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REVIEW

Leveraging the variable natural history of ductal carcinoma in situ (DCIS) to select optimal therapy

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Abstract

Purpose Ductal carcinoma in situ (DCIS) is a non-obligate precursor to invasive ductal carcinoma. The authors sought to discuss the evidence suggesting that not all DCIS will progress to invasive disease if left untreated.

Results Four lines of evidence align to suggest that not all of this in-situ disease progresses to invasive cancer: its prevalence on screening mammography, studies of missed diagnoses, incidental findings in autopsy specimens, and large retrospective reviews of those treated with excision alone.

Conclusion A clearer understanding of the variable history of DCIS coupled with advances in genomic profiling of the disease holds the promise of reducing widespread over-treatment of this non-invasive cancer. Additionally, identification of higher risk of recurrence subsets may select patients for whom more aggressive treatment may be appropriate.

Keywords Ductal carcinoma in situ · DCIS · Breast cancer · Breast cancer screening · Breast cancer genomic profiling · Oncotype DCIS · Oncotype Dx

Introduction

Historically, the strategy for the treatment of DCIS has been based upon incorrect assumptions regarding the natural history of the disease. The overriding conceptual framework supported the idea that virtually all DCIS was likely to progress to invasive ductal carcinoma in a clinically relevant time frame. Four lines of evidence provide credible proof that this logic was flawed and suggest that more than half of DCIS cases are either destined to never proceed to invasive carcinoma or may progress at such a slow pace as to be clinically irrelevant. Advances in molecular profiling of DCIS have provided further evidence that a subset of cases might be treated adequately with complete excision alone, without radiation therapy. It is possible that some very low-risk lesions, confirmed on genomic profiling, may be simply followed closely in a program of active surveillance. In short, our understanding of DCIS has evolved from imagining the disease as a single entity in an inevitable progression to invasion, to a heterogeneous family of neoplasms. Predicting class in this complex mosaic of non-invasive breast cancer represents the next significant frontier in the study of early-stage breast cancer.

Pathophysiology

In simplistic terms, virtually all DCIS originates from the hormone-sensitive epithelial cells lining the basement membrane within the terminal duct lobular unit of the breast. Although a simplistic model of progression beginning with ductal hyperplasia, progressing to DCIS, and ending with invasive ductal carcinoma (IDC) is appealing, epidemiological evidence suggests that most atypical ductal hyperplasia (ADH) is not destined to become DCIS, and similarly, most DCIS does not progress to IDC [1–7]. In some genomic biomarker studies, DCIS and IDC from the same breast were found to have similar gene copy number profiles and expression signatures. However, more recent genomic sequencing technologies have failed to confirm that all synchronous in-situ and invasive lesions share concordant mutations. Unfortunately, the specific molecular explanation of if, when, and how DCIS will invade through the basement membrane has yet to be clarified [8–25]. Invasion of these collections of

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clonal neoplastic cells is not inevitable, however, and even extensive cases of DCIS are usually confined to a single segment of the mammary duct system. Furthermore, the alteration in normal anatomy by proliferative processes such as sclerosing adenosis, duct hyperplasia, or radial scars may facilitate further proliferation of the neoplastic cells [26].

DCIS: progression or indolence?

Ductal carcinoma in situ comprises just over 20% of modern breast cancer diagnoses in the United States, which is a greater than sevenfold increase from the 2.8% incidence reported in 1973 [27]. This increase in incidence is directly attributable to the widespread popularization and application of screening mammography beginning in 1990. In fact, DCIS was almost never seen prior to the popularization of mammographic screening. Moreover, DCIS is more common in the U.S. compared to England or Switzerland, countries whose screening mammography practices involve less frequent intervals, later age at commencement, and no screening over a set age [28, 29]. Furthermore, the advent of high-quality digital mammography in the twenty-first century, with its improved visualization through dense breast tissue, has led to an even greater increase in the detection and therefore reported incidence of DCIS [30].

The prevalence of DCIS and its potential for indolence is demonstrated by historical autopsy studies. Nielsen et al. reviewed 77 autopsy specimens of women who died between age 22 and 89 (median age 67) from unrelated causes. Fourteen of the women were found to have occult DCIS without evidence of invasion [31]. A subsequent review of seven similar investigations revealed that the average prevalence of DCIS was 8.9% [32]. This is significantly higher that one would expect from age-adjusted screening prevalence data (1 per 1300 women screened) [27].

Studies revealing the misdiagnosis of DCIS as proliferative lesions, without subsequent intervention, further illustrate the heterogeneity in the natural progression of DCIS. A retrospective study of 28 cases of undiagnosed DCIS in a population of more than 11,000 women with benign breast disease found that only 9 of the 28 (32%) of patients developed any form of invasive breast cancer for up to 31 years after the index biopsy [9]. A larger retrospective review of thousands of specimens initially categorized as benign revealed 30 cases with occult micropapillary DCIS. Since the missed diagnosis occurred later, no treatment was rendered in any of these cases. In 15 patients in whom follow-up information was available, only eight women developed invasive cancer in the ipsilateral breast with an average time to diagnosis of 9 years [33]. Lastly, of 80 cases of missed DCIS found in approximately 9000 'benign' breast biopsies, only 11 lesions progressed to clinically relevant invasive cancer over the course of 17.5 years [27]. When the results of these studies are combined, among those found to have undiagnosed and subsequently untreated DCIS, the risk of being diagnosed with clinically relevant ipsilateral invasive breast cancer 10–15 years later ranged from 14 to 53% [34].

More recently, Van Zee et al. found that the majority of DCIS treated by local excision alone with close or involved margins does not portend an eventual diagnosis of invasive breast cancer with long-term follow-up. A review of nearly 3000 DCIS cases treated with lumpectomy alone identified 271 patients with excision margins less than 2 mm, and 59 patients with positive margins. Although this population did not undergo re-excision, radiation, or endocrine ablative therapy, more than 60% were alive without a diagnosis of invasive breast cancer at a mean follow-up of 20 years [35].

These four lines of evidence, the prevalence of DCIS on screening mammography, studies of missed diagnoses of DCIS, incidence of DCIS in autopsy specimens, and the large retrospective cohort of those treated with excision alone, indicate that not all DCIS progresses to invasive cancer.

Adjuvant radiation in the treatment of DCIS

Several prospective trials with long-term follow-up have established that the standard of care in the treatment of DCIS includes adjuvant radiation following excision. The National Surgical Adjuvant Breast and Bowel Project B-17 Trial (1971) compared lumpectomy alone to lumpectomy with radiation in women with DCIS. Of the non-irradiated patients who underwent lumpectomy alone, more than 80% of patients were alive and free of breast cancer at 20 years. See Fig. 1 for the Kaplan–Meier curves depicting 20-year outcomes of invasive ipsilateral breast tumor recurrences (a), and DCIS ipsilateral breast tumor recurrences (b) in patients treated with lumpectomy alone, lumpectomy with radiation (LRT), LRT with placebo, and LRT with 5 years of tamoxifen. Although post-lumpectomy radiation did afford a 52% decrease in the risk of ipsilateral invasive breast tumor recurrence, it did not demonstrate an overall difference in survival among those who received radiation vs. those that did not [36]. A later follow-up study reported that despite reanalyzing the recurrence data with respect to patient age, method of detection, and histologic features, the authors concluded that they could not identify a subset of patients with DCIS whose risk of local recurrence was not decreased by adjuvant radiation using traditional clinicopathologic factors, but that they were aware that a subset must exist.

Determining the specific cohort of patients who will absolutely benefit from radiation and sparing those that may not is paramount in improving treatment-related outcomes for breast cancer patients. Short-term side effects of

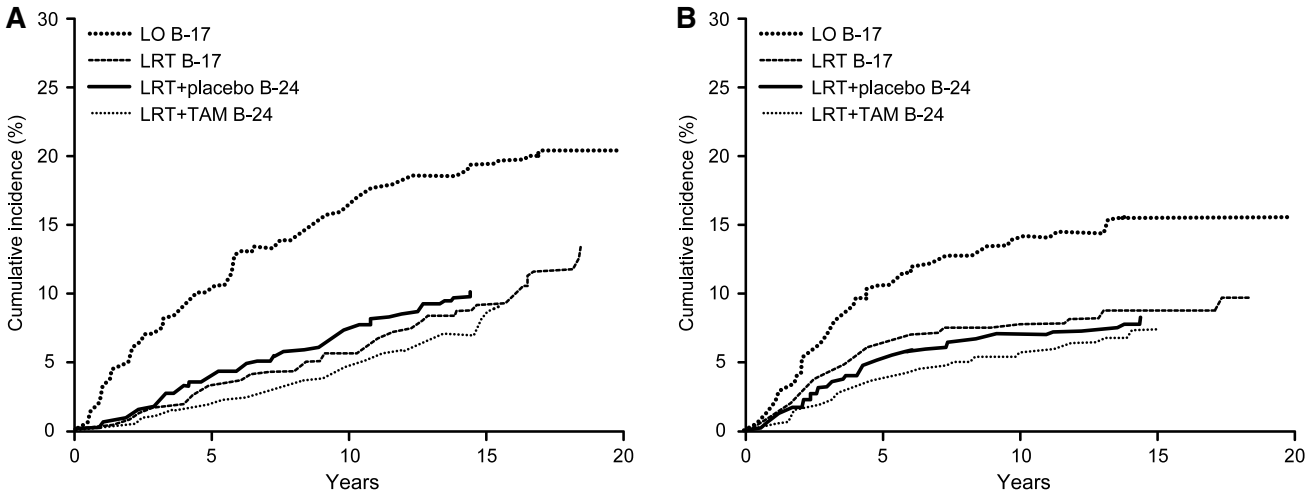

Fig. 1 Long-term invasive and in-situ recurrences after lumpectomy alone, lumpectomy with radiation (LRT), LRT with placebo, and LRT with 5 years of tamoxifen (from NSABP B-17) [36, 37]

breast radiation include axillary and chest pain, skin itching, burns, and discoloration, breast contraction as well as systemic effects such as fatigue and leukopenia, while the long-term morbidity includes the increased likelihood of a coronary event or, rarely, a secondary malignancy such as angiosarcoma of the breast [38].

Predictors of invasion

Since some DCIS is indolent and progression to invasive disease is not obligatory, researchers have sought to identify which patients with DCIS are at greatest risk for invasive disease, and thus require further treatment outside of excision. Historically, long-term data have demonstrated a substantial difference in the rates of progression between low-grade and high-grade DCIS, and grade assignment by pathologists is unfortunately subject to significant and well-documented inter-observer bias. Therefore, histologic grade has proved to be an incompletely reliable metric when conducting clinical research [39].

Prognostic index

Predicting a measurable risk of local recurrence in DCIS patients conservatively treated led to the development of the University of Southern California/Van Nuys Prognostic Index (USC/VNPI). The USC/VNPI includes five factors: tumor size, margin width, nuclear grade, age, and the presence of comedonecrosis. It produces a numerical score closely related to outcome. The development of the algorithm in itself was a considerable contribution to the idea that DCIS behaves as a family of diseases and that a standardized, uniform approach will unnecessarily overtreat some patients and undertreat others. However, the technical manpower required to achieve the accurate tumor and margin size employed in the development of the algorithm requires subspecialized pathology support that is outside of the scope of most healthcare institutions, therefore limiting the universal application of the USC/VPNI.

Genomic profiling

As the sole platform providing Level 1b evidence-supported prognostic and predictive risk estimates in the treatment of invasive breast cancer, the 21-gene assay (Oncotype DX, Genomic Health) has been integrated into the 8th revision of the American Joint Commission on Cancer Staging system, effective since January 1, 2018 [40]. The 21-gene assay has allowed providers to tailor treatment of invasive breast cancer to a patient's unique tumor biology. Pooling data from four large, independently run, international studies measuring prospective outcomes of more than 50,000 patients, the results from the SEER Registry, TAILORx, Clalit, and West German Group's Plan B studies have demonstrated that the 21-gene assay accurately predicts patients' recurrence risk, response to chemotherapy, and survival [41–44]. With the demonstration that 99% of patients with estrogen receptor-positive tumors with a low Recurrence Score (less than 11 as in TAILORx trial) will be disease-free at 5 years with the use of adjuvant hormonal therapy alone, more patients are able to avoid cytotoxic chemotherapy without fear of sacrificing a potential survival benefit. These outcomes have been reflected in the new 8th Edition Staging System, where a 21-gene Recurrence Score of less than 11 may downstage breast cancer from Stage II or even Stage III to Stage I [40].

Advances in gene expression profiling and genomic profiling have prompted researchers to focus their attention

on patients with DCIS. A 12-gene DCIS assay, the DCIS Score (Genomic Health Inc.), has been developed, tested, and validated in both the ECOG 5194 patient subset and a convenience sample of tumors found in the Ontario Province in Canada [45, 46].

Solin, et al. reported their results of the application of the 12-gene DCIS assay to the ECOG 5194 patients and confirmed that the score accurately quantifies the risk of recurrence. The study population of 327 patients were divided into two groups: Group 1 ($n=273$, 83%) consisted of grade 1 or 2 tumors with size ≤ 2.5 cm, and Group 2 consisted of grade 3 tumors of size ≤ 1 cm ($n=54$, 17%). Median patient age was 61, with 80% being at least 40 years of age. Median tumor size was 7 mm, and 65% of resections had margins ≥ 5 mm. Almost all (97%) tumors were estrogen receptor positive (by RT-PCR), and 29% of patients used tamoxifen during their treatment course. After applying the 12-gene DCIS assay to the tumor samples, 70% of patients were in the low-risk group, and 30% in the intermediate- or high-risk group. See Table 1 for recurrence rates compared by 12-gene DCIS assay [45].

Alone, the 12-gene DCIS assay predicted the likelihood of any local recurrence with a hazard ratio (HR) of 2.31 (95% CI 1.15–4.49, $p=0.02$), with the HR associated with a 50-point difference in the assay result. In the multivariable analysis excluding the assay, only tumor size and postmenopausal status were significant predictors for the risk of local recurrence. However, when the multivariable analysis included the assay with tumor size and menopausal status, the estimated HR was 2.37 (95% CI 1.14–4.76, $p=0.02$), which is essentially unchanged from the model employing the assay alone, demonstrating that the result may be an independent predictor of local recurrence risk. Interestingly, the traditionally employed clinical and pathologic variables including surgical margins, grade, presence of comedonecrosis, and DCIS type (papillary, cribriform, solid, etc), as well as tamoxifen use, were not statistically significant predictors for recurrence [45].

In the Ontario Province DCIS Cohort Analysis of DCIS patients undergoing lumpectomy alone, the 12-gene DCIS assay was applied to 571 tumor samples with negative margins (defined as "no ink on tumor"). See Table 2 for the correlation of the assay result with 10-year risk of in-situ and invasive local recurrences in the Ontario analysis.

Within this analysis, the 12-gene DCIS assay result was associated with in-situ local recurrence (HR 2.43, $p=0.005$) and invasive local recurrence (HR 1.78, $p=0.04$). Age, tumor size, and multifocality were all independent risk predictors of local recurrence. As in the ECOG 5194 analysis, the assay provided independent information beyond these clinical and pathological variables (adjusted HR 1.68, 95% CI 1.08–2.62, $p=0.02$). The authors concluded that the 12-gene DCIS assay independently predicts and quantifies tumor-specific recurrence risk in a population of pure DCIS treated by lumpectomy alone [46].

More recently, a meta-analysis combining the data from these two prior analyses has been published. Seven hundred seventy-three patients underwent BCS alone, where those with positive margins and multifocal disease were excluded. The authors found that using tumor size and age alone, they were unable to predict which patients with DCIS have a 10-year local recurrence risk of $\leq 8\%$. However, using the 12-gene DCIS assay combined with tumor size and patient age, 25.9% of patients with DCIS could be identified as having a 10-year local recurrence risk of $\leq 8\%$, and almost half (47%) could be identified as having a 10-year local recurrence risk of $\leq 10\%$ [47].

Additionally, 10.9% of patients with DCIS were found to have a 10-year local recurrence risk (LRR) of more than 15% by using tumor size and patient age alone. However, when the assay was combined with tumor size and patient age, 21.1% were identified as having a 10-year LRR of more than 15%, almost doubling the amount of high-risk patients who could potentially be identified at the time of treatment. These results confirm the benefit of the individualization of treatment decision-making for women with DCIS. The identification of DCIS patients at exceptionally low or high risk of recurrence will give providers and patients the opportunity to make an educated and personalized decision of either deferring or electing adjuvant radiation therapy [47].

Table 1 10-year risk of local recurrence of ECOG 5194 data correlated with the 12-gene DCIS assay [45]

12-gene DCIS assay (DCIS score)	All local events (95% CI)	Invasive local recurrence (95% CI)
All patients, $n=327$	15% (12–20)	7% (5–11)
Low (<39), $n=230$	11% (7–16)	4% (2–8)
Intermediate (39–54), $n=53$	27% (16–42)	12% (5–28)
High score (≥55), $n=44$	26% (15–43)	19% (10–36)

Log rank (any event) $p=0.006$

Log rank (invasive recurrence) $p=0.003$

Table 2 10-year risk of local recurrence of Ontario study correlated with the 12-gene DCIS assay

12-gene DCIS assay (DCIS Score)	In-situ local recurrence (95% CI)	Invasive local recurrence (95% CI)
All, $n=571$	9% (6–11)	12% (9–15)
Low (<39), $n=355$	5% (3–9)	8% (6–12)
Intermediate (39–54), $n=95$	14% (8–24)	21% (13–33)
High (≥55), $n=121$	14% (9–22)	16% (9–25)

Log rank (DCIS) $p=0.002$

Log rank (invasive only) $p=0.03$

Retrospective studies have sought to evaluate the effect of preoperative breast magnetic resonance imaging (MRI) on recurrence outcomes in patients with DCIS [48, 49]. More recently, data from the first prospective cohort that measured the combined impact of breast MRI when used with the 12-gene DCIS assay in surgical and radiation therapy decision-making were presented. In this analysis, women with screen-detected pure DCIS on core biopsy who were eligible for lumpectomy underwent breast MRI and any additional necessary biopsies of new findings noted on the preoperative imaging. In patients who then underwent lumpectomy with margins of at least 2 mm without evidence of invasive disease, the 12-gene DCIS assay was performed. If the assay score was low (< 39), the patient was advised that she may avoid radiation [50].

Three hundred sixty-three patients were evaluated, and 171 patients met criteria for inclusion. Three hundred and thirty-five women were enrolled. More than 80% of patients underwent lumpectomy, and 3.9% were subsequently converted to mastectomy. Eighty-two patients received a low assay score, and only seven of those patients (8.8%) chose to undergo radiation, while 58 of 72 (80.6%) patients with hormone receptor-positive DCIS and a low score accepted the recommendation to receive adjuvant endocrine therapy. Interestingly, 14.8% of the patients with low assay scores had high-grade DCIS. Among the patients with intermediate/high scores, 84 of 89 (94.4%) chose to undergo adjuvant radiation, and 49 of 66 (74.2%) in the high-risk group with hormone receptor-positive tumors planned to receive endocrine therapy. Of note, only 81.5% of patients with intermediate/high scores had high-grade DCIS.

The authors concluded that radiation therapy recommendations based on the 12-gene DCIS assay were acceptable to most women in the study who received adequate information about the test, and who participated in shared decision-making [50].

Conclusion

According to the American Cancer Society, about 60,000 cases of DCIS are diagnosed in the United States each year, accounting for one out of every five new breast cancer diagnoses. This increase in incidence is directly attributed to the uptake of screening mammography, along with the increase in life expectancy of American women [51].

Treatment of DCIS has been influenced by unjustified comparisons to invasive cancer, partially misinterpreted clinical trials, as well as public misconceptions about the nature of what is sometimes referred to as "Stage 0" breast cancer. Both epidemiological and outcomes-based studies suggest that a significant proportion of breasts may possess a non-trivial reservoir of DCIS that is either never going to invade the basement membrane, or whose indolent progression may remain clinically insignificant.

Although randomized clinical trials have demonstrated that radiotherapy after local excision reduces the risk of both invasive and in-situ recurrence when compared to excision alone, adjuvant radiation therapy does not definitively improve survival in women with DCIS. Moreover, a significant majority of patients who were not irradiated have remained free of invasive breast cancer for more than two decades. As traditional clinicopathologic factors have failed to identify the subset of patients that would benefit most from adjuvant radiation, the difficulty proving a radiation-related survival benefit, along with the very high long-term survival rates of patients with DCIS, has led to further technological advancements aimed at identifying patients most likely to benefit from aggressive local control.

The validation of the 21-gene assay (Oncotype Dx) in predicting both risk of recurrence and response to chemotherapy has revolutionized breast cancer care, allowing providers to tailor adjuvant cytotoxic therapy to the genomic profile of a patient's tumor. Similarly, the in-situ genomic profiling tool of the 12-gene DCIS assay has since been proven to independently quantify recurrence risk in a population of pure DCIS treated by lumpectomy alone. Although it has not been directly proven to be explicitly predictive of the benefit from radiotherapy, the identification of DCIS patients at exceptionally low or high risk of recurrence allows providers and their patients to consider the DCIS assay result in discussions of treatment decisions. With the recent additions to the DCIS literature employing the 12-gene DCIS assay, providers and patients can feel comfortable making an educated and personalized decision of deferring or electing adjuvant radiation therapy after surgical excision of this oftentimes indolent non-obligate precursor.

Compliance with ethical standards

Conflict of interest Dr. Rojas and Dr. Fortes declare that they have no conflicts of interest. Dr. Borgen has received a speaker honorarium from Company Genomic Health, Inc.

References

1. Francis A, Thomas J, Fallowfield L, Wallis M (2015) Addressing overtreatment of screen detected DCIS: the LORIS trial. Eur J Cancer 51:2296–2303
2. Ernster V, Barclay J (1997) Increases in ductal carcinoma in situ (DCIS) of the breast in relation to mammography: a dilemma. J Natl Cancer Inst Monogr 22:151–156
3. Wellings S, Jensen H (1973) On the origin and progression of ductal carcinoma in the human breast. J Natl Cancer Inst 50:1111–1118
4. Page D, Dupont W, Rogers L, Jensen R et al (1995) Continued local recurrence of carcinoma 15–25 years after a diagnosis of low

grade ductal carcinoma in situ of the breast treated only by biopsy. Cancer 76:1197–1200
5. Dupont W, Page D (1985) Risk factors for breast cancer in women with proliferative breast disease. N Engl J Med 312:146–151
6. Tavassoli F (1998) Ductal carcinoma in situ: introduction of the concept of ductal intraepithelial neoplasia. Mod Pathol 11:140–154
7. McCaffery K, Nickel B, Moynihan R, Hersch J (2015) How different terminology for ductal carcinoma in situ impacts women's concern and treatment preferences: a randomised comparison within a national community survey. BMJ Open 5:e008094
8. Bartlett J, Nofech-Moses S, Rakovitch E (2014) Ductal carcinoma in situ of the breast: can biomarkers improve current management? Clin Chem 60:60–67
9. Thompson A, Brennan K, Cox A, Gee J et al (2008) Evaluation of the current knowledge limitations in breast cancer research: a gap analysis. Breast Cancer Res 10:R26
10. Leonard G, Swain S (2004) Ductal carcinoma in situ, complexities and challenges. J Natl Cancer Inst 96:906–920
11. Aubele M, Mattis A, Zitzelsberger H, Walch A et al (1999) Intratumoral heterogeneity in breast carcinoma revealed by laser-microdissection and comparative genomic hybridization. Cancer Genet Cytogenet 110:94–102
12. Aubele M, Cummings M, Walch A, Zitzelsberger H (2000) Heterogeneous chromosomal aberrations in intraductal breast lesions adjacent to invasive carcinoma. Anal Cell Pathol 20:17–24
13. Aubele M, Mattis A, Zitzelsberger H, Walch A (2000) Extensive ductal carcinoma in situ with small foci of invasive ductal carcinoma: evidence of genetic resemblance by CGH. Int J Cancer 85:82–86
14. Foschini M, Morandi L, Leonardi E, Flamminio F (2013) Genetic clonal mapping of in situ and invasive ductal carcinoma indicates the field cancerization phenomenon in the breast. Hum Pathol 44:1310–1319
15. Luzzi V, Holtschlag V, Watson MA (2001) Expression profiling of ductal carcinoma in situ by laser capture microdissection and high-density oligonucleotide arrays. Am J Pathol 158:2005–2010
16. Reis-Filho J, Lakhani S (2003) The diagnosis and management of pre-invasive breast disease: genetic alterations in pre-invasive lesions. Breast Cancer Res 5:313–319
17. Werner M, Mattis A, Aubele M, Cummings A et al (1999) 20q13.2 amplification in intraductal hyperplasia adjacent to in situ and invasive ductal carcinoma of the breast. Virchows Arch 435:469–472
18. Westbury C, Reis-Filho J, Dexter T, Mahler-Araujo B et al (2009) Genome-wide transcriptomic profiling of microdissected human breast tissue reveals differential expression of KIT (c-Kit, CD117) and oestrogen receptor-alpha (ERalpha) in response to therapeutic radiation. J Pathol 219:131–140
19. Ghazani A, Arneson N, Warren K, Pintilie M et al (2007) Genomic alterations in sporadic synchronous primary breast cancer using array and metaphase comparative genomic hybridization. Neoplasia 9:511–520
20. Hernandez L, Wilkerson P, Lambros M, Campion-Flora A (2012) 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 227:42–52
21. Kim S, Jung S, Kim M, Baek I et al (2015) Genomic differences between pure ductal carcinoma in situ and synchronous ductal carcinoma in situ with invasive breast cancer. Oncotarget 6:7597–7607
22. Kroigard A, Larsen M, Laenkholm A, Knoop A et al (2015) Clonal expansion and linear genome evolution through breast cancer progression from pre-invasive stages to asynchronous metastasis. Oncotarget 6:5634–5649
23. Koboldt D, Steinberg K, Larson D, Wilson R et al (2013) The next-generation sequencing revolution and its impact on genomics. Cell 155:27–38
24. Newburger D, Kashef-Haghighi D, Weng Z, Salari R et al (2013) Genome evolution during progression to breast cancer. Genome Res 23:1097–1108
25. Yates L, Gerstung M, Knappskog S, Desmet C et al (2015) Subclonal diversification of primary breast cancer revealed by multiregion sequencing. Nat Med 21:751–759
26. Macklin P (2012) Essential ductal carcinoma in situ (DCIS) pathobiology for modelers. http://www.mathcancer.org/files/tutorials/biology/Macklin_DCIS_biology_tutorial_2012_v1.pdf. Accessed 1 Aug 2017
27. Ernster V, Barclay J, Kerlikowske K, Wilkie H et al (2000) Mortality among women with ductal carcinoma in situ of the breast in the population-based surveillance, epidemiology and end results program. Arch Intern Med 160:953–958
28. Schopper D, de Wolf C (2007) Breast cancer screening by mammography: international evidence and the situation in Switzerland. Krebsliga Schweiz/Oncosuisse. http://www.swisscancer.ch/stellungnahmen/mammografie. Accessed 1 Aug 2017
29. Biller-Adorno N, Juni P (2014) Abolishing mammography screening programs? A view from the Swiss medical board. N Engl J Med 370:1965–1967
30. Berger N, Schwizer S, Varga Z, Rageth C et al (2016) Assessment of the extent of microcalcifications to predict the size of a ductal carcinoma in situ: comparison between tomosynthesis and conventional mammography. Clin Imaging 50(6):1269–1273
31. Nielsen M, Jensen J, Anderson J (1984) Precancerous and cancerous breast lesions during lifetime and at autopsy. A study of 83 women. Cancer 54:612–615
32. Welch H, Black W (1997) 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 127:1023–1028
33. Rosen P, Snyder R, Foote F, Wallace T (1970) Detection of occult carcinoma in the apparently benign breast biopsy through specimen radiography. Cancer 26:944–952
34. Fong J, Kurniawan E, Rose A, Mou A (2011) Outcomes of screening-detected ductal carcinoma in situ treated with wide excision along. Ann Surg Oncol 18:3778
35. Van Zee K, Subhedar P, Olcese C, Patil S et al (2015) Relationship between margin width and recurrence of ductal carcinoma in situ: analysis of 2996 women treated with breast conserving surgery for 30 years. Ann Surg 262(4):623–631
36. Wapnir I. Dignam J, Fisher B, Mamounas E et al (2011) 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 103(6):478–488
37. Fisher B, Dignam J, Wolmark N et al (1998) Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from the national surgical adjuvant breast and bowel project B-17. J Clin Oncol 16:441–452
38. Taylor C, Correa C, Duane F, Aznar M et al (2017) Estimating the risks of breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous randomized trials. J Clin Oncol 35(15):1641–1649
39. Jackson S, Frederick P, Pepe M, Nelson H et al (2017) Diagnostic reproducibility: what happens when the same pathologist interprets the same breast biopsy specimen at two points in time? Ann Surg Onc 24(5):1234–1241
40. Amin M, Greene F, Edge S, Compton C et al (2017) The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA 67:93–99

41. Petkov V, Miller D, Howlader N, Gliner N et al (2016) Breast-cancer-specific mortality in patients treated based on the 21-gene assay: a SEER population-based study. Breast Cancer 2(16017):1–9
42. Sparano J, Gray R, Makower D, Pritchard K (2015) Prospective validation of a 21-gene expression assay in breast cancer. N Engl J Med 373(21):2005–2014
43. Stemmer S, Steiner M, Rizel S, Soussan-Gutman L et al (2016) Real -life analysis evaluating 1594 N0/Nmic breast cancer patients for whom treatment decisions incorporated the 21-gene recurrence score result: 5-year KM estimate for breast cancer specific survival with recurrence score results ≤ 30 is> 98%. Cancer Res 76(4S):P5–P08
44. Nitz U, Gluz O, Christgen M, Clemmons M et al (2017) Reducing chemotherapy use in clinically high-risk, genomically low-risk pN0 and pN1 early breast cancer patients: five-year data from the prospective, randomised phase 3 West German Study Group (WSG) PlanB trial. Breast Cancer Res Treat 165:573
45. Solin L, Gray R, Baehner F, Butler S et al (2013) A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. J Natl Cancer Inst 105(10):701–710
46. Rakovitch E, Nofech-Mozes S, Hanna W, Baehner F et al (2015) A population-based validation study of the DCIS Score predicting recurrence risk in individuals treated by breast-conserving surgery alone. Breast Cancer Res Treat 152(2):389–398
47. Rakovitch E, Gray R, Baehner F, Sutradhar R et al (2018) Refined estimates of local recurrence risks by DCIS score adjusting for clinicopathological features: a combined analysis of ECOG-ACRIN E5194 and Ontario DCIS cohort studies. Breast Cancer Res Treat 169:359–369
48. Pilewskie M, Olcese C, Eaton A, Patil S et al (2014) Perioperative breast MRI is not associated with lower locoregional recurrence rates in DCIS patients treated with or without radiation. Ann Surg Oncol 21(5):1552–1560
49. Hill M, Beeman J, Jhala K, Holubar S et al (2017) Relationship of breast MRI to recurrence rates in patients undergoing breast-conservation treatment. Breast Cancer Res Treat 163:615
50. Khan S, Gatsonis C, Snyder B, Lehman C et al (2017) Prospective study of MRI and Multiparameter gene expression assay in DCIS: a trial of the ECOG-ACRIN Cancer Research Group (E4112). J Clin Oncol 35(15_suppl):534–534
51. American Cancer Society. (2017) Breast Cancer Facts & Figs. 2017–2018. American Cancer Society, Inc., Atlanta. http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2014. Accessed 26 July 2017