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A Dosimetric Study of Accidental Internal Mammary Lymph Node Irradiation during Locoregional Breast Irradiation

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Abstract

Background: One remaining grey zone in locoregional breast irradiation is whether to irradiate internal mammary lymph nodes (IMN) in the lack of gross involvement as well as optimum dosimetric recommendations for IMN irradiation. Our study aimed to assess whether IMNs are incidentally irradiated during locoregional breast irradiation, and whether this non-intended irradiation could contribute to lower IMN recurrence risk.

Method: This retrospective study was conducted on 137 adult female patients treated at Alexandria Main University Hospital who had pathologically proven breast cancer. Patients should have undergone surgery and were proven to be: T3 (tumor > 5 cm), had positive axillary lymph nodes (ALNs; ≥ 1 ALN involvement) or had positive surgical margins, from January 1st, 2015, to December 31st, 2017. IMNs were delineated, and the IMN mean dose was recalculated. Data were analyzed using SPSS Ver. 25 and data was considered statistically significant at a *P*-value of ≤ 0.05.

Results: Only the IMN mean dose percent, at a cutoff dose of 28.5% mean dose percent, was associated with significant reduction in the risk of IMN recurrence ($P = 0.05$). Other factors including tumor site, size, grade, or nodal status were not associated with higher risk of recurrence.

Conclusion: Although the indication of IMN irradiation is still debatable, our results suggest that a minimum prescribed dose percent of 28.5% is needed to reduce the risk of IMN recurrence in patients with no IMN gross involvement. Yet, studies with larger sample size are needed to better characterize optimum IMN dosimetric criteria.

Keywords: Breast neoplasms, Radiation dosage, Internal mammary lymph node, Adjuvant radiotherapy, Survival

Introduction

Adjuvant radiotherapy (RT) is an integral part of the treatment plan of patients with early and locally advanced breast cancer after undergoing either breast-conservative surgery (BCS) or after modified radical mastectomy (MRM) in selected high-risk patients.[1, 2] However, one controversial aspect to locoregional RT up to this day is whether or not and when to include internal mammary lymph nodes (IMN) within the RT field in case of no gross involvement.[3, 4] Although the National Comprehensive Cancer Network (NCCN) putting recommendations on the indications for IMN irradiation;[5] there still remains an ongoing conflict on the risks versus benefits of IMN irradiation in different case scenarios.

For example, the French trial designed to assess the effect of IMN irradiation on 10-year overall survival of patients who underwent mastectomy, found that irradiating IMN in node positive patients did not improve overall survival.[4] On the other hand, the prospective Danish BREAST Cancer Group (DBCG)-IMN trial, on around 3,000 node positive patients, tested the effect of IMN irradiation on 8-year overall survival and found that there was significant improvement in cancer-related mortality (20.9% in irradiated group vs. 23.4% in non-irradiated group; hazard ratio (HR) = 0.85, P = 0.03) as well as overall survival (HR = 0.82, P = 0.005).[3]

Currently, the criteria for including IMN within the clinical target volume (CTV) in the NCCN guidelines are: Category 1 recommendation for patients with ≥ 4 positive axillary lymph nodes (ALNs) and strong consideration – Category 2A – for patients with 1-3 positive ALNs.[5] However, there is still a controversy regarding the inclusion of IMN especially given the higher risk of cardiac and lung toxicity if included. Additionally, despite the higher risk of IMN involvement in inner-quadrant tumors, the risk of IMN recurrence remains quite low (< 1%) following adjuvant locoregional irradiation.[6] This has, in turn, suggested the possible role for incidental – or non-intentional – IMN irradiation in patients receiving adjuvant therapy.[7, 8]

Our study aims to test this theory and assess whether IMN receive incidental irradiation and whether this non-intended IMN irradiation could actually contribute to lower IMN Recurrence risk in adult female patients with surgically managed breast cancer – regardless of the number of involved ALNs.

Materials and Methods

This is a retrospective cohort study that was executed on 137 female patients diagnosed and treated at the Clinical Oncology and Nuclear Medicine Department at Alexandria Main University Hospital during the period from January 1st, 2015, to December 31st, 2017.

Inclusion criteria

We included adult female patients older than 18 years of age who had pathologically proven breast cancer diagnosis, any subtype. These patients should have undergone either BCS or MRM and were proven to be T3 (tumor > 5 cm) or had positive ALNs (≥ 1 axillary LN involvement) or had positive surgical margins. All patients should have been indicated to receive adjuvant post-operative RT without intended IMN radiation field inclusion.

Exclusion criteria

We excluded patients who were node negative following MRM (i.e., not eligible for adjuvant locoregional RT) as well as patients with pathologically proven IMN involvement.

RT technique

All the cases were simulated at our institution using non-contrast computed tomography (CT) scan at 5 mm thickness from the base of the skull up to the umbilicus. All patients had lead markers placed at the reference points (3 arbitrary points on the chest wall determined by the laser) to maintain inter-fractional consistency. Following simulation, the images were sent directly to the Monaco planning system for 3D delineation and planning. The Radiation Therapy Oncology Group (RTOG) consensus guideline was used for delineation of CTV and the supraclavicular fossa. The borders of radiation field to breast or chest wall are superiorly: the inferior border of clavicular head; inferiorly: 2 cm below the inframammary fold; medially: the midsternum, laterally: the midaxillary line. The borders of supraclavicular fossa are: superiorly: caudal to cricoid cartilage, inferiorly: the junction of brachiocephalic veins and caudal edge of clavicular head, posteriorly: the anterior axis of the scalene muscle, medially: exclude trachea, laterally: junction of first rib and clavicle.

A planning target volume (PTV) of 5 mm margin from CTV was used.

Following our institutional guidelines, uninvolved IMN were not routinely delineated within the target volumes; however, for this study in particular, IMNs were contoured through the internal thoracic vessel topography (from the superior border of the first rib cranially up to the superior border of the fourth rib caudally) using the following borderlines: Anteriorly at the posterior border of the chest wall; posteriorly at the outer border of the parietal pleura; medially at the lateral border of the sternum or the medial limit of the internal thoracic vascular area; and laterally at the medial limit of the internal thoracic vascular area.

Following the IMN delineation, the total radiation dose was recalculated without any modification in the plan that was done prior to this delineation/contouring – including the gantry angles, collimator and multi-leaf collimator positions, or beam specifications and the accurate dose to IMN was calculated through the dose volume histogram (DVH).

By referring to patients data kept at the hospital records and reviewing the imaging done for the patients at their regular follow up visits, we collected data about the recurrence in the internal mammary and disease-free survival.

Primary outcomes

Our primary outcome included estimating the IMN recurrence risk in patients receiving the mean IMN dose percent (IMD mean %) or higher versus those who receive less than the IMD % – after determining the IMD % as a percentage of the prescribed dose. Multivariate analysis was also done to assess the effect of different factors on IMN recurrence risk, including tumor grade, tumor site, tumor side, and nodal status.

Secondary outcomes

Secondary outcomes included the ipsilateral lung volume receiving ≥ 20 Gy (V20) and the mean heart dose (in left-sided breast cancer patients only).

Ethical considerations

A written informed consent was obtained from all patients in the present study. Our study protocol was approved prior to the conduction of the study by the Ethics Committee of the Faculty of Medicine, Alexandria University under the serial number 0105896 and was conducted in accordance with the declaration of Helsinki. Our Institutional Ethical Review Board (IRB) number for the study is 00007555 and the Federal Wide Assurance (FWA) number is 00018699.

Statistical analysis

All data was analyzed using SPSS Ver. 25. Quantitative data was expressed using mean and standard deviations (SD); while qualitative data were expressed using frequency and percentage. Unpaired t-test was used to compare the mean IMN recurrence risk as well as other quantitative data, and the chi-square test was used for qualitative data analysis. Data were considered statistically significant at a *P*-

value of ≤ 0.05 to ensure a study power of at least 80%.

Results

Demographic data

The mean age of the patients was 53 years (27-82; SD = 11), as illustrated in table 1.

Tumor characteristics

The majority of the patients had Grade II tumors, T2 tumor size (2-5 cm; 74%), and N1 (1-3 lymph nodes) or N2 (4-9 lymph nodes) axillary nodal involvement (38% and 36%, respectively). Full clinical tumor characteristics for included patients are further illustrated in table 1.

RT fractionation and dosimetry

On reviewing the form of RT fractionation, 45.3% of the patients (n = 62) received conventional fractionation and 54.7% (n = 75) received hypofractionated RT. When it comes to boost administration, only 2.9% (n = 4) were candidates for a radiation boost. Conventional fractionation involved 50 Gy / 25 fraction regimen, while the hypofractionated regimen included 40 Gy / 15 fractions. IMN was covered by less than 95% of the prescribed dose as part of PTV. The mean prescribed dose percent for IMNs was 28.5%, while the mean heart dose was 1.36 Gy and the lung V20 was 16.33 Gy – as described in table 2.

Taking the side of the tumor into consideration, tumors on the right side had a mean IMN dose (IMD) of 28.63% of the prescribed dose; while the left side had a mean dose of 27.8% of the prescribed dose – this difference was not statistically significant. The V20 lung dose on the right side was not statistically significant from the left side as well (15.94% on the right sided breast cancers versus 16.66% on the left as shown in table 3.

Internal mammary node recurrence-free survival and mean dose percent

Internal mammary node recurrence-free survival was significantly higher in the patients who received more than 28.5% of the prescribe dose, compared with those who received suboptimum doses (*P* = 0.05; Figure 1).

Censored patients refer to patients who lost follow-up.

Nodal status and IMN recurrence-free survival

The presence and number of axillary lymph node involvement had no effect on the risk of IMN recurrence risk (*P* > 0.05; Table 4, Figure 2).

Censored patients refer to patients who lost follow-up.

Neither tumor grade nor tumor size has any effect on the IMN recurrence risk (*P* > 0.05; Figures 3 and 4, respectively). Tumor site (quadrant) was also not associated with any significant difference (*P* > 0.05; Figure 5).

Discussion

This study suggests that breast cancer patients with axillary lymph node involvement, and without gross involvement of IMN had significant increase in disease-free survival if the incidental dose to internal mammary lymph node exceeds 28.5% of the prescribed dose.

Breast cancer is currently the most prevalent cancer in women worldwide, making up almost 13% of all cancer cases and one-quarter of cancer cases in females.[9] However, looking at Egyptian statistics according to the "National Cancer Institute (NCI) in Cairo" registry, breast cancer has a much higher prevalence in Egypt, faring at a surprising percentage of almost 40% in 2014.[10] Despite the general awareness on breast cancer screening, being lacking amongst the general population and having more late cases not candidates for curative treatment, one initiative by the Ministry of Health for the early detection of breast cancer cases known as the "Women's Health Initiative" has led to the early detection of numerous breast cancer cases since 2019, reaching as high as 28 million adult women. This has, in turn, created an uptrend in the number of females undergoing interventions with curative intent – i.e. (neo) adjuvant chemotherapy, surgery, and locoregional RT.[11] However, with earlier breast cancer comes more axillary, and IMN, negative patients, which has made us face more IMN negative patients than before.

The incidence of IMN metastasis varies greatly depending on the size and quadrant the tumor is located in, as well as axillary lymph node involvement. In case of tumors < 0.5 cm, incidence of IMN metastasis is 3-7%; significantly less than the risk of involvement in tumors ranging from >3 - 5 cm – which reaches 40%-60%. Additionally, tumors located within the inner quadrants have reported higher risk of recurrence; estimated to reach 45% in the upper inner quadrant tumors and 72% in the lower inner quadrant tumors.[6] However, despite these startling numbers for inner tumors, overall, this subset of individuals represents a small percentage of females with breast cancer. Nearly 9 % of axillary node negative patients have IMN involvement and about 40% have IMN involvement in patients with as much as four or more ALNs.[7, 8] Additionally, less than 1% experience IMN recurrence following adjuvant RT – despite not directly being included in the CTV. This discrepancy in percentages has therefore created a dilemma of determining who will benefit from IMN irradiation so much that it outweighs the risks of its irradiation. Additionally, there have been suggestions that IMN might be receiving higher incidental irradiation[12] – which might have contributed to the lower recurrence rates. The literature on incidental radiation dose to IMLN is sparse, most of these studies assessed the incidental dose to IMLN, but none of them correlated the mean dose of IMLN and the rate of IMLN recurrence.[12, 13]

Therefore, our study was conducted in order to determine the mean dose received by IMN (as a percentage of the prescribed dose) as well as the IMN risk of recurrence. The correlation between the mean IMN dose and IMN risk of recurrence was then tested for significance. Our study has included a total of 137 female patients diagnosed and treated at the Clinical Oncology and Nuclear Medicine Department at Alexandria Main University Hospital during the period from January 1st, 2015, to December 31st, 2017. These patients were candidates to receive adjuvant post-operative RT; yet, without IMN irradiation inclusion criteria. Our results showed that IMN received a mean dose (IMD %) of 28.5% of the prescribed dose.

Arora et al., in his retrospective study on 50 breast cancer patients treated by 3 D conformal radiotherapy, stated that the mean dose to IMN was 24.98 Gy.[13] While Wang et al. reported that 29.6 Gy was the mean incidental radiation dose to IMC.[14]

In our study, we assessed patients who received less than this mean dose (28%) versus those who received ≥28%, and we found that in patients with IMN receiving a minimum of 28% of the prescribed dose, there was a lower risk of IMN recurrence; while on retrospectively assessing all of the patients who have experienced IMN recurrence, all of them had received a suboptimum IMD of % < 28% ($P = 0.05$).

In our study, the tumor size, site, grade, and also nodal involvement did not correlate with IMN recurrence risk, this may be explained by the small sample size.

The maximum heart irradiation dose was around 20 Gy – well-lower than the standard limits – and the lung had a V20 irradiated volume of 16.3%.

These findings suggest possible unintentional benefits being supplied through the incidental irradiation of IMN – irrespective of tumor grade; stage; or site.

To our knowledge, this is the only study that assessed the incidental dose to IMLN and its correlation with IMLN recurrence.

Limitations of our study include its retrospective origin and the small sample size. That is why we recommend other similar clinical trials to be conducted with a larger sample size.

Conclusion

Despite our results being based on a small sample size, we could infer that achieving an IMN minimal mean dose of 28.5% of the prescribed dose is recommended in node positive breast cancer patients to reduce the risk of IMN recurrence. Larger sample sizes in future studies would be recommended to establish an accurate dosimetric recommendation for IMN irradiation.

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No funding was provided for the conduction of this study.

Authors' Contribution

Y.H.: Study design, data gathering, and manuscript drafting; K.A.: Study design, and reviewing the manuscript; D.A.: Study design, and reviewing the manuscript. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.

Conflict of Interest

None declared.

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Table 1. Demographic and clinical characteristics of the patients

Characteristic		No. of patients	%
Comorbidities	Yes	31	28.4%
	No	78	71.6%
	Total	109	100.0%
Menstrual history	Premenopausal	44	40.4%
	Postmenopausal	65	59.6%
	Total	109	100.0%
Family history	Yes	11	10.1%
	No	98	89.9%
	Total	109	100.0%
Type of surgery	Breast conservative surgery	48	35.1
	Mastectomy	89	64.9
	Total	137	100.0%
Tumor side	Right breast	63	46.0%
	Left breast	74	54.0%
Tumor site	Outer quadrates	27	45.8%
	Inner quadrates	18	30.5%
	Central quadrates	14	23.7%
Pathology type	IDC	105	97.2%
	ILC	1	0.9%
	Others	2	1.9%
Tumor grade	Grade I	0	0.0%
	Grade II	96	88.9%
	Grade III	12	11.1%
T	T1	23	21.5%
	T2	74	69.2%
	T3	8	7.5%
	T4	2	1.9%
N	N0	16	15.1%
	N1	38	35.8%
	N2	36	34.0%
	N3	16	15.1%
Lymph vascular invasion	Positive LVI	106	98.1%
	Negative LVI	2	1.9%
Estrogen receptor staining	ER positive	74	72.5%
	ER negative	28	27.5%
Progesterone receptor staining	PR positive	67	65.7%
	PR negative	35	34.3%
Her2 receptor staining	Positive	29	28.7%
	Negative	72	71.3%

IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; T: Tumor size; N: Lymph nodes; M: Metastasis; LVI: Lymphovascular invasion; ER: Estrogen receptor; PR: Progesterone receptor; Her2: Human epidermal growth factor receptor 2; No.: Number

Table 2. Radiotherapy dosimetric data

	Mean	Standard deviation
IMN volume	7.35	0.45
IMN mean dose (%)	28.50	20.71
IMN minimal (%)	5.22	2.67
IMN maximum dose (%)	84.2	27.4
Heart mean dose (GY)	1.36	2.02
Heart minimum dose (GY)	0.01	0.09
Heart maximum dose (GY)	19.98	20.46
Lung mean dose (GY)	7.79	2.28
Lung V20 (%)	16.33	4.22

IMN: Internal mammary lymph nodes; V20: Lung volume receiving ≥20 Gy; the IMN dose is calculated as % of the prescribed dose

Table 3. Min., mean, and max. dose to the internal mammary nodes, heart, and lungs according to the irradiated side

	Tumor side							
	Right breast				Left breast			
	Mean	**Min.**	**Max.**	**SD**	**Mean**	**Min.**	**Max.**	**SD**
IMN mean dose%	28.62%	5.00%	81.00%	20.762%	27.79%	1.00%	91.00%	20.225%
IMN minimal%	5.74%	2.00%	20.00%	3.35%	4.77%	2.00%	15.00%	1.81%
IMN maximum dose%	85.93%	7.80%	118.00%	26.96%	82.72%	15.00%	113.00%	27.92%
Heart mean dose (GY)	0.00	0.00	0.00	0.00	1.36	1.0	5.40	2.15
Heart minimal dose (GY)	0.00	0.00	0.00	0.00	.03	0.00	0.70	0.12
Heart maximum dose (GY)	0.00	0.00	.00	0.00	36.99	0.00	53.00	11.91
Lung maximum dose (GY)	46.78	20.00	55.90	6.32	47.07	38.50	55.70	5.17
Lung minimal dose (GY)	0	0	0	0	0	0	0	0
Lung mean dose (GY)	7.76	3	12	2.26204	7.82	3.6	11.6	2.3049
LungV20 %	15.94%	5.00%	22.00%	4.15%	16.66%	6.00%	22.00%	4.29%

Min.: Minimum; Max.: Maximum; IMN: Internal mammary lymph nodes; Gy: Gray

Table 4. Axillary nodal status and internal mammary node recurrence-free survival

N	**Mean**	**95% Confidence interval**		***P* value**
		Lower limit	**Upper limit**	
N0	62.000	50.843	73.157	
N1	53.045	47.820	58.271	0.913
N2	52.580	45.548	59.613	0.871
N3	50.800	41.131	60.469	0.910
Overall	62.054	57.542	66.566	

N: Nodes

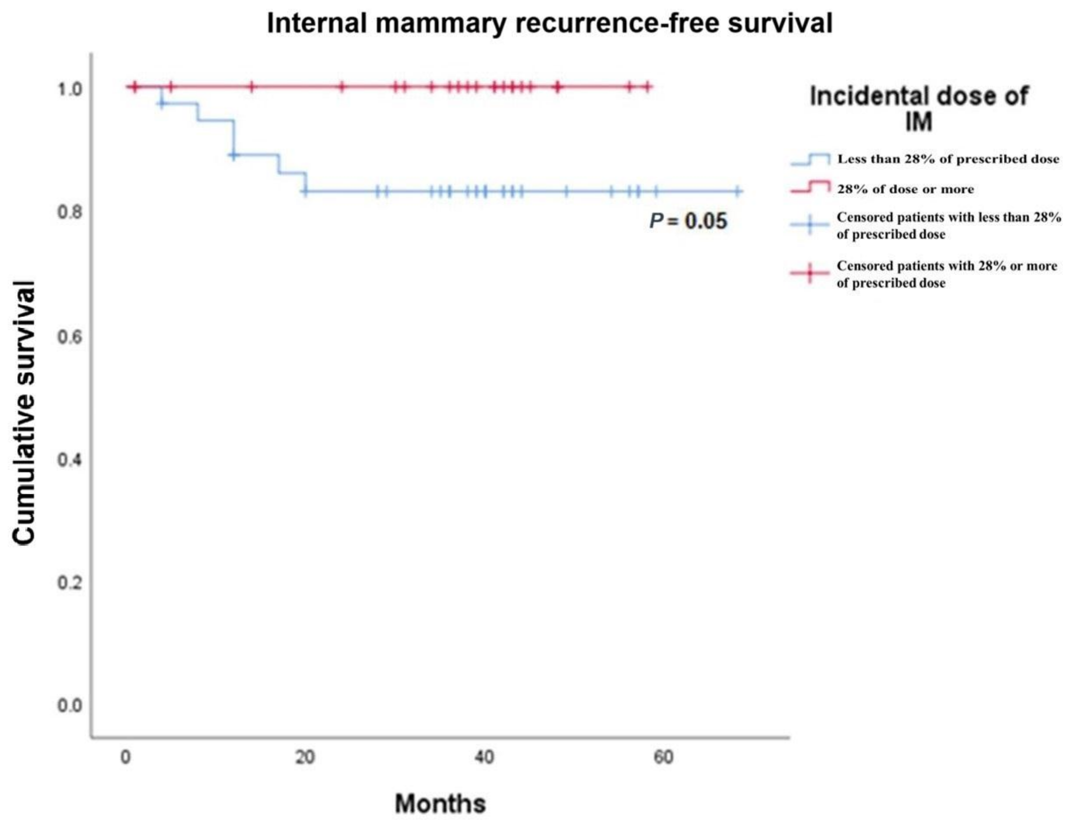

Figure 1. This figure shows the correlation between incidental dose of radiation to internal mammary lymph nodes and internal mammary recurrence-free survival.
IM: Internal mammary; Censored: lost follow-up

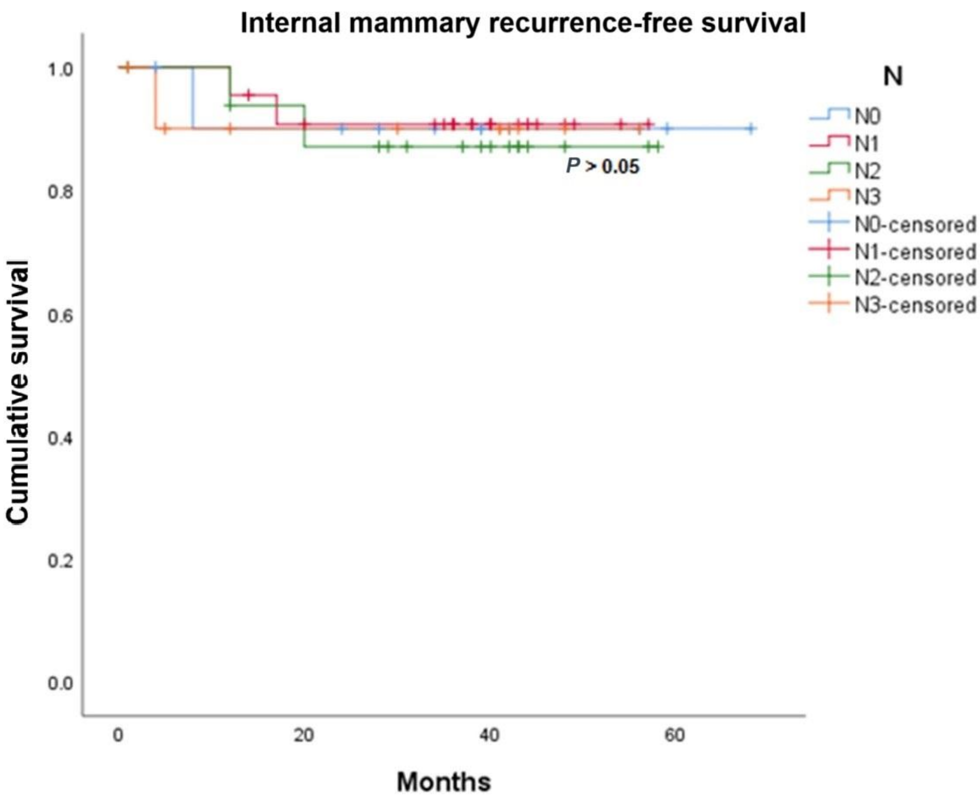

Figure 2. This figure shows the correlation between axillary lymph node involvement and internal mammary recurrence-free survival.

LN: Lymph node; N0: No axillary LN; N1: 1-3 axillary LN; N2: 4-9 axillary LN; N3: > 9 axillary LN; Censored: lost follow-up

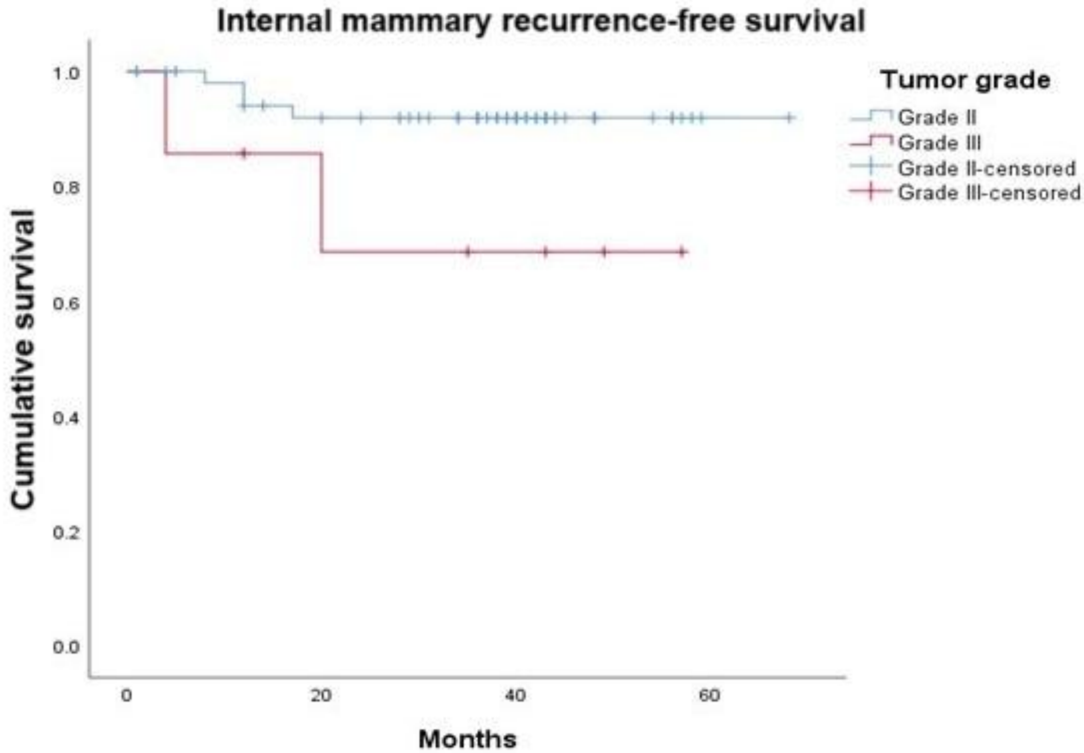

Figure 3. This figure shows the correlation between tumor grade and internal mammary recurrence-free survival.
Censored: Lost follow-up

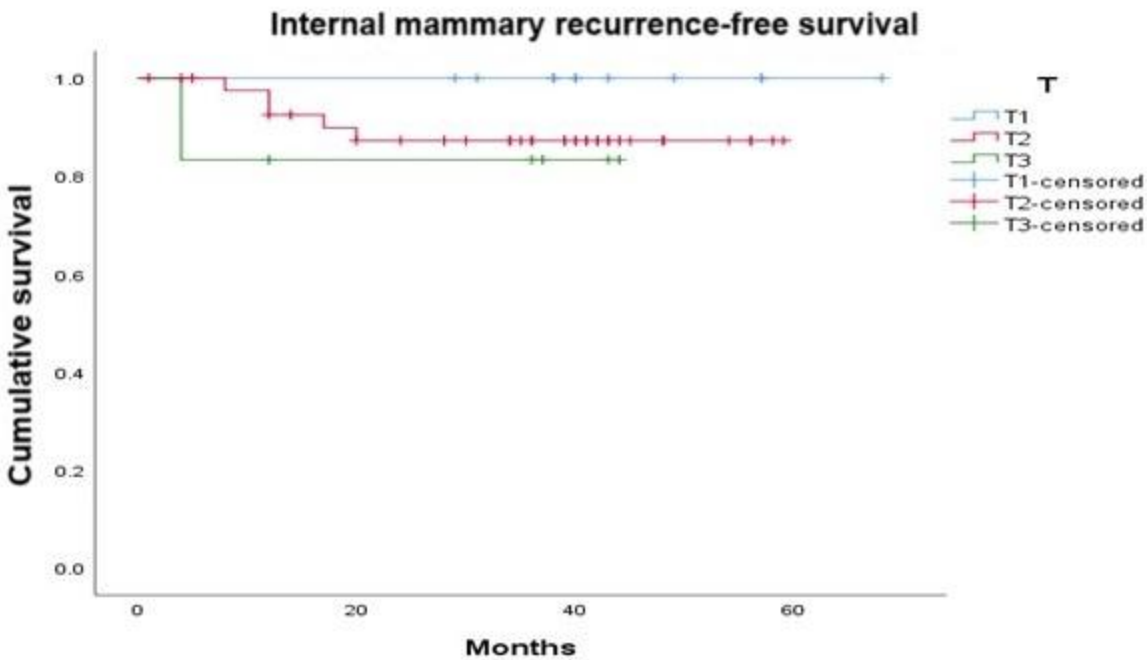

Figure 4. This figure shows the correlation between tumor size internal mammary node recurrence-free survival.
Censored: Lost follow-up

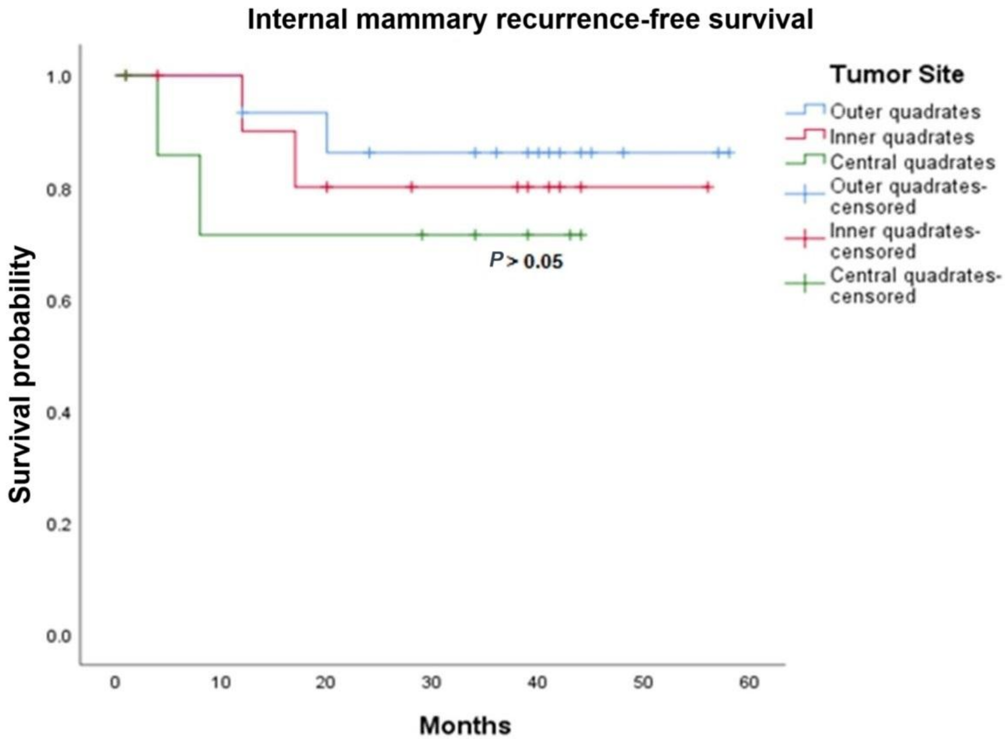

Figure 5. This figure shows the correlation between tumor site and internal mammary recurrence-free survival.

Censored: Lost follow-up