De-escalation of radiotherapy after primary chemotherapy in cT1-2N1 breast cancer (RAPCHEM; BOOG 2010-03)

De-escalation of radiotherapy after primary chemotherapy in cT1–2N1 breast cancer (RAPCHEM; BOOG 2010–03): 5-year follow-up results of a Dutch, prospective, registry study

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Summary

Background Primary chemotherapy in breast cancer poses a dilemma with regard to adjuvant locoregional radiotherapy, as guidelines for locoregional radiotherapy were originally based on pathology results of primary surgery. We aimed to evaluate the oncological safety of de-escalated locoregional radiotherapy in patients with cT1–2N1 breast cancer treated with primary chemotherapy, according to a predefined, consensus-based study guideline.

Methods In this prospective registry study (RAPCHEM, BOOG 2010–03), patients referred to one of 17 participating radiation oncology centres in the Netherlands between Jan 1, 2011, and Jan 1, 2015, with cT1–2N1 breast cancer (one to three suspicious nodes on imaging before primary chemotherapy, of which at least one had been pathologically confirmed), and who were treated with primary chemotherapy and surgery of the breast and axilla were included in the study. The study guideline comprised three risk groups for locoregional recurrence, with corresponding locoregional radiotherapy recommendations: no chest wall radiotherapy and no regional radiotherapy in the low-risk group, only local radiotherapy in the intermediate-risk group, and locoregional radiotherapy in the high-risk group. Radiotherapy consisted of a biologically equivalent dose of 25 fractions of 2 Gy, with or without a boost. During the study period, the generally applied radiotherapy technique in the Netherlands was forward-planned or inverse-planned intensity modulated radiotherapy. 5-year follow-up was assessed, taking into account adherence to the study guideline, with locoregional recurrence rate as primary endpoint. We hypothesised that 5-year locoregional recurrence rate would be less than 4% (upper-limit 95% CI 7·8%). This study was registered at ClinicalTrials.gov, NCT01279304, and is completed.

Findings 838 patients were eligible for 5-year follow-up analyses: 291 in the low-risk group, 370 in the intermediate-risk group, and 177 in the high-risk group. The 5-year locoregional recurrence rate in all patients was 2·2% (95% CI 1·4–3·4). The 5-year locoregional recurrence rate was 2·1% (0·9–4·3) in the low-risk group, 2·2% (1·0–4·1) in the intermediate-risk group, and 2·3% (0·8–5·5) in the high-risk group. If the study guideline was followed, the locoregional recurrence rate was 2·3% (0·8–5·3) for the low-risk group, 1·0% (0·2–3·4) for the intermediate-risk group, and 1·4% (0·3–4·5) for the high-risk group.

Interpretation In this study, the 5-year locoregional recurrence rate was less than 4%, which supports our hypothesis that it is oncologically safe to de-escalate locoregional radiotherapy based on locoregional recurrence risk, in selected patients with cT1–2N1 breast cancer treated with primary chemotherapy, according to this predefined, consensus-based study guideline.

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Introduction

Primary chemotherapy is increasingly used in patients with breast cancer. This practice challenges defining indications for adjuvant locoregional radiotherapy, as locoregional radiotherapy guidelines were originally based on studies in which patients were treated with primary surgery. Several retrospective studies have identified tumour biology,[1–6] and tumour stage before and after primary chemotherapy,[6–11] as important factors related to locoregional recurrence in patients treated with primary chemotherapy. Most guidelines now state that patients with stage III disease benefit from locoregional radiotherapy, regardless of their response to primary chemotherapy,[12–14] and that patients with cT1–2N0 disease who have a good response to primary chemotherapy do not benefit from locoregional radiotherapy.[13–15] In cT1–2N1 disease (one to three suspicious nodes on imaging before primary chemotherapy, of which at least one has been pathologically confirmed), it is less clear when locoregional radiotherapy is indicated.[13–15] Studies have shown that locoregional radiotherapy in case of pT1–2N1a lowers locoregional recurrence rate and improves survival,[15,16] yet results also suggested that locoregional radiotherapy could be omitted in patients with an estimated low risk of locoregional recurrence. A study concluded that in case of axillary pathological complete response after primary

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Research in context

Evidence before this study

In breast cancer guidelines that described indications for adjuvant locoregional radiotherapy after primary chemotherapy, it is unclear when locoregional radiotherapy is indicated in case of cT1–2N1 disease (one to three suspicious nodes on imaging before primary chemotherapy). Therefore, we searched PubMed for studies published from database inception until Jan 1, 2010, with the search terms "breast cancer", "neoadjuvant chemotherapy" or "primary chemotherapy", "radiotherapy" or "radiation therapy", and "locoregional recurrence", with no language restriction. Since no randomised controlled trials were published, we searched for cohort studies that investigated indications for locoregional radiotherapy in these patients. Studies showed that locoregional radiotherapy for pT1–2N1a reduces locoregional recurrence and improves survival, but that locoregional radiotherapy could be omitted in patients with an estimated low locoregional recurrence risk. Several studies have suggested that in case of an axillary pathological complete response after primary chemotherapy (ie, ypN0), regional radiotherapy and chest wall radiotherapy could be omitted. Hence, it was uncertain in which patients with cT1–2N1 disease treated with primary chemotherapy locoregional radiotherapy was indicated.

Added value of this study

To our knowledge, this is the first prospective study developed to evaluate the oncological safety of de-escalated locoregional radiotherapy in patients with cT1–2N1 breast cancer, according to a predefined consensus-based study guideline. Results from this study suggest that it is oncologically safe to de-escalate locoregional radiotherapy in this group, based on ypN-status, following axillary lymph node dissection (ALND). This study supports the hypothesis that locoregional radiotherapy can be omitted in selected patients in whom ALND is performed (ie, no chest wall radiotherapy and no regional radiotherapy in case of ypN0, and no regional radiotherapy in case of ypN1).

Implications of the available evidence

In the future, the results of this study might lead to more frequent omission of locoregional radiotherapy, which could result in lower morbidity and a better quality of life for patients with breast cancer who are receiving primary chemotherapy. Ongoing, randomised studies will show whether these results can be confirmed, by providing more information with regard to appropriate locoregional treatment strategies for patients with node-positive disease in terms of long-term prognosis, and will help create guidelines for patients in whom ALND is omitted.

chemotherapy (ie, ypN0), only whole breast radiotherapy after breast conserving therapy, and no locoregional radiotherapy after mastectomy, resulted in 10-year locoregional recurrence rates of 0–12·4%, depending on age, tumour size, and primary tumour response.[11] Hence, more evidence is needed to reach a consensus about the most optimal strategy for locoregional radiotherapy in cT1–2N1 disease treated with primary chemotherapy.

See Online for appendix 2

We hypothesised that adjuvant locoregional radiotherapy could be de-escalated in patients with cT1–2N1 breast cancer (one to three suspicious nodes on imaging before primary chemotherapy, of which at least one has been pathologically confirmed) treated with primary chemotherapy. Therefore, a Dutch, prospective, registry study (RAPCHEM, BOOG 2010–03) was developed to evaluate the oncological safety of de-escalated locoregional radiotherapy, according to a predefined consensus-based study guideline. Adherence to the study guideline was evaluated in a previous paper by comparing the volumes irradiated to the study guideline, along with possible explanations for observed practice variation of the participating radiation oncology centres.[17] We found that presence or absence of known risk factors was not associated with deviation from the study guideline. The aim of this study was to assess 5-year locoregional recurrence rate, 5-year recurrence-free interval, and 5-year overall survival, taking into account adherence to the study guideline. We hypothesised that the 5-year locoregional recurrence rate would be less than 4% if the study guideline was followed.

Methods

Study design and participants

In this prospective registry study, patients with cT1–2N1 invasive breast cancer treated with at least three cycles of primary chemotherapy and surgery of the breast and axilla were eligible if referred to one of 17 participating radiation oncology centres in the Netherlands between Jan 1, 2011, and Jan 1, 2015 (appendix 2 p 1).[17] At least one axillary lymph node had to contain a confirmed metastasis, based on a core needle biopsy or fine needle aspiration, or a sentinel lymph node biopsy (SLNB) before primary chemotherapy. Exclusion criteria were four or more suspicious lymph nodes on imaging before primary chemotherapy, distant metastases, or irradical surgery of the primary tumour. Patients were identified from the Netherlands Cancer Registry (NCR), in which they were included via an opt-out recruitment approach, and clinical data were collected from their medical files by specially trained registration clerks of the Netherlands Comprehensive Cancer Organisation. Therefore, written, informed consent was not required. The Institutional Review Board (IRB) of Maastro performed an ethics review, and both the IRB of Maastro and the Privacy Review Board of the NCR approved the study.

Procedures

Treatment was planned according to the Dutch guidelines, which consisted of 6–8 cycles of primary chemotherapy, followed by surgery of the breast and axilla. The study guideline for locoregional radiotherapy was based on the

existing literature at the time of protocol development, and endorsed by the Dutch Breast Cancer Research Group. In the study guideline, based on ypN status, patients were assigned to one of three predefined risk groups: low (ie, ypN0), intermediate (ie, ypN1, one to three positive nodes in surgical specimen after primary chemotherapy), or high (ie, ypN2–3, four or more positive nodes in surgical specimen after primary chemotherapy) risk of developing a locoregional recurrence. Each risk group had its own locoregional radiotherapy recommendations (table 1). In each risk group, radiotherapy consisted of a biologically equivalent dose of 25 fractions of 2 Gy, with or without a boost. During the study period, the generally applied radiotherapy technique in the Netherlands was forward-planned or inverse-planned intensity modulated radiotherapy. Until mid-2013, the vast majority of patients with node-positive (cN+) disease underwent an axillary lymph node dissection (ALND). The outcomes of ACOSOG Z0011[18] resulted in a protocol amendment on March 5, 2013, in which less invasive axillary staging procedures (ie, SLNB before primary chemotherapy, or SLNB or MARI-procedure [marking the axilla with radioactive iodine seed],[19] or both, after primary chemotherapy) were also allowed. Decisions on type of axillary surgery were left to the discretion of the multidisciplinary team. If ALND was omitted, patients were assigned to the risk groups based on the pathology outcomes of the less invasive staging procedure and other factors related to locoregional recurrence. Radiotherapy of the axilla (level I–II) was recommended if ALND was omitted in the intermediate-risk or high-risk group. Intervals between treatment modalities (ie, primary chemotherapy, surgery, radiotherapy) were aimed to be less than 5 weeks.

Follow-up was performed by physical examination and mammography, and was carried out according to the Dutch guideline (ie, at least yearly). The primary endpoint was not centrally reviewed.

	Radiotherapy after breast conserving therapy	Radiotherapy after mastectomy
Low-risk group		
ypN0 (ALND)	Whole breast radiotherapy	..
If SLNB before primary chemotherapy and no ALND: cN1mi (SLNB), no risk factor*; or if SLNB after primary chemotherapy and no ALND: ypN0 (SLNB)	Whole breast radiotherapy	..
Intermediate-risk group		
ypN1 (ALND)	Whole breast radiotherapy	Chest wall radiotherapy
If SLNB before primary chemotherapy and no ALND†: cN1mi (SLNB), ≥1 risk factor*, or cN1 (SLNB), ≤2 macrometastases, no risk factor*; or if SLNB after primary chemotherapy and no ALND†: ypN1mi (SLNB), no risk factor*	Whole breast radiotherapy; in addition axilla level I and II†	Chest wall radiotherapy; in addition axilla level I and II†
High-risk group		
ypN2–3 (ALND)	Whole breast radiotherapy; axilla level III and IV	Chest wall radiotherapy; axilla level III and IV
If SLNB before primary chemotherapy and no ALND†: cN1 (SLNB), with ≤2 macrometastases and ≥1 risk factor*, or ≥3 macrometastases; or if SLNB after primary chemotherapy and no ALND†: ypN1mi (SLNB), ≥1 risk factor*, or ypN1 (SLNB)	Whole breast radiotherapy; axilla level III and IV; in addition axilla level I and II†	Chest wall radiotherapy; axilla level III and IV; in addition axilla level I and II†

ALND=axillary lymph node dissection. SLNB=sentinel lymph node biopsy. *Risk factor: grade 3, lymphovascular invasion, tumour size more than 3 cm. †If ALND was omitted in the intermediate-risk or high-risk group, radiotherapy of the axilla (level I and II) was recommended. Radiotherapy of the axilla (level I and II) after ALND, and radiotherapy of the internal mammary chain were optional.

Table 1: **Study guideline with risk groups based on locoregional recurrence risk, and locoregional radiotherapy recommendations**

Outcomes

The primary endpoint was 5-year locoregional recurrence rate. Secondary endpoints were 10-year locoregional recurrence rate; 5-year, 10-year, and 15-year recurrence-free interval; and 5-year, 10-year, and 15-year overall survival. Since the 10-year and 15-year follow-up timepoints were not yet reached at the time of this primary analysis, these endpoints are not reported here, and only 5-year results are presented in this Article. Locoregional recurrence events comprised ipsilateral in-breast and chest wall recurrence (ie, invasive or ductal carcinoma in situ), and ipsilateral regional recurrence (ie, axillary, internal mammary, or periclavicular metastases). Locoregional recurrence rate was defined as time interval between primary breast cancer diagnosis and occurrence of a (pathologically confirmed) locoregional recurrence as first event, measured in days. If distant metastases occurred first, or within 90 days of the locoregional recurrence (ie, synchronous distant metastases), the locoregional recurrence was not included in the locoregional recurrence rate. Patients were censored if they were still alive without a recurrence at last date of follow-up. Recurrence-free interval was defined as time interval between primary breast cancer diagnosis and occurrence of locoregional recurrence, distant metastases, or death from breast cancer, whichever came first, measured in days.[20] Patients were censored if death from another or unknown cause occurred as first event, or if they were still alive without an event at last date of follow-up. Overall survival was defined as time interval between primary breast cancer diagnosis until death from any cause, measured in days. Patients were censored if they were still alive at last date of follow-up.

Statistical analysis

To show with a *Z*-test that the study guideline resulted in a 5-year locoregional recurrence rate of less than 4%, with 7·8% as upper-limit of 95% CI, 237 patients per risk group were required (one-sided α of 5%, and 80% power; n=711). Enrolment was continued until a total sample size of 848 patients was reached, as previously described.[17]

Categorical variables (eg, age, grade, and breast cancer molecular subtype) were summarised as frequencies and percentages, and χ^2 test or Fisher's exact test was conducted to compare the risk groups. 5-year locoregional recurrence rate, 5-year recurrence-free interval, and 5-year overall survival were assessed for the whole group and per risk group. Post-hoc analyses were performed to take into

account adherence to the study guideline. Locoregional recurrence rate was estimated with the cumulative incidence function, treating distant metastases and death as competing risks, and Kaplan-Meier survival analyses were performed to assess recurrence-free interval and overall survival including 95% CIs of these outcomes. Cox proportional hazards regression analyses and log-rank tests were used to compare the outcomes. To examine whether prognosis differed between patients who underwent ALND (ie, ALND group), and patients in whom ALND was omitted (ie, no ALND group), stratified analyses of 5-year locoregional recurrence rate, 5-year recurrence-free interval, and 5-year overall survival were performed post hoc. Finally, to investigate which patient and tumour characteristics were related to recurrence-free interval (ie, chance of developing any recurrence), post-hoc multivariable analyses were performed in the ALND group. If the p value was 0·2 or less in univariable analysis, variables were included in the multivariable Cox proportional hazards regression analyses. Results were reported as hazard ratios (HRs) with 95% CI. In case of missing data in the patient and tumour characteristics, we first applied multiple imputation in STATA. We considered these missing values as missing at random. Multivariable analyses for locoregional recurrence rate was not performed, due to a low number of locoregional recurrences.

All tests were two-sided, and a p value of less than 0·05 was considered statistically significant. All analyses were conducted in STATA (16.1). The study is registered at ClinicalTrials.gov, NCT01279304.

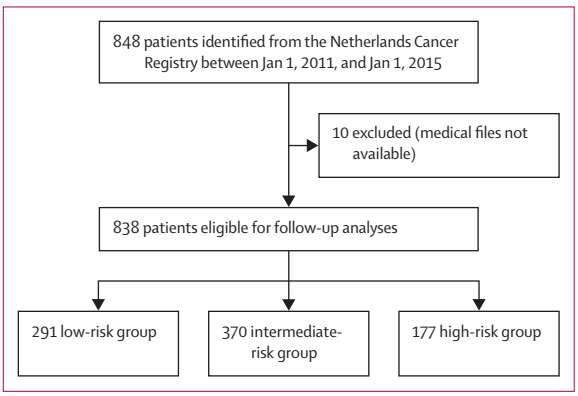

Figure 1: **Study profile**

	Whole group* (n=838)	Low-risk group (n=291)	Intermediate-risk group (n=370)	High-risk group (n=177)	χ^2 p value
Age, years	..	..	..	..	0·0053
<40	101 (12%)	45 (15%)	45 (12%)	11 (6%)	..
40–59	58 (70%)	206 (71%)	256 (69%)	123 (69%)	..
≥60	152 (18%)	40 (14%)	69 (19%)	43 (24%)	..
Molecular subtype	..	..	..	..	<0·0001
HR+, HER2–	534 (64%)	128 (44%)	276 (75%)	139 (80%)	..
HR+, HER2+	108 (13%)	58 (20%)	38 (10%)	12 (7%)	..
HR–, HER2+	57 (7%)	35 (12·1%)	18 (5%)	4 (2%)	..
Triple negative	123 (15%)	69 (24%)	35 (9%)	19 (11%)	..
Hormone receptor missing†	7	1	3	3	..
Grade	..	..	..	..	0·0035
1	123 (19%)	36 (17%)	57 (19%)	30 (20%)	..
2	348 (53%)	92 (44%)	174 (58%)	82 (55%)	..
3	185 (28%)	79 (38%)	68 (23%)	38 (25%)	..
Unknown†	182	84	71	27	..
Lymphovascular invasion	..	..	..	..	0·0013
No	441 (81%)	145 (86%)	208 (82%)	88 (70%)	..
Yes	106 (19%)	23 (14%)	45 (18%)	38 (30%)	..
Unknown†	291	123	117	51	..
Initial tumour size, cm	..	..	..	..	0·064
≤2·0	165 (20%)	46 (16%)	84 (23%)	35 (20%)	..
2·1–5·0	657 (80%)	242 (84%)	275 (77%)	140 (80%)	..
Exact size unknown (≤5·0)†	16	3	11	2	..
Type of breast surgery	..	..	..	..	0·042
Lumpectomy	475 (57%)	175 (60%)	214 (58%)	86 (49%)	..
Mastectomy	363 (43%)	116 (40%)	156 (42%)	91 (51%)	..

(Table 2 continues on next page)

Role of funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

838 patients were eligible for 5-year follow-up analyses: 291 in the low-risk group, 370 in the intermediate-risk group, and 177 in the high-risk group (figure 1). Ten patients were excluded from the 5-year follow-up analyses because their medical files were not available. Characteristics of the study population are summarised in table 2. Median age of the whole group was 49 years (IQR 43–57). All patients were women. We did not collect data on race or ethnicity.

In agreement with the Dutch guidelines, all patients underwent mammography and ultrasound of the breast and axilla. 732 (87%) of 838 patients also underwent breast MRI. Regarding primary chemotherapy regimens, of 838 patients, 137 (16%) were treated with anthracyclines, 59 (7%) with taxanes, and 634 (76%) with both anthracyclines and taxanes.[17] All patients received at least three cycles of primary chemotherapy, and 759 (91%) of 838 patients received at least six cycles of primary chemotherapy. 699 (83%) of 838 patients were irradiated. Radiotherapy dose was biologically equivalent to 25 fractions of 2 Gy, with or without a boost of eight fractions of 2 Gy: 90 (13%) of 699 patients received a 2 Gy fraction schedule, and all other patients (87%) received a 2·66 Gy schedule. A boost to the tumour bed was applied in 377 (54%) patients, in 50 (7%) patients a boost was delivered to the chest wall, and in 41 (6%) of 699 patients to the nodal regions. The irradiated volumes are listed in table 1. Internal mammary chain radiotherapy was given to

40 (6%) of 699 patients (ten in the low-risk group, 18 in the intermediate-risk group, and 12 in the high-risk group).

Median follow-up for disease recurrence was 5·8 years (IQR 5·2–6·4). Median follow-up with regard to vital status was 6·8 years (IQR 6·1–7·9). 43 (5%) of 838 patients were lost to follow-up before reaching 5-year follow-up, without an event reported. Of the 838 patients, 18 patients had a locoregional recurrence as first event (2%), 25 patients had a locoregional recurrence with synchronous distant metastases (3%), and 70 patients had distant metastases as first event (8%; appendix 2 p 2). 65 (8%) of 838 patients died, of whom 26 patients died of breast cancer (40%), and four patients died of another cause (6%). In 35 (54%) of 65 patients the cause of death was not recorded: 33 (94%) of these 35 patients had distant metastases (with or without locoregional recurrence), and one patient had a locoregional recurrence.

For the whole group (n=838), 5-year locoregional recurrence rate was 2·2% (95% CI 1·4–3·4). 5-year locoregional recurrence rate did not significantly differ between risk groups: low-risk versus intermediate-risk group: HR 1·08 (95% CI 0·37–3·10), p=0·89; low-risk versus high-risk group: 1·23 (0·35–4·36), p=0·75; and intermediate-risk versus high-risk group: 1·14 (0·34–3·80), p=0·83 (figure 2). Table 3 shows the outcomes of the performed post-hoc analyses per risk group considering adherence to the study guideline. If the study guideline was followed, locoregional recurrence rate was 2·3% (95% CI 0·8–5·3) for the low-risk group, 1·0% (0·2–3·4) for the intermediate-risk group, and 1·4% (0·3–4·5) for the high-risk group. In each risk group, less or more locoregional radiotherapy than prescribed by the study guideline did not result in significantly altered locoregional recurrence rate. 5-year locoregional recurrence rate if locoregional recurrences with synchronous distant metastases were included are shown in appendix 2 (p 3).

For the whole group (n=838), 5-year recurrence-free interval was 86·4% (95% CI 83·9–88·6), and 5-year overall survival was 92·2% (90·2–93·8). Outcomes of recurrence-free interval and overall survival per risk group are presented in figure 2, and table 3 shows the outcomes when adherence to the study guideline is considered.

Regarding the extent of axillary surgery, post-hoc analyses were performed. 5-year locoregional recurrence rate did not differ between the ALND group and the no ALND group (appendix 2 p 4). Figure 3 illustrates the 5-year recurrence-free interval of the ALND group and the no ALND group. Overall, the ALND group had a worse recurrence-free interval (85·2%, 95% CI 82·3–87·7) than the no ALND group (91·7%, 86·1–95·1; p=0·032). In the low-risk and intermediate-risk group, there was no significant difference between groups. In the high-risk group, the ALND group had a significantly worse recurrence-free interval (69·3%, 60·1–76·5) compared with the no ALND-group (93·8%, 82·0–98·0; p=0·0010). Similar results were found for 5-year overall survival (appendix 2 p 5). Patient and tumour characteristics of patients in the high-risk group are listed in appendix 2 (p 6).

	Whole group* (n=838)	Low-risk group (n=291)	Intermediate-risk group (n=370)	High-risk group (n=177)	χ^2 p value
(Continued from previous page)					
Tumour size after primary chemotherapy, cm	..	..	..	..	<0·0001
≤2·0	580 (72%)	229 (81%)	252 (70%)	99 (59%)	..
2·1–5·0	208 (26%)	47 (17%)	100 (28%)	61 (36%)	..
>5·0	20 (2%)	5 (2%)	6 (2%)	9 (5%)	..
Unknown†	30	10	12	8	..
Response of primary tumour	..	..	..	..	<0·0001
No pathological complete response	542 (74%)	142 (54%)	259 (82%)	141 (91%)	..
Pathological complete response	191 (26%)	122 (46%)	55 (18%)	14 (9%)	..
Unknown†	105	27	56	22	..
Axillary surgery	..	..	..	..	<0·0001
ALND	681 (81%)	234 (80%)	319 (86%)	128 (72%)	..
SLNB before primary chemotherapy, no ALND	90 (11%)	16 (5%)	49 (13%)	25 (14%)	..
SLNB or MARI after primary chemotherapy, no ALND	67 (8%)	41 (14%)	2 (1%)	24 (14%)	..
Radiotherapy	..	..	..	..	<0·0001‡
According to study guideline	533 (64%)	181 (62%)	200 (54%)	152 (86%)	..
Less than study guideline	90 (11%)	2 (1%)	63 (17%)	25 (14%)	..
More than study guideline	214 (26%)	108 (37%)	106 (29%)	0	..
Less or more than study guideline	1 (0%)	0	1 (0%)	0	..

Data are n (%). ALND=axillary lymph node dissection. MARI=marking an axillary metastasis with radioactive iodine. SLNB=sentinel lymph node biopsy. *All patients were women. †Missing and unknown values were excluded from the χ^2 test. ‡Fisher's exact test was conducted if the expected frequency count was less than 5 for more than 20% of cells.

Table 2: **Baseline characteristics**

The outcomes of the post-hoc univariable and multivariable analyses for predictors of recurrence-free interval in the ALND group are shown in appendix 2 (p 7). In multivariable analyses, risk group, triple negative disease, and grade 3 disease were significantly associated with worse recurrence-free interval. A pathological complete response of the primary tumour was significantly associated with improved recurrence-free interval. All other factors analysed were not significantly associated with worse or improved recurrence-free interval.

Discussion

In this prospective registry study of patients with cT1–2N1 breast cancer treated with primary chemotherapy, locoregional recurrence rates were less than 4% for the whole group and for each risk group, with the upper-limit of the 95% CI not exceeding 7·8%, which is in accordance with our hypothesis.

A similar analysis was performed by Haffty and colleagues in 701 patients with cT1–4N1–2 breast cancer, who received primary chemotherapy followed by ALND and locoregional radiotherapy if indicated.[21] In their study with median follow-up of 5·9 years, 43 patients (6%) had

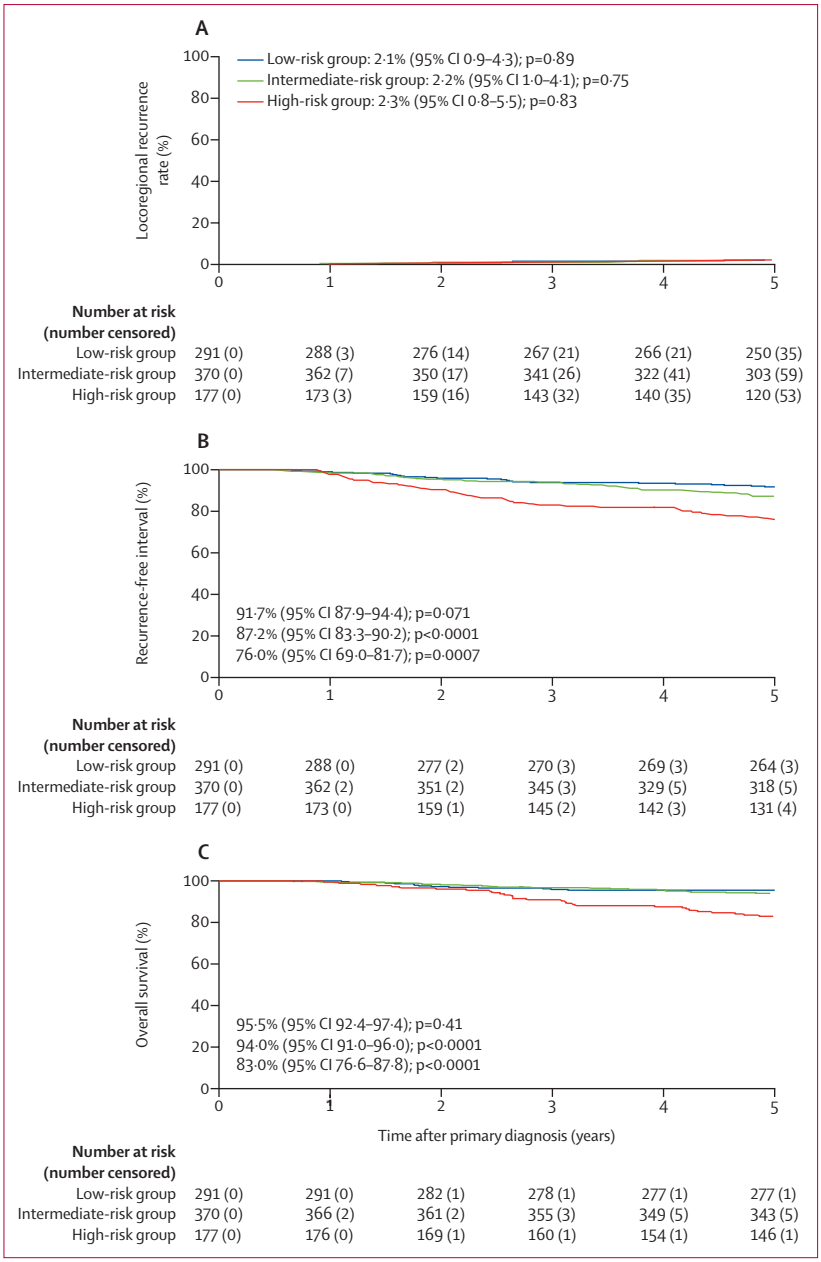

Figure 2: **5-year follow-up results per risk group**
(A) 5-year locoregional recurrence (without synchronous distant metastases). (B) 5-year recurrence-free interval. (C) 5-year overall survival.

a locoregional recurrence, which was a higher risk than we found in our study (2%). However, Haffty and colleagues also included patients with more advanced breast cancer, whereas we also included those with cN1 disease based on a positive SLNB. Moreover, locoregional recurrences with synchronous distant metastases were not included in our locoregional recurrence rate. When locoregional recurrences with synchronous distant metastases were included, locoregional recurrence rates were between 4·9% and 5·8%. Regardless of the differences between studies, Haffty and colleagues concluded that omission of locoregional radiotherapy after mastectomy, and omission of regional radiotherapy after breast conserving therapy, was not associated with worse locoregional recurrence outcomes in ypN0 disease. This is identical to our conclusions about locoregional radiotherapy in the low-risk group.

681 (81%) of 838 patients in our study population underwent ALND, providing an accurate ypN status. When only a less invasive axillary staging procedure was performed, it became more complex to assign patients to the risk groups, as these procedures are less accurate. Therefore, in these patients, we also considered other factors related to locoregional recurrence. However, the criteria to assign patients to the risk groups might not have been entirely correct. For example, patients with ypN0 based on SLNB or MARI-procedure, or both, were assigned to the low-risk group, yet some of these patients might have had residual disease, which would have been detected by ALND; therefore, they should have been assigned to the intermediate-risk or high-risk group. Conversely, patients with limited nodal disease based on the SLNB or MARI-procedure, or both, after primary chemotherapy (ie, ypN1mi with one or fewer risk factors, or ypN1), were assigned to the high-risk group, whereas if ALND would have been performed resulting in the same ypN status, patients would have been assigned to the intermediate-risk group. In the high-risk group, the ALND group had a significantly worse 5-year recurrence-free interval compared with the no ALND group. This finding could be explained by the fact that the ALND group represented fewer patients achieving pathological complete response of the primary tumour, and represented patients with extensive residual axillary disease (ie, ypN2 or ypN3). In the no ALND group, 25 (51%) of 49 patients had no axillary surgery performed after primary chemotherapy (ie, cN1 based on SLNB before primary chemotherapy), and 24 (49%) of 49 patients had ypN1mi or ypN1 disease after primary chemotherapy. These findings suggest that a proportion of the no ALND group had a more favourable ypN status compared with the ALND group, which might have positively affected prognosis. Therefore, these findings must be interpreted with caution.

In patients who underwent ALND, this study guideline did not consider other factors related to locoregional recurrence, besides ypN status. As a result, the low-risk group (ypN0) contained more patients with less favourable triple negative and HER2-positive subtypes, which is counterintuitive, but could have been expected as these subtypes are more often associated with axillary pathological complete response. The intermediate-risk group (ypN1) and high-risk group (ypN2–3) were significantly associated with worse recurrence-free interval in the multivariable analyses. Therefore, dividing patients into risk groups based on ypN status appears a good foundation for estimating locoregional recurrence

	Locoregional recurrence rate*		Recurrence-free interval		Overall survival	
	Number of events	5-year locoregional recurrence rate (% [95% CI])	Number of events	5-year recurrence-free interval (% [95% CI])	Number of events	5-year overall survival (% [95% CI])
Low-risk						
Total (n=291)	6	2·1% (0·9–4·3)	24	91·7% (87·9–94·4)	13	95·5% (92·4–97·4)
According to study guideline (n=181)	4	2·3% (0·8–5·3)	11	93·9% (89·2–96·6)	7	96·1% (92·0–98·1)
Less radiotherapy than study guideline (n=2)	0	NR	0	NR	0	NR
More radiotherapy than study guideline (n=108)	2	1·9% (0·4–6·0)	13	88·0% (80·2–92·8)	6	94·4% (88·1–97·5)
p values†						
According to study guideline *vs* more than study guideline	..	0·86 (HR 0·9 [0·2–4·7])	..	0·076	..	0·50
Intermediate-risk						
Total (n=370)	8	2·2% (1·0–4·1)	47	87·2% (83·3–90·2)	22	94·0% (91·0–96·0)
According to study guideline (n=200)	2	1·0% (0·2–3·4)	19	90·4% (85·4–93·8)	10	95·0% (90·8–97·3)
Less radiotherapy than study guideline (n=63)	2	3·2% (0·6–9·8)	11	82·5% (70·7–89·9)	3	95·2% (86·0–98·4)
More radiotherapy than study guideline (n=106)	4	3·8% (1·3–8·8)	17	83·8% (75·2–89·6)	9	91·4% (84·1–95·4)
More or less radiotherapy than study guideline (n=1)	0	NR	0	NR	0	NR
p values†						
According to study guideline *vs* less radiotherapy than study guideline	..	0·24 (HR 3·3 [0·5–23·2])	..	0·082	..	0·92
According to study guideline *vs* more radiotherapy than study guideline	..	0·11 (HR 4·0 [0·7–21·6])	..	0·079	..	0·22
Less radiotherapy than study guideline vs more or less radiotherapy than study guideline	..	0·83 (HR 1·2 [0·2–6·6])	..	0·86	..	0·35
High-risk						
Total (n=177)	4	2·3% (0·8–5·5)	42	76·0% (69·0–81·7)	30	83·0% (76·6–87·8)
According to study guideline (n=152)	2	1·4% (0·3–4·5)	37	75·4% (67·7–81·5)	27	82·1% (75·0–87·4)
Less radiotherapy than study guideline (n=25)	2	8·4% (1·5–23·5)	5	80·0% (58·4–91·2)	3	88·0% (67·3–96·0)
p values†						
According to study guideline *vs* less radiotherapy than study guideline	..	0·073 (HR 6·0 [0·9–42·6])	..	0·62	..	0·49

HR=hazard ratio. NR=not reported (due to scarce data). *Without synchronous distant metastases. †p values were either derived from Cox proportional hazards regression analyses in case of 5-year locoregional recurrence rate, or from log-rank test in case of 5-year recurrence-free interval and overall survival. Analyses to take into account adherence to the study guideline were performed post-hoc.

Table 3: **5-year results per risk group, taking into account adherence to the study guideline**

rate. However, even in multivariable analysis, triple negative disease, and grade 3 tumours were still significantly associated with worse recurrence-free interval. Therefore, these factors should also be considered when deciding if locoregional radiotherapy is indicated.

30–70% of patients with cN+ disease achieve axillary pathological complete response after primary chemotherapy.[22,23] It is hypothesised that ALND can be omitted in these patients, as axillary pathological complete response is associated with improved prognosis when compared with residual axillary disease.[24,25] Therefore, less invasive axillary surgery procedures are being implemented, in an effort to establish response-guided treatment. This approach has resulted in a decreased use of ALND,[26,27] and an increased use of axillary radiotherapy,[26] also in patients with residual axillary disease.[26] However, as data are scarce,[28] it is unclear whether omitting ALND in cN+ breast cancer is safe with regard to long-term prognosis. In a review on currently available data derived mainly from retrospective patient series,[29] an overview was provided on de-escalating axillary treatment after primary chemotherapy. The reviewed studies showed that if an ALND was omitted, very few axillary recurrences occurred in patients with cN+ disease who converted to ypN0 (based on less invasive surgery). However, the extent of radiotherapy in these studies was not clearly stated. Thus, it is unclear whether the axilla was irradiated or not. It was suggested

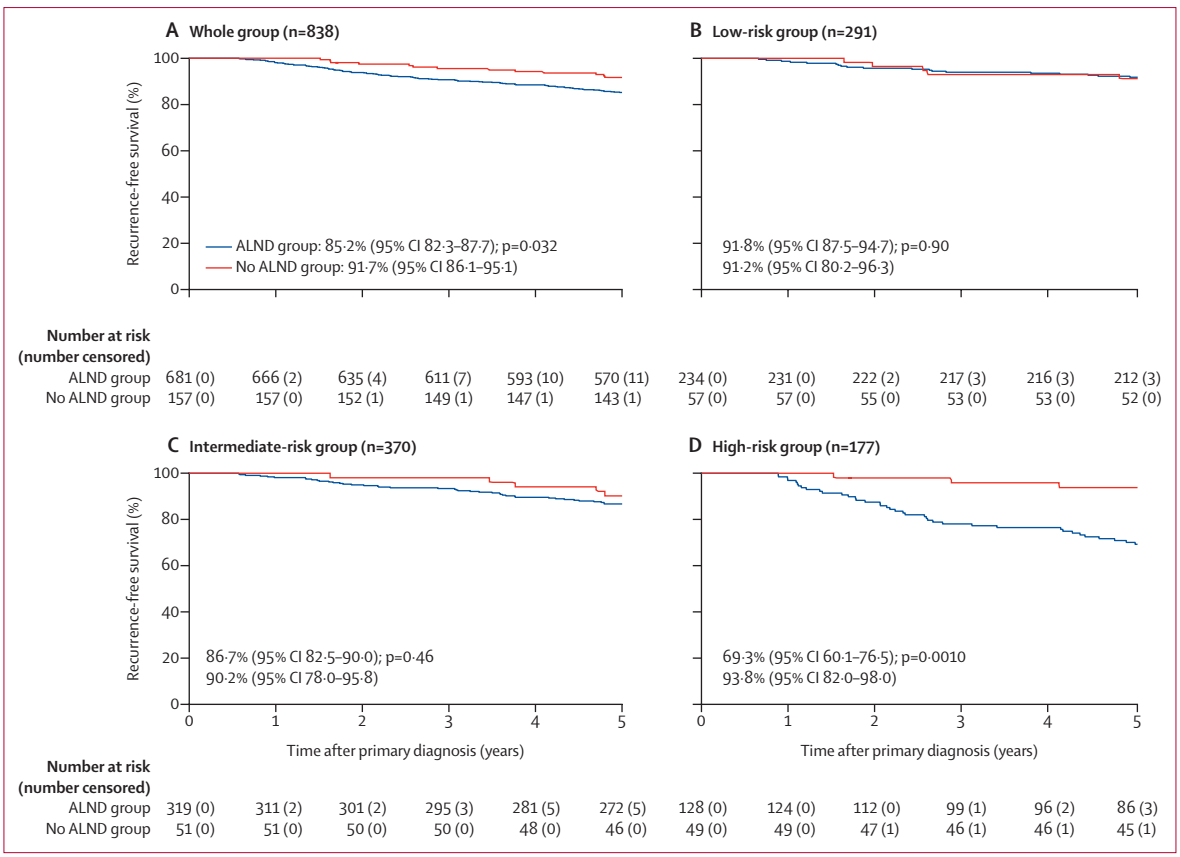

Figure 3: **5-year recurrence-free interval of ALND group versus no ALND group (post-hoc analysis)**
(A) All patients. (B) Low-risk group. (C) Intermediate-risk group. (D) High-risk group. ALND=axillary lymph node dissection.

that local radiotherapy might be omitted in selected patients with ypN0; however, while we await results from ongoing randomised controlled trials and registry-based studies, decisions on de-escalating axillary treatment should be taken with caution, especially when an ALND is omitted. Several ongoing randomised controlled trials are assessing the value of ALND and locoregional radiotherapy in cN+ breast cancer treated with primary chemotherapy. NSABP-B51/RTOG-1304 and ATNEC include patients with axillary pathological complete response (NCT01872975 and NCT04109079), and Alliance A011202 and TAXIS include patients with residual disease (NCT01901094 and NCT03513614). All have disease-free survival as primary endpoint. In addition, MINIMAX (NCT04486495)[30] and AXSANA (NCT04373655) are registry studies that include both patients with axillary pathological complete response and those with residual disease. Together, these trials and registry studies will provide more information regarding appropriate loco-regional treatment strategies for cN+ disease in terms of long-term prognosis and will help to create guidelines for patients in whom ALND is omitted.

A strength of this study was the availability of detailed data regarding locoregional radiotherapy and disease recurrences. Although radiotherapy practices vary widely in cT1–2N1 disease, and adherence to the study guideline was not mandatory, 533 (64%) of 838 patients were treated according to the study guideline. As practice variation is inherent to studies using real-world data, 108 (37%) of 291 patients in the low-risk group and 106 (29%) of 370 patients in the intermediate-risk group received more radiotherapy than prescribed by the study guideline. Remarkably, this did not seem to affect locoregional recurrence rate, recurrence-free interval, and overall survival in a statistically significant or clinically relevant way.

Limitations of our study include the fact that, in each risk group, the actual sample size treated according to the study guideline was smaller than required based on the power calculation. Nevertheless, when performing the analyses in the subset of patients treated according to the study guideline, the upper limit of 95% CI of 5-year locoregional recurrence rate did not exceed 7·8%. These findings support the oncological safety of the study guideline and will likely contribute to more uniform radiotherapy practices. Finally, since we adapted the study based on extrapolation from ACOSOG Z0011,[18] we also included patients in whom ALND was omitted, which made the study population more heterogeneous. However, as the size of the no ALND group was small, we cannot

draw any conclusions regarding these patients. Nevertheless, this study population reflects the population of daily practice, and by taking into account other factors related to locoregional recurrence if ALND is omitted, this study guideline might pave the way to safely de-escalate locoregional radiotherapy in these patients as well.

To conclude, based on the results of this study with cT1–2N1 patients treated with primary chemotherapy, it seems oncologically safe to de-escalate locoregional radiotherapy based on ypN status following ALND. This study supports the hypothesis that locoregional radiotherapy can be omitted in selected patients in whom ALND is performed (ie, no chest wall radiotherapy and no regional radiotherapy in case of ypN0, and no regional radiotherapy in case of ypN1). Randomised controlled trials are needed to further evaluate the effect of de-escalation on disease-free survival and overall survival, both for patients in whom ALND is performed, and for patients in whom ALND is omitted. In the future, this approach based on response to primary chemotherapy and type of surgery might lead to locoregional radiotherapy being more often omitted, and might therefore result in less morbidity and better quality of life for patients with breast cancer who are treated with primary chemotherapy.

Contributors

This study was conceived and designed by TvD, PHME, RMAH, SCL, RMP, PMPP, LJAS, JW, ACV, and LJB. AEvL arranged data management performed by the registry team of the Netherlands Comprehensive Cancer Organisation. SRdW performed data analysis and prepared the manuscript. LdM and JV accessed and verified the data. SRdW, JMS, LdM, JV, ACV, PMPP, and LJB interpreted the data. All authors had full access to all the data in this study, read and edited the manuscript thoroughly, and approved the final manuscript. The corresponding author had the final responsibility to submit for publication.

Declaration of interests

For data management of the RAPCHEM study, LJB received a grant from Dutch Cancer Society (grant number 2010-4679). SCL reports grants from AstraZeneca, Eurocept Plaza, Roche, Genentech, Gilead Sciences, Tesaro, Novartis, Dutch Cancer Society, ZonMw, and A Sister's Hope; consulting fees from AstraZeneca, European Research Council (ERC), and NWO (Dutch Research Council); other financial support (eg, for attending meetings or travel) from Daiichi Sankyo, ESMO, ERC, and NWO; and non-financial support (ie, drugs, and gene expression tests) from Genentech, Roche, Gilead Sciences, Novartis, Agendia, and AstraZeneca, outside the submitted work. SCL has a patent (UN23A01/P-EP) pending. SCL is Chair of the Trial Steering Committee of the PIONEER trial (NCT03306472), and member of the Health Council of the Netherlands. All other authors declare no competing interests.

Data sharing

Anyone who wishes to access the participant data can submit a proposal at the Netherlands Cancer Registry (NCR). If the proposal is approved by the Privacy Review Board and the scientific committee of the NCR, as well as by the principal investigators of the RAPCHEM study, de-identified 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. The study protocol is available in appendix 2.

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References

1 Jwa E, Shin KH, Kim JY, et al. Locoregional recurrence by tumor biology in breast cancer patients after preoperative chemotherapy and breast conservation treatment. *Cancer Res Treat* 2016; **48:** 1363–72.

2 Yang TJ, Morrow M, Modi S, et al. The effect of molecular subtype and residual disease on locoregional recurrence in breast cancer patients treated with neoadjuvant chemotherapy and postmastectomy radiation. *Ann Surg Oncol* 2015; **22** (suppl 3): S495–501.

3 Meyers MO, Klauber-Demore N, Ollila DW, et al. Impact of breast cancer molecular subtypes on locoregional recurrence in patients treated with neoadjuvant chemotherapy for locally advanced breast cancer. *Ann Surg Oncol* 2011; **18:** 2851–57.

4 Caudle AS, Yu TK, Tucker SL, et al. Local-regional control according to surrogate markers of breast cancer subtypes and response to neoadjuvant chemotherapy in breast cancer patients undergoing breast conserving therapy. *Breast Cancer Res* 2012; **14:** R83.

5 Mittendorf EA, Buchholz TA, Tucker SL, et al. Impact of chemotherapy sequencing on local-regional failure risk in breast cancer patients undergoing breast-conserving therapy. *Ann Surg* 2013; **257:** 173–79.

6 Swisher SK, Vila J, Tucker SL, et al. Locoregional control according to breast cancer subtype and response to neoadjuvant chemotherapy in breast cancer patients undergoing breast-conserving therapy. *Ann Surg Oncol* 2016; **23:** 749–56.

7 Buchholz TA, Katz A, Strom EA, et al. Pathologic tumor size and lymph node status predict for different rates of locoregional recurrence after mastectomy for breast cancer patients treated with neoadjuvant versus adjuvant chemotherapy. *Int J Radiat Oncol Biol Phys* 2002; **53:** 880–88.

8 Buchholz TA, Tucker SL, Masullo L, et al. Predictors of local-regional recurrence after neoadjuvant chemotherapy and mastectomy without radiation. *J Clin Oncol* 2002; **20:** 17–23.

9 Garg AK, Strom EA, McNeese MD, et al. T3 disease at presentation or pathologic involvement of four or more lymph nodes predict for locoregional recurrence in stage II breast cancer treated with neoadjuvant chemotherapy and mastectomy without radiotherapy. *Int J Radiat Oncol Biol Phys* 2004; **59:** 138–45.

10 Huang EH, Tucker SL, Strom EA, et al. Postmastectomy radiation improves local-regional control and survival for selected patients with locally advanced breast cancer treated with neoadjuvant chemotherapy and mastectomy. *J Clin Oncol* 2004; **22:** 4691–99.

11 Mamounas EP, Anderson SJ, Dignam JJ, et al. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. *J Clin Oncol* 2012; **30:** 3960–66.

12 Reinert T, de Souza ABA, Sartori GP, Obst FM, Barrios CH. Highlights of the 17th St Gallen International Breast Cancer Conference 2021: customising local and systemic therapies. *Ecancermedicalscience* 2021; **15:** 1236.

13 Nationaal Borstkanker Overleg Nederland. Guideline: treatment of breast cancer. 2017. https://www.vkgn.org/files/5035/Richtlijn%20Mammacarcinoom%20(NABONCBOVKGN,%202017).pdf (accessed Feb 2, 2022).

14 National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: breast cancer, version 2. 2022. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1419 (accessed Jan 13, 2022).

15 Recht A, Comen EA, Fine RE, et al. Postmastectomy radiotherapy: an American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology focused guideline update. *Pract Radiat Oncol* 2016; **6:** e219–34.

16 McGale P, Taylor C, Correa C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 2014; **383:** 2127–35.

17 Boersma LJ, Verloop J, Voogd AC, et al. Radiotherapy after primary CHEMotherapy (RAPCHEM): practice variation in a Dutch registration study (BOOG 2010-03). *Radiother Oncol* 2020; **145:** 201–08.

18 Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomised clinical trial. *JAMA* 2011; **305:** 569–75.

19 Donker M, Straver ME, Wesseling J, et al. Marking axillary lymph nodes with radioactive iodine seeds for axillary staging after neoadjuvant systemic treatment in breast cancer patients: the MARI procedure. *Ann Surg* 2015; **261:** 378–82.

20 Gourgou-Bourgade S, Cameron D, Poortmans P, et al. Guidelines for time-to-event end point definitions in breast cancer trials: results of the DATECAN initiative (Definition for the Assessment of Time-to-event Endpoints in CANcer trials). *Ann Oncol* 2015; **26:** 873–79.

21 Haffty BG, McCall LM, Ballman KV, Buchholz TA, Hunt KK, Boughey JC. Impact of radiation on locoregional control in women with node-positive breast cancer treated with neoadjuvant chemotherapy and axillary lymph node dissection: results from ACOSOG Z1071 clinical trial. *Int J Radiat Oncol Biol Phys* 2019; **105:** 174–82.

22 Samiei S, Simons JM, Engelen SME, Beets-Tan RGH, Classe JM, Smidt ML. Axillary pathologic complete response after neoadjuvant systemic therapy by breast cancer subtype in patients with initially clinically node-positive disease: a systematic review and meta-analysis. *JAMA Surg* 2021; **156:** e210891.

23 Dominici LS, Negron Gonzalez VM, Buzdar AU, et al. Cytologically proven axillary lymph node metastases are eradicated in patients receiving preoperative chemotherapy with concurrent trastuzumab for HER2-positive breast cancer. *Cancer* 2010; **116:** 2884–89.

24 Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet* 2014; **384:** 164–72.

25 von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol* 2012; **30:** 1796–804.

26 Simons JM, Koppert LB, Luiten EJT, et al. De-escalation of axillary surgery in breast cancer patients treated in the neoadjuvant setting: a Dutch population-based study. *Breast Cancer Res Treat* 2020; **180:** 725–33.

27 Al-Hilli Z, Hoskin TL, Day CN, Habermann EB, Boughey JC. Impact of neoadjuvant chemotherapy on nodal disease and nodal surgery by tumor subtype. *Ann Surg Oncol* 2018; **25:** 482–93.

28 van Loevezijn AA, van der Noordaa MEM, Stokkel MPM, et al. Three-year follow-up of de-escalated axillary treatment after neoadjuvant systemic therapy in clinically node-positive breast cancer: the MARI-protocol. *Breast Cancer Res Treat* 2022; **193:** 37–48.

29 Senkus E, Cardoso MJ, Kaidar-Person O, Łacko A, Meattini I, Poortmans P. De-escalation of axillary irradiation for early breast cancer - has the time come? *Cancer Treat Rev* 2021; **101:** 102297.

30 de Wild SR, Simons JM, Vrancken Peeters M, Smidt ML, Koppert LB, Group M. MINImal vs MAXimal invasive axillary staging and treatment after neoadjuvant systemic therapy in node positive breast cancer: protocol of a Dutch Multicenter Registry Study (MINIMAX). *Clin Breast Cancer* 2022; **22:** 59–64.