Prognostic impact of repeat sentinel lymph node biopsy in patients with ipsilateral breast tumour recurrence

Original article

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Background: **Ipsilateral breast tumour recurrence (IBTR) has an unfavourable prognosis, with a significant subsequent risk of distant recurrence. Repeat sentinel lymph node biopsy (rSLNB) has recently been demonstrated to be technically feasible and useful in tailoring adjuvant treatment plans in patients with IBTR. The prognostic impact of rSLNB in patients with IBTR remains unclear. This study analysed the risk of distant recurrence after IBTR, and evaluated the prognostic impact of rSLNB and other patient and tumour characteristics on distant recurrence-free survival.**

Methods: **Data were obtained from the SNARB (Sentinel Node and Recurrent Breast Cancer) study. Cox proportional hazards analyses were performed to assess the prognostic effect of tumour, patient and treatment factors on distant recurrence-free survival.**

Results: **Of the 515 included patients, 230 (44·7 per cent) had a tumour-negative rSLNB and 46 (8·9 per cent) a tumour-positive rSLNB. In 239 patients (46·4 per cent) the rSLNB procedure was unsuccessful. After a median follow-up of 5·1 years, 115 patients (22·3 per cent) had developed a recurrence. The overall 5-year distant recurrence-free survival rate was 84·2 (95 per cent c.i. 80·7 to 87·7) per cent. An interval of less than 2 years between primary breast cancer treatment and ipsilateral recurrence ($P = 0·018$), triple-negative IBTR ($P = 0·045$) and absence of adjuvant chemotherapy after IBTR ($P = 0·010$) were independently associated with poor distant recurrence-free survival. The association between the outcome of rSLNB and distant recurrence-free survival was not statistically significant ($P = 0·682$).**

Conclusion: **The outcome of rSLNB is not an important prognostic factor for distant recurrence, and its value as a staging tool in patients with IBTR seems disputable.**

Members of the SNARB study group are co-authors in this study and are listed in *Appendix S1* (supporting information)

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Introduction

Ipsilateral breast tumour recurrence (IBTR) has an unfavourable prognosis, with a significant risk of subsequent local, regional and distant recurrence as well as poor survival[1–4]. The 5-year overall survival rate for patients with IBTR ranges between 45 and 80 per cent[5–7]. Primary nodal status, size of IBTR, and the disease-free interval (DFI) between the primary breast cancer and IBTR diagnosis are known prognostic factors for the development of further recurrences[8,9]. Fortunately, as a result of increasing knowledge of tumour behaviour and enhanced treatment options, the percentage of patients developing an IBTR has decreased significantly over the years[8,10]. Nevertheless, because the incidence of breast cancer is high, IBTR still occurs in a considerable number of patients. Improvements in treatment strategies for patients with IBTR are therefore needed to increase the cure rate.

Patients with IBTR without evidence of distant metastasis are treated with curative intent, aiming for local disease control through wide local excision or mastectomy, combined with selective use of (re)irradiation depending on

previous treatments[11,12]. Although lymph node staging is an integral component of primary breast cancer treatment, the optimal management of the lymph nodes in patients with IBTR has not been standardized. Until recently, ipsilateral axillary lymph node dissection (ALND) was a standard procedure in patients with IBTR, aiming to achieve maximum locoregional disease control. The rationale for performing an ipsilateral ALND has become questionable for several reasons. The prognostic impact of nodal status at the time of IBTR is unclear. Moreover, the staging accuracy of ipsilateral ALND is debatable, because aberrant lymphatic drainage patterns are frequently found in patients with IBTR[13], and exposing patients to the risks of ALND-associated morbidity is disputed. Several studies[14–16] have assessed repeat sentinel lymph node biopsy (rSLNB) in patients with IBTR, and reported that it is technically feasible and useful in tailoring adjuvant treatment plans. Regional relapse rates after negative rSLNB without completion ALND in patients with recurrent breast cancer are very low[17]. However, detailed information on distant relapse rates is lacking and so the prognostic value of rSLNB remains unclear[13].

The aim of this study was to describe the incidence of subsequent breast cancer-related events in patients with IBTR who have undergone rSLNB, and to determine the prognostic value of rSLNB and other patient and tumour characteristics on distant recurrence-free survival (DRFS).

Methods

The SNARB study is a multicentre national registry study in which 36 Dutch hospitals participated. Patients with clinically apparent ipsilateral or contralateral lymph node metastases and patients with distant metastasis at the time of diagnosis of IBTR were excluded. Patients with operable locally recurrent breast cancer were staged with rSLNB and included in the study[15]. The dual mapping technique with both ^{99m}Tc and blue dye was used for the rSLNB procedure. Technical specifications and determinants of successful rSLNB have been reported in detail elsewhere[15,18].

Pathological lymph node status

A positive sentinel lymph node (SLN) at rSLNB was defined as a lymph node containing either macrometastases (larger than 2·0 mm) and/or micrometastases (over 0·2 mm and/or more than 200 cells, but none larger than 2·0 mm) in accordance with the TNM classification, seventh edition[19]. Isolated tumour cells (small clusters of cells no larger than 0·2 mm and/or fewer than 200 cells) in the SLNs were classified as node-negative.

In patients with an unsuccessful rSLNB, a sentinel node could not be visualized and/or harvested because of an unsuccessful procedure. In these patients, injection of a second dose of radiolabelled tracer was allowed, or the physician could act in accordance with the local protocol[18]. There was no requirement to perform an ALND in patients with an unsuccessful rSLNB.

Follow-up

In 2017, follow-up data on patients in the SNARB study were collected and entered into the database. General practitioners were contacted for additional follow-up information when hospital records showed no outpatient clinic visits for more than 1 year. Last follow-up was documented as date of last visit to the outpatient clinic, date of last visit to the general practitioner or date of death. Follow-up time was defined as the interval between date of surgery for IBTR and date of last follow-up. Patients for whom follow-up data were not available, owing to emigration, lack of information or withdrawal of informed consent, were excluded.

Definitions of recurrence

A local re-recurrence (LRR) after a previously treated IBTR was defined as reappearance of tumour growth in the treated breast or overlying skin. A regional recurrence (RR) was defined as any evidence of disease in ipsilateral intramammary nodes, ipsilateral and contralateral internal mammary nodes, ipsilateral and contralateral axillary nodes, and ipsilateral and contralateral infraclavicular and supraclavicular nodes[17,20]. Lymph node recurrences outside these nodal basins were considered as distant metastatic disease. An event in the contralateral breast was defined as a new primary tumour and was not considered as a recurrence, unless it could be proven that it was metastatic disease[21].

Distant recurrences (DRs) were defined as any evidence of disease outside the ipsilateral breast, contralateral breast and regional lymph nodes. LRR and/or RR diagnosed at the same time as, or after the appearance of, DR were not recorded because distant metastatic disease is considered to be the worst site according to a hierarchy of prognosis from worst to best[22]. In the event of synchronous LRR and RR, the recurrence was registered as RR.

Study endpoints

The clinical events to be included in the definitions of time-to-event endpoints were selected according to the

DATECAN and STEEP guidelines[21,22]. Recurrence-free interval was defined as the interval from date of surgery of the IBTR to detection of the first recurrence (LRR, RR, DR) or date of last follow-up. Distant recurrence-free interval (DRFI) was defined as the interval between date of surgery of the IBTR and date of diagnosis of a DR or date of last follow-up. The occurrence of DR after IBTR and breast cancer-related death were included in the DRFI[21,22]. Breast cancer-specific survival was censored in patients who died from other causes.

Statistical analysis

Patient, tumour and treatment characteristics were compared between groups using Pearson's χ^2 test or Fisher's exact test, as appropriate, for categorical data; Mann–Whitney *U* test or independent-samples *t* test was used for continuous variables depending on the normality of the distribution. Survival analyses were undertaken using the Kaplan–Meier method to calculate the prognosis of patients after curative treatment for IBTR. DRFS rates were calculated based on the DRFI defined above. The 5-year DRFS rate was calculated for tumour, patient and treatment variables, and compared between strata using the two-tailed log rank test. To assess the independent prognostic effect of the variables, a multivariable analysis was performed using Cox proportional hazards model. The multivariable model was fitted for factors that were statistically significant in the univariable analyses, prespecified prognostic factors according to the CALOR (Chemotherapy as Adjuvant for LOcally Recurrent Breast Cancer) study[23] (DFI, location and receptor status of IBTR and use of adjuvant chemotherapy for IBTR), size of IBTR and the outcome of rSLNB (positive, negative or unsuccessful). Hazard ratios and 95 per cent confidence intervals were estimated for each variable compared with the reference group. Two-sided $P < 0{\cdot}050$ was considered statistically significant. Data analysis was done using SPSS® version 24 (IBM, Armonk, New York, USA).

Results

Follow-up data were collected from 536 patients included in the SNARB study. Twenty-one patients were lost to follow-up, and 515 (96·1 per cent) remained for analysis.

Successful *versus* unsuccessful repeat sentinel node biopsy

Of the 515 patients, 276 (53·6 per cent) had an rSLNB with successful harvesting of the SLN, and in 239 patients (46·4 per cent) the SLN could not be visualized and/or harvested because of an unsuccessful procedure. Patient and tumour characteristics categorized by successful and unsuccessful rSLNB procedure are summarized in *Table S1* (supporting information). Patients who had undergone ALND during treatment of the primary breast cancer were significantly less likely to have a successful rSLNB, owing to a lower SLN identification rate. The median time from primary breast cancer surgery to diagnosis of IBTR was significantly longer in the unsuccessful group. No differences in adjuvant treatment regimens were observed between the two groups.

Positive and negative *versus* unsuccessful repeat sentinel node biopsy

Of the 515 patients, 230 (44·7 per cent) had a successful negative rSLNB and 46 (8·9 per cent) a successful positive rSLNB; the rSLNB procedure was unsuccessful in the remaining 239 patients (46·4 per cent). Patient and tumour characteristics categorized by outcome of the rSLNB after IBTR are summarized in *Table 1*. The majority of the patients had an IBTR no larger than 2 cm (70·3 per cent), grade II disease (44·9 per cent) and hormone receptor (HR)-positive, human epidermal growth receptor (HER) 2-negative breast cancer (67·0 per cent). After surgical treatment for IBTR, 315 patients (61·2 per cent) received adjuvant endocrine therapy. Adjuvant chemotherapy was administered to 125 patients (24·3 per cent). In total, 354 patients (68·7 per cent) received adjuvant endocrine and/or chemotherapy. Adjuvant endocrine therapy and/or adjuvant chemotherapy were administered significantly more often in patients with a positive rSLNB than in those with a negative or unsuccessful rSLNB ($P < 0{\cdot}001$).

Patterns of recurrence after curative treatment of ipsilateral breast tumour recurrence

Median follow-up for patients still alive after treatment of IBTR was 5·1 (range 1·1–13·2) years. After treatment of IBTR, 115 patients (22·3 per cent) developed a recurrence. The risk of developing another recurrence was highest in the third year following treatment for IBTR (5·9 (95 per cent c.i. 5·1 to 6·7) per cent). LRR was observed in 20 patients (3·9 per cent), RR occurred in 18 patients (3·5 per cent), and 77 patients (15·0 per cent) developed DR as a first event after IBTR (*Fig. 1*). There was no significant difference in the occurrence of RRs between patients with a tumour-positive rSLNB (1 patient, 2 per cent), a tumour-negative rSLNB (10, 4·3 per cent) and those with an unsuccessful rSLNB (7, 2·9 per cent) ($P = 0{\cdot}618$).

Table 1 Patient, tumour and treatment characteristics of patients with ipsilateral breast tumour recurrence according to outcome of repeat sentinel node biopsy

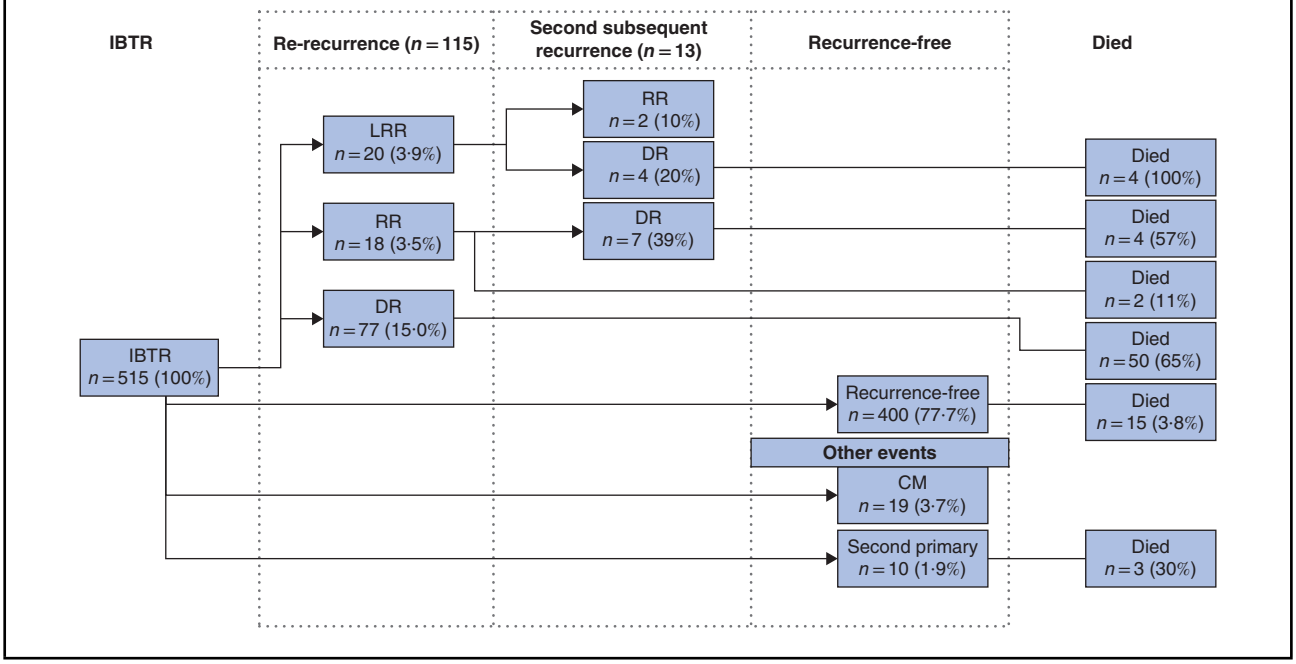
	All patients (*n* = 515)	rSLNB-positive (*n* = 46)	rSLNB-negative (*n* = 230)	rSLNB unsuccessful (*n* = 239)	*P*†
Final status of primary axillary surgery*					< 0·001
No axillary staging	34 (6·6)	7 (15)	21 (9·1)	6 (2·5)	
SLNB	203 (39·4)	14 (30)	115 (50·0)	74 (31·0)	
ALND	278 (54·0)	25 (54)	94 (40·9)	159 (66·5)	
Primary nodal status*					0·037
Negative	372 (72·2)	30 (65)	170 (73·9)	172 (72·0)	
Positive	91 (17·7)	8 (17)	32 (13·9)	51 (21·3)	
Unknown	52 (10·1)	8 (17)	28 (12·2)	16 (6·7)	
Time from primary surgery to IBTR diagnosis (years)*					
Median (range)	10·5 (0·4–31·8)	11·4 (0·7–31·8)	7·9 (0·4–30·2)	11·8 (0·4–30·0)	< 0·001‡
< 2·0	38 (7·4)	2 (4)	22 (9·6)	14 (5·9)	0·007
≥ 2·0, < 5·0	94 (18·3)	8 (17)	49 (21·4)	37 (15·5)	
≥ 5·0, < 10·0	117 (22·8)	10 (22)	63 (27·5)	44 (18·4)	
≥ 10·0	265 (51·6)	26 (57)	95 (41·5)	144 (60·3)	
Unknown	1 (0·2)	0 (0)	1 (0·4)	0 (0)	
Age at IBTR (years)					
Median (range)	64 (26–93)	63 (42–89)	63 (27–87)	65 (26–93)	0·142‡
< 35	6 (1·2)	0 (0)	2 (0·9)	4 (1·7)	0·233
35–59	176 (34·2)	20 (43)	84 (36·5)	72 (30·1)	
60–69	178 (34·6)	17 (37)	81 (35·2)	80 (33·5)	
≥ 70	155 (30·1)	9 (20)	63 (27·4)	83 (34·7)	
Location of IBTR					< 0·001
Breast	454 (88·2)	39 (85)	188 (81·7)	227 (95·0)	
Mastectomy scar or chest wall	61 (11·8)	7 (15)	42 (18·3)	12 (5·0)	
Aberrant location of SLN at rSLNB					< 0·001
Yes	126 (24·5)	26 (57)	100 (43·5)	0 (0)	
No	148 (28·7)	20 (43)	128 (55·7)	0 (0)	
Unknown	2 (0·4)	0 (0)	2 (0·9)	0 (0)	
Unsuccessful rSLNB	239 (46·4)	0 (0)	0 (0)	239 (100)	
Final axillary surgery at IBTR					< 0·001
Unsuccessful rSLNB	179 (34·8)	0 (0)	0 (0)	179 (74·9)	
(c)ALND	104 (20·2)	15 (33)	29 (12·6)	60 (25·1)	
rSLNB	232 (45·0)	31 (67)	201 (87·4)	0 (0)	
Lesion size of IBTR (cm)					0·022
≤ 2	362 (70·3)	32 (70)	167 (72·6)	163 (68·2)	
> 2	120 (23·3)	14 (30)	42 (18·3)	64 (26·8)	
Unknown	33 (6·4)	0 (0)	21 (9·1)	12 (5·0)	
Tumour grade of IBTR					0·745
I	104 (20·2)	7 (15)	45 (19·6)	52 (21·8)	
II	231 (44·9)	25 (54)	99 (43·0)	107 (44·8)	
III	151 (29·3)	11 (24)	71 (30·9)	69 (28·9)	
Unknown	29 (5·6)	3 (7)	15 (6·5)	11 (4·6)	
Receptor status of IBTR					0·167
Triple-negative	67 (13·0)	2 (4)	29 (12·6)	36 (15·1)	
HR−, HER-2+	18 (3·5)	2 (4)	7 (3·0)	9 (3·8)	
HR+, HER-2+	33 (6·4)	4 (9)	14 (6·1)	15 (6·3)	
HR+, HER2−	345 (67·0)	36 (78)	148 (64·3)	161 (67·4)	
Unknown	52 (10·1)	2 (4)	32 (13·9)	18 (7·5)	

Table 1 Continued

	All patients ($n = 515$)	rSLNB-positive ($n = 46$)	rSLNB-negative ($n = 230$)	rSLNB unsuccessful ($n = 239$)	P†
Systemic therapy at IBTR					< 0·001
Yes	354 (68·7)	45 (98)	149 (64·8)	160 (66·9)	
No	161 (31·3)	1 (2)	81 (35·2)	79 (33·1)	
Endocrine therapy after IBTR					< 0·001
Yes	315 (61·2)	42 (91)	133 (57·8)	140 (58·6)	
No	200 (38·8)	4 (9)	97 (42·2)	99 (41·4)	
Chemotherapy after recurrent IBTR					< 0·001
Yes	125 (24·3)	23 (50)	47 (20·7)	55 (23·0)	
No	390 (75·7)	23 (50)	183 (79·6)	184 (77·0)	

Values in parentheses are percentages unless indicated otherwise. *Primary refers to the time of primary breast cancer treatment before the recurrence. (r)SLNB, (repeat) sentinel lymph node biopsy; (c)ALND, (completion) axillary lymph node dissection; IBTR, ipsilateral breast tumour recurrence; SLN, sentinel lymph node; HR, hormone receptor; HER-2, human epidermal growth receptor 2. †Pearson χ^2 test, except ‡Mann–Whitney U test.

Fig. 1 Patterns of recurrence after curative treatment of ipsilateral breast tumour recurrence in 515 patients



IBTR, ipsilateral breast tumour recurrence; LRR, local re-recurrence; RR, regional recurrence; DR, distant recurrence; CM, contralateral metastases.

The 5-year overall recurrence-free survival rate after IBTR was 79·1 (95 per cent c.i. 75·2 to 83·0) per cent. No significant difference in 5-year recurrence-free survival was observed between patients with an unsuccessful, tumour-positive or tumour-negative rSLNB ($P = 0·543$).

Thirteen of the 38 patients with LRR or RR developed another recurrence (*Fig. 1*). Seventy-eight of the 515 patients (15·1 per cent) died during follow-up after IBTR, 60 (77 per cent) from breast-cancer related causes.

A total of 88 patients (17·1 per cent) developed DR, 77 (88 per cent) as a first event after treatment of IBTR and 11 (12 per cent) after diagnosis of LRR or RR following IBTR (*Fig. 1*). The sites of first distant metastases were bone (26 patients), lung (16), liver (10), brain (7) and other sites (12). In 17 patients DRs were diagnosed at multiple

Table 2 Univariable analysis of clinicopathological characteristics related to distant recurrence-free survival after curative treatment of ipsilateral breast tumour recurrence

	All patients ($n = 515$)	Patients with DR or breast cancer-related death ($n = 90$)	5-year DRFS (%)	P†
Final status of primary axillary surgery*				0·700
No axillary staging	34 (6·6)	4	86	
SLNB	203 (39·4)	31	87·6	
ALND	278 (54·0)	55	81·9	
Primary nodal status*				0·016
Negative	372 (72·2)	61	85·5	
Positive	91 (17·7)	25	75	
Unknown	52 (10·1)	4	92	
Time from primary surgery to IBTR diagnosis (years)*				0·025
< 2·0	38 (7·4)	12	69	
≥ 2·0, < 5·0	94 (18·3)	14	85·0	
≥ 5·0, < 10·0	117 (22·7)	18	90·2	
≥ 10·0	265 (51·5)	46	83·5	
Age at IBTR (years)				0·251
< 35	6 (1·2)	2	67	
35–59	176 (34·2)	27	87·1	
60–69	178 (34·6)	31	84·4	
≥ 70	155 (30·1)	30	81·2	
Location of IBTR				0·672
Breast	454 (88·2)	79	84·5	
Mastectomy scar or chest wall	61 (11·8)	11	83	
Result of rSLNB				0·682
Positive	46 (23·7)	10	76	
Negative	230 (44·7)	35	85·4	
Unsuccessful	239 (46·4)	45	84·7	
Aberrant location of SLN on rSLNB				0·956
Yes	126 (24·5)	22	83·7	
No	150 (29·1)	23	83·8	
Unsuccessful rSLNB	239 (46·4)	45	84·5	
Final axillary surgery at IBTR				0·960
Unsuccessful rSLNB	179 (34·8)	33	83·8	
rSLNB	232 (45·0)	36	82·8	
(c)ALND	104 (20·2)	21	86·1	
IBTR nodal status				0·713
Negative	279 (54·2)	45	86·0	
Positive	57 (11·1)	12	77	
Unknown	179 (34·8)	33	83·8	
Lesion size of IBTR (cm)				0·086
≤ 2	362 (70·3)	60	85·1	
> 2	120 (23·3)	28	77·8	
Unknown	33 (6·4)	2	97	
Tumour grade of IBTR				0·089
I	104 (20·2)	11	90·0	
II	231 (44·9)	43	83·8	
III	151 (29·3)	28	82·8	
Unknown	29 (5·6)	8	74	
Receptor status of IBTR				0·205
Triple-negative	67 (13·0)	18	75	
HR−, HER-2+	18 (3·5)	2	88	

Table 2 Continued

	All patients ($n = 515$)	Patients with DR or breast cancer-related death ($n = 90$)	5-year DRFS (%)	P†
HR+, HER-2+	33 (6·4)	5	81	
HR+, HER2−	345 (67·0)	59	85·6	
Unknown	52 (10·1)	6	87	
Systemic therapy after IBTR				0·672
Yes	354 (68·7)	61	83·8	
No	161 (31·3)	29	85·0	
Endocrine therapy after IBTR				0·977
Yes	315 (61·2)	55	83·3	
No	200 (38·8)	35	85·3	
Chemotherapy after IBTR				0·067
Yes	125 (24·3)	16	89·5	
No	390 (75·7)	74	82·6	

Values in parentheses are percentages unless indicated otherwise. *Primary refers to the time of primary breast cancer treatment before the recurrence. DR, distant recurrence; DRFS, distant recurrence-free survival; (r)SLNB, (repeat) sentinel lymph node biopsy; ALND, axillary lymph node dissection; IBTR, ipsilateral breast tumour recurrence; SLN, sentinel lymph node; HR, hormone receptor; HER-2, human epidermal growth receptor 2. †Log rank test.

Table 3 Univariable and multivariable Cox proportional hazards regression model of distant recurrence-free survival after curative treatment of ipsilateral breast tumour recurrence

	Distant recurrence-free survival ($n = 90$)			
	Univariable analysis		Multivariable analysis	
	Hazard ratio	P	Hazard ratio	P
Primary nodal status*				
Negative	1·00 (reference)		1·00 (reference)	
Positive	1·70 (1·07, 2·71)	0·025	1·52 (0·94, 2·45)	0·086
Unknown	0·49 (0·18, 1·34)	0·165	0·48 (0·17, 1·34)	0·161
Time from primary surgery to IBTR diagnosis (years)*				
< 2·0	2·25 (1·19, 4·25)	0·012	2·54 (1·17, 5·53)	0·018
≥ 2·0, < 5·0	0·82 (0·45, 1·49)	0·507	0·94 (0·51, 1·74)	0·845
≥ 5·0, < 10·0	0·84 (0·49, 1·46)	0·541	0·88 (0·51, 1·54)	0·657
≥ 10·0	1·00 (reference)		1·00 (reference)	
Location of IBTR				
Breast	1·00 (reference)		1·00 (reference)	
Chest wall	1·15 (0·61, 2·15)	0·672	0·73 (0·34, 1·54)	0·401
Receptor status of IBTR				
HR+, HER-2−	1·00 (reference)		1·00 (reference)	
Triple-negative	1·65 (0·97, 2·80)	0·063	1·82 (1·04, 3·26)	0·045
HR−, HER-2+	0·56 (0·14, 2·30)	0·422	0·84 (0·20, 3·51)	0·810
HR+, HER-2+	0·90 (0·36, 2·25)	0·822	1·05 (0·41, 2·66)	0·921
Unknown	0·70 (0·30, 1·61)	0·398	0·88 (0·36, 2·15)	0·771
Lesion size of IBTR (cm)				
≤ 2 cm	1·00 (reference)		1·00 (reference)	
> 2 cm	1·41 (0·90, 2·20)	0·137	1·57 (0·99, 2·50)	0·056
Unknown	0·37 (0·09, 1·51)	0·165	0·35 (0·08, 1·59)	0·175
Chemotherapy after IBTR				
No	1·00 (reference)		1·00 (reference)	
Yes	0·61 (0·35, 1·04)	0·070	0·46 (0·25, 0·83)	0·010
Outcome of rSLNB procedure				
Negative	1·00 (reference)		1·00 (reference)	
Positive	1·35 (0·67, 2·72)	0·403	1·69 (0·81, 3·51)	0·163
Unsuccessful	1·13 (0·72, 1·76)	0·596	1·05 (0·66, 1·66)	0·840

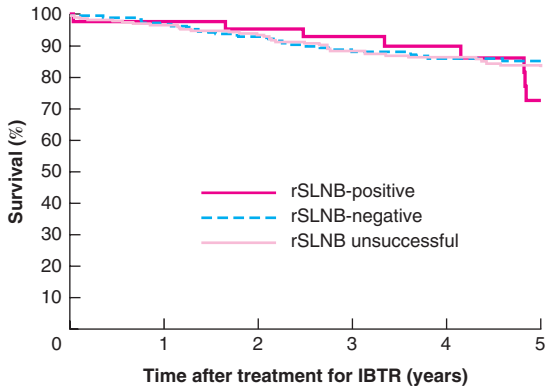
Values in parentheses are 95 per cent confidence intervals. *Primary refers to the time of primary breast cancer treatment before the recurrence. IBTR, ipsilateral breast tumour recurrence; HR, hormone receptor; HER-2, human epidermal growth receptor 2; rSLNB, repeat sentinel lymph node biopsy.

Table 4 Multivariable Cox proportional hazards regression analysis of distant recurrence-free survival for patients with ipsilateral breast tumour recurrence, testing the interaction between adjuvant chemotherapy and oestrogen receptor status

	Model with ER-negative patients ($n = 89$)*		Model with ER-positive patients ($n = 386$)*	
	Hazard ratio	*P*	Hazard ratio	*P*
Adjuvant chemotherapy	0·21 (0·06, 0·74)	0·015	0·59 (0·30, 1·17)	0·130
No adjuvant chemotherapy	1·00 (reference)		1·00 (reference)	

Values in parentheses are 95 per cent confidence intervals. ER, oestrogen receptor. *Adjusted for pN status of primary tumour, disease-free interval, ipsilateral breast tumour recurrence location, tumour size and outcome of repeat sentinel lymph node biopsy.

Fig. 2 Kaplan–Meier curve showing distant recurrence-free survival after curative treatment for ipsilateral breast tumour recurrence, according to the outcome of repeat sentinel lymph node biopsy



No. at risk						
rSLNB-positive	46	44	40	35	28	16
rSLNB-negative	230	226	210	172	130	89
rSLNB unsuccessful	239	228	212	182	151	117

rSLNB, repeat sentinel lymph node biopsy; IBTR, ipsilateral breast tumour recurrence.

sites at the same time. The 5-year DRFS rate was 84·2 (80·7 to 87·7) per cent.

Prognostic factors for distant recurrence-free survival

Univariable analysis showed that the nodal status (ALND and/or SLNB) at the time of primary surgery and the DFI between primary breast cancer surgery and diagnosis of an IBTR were significantly related to a higher risk of DR (*Table 2*). After inclusion of the predefined risk factors in a multivariable Cox regression analysis, the most important prognostic factors for DR were a DFI of less than 2 years, a triple-negative IBTR and adjuvant chemotherapy (*Table 3*).

The DRFI was longer for patients who received adjuvant chemotherapy following the IBTR, with a 5-year DRFS rate of 89·5 (95 per cent c.i. 83·4 to 95·6) per cent, compared with 82·6 (78·5 to 86·7) per cent for those treated without adjuvant chemotherapy (*Table 2*). In multivariable analysis, patients with IBTR who had adjuvant chemotherapy had a lower risk of developing DR (hazard ratio 0·46, 95 per cent c.i. 0·25 to 0·83; $P = 0·010$) (*Table 3*). The beneficial effect of adjuvant chemotherapy on DRFS was significantly more pronounced in patients with an oestrogen receptor (ER)-negative IBTR (hazard ratio 0·21, 0·06 to 0·74) (*Table 4*).

For patients in the negative rSLNB group, the 5-year DRFS rate was 85·4 (80·5 to 90·3) per cent, compared with 76 per cent (60 to 92) per cent in the positive rSLNB group and 84·7 (79·8 to 89·6) per cent in the unsuccessful rSLNB group ($P = 0·682$) (*Table 2*). Survival plots in relation to the outcome of rSLNB are shown in *Fig. 2*. The outcome of rSLNB was not a statistically significant prognostic

factor, either in the univariable or multivariable analysis (*Table 3*).

Discussion

In this large cohort of 515 patients with IBTR, who all underwent rSLNB, the 5-year DRFS rate was 84·2 per cent. Prognosis was significantly worse for patients with an interval of less than 2 years between primary breast cancer treatment and an IBTR, triple-negative IBTR or absence of treatment with adjuvant chemotherapy after IBTR. No statistically significant differences in outcomes (RR, DR) were found in comparisons of patients with a tumour-positive, tumour-negative or unsuccessful rSLNB.

Studies[9,24,25] of the incidence of locoregional recurrence or DR after IBTR have reported rates ranging from 15 to 71 per cent. Voogd and colleagues[9] reported a 5-year DR rate of 55·8 per cent in a cohort of patients with IBTR, initially treated between 1980 and 1992. That rate is much higher than the 5-year DR rate of 15·8 per cent reported in the present SNARB cohort treated between 2002 and 2014. Advances in the diagnosis and treatment of breast cancer in recent years might explain this difference. Furthermore, patients in the SNARB cohort had a more favourable prognosis as they were all clinically node-negative.

Follow-up data for patients with ipsilateral locoregional recurrences in the CALOR trial[3] were reported recently: 9·3 per cent of patients developed an isolated locoregional re-recurrence after 5 years and 23 per cent developed DR. However, the CALOR trial included patients with an isolated IBTR as well as those with regional disease. The present cohort included only patients with IBTR who had no clinical evidence of involved regional lymph nodes. Unfortunately, as other studies on prognosis after IBTR did not report on axillary staging methods, no comparisons could be made of the results regarding the impact of rSLNB on outcome after IBTR.

Lymph node status is a known prognostic factor in primary breast cancer[26]. Therefore, it was hypothesized that lymph node status determined by rSLNB could have the same role in patients with IBTR. In an earlier study[17], a low regional relapse rate for rSLNB-negative patients treated without ALND suggested that omitting ipsilateral ALND was safe, and it was proposed that rSLNB should be adopted as standard of care in IBTR. Going further, the present study analysed the impact of any axillary staging in patients with IBTR. No significant difference in the rate of DR after curative treatment for IBTR was found for patients with a tumour-positive, tumour-negative or unsuccessful rSLNB, in either univariable or multivariable analyses. This finding gives rise to several clinical questions and possible consequences regarding the value of surgical interventions in the axilla in patients with IBTR.

The value of rSLNB in clinically node-negative patients with IBTR might be disputed overall, as the outcome of the procedure appears to have a minor impact on the prognosis. In addition, the rate of unsuccessful rSLNB procedures (46·4 per cent) was quite high here, although comparable with that in other studies[27,28] reporting on rSLNB in patients with similar characteristics. Despite these findings, rSLNB could still be considered as a regional therapeutic procedure (preventing RR). Because the SNARB study did not collect data for patients with no axillary staging attempt at the time of IBTR, the therapeutic impact of the SNARB procedure could only be estimated from other observational studies. In a meta-analysis[13], the reported false-negative rate of rSLNB was 4·1 per cent. The clinical ipsilateral recurrence rate after a negative rSLNB was 1·0 per cent after a follow-up of 5·1 years[17]. Thus, a false-negative rSLNB seemed to be associated with clinically manifest recurrence in around 25 per cent of patients (1·0 per cent/4·1 per cent × 100). In the total SNARB cohort, 8·9 per cent of the patients had a positive rSLNB. These positive metastatic lymph nodes would be left behind if rSLNB were omitted, and RR would be expected to occur in more than 2 per cent of the patients (8·9 per cent × 24·4 per cent/100) after 5·1 years of follow-up. In other words, 100 rSLNBs would have to be performed to prevent two RRs. It is debatable whether the routine performance of rSLNB is justified with such small numbers benefitting. Ugras and co-workers[29] compared a group of patients with IBTR who had rSLNB with a group who had similar tumour characteristics but no axillary staging, and found low rates of axillary recurrences in both groups. Although their sample size was insufficient to exclude small differences, particularly in nodal recurrences, they concluded that restaging of patients with IBTR is of limited value and that further study in larger cohorts is needed[29].

As no statistically significant effect of rSLNB outcome on prognosis could be proven in patients with a clinically node-negative IBTR, ALND seems obsolete in this subgroup of patients. This recommendation is not only supported by the absence of an important prognostic value of rSLNB, but also based on other studies showing aberrant lymph drainage to basins other than the ipsilateral axilla in over half of all patients with IBTR[13,15]. Furthermore, exploration of SLNs in lymph node basins other than the ipsilateral and contralateral axilla is not recommended during rSLNB. Surgical exploration of aberrant nodes is more difficult, with potential additional morbidity (including risk of nerve injury, pneumothorax and bleeding) and there is

currently insufficient evidence to recommend extra-axillary SLNB[30,31].

From the present data it appears that clinicians in the SNARB study based adjuvant systemic treatment plans on the outcome of rSLNB, with rSLNB-positive patients receiving adjuvant systemic therapy significantly more often. Data from the SNARB study do not support such treatment decisions based on the outcome of rSLNB. The use of adjuvant chemotherapy in IBTR is, however, supported, especially in the ER-negative subgroup. The beneficial effect of adjuvant chemotherapy is consistent with a recent report[32] of the long-term results of the CALOR trial after a median follow-up of 9 years, which showed that adjuvant chemotherapy improved disease-free survival in ER-negative patients only.

Other factors known to be associated with recurrence-free survival after IBTR are primary nodal status, IBTR lesion size, and the interval between primary breast cancer and IBTR (DFI)[8,9]. The present findings confirm the unfavourable effect of a short DFI on prognosis. A short DFI may represent chemotherapy-insensitive or radiotherapy-resistant disease[33,34]. In addition, late IBTRs may represent *de novo* neoplastic transformation in the earlier treated breast, in which these new primary tumours have a more favourable role regarding outcome and prognosis than early IBTRs[33,34]. However, accurate methods establishing the type of IBTR have proven difficult to reproduce[35], and inaccurate characterization could significantly influence reported rates and patterns of relapse[36].

Some caveats have to be considered regarding this study. Registration of HER-2 status only started in 2005; before that time, the HER-2 status of the primary tumour was generally not reported and this variable was not therefore included in the analysis. The number of rSLNB-positive patients in the SNARB study was relatively small, so a clinically relevant difference cannot be ruled out. Furthermore, a type II error owing to the low incidence of recurrence after IBTR cannot be excluded. An RCT comparing patients who undergo rSLNB *versus* patients without any axillary interventions would be preferable to determine the impact on the occurrence of events after IBTR. However, such a trial would most probably be underpowered because of the low incidence of IBTR, and LR, RR and DR after IBTR.

Despite these limitations, the SNARB study represents a large cohort of patients with IBTR undergoing rSLNB with a median follow-up of more than 5 years. Furthermore, the inclusion of unselected patients in different types of hospital in the Netherlands appears representative of the majority of patients with IBTR encountered in daily practice. Based on the present findings, use of rSLNB as a primary staging tool in patients with IBTR is disputable as it does not seem to provide important prognostic information.

Disclosure

The authors declare no conflict of interest.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.