The road towards conquering DCIS overtreatment

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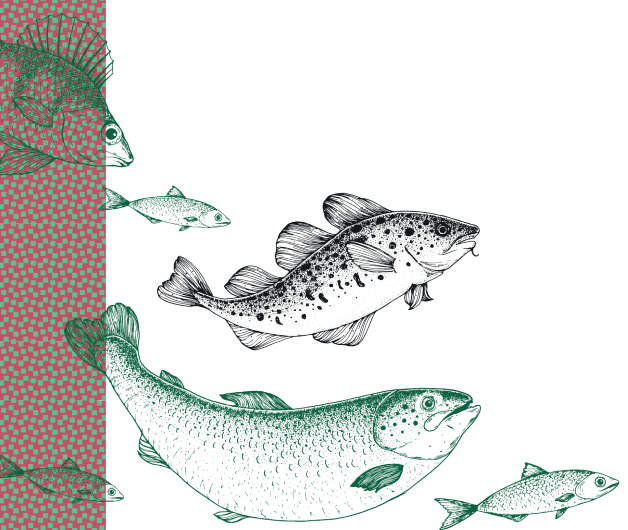

Chapter 7

Summarizing discussion

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DCIS: from an unknown entity to a frequently treated disease

The concept of preinvasive carcinoma of the breast was established in the early 1930s and terms as intra-duct carcinoma and carcinoma in situ were used shortly thereafter by some of the very first pathologists.[1,2] Before the emergence of pathology as a medical specialty, surgeons themselves operating on palpable breast abnormalities, decided whether a lesion was benign or malignant based on gross inspection or rarely based on microscopic examination of frozen sections. The operation for breast lesions perceived as benign was then terminated after lumpectomy, while a radical mastectomy was the therapy of choice if a lesion was considered malignant, whereby the distinction between preinvasive and invasive breast lesions was not yet made in the early days.[3]

Up until the last quarter of the 20th century, the standard treatment for DCIS was a mastectomy and even an 'en bloc' axillary dissection was routinely performed, similar to the surgical treatment of invasive breast cancer (IBC). A diagnosis of DCIS, either found isolated or adjacent to IBC, was therefore not of great interest in clinical practice, it implied a similar treatment as IBC and resulted in excellent curation rates.[4]

The interest in DCIS increased after the widespread adoption of breast conserving surgery (BCS) in DCIS with an inherent risk of recurrence, progression or the evolution of new primary in situ/ invasive lesions. Still, pure DCIS (i.e. isolated or without IBC) was a rare finding, because it generally does not cause symptoms for which women seek medical help. However, since the introduction of breast cancer screening the incidence of DCIS dramatically increased, as DCIS is often associated with calcifications that can be detected by mammography. More than 90% of DCIS we encounter today are detected only on imaging studies.[5] Almost all women with DCIS are currently being treated to avoid the development of IBC with its inherent risk of metastases with potentially

fatal outcome. In this light, it is important to note that the DCIS lesions we encounter today may harbor very different risks compared to the DCIS we diagnosed before the screening era.

The DCIS dilemma

Treating DCIS has not led to a reduced IBC incidence. Breast screening programs have therefore received criticism by some for being associated with overdiagnosis and overtreatment of DCIS.[6–8] It has also been reported that a large proportion of untreated DCIS will not progress to IBC.[9,10] A 10-year net risk of ipsilateral IBC (iIBC) of 12.2% (95% Confidence Interval (95%CI) 8.6-17.1%) for women with DCIS grade 1/2 and 17.6% (95%CI 12.1-25.2%) for grade 3 was reported. These results are based on a selected patient group, because the standard management of DCIS is surgical removal often followed by radiotherapy in case of BCS. However, these results underline that at least some DCIS lesions have a low risk of progression and may thus be overtreated.

A reduction of IBC incidence may fail to occur as a result of detecting and treating only a subset of predominantly harmless DCIS lesions while DCIS with a high risk of progression remains undetected, i.e. DCIS may not be associated with mammographic abnormalities and/or DCIS may show such a fast progression that we are unable to detect the lesion in an in situ stage. The much higher incidence of IBC compared to DCIS and the frequent finding of DCIS adjacent to IBC, suggests indeed an undetected DCIS reservoir exists. In addition, a subset of IBC's may arise de novo and not through a DCIS stage.

At this point, our dilemma is, that we are unable to detect and treat only high-risk DCIS lesions, in order to reduce the incidence of IBC as much as possible. Reliably distinguishing low-risk from high- risk DCIS to guide treatment is still impossible and is urgently needed to prevent overtreatment.

Challenges in solving the DCIS dilemma

In chapter 1 and 2, current knowledge on DCIS is summarized and areas are identified where profound research is needed including challenges herein, to gain more insight imperative to reduce overtreatment in women with low-risk DCIS and to provide optimal treatment for potentially hazardous DCIS.[11,12] Considerable uncertainty exists about the likelihood that a treatment strategy will prevent IBC, whether that likelihood will change based on specific patient and DCIS characteristics, and whether the reduction in risk is enough to justify costs and the potential side effects of that treatment.[13] Uncertainty about what a diagnosis of DCIS entails exists among both caregivers and patients. For women it is difficult to understand that on the one hand DCIS is not yet breast cancer, and on the other hand intensive treatment is advised. Patients diagnosed with DCIS have been reported to have inaccurate perceptions of the breast cancer risks they face. Despite their better prognosis, DCIS patients had comparable perceptions of the risk of recurrence and dying of breast cancer as women with IBC.[14,15]

Gaining more insight on factors associated with the development of ipsilateral invasive breast cancer (iIBC) after DCIS is urgently needed to better inform patients, allowing for more realistic risk perception, taken into account quality of life and competitive factors in terms of morbidity and mortality. Clinical, radiological, histopathological and molecular data should be integrated in order to build an individualized risk prediction tool helping clinicians and women make well-informed treatment decisions. One of the challenges in finding risk factors for progression in DCIS, is the need of large patient series with long follow-up, due to the low rate of IBC-events after DCIS. Interrater variability is another complicating issue. It is difficult to evaluate the role of histopathological features in risk stratification, such as grade, when many different grading systems with partly unclear criteria are used resulting in only poor to modest interrater reliability.[16–26] Additionally, a major impeding factor is that most of the studies have to rely on a comparison between patient groups with treated DCIS, hampering our understanding of the natural history of DCIS.

Currently, several trials in the US, UK and the Netherlands are investigating the safety of active surveillance in women with DCIS, which will provide us the advantage of studying the natural course of DCIS and potential prognostic factors in DCIS in the non-treated breast.[27–29] Main outcome measure is the risk of developing iIBC in both study arms: women receiving either standard treatment or no treatment. Annual mammograms will be performed in both patient groups and appropriate clinical measures are taken upon any suspicion of progression. Furthermore, type of breast cancer, frequency of diagnostic measures during follow-up, and psychological effects will be compared between both study arms.

Eligible for these trials is a subset of DCIS patients with an assumed lower risk of progression to iIBC and a lower risk of underestimation, based on the available evidence. Underestimation occurs when a preoperative biopsy shows DCIS grade 1 or 2, but the surgical specimen reveals either DCIS of a higher grade, a so-called upgrade, or alternatively an invasive carcinoma, a so-called upstage. In general, women over the age of 45 with asymptomatic, screen-detected DCIS grade 1 or grade 2 are eligible, who show no other mammographic abnormalities besides calcifications. Women with a positive history for breast cancer or familiar predisposition are not eligible.[27–29]

For safe inclusion in these active surveillance trials and upon implementation in clinical practice, it is imperative that histological grading is reproducible and that the risk of underestimation will not pose any health risks to women. Various studies have assessed reproducibility of histopathological evaluation of DCIS features. Unfortunately, these studies were frequently based on highly selected case sets, assessed by expert breast pathologists only, often after having received instructions or tutorials beforehand, and using reference diagnoses without follow-up data.[19,23,24,30–36] Uncertainty about the validity of the reported risk of underestimation also exists (up to >50%), as these results were often found in studies evaluating small cohorts of women with DCIS that were not representative for the typical DCIS lesions we encounter in today's clinical practice, i.e. screen-detected DCIS based on calcifications only, diagnosed on vacuum-assisted biopsies.[37–42] In these studies, DCIS was more often diagnosed on small core biopsies in patients with symptomatic presentation, such as mass lesions.

First steps on the road towards a reduction of overtreatment in DCIS

In consideration of the current knowledge gaps described above, the main objectives of this thesis, aimed to reduce overtreatment of DCIS of the breast , were: 1) to evaluate the risk of underestimation after a diagnosis of DCIS and the interrater reliability in the histopathological classification of DCIS, important conditions in order to safely adopt an active surveillance strategy for low-risk DCIS, 2) to investigate associations of clinicopathological factors with the risk of developing iIBC after treatment.

Insight on promising prognostic factors and common methodological pitfalls may improve risk stratification

Many studies have investigated prognostic factors for invasive disease after a diagnosis of DCIS, but none of the reported factors have been shown to be of sufficient value for implementation in clinical practice.[43,44] To inform risk stratification, we performed a systematic review with meta-analyses (Chapter 3), summarizing current knowledge on prognostic factors for iIBC after treatment of DCIS, assessing the risk of bias using the QUIPS tool in these prognostic factor studies and identifying the strongest prognostic factors found in only high quality studies devoid of a high risk of bias.[45–47]

The six strongest prognostic factors, associated with a higher iIBC risk, were African-American race, premenopausal status, detection by palpation, involved margins, high histologic grade and high p16 expression. Strikingly, a moderate or high risk of bias could be determined in at least one of the QUIPS domains (study participation, study attrition, prognostic factor measurement, end-point definition, study confounding, statistical analysis and reporting) in almost all studies, and was most frequently attributable to insufficient handling of confounders (mainly type of treatment) and poorly described study groups.

Based on our study, we would strongly recommend to use guidelines for prognostic factor studies, such as STROBE guidelines, to improve study designs and avoid common methodological pitfalls.[48] In particular, study groups should be described in detail, providing at least data reported routinely in clinical practice, such as age at diagnosis, clinical presentation, histologic grade, treatment, lesion size and marginal status. In addition, the effect of treatment should be accounted for. It is also important to define a clear end-point, because risk factors may be different for DCIS recurrence than for subsequent iIBC.[49] Specifically focusing on subsequent iIBC is especially important, due to the inherent mortality risk. Lastly, when searching for prognostic factors for invasive disease after a diagnosis of DCIS, one should not include patients who already show adjacent (micro)invasive carcinoma at the time of diagnosis.

Risk of underestimation is lower than assumed

There are concerns among healthcare givers and women with DCIS about underestimation, which may make them hesitant to participate in active surveillance trials. At the same time, it is necessary to recruit a high number of patients in order to perform sufficiently powered analysis. It is therefore of utmost importance to address this issue of underestimation within the context of active surveillance. We therefore evaluated the risk of underestimation and determinants for upgrade (i.e. when final pathology shows DCIS of a higher grade than found on preoperative biopsy) and upstage (i.e. when final pathology shows invasive disease) after a diagnosis of pure DCIS (Chapter 4).[50] In contrast to previous studies, we excluded women in whom there was a clinical suspicion of invasive disease based on radiological or clinical examination, as active surveillance would not be an option for these women.

We found a lower percentage of upstage of 15% compared to literature and an upgrade rate of 14.6%. Applying the strict eligibility criteria of the active surveillance trials for which data was available, namely age, screening mammography findings, biopsy method, DCIS grade on preoperative biopsy, symptomatic status at the time of clinical examination and previous breast cancer history, the upstage rate decreased even further to 10.3% for the LORIS trial and 10.5% for the COMET trial. Most of the other studies, who specifically assessed underestimation in patients eligible for active surveillance, showed similar low upstage rates.[51–54] We were able to identify several factors associated with underestimation, such as the use of a core-needle biopsy, a large mammographic lesion size, mammographic BIRADS score 5, presence of symptoms such as a palpable lump on examination, and the presence of necrosis on biopsy.

Our findings provide reassurance for both clinicians and patients with DCIS regarding trial participation. Consideration of these factors could aid risk stratification of women with DCIS being considered for active surveillance.

Clinically occult carcinomas have an excellent prognosis, likely also upon delayed detection in active surveillance

Furthermore, in case we found invasive disease on final pathology, we found the IBC to be typically small (< 1 cm), of low to intermediate grade and positive for estrogen receptor (ER). What would happen, if we miss these tumors while adopting an active surveillance strategy with annual mammographic follow-up? If we apply these tumor characteristics in a woman of 60 years of age and if we assume an overestimated tumor volume doubling rate of for example 1 year, a) the chance to detect a 2 cm large tumor on follow-up mammography is high and b) overall survival based on online prediction tools such as PREDICT (https://breast.predict.nhs.uk/) will still be excellent (>90%).

Our findings need to be further validated, preferable within the context of the current prospective active surveillance trials, including an evaluation of the effect that a delayed diagnosis will have on survival, available treatment options and the mental state of women in whom this occurs.

There is substantial interrater variability in the classification of histopathological DCIS features

In the light of concerns regarding interobserver reliability of histological grading of DCIS, we performed a study combining an interrater reliability study in women with screen-detected DCIS, reflecting daily practice as closely as possible, with an analysis of iIBC risk based on the majority opinion of a large group of raters (Chapter 5). This approach minimizes the muddling effect of interrater variability and subjectivity on the evaluation of the prognostic value of histopathological features. Without any instructions, 38 raters with different levels of expertise scored histopathological features of DCIS, namely grade, dominant growth pattern, frequency of mitoses and the presence of necrosis, calcifications, periductal lymphocytic infiltrate and (type of) periductal fibrosis. Our study showed that a substantial interrater variability exists in the classification of all these features.

Grade, growth pattern and mitotic activity are associated with iIBC risk in women treated by BCS alone

When using majority opinions, we found that DCIS grade, comparing grade 1 and 2 combined versus grade 3, and growth pattern were independent factors associated with the risk of subsequent iIBC after DCIS, in patients treated with BCS alone. The presence of many mitoses was significantly associated with a higher risk of iIBC, only in univariable analysis, likely due to collinearity with grade. In patients treated with BCS with radiotherapy, none of the histopathological features were associated with iIBC risk.

Semi-quantitative grading system may improve reliability of DCIS features associated with iIBC risk

There are many different grading systems that incorporate multiple histological features such as nuclear pleomorphism, growth pattern, cell polarization, mitotic activity and necrosis. However, it is not clearly defined, how these separate features should be valued and how they lead towards a resulting grade. The histological features we found to have prognostic value are strikingly similar to the ones used in the modified Bloom and Richardson grading system, which is widely accepted and used for IBC grading.[55,56] We would suggest to objectify DCIS grading by using a similar semi-quantitative scoring system, analogue to the modified Bloom and Richardson system, separately evaluating nuclear pleomorphism, growth pattern and mitotic activity. Alternative approaches using pathology information, such as dichotomous or automated scoring and artificial intelligence-based methods, may improve reliability and may discover yet unknown prognostic biomarkers for DCIS.[57–60]

DCIS adjacent to HER2-positive invasive breast cancer can be eradicated by neoadjuvant systemic treatment allowing breast conserving surgery more often

In the last study described in this thesis (Chapter 6), we shift our focus from pure DCIS to DCIS occurring adjacent to HER2-positive IBC in a neoadjuvant setting. Neoadjuvant systemic treatment (NST) is increasingly used in breast cancer and results in high rates of pathological complete response in HER2-positive breast cancer, enabling less extensive surgery.[61–66] However, the presence of adjacent DCIS in pre-NST biopsies and extensive calcifications on imaging are often considered contra-indications for BCS, even in patients with radiological complete response of the tumor on MRI. This is because DCIS is considered insensitive to systemic treatment. However, in small series it has been reported that DCIS does show response to NST in a subset of patients (33-51%).[67,68] This would implicate that, for these patients, BCS may still be a safe option. As HER2-positive IBC responds well to NST and adjacent DCIS is frequently found (57-72%), we estimated the response of DCIS to NST containing HER2-blockade in this breast cancer subtype and we assessed the associations of clinicopathological and radiological factors with DCIS response in the largest study set to date.

We found a DCIS response rate of 46%, when all patients were considered that showed DCIS on pre-NST biopsy. The absence of suspicious calcifications on pre-NST mammography, dual HER2-

blockade with trastuzumab and pertuzumab, a (near) complete response on MRI, the absence of calcifications in DCIS in the pre-NST biopsy and a Ki-67 >20% in DCIS were associated with DCIS response. As surgical planning issues concerning the safety of BCS especially arise in patients with a high likelihood of extensive DCIS, we also performed a subgroup analysis in patients who showed adjacent DCIS in the pre-NST biopsy as well as suspicious calcifications on mammography. In this patient group, the same factors were associated with DCIS response, while also the absence of necrosis in DCIS in the pre-NST biopsy was associated with DCIS response in this subgroup. DCIS response was also more often observed in patients with HR-negative IBC and IBC grade 1+2 in this subgroup, but these associations did not reach statistical significance. In this context, it will be interesting to perform gene expression analysis to evaluate the predictive value of specific molecular subtypes for DCIS response, as has been reported for HER2-positive IBC.[69]

Further research is needed to validate our findings. We would recommend a prospective study in women with HER2-positive IBC with radiological suspicion of extensive DCIS and pathological confirmation before NST. Radio-pathological correlation should be a fundamental component in this study, using both mammography and MRI before and after NST. The prediction of response of DCIS to NST could also be improved by obtaining biopsies of the DCIS area prior to surgery. This will provide more insight and may enable us to identify women in whom BCS may be justified, despite the presence of adjacent DCIS.

Concluding remarks and future perspectives

To reduce overtreatment of pure DCIS, we can build in additional selections during the diagnostic route, at each selection point deciding whether or not further testing or treatment is justified based on the risk of iIBC or the risk of dying from this cancer, whilst taken into account competitive factors in terms of morbidity and mortality. Large international and multidisciplinary collaborations, such as the consortium PREvent ductal Carcinoma In Situ Invasive Overtreatment Now (PRECISION; https://www.dcisprecision.org/) and trials exploring active surveillance strategies will be key in providing necessary insights.

Firstly, at the imaging level, we could look for factors able to discriminate between low-risk lesions (which includes both benign and malignant disease) and high-risk lesions by estimating risks in treated and non-treated women. Recently for example, the Breast-CAlcification Risk Evaluation study (Breast-CARE) was set up, which will compare these risks in women who showed only calcifications at screening, linking data from the breast screening program (region South-West), the Netherlands Cancer Registry and the nationwide network and registry of histo- and cytopathology in the Netherlands. Artificial intelligence-based methods applied on mammograms could be explored. Also, as calcifications can be formed in different contexts, both in benign and malignant disease, and show differences in mammographic and microscopic appearance, more detailed analysis into the biochemical composition of calcifications may reveal prognostic information as preliminary results suggest.[70]

Secondly, if further testing is indicated, a diagnostic biopsy will be taken which allows for another selection point. At this point, we can integrate clinical, radiological and tissue data (histopathological and molecular information). Such an integration could take place outside the hospital, in a comprehensive screening center, primarily aimed at excluding high-risk disease, preventing unnecessary medicalization. We have identified in the studies, described in chapter 3 and 5, several promising factors that may provide important prognostic information, such as race, menopausal status, mode of presentation, and grade, growth pattern, mitotic activity and p16 expression of DCIS. As for histopathology, we should not only focus on the epithelial compartment, but also evaluate the prognostic value of myoepithelial and stromal factors. In addition, it is important at this stage to also taken into account genetic and familial predisposition. The results from our interrater reliability study have shown that we need to improve reliability in the classification of histopathological DCIS features, in order to use this information on an individual level. Reliability of simplified classification systems with the provision of clear guidelines needs to be assessed, with information on follow-up used as golden standard. Also, automated scoring and again artificial intelligence-based methods should be explored.

Thirdly, once a DCIS lesion is considered to be low risk for progression to IBC, ideally determined by an individualized risk prediction tool, the option of active surveillance should be considered. We have shown that the underestimation after a diagnosis of DCIS based on a preoperative biopsy is lower than assumed, that most missed cancers have a good prognosis and a delayed detection upon follow-up will most likely not deteriorate survival. This is reassuring for doctors and women considering active surveillance. At this selection point, the prognosis of the expected IBC that will develop upon progression, age, competing risks and patient preference are all important factors. Realistic risk perception is essential at this stage. This implies clinicians, experts in how to frame risks, and, last but not least, patient representatives need to optimize the communication of risks.

Fourthly, overtreatment of women with IBC due to the presence of adjacent DCIS needs to be prevented. This requires accurate identification of DCIS lesions that do respond to NST. This is in particular true for HER2-positive IBC with adjacent DCIS, as we have shown that the presence of adjacent DCIS is not per se a contra-indication for BCS. Ideally, our findings will be validated in a prospective setting, including detailed (quantitative) radiological-pathological correlation before and after NST and a post-NST biopsy procedure when a complete response of DCIS is suspected.

In conclusion, we have taken significant steps on the road towards conquering overtreatment of DCIS: by having identified several clinicopathological prognostic factors in pure DCIS, by providing reassuring evidence regarding underestimation in the context of active surveillance, by stressing the need for improvement of interrater reliability in histopathological classification, and by showing that the presence of DCIS adjacent to HER2-positive breast cancer should not preclude the option of breast conserving surgery.

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