Finding the balance between overtreatment and undertreatment of ductal carcinoma in situ
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Citation for published version (APA):

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CHAPTER 1

General introduction and outline of the thesis
Ductal carcinoma in situ

Ductal carcinoma in situ (DCIS) is considered a non-obligate precursor of invasive breast cancer. Risk factors associated with DCIS are similar to those associated with invasive breast cancer and include positive family history of breast cancer, increased breast density, and nulliparity or late age at first full-term pregnancy. DCIS is characterized by an abnormal epithelial proliferation confined to the mammary ductal-lobular system. In DCIS, the outer myoepithelial layer is still organized and the neoplastic epithelial cells do not grow beyond the basement membrane into the surrounding stroma (Figure 1). Therefore, DCIS has no metastatic capacity, unlike invasive carcinoma. The term DCIS encompasses a heterogeneous group of lesions that vary with regard to their histologic appearance and clinical behaviour. There is very limited information on the natural history of DCIS because surgical removal of the lesions hinders evaluation of their evolution. The proportion of DCIS lesions that will progress to invasive disease if untreated is estimated to be 15-50%.

Figure 1. Crossing the border. Tissue abnormalities known as DCIS may stay confined within a milk duct for a lifetime; a minority break out to become invasive cancer. Credit: K. Sutliff, http://science.sciencemag.org/.
Breast cancer screening

DCIS rarely produces symptoms or signs and most DCIS lesions are diagnosed following detection of suspiciously grouped, pleomorphic, or fine linear calcifications on mammograms. Undergoing mammography is thereby the strongest risk factor for being diagnosed with DCIS. While DCIS was seldom detected before the advent of screening mammography (about 300 women with DCIS among a total Dutch female population of approximately 5 million women aged 25 years and older in the Netherlands in 1989), the widespread adoption and subsequent digitalization of mammography-based population-wide breast cancer screening programs have led to an impressive increase in incidence of DCIS (Figure 2a). In 2015, DCIS was diagnosed in approximately 2400 women in the Netherlands (total ≥25 years female population approximately 6 million), accounting for 14% of all newly diagnosed cases of breast cancer.

Overdiagnosis

Breast cancer screening aims to detect breast disease that will ultimately cause harm and that is more likely to be cured if detected early. However, after having treated many women with screen-detected DCIS, the incidence of invasive breast cancer has not declined (Figure 2b). Unfortunately, population-based mammographic screening programs also identify a reservoir of indolent DCIS and thus lead to overdiagnosis (Figure 3). Overdiagnosis of DCIS can be defined as the detection of DCIS that would not go on to cause symptoms or would not progress to symptomatic or ultimately lethal invasive breast cancer if it had remained undetected and can be explained by regressing, non-progressing, or slowly growing lesions (Figure 4). Based on autopsy series it is estimated that 10-39% of middle-aged women harbour indolent DCIS.
Figure 2. Incidence of a DCIS by age group and b DCIS and invasive breast cancer for all age groups, in the Netherlands from 1989 to 2015. The Dutch breast cancer screening program started in 1989. From 1989 to 1997 women aged 50 to 69 years were the target population. Full coverage for these women was achieved in 1997. In 1998 the program was extended to women aged 70 to 75 years.16,19,20
Figure 3. Overdiagnosis. The detection of indolent DCIS lesions in the screened group produces apparent increases in the number of cases of DCIS (three in the screened group in the figure and one in the control group) and in survival (two of three patients in the screened group were treated and died of natural causes, without evidence of disease [66% survival], and the one patient in the control group did not survive [0% survival]), with no effect on mortality (one death from breast cancer in each group). Two patients in the control group died with undiagnosed DCIS that did not affect their natural life span. Adapted from Patz et al.21

Figure 4. Heterogeneity of DCIS progression. The arrow labeled “fast” represents a fast-growing DCIS, one that quickly progresses to invasive breast cancer and death. The arrow labeled “slow” represents a slow-growing DCIS, one that leads to invasive breast cancer but only after many years. The subsequent invasive breast cancer may lead to death, or the patient may die of some other cause. Depending on the definition of overdiagnosis and on the cause of death this DCIS can be labeled as overdiagnosed. The arrow labeled “very slow” represents a DCIS that never causes problems because the patient will die of some other cause before the DCIS has progressed to invasive breast cancer or has caused symptoms. The arrows labeled “non-progressive” and “recessive” represent DCIS that never cause problems because they never progress or even regress. Adapted from Welch and Black.17
Guidelines for DCIS treatment

The aim of treating women with DCIS is to prevent the development of invasive breast cancer and ultimately to prevent breast cancer mortality. In the past, DCIS was typically treated by mastectomy like invasive breast cancer, with no decisive evidence of necessity. When in the mid-eighties breast-conserving treatment proved to be safe for patients with invasive breast cancer, several randomized clinical trials were initiated to investigate the role of radiotherapy after breast-conserving surgery in women with DCIS. Since then, women diagnosed with DCIS in the Netherlands have been treated by mastectomy, breast-conserving surgery plus radiotherapy, or breast-conserving surgery alone. The current Dutch treatment guidelines recommend mastectomy or breast-conserving treatment, consisting of microscopic tumour excision and radiotherapy. Contraindications for breast-conserving treatment include multicentricity and residual disease. The long-term outcomes in patients with DCIS treated by these conventional therapies are excellent with 10-year local (in situ or invasive) recurrence rates of 3% after mastectomy, 14% after breast-conserving surgery with radiotherapy, and 26% after breast-conserving surgery without radiotherapy, and very high overall survival, regardless of treatment. Hormonal therapy is not recommended for DCIS patients in the Netherlands because of limited benefit in terms of local control and survival, and the side effects involved. However, the national guidelines in the United States recommend consideration of this adjuvant treatment in women who are oestrogen receptor-positive or who undergo breast-conserving surgery alone. In addition, a trend toward more aggressive treatment of DCIS is observed. While the proportion of women undergoing unilateral mastectomy for DCIS has declined over the years, increasingly more DCIS patients opt for contralateral prophylactic mastectomy. Further, the use of neoadjuvant chemotherapeutic agents or other anticancer drugs such as trastuzumab in the treatment of DCIS has also been suggested. Despite the favourable prognosis many DCIS patients overestimate their risk for future breast cancer and disease spread to other parts of the body. They tend to view the disease very much like invasive breast cancer. This inaccurate, heightened risk perception may reflect a lack of clarity and standardized information among health-care providers resulting in suboptimal communication. On the other hand, anxiety among DCIS patients might impede accurate risk perception.
The DCIS dilemma: overtreatment versus undertreatment

Overdiagnosis and inaccurate risk perception can lead to unnecessary treatment among women diagnosed with DCIS. On the other hand, some DCIS have high malignant potential and undertreatment of these lesions should be prevented. The inability to accurately stratify DCIS patients into low-risk and high-risk groups results in a clinical DCIS dilemma (Figure 5). Finding the balance between overtreatment and undertreatment of DCIS requires an integrative and multidisciplinary approach. To optimize individualized risk prediction the compilation of representative DCIS cohorts is imperative. The nationwide Netherlands Cancer Registry and the possibility to link this registry to other nationwide registries provide clinicians and researchers with a wealth of clinical data and enables reliable and complete data collection. The Dutch DCIS cohort established within the scope of this thesis provides the foundation upon which future clinical, morphological and molecular studies can build.

Figure 5. DCIS dilemma: overtreatment versus undertreatment. These curves represent the population of patients with DCIS who benefit from (adjuvant) treatment (i.e. they will develop invasive breast cancer without treatment) and who do not benefit from (adjuvant) treatment (i.e. even without treatment they will never develop invasive breast cancer). Risk factors to accurately stratify low-risk and high-risk groups have to be identified yet. Relaxing risk factor criteria for recommending treatment decreases overtreatment but risks increasing undertreatment. Restricting risk factor criteria decreases undertreatment but increases overtreatment. Adapted from Smith, 2016.49
Outline

This thesis aims to frame the DCIS dilemma by reviewing current knowledge and evaluating clinical outcome in a nationwide cohort of women treated for DCIS. Further, we developed a randomized non-inferiority clinical trial to assess safety of active surveillance in women with DCIS and explored international interest and feasibility of this study. Chapters 2 and 3 of this thesis review our current understanding of DCIS and identify current knowledge gaps. Chapter 2 proposes an integrative step-wise approach to solve the DCIS dilemma.

Chapters 4, 5 and 6 provide the results of our population-based cohort studies for which we used data from the Netherlands Cancer Registry, the Dutch nationwide network and registry of histology and cytopathology (PALGA), the Dutch screening organization and Statistics Netherlands (cause of death). In chapter 4 we assessed the risk of subsequent ipsilateral and contralateral invasive breast cancer among 10,090 women diagnosed with primary pure DCIS between 1989 and 2004 in the Netherlands. Specifically, we evaluated the effect of different treatment strategies. In chapter 5 we compared cause-specific mortality between DCIS patients and women in the general population to evaluate excess mortality. Chapter 6 describes the prognostic role of method of detection among women with screen-detected, interval and non-screening-related DCIS.

Chapter 7 discusses the rationale and design of a randomized clinical trial between standard treatment and active surveillance for LOw-Risk DCIS (LORD). In addition, it provides the results of an explorative feasibility study among 53 European centres.

In chapter 8 the ongoing research and future prospects of DCIS management and research are comprehensively discussed after a short discussion of the results.

The thesis ends with a summary of the presented results in chapter 9.
References


