

A retrospective alternative for active surveillance trials for ductal carcinoma *in situ* of the breast

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Ductal carcinoma *in situ* (DCIS) of the breast is a nonobligate precursor of invasive breast cancer, accounting for 20 % of screen-detected breast cancers. Little is known about the natural progression of DCIS because most patients undergo surgery upon diagnosis. Many DCIS patients are likely being overtreated, as it is believed that only around 50 % of DCIS will progress to invasive carcinoma. Robust prognostic markers for progression to invasive carcinoma are lacking. In the past, studies have investigated women who developed a recurrence after breast-conserving surgery (BCS) and compared them with those who did not. However, where there is no recurrence, the patient has probably been adequately treated. The present narrative review advocates a new research strategy, wherein only those patients with a recurrence are studied. Approximately half of the recurrences are invasive cancers, and half are DCIS. So-called “recurrences” are probably most often the result of residual disease. The new approach allows us to ask: why did some residual DCIS evolve to invasive cancers and others not? This novel strategy compares the group of patients that developed *in situ* recurrence with the group of patients that developed invasive recurrence after BCS. The differences between these groups could then be used to develop a robust risk stratification tool. This tool should estimate the risk of synchronous and metachronous invasive carcinoma when DCIS is diagnosed in a biopsy. Identification of DCIS patients at low risk for developing invasive carcinoma will individualize future therapy and prevent overtreatment.

Introduction

Ductal carcinoma *in situ* (DCIS) of the breast is a nonobligate precursor of invasive breast cancer, representing a heterogeneous group of lesions in terms of morphology and genetics.¹ DCIS is constituted by neoplastic epithelial cells which are confined within the ductal-lobular system by myoepithelial cells and the basement membrane.¹ Before the advent of screening mammography, DCIS was only diagnosed when symptomatic (i.e., due to nipple discharge and/or the presence of a palpable mass) and constituted less than 2 % of all diagnosed breast cancers.² Since the widespread introduction of mammographic screening, DCIS

detection rates substantially increased to approximately 20 % of all screen-detected breast cancers diagnosed at present.^{3–5} Nowadays, around 9–19% of DCIS patients are symptomatic, whereas the majority has an occult screen-detected lesion.^{5–8}

Whether this increased detection rate mainly represents over-diagnosis remains subject for debate. Early breast cancer diagnosis is considered as beneficial for patients since it is supposed to decrease the risk of both regional lymph node metastasis and distant metastasis. On the other hand, diagnosis of DCIS might also be considered as a negative side-effect of mammography screening, as it is often questioned whether every DCIS would

Key words: ductal carcinoma *in situ*, recurrence, active surveillance, risk stratification, prognostic markers

Abbreviations: BCS: breast-conserving surgery; COMET: comparison of operative to monitoring and endocrine therapy trial; DCIS: ductal carcinoma *in situ*; ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; LORD: low-risk DCIS trial; LoRis: low-risk DCIS trial; NSABP: National Surgical Adjuvant Breast and Bowel Project; PR: progesterone receptor; TAM: tamoxifen; UK/ANZ: United Kingdom/Australia, New Zealand

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have become symptomatic in the absence of screening.⁹ It is currently unclear which DCIS lesions are able to progress to invasive cancer, and which DCIS lesions will remain indolent.^{10,11} The identification of those indolent DCIS lesions remains a substantial challenge for future research. In the current narrative review, we discuss the available evidence on natural progression of DCIS, as well as the possible pitfalls of active surveillance trials. Additionally, we present a new research strategy which may serve as an efficient retrospective surrogate for active surveillance studies.

Current state-of-the-art treatment of DCIS

Per definition, DCIS itself does not yield a risk of (lymph) angioinvasion and metastasis. Therefore, the cornerstone of current DCIS treatment is to prevent the development of invasive carcinoma.¹² Patients with DCIS show excellent survival,¹³ with a 20-year actuarial breast cancer-specific mortality rate of 3.8%.¹⁴ However, women who develop ipsilateral invasive breast carcinoma after initial diagnosis of DCIS show reduced overall and breast cancer-specific survival,^{15–17} as they are 18 times more likely to die of breast cancer than women who do not develop an ipsilateral invasive in-breast recurrence.¹⁶ At present, most DCIS patients undergo surgery. Depending on the size of the lesion and patient preferences, surgical treatment consists either of breast-conserving surgery (BCS; i.e., lumpectomy) or mastectomy.¹² Adjuvant radiotherapy halves the overall recurrence risk after BCS, regardless DCIS size, grade and margin status.^{17–19} Despite its substantial influence on recurrence-free survival, adjuvant radiotherapy does not significantly alter overall survival for DCIS patients.¹⁸ Adjuvant endocrine therapy with tamoxifen (TAM) was shown to be associated with both a reduced ipsilateral recurrence risk and a reduced risk of contralateral invasive and *in situ* carcinoma, although the United Kingdom/Australia, New Zealand (UK/ANZ) DCIS trial and National Surgical Adjuvant Breast and Bowel Project (NSABP) B-24 trial did not discern estrogen receptor-positive (ER) from ER-negative DCIS patients.^{19–21} *Post hoc* analysis of the NSABP B-24 cohort confirmed these results only for patients with ER-positive DCIS treated with TAM.²² Despite these observations, adjuvant TAM did not significantly influence the all-cause mortality risk for patients with ER-positive DCIS.²³ A recently published report on the UK Sloane Project, which prospectively studied a population-based cohort of patients with screen-detected DCIS, confirmed that both radiotherapy and endocrine therapy were associated with decreased ipsilateral recurrence risk.²⁴ A retrospective population-based analysis of endocrine treatment of DCIS patients in British Columbia showed similar results, thereby demonstrating the generalizability of these trial data at the population level.²⁵

The gaps in our knowledge on natural progression

Since most DCIS patients are treated upon diagnosis, little is known about the natural course of progression to invasive breast cancer. Evidence on the prevalence and spontaneous course of DCIS is restricted. A systematic review on 13 autopsy studies reports a prevalence of undetected DCIS in 8.9% of adult women

without a history of preexistent breast disease.²⁶ Series of DCIS patients treated with biopsy only are scarce. Betsill and Rosen *et al.* observed that 8 of 15 DCIS patients, who were treated by biopsy only, developed an invasive carcinoma after a mean interval of 10 years.^{27,28} Collins *et al.* identified a series of 13 DCIS patients who were initially diagnosed as having benign breast disease: 4–18 years later, six of these 13 untreated patients had developed invasive carcinoma, regardless DCIS grade.²⁹ Sanders *et al.* reported on a cohort of 45 patients with low-grade DCIS, initially diagnosed as having benign breast disease and therefore “treated” with biopsy only.³⁰ Sixteen of these low-grade DCIS patients developed invasive carcinoma in the same breast quadrant within three to 42 years after initial biopsy.³⁰ More recently, Maxwell *et al.* reported a series of 89 DCIS patients who either declined or were unfit to undergo surgery.³¹ One in three patients developed invasive carcinoma after a median interval of 45 months, and high-grade DCIS patients showed a significantly higher risk for developing invasive carcinoma (48%) than intermediate or low-grade DCIS patients (32 and 18%, respectively).³¹

These retrospective series probably underestimate the risk of spontaneous progression of DCIS, as most reports mainly concern low-grade DCIS. Despite these limitations, useful information can be deduced: both low-grade and high-grade DCIS show the ability to progress to invasive carcinoma, but this occurs more frequently and after a shorter time interval in high-grade DCIS.^{13,31} Patients with high-grade DCIS also have a higher risk of breast cancer-related death than patients with low- or intermediate-grade DCIS.¹³ Notwithstanding the risk of progression, a significant number of unresected DCIS in the aforementioned retrospective series remained *in situ*, even among the patients with high-grade DCIS. It is therefore generally accepted that a substantial number of DCIS patients is currently overtreated.

Is active surveillance a noninferior alternative?

At present, three active surveillance trials are conducted to investigate whether watchful waiting is a noninferior alternative strategy for low-risk DCIS compared to conventional surgery with or without adjuvant irradiation and/or hormonal therapy, as per local protocol.^{32,33} In the UK, the low-risk DCIS (LoRis) trial is open to women with a vacuum-assisted biopsy diagnosis of asymptomatic low- or intermediate-grade DCIS without necrosis and with low-mitotic rate.³⁴ Upon central histopathological review of the biopsies, eligible patients are randomized between an active monitoring arm and a surgery arm with conventional surgical and adjuvant treatment.³⁵ In mainland Europe, inclusion in the low-risk DCIS (LORD) trial is limited to women aged over 45 with asymptomatic screen-detected pure low-grade DCIS.³⁶ The LORD trial does not require central histopathological review and randomizes patients between active surveillance and standard treatment according to local policy.³⁶ In the USA, the comparison of operative to monitoring and endocrine therapy (COMET) trial is open to women aged over 40 with newly diagnosed hormone receptor-positive human epidermal growth factor receptor

2 (HER2)-negative low- or intermediate-grade DCIS.³⁷ A fourth active surveillance study was announced in Australian and New Zealand with more stringent inclusion criteria than the aforementioned trials.³⁸ This LARRIKIN trial will include women aged over 55 with screen-detected or incidentally detected DCIS smaller than 25 mm on imaging. Additionally, only patients with hormone receptor-positive, HER2 nonamplified low- or intermediate-DCIS without comedonecrosis will be allowed to participate.³⁸

Accrual for these trials seems challenging: a report on the first 22 months of the LoRis trial mentions randomization of 38 of only 55 eligible patients,³⁹ whereas the required sample size amounts 932 patients.³⁵ At that rate, accrual will take more than 40 years. The stringent inclusion criteria limit the number of eligible patients. It is likely that patients feel anxious upon being allocated to the watchful waiting arm. Collaboration between these trials for combined data analysis in case of lack of power will be arduous, as all trials apply slightly different inclusion criteria. Even if these active surveillance trials prove that watchful waiting is not inferior compared to standard treatment, it will take many years before these data will be available for routine clinical use. Moreover, only a minority of DCIS patients will benefit from these findings, since only 9–12% of DCIS are low grade.^{13,24,40–42} Additional inclusion criteria besides nuclear grade will further decrease the number of eligible patients. The overall impact of active surveillance trials on the population of DCIS patients might therefore be limited.⁴³

Risk stratification and thus treatment allocation based on nuclear grade remains an additional challenge, since nuclear grade is characterized by considerable interobserver variability.^{42,44} Pathologists disagree more often on the difference between low and intermediate grade, than on the difference between intermediate and high grade.^{45,46} It would therefore be interesting to investigate the prognostic value of two-tier grading as nonhigh grade *vs.* high grade instead of a three-tier grading system.⁴⁷ This two-tier morphological grading is corroborated by several molecular and

gene expression studies that indicate a low-grade and high-grade pathway in breast cancer development.^{48–50} The identification of alternative robust prognostic markers besides nuclear grade is of utmost importance, because it is likely that overtreatment of DCIS patients will continue despite the potential usage of active surveillance strategies in this limited subpopulation of “low-risk” DCIS. Notwithstanding these drawbacks, active surveillance trials are presumed to teach us a lot about natural progression in this particular subgroup. This new knowledge should enable us to approach DCIS biology from a completely different perspective.

Risk assessment for synchronous invasion at the biopsy level

Active surveillance might be hazardous, as up to 24% of patients with a biopsy diagnosis of “low-risk” DCIS present a synchronous invasive carcinoma component in the subsequent resection specimen.^{51–55} Five studies applied the inclusion criteria of one or more active surveillance studies on pure DCIS diagnosed in biopsies to investigate the risk of under-treatment in case of a synchronous invasive carcinoma in the subsequent resection specimen (Table 1). Podoll *et al.* examined a series of 105 DCIS that were upstaged to invasive cancer in the subsequent resection specimen and applied the LORD and LoRis criteria on this cohort.⁵⁶ Only three (3%) upgraded DCIS met the LORD criteria, but 20 (19%) upgraded DCIS met the LoRis criteria.⁵⁶ A similar analysis by Alexander *et al.* reports 229 DCIS that were upstaged to invasive cancer, of which four (2%) met the LORD criteria, 37 (16%) met the LoRis criteria and 15 (7%) met the COMET criteria.⁵⁷ A combination of the LORD, LoRis and COMET trial eligibility criteria was retrospectively applied on a subset of 37,544 patients in the National Cancer Database of the American College of Surgeons and the American Cancer Society, which revealed an upstaging rate to invasive carcinoma of 21.8% in this eligible subgroup.⁵⁸

Overall, the prediction of synchronous invasive cancer when pure DCIS is diagnosed at the biopsy level remains challenging.

Table 1. Overview of retrospective analyses of active surveillance trials’ eligibility criteria in relation to upstage rates to invasive cancer in the surgical resection specimen, after an initial diagnosis of pure DCIS at the biopsy level

Ref.	Year of publication	Active surveillance eligibility criteria	Number of samples according to eligibility criteria <i>n</i>	Total upstage rate to invasive cancer <i>n</i> (%)	Upstage rate to invasive cancer according to nuclear grade <i>n</i> (%)
51	2013	LoRis	31	0 (0)	<ul style="list-style-type: none"> • Low grade: 0 (0) • Intermediate grade: 0 (0)
52	2016	LoRis	296	58 (20)	<ul style="list-style-type: none"> • Low grade: 4 (8) • Intermediate grade: 54 (22)
53	2017	LoRis	74	5 (7)	<ul style="list-style-type: none"> • Low grade: 1 (8) • Intermediate grade: 4 (7)
		LORD	10	1 (10)	<ul style="list-style-type: none"> • Low grade: 1 (10)
		COMET	81	5 (6)	<ul style="list-style-type: none"> • Low grade: 1 (8) • Intermediate grade: 4 (6)
54	2018	LoRis	25	6 (24)	Not mentioned in this report
		COMET	23	5 (22)	Not mentioned in this report
55	2017	LoRis	241	16 (7)	Not mentioned in this report

Abbreviations: COMET, comparison of operative to monitoring and endocrine therapy trial; DCIS, ductal carcinoma *in situ*; LORD, low-risk DCIS trial; LoRis, low-risk DCIS trial; Ref, reference.

Many studies have ascertained that upstaging is more frequent in high-grade DCIS than in low- and intermediate-grade DCIS.^{55,59–62} Nevertheless, a significant proportion of nonhigh-grade pure DCIS shows synchronous invasive carcinoma in the subsequent resection specimen.⁵⁷ Attempts have been made to identify additional histological and immunohistochemical features for prediction of concurrent invasive carcinoma. Among them, increased stromal inflammation seems perpetually associated with increased risk for (micro-)invasive carcinoma,^{63–65} but this promising histopathological feature requires further validation in larger independent patient cohorts. Likewise, HER2 positivity in pure DCIS at the biopsy level seems to be associated with increased risk of synchronous invasive cancer in the subsequent resection specimen.⁶⁶ This could be due to the fact that HER2-positive invasive carcinomas have an extensive HER2-positive *in situ* component,⁶⁷ which is a risk factor for sampling error. However, further investigations are necessary as this upstage risk was not confirmed by others.^{63,68} Of note, increased stromal inflammation is strongly correlated with HER2-positivity in pure DCIS,^{69,70} and stromal inflammation is more frequently observed in DCIS admixed with invasive carcinoma than in pure DCIS.⁶⁵ It is currently unclear which feature is the most decisive factor in the progression of *in situ* to invasive carcinoma.

Innovation will discern indolence from agility in DCIS

Besides a lack of adequate markers to predict synchronous invasive carcinoma when pure DCIS is diagnosed at the biopsy level, there is also a need for reliable prognostic markers to assess recurrence risk after conventional treatment of DCIS patients. Despite decades of intensive research, adequate markers for the prediction of invasive recurrence after conventional treatment are lacking. This results in the current uniform treatment of DCIS patients: one size fits all. Why is this? Nearly all studies on prognostic markers in DCIS have applied the following strategy: all BCS-treated patients diagnosed with pure DCIS in the lumpectomy specimen are investigated and clinicopathological characteristics are noted. Subsequently, the initial DCIS lesions of the patients who have developed a recurrence (designated as “cases”) are compared to the DCIS lesions of the patients who did not develop a recurrence (designated as “controls”). As a result, one or more clinicopathological features are significantly more or less often present in the DCIS lesions of the patients who developed a recurrence. Unfortunately, the prognostic power of these features often cannot be confirmed by others in independent patient cohorts.

This lack of validation is probably due to the fact that most DCIS patients who undergo surgery, will be adequately treated: if the initial DCIS lesion is completely removed, the patient will never develop a recurrence. Contrariwise, patients who do develop a so-called “recurrence” should be considered as inadequately treated patients. These patients have residual, initially incompletely removed DCIS in their breasts. A so-called “recurrence” can then be regarded as an outgrowth from this residual disease. Evidently, these “outgrowths” should be discerned from new, independent breast lesions that are not clonally related to

the initial DCIS lesion. Only few studies have investigated the relationship between primary DCIS lesions and their recurrences. Although some studies were limited to histopathological and immunohistochemical features without molecular comparison, their results indicated that about 80–90% of recurrences are actually outgrowths from initially incompletely removed DCIS.^{71,72} Other studies investigated copy number aberrations and loss of heterozygosity, which resulted in a similar high concordance between primary DCIS lesions and their recurrences.^{73–76} To our opinion, retrospective studies should therefore only focus on these patients who recurred, and not on the entire initial patient cohort (Fig. 1).

The key message is “pick the right cases and the right controls”. The correct “controls” are the patients with incompletely removed DCIS that remained *in situ*, that is, the patients who developed a so-called “*in situ* recurrence”. Consequently, the right “cases” are not all patients who relapsed. Only those patients who had initially incompletely removed DCIS that has evolved into invasive carcinoma should be regarded as “cases”, that is, the patients who developed a so-called “invasive recurrence” (Fig. 1). The patient group that has not developed a recurrence (yet) will probably contain a small but hitherto unidentifiable minority who does have incompletely removed DCIS. This small subgroup might either relapse somewhere in the future, or they might have initially incompletely removed DCIS that will remain clinically occult. However, this subgroup will not bias the study as it is not taken into account in the analysis. Such a comparison should enable us to answer the following question: why did some residual DCIS remain *in situ*, and why did other residual DCIS progress to invasive carcinoma? This novel approach can therefore be considered as a retrospective alternative for the current active surveillance trials: incomplete removal of DCIS allowed the residual DCIS lesion to “progress naturally,” enabling us to retrospectively compare the DCIS lesions that remained *in situ* with the DCIS lesions that have progressed to invasive cancer.

The advantage of this strategy is that it will include all BCS-treated DCIS patients and not just the patients with low-grade DCIS. This novel approach should enable the identification of unequivocal robust markers that predict progression to invasive cancer. Eventually, these markers might allow adequate risk stratification when pure DCIS is diagnosed in core biopsies, by discerning indolent DCIS lesions from aggressive DCIS lesions that have an invasive carcinoma component, either on the short term (i.e., synchronous invasive component) or on the long term (i.e., metachronous invasive component). The results of such a study will aid to individualize therapy for DCIS patients and are therefore expected to significantly reduce overtreatment.

Practical implementation of the alternative research strategy

To the best of our knowledge, this alternative strategy has been applied only once before. Zhou et al.⁷⁷ investigated a series of 266 women with primary pure DCIS and a known ipsilateral breast event: 136 of these so-called recurrences were invasive

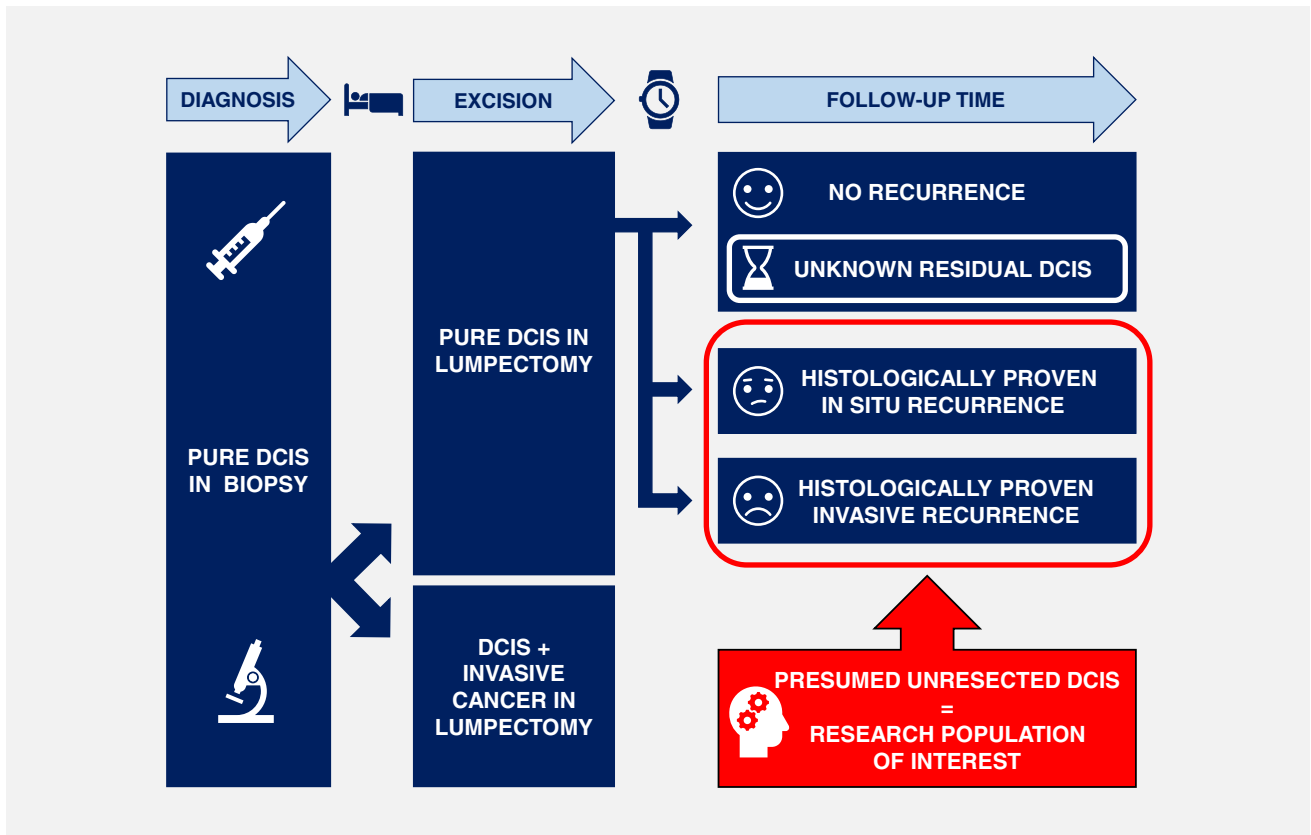


Figure 1. Schematic conceptualization of the novel research strategy. The characteristics of the primary DCIS lesions of patients with *in situ* and invasive recurrences after breast-conserving surgery are compared to each other. The majority of patients without recurrences are considered to be adequately treated and are therefore not included in our study. [Color figure can be viewed at wileyonlinelibrary.com]

carcinoma and 130 were DCIS. Unfortunately, these authors did not investigate the clonal relationship between the primary DCIS lesion and its corresponding recurrence, since they regarded all ipsilateral new events as *de facto* recurrences.⁷⁷ Establishing whether a “recurrence” is either a new second primary tumor or an outgrowth of the initial DCIS lesion is essential for the success of this research strategy. To determine the clonal relationship between the primary DCIS lesion and the second breast event, morphological features such as nuclear grade and DCIS growth pattern can be studied, complemented by immunohistochemistry to assess the expression of ER, progesterone receptor (PR) and HER2. However, these histopathological characteristics enable only a rough comparison, and they should therefore be complemented by molecular studies (i.e., next-generation sequencing and/or copy number analyses). Such an approach seems feasible as it has been shown that there is a high degree of genomic concordance between both components in synchronous *in situ* and invasive carcinoma.^{78–82} Although genomic profiling requires larger financial resources, it allows a more refined comparison than mere immunohistochemistry. This is especially important as protein expression profiles (e.g., ER, PR and HER2 status) can change during breast cancer progression.⁷² An integrated approach of histopathological and molecular characteristics should enable to

distinguish second primary breast lesions from true DCIS outgrowths with a higher degree of certainty than morphological and immunohistochemical features alone, and subsequent analyses can then be continued with the latter.

Despite the fact that Zhou *et al.*⁷⁷ did not discern true DCIS outgrowths from new primary breast lesions, their findings remain very interesting: patients with ER-negative HER2-positive primary DCIS presented significantly more often with an *in situ* “recurrence,” whereas ER-positive HER2-negative primary DCIS presented significantly more often with an invasive “recurrence.”⁷⁷ This might seem contradictory, as HER2 is associated with poor prognosis in invasive breast cancer. This apparent paradox is indirectly supported by other studies. For instance, HER2 protein overexpression in pure DCIS treated with BCS was associated with increased *in situ* recurrence risk, but not with invasive recurrence risk.^{83–85} HER2-positive invasive breast cancers are more often associated with adjacent DCIS than HER2-negative invasive breast cancers, and this adjacent DCIS shows more often a larger size and a higher rate of incomplete resection in HER2-positive breast cancers.⁶⁷ HER2 amplification and its concurrent protein overexpression might act as a driver for intraductal clonal proliferation, instead of being a driver of cancer cell invasion. This hypothesis may explain the observations of Zhou *et al.*,⁷⁷ and it may also

Table 2. A selection of prospective trials and retrospective studies with a substantial number of ipsilateral local recurrences (either *in situ* or invasive) after breast-conserving surgery for DCIS, with or without adjuvant radiotherapy and/or hormonal therapy

Ref	Study /trial	FU time (months) ¹ Mean Median	Total number of patients n	Overall recurrence n (%)	No radiotherapy, no TAM			Radiotherapy without TAM			Radiotherapy with TAM		
					<i>In situ</i> recurrence n (%)	Invasive recurrence n (%)	Invasive recurrence n (%)	<i>In situ</i> recurrence n (%)	Invasive recurrence n (%)	Invasive recurrence n (%)	<i>In situ</i> recurrence n (%)	Invasive recurrence n (%)	Invasive recurrence n (%)
20	NSABP B-17	207	813	222 (27)	99 (12)	123 (15)	62 (15)	79 (20)	37 (9)	44 (11)	NA	NA	
20	NSABP B-24	163	1,799	268 (15)	128 (7)	140 (8)	NA	NA	68 (8)	81 (9)	60 (7)	59 (7)	
90	SweDCIS	204	1,046	258 (25)	129 (12)	129 (12)	91 (17)	74 (14)	38 (7)	55 (11)	NA	NA	
19	UK/ANZ DCIS ²	152	1,694	376 (22)	197 (12)	163 (10)	86 (16)	52 (10)	14 (5)	10 (4)	11 (3)	11 (3)	
17	EORTC10853	190	1,010	234 (23)	110 (11)	121 (12)	74 (15)	75 (15)	37 (7)	48 (10)	NA	NA	
24	Sloane project	64	7,007	368 (5)	3	3	3	3	3	3	3	3	
70	Pruneri <i>et al.</i>	98	945	180 (19)	3	3	3	3	3	3	3	3	
41	Punglia <i>et al.</i>	60	2,762	79 (3)	3	3	3	3	3	3	3	3	
91	E5194 cohort	138	327	53 (16)	26 (8)	27 (8)	3	3	3	3	3	3	
91	Ontario cohort	118	446	65 (15)	27 (6)	38 (9)	3	3	3	3	3	3	
95	Toss <i>et al.</i>	103	776	83 (11)	30 (4)	53 (7)	3	3	3	3	3	3	
97	Wai <i>et al.</i>	113	460	60 (13)	32 (7)	28 (6)	32 (7)	28 (6)	NA	NA	NA	NA	
96	Tunon-de-Lara <i>et al.</i>	118	812	71 (9)	24 (3)	47 (6)	3	3	3	3	3	3	
92	Butler-Henderson <i>et al.</i>	113	1,356	235 (17)	86 (6)	149 (11)	3	3	3	3	3	3	
93	Collins <i>et al.</i>	58	2,995	325 (11)	172 (6)	153 (5)	3	3	3	3	3	3	
94	Rudloff <i>et al.</i>	67	1,868	202 (11)	122 (7)	80 (4)	3	3	3	3	3	3	

¹Some study reports provided median follow-up time in years; for these reports, the number of years was multiplied by 12 months to achieve median follow-up in months to enable comparison.

²The category "tamoxifen alone, without radiotherapy" from this report is not included in this table.

³No details on different subgroups were provided in these study reports, and therefore data on different subgroups could not be provided in this table.

Abbreviations: DCIS, ductal carcinoma *in situ*; EORTC, European Organization for Research and Treatment of Cancer; FU, follow-up; NA, not applicable; NSABP, National Surgical Adjuvant Breast and Bowel Project; Ref, reference number; TAM, tamoxifen; UK/ANZ, United Kingdom/Australia, New Zealand.

Bold values are means and values in italics are medians.

explain the paradoxical observation of HER2 overexpression being much more common in DCIS than in invasive carcinoma.^{86,87} Nevertheless, a nested case-control study identified HER2 as a marker for progression to invasive carcinoma,⁸⁸ and therefore additional investigations remain warranted to clarify the role of this intriguing receptor.^{87,89}

Practical implementation of the novel research strategy might be hampered by the low overall number of recurrences in a single center. A multicenter approach seems therefore mandatory, to enable the inclusion of a sufficiently large number of DCIS patients with subsequent recurrence. Patient recruitment might be facilitated by including patients of previously conducted randomized clinical trials and retrospective studies, of which a non-exhaustive selection is summarized in Table 2.^{17,19,20,24,41,70,90-97} Inclusion of these patients in a study conducted according to the new research strategy would allow for correction of treatment effects, since a substantial number of patients are treated with radiotherapy and/or TAM after BCS. Additionally, it would be interesting to also include HER2-positive DCIS patients with recurrences from the currently ongoing NSABP B-43 trial, wherein the value of adjuvant trastuzumab is investigated.⁹⁸ Inclusion of a sufficiently large number of patients does not only allow stratification according to type of adjuvant treatment, but it would also allow stratification according to DCIS grade and other clinicopathological parameters. It may therefore be possible to provide stronger evidence for the so-called low-grade and high-grade pathway of breast cancer progression, wherein low-grade DCIS

gives rise to less aggressive low-grade invasive carcinoma, and high-grade DCIS gives rise to more aggressive high-grade invasive carcinoma.^{50,99} Implementation of this novel research strategy in a combined multicenter international effort could force a major breakthrough in the research on DCIS biology and its natural progression.

Conclusion

The breast is a rather unique organ regarding the clonality issue between DCIS and its recurrence, although a similar issue exists in the liver and the lungs, where intra-organ metastases have to be discerned from new, metachronous and synchronous carcinomas.^{100,101} Based on the currently available evidence regarding prognostic markers in DCIS (or the lack thereof), we propose a new model as a retrospective surrogate for active surveillance trials, which may provide useful data on the short term. This novel strategy is based on the comparison of the initial DCIS lesion between the patients who developed an *in situ* recurrence and the patients who developed an invasive recurrence. We hope this model will be included in future scientific studies on risk stratification of DCIS, as we believe this strategy will enable identification of robust markers for prediction of the natural course of DCIS. If this new approach succeeds in the development of a reliable risk stratification tool, the direct impact on clinical management of DCIS will be enormous, as it is likely that many patients will be treated less aggressively than they are now.

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