77 to 0.96;  $P = .007$ ) in favor of IMN irradiation.

The chief difference between DBCG-IMN and the other studies is that the number of patients was much more substantial. This increased size could improve the analytical power sufficiently to enable the detection of even a small benefit from administering IMN-RT.

The IMN area is usually included in radiation fields when tumors are in the central or inner quadrants due to the lymphatic drainage pathways. Regarding KROG-0806, an ad hoc subgroup analysis showed significantly higher DFS rates with IMN-RT among patients with mediocentrally located tumors. In this subgroup, the 7-year DFS rates were 81.6% without

IMN-RT vs 91.8% with IMN-RT (HR, 0.42; 95%CI, 0.22-0.82; log-rank P = .008) and the 7-year breast cancer mortality rates were 10.2% without IMN-RT vs 4.9% with IMN-RT (HR, 0.41; 95%CI, 0.17-0.99; log-rank P = .04). Therefore, we performed a subgroup analysis; it indicated that IMN-RT did not show any benefits in these locations.

According to the MA.20 trial<sup>[3]</sup>, ER- and PR-negative patients benefited from regional lymph node irradiation. We performed a subgroup analysis based on intrinsic subtypes. No benefit of IMN-RT was found for any subtype.

N stage is another principal factor that might increase the risk of IMN metastasis. Based on DBCG-IMN subgroup analysis, IMN-RT was more pronounced in patients with 4 or more positive axillary nodes. Thus, an N-stage subgroup analysis was performed. However, no benefit of IMN-RT is observed in any N-stage subgroup.

In terms of toxicity, cardiac toxicity is of most concern. In this study, the heart was re-delineated for all patients. The mean heart dose was 7.1 Gy for the IMN-irradiated group and 3.7 Gy for the non IMN-irradiated group. However, the cardiac outcome did not show any difference between the groups. There were only 2 patients with Radiation Therapy Oncology Group Grade 3 (1 in each group; *Table 3*). We explored the heart toxicity of each patient, but no dose correlation was found.

The limitations of this study were small sample size after propensity score matching (n = 278), short-term follow-up time (4.3 years), retrospective study, and small target volume (CTV<sub>IMN</sub>). At the time of the study design, we adapted the IMN group criteria from the MA.20 trial focusing on the clinical target volume (CTV<sub>IMN</sub>) rather than on the planning target volume (PTV<sub>IMN</sub>). However, this should be interpreted carefully because with an evaluation lack of PTV<sub>IMN</sub> could be a contributing factor to the lack of benefit of IMN RT.

Finally, when considering first-event failure (*Table 4*), it is apparent that there were high proportions of distant metastases in both groups without IMN recurrence. This finding may reject our hypothesis that IMN was the cause of distant metastasis. Currently, high percentages of distant failure lead to an increasing tendency of neoadjuvant chemotherapy. Therefore, the investigation role of IMN RT in patients treated with neoadjuvant chemotherapy should be future directions.

## Conclusions

In the modern radiation technique era with real-world data, we could not find a benefit of internal mammary irradiation.

## Acknowledgments

The authors are grateful to Mr. David Park for English-language editing.

## Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Funding : None

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

**Acknowledgements :** Special thanks to my advisor, *Kullathorn Thephamongkhol, M.D.*, and co-advisor, *Jiraporn Setakoranukul, M.D.* for guidance and support. Many thanks to *Suthinee Ithimakin, M.D.*, *Rungroj Krittayaphong, M.D.* and *Kyrhatii Trikhirhisthit, M.D.* for trial design and advice. Thank you *Ms. Nataya Samasant* for coordinate things in need and we also gratefully acknowledge the professional editing of this paper by Mr. David Park

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Table 1 : Patient demographics and diseases characteristics.

	<i>Whole population</i>				<i>Propensity-Match</i>		
		IMN RT (N=143)	No IMN RT (N=427)	P	IMN RT (N=139)	No IMN RT (N=139)	P
<b>Age, years</b> mean(SD)		55.1 (10.9)	53.1 (10.5)	0.06	55.1 (10.8)	54.6 (9.5)	0.72
<b>Menstruation</b>	Premenstruation	95 (66.4%)	262 (61.4%)	0.32	92 (66.2%)	93 (66.9%)	1.00
	Postmenstruation	48 (33.6%)	165 (38.6%)		47 (33.8%)	46 (33.1%)	
<b>Laterality</b>	Right	59 (41.3%)	202 (47.3%)	0.24	57 (41.0%)	60 (43.2%)	0.81
	Left	84 (58.7%)	225 (52.7%)		82 (59.0%)	79 (56.8%)	
<b>In-breast location</b>	Outer	47 (32.9%)	286 (67.0%)	<0.001	47 (33.8%)	48 (34.5%)	0.93
	Center	40 (27.9%)	64 (15.0%)		39 (28.1%)	36 (25.9%)	
	Inner	54 (37.8%)	71 (16.6%)		53 (38.1%)	55 (39.6%)	
	Indeterminate	2 (1.4%)	6 (1.4%)		0 (0%)	0 (0%)	
<b>T Stage</b>	T0	0 (0%)	3 (0.7%)	0.44	0 (0%)	0 (0%)	0.99
	Tis	0 (0%)	1 (0.2%)		0 (0%)	0 (0%)	
	T1	31 (21.7%)	122 (28.6%)		31 (22.3%)	30 (31.6%)	
	T2	92 (64.3%)	257 (60.2%)		88 (63.3%)	90 (64.7%)	
	T3	14 (9.8%)	29 (6.8%)		14 (10.1%)	14 (10.1%)	
	T4	6 (4.2%)	15 (3.5%)		6 (4.3%)	5 (3.6%)	
<b>N Stage</b>	N1mi	1 (0.7%)	21 (4.9%)	0.003	1 (0.7%)	5 (3.6%)	0.46
	N1	56 (39.2%)	212 (49.6%)		56 (40.3%)	57 (41.0%)	
	N2	50 (35.0%)	126 (29.5%)		50 (36.0%)	47 (33.8%)	
	N3	36 (25.2%)	68 (15.9%)		32 (23.0%)	30 (21.6%)	
<b>Grade</b>	G1	7 (4.9%)	21 (4.9%)	0.96	7 (5.0%)	6 (4.3%)	0.79
	G2	89 (62.2%)	259 (60.7%)		88 (63.3%)	94 (67.6%)	
	G3	47 (32.9%)	147 (34.4%)		44 (31.7%)	39 (28.1%)	
<b>LVSI</b>	Negative	54 (37.8%)	191 (44.7%)	0.23	54 (38.8%)	56 (40.3%)	0.94
	Positive	75 (52.4%)	188 (44.0%)		71 (51.1%)	68 (48.9%)	
	Indeterminate	14 (9.8%)	48 (11.2%)		14 (10.1%)	15 (10.8%)	
<b>Luminal Status</b>	Luminal A/B	121 (84.6%)	345 (80.8%)	0.12	117 (84.2%)	116 (83.5%)	1.00
	Her-2 Positive	14 (9.8%)	34 (8.0%)		14 (10.1%)	15 (10.8%)	
	Triple Negative	8 (5.6%)	48 (11.2%)		8 (5.8%)	8 (5.8%)	
<b>LN positive</b> median(IQR)		4 (2-8)	3 (1-7)	<0.001	4 (2-8)	4 (1-8)	0.26
<b>Extranodal</b>	No	26 (18.2%)	122 (28.6%)	0.043	24 (17.3%)	34 (24.5%)	0.26

## Whole population

## Propensity-Match

	Whole population			Propensity-Match			
		IMN RT (N=143)	No IMN RT (N=427)	P	IMN RT (N=139)	No IMN RT (N=139)	P
extension	Yes	108 (75.5%)	108 (75.5%)		106 (76.3%)	94 (67.6%)	
	Indeterminate	9 (6.3%)	9 (6.3%)		9 (6.5%)	11 (7.9%)	
Surgical margin status	Negative	13 (93.0%)	409 (95.8%)	0.19	129 (92.8%)	136 (97.8%)	0.085
	Positive	10 (7%)	18 (4.2%)		10 (7.2%)	3 (2.2%)	

Data are presented as n (%).

Table 2 : Treatment characteristics.

	Whole population				Propensity-Match			
		IM N RT (N=143)	No IMN RT (N=427)	P	IM N RT (N=139)	No IMN RT (N=139)	P	
Irradiated IMN volume <sup>a</sup> , % mean(SD)		99.7% (0.5)	53.3% (31.7)	<0.001	99.8% (0.5)	59.5% (29.6)	<0.001	
BH	No	142 (99.3%)	416 (97.4%)	0.3	138 (99.3%)	135 (97.1%)	0.3	
	Yes	1 (0.7%)	11 (2.6%)		1 (0.7%)	4 (2.9%)		
Mean heart dose, Gy mean(SD)		7.1 (5.4)	3.8 (3.6)	<0.001	7.1 (5.4)	4.0 (3.6)	<0.001	
Surgery	MRM	127 (88.8%)	298 (69.8%)	<0.001	123 (88.5%)	108 (77.7%)	0.0	
	BC	16 (11.2%)	129 (30.2%)		16 (11.5%)	31 (22.3%)		
LN dissection mean(SD)		19.5 (8.3)	18.3 (8.7)	0.1	19.4 (8.3)	19.0 (8.4)	0.6	
Systemic treatment <sup>(b)</sup>	Adequate	118 (82.5%)	355 (83.1%)	0.9	115 (82.7%)	111 (79.9%)	0.6	
	Inadequate	25 (17.5%)	72 (16.9%)		24 (17.3%)	28 (20.1%)		

Data are presented as n (%).

<sup>a</sup>Volume of internal mammary lymph node received 80% prescribed dose.

<sup>b</sup>Adequate treatment defined as 1. Received chemotherapy as planned 2. Duration from surgery to start chemotherapy not more than 60 days, Inadequate defined as 1. Incomplete course of chemotherapy 2. Her-2 positive but didn't received Herceptin 3. Duration from surgery to start chemotherapy more than 60 days

Table 3. Cardiac Toxicity

		Whole population			Propensity-Match		
		IMN RT (N=143)	No IMN RT (N=427)	P	IMN RT (N=139)	No IMN RT (N=139)	P
Cardiac Event		2 (1.4%)	5 (1.2%)	.0	2 (1.4%)	2 (1.4%) <sup>a</sup>	.0
IMN RT, 2 pts		Mean Heart (Gy)		RTOG Grading			
Patient 1	Moderate pericardiac effusion + Valvular heart disease	28	4.1	3			
Patient 2	Cardiomyopathy + Coronary artery disease	93	8.6	1			
Non-IMN RT, 5 pts		Mean Heart (Gy)		RTOG Grading			
Patient 1	Valvular heart disease	29	10.	1			
Patient 2	Cardiomyopathy	37	0.7	1			
Patient 3	Cardiomyopathy + Minimal pericardial effusion	969	12.	3			
Patient 4	Coronary artery disease	06	4.2	2			
Patient 5	Coronary artery disease	58	2.2	1			

a: patients number 1 and number 4 in Non-IMN groups were left after propensity-matching

**Table 4** : First event recurrence (Propensity-match population)

First Event	IMN RT (139/278, 50%)	No-IMN RT (139/278, 50%)
Local recurrence	2 (1.4%)	0 (0%)
Regional recurrence ( IMN )	0 (0%)	0 (0%)
Regional recurrence ( non-IMN )	0 (0%)	0 (0%)
Distant met.	22 (15.8%)	16 (11.5%)
Local + Regional ( IMN )	0 (0%)	0 (0%)
Local + Regional ( non-IMN )	0 (0%)	1 (0.7%)
Local + Distant met.	1 (0.7%)	1 (0.7%)
Regional ( IMN ) + Distant met.	0 (0%)	3 (2.2%)
Regional ( non-IMN ) + Distant met.	2 (1.4%)	0 (0%)
Local then Regional ( non-IMN )	1 (0.7%)	0 (0%)
Local then Distant met.	0 (0%)	1 (0.7%)
Local + Regional ( non-IMN ) + Distant met.	1 (0.7%)	0 (0%)
Total	29/139 (20.7%)	22/139 (15.8%)

Data are present as n (%).

Figure 1 : Consort diagram

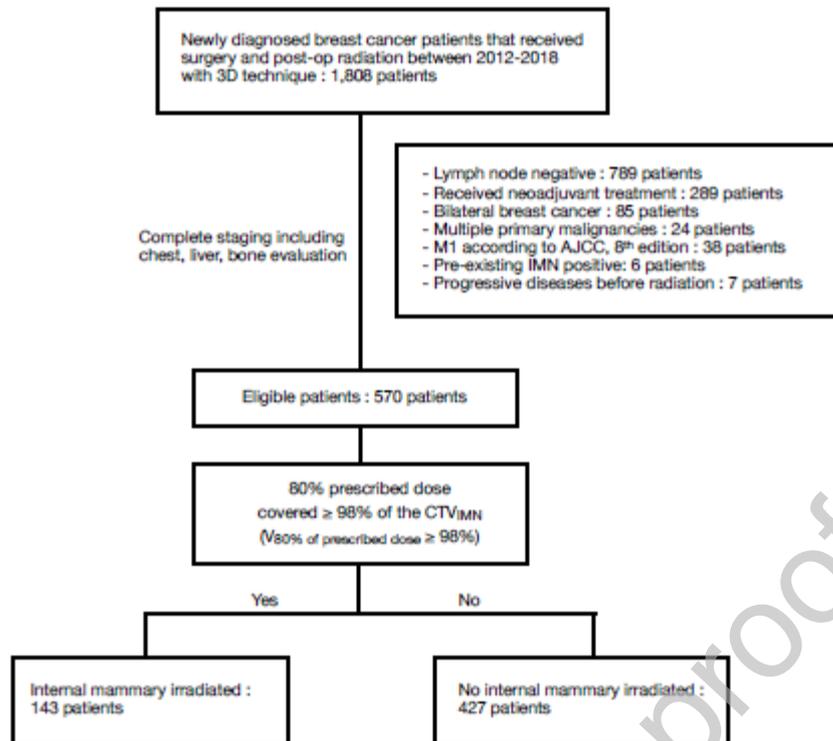
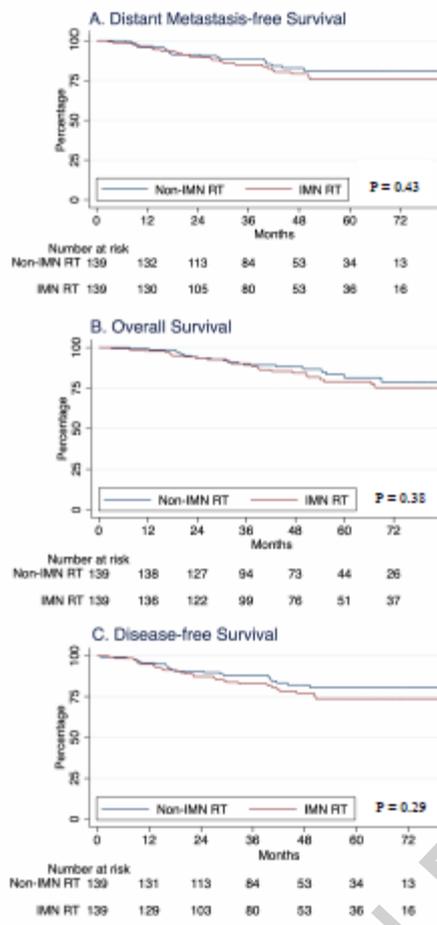


Figure 2 : DMFS, OS, DFS



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