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Original Article

# De-escalation of axillary treatment in the event of a positive sentinel lymph node biopsy in cT1–2 N0 breast cancer treated with mastectomy: nationwide registry study (BOOG 2013-07)

Sabine R. de Wild[1,*], Lori M. van Roozendaal[2], Johannes H. W. de Wilt[3], Thijs van Dalen[4], Jos A. van der Hage[5], Frederieke H. van Duijnhoven[6], Janine M. Simons[1,7], Robert-Jan Schipper[8], Linda de Munck[9], Sander M. J. van Kuijk[10], Liesbeth J. Boersma[11], Sabine C. Linn[12], Marc B. I. Lobbes[13], Philip M. P. Poortmans[14,15], Vivianne C. G. Tjan-Heijnen[16], Koen K. B. T. van de Vijver[17,18], Jolanda de Vries[19], A. Helen Westenberg[20], Luc J. A. Strobbe[21] and Marjolein L. Smidt[1]

[1]Maastricht University Medical Centre+, Department of Surgery, GROW School for Oncology and Reproduction, Maastricht, The Netherlands
[2]Department of Surgery, Zuyderland Medical Centre, Heerlen, the Netherlands
[3]Department of Surgery, Radboud University Medical Centre, Nijmegen, the Netherlands
[4]Department of Surgery, Erasmus Medical Centre, Rotterdam, the Netherlands
[5]Department of Surgery, Leiden University Medical Centre, Leiden, the Netherlands
[6]Department of Surgery, Netherlands Cancer Institute—Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands
[7]Department of Radiotherapy, Erasmus Medical Centre, Rotterdam, the Netherlands
[8]Department of Surgery, Catharina Hospital, Eindhoven, the Netherlands
[9]Department of Research and Development, Netherlands Comprehensive Cancer Organization (IKNL), Utrecht, the Netherlands
[10]Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre+, Maastricht, the Netherlands
[11]Maastricht University Medical Centre+, Department of Radiation Oncology (Maastro), GROW School for Oncology and Reproduction, Maastricht, the Netherlands
[12]Department of Medical Oncology, Netherlands Cancer Institute—Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands
[13]Department of Medical Imaging, Zuyderland Medical Centre, Sittard-Geleen, the Netherlands
[14]Department of Radiation Oncology, Iridium Netwerk, Antwerp, Belgium
[15]Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium
[16]Department of Medical Oncology, Maastricht University Medical Centre+, Maastricht, the Netherlands
[17]Department of Pathology, Netherlands Cancer Institute—Antoni van Leeuwenhoek, Amsterdam, the Netherlands
[18]Department of Pathology, University Hospital Ghent—Cancer Research Institute Ghent, Ghent, Belgium
[19]Department of Psychology and Health, Tilburg University, Tilburg, the Netherlands
[20]Department of Radiation Oncology, Radiotherapiegroep Arnhem, Arnhem, the Netherlands
[21]Department of Surgery, Canisius Wilhelmina Hospital, Nijmegen, the Netherlands

*Correspondence to: Sabine R. de Wild, Department of Surgery, Maastricht University Medical Centre+, PO Box 5800, 6202 AZ Maastricht, the Netherlands (e-mail: s.dewild@maastrichtuniversity.nl)

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## Abstract

**Background:** Trials have demonstrated the safety of omitting completion axillary lymph node dissection in patients with cT1–2 N0 breast cancer operated with breast-conserving surgery who have limited metastatic burden in the sentinel lymph node. The aim of this registry study was to provide insight into the oncological safety of omitting completion axillary treatment in patients operated with mastectomy who have limited-volume sentinel lymph node metastasis.
**Methods:** Women diagnosed in 2013–2014 with unilateral cT1–2 N0 breast cancer treated with mastectomy, with one to three sentinel lymph node metastases (pN1mi–pN1a), were identified from the Netherlands Cancer Registry, and classified by axillary treatment: no completion axillary treatment, completion axillary lymph node dissection, regional radiotherapy, or completion axillary lymph node dissection followed by regional radiotherapy. The primary endpoint was 5-year regional recurrence rate. Secondary endpoints included recurrence-free interval and overall survival, among others.
**Results:** In total, 1090 patients were included (no completion axillary treatment, 219 (20.1%); completion axillary lymph node dissection, 437 (40.1%); regional radiotherapy, 327 (30.0%); completion axillary lymph node dissection and regional radiotherapy, 107 (9.8%)). Patients in the group without completion axillary treatment had more favourable tumour characteristics and were older. The overall 5-year regional recurrence rate was 1.3%, and did not differ significantly between the groups. The recurrence-free interval was also comparable among groups. The group of patients who did not undergo completion axillary treatment had statistically significantly worse 5-year overall survival, owing to a higher percentage of non-cancer deaths.
**Conclusion:** In this registry study of patients with cT1–2 N0 breast cancer treated with mastectomy, with low-volume sentinel lymph node metastasis, the 5-year regional recurrence rate was low and comparable between patients with and without completion axillary treatment.

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## Introduction

In clinically node-negative (cN0) breast cancer, axillary lymph node dissection (ALND) has been replaced by sentinel lymph node biopsy (SLNB), based on the results of landmark trials such as NSABP B-32[1–4]. If there is no sentinel lymph node (SLN) metastasis, SLNB without completion ALND provides comparable survival, regional control, and less morbidity[1–3]. In addition, in the event of low-volume SLN metastasis, completion ALND can be omitted in patients who undergo breast-conserving surgery (BCS) combined with whole-breast radiotherapy (RT)[5–9]. The added value of SLNB itself has been investigated in trials such as INSEMA, SOUND, BOOG 2013-08, SOAPET, and NAUTILUS[10–14]. Recently published results of the SOUND trial[15] support an axillary de-escalation strategy in patients treated with BCS combined with RT.

It has been hypothesized that RT after BCS also improves regional control, as a result of incidental irradiation of the axilla[16–18]. Thus, it is not possible to simply extrapolate the results from trials such as Z0011 to patients treated with mastectomy, who do not routinely receive chest wall RT[7,8]. Moreover, the beneficial effect of adjuvant systemic therapy on regional control should also be considered. Trials such as IBCSG 23-01 only included a limited number of patients who underwent mastectomy[5,6,19]. The Dutch BOOG 2013-07 RCT was designed and initiated (NCT02112682)[20] but, owing to lack of accrual, the RCT was ended in 2017. In an effort to provide insight into oncological safety, a nationwide registry study was conducted. The 5-year results are now presented with regard to the oncological safety of omitting completion axillary treatment in patients who undergo mastectomy and have low-volume SLN metastasis.

## Methods

### Study design and participants

Inclusion and exclusion criteria for this registry study were similar to those of the BOOG 2013-07 RCT[20]. Women aged at least 18 years, with unilateral cT1–2 N0 invasive breast cancer treated with mastectomy, with a maximum of three SLN metastases (pN1mi–pN1a), and diagnosed between 1 January 2013 and 31 December 2014, were identified from the Netherlands Cancer Registry (NCR). cN0 status was defined by the absence of lymph node metastases at the time of diagnosis. This was based on ultrasound examination and, if indicated, confirmed with a negative fine-needle aspiration or core needle biopsy if there were suspicious lymph nodes, all part of the recommended method for assessment of axillary nodal status in the Netherlands since 2008. Exclusion criteria were: distant metastases, neoadjuvant systemic therapy, positive surgical margins after mastectomy, previous surgery or RT of the ipsilateral axilla, history of invasive breast cancer, and other malignancies (except successfully treated malignancies more than 5 years before diagnosis of invasive breast cancer, basal cell or squamous cell skin cancer, or carcinoma *in situ* of the breast or cervix).

The NCR is a nationwide registry that is managed by the Netherlands Comprehensive Cancer Organization (IKNL)[21]. Patients are included in this registry via an opt-out approach. Specially trained registration clerks of IKNL gather clinical data from the patients' medical files. The data collected can be used for research after receiving approval from the Privacy Review Board of the NCR, as was done for this study. Written informed consent was not required.

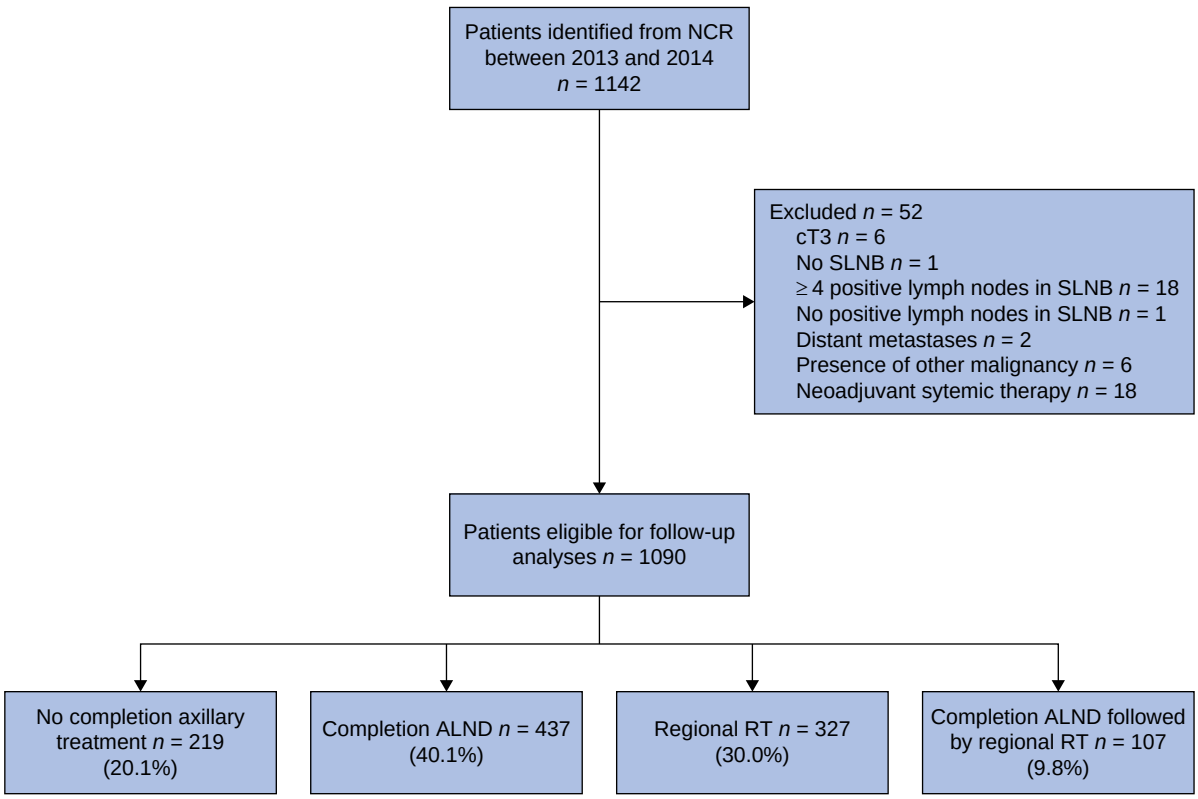


**Fig. 1 Study flow diagram**

NCR, Netherlands Cancer Registry; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; RT, radiotherapy.

**Table 1 Patient, tumour, and treatment characteristics**

| | Whole cohort (*n* = 1090) | No completion axillary treatment (*n* = 219) | Completion ALND (*n* = 437) | Regional RT (*n* = 327) | Completion ALND + regional RT (*n* = 107) | P† |
|---|---|---|---|---|---|---|
| **Age (years)** | | | | | | < 0.001 |
| < 40 | 54 (5.0) | 4 (1.8) | 23 (5.3) | 21 (6.4) | 6 (5.3) | |
| 40–59 | 473 (43.4) | 67 (30.6) | 228 (52.2) | 134 (41.0) | 44 (41.1) | |
| 60–74 | 357 (32.8) | 61 (27.9) | 142 (32.5) | 110 (33.6) | 44 (41.1) | |
| ≥ 75 | 206 (18.9) | 87 (39.7) | 44 (10.1) | 62 (19.0) | 13 (12.2) | |
| Median (i.q.r.) | 60 (49–71) | 68 (52–81) | 56 (48–66) | 60 (50–70) | 61 (50–78) | |
| **Molecular subtype** | | | | | | 0.137 |
| HR+, HER2− | 886 (81.3) | 193 (88.1) | 356 (81.5) | 252 (77.1) | 85 (79.4) | |
| HR+, HER2+ | 109 (10.0) | 18 (8.2) | 42 (9.6) | 38 (11.6) | 11 (10.3) | |
| HR−, HER2+ | 42 (3.9) | 3 (1.4) | 17 (3.9) | 16 (4.9) | 6 (5.6) | |
| Triple negative | 53 (4.9) | 5 (2.3) | 22 (5.0) | 21 (6.4) | 5 (4.7) | |
| **Grade** | | | | | | < 0.001 |
| 1 | 188 (17.7) | 55 (24.4) | 75 (17.7) | 51 (15.9) | 9 (8.7) | |
| 2 | 596 (56.0) | 132 (60.8) | 239 (56.2) | 164 (51.3) | 61 (59.2) | |
| 3 | 281 (26.4) | 32 (14.8) | 111 (26.1) | 105 (32.8) | 33 (32.0) | |
| Unknown‡ | 25 | 2 | 12 | 7 | 4 | |
| **Lymphovascular invasion** | | | | | | 0.001 |
| No | 651 (71.6) | 151 (81.2) | 252 (70.8) | 195 (70.9) | 53 (57.6) | |
| Yes | 258 (28.4) | 35 (18.8) | 104 (29.2) | 80 (29.1) | 39 (42.4) | |
| Unknown‡ | 181 | 25 | 82 | 55 | 16 | |
| **Clinical tumour status** | | | | | | 0.106 |
| cT1 | 518 (47.5) | 110 (50.2) | 219 (50.1) | 148 (45.3) | 41 (38.3) | |
| cT2 | 572 (52.5) | 109 (49.8) | 218 (49.9) | 179 (54.7) | 66 (61.7) | |
| **Multifocality** | | | | | | 0.051 |
| No | 741 (68.0) | 166 (75.8) | 290 (66.4) | 214 (65.4) | 71 (66.4) | |
| Yes | 349 (32.0) | 53 (24.2) | 147 (33.6) | 113 (34.6) | 36 (33.6) | |
| **Pathological tumour status** | | | | | | < 0.001 |
| pT1 | 445 (40.8) | 101 (46.1) | 186 (42.6) | 132 (40.4) | 26 (24.3) | |
| pT2 | 585 (53.7) | 115 (52.5) | 226 (51.7) | 175 (53.5) | 69 (64.5) | |
| pT3 | 56 (5.1) | 2 (0.9) | 25 (5.7) | 17 (5.2) | 12 (11.2) | |
| pT4 | 4 (0.4) | 1 (0.5) | 0 (0.0) | 3 (0.9) | 0 (0.0) | |
| **pN status after SLNB** | | | | | | < 0.001 |
| pN1mi(sn) | 288 (26.4) | 164 (74.9) | 45 (10.3) | 75 (22.9) | 4 (3.7) | |
| pN1a(sn) | 802 (73.6) | 55 (25.1) | 392 (89.7) | 252 (77.1) | 103 (96.3) | |
| **No. of positive SLNs** | | | | | | < 0.001 |
| 1 | 872 (80.0) | 204 (93.2) | 335 (76.7) | 266 (81.4) | 67 (62.6) | |
| 2 | 183 (16.8) | 13 (5.9) | 93 (21.3) | 52 (15.9) | 25 (23.4) | |
| 3 | 35 (3.2) | 2 (0.9) | 9 (2.1) | 9 (2.8) | 15 (14.0) | |
| **Chemotherapy** | | | | | | < 0.001 |
| No | 457 (41.9) | 153 (69.9) | 136 (31.1) | 143 (43.7) | 25 (23.4) | |
| Yes | 633 (58.1) | 66 (30.1) | 301 (68.9) | 192 (56.3) | 82 (76.6) | |
| **Targeted therapy** | | | | | | 0.038 |
| No | 965 (88.5) | 206 (94.1) | 382 (87.4) | 285 (87.2) | 92 (86.0) | |
| Yes | 125 (11.5) | 13 (5.9) | 55 (12.6) | 42 (12.8) | 15 (14.0) | |
| **Endocrine therapy** | | | | | | 0.139 |
| No | 165 (15.1) | 30 (13.7) | 60 (13.7) | 62 (19.0) | 13 (12.2) | |
| Yes | 925 (84.9) | 189 (86.3) | 377 (86.3) | 265 (81.0) | 94 (87.9) | |
| **RT of chest wall*** | | | | | | < 0.001 |
| No | 656 (60.2) | 210 (95.9) | 368 (84.2) | 78 (23.9) | 0 (0.0) | |
| Yes | 434 (39.8) | 9 (4.1) | 69 (15.8) | 249 (76.2) | 107 (100.0) | |

Values are *n* (%) unless otherwise indicated. *Fifteen patients received radiotherapy (RT) to the internal mammary chain: one, one, five, and eight in the groups that had no completion axillary treatment, completion axillary lymph node dissection (ALND), regional RT, and completion ALND and regional RT respectively. HR, hormone receptor; HER2, human epidermal growth factor receptor 2; SLNB, sentinel lymph node biopsy; SLN, sentinel lymph node. †Pearson's $\chi^2$ test, with $P < 0.050$ considered statistically significant; ‡missing values were excluded from the statistical analysis.

Data on the following variables were gathered for each patient: year of diagnosis, age, histomorphological subtype, breast cancer molecular subtype, tumour grade, lymphovascular invasion (LVI), multifocality, TNM status at diagnosis and after surgery[22], number of (positive) lymph nodes identified at axillary surgery, type of axillary treatment, type of systemic therapy, details of RT (target volumes, dose, and number of fractions), and follow-up in terms of recurrence and survival.

The overall mortality data in the NCR were derived from the municipality registry, with the last update on 31 January 2023. Cause of death was derived from Statistics Netherlands.

Patients were assigned retrospectively to one of four groups based on axillary treatment: no completion axillary treatment, completion ALND, regional RT, or completion ALND followed by regional RT. In this study, regional RT was defined as RT of axillary levels I–II and/or levels III–IV (periclavicular region) with or without RT of the internal mammary nodes[23].

During the study interval, treatments were based on the Dutch breast cancer treatment guideline of 2012, and definitive treatment choices were left to the discretion of the multidisciplinary team at each hospital. If no completion ALND was undertaken, and regional RT was administered, this consisted of RT of axillary levels I–II. In the event of high-risk disease (2 or fewer

**Table 2 All recurrences, contralateral breast cancers, and vital status at 5-year follow-up**

| | Whole cohort (*n* = 1090) | No completion axillary treatment (*n* = 219) | Completion ALND (*n* = 437) | Regional RT (*n* = 327) | Completion ALND + regional RT (*n* = 107) |
|---|---|---|---|---|---|
| **Regional recurrence** | 9* (0.8) | 3 (1.4) | 4 (0.9) | 2 (0.6) | 0 (0.0) |
| Synchronous distant metastases | 6 | 1 | 3 | 2 | 0 |
| **Local recurrence†** | 12‡ (1.1) | 2 (0.9) | 7 (1.6) | 2 (0.6) | 1 (0.9) |
| Synchronous distant metastases | 3 | 0 | 3 | 0 | 0 |
| **Both regional and local recurrence†§** | 5 (0.5) | 2 (0.9) | 2 (0.5) | 1 (0.3) | 0 (0.0) |
| Synchronous distant metastases | 4 | 2 | 1 | 1 | 0 |
| **Distant metastases as first event** | 63 (5.8) | 9 (4.1) | 27 (6.2) | 16 (4.9) | 11 (10.2) |
| **Contralateral breast cancer** | 12 (1.1) | 2 (0.9) | 6 (1.4) | 2 (0.6) | 2 (1.9) |
| **Vital status** | | | | | |
| Alive | 944 (86.6) | 173 (79.0) | 392 (89.7) | 285 (87.2) | 94 (87.9) |
| Dead | 146 (13.4) | 46 (21.0) | 45 (10.3) | 42 (12.8) | 13 (12.1) |
| **Cause of death** | | | | | |
| Breast cancer | 57 (5.2) | 14 (6.4) | 21 (4.8) | 15 (4.6) | 7 (6.5) |
| Other or unknown type of cancer | < 25 | < 5 | < 10 | < 10 | < 5 |
| Other than cancer | 63 (5.8) | 27 (12.3) | 16 (3.7) | 17 (5.2) | 5 (4.7) |
| Unknown | < 5 | < 5 | < 5 | < 5 | < 5 |

Values are *n* (%). In analyses in which data from Statistics Netherlands was used, adjustments were made (for example < 5 is recorded if there are fewer than 5 patients in a cell) to avoid the risk of revealing the identity of individual patients. *In one patient, local recurrence and distant metastases occurred at a later time. †All local recurrences were invasive breast cancer. ‡In three patients, distant metastases (and a regional recurrence in 1 patient) occurred at a later time. §Regional and local recurrence occurred synchronously in these patients, who were not included in the regional recurrence and local recurrence rows above. ALND, axillary lymph node dissection; RT, radiotherapy.

**Table 3 Five-year regional recurrence rates**

| | No. of events | Regional recurrence rate (%) | HR | P |
|---|---|---|---|---|
| **Whole cohort (*n* = 1090)** | 14 | 1.3 (0.8, 2.2) | – | – |
| **No completion axillary treatment (*n* = 219)** | 5 | 2.5 (0.9, 5.4) | 1.00 (reference) | – |
| **Completion ALND (*n* = 437)** | 6 | 1.4 (0.6, 2.9) | 0.53 (0.16, 1.75) | 0.299 |
| **Regional RT (*n* = 327)** | 3 | 1.0 (0.3, 2.6) | 0.37 (0.09, 1.53) | 0.170 |
| **Completion ALND plus regional RT (*n* = 107)** | 0 | – | – | – |

Values in parentheses are 95% confidence intervals. Cox proportional hazards regression analyses were used to compare the groups, with $P < 0.050$ considered statistically significant. *P* values for other group comparisons were also not significant (not reported). ALND, axillary lymph node dissection; RT, radiotherapy.

macrometastases with risk factors such as age less than 40 years or triple-negative breast cancer, or more than 2 metastases), RT was extended to the periclavicular region and chest wall. If completion ALND was performed, locoregional RT was indicated if there were risk factors such as a total of at least four positive lymph nodes, or lymph node involvement at the mediocranial border of the dissected axilla. This consisted of RT of the chest wall and periclavicular lymph nodes, including the undissected part of the axilla; however, it could exceptionally also include (part of) the dissected axilla. RT was delivered to the internal mammary nodes if considered indicated (for example, if there was extensive lymph node involvement and/or primary tumour located medially). An RT dose of 42.56 Gy was applied in 16 fractions or another dose biologically equivalent to 25 × 2 Gy.

## Outcomes

The primary endpoint was the 5-year regional recurrence (RR) rate. Secondary endpoints were 5-year local recurrence (LR) rate, locoregional recurrence (LRR) rate, distant metastasis (DM) rate, recurrence-free interval (RFi)[24], overall survival (OS), occurrence of contralateral breast cancer, and number of delayed ALNDs. RR included recurrences in ipsilateral axillary levels I–II, the periclavicular region, and internal mammary and intramammary lymph nodes[23]. LR comprised chest wall recurrences (invasive or *in situ* carcinoma), and DM comprised recurrences in any other location, all in accordance with the Maastricht Delphi consensus on event definition by Moossdorff *et al.*[25]. In this study, if DM occurred as first event, no further data were collected with regard to other recurrences that developed at a later time. RR, LR, LRR, and DM rates were based on events occurring between the primary breast cancer diagnosis and 5-year follow-up. Patients were censored if they were lost to follow-up or were still alive at 5-year follow-up without recurrence. Contralateral breast cancer was defined as an invasive tumour in the contralateral breast. RFi was based on the time interval between the primary breast cancer diagnosis and development of an RR, LR, DM, or death from breast cancer, whichever came first, measured in days. Patients were censored if they died from a non-breast cancer cause as first event, or if they were lost to follow-up or still alive at 5-year follow-up without an event. OS was based on the time interval between the primary breast cancer diagnosis until death from any cause, measured in days. Patients were censored if they were lost to follow-up or were still alive at 5-year follow-up. Delayed ALND was defined as an ALND performed for recurrent axillary disease.

## Statistical analysis

Categorical variables are summarized as numbers with percentages, and Pearson's $\chi^2$ test or Fisher's exact test was used to compare groups. Five-year follow-up analyses were performed for RR, LR, LRR, and DM rates, RFi, and OS, in the whole cohort and by axillary treatment group. In addition, supplementary 5-year follow-up analyses were undertaken for patients with macrometastatic disease identified in the SLNB. The cumulative incidence function was used to estimate RR, LR, LRR, and DM rates. In calculations of RR, LR, and LRR rates, distant metastases as first event and death were treated as competing risks, and, in estimations of DM rate,

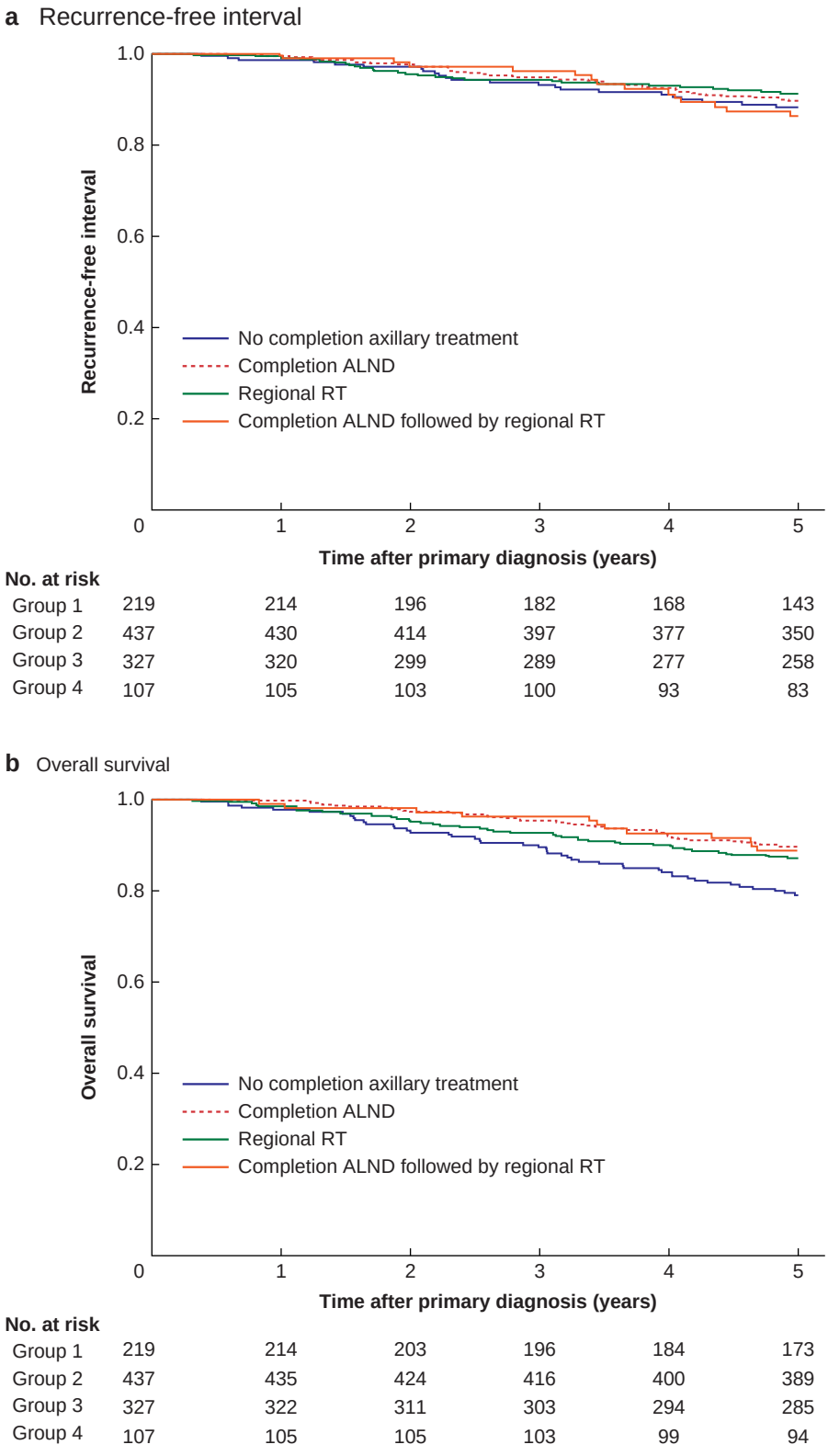


**Fig. 2 Five-year recurrence-free interval and overall survival according to axillary treatment group**

**a** Recurrence-free interval and **b** overall survival. Five-year recurrence-free interval rates were 89.7 (95% c.i. 86.3 to 92.3)% for completion axillary lymph node dissection (ALND) ($P = 0.552$), 91.3 (87.5 to 93.9)% for regional radiotherapy (RT) ($P = 0.300$), and 86.4 (78.1 to 91.7)% for completion ALND followed by regional RT ($P = 0.734$) *versus* 88.3 (82.8 to 92.1)% for no completion axillary treatment; 5-year overall survival rates were 89.7 (86.4 to 92.2)% for completion ALND ($P < 0.001$), 87.2 (83.0 to 90.3)% for regional RT ($P = 0.012$), and 87.9 (80.0 to 92.8)% for completion ALND followed by regional RT ($P = 0.046$) *versus* 79.0 (73.0 to 83.8)% for no completion axillary treatment (log rank test).

death was treated as a competing risk. Cox proportional hazards regression analyses were used to compare groups. Kaplan–Meier survival analyses were performed to assess RFi and OS, with log rank tests used to compare groups. All tests were two-sided, and $P < 0.050$ was considered statistically significant. All analyses were conducted in Stata® SE16.1 (StataCorp, College Station, TX, USA).

# Results

## Patient, tumour, and treatment characteristics

A total of 1142 patients were identified from the NCR, of whom 1090 were eligible for analyses (*Fig. 1*). Fifty-two patients were excluded, as they did not match the inclusion criteria. The median age was 60 (i.q.r. 49–71) years. Characteristics of the study population are summarized in *Table 1*.

Most tumours were hormone receptor-positive and human epidermal growth factor receptor 2 (HER2)-negative (81.3%), grade 2 (56.0%), and/or cT2 at diagnosis (52.5%). The median number of SLNs excised was 2 (i.q.r. 1–3). After SLNB, 73.6% of patients had pN1a(sn) and 26.4% had pN1mi(sn) disease. Most patients (80.0%) had only one SLN with metastasis. Adjuvant chemotherapy was administered to 633 (58.1%), endocrine therapy to 925 (84.9%), and adjuvant RT of the chest wall to 434 (39.8%) of 1090 patients.

Some 219 patients (20.1%) had no completion axillary treatment, 437 (40.1%) underwent completion ALND, 327 (30.0%) had regional RT, and 107 (9.8%) underwent completion ALND and regional RT. Patients who had no completion axillary treatment were more often aged 75 years or higher, and had grade 1 tumours, pN1mi(sn), and a maximum of one positive SLN. Furthermore, LVI was less often present in this group, and fewer patients received chemotherapy or RT of the chest wall. Compared with the group that had completion ALND, those who underwent regional RT were more likely to have pN1mi(sn) disease, and to receive RT of the chest wall. Most patients in the completion ALND and regional RT group had grade 2 or 3 tumours, and they more often presented with LVI, as well as with more extensive axillary disease and larger tumours at surgery. More of these patients had chemotherapy, and chest wall RT was always administered.

## Follow-up results

Median follow-up for recurrence was 6.0 (i.q.r. 5.1–6.7, range 0.1–8.8) years and that for vital status was 8.8 (8.1–9.4, 0.3–10.1) years. All recurrences (RR, LR, and DM), contralateral breast cancers, and vital status (including cause of death) at 5-year follow-up are summarized in *Table 2*.

The overall 5-year RR rate was 1.3 (95% c.i. 0.8 to 2.2)%. Five-year RR rates for the groups who had no completion axillary treatment, completion ALND, and regional RT were 2.5 (0.9 to 5.4), 1.4 (0.6 to 2.9), and 1.0 (0.3 to 2.6)% respectively (*Table 3*). There were no statistically significant differences between groups. No recurrences occurred among patients who had completion ALND and regional RT. In the whole cohort, one delayed ALND was performed owing to a solitary axillary metastasis that developed 2.1 years after the primary cancer diagnosis.

The overall 5-year LR, LRR, and DM rates were 1.7 (1.0 to 2.6), 2.5 (1.7 to 3.5), and 7.2 (5.7 to 8.8)% respectively. Five-year RR, LR, LRR, and DM rates by axillary treatment group are listed in *Table S1*. There were no statistically significant differences between the groups. In the whole cohort, 12 patients (1.1%) developed contralateral invasive breast cancer, 2 (0.9%) of those who had no completion axillary treatment, 6 (1.4%) who received completion ALND, 2 (0.6%) who underwent regional RT, and 2 (1.9%) who had completion ALND and regional RT (*Table 2*).

The overall 5-year RFi and OS rates were 89.5 (87.5 to 91.3) and 86.6 (84.4 to 88.5)% respectively (*Fig. 2*). The 5-year OS rate for the group with no completion axillary treatment (79.0%) was significantly worse than that for patients who underwent completion ALND (89.7%; $P < 0.001$), regional RT (87.2%; $P = 0.012$), or completion ALND and regional RT (87.9%; $P = 0.046$). Of the 146 patients who died, the percentage of non-cancer deaths was 58.7, 35.6, 40.4, and 38.5% in the groups that had no completion axillary treatment, completion ALND, regional RT, and completion ALND and regional RT respectively.

Follow-up results are shown specifically for patients with macrometastasis in the SLNB in *Tables S2*, *S3*, and *Fig. S1*. Again, no statistically significant differences were observed in terms of RR, LR, LRR, and DM rates, and RFi. The 55 patients who had no completion axillary treatment had statistically significantly worse 5-year OS. The median age in this group was 83 (i.q.r. 69–88) years.

# Discussion

In this nationwide registry study, the 5-year RR rate was 1.3% in a cohort of 1090 patients with cT1–2 N0 breast cancer treated with mastectomy, and with low-volume SLN metastasis. Patients in whom completion axillary treatment was omitted were older and had more favourable tumour characteristics. These patients had a 5-year RR rate of 2.5%, which was not significantly different from that of the patients who underwent completion ALND (1.4%), or regional RT (1.0%). Five-year LR, LRR, and DM rates, and RFi also did not differ between groups. The group without completion axillary treatment did have statistically significantly worse 5-year OS, but this was explained by a higher percentage of non-cancer deaths.

A similar but smaller study was reported previously by FitzSullivan *et al.*[26], who performed a retrospective single-centre study of 525 patients, treated between 1994 and 2010, who underwent mastectomy and who had a limited number of SLN metastases (median 1, range 1–4). With a median follow-up of 5.5 years, the 58 patients who had no completion axillary treatment had an extrapolated 10-year RR rate of 3.8%. Forty-seven (81%) of the 58 patients had pN1mi(sn). No statistically significant differences were demonstrated between groups with regard to RR rate, recurrence-free survival, and OS. Zaveri *et al.*[27] identified 548 patients diagnosed between 2006 and 2015, who were treated with mastectomy, and had up to two positive SLNs. With a median follow-up of 5.4 years, the 5-year LRR rate among 126 patients without completion axillary treatment was 1.8%. Sixty-seven (53.2%) of the 126 patients had pN1mi(sn), and 36 (28.6%) received RT. No statistically significant differences were demonstrated between groups (no ALND or ALND (with or without RT)) with regard to LRR, DM, and OS rates. In the present study, 5-year OS for the group with no completion axillary treatment was statistically significantly worse than that of the other groups, even though the number of breast cancer-related events was comparable. This may be largely explained by the fact that these patients were more often aged 75 years or older (39.7% *versus* 18.9% in the whole cohort) and more often died from causes other than cancer (58.7% *versus* 44.4% in the whole cohort).

In this study, patients who had no completion axillary treatment had more favourable tumour characteristics (for example pN1mi(sn) in 74.9%), and less often received adjuvant treatment such as chemotherapy and chest wall RT compared with the other groups. This was also found in an American population-based study[28] of axillary management patterns of 12 190 patients with cT1–2 N0 breast cancer treated with mastectomy, and with one or two SLN metastases. In addition, patients with no axillary treatment in that study more often had co-morbidities. Hence, patients are probably already selected for omission of (axillary) treatment not only based on tumour characteristics but also other important factors such as age and

co-morbidities. In the present study, it is likely that some patients who did not undergo completion axillary treatment already had a shorter life expectancy, which may have contributed to the decision to omit further axillary treatment.

Despite limited evidence regarding oncological safety, completion ALND is being omitted or replaced by regional RT if there is limited SLN involvement in cT1–2 N0 breast cancer treated with mastectomy in daily practice[28–32]. IBCSG 23-01 and AATRM 048/13/2000[5,6,19] were RCTs that included patients with micrometastatic SLNs who underwent mastectomy, and compared ALND with no further axillary treatment. Both trials showed no benefit of completion ALND regarding disease-free survival. Unfortunately, the percentage of included patients treated with mastectomy was quite small in both trials (7 and 9% respectively). Ongoing non-inferiority RCTs on this topic are SINODAR ONE, POSNOC, and SENOMAC[33–35], which are all assessing the oncological safety of omitting completion axillary treatment if there are macrometastatic SLNs. In SINODAR ONE[33], patients with cT1–2 N0 breast cancer and one or two macrometastatic SLNs were randomized between SLNB only and ALND. In a subanalysis limited to 218 patients who underwent mastectomy, with a median follow-up of 33 months, SLNB only was not inferior to ALND in terms of 5-year recurrence-free survival (94.1 *versus* 95.7%) and OS (98.7 *versus* 97.8%)[36]. RT (27 *versus* 8%) and chemotherapy (56.8 *versus* 49.5%) were more often administered in the ALND group. Currently, patients undergoing mastectomy are still being enrolled in the study to increase its power. In the POSNOC trial[34], 1900 patients with cT1–2 N0 breast cancer and 1 or 2 macrometastatic SLNs are being randomized between adjuvant systemic therapy and adjuvant systemic therapy with either ALND or axillary RT, with 5-year axillary recurrence rate as the primary endpoint. The first results are expected in 2026. In SENOMAC[35], 3500 patients with cT1–3 N0 breast cancer and 1 or 2 macrometastatic SLNs are being randomized between SLNB only and ALND. One-year quality-of-life outcomes were published in 2022[37]. The results for the primary endpoint, 5-year breast cancer-specific survival, are awaited. Interestingly, in an interim analysis[38] of generalizability, the authors concluded that older patients were under-represented in the study. All three RCTs excluded either patients aged 75 years or more, or those deemed unfit for adjuvant systemic therapy. This is in accordance with studies evaluating the generalizability of RCTs[39,40], indicating that older patients are under-represented in RCTs. With 206 of 1090 patients (18.9%) being aged at least 75 years, the present study has provided highly relevant results to help guide axillary treatment strategies, including the elderly patient population.

In Western countries, almost one-third of breast cancers occur in patients older than 65 years, with the greatest incidence between 75 and 79 years[41]. These patients tend to have more co-morbidities, and a shorter life expectancy regardless of breast cancer. Therefore, it is of utmost importance to keep these factors in mind when deciding on axillary treatment especially in these patients. Going a step further, one of the recommendations of the Choosing Wisely campaign[42] is not to perform SLNB routinely in patients older than 70 years with hormone receptor-positive/HER2-negative disease. This was based on two RCTs in which most patients received BCS plus RT, and all were treated with adjuvant tamoxifen, showing that omission of SLNB did not compromise long-term survival outcomes[43–45]. In a Canadian population-based cohort study[46], 17 370 woman aged 65–95 years diagnosed with stage I–II breast cancer between 2010 and 2016 were identified. Of these, 1771 (10.2%) did not undergo axillary surgery. These patients were older, had more co-morbidities, and were less likely to receive adjuvant treatment. After propensity score weighting, patients not undergoing axillary surgery had comparable breast cancer-specific survival (HR 0.98), yet worse OS (HR 1.14). Similar results were reported for patients older than 70 years with hormone receptor-positive/HER2-negative disease. The authors suggested that the worse OS was probably explained by competing risks of death from causes other than breast cancer. These findings are similar to those of the present study, which confirmed a higher percentage of non-cancer deaths in the group with no axillary treatment. With the aim of predicting 5-year survival and recurrence, and to subsequently optimize treatment in older patients (aged at least 65 years), the PORTRET tool was developed in 2021[47]. Age, tumour characteristics, co-morbidities according to the ICD-10 classification, and geriatric predictors, such as walking difficulties, dementia or cognitive impairment, polypharmacy, and sensory deficits, were included in this tool.

A strength of the present study was the availability of detailed recurrence and survival data, including cause of death (known in over 95% of patients) for all axillary treatment groups. Owing to its population-based design, this study has provided an overview of real-world clinical practice in Dutch breast cancer care. A limitation is the heterogeneity between groups, and not having co-morbidity data, which precludes firm conclusions being drawn. Nonetheless, the results have demonstrated comparable outcomes when all available data are taken into account, and emphasized the importance of also considering factors such as age and overall health when deciding on treatment strategies. Another limitation is the relatively short median follow-up time of 6.0 years for recurrence for a cohort comprising 91.3% of patients with hormone receptor-positive breast cancer, as these tend to develop recurrences after a longer follow-up[48]. Finally, no data were available on factors that played a role in decision-making regarding axillary treatment strategies.

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## Disclosure

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## Supplementary material

Supplementary material is available at *BJS* online.

## Data availability

Anyone who wishes to access the data can submit a proposal to the NCR. If the proposal is approved by the Privacy Review Board and the scientific committee of the NCR, as well as the authors of this paper, deidentified participant data with a data dictionary will be made available, 3 months after publication at the earliest. More information can be found at https://iknl.nl/en/ncr/apply-for-data.

## Author contributions

Lori van Roozendaal (Conceptualization, Formal analysis, Funding acquisition, Methodology, Supervision, Writing—review & editing), Sabine Linn (Conceptualization, Methodology, Writing—review & editing), Marc Lobbes (Conceptualization, Methodology, Writing—review & editing), Vivianne Tjan-Heijnen (Conceptualization, Methodology, Writing—review & editing), Koen van de Vijver (Conceptualization, Methodology, Writing—review & editing), Jolanda de Vries (Conceptualization, Methodology, Writing—review & editing), AH Westenberg (Conceptualization, Methodology, Writing—review & editing), Sabine de Wild (Data curation, Formal analysis, Methodology, Writing—original draft, Writing—review & editing), Johannes De Wilt (Conceptualization, Funding acquisition, Methodology, Writing—review & editing), Thjis van Dalen (Conceptualization, Methodology, Writing—review & editing), Jos van der Hage (Conceptualization, Methodology, Writing—review & editing), Frederieke van Duijnhoven (Formal analysis, Writing—review & editing), Janine Simons (Methodology, Supervision, Writing—review & editing), Robert-jan Schipper (Formal analysis, Writing—review & editing), Linda de Munck (Data curation, Formal analysis, Writing—review & editing), Sander van Kuijk (Formal analysis, Writing—review & editing), Liesbeth Boersma (Conceptualization, Methodology, Writing—review & editing), Philip Poortmans (Conceptualization, Methodology, Writing—review & editing), Luc Strobbe (Conceptualization, Formal analysis, Methodology, Writing—review & editing), and Marjolein Smidt (Conceptualization, Formal analysis, Funding acquisition, Methodology, Supervision, Writing—review & editing)

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