European Journal of Surgical Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Conditional regional recurrence risk: The effect of event-free years in different subtypes of breast cancer

Marissa L.G. Vane [a, b, *], Martine Moossdorff [a], Marissa C. van Maaren [c, e], Sander M.J. van Kuijk [d], Thiemo J.A. van Nijnatten [f], Lori M. van Roozendaal [a], Evert-Jan G. Boerma [g], Johannes H.W. de WIlt [h], Marjolein L. Smidt [a, b]

[a] Department of Surgical Oncology, Maastricht University Medical Centre, Maastricht, the Netherlands
[b] GROW - School for Oncology and Developmental Biology, Maastricht University Medical Centre, the Netherlands
[c] Department of Research, Netherlands Comprehensive Cancer Organisation, Utrecht, the Netherlands
[d] Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre, Maastricht, the Netherlands
[e] Department of Health, Technology and Services Research. Technical Medical Centre, University of Twente, Enschede, the Netherlands
[f] Department of Radiology and Nuclear Medicine, Maastricht University Medical Centre, Maastricht, the Netherlands
[g] Department of Surgery, Zuyderland Hospital, Heerlen, the Netherlands
[h] Department of Surgical Oncology, Radboud University Medical Centre, Nijmegen, the Netherlands

ARTICLE INFO

Article history:
Accepted 13 November 2020
Available online xxx

Keywords:
Breast cancer
Conditional survival
Regional recurrence
Subtypes of breast cancer

ABSTRACT

Background: Regional recurrence (RR), also known as lymph node recurrence, is an endpoint in several trials concerning reducing axillary treatment in cT1-2N0 breast cancer patients. The risk of RR may decrease with each subsequent event-free year, affecting the yield and consequently usefulness of long (er) follow-up. The aim of this study is to determine the risk of RR as a first event within five years after diagnosis in subtypes of breast cancer, conditional to being event-free for one, two, three and four years.
Methods: From the Netherlands Cancer Registry, cT1-2N0 breast cancer patients diagnosed from 2005 to 2008 were analyzed. Subgroup analysis was performed for pT1-2N+(sn) patients. RR risk was calculated with Kaplan-Meier analysis. Conditional RR (assuming x event-free years) was determined by selecting patients without an event at x years, and calculating the remaining risk for RR within five years after diagnosis.
Results: A total of 18,009 cT1-2N0 (all pN stages) breast cancer patients were included. RR occurred in 1.3% of cT1-2N0 and 1.5% of pT1-2N+(sn) patients. The risk of RR varied between subtypes; it was highest for triple negative tumors and lowest for ER + PR + Her2-and ER + Her2+ tumors. After event-free years, the risk of RR decreased subsequently in both groups and in all subtypes. After two event-free years, the risk of RR was 0.8%.
Conclusion: The absolute yield of follow-up to detect RR beyond two years is low; for every 125 event-free patients, one RR can be expected until five years. This suggests that follow-up longer than two years is of limited value for detecting RR in both clinical and research setting.

Introduction

As a result of several recent randomized controlled trials, the extent of axillary treatment in breast cancer patients is being reduced [1–6]. Since a complete axillary dissection is replaced by radiotherapy, sentinel node only or no axillary treatment at all, regional recurrence (RR), also known as lymph node recurrence, is an important endpoint in these different trials. Endpoints are standardly reported as rates after five and ten-years of follow-up. However, these rates improve when patients remain event-free during follow-up for each consecutive year.

Conditional survival is defined as the probability of surviving an additional x years given that a patient has already survived a number of years after diagnosis [7]. Previous studies assessed conditional OS and DFS among breast cancer patients [8–11] and showed that conditional survival improves over time, in particular

* Corresponding author. Department of Surgical Oncology Maastricht University, Medical Centre P.O. Box 5800 6202, AZ Maastricht, the Netherlands.
E-mail address: marissa.vane@gmail.com (M.L.G. Vane).

https://doi.org/10.1016/j.ejso.2020.11.122
0748-7983/

among patients with worst prognosis at baseline (e.g. stage III versus stage I-II) [11]. This is in accordance with ovarian, colorectal, endometrial, and testicular cancer and melanoma patients, in which prognosis for cancer survivors generally improves with each event-free year [10,12,13]. It is conceivable that in line with OS and DFS the risk for RR might decrease after a number of event-free years.

Adequate duration of follow-up in both clinical and research setting remains controversial. Most studies report their first results after five years, but it has been suggested that most RRs occur in the first few years after diagnosis. This questions the yield and therefore use of longer follow-up for this purpose. Another topic of debate in these randomized controlled trials is whether different subtypes of breast cancer might require a different approach. The benefit of computing an individual's RR rate is gaining more tailored prognostic information and follow-up time for breast cancer survivors.

The aim of this study is to determine the risk of RR as a first event within five years after diagnosis, conditional to being event-free for one, two, three, and four years. This study will focus on clinically node negative breast cancer patients in general, and additionally on patients with sentinel node involvement. Conditional RR will be presented separately for ER + PR + Her2-, ER + PR-Her2-, ER + Her2+, ER-Her2+, and triple negative tumors.

Methods

Data collection

The Netherlands Cancer Registry (NCR) data is based on all new breast cancer patients from all Dutch hospitals. Data on patient-, tumor-, and treatment-related characteristics, prospectively retrieved from patients' records by trained data managers of the Netherlands Comprehensive Cancer Organisation (IKNL). For patients diagnosed between 2005 and 2008, an active follow-up was conducted in which data on first breast cancer event within five years after diagnosis were gathered directly from patient files. Follow-up consisted of yearly physical examination and mammography up to five years after diagnosis [14]. First breast cancer event was registered as new primary ipsilateral breast cancer, contralateral breast cancer, local recurrence (LR), RR or distant recurrence.

Study population

We analyzed the risk of RR (lymph node recurrence) in women between 2005 and 2008 diagnosed with primary invasive breast cancer in the Netherlands. This study focused on the study populations of previous mentioned randomized controlled trials, therefore all breast cancer patients with a clinically T1-2 tumor and clinically node negative status from the NCR data were included. First, the overall clinically T1-2N0 population (consistent with the study population of BOOG 2013–08, SOUND, INSEMA and NCT01821768) was analyzed [6]. Second, patients from this population with a positive sentinel lymph node (SLN) (consistent with the study population of ACOSOG Z0011, IBCSG 23–01, AMAROS, POSNOC, SENOMAC and SINODAR) were analyzed separately [1,3–6]. These patients will be further referred to as the pT1-2N+(sn) subpopulation. Patients were excluded in case of distant metastasis at (or within 91 days of) diagnosis, an incomplete five-year follow-up, treatment with primary systemic therapy, or in case of no sentinel lymph node biopsy (SLNB) or incomplete registered results.

Locoregional treatment

Patients were treated according to the Dutch breast cancer guidelines of 2005 [14]. All patients had clinically T1-2 tumors and were clinically node negative (based on physical examination, axillary ultrasound was common but not mandatory). Locoregional treatment consisted of breast conserving therapy (lumpectomy and whole breast radiotherapy) or mastectomy, both combined with an SLNB. Patients with a positive SLN were treated with an axillary lymph node dissection (ALND) or axillary radiotherapy, in context of the AMAROS trial.

Systemic treatment

Adjuvant systemic treatment was recommended for all pN + breast cancer patients. Adjuvant systemic treatment for N0 patients was recommended for patients <35 years and for patients ≥35 years with risk factors. Risk factors were tumor ≥3 cm, or tumor ≥1 cm and grade III, or tumor ≥2 cm and grade II. Chemotherapy regimen consisted of five courses 5 Fluorouracil, Epirubicin, Cyclophosphamide (FEC) or six courses of Taxotere, Adriamycin and Cyclophosphamide (TAC). Endocrine therapy (Tamoxifen and/or Luteinizing hormone-releasing hormone agonist) was recommended for ER+ and/or PR + tumors. In case of Her2Neu receptor (Her 2) amplification, targeted therapy (trastuzumab) was recommended in addition to chemotherapy.

Endpoints

The primary endpoint was conditional RR, defined as the risk of RR as a first event within five years after diagnosis, conditional to being event-free for one, two, three, and four years. RR included recurrence in an ipsilateral axillary-, infraclavicular-, or supraclavicular lymph node, internal mammary/parasternal or intramammary lymph node [15]. Events within 91 days following diagnosis were regarded as synchronous with the original tumor. Patients were censored at the date of their first event, at the date of last follow-up, or at the date of death. If another event (new primary ipsilateral breast cancer, contralateral breast cancer, local recurrence, RR or distant recurrence) occurred within 91 days of the first recurrence, this was considered synchronous to the first event, and also counted as a first recurrence.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 22.0 (IBM Corporation, Armonk, NY, USA). RR was determined for the overall population and for the subgroup of clinically node negative patients with positive lymph nodes. Kaplan-Meier analysis was used to determine the probability of RR over time. Missing values were disregarded, not imputed. Significance of the difference between the subtypes (ER + PR + Her2-, ER + PR-Her2-, ER + Her2+, ER-Her2+, and ER-PR-Her2-) was tested with the log-rank test. Univariable and multivariable Cox regression was used to determine the effect of subtype corrected for several prognostic variables that may differ among the groups. The risk of conditional RR was calculated by selecting patients who were event free (i.e. no local recurrence, RR, distant recurrence, second primary breast cancer, or death) at one, two, three, and four years. The risk of RR within five years of diagnosis was calculated for each time point and for five approximate subtypes of breast cancer. A p-value ≤0.05 was considered as statistically significant.

Results

Patient demographics and primary tumor characteristics

A total of 18,009 primary clinically T1-2N0 breast cancer patients were included. Patient and tumor characteristics are summarized in Table 1. Median age was 59 years (range 22–98). The most prevalent subtype was ER + PR + Her2-in 9929 patients (55.1%), followed by ER + PR-Her2-in 2032 patients (11.3%), triple negative tumors in 1701 patients (9.5%), ER + Her2+ in 1231 patients (6.8%) and ER-Her2+ in 667 patients (3.7%). Subtype was unknown in 2449 of the patients (13.6%). All patients underwent SLNB for determining axillary lymph node status. Patient and tumor characteristics per subtype are shown in Appendix 1.

The effect of x-event-free years on risk of regional recurrence within five years

The incidence of RR as a first event within five years of diagnosis was 1.3% in the overall cT1-2N0 group, and 1.5% in the subpopulation of pT1-2N+(sn) patients. These results were corrected for confounders, for both the overall cT1-2N0 group and subpopulation of pT1-2N+(sn) (Appendix 2). After one, two, three, and four event-free years, the risk of developing RR in the remaining period decreased in both groups. In the overall cT1-2N0 group, the risk of RR decreased with additional event-free years to 1.1%, 0.8%, 0.6%, and 0.3%, respectively (Table 2). In the pT1-2N+(sn) subpopulation, the risk of RR decreased to 1.2%, 0.8%, 0.6%, and 0.4%, respectively (Table 3). In both the overall cT1-2N0 group and in the pT1-2N+(sn) subpopulation, the risk of RR as a first event, after 2 event-free years was 0.8%.

Regional recurrence as a first event between different subtypes

The risk of RR at diagnosis in the overall cT1-2N0 group varied between subtypes, and was highest for triple negative (3.7%) and lowest for ER + PR + Her2-tumors (0.8%) (Table 2). The difference between the subtypes ER + PR + Her2-and ER + PR-Her2- (0.8% vs 1.5%, p = 0.001); and between ER-Her2+ and triple negative were significant (1.8% vs 3.7%, p = 0.029) (Fig. 1). In the subpopulation of pT1-2N+(sn), the risk of RR at diagnosis also varied between subtypes, and was highest for triple negative (10.7%) and lowest for ER + Her2+ tumors (0.4%) and ER + PR + Her2- (0.5%) (Table 3). The difference between the subtypes in the pT1-2N+(sn) subpopulation were significant in ER + PR + Her2-and ER + PR-Her- (0.5% vs 1.9% p = 0.011), ER + PR-Her- and ER + Her2+ (1.9% vs 0.4%, p = 0.077), ER + Her2+ and ER-Her2+ (0.4% vs 3.4%, p = 0.006) and ER-Her2+ and triple negative (3.4% vs 10.7%, p = 0.015) (Fig. 2).

The effect of x-event-free years on risk of regional recurrence between subtypes

The risk of RR as a first event within five years after diagnosis decreased in all subtypes from both the overall and subgroup, when more event-free years had passed. Triple negative tumors had the worst prognosis at baseline, but showed proportionally the largest decrease (3.7%–0.4%) in the cT1-2N0 group and (10.7%–1.2%), respectively in the pT1-2N+(sn) subgroup. Tumors with the best prognosis at baseline, ER + PR + Her2-in the overall cT1-2N0 group (0.8%–0.2%), and ER + Her2+ tumors (0.4%–0.4%) and ER + PR + Her2- (0.5%–0.2%) in the pT1-2N+(sn) subgroup, showed proportionally the least decrease. After 2 event-free years, the overall risk of developing RR within five years, was less than 1%

Table 1
Patient demographics and tumor characteristics of the cT1-2N0 population (N = 18,009).

Age, years median range	59 22–98	pT-stage, n (%) pT0 pT1 pT2 pT3 pT4 unknown	 1 (0.0) 12332 (68.5) 5422 (30.1) 157 (0.9) 18 (0.1) 79 (0.4)
cT-stage, n (%) cT1 cT2	 13809 (76.7) 4200 (23.3)	pN-stage, n (%) pN0 pN1mi pN1a pN1b pN2 pN3 unknown	 13177 (73.2) 1211 (6.7) 2813 (15.6) 29 (0.1) 519 (2.9) 177 (1.0) 36 (0.2)
Surgical treatment, n (%) breast conserving mastectomy	 12173 (67.6) 5836 (32.4)	Radiotherapy for breast conserving treatment, % (n) yes no	98.0 (11935) 2.0 (238)
Tumor type, n (%) ductal lobular mixed or other	 13640 (75.7) 1858 (10.3) 2511 (14.0)	Chemotherapy, n (%) yes No	 5767 (32.0) 12242 (68.0)
Grade (Bloom-Richardson), n (%) I II III unknown	 4730 (26.3) 7774 (43.2) 4872 (27.0) 663 (3.5)	Hormone therapy for ER + , n (%) yes No	 7102 (47.2) 7935 (52.8)
Subtypes, n (%) ER + PR + Her2-ER + PR-Her2-ER + Her2+ ER-Her2+ triple negative Unknown	 9929 (55.1) 2032 (11.3) 1231 (6.8) 667 (3.7) 1701 (9.5) 2449 (13.6)	Trastuzumab and chemotherapy for HER2 + , n (%) yes no	 933 (49.3) 974 (50.7)

Table 2
Impact of a number of event-free years on the risk of RR as a first event within five years after diagnosis in clinically node negative patients (cT1-2N0).

			Risk of regional recurrence within five years after diagnosis, after x event-free years			
	N	Risk of 5-year RR at diagnosis	After 1 event-free year	After 2 event-free years	After 3 event-free years	After 4 event-free years
All patientsrowhead	18009	1.3% (206/18009)	1.1% (163/17460)	0.8% (117/16693)	0.6% (77/15891)	0.3% (35/14749)
Breast cancer subtypesrowhead						
ER + PR + Her2-rowhead	9929	0.8% (67/9929)	0.8% (61/9695)	0.7% (51/9346)	0.4% (34/8967)	0.2% (16/8316)
ER + PR-Her2-rowhead	2032	1.5% (27/2032)	1.2% (21/1958)	0.9% (15/1873)	0.4% (7/1765)	0.3% (4/1644)
ER + Her2+rowhead	1231	1.4% (15/1231)	1.3% (14/1204)	1.1% (11/1155)	0.7% (7/1098)	0.3% (2/1031)
ER-Her2+rowhead	667	1.8% (11/667)	1.3% (8/641)	0.7% (4/601)	0.6% (3/568)	0.2% (1/525)
Triple negativerowhead	1701	3.7% (54/1701)	2.6% (36/1594)	1.4% (17/1449)	0.9% (10/1351)	0.4% (3/1255)

Table 3
Impact of a number of event-free years on the risk of RR as a first event within five years after diagnosis in clinically node negative patients with a positive SLN (pT1-2N+(sn)).

			Risk of regional recurrence within five years after diagnosis, after x event-free years			
	N	Risk of 5-year RR at diagnosis	After 1 event-free year	After 2 event-free years	After 3 event-free years	After 4 event-free years
All patients	4348	1.5% (58/4348)	1.2% (45/4194)	0.8% (27/4002)	0.6% (19/3798)	0.4% (12/3559)
Breast cancer subtypes						
ER + PR + Her2-	2630	0.5% (13/2630)	0.4% (9/2558)	0.3% (7/2472)	0.2 (5/2372)	0.2% (4/2244)
ER + PR-Her2-	480	1.9% (7/480)	1.5% (5/457)	1.0% (3/438)	0.8% (2/406)	0.8% (2/371)
ER + Her2 +	366	0.4% (1/366)	0.4% (1/328)	0.4% (1/312)	0.4% (1/298)	0.4% (1/279)
ER-Her2 +	336	3.4% (5/157)	3.4% (5/152)	1.5% (2/143)	1.5% (2/137)	0.0% (0/126)
Triple negative	293	10.7% (24/293)	8.7% (18/257)	5.2% (9/220)	2.8% (4/191)	1.2% (1/173)

in the cT1-2N0 group and pT1-2N+(sn) patients (Tables 2 and 3). In the subgroup of pT1-2N+(sn) patients, the risk of developing RR within five years was less than 1% after three event-free years, except for ER-Her2+ (1.5%) and triple negative tumors (5.2%) (Table 3).

Discussion

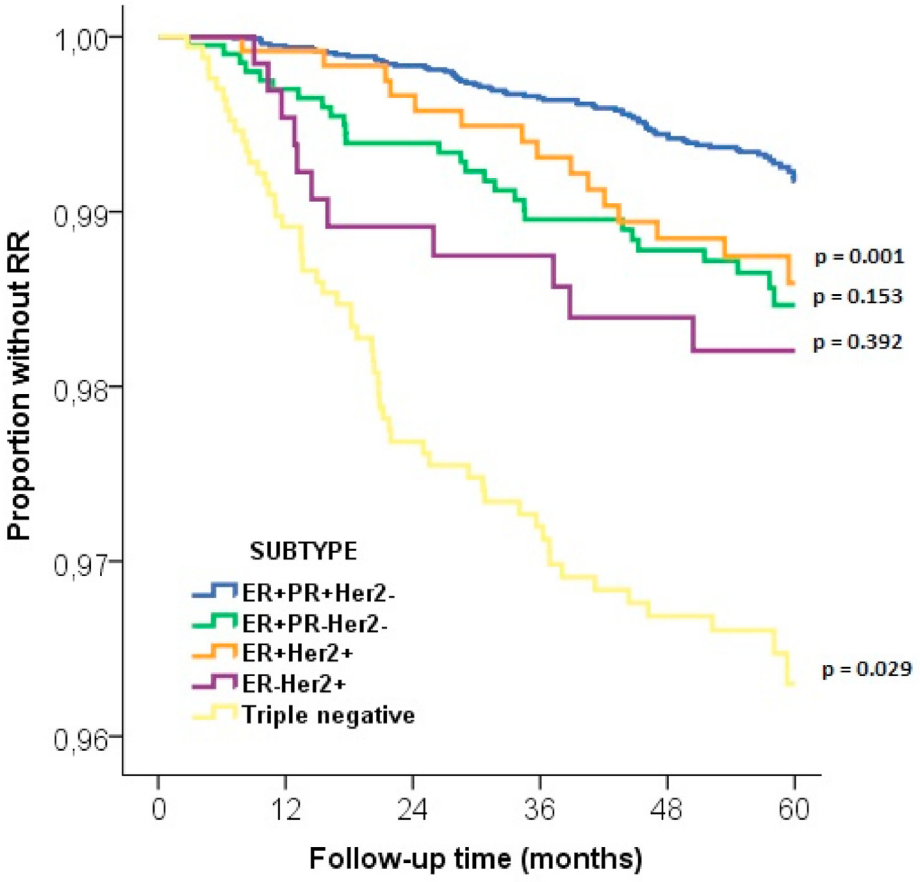
In a large cohort of patients from the national cancer registry in the Netherlands the RR as a first event within five years after diagnosis was determined. Moreover, conditional survival, being event-free for every consecutive year during follow-up, was calculated. In the overall cT1-2N0 group, and in the pT1-2N+(sn) subpopulation the risk of RR was 1.3%, and 1.5% respectively. In the overall group and subpopulation, the risk of RR significantly differed between subtypes. The risk of RR decreased in both groups and in all subtypes when more event-free years passed.

Previous studies showed that conditional DFS and OS improves as time elapses since breast cancer diagnosis [8,9,11]. Janssen-Heijnen et al. showed a clear difference in conditional survival between stage (favorable for stage III versus stage I-II) and between age groups (favorable for age groups 45–54 and 55–64 years). These differences in conditional survival remained significant, but decreased in time [10,11]. Only one study reported the impact of subtype as a prognostic factor on conditional survival. Ten-year RR declined over time, the risk changed from 1.7 to 0.5% for luminal A subtypes and from 4.9 to 0.2% for triple negative tumors [16]. In the current era, subtypes of breast cancer have become more important in addition to traditional prognostic factors, such as age and stage.

The strength of the present study is the large cohort of 18,009 breast cancer patients. All new Dutch breast cancer patients diagnosed between 2005 and 2008 were included. Therefore, all subtypes, including ER + PR + Her2-, ER + PR-Her2-, ER + Her2+, ER-Her2+, and even triple negative tumors are adequately represented in this cohort. Although triple negative breast cancer patients were less frequently diagnosed with a positive SLN at diagnosis compared to other subtypes, these tumors had the highest risk of RR as a first event within five years after diagnosis (3.7% in the overall group and 10.7% in the subpopulation of sentinel node positive patients). The systematic review of Lowery et al. concluded that locoregional recurrence was significantly higher in triple negative tumors compared with other subtypes [17]. Metzger et al. also observed an increased incidence of RR in triple negative tumors compared to other subtypes [18]. In contrast, van Roozendaal et al. showed that RR occurred in only 2.9% of the triple negative cT1-2N0 breast cancer patients [19].

This study showed that the decrease in risk of RR was most explicit in the subtype with the highest risk at baseline (triple negative tumors). This is consistent with previous studies, which suggested that improvement with event-free years is greatest for tumors with the worst prognosis at baseline [11].

Based on these results, physicians can use conditional RR for more patient tailored information after one, two, three and four event-free years classified on subtype. In the clinical setting, follow-up is continued to at least five years after diagnosis. However, after two event-free years, only one in 125 patients will have a RR in the remaining three years of follow-up. This suggests that longer follow-up is of limited value for detection of RR, although this may be required for other reasons. Furthermore, this study showed that most patients with highest risk of RR at baseline (triple negative

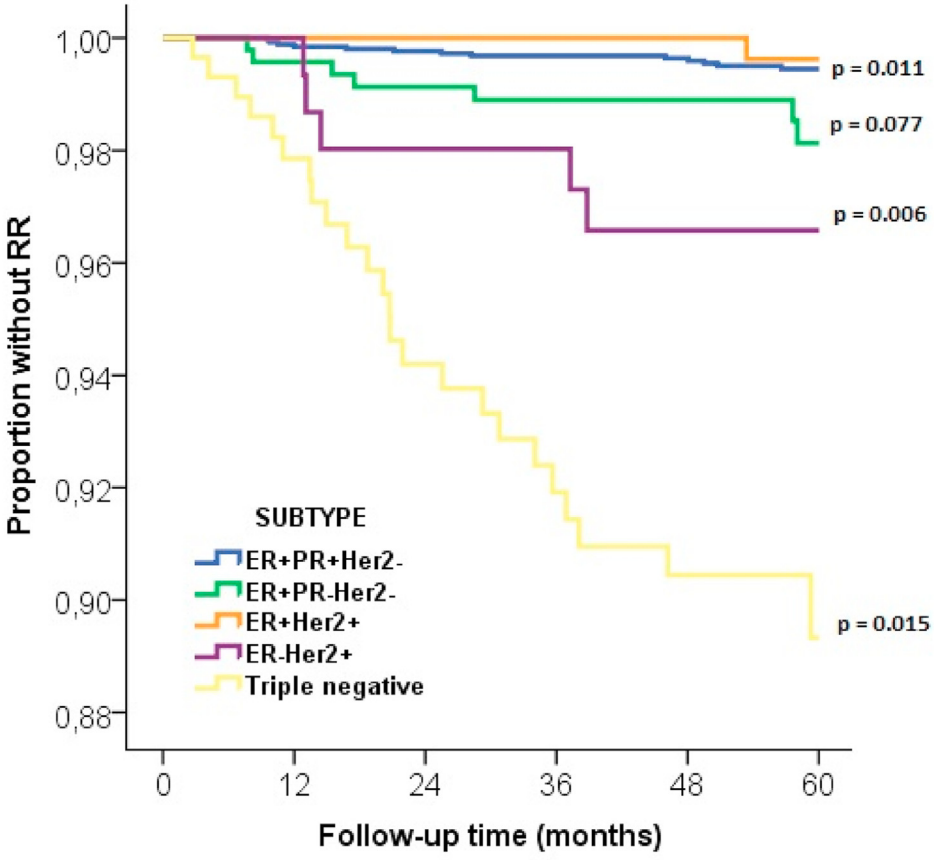


Time (months)	0	12	24	36	48
N at risk	18,009	17,460	16,693	15,814	14,749

Fig. 1. Kaplan Meier curves for regional recurrence as a first event between different subtypes (ER + PR + Her2-, ER + PR-HER2-, ER + Her2+, ER-Her2+ and triple negative) in cT1-2N0 breast cancer after 5 years.

pT1-2N+(sn) tumors) will develop RR early during follow-up. So even in these tumors, follow-up after three years is of limited value for detection of RR. The information on conditional RR can also be used to determine follow-up duration and calculate sample sizes in clinical research using RR as an endpoint, although longer follow-up may be required for other outcomes. Cost-effectives of reducing the follow-up period could be the subject of future investigations.

A limitation of this study is the lack of follow-up beyond five years. However, Matsen et al. showed that the majority of RR in node negative patients occurred within the first five years after surgery [20]. They reported late RR, defined as RR after more than five years of surgery, occurring in only five of the 1529 included patients. The recently published ten-year results of the ACOSOG Z0011 trial showed that from five to ten years of follow-up, only two patients developed a RR in the ALND group versus five in the SLNB alone group [21]. These results imply that late RR after a negative SLNB are extremely rare. The question remains whether this is also applicable to ER + tumors treated with at least five years of hormone therapy, since RR in this subtype continue to occur through 10 years [22,23]. Further, this analysis includes all patients with a positive SLN, i.e. 1-3 and 4 or more, as only the total number of positive nodes was registered and not the number of positive SLNs. Another limitation of this study is that only the first event (RR) within five years after diagnosis was registered, which could have resulted in an underestimated number of events. Finally,



Time (months)	0	12	24	36	48
N at risk	4,348	4,194	4,002	3,798	3,559

Fig. 2. Kaplan Meier curves for regional recurrence as a first event between different subtypes (ER + PR + Her2-, ER + PR-HER2-, ER + Her2+, ER-Her2+ and triple negative) in pT1-2N+(sn) breast cancer after 5 years.

patients were treated according to the Dutch breast cancer guideline of 2005. This differs from current guideline concerning that axillary ultrasound was common but not mandatory. Nowadays, patients without complete response after neoadjuvant chemotherapy, capecitabine will be added. Patients with tumor size >2 cm and HER2+ will receive double treatment. Finally, systemic treatment has become better and more personalized. This all together will decrease the number of events and risk of recurrence.

In conclusion, the overall risk of RR as a first event was low in cT1-2N0 breast cancer patients (1.3%). After one, two, three and four event-free years, the risk of RR decreased in both groups and all subtypes. The absolute yield of follow-up beyond two years concerning RR is low (0.8%); for every 125 event-free patients, one RR can be expected until five-years. This suggests that follow-up longer than two years is of limited value for detecting RR in both clinical and research setting.

CRediT authorship contribution statement

Marissa L.G. Vane: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **Martine Moossdorff:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **Marissa C. van Maaren:** Investigation, Resources, Writing - review & editing. **Sander M.J. van Kuijk:** Software, Validation, Formal analysis, Writing - review & editing. **Thiemo J.A. van**

Nijnatten: Validation, Writing - review & editing. **Lori M. van Roozendaal:** Validation, Writing - review & editing. **Evert-Jan G. Boerma:** Writing - review & editing. **Johannes H.W. de WIlt:** Writing - review & editing, Supervision. **Marjolein L. Smidt:** Conceptualization, Methodology, Investigation, Writing - review & editing, Supervision.

Declaration of competing interest

None of the authors reported have a conflict of interest related to the outcomes of this study.

Acknowledgements

The authors thank the Netherlands Cancer Registry for providing data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2020.11.122.

Funding

This work was supported by CZ fonds 201400316.

Conflicts of interest

M.L. Smidt, has been awarded a grant from Servier Pharma for microbiome research in breast cancer treatment. The remaining authors have no disclosures or conflicts of interest.

Ethical approval

The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Due to its retrospective design, ethical approval was not obtained.

Informed consent

Not applicable.

References

[1] Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. J Am Med Assoc 2011;305(6):569–75.

[2] Galimberti V, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol 2013;14(4):297–305.

[3] Donker M, Slaets L, van Tienhoven G, Rutgers EJ. [Axillary lymph node dissection versus axillary radiotherapy in patients with a positive sentinel node: the AMAROS trial]. Ned Tijdschr Geneeskd 2015;159:A9302.

[4] van Roozendaal LM, de Wilt JH, van Dalen T, van der Hage JA, Strobbe LJ, Boersma LJ, et al. The value of completion axillary treatment in sentinel node positive breast cancer patients undergoing a mastectomy: a Dutch randomized controlled multicentre trial (BOOG 2013-07). BMC Canc 2015;15:610.

[5] Goyal A, Dodwell D. POSNOC: a randomised trial looking at axillary treatment in women with one or two sentinel nodes with macrometastases. Clin Oncol 2015;27(12):692–5.

[6] Gentilini O, Veronesi U. Abandoning sentinel lymph node biopsy in early breast cancer? A new trial in progress at the European Institute of Oncology of Milan (SOUND: sentinel node vs Observation after axillary UltraSouND). Breast 2012;21(5):678–81.

[7] Henson DE, Ries LA, Carriaga MT. Conditional survival of 56,268 patients with breast cancer. Cancer 1995;76(2):237–42.

[8] Allemani C, Minicozzi P, Berrino F, Bastiaannet E, Gavin A, Galceran J, et al. Predictions of survival up to 10 years after diagnosis for European women with breast cancer in 2000-2002. Int J Canc 2013;132(10):2404–12.

[9] Arrington AK, Goldstein L, Kruper L, Vito C, Yim J, Chen SL. Life expectancy after curative-intent treatment of breast cancer: impact on long-term follow-up care. Am Surg 2014;80(6):604–9.

[10] Janssen-Heijnen ML, Gondos A, Bray F, Hakulinen T, Brewster DH, Brenner H, et al. Clinical relevance of conditional survival of cancer patients in europe: age-specific analyses of 13 cancers. J Clin Oncol 2010;28(15):2520–8.

[11] Janssen-Heijnen ML, van Steenbergen LN, Voogd AC, Tjan-Heijnen VC, Nijhuis PH, Poortmans PM, et al. Small but significant excess mortality compared with the general population for long-term survivors of breast cancer in The Netherlands. Ann Oncol 2014;25(1):64–8.

[12] Kurta ML, Edwards RP, Moysich KB, McDonough K, Bertolet M, Weissfeld JL, et al. Prognosis and conditional disease-free survival among patients with ovarian cancer. J Clin Oncol 2014;32(36):4102–12.

[13] Zamboni BA, Yothers G, Choi M, Fuller CD, Dignam JJ, Raich PC, et al. Conditional survival and the choice of conditioning set for patients with colon cancer: an analysis of NSABP trials C-03 through C-07. J Clin Oncol 2010;28(15):2544–8.

[14] Guideline mammacarcinoma 2012 The Netherlands the Netherlands 2012. Available from: http://richtlijnendatabase.nl/en/richtlijn/breast_cancer/locoregional_treatment.html.

[15] Moossdorff M, van Roozendaal LM, Strobbe LJ, Aebi S, Cameron DA, Dixon JM, et al. Maastricht Delphi consensus on event definitions for classification of recurrence in breast cancer research. J Natl Cancer Inst 2014;106(12).

[16] van Maaren MC, de Munck L, Strobbe LJA, Sonke GS, Westenend PJ, Smidt ML, et al. Ten-year recurrence rates for breast cancer subtypes in The Netherlands: a large population-based study. International journal of cancer Journal international du cancer 2019;144(2):263–72.

[17] Lowery AJ, Kell MR, Glynn RW, Kerin MJ, Sweeney KJ. Locoregional recurrence after breast cancer surgery: a systematic review by receptor phenotype. Breast Canc Res Treat 2012;133(3):831–41.

[18] Metzger-Filho O, Sun Z, Viale G, Price KN, Crivellari D, Snyder RD, et al. Patterns of Recurrence and outcome according to breast cancer subtypes in lymph node-negative disease: results from international breast cancer study group trials VIII and IX. J Clin Oncol 2013;31(25):3083–90.

[19] van Roozendaal LM, Smit LH, Duijsens GH, de Vries B, Siesling S, Lobbes MB, et al. Risk of regional recurrence in triple-negative breast cancer patients: a Dutch cohort study. Breast Canc Res Treat 2016;156(3):465–72.

[20] Matsen C, Villegas K, Eaton A, Stempel M, Manning A, Cody HS, et al. Late axillary recurrence after negative sentinel lymph node biopsy is uncommon. Ann Surg Oncol 2016 Aug;23(8):2456–61. https://doi.org/10.1245/s10434-016-5151-1. Epub 2016 Mar 8.

[21] Armando E, Giuliano KH, Ballman Karla V, Beitsch Peter D, Whitworth Pat W, Blumencranz Peter William, et al. Ten-year survival results of ACOSOG Z0011: a randomized trial of axillary node dissection in women with clinical T1-2 N0 M0 breast cancer who have a positive sentinel node. 2016 [Abstract].

[22] Pagani O, Price KN, Gelber RD, Castiglione-Gertsch M, Holmberg SB, Lindtner J, et al. Patterns of recurrence of early breast cancer according to estrogen receptor status: a therapeutic target for a quarter of a century. Breast Canc Res Treat 2009;117(2):319–24.

[23] Saphner T, Tormey DC, Gray R. Annual hazard rates of recurrence for breast cancer after primary therapy. J Clin Oncol 1996;14(10):2738–46.