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ORIGINAL ARTICLE – BREAST ONCOLOGY

Internal Mammary Chain Sentinel Nodes in Early-Stage Breast Cancer Patients: Toward Selective Removal

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ABSTRACT

Background. Removal of internal mammary chain sentinel nodes (IMCSNs) affects prognosis and treatment of breast cancer, and internal mammary chain radiotherapy (IMCRT) can improve survival for selected patients. This study aimed to determine the effect of IMCSN biopsy on recurrence-free survival (RFS) and overall survival (OS) and to identify predictive factors for IMCSN and distant metastasis.

Methods. Patients with IMCSNs were selected from a prospective database for the period 1999–2007. Lymphoscintigraphy was performed after intratumoral technetium-99 m injection, and all sentinel nodes were removed. Both RFS and OS were calculated for subgroups with tumor-positive, tumor-negative, or non-removed IMCSNs. Predictive factors were identified for tumor-positive IMCSNs and distant metastasis by regression analysis.

Results. For 287 (85%) of 336 patients, IMCSN biopsy was performed, and metastasis was detected in 38 patients (13%). The patients with tumor-positive IMCSNs had poorer OS than the patients with no IMCSN metastasis or non-removed IMCSNs ($p = 0.002$). These patients also had worse RFS due to distant metastasis ($p = 0.002$). Axillary metastasis was predictive for tumor-positive IMCSNs (positive predictive value, 38.5%). The predictive factors for distant metastasis were tumor-positive IMCSNs (hazard ratio [HR], 2.5), non-removed IMCSNs (HR, 2.3), tumor diameter greater than 1.5 cm (HR, 3.5), and age older than 65 years (HR, 3.1; reference, < 50 years).

Conclusions. Patients with IMCSNs have worse survival due to distant metastasis. The clinically relevant predictive factor for distant metastasis is tumor larger than 1.5 cm. According to the authors' current protocol, IMCSN biopsy is performed for patients younger than 70 years who have a tumor larger than 1.5 cm, with the cardiotoxicity of the adjuvant IMCRT weighed against the survival benefit.

The internal mammary chain (IMC) is the most significant lymphatic drainage site of the breast outside the axilla, and internal mammary chain sentinel nodes (IMCSNs) are identified in about one of five patients after peritumoral injection of the tracer.[1–7] This number increases for patients with previous surgery of the breast or a medially located tumor.[1,8,9]

Multiple studies have demonstrated that biopsy of the IMCSN affects disease stage, prognosis, and treatment strategy.[10–15] Patients with IMCSN metastasis have poorer

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survival than those without it, and patients with both axillary and IMC metastasis have worse survival than patients with axillary or IMC metastasis alone.[14,15]

Surgical removal of IMCSNs, however, is not often pursued because it can be technically demanding and time-consuming, may require an additional skin incision, and can lead to complications such as pneumothorax or bleeding.[2–6,11–14]

Recent studies indicate that radiotherapy of the IMC (IMCRT) for patients with a high likelihood of IMC lymphatic drainage is associated with improved recurrence-free survival (RFS), distant metastasis-free survival, and overall survival (OS).[16–20] However, IMCRT also is associated with morbidity such as pulmonary fibrosis, pneumonitis, and most important, an increased risk of heart disease, especially in left-sided breast cancer, but also in right sided breast cancer.[21–27] The breathhold technique is used increasingly for left-sided breast cancer, but with most radiation techniques, this cannot be applied with irradiation of the IMC.

This study aimed to determine the effect of IMCSN biopsy on the prognosis for patients with IMC drainage shown on preoperative lymphoscintigraphy and to identify predictive factors for IMCSN and other metastases. In addition, the study aimed to select the patients who might benefit from removal of the IMCSN, and if negative, might be spared IMCRT.

METHODS

We conducted a single-institution analysis of all breast cancer patients with sentinel node (SN) procedure included in a prospectively maintained database from the Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital from January 1999 to December 2006. The study protocol was approved by the institutional review committee and met the guidelines of the responsible governmental agency. Part of this study population was included in a study by Madsen et al.[14]

Tumor size was assessed with mammography, ultrasound, and contrast-enhanced magnetic resonance imaging (MRI) if required. Nodal status was determined preoperatively by ultrasound-guided fine-needle biopsy of abnormal lymph nodes in the axilla. Periclavicular and IMCSNs were assessed by indication. All patients with IMC lymphatic drainage were eligible for this study.

On the day before breast surgery, technetium-99 m-nanocolloid (Nanocoll; GE-Healthcare, Eindhoven, the Netherlands) was injected in or near the tumor based on palpation if the tumor was palpable or under ultrasound or stereotactic mammographic guidance when the tumor was non-palpable, with a mean volume of 0.2 mL and a mean radioactivity dose of 100–120 MBq. Conventional lymphoscintigraphy was performed after 20–30 min, after 2 h, and after 4 h. A dual-head gamma camera equipped with low-energy high-resolution collimators (Vertex; Philips, Eindhoven, The Netherlands) was used. Both anterior and lateral images were routinely obtained, with additional images obtained if needed.

Surgical procedure was performed the day after 1 mL of patent blue dye (Blue Patente V, Laboratoire Guerbet, Aulnay-sous-Bois, France) was administered intratumorally. Sentinel nodes were located using a gammaprobe (Neoprobe; Johnson & Johnson Medical B.V., Hamburg, Germany) in all regions indicated by lymphoscintigraphy and subsequently removed. Suspicious non-radioactive nodes were routinely removed in the axilla as well.

The study explored IMCSNs through a transverse incision over the intercostal space concerned, and radioactive lymph nodes were dissected. It is our policy to perform a basal axillary lymph node dissection if no SN is identified. Sentinel nodes were formalin-fixated, bisected, paraffin-embedded, and cut at a minimum of six levels at 50–100-μg intervals. The paraffin sections were stained with hematoxylin–eosin and immunohistochemistry (CAM5.2; Becton–Dickinson, San Jose, CA, USA). The tumors were classified according to the WHO classification based on pathologic evaluation and hormonal status to define the need for adjuvant therapy.

Postoperative Treatment

Breast-conserving treatment consisted of a lumpectomy followed by whole-breast irradiation (50 Gy/25 fractions or equivalent dose ± a boost to the original tumor bed). We administered IMCRT for patients who had positive internal mammary chain sentinel nodes and for patients who had axillary metastases and IMC lymphatic drainage without histopathologic confirmation.

The doses for IMC irradiation generally consisted of 50 Gy. During the study period, our department used conventional simulation with gradual introduction of three-dimensional (3D) computed tomography (CT). The technique most applied for the IMC consisted of an anterior electron field (2/3 of the fractions) in combination with photons (1/3 of the fractions) to lower the dose to the heart. The depth of the internal mammary nodes was measured by ultrasound and in later years on the planning CT scan to determine the energy of the electrons. Adjuvant systemic treatment decisions were made according to the Dutch national guidelines.[28]

Data Analysis

Data analysis was performed using IBM SPSS Statistics 24.0 (Armonk, NY). Groups for comparison were defined as tumor-positive, tumor-negative, or unknown (i.e., non-removal of the IMCSN). Differences in RFS and OS were calculated using the Kaplan–Meier method with log-rank analysis. Prognostic factors for a tumor-positive IMCSN were calculated using logistic regression. Prognostic factors for RFS were assessed using Cox regression analysis. Significance was defined as a p value lower than 0.05.

RESULTS

IMC Lymphatic Drainage and Removal

The database included 1639 breast cancer patients with SN biopsy, 339 (21%) of whom had IMC drainage shown on lymphoscintigraphy. Three patients were lost to follow-up evaluation. The remaining 336 patients were analyzed.

The median follow-up period was 9.5 years (interquartile range [IQR], 5.9–11.0 years). Biopsy of the IMCSN was successful for 287 patients (85%). For 49 patients (15%), biopsy of the IMCSN could not be performed due to surgical technical reasons or to a lack of radioactive counts measured by the gammaprobe intraoperatively. The baseline patient characteristics were similar between the patients with and those without biopsy of the IMCSN (Table 1).

Pathology analysis showed IMCSN metastases in 38 (13%) of the 287 patients with an IMCSN biopsy. Overall, 51 patients were treated with IMCRT (15%), including all patients with IMCSN metastases. Adjuvant systemic treatment did not differ between the groups (Table 1).

Overall and Breast Cancer Survival

After 10 years, 52 (15%) of the 336 patients with IMC drainage had died. Of these 52 patients, 32 (9.5%) died of breast cancer and 20 (6%) died of other causes.

The 10-year OS rate for the patients with biopsy of IMCSNs was 86% (95% confidence interval [CI], 81–91%) compared with 73% (95% CI, 60–87%) for the patients with non-removed IMCSNs ($p = 0.024$). The respective breast cancer-specific survival rates were 91% (95% CI, 88–95%) and 76% (95% CI, 63–89%) ($p = 0.008$).

The patients with a tumor-positive IMCSN and those without IMCSN biopsy had significantly worse OS and breast cancer-specific survival rates than the patients with a tumor-negative IMCSN. The 10-year OS was 57% (95% CI, 38–76%) for the patients with a tumor-positive IMCSN, 59% (95% CI, 37–80%) for the patients without biopsy of the IMCSN, and 82% (95% CI, 74–89%) for the patients with a tumor-negative IMCSN ($p = 0.002$). The breast cancer-specific survival rate was 78% (95% CI, 65–92%) for the patients with a tumor-positive IMCSN, 76% (95% CI, 63–89%) for the patients without biopsy of the IMCSN, and 94% (95% CI, 90–97%) for the patients with a tumor-negative IMCSN ($p = 0.001$).

Recurrence-Free Survival

In 78 (23%) of the 336 patients with IMC drainage, recurrent disease was detected during the follow-up evaluation. Local recurrence in the ipsilateral breast was detected in 32 patients (9.5%), and regional recurrence was seen in 26 patients (7.7%), 3 (0.9%) of whom had recurrence in the IMC nodes. Of the three patients with IMC recurrence, two had no removal of IMCSNs and one had undergone IMCSN biopsy. All the IMC recurrences were clinically evident disease presenting with pain and swelling in the IMC region, confirmed on CT imaging. Distant metastases developed in 42 patients (12.5%).

The overall 10-year RFS was 78% (95% CI, 73–83%). For the 287 patients with IMCSN biopsy, the 10-year RFS was 82% (95% CI, 76–87%) compared with 61% (95% CI, 45–77%) for the 49 patients without biopsy of the IMCSNs ($p = 0.004$). The distant metastasis-free survival rate was higher for the patients with IMCSN biopsy (89%; 95% CI, 84–93% vs 76%; 95% CI, 62–89%; $p = 0.017$). The local and regional RFS rates did not differ between these groups.

Analysis based on IMCSN biopsy results showed better overall and distant metastasis-free survival rates for the patients with a tumor-negative IMCSN than for the patients with a tumor-positive IMCSN or non-removed IMCSNs (Table 2, Fig. 1). Recurrence-free survival did not differ between the patients with a tumor-positive IMCSN and the patients without an IMCSN biopsy.

Prognostic Factors for Tumor-Positive IMCSN

In the univariable analysis, positive axillary status and positive estrogen receptor expression were associated with a higher probability of a tumor-positive IMCSN (Table 3). In the multivariable analysis, only axillary metastasis remained a significant prognostic factor (odds ratio [OR], 6.69; 95% CI, 3.16–14.14; $p < 0.001$). Axillary metastases were present in 52 (18%) of the 287 patients with IMCSN biopsy. The positive predictive value (PPV) of axillary metastasis for a tumor-positive IMCSN was 38.5%, and the negative predictive value (NPV) was 92.3% (Fig. S1).

Prognostic Factors for Other Metastases

Neither local nor regional disease recurrence differed between any of the groups. We therefore did not explore

TABLE 1 Baseline characteristics of patients with internal mammary chain lymphatic drainage

	Total (n = 336)		IMCSN removed (n = 287)		IMCSN not removed (n = 49)		p value[a]
Age (years)	55	(%)	54	(%)	58	(%)	
< 50	115	34	102	36	13	27	0.22
50–65	150	45	130	45	20	41	0.09
> 65	71	21	54	19	16	33	0.46
Mean tumor diameter (cm)	1.63		1.61		1.77		0.26
Palpable	195	58	166	58	29	60	0.88
Breast-conserving surgery	248	74	207	72	41	84	0.09
Tumor location							0.63
Lateral upper	100	30	87	30	13	27	
Medial upper	104	31	86	30	18	37	
Lateral lower	43	13	38	13	5	10	
Medial lower	48	14	43	15	5	10	
Central	41	12	33	11	8	16	
Tumor-positive IMCSN	38	11	38	13	–		–
Tumor-positive axillary nodes	61	18	52	18	9	18	0.97
ER-positive	265	79	225	78	40	82	0.61
HER2neu-positive	40	12	34	12	6	12	0.94
Adjuvant therapy	297	88	253	88	44	90	0.74
Chemotherapy	103	31	87	30	14	29	0.89[b]
Hormonal therapy	122	36	101	35	21	43	0.43[b]
Radiotherapy	262	78	220	77	42	86	0.16

IMCSN internal mammary chain sentinel node, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2

[a]p value was calculated with an independent t test for the mean tumor diameter, and with Pearson's Chi square test for the other variables. If the expected cell count less than 5 was greater than 20%, Fisher's exact test was used

[b]Fisher's exact test

TABLE 2 Recurrence-free survival

Recurrence-free survival	Total (SE) (n = 336) % (n)	IMCSN-negative (n = 249) % (SE)	IMCSN-positive (n = 38) % (SE)	Log-rank (− vs. +) p value	IMCSN not removed (n = 49) % (SE)	Log-rank (− vs. not removed) p value	Log-rank (− vs. + vs. not removed) p value
Overall							
5-year	89.3 (1.7)	91.5 (1.8)	78.9 (6.6)		87.5 (4.8)		
10-year	78.1 (2.6)	84.0 (2.8)	67.8 (7.7)	0.018	61.1 (8.0)	0.001	0.002
Local							
5-year	96.7 (1.0)	96.9 (1.2)	91.9 (4.5)		100 (2.5)		
10-year	91.0 (2.0)	93.0 (2.1)	85.5 (6.0)	0.134	85.3 (7.3)	0.207	0.245
Regional							
5-year	96.2 (1.1)	96.5 (1.2)	94.6 (3.7)		95.7 (2.9)		
10-year	90.7 (2.0)	92.6 (2.1	91.4 (4.8)	0.612	80.8 (6.7)	0.034	0.107
Distant							
5-year	93.9 (1.4)	96.1 (1.3)	83.7 (6.1)		91.4 (4.1)		
10-year	86.7 (2.2)	91.0 (2.3)	77.3 (7.1)	0.010	75.5 (6.9)	0.004	0.004

Recurrence-free survival table was calculated with the Kaplan–Meier method. Follow-up evaluation was maximized at 10.5 years

IMCSN internal mammary chain sentinel node, *SE* standard error

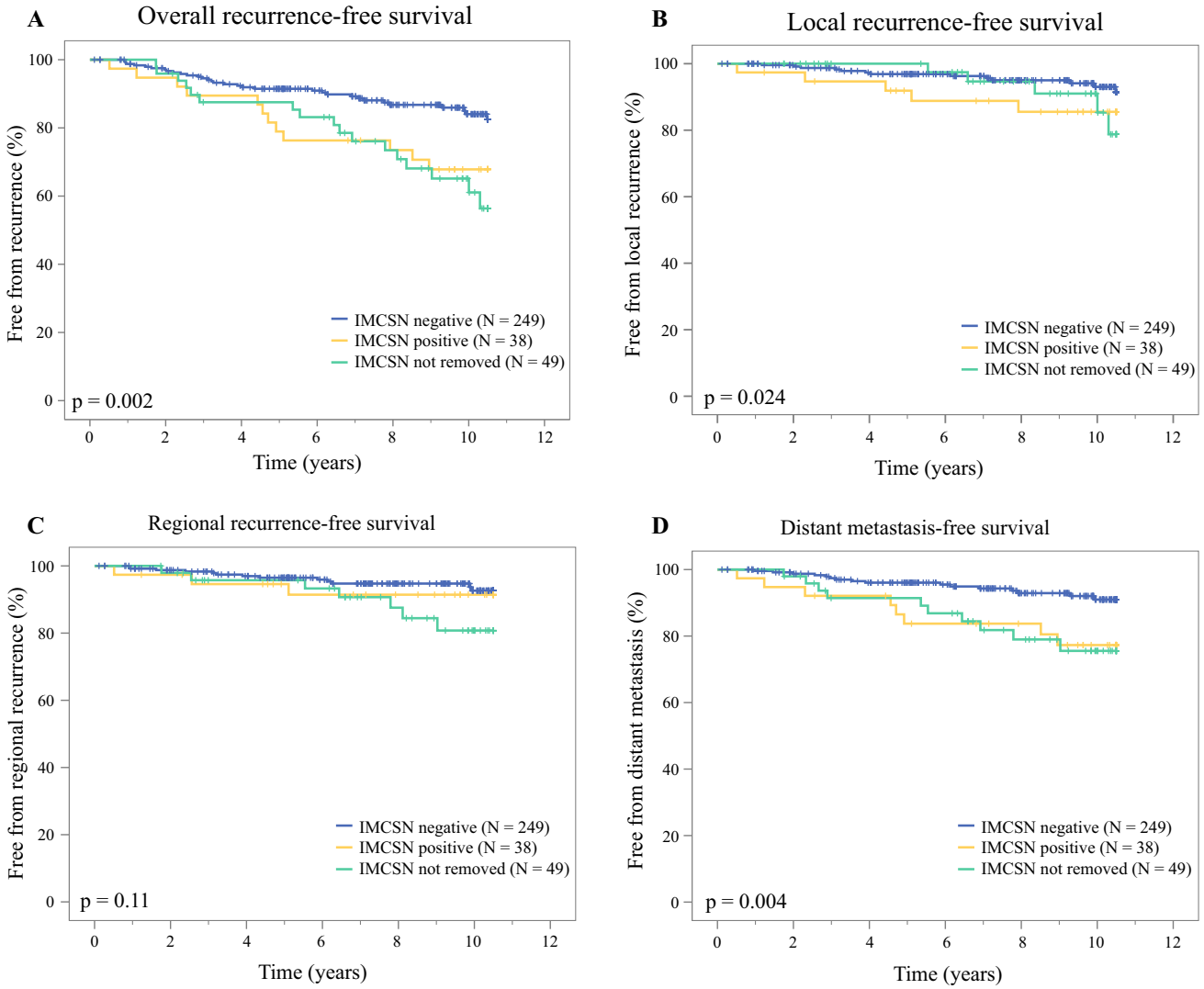

FIG. 1 Kaplan–Meier curves for **a** overall recurrence-free survival, **b** local recurrence-free survival, **c** regional recurrence-free survival, and **d** distant metastasis-free survival according to internal mammary chain sentinel node status. Follow-up evaluation was maximized at 10.5 years. *IMCSN* internal mammary chain sentinel node

prognostic factors for locoregional relapse. Prognostic factors for distant metastasis in the patients with IMC drainage were explored. In the multivariable analysis, a tumor-positive IMCSN was a prognostic factor for distant metastasis (HR, 2.5; 95% CI, 1.0–5.8; $p = 0.04$), as was an unremoved IMCSN (HR, 2.3; 95% CI, 1.0–5.1; $p = 0.05$). In addition, tumor diameter greater than 1.5 cm versus tumor diameter smaller than 1.5 cm (HR, 3.5; 95% CI, 1.6–8.4; $p < 0.00$) and age older than 65 years versus age younger than 50 years (HR, 3.1; 95% CI, 1.2–7.7; $p = 0.02$) were identified as prognostic factors for distant metastasis (Table 4).

Change in Adjuvant Treatment Strategy

All 38 patients with tumor-positive IMCSNs were treated with adjuvant IMCRT. Of these 38 patients, 20 had concomitant axillary metastasis and thus would also have received IMCRT if IMCSN biopsy had not been performed. Of the patients with no axillary metastasis, 18 underwent IMCRT based on the results of IMCSN biopsy alone. In nine patients, axillary metastasis was found, but the IMCSN biopsy was unsuccessful. These nine patients underwent IMCRT. For 32 patients, IMCRT could be withheld due to a tumor-negative IMCSN biopsy in the presence of axillary metastasis. Altogether, 59 (18%) of the 336 patients had a change of radiotherapy (RT) regimen due to IMCSN biopsy. For seven patients, adjuvant

TABLE 3 Prognostic factors for a tumor-positive internal mammary chain sentinel node

Variable (n = 287)	Univariable		Multivariable		95% CI
	OR	p value	OR	p value	
Age (years) reference (< 50)					
50–65	0.95	0.89			
>65	0.92	0.86			
Medial/central versus lateral	1.07	0.85			
Diameter > 1.5 versus < 1.5 cm	1.68	0.15			
Diameter > 2 versus < 2 cm	1.15	0.72			
Positive versus negative axilla	7.54	< 0.001	6.69	< 0.001	3.16–14.14
ER+ versus ER−	3.62	0.04	2.35	0.18	0.67–8.26
PR+ versus PR−	1.82	0.12			
HER2neu+ versus HER2neu−	0.86	0.79			

Logistic regression analysis. Outcome: tumor-positive internal mammary chain sentinel node. Follow-up evaluation was maximized at 10.5 years

CI confidence interval, *OR* odds ratio, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

TABLE 4 Prognostic factors for distant metastasis

Variable (n = 336)	Univariable		Multivariable		95% CI
	HR	p value	HR	p value	
Reference (IMCSN-negative)		0.006		0.06	
IMCSN-positive	2.92	0.14	2.45	0.04	1.0–5.8
IMCSN not removed	3.01	0.005	2.27	0.05	1.0–5.1
Age (years) reference (< 50)		0.02		0.05	
50–65	1.36	0.49	1.61	0.29	0.7–3.9
> 65	3.17	0.01	3.07	0.02	1.2–7.7
Medial/central versus lateral	0.62	0.16			
Diameter > 1.5 versus < 1.5 cm	3.62	0.002	3.52	0.003	1.6–8.4
Positive versus negative axilla	1.32	0.48			
ER+ versus ER−	0.70	0.35			

Cox regression analysis. Outcome: distant metastasis. Follow-up evaluation was maximized at 10.5 years

CI confidence interval, *HR* hazard ratio, *IMCSN* internal mammary chain sentinel node, *ER* estrogen receptor, *PR* progesterone receptor

systemic therapy was added to the treatment because of a tumor-positive IMCSN (2%).

Complications

The overall complication rate for the IMC procedure in this study population was 3%. For 6 of the 287 patients with IMCSN biopsy, the surgical procedure was complicated by a minor pleural defect. Bleeding occurred in three patients. No invasive intervention was needed in these cases.

DISCUSSION

This study showed that biopsy of the IMCSN is successful for the majority of patients (86%) with IMC drainage shown on preoperative scintigraphy and has a low complication rate (Table S1). Patients with IMCSN metastasis have worse OS and breast cancer specific-survival than patients without IMCSN metastasis. Veronesi et al.[15] noted earlier that having both IMCSN and axillary metastasis is associated with worse survival than having solitary IMCSN or axillary metastasis alone. In the study of Madsen et al.,[14] the solitary presence of IMCSN metastasis influenced OS, but it was not a prognostic factor in the presence of axillary metastasis.

In our study, survival was significantly worse in the presence of IMCSN metastasis. Of the 287 patients with IMCSN biopsy, 18 had solitary IMCSN metastasis, and 20 had both IMC and axillary nodal involvement. In addition, we found that IMCSN biopsy for patients with IMC drainage is associated with better RFS than patients have without biopsy of the IMCSN. Survival was comparable between the patients with IMC metastasis and the patients without biopsy of the IMCSN.

We cannot fully explain the poor prognostic results in the group without removal of the IMCSN. We must add that the group of patients with non-removed IMCSNs was small and that the patients in this group likely had more risk factors for the development of distant metastasis than the other groups. The mean tumor diameter was greater in the patients without IMCSN removal, and the patients in this group were slightly older, which also was a predictive factor for distant metastasis. In addition, the removal of IMCSNs itself may have a beneficial effect on survival because it stops potential micro-metastasis from spreading.

Because removal of an IMCSN has side effects, it should be performed only if substantial benefit is expected. To our knowledge, no studies have identified prognostic factors for IMCSN metastasis, thus enabling a more tailored strategy for IMCSN removal. A prognostic factor for IMCSN metastasis in the multivariable analysis was axillary metastasis. However, the PPV of axillary metastasis for the presence of IMCSN metastasis is low (38%), so it is not a useful decision tool (Fig. S1).

In our study, the lower survival rate in the presence of IMCSN metastasis was attributable to the higher likelihood of the development of distant metastases, as shown in Fig. 1. Local and regional recurrence did not influence the difference in RFS between any of the groups.

Because distant metastasis has a major impairing influence on survival, we also focused on the prognostic factors for this in our study population. We identified four significant factors in the multivariable analysis. A tumor-positive IMCSN and failure of IMCSN biopsy both were related to distant metastasis. As discussed earlier, both factors also were associated with lower survival rates. The remaining two prognostic factors for distant metastasis were tumor diameter greater than 1.5 cm and age older than 65 years. We consider tumor diameter a clinically relevant and easily applicable selection tool for performing IMCSN biopsy because patients with IMC drainage and tumor larger than 1.5 cm have a 3.5-fold increased risk of distant metastasis. Patients with a tumor larger than 1.5 cm may therefore benefit from IMCRT in the presence IMCSN metastasis, and patients with a tumor-negative IMCSN can be spared unnecessary IMC irradiation. We believe that age older than 65 years is not useful as a selection tool because biopsy of the IMCSN mainly affects adjuvant RT indication (Table S1), and the beneficial effects of IMCRT occur only after 10 years of follow-up evaluation.[16,17] With the current life expectancy at approximately 80 years in the Netherlands, patients older than 70 years may not benefit from IMCRT.

The percentage of patients who will be undertreated using the cutoff points of tumor size greater than 1.5 cm and age younger than 70 years is low. With these selection criteria, 8 (3%) of the 296 patients younger than 70 years with solitary IMCSN metastases in our study would not have received IMCRT.

Recent studies investigating adjuvant IMCRT have concluded that irradiation of the IMC improves RFS.[16–18] The European Organisation for Research and Treatment of Cancer (EORTC) study by Poortmans et al.[16] found a small benefit for the IMCRT group in terms of distant metastasis-free survival (HR, 0.86; 95% CI, 0.76–0.98; $p = 0.02$) and breast cancer mortality (HR, 0.82; 95% CI, 0.70–0.97; $p = 0.02$) among the patients with a medially or centrally located tumor, but OS showed no difference after 10 years of follow-up evaluation.

The aforementioned results are similar to those in the study of Whelan et al.[17] (MA.20 trial; IMCRT as part of regional irradiation) that investigated node-positive or high-risk node-negative patients, although they found no statistically significant benefit of regional nodal irradiation in terms of breast cancer survival. Thorsen et al.[18] compared IMCRT in patients with right-sided breast cancer with no-IMCRT in patients who had left-sided breast cancer and found that IMCRT improved OS by 3.7% and decreased breast cancer mortality by 2.5% already after 8-years of follow-up evaluation. However, patients with left-sided breast cancer, who were most prone to adverse effects of IMCRT, did not receive IMCRT, and their study excluded patients unfit to receive IMCRT or older than 70 years. This exclusion may have led to an impressive effect of IMCRT in this study.

Patients treated with left-sided RT have an increased risk of coronary damage, heart disease, and pulmonary fibrosis, and patients older than 70 years have increased vulnerability for lung and cardiac toxicity.[21–27] However, with more contemporary techniques, radiation dose to organs at risk is reduced. Currently, most RT departments perform CT-based planning, with delineation of lymph node areas. Also, breathhold techniques are used increasingly. This, in combination with new techniques such as volumetric arc therapy (VMAT) may lead to fewer side effects in future studies.

Currently, no clear guidelines exist for administering IMCSN biopsy and IMCRT to patients with early-stage breast cancer who are clinically node-negative.[29,30] Our study is the largest single-institution analysis on this subject and provides a clinically relevant guideline for daily

practice. Although the relatively small number of patients was a limitation of this study, the long follow-up period was an advantage. Although molecular prognostication has considerably changed disease staging and indications for (neo)adjuvant systemic therapy in the last decade, the focus of our treatment strategy is on sparing patients the morbidity of IMC irradiation, not on selecting patients for systemic treatment. However, further research is needed to check whether IMCSN biopsy is of added value for patients with a tumor larger than 1.5 cm and low-risk molecular prognostication.

In this study, we showed that patients with IMCSNs and a breast tumor larger than 1.5 cm benefit from IMCSN biopsy. Patients with IMCSN metastasis have lower survival rates due to the development of distant metastases. The occurrence of distant metastasis is significantly higher among patients with a breast tumor larger than 1.5 cm. It is known that targeted IMCRT can improve survival for patients with IMC metastases. We aim to select those patients who benefit from IMCRT and those who can be spared the possible morbidity of radiation treatment. The cardiotoxicity of IMCRT should be weighed against the expected RFS benefit. Therefore, we recommend removing all IMCSNs, if technically possible, from patients younger than 70 years with a breast tumor larger than 1.5 cm.

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