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Feasibility of a prospective, randomised, open-label, international multicentre, phase III, non-inferiority trial to assess the safety of active surveillance for low risk ductal carcinoma in situ – The LORD study

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Abstract ***Background:*** The current debate on overdiagnosis and overtreatment of screen-detected ductal carcinoma in situ (DCIS) urges the need for prospective studies to address this issue. A substantial number of DCIS lesions will never form a health hazard, particularly if it concerns non- to slow-growing low-grade DCIS. The LORD study aims to evaluate the safety of active surveillance in women with low-risk DCIS.
Design: This is a randomised, international multicentre, open-label, phase III non-inferiority trial, led by the Dutch Breast Cancer Research Group (BOOG 2014-04) and the European Organization for Research and Treatment of Cancer (EORTC-BCG 1401). Standard

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Active surveillance

treatment will be compared to active surveillance in 1240 women aged ⩾45 years with asymptomatic, screen-detected, pure low-grade DCIS based on vacuum-assisted biopsies of microcalcifications only. Both study arms will be monitored with annual digital mammography for a period of 10 years. The primary end-point is 10-year ipsilateral invasive breast cancer free percentage. Secondary end-points include patient reported outcomes, diagnostic biopsy rate during follow-up, ipsilateral mastectomy rate and translational research.

Feasibility: To explore interest in and feasibility of the LORD study we conducted a survey among EORTC and BOOG centres. A vast majority of EORTC and BOOG responding centres expressed interest in participation in the LORD study. The proposed study design is endorsed by nearly all centres.

1. Background

The introduction of population-based mammographic breast cancer screening programmes and the implementation of digital mammography have led to impressive increase in incidence of ductal carcinoma in situ (DCIS) [1–7]. This increase is not clearly associated with a substantial decrease in incidence of advanced invasive breast cancer (iBC), and since a proportion of DCIS will either not progress to iBC or progress at a much later stage in life, it is suggested that overdiagnosis and resultant overtreatment exist [8–13]. Currently, in the United States, approximately one woman is diagnosed with DCIS for every four women diagnosed with iBC [7]. In the Netherlands in 2012, 14,296 women were diagnosed with iBC and 2245 women were diagnosed with non-invasive pre-stage breast cancer. Of these, approximately 80% were DCIS. The European standardised rate of non-invasive, pre-stage breast cancer has increased almost fivefold from 1989 to 2012 in the Netherlands – 4.9 per 100,000 to 22.3 per 100,000. About one in six of all DCIS cases was a low-grade disorder [14].

The goal in treating patients with DCIS is to prevent development of iBC. The conventional treatment of DCIS is similar to that of early-stage iBC, i.e. wide local excision (WLE) often followed by radiotherapy (RT), or mastectomy, and possibly hormonal therapy (HT). The outcomes in patients with DCIS treated by these conventional therapies are excellent, but the best way to manage DCIS is still subject to debate.

The natural history of DCIS is not clear, since traditionally, patients diagnosed with DCIS are treated. Therefore, series of patients not treated for DCIS are not available [15]. However, there exists strong circumstantial evidence that DCIS is a non-obligate precursor lesion of iBC [16]. Studies where DCIS was initially misdiagnosed as benign and treated by biopsy alone suggest that between 50% and 85% of all DCIS will never progress into iBC [15]. From autopsy series we have learned that the proportion of middle-aged women who harboured undetected DCIS ranged from 10% to 39% [17].

A range of proliferative breast lesions like DCIS have been considered risk indicators or precursor lesions and carry a relative risk of iBC ranging from 1.2 to 10 [16]. Lobular carcinoma in situ (LCIS) is generally considered a risk indicator, inferring an increased rate of development of iBC, either in the ipsilateral or contralateral breast, of about 1–2% per year, and a relative risk similar to that of DCIS (8–10) [18–23]. Strikingly, low-grade DCIS is intensively treated, and coincidentally-found classical LCIS is managed by active surveillance [18].

Unfortunately, accurate prognostic factors to distinguish potentially life-threatening DCIS from non-hazardous pre-invasive lesions are lacking. The aggressive subtypes require intensive treatment, but apparently indolent DCIS might be managed by active surveillance [24]. Progression from DCIS to iBC constitutes a complex biological phenomenon [16,25]. It has been hypothesised that breast cancer evolution can be classified into two groups: a low- and high-grade breast neoplasia family [16,26–30]. The low- and high-grade multistep model of breast cancer progression based on morphological, immunophenotypical and molecular features described by Lopez-Garcia et al. suggests that if low-grade DCIS progresses to invasive disease this will be low-grade iBC with favourable characteristics in most cases and survival rates after treatment of this invasive cancer will still be excellent. This model is supported by other studies [25,31]. Furthermore, it has been hypothesised that progression from low-grade pre-stage breast cancer to high-grade iBC is an uncommon biological phenomenon [16,31,32].

Four randomised controlled trials that begun between 1985 and 1990 showed that adjuvant RT after WLE reduced local failure rates, but did not reduce the risk of metastases or breast cancer death for patients with DCIS as a whole. A subgroup of patients in whom RT can be omitted could not be identified [33–36]. Few studies prospectively evaluated the outcomes after WLE only in a subgroup of DCIS patients. The Eastern Cooperative Oncology Group (ECOG) 5194 trial (low- or intermediate-grade DCIS ⩽2.5 cm or high-grade DCIS ⩽1.0 cm excised with final margins ⩾3 mm)

found that after a median follow-up time of 6.7 years, 26 invasive ipsilateral breast events occurred in 565 women with low/intermediate-grade DCIS treated by WLE only [37]. Wong et al. performed a phase II, single-arm, prospective trial in patients with small low- or intermediate grade DCIS, and wide excision with final microscopic margins $\geqslant$1 cm. Among 143 patients treated by WLE only, only six developed an invasive local recurrence as first event within 8 years [38].

Strong imaging markers to guide therapy decisions in DCIS have been lacking. Studies have shown that magnetic resonance imaging (MRI) is more sensitive than mammography for identifying iBC, and – in particular high and intermediate grade – DCIS [39–44]. The potential role of MRI in the routine diagnostic workup of DCIS is controversial [45,46]. It might be a useful tool to diminish the overtreatment of indolent screen-detected lesions, and prevent the undertreatment of aggressive DCIS and underestimated invasive disease.

1.1. Rationale

The question has been raised whether intensive treatment for low-risk DCIS might be considered overtreatment [47]. A substantial number of DCIS lesions will never form a health hazard, particularly if it concerns non- to slow-growing low-grade DCIS. This implies that many women might be unnecessarily going through intensive treatment resulting in a decrease in quality of life and an increase in health care costs, without any survival benefit. The LORD (LOw Risk Dcis) study is a randomised, international, multicentre, open-label, phase III non-inferiority trial that assesses the safety of active surveillance in women with low-risk DCIS. The leading groups are the Dutch Breast Cancer Research Group (BOOG) and the European Organisation for Research and Treatment of Cancer (EORTC). To explore interest in and feasibility of the LORD study, to map standard approach of low-risk DCIS in different countries and to investigate the possible role of MRI in the LORD study, we conducted a survey among EORTC and BOOG centres. Here we present the LORD study protocol and discuss the results of the explorative feasibility survey.

2. Design

2.1. Objectives of the trial

2.1.1. Primary objective

The primary objective of the LORD study is to determine whether low-grade DCIS can safely be managed by an active surveillance strategy or that conventional treatment, being either WLE alone, WLE + RT, or mastectomy, and possibly HT, followed by active surveillance, will remain standard of care. Safety will be measured by ipsilateral invasive breast cancer-free percentage at 10 years (10-year iiBC-free%). Details on the primary end-point will be discussed in the statistical section.

2.1.2. Secondary objectives

Secondary objectives/end-points of the LORD include:

- Patient reported outcomes
- Cost-effectiveness
- Central collection of imaging data and bio samples for future translational research purposes

By integrating clinical, imaging, morphological and molecular data of both retrospective DCIS series and the prospective LORD study, we aim at developing a tool, reliably distinguishing harmless from aggressive screen-detected DCIS, that may help clinicians and women with DCIS to decide between management by active surveillance or more intensive treatment.

- Rate of invasive disease at final pathology specimen in the conventional treatment arm
- Rate of DCIS grade II/III at final pathology specimen in the conventional treatment arm
- Biopsy rate during follow-up
- Ipsilateral mastectomy rate
- Time to ipsilateral DCIS grade II/III
- Time to contralateral DCIS grade I/II/III
- Cumulative incidence of contralateral invasive breast cancer
- Time to failure of active surveillance strategy in the experimental arm, i.e. time to crossover to conventional treatment, due to any cause
- Distant metastases free interval
- Overall survival

2.2. Patient selection criteria

2.2.1. Inclusion criteria

Women aged 45 years or older with asymptomatic, pure and low-grade DCIS based on vacuum-assisted biopsies (VACB) of microcalcifications only, detected by population-based or opportunistic screening mammography, are eligible if they have an American Society of Anaesthesiologists (ASA) score of 1–2 and life expectancy of more than 5 years. Prior surgery of the ipsilateral breast because of benign lesions is allowed. Before randomisation, written informed consent must be given according to ICH/GCP and national/local regulations.

2.2.2. Exclusion criteria

Individuals will be excluded from the trial if they have personal history of DCIS or iBC, or if a BRCA1 or

BRCA2 mutation was previously identified in their family. Other exclusion criteria are symptomatic DCIS, i.e. DCIS detected by palpation or nipple discharge, bilateral DCIS, synchronous contralateral iBC, LCIS, Paget's disease, or invasive breast disease on cytology or histology and serious disease that precludes definitive surgical treatment.

2.3. Participant recruitment

Patients will be recruited at participating trial sites across different countries, i.e. breast centres, highly specialised gynaecologic departments or gynaecological and oncological outpatient units. Patients whose diagnostic core biopsy – as standard of care – of screen-detected microcalcifications shows histologically confirmed unilateral primary low-grade DCIS of the breast by local pathology will be able to participate in the LORD study. Only if the informed consent form is obtained, and inclusion and exclusion criteria are compliant, the patient can be enrolled into the study. Patients who are not registered prior to any trial-related procedure cannot be accepted for the trial at a later time.

2.4. Diagnostic workup before randomisation (Fig. 1)

Population-based or opportunistic screening mammography should reveal lesions consisting of microcalcifications only. A minimum of six cores with VACB of the microcalcifications must be taken, and a marker should be placed at the biopsy site. The biopsy specimen will be considered representative if a substantial amount of microcalcifications is found in two or more of the biopsies or if more than 75% of the microcalcifications is removed in one of the cores, and this should be proven by specimen radiography. The definition of grade I DCIS described by Schnitt and Collins will be adhered to [48]. Key features of low-grade DCIS include:

Cytologic features:

- Monotonous, uniform, rounded cell population
- Subtle increase in nuclear-cytoplasmic ratio
- Equidistant or highly organised nuclear distribution
- Rounded nuclei with inconspicuous nucleoli
- Hyperchromasia may or may not be present

Architectural features:

- Cribiform, micropapillary or solid patterns most frequent
- Bridges and arcades, when present, of uniform thickness
- Cells polarise around extracellular lumens
- Comedo necrosis rare

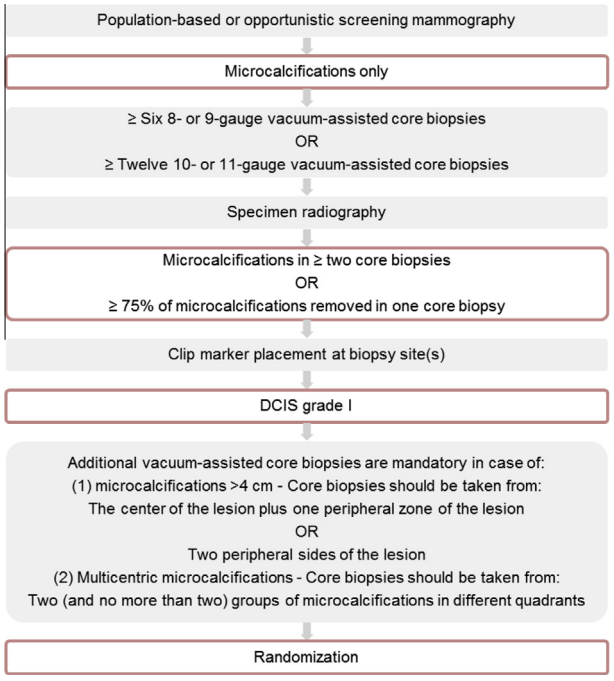

Fig. 1. Flow chart of diagnostic workup prior to randomisation.

In case of extended (>4 cm) DCIS grade I, VACB from the centre of the lesion and a peripheral part, or two peripheral parts of the lesion must be taken. In case of multicentricity two locations of clusters in different quadrants must be biopsied. Radiological and pathological findings should correlate, i.e. both findings should confirm low-grade DCIS and no suspicion of intermediate-grade or high-grade DCIS or iBC should exist.

2.5. Study design

The LORD trial will be an international multicentre, phase III, open-label, randomised non-inferiority study. Individuals will be randomised in equal numbers to one of the following arms: active surveillance or standard treatment according to local policy, followed by active surveillance. Study centre will be included in the stratification of this trial. Randomisation will take place within 12 weeks after histologically proven low-grade DCIS on VACB. A computer-based allocation using the minimisation method with a random component will be used for the randomisation procedure. Surgery in the standard arm will take place within 8 weeks after randomisation.

2.6. Study arms

The trial will compare standard treatment according to local policy and an active surveillance strategy in

patients with low-grade screen-detected DCIS (see Fig. 2):

2.6.1. Experimental arm

Active surveillance, i.e. monitoring by annual digital mammography for a period of 10 years, and treatment if there is any sign of progression to higher-grade DCIS or invasive cancer.

2.6.2. Standard arm

Standard treatment according to local policy. This can be either WLE alone, WLE + RT, or mastectomy, and HT by Tamoxifen will be allowed. In case invasive disease is found at final pathology after surgery, patients should be treated and followed up according to local policy. The same follow-up scheme will be applied in both study arms, i.e. annual mammography for a period of 10 years.

2.7. Clinical evaluation and follow-up

Timing of follow-up visits will be based on the date of registration. Follow-up mammograms will be scheduled annually from the date of registration for 10 years in both study groups. Fig. 3 shows a decision tree to be used for additional diagnostics during follow-up. Biopsy during follow-up will be recommended in case of an increase of >30% of the largest diameter of the index lesion on mammography as compared to the mammography performed one year after the initial VACB. The lesion to act upon must be at least 1 cm in diameter. Biopsy will also be strongly recommended in case of suspicion of malignancy according to the BIRADS® criteria of the American College of Radiology [49].

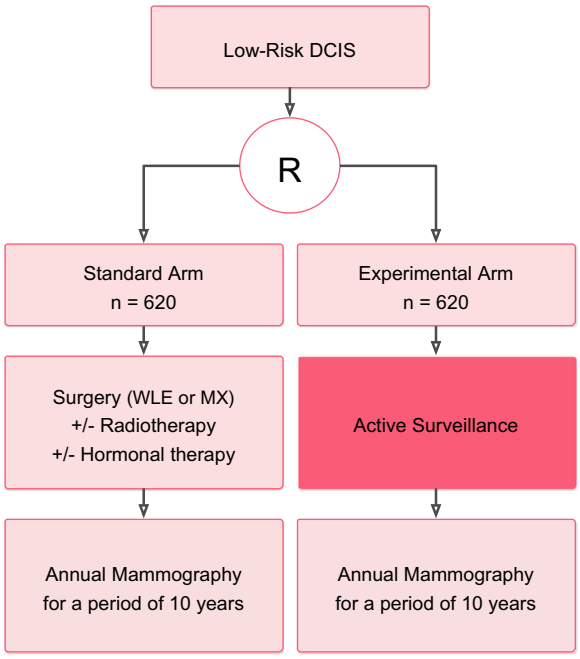

Fig. 2. Flow chart of study design. R = randomisation. WLE = wide local excision. MX = mastectomy.

2.8. Statistical considerations

2.8.1. Primary end-point

Safety will be measured by ipsilateral invasive breast cancer–free percentage at 10 years (10-year iiBC-free%). Regional and distant metastases and death from breast cancer in the absence of iiBC will also count as events in this definition. This definition is in line with the definition of recurrence free-interval in the adjuvant setting [50]. If the primary DCIS is excised and final pathology concludes invasive disease, this incidence will not count as an event for the primary end-point. These patients will not be excluded from the study and/or analysis and will be followed for events from surgery onwards.

2.8.2. Hypotheses

We have applied the following null and alternative hypotheses (H0 and H1 respectively):

H0 *(inferiority of active surveillance):*
10-year iiBC-free% active surveillance arm ⩽ 10-year iiBC-free% standard arm − 10%.
H1 *('non-inferiority' of active surveillance):*
10-year iiBC-free% active surveillance arm ⩾ 10-year iiBC-free% standard arm − 5%.

We have re-formulated the design assumptions based on 5-year iiBC-free%, presuming a fairly constant event rate over time [33–38,51–58]. We have assumed that the mastectomy rate in the standard treatment arm is 20% and that the 5-year iiBC-free% equals 100% for this treatment. Furthermore, we have assumed that the breast-conserving treatment rate in the standard treatment arm is 80% and that the 5-year iiBC-free% equals 97% for this treatment. Given these percentages it is presumed that the 5-year iiBC-free% in the standard treatment arm equals 97.5%, and the 10-year iiBC-free% equals 95%.

2.8.3. Primary test

The 10 year iiBC-free% will be estimated based on the Weibull survival model for the time to iiBC in each treatment arm separately. The difference between these two estimates will be compared with a critical value of 6.45. The primary test will be conducted in the per protocol population, consisting of all eligible patients who effectively started in the randomised treatment arm.

2.8.4. Sample size

With a one-sided test for non-inferiority with alpha = 0.025 and a power of 80%, 930 patients need

to be assessed for the primary end-point, and hence need to fulfil a follow-up period of at least 10 years. We anticipate that 25% of all randomised patients will be excluded from the per protocol population, or will have dropped out before the end of the 10-year follow-up period, and therefore **1240** low-grade DCIS patients need to be randomised. Accrual is expected to take 4 years, resulting in an estimated total study duration of 14 years.

The power for this trial design fluctuates slightly for different plausible 10-year iiBC-free percentages in the standard treatment arm as shown in Table 1. Table 1 also takes into account a non-binding interim analysis for futility (see below) and a parametric Weibull estimation of the 10-year iiBC-free%.

2.8.5. Interim analysis

One non-binding interim look for futility is planned when 742 patients have fulfilled a follow-up period of 5 years. This is estimated to occur 7.6 years after accrual of the first patient. The 5-year iiBC-free% will be estimated based on the Weibull survival model for the time to iiBC in each treatment arm separately. The difference between these two estimates will be compared with a critical value of 4.91.

Simulated operating characteristics of the interim look are illustrated in Table 2.

2.8.6. Statistical analysis

The primary analysis will be based on the per protocol population (see primary test section), and will be supplemented with an intention-to-treat analysis. A multivariate analysis will be performed using a cox proportional hazards regression model.

3. Feasibility

In May 2014 a survey was released to the EORTC and BOOG networks. This survey aimed to explore interest in and feasibility of the LORD trial, to map standard approach of low-risk DCIS in different countries, and to investigate the possible role of MRI in this trial.

3.1. Methods

A team of clinical breast cancer experts, which consisted of a surgeon, pathologist, radiologist, radiotherapist, medical oncologist, nurse practitioner, and statistician, developed the survey items.

Table 1
Simulated design characteristics (30,000 simulation runs for each setting). As per planned design in grey. Five scenarios for the 10-year ipsilateral invasive breast cancer-free percentage in the standard arm are considered.

True 10-yr iiBC-free % Standard Treatment	Null Hypothesis 10-yr iiBC-free % (-10%) Active surveillance	Alternative Hypothesis 10-yr iiBC-free % (-5%) Active surveillance	**Simulated Power**	**Simulated Significance Level (1-sided)**
99%	89%	94%	89%	0.6%
97%	87%	92%	84%	1.4%
95%	85%	90%	80%	2.5%
93%	83%	88%	77%	3.5%
91%	81%	86%	74%	4.6%

The table contains the simulated power and significance level under the planned design for each scenario, taking into account a Weibull estimate of the 10-year ipsilateral invasive breast cancer-free percentage and a non-binding interim test for futility.
10-year iiBC-free% = 10-year ipsilateral invasive breast cancer-free percentage.

Table 2
Simulated operating characteristics of the interim look (30,000 simulation runs for each setting). As per planned design marked in grey.

	Probability to stop at interim for futility		
	under the alternative	under the null	under major inferiority Defined as a difference of 13% in 10-yr iiBC-free %
True 5-yr iiBC-free % Standard arm	(5-yr iiBC-free % Experimental arm under the alternative)	(5-yr iiBC-free % Experimental arm under the null)	(5-yr iiBC-free % Experimental arm under major inferiority)
99.5%	0.6% (97.0%)	58% (94.3%)	93% (92.7%)
98.5%	2% (95.9%)	59% (93.3%)	91% (91.7%)
97.5%	4% (94.9%)	60% (92.2%)	90% (90.6%)
94.4%	6% (93.8%)	61% (91.1%)	89% (89.4%)
95.4%	8% (92.7%)	61% (90.0%)	88% (88.3%)

Five different scenarios are considered for the 5-year ipsilateral invasive breast cancer-free percentage in the standard arm (first column). The five scenarios in this column correspond to those in Table 1 given a constant event rate over time.Columns 2–4 contain the operating characteristics of the interim look under three different scenario's regarding the difference in 5-year ipsilateral invasive breast cancer-free percentage between the standard and experimental arm.5-yr iiBC-free% = 5-year ipsilateral invasive breast cancer-free percentage.
10-yr iiBC-free% = 10-year ipsilateral invasive breast cancer-free percentage.

3.2. Results

A total of 53 centres from 14 different countries responded to the survey. Most responding centres were from the Netherlands (36%), Belgium (25%), and France (11%). Other responding centres were from Egypt, Greece, Israel, Italy, Poland, Portugal, Serbia, Slovenia, Spain, Sweden and Turkey.

3.2.1. Interest and feasibility

More than three quarters of the responders were interested in participation in the study (77%). Twelve centres that reported not to be interested were from Belgium (6/13 responding centres), France (3/6), Greece (1/2), Israel (1/1) and Sweden (1/1). Reasons for no interest could be subdivided into three main issues: accrual difficulties ($n = 5$), not convinced by study design or rationale (5) and administrative issues (1) (1 missing).

Further presentation of the survey results is based on the answers of centres that expressed interest ($n = 41$) and shown in Table 3.

The reported numbers resulted in an estimated total of around 400 low-grade screen-detected DCIS patients per year in the interested centres. 90% of the centres believed that low-grade DCIS patients would be willing to participate in the LORD study. Three centres, from Greece, the Netherlands and Turkey, that thought that patients would not be willing to participate, expected that most patients would demand surgery.

3.2.2. Current management of DCIS

3.2.2.1. Screening. Most screening programmes apply a lower age limit of 50 years. In Italy and Portugal a lower age limit of 45 years was reported (four centres), and one centre in Turkey reported a limit of 40 years.

3.2.2.2. Treatment. To assess the current treatment of DCIS, centres were allowed to give multiple answers. The most frequently offered treatment approach of DCIS was WLE followed by RT: 95% of the centres reported to offer this approach as one of the treatment options, which means that 5% of the centres reported

not to offer WLE + RT to DCIS patients. A minority of the centres reported to offer HT (all Tamoxifen) (29%). Of the centres that reported to offer HT as one of the treatment options, five were from Belgium, two from Italy, and one from Poland, Portugal, Serbia, Spain and Turkey each.

3.2.2.3. Diagnostic workup and follow-up. The proposed diagnostic workup and follow-up strategy in the LORD study was endorsed by most centres (85% and 90%, respectively). Centres that reported to employ different diagnostic workup of DCIS ($n = 5$) explained that they would take less biopsies in the diagnostic process. Centres that reported not to feel comfortable to comply with the follow-up scheme ($n = 4$), would like to add a mammography 6 months after the first diagnosis, or every 6 months, and would recommend attenuating the definition of progression.

3.2.3. MRI

The majority of the interested centres preferred not to add an MRI to the diagnostic workup in the trial (66%).

4. Discussion leading to rationale and design of the LORD trial

4.1. Considerations and arguments

The current debate on overdiagnosis and overtreatment of screen-detected breast cancer and pre-invasive breast lesions urges the need for prospective studies to address these issues. With the increased use of screening mammography, the likelihood of detecting DCIS is considerable with 20% of all screen-detected breast cancer cases. No randomised trial has compared WLE + RT with mastectomy for the treatment of DCIS, but four randomised controlled trials have addressed the value of adding RT to WLE [59–62]. Controversy exists primarily because of the absence of randomised trials documenting that treatment improves survival and quality of life. Because almost all DCIS is excised when detected, uncertainty about the natural history exists, and the clinical significance of screen-detected DCIS is debated. It is sufficiently clear that DCIS represents a heterogeneous group of diseases, and it is time to address the safety of active surveillance in women with screen-detected low-risk DCIS in order to reduce the negative impact of identifying and treating non-lethal disease.

The LORD study aims to contribute to solve a substantial clinical dilemma in breast cancer diagnosis and treatment: finding the balance between overdiagnosis and undertreatment in individuals with low-risk DCIS of the breast. We believe it is reasonable to assume that active surveillance is nearly as safe as the conventional management of screen-detected low-grade DCIS in terms of the 10-year ipsilateral invasive breast cancer free rate and consequently the related survival. For our sample size calculation we have assumed a slightly decreased 5-year iiBC-free rate in the experimental arm, as opposed to the standard treatment arm. Data on the natural history of DCIS are not well established, and therefore we also based our assumptions on data on similar low-risk non-obligate precursor lesions, like LCIS and atypical hyperplasia. We hold the position that our assumed iiBC-free rate in the active surveillance arm, in relation to the expected iiBC-free rate in the standard treatment arm, is clinically acceptable with broad clinical support [63].

4.2. Ipsilateral invasive breast cancer-free rate

When discussing the trade-off of an acceptable iiBC-free rate, the potential benefits of not treating should also be taken into account. Active surveillance does not remove DCIS, and may therefore miss an opportunity to end or delay disease progression. However, despite a slightly higher chance of developing iiBC, we concur that active surveillance may save a substantial number of women from going through surgery and radiotherapy, avoiding possible harmful side-effects of treatment, and as a consequence, this may lead to an improved quality of life (cosmetic outcomes, body self-image, self-esteem, etc.). Of course, the potential distress caused by 'no treatment' will be actively evaluated in the LORD study in order to gain a well-balanced insight into patient reported outcomes. Furthermore, the evaluation of health economics data might show that an active surveillance strategy will lead to a decrease in health care costs. Cost-effectiveness research will allow patients, health care providers and payers to better understand the true value of each disease-management strategy.

One other important argument to assume that the expected iiBC-free rates in this low-risk DCIS population are clinically acceptable is provided by the circumstantial evidence that there is a difference in natural history between high-grade and low-grade DCIS. If low-grade DCIS progresses to iBC, this is most likely to be low-grade iBC [16,25,31]. After an active surveillance strategy of a low-grade DCIS lesion, multiple treatment options of the subsequent low-grade iBC will still be feasible and excellent long-term survival outcomes can be preserved. Subsequent high-grade iBC is unlikely to develop from low-grade DCIS, and will more likely be a new primary tumour [16,31,32]. Women managed by an active surveillance strategy, as well as women treated by WLE for DCIS will have a chance of developing new primary breast cancer, but the breast-conserving options might be more limited in the latter group.

Table 3
Survey results based on the answers of centres that expressed interest ($n = 41$).

		n	%
Interest and feasibility			
How many patients with screen-detected ductal carcinoma in situ (DCIS) do you see in your hospital per year?			
	⩽25	16	39
	26–50	13	32
	>50	12	29
What percentage of the screen-detected DCIS lesions are low-grade (grade 1)?			
	⩽5%	5	12
	6–15%	13	32
	16–25%	10	24
	>25%	9	22
	Missing	4	10
Do you think that these low-grade DCIS patients will be willing to participate in this trial?			
	Yes	37	90
	No	3	7
	Missing	1	2
Current management of DCIS			
Is there a population-based screening programme in your country?			
	Yes	36	88
	No	4	10
	Missing	1	2
If yes, How is the screening programme organised? ($n = 36$)			
Frequency	Biannual	35	97
	Missing	1	3
Location	Screening unit	29	81
	Hospital	4	11
	Other	2	6
	Missing	1	3
Participation rate estimate	<50%	5	14
	50–79%	14	39
	⩾80%	10	28
	Missing	7	19
Lower age limit	40 years	1	3
	45 years	4	11
	50 years	30	83
	Missing	1	3
Upper age limit	65 years	3	8
	69–70 years	11	31
	74–75 years	21	58
How are patients with DCIS treated in your hospital? (several options are possible)			
	No treatment	0	0
	Excision biopsy	8	20
	Wide local excision	16	39
	Wide local excision + radiotherapy	39	95
	Mastectomy	23	56
	Hormonal therapy	12	29
Does the work-up scheme which is described in the outline reflect the standard of practice in your hospital?			
	Yes	35	85
	No	5	5
	Missing	1	1
Is the work-up of DCIS in your hospital considered standard in your entire country?			
	Yes	38	93
	No	3	7
Are you comfortable to comply to the follow-up flow-chart described in the outline?			
	Yes	37	90
	No	4	10
Magnetic resonance imaging (MRI)			
Are you using MRI in the work-up of low-grade DCIS?			
	Yes, routinely	2	5
	Yes, in special cases	21	51
	No, never	18	44
Is MRI in the work-up of DCIS reimbursed in your country?			
	Yes	28	68
	No	11	27

(*continued on next page*)

Table 3 (*continued*)

	n	%
Missing	2	5
Would you prefer to add an MRI to the work-up in this trial?		
Yes	14	34
No	27	66
If an additional MRI in the work-up of DCIS leads to a diagnosis of histologically proven high grade DCIS or invasive breast cancer (upgrading) would you then include MRI in your standard work-up?		
Yes, if MRI leads to an upgrade in at least 5% of patients	10	24
Yes, if MRI leads to an upgrade in at least 10% of patients	14	34
Missing	17	42

4.3. Standard treatment arm

The LORD study includes all current DCIS treatment strategies within the standard treatment arm. A multi-arm design was not considered feasible because this would lead to a non-feasible increase in sample size. Furthermore, we concluded from our discussions that the study should reflect the current standard clinical practice as much as possible. We will stratify by centre to strive for an equal contribution of all preferred current practice approaches in both study arms, and moreover, the stratification accounts for small differences in the diagnostic workup and follow-up of the study individuals. The option to exclude mastectomy from the standard treatment arm, because of its deviant iiBC-free rate, was abandoned. Either way, some women will end up undergoing a mastectomy in this treatment arm as a result of positive margins.

The use of HT in the treatment of DCIS differs among and within the anticipated participating countries. In the Netherlands for example, HT is generally not offered to patients with pure DCIS. Because of the international multi-centre design of the LORD the use of HT is allowed in the standard arm. However, its use is not allowed in patients within the active surveillance arm.

4.4. Age

The lower age limit for inclusion in this trial was set at 45 years. In most screening programmes women from the age of 50 years are targeted. However, in our survey, four centres reported a lower age limit of 45 years to be applicable in their screening programme. Women with a history of any grade DCIS younger than 40 or 50 years have an increased risk of developing iBC than older women [7]. We discussed not to exclude potential trial participants between 45 and 50 years, because the division between 'young' and 'old' is arbitrary and variable between studies, and it is believed that women with screen-detected, asymptomatic low-grade DCIS have a favourable long-term outcome as opposed to women with symptomatic disease.

4.5. Central review

The LORD trial does not apply pre-randomisation central pathology or imaging review. Literature shows that classifying low-risk in situ lesions is associated with significant interobserver variation [64–68]. This suggests that some true low-grade DCIS lesions are missed, whereas other lesions are classified as DCIS incorrectly. This could be an indication to use pre-randomisation central pathology review by expert pathologists. However, in daily practice treatment decisions are based on the pathology reports assessed by local pathologists. Both downgraded and upgraded lesions will appear to some extent in the study population as well as in the real population. Furthermore, central pathology review involves complicated and expensive logistics owing to enrolment of large numbers of patients in multiple countries and requires long turnaround time for slide review at the central location.

In the LORD study we pursue the definition of low-grade DCIS as described in the book *Biopsy Interpretation of the Breast* written by Schnitt and Collins [48]. Tissue blocks of pre-randomisation VACB and resection specimens, as well as digital mammography data will be collected for retrospective central review and future translational research purposes.

4.6. MRI

Mammography is the mainstay for diagnosing DCIS. However, MRI of the breast has the ability to enhance additional findings in women when performed after initial clinical evaluation. Yet, the clinical relevance of these additional findings is uncertain [46,69,70]. During protocol development, the possibility of adding pre-randomisation MRI to the diagnostic workup has been discussed. The advantages of pre-randomisation MRI include improved sensitivity and therefore increased ability to detect intermediate-grade or high-grade DCIS, and iBC, which are considered exclusion criteria in the LORD trial. In spite of improved sensitivity a retrospective cohort study showed no association between the perioperative use of MRI and

local–regional recurrence rate in women undergoing breast-conserving surgery for DCIS [71].

Currently, breast MRI is not routinely performed in patients with DCIS, which was also reflected in the results of our explorative survey. An MRI side-study could give more insights into the role of MRI in the diagnostic workup of screen-detected DCIS. However, the majority of centres that showed interest in participation in the LORD trial were not in favour of adding MRI to the workup in the study. Main reasons were a foreseen high rate in false-positive findings resulting in increased number of diagnostic procedures, psychological distress and costs.

In the LORD study, the use of MRI is allowed in the workup of the study individuals before randomisation at the discretion of the physician. The use of MRI after diagnosis of low-grade DCIS on core biopsy is not recommended.

4.7. Statistical considerations

The LORD study comprises some non-conventional choices in the statistical design.

First, we have applied a special type of non-inferiority design, where the alternative hypothesis corresponds to 'minor inferiority'. A classical non-inferiority design would have had the following H1:

$H1_{classical}$ *(non-inferiority of active surveillance)*:
10-year iiBC-free% active surveillance arm ⩾ 10-year iiBC-free% standard arm.

However, we expect slightly more events with an active surveillance approach as opposed to excision with or without RT and/or HT in patients with low-grade DCIS, and therefore $H1_{classical}$ was not considered realistic in this study setting.

Second, the primary test in the LORD study will not be based on the relative risk (hazard ratio), but on a fixed difference in absolute risk (10-year iiBC-free%). In this trial we expect a low event rate for the primary end-point, and therefore the absolute difference in 10-year event-free% is considered to be of more clinical significance than the relative difference. When the 10-year iiBC-free% in the standard arm would be higher than anticipated the hazard ratio would increase exponentially, rendering a statistical design based on the hazard ratio, e.g. the logrank test, majorly underpowered. The outcome of the trial would then not be in line with the actual difference in 10-year iiBC-free% (see Fig. 4). The power of the current proposed statistical test is less

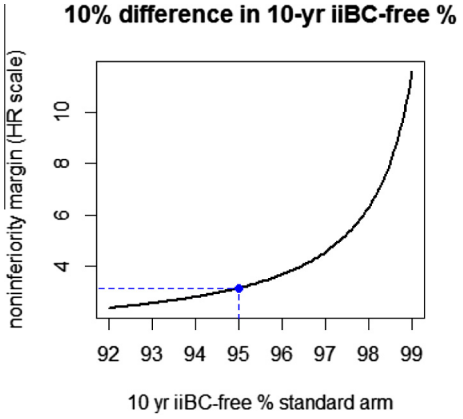

Fig. 4. Relation between the hazard ratio and the 10-year ipsilateral invasive breast cancer-free percentage in the standard treatment arm, for a fixed difference of 10% in 10-year ipsilateral invasive breast cancer-free percentage between the standard and experimental arm. HR = hazard ratio. 10-yr iiBC-free% = 10-year ipsilateral invasive breast cancer-free percentage.

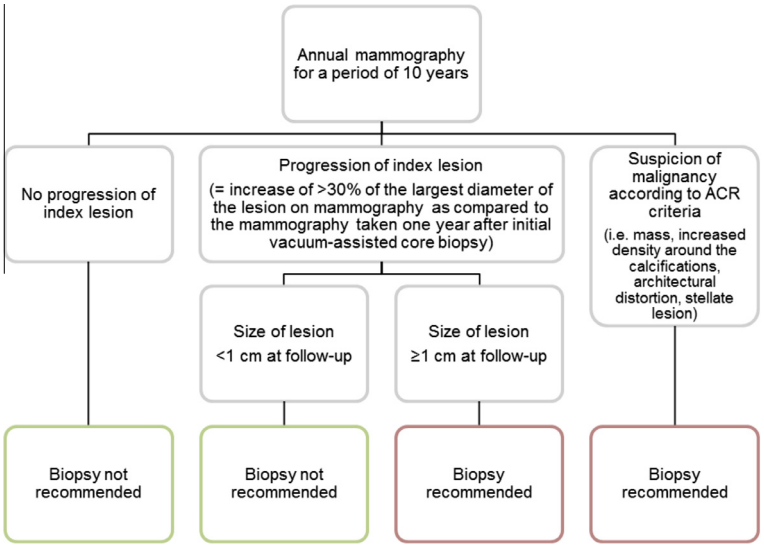

Fig. 3. Decision tree to be used during follow-up. ACR = American College of Radiology.

sensitive to deviations from the hypothesised 10-year iiBC-free% in the standard arm (see Table 1).

Third, we chose not to conduct an event-driven trial, because of the expected low primary event rate in both study arms. Instead we will use a follow-up time-driven design. As a result we will greatly depend on achieving the pre-specified follow-up for 75% of patients.

Furthermore, we will primarily test the difference between iiBC-free% between both study arms at 10-year follow-up instead of 5-year follow-up. Because low-grade DCIS has a long natural history, it is necessary to follow up these patients beyond 5 years for late recurrences, and draw conclusions based on longer follow-up.

5. Trial status

The start of active recruitment is estimated to be in the fourth quarter of 2015. Recruitment is estimated to take 4 years. The projected date of study completion will be after an additional follow-up period of 10 years.

Role of the funding source

The funding sources had no involvement in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

Conflict of interest statement

None declared.

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References

[1] Ernster VL, Ballard-Barbash R, Barlow WE, Zheng Y, Weaver DL, Cutter G, et al. Detection of ductal carcinoma in situ in women undergoing screening mammography. J Natl Cancer Inst 2002;94:1546–54.

[2] Sørum R, Hofvind S, Skaane P, Haldorsen T. Trends in incidence of ductal carcinoma in situ: the effect of a population-based screening programme. Breast 2010;19:499–505.

[3] van Steenbergen LN, Voogd AC, Roukema JA, Louwman WJ, Duijm LEM, Coebergh JWW, et al. Screening caused rising incidence rates of ductal carcinoma in situ of the breast. Breast Cancer Res Treat 2009;115:181–3.

[4] van Luijt PA, Fracheboud J, Heijnsdijk EAM, Heeten den GJ, de Koning HJ, National Evaluation Team for Breast Cancer Screening in Netherlands Study Group (NETB). Nation-wide data on screening performance during the transition to digital mammography: observations in 6 million screens. Eur J Cancer 2013;49:3517–25.

[5] Bluekens AMJ, Holland R, Karssemeijer N, Broeders MJM, den Heeten GJ. Comparison of digital screening mammography and screen-film mammography in the early detection of clinically relevant cancers: a multicenter study. Radiology 2012;265:707–14.

[6] Vigeland E, Klaasen H, Klingen TA, Hofvind S, Skaane P. Full-field digital mammography compared to screen film mammography in the prevalent round of a population-based screening programme: the Vestfold County Study. Eur Radiol 2008;18:183–91.

[7] Virnig BA, Tuttle TM, Shamliyan T, Kane RL. Ductal carcinoma in situ of the breast: a systematic review of incidence, treatment, and outcomes. J Natl Cancer Inst 2010;102:170–8.

[8] Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. N Engl J Med 2012;367:1998–2005.

[9] Chu KC, Kramer BS, Smart CR. Analysis of the role of cancer prevention and control measures in reducing cancer mortality. J Natl Cancer Inst 1991;83:1636–43.

[10] de Gelder R, Fracheboud J, Heijnsdijk EAM, Heeten den G, Verbeek ALM, Broeders MJM, et al. Digital mammography screening: weighing reduced mortality against increased overdiagnosis. Prev Med 2011;53:134–40.

[11] Verbeek ALM, Broeders MJM, Otto SJ, Frachebou J, Otten JDMH, Holland R, et al. Effects of the population screening into breast cancer. Ned Tijdschr Geneeskd 2013;157:A5218.

[12] Welch HG, Black WC. Overdiagnosis in cancer. J Natl Cancer Inst 2010;102:605–13.

[13] Welch HG. Overdiagnosis and mammography screening. BMJ 2009;339, b1425–5.

[14] IKNL CCCTN. Netherlands Cancer Registry. n.d.

[15] Erbas B, Provenzano E, Armes J, Gertig D. The natural history of ductal carcinoma in situ of the breast: a review. Breast Cancer Res Treat 2006;97:135–44.

[16] Lopez-Garcia MA, Geyer FC, Lacroix-Triki M, Marchio C, Reis-Filho JS. Breast cancer precursors revisited: molecular features and progression pathways. Histopathology 2010;57:171–92.

[17] Welch HG, Black WC. Using autopsy series to estimate the disease "reservoir" for ductal carcinoma in situ of the breast: how much more breast cancer can we find?. Ann Intern Med 1997;127:1023–8.

[18] Lakhani SR, Audretsch W, Cleton-Jensen A-M, Cutuli B, Ellis I, Eusebi V, et al. The management of lobular carcinoma in situ (LCIS). Is LCIS the same as ductal carcinoma in situ (DCIS)? Eur J Cancer 2006;42:2205–11.

[19] Page DL, Dupont WD. Proliferative breast disease: diagnosis and implications. Science 1991;253:915–6.

[20] Fitzgibbons PL, Henson DE, Hutter RV. Benign breast changes and the risk for subsequent breast cancer: an update of the 1985 consensus statement. Cancer Committee of the College of American Pathologists. Arch Pathol Lab Med 1998;122:1053–5.

[21] Chen Y-Y, Hwang E-SS, Roy R, DeVries S, Anderson J, Wa C, et al. Genetic and phenotypic characteristics of pleomorphic lobular carcinoma in situ of the breast. Am J Surg Pathol 2009;33:1683–94.

[22] Arpino G, Laucirica R, Elledge RM. Premalignant and in situ breast disease: biology and clinical implications. Ann Intern Med 2005;143:446–57.

[23] Sanders ME, Schuyler PA, Dupont WD, Page DL. The natural history of low-grade ductal carcinoma in situ of the breast in women treated by biopsy only revealed over 30 years of long-term follow-up. Cancer 2005;103:2481–4.
[24] Van de Vijver MJ, Peterse H. The diagnosis and management of pre-invasive breast disease: pathological diagnosis-problems with existing classifications. Breast Cancer Res 2003;5:269.
[25] Hernandez L, Wilkerson PM, Lambros MB, Campion-Flora A, Nava Rodrigues D, Gauthier A, et al. Genomic and mutational profiling of ductal carcinomas in situ and matched adjacent invasive breast cancers reveals intra-tumour genetic heterogeneity and clonal selection. J Pathol 2012;227:42–52.
[26] Lagios MD. Heterogeneity of duct carcinoma in situ (DCIS): relationship of grade and subtype analysis to local recurrence and risk of invasive transformation. Cancer Lett 1995;90:97–102.
[27] Buerger H, Otterbach F, Simon R, Schäfer KL, Poremba C, Diallo R, et al. Different genetic pathways in the evolution of invasive breast cancer are associated with distinct morphological subtypes. J Pathol 1999;189:521–6.
[28] Roylance R, Gorman P, Hanby A, Tomlinson I. Allelic imbalance analysis of chromosome 16q shows that grade I and grade III invasive ductal breast cancers follow different genetic pathways. J Pathol 2002;196:32–6.
[29] O'Connell P, Pekkel V, Fuqua SA, Osborne CK, Clark GM, Allred DC. Analysis of loss of heterozygosity in 399 premalignant breast lesions at 15 genetic loci. J Natl Cancer Inst 1998;90:697–703.
[30] Farabegoli F, Champeme M-H, Bieche I, Santini D, Ceccarelli C, Derenzini M, et al. Genetic pathways in the evolution of breast ductal carcinoma in situ. J Pathol 2002;196:280–6.
[31] Bijker N, Peterse H, Duchateau L, Robanus-Maandag EC, Bosch CAJ, Duval C, et al. Histological type and marker expression of the primary tumour compared with its local recurrence after breast-conserving therapy for ductal carcinoma in situ. Br J Cancer 2001;84:539–44.
[32] Millis RR, Barnes DM, Lampejo OT, Egan MK, Smith P. Tumour grade does not change between primary and recurrent mammary carcinoma. Eur J Cancer 1998;34:548–53.
[33] Donker M, Litière S, Werutsky G, Julien J-P, Fentiman IS, Agresti R, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma in situ: 15-year recurrence rates and outcome after a recurrence, from the EORTC 10853 randomized phase III trial. J Clin Oncol 2013;31:4054–9.
[34] Wapnir IL, Dignam JJ, Fisher B, Mamounas EP, Anderson SJ, Julian TB, et al. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. J Natl Cancer Inst 2011;103:478–88.
[35] Wärnberg F, Garmo H, Emdin S, Hedberg V, Adwall L, Sandelin K, et al. Effect of radiotherapy after breast-conserving surgery for ductal carcinoma in situ: 20 years follow-up in the randomized SweDCIS trial. J Clin Oncol 2014, JCO.2014.56.2595.
[36] Cuzick J, Sestak I, Pinder SE, Ellis IO, Forsyth S, Bundred NJ, et al. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. Lancet Oncol 2011;12:21–9.
[37] Hughes LL, Wang M, Page DL, Gray R, Solin LJ, Davidson NE, et al. Local excision alone without irradiation for ductal carcinoma in situ of the breast: a trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2009;27:5319–24.
[38] Wong JS, Chen Y-H, Gadd MA, Gelman R, Lester SC, Schnitt SJ, et al. Eight-year update of a prospective study of wide excision alone for small low- or intermediate-grade ductal carcinoma in situ (DCIS). Breast Cancer Res Treat 2014;143:343–50.
[39] Berg WA, Gutierrez L, NessAiver MS, Carter WB, Bhargavan M, Lewis RS, et al. Diagnostic accuracy of mammography, clinical examination, US, and MR imaging in preoperative assessment of breast cancer. Radiology 2004;233:830–49.
[40] Boetes C, Mus RD, Holland R, Barentsz JO, Strijk SP, Wobbes T, et al. Breast tumors: comparative accuracy of MR imaging relative to mammography and US for demonstrating extent. Radiology 1995;197:743–7.
[41] Hata T, Takahashi H, Watanabe K, Takahashi M, Taguchi K, Itoh T, et al. Magnetic resonance imaging for preoperative evaluation of breast cancer: a comparative study with mammography and ultrasonography. J Am Coll Surg 2004;198:190–7.
[42] Menell JH, Morris EA, Dershaw DD, Abramson AF, Brogi E, Liberman L. Determination of the presence and extent of pure ductal carcinoma in situ by mammography and magnetic resonance imaging. Breast J 2005;11:382–90.
[43] Kuhl CK, Schrading S, Bieling HB, Wardelmann E, Leutner CC, Koenig R, et al. MRI for diagnosis of pure ductal carcinoma in situ: a prospective observational study. Lancet 2007;370:485–92.
[44] Lehman CD. Magnetic resonance imaging in the evaluation of ductal carcinoma in situ. J Natl Cancer Inst Monographs 2010;2010:150–1.
[45] van der Velden AP Schouten, Schlooz-Vries MS, Boetes C, Wobbes T. Magnetic resonance imaging of ductal carcinoma in situ: what is its clinical application? A review. Am J Surg 2009;198:262–9.
[46] Margenthaler JA. Magnetic resonance imaging in patients with ductal carcinoma in situ: routine, selective, or not at all? Ann Surg Oncol 2014;21:1510–1.
[47] Alvarado M, Ozanne E, Esserman L. Overdiagnosis and overtreatment of breast cancer. Am Soc Clin Oncol Educ Book 2012, e40–5.
[48] Schnitt SJ, Collins LC. Biopsy interpretation of the breast. 2nd ed. Lippincott Williams & Wilkins; 2013, a Wolters Kluwer business.
[49] D'Orsi CJ, Sickles EA, Mendelson EB, Morris EA. ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston, VA, American College of Radiology; 2013.
[50] Hudis CA, Barlow WE, Costantino JP, Gray RJ, Pritchard KI, Chapman J-AW, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. J Clin Oncol 2007;25:2127–32.
[51] Early Breast Cancer Trialists' Collaborative Group, Correa C, McGale P, Taylor C, Wang Y, Clarke M, et al. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. J Natl Cancer Inst Monographs 2010;2010:162–77.
[52] Fisher B, Costantino JP, Wickerham DL, Cecchini RS, Cronin WM, Robidoux A, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 2005;97:1652–62.
[53] Goodwin A, Parker S, Ghersi D, Wilcken N. Post-operative radiotherapy for ductal carcinoma in situ of the breast. Cochrane Database Syst Rev 2013;11, CD000563.
[54] Benson JR, Wishart GC. Predictors of recurrence for ductal carcinoma in situ after breast-conserving surgery. Lancet Oncol 2013;14:e348–57.
[55] Wang S-Y, Shamliyan T, Virnig BA, Kane R. Tumor characteristics as predictors of local recurrence after treatment of ductal carcinoma in situ: a meta-analysis. Breast Cancer Res Treat 2011;127:1–14.
[56] Boyages J, Delaney G, Taylor R. Predictors of local recurrence after treatment of ductal carcinoma in situ: a meta-analysis. Cancer 1999;85:616–28.
[57] Kuerer HM, Albarracin CT, Yang WT, Cardiff RD, Brewster AM, Symmans WF, et al. Ductal carcinoma in situ: state of the science and roadmap to advance the field. J Clin Oncol 2009;27:279–88.
[58] Morrow M, Strom EA, Bassett LW, Dershaw DD, Fowble B, Harris JAYR, et al. Standard for the management of ductal carcinoma in situ of the breast (DCIS). CA Cancer J Clin 2002;52:256–76.

[59] Fisher B, Costantino J, Redmond C, Fisher E, Margolese R, Dimitrov N, et al. Lumpectomy compared with lumpectomy and radiation therapy for the treatment of intraductal breast cancer. N Engl J Med 1993;328:1581–6.

[60] Julien JP, Bijker N, Fentiman IS, Peterse JL, Delledonne V, Rouanet P, et al. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. Lancet 2000;355:528–33.

[61] Emdin SO, Granstrand B, Ringberg A, Sandelin K, Arnesson L-G, Nordgren H, et al. SweDCIS: Radiotherapy after sector resection for ductal carcinoma in situ of the breast. Results of a randomised trial in a population offered mammography screening. Acta Oncol 2006;45:536–43.

[62] Houghton J, George WD, Cuzick J, Duggan C, Fentiman IS, Spittle M, et al. Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: randomised controlled trial. Lancet 2003;362:95–102.

[63] Jenks S. Downgrading cancer definitions: overdiagnosis fuels the discussion. J Natl Cancer Inst 2014;106:dju070.

[64] Page DL, Rogers LW. Combined histologic and cytologic criteria for the diagnosis of mammary atypical ductal hyperplasia. Hum Pathol 1992;23:1095–7.

[65] Sloane JP, Amendoeira I, Apostolikas N, Bellocq JP, Bianchi S, Boecker W, et al. Consistency achieved by 23 European pathologists from 12 countries in diagnosing breast disease and reporting prognostic features of carcinomas. European Commission Working Group on Breast Screening Pathology. Virchows Arch 1999;434:3–10.

[66] Elston CW, Sloane JP, Amendoeira I, Apostolikas N, Bellocq JP, Bianchi S, et al. Causes of inconsistency in diagnosing and classifying intraductal proliferations of the breast. European Commission Working Group on Breast Screening Pathology. Eur J Cancer 2000;36:1769–72.

[67] O'Malley FP, Mohsin SK, Badve S, Bose S, Collins LC, Ennis M, et al. Interobserver reproducibility in the diagnosis of flat epithelial atypia of the breast. Mod Pathol 2006;19:172–9.

[68] Jain RK, Mehta R, Dimitrov R, Larsson LG, Musto PM, Hodges KB, et al. Atypical ductal hyperplasia: interobserver and intraobserver variability. Mod Pathol 2011;24:917–23.

[69] Morrow M. Magnetic resonance imaging in the breast cancer patient: curb your enthusiasm. J Clin Oncol 2008;26:352–3.

[70] Elshof LE, Rutgers EJT, Deurloo EE, Loo CE, Wesseling J, Pengel KE, et al. A practical approach to manage additional lesions at preoperative breast MRI in patients eligible for breast conserving therapy: results. Breast Cancer Res Treat 2010;124:707–15.

[71] Pilewskie M, Olcese C, Eaton A, Patil S, Morris E, Morrow M, et al. Perioperative breast MRI is not associated with lower locoregional recurrence rates in DCIS patients treated with or without radiation. Ann Surg Oncol 2014;21:1552–60.