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Low Risk of Development of a Regional Recurrence After an Unsuccessful Repeat Sentinel Lymph Node Biopsy in Patients with Ipsilateral Breast Tumor Recurrence

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ABSTRACT

Background. Unlike sentinel lymph node biopsy (SLNB) in the primary setting, the repeat SLNB (rSLNB) in patients with ipsilateral breast tumor recurrence (IBTR) is challenging, because it is difficult to visualize and/or harvest a sentinel lymph node in every patient. Regional treatments options and safety in terms of regional disease control after such an unsuccessful rSLNB remain unclear. This study assesses factors associated with the performance of axillary lymph node dissection (ALND) after unsuccessful rSLNB and evaluates the occurrence of regional recurrences.

Methods. Data were obtained from the Sentinel Node and Recurrent Breast Cancer (SNARB) study. In 239 patients, the rSLNB was unsuccessful, of whom 60 patients underwent ipsilateral ALND.

Results. A shorter time interval between primary treatment and IBTR, and a primary negative SLNB were significantly associated with a higher probability to be treated with ALND after unsuccessful rSLNB ($P < 0.001$). The 5-year regional-recurrence rate was 0.0% in the ALND group compared with 3.7% in the group treated without ALND ($P = 0.113$). Of the 179 patients treated without ALND, after a median follow-up of 5.1 years (range 0.3–13.2), 7 (3.9%) developed a regional recurrence as first event after unsuccessful rSLNB. None of the seven recurrences occurred in the ipsilateral axilla. Univariable analysis showed no factors associated with regional recurrence as first event after unsuccessful rSLNB ($P > 0.05$).

Conclusions. The present study demonstrates that the risk of regional recurrence in patients with an IBTR and an unsuccessful rSLNB is negligible, irrespective of the use of ALND. This suggests that there is no need for additional treatment of the axilla after an unsuccessful rSLNB.

In recent years, repeat sentinel lymph node biopsy (rSLNB) emerged as an axillary staging procedure in patients with ipsilateral breast tumor recurrence (IBTR). Unlike sentinel node biopsy in the primary setting, the procedure in patients with IBTR is challenging. Repeat sentinel node (rSN) identification is reported to vary between 53 and 93%, with a mean percentage of 63%.[1–3] For the remaining patients rSLNB was unsuccessful, which means that no sentinel lymph node could be visualized and/or harvested. Previous treatments of the breast and axilla with surgery and/or radiotherapy have been associated with a more difficult identification of rSLNB.[1] Scar tissue and post irradiation fibrosis may change the anatomy of breast and axillary lymphatics, whereby lymph vessels may be

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totally blocked or disrupted, increasing the risk of unsuccessful rSLNB procedures.[4,5] The optimal regional treatment options after an unsuccessful rSLNB are unclear, as its impact on regional disease control.

Previously, in a cohort of IBTR patients who were all successfully staged with a negative rSLNB, safety with respect to regional control was investigated. The 5-year risk of developing regional recurrences after a negative rSLNB without subsequent ALND was less than 5%, and only 1% was located in the ipsilateral axilla. These low regional relapse rates justified the recommendation to replace ipsilateral ALND by rSLNB in case of a clinically node-negative IBTR.[6] Going forward, Ugras et al.[7] investigated whether the promises of rLSNB, such as improved regional control and better survival, were fulfilled by comparing a group of IBTR patients who had axillary staging versus a group of patients who did not. No difference in tumor characteristics or treatment of IBTR were observed, and low rates of axillary failure occurred in both groups. Although their sample size was insufficient to exclude small differences particularly in nodal recurrences, they concluded that restaging of the axilla in patients with IBTR is of limited value and that further research in larger cohorts is needed.[7]

Hence, uncertainty exists on the need for and extent of regional treatments, necessary for patients with an unsuccessful rSLNB procedure. Some advocate to perform an ipsilateral ALND or recommend extensive radiotherapy to the closest lymph node basin. This study was designed to assess factors associated with the decision to perform an ALND after unsuccessful rSLNB and to evaluate the risk of regional recurrences as first event after an unsuccessful rSLNB in patients with IBTR, treated with curative intent.

METHODS

SNARB Study Design

The Sentinel Node and Recurrent Breast Cancer (SNARB) study is a multicenter national registration study in which 36 Dutch hospitals participated.[8,9] Patients with clinically apparent (clinical exam and axillary ultrasound) ipsilateral or contralateral axillary lymph node metastases and patients with distant metastases at the time of diagnosis of IBTR were excluded. A total of 536 patients with operable locally recurrent breast cancer were staged with rSLNB and included in the SNARB study.[8] The dual-mapping technique with both ^{99m}techneticum and blue dye was used for all rSLNB procedures. Technical specifications have been reported in detail earlier.[1]

Patients

A rSLNB was defined as unsuccessful when the sentinel node could not be surgically harvested. All patients with IBTR, breast or chest wall, and an unsuccessful rSLNB were considered eligible for inclusion.

Aims

First, to explore specific patient and tumor characteristics predictive for the performance of an ALND after unsuccessful rSLNB, a subgroup analysis was done comparing patients who underwent ALND after unsuccessful rSLNB compared with patients who did not undergo ALND. Second, in patients with unsuccessful rSLNB treated with an ALND, factors related to metastatic lymph nodes were evaluated. Third, the occurrence of regional recurrences as first event in patients with unsuccessful rSLNB was investigated between patients treated with and without ALND. Finally, in patients with unsuccessful rSLNB treated without ALND, factors related to regional recurrences as first event after IBTR were explored.

Follow-Up

In 2017, follow-up data of the 536 patients in the SNARB study were collected and entered into the database. General practitioners were actively contacted for additional follow-up information when hospital records showed no outpatient clinic visits for more than 1 year. Date of last follow-up was documented as last visit to the outpatient clinic, date of last visit to the general practitioner, or date of death in case the patient had deceased. Follow-up time was defined as the time between date of surgery for IBTR and date of last follow-up. Time to regional recurrence was defined as time between treatment of IBTR and date of diagnosis of regional recurrence as first event after IBTR. Twenty-one patients (4%) for whom follow-up data were not available due to emigration, lack of information, or withdrawal of informed consent were excluded; 515 patients (96%) remained available for analysis.

Definition of Regional Recurrence

The primary endpoint of this study was regional lymph node recurrence as first event after curative treatment of an IBTR. A regional recurrence (RR) was defined as any evidence of disease found in ipsilateral intramammary nodes, ipsi- and contralateral internal mammary nodes, ipsi- and contralateral axillary nodes, and ipsi- and contralateral infra- and supra-clavicular nodes[6,10–12] (see *Supporting Information*). Lymph node recurrences found

outside these nodal basins were defined as distant metastatic disease.

Regional recurrences diagnosed at the same time as or after the appearance of distant recurrences were not recorded, as distant metastatic disease is considered to be the most unfavorable site of relapse, according to a hierarchy of prognosis.[13] In case of synchronous LR and RR, the recurrence was registered as a RR.

Statistics

The following variables were compared between patients with ALND and without ALND following an unsuccessful rSLNB: age, tumor and axillary surgery, nodal classification, tumor stage, receptor status and adjuvant therapy of primary tumor and IBTR; time interval from primary surgery to IBTR; repeat SN tracer amount. Statistical significance was tested using Pearson Chi square test and Fisher exact test for categorical variables when appropriate. For continuous variables, Mann–Whitney *U* test or independent samples *t* test was used when appropriate. The multivariable model was fitted for all significant univariable factors. A two-sided *P* value < 0.05 was considered statistically significant. Survival analysis, using the Kaplan–Meier method, was performed to calculate the 5-year risk of regional recurrences after curative treatment for IBTR, either with or without ALND. Differences were analyzed using the log-rank test. Data analysis were performed using SPSS version 24 (SPSS Inc., Chicago, IL).

RESULTS

Of the included 515 patients, 239 (46%) had an unsuccessful rSLNB, of which 60 (25%) patients underwent ipsilateral ALND. The median age at time of IBTR was 65.0 years (range 29–93). After treatment of IBTR, 160 patients (66.9%) received adjuvant systemic treatment. Adjuvant endocrine therapy was administered in 140 patients (58.6%) and adjuvant chemotherapy in 55 (23.0%) patients.

Factors Related to the Performance of ALND in Patients with an Unsuccessful rSLNB

Table 1 presents patient, tumor, and treatment characteristics categorized by patients treated with an ALND and without an ALND after an unsuccessful rSLNB. In univariable analysis, time between primary treatment and diagnosis of IBTR was significantly shorter for patients treated with ALND compared with patients treated without ALND, with a median of 5.2 years versus 14.0 years, respectively ($P < 0.001$). Furthermore, patients treated with ALND were significantly more often staged with a primary negative sentinel lymph node ($P < 0.001$). No significant differences were observed between the groups regarding size, grade, or receptor status of the IBTR, nor in the adjuvant treatments following curative treatment of IBTR.

Factors Related to Metastatic Lymph Nodes in Patients with Unsuccessful rSLNB Treated with an ALND

In 52 (87%) of the 60 patients, ALND revealed no involved lymph nodes. In the other eight patients (13%), macrometastases were found in one or more lymph nodes. Univariable analysis showed no significant differences between the groups with or without positive lymph nodes regarding patient and tumor characteristics. Patients with positive lymph nodes were treated more often with radiotherapy compared to patients with negative lymph nodes: 50.0% versus 15.4%, respectively ($P = 0.043$). Adjuvant chemotherapy was administered to 50.0% of the patients with positive lymph nodes versus 21.2% to patients with negative lymph nodes ($P = 0.098$) (see *Supporting Information*, Table 2).

Regional Recurrences in Patients Treated with ALND and Patients Treated Without ALND After Unsuccessful rSLNB

With a median follow-up of 5.1 (range 0.3–13.2) years from IBTR, none of the patients treated with ALND after unsuccessful rSLNB experienced regional recurrence as first event after IBTR compared with seven patients (3.9%) in the group of patients treated with no ALND after unsuccessful rSLNB. The 5-year actuarial regional recurrence rate was 0.0% in the ALND group compared with 3.7% (95% confidence interval (CI) 0.6–7.4) in the group treated without ALND ($P = 0.113$). Furthermore, the 5-year disease free survival was 90.8% (95% confidence interval [CI] 85.9–95.7) in the ALND group compared with 91.1% (95% CI 83.7–98.5) in the group treated without ALND ($P = 0.980$).

Of the seven patients with regional recurrence, none experienced regional recurrence in the ipsilateral axilla, resulting in an ipsilateral axillary recurrence rate of 0.0%. Five patients experienced regional recurrences in the contralateral axilla: one patient in the contralateral infraclavicular basin, and in one patient regional recurrences were found in multiple basins (bilaterally supra- and infraclavicular) (Table 2). In one patient, the occurrence of the contralateral regional recurrence was in concordance with the site of rSLNB on lymphoscintigraphy. At time of IBTR, a contralateral ALND was not performed due to the

TABLE 1 Clinical-pathological characteristics of all patients with ipsilateral breast tumor recurrence and unsuccessful repeat sentinel lymph node biopsy ($N = 239$)

	Total group: ($N = 239$)	Additional lymph node dissection ($N = 60$)	No additional lymph node dissection ($N = 179$)	P value
Age primary tumor, median years (range)	52.0 (25–88)	56.0 (33–88)	51.0 (27–87)	0.005
Age primary tumor, years				0.002
< 35	18 (7.5%)	4 (6.7%)	14 (7.8%)	
35–59	155 (64.9%)	29 (48.3%)	126 (70.4%)	
60–69	54 (22.6%)	20 (33.3%)	34 (19.0%)	
≥ 70	12 (5.0%)	7 (11.7%)	5 (2.8%)	
Primary surgery				1.000
Mastectomy	12 (5.0%)	3 (5.0%)	9 (5.0%)	
Breast-conserving surgery	227 (95.0%)	57 (95.0%)	170 (95.0%)	
Primary SN				< 0.001
Negative	74 (31.0%)	50 (83.3%)	24 (13.4%)	
Positive	14 (5.9%)	3 (5.0%)	11 (6.1%)	
No SN	151 (63.2%)	7 (11.7%)	144 (80.4%)	
Primary axillary surgery				< 0.001
No axillary staging	6 (2.5%)	2 (3.3%)	4 (2.2%)	
SN-negative	72 (30.1%)	50 (83.3%)	22 (12.3%)	
SN-negative, cALND	2 (0.8%)	0 (0.0%)	2 (1.1%)	
SN-positive, cALND	12 (5.0%)	1 (1.7%)	11 (6.1%)	
SN-positive, no cALND	2 (0.8%)	2 (3.3%)	0 (0.0%)	
ALND	145 (60.7%)	5 (8.3%)	140 (78.2)	
Primary nodal status				0.001
Negative	172 (72.0%)	54 (90.0%)	118 (65.9%)	
Positive	51 (21.3%)	4 (6.7%)	47 (26.3%)	
Unknown	16 (6.7%)	2 (3.3%)	14 (7.8%)	
Primary tumor size (mm)				0.066
< 20	131 (54.8%)	39 (65.0%)	92 (51.4%)	
21–50	39 (16.3%)	6 (10.0%)	33 (18.4%)	
> 50	1 (0.4%)	1 (1.7%)	0 (0.0%)	
Unknown	68 (28.5%)	14 (23.3%)	54 (30.2%)	
Primary tumor grade				0.007
I	35 (14.6%)	14 (23.3%)	21 (11.7%)	
II	45 (18.8%)	17 (28.3%)	28 (15.6%)	
III	30 (12.6%)	6 (10.0%)	24 (13.4%)	
Unknown	129 (54.0%)	23 (38.3%)	106 (59.2%)	
Receptor status of primary tumor				0.004
Triple negative	16 (6.7%)	5 (8.3%)	11 (6.1%)	
HRneg_Her2pos	3 (1.3%)	0 (0.0%)	3 (1.7%)	
Hrpos_Her2pos	5 (2.1%)	1 (1.7%)	4 (2.2%)	
HRpos_Her2neg	45 (18.8%)	21 (35.0%)	24 (13.4%)	
Unknown	170 (71.1%)	33 (55.0%)	137 (76.5%)	
Hormone status primary tumor				0.002
ER and PR negative	26 (10.9%)	8 (13.3%)	18 (10.1%)	
ER/PR positive	110 (46.0%)	38 (63.3%)	72 (40.2%)	
Unknown	103 (43.1%)	14 (23.3%)	89 (49.7%)	

TABLE 1 continued

	Total group: (N = 239)	Additional lymph node dissection (N = 60)	No additional lymph node dissection (N = 179)	P value
Time from primary surgery to IBTR diagnose				
Median, months (range)	146 (5–360)	62.0 (8–330)	167 (5–360)	< 0.001
Median, years (range)	12.2 (0.42–30.0)	6.0 (0.7–27.5)	14.0 (0.42–30.0)	< 0.001
< 2	14 (5.9%)	5 (8.3%)	9 (5.0%)	< 0.001
2.1–5	37 (15.5%)	21 (35.0%)	26 (8.9%)	
5.1–10	44 (18.4%)	21 (35.0%)	23 (73.2%)	
> 10	144 (60.3%)	13 (21.7%)	131 (73.2%)	
Preoperative staging imaging modalities				0.289
None	85 (35.6%)	17 (28.3%)	68 (38.0%)	
Conventional imaging	115 (48.1%)	34 (56.7%)	81 (45.3%)	
^{18}F-FDG PET-CT	39 (16.3%)	9 (15.0%)	30 (16.8%)	
Age IBTR, median years (range)	65.0 (29–93)	64.5 (36–93)	66.0 (29–92)	0.257
Age IBTR, years				0.991
< 35	4 (1.7%)	1 (1.7%)	3 (1.7%)	
35–59	72 (30.1%)	19 (31.7%)	53 (29.6%)	
60–69	80 (33.5%)	20 (33.3%)	60 (33.5%)	
≥ 70	83 (34.7%)	20 (33.3%)	63 (35.2%)	
Location IBTR				1.000
Breast	227 (95.0%)	57 (95.0%)	170 (95%)	
Mastectomy scar or chest wall	12 (5.0%)	3 (5.0%)	9 (5.0%)	
Repeat SN aberrant LM				0.062
Yes	39 (16.3%)	4 (6.7%)	35 (19.6%)	
No	23 (9.6%)	7 (11.7%)	16 (8.9%)	
No successful LM	177 (74.1%)	49 (81.7%)	128 (71.5%)	
Repeat SN tracer amount, MBq median (range)	100.0 (19–219)	100.5 (20–177)	100 (19–219)	0.656
Tumor size IBTR (mm)				0.464
< 20	163 (68.2%)	41 (68.3%)	122 (68.2%)	
21–50	59 (24.7%)	17 (28.3%)	42 (23.5%)	
> 50	5 (2.1%)	0 (0.0%)	5 (2.8%)	
Unknown	12 (5.0%)	2 (3.3%)	10 (5.6%)	
Tumor grade IBTR				0.320
I	52 (21.8%)	9 (15.0%)	43 (24.0%)	
II	107 (44.8%)	26 (43.3%)	81 (45.3%)	
III	69 (28.9%)	21 (35.0%)	48 (26.8%)	
Unknown	11 (4.6%)	4 (6.7%)	7 (3.9%)	
Receptor status IBTR				0.904
Triple negative	36 (15.1%)	9 (15.0%)	27 (15.1%)	
HRneg_Her2pos	9 (3.8%)	3 (5.0%)	6 (3.4%)	
Hrpos_Her2pos	15 (6.3%)	4 (6.7%)	11 (6.1%)	
HRpos_Her2neg	161 (67.4%)	41 (68.3%)	120 (67.0%)	
Unknown	18 (7.5%)	3 (5.0%)	15 (8.4%)	
Radiotherapy IBTR				0.553
Yes	41 (17.2%)	12 (20.0%)	29 (16.2%)	
No	198 (82.8%)	48 (80.0%)	150 (83.8%)	

TABLE 1 continued

	Total group: (N = 239)	Additional lymph node dissection (N = 60)	No additional lymph node dissection (N = 179)	P value
Systemic therapy IBTR				0.875
Yes	160 (66.9%)	19 (31.7%)	60 (33.5%)	
No	79 (33.1%)	41 (68.3%)	119 (66.5%)	
Endocrine therapy IBTR				0.547
Yes	140 (58.6%)	33 (55.0%)	107 (59.8%)	
No	99 (41.4%)	27 (45.0%)	72 (40.2%)	
Chemotherapy IBTR				0.724
Yes	55 (23.0%)	15 (25.0%)	40 (22.3%)	
No	184 (770%)	45 (75.0%)	139 (77.7%)	

Univariable analysis compared patients with ipsilateral axillary lymph node dissection (N = 60) and patients with no axillary lymph node dissection (N = 179)

IBTR ipsilateral breast tumor recurrence, *ALND* axillary lymph node dissection, *cALND* completion axillary lymph node dissection, *SN* sentinel node, *mm* millimeter, *HR* hormone receptor, *ER* estrogen, *PR* progesterone, *MBq* mega becquerel, *Her2* human epidermal growth receptor 2, *neg* negative, *pos* positive

TABLE 2 Regional recurrences after an unsuccessful repeat sentinel lymph node biopsy, without additional lymph node dissection

Regional recurrence	Follow-up IBTR (months)	rSN location LM	DFI 1st–2nd tumor (months)	Primary axillary staging	Primary adjuvant (RT, CT, HT)	IBTR adjuvant (CT, RT, HT)
Contralateral axilla	15	No LM	6	SN +, cALND	RT, HT	HT
Contralateral axilla	61	Contralateral axilla	19	ALND	RT	HT
Contralateral axilla	26	No LM	13	ALND	RT	None
Contralateral axilla	32	No LM	24	ALND	RT (unknown region), unknown CT, HT	HT
Contralateral axilla	17	No LM	18	ALND	RT	HT
Contralateral infraclavicular	25	No LM	14	No staging	RT (ipsilateral axillar)	None
Contralateral, ipsilateral infra/supraclavicular	25	No LM	19	ALND	RT, HT	CT

DFI disease free interval, *IBTR* ipsilateral breast tumor recurrence, *rSN* repeat sentinel node, *LM* lymphoscintigram, *RT* radiotherapy, *CT* chemotherapy, *HT* hormone therapy, *SN+* sentinel node positive, *cALND* completion axillary lymph node dissection, *ALND* axillary lymph node dissection, *SN-* sentinel node negative, *n.a.* not available

age of the patient and more than two comorbidities. In the other six patients, no lymph nodes were visualized during lymphoscintigraphy.

Four of the seven regional recurrence patients presented with a symptomatic RR (i.e., patients visited the outpatient clinic with lymph node swelling or other localized complaints in an interval between planned follow-up moments or after follow-up was already terminated). The other three recurrences were detected during routine follow-up; one patient during scheduled echography, one patient during scheduled breast magnetic resonance imaging, and one patient during scheduled positron emission tomography scan.

All seven patients with a regional recurrence received adjuvant radiotherapy during the treatment of their primary breast cancer (5 to the breast only, 1 to the ipsilateral axilla, and for 1 patient the extension of adjuvant radiotherapy was unknown), and none of them received re-irradiation after IBTR. The patient treated with adjuvant radiotherapy to the ipsilateral axilla had a regional recurrence in the contralateral axilla (Table 2). See supporting information for detailed information regarding radiotherapy for patients with no regional recurrences.

TABLE 3 Clinical-pathological characteristics of all patients with ipsilateral breast tumor recurrence and unsuccessful repeat sentinel lymph node biopsy, without additional lymph node dissection ($N = 179$)

	Total group: ($N = 179$)	Regional recurrence ($N = 7$)	No regional recurrence ($N = 172$)	P value
Age primary tumor, median years (range)	51.0 (27–87)	54.0 (37–67)	51.0 (27–87)	0.598
Age primary tumor, years				0.777
< 35	14 (7.8%)	0 (0.0%)	14 (8.1%)	
35–59	126 (70.4%)	6 (85.7%)	120 (69.8%)	
60–69	34 (19.0%)	1 (14.3%)	33 (19.2%)	
≥ 70	5 (2.8%)	0 (0.0%)	5 (2.9%)	
Primary surgery				1.000
Mastectomy	9 (5.0%)	0 (0.0%)	9 (5.2%)	
Breast-conserving surgery	170 (95.0%)	7 (100.0%)	163 (94.8%)	
Primary SN				0.409
Negative	24 (13.4%)	0 (0.0%)	24 (14.0%)	
Positive	11 (6.1%)	1 (14.3%)	10 (5.8%)	
No SN	144 (80.4%)	6 (85.7%)	138 (80.2%)	
Primary axillary surgery				0.162
No axillary staging	4 (2.2%)	1 (14.3%)	3 (1.7%)	
SN-negative	22 (12.3%)	0 (0.0%)	22 (12.8%)	
SN-negative, cALND	2 (1.1%)	0 (0.0%)	2 (1.2%)	
SN-positive, cALND	11 (6.1%)	1 (14.3%)	10 (5.8%)	
SN-positive, no cALND	0 (0.0%)	0 (0.0%)	0 (0.0%)	
ALND	140 (78.2)	5 (71.4%)	135 (78.5%)	
Primary nodal status				0.106
Negative	118 (65.9%)	4 (57.1%)	114 (66.3%)	
Positive	47 (26.3%)	1 (14.3%)	46 (26.7%)	
Unknown	14 (7.8%)	2 (28.6%)	12 (7.0%)	
Primary tumor size (mm)				0.941
< 20	92 (51.4%)	4 (57.1%)	80 (51.2%)	
21–50	33 (18.4%)	1 (14.3%)	32 (18.6%)	
> 50	0 (0.0%)	–	–	
Unknown	54 (30.2%)	2 (28.6%)	52 (30.2%)	
Primary tumor grade				0.425
I	21 (11.7%)	0 (0.0%)	21 (12.2%)	
II	28 (15.6%)	2 (28.6%)	26 (15.1%)	
III	24 (13.4%)	0 (0.0%)	24 (14.0%)	
Unknown	106 (59.2%)	5 (71.4%)	101 ()58.7%	
Receptor status of primary tumor				0.894
Triple negative	11 (6.1%)	1 (14.3%)	10 (5.8%)	
HRneg_Her2pos	3 (1.7%)	0 (0.0%)	3 (1.7%)	
Hrpos_Her2pos	4 (2.2%)	0 (0.0%)	4 (2.3%)	
HRpos_Her2neg	24 (13.4%)	1 (14.3%)	23 (13.4%)	
Unknown	137 (76.5%)	5 (71.4%)	132 (76.7%)	
Hormone status primary tumor				0.361
ER and PR negative	18 (10.1%)	1 (14.3%)	17 (9,9%)	
ER/PR positive	72 (40.2%)	1 (14.3%)	71 (41.3%)	
Unknown	89 (49.7%)	5 (71.4%)	84 (48.8%)	

TABLE 3 continued

	Total group: (N = 179)	Regional recurrence (N = 7)	No regional recurrence (N = 172)	P value
Time from primary surgery to IBTR diagnose				
Median, months (range)	167 (5–360)	165 (68–284)	170 (5–360)	0.376
Median years (range)	14.0 (0.42–30.0)	13.8 (5.7–23.8)	14.2 (0.42–30.0)	0.374
< 2	9 (5.0%)	0 (0.0%)	9 (5.2%)	0.754
2.1–5	26 (8.9%)	0 (0.0%)	16 (9.3%)	
5.1–10	23 (73.2%)	1 (14.3%)	22 (12.8%)	
> 10	131 (73.2%)	6 (85.7%)	125 (72.7%)	
Age IBTR, median years (range)	66.0 (29–92)	68.1 (60–75)	66.0 (29–92)	0.209
Age IBTR, years				0.325
< 35	3 (1.7%)	0 (0.0)	3 (1.7%)	
35–59	53 (29.6%)	0 (0.0%)	53 (30.8%)	
60–69	60 (33.5%)	3 (42.9%)	57 (33.1%)	
≥ 70	63 (35.2%)	4 (57.1%)	59 (34.3%)	
Location IBTR				1.000
Breast	170 (95%)	7 (100.0%)	163 (94.8%)	
Mastectomy scar or chest wall	9 (5.0%)	0 (0.0%)	9 (5.2%)	
Repeat SN aberrant LM				0.619
Yes	35 (19.6%)	1 (14.3%)	34 (19.8%)	
No	16 (8.9%)	0 (0.0%)	16 (9.3%)	
No successful LM	128 (71.5%)	6 (85.7%)	122 (70.9%)	
Repeat SN tracer amount, MBq median (range)	100 (19–219)	100.0 (21–198)	100.0 (19–219)	0.827
Tumor size IBTR (mm)				0.255
< 20	122 (68.2%)	4 (57.1)	118 (68.6%)	
21–50	42 (23.5%)	2 (28.6%)	40 (23.3%)	
> 50	5 (2.8%)	1 (14.3%)	4 (2.3%)	
Unknown	10 (5.6%)	0 (0.0%)	10 (5.8%)	
Tumor grade IBTR				0.734
I	43 (24.0%)	1 (14.3%)	42 (24.4%)	
II	81 (45.3%)	3 (42.9%)	78 (45.3%)	
III	48 (26.8%)	3 (42.9%)	45 ()26.2%	
Unknown	7 (3.9%)	0 (0.0%)	7 (4.1%)	
Receptor status IBTR				0.794
Triple negative	27 (15.1%)	1 (14.3%)	26 (15.1%)	
HRneg_Her2pos	6 (3.4%)	0 (0.0%)	6 (3.5%)	
Hrpos_Her2pos	11 (6.1%)	0 (0.0%)	11 (6.4%)	
HRpos_Her2neg	120 (67.0%)	6 (85.7%)	114 (66.3%)	
Unknown	15 (8.4%)	0 (0.0%)	15 (8.7%)	
Radiotherapy IBTR				0.600
Yes	29 (16.2%)	0 (0%)	29 (16.9%)	
No	150 (83.8%)	7 (100.0%)	143 (83.1%)	
Systemic therapy IBTR				1.000
Yes	119 (66.5%)	5 (71.4%)	114 (66.3%)	
No	60 (33.5%)	2 28.6%)	58 (33.7%)	

TABLE 3 continued

	Total group: (N = 179)	Regional recurrence (N = 7)	No regional recurrence (N = 172)	P value
Endocrine therapy IBTR				1.000
Yes	107 (59.8%)	4 (57.1%)	103 (59.9%)	
No	72 (40.2%)	3 (42.9%)	69 (40.1%)	
Chemotherapy IBTR				1.000
Yes	40 (22.3%)	1 (14.3%)	39 (22.7%)	
No	139 (77.7%)	6 (85.7%)	133 (77.3%)	

Univariable analysis compared patients with regional recurrences (N = 7) and patients without regional recurrences (N = 172)

IBTR ipsilateral breast tumor recurrence, *ALND* axillary lymph node dissection, *cALND* completion axillary lymph node dissection, *SN* sentinel node, *mm* millimeter, *HR* hormone receptor, *ER* estrogen; *PR* progesterone, *MBq* mega becquerel, *Her2* human epidermal growth receptor 2, *neg* negative, *pos* positive

Comparison of Variables Among Patients With and Without Regional Recurrences as First Event After IBTR

Comparing the patients who developed regional recurrences and those who did not, we found no significant differences between the groups regarding DFI, age, and tumor characteristics during primary and recurrent breast cancer (Table 3). Likewise, there were no significant differences in the administration of adjuvant therapy following IBTR between the two patient cohorts.

DISCUSSION

Data from this study showed that the risk of developing regional recurrences after an unsuccessful rSLNB in patients with IBTR is low. The low relapse rate supports the hypothesis that there is no need for additional axillary treatment after an unsuccessful rSLNB in the IBTR setting.

In the past, the performance of an ipsilateral ALND in the setting of IBTR was considered as standard care for an optimal regional disease control. In this study, 25% of the patients with an unsuccessful rSLNB received an additional ALND. Because the regional recurrences were found in aberrant basins in all cases, most patients would not have had a theoretical benefit from ipsilateral ALND.

The present finding that patients treated with ALND after an unsuccessful rSLNB had a much shorter DFI compared with patients not treated with ALND and is in accordance with the findings from previous studies, which observed a shorter DFI as an indicator for poor prognosis.[13–15] Nevertheless, none of the regional recurrences in this study occurred in the ipsilateral axilla, and thus an ALND would not have prevented those regional events. Obviously, uncertainty exists on regional treatment options for patients with an unsuccessful rSLNB. The percentage of patients receiving adjuvant radiotherapy did not differ between patients treated with or without ALND. Because the regional recurrence rate was low in both groups, there is no indication for adjuvant axillary radiotherapy in the setting of an unsuccessful rSLNB procedure as well. Regarding the use of adjuvant chemotherapy, it is supported in all IBTR patients, especially in the estrogen receptor negative subgroup.[16]

In 13% of the patients treated with an ALND after an unsuccessful rSLNB, metastatic lymph nodes were found. This is a remarkably high percentage, considering the fact that not a single ipsilateral axillary recurrence occurred—not even in patients who did not undergo cALND. Randomized trials comparing complementary axillary surgery after positive sentinel lymph node biopsy versus no ALND or axillary radiotherapy in the primary setting, such as the ACOSOG-Z0011, AMAROS, and OTASOR trials, found comparable regional recurrence rates between those groups, whereas pathologically involved axillary lymph nodes were found in 27–39% of patients who received ALND, an even higher percentage compared with the 13% found in this study.[17–19] These results strengthen the available evidence that only a limited part of the involved lymph nodes have the potential to progress into clinically detectable axillary disease and confirm the hypothesis that a standard ALND after an unsuccessful rSLNB is not useful.

The 5-year actual regional recurrence rate was 3.7% in the group of patients treated without ALND after an unsuccessful rSLNB. Until now, other studies evaluating rSLNB focused mainly on the successfully harvested rSNs.[3,20] Hence, no data are available to compare our findings regarding the impact of an unsuccessful rSLNB on the outcome for IBTR. In a cohort of 201 IBTR patients, all staged with a negative rSLNB, a 5-year regional recurrence rate of 4.5% was found, with an ipsilateral recurrence rate of 1.0%.[6] One could speculate that in patients with an unsuccessful rSLNB, positive sentinel nodes may have

been left behind, which could develop into clinically detectable disease. However, in the current study, the recurrence rate in patients with an unsuccessful rSLNB turned out to be similar to the recurrence rate in the group of patients with successfully harvested negative lymph nodes.

Furthermore, this study showed no significant differences in tumor and patient characteristics between patients developing regional recurrence and those who did not. Although the event numbers are small, based on these results, we cannot distinguish patients with an unsuccessful rSLNB being more at risk for regional recurrence. Recently, Ugras et al.[7] questioned whether axillary staging by rSLNB is even worthwhile and found a comparable regional recurrence rate between patients staged with rSLNB and patients without axillary staging. The low regional recurrence rate reported is in line with the results of Ugras et al. and with their conclusion that restaging of clinically node-negative patients may be of limited value.[7] Furthermore, with improving noninvasive diagnostic options as positron emission tomography–computed tomography (PET-CT), the rationale seems to be even more weaning.

Axillary surgery, with SLNB and/or (c)ALND, has been one of the cornerstones in the management of breast cancer. With the potential therapeutic impact of rSLNB and the possible ability to provide prognostic information tailoring adjuvant systemic therapy, rSLNB gained credibility in the setting of IBTR.[8] However, the need for axillary surgery as a staging procedure is diminishing due to the improved knowledge of tumor biology, the development of more effective adjuvant therapies, and the increasing use of biomarkers and genomic tests as prognostic tools in clinical practice. Hence, in the primary treatment setting, trials, such as SOUND, POSNOC, and BOOG, are currently exploring differences in outcome between patients staged with SLNB compared with no axillary surgery.[21–23] Results are awaited, but it is clear that the questions addressed in these trials are similar to the questions raised in the IBTR setting. Our IBTR patients with an unsuccessful rSLNB, most probably, will be different from patients with no axillary staging (no rSLNB or (c)ALND) at all. However, the 5-year regional recurrence rate in the unsuccessful rSLNB was less than 5%, and no recurrences were found in the ipsilateral axilla, even though no lymph nodes were removed. These findings may indicate that the omission of any surgical lymph node staging in patients with IBTR without clinical manifest lymph node metastases can be justified in the future.

This study is limited by its retrospective nature, because a randomized controlled trial comparing unsuccessful rSLNB patients treated with ALND and without ALND would have been preferable. On the other hand, such a trial would most probably be underpowered due to the low incidence of recurrent breast cancer and regional recurrence after recurrent breast cancer. Given the small number of regional recurrences, multivariable analysis to determine independent risk factors were not feasible. These considerations should be taken into account when discussing treatment options after an unsuccessful rSLNB. Despite these limitations, the present study is unique by presenting follow-up data of a large cohort of patients with IBTR and unsuccessful rSLNB. The SNARB-study is a multicenter Dutch study providing data of different types of hospitals and therefore representative for patients with unsuccessful rSLNB in daily practice.

CONCLUSIONS

The present study shows that the risk of regional recurrence in the ipsilateral axilla in patients with an IBTR and an unsuccessful rSLNB is negligible, irrespective of the use of ALND. This suggests that there is no need for additional treatment of the axilla after an unsuccessful rSLNB. These results may trigger the discussion on the impact of any surgical axillary staging in the IBTR setting.

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ETHICAL STANDARD Research done for this study complies with the current laws of The Netherlands.

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