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CLINICAL TRIAL

De-ESCAlating RadioTherapy in breast cancer patients with pathologic complete response to neoadjuvant systemic therapy: DESCARTES study

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Abstract

Purpose Neoadjuvant systemic therapy (NST) is increasingly used in breast cancer patients and depending on subtype, 10–89% of patients will attain pathologic complete response (pCR). In patients with pCR, risk of local recurrence (LR) after breast conserving therapy is low. Although adjuvant radiotherapy after breast conserving surgery (BCS) reduces LR further in these patients, it may not contribute to overall survival. However, radiotherapy may cause early and late toxicity. The aim of this study is to show that omission of adjuvant radiotherapy in patients with a pCR after NST will result in acceptable low LR rates and good quality of life.

Methods The DESCARTES study is a prospective, multicenter, single arm study. Radiotherapy will be omitted in cT1-2N0 patients (all subtypes) who achieve a pCR of the breast and lymph nodes after NST followed by BCS plus sentinel node procedure. A pCR is defined as ypT0N0 (i.e. no residual tumor cells detected). Primary endpoint is the 5-year LR rate, which is expected to be 4% and deemed acceptable if less than 6%. In total, 595 patients are needed to achieve a power of 80% (one-side alpha of 0.05). Secondary outcomes include quality of life, Cancer Worry Scale, disease specific and overall survival. Projected accrual is five years.

Conclusion This study bridges the knowledge gap regarding LR rates when adjuvant radiotherapy is omitted in cT1-2N0 patients achieving pCR after NST. If the results are positive, radiotherapy may be safely omitted in selected breast cancer patients with a pCR after NST.

Trial registration: This study is registered at ClinicalTrials.gov on June 13th 2022 (NCT05416164). Protocol version 5.1 (15-03-2022).

Keywords Breast cancer · Neoadjuvant systemic therapy · Breast-conserving surgery · Radiotherapy · Neoplasm Recurrence · Local · Quality of Life

Abbreviations

BCS	Breast conserving surgery
BCT	Breast conserving therapy
CESM	Contract-enhanced spectral mammography
DCIS	Ductal carcinoma in situ
FDG-PET CT	Fluorodeoxyglucose-positron emission tomography computed tomography
HER2	Human epidermal growth factor Receptor 2
HR	Hormone receptor
LR	Local recurrence
LRR	Locoregional recurrence
LVI	Lymphovascular invasion
MRI	Magnetic resonance imaging
Mx	Mastectomy
NST	Neoadjuvant systemic therapy
OS	Overall survival
pCR	Pathologic complete response
QOL	Quality of life
TN	Triple negative
XMG	Mammograph

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Introduction

Neoadjuvant systemic treatment (NST) is increasingly used in breast cancer treatment, resulting in tumor downsizing and an increase in breast conserving therapy (BCT) rates without compromising local recurrence (LR) rates or overall survival (OS) [1–4]. The extent of tumor downsizing is largely dependent on breast cancer molecular subtypes, with highest pathologic complete response (pCR) rates in triple negative (TN) and Human epidermal growth factor Receptor 2-positive (HER2 +) subtypes (40–89%) and lower pCR rates of 10–15% in Hormone Receptor positive (HR +)/HER2-breast cancer [5–11]. In patients with a pCR, de-escalation of locoregional treatment after NST seems attractive. However, de-escalation of locoregional treatment by omitting surgery is not considered safe, since post-NST biopsies or MRI cannot accurately assess pCR yet [12–16]. Adjuvant whole breast irradiation, however, may be de-escalated in pCR patients who do not have an indication for regional irradiation [17]. As radiotherapy following breast conserving surgery (BCS) is associated with pain, deformation of the breast and fibrosis in up to 40% of patients [18–21], omitting radiotherapy in patients with pCR should lead to less deterioration in quality of life (QOL).

In this patient group, risk of distant and local failure after breast conserving therapy (BCT, i.e. BCS and radiotherapy) is low [22–26]. A retrospective study by Mamounas et al. concluded that absence of pCR was the most important independent predictor of 10-year locoregional recurrence (LRR) in patients treated with BCT or mastectomy (ypN-/no breast pCR vs ypN-/breast pCR Hazard Ratio 1.55 and ypN + vs ypN-/breast pCR Hazard Ratio 2.71, $n = 2961$) [23]. In 225 clinically node-negative patients with pCR treated with BCT, 10-year LRR rates were reported of 7.6% and 6.3% for patients < 50 and ≥ 50 years respectively [23].

Recent studies in patients with stage I-III disease treated with contemporary systemic treatments, who underwent pre-NST staging with MRI and axillary ultrasound (*N* ranged between 243 and 426) reported 5-year LRR rates between 1.0 and 3.5% after BCT [22, 24–26]. In the highest reported LRR rate, isolated tumor cells were also considered as pCR [26].

A small recent retrospective series of 197 cT1-4N0-3 patients who achieved pCR following NST and who underwent BCS with ($n = 87$) or without ($n = 110$) radiotherapy, reported 5-year LR rates varied between 0 and 3.2% in patients who did not receive adjuvant radiotherapy [27]. *(M. Asaoka, personal communication).*

As the risk of LR in patients with pCR after NST is extremely low and considering that radiotherapy may cause considerable morbidity, we will investigate the safety of omitting radiotherapy after BCS. We expect that the omission of radiotherapy will result in acceptable low LR rates and that patients' QOL will be safeguarded both in terms of physical and psychological wellbeing (Fig. 1).

Methods

Objective

The primary aim is to investigate our hypothesis that omitting radiotherapy after BCS in breast cancer patients with a pCR after NST results in a 5-year local control rate of $> 96\%$. Secondary objectives are to show that by omitting radiotherapy, patient's QOL, particularly in terms of cancer worry levels, will remain good. The 5-year LR rate, distant and regional metastasis free survival and local non-salvageable recurrence free survival will be assessed, as will the 10-year OS.

Study design

The DESCARTES study is a prospective multicenter single arm study (Fig. 1).

Study population

Eligibility of patients will be assessed at multi-disciplinary meetings. Breast cancer patients with an unifocal and unilateral cT1-2N0 tumor, irrespective of the hormone receptor and HER2-status, treated with NST and BCS and who achieved pCR after NST will be considered for inclusion. NST (including chemotherapy, immunotherapy HER2-targeted and endocrine therapy) is administered according to institutional guidelines at time of diagnosis. A pCR is defined as ypT0N0 (i.e., absence of invasive carcinoma, in-situ carcinoma or isolated tumor cells in the breast and absence of carcinoma or isolated tumor cells in the lymph nodes). If pCR of breast and lymph nodes is achieved, patients may be included into the single-arm study after obtaining informed consent, in which radiotherapy of the breast is omitted.

To participate in this study, a subject must meet all of the criteria described in Table 1.

Locoregional treatment and adjuvant systemic treatment

A marker should be placed in the center of the tumor before start of NST. Contrast-enhanced breast MRI or contrast enhanced spectral mammography (CESM) is conducted pre-NST for response evaluation. Axillary status is evaluated

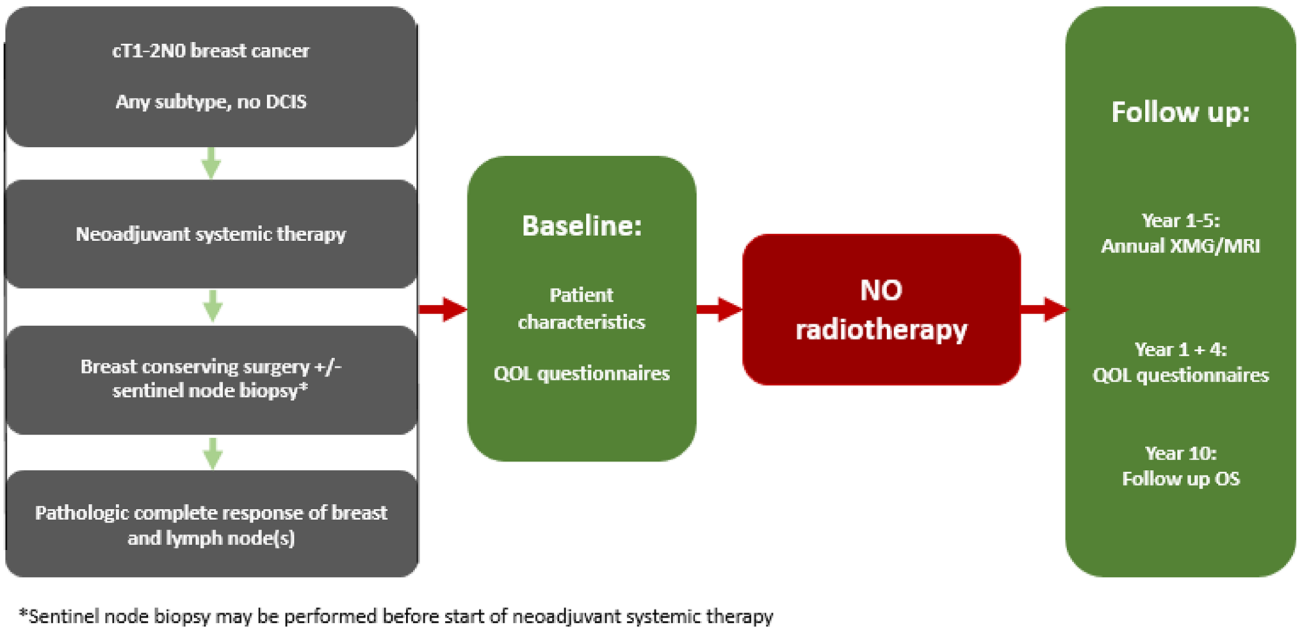

Fig. 1 Overview of the procedures in the DESCARTES study

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Women, aged ≥ 18 years	Primary tumor (T) clinical stage cT3-4
Invasive HR + /HER2-, HR + /HER2 + , HR-/HER2 + or TN breast cancer	DCIS associated with invasive carcinoma or elsewhere in the ipsilateral breast
Primary tumor (T) clinical stage cT1-2	Pre- or post-NST diagnosis of nodal disease including isolated tumor cells
Unifocal disease	Patients without axillary ultrasound or FDG-PET CT pre-NST
Clinical nodal stage N0; absence of lymph node metastases should be confirmed by ultrasound or FDG-PET CT	History of breast cancer in the ipsilateral breast
Treatment with NST and BCS	Synchronous contralateral breast cancer or DCIS
Sentinel node biopsy performed before or after NST	Synchronous M1 disease
pCR in breast and lymph nodes, i.e., no residual tumor cells detected	Carrier of a gene mutation associated with increased risk of breast cancer, i.e., BRCA1, BRCA2, CHEK2, TP53 or PALB2
Written informed consent	

HR hormone receptor; *HER*2 human epidermal growth factor Receptor 2; *TN* triple negative; *FDG-PET CT*, fluorodeoxyglucose-positron emission tomography computed tomography; *NST* neoadjuvant systemic therapy; *BCS* breast conserving surgery; *pCR* pathologic complete response; *DCIS* ductal carcinoma in situ

pre-NST by ultrasound or FDG-PET/CT. In case of suspicious axillary lymph node(*s*), fine needle aspiration or core biopsy is performed for pathology analysis to confirm node-negative disease.

Following NST, BCS is performed. A post-NST sentinel node biopsy procedure (if not performed pre-NST) is performed using single or dual-tracer technique. The surgical specimen will be assessed by a specialized breast pathologist according to national guidelines. Adjuvant systemic therapy is administered according to national breast cancer guidelines [28].

Table 2 Overview of follow-up

	Imaging	Questionnaires
Baseline		Education level, 12-item intolerance of uncertainty scale, EORTC-QLQ-C30, EORTC-QLQ-BR23, Cancer Worry Scale
1 year after surgery	Mammography/MRI	EORTC-QLQ-C30, EORTC-QLQ-BR23, Cancer Worry Scale
2 years after surgery	Mammography/MRI	
3 years after surgery	Mammography/MRI	
4 years after surgery	Mammography/MRI	EORTC-QLQ-C30, Cancer Worry Scale, EORTC-QLQ-BR23
5 years after surgery	Mammography/MRI	

Follow up

Patients will be followed for a period of 10 years. The LR is assessed in the first 5 years with a yearly mammography or MRI according to the national guidelines. At 10 years the overall survival will be assessed.

The QOL is measured using EORTC-QLQ-C30 [29] and EORTC-QLQ-BR23 [30] at baseline, year 1 and year 4. The 8-item Cancer Worry Scale [31] will be used to measure if worry related to omission of radiotherapy may affect QOL at the same time points. Two demographic variables (education level and tolerance for uncertainty) will be measured at baseline as these patient characteristics could be associated with QOL and level of experienced cancer worry and need to be considered in the analyses (Table 2).

Study endpoints

The primary endpoint of the study is the LR rate, defined as recurrence in the ipsilateral breast. Any LR is considered an event and is included in the analysis. Time to LR is calculated from the date of surgery to the occurrence of the LR.

Secondary endpoints include time to LR from date of first diagnosis, distant metastases free survival, local non-salvageable recurrence free survival and disease free survival after 5 years and OS after 5 and 10 years. QOL will be compared to norm values and a score of > 14 on the Cancer Worry scale is considered clinically relevant [31].

Sample size calculation and safety analysis

Reported 5-year LR and LRR rates for patients with stage 2 and 3 disease (cT1-4N0-3) treated with NST, BCS and radiotherapy who achieve pCR, range from 0 to 3.5%, where patients with DCIS [24–26] and even isolated tumor cells (one report, with highest reported LRR of 3.5%) [26] were included in the pCR group.

As radiotherapy in primary breast cancer reduces recurrence with at least a factor 2.5, LR at 5 years without radiotherapy could be in the range of 0–8.75% for pCR patients [32].

Recently, 5-year LR rates in NST patients treated with breast conserving surgery without radiotherapy were reported in a small group of 110 pCR patients, with a very low LR rate of 1.8%. Notably, this concerned a group of cT1-4N0-3 patients, with 57% of patients being node-positive. In addition, residual DCIS was included in the pCR group [27].

As we will include only node negative patients with tumors < 5 cm AND will exclude patients with residual DCIS, we may expect the recurrence rate to be on the lower side of the hypothesized range of 0–8.75%. For our statistical analysis, we have therefore used an expected rate of LR rate of 4%.

A 5-year LR rate of less than 6% is deemed acceptable, as studies have shown that the effect of radiotherapy on LR is mainly achieved in the first 5 years following treatment [33], especially in TN and HER2 + subtypes, which will constitute the majority of our population. Simulations were performed to calculate the sample size of a two stage single arm trial (including an interim analysis of safety), using the one sample log rank test. Assuming a 5-year follow up and a 5-year uniform accrual, assuming as well an exponential distribution for survival, it is calculated that the expected number of events when 325 patients are included should be at most six under the null hypothesis. An analysis of safety will be performed after inclusion of 325 patients and a minimum median follow up time of 16.2 months. If less or equal events are observed at that time, the trial continues and 595 patients in total are needed to achieve a power of 80% (with a one-side alpha of 0.05) to achieve non-inferiority of the primary endpoint. The expected number of events during the study are 35 to exclude a LR rate at 5 years of 6% or more, if the actual LR rate is 4%.

Table 3 Local and locoregional recurrence rates following NST

Author	Year	cTNM	Molecular subtype	Sample size	Treatment	pCR	5-year in breast recurrence (%)	5-year locoregional recurrence (%)
Chen et al. (22)	1987–2000	T1-4N0-1*	not specified	157	BCS + RT	Unknown**	1	3
Vila et al. (24)	1997–2005	T0-4N0-3	not specified	656	BCS + RT	Unknown	2.9	5.5
Vila et al. (24)	1997–2005	T0-4N0-3	not specified	250	BCS + RT or Mx ± RT	Yes, pTis included	–	3.2
Swisher et al. (25)	2005–2012	T0-4N0-3	All	243	BCS + RT	Yes, pTis included	–	1.0
–	–	–	HR + /HER2-	61	BCS + RT	Yes, pTis included	–	0
–	–	–	HR + /HER2 +	48	BCS + RT	Yes, pTis included	–	0
–	–	–	HR-/HER2 +	42	BCS + RT	Yes, pTis included	–	2.6
–	–	–	HR-/HER2-	92	mastectomy/ BCS + RT	Yes, pTis included	–	1.4
Gillon et al. (26)	2001–2006	T1-4N0-3	All	1553	mastectomy/ BCS + RT	unknown	1.9	4.9
–	–	–	–	283	mastectomy/ BCS + RT	Yes, pTis and pTitc included	3.5	–
–	–	–	–	426	mastectomy/ BCS + RT	Yes, pCR of lymph nodes	–	2.3

*patients with non-inflammatory breast cancer excluded and ** no LVI, pCR or solitary residual invasive tumor of < 2 cm

LVI lymphovascular invasion; *pCR* pathologic complete response; *HR* hormone receptor; *HER*2 human epidermal growth factor Receptor 2; *BCS* breast conserving surgery; *RT* radiotherapy; *Mx* mastectomy

Discussion

Over 60% of women who are diagnosed with breast cancer in the Netherlands are treated with systemic treatment, which is administered before locoregional treatment (NST) in 40% of breast cancer patients. NST may result in pCR in over 60% of patients depending on breast cancer subtype with the highest rates in TN and HER2 + subtypes [10, 11]. In patients with pCR, risk of LR is low [23–26].

As mentioned in the introduction, Mamounas et al. reported retrospectively on 10-year LRR rates varying from 6.3% (≥ 50 years old) to 7.6% (< 50 years old) in clinically node negative patients with nodal and breast pCR after NST and BCS ($n = 225$) [23]. The pCR definition included patients with residual in situ disease and axillary lymph node status was assessed by palpation only. However, this overview confirmed that the absence of pCR was the most important negative predictor for LRR [23]. Five-year LRR rates reported by more recent studies including up-to-date systemic treatments and staging varied between 1.0 and 3.5%.(Table 3) Notably, isolated tumor cells were considered as pCR in studies with the highest reported LRR rates [24–26].

The effect of omitting radiotherapy on survival was investigated by Mandish et al. in 364 out of 5383 patients with cT0-4N0-3 breast cancer treated with NST and breast conserving surgery who showed pCR of both breast and lymph nodes. Within this study population, which mainly concerns women ≥ 70 with grade 1 disease, omission of radiotherapy did not compromise survival, as 5-year OS rates did not significantly differ (93.6% with RT and 93% without RT, adjusted hazard ratio 1.33, 95% CI 0.76–2.31, $p = 0.3181$) [32].

Radiotherapy of the breast is associated with short- and long-term morbidity in up to 50% of patients [18, 20, 21, 34] consisting of, pain and fibrosis of the breast and impaired cosmetics, and slightly increased risks of radiation induced tumors and cardiac morbidity [18–20, 34, 35]. De-escalation of local therapy by partial breast and hypo-fractionated radiotherapy in selected patients has been shown to positively affect quality of life by reducing fibrosis whilst maintaining local control rates and without compromising survival [36–38].

Omitting radiotherapy altogether was investigated in patients undergoing primary breast conserving surgery, i.e. without NST. In the PRIME-II trial patients aged > 65 years with node negative breast cancers of < 3 cm were

Table 4 Local recurrence rates for patients treated with NST and breast conserving surgery ± radiotherapy

Molecular subtype	BCS followed by RT		BCS without RT	
	Total (N)	5-year LR (%)	Total (N)	5-year LR (%)
All	87	1.1%	110	1.8%
Luminal	8	0 (0%)	16	0 (0%)
Luminal HER2 +	19	0 (0%)	31	1 (3.2%)
HER2 +	18	0 (0%)	31	0 (0%)
TN	42	1 (2.4%)	32	1 (3.1%)

Patients were cT0-4N0-3, with 57% being node positive. For pCR definition, ypTis was included. *BCS* breast conserving surgery; *RT* radiotherapy; *LR* local recurrence; *HER2* human epidermal growth factor Receptor 2; *TN* triple negative

randomized to standard treatment with whole breast irradiation or study treatment in which radiotherapy was omitted. Although 5-year LR rate was higher in the experimental arm (4.1% vs 1.3%), absolute LR was low in both arms and there was no difference in OS [39]. In the Netherlands, omitting radiotherapy is already implemented for a group of older patients with low risk of recurrence (> 70 y/o, stage I breast cancer) following primary surgical treatment [40].

For patients receiving NST, data on LR when omitting radiotherapy are limited. Asoaka et al. reported on LR following NST and BCS when radiotherapy was omitted. Of the 197 cT1-4N0-3 patients with pCR following NST and BCS that were included, 110 did not receive adjuvant radiotherapy [27]. Notably, 57% of patients included in the study presented with node positive disease and patients with residual disease in situ were considered as pCR. Five-year LR rates without radiotherapy were 0% for luminal and HER2 subtype, 3.1% for TNBC and 3.2% for luminal HER2 + breast cancer as shown in Table 4.

Knowledge regarding the effect of treatment de-escalation on cancer worry and fear of recurrence is limited, but the literature consistently shows that fear of recurrence is one of the key issues that cancer patients and survivors face. However, as shown by Raphael et al. patients are more likely to opt out of radiotherapy when using patient decision aids, despite considering risk of recurrence and peace of mind as important characteristics to base their decision on [41]. This study will provide valuable information on whether omitting radiotherapy poses an unacceptable psychological burden for patients.

Our experience is that, in the Netherlands, patients are willing to participate in de-escalation trials, provided they can choose de-escalation themselves rather than being allocated to omission of treatment or not. With approximately 1250 patients with cT1-2N0 breast cancer to be treated annually with NST, which will be mainly TN and HER2 + patients, and a conservatively estimated pCR rate of 55% in this group, over 680 patients may be eligible annually. Expecting to include 125 patients yearly, the required number of 595 patients will be included within the 5 years allotted for accrual.

Based on the low recurrence rates of patients with pCR after NST, radiotherapy in the context of a pCR may be seen as overtreatment. This trial will fill the information gap regarding LR rates when radiotherapy is omitted. If this trial confirms that LR risk is low when omitting radiotherapy, (i.e. 4%), and patients have good quality of life and cancer worry levels remain below the clinical significant threshold [31], this strategy should be offered as a safe alternative to patients with pCR in a shared decision making process supported with patient decision aids [41].

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Author contributions FHvD conceived the DESCARTES study, participated in the design of the study and supervised the drafting of this manuscript. AKEvH participated in the design of the study and drafted the first version of this manuscript. JPvO, LJB, JHM, NSR, JT, EGE, EJTR and MTFDVP participated in the design of the study and critically reviewed the previous versions of this manuscript. All authors approved the final version of the manuscript.

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Data availability statement Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Declarations

Competing interests The authors have no relevant financial or non-financial interests to disclose.

Ethical approval This study protocol is examined and approved by the accredited Medical Research Ethics Committee of The Netherlands Cancer Institute Antoni van Leeuwenhoek (reference: METC21.1046/M21CAR).

Consent to participate Informed consent of all individual participants will be obtained before inclusion in the study.

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