A comprehensive approach for quality assessment of breast cancer care

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A COMPREHENSIVE APPROACH FOR QUALITY ASSURANCE OF BREAST CANCER CARE

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Financial support for printing of this thesis was kindly provided by:
Dutch Institute for Clinical Auditing (DICA), Netherlands Comprehensive Cancer Organisation (IKNL), Nederlandse Vereniging voor Plastische Chirurgie (NVPC), SOLV Advocaten, Walaeus bibliotheek - University Library.

The sponsors had no role in the design, execution, analyses, interpretation of data, writing of the articles and the decision to submit the findings for publication of the studies included in this thesis.

Cover design: Erik Heeg
Lay-out: Tiny Wouters
Printed by: Proefschriftmaken | proefschriftmaken.nl

ISBN: 978-94-6423-281-3

A COMPREHENSIVE APPROACH FOR QUALITY ASSURANCE OF BREAST CANCER CARE

Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof.dr.ir. H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op woensdag 22 september 2021
klokke 10.00 uur

door

Erik Heeg
geboren te Groningen in 1989

Promotoren:	Prof. dr. R.A.E.M. Tollenaar
	Prof. dr. M.A.M. Mureau, Erasmus MC, Rotterdam
Copromotor:	Prof**.** dr. M.T.F.D. Vrancken-Peeters, NKI-AVL, Amsterdam
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Voor mijn ouders

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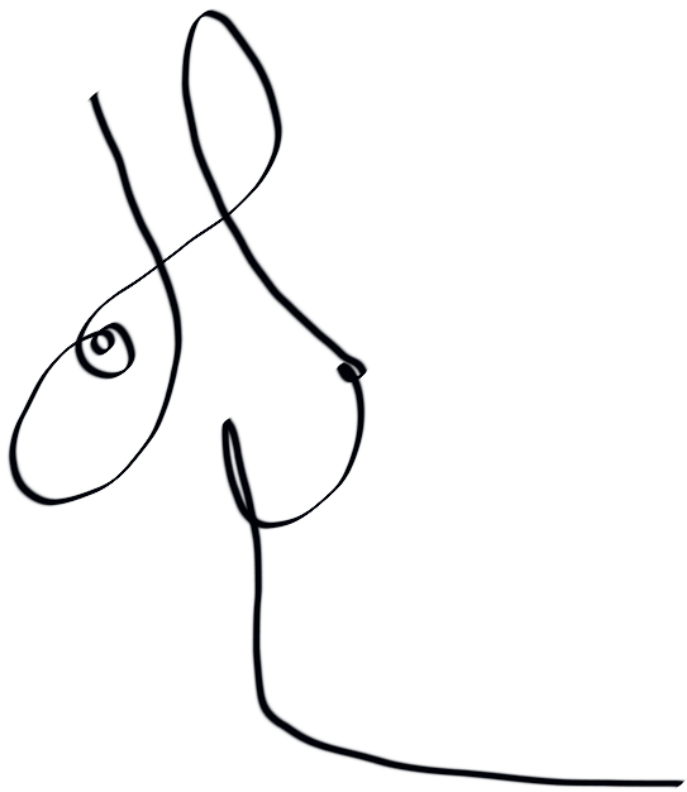
Chapter 1

General introduction and outline of this thesis



General introduction

In the last decades, there has been an increasing interest in the assessment and improvement of healthcare quality.[1-3] Advances in healthcare quality have been associated with positive effects on patient satisfaction, outcomes, productivity, and ultimately with lower healthcare costs.[4,5] However, defining healthcare quality is complicated due to subjective perspectives, multi-dimensional components, and changing cultural expectations. Defining quality of care might even be more challenging in breast cancer care due to the multidisciplinary setting, heterogeneity in tumor and patient populations, multitude of treatment pathways, and evolving diagnostic and treatment modalities.

Since defining healthcare quality depends on different perceptions of various stakeholders (e.g., physicians, patients, policymakers, taxpayers), several definitions and frameworks have been formulated to describe, monitor, and improve quality of care.[6] One of these frameworks was formulated by the Institute of Medicine (IOM) in the United States (US) in 2001.[7] Six dimensions of quality were described that could be used to assess and improve healthcare quality: *safety*, *effectiveness, patients-centeredness, timeliness, efficiency, and equity*.[7]

Although these six dimensions can be interpreted and used in various ways, in the current thesis they are used to assess the quality of breast cancer care in the following manner. The dimension of *safety* refers to not harming or limiting the harming of patients as a consequence of provided care. Safe care reduces or limits risks and hazards of adverse events for those involved. *Effectiveness* can be described as using care resources that have proven to result in the most superior clinical and non-clinical outcomes, such as the patients' health and satisfaction. Moreover, effective healthcare aims to limit the overuse of care with undesired or less optimal outcomes. On the other hand, it aims to limit the underuse of care that would result in superior outcomes. The dimension *patient-centeredness* refers to patients being well-informed and involved in care decisions. Patient-centeredness will provide patients a certain degree of control over the provided healthcare. The dimension of *timeliness* refers to receiving care without unnecessary delays. Extensive diagnostics or procedure preparation can require additional time and has been associated with delayed primary treatment.[8-10] Although some delay due to diagnostics may seem inevitable, there are unintentional delaying factors that could be dealt with when identified. The dimension of *efficiency* refers to limiting waste of care and resources (e.g. diagnostics, consultations, medicines, medical procedures, multidisciplinary reviews), thus the most optimal resource utilization. Efficient healthcare uses resources in the best order that

contribute to better outcomes while limiting the use of time, costs, and resources. The last dimension when assessing quality is *equity*. Equity refers to limiting unintentional disparities in quality of care among patients with differences in, for instance, gender, age, race, level of intelligence, social-economic status, sexual orientation, insurance, or location of residency.

The different stakeholders previous described of healthcare may each encounter different challenges when assessing and improving quality of care. One of these challenges in assessing healthcare quality may be the difference in priority of the previously described six dimensions among the stakeholders. While patients may give priority to *timeliness*, *patient-centeredness*, and *safety*, physicians may well focus on *safety* and *effectiveness*, and policymakers may prioritize *effectiveness*, *efficiency*, and *equity*. Nonetheless, for improving the quality of breast cancer care, all six dimensions of quality should be assessed in a sensible and evidence-based manner.

In light of the increasing attention for assessing quality of healthcare, physicians increasingly receive questions that go beyond the focus of most conventional medical research such as “Do we have optimal resource utilization?”, “What factors endanger *effectiveness* and *timeliness*?”, “Can we give patients sufficient counseling regarding *safety*?” and “Can we identify *inefficiencies*?”. Hereby, physicians and healthcare policymakers are facing pressure to improve knowledge regarding all different dimensions of quality of healthcare. As a consequence, physicians, but also healthcare policymakers, seek for tools and structure on how to assess and compare the quality of healthcare that helps us to improve and learn from each other on both a national level, as on an international level.

The studies in the current thesis aim to improve the quality of breast cancer care by addressing one or more of the previously mentioned dimensions of quality of healthcare in each of the following chapters. The chapters in this thesis evaluate breast cancer care quality considering three different parts of care. In **Part I**, the extent of patients changing hospital after breast cancer diagnosis and its impact on the quality of care in the Netherlands is described. In **Part II**, the timing of adjuvant chemotherapy in relation to immediate breast reconstruction and patient survival is shown. In **Part III**, the variation in use and outcomes of different breast reconstructive strategies on a national and international level is presented.

Figure 1.1 visualizes the six dimensions of quality of healthcare, addressed in the chapters in this thesis. While the dimensions widely overlap and cannot be assessed separately, they influence one another and are dependent on several levels.

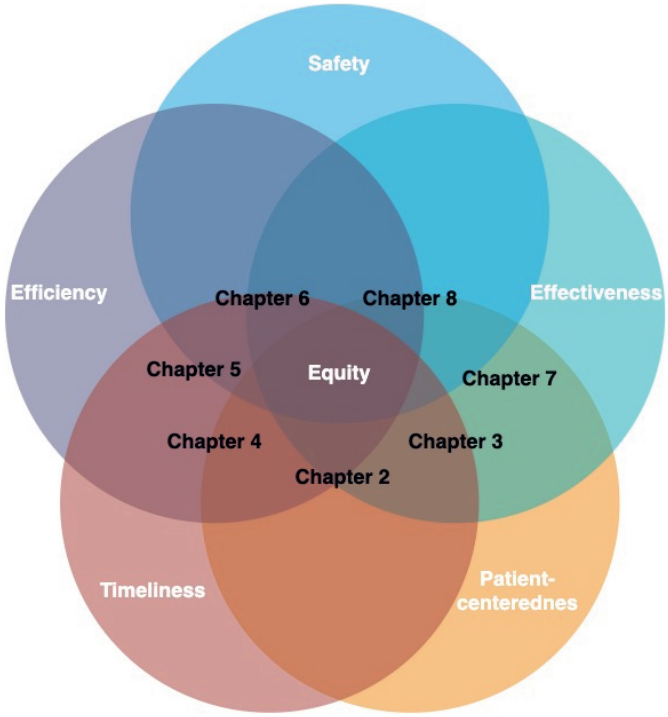


Figure 1.1. A robust illustration of the content of the seven chapters of this thesis, each chapter captures multiple dimensions of quality of healthcare.

This thesis does not address all aspects and components that may contribute to improved quality of care nor does it claim to provide a blueprint for the most optimal care pathway for all stakeholders. However, the scientific questions raised and answered in the following chapters may contribute to a better understanding of how to improve breast cancer care.

In general

After lung cancer, breast cancer is the second most commonly diagnosed cancer in the world, with nearly 2.1 million newly diagnosed patients in 2018.[11] The incidence rate is highest in western countries and surpassed 15,000 patients in the Netherlands in 2018.[11-13] These high incidence rates in western countries are most likely related to a combination of an increase in risk factors such as aging of the population, obesity,[14] higher age at pregnancy, and lower number of gravidities[15,16] compared to other

countries and to improved breast cancer screening.[17,18] Although the prognosis of breast cancer patients has improved during the last decades, still more than 3,000 patients die from breast cancer in the Netherlands each year.[13] Due to the high incidence of breast cancer and the active role of patient advocacy groups and physicians in breast cancer organizations, improvement of the prognosis and quality of breast cancer care has been recognized as a major global challenge.

Progress in quality assurance

Before addressing different aspects or components of breast cancer care that may attribute to improving the dimensions, one should be aware of previous and current quality programs. Several (inter)national initiatives have contributed to the current quality of breast cancer care. During the last decades, a growing number of healthcare providers across the world have advocated for more transparency in the quality of breast cancer care.[19] The earliest initiatives were nationwide cancer registries that started in Northern Europe in the fifties and sixties of the last century.[20] These registries provided data concerning demographic characteristics, incidence, prevalence, and mortality of breast cancer patients.[20] However, data of these registries was limited for meaningful comparison between hospitals or relatively short-term improvement projects, because outcomes needed to be assessed during a prolonged period, making the feedback loop for improvements inadequate.

The interest in comparing healthcare outcomes has come on a fast track in Europe during the last decades, as the first studies showed improved outcomes and decreased variation between hospitals as a result of nationwide assessment of colorectal cancer care.[21-23] Subsequently, in the search for breast cancer quality assurance, the first hospital performer indicators were formulated, which focused not only on outcomes but also on the process and structure of the care pathway.[19,24] Many quality improvement projects hypothesized that by improving the process and structure of care, outcomes would consequently improve.[25]

In the Netherlands, the Dutch National Breast Cancer Organization (NABON), Dutch Institute for Clinical Auditing (DICA) and the Netherlands Cancer Registry (IKNL) founded the NABON Breast Cancer Audit (NBCA) in 2011.[26] Since then, data regarding clinicopathological characteristics, diagnostics and treatment modalities of all patients diagnosed with invasive or ductal carcinoma *in situ* (DCIS) in the Netherlands has been registered in the NBCA-database.[26] The NBCA aims to monitor the nationwide quality of breast cancer care by using a set of quality indicators (QIs) measured for all Dutch hospitals providing breast cancer care.

The quality of breast implant surgery is monitored by the Dutch Breast Implant Registry (DBIR) in the Netherlands since 2015.[27] Mandatory registration of every breast implant and explant resulted in more than 7,500 patients (aesthetic and reconstructive) being registered in the Netherlands in 2017.[28]

With both nationwide registries, benchmarking and inter-hospital comparison of healthcare quality is encouraged. In addition, the general public, such as policymakers, patients and media, receive insight into the quality of care in Dutch hospitals through an annual publication of a set of transparent QIs for external transparancy.[29] Physicians and hospital policymakers can also see their own outcomes in comparison to anonymized other hospitals regarding 'internal' Qis. QI that are considered 'internal' are still under development. The population-based databases are also used to address scientific questions. Some scientific questions are difficult to answer in conventional research settings due to ethical complexity and the need for a high number of patients. Moreover, the registries use a real-world patient population instead of a selection of patients used in most conventional research, such as randomized controlled trials or retrospective single-center studies.[30]

PART I: Hospital transfer in breast cancer care

In the last two decades, breast cancer care has evolved somewhat into tailored-made care due to the increasing number of diagnostic and treatment modalities. Although most of previously mentioned developments have improved the quality of breast cancer care, unintentionally, the complexity of breast cancer care has simultaneously increased due to the expanding number of involved supporting (e.g., pathology, radiology), surgical (e.g., surgical oncology, plastic surgery) and nonsurgical (e.g., medical oncology, radiotherapy) disciplines. The constant evolving diagnostic and treatment modalities made it challenging to comprehend all information for patients.[31-33] This uncertainty might specifically be present among breast cancer patients compared to other patients as breast cancer patients are increasingly aware of different treatment modalities informed by strong organized patient advocacy groups.[34,35]

Since patients are free to choose their physicians and hospital in most Western countries, patients can change from one hospital to another during their care process. As a consequence of the increasing patient autonomy and complexity of care, it could well be possible that an increasing number of patients change from one hospital to another along the breast cancer care pathway. The contrary has also been hypothesized.[36] Since most Western countries have up-to-date guidelines, variation in

care between hospitals could decrease as physicians use evidence-based guidelines with similar diagnostic and treatment algorithms. These guidelines and algorithms aim, among other things, to increase evidence-based medicine and reduce unwanted variation in care between healthcare providers. As a result of this, the clinical necessity for a change of hospital could decrease as breast cancer care would be more or less similar in all hospitals. Literature focusing on patients changing hospital, however, is sparse. Moreover, the evidence whether a hospital change influences breast cancer care is limited. Therefore, the current knowledge regarding the impact of patients changing hospital on *effectiveness, timeliness, efficiency, and equity* of breast cancer care is limited.

Are breast cancer patients changing hospital after diagnosis and who are they?

The overall percentage of patients changing hospital after diagnosis can be defined as the hospital transfer rate. In **chapter 2**, a hospital transfer is defined as patients receiving treatment in another hospital compared to the hospital of diagnosis. For individual physicians and patients, overseeing the impact of a hospital transfer is challenging since it requires large quantities of data to assess its impact on quality of care. It has been suggested that hospital transfers negatively affect the quality of breast cancer care since hospital transfers have been associated with decreased quality of care among patients with diabetes, ischemic stroke, and different types of cancer.[37-43]

High-quality breast cancer care requires identification of delaying factors and components. Evaluating the extent of hospital transfers, predictive characteristics of hospitals transfers and whether it has an impact on the *timeliness* of care has the potential to improve breast cancer care. With this information, physicians and healthcare policymakers could alter the care process and structure to minimize a potential negative impact of hospital transfers on the quality of breast cancer care. Hypothesizing that hospital transfers delay care, *equity* of care could also be improved when those at risk are identified.

Therefore, **Chapter 2** focuses on patients who transferred hospital after their breast cancer diagnosis.[44] In this chapter, we describe the extent and trend over time of hospital transfers of breast cancer patients on a national level in the Netherlands. Secondly, we analyzed which factors are of predictive value for a hospital transfer. To gain insight into the independent impact of hospital transfers on *timeliness*, time from diagnosis to primary treatment is compared between patients with and without a hospital transfer.

Second opinions in breast cancer care

Part of the extent of patients changing hospitals could be patients who seek an second opinion (SO). An SO is defined as an assessment of a diagnosis or treatment proposal by an independent second physician of the same medical discipline. Second opinion (SO) programs have officially been introduced in surgery in the 70ties and 80ties of the last century, as the first reports not only showed a major impact of SOs on treatment recommendations, but also demonstrated that SOs were cost effective by preventing unnecessary procedures.[45-48] Among patients with cancer seeking for an SO, the majority is breast cancer-related.[49,50] Previous studies reported SO rates among breast cancer patients between 1% and 31%,[50-55] although an exact nationwide percentage is unknown.

The clinical value of breast cancer second opinions is still under debate, despite a vast number of previous studies focusing on this subject. Evaluating the clinical impact of SOs is warranted as SOs can have unintentional effects on quality of care. Previous studies have shown that repeating diagnostics, additional consultation and other discontinuities of care were associated with an increased workload for physicians, healthcare costs and delayed primary treatment.[9,10,38-40,43,49,56] Moreover, SOs might even increase uncertainty in case of a contradicting diagnosis or treatment proposal.[57] When aiming for *efficient* and *effective* breast cancer care, high-quality research regarding its medical value is warranted to limit potential overuse or undesired or less optimal outcomes, hereby, optimizing resource utilization. To do so, one could analyze the absolute 'medical' difference between the first and SOs. The evidence regarding the impact of SOs may also improve patient-counseling and the shared-decision process, which fosters *patient-centeredness*. In **Chapter 3** of this thesis, we report on SOs in a comprehensive manner of breast cancer patients who visit the Netherlands Cancer Institute and investigate the impact of SOs on diagnostics and treatment proposals.[58] In this chapter, discrepancies between first and SOs are quantified using a newly defined categorization of discrepancy specific for SOs among breast cancer patients.

PART II: Continuity of the adjuvant chemotherapy pathway

A discontinuity of the care process, defined as a delay of treatment, has been a universal concern of patients and physicians since the beginning of breast cancer treatment. In 1907, the pioneer of the radical mastectomy William Halsted stated "*we no longer need the proof which our figures so unmistakably give that the slightest delay is dangerous…"*.[59] This fear may still be present among many patients, as most breast

cancer lawsuits claim unnecessary delay up to diagnosis or treatment, rather than medical misconducts.[60]

Current evidence-based breast cancer guidelines[61-63] are less rigorous regarding the slightest delay compared to these statements of William Halsted. The current general opinion is that time to treatment should not be needlessly delayed for two reasons: 1) to limit psychological distress for the patient,[64] and 2) to minimize the negative impact on breast cancer outcomes, such as disease-free and overall survival.[65]

Regarding time from surgery to adjuvant chemotherapy (TTC), literature shows decreased disease-specific and overall survival in patients with delayed TTC, though using heterogeneous time limits ranging between 6 to 12 weeks.[66-68] Despite the contradicting evidence and lack of consensus of the optimal time intervals, the European Society of Medical Oncologists (ESMO) stated that adjuvant chemotherapy should preferably be started within 6 weeks after surgery and that chemotherapy has a decreased efficiency when initiated after more than 12 weeks.[61,69]

Due to the lack of high-quality evidence, physicians and healthcare policymakers receive questions such as 'Should I start treatment as soon as possible?' and 'What procedures or factors endanger timely care?'. As a consequence, optimizing the *timeliness* of breast cancer care has been the subject of many studies. When aiming for a minimal number of discontinuities of care, all different factors that can result in a delay of treatment should be evaluated. **Part II** of this thesis focuses on the *timeliness* of postoperative care, explicitly concerning the timely initiation of adjuvant chemotherapy.

Impact of postmastectomy immediate breast reconstruction

Post mastectomy immediate breast reconstruction (IBR) has often been mentioned as a potential delaying factor for initiating adjuvant chemotherapy. As a result of this discussion, physicians may be cautious to use post mastectomy IBR in patients who have an indication for adjuvant chemotherapy.[70] It has been suggested that IBR after mastectomy increases TTC due to a longer time to recover and a higher risk of postoperative complications. However, reports regarding both associations have shown contradicting findings.[71-76] High-quality evidence is warranted regarding the impact of IBR on TTC since there has been an increasing interest of IBR in most industrialized countries in the last decade.[77] IBR is associated with good esthetic results and better psychosocial well-being compared to mastectomy only or delayed reconstruction.[78-81]

Therefore, we investigated in **Chapter 4** whether IBR after mastectomy reduces the likelihood of timely initiation of adjuvant chemotherapy compared to mastectomy alone.[82] The association was evaluated in a population-based setting while limiting

confounding by indication since patients do not have the same likelihood of receiving IBR based on baseline characteristics that also affect the timely initiation of adjuvant chemotherapy. Hereby, we aim to improve the *timeliness* of the postoperative treatment pathway of breast cancer patients.

Clinical implications of postoperative treatment delay in high-risk breast cancer

When reviewing literature, delay of adjuvant treatment is associated with worse breast cancer outcomes regarding recurrence and survival.[65-67,83] In the last five years, there is increasing evidence suggesting that the association between decreased outcomes and time from surgery to chemotherapy might be subtype dependent.[66,84-87] The subtype dependent relationship between TTC and survival is not contra-intuitive as consensus exists on the more aggressive biology and proliferation rate of high-risk tumors, such as triple-negative breast cancer (TNBC).[88,89] A recent report demonstrated decreased outcomes in TNBC patients receiving adjuvant chemotherapy beyond 30 days after surgery.[86] However, the suggested association of the subtype dependent relationship justify further investigation, since most previous studies had a single-center character and used a small number of patients without stratifying for type of surgery.[66,84-87] Although TNBC represents only 15% of breast cancer subtypes, patients with TNBC have a worse prognosis compared to other subtypes.[88,90,91] Moreover, optimizing the effect of adjuvant chemotherapy is especially warranted in patients with TNBC as chemotherapy is the only current established therapeutic option in most of the patients with TNBC.[92] Furthermore, despite the fact that previous studies have demonstrated that patients with TNBC are less likely to have delayed time from surgery to chemotherapy,[67,93] between 35% to 74% of patients with TNBC receive chemotherapy beyond 30 days after surgery.[67,84,87,93,94]

When high-quality evidence would support the suggested relationship between decreased survival and TTC beyond 30 days in patients with TNBC, it could be argued that timely adjuvant treatment is warranted and guidelines should be adjusted accordingly. A randomized study regarding survival data of patients with TNBC receiving adjuvant chemotherapy within and beyond 30 days is not likely to be conducted, because of the complex ethical considerations.

While patients who undergo BCS compared to mastectomy have better survival outcomes most likely partly based on underlying baseline characteristics, patients undergoing mastectomy are more likely to have a delayed time from surgery to chemotherapy. Therefore, survival analyses should be stratified by type of primary surgery. In **Chapter 5,** we describe whether time from surgery to chemotherapy beyond

30 days is related to a decreased overall survival in high-risk patients diagnosed with TNBC using a prospectively registered population-based cohort. The findings of this chapter aim to improve the *safety* and *timeliness* of high-risk breast cancer care.

PART III: Quality assessment of breast reconstruction strategies

During the last decade, there has been an increasing interest in reconstructive surgery with more acceptable cosmetic results. Loss of the breast mound due to mastectomy negatively affects different aspects of the quality of life of patients such as decreased body image and self-estreem.[78,81,95-97]
Following the increasing interest in reconstructive surgery, a growing number of patients have undergone a breast reconstruction after mastectomy in most western countries.[77,98] More than 90% of breast reconstructions was implant-based.[77,99,100] Breast reconstructions can be performed during the mastectomy (immediate) or in a second operation at a later time (delayed reconstruction). IBR following mastectomy has shown to result in similar postoperative patient satisfaction compared to BCS.[81] Since there is no current golden strategy for the most optimal breast reconstruction, high-quality evidence regarding *safety*, *effectiveness* and *efficiency* is warranted. **Part III** of this thesis aims this provide crucial evidence for physicians regarding the different breast reconstruction strategies on a national and international level.

Comparing revision rates of implant-based breast reconstructions

An implant-based breast reconstructions (IBBR) can be achieved in a one-stage (direct-to-implant) or a two-stage reconstruction. During a two-stage reconstruction, a temporary tissue expander (TE) is inserted followed by definitive implant during a second operation. Use of direct-to-implant IBBR has increased due to advancements in oncological surgery (e.g. skin-sparing mastectomy) and plastic surgery (e.g., acellular dermal matrices (ADM), meshes). Two-stage IBBRs are commonly used for patients in whom significant skin loss is expected or for those who have a wish for an increase in breast size.[101]
Currently, no consensus exists regarding the risk for a revision after direct-to-implant compared to two-stage IBBRs, as previous meta-analyses report a low level of evidence regarding this topic.[102,103] The lack of consensus regarding the risk for revisions may increase variation among hospital protocols in using direct-to-implant and two-stage

IBBR as current practice might be more a reflection of personal experience or local policy.

Outcomes regarding the *safety* of both direct-to-implant and two-stage IBBR using data from a population-based nationwide database could improve treatment-counseling by increasing the knowledge regarding revision indications and risk factors. Moreover, it could reduce potential unwanted variation between physicians. **Chapter 6** compares the revision incidence, revision indications, and the additional number of operations between direct-to- implant and two-stage IBBR.

Cross country evaluation of breast cancer care

In 2018, almost one-third of the breast cancer patients underwent mastectomy as final surgical treatment for local control of the disease In the Netherlands.[104] Immediate breast reconstruction, as being described in chapter 6, is performed in one-fourth of patients with invasive breast cancer and almost half of those with ductal carcinoma in situ (DCIS) undergoing a mastectomy in the Netherlands.[104]

Previous studies demonstrated equal survival outcomes when comparing BCS followed by radiation therapy and mastectomy.[105,106] Recent reports even suggested better outcomes in those who underwent BCS and radiation therapy compared to mastectomy in early-stage breast cancer, although residual confounding might be present.[107-109] However, since not all patients are eligible for BCS, increasing the number of patients who undergo breast contour preservation (BCP) using other methods is warranted.

There are various factors determining whether patients are eligible for NAC, primary BCS or IBR. While the introduction of neoadjuvant chemotherapy (NAC) as a down staging procedure made more patients eligible for BCS,[110,111] BCP has also been achieved by increasing the number of patients undergoing IBR postmastectomy.[100,112,113]

In 2015, the NBCA formulated a comprehensive parameter aiming for better reflection of the multidisciplinary effort to preserve the breast mound, defined as BCP.[114] BCP is thought to be achievable for most breast cancer patients, specifically those who are diagnosed with early-stage breast cancer.

Chapter 7 describes the prevalence of BCP among women with early-stage breast cancer in Denmark and the Netherlands using nationwide databases from both countries. Hereby, this chapter aims to identify opportunities for improvement within both countries. This information is warranted for increasing the use of BCP and reduce potential unwanted variation between hospitals. Moreover, potential room for

improvement in the breast cancer care organization may be identified and clues for future research might be highlighted.

Quality assessment of oncoplastic surgery

Alongside post mastectomy reconstruction techniques, reconstructive techniques during BCS have evolved in the last decades.[77] The combination of oncological and plastic surgery during BCS is commonly defined as oncoplastic breast surgery.[115] Applying oncoplastic breast surgery enables physicians to *safely* perform breast conservation even in patients with large and multifocal tumors, who otherwise had to undergo mastectomy due to the indication for an large excision.[115,116]

In reviewing literature, oncoplastic breast surgery shows promising long term outcomes regarding survival, local recurrence, and quality of life compared to patients who underwent BCS or mastectomy.[117-120] Moreover, it has been hypothesized that it results in fewer re-excisions due to insufficient tumor margins as oncoplastic breast surgery has been associated with wider excisions compared to BCS alone.[121-123]

However, the level of evidence regarding the impact of oncoplastic breast surgery on the number of re-excisions is limited due to weak methodology, single-center settings, and a small number of patients.[118,121-125] **Chapter 8** focuses on the re-excision rate after oncoplastic breast surgery compared to BCS using a real-world Danish population-based database. Secondary, we evaluate the impact of oncoplastic breast surgery on the risk for conversion to mastectomy compared to BCS. Hereby, this chapter aims to foster the knowledge regarding the *safety* and e*ffectiveness* of this breast reconstructive strategy.

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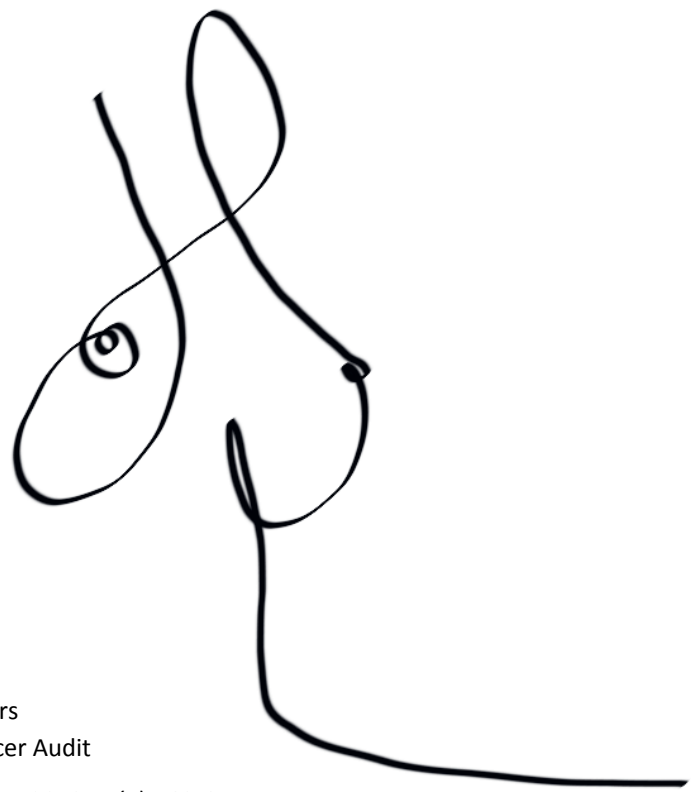
Part I

Change of hospital in breast cancer care

Chapter 2

Hospital transfer after a breast cancer diagnosis: a population-based study in the Netherlands of the extent, predictive characteristics and its impact on time to treatment



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European Journal of Surgical Oncology 2019;45(4):560-6

Abstract

Purpose

Patients may transfer of hospital for clinical reasons but this may delay time to treatment. The purpose of this study is to provide insight in the extent of hospital transfer in breast cancer care; which type of patients transfer and what is the impact on time to treatment.

Methods

We included 41,413 breast cancer patients registered in the Netherlands Cancer Registry between 2014 and 2016. We investigated transfer of hospital between diagnosis and first treatment being surgery or neoadjuvant chemotherapy (NAC). Co-variate adjusted characteristics predictive for hospital transfer were determined. To adjust for possible treatment by indication bias we used propensity score matching (PSM). Time to treatment in patients with and without hospital transfer was compared.

Results

Among 41,413 patients, 8.5% of all patients transferred to another hospital between diagnosis and first treatment; 4.9% before primary surgery and 24.8% before NAC. Especially young (aged <40 years) patients and those who underwent a mastectomy with immediate breast reconstruction (IBR) were more likely to transfer. The association of mastectomy with IBR with hospital transfer remained when using PSM. Hospital transfer after diagnosis significantly prolonged time to treatment; breast-conserving surgery by 5 days, mastectomy by 7 days, mastectomy with IBR by 9 days and NAC by 1 day.

Conclusions

While almost 5% of Dutch patients treated with primary surgery transfer hospital after diagnosis and up to 25% for patients treated with NAC, our findings suggest that especially those treated with primary surgery are at risk for additional treatment delay by hospital transfer.

Introduction

Breast cancer is the most common neoplasm among women in the Netherlands with an incidence of more than 14,000 new patients.[1] Since 1989, the Netherlands Cancer Registry (NCR) registers data on patient-, tumor-, diagnostic- and treatment characteristics of all Dutch cancer patients. A high standard of care is provided in all breast cancer treating hospitals, offering both surgical and systemic treatment options in every hospital.[2]

Hospital transfer can be clinically motivated e.g., because of the unavailability of certain treatment options, or patient's wish. However, hospital transfer can cause delay in treatment, extra costs and discontinuity of care as being demonstrated in different studies including patients diagnosed with ischemic stroke, diabetes and different types of cancer.[3-9] The first discussion about breast cancer patients changing hospital emerged after publication of studies focusing on predictors of delay of treatment.[10,11] A recent study by Bleicher *et al.* showed an association between hospital transfer and treatment delay. They also showed that more than one-third of breast cancer patients transfer hospital in the United States (US).[12] Identifying predictive characteristics for hospital transfer based on previous studies is debatable as hospital transfer was not analyzed independently of other characteristics. The findings from the US cannot be generalized, as the healthcare systems differ between countries on care access by patients and hospital transfer depends of the organization of healthcare.

Because the existing research on hospital transfer by breast cancer patients is restricted to studies in non-population based settings in which not all breast cancer treating hospitals were participating, the relevance of a more detailed, population-based study is emphasized. Quantifying the extent of hospital transfer and assessing which patient characteristics are predictive of hospital transfer, could provide relevant information for physicians focusing on optimizing breast cancer care.

The primary aim of the present study is to analyze to what extent patients diagnosed with breast cancer transfer to another hospital between diagnosis and treatment in the Netherlands. Secondly, we sought to investigate predictive factors for hospital transfer and determine the impact of hospital transfer on time to treatment.

Methods

Patient population

The study was designed by the NABON Breast Cancer working group, an initiative that started in 2011.[2] For this study data on patient, tumor and treatment characteristics as well as hospital characteristics were derived from the NCR database. All surgically treated female patients diagnosed in the Netherlands with invasive breast cancer between January 1th, 2014 and December 31th, 2016 were selected. Patients diagnosed with metachronous breast cancer in the same breast or contralateral, were included multiple times. Hospital transfers were recorded on patient level, so patients with bilateral tumor were counted as one. Patients with an unknown treatment status were excluded. The study was approved by the Privacy Review Board of the NCR.

Variables studied

Patient characteristics*:* Age at time of diagnosis was depicted in 10-year groups, as this provided more insight into differences between clinically relevant groups. Socio-economic status (SES) was determined using the postal code. The SES indicator uses fiscal data based on a combination of the mean value of the houses and mean household income and was provided at an aggregated level for each Dutch postal code.[13] SES was categorized in low (first - third decile), medium (fourth - seventh decile) and high (eight - tenth decile).

Tumor characteristics: Histologic finding, tumor differentiation grade according to Bloom–Richardson scoring system[14] and stage according to the 7th edition of the American Joint Committee on Cancer's (AJCC) Cancer Staging Manual [15] were included.

Treatment characteristics: Type of first surgery was classified into breast-conserving surgery, mastectomy, and mastectomy with immediate breast reconstruction (IBR) on the same day as the mastectomy. Chemotherapy was defined as neoadjuvant when initiated before surgery.

For analysis of patients transferring to another hospital we defined two groups; 1. patients who underwent primary surgery and 2. patients who underwent neoadjuvant chemotherapy (NAC) followed by surgery. Hospital transfer was defined as a transfer between diagnosis and primary surgery or between diagnosis and start of NAC.

Hospital characteristics: Hospitals were categorized according to hospital type as district hospitals, teaching hospitals (not affiliated with a medical faculty), medical faculty affiliated university hospitals and cancer-specific hospitals (only treating cancer patients).

To evaluate the impact of transfer on time to treatment, we calculated time in days between biopsy-proven breast cancer and first treatment, being primary surgery or initiation of NAC for patients with and without hospital transfer.

Statistical analysis

Differences in characteristics between patients with or without hospital transfer were analyzed using chi-square tests. A p-value <0.05 was considered statistically significant. A logistic regression model was used to determine characteristics predictive for hospital transfer and was presented as the odds ratio (OR) with a 95% confidence interval (CI). Characteristics that had a p<0.10 in univariable analysis were included in a multivariable model. Secondly, to adjust for possible treatment by indication bias between the different types of surgery, we used propensity score matching (PSM) to match patients on having the same chance of a specific surgery based on patient, tumor and axillary lymph node treatment characteristics. Time to treatment in patients with and without hospital transfer were compared using Wilcoxon-Mann-Whitney tests. All statistical analyses were performed with STATA (version 13.1, 2013, Texas).

Results

Study population

Between 2014 and 2016, 41,413 female patients with invasive breast cancer who met our eligibility criteria were included. In total, 33,930 patients underwent primary surgery and 7,483 patients received NAC. Patient, tumor and treatment characteristics are listed in Table 2.1.

Mean age was 60.5 (standard deviation 12.5) years. In the primary surgery group 22,106 patients (65.2%) underwent breast-conserving surgery and 11.824 patients (34.8%) underwent ablative surgery. The use of IBR increased from 19.5% to 24.2% over the 3-year period. Over the years the percentage of patients receiving NAC increased from 15.1% to 18.3%. Off all patients, 14,683 (35.5%) patients were diagnosed in a district hospital, 23,287 (56.2%) patients in a teaching hospital, 2,491 (6.0%) patients in a university hospital and 952 (2.3%) in a cancer-specific hospital.

Table 2.1. Patient, tumor and treatment characteristics with percentage of patients who transfer hospital.

	Diagnosis and primary surgery				Diagnosis and neoadjuvant chemotherapy			
	All patients	Hospital transfer			All patients	Hospital transfer		
	N (%)	No	Yes	p-value	N (%)	No	Yes	p-value
Number of patients	33,930 (100.0)	95.1	4.9		7,483 (100.0)	75.3	24.8	
Year of diagnosis								
2014	11,728 (34.6)	95.6	4.5	0.014	2,147 (28.7)	69.4	30.7	<0.001
2015	11,001 (32.4)	94.8	5.3		2,729 (36.5)	70.2	29.8	
2016	11,201 (33.0)	95.0	5.0		2,607 (34.8)	85.4	14.6	
Age (years)								
<40	953 (2.8)	86.3	13.8	<0.001	1,088 (14.5)	68.7	31.3	<0.001
40-49	4,084 (12.0)	92.3	7.7		2,476 (33.1)	74.8	25.2	
50-59	8,532 (25.2)	94.7	5.3		2,189 (29.3)	76.8	23.2	
60-69	10,689 (31.5)	95.8	5.2		1,473 (19.7)	78.7	21.3	
70-79	7,039 (20.8)	96.8	3.2		240 (3.2)	73.8	26.3	
≥80	2,633 (7.8)	96.6	3.4		17 (0.2)	76.8	23.5	
Socio-economic status								
Low	11,739 (35.4)	94.6	5.4	<0.001	2,319 (31.0)	73.6	26.4	0.001
Average	11,593 (34.9)	95.8	4.2		2,584 (34.5)	78.3	21.7	
High	10,598 (31.9)	94.9	5.1		2,580 (34.5)	73.7	26.3	
Differentiation grade								
Well	8,893 (26.2)	95.4	4.6	0.011	598 (8.0)	82.1	17.9	<0.001
Moderately	16,160 (47.6)	95.1	4.9		2,558 (34.2)	74.4	25.7	
Poorly	7,850 (23.1)	95.2	4.8		2,031 (27.1)	73.7	26.3	
Unknown	1,027 (3.0)	91.1	8.9		2,296 (30.7)	75.9	24.1	
Histology								
Ductal	27,227 (80.2)	95.1	4.9	0.002	6,446 (86.1)	75.8	24.2	<0.001
Lobular	4,138 (12.2)	95.7	4.3		743 (9.9)	75.1	24.9	
Other	2,565 (7.6)	93.8	6.2		294 (3.9)	64.3	35.7	
Tumor stage								
1	23,451 (69.1)	95.0	5.0	0.175	586 (7.8)	73.9	26.1	0.361
2a	7,981 (23.5)	95.1	4.9		2,517 (33.6)	75.4	24.6	
2b	1,773 (5.2)	96.3	3.7		2,218 (29.6)	75.1	24.9	
3	509 (1.5)	94.3	5.7		1,832 (24.5)	76.4	23.6	
4	216 (0.6)	94.9	5.1		330 (4.4)	71.5	28.5	
Receptor status								
Triple negative	2,784 (8.2)	95.7	4.3	0.244	1,521 (20.3)	72.9	27.2	0.001
Her-2 positive	3,259 (9.6)	94.6	5.4		1,915 (25.6)	75.2	24.8	
HR+/HER2 negative	25,617 (78.5)	95.1	4.9		3,889 (52.0)	75.7	24.3	
Unknown	1,270 (3.7)	94.9	5.1		158 (2.1)	87.3	12.7	
Sentinel node biopsy								
No	3,468 (10.2)	95.8	4.2	0.037	NA	NA	NA	-
Yes	30,462 (89.8)	95.0	5.0		NA	NA	NA	
ALND								
No	30,178 (88.9)	95.0	5.0	0.016	NA	NA	NA	-
Yes	3,752 (11.1)	95.9	4.1		NA	NA	NA	
Type of surgery								
BCS	22,106 (65.2)	95.7	4.3	<0.001	NA	NA	NA	-
Mastectomy	9,170 (27.0)	96.1	3.9		NA	NA	NA	
Mastectomy with IBR	2,654 (7.8)	86.3	13.8		NA	NA	NA	

Hospital transfer is expressed as percentage. The total of percentages might be above 100% due to rounded percentages. Abbreviations: CI, confidence interval; HR, hormone receptor; IBR, immediate breast reconstruction; ALND, axillary lymph node dissection; BCS, breast-conserving surgery; NA, not available.

Hospital transfer after diagnosis

In total, 3,517 patients (8.5%) transferred hospital between diagnosis and first treatment. The hospital transfer during the 3-year period is presented in Figure 2.1. In patients treated with primary surgery, the overall percentage of hospital transfer was 4.9% (n=1,665) whereas in patients treated with NAC, 24.8% of patients (n=1,852) transferred hospital between diagnosis and initiation of NAC. The total percentage of patients transferring hospital between NAC and surgery was 16.9%. Of the patients transferring hospital between diagnoses and NAC, 50.7% returned to the hospital of diagnosis after completion of NAC.

Over the years, the percentage of patients treated with primary surgery who transferred hospital increased significantly from 4.5% to 5.0% (p=0.014) whereas for those who started with NAC this percentage decreased from 30.7% to 14.6% (p<0.001). The percentage of patients who transferred hospital between NAC and surgery decreased from 22.5% to 8.4% (p<0.001).

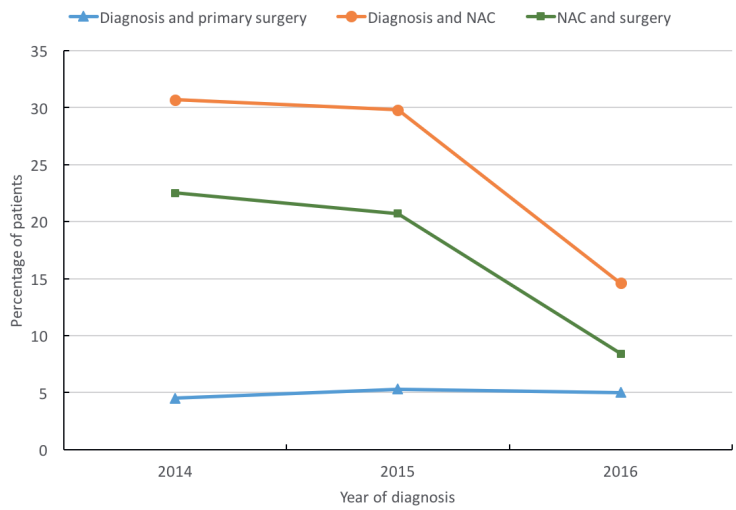

Figure 2.1. Proportion of patients that transfer hospital after diagnosis between 2014 and 2016. Abbreviations: NAC, neo-adjuvant chemotherapy.

Patients transferring hospital between diagnosis and surgery

The number of patients treated with primary surgery according to hospital type before and after hospital transfer is shown in Figure 2.2. Patients diagnosed in a district hospital most frequently transferred hospital and those diagnosed in a teaching

hospital least frequently transferred hospital. When hospital transfer occurred, patients most commonly transferred towards a teaching hospital.

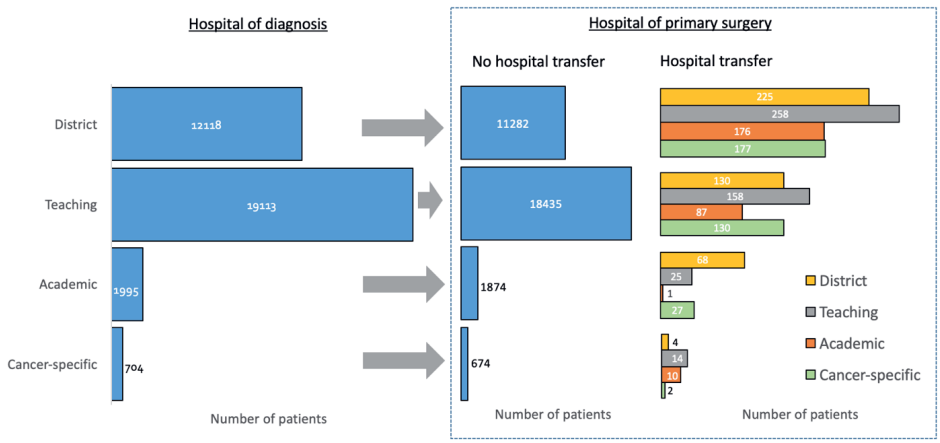

Figure 2.2. Number of patients treated with primary surgery who transfer hospital according to type of hospital.

Characteristics predictive of hospital transfer are listed in Table 2.2. Multivariable analyses demonstrated that especially patients younger than 40 years of age (OR 2.72, 95%-CI 2.19-3.39) and patients who underwent a mastectomy with IBR (OR 2.81, 95%-CI 2.45-3.22) were more likely to transfer hospital. The association between younger age (<40 years) and hospital transfer was independent of the type of surgical therapy (data not shown). After adjusting for treatment by indication bias using PSM, patients undergoing a mastectomy with IBR still had a higher likelihood of hospital transfer (OR 1.07, 95%-CI 1.04-1.09). In other words, as patients were equally likely to obtain a certain type of surgery given their characteristics, these analyses provide the effect that can be attributed to the type of surgery itself rather than the indication for treatment. Hospital transfer was more likely among patients with a low SES, and patients with an unknown differentiation grade, histologic findings categorized as 'other' or tumor stage 3 were more likely to transfer hospital.

Table 2.2. Univariable and multivariable analysis of predictors for a transfer in hospital between diagnosis and first treatment.

	Diagnosis and primary surgery		Diagnosis and neoadjuvant chemotherapy	
	univariable OR (95% CI)	multivariable OR (95% CI)	univariable OR (95% CI)	multivariable OR (95% CI)
Year of inclusion				
2014	ref.	ref.	2.59 (2.25-2.99)	2.90 (2.50-3.37)
2015	1.19 (1.05-1.34)	1.19 (1.05-1.34)	2.49 (2.17-2.85)	2.63 (2.29-3.01)
2016	1.14 (1.01-1.29)	1.15 (1.02-1.30)	ref.	ref.
Age (years)				
<40	3.6 (2.93-4.43)	2.72 (2.19-3.39)	1.68 (1.41-2.01)	1.71 (1.42-2.05)
40-49	1.89 (1.63-2.20)	1.59 (1.36-1.85)	1.24 (1.06-1.45)	1.23 (1.05-1.44)
50-59	1.27 (1.11-1.45)	1.16 (1.01-1.32)	1.11 (0.95-1.30)	1.11 (0.94-1.31)
60-69	ref.	ref.	ref.	ref.
70-79	0.74 (0.63-0.87)	0.78 (0.66-0.91)	1.31 (0.96-1.80)	1.36 (0.99-1.88)
≥80	0.79 (0.63-1.00)	0.86 (0.68-1.09)	1.14 (0.37-3.51)	1.18 (0.37-3.75)
Socio-economic status				
Low	1.2 (1.061.35)	1.23 (1.09-1.39)	1.25 (1.09-1.42)	1.23 (1.07-1.41)
Average	ref.	ref.	ref.	ref.
High	1.13 (0.99-1.27)	1.07 (0.95-1.22)	1.25 (1.10-1.42)	1.24 (1.09-1.41)
Differentiation grade				
Well	ref.	ref.	ref.	ref.
Moderately	1.06 (0.94-1.20)	1.05 (0.92-1.19)	1.58 (1.26-1.99)	1.67 (1.32-2.11)
Poorly	1.03 (0.89-1.19)	0.94 (0.81-1.09)	1.64 (1.30-2.07)	1.65 (1.29-2.12)
Unknown	2.01 (1.58-2.54)	1.87 (1.47-2.38)	1.46 (1.16-1.84)	1.18 (0.93-1.50)
Histology				
Ductal	ref.	ref.	ref.	ref.
Lobular	0.88 (0.75-1.04)	0.93 (0.79-1.10)	1.04 (0.87-1.24)	1.16 (0.96-1.40)
Other	1.29 (1.09-1.53)	1.29 (1.09-1.54)	1.74 (1.36-2.22)	1.82 (1.41-2.35)
Tumor stage				
1	ref.	ref.	ref.	-
2a	0.98 (0.87-1.10)	1.00 (0.88-1.14)	0.92 (0.75-1.13)	-
2b	0.74 (0.57-0.95)	0.87 (0.66-1.17)	0.94 (0.76-1.16)	-
3	1.15 (0.79-1.68)	1.58 (1.04-2.40)	0.88 (0.71-1.08)	-
4	1.02 (0.56-1.88)	1.26 (0.67-2.36)	1.13 (0.83-1.52)	-
Receptor status				
Triple negative	0.88 (0.72-1.06)	-	1.16a (1.02-1.33)	1.15 (0.99-1.34)
Her-2 positive	1.12 (0.95-1.31)	-	1.03 (0.91-1.17)	1.05 (0.92-1.20)
HR+/HER-2 negative	ref.	-	ref.	ref.
Unknown	1.05 (0.81-1.35)	-	0.45 (0.28-0.73)	0.34 (0.21-0.56)
Sentinel node biopsy				
No	0.83 (0.70-0.99)	1.04 (0.84-1.30)	-	-
Yes	ref.	ref.	-	-
ALND				
No	ref.	ref.	-	-
Yes	0.81 (0.69-0.96)	0.77 (0.62-0.96)	-	-
Type of surgery				
BCS	ref.	ref.	-	-
Mastectomy	0.91 (0.80-1.03)	0.99 (0.86-1.13)	-	-
Mastectomy with IBR	3.58 (3.14-4.07)	2.81 (2.45-3.22)	-	-

Abbreviations: OR, odds ratio; CI, confidence interval; HR, hormone receptor; BCS, breast-conserving surgery; IBR, immediate breast reconstruction; ALND, axillary lymph node dissection.

Patients transferring hospital between diagnosis and NAC

The number of patients treated with NAC according to hospital type before and after hospital transfer is shown in Figure 2.3. Patients diagnosed in a district hospital most frequently transferred hospital and those diagnosed in a cancer-specific hospital least frequently transferred hospital. When hospital transfer occurred, patients most commonly transferred towards a district hospital.

Multivariable analyses demonstrated that hospital transfer was particularly more likely in patients included in 2014 (OR 2.90, 95%-CI 2.50-3.37) and 2015 (OR 2.63, 95%-CI 2.29-3.01) and patients younger than 40 years of age (OR 1.71, 95%-CI 1.42-2.05). Patients with a low or high SES were more likely to transfer hospital compared to patients with a moderate SES. Patients with moderately or poorly differentiated tumors and those who had 'other' histologic findings were more likely to transfer hospital. The receptor status of the tumor was not predictive for hospital transfer.

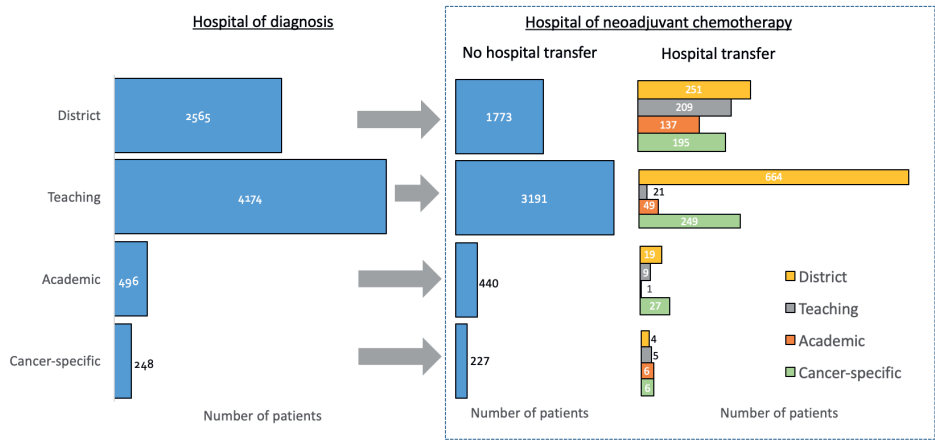

Figure 2.3. Number of patients treated with neoadjuvant chemotherapy who transfer hospital according to type of hospital.

Time from diagnosis to first treatment

The times from diagnosis to primary surgery and from diagnoses to NAC are listed in Table 2.3. Both were significantly longer for patients who transferred hospital compared with those who did not. Median time from diagnosis to treatment was prolonged for all different treatment modalities; breast-conserving surgery by 5 days

(p<0.001), mastectomy by 7 days (p<0.001), mastectomy with IBR by 9 days (p<0.001) and NAC by 1 day (p<0.001).

Table 2.3. Time (days) from diagnosis to first treatment by transfer of hospital status.

	No transfer of hospital		**Transfer of hospital**		
	Median	ICR	Median	ICR	p-value*
Time from diagnosis to surgery	23	18-31	32	23-45	<0.001
Breast-conserving surgery	22	17-29	29	21-40	<0.001
Mastectomy without immediate reconstruction	25	19-32	30	21-43	<0.001
Mastectomy with immediate reconstruction	34	27-44	43	33-58	<0.001
Time from diagnosis to neoadjuvant chemotherapy	27	21-33	28	22-36	<0.001

Abbreviations: ICR, interquartile range. *Wilcoxon-Mann-Whitney tests

Discussion

Our study shows that over a 3-year period in total 3,517 (8.5%) patients transferred to another hospital between diagnosis and first treatment; 4.8% of patients transferred before primary surgery and almost 25% of patients transferred before the start of NAC. Looking at all patients, a hospital transfer most commonly occurred when diagnosed in a district hospital. Hospital transfer in patients undergoing primary surgery was most likely in younger patients (aged <40 years) and in patients who underwent a mastectomy with IBR. In patients treated with NAC, hospital transfer between diagnosis and NAC was most likely in patients included in the earlier years (2014 and 2015) and younger age (<40 years). Patients who transferred hospital had a significant delay from diagnosis to first treatment for all different treatment modalities, though the largest impact was reported for patients undergoing primary surgery.

International variation exists in the extent of patients who transfer hospital after diagnosis,[10-12,16-18] though no population-based studies focusing on this subject exist. Surprisingly, the overall percentage of patients who transfer hospital in our study was much lower than the recently reported 36.6% in the study by Bleicher *et al.*[12] Their study focused on the impact of hospital transfer between diagnosis and surgery on treatment delay, in non-neoadjuvant treated patients diagnosed at Commission on Cancer (CoC)-accredited Hospitals in the US. Contrary to our findings, they reported a large increase in hospital transfer of 29.1% to 39.6% over time rather than a decrease as reported in the present study. It is not yet clear how this should be explained.

Although their analysis did not adjust for other factors, Bleicher *et al.* also reported that younger patients were more likely to transfer hospital.[12] Among other factors, they showed that type of insurance and ethnicity were predictive for hospital transfer. These

data are not registered in the NCR-database and could therefore not be included in our analyses. Contrary to our study, hospital selection bias may exist in the study of Bleicher *et al.* as only patients were included from CoC-accredited hospitals, whereas the present study included all Dutch hospitals. It is unclear if the higher hospital transfer reported by Bleicher could be the result of the increasing use of IBR in the US,[19] as presence of IBR was not reported. The higher hospital transfer in the US could also be due to more centralization of breast cancer surgery, which would result in more hospital transfer after diagnosis. Bleicher *et al.* suggested that the increase in hospital transfer might be among other things due to the increasing use of second opinions, though a report by Kurian *et al*. in 2016 showed that only up to 10% of breast cancer patients seek a second opinion in the US.[12,20] Another explanation for the discrepancy in hospital transfer is that patients in the US might be directed to specific hospitals for treatment by insurance companies in comparison to patients in the Netherlands due to differences in medical insurance coverage. Dutch patients can freely transfer between hospitals based on their own preferences and are not obligated to receive treatment in specific hospitals because of insurance coverage as every patient has a minimal coverage, which covers the costs for treatment in any hospital.

Our findings on the impact of hospital transfer on time to treatment are in line with Bleicher *et al.* and prior studies from the US.[10-12] Bleicher *et al.* showed an independent association between hospital transfer and treatment delay in all different treatment modalities. Unfortunately, they did not differentiate between mastectomy with and without IBR, as our study adds that hospital transfer for this latter group will prolong time to treatment by 9 days additionally to the delay compared to breast-conserving surgery. The increase in time to treatment is most likely due to the more complex logistic organization of IBR.[8,21] Hospital transfer might complicate time management by requiring patients to register in the new hospital and consult new physicians. Future research could focus on how hospital transfer specifically prolongs time to treatment. The delaying impact of transferring hospital in our study is most likely without clinical implications for patients treated with NAC as hospital transfer delayed treatment by only one day.

Our conclusions that patients who underwent a mastectomy with IBR are more likely to transfer hospital confirm the results of a prior study by Liederbach *et al.* though they did not adjust for other characteristics nor for treatment by indication bias.[10] It is likely that the higher percentage of hospital transfer in these patients is due to organizational capabilities or medical expertise to perform an IBR, because wide variation in the use of IBR between hospitals exists on national and international level.[1,22-24] The association between mastectomy with IBR and hospital transfer is not likely to be entirely explained by lack of reconstructive surgical expertise, because only two Dutch hospitals

do not carry out IBR at least once annually.[7,22] Hospital transfer could not be explained by the type of IBR as hospital transfer was comparable between different types of IBR such as reconstruction with autologous tissue or prosthesis, as subsequent analysis showed no significant difference (p=0.994). A previous study showed that variation in the use of IBR between Dutch hospitals could not be explained by collaborations between hospitals and that the variation was only partly explained by hospital organizational factors.[22] Unfortunately, our study did not have the information on the number of plastic surgeons in hospitals and therefore we could not include this in our analysis as the expertise and incorporation of plastic surgeons in the breast care team is likely to explain the chance of receiving IBR.

Unfortunately, we could not compare our results regarding predictive characteristics for hospital transfer between diagnosis and NAC to previous research, as this was not studied before. The much higher percentage of hospital transfer when treated with NAC in comparison to those who underwent primary surgery could not be explained by lack of expertise in NAC treatment, because all Dutch hospitals that provide breast cancer care also administer NAC.[7] Nonetheless, variation between Dutch hospitals does exist in the use of NAC in patients with locally advanced breast cancer.[25] Surprisingly, hospital transfer decreased significantly in the most recent year in our results. This decrease could not be explained by a change in characteristics between 2014 versus 2016 as subsequent analyses showed comparable predictive characteristics (data not shown). Moreover, the number of hospitals that administered NAC remained the same over the 3-year period. Despite the fact that no significant changes occurred in the Dutch guidelines regarding NAC during the 3-year period, the increasing use of NAC may have created more expertise in district hospitals, thereby overcoming the necessity to transfer hospital.

Limitations

Our study has several limitations. The reader should bear in mind that the reported hospital transfer could be an overestimation when hospital transfer was reported between hospitals that actually had a non-official collaboration. Examples of official collaborations are known in which one hospital performs most of the diagnostics and the other hospital performs the treatment. However, official collaborations of hospitals are updated annually in the NCR-database. Limitations subsequent to the use of a database are that it could not account for possibly unmeasured confounders (e.g., patients' preference, comorbidities or travel distance to hospital) that could influence hospital transfer. Extrapolating our results to other countries must be done with cautiousness as healthcare and referral agreements might differ between countries.

However, the predictive factors in our population for hospital transfer are in accordance with those previously described from the US.

Conclusions

Almost 5% of the Dutch patients undergoing primary surgery and up to one-fourth for patients treated with NAC transfer to another hospital after diagnosis. One of the more significant findings of this study is that hospital transfer is mainly associated with age below 40 years and with mastectomy with IBR. While patients undergoing mastectomy with IBR are known to have prolonged time to surgery compared to breast-conserving surgery or mastectomy, our findings suggest that especially these patients are at risk for additional treatment delay due to the delaying impact of hospital transfer. These findings extend the knowledge of patients at risk for discontinuity of care and challenges hospitals to improve timely care for patients who transfer hospital.

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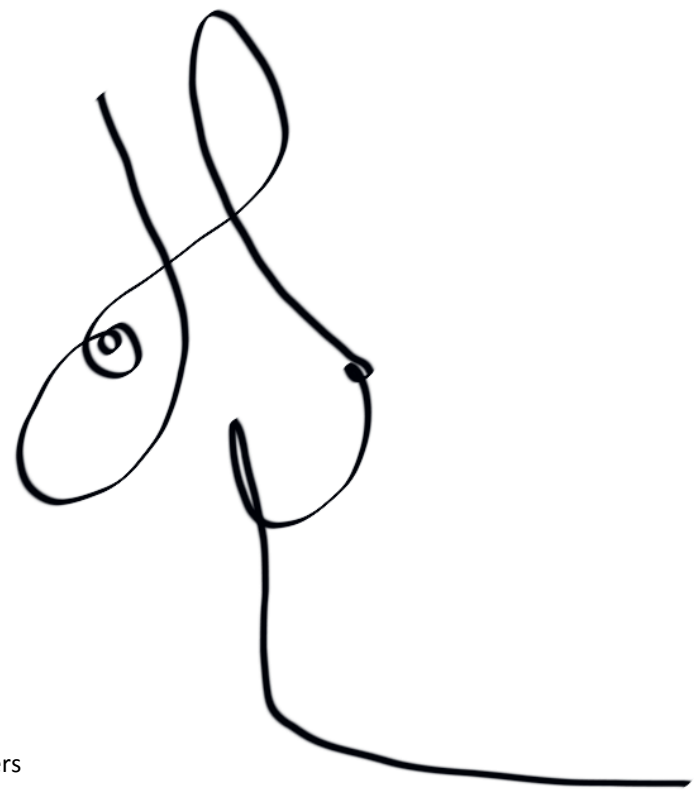
Chapter 3

Impact of second opinions in breast cancer diagnostics and treatment: A retrospective analysis



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Annals of Surgical Oncology 2019;26(13):4355-63

Abstract

Background

Breast cancer care is becoming increasingly complex, and patients with breast cancer are increasingly aware of the different treatment options, resulting in requests for second opinions (SOs). The current study investigates the impact of breast cancer SOs on final diagnosis and treatment in the Netherlands Cancer Institute (NCI) using a newly designed Breast Cancer Second Opinion (BCSO) classification system.

Methods

Patients who visited the NCI for an SO between October 2015 and September 2016 were included. Demographics, diagnostics, and treatment proposals were compared between first and SO. Discrepancy was categorized using our BCSO classification system, categorizing SOs into (1) noncomparable, (2) identical, and (3) minor or (4) major discrepancy.

Results

The majority of SOs (n=591) were patient initiated (90.7%). A total of 121 patients underwent treatment prior to their SO, leaving 470 patients for assessment of discrepancies according to our BCSO classification system. More than 45% of these SOs resulted in at least one discrepancy, with comparable rates for physician- and patient-initiated SOs (42.5% vs. 45.6%, p=0.708). Significantly more discrepancies were observed in patients with additional imaging (51.3% vs. 37.2%, p=0.002) and biopsies (53.7% vs. 40.3%, p=0.005). Almost 60% of all discrepancies were categorized as major (neoadjuvant systemic treatment instead of primary surgery, breast-conserving surgery instead of mastectomy, and proposing postmastectomy immediate breast reconstruction).

Conclusions

Our findings show substantial differences in diagnostic and treatment options in breast cancer patients visiting the Netherlands Cancer Institute for an SO, thereby emphasizing more consensus for the indications of these treatment modalities.

Introduction

Medical care for breast cancer patients is becoming increasingly complex, due to the emergence of patient- and tumor-tailored treatment and the wide variety of available treatment modalities. To address this complexity, all Dutch hospitals that provide breast cancer care have a multidisciplinary tumor board (MDT) where newly diagnosed breast cancer patients are discussed.[1] Case review at a MDT is associated with improved breast cancer care.[2-6] Additionally, these boards review second opinions (SOs) coming from different hospitals.

SOs can be initiated by patients themselves or by their physicians. Patient-initiated second opinions (PtSO) may be requested for a variety of reasons, but most frequently to achieve more certainty or reassurance about the diagnosis and/or treatment options provided by the first-opinion physician.[7,8] Physician-initiated second opinions (PhSO) may occur either when the first-opinion physician seeks consultation or lacks expertise in complex care or when a patient is believed to have a psychological need for an additional opinion on their diagnosis and treatment plan.[9,10]

Of all patients diagnosed with some form of cancer, SOs are most frequently requested by patients with breast cancer.[11,12] The rate of SOs among breast cancer patients reported in previous studies ranges between 9 and 20%.[8,13-15] The demand for SOs may be increasing due to the increasing complexity of breast cancer treatment and subsequent complex decisions that patients and their physicians have to make. Furthermore, expansion of information provided by patient coalitions and media has enhanced patients' awareness of available treatment options and the importance of shared decision-making.[16]

Besides their potential benefits, SOs have been suggested to have disadvantages: they may result in additional imaging and biopsies/biopsy procedures and could delay treatment onset.[11,17,18] It has been debated whether an SO decreases patients' uncertainty about the diagnosis and treatment plan.[15] For physicians, SOs may increase workload and costs, and could result in a decrease of patients' trust in them.[8]

A study by Mellink et al. of 317 Dutch patients diagnosed with various types of cancer reported that almost one-third of all SOs resulted in discrepancy regarding pathology and imaging interpretation or treatment advice between first and SO.[11] In breast cancer patients, literature shows clinically relevant discrepancy in imaging interpretation of 13–38%[19-22] and in pathology interpretation of 8–16%.[23-25] Whether breast cancer SOs have a meaningful impact on clinical care is unknown. Previous studies focusing on breast cancer SOs used small sample sizes and heterogeneous definitions or no definition of what ''clinical impact'' of an SO entails.

In this study, we report on SOs for breast cancer in the Netherlands Cancer Institute-Antoni van Leeuwenhoek (NCI-AVL) hospital and their impact on final diagnosis and treatment using a newly designed Breast Cancer Second Opinion classification system. We analyze both PtSO and PhSO and describe (1) differences in interpretation of imaging and pathology and (2) the discrepancy in treatment proposals between first and SOs. Additionally, we analyze the impact of additional diagnostic procedures on these discrepancies.

Methods

Patient population

All patients with breast cancer who visited the outpatient clinic of the Department of Surgical Oncology of the NCI- AVL for an SO between October 2015 and September 2016 were retrospectively selected. The NCI-AVL is a tertiary hospital with high expertise in cancer research and treatment. Patients were identified using a specific code in their medical file assigned when an SO request was mentioned in the referral letter. All patients who visit this outpatient clinic either have a clinical suspicion or have been diagnosed with breast cancer. Exclusion criteria for the current study were: the absence of a referral letter, referral by a general practitioner, and absence of a definitive diagnosis at first opinion or SO. Patients with a benign diagnosis at both first and second opinion were also excluded. Patients were categorized into two groups according to their ‘‘care phase’’ at SO to limit potential differences in discrepancy caused by received treatment: (1) patients who did not receive treatment prior to SO and (2) patients who had been treated at the time of the SO.

Variables studied

Information from the first opinion regarding the patients’ demographic characteristics, imaging and histopathologic results, and proposed treatment plan were retrieved from the referral letter, as well as from the imaging and pathology reports sent by the first opinion’s hospital. Whether the SO was patient or physician initiated was derived from the referral letter. We revised the pathology and imaging reports of the first opinion and included information obtained by additional imaging and pathology performed during the SO [e.g., magnetic resonance breast imaging (MRI), computed tomography (CT), or positron emission tomography (PET)-CT]. Additional diagnostic procedures that were strictly part of a trial protocol were not included. Genetic counseling was defined as ‘‘rapid genetic counseling and testing’’ (RGCT) when performed between diagnosis

and primary surgery. Furthermore, we compared the treatment proposal at first opinion with the treatment undergone by the patient at the NCI-AVL, at the hospital providing the first opinion (after back-referral), or at a third hospital (in case of further referral after the SO). The treatment plan could be either (neo)adjuvant systemic treatment (NST) or primary surgery. Type of surgery was recorded for both the axilla [sentinel node (SN) biopsy, MARI procedure (marking of an axillary lymph node with a radioactive iodine seed before start of NST and removing this marked lymph node after NST), axillary lymph node dissection (ALND)] and the breast [breast-conserving surgery (BCS), mastectomy with or without immediate breast reconstruction (IBR)].

Development of the Breast Cancer Second Opinion (BCSO) classification to assess discrepancies

We composed a breast cancer SO (BCSO) classification system to quantify the degree of discrepancy between the first opinion and SO. This classification system was inspired by the surgical oncology SO classification suitable for patients diagnosed with any malignant neoplasm developed by Mellink et al.[11] The BCSO classification system consists of four outcome categories: (1) incomparable, (2) identical, and (3) minor or (4) major discrepancy. The definitions of these categories were developed during five feedback sessions with a MDT. The categorization is based on discrepancy between first and SO in diagnostic findings, genetic screening, or treatment proposal. Patients were categorized as ‘‘minor discrepancy’’ when differences between the first and SO most likely had little impact on the treatment plan and prognosis. Patients were categorized as ‘‘major discrepancy’’ when differences most likely had a clinically relevant impact on patients’ treatment plan and prognosis. In case with both minor and major discrepancies, patients were categorized as having ‘‘major discrepancy.’’ Patients were categorized as incomparable when all clinicopathological findings, genetic screening, and the treatment proposal were unknown and when a patient received more than one treatment option. Patients were categorized as identical when the treatment proposal resulting from the second opinion was part of a trial (phase I/II) or when the treatment was a palliative option. A detailed description of the classification system is presented in Table 3.1.

Statistical analysis

Descriptive statistics of patient and tumor characteristics and diagnostics were stratified according to the previously described two patient groups (i.e., untreated and treated prior to SO). All tests were two-sided, and p value <0.05 was considered statistically significant. The discrepancy between first opinion and SO is described for

patients according to the BSO classification system. The number of patients included per analysis might differ, as not all information of all patients was known at first and SO. All analyses were performed using SPSS® version 24 (IBM, Armonk, NY, USA).

Table 3.1. Breast cancer second opinion classification for discrepancy after a second opinion

Categorization	Description
Incomparable	Unknown or more than one treatment option given in first or second opinion
	Clinicopathological findings cannot be compared due to unknown findings in first or second opinion
Identical	Identical opinion on clinicopathological findings and treatment proposal
	Treatment proposal given by second opinion is part of a trial (phase I/II)
	Palliative treatment only option
Minor discrepancy	Minor change in findings from diagnostics, e.g.
	clinical tumor stadium (0 ↔ 1 or 1 ↔ 2 or 2 ↔ 3)
	histological tumor type (ductal ↔ lobular)
	differentiation grade (I ↔ II or II↔III)
	Genetic screening on urgent request instead of regular genetic screening
	Other changes not included in 'major discrepancy
Major discrepancy	Major change in diagnostics e.g.
	benign instead of (pre)malignant
	receptor status
	differentiation grade (I ↔ III)
	axillary lymph node involvement (N0 ↔ N+)
	tumor stadium (1 ↔ 3-4 or 2 ↔ 4 or 3↔4)
	Neo-adjuvant treatment instead of primary surgery
	Change in type of surgery, e.g.
	breast conserving instead of ablative surgery
	postmastectomy immediate reconstruction instead of mastectomy only
	Change in treatment modality, e.g.
	adjuvant local treatment
	adjuvant systemic treatment
	systemic therapy instead of surgery

Results

Study population

We identified 763 patients who visited the breast cancer outpatient clinic of the NCI-AVL for a SO, of whom 591 patients met our eligibility criteria. Figure 3.1 shows the flowchart of patient selection and the treatment provided for those who received treatment at first opinion.

Table 3.2 presents patient and tumor characteristics as described in the referral letter. The vast majority of SOs were patient initiated (90.7%). The mean age of all patients was 50.9 (range 29–82) years, and two patients were male. Of all patients diagnosed

with invasive breast cancer, 51.5% were diagnosed with hormone receptor (HR)-positive (estrogen or progesterone) and human epidermal growth factor receptor 2 (HER2)-negative tumors, 15.0% with HR-negative and HER2-positive tumors, 14.2% with triple-negative tumors, and 19.3% with an unknown subtype. Of all patients, 61.9% were classified as stage I or II. Only 3.7% had metastatic disease.

Of the 470 patients, untreated prior to SO, 269 (57.2%) underwent MRI, 187 (39.8%) underwent CT/PET-CT, and 175 (37.2%) patients underwent at least one additional biopsy at the NCI-AVL. Of the 121 patients who had already started their treatment at first opinion, 25 (20.7%) underwent MRI, 22 (18.2%) underwent CT/PET-CT, and 14 (11.6%) underwent additional biopsies at the NCI-AVL. Of the 470 patients, 119 (25.3%) participated in a trial at SO, of whom 17 participated in a phase 1/2 trial.

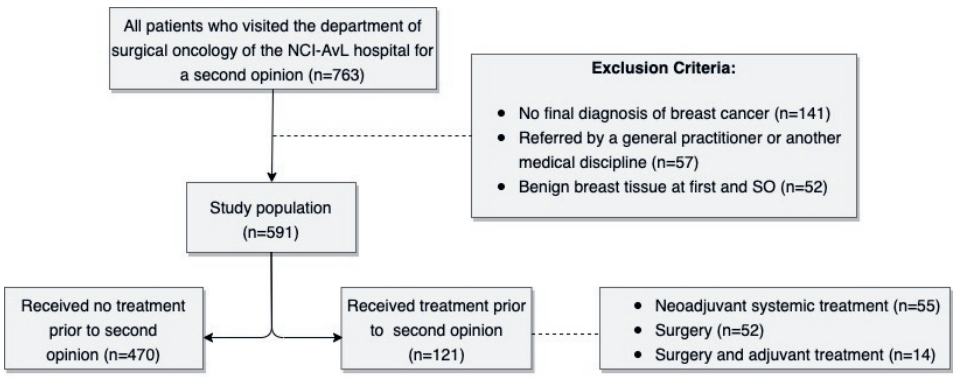

Figure 3.1. Number of patients with a second opinion for breast cancer at the Department of Surgical Oncology of the Netherlands Cancer Institute/ Antoni van Leeuwenhoek hospital between October 2015 and September 2016. Note: some patients were excluded based on multiple exclusion criteria.

Discrepancy according to the breast cancer second opinion classification

Discrepancy between the first and SO according to the BCSO classification could be assessed for patients who had not received treatment prior to SO, as previous treatment would be expected to give rise to changes in diagnostic findings and further treatment proposal.

In 213 (45.3%) of the 470 patients untreated prior to SO, a discrepancy between first opinion and SO was observed. Of these discrepancies, 76 (16.2%) were minor and 137 (29.1%) were major. Of the 137 patients with a major discrepancy, 38 (27.7%) patients additionally had a minor discrepancy. In total, 257 (54.7%) patients were classified as identical.

SOs initiated by a physician did not result in higher discrepancy rates compared with those initiated by a patient (42.5% vs. 45.6%, respectively, p=0.708). Participation in trials, besides phase 1/2, did not result in more discrepancy, as discrepancies were seen in 52.9% patients enrolled in a trial versus 42.7%% in patients who did not participate in a trial (p=0.053). Table 3.3 presents the discrepancy rates based on our BCSO classification.

Table 3.2. Patient and tumor characteristics described in the referral letter at first opinion (N=591).

			Treatment prior to second opinion	
		All patients (n=591)	No (n=470)	Yes (n=121)
Second opinion initiated by	physician	55 (9.3%)	40 (8.5%)	15 (12.4%)
	patient	536 (90.7%)	430 (91.5%)	106 (87.6%)
Age at diagnosis (years)	mean (sd)	51 (12)	51 (12)	51 (11)
Gender	female	589 (99.7%)	469 (99.8%)	120 (99.2%)
ASA classification	I	475 (80.4%)	376 (80%)	99 (81.8%)
	II	92 (15.6%)	79 (16.8%)	13 (10.7%)
	III	24 (4.1%)	15 (3.2%)	9 (7.4%)
Diagnosis	DCIS	75 (12.7%)	66 (14.0%)	9 (7.4%)
	invasive ± DCIS	507 (85.8%)	399 (84.9%)	108 (89.3%)
	other	9 (1.5%)	5 (1.1%)	4 (3.3%)
Histological tumor type	ductal	443 (75%)	356 (75.7%)	87 (71.9%)
	lobular	88 (14.9%)	62 (13.2%)	26 (21.5%)
	combination of ductal/lobular	47 (8%)	39 (8.3%)	8 (6.6%)
	unknown	13 (2.2%)	13 (2.8%)	0 (0.0%)
Differentiation grade	I	64 (10.8%)	51 (10.9%)	13 (10.7%)
	II	178 (30.1%)	121 (25.7%)	57 (47.1%)
	III	98 (16.6%)	72 (15.3%)	26 (21.5%)
	unknown	251 (42.5%)	226 (48.1%)	25 (20.7%)
Receptor status [a]	Triple-negative	72 (14.2%)	58 (14.5%)	21 (13.0%)
	HER2+	76 (15.0%)	55 (13.8%)	16 (19.4%)
	HR+ (ER and/or PR) and HER2-	261 (51.5%)	195 (48.9%)	66 (61.1%)
	Unknown	98 (19.3%)	91 (22.8%)	7 (6.5%)
Stage	0	76 (12.9%)	70 (14.9%)	6 (5.0%)
	I	153 (25.9%)	143 (30.4%)	10 (8.3%)
	II	213 (36.0%)	178 (37.9%)	35 (28.9%)
	III	76 (12.9%)	49 (10.4%)	27 (22.3%)
	IV	22 (3.7%)	15 (3.2%)	7 (5.8%)
	unknown	51 (8.6%)	15 (3.2%)	36 (29.8%)
Trial participation	Yes	131 (22.2%)	119 (25.3%)	12 (9.9%)

SD standard deviation, ASA American Society of Anesthesiologists, DCIS ductal carcinoma in situ, HR hormone receptors, HER2 human epidermal growth factor receptor 2. [a] Invasive breast cancer.

Minor discrepancies between first opinion and SO were mostly found in tumor staging, which occurred in 70 (15.4%) patients. Major discrepancies mostly concerned differences in primary treatment proposal. A total of 76 (22.8%) out of 334 patients with a primary treatment proposed at first opinion received a different primary

treatment compared with the proposed treatment at first opinion. A total of 59 (17.7%) patients received NST instead of primary surgery, and 17 (5.1%) patients underwent primary surgery instead of NST. Other common major discrepancies were observed in type of first surgery and in use of IBR in patients who underwent mastectomy. Information regarding the proposed treatment of the axilla (SN, MARI, or ALND) was not well documented in the referral letters and could therefore not be compared. Genetic counseling was not frequently mentioned in the referral letter and was only known in 24 patients at first and SO. Two (0.4%) patients had a change in their primary diagnosis from malignant at first opinion to benign at SO.

Of the patients who received additional biopsy at SO, discrepancy between first and SO was observed in histology in 10.2% (out of 167 patients), differentiation grade in 23.2% (out of 82 patients), invasiveness in 1.1% (out of 174 patients), tumor stage in 26.7% (out of 172 patients), and receptor status in 3.4% (out of 119 patients). Additional diagnostics at SO resulted in a significantly higher discrepancy rate: discrepancy (minor or major) was more common in patients who received additional imaging (51.3% vs. 37.2%, p=0.002) or biopsy (53.7% vs. 40.3%, p=0.005) at SO compared with those who did not.

Table 3.3. Discrepancy between first and second opinion according to breast cancer second opinion classification of 470 patients who had not yet received treatment prior to second opinion.

	Discrepancy		
	No	Yes	Incomparable
Minor discrepancies [a]	394 (83.8%)	76 (16.2%)	
Stage (e.g. I ⇔ II)	385 (84.6%)	70 (15.4%)	15
Histological tumor type (e.g. ductal ⇔ lobular)	428 (94.7%)	24 (5.3%)	18
Differentiation grade (e.g. I ⇔ II)	214(88.1%)	29 (11.9%)	227
Genetic screening (e.g. genetic screening after surgery ⇔ RGCT)	19 (79.2%)	5 (20.8%)	446
Major discrepancies [a]	333 (70.9%)	137 (29.1%)	
Malignancy (e.g. benign ⇔ malignant)	468 (99.6%)	2 (0.4%)	0
Receptor status [b] (e.g. triple negative ⇔ HER2 positive)	301 (98.7%)	4 (1.3%)	94
Differentiation grade (e.g. I ⇔ III)	242 (99.6%)	1 (0.4%)	227
Lymph node involvement (e.g. N0 ⇔ N1)	430 (97.5%)	11 (2.5%)	29
Stage (e.g. I ⇔ III)	443 (97.4%)	12 (2.6%)	15
Neoadjuvant therapy (e.g. neoadjuvant therapy ⇔ primary surgery)	258 (77.2%)	76 (22.8%)	136
First surgery (e.g. mastectomy ⇔ breast conserving surgery)	266 (89.9%)	30 (10.1%)	174
Reconstruction [c] (e.g. mastectomy only ⇔ mastectomy with IBR)	50 (61.7%)	31 (38.3%)	58

Note: Incomparable may be due to missing information in first or second opinion. *RGCT* rapid genetic counseling and testing, *IBR* immediate breast reconstruction. [a] In case of both minor and major discrepancies, patients were categorized as having a ''major discrepancy.'' Total or subgroup total discrepancy can differ with different categories added up as patients are counted once. [b] Invasive breast cancer. [c] Patients who underwent a mastectomy as their first surgical therapy.

Location of further treatment after the second opinion

A total of 293 (62.3%) patients of the 470 patients untreated prior to SO remained at the NCI-AVL after the SO for all further treatment, while 92 (19.6%) patients remained for part of the treatment and 85 (18.1%) patients returned to the hospital of first opinion for the entire treatment. The majority (95.7%) of the patients who stayed in our hospital for a part of the treatment underwent surgery at the NCI-AVL and received systemic therapy at the hospital of first opinion. Patients with a discrepancy (minor or major) between first opinion and SO more often remained in the NCI-AVL for all further treatment as compared with patients without discrepancy (46.4% vs. 32.9%, p=0.027).
Of the 121 patients who had received treatment at first opinion, 41 (33.9%) patients remained at the NCI-AVL after SO for all further treatment, 28 (23.1%) patients remained for part of the treatment, and 52 (43.0%) patients returned to the hospital of first opinion for the entire treatment.

Discussion

In this retrospective series at a tertiary cancer center in The Netherlands, we observed that an SO for breast cancer in untreated patients resulted in at least one discrepancy in diagnostic findings or therapeutic advice in 45% of patients, 29% of which were major. The most common discrepancies were observed regarding primary treatment proposal (NST instead of primary surgery), type of surgery (BCS instead of mastectomy), and the use of IBR in those who underwent mastectomy (IBR instead of mastectomy only). The discrepancy rate (minor or major) was significantly higher in patients who received additional imaging and biopsies at SO compared with those who did not. Our newly designed BCSO classification can be used in a reproducible manner in future studies to assess the clinical impact of SOs, enabling comparison of results between studies.
It could be expected that improvements in care and increased standardization of breast cancer management in the last decade might have resulted in reduced discrepancy between first and SOs. However, the discrepancy rate in the current study is higher than the 16% minor and 16% major discrepancy rate for SOs reported in 2006 in a sample of Dutch cancer patients, of whom 72% had breast cancer.[11] Our higher discrepancy rate might be explained by differences in the definition of discrepancy, as the classification system used in the former study was applicable to patients with several types of cancer and thus was different from our BCSO classification system.[11]

The highly variable definitions of discrepancy complicate comparison of the present results with other previous findings in breast cancer, in which discrepancy rates between 3 and 43% were reported.[2,5,6,19,23,26] The BCSO classification for discrepancy developed in the current study will enable detailed and reproducible comparisons between first opinions and SOs in the future.

To the best of the authors' knowledge, this is the first study to report discrepancy in proposed primary treatment between first and SO in detail, being NST or surgical therapy. We found that almost 23% of patients received a different primary treatment proposal (NST or primary surgery). Large variation exists between Dutch hospitals in use of NST, due to divergent expert opinions on the indications for NST.[27,28] This disagreement between physicians on the indications for NST might partly explain the discrepancy in proposed primary treatment. These results emphasize that more consensus is needed to reduce the variation in the indications for NST.

The SOs evaluated in the current study were provided in a tertiary hospital with high expertise on breast cancer care.[1] Previous studies have suggested that expertise in treatments such as the use of NST and IBR might be indications for an SO or a change of hospital after diagnosis.[7,29] This is partly true, as results from a national audit show that the use of NST and IBR in the NCI-AVL is above the national Dutch average.[1] On the other hand, the number of patients who received NST followed by BCS was comparable between patients who remained in the NCI-AVL and those who returned to the hospital of first opinion. The discrepancy in use of IBR in the current study might partly be explained by the ongoing discussion on the timing of breast reconstruction when adjuvant radiation therapy is indicated.[30,31] Other hospitals may have a different policy on performing IBR when the patient needs adjuvant radiation.

The current finding that discrepancy rates were higher for patients who received additional imaging at SO emphasizes the value of SO review and importance of additional imaging. This is in concordance with previous studies focusing on the impact of additional imaging procedures.[2,19,20] Nonetheless, it was not always clear in previous studies whether diagnostic discrepancies resulted in an alteration of treatment.

A discrepancy in genetic counseling has not been analyzed in previous studies on SOs before. Although genetic counseling could be compared in only 24 patients, we observed that 5 (20.8%) patients received RGCT instead of postoperative genetic screening. Despite the fact that none of these latter patients had a discrepancy in the type of surgery, use of genetic counseling before surgery could influence decision-making regarding primary surgery and timing of risk-reducing contralateral mastectomy.[32] Unfortunately, the small number of patients does not allow any hard conclusions to be drawn regarding the causality between SOs and genetic counseling.

This is the first study comparing the discrepancy rate between patient- and physician-initiated SOs. We found comparable rates of minor and major discrepancies between both types of SOs. A surprising finding in the current study is that, out of the 257 patients with an identical SO, only 22.2% returned to the hospital providing the first opinion for the entire treatment. These findings are not in line with findings by Mellink et al., who reported that 85% of patients with an identical SO returned to the first opinion.[11] Although not the focus of our study, this could on one hand suggest that there is room for improvement at the first opinion to encourage patients in seeking an SO and reassuring them that they can return after the SO. On the other hand, it could indicate that the hospital providing the SO should stimulate back-referral of patients to the hospital of first opinion and aim to enhance patients' trust in the physician who provided the first opinion.

The high discrepancy rates reported in our study should be interpreted with caution. Although the discrepancy rate might seem high, it may primarily show the complexity of breast cancer management: Not every discrepancy is associated with better care; some discrepancies might reflect interobserver variability and institutional preferences, and may not be based on guideline recommendations. The findings of the current study are subject to at least three limitations. First, it is important to bear in mind that an SO can be an opinion based on information on top of the information from the first opinion, as is the case with the use of additional imaging by an SO. It is unknown whether the first opinion would also have performed the additional imaging resulting in an altered diagnosis or treatment proposal. Nonetheless, almost 97% of included SOs received a diagnosis or treatment proposal from the first opinion based on the information available at that moment. Second, our retrospective study design does not allow any hard conclusions to be drawn regarding the causality of discrepancy in imaging and altered treatment. Thirdly, our findings cannot be extrapolated to all breast cancer SOs, as the study was conducted in a tertiary setting. However, the developed BCSO classification allows better comparison of discrepancy in a reproducible manner.

Conclusions

Our study showed, with the use of the newly developed BCSO classification, a substantial impact of SOs on breast cancer diagnostics and treatment. Major discrepancies mainly concerned primary treatment, type of first surgery, and use of IBR, thereby emphasizing the importance of more consensus for the indications of these treatment modalities. Future studies focusing on the impact of SOs could use the BCSO

classification to assess discrepancy between first opinion and SO in a detailed and reproducible way. With the increasing use of nationwide cancer registries, future studies could include SOs from all different types of hospitals, which could validate the current single-center evidence on the impact of SOs.

Acknowledgment

We thank S. Gerritsen, J. Remmelzwaal, and M. Piek-den Hartog for their expertise on the breast cancer second opinion outpatient clinic.

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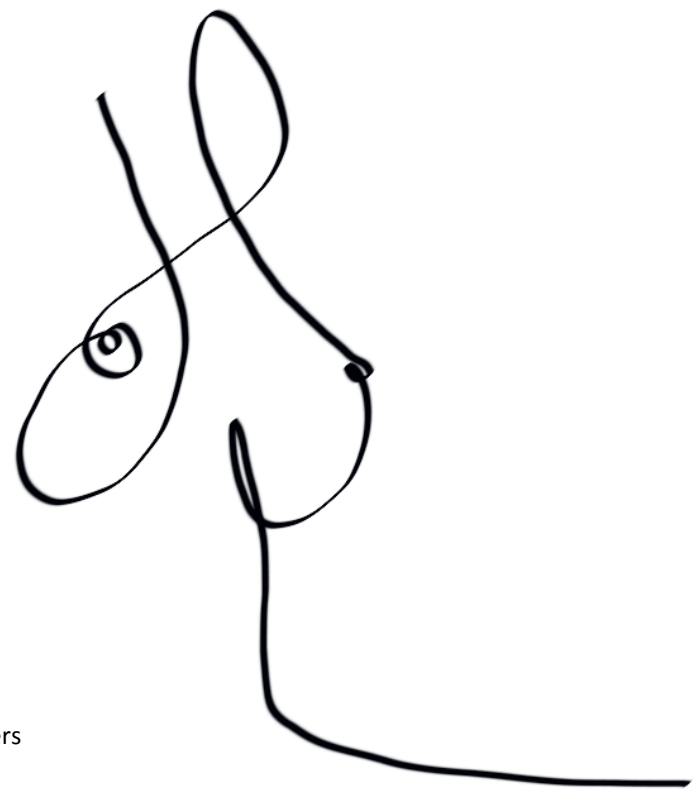
Part II

Continuity of the adjuvant chemotherapy pathway

Chapter 4

Nationwide population-based study of the impact of postmastectomy immediate breast reconstruction on the timing of adjuvant chemotherapy



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British Journal of Surgery 2019;106(12):1640-1648

Abstract

Background

Initiation of adjuvant chemotherapy within 6–12 weeks after mastectomy is recommended by guidelines. The aim of this population-based study was to investigate whether immediate breast reconstruction (IBR) after mastectomy reduces the likelihood of timely initiation of adjuvant chemotherapy.

Methods

All patients with breast cancer who had undergone mastectomy and adjuvant chemotherapy between 2012 and 2016 in the Netherlands were identified. Time from surgery to adjuvant chemotherapy was categorized as within 6 weeks or after more than 6 weeks, within 9 weeks or after more than 9 weeks, and within 12 weeks or after more than 12 weeks. The impact of IBR on the initiation of adjuvant chemotherapy for these three scenarios was estimated using propensity score matching to adjust for treatment by indication bias.

Results

A total of 6,300 patients had undergone primary mastectomy and adjuvant chemotherapy, of whom 1,700 (27.0%) had received IBR. Multivariable analysis revealed that IBR reduced the likelihood of receiving adjuvant chemotherapy within 6 weeks (odds ratio (OR) 0.76, 95T%-CI 0.66-0.87) and 9 weeks (0.69, 95%-CI 0.54-0.87), but not within 12 weeks (OR 0.75, 95%-CI 0.48-1.17). Following propensity score matching, IBR only reduced the likelihood of receiving adjuvant chemotherapy within 6 weeks (OR 0.95, 95%-CI 0.90-0.99), but not within 9 weeks (OR 0·97, 95%-CI 0.95-1.00) or 12 weeks (OR 1.00, 95%-CI 0.99-1.01).

Conclusion

Postmastectomy IBR marginally reduced the likelihood of receiving adjuvant chemotherapy within 6 weeks, but not within 9 or 12 weeks. Thus, IBR is not contraindicated in patients who need adjuvant chemotherapy after mastectomy

Introduction

Breast cancer is the most commonly diagnosed malignant cancer among women.[1] Despite advancements in diagnostics and systemic treatment, up to one-third of patients with breast cancer undergo mastectomy as the first surgical treatment to achieve local control.[2] Adjuvant systemic treatment, including chemotherapy, reduces the risk of distant recurrence and breast cancer mortality.[3] In the Netherlands, 6 weeks is the maximum time limit aimed for between surgery and initiation of adjuvant chemotherapy, as recommended by the European Society for Medical Oncology (ESMO)[4] and the Netherlands Society for Plastic Surgery.[5,6]

Several studies have reported that delayed initiation of adjuvant chemotherapy is associated with lower overall and recurrence-free survival.[7-12] The recommended acceptable maximum delay, however, varies from 7 to 12 weeks. There still is no international consensus on the definition of an unacceptable delay, but all guidelines advocate that initiation of adjuvant chemotherapy should not be delayed unnecessarily, as this may have a negative impact on survival, specifically in patients at higher risk of recurrence.[9,10,12]

The addition of immediate breast reconstruction (IBR) to mastectomy could result in preoperative delay owing to more complex logistic coordination of the operation. After surgery, a delay could be the result of longer recovery, as IBR may increase the risk of postoperative complications, even though reports on the risk of adverse events are contradicting.[13-16]

In the past decade, an increasing number of women have undergone IBR after mastectomy.[2,17,18] IBR is generally associated with good aesthetic results and less negative psychological impact on the patient, as it involves fewer operations and hospital admissions compared with breast reconstruction at a later time.[19-21] Owing to the lack of consensus on timing of adjuvant chemotherapy, physicians remain cautious in recommending IBR when adjuvant chemotherapy is part of the preoperative treatment plan.[22]

Most previous studies on the possible delaying impact of post mastectomy IBR have been single-centre studies with weak methodology and no adjustment for treatment by indication bias.[16,23,24] A systematic review from 2015 concluded that IBR does not delay time from surgery to adjuvant chemotherapy to a clinically relevant extent,[24] although the included studies showed strongly contradictory results. Moreover, a cut-off point of 12 weeks to initiation of adjuvant treatment was used, whereas current European guidelines recommend 6 weeks.[4] Furthermore, it seems likely that there may be an underlying reason why some patients have IBR and others do not, giving rise to treatment by indication bias when comparing the outcomes of these two groups. The

aim of the present nationwide population-based study was to investigate the extent to which post mastectomy IBR reduces the likelihood of timely initiation of adjuvant chemotherapy compared with mastectomy alone, while also adjusting for confounding by indication.

Methods

Prospectively collected data from the NABON Breast Cancer Audit (NBCA) database were used. The NBCA was started in 2011 and is an initiative from the National Breast Cancer Organization Netherlands (NABON), the Netherlands Comprehensive Cancer Organization and the Dutch Institute for Clinical Auditing. The NBCA collects anonymized data on clinicopathological characteristics, diagnostics and treatment modalities in a database from all hospitals in the Netherlands. It includes all patients diagnosed with ductal carcinoma in situ (DCIS) or invasive breast cancer treated surgically since 2012. The NBCA aims to monitor the quality of breast cancer care and to provide feedback to participating hospitals to stimulate and facilitate quality improvement.[25] No formal consent is required for this type of study from an ethics committee in the Netherlands according to Central Committee on Research involving Human Subjects.

Patient population

All women diagnosed with invasive breast cancer between 2012 and 2016 who had undergone primary mastectomy with or without IBR followed by adjuvant chemotherapy were identified from the NBCA database. IBR was defined as a reconstruction performed by a plastic surgeon on the same day as the mastectomy. Women who had received systemic neoadjuvant treatment, had undergone lumpectomy as initial surgery or had a re-excision were excluded from the analysis. Patients who had received another adjuvant therapy before the initiation of adjuvant chemotherapy, and those with a missing date of operation or adjuvant chemotherapy were also excluded.

Outcomes

The primary outcome was whether the patient received adjuvant chemotherapy within a specific time interval after surgery. Time to adjuvant chemotherapy was analysed with three different cut-off values: within 6 weeks or after more than 6 weeks, within 9 weeks or after more than 9 weeks, and within 12 weeks or after more than 12 weeks. These cut-offs were chosen based on the currently recommended starting point

according to Dutch and ESMO guidelines,[4,5] and on previous literature demonstrating that a clinical impact is found when adjuvant chemotherapy is started later than 7-12 weeks, indicating the importance of initiating adjuvant chemotherapy at least within this time period.[7-12]

Confounders

Potential confounders included in analyses were year of diagnosis, age, WHO performance status,[26] presence of DCIS, histological type, receptor status, tumour stage according to the seventh edition of AJCC,[27] sentinel node biopsy, axillary lymph node dissection (ALND), hospital transfer between site for surgery and that for adjuvant chemotherapy, and annual number of patients operated on for breast cancer at the hospital (hospital volume). Data regarding reconstruction at a later time, rather than IBR, are not registered in the NBCA and could therefore not be included.

Statistical analysis

Statistical differences for all possible confounders between women who had mastectomy alone and those who had mastectomy plus IBR were determined using χ^2tests. All tests were two-sided, and $p<0.050$ was considered statistically significant. Multivariable logistic regression analysis was used to determine the likelihood that women who had undergone IBR received adjuvant chemotherapy within6, 9 and 12 weeks, when adjusted for the confounders. There may, however, be an underlying reason why patient shave IBR, so that not all women are equally likely to receive IBR, for example because of a different type of tumour or age of the patient, introducing a treatment by indication bias. Thus, propensity score matching (PSM) was performed, including all available patient and tumour characteristics to adjust for treatment by indication bias. Use of PSM ensures that patients from both cohorts are matched and have the same likelihood of receiving IBR, given certain patient and tumour characteristics. For each pair, one patient did and one did not undergo IBR; this is essential to estimate the true treatment effect on an out-come in observational studies.[28,29] Statistical analyses were performed with SPSS® version 24 (IBM, Armonk, New York, USA).

Results

In the selected time interval, 6,300 women were diagnosed with invasive breast cancer and met the eligibility criteria. Of these, 4,600 patients (73.0%) underwent mastectomy

alone and 1,700 patients (27.0%) had postmastectomy IBR. Of the women who had IBR, 91.2% had received an implant-based reconstruction (including tissue expanders).The proportion of women who had postmastectomy IBR decreased with patient age and increased over time (Figure 4.1).Patients who underwent IBR were younger at diagnosis, more often had a WHO status of 0, or were diagnosed with no special type of histology, DCIS component and tumour stage I than women who had mastectomy alone (Table 4.1). There was no difference in receptor status or differentiation grade between the two groups. Of women who had postmastectomy IBR, the proportions that underwent sentinel node biopsy, transferred hospital between surgery and adjuvant chemotherapy, or were treated in a hospital with surgical volume exceeding 250 patients annually were also higher compared with those of women who had mastectomy alone. However, the proportion that had ALND was lower in women who underwent postmastectomy IBR (Table 4.1).

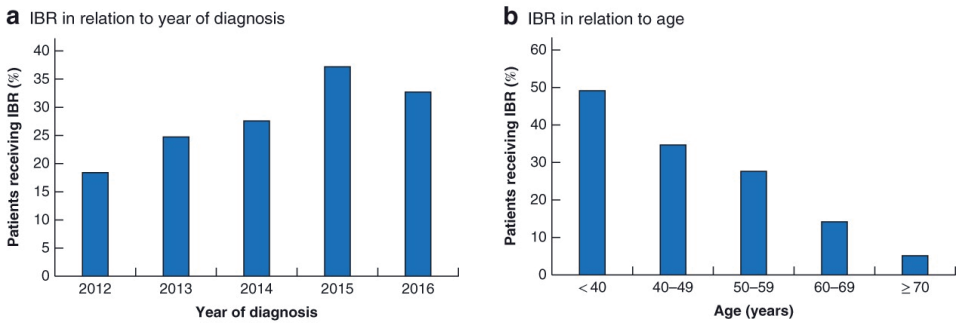

Figure 4.1. Proportion of patients having immediate breast reconstruction in relation to (a) year of diagnosis and (b) age.

Time to adjuvant chemotherapy

The median (i.q.r.) time from surgery to adjuvant chemotherapy in women who had postmastectomy IBR was 36 (29–47) days, compared with 34 (28–44) days in those who had mastectomy alone (Table 4.2). Adjuvant chemotherapy was initiated within 6 weeks in more than two-thirds of patients, and the vast majority received adjuvant chemotherapy within 9 and 12 weeks. The total proportion of patients who received adjuvant chemotherapy within 6, 9 and 12 weeks did not differ over time (2012–2016: p=0.282, p=0.128 and p=0.052 respectively) (Figure 4.2).

Table 4.1. Baseline characteristics of patients who had mastectomy alone or immediate breast reconstruction after mastectomy and received adjuvant chemotherapy.

	Mastectomy alone (n=4,600)	IBR after mastectomy (n=1,700)	p-value*
Year of diagnosis			<0.001
2012	1,282 (27.9)	290 (17.1)	
2013	1,113 (23.4)	365 (21.5)	
2014	987 (21.5)	378 (22.2)	
2015	690 (15.0)	411 (24.2)	
2016	528 (11.5)	256 (15.1)	
Age (years)			<0.001
<40	304 (6.6)	295 (17.4)	
40-49	1,081 (23.5)	578 (34.0)	
50-59	1,506 (32.7)	578 (34.0)	
60-69	1,409 (30.6)	233 (13.7)	
≥70	300 (6.5)	16 (0.9)	
WHO performance status			0.001
0	4,126 (89.7)	1572 (92.5)	
1	450 (9.8)	116 (6.8)	
≥2	24 (0.5)	12 (0.7)	
Histology			<0.001
No special type	3,580 (77.8)	1414 (83.2)	
Lobular	731 (15.9)	168 (9.9)	
Both/other	289 (6.3)	118 (6.9)	
DCIS component			<0.001
No	2,241 (48.7)	623 (36.6)	
Yes	2,359 (51.3)	1077 (63.4)	
Receptor status			0.071
Triple negative	695 (15.1)	223 (13.1)	
HER2-neu+	1,053 (22.9)	405 (23.8)	
HR + and HER2 -	2,727 (59.3)	1038 (61.1)	
Unknown	125 (2.7)	34 (2.0)	
Differentiation grade			0.987
Well	431 (9.4)	161 (9.5)	
Moderate	2,136 (46.4)	791 (46.5)	
Poor	2,033 (44.2)	748 (44.0)	
Tumour stage			<0.001
I	1,036 (22.5)	735 (43.2)	
IIa	1,542 (33.5)	632 (37.2)	
IIb	856 (18.6)	200 (11.8)	
III	1,128 (24.5)	128 (7.5)	
IV	38 (0.8)	5 (0.3)	
Sentinel node biopsy			<0.001
No	1,439 (31.3)	131 (7.7)	
Yes	3,161 (68.7)	1569 (92.3)	
ALND			<0.001
No	2,303 (50.1)	1265 (74.4)	
Yes	2,297 (49.9)	435 (25.6)	
Hospital transfer			0.030
No	4,466 (97.1)	1632 (96.0)	
Yes	134 (2.9)	68 (4.0)	
Hospital volume of surgery (no. of patients)			<0.001
1-99	223 (4.8)	29 (1.7)	
100-149	1,036 (22.5)	263 (15.5)	
150-199	978 (21.3)	253 (14.9)	
200-249	478 (10.4)	236 (13.9)	
≥250	1,885 (41.0)	919 (54.1)	

Values in parentheses are percentages. IBR, immediate breast reconstruction; DCIS, ductal carcinoma in situ; HR+, hormone receptor-positive; ALND, axillary lymph node dissection. *χ^2 test.

Table 4.1. (continued)

	Mastectomy alone (n=4,600)	IBR after mastectomy (n=1,700)	p-value*
Hospital volume of surgery (no. of patients)			<0.001
1-99	223 (4.8)	29 (1.7)	
100-149	1,036 (22.5)	263 (15.5)	
150-199	978 (21.3)	253 (14.9)	
200-249	478 (10.4)	236 (13.9)	
≥250	1,885 (41.0)	919 (54.1)	

Values in parentheses are percentages. IBR, immediate breast reconstruction; DCIS, ductal carcinoma in situ; HR+, hormone receptor-positive; ALND, axillary lymph node dissection. *χ^2 test.

Table 4.2. Time from surgery to adjuvant chemotherapy, and proportion of patients receiving adjuvant chemotherapy within 6, 9 and 12 weeks.

	Mastectomy alone (n=4,600)	IBR after mastectomy (n=1,700)
Time from surgery to adjuvant chemotherapy (days)*	34 (28 to 44)	36 (29 to 47)
No. of patients receiving adjuvant chemotherapy		
Within 6 weeks	3,297 (71.7)	1,145 (67.4)
Within 9 weeks	4,304 (93.6)	1,564 (92.0)
Within 12 weeks	4,509 (98.0)	1,669 (98.2)

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). IBR, immediate breast reconstruction.

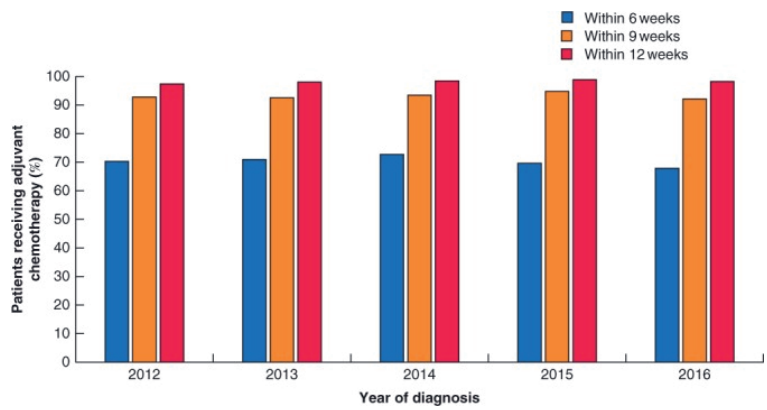

Figure 4.2. Proportion of women receiving adjuvant chemotherapy within 6, 9 and 12 weeks in relation to year of diagnosis.

Unmatched multivariable analyses

Multivariable analysis revealed that patients who had undergone IBR were less likely than those having mastectomy alone to receive adjuvant chemotherapy within6 weeks (odds ratio (OR) 0.76, 95%-CI 0.66-0.87; p<0.001) or 9 weeks (OR 0.69, 95%-CI 0.54-0.87; p=0.002) of surgery (Table 4.3). However, IBR had no association with receiving adjuvant chemotherapy within 12 weeks (OR 0.75, 95%-CI 0.48-1.17; p=0.205).

Table 4.3. Univariable and multivariable analyses without propensity score matching of characteristics associated with time to adjuvant chemotherapy within 6, 9 and 12 weeks.

	No. of patients (n=6,300)*	Time to adjuvant chemotherapy					
		≤6 weeks		≤9 weeks		≤12 weeks	
		OR (univariable)	OR (multivariable)	OR (univariable)	OR (multivariable)	OR (univariable)	OR (multivariable)
IBR after mastectomy							
No	4,600 (73.0)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	1,700 (27.0)	0.82 (0.72-0.92)	0.76 (0.66-0.87)	0.79 (0.64-0.98)	0.69 (0.54-0.87)	1.09 (0·72-1·64)	0.75 (0.48-1.17)
Year of diagnosis							
2012	1,572 (25.0)	1.00 (reference)	-	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
2013	1,478 (23.5)	1.03 (0.88-1.21)	-	0.96 (0.73-1.26)	0.95 (0.72-1.25)	1.28 (0.80-2.05)	1.30 (0.81-2.08)
2014	1,365 (21.7)	1.12 (0.95-1.31)	-	1.11 (0.83-1.48)	1.05 (0.78-1.42)	1.53 (0.92-2.55)	1.50 (0.90-2.50)
2015	1,101 (17.5)	0.99 (0.83-1.17)	-	1.43 (1.03-1.99)	1.47 (1.04-2.07)	2.49 (1.31-4.75)	2.44 (1.26-4.70)
2016	784 (12.4)	0.91 (0.76-1.09)	-	0.94 (0.68-1.31)	0.85 (0.60-1.20)	1.63 (0.87-3.05)	1.52 (0.80-2.89)
Age (years)							
<40	599 (9.5)	1.13 (0.92-1.39)	1.17 (0.94-1.46)	1.17 (0.79-1.72)	1.17 (0.78-1.75)	1.23 (0.56-2.66)	1.28 (0.59-2.79)
40-49	1,659 (26.3)	1.18 (1.02-1.37)	1.20 (1.03-1.40)	1.24 (0.94-1.63)	1.21 (0.92-1.60)	0.93 (0.57-1.54)	0.94 (0.57-1.55)
50-59	2,084 (33.1)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
60-69	1,642 (26.1)	0.78 (0.68-0.93)	0.68 (0.59-0.79)	0.72 (0.56-0.91)	0.64 (0.49-0.82)	0.60 (0.38-0.95)	0.57 (0.36-0.89)
≥70	316 (5.0)	0.71 (0.55-0.91)	0.51 (0.39-0.67)	0.82 (0.53-1.28)	0.62 (0.39-0.99)	0.73 (0.32-1.67)	0.68 (0.30-1.56)
WHO performance status							
0	5,698 (90.4)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	-
1	566 (9.0)	0.62 (0.52-0.74)	0.62 (0.51-0.75)	0.63 (0.47-0.85)	0.63 (0.46-0.85)	0.75 (0.43-1.31)	-
≥2	36 (0.6)	0.44 (0.23-0.86)	0.51 (0.25-1.02)	0.35 (0.14-0.84)	0.39 (0.15-0.98)	0.32 (0.08-1.36)	-
Histology							
No special type	4,994 (79.3)	1.00 (reference)	-	1.00 (reference)	-	1.00 (reference)	-
Lobular	899 (14.3)	0.96 (0.82-1.12)	-	1.04 (0.78-1.38)	-	1.67 (0.89-3.12)	-
Both/other	407 (6.5)	0.86 (0.69-1.06)	-	0.80 (0.55-1.15)	-	0.82 (0.42-1.58)	-
DCIS component							
No	2,864 (45.5)	1.00 (reference)	-	1.00 (reference)	-	1.00 (reference)	-
Yes	3,436 (54.5)	0.99 (0.89-1.11)	-	0.90 (0.74-1.10)	-	0.89 (0.62-1.28)	-
Receptor status							
Triple negative	918 (14.6)	1.34 (1.14-1.58)	1.12 (1.03-1.22)	1.33 (0.99-1.80)	0.96 (0.69-1.35)	0.79 (0.49-1.29)	-
HER2-neu+	1,458 (23.1)	1.34 (1.17-1.53)	1.17 (1.09-1.26)	1.43 (1.11-1.85)	1.19 (0.91-1.57)	1.12 (0.71-1.77)	-
HR + and HER2 -	3,765 (59.8)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	-
Unknown	159 (2.5)	1.50 (1.03-2.17)	1.94 (1.70-2.22)	1.39 (0.70-2.74)	1.51 (0.75-3.06)	1.01 (0.32-3.25)	-

Table 4.3 (continued)

	No. of patients (n=6,300)*	Time to adjuvant chemotherapy					
		≤6 weeks		≤9 weeks		≤12 weeks	
		OR (univariable)	OR (multivariable)	OR (univariable)	OR (multivariable)	OR (univariable)	OR (multivariable)
Receptor status							
Triple negative	918 (14.6)	1.34 (1.14-1.58)	1.12 (1.03-1.22)	1.33 (0.99-1.80)	0.96 (0.69-1.35)	0.79 (0.49-1.29)	-
HER2-neu+	1,458 (23.1)	1.34 (1.17-1.53)	1.17 (1.09-1.26)	1.43 (1.11-1.85)	1.19 (0.91-1.57)	1.12 (0.71-1.77)	-
HR + and HER2 -	3,765 (59.8)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	-
Unknown	159 (2.5)	1.50 (1.03-2.17)	1.94 (1.70-2.22)	1.39 (0.70-2.74)	1.51 (0.75-3.06)	1.01 (0.32-3.25)	-
Differentiation grade							
Well	592 (9.4)	0.70 (0·58-0.84)	0.90 (0.73-1.11)	0.55 (0.40-0.75)	0.68 (0.48-0.96)	0.61 (0.35-1.05)	-
Moderate	2,927 (46.5)	0.83 (0·74-0.93)	0.94 (0.85-1.11)	0.71 (0.57-0.88)	0.81 (0.64-1.03)	1.05 (0.72-1.55)	-
Poor	2,781 (44.1)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	-
Tumour stage							
I	1,771 (28.1)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	-
IIa	2,174 (34.5)	1.08 (0.94-1.24)	1.44 (1.24-1.68)	1.12 (0.87-1.45)	1.51 (1.14-2.00)	1.38 (0.87-2.20)	-
IIb	1,056 (16.8)	0.72 (0.61-0.84)	1.30 (1.06-1.60)	0.73 (0.55-0.97)	1.34 (0.94-1.90)	0.99 (0.58-1.66)	-
III	1,256 (19.9)	1.11 (0.94-1.30)	1.72 (1.37-2.15)	0.90 (0.67-1.19)	1.43 (0.98-2.09)	1.03 (0.63-1.70)	-
IV	43 (0.7)	0.52 (0.28-0.95)	0.65 (0.34-1.25)	2.97 (0.41-21.78)	3.76 (0.50-28.18)	-	-
Sentinel node biopsy							
No	1,570 (24.9)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	-
Yes	4,730 (75.1)	0.51 (0.44-0.58)	0.23 (0.19-0.27)	0.59 (0.46-0.77)	0.33 (0.24-0.45)	0.85 (0.56-1.31)	-
ALND							
No	3,568 (56.6)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	2,732 (43.4)	0.57 (0.51-0.63)	0.23 (0.19-0.27)	0.53 (0.44-0.65)	0.30 (0.23-0.39)	0.56 (0.39-0.81)	0.58 (0.40-0.85)
Hospital transfer							
No	6,098 (96.8)	1.00 (reference)	1.00 (reference)	1.00 (reference)	-	Ref	-
Yes	202 (3.2)	0.55 (0.42-0.73)	0.48 (0.36-0.66)	0.75 (0.45-1.22)	-	0.98 (0.36-2.67)	-
Hospital volume of surgery (no. of patients)							
1-99	252 (4.0)	0.91 (0.67-1.23)	0.94 (0.68-1.30)	1.37 (0.70-2.70)	1.40 (0.70-2.79)	1.37 (0.40-4.65)	-
100-149	1,299 (20.6)	0.88 (0.74-1.04)	0.87 (0.72-1.04)	0.70 (0.51-0.97)	0.71 (0.51-0.99)	0.70 (0.40-1.24)	-
150-199	1,231 (19.5)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	-
200-249	714 (11.3)	0.96 (0.78-1.20)	0.61 (0.76-1.18)	0.68 (0.47-0.98)	0.69 (0.47-1.00)	0.60 (0.32-1.14)	-
≥250	2,804 (44.5)	0.76 (0.66-0.89(	0.75 (0.66-0.87)	0.72 (0.54-0.96)	0.76 (0.57-1.02)	0.91 (0.54-1.54)	-

Values in parentheses are 95 per cent confidence intervals unless indicated otherwise; *values are number (per cent). †Between surgery and adjuvant chemotherapy. IBR, immediate breast reconstruction; DCIS, ductal carcinoma in situ; HR+, hormone receptor-positive; ALND, axillary lymph node dissection.

Although not the focus of this study, analyses of predictive confounders demonstrated that, amongst other factors, patients who had a sentinel node biopsy or ALND were less likely to receive adjuvant chemotherapy within6 and 9 weeks, as well as within 12 weeks for ALND (Table 4.3).

Matched comparison of the two groups

Following PSM of patients with an equal likelihood of receiving IBR based on patient and tumour characteristics, women who had IBR were still less likely to receive adjuvant chemotherapy within 6 weeks (OR 0.95, 95%-CI 0.90-0.99; p=0.035), but not within 9 weeks (OR 0.97, 95%-CI 0.95-1.00; p=0.050) or 12 weeks (OR 1.00, 95%-CI 0.99-1.01; p=0.894).

Discussion

This large population-based study, analysing patients from all hospitals treating breast cancer in the Nether-lands, found that, compared with mastectomy alone, IBR after mastectomy reduced the likelihood of receiving adjuvant chemotherapy within 6 weeks of surgery, as recommended by Dutch and European guidelines,[4-6] but not within 9 or 12 weeks. This suggests that postmastectomy IBR is not necessarily contraindicated inpatients who need adjuvant chemotherapy, because in general IBR does not delay its initiation to a clinically relevant extent.

Previous studies on the impact of IBR on time to adjuvant chemotherapy reported a large variation in time to adjuvant chemotherapy, ranging from 21 to 80 days for those who had mastectomy alone and from 31 to 97 days for patients who received IBR,[30-34] with reported differences between these cohorts of 14–27 days.[24] However, this large variation may have been the result of the small single-centre studies, weak methodology and biases, such as the lack of adjusting for treatment by indication bias. The findings of the present study are not in line with the recently published results from a large multicentre study of Jabo and colleagues in the USA,[35] which suggested that IBR delays time from diagnosis to treatment but not from surgery to adjuvant chemotherapy. This discrepancy may be explained by differences in the statistical approach, as these authors used time as a continuous value, compared with a categorical value in the present study. Moreover, Jabo and co-workers compared time from surgery to adjuvant chemotherapy with non-parametric tests with-out adjusting for confounders,[35] because the latter was not the main focus of their study. It is noteworthy that their reported time from surgery to adjuvant chemotherapy was

considerably longer than that found in the present study, both for patients who had mastectomy alone (40 versus34 days respectively) and those who underwent IBR (42 versus 36 days).[35]

The present study suggests that patients who had sentinel node biopsy or ALND were less likely to receive adjuvant chemotherapy within the predefined cut-off points, confirming the previously reported delaying impact of ALND.[34] In the present study, postoperative complications may have occurred more frequently in patients who under-went ALND combined with postmastectomy IBR, and thereby potentially could have delayed chemotherapy.

Postoperative complications, such as axillary seroma, are common after mastectomy combined with ALND.[36-38] The present study suggests that the associated risk of postoperative complications after sentinel node biopsy and ALND may increase the likelihood of delay. The risk of seroma formation can be reduced by minimizing dead space through quilting sutures or an axillary drain.[39] Complications, and strategies to prevent their occurrence, are not collected in the NBCA database and could therefore not be studied as a potential explanatory factor.

The present study has shown that patients diagnosed with triple-negative breast cancer, human epidermal growth factor receptor 2-positive breast cancer and higher stage disease were more likely to receive adjuvant chemotherapy within 6 weeks. It is reassuring that these tumour characteristics were predictive of timely initiation of adjuvant chemotherapy, as previous studies have shown that delay is of particular relevance in women with these more aggressive types of cancer.[7,10]

It was expected that the impact of IBR on time to adjuvant chemotherapy would change after adjusting for treatment by indication bias, as the present results and a previous Dutch study both showed that patients undergoing IBR differ in many characteristics from those undergoing mastectomy alone.[40]

The majority of patients in the present study underwent a two-stage implant IBR with a tissue expander. This type of IBR is the most common approach in patients eligible for postoperative radiotherapy in most industrialized countries.[41] Despite autologous reconstructions being used increasingly in the last decade,[18] the proportions of different types of IBR were comparable between the predefined cut-off points (data not shown). Nonetheless, the number of women who had IBR using autologous tissue with or without a prosthesis was low (less than 8 per cent), reflecting practice in the past. Therefore, a future study with more patients receiving IBR using autologous tissue could investigate whether this will affect the results.

Patients who changed hospital after surgery were less likely to receive adjuvant chemotherapy within 6 weeks, but not within 9 or 12 weeks. Although this concerned

only 3.2% of all patients, the association corroborates the theory that hospital transfer delays treatment, as shown by previous studies.[34,42,43]

The present results are inconclusive regarding the association between hospital volume and time to adjuvant chemotherapy. On the one hand, higher volume reduced the likelihood of receiving adjuvant chemotherapy within6 weeks, but on the other hand, lower volume reduced the likelihood of receiving adjuvant chemotherapy within9 weeks. A recent study by Schreuder and co-workers demonstrated that hospital volume only partly explains the use of IBR in the Netherlands.[44] Presumably, other hospital related factors such as theatre availability or number of medical specialists have more impact on time to adjuvant chemotherapy after IBR than just hospital volume.

The number of patients aged 70 years or above seems lower in the present study than in previous studies. This might be explained by the fact that adjuvant chemotherapy is used less frequently in these older women in the Netherlands.[45] Furthermore, postmastectomy IBR is used less frequently in this patient group in the Netherlands.[40]

There were several limitations to the present study. First, it was observational, using PSM to adjust for confounding as best as possible. However, matching may be improved by adding other factors potentially associated with delay of adjuvant chemotherapy or the type of surgery (such as radiotherapy, BMI, travel distance). Unfortunately, it was not possible to include these factors as these are not registered in the NBCA database. Insurance coverage was probably not important in the present study, in contrast to studies from the USA, because all Dutch patients are obliged to have basic insurance coverage, providing equal access to breast cancer treatment and breast reconstruction. Second, treatment delay or choice for a specific type of surgery can also be the result of patient preference, such as seeking a second opinion or personal scheduling limitations. Third, this study focused on the time between surgery and initiation of adjuvant chemotherapy, and was therefore not able to assess the potential delaying impact of IBR in the preoperative phase owing to organizational factors such as planning.

The results of the present study in a population-based setting, which were adjusted for confounding and treatment by indication bias, add to the evidence in current literature that IBR is not contraindicated in patients who require a mastectomy and adjuvant chemotherapy, because it does not generally delay time to adjuvant chemotherapy to a clinically relevant extent.

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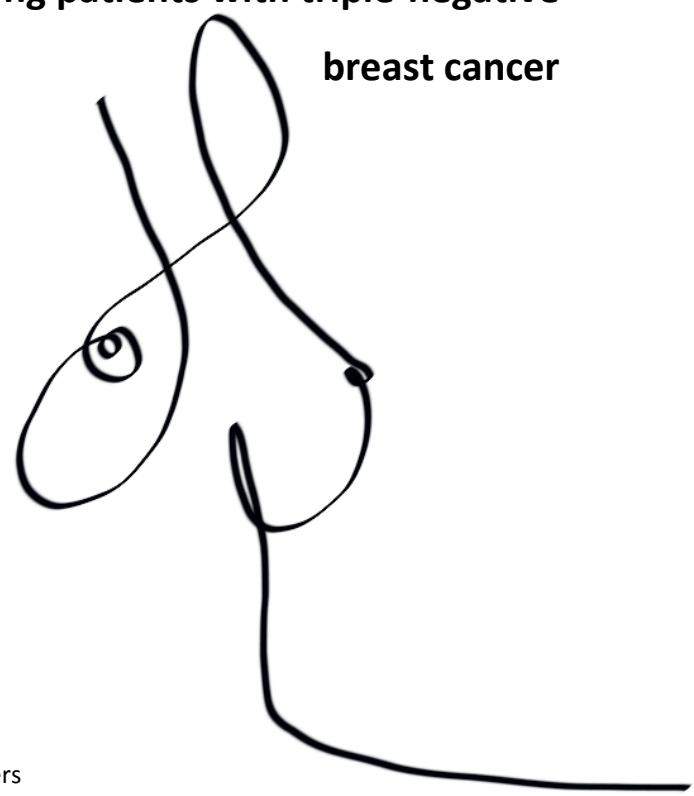
Chapter 5

Association between initiation of adjuvant chemotherapy beyond 30 days after surgery and overall survival among patients with triple-negative breast cancer



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International Journal of Cancer, 2020 Jul 1;147(1):152-159

Abstract

Delayed time to chemotherapy (TTC) is associated with decreased outcomes of breast cancer patients. Recently, studies suggested that the association might be subtype-dependent and that TTC within 30 days should be warranted in patients with triple-negative breast cancer (TNBC). The aim of the current study is to determine if TTC beyond 30 days is associated with reduced 10-year overall survival in TNBC patients. We identified all TNBC patients diagnosed between 2006 and 2014 who received adjuvant chemotherapy in the Netherlands. We distinguished between breast-conserving surgery (BCS) vs. mastectomy given the difference in preoperative characteristics and outcomes. The association was estimated with hazard ratios (HRs) using propensity-score matched Cox proportional hazard analyses. In total, 3,016 patients were included. In matched patients who underwent BCS (n=904), 10-year overall survival was favourable for patients with TTC within 30 days (84.4% vs. 76.9%, p=0.001). Patients with TTC beyond 30 days were more likely than those with TTC within 30 days to die within 10 years after surgery (HR 1.69 (95%-CI 1.22–2.34), p=0.002). In matched patients who underwent mastectomy (n=1,568), there was no difference in 10 years overall survival between those with TTC within or beyond 30 days (74.5% vs. 74.7%, p=0.716), nor an increased risk of death for those with TTC beyond 30 days (HR 1.04 (95%-CI 0.84–1.28), p=0.716). Initiation of adjuvant chemotherapy beyond 30 days is associated with decreased 10 years overall survival in TNBC patients who underwent BCS. Therefore, timelier initiation of chemotherapy in TNBC patients undergoing BCS seems warranted.

Introduction

Breast cancer is the most commonly diagnosed cancer and has the second-highest mortality rate among women.[1] Patients diagnosed with high-risk tumors such as triple-negative breast cancer (TNBC) have an adverse prognosis compared to patients with other subtypes.[2] For these patients, locoregional treatment consists of breast-conserving surgery (BCS) with radiation therapy or mastectomy with or without radiation therapy. Adjuvant chemotherapy is standard of care for patients with TNBC as the treatment reduces the risk on a distant recurrence and improves overall survival.[3-6]
Although an optimal interval from surgery to adjuvant chemotherapy (Time to Chemotherapy, TTC) is not precisely defined, guidelines recommend to initiate chemotherapy within 6–12 weeks after surgery.[7,8] Several studies showed an association between delayed initiation of chemotherapy and worse breast cancer outcomes, though with different cut-off points between 6 and 12 weeks.[9-12] Although patients with TNBC are less likely to have delayed TTC compared to other subtypes,[13-16] between 35% and 74% of patients with TNBC receive adjuvant chemotherapy beyond 30 days after surgery.[9,10,16-18]
In the recent years, several studies have suggested that the impact of TTC on survival might be subtype-dependent and that initiation of adjuvant chemotherapy within 30 days could be warranted particularly in patients with high-risk breast cancer such as TNBC, [9,10,17,18] as this type has a more aggressive biology and rapid proliferation rate compared to other subtypes.[19] However, the current evidence that a TTC within 30 days is warranted in patients with TNBC is based on single-center studies with weak methodology.[11] None of the previous studies stratified analyses for the type of surgery or adjusted for confounding by indication by matching patients on the likelihood to receive adjuvant chemotherapy within 30 days. This latter is crucial as patients with certain baseline characteristics, such as old age, use of breast reconstruction or hospital transfer, do not have the same chance of TTC within 30 days so that it is not clear whether it is the TTC or the underlying indication causing the reduced survival.[9,15,20] Furthermore, it is not always clear if previous studies excluded patients who received adjuvant radiation therapy before chemotherapy.
In the current study, we conducted a propensity score-matched analysis in a prospective, population-based cohort to assess the extent to which TTC beyond 30 days is associated with survival among patients diagnosed with TNBC. To further limit confounding by indication, we focused only on patients who underwent surgery followed by chemotherapy and stratified the analyses by type of surgery.

Methods

Data were anonymously obtained from the Netherlands Cancer Registry (NCR). The NCR is a prospective nationwide register for all malignancies diagnosed in all hospitals in the Netherlands. Based on notification from the Pathology Archive (PALGA) it includes patient, tumor and treatment characteristics, which are registered by trained data managers. Vital status is regularly obtained in the NCR database through linkages with the municipality register. Our study has been approved by the privacy committee of the NCR.

All women diagnosed with Stage I–III TNBC between 2006 and 2014 who underwent breast-conserving surgery (BCS) or a mastectomy were selected. The hormonal receptors were categorized as negative when <10% of tumor cells were positively stained following the Dutch Breast Cancer guidelines. Human Epidermal growth factor Receptor (HER) 2 was defined negative in case of protein overexpression in an immunohistochemistry test or gene amplification in a fluorescence in situ hybridization test. TNBC was defined when estrogen-negative, progesterone-negative and HER2-negative. For the current study, only TNBC patients who received adjuvant chemotherapy were selected. We excluded patients who were treated with radiotherapy before chemotherapy, as the current study focused on impact of delayed TTC and part of the delay could otherwise be due to delay in or recovery from radiotherapy. Furthermore, we excluded patients diagnosed with metachronous primary breast cancers, metastatic disease, treatment with neoadjuvant chemotherapy, unknown date of operation or start of chemotherapy as this makes calculation of TTC impossible. Patients with extreme TTCs beyond 6 months were also excluded as these were most likely data entry errors.

All patients received adjuvant chemotherapy according to the Dutch Breast Cancer Guidelines applicable at that point in time. Alterations to the guidelines were made in 2008 and 2012 which is shown in Supporting Information Table S5.1. Every treatment schedule contained an Anthracycline. Since 2008 additionally a taxane was included for high-risk patients.

Since baseline characteristics and breast cancer outcomes differ between the different types of surgery, patients were categorized into (i) patients who underwent BCS and (ii) patients who underwent mastectomy. The type of surgery was defined by the definitive surgery performed. TTC was defined as the number of days between definitive breast surgery and initiation of adjuvant chemotherapy. Type or moment of axillary surgery was not taken into account. Within each patient group, patients were categorized into two-time interval groups; TTC ≤30 days and TTC >30 days. The primary outcome of our study was 10-year overall survival, which was defined as time from definitive surgery

until last contact, being the date of death or last linkage of the NCR with the municipality register. The last linkage for the current study was on February 1, 2018.
To limit confounding by indication, a propensity score was created for having TTC beyond 30 days using a logistic regression model.[21] The following covariates were included in the propensity score; year of diagnosis, age, socioeconomic status (SES), histological tumor type, differentiation grade, stage, re-excision and change of hospital after surgery. Patients were matched on having the same propensity for TTC > 30 days using a matching ratio of 1:1.[22] The caliper width used in our analyses was 0.2 times the standard deviation of the logit of the propensity score. We checked for possible imbalance in baseline characteristics before and after matching using standardized differences. A standardized difference of a variable of ≥10% indicates an imbalance in baseline characteristics between the time interval groups.[23] Median follow-up was determined using the reverse Kaplan–Meier method.[24] The 10-year overall survival was estimated using the Kaplan–Meier method and compared between the matched time interval groups using the log-rank test. The hazard ratios (HR) with 95% confidence intervals (CIs) for occurrence of death were determined using a Cox regression model in matched patients. We tested the proportionality assumption using log–log plots and Schoenfeld residuals which were all satisfied. To minimize the impact of radiotherapy after chemotherapy, subsequent analyses were conducted with patients who did and did not receive radiation therapy. All analyses were performed in STATA® version 14.2 (StataCorp LLC, College Station, TX).

Data availability

Data can be made available upon reasonable request to the NCR (data application number K18.145).

Results

The analyses included 3,016 patients, of whom 1,079 (35.8%) underwent BCS and 1,937 (64.2%) underwent mastectomy. The mean (standard deviation) age was 51.1 (10.7) and 50.9 (12.4) years at diagnosis for patients who underwent BCS and mastectomy, respectively.
Of the 1,079 patients who underwent BCS before matching, 485 (45.0%) patients received adjuvant chemotherapy ≤30 days and 594 (55.1%) patients >30 days. Before matching, the absolute standardized difference was more than 10% in seven categories of baseline characteristics, suggesting an inadequate balance (Table 5.1). In total, 452

(50.0%) patients with TTC >30 days were successfully matched to 452 (50.0%) patients with TTC ≤30 days. In these patients, absolute standardized differences for the covariates, except the year of inclusion 2010, were <10%, suggesting an overall adequate balance across the two TTC groups. For matched patients who underwent BCS within and beyond 30 days, median (interquartile range) TTC was 26 (22–28) days and 43 (35–72) days, respectively.

Table 5.1. Comparison of baseline characteristics of patients who underwent breast-conserving surgery according to time to chemotherapy ≤30 days and >30 days before and after matching.

	Before matching (n=1079)			After matching (n=904)		
	≤30 days (n=485)	>30 days (n=594)	Standardized difference	≤30 days (n=452)	>30 days (n=452)	Standardized difference
Year of inclusion						
2006	32 (6.6)	51 (8.6)	0.075	31 (6.9)	27 (6.0)	0.036
2007	31 (6.4)	42 (7.1)	0.027	31 (6.9)	36 (8.0)	0.042
2008	55 (11.3)	69 (11.6)	0.009	54 (11.9)	59 (13.1)	0.033
2009	51 (10.5)	71 (12.0)	0.046	51 (11.3)	54 (11.9)	0.021
2010	57 (11.8)	106 (17.9)	0.172	57 (12.6)	37 (8.2)	0.145
2011	68 (14.0)	74 (12.5)	0.046	67 (14.8)	71 (15.7)	0.025
2012	70 (14.4)	69 (11.6)	0.084	63 (13.9)	67 (14.8)	0.025
2013	48 (9.9)	64 (10.8)	0.029	48 (10.6)	54 (11.9)	0.042
2014	73 (15.1)	48 (8.1)	0.219	50 (11.1)	47 (10.4)	0.021
Age (years)						
<40	79 (16.3)	93 (15.7)	0.017	77 (17.0)	78 (17.3)	0.006
40-49	157 (32.4)	147 (24.8)	0.169	138 (30.5)	141 (31.2)	0.014
50-59	134 (27.6)	198 (33.3)	0.124	131 (29.0)	125 (27.7)	0.029
60-69	101 (20.8)	140 (23.6)	0.066	93 (20.6)	94 (20.8)	0.005
≥70	14 (2.9)	16 (2.7)	0.012	13 (2.9)	14 (3.1)	0.013
SES						
Low	149 (30.7)	183 (30.8)	0.002	139 (30.8)	134 (29.6)	0.024
Medium	167 (34.4)	199 (33.5)	0.020	156 (34.5)	157 (34.7)	0.005
High	169 (34.9)	212 (35.7)	0.018	157 (34.7)	161 (35.6)	0.029
Histological tumor type						
Ductal	436 (89.9)	544 (91.6)	0.058	410 (90.7)	407 (90.0)	0.023
Lobular	6 (1.2)	6 (0.8)	0.039	3 (0.7)	4 (0.9)	0.025
Other	43 (8.9)	45 (7.6)	0.047	39 (8.6)	41 (9.1)	0.016
Differentiation grade						
Well	3 (0.6)	6 (1.0)	0.044	3 (0.7)	2 (0.4)	0.030
Intermediate	58 (12.0)	65 (10.9)	0.032	48 (10.6)	53 (11.7)	0.035
Poor	419 (86.4)	505 (85.0)	0.039	396 (87.6)	395 (87.4)	0.007
Unknown	5 (1.0)	18 (3.0)	0.142	5 (1.1)	2 (0.4)	0.076
Stage						
I	136 (28.0)	193 (32.5)	0.096	134 (29.6)	124 (27.4)	0.049
II	286 (59.0)	312 (52.5)	0.130	259 (57.3)	266 (58.8)	0.031
III	63 (13.0)	89 (15.0)	0.058	59 (13.1)	62 (13.7)	0.019
Re-excision	33 (6.8)	27 (4.6)	0.098	22 (4.9)	24 (5.3)	0.020
Change in hospital	154 (31.8)	217 (36.5)	0.101	146 (32.3)	136 (30.1)	0.048

Note: Values are numbers (percentages) unless stated otherwise. Percentages may not add up to exactly 100% as a result of rounding. A standardized difference of a variable of ≥10% is presented in bold. This indicates an imbalance in baseline characteristics between the time interval groups. Abbreviations: SD, standard deviation; SES, socioeconomic status.

Of the 1937 patients who underwent mastectomy, 806 (41.6%) patients received adjuvant chemotherapy ≤30 days and 1,131 (58.4%) patients >30 days after mastectomy. Before matching, patients showed a significant imbalance in four categories of baseline characteristics (Table 5.2).

Table 5.2. Comparison of baseline characteristics of patients who underwent mastectomy according to time from surgery to chemotherapy ≤30 days and >30 days before and after matching. Values are numbers (percentages) unless stated otherwise.

	Before matching (n=1,937)			After matching (n=1,568)		
	≤30 days (n=806)	>30 days (n=1,131)	Standardized difference	≤30 days (n=784)	>30 days (n=784)	Standardized difference
Year of inclusion						
2006	60 (7.4)	83 (7.3)	0.004	60 (7.7)	68 (8.7)	0.037
2007	71 (8.8)	101 (8.9)	0.004	69 (8.8)	77 (9.8)	0.035
2008	66 (8.2)	129 (11.4)	0.108	66 (8.4)	33 (4.2)	0.174
2009	89 (11.0)	144 (12.7)	0.052	89 (11.4)	91 (11.6)	0.008
2010	98 (12.2)	160 (14.1)	0.059	96 (12.2)	87 (11.1)	0.036
2011	118 (14.6)	151 (13.4)	0.037	116 (14.8)	120 (15.3)	0.014
2012	111 (13.8)	148 (13.1)	0.020	109 (13.9)	123 (15.7)	0.050
2013	112 (13.9)	113 (10.0)	0.121	104 (13.3)	104 (13.3)	0.000
2014	81 (10.0)	102 (9.0)	0.035	75 (9.6)	81 (10.3)	0.026
Age (years)						
<40	216 (26.8)	214 (18.9)	0.188	199 (25.4)	206 (26.3)	0.020
40-49	195 (24.2)	277 (24.5)	0.007	193 (24.6)	206 (26.3)	0.038
50-59	196 (24.3)	280 (24.8)	0.010	193 (24.6)	215 (27.4)	0.064
60-69	172 (21.3)	283 (25.0)	0.087	172 (21.9)	153 (19.5)	0.060
≥70	27 (3.3)	77 (6.8)	0.158	27 (3.4)	4 (0.5)	0.212
SES						
low	263 (32.6)	256 (31.5)	0.025	255 (32.5)	262 (33.4)	0.019
medium	276 (34.2)	378 (33.4)	0.017	271 (34.6)	272 (34.7)	0.003
high	267 (33.1)	397 (35.1)	0.042	258 (32.9)	250 (31.9)	0.022
Histological tumor type						
ductal	722 (89.6)	1034 (91.4)	0.063	705 (89.9)	702 (89.5)	0.013
lobular	20 (2.5)	20 (1.8)	0.049	20 (2.6)	18 (2.3)	0.017
other	64 (7.9)	77 (6.8)	0.043	59 (7.5)	64 (8.2)	0.024
Differentiation grade						
well	6 (0.7)	10 (0.9)	0.016	6 (0.8)	4 (0.5)	0.032
intermediate	113 (14.0)	143 (12.6)	0.040	109 (13.9)	118 (15.1)	0.033
poor	672 (83.4)	960 (84.9)	0.041	656 (83.7)	649 (82.8)	0.024
unknown	15 (1.9)	18 (1.6)	0.021	13 (1.7)	13 (1.7)	0.000
Stage						
I	185 (23.0)	307 (27.1)	0.097	182 (23.2)	173 (22.1)	0.027
II	467 (57.9)	616 (54.5)	0.070	453 (57.8)	466 (59.4)	0.034
III	154 (19.1)	208 (18.4)	0.018	149 (19.0)	145 (18.5)	0.013
Re-excision	69 (8.6)	73 (6.5)	0.080	63 (8.0)	67 (8.5)	0.019
Change of hospital	269 (33.4)	413 (36.5)	0.066	267 (34.1)	261 (33.3)	0.016
IBR	93 (11.5)	146 (12.9)	0.042	93 (11.9)	90 (11.5)	0.012

Note: Values are numbers (percentages) unless stated otherwise. Percentages may not add up to exactly 100% as a result of rounding. A standardized difference of a variable of ≥10% is presented in bold. This indicates an imbalance in baseline characteristics between the time interval groups. Abbreviations: IBR, immediate breast reconstruction; SES, socioeconomic status.

In total, 784 (50.0%) patients with TTC >30 days were successfully matched to 784 (50.0%) patients with TTC ≤30 days. After matching, imbalance in two groups remained (year of inclusion 2008 and age beyond 70). For matched patients who underwent mastectomy within and beyond 30 days, median (interquartile range) TTC was 26 (22–28) days and 38 (34–47) days, respectively. All subsequent analyses were performed in the matched patient populations.

Median follow-up was 82.9 (95%-CI 80.5–86.5) and 81.4 (95%-CI 79.5–83.9) months for patients who underwent BCS and mastectomy, respectively. During the study period, 157 (17.2%) of the BCS matched patients died. In these matched patients undergoing BCS, 10-year overall survival was significantly better in patients with TTC ≤30 days compared to patients with TTC >30 days (84.4% [95%-CI 79.7–88.1] vs. 76.9% [95%-CI 72.2–81.0], p=0.001) as shown in Figure 5.1. Patients with TTC >30 days were more likely than those with TTC ≤30 days to die within 10 years after surgery (HR 1.69 (95%-CI 1.22–2.34), p=0.002). During the study period, 349 (22.3%) of the mastectomy matched patients died. In matched patients undergoing mastectomy, 10-year overall survival was similar between patients with TTC ≤30 days and patients with TTC >30 days (74.5% [95%-CI 70.6–77.9] vs. 74.7% [95%-CI 70.9–78.1], p=0.716) as shown in Figure 5.2. Patients with TTC >30 days had the same likelihood as patients with TTC ≤30 days to die within 10 years after surgery (HR 1.04 [95%-CI 0.84–1.28], p=0.716).

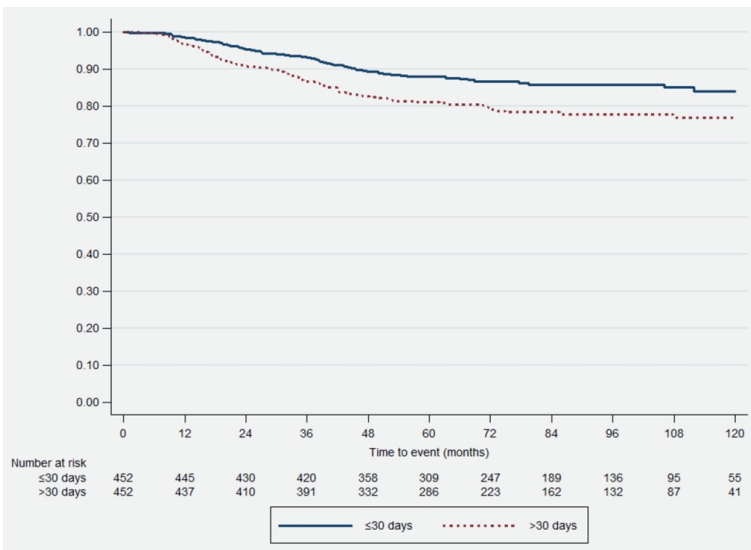

Figure 5.1. Ten-years overall survival for matched patients who underwent breast-conserving surgery with time from surgery to chemotherapy ≤30 days and >30 days.

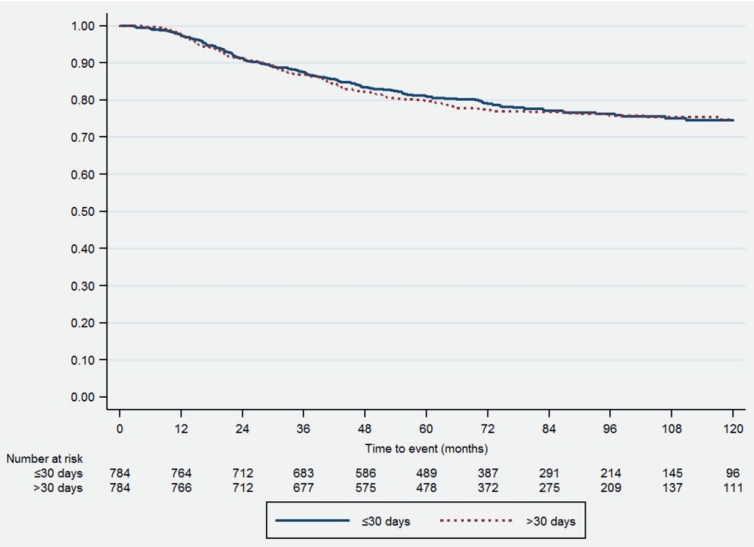

Figure 5.2. Ten-years overall survival for matched patients who underwent mastectomy with time from surgery to chemotherapy ≤30 days and >30 days.

A small number of patients who underwent BCS did not receive radiotherapy after chemotherapy (n=53). To limit the potential impact of the use of radiotherapy after chemotherapy on overall survival, subsequent analyses were performed in BCS matched patients who received radiotherapy (n=880). In this subgroup, the increased likelihood to die within 10 years associated with TTC > 30 days remained (HR 1.58 [95%-CI 1.13–2.22], p=0.008). In patients who underwent mastectomy, 1,461 (75.4%) patients did not receive radiotherapy after chemotherapy. In the subgroup analyses of patients who did not receive radiotherapy (n=1,128), patients with TTC >30 days had a similar 10-year overall survival compared to patients with TTC ≤30 days (HR 1.10 [95%-CI 0.83–1.47], p=0.500). The same was found in matched patients who did receive radiotherapy after chemotherapy (n=342, HR 0.98 [95%-CI 0.70–1.39], p=0.930).

Discussion

In this population-based cohort study, we demonstrated that in propensity-score matched patients diagnosed with TNBC who underwent BCS with TTC beyond 30 days was associated with a significantly increased risk of death compared to those with a TTC within 30 days, while a TTC beyond 30 days had no impact on survival for patients

undergoing a mastectomy. Furthermore, we demonstrated that this association was independent of the use of adjuvant radiotherapy after chemotherapy. These results suggest timelier initiation of chemotherapy in TNBC patients is warranted after BCS, which is relevant because previous studies showed delay beyond 30 days to occur in a substantial proportion of these patients.

Even though current literature does not clearly state the optimal timing for adjuvant chemotherapy for all patients, consensus exists on a more aggressive treatment for TNBC as it has a more aggressive biology and rapid proliferation rate compared to other subtypes.[4,8,19] Therefore, it makes sense that timely adjuvant chemotherapy is particularly relevant for these patients. Adjuvant chemotherapy improves breast cancer outcomes especially by the cytotoxic effects on micrometastases. Possible explanations for the decrease in overall survival in patients with delayed TTC include increased angiogenesis in the tumor and growth of distant micrometastases, given that TNBC is characterized by rapid growth which is now given more time due to delay in TTC.[19] The current study adds to the current evidence that the association is only present in patients who underwent BCS and not in those who underwent mastectomy, as previous studies did not stratify analyses for type of surgery.[11] It is possible that the impact on survival after BCS is due to patient selection. Patients preference for BCS and less significant surgery can be related to comorbidity or frailty as well as be the reason for delayed TTC, which independently may impact patients' survival.[25] This might also explain a smaller impact on survival in patients who underwent mastectomy as these patients are known to have more comorbidities compared to those who underwent BCS.[25] Unfortunately, comorbidities and frailty measures are not registered in the NCR-database and could therefore not be included in the current study.

Another explanation for the different association of TTC and overall survival between the two surgical procedures may be found in the different range of TTC among patients who underwent BCS with TTC beyond 30 days (median 43 days, interquartile range 35-72 days) compared to those who underwent mastectomy with TTC beyond 30 days (median 38 days, interquartile range 34–47 days). However, subsequent multivariable analyses categorizing patients into three-time interval groups showed that both patients who underwent mastectomy with TTC between 31 and 60 days and beyond 60 days had a similar survival compared to those with TTC within 30 days (data not shown), despite the small number of patients with TTC beyond 60 days (n = 121).

Most previous studies reported an association between delayed TTC in TNBC patients and adverse outcomes.[11] Two studies reported an average 26% significantly increased risk of death in patients with TNBC who have TTC between 31 and 60 days compared to those with TCC within 30 days.[9,10] More recently, Yu et al. reported in a subgroup analyses (n=270) that TNBC patients who had TTC beyond 8 weeks have a worse OS

(HR 2.55, 95%-CI 1.25–5.18).[18] Unfortunately, these three studies did not stratify analyses for the type of definitive surgery nor performed subgroup analyses for use of radiotherapy. The observed association in these three studies might thus be biased due to difference in prognosis between provided treatment or due to insufficiently adjusting for unbalanced baseline characteristics. In the current study, an imbalance in baseline characteristics was seen before matching between patients who received adjuvant chemotherapy within and beyond 30 days. These characteristics could also be underlying indications for timelier initiation of chemotherapy. Poor prognostic characteristics such as older age, higher differentiation grade, triple-negative receptor status and lymph node involvement are associated with reduced TTC in many previous studies, despite using different time thresholds. Since these poor prognostic characteristics influence both the indication for timelier initiation as well as the outcome, estimating a reliable effect of TTC on survival as performed in our study demanded adjustment for this confounding by indication. Still, we cannot rule out residual confounding by unmeasured factors (i.e., comorbidity of dose-intensity of chemotherapy).

In contrast with the previously mentioned studies, a recent propensity score-matched single-center study in 724 TNBC patients observed no difference in disease-free survival and overall survival between patients who had TTC within 30, 32–42, 43–56 or beyond 56 days.[26] The difference in results with the current study might be due to the smaller sample size or absence of stratified analyses for type of surgery. Moreover, the single-center setting decreases the generalizability of the former results due to local clinical practice.

Most previous studies did not specify if adjuvant chemotherapy was initiated before or after radiotherapy.[11] The exclusion of patients who received radiotherapy before chemotherapy in the current study is essential to obtain reliable results, as there is a significant difference in baseline characteristics and breast cancer outcomes between those who receive chemotherapy before or after radiotherapy.[27]

In high-income countries, today's tendency is to give chemotherapy in the neoadjuvant setting, thus before surgery, specifically for patients with locally advanced breast cancer aged <70 years.[28] For our study, the number of neoadjuvant treated patients was too low and follow-up since introduction in the Netherlands was too short to make reliable conclusions. In future research, it would be interesting to evaluate the impact of time to treatment on survival in patients with TNBC.

Our study has several limitations. First, we could only adjust for confounding by indication of measured and known variables, but several unknown as well as unmeasured confounders could influence the outcomes. For instance, the absence of information regarding the reason for the delayed TTC limits the interpretation of the

association. There are several valid reasons that could delay TTC rather than being poor quality of delivered care which are associated with worse overall survival, such as complications due to the surgery, poor physical health, ECOG performance status or comorbidities that do not allow timelier initiation of chemotherapy. This information is not registered in the NCR database and could therefore not be included in our analyses, but might influence results if distributed differently between patient groups or time intervals. Comorbidity was only registered for a small percentage of the current population that this factor, unfortunately, could not be analyzed. Second, the results of the current study need to be evaluated in a large cohort including additional information regarding the chemotherapy type, dose, number of cycles and rate of completion as these are known to influence survival. This information was not included in the current overall analyses, as the type of chemotherapy is considered incomplete in the NCR before 2011. Nonetheless, analysis of a subgroup of patients treated between 2011 and 2014 while adjusting for type of chemotherapy (anthracycline, taxanes or a combination of both; data not shown), both for patients who underwent BCS and mastectomy, revealed similar results even despite the short follow-up. A strength of the present study is both its sample size, stratified analyses by type of surgery and strong methodology to reduce confounding by indication given the impossibility to randomize patients by TTC.

Conclusions

The current results suggest that the initiation of chemotherapy beyond 30 days is associated with decreased overall survival in TNBC patients who underwent BCS. However, no association was observed for those who underwent mastectomy. These results suggest timelier initiation of chemotherapy in TNBC patients is warranted after BCS.

Acknowledgements

We thank The Netherlands Cancer Registry for providing the data, as well as the registration clerks for their effort in gathering the data in the Netherlands Cancer Registry.

Supporting information

Table S5.1. Dose and intensity schedule of chemotherapy for patients diagnosed with triple-negative breast cancer according to the Dutch Breast Cancer Treatment guidelines between 2004 and 2014.

Time period	Chemotherapy schedule	Dose of cytostatic	Interval
From 2004	6 x TAC	docetaxel $_{75mg/m2}$	Every 3 weeks
		adriamycine $_{50mg/m2}$	
		cyclophosphamide $_{500mg/m2}$	
	6 x ddAC/AC	adriamycine $_{60mg/m2}$	Every 2 weeks
		cyclophosphamide $_{600mg/m2}$	
	6 x FEC	5-fluoruacil $_{600mg/m2}$	Every 3 weeks
		epirubicine $_{100mg/m2}$	
		cyclophosphamide $_{600mg/m2}$	
	6 x CAF	cyclophosphamide $_{500mg/m2}$	Every 3 weeks
		adriamycine $_{50mg/m2}$	
		5-Fluoruacil $_{600mg/m2}$	
	5 x FEC	5-Fluoruacil $_{600mg/m2}$	Every 3 weeks
		epirubicine $_{120mg/m2}$	
		cyclophosphamide $_{600mg/m2}$	
	5 x CAF	cyclophosphamide $_{500mg/m2}$	Every 3 weeks
		adriamycine $_{50mg/m2}$	
		5-fluoruacil $_{500mg/m2}$	
From 2008	3 x FEC and	3 x FEC $_{100mg/m2}$	Every 3 weeks followed by
	3 x Docetaxel	3 × docetaxel $_{100mg/m2}$	Every 3 weeks
	4 x AC and	adriamycine $_{60mg/m2}$	Every 3 weeks followed by
	4 x Paclitaxel	cyclophosphamide $_{600mg/m2}$	
		paclitaxel $_{175mg/m2}$	Every 3 weeks
From 2012	4 x ddAC and	adriamycine $_{60mg/m2}$	Every 2 weeks followed by
	12 x Paclitaxel	cyclophosphamide $_{600mg/m2}$	
		paclitaxel$_{80mg/m2}$	Every week

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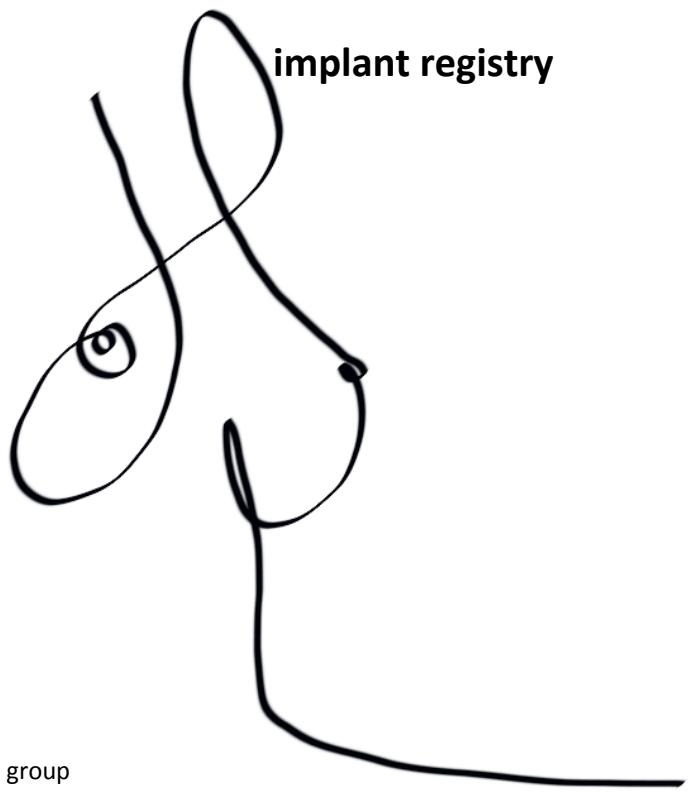
Part III

Quality assessment of breast reconstruction strategies

Chapter 6

Revision incidence after immediate direct-to-implant versus two-stage implant-based breast reconstruction: results from a nationwide breast implant registry



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Abstract

Background

In immediate implant-based breast reconstruction (IBBR), large variation is observed in current practices between a direct-to-implant or two-stage approach. This population-based study aimed to compare unplanned short- and long-term revision incidence between direct-to-implant and two-stage IBBR in the Netherlands.

Methods

All patients with immediate IBBR following a mastectomy between 2015 and 2019 were selected from the nationwide Dutch Breast Implant Registry (DBIR). Short- and long-term unplanned revision incidence was studied per immediate IBBR, including revision indications, and total number of additional operations. Confounding by indication was limited using propensity score matching.

Results

A total of 4,938 breast implants (4,321 women) were included, of which 2,350 (48%) for direct-to-implant IBBR and 2,588 (52%) for two-stage IBBR. Median (i.q.r) follow-up was 30 (15-45) months and 32 (20-47) months, respectively. Short-term revision incidence was 4.2% and 11.7%, respectively (conditional OR 0.32, 95%-CI 0.25-0.43). Long-term revision incidence was 10.8% (95%-CI 9.4-12.1) and 16.3% (95%-CI 14.8-17.7), respectively. In the propensity score matched cohort, similar results were found. In the direct-to-implant group, more breasts were reconstructed within the planned number of operations than in the two-stage group.

Conclusion

Unplanned revision surgery occurred less often after direct-to-implant IBBR, and more breasts were reconstructed within the planned number of operations compared to two-stage IBBR. These results, based on real-world data, are important for improving patient counselling and shared decision-making.

Introduction

Immediate postmastectomy breast reconstruction is becoming increasingly popular, with up to 50% of mastectomy patients undergoing this type of reconstruction in current practice.[1,2] Although autologous techniques are increasingly being used, immediate implant-based breast reconstruction (IBBR) is still most often performed (70-90%).[1-5] Immediate IBBR can be achieved either using a one-stage direct-to-implant approach or a two-stage technique with a tissue expander (TE), which is replaced by a definite breast implant during a second surgery.

There is an ongoing debate about the differences in complications and cosmetic outcomes between direct-to-implant and two-stage breast reconstruction, as direct comparisons in randomized controlled trials (RCTs) have not been performed.[6-9] Possible advantages of direct-to-implant IBBR include fewer outpatient clinic visits and fewer surgeries, expected lower overall costs, and a quicker return to the patient's social and working life.[10,11] Possible disadvantages are difficulties in using implant sizes larger than the original breast(s), higher probability of asymmetry, and the potentially higher risk of adverse events, especially if ADMs or meshes are used.[12,13]

The latest evidence-based Dutch guideline for breast reconstruction from 2015 states that it is difficult to make evidence-based recommendations due to a lack of high-quality evidence.[14] This lack of high-quality evidence may contribute to unwanted variation in current practices among healthcare providers. These arguments emphasize the need for a better understanding of the differences in risks and outcomes to improve patient counselling and quality of care. Therefore, this study aimed to compare revision incidence, revision indications, and the additional number of operations per breast between direct-to-implant and two-stage IBBR in a nationwide, population-based cohort using the Dutch Breast Implant registry (DBIR).

Methods

Design and study population

This observational cohort study included all women who had been prospectively registered in the DBIR after undergoing a direct-to-implant or two-stage immediate IBBR between January 1, 2015, and December 31, 2019. Indications for an immediate IBBR were mastectomy for breast cancer or prophylactic mastectomy.

Patients who had undergone reconstruction for a benign condition, who had received any previous breast implant surgery, and in whom additional surgical techniques (fat

grafting or mastopexy) had been used during implant insertion, were excluded from analysis.
Of the women with a two-stage IBBR, information on both the first stage (tissue expander insertion) and second stage (tissue expander exchange for permanent breast implant) was necessary for inclusion.

Data collection: the Dutch Breast Implant Registry

The DBIR is a nationwide, population-based registry. Since 2015, patient, surgery, and implant characteristics are prospectively collected of all patients undergoing breast implant surgery in the Netherlands for breast reconstruction or breast augmentation. More details about the registry have been described previously.[1,15,16] Currently, 100% (n=74) of the hospitals and 95% (n=37) of the private clinics where breast implant surgery is being performed are included in DBIR. For the current study, the last data update was on May 8th, 2020.

Definitions

Direct-to-implant IBBR was defined as the insertion of a permanent breast implant during the same operation as the mastectomy. Two-stage IBBR was defined as the insertion of a tissue expander (TE) during the same operation as the mastectomy, followed by a second operation in which a permanent breast implant replaced the TE.
Completion of each reconstruction trajectory was defined as the moment a permanent breast implant was inserted. The reconstruction trajectory of a two-stage IBBR was defined as the time between mastectomy with immediate TE insertion and TE replacement with a permanent breast implant. Revision surgery was defined as the first unplanned reoperation after insertion, in which the breast implant or TE was repositioned, explanted or replaced. Indications for an unplanned revision were mastectomy skin flap necrosis, skin scarring problems, autologous flap problems, deep wound infections, seroma or hematoma, capsular contracture, newly diagnosed breast cancer, BIA-ALCL, breast pain, asymmetry, dissatisfaction with volume, patient-requested implant removal due to nonspecific health symptoms, device malposition, and device rupture or deflation.
Exact definitions of all patient, surgery, revision, and implant variables used for analysis can be found in the DBIR Data Dictionary (Appendix S6.1, supporting information).

Outcome measures

The primary outcome was the short-term revision incidence of both IBBR techniques during the time from mastectomy until 60 days after the last planned surgery in each reconstruction trajectory (Figure 6.1). A time interval of 60 days was chosen because a substantial amount of complications in breast implant surgery occur after 30 days.[17,18] Subsequently, the long-term cumulative revision incidence within two years after mastectomy, revision indications, and the total number of additional operations per breast were evaluated for both IBBR techniques. Potential confounding factors were identified based on existing literature and clinical rationale. A Directed Acyclic Graph (DAG) was used to visualize this process before performing analyses.[19]

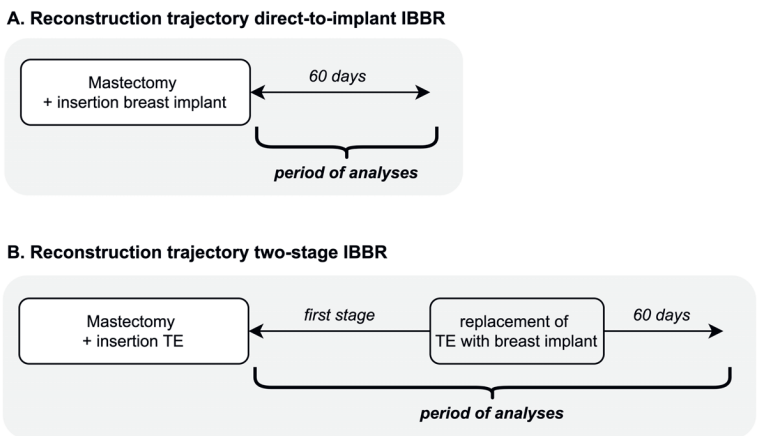

Figure 6.1. Schematic view of the two analyzed reconstruction trajectories: from mastectomy and immediate IBBR until 60 days after completion of the reconstruction

Statistical analysis

All analyses were performed with the implant as the unit of analysis, using R software, version 1·2·5019-©2009-2019, RStudio, Inc. Missing data patterns were evaluated, resulting in the assumption of data being missing at random. Multiple imputation by chained equations was performed ('mice' package, version 3.6.0).[20,21] The outcome variable itself was not imputed. Statistical models were fitted and results were pooled following Rubin's rules.[22] See Table S6.1 in the supporting information for non-imputed data.

Baseline characteristics were compared between groups using Student's t-tests, Mann Whitney U tests, χ^2 tests or Fisher's exact tests accordingly. Two-sided $p<0.050$ was considered statistically significant.

To assess the likelihood of short-term revision, multivariable logistic regression analyses were performed ('stats' package, version 3.6.1). Subsequently, to account for clustering of patients and implants within healthcare institutions which were likely to be correlated with practices performed, a conditional OR with 95%-CI was calculated using a mixed-effects logistic regression model ('lme4' package, version 1·1-21). In this mixed-effects model, confounding factors that were distributed differently between the revision and no-revision groups were entered as fixed effects and healthcare institutions were included as random intercepts.

The crude, long-term cumulative revision incidence was calculated using Nelson-Aalen estimates. Implants without any revision at closure of the dataset on May 8, 2020, were censored. After reassuring the proportional hazard assumption was met, a hazard ratio (HR) was calculated using a Cox proportional hazards model. The total number of additional surgeries was calculated per reconstruction trajectory per breast.

Sensitivity analysis

Two sensitivity analyses were performed. First, the E-value was calculated ('EValue' package, version 2.0.0). An E-value assesses the minimum strength an unmeasured confounding factor must have, to negate the observed treatment-outcome association.[23] Second, propensity score matching (PSM) was used to assess the likelihood of short- and long-term revision while limiting potential confounding by indication.[24,25] A logistic regression model was used to calculate the propensity score for undergoing direct-to-implant IBBR using all preoperative covariates: age, ASA classification, BMI, smoking status, previous radiotherapy, postoperative radiotherapy planned, year of surgery, healthcare institution, healthcare institution volume, reconstruction indication, and laterality. In the PSM analyses, records with any missing preoperative characteristic were excluded. Matching was performed using a 1:1 ratio with a calliper width of 0·2 times the standard deviation of the logit ('MatchIt' package, version 3.0.2). Potential imbalances before and after matching were assessed using standardized mean differences (s.m.d.).[26] A baseline characteristic with an s.m.d. of 10% or more indicates an imbalance between the direct-to-implant and two-stage group.

Results

A total of 4,321 patients and 4,938 breast implants met the inclusion criteria (Figure S6.1, supporting information), of whom 4,064 patients (94.1%) underwent immediate IBBR after mastectomy for breast cancer and 257 (5.9%) after prophylactic mastectomy. These reconstructions were performed in 76 healthcare institutions with a mean volume per institution of 110 (range 13-546) breast implant surgeries per year.
A total of 2,350 (47.6%) breast implants were inserted for a direct-to-implant IBBR, and 2,588 (52.4%) TE's were inserted for a two-stage IBBR. Direct-to-implant IBBR was more frequently performed in younger, non-smoking patients, if postoperative radiotherapy was planned, in case of nipple-sparing surgery, the use of ADM/mesh, and autologous flap cover. Furthermore, direct-to-implant IBBR was more frequently registered in more recent years, and in healthcare institutions with a volume of >200 implant surgeries per year (Table S6.2, supporting information).

Short-term revision incidence

Of 2,350 breast implants inserted during direct-to-implant IBBR, 99 (4.2%) underwent unplanned revision surgery within 60 days after completion of the reconstruction trajectory. Of 2588 breasts that underwent two-stage IBBR, 302 (11.7%) had an unplanned revision within 60 days after completion of the entire reconstruction trajectory. The majority of these unplanned revisions occurred during the first stage of two-stage reconstruction (n=279) (Figure 6.2).
Revision surgery was more frequently observed after two-stage IBBR, in patients with higher age, ASA classification, and BMI, in patients who smoked, in middle-volume healthcare institutions (50-200 implant surgeries per year), and after non-nipple sparing surgery (Table 6.1). Compared with a two-stage procedure, implants inserted during a direct-to-implant procedure had a lower likelihood of short-term revision surgery (unadjusted OR 0.33, 95%-CI 0.26-0.42; adjusted OR 0.28, 95%-CI 0.22-0.36; conditional OR 0.32, 95%-CI 0.25-0.43) (Table 6.2).

Long-term revision incidence

The median (i.q.r.) follow-up time was 30 (15-45) months in the direct-to-implant group and 32 (20-47) months in the two-stage group. After direct-to-implant IBBR, the crude cumulative unplanned revision incidence within two years was 10.8% (n=251, 95%-CI 9.4-12.1). Within the two-stage group, this was 16.3% (n=443, 95%-ci 14.8-17.7) (Figure 6.3A). A hazard ratio could not be calculated, because the proportional hazard assumption was not met. Differences in baseline characteristics between the groups

with and without long-term revision surgery were the same differences as seen between the groups with and without short-term revision surgery.

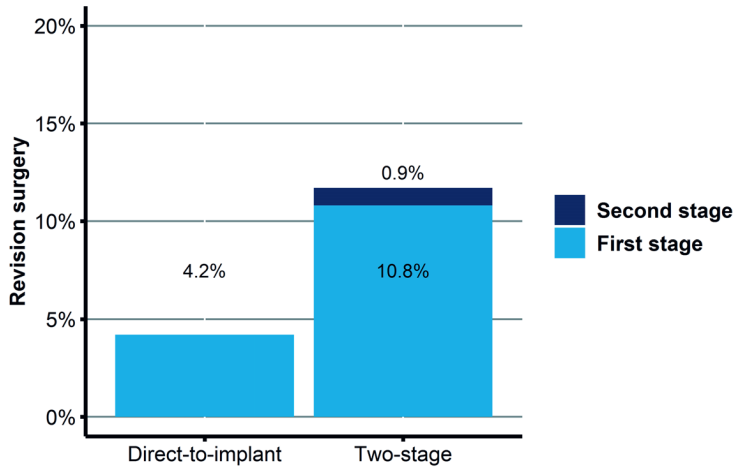

Figure 6.2. Short-term (≤60 days) revision incidence per breast reconstruction trajectory.

Revision indications

Within 60 days after direct-to-implant IBBR, most frequently registered revision indications were mastectomy skin flap necrosis, deep wound infections, and autologous flap problems (Table 6.3). After 60 days, asymmetry, dissatisfaction with volume, and breast pain were most frequently observed.

During the complete first stage of a two-stage IBBR, revision surgery was mostly performed for deep wound infections, seroma or hematoma, mastectomy skin flap necrosis, and device rupture or deflation. Within 60 days of the second stage of two-stage IBBR, the majority of revisions was for seroma or hematoma, deep wound infections, and skin scarring problems. Over the longer term, asymmetry, breast pain, capsular contracture, and dissatisfaction with volume were mostly observed.

Very few implants were removed on patients' request due to nonspecific health symptoms. No implant removals for BIA-ALCL were registered.

Table 6.1. Patient and surgery factors at time of mastectomy and immediate IBBR, per group with and without short-term (≤60 days) revision surgery after completion of the reconstruction trajectory

	Total group (n=4938)	No short-term revision (n=4537)	Short-term revision (n=401)	p-value
Intervention of interest				
Type of IBBR				<0·001
Direct-to-implant	2350 (47·6)	2251 (49·6)	99 (24·7)	
Two-stage	2588 (52·4)	2286 (50·4)	302 (75·3)	
Patient characteristics				
Age (years, s.d.)	49·3 (11·4)	49·1 (11·4)	51·1 (10·6)	0·001
ASA classification				<0·001
I	3092 (62·6)	2896 (63·8)	196 (48·9)	
II	1695 (34·3)	1510 (33·3)	185 (46·1)	
III+	151 (3·1)	131 (2·9)	20 (5·0)	
Body Mass Index (kg/m^2, i.q.r.)	23·0 (20·7-26·1)	22·9 (20·7-25·9)	24·5 (22·2-28·2)	<0·001
Smoking status				<0·001
Not smoking	4293 (86·9)	3970 (87·5)	323 (80·5)	
Smoking	645 (13·1)	567 (12·5)	78 (19·5)	
Previous radiotherapy				0·354
No	4605 (93·3)	4236 (93·4)	369 (92·0)	
Yes	333 (6·7)	301 (6·6)	32 (8·0)	
Surgery characteristics				
Healthcare institution volume (per year)				0·001
<50 implant surgeries	569 (11·5)	523 (11·5)	46 (11·5)	
50-99 implant surgeries	900 (18·2)	804 (17·7)	96 (23·9)	
100-200 implant surgeries	1989 (40·3)	1819 (40·1)	170 (42·4)	
>200 implant surgeries	1480 (30·0)	1391 (30·7)	89 (22·2)	
Reconstruction indication				1·000
Breast cancer	4488 (90·9)	4124 (90·9)	364 (90·8)	
Prophylactic mastectomy	450 (9·1)	413 (9·1)	37 (9·2)	
Laterality				0·220
Unilateral	3230 (65·4)	2956 (65·2)	274 (68·3)	
Bilateral	1708 (34·6)	1581 (34·8)	127 (31·7)	
Incision site				0·040
Nipple sparing	1132 (22·9)	1058 (23·3)	74 (18·5)	
Non-nipple sparing	3470 (70·3)	3166 (69·8)	304 (75·8)	
Other	336 (6·8)	313 (6·9)	23 (5·7)	
Plane				0·003
Sub flap	234 (4·7)	220 (4·8)	14 (3·5)	
Completely covered with PM muscle	2598 (52·6)	2408 (53·1)	190 (47·4)	
Partially covered with PM muscle	1931 (39·2)	1759 (38·8)	172 (42·9)	
Other	175 (3·5)	150 (3·3)	25 (6·2)	
Number of applied ICMs during implant insertion				0·050
<4	947 (19·2)	879 (19·4)	68 (17·0)	
4	1742 (35·3)	1615 (35·6)	127 (31·7)	
>4	2249 (45·5)	2034 (45·0)	206 (51·3)	
ADM/Mesh				0·105
No	4448 (90·1)	4077 (89·9)	371 (92·5)	
Yes	490 (9·9)	460 (10·1)	30 (7·5)	
Autologous flap cover				0·291
No	43659 (88·3)	3998 (88·1)	361 (90·0)	
Yes	579 (11·7)	539 (11·9)	40 (10·0)	

Values in parentheses are percentages, unless indicated otherwise. IBBR, implant-based breast reconstruction; s.d., standard deviation; ASA, American society of anesthesiologists; i.q.r, interquartile range; PM, pectoralis major; ICMs, infection control measures; ADM, acellular dermal matrix.

Table 2. Likelihood of short-term revision surgery after completion of the reconstruction trajectory

Direct-to-implant IBBR (n=2,350 implants) Two-stage IBBR (n=2,588 implants)	**OR**
Unadjusted (univariable logistic regression model)	
Two-stage	1 (reference)
Direct-to-implant	0·33 (0·26-0·42)
Adjusted (multivariable logistic regression model)	
Age	0·34 (0·27-0·43)
Age & ASA	0·33 (0·26-0·42)
Age, ASA, & BMI	0·33 (0·26-0·42)
Age, ASA, BMI & smoking	0·34 (0·27-0·43)
Age, ASA, BMI, smoking & institution volume	0·34 (0·27-0·44)
Age, ASA, BMI, smoking, institution volume & incision site	0·34 (0·27-0·43)
Age, ASA, BMI, smoking, institution volume, incision site & plane	0·28 (0·22-0·37)
Age, ASA, BMI, smoking, institution volume, incision site, plane & number of applied ICMs	0·28 (0·22-0·36)
Conditional (mixed-effects logistic regression model)	
Age, ASA, BMI, smoking, institution volume, incision site, plane, number of applied ICMs & healthcare institution*	0·32 (0·25-0·43)

Values in parentheses are 95%-CI. *The conditional OR was obtained by entering age, ASA classification, BMI, smoking, institution volume, incision site, plane, and number of applied ICMs as fixed effects into the model, and healthcare institution as random effect. IBBR, implant-based breast reconstruction; ASA, American society of anesthesiologists' classification; BMI, body mass index; ICMs, infection control measures.

Additional operations

During the follow-up period, 2,099 of 2,350 breasts (89.3%) in the direct-to-implant IBBR cohort were reconstructed within one operation. Eighty-three breasts (3.5%) needed one, 125 (5.3%) two, and 43 (1.8%) three or more additional operations.
In the two-stage IBBR group, 2,155 of 2,588 breasts (83.3%) were reconstructed within the planned two procedures. Hundred eighty-one breasts (7.0%) needed one, 82 (3.2%) two, and 82 (3.2%) three or more additional operations. Eighty-eight breasts (3.4%) needed revision surgery right after TE insertion and did not reach the second stage within the median follow-up.

Sensitivity analysis

For the conditional OR of short-term revision surgery, the E-value was 5.7. This indicates that residual confounding could explain the observed association if an unidentified confounding factor exists with a relative risk association of at least 5·7. The E-value for the adjusted HR of long-term revision surgery could not be calculated because the proportional hazard assumption was not met.
After limiting confounding by indication using propensity score matching, 381 (50.0%) direct-to-implant records were matched to 381 (50.0%) two-stage IBBRs. While before matching, an imbalance in preoperative baseline characteristics was observed, no imbalances were observed after matching (Table S6.3, supporting information). In the

matched cohort (n=762), implants inserted during direct-to-implant IBBR had a lower conditional likelihood of short-term revision compared to a two-stage procedure (conditional OR 0.33, 95%-CI 0.20-0.53). For the long-term, the crude cumulative revision incidence was 14.3% (95%-CI 10.3-18.1) after direct-to-implant IBBR and 22.7% (95%-CI 17.8-27.2) after a two-stage procedure (non-proportional hazards) (Figure 6.3B).

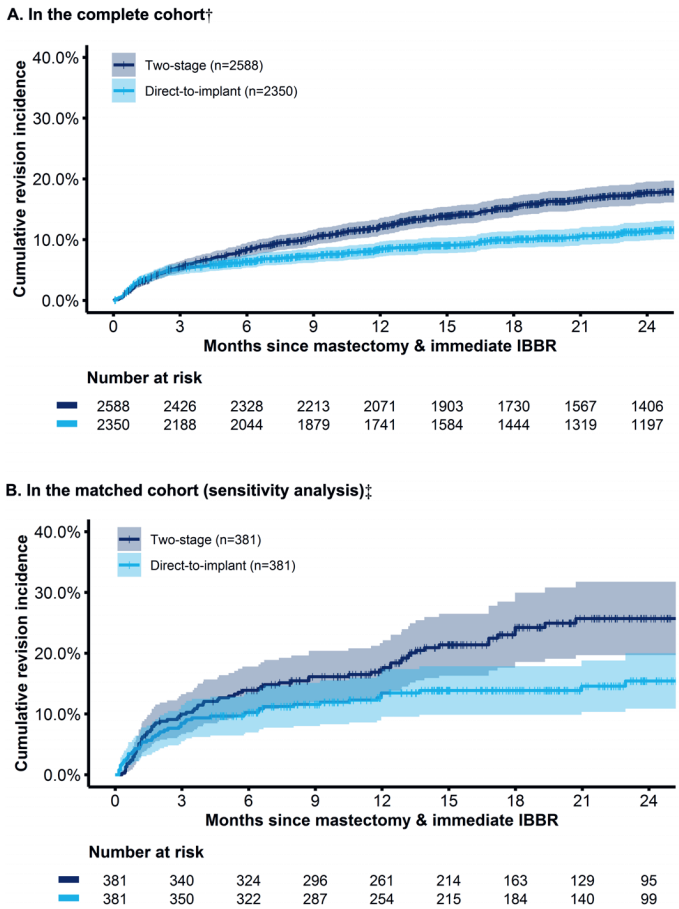

Figure 6.3. Crude, long-term cumulative revision incidence after mastectomy and immediate direct-to-implant IBBR or immediate two-stage IBBR*
*Curve includes revisions during the first and second stage of the reconstruction trajectory. †Direct-to-implant: within 1 month 2.8% (2.1 to 3.4), 6 months 6.2% (5.2 to 7.2), 12 months 8.1% (7.0 to 9.2), 24 months 10.8% (9.4 to 12.1). Two-stage: within 1 month 2.4% (1.8 to 3.0), 6 months 8.0% (6.9 to 9.0), 12 months 11.4% (10.2 to 12.7), 24 months 16.3% (14.8 to 17.7). ‡Direct-to-implant: within 1 month 4.2% (2.2 to 6.2), 6 months 9.7% (6.7 to 12.7), 12 months 12.6% (9.1 to 15.9), 24 months 14.3% (10.3 to 18.1). Two-stage: within 1 month 4.2% (2.2 to 6.2), 6 months 13.0% (9.5 to 16.3), 12 months 15.8% (12.0 to 19.5), 24 months 22.7% (17.8 to 27.2). Values in parentheses are 95%-CIs. IBBR, implant-based breast reconstruction.

Table 6.3. Indications* for short- and long-term revision surgery per reconstruction trajectory.

	Direct-to-implant IBBR		Two-stage IBBR		
	Short-term ≤60 days (n=99)	Long-term >60 days (n=152)	Short-term during first stage (n=279)	Short-term ≤60 days second stage (n=23)	Long-term >60 days second stage (n=131)
Deep wound infection	42 (42)	19 (13)	117 (42)	6 (26)	7 (5)
Seroma or hematoma	15 (15)	17 (12)	64 (23)	10 (44)	10 (8)
Mastectomy skin flap necrosis	52 (53)	14 (10)	48 (17)	1 (4)	4 (3)
Asymmetry	2 (2)	57 (39)	18 (7)	2 (9)	48 (37)
Breast pain	7 (7)	33 (23)	36 (13)	2 (9)	40 (31)
Capsular contracture	1 (1)	28 (19)	35 (13)	0 (0)	35 (27)
Skin scarring problems	11 (11)	7 (5)	32 (12)	5 (22)	12 (9)
Dissatisfaction with volume	2 (2)	34 (23)	9 (3)	1 (4)	30 (23)
Device malposition	2 (2)	28 (19)	18 (7)	1 (4)	25 (19)
Autologous flap problems	29 (29)	6 (4)	16 (6)	1 (4)	3 (2)
Device rupture or deflation	2 (2)	9 (6)	43 (15)	1 (4)	6 (5)
Newly diagnosed breast cancer	7 (7)	12 (8)	11 (4)	1 (4)	1 (1)
Patient-requested implant removal due to nonspecific health symptoms	1 (1)	3 (2)	1 (<1)	0 (0)	1 (1)
BIA-ALCL	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Values in parentheses are percentages. *Multiple indications could be reported per revision procedure. IBBR, implant-based breast reconstruction; BIA-ALCL, Breast Implant - Associated Anaplastic Large Cell Lymphoma.

After limiting confounding by indication using propensity score matching, 381 (50.0%) direct-to-implant records were matched to 381 (50.0%) two-stage IBBRs. While before matching, an imbalance in preoperative baseline characteristics was observed, no imbalances were observed after matching (Table S6.3, supporting information). In the matched cohort (n=762), implants inserted during direct-to-implant IBBR had a lower conditional likelihood of short-term revision compared to a two-stage procedure (conditional OR 0.33, 95%-CI 0.20-0.53). For the long-term, the crude cumulative revision incidence was 14.3% (95%-CI 10.3-18.1) after direct-to-implant IBBR and 22.7% (95%-CI 17.8-27.2) after a two-stage procedure (non-proportional hazards) (Figure 6.3B).

Discussion

This nationwide population-based study included close to 100% of all healthcare institutions performing breast reconstruction in the Netherlands. After adjusting for confounders and variation among centers, direct-to-implant IBBR was associated with a lower short-term and long-term unplanned revision incidence compared to two-stage IBBR. After limiting confounding by indication, comparable results were found. In the

direct-to-implant group, more breasts were reconstructed within the planned number of operations than in the two-stage group.

Interestingly, both Basta et al. and Lee et al. reported in their meta-analysis that direct-to-implant procedures were associated with a 1.24 (95%-CI 1.02-1.53) and 1.25 (95%-CI 0.40-3.89) higher risk of revision surgery, respectively, although the latter result was not statistically significant.[8,9] However, both meta-analyses included mainly single-centre studies, with low numbers of reconstructions, high heterogeneity in follow-up time, and without adjusting for confounders or indication bias. Additionally, the second stage of a two-stage IBBR was not always included, and often comparison of direct-to-implant versus two-stage IBBR was not the study aim.

Bennett et al. compared different types of IBBR during a two-year follow-up, using data from the Mastectomy Reconstruction Outcomes Consortium Study.[27] After adjusting for confounders and variation among centers, re-operative complication rates were 19% after direct-to-implant IBBR and 16% after two-stage IBBR (OR 1.06, 95%-CI 0.56-1.99). However, these results were statistically not significant and not adjusted for confounding by indication. Other smaller studies reported comparable proportions of long-term revision surgery between both IBBR groups (range 20-28%).[28,29] Nevertheless, comparing the results of the current study to previous studies remains difficult, because many different outcome definitions are used, such as reconstructive failure, reoperation, or re-operative complications.[7,18,27,30]

There are two likely explanations for the lower risk of short- and long-term revision surgery in the direct-to-implant IBBR group compared to the two-stage group. First, the reconstruction trajectory of a two-stage IBBR is longer by definition with two potentially hazardous events instead of one. Second, patient selection may have affected the probability of revision surgery. Direct-to-implant IBBR was more often performed in younger, non-smoking patients. Additionally, fewer infection control measures were used compared to two-stage IBBR, suggesting that direct-to-implant IBBR was more frequently performed in low-risk patients. However, after limiting confounding by indication using propensity score matching, comparable results were found.

To decrease the risk of short-term revision surgery after direct-to-implant IBBR, current findings suggest that one should focus specifically on mastectomy skin flap quality and prevention of deep wound infections. After two-stage IBBR, most short-term revisions were due to deep wound infections and seroma or hematoma formation. As most of these revision indications were related, different preventive strategies may be useful. For example, prophylactic intravenous tranexamic acid administration and a more aggressive surgical dead space management to prevent hematoma and seroma formation, respectively, and consequently deep wound infections.[31,32] Another specific

complication after two-stage procedures was TE deflation during the expansion period. Innovations that would obviate the need to puncture a TE for expanding, such as carbon dioxide-inflated TEs, could, therefore, be interesting, also to further reduce infections.[33] Long-term outcomes of both IBBR techniques could be improved by focusing on patient selection and counselling, especially regarding the risk of asymmetry, pain and capsular contracture, dissatisfaction with volume and device malposition.

Strengths and limitations

One of the strengths of this study is that real-world data was used from a nationwide population-based registry, including implants that were followed over time within different healthcare institutions. Consequently, the findings reflect daily clinical practice in the Netherlands. Randomized Controlled Trials are still the golden standard for comparative studies. However, RCTs are not always feasible if the outcome has a low event rate. As the next best alternative, selection and indication bias was limited using imputation techniques for missing data and propensity score matching to mimic pseudo-randomization. Also, clustering of patients and implants within healthcare institutions were taken into account. Finally, the DBIR uses definitions similar for all breast implant registries affiliated with the International Collaboration of Breast Registry Activities (ICOBRA), thereby improving comparability to future studies and meta-analyses using data from breast implant registries.[34]

There are several limitations. First, revision surgeries might have been underreported. Registration of inserted medical devices is mandatory by law in the Netherlands, but explantations are not. However, it is unlikely that revisions were less frequently registered for only one of the IBBR techniques. Thus, the presented revision incidences need to be interpreted as minimum incidences. Second, there may be residual confounding, due to missing potential confounders such as mastectomy skin flap quality, breast volume or mastectomy weight, and detailed information on (neo)adjuvant therapy.[3,18,35,36] However, the sensitivity analysis indicated that residual confounding could explain the observed association if an unidentified confounding factor with an OR of at least 5·7 would exist. The majority of the measured confounders had an OR below 2. Therefore, it is unlikely that unidentified confounders would alter our conclusions.

Future research

In daily practice, healthcare institutions tend to prefer one technique over the other. Future studies should focus on nationwide variation in the use of both IBBR techniques

and the underlying reasons. Insight into variation, patient selection, and outcomes helps to further improve guidelines and the quality of care provided.

Conclusions

Unplanned revision surgery occurred less often after direct-to-implant IBBR, and a higher proportion of breasts were reconstructed within the planned number of operations compared to two-stage IBBR. These population-based results are important to improve patient counselling and shared decision-making. Besides, they may help to start the discussion about whether a direct-to-implant approach should be considered more often.

Acknowledgement

The authors thank all plastic surgeons, residents, physician assistants, and nurses for data registration in the DBIR.

Supporting information

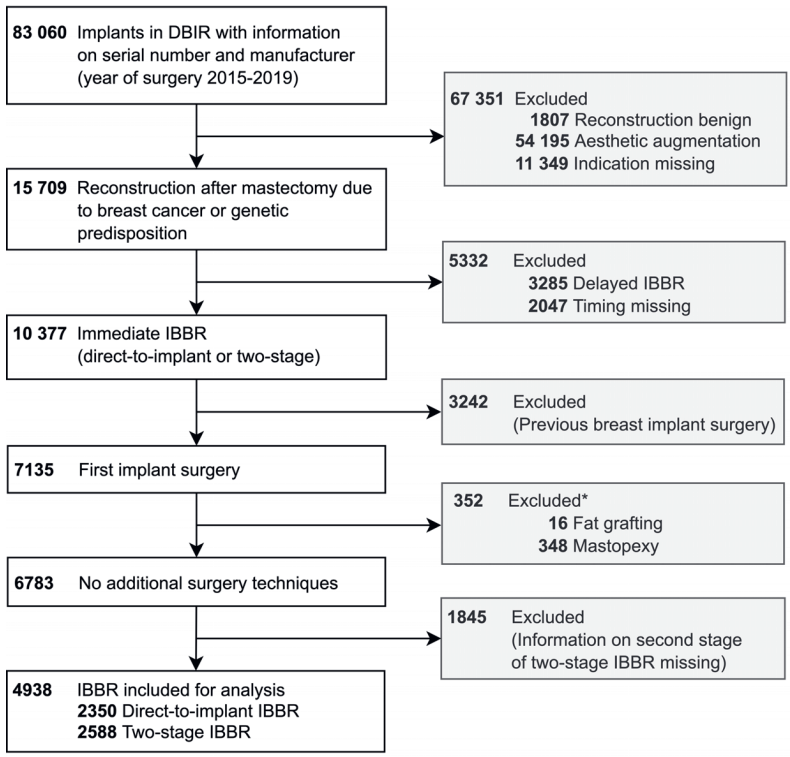

Figure S6.1. Flow chart of implant selection.
*More than one additional surgery technique could be registered per record. DBIR, Dutch Breast Implant Registry; IBBR, implant-based breast reconstruction; TE, tissue expander.

Table S6.1. Raw data of patient and surgery characteristics at time of mastectomy and immediate IBBR

	Total group (n=4,938)
Intervention of interest	
Type of IBBR	
Direct-to-implant	2,350 (47.6)
Two-stage	2,588 (52.4)
Patient characteristics	
Age (years, s.d.)	49.3 (11.4)
Missing	15 (0.3)
ASA classification	
I	3,056 (61.9)
II	1,673 (33.9)
III+	147 (3.0)
Missing	62 (1.2)
Body Mass Index* (kg/m^2, i.q.r.)	23.9 (21.6-26.8)
Missing	2494 (50.5)

Table S6.1. (continued)

	Total group (n=4,938)
Smoking status*	
Not smoking	1,808 (36.6)
Smoking	258 (5.2)
Missing	2,872 (58.2)
Previous radiotherapy	
No	3,994 (80.9)
Yes	254 (5.1)
Missing	690 (14.0)
Postoperative radiotherapy planned*	
No	2,188 (44.3)
Yes	155 (3.1)
Missing	2,595 (52.6)
Surgery characteristics	
Year of surgery	
2015	772 (15.6)
2016	987 (20.0)
2017	1,016 (20.6)
2018	1,185 (24.0)
2019	978 (19.8)
Healthcare institution volume (per year)	
<50 implant surgeries	569 (11.5)
50-99 implant surgeries	900 (18.2)
100-200 implant surgeries	1,989 (40.3)
>200 implant surgeries	1,480 (30.0)
Reconstruction indication	
Breast cancer	4,488 (90.9)
Prophylactic mastectomy	450 (9.1)
Laterality	
Unilateral	3,230 (65.4)
Bilateral	1,708 (34.6)
Incision site	
Nipple sparing	1,010 (20.5)
Non-nipple sparing	3,232 (65.5)
Other	256 (5.2)
Missing	440 (8.9)
Plane	
Sub flap	203 (4.1)
Completely covered with PM muscle	2,338 (47.3)
Partially covered with PM muscle	1,623 (32.9)
Other	154 (3.1)
Missing	620 (12.6)
Number of applied ICMs during implant insertion	
<4	947 (19·2)
4	1,735 (35·1)
>4	2,233 (45·2)
Missing	23 (0·5)
ADM/Mesh	
No	3,941 (79·8)
Yes	446 (9·0)
Missing	551 (11·2)
Autologous flap cover	
No	3,845 (77·9)
Yes	426 (8·6)
Missing	667 (13·5)

Values in parentheses are percentages, unless indicated otherwise. IBBR, implant-based breast reconstruction; s.d., standard deviation; ASA, American society of anesthesiologists; i.q.r, interquartile range; PM, pectoralis major; ICMs, infection control measures; ADM, acellular dermal matrix. *Registered since September 2017.

Table S6.2. Patient and surgery characteristics at time of mastectomy and immediate IBBR per reconstruction trajectory

	Direct-to-implant IBBR (n=2,350, 47.6%)	Two-stage IBBR (n=2,588, 52.4%)	p-value
Patient characteristics			
Age (years, s.d.)	48.5 (11.5)	49.9 (11.2)	<0.001
ASA classification			0.197
I	1,487 (63.3)	1,606 (62.1)	
II	783 (33.3)	912 (35.2)	
III+	80 (3.4)	70 (2.7)	
Body Mass Index (kg/m^2, i.q.r.)	23·1 (20.8-26.0)	23.2 (20.7-26.3)	0.894
Smoking status			<0.001
Not smoking	2,109 (89.7)	2,181 (84.3)	
Smoking	241 (10.3)	407 (15.7)	
Previous radiotherapy			0.111
No	2,179 (92.7)	2,428 (93.8)	
Yes	171 (7.3)	160 (6.2)	
Postoperative radiotherapy planned			<0.001
No	2,096 (89.2)	2,476 (95.7)	
Yes	254 (10.8)	112 (4.3)	
Surgery characteristics			
Year of surgery			<0.001
2015	322 (13.7)	450 (17.4)	
2016	456 (19.4)	531 (20.5)	
2017	461 (19.6)	555 (21.4)	
2018	506 (21.5)	679 (26.2)	
2019	605 (25.7)	373 (14.4)	
Healthcare institution volume (per year)			<0.001
<50 implant surgeries	272 (11.6)	297 (11.5)	
50-99 implant surgeries	435 (18.5)	465 (18.0)	
100-200 implant surgeries	744 (31.7)	1,245 (48.1)	
>200 implant surgeries	899 (38.3)	581 (22.4)	
Reconstruction indication			0.306
Breast cancer	2,125 (90.4)	2,363 (91.3)	
Prophylactic mastectomy	225 (9.6)	225 (8.7)	
Laterality			0.175
Unilateral	1,514 (64.4)	1,716 (66.3)	
Bilateral	836 (35.6)	872 (33.7)	
Incision site			<0.001
Nipple sparing	674 (28.7)	460 (17.8)	
Non-nipple sparing	1,428 (60.8)	2,039 (78.8)	
Other	248 (10.6)	89 (3.4)	
Plane			<0.001
Sub flap	133 (5.7)	99 (3.8)	
Completely covered with PM muscle	919 (39.1)	1,686 (65.1)	
Partially covered with PM muscle	1,174 (50.0)	750 (29.0)	
Other	124 (5.3)	53 (2.0)	
Number of applied ICM's during implant insertion			<0.001
<4	621 (26.4)	326 (12.6)	
4	784 (33.4)	958 (37.0)	
>4	945 (40.2)	1,304 (50.4)	
ADM/Mesh			<0.001
No	1,961 (83.4)	2,486 (96.1)	
Yes	389 (16.6)	102 (3.9)	
Autologous flap cover			<0.001
No	1,958 (83.3)	2,402(92.8)	
Yes	392 (16.7)	186 (7.2)	

Values in parentheses are percentages, unless indicated otherwise. IBBR, implant-based breast reconstruction; s.d., standard deviation; ASA, American society of anesthesiologists; i.q.r., interquartile range; PM, pectoralis major; ICMs, infection control measures; ADM, acellular dermal matrix.

Table S6.3. Preoperative patient and surgery characteristics at time of mastectomy and immediate IBBR, per reconstruction trajectory, before and after propensity score matching*

	Before PSM			After PSM		
	Direct-to-implant IBBR n=800 (41.9)	Two-stage IBBR n=1,107 (58.1)	s.m.d.†	Direct-to-implant IBBR n=381 (50.0)	Two-stage IBBR n=381 (50.0)	s.m.d.†
Patient characteristics						
Age (years, s.d.)	48.7 (11.3)	48.8 (11.6)	0.01	48.6 (11.5)	48.7 (11.9)	0.01
ASA classification			0.15			0.04
I	(49.6)	631 (57.0)		194 (50.9)	194 (51.2)	
II	361 (45.2)	435 (39.3)		169 (44.4)	171 (44.9)	
III+	42 (5.2)	41 (3.7)		18 (4.7)	15 (3.9)	
Body Mass Index (kg/m^2, i.q.r.)	23.6 (21.5-26.4)	23.9 (21.5-26.8)	0.07	23.7 (22.0-26.8)	24.0 (21.8-27.0)	0.01
Smoking status			0.10			0.09
Not smoking	714 (89.2)	952 (86.0)		328 (86.1)	340 (89.2)	
Smoking	86 (10.8)	155 (14.0)		53 (13.9)	41 (10.8)	
Previous radiotherapy			0.06			0·01
No	751 (93.9)	1055 (95.3)		354 (92.9)	353 (92.7)	
Yes	49 (6.1)	52 (4.7)		27 (7.1)	28 (7.3)	
Postoperative radiotherapy planned			0.28			<0.01
No	715 (89.4)	1068 (96.5)		357 (93.7)	357 (93.7)	
Yes	85 (10.6)	39 (3.5)		24 (6.3)	24 (6.3)	
Surgery characteristics						
Year of surgery			0.23			0.03
2015	0 (0)	1 (0.1)		0 (0)	0 (0)	
2016	5 (0.6)	4 (0.4)		4(1.0)	4 (1.0)	
2017	131 (16.4)	194 (17.5)		57 (15.0)	60 (15.7)	
2018	348 (43.5)	585 (52.8)		187 (49.1)	181 (47.6)	
2019	316 (39.5)	323 (29.2)		133 (34.9)	136 (35.7)	
Healthcare institution volume (per year)			0.18			0.05
<50 implant surgeries	113 (14.1)	106 (9.6)		37 (9.7)	42 (11.0)	
50-99 implant surgeries	180 (22.5)	233 (21.1)		82 (21.5)	81 (21.3)	
100-200 implant surgeries	357 (44.6)	503 (45.4)		165 (43.3)	160 (42.0)	
>200 implant surgeries	150 (18.8)	265 (23.9)		97 (25.5)	98 (25.7)	
Reconstruction indication			0.05			0.01
Breast cancer	675 (84.4)	912 (82.4)		320 (84.0)	319 (83.7)	
Prophylactic mastectomy	125 (15.6)	195 (17.6)		61 (16.0)	62 (16.3)	
Laterality			0.02			0.01
Unilateral	476 (59.5)	647 (58.4)		215 (56.4)	217 (57.0)	
Bilateral	324 (40.5)	460 (41.6)		166 (43.6)	164 (43.0)	

Values in parentheses are percentages, unless indicated otherwise. *Sub-selection of original non-imputed data, records with any missing preoperative characteristic were excluded. †Standardized mean differences of ≥0·1 represent disbalances in characteristics between groups. PSM, propensity score matching; IBBR, implant-based breast reconstruction; s.m.d., standardized mean difference; s.d., standard deviation; ASA, American society of anesthesiologists; i.q.r., interquartile range

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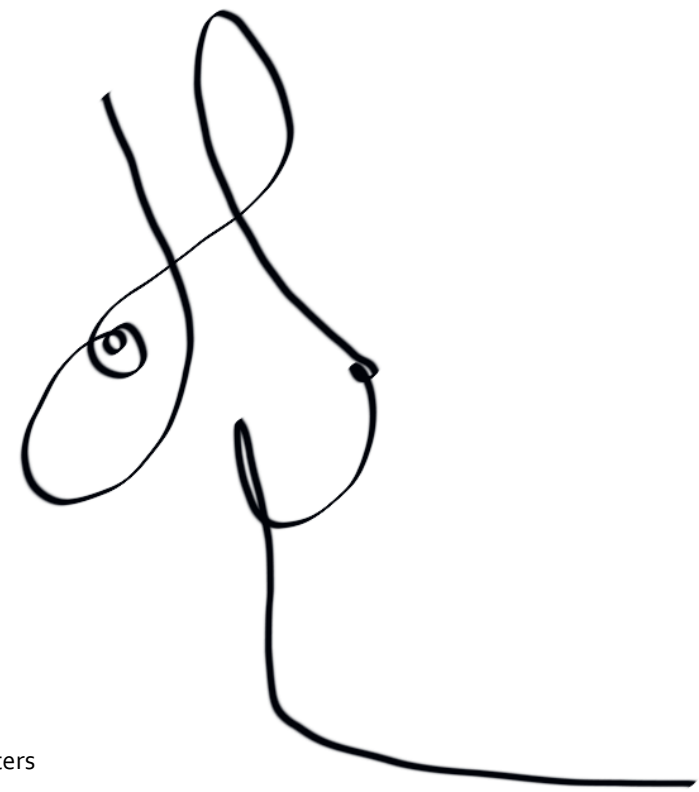
Chapter 7

Breast-contour preserving procedures for early-stage breast cancer: a population-based study of the trends, variation in practice and predictive characteristics in Denmark and the Netherlands



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Abstract

Purpose

Breast-contour preservation (BCP) is possible for most women treated for early-stage breast cancer. BCP can be defined as primary breast-conserving treatment (BCT), neoadjuvant chemotherapy (NAC) followed by BCT and immediate postmastectomy breast reconstruction (IBR). This study provides insight in current BCP strategies in Denmark and the Netherlands and aims to identify opportunities for improvement within both countries.

Methods

A total of 92,881 patients with early-stage breast cancer who were operated in Denmark and the Netherlands between 2012 and 2017 were selected from the Danish Breast Cancer Group and the Dutch National Breast Cancer Audit databases. BCP procedures and predictive factors were analyzed within and between both countries.

Results

BCP was achieved in 76.7% (n=16,355) of the Danish and in 74.5% (n=53,328) of the Dutch patients. While BCP rate did not change significantly over time in Denmark ($p=0.250$), a significant increase in BCP rate from 69.5% in 2012 to 78.5% in 2017 ($p<0.001$) was observed in the Netherlands. In both countries, variation in BCP rates between hospitals decreased over time. NAC followed by BCT and postmastectomy IBR was substantially more often used in the Netherlands compared to Denmark, specifically in patients younger than 50 years.

Conclusions

In more than 75% of all Danish and Dutch patients, surgically treated for early-stage breast cancer, the breast- contour was preserved. The different use of BCP strategies within Denmark and the Netherlands and the differences observed between hospitals in both countries emphasize the need for more (inter)national consensus on treatment modalities.

Introduction

Since several landmark studies in the 1980s confirmed comparable survival outcomes for early-stage breast cancer after breast conserving treatment (BCT) and mastectomy,[1-3] BCT has become the preferred standard of care. BCT is defined as breast-conserving surgery (BCS) followed by radiation therapy. Besides the surgical shift towards BCS, attention for outcomes such as the patients' quality of life has increased in the last decade.

Loss of the breast mound may lead to a decreased self-image and quality of life.[4] Nowadays, preservation of the breast mound is possible for most early-stage breast cancer patients. This has been achieved by primary BCS for smaller tumors, and by the introduction of oncoplastic surgery techniques for large tumors.[5] Furthermore, neoadjuvant chemotherapy (NAC) is increasingly being used to downsize the tumor allowing for BCT.[6] In addition to this, immediate breast reconstruction (IBR) leads to restoration of the breast mound if mastectomy is indicated. Furthermore, IBR compared to delayed breast reconstruction reduces additional operations and hospitalizations [7], leading to reduced patient burden and healthcare costs.[8]

National registries have demonstrated that overall, the proportion of breast cancer patients undergoing BCT (either primary or after NAC) or mastectomy followed by IBR, is currently over 70% in the United States and some European countries.[9-13] It is also known that there is a large variation between hospitals in the use of different treatment modalities.[14,15]

A previous study reported on breast-contour preservation (BCP) as a new comprehensive parameter for evaluating breast cancer treatment on a national level.[16] This new parameter aims to reflect the combined efforts of nonsurgical and surgical treatments to achieve preservation of the breast mound and is defined as either primary BCS, BCS after NAC or mastectomy followed by IBR. Because not all patients are primarily eligible for BCS, increasing the rate of BCP using either NAC or mastectomy followed by IBR is therefore of major importance. Despite that European, Danish and Dutch guidelines empathize the importance of BCP by highlighting the separate treatment strategies leading to BCP,[17-19] previous literature focusing on all different strategies is sparse and non-existing when comparing countries within Europe. An international evaluation of BCP rates could provide valuable insight into daily practice and could identify possibilities to improve BCP strategies. The Netherlands and Denmark are both high-income countries and have well-maintained population-based breast cancer registries with similar medical care systems that provide equal access to healthcare for all patients, making them suitable for evaluation. The aims of the current study were to investigate the prevalence of BCP among women with early-stage breast

cancer in Denmark and the Netherlands and to identify opportunities for improvement. This information can be used to increase the use of BCP procedures and reduce variation between hospitals in BCP rate in patients with early-stage breast cancer.

Methods

Data sources

Anonymized patient data regarding the demographic, clinicopathological, and treatment characteristics was obtained from the Danish Breast Cancer Group (DBCG) and the National Breast Cancer Organization Netherlands (NABON) Breast Cancer Audit (NBCA) from Denmark and the Netherlands, respectively. The scientific committee of the NBCA and the DBCG Board, and the Danish Clinical Quality Program– National Clinical Registries (RKKP) approved this study.
The DBCG was established in 1977 and prospectively collects data on patient-, tumor, and treatment-related characteristics, and follow-up of all female patients diagnosed with primary breast cancer in Denmark.[20] The NBCA was established in 2011 and prospectively collects data on patient-, tumor-, and treatment-related characteristics of all surgically treated patients diagnosed with primary invasive breast cancer or ductal carcinoma in situ (DCIS) in the Netherlands.[9] A more detailed description of the organization and data collection of both the DBCG and NBCA was published previously.[9,21]

Study population

All female patients with primary invasive early-stage breast cancer who were operated between January 1st, 2012 and December 31st, 2017 and were registered in the DBCG- or NBCA-database were selected for this study. Early-stage breast cancer was defined as T1-2 N0-1 without distant metastasis. Patients diagnosed with locally advanced breast cancer were excluded. Patients diagnosed with only DCIS were not included as these patients are not registered in the database for the clinical quality program in Denmark, and therefore completeness of data is uncertain.

Definitions and outcomes

In both countries, rarely reported histological subtypes such as mucinous, medullary, papillary, and tubular subtype were categorized as ‘other'. In Denmark, differentiation grade was determined for ductal and lobular breast cancer, but not for other subtypes according to the modified version of the Bloom-Richardson scoring system by Ellis *et*

al.[22] In the Netherlands, differentiation grade was categorized for all histological subtypes according to the modified version by Lakhani *et al.*[23] In both registers, tumor size and lymph node status was categorized according to the 7th edition of the American Joint Committee on Cancer's Cancer Staging Manuel.[24] For the current study, breast cancer specimens with ≥10% positively stained cells for estrogen receptor (ER) by immunohistochemistry were considered positive. Progesterone status is not registered in the DBCG database for the clinical quality program in Denmark and could therefore not be included in the current study. Human epidermal growth factor receptor 2 (HER2) expression was tested using an immunohistochemistry test or gene amplification in a fluorescence in situ hybridization test according to standard criteria.[25]
Surgical treatment was categorized as BCS or mastectomy at definitive treatment. The primary outcome of this study was preservation of the breast contour. A definition of BCP was met if the patient underwent one of the following treatments: (1) primary BCS, (2) NAC followed by BCS, or (3) mastectomy (either primary or after NAC) followed by IBR. IBR was defined as breast reconstruction at the same procedure as mastectomy. Patients were categorized as not having received BCP if they had undergone mastectomy without IBR. While in the DBCG-database, surgical procedures up to one month following primary surgery are included, no time limit exists for inclusion of secondary procedures in the NBCA-database for the primary breast tumor.
Hospital surgical volume was defined as the average number of included patients operated per hospital per year and was categorized in low (<150 patients), intermediate (150-299 patients), and high (≥300 patients) volume hospital. The average number of patients was for hospitals, that were not active the whole period, only accounted for the years the hospitals actually treated patients.

Statistical analysis

Analyses were stratified into two patient populations: 1) patients registered in the DBCG-database and 2) patients registered in the NBCA-database. Missing characteristics were categorized as a separate characteristic. Patient-, tumor- and hospital-related characteristics were compared between patients who underwent mastectomy alone and those who underwent a BCP procedure, using χ^2-tests for categorical variables. Patients with unknown characteristics were included in the descriptive statistics. Descriptive statistics were used to report on the overall BCP rate in both populations. To describe the BCP rate between hospitals and over time, hospital mean and 95% control limits (CLs) are presented in three funnel plots for year of operation 2013, 2015, and 2017.[26,27] Univariable and multivariable logistic regression analyses were used to estimate the odds ratio (OR) with 95% confidence intervals (CIs)

for BCP, applying the Wald test for statistics significance. Patients with unknown characteristics were not included in univariable and multivariable analyses. All tests were two-sided and a p-value of <0.05 was considered statistically significant. Analyses were performed using SPSS ® (version 24, IBM, Armonk, New York, USA).

Data availability

Data can be made available upon reasonable request to the NBCA and the DBCG Board, and the Danish Clinical Registries.

Results

In total, 92,881 patients met the inclusion criteria, of whom 21,288 (22.9%) had been registered in Denmark and 71,593 (77.1%) in the Netherlands. The mean age (standard deviation) at diagnosis was 61.7 (12.5) years for patients in Denmark and 61.1 (12.3) years for patients in the Netherlands. In both countries, most of the patients were diagnosed with stage T1 (≤20 mm) breast cancer without lymph node involvement and with a ductal subtype which was estrogen positive and HER2 negative (Table 7.1).
In Denmark (n=12 hospitals), there were 1 low-volume, 7 intermediate-volume and 4 high-volume hospitals, whereas in the Netherlands (n=82 hospitals), there were 50 low-volume, 28 intermediate-volume and 4 high-volume hospitals.
Between 2012 and 2017, 16,355 (76.7%) patients from Denmark and 53,328 (74.5%) patients from the Netherlands underwent BCP (Figure 7.1). While, the overall BCP rate was stable over time in Denmark (75.8% to 76.8%, p=0.250), BCP rate increased significantly from 69.5% in 2012 to 78.5% in 2017 in the Netherlands (p<0.001).
The BCP strategies changed significantly over time within both countries (p<0.001). While the primary BCS rate decreased from 72.4% in 2012 to 68.7% in 2017 in Denmark, primary BCS rate only slightly decreased from 59.9% to 59.6% in the Netherlands (Figure 7.1). The NAC followed by BCS rate increased from 1.3% to 5.7% in Denmark between 2012 and 2017 and from 3.1% to 9.6% in the Netherlands. The mastectomy followed by IBR rate slightly increased from 2.0% in 2012 to 2.4% in 2017 in Denmark and increased from 6.5% to 9.2% in the Netherlands (Figure 7.1). The average mastectomy followed by IBR rate was different between both countries in both the lymph node positive patient group (1.5% in Denmark vs. 9.3% in the Netherlands,) as in the lymph node negative patient group (2.4% vs. 8.5%, respectively). In both countries, the majority of IBRs were implant- or tissue expander (TE) based reconstructions (94.0 vs. 89.4%).

Table 7.1. Baseline characteristics of patients diagnosed with early-stage breast cancer in Denmark and the Netherlands who underwent a breast-contour preserving procedure or mastectomy alone between 2012 and 2017.

	Denmark (n=21,288)				Netherlands (n=71,593)			
		Breast-contour preservation				Breast-contour preservation		
	N (col %)	No (row %)	Yes (row %)	p-value	N (col %)	No (row %)	Yes (row %)	p-value
Number of patients	21,288	23.3	76.7		71,539	25.5	74.5	
Year of operation				0.25				<0.001
2012	3,455 (16.2)	24.2	75.8		11,412 (15.9)	30.5	69.5	
2013	3,568 (16.8)	24.1	75.9		11,586 (16.2)	29.0	71.0	
2014	3,617 (17.0)	22.3	77.7		11,985 (16.7)	27.0	73.0	
2015	3,552 (16.7)	22.4	77.6		11,889 (16.6)	24.3	75.7	
2016	3,529 (16.6)	23.4	76.6		12,313 (17.2)	21.4	78.6	
2017	3,567 (16.8)	23.2	76.8		12,408 (17.3)	21.5	78.5	
Age (years)				<0.001				<0.001
<40	838 (3.9)	30.8	69.2		2,850 (4.0)	22.5	77.5	
40-49	2,857 (13.4)	25.3	74.7		9,818 (13.7)	23.0	77.0	
50-59	5,087 (23.9)	17.1	82.9		1,8870 (26.4)	18.6	81.4	
60-69	7,023 (33.0)	16.8	83.2		2,1189 (29.6)	22.0	78.0	
70-79	3,827 (18.0)	30.7	69.3		1,3943 (19.5)	30.6	69.4	
≥80	1,656 (7.8)	45.2	54.8		4,923 (6.9)	59.4	40.6	
Histological subtype				<0.001				<0.001
ductal	17,012 (79.9)	22.1	77.9		58,362 (81.5)	23.9	76.1	
lobular	2,220 (10.4)	31.7	68.3		7,555 (10.6)	36.4	63.6	
other	2,046 (9.6)	23.4	76.6		5,242 (7.3)	28.3	71.7	
unknown	10 (0.0)	60.0	40.0		434 (0.6)	23.0	77.0	
Differentiation grade				<0.001				<0.001
I	5,355 (25.2)	16.3	83.7		18,077 (25.2)	18.6	81.4	
II	9,203 (43.2)	24.7	75.3		32,243 (45.0)	26.6	73.4	
III	4,407 (20.7)	27.7	72.3		16,663 (23.3)	29.7	70.3	
not determined	2,046 (9.6)	23.4	76.6		-	-	-	
unknown	277 (1.3)	36.1	63.9		4,610 (6.4)	30.0	70.0	
Estrogen receptor				<0.001				<0.001
<10%	3,036 (14.3)	28.3	71.7		10,868 (15.2)	29.6	70.4	
≥10%	18,198 (85.5)	22.4	77.6		59,114 (82.6)	24.8	75.2	
unknown	54 (0.3)	31.5	68.5		1,611 (2.3)	24.6	75.4	

Table 7.1. (continued)

	Denmark (n=21,288)				Netherlands (n=71,593)			
	Breast-contour preservation				Breast-contour preservation			
	N (col %)	No (row %)	Yes (row %)	p-value	N (col %)	No (row %)	Yes (row %)	p-value
HER2 status				<0.001				<0.001
negative	18,433 (86.6)	21.8	78.2		62,047 (86.7)	24.9	75.1	
positive	2,622 (12.3)	32.8	67.2		8,219 (11.5)	30.5	69.5	
unknown	233 (1.1)	33.5	66.5		1,327 (1.9)	23.7	76.3	
T-stage				<0.001				<0.001
pT1	14,954 (70.2)	14.5	85.5		51,155 (71.5)	18.8	81.2	
pT2	6,225 (29.2)	43.4	56.6		20,360 (28.4)	42.3	57.7	
unknown	109 (0.5)	73.4	26.6		78 (0.1)	42.3	57.7	
Lymph node status				<0.001				<0.001
pN0	14,312 (67.2)	17.7	82.3		53,385 (74.6)	21.7	78.3	
pN1	6,262 (29.4)	35.1	64.9		18,089 (25.3)	36.5	63.5	
unknown	714 (3.4)	31.5	68.5		119 (0.2)	51.3	48.7	
Hospital volume				<0.001				<0.001
low	703 (3.3)	17.8	82.2		28,608 (40.0)	30.2	69.8	
intermediate	8,689 (40.8)	27.1	72.9		34,909 (48.8)	22.8	77.2	
high	11,896 (55.9)	20.8	79.2		8,076 (11.3)	20.8	79.2	

HER2 human epidermal growth factor receptor 2.

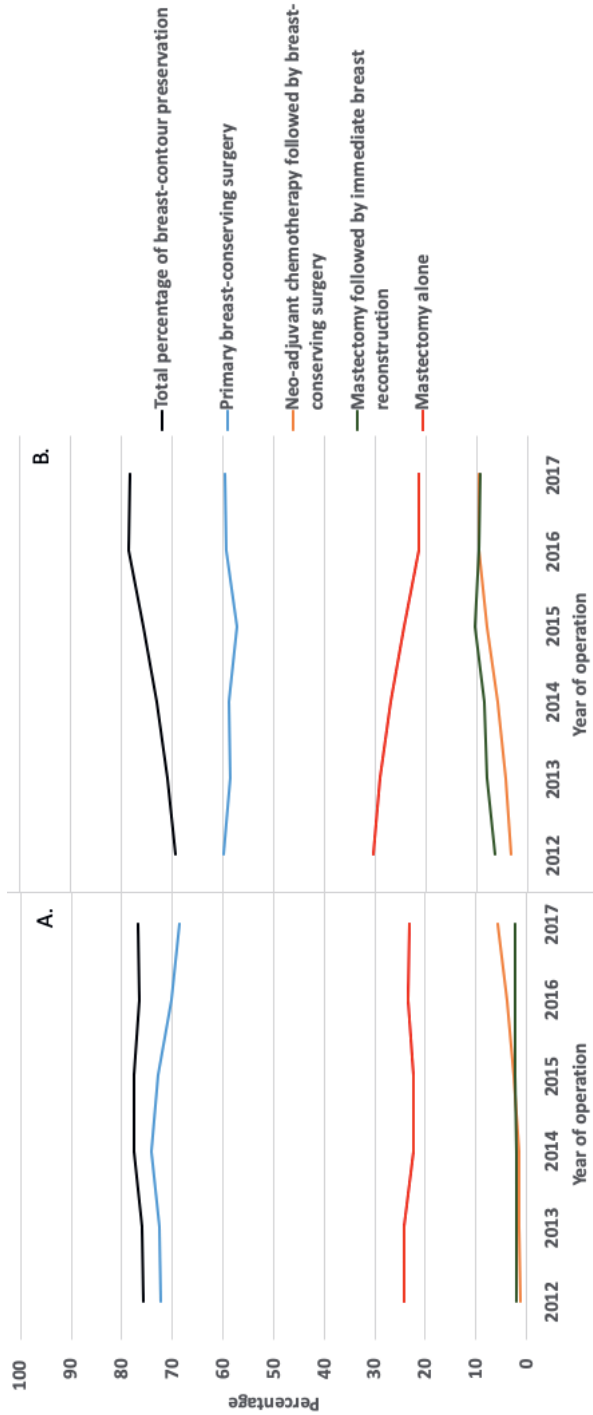

Figure 7.1. Breast cancer treatment strategies of patients diagnosed with early-stage breast cancer in a Denmark and b the Netherlands between 2012 and 2017.

Baseline characteristics associated with BCP within both countries are listed in Table 7.2. While the year of diagnosis was not associated with BCP in Denmark, patients operated in more recent years compared to year 2012, were more likely to undergo a BCP procedure in the Netherlands, with increasing ORs (Table 7.2).

Table 7.2. Univariable and multivariable analyses of characteristics associated with breast-contour preservation within Denmark and the Netherlands.

	Denmark (n=20,096)			Netherlands (n=64,594)		
	OR (95% CI) Univariable	OR (95% CI) multivariable	p-value	OR (95% CI) Univariable	OR (95% CI) multivariable	p-value
Year of diagnosis			0.07			<0.001
2012	1.00 (reference)	1.00 (reference)		1.00 (reference)	1.00 (reference)	
2013	0.99 (0.88-1.11)	0.94 (0.83-1.06)		1.08 (1.01-1.14)	1.05 (0.98-1.12)	
2014	1.08 (0.96-1.21)	1.09 (0.96-1.23)		1.21 (1.14-1.28)	1.20 (1.13-1.28)	
2015	1.10 (0.98-1.24)	1.12 (0.98-1.27)		1.35(1.27-1.43)	1.34 (1.25-1.43)	
2016	1.02 (0.91-1.15)	1.07 (0.95-1.22)		1.57 (1.47-1.67)	1.63 (1.52-1.74)	
2017	1.02 (0.91-1.14)	1.05 (0.93-1.20)		1.56(1.47-1.66)	1.59 (1.49-1.70)	
Age (years)			<0.001			<0.001
<40	0.45 (0.38-0.53)	0.64 (0.53-0.77)		0.97 (0.88-1.08)	1.20 (1.08-1.34)	
40-49	0.61 (0.55-0.68)	0.84 (0.74-0.94)		0.96 (0.90-1.02)	1.20 (1.12-1.28)	
50-59	0.99 (0.89-1.09)	1.13 (1.02-1.26)		1.23 (1.17-1.29)	1.31 (1.25-1.39)	
60-69	1.00 (reference)	1.00 (reference)		1.00 (reference)	1.00 (reference)	
70-80	0.45 (0.41-0.49)	0.55 (0.49-0.61)		0.63 (0.60-0.66)	0.62 (0.59-0.66)	
≥80	0.23 (0.20-0.26)	0.30 (0.26-0.34)		0.19 (0.18-0.20)	0.24 (0.22-0.26)	
Histological subtype			<0.001			<0.001
ductal	1.00 (reference)	1.00 (reference)		1.00 (reference)	1.00 (reference)	
lobular	0.61 (0.56-0.68)	0.62 (0.56-0.70)		0.54 (0.51-0.57)	0.58 (0.55-0.62)	
other	0.96 (0.85-1.08)	0.98 (0.84-1.14)		0.79 (0.79-0.84)	0.80 (0.74-0.86)	
Differentiation grade			0.002			<0.001
I	1.00 (reference)	1.00 (reference)		1.00 (reference)	1.00 (reference)	
II	0.67 (0.62-0.73)	0.84 (0.77-0.93)		0.63 (0.60-0.66)	0.80 (0.84-0.84)	
III	0.57 (0.52-0.62)	0.92 (0.81-1.04)		0.54 (0.51-0.57)	0.76 (0.81-0.81)	
Estrogen receptor			0.392			<0.001
<10%	0.75 (0.69-0.82)	0.95 (0.85-1.07)		0.77 (0.74-0.81)	0.89 (0.83-0.94)	
≥10%	1.00 (reference)	1.00 (reference)		1.00 (reference)	1.00 (reference)	
HER2 status			<0.001			<0.001
negative	1.00 (reference)	1.00 (reference)		1.00 (reference)	1.00 (reference)	
positive	0.56 (0.51-0.62)	0.58 (0.52-0.65)		0.75 (0.71-0.79)	0.73 (0.69-0.78)	
T-stage			<0.001			<0.001
pT1	1.00 (reference)	1.00 (reference)		1.00 (reference)	1.00 (reference)	
pT2	0.21 (0.20-0.23)	0.28 (0.26-0.30)		0.30 (0.29-0.31)	0.40 (0.38-0.41)	
Lymph node status			<0.001			<0.001
pN0	1.00 (reference)	1.00 (reference)		1.00 (reference)	1.00 (reference)	
pN1	0.41 (0.38-0.44)	0.51 (0.48-0.55)		0.48 (0.46-0.50)	0.53 (0.51-0.56)	
Hospital volume			<0.001			<0.001
low	1.73 (1.40-2.13)	1.91 (1.52-2.40)		0.67 (0.65-0.70)	0.66 (0.64-0.69)	
intermediate	1.00 (reference)	1.00 (reference)		1.00 (reference)	1.00 (reference)	
high	1.45 (1.36-1.55)	1.55 (1.44-1.67)		1.13(1.06-1.20)	1.09 (1.02-1.17)	

Abbreviations: human epidermal growth factor receptor 2, HER2.

The overall BCP rate was significantly different between age groups (Table 7.1). After adjusting for confounders, in both countries, patients between 50 and 59 years old

were more likely to undergo BCP compared to patients of 60 to 69 years of age (OR 1.13, 95%-CIs 1.02-1.26 and OR 1.31, 95%-CIs 1.25-1.39, respectively). In the Netherlands, patients younger than 40 years and between 40 to 49 years of age were also more likely to undergo BCP compared to those who were 60 to 69 years old (OR 1.20, 95%-CIs 1.08-1.34 and OR 1.20, 95%-CIs 1.12-1.28, respectively). Whereas, in Denmark, patients younger than 40 years and between 40 to 49 years of age (OR 0.64, 95%-CIs 0.53-0.77 and OR 0.84, 95%-CIs 0.74-0.94, respectively) were less likely to undergo BCP compared to those who were 60 to 69 years old (Table 7.2).

Among other predictive characteristics, patients diagnosed with a T2 tumor (OR 0.28, 95%-CIs 0.26-0.30 and OR 0.40, 95%-CIs 0.38-0.41, respectively) compared to T1 tumor and lymph node involvement (OR 0.51, 95%-CIs 0.48-0.55 and OR 0.53, 95%-CIs 0.51-0.56, respectively) were less likely to undergo BCP within both Denmark and the Netherlands.

In both Denmark and the Netherlands, NAC followed by BCS (6.1% and 18.2%, respectively) and mastectomy followed by IBR (10.1% and 32.9%, respectively) was most commonly performed in patients younger than 40 years (Figure 7.2). Both treatment modalities were less commonly performed as age increased and were almost never performed in patients older than 80 years (Figure 7.2).

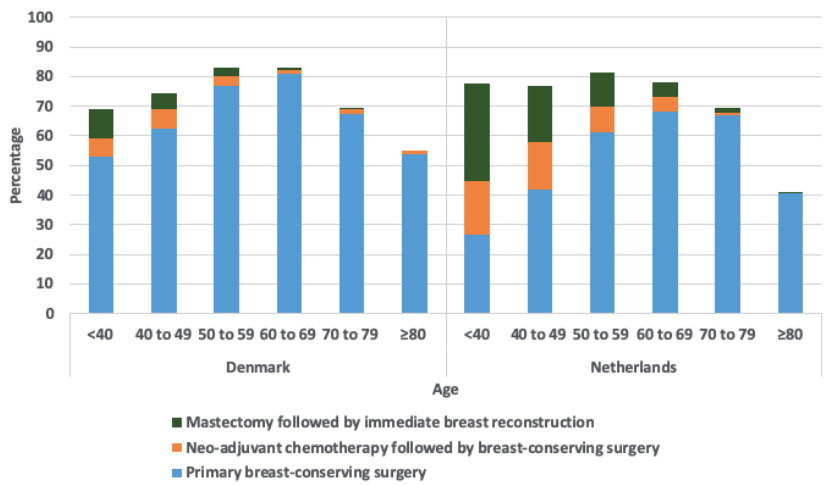

Figure 7.2. Breast-contour preservation strategies per age group for patients with early-stage breast cancer in Denmark and the Netherlands.

Although in general the variation in BCP rates between hospitals was smaller in Denmark compared to the Netherlands, a decrease in variation in BCP rates was

observed between hospitals within both Denmark and the Netherlands over time (Figure 7.3).

In both countries, patients were more likely to undergo BCP if they underwent surgery at a high-volume hospital (OR 1.55, 95%-CIs 1.44-1.67 and OR 1.09, 95%-CIs 1.02-1.17, respectively) compared to an intermediate-volume hospital. In the Netherlands, patients treated at a low-volume hospital were less likely to preserve their breast contour compared to patients in an intermediate-volume hospital (OR 0.66, 95%-CIs 0.64-0.69).

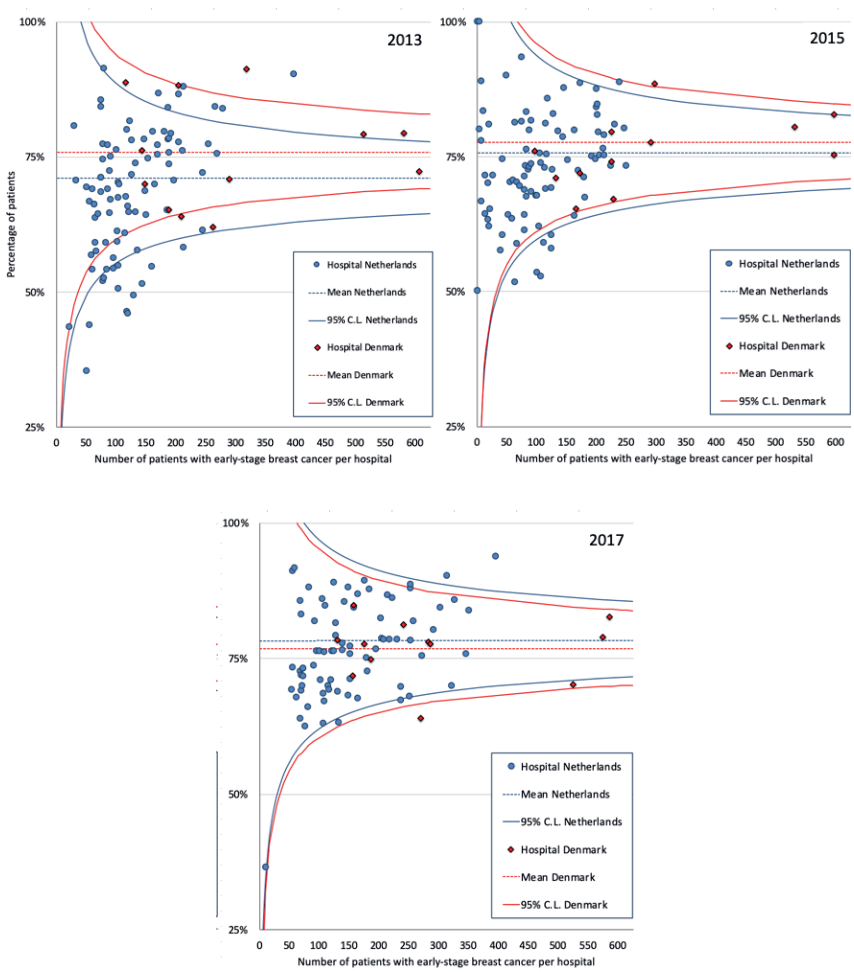

Figure 7.3. Funnel plots of breast-contour preservation for early-stage breast cancer in Denmark (red) and the Netherlands (blue) in 2013, 2015 and 2017, showing the hospital mean and 95% control limits. Note: the y-axis starts from 25%.

Discussion

In this large population-based study of patients with early-stage breast cancer, insight into BCP strategies is provided and it is shown that BCP was achieved in more than 75% of patients in both Denmark and the Netherlands, albeit using different treatment strategies. While in Denmark BCP was predominantly achieved by using primary BCS, the use of NAC followed by BCS and mastectomy followed by IBR played a substantial role in the Netherlands, specifically in patients younger than 50 years. We observed a stable high overall BCP rate between 2012 and 2017 in Denmark and a significant increase over time in the Netherlands. Current findings demonstrated considerable variation in the use of BCP strategies between hospitals within both countries and between countries. These results therefore suggest that more (inter)national consensus on the indication for different breast cancer treatment modalities is warranted, specifically on indications for NAC and mastectomy followed by IBR.

Van Bommel *et al.* first described BCP as a new comprehensive parameter for evaluating quality of breast cancer treatment in patients with early-stage as well as more advanced stages of breast cancer.[16] They reported an increase in the overall BCP rate from 63% in 2011 to 71% in 2015 which was translated as a quality of care improvement.[16] This observed trend continued in the Netherlands up to 2017 as is shown in the current study, although the different strategies used in Denmark made an interesting perspective.

The current study observed differences in BCP strategies per age group and over time between Denmark and the Netherlands. The rate of patients undergoing NAC followed by BCS more than tripled in both countries over time. However, in Denmark, less patients younger than 50 years, underwent NAC followed by BCS (6.3 vs. 16.7%, respectively) or mastectomy followed by IBR (6.7 vs. 22.2%, respectively) compared to the Netherlands. In reviewing literature, several studies from around the world have reported an increasing use of NAC, specifically in patients younger than 70 years and in patients with more advanced tumors.[6,28,29] The difference in use of NAC followed by BCS between both countries may partly be explained by the moment of introducing NAC in the national guidelines. While in the Netherlands NAC was introduced as a downstaging procedure in the breast cancer guideline in 2012,[14,30] Danish guidelines incorporated NAC as a downstaging procedure in the second half of 2016 and has been increasingly used thereafter.[19]

Breast cancer with lymph node involvement requires radiotherapy, which limits the use of IBR as radiotherapy is frequently mentioned as a contraindication for implant-based IBR.[31,32] Interestingly, different IBR rates among patients who underwent mastectomy were found between both countries, both in patients with a positive and negative

lymph node. It is unlikely that the type of IBR technique explains the observed differences, since the majority of IBRs were implant- or TE based in both countries. This together with the relative low increase in IBR rates in Denmark suggests potential room for improvement in Denmark. Internationally, there has been an increasing use of IBR in most high-income countries in the last decade. The mean IBR rate of 25.5% among patients who underwent mastectomy in the Netherlands is within the range of other high-income countries, such as United Kingdom (up to 23% in 2016),[33] United States (up to 43% in 2014),[34] and Australia (up to 18% in 2013).[35] Nonetheless, previous research has shown substantial variation in postmastectomy IBR rates between hospitals in the Netherlands and other countries, unexplained by patient and tumor characteristics.[15,36,37] The different use of IBR between hospitals emphasizes the need for more international consensus on the indications for IBR. Future cross-country studies could focus on hospital organizational factors as some of these are associated with the use of IBR.[38,39] Unfortunately, these factors could not be accounted for in the current study.

Overall, a smaller proportion of patients underwent a mastectomy (with or without IBR) in Denmark compared to the Netherlands (25.5% vs. 34.2%, respectively). This finding suggest room for improvement in the Netherlands in performing more BCS instead of mastectomy, since previous studies showed comparable survival outcomes when comparing patients who underwent BCT and mastectomy.[2,40]

Different grading systems were used in both countries. Hereby, relatively more Dutch patients with an unknown differentiation grade were excluded from the logistic regression model compared to Danish patients. Nonetheless, the impact is most likely limited as subsequent analysis showed the same findings when including these patients (data not shown).

The current study highlights an interesting difference in hospital volume. While in Denmark only 3.3% of patients were operated at a low-volume hospital, this was 40% in the Netherlands. Despite that previous studies found minimal differences in survival between intermediate- and high-volume hospitals,[41,42] no literature exists on the relationship between hospital volume and 'soft' outcomes such as BCP. In the current study, a significant association between hospital volume and BCP rate was found. Although it is beyond the scope of the current study, current findings suggest that BCP might be increased in the Netherlands by centralizing breast cancer care. This hypothesis requires additional future analyses on the relationship between hospital volume and BCP.

A decrease of variation in BCP rates between hospitals was observed over time, specifically in the Netherlands. A potential contributor to this trend in the Netherlands might be the continuous feedback hospitals received on their BCP rate provided by the

NBCA. Several other improvements in health care have been accomplished by monitoring the quality of cancer care and providing benchmark feedback to hospitals.[43,44]

The current study has several limitations. First, there might have been unaccounted confounders in the current analyses (e.g., comorbidities, social-economic status, smoking status). Unfortunately, these confounders are not registered in both databases. Second, there might be subtle differences in interpretation of definitions between those who register patients which might explain part of the treatment choices. Thirdly, only surgical procedures performed within one month after primary surgery were included in the DBCG-database. Although most secondary surgery is performed within a short time period after primary surgery, secondary mastectomies or reconstructive efforts without oncologic purpose do occur after a longer time period, specifically in patients younger than 50 years with for instance a genetic predisposition. A previous study using the DBCG database reported a higher mastectomy rate after BCS in Denmark between 2008 and 2012 (data not shown) when including procedures up to three months after primary surgery.[45] Consensus regarding the inclusion period among national registries could improve future cross-country comparison. Lastly, the current study could unfortunately not account for whether patients in different hospitals had access to high skilled physicians who offered the entire field of breast reconstruction procedures. Strengths of the current study are the real-world population-based databases and high number of patients. To the best of the authors' knowledge, there have been no previous cross-country population-based analyses, evaluating the comprehensive breast cancer treatment for early-stage breast cancer. Therefore, current findings can be used for comparison and benchmarking in future studies.

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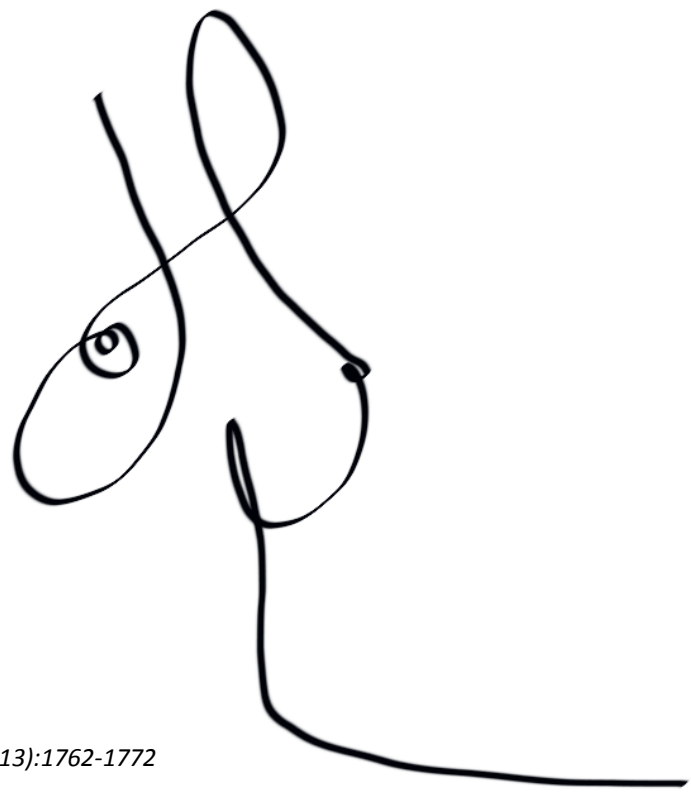
Chapter 8

Rates of re-excision and conversion to mastectomy after breast-conserving surgery with or without oncoplastic surgery: a nationwide population-based study



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British Journal of Surgery, 2020;107(13):1762-1772

Abstract

Background

There is no consensus regarding the impact of oncoplastic surgery (OPS) on rates of re-excision and conversion to mastectomy following breast-conserving surgery (BCS). Here these two outcomes after BCS and OPS were compared in a nationwide population-based setting.

Methods

In Denmark, all OPS is registered and categorized into volume displacement, volume reduction or volume replacement. Patients who underwent BCS or OPS between 2012 and 2018 were selected from the Danish Breast Cancer Group database. Multivariable analyses were performed to adjust for confounders, and propensity score matching to limit potential confounding by indication bias.

Results

A total of 13,185 patients (72.5%) underwent BCS and 5,003 (27.5%) OPS. Volume displacement was used in 4,171 patients (83.4%), volume reduction in 679 (13.6%) and volume replacement in 153 (3.1%). Re-excision rates were 15.6 and 14.1% after BCS and OPS respectively. After adjusting for confounders, patients were less likely to have a re-excision following OPS than BCS (odds ratio (OR) 0.80, 95%-CI 0.72-0.88), specifically after volume displacement and reduction. The rate of conversion to mastectomy was similar after OPS and BCS (3.2 versus 3.7%; p=0·105), but with a lower risk in adjusted analysis (OR 0.69, 0.58 to.0·84), specifically after volume displacement and reduction procedures. Findings were similar after propensity score matching.

Conclusion

A modest decrease in re-excision rate and less frequent conversion to mastectomy were observed after OPS compared with BCS.

Introduction

Randomized trials[1-5] conducted in the 1980s established breast-conserving surgery (BCS) followed by radiotherapy as the preferred treatment for early-stage breast cancer. Improved breast cancer survival rates[6,7] have led to an increased focus on cosmetic outcomes after treatment.[8] Consequently, a challenging balance has emerged between achieving complete resection of the tumor with appropriate tumor-free margins and a favorable cosmetic result. Not every patient is eligible for BCS owing to anatomical and tumor characteristics.[9]

Oncoplastic surgery (OPS) improves cosmetic outcomes and is nowadays used in up to 34% of patients with breast cancer undergoing BCS.[10-14] Previous studies[15,16] have demonstrated that by using OPS breast conservation becomes an alternative to mastectomy in patients with large and multifocal tumors. Compared with BCS, OPS is associated with larger resections,[17,18] and good long-term survival outcomes[11,13,18,19] and quality of life.[20-22] Achieving larger tumor resections with OPS may also reduce the number of re-excisions owing to insufficient margins. High-quality evidence regarding the impact of OPS on re-excisions is, however, sparse.[18,19]

Between 2000 and 2009, re-excision after BCS occurred in about 17% of patients with breast cancer in Denmark,[23] which is within the reported range of 5-35%.[22,24-26] Re-excision requiring mastectomy is commonly defined as conversion to mastectomy. Re-excision and conversion to mastectomy are associated with more morbidity, complications, poorer aesthetic outcome, greater patient distress and increased healthcare costs.[27,28] Furthermore, for patients in whom free margins were not achieved during primary BCS, an increased risk of ipsilateral breast tumor recurrence has been reported.[23]

In Denmark, OPS techniques have been registered prospectively by the Danish Breast Cancer Group (DBCG) for all patients undergoing BCS since July 2010. The primary goal of the present study was to compare re-excision rates after BCS versus OPS in patients with early-stage breast cancer, in a population-based national setting. A further aim was to investigate whether OPS results in a lower conversion to mastectomy rate (CMR) than BCS. As several studies[11-13,29] have shown that patients may not have the same likelihood of receiving OPS based on their baseline characteristics, additional propensity score matching was used to limit the potential confounding by indication bias.

Methods

Since 1978, the DBCG has collected clinicopathological and treatment characteristics and follow-up data prospectively from all patients diagnosed with a primary invasive breast cancer.[30] OPS is categorized into three types: volume displacement, defined as local rearrangement of tissue near the lumpectomy cavity in order to close the defect; volume reduction, defined as the use of a breast reduction technique to remove tumor and improve breast shape at the same time; and volume replacement, defined as tissue transfer from outside the breast into the breast (such as local perforator flaps). A more detailed description of data collection by the DBCG has been published.[30,31] The study was approved by the Scientific Committee of Surgery within the DBCG and the Danish Clinical Registries.

Study population

All women with invasive breast cancer without distant metastasis, who underwent primary BCS between January 2012 and December 2018, identified from the DBCG database were included. Patients who received neoadjuvant therapy or surgical biopsy as the only surgical procedure were excluded. Patients were categorized into four groups: BCS (without OPS), OPS with volume displacement, OPS with volume reduction, and OPS with volume replacement.

Outcomes

The primary outcome was re-excision, defined as a second BCS procedure or mastectomy following the primary BCS within 2 months of the initial operation. This interval was chosen to limit potential re-excisions owing to breast cancer recurrence. Information about re-excision, including type, was retrieved from Danish National Patient Registry.[32] Re-excision rates among patients aged over 50 years might be influenced by use of boost radiation for treatment of insufficient margins, so secondary interventions (re-excision or boost radiation) were compared in patients aged 50 years or older undergoing BCS or OPS. The secondary outcome, CMR, was defined as the rate of mastectomy following the primary BCS within 2 months of the initial operation.

Confounders

Co-morbidity was classified according to the Charlson Co-morbidity Index (CCI).[33] Histological subtypes, such as papillary, medullary and mucinous subtypes, were categorized as ‘other’. In Denmark, grading is applied to invasive ductal and lobular

carcinomas, but not to subtypes classified as 'other', according to the modified version of the Bloom Richardson scoring system of Elston and Ellis.[34] Breast cancer was classified as estrogen receptor-positive when at least 10% of cells stained positive in immunohistochemical analyses. Expression of human epidermal growth factor receptor 2 (HER2) was determined according to standard recommendations.[35] Tumor size and lymph node status were categorized according to the seventh edition of the AJCC cancer staging classification.[36] Any missing characteristics were classified as unknown.

Guidelines

In accordance with Danish guidelines,[30,31] re-excision was advised if invasive carcinoma was identified at the inked margins or ductal carcinoma in situ (DCIS) within 2 mm from the margin. Danish guidelines also recommend boost radiation in all patients younger than 50 years after BCS with or without OPS; and in those with a microscopic free margin of less than 2 mm for invasive breast cancer or DCIS, irrespective of age.[37,38]

Statistical analysis

Patient and tumor characteristics were compared between BCS and OPS groups using $\chi 2$ test for categorical variables, and Mann–Whitney U test or Kruskal–Wallis test for continuous variables. Unknown characteristics were included in the descriptive statistics. Two-sided $P < 0{\cdot}050$ was considered statistically significant. To adjust for confounders, a multivariable logistic regression model was used to estimate whether patients who underwent OPS were more likely to have a re-excision than those who had BCS. Results were expressed as odds ratios (ORs) with 95% confidence intervals, and the Wald test was used for analysis of statistical significance. The latter analyses were repeated for the secondary outcome CMR. Patients with unknown variables were included as a separate category in all analyses.

To evaluate whether associations were subject to confounding by indication, meaning that not all patients were equally likely to have received OPS, analyses were repeated in propensity score-matched cohorts. Patients who underwent BCS were matched with those who had OPS as a whole and by each type of OPS. Patients were matched on the likelihood of undergoing OPS using the following co-variables: year of operation, age, CCI score, histological finding, differentiation grade, estrogen receptor positivity, HER2 status, T and N status.[39,40] Patients who underwent BCS were matched 1:1 with those who had OPS using a caliper width of 0.2 times the standard deviation of the logit of the propensity score.[41] Potential imbalances in characteristics before and after matching were shown using a standardized difference; a value of 10% or more was

indicative of an imbalance in characteristics.[42] All analyses were performed using SPSS® version 24 (IBM, Armonk, New York, USA).

Results

A total of 18,188 patients met the inclusion criteria, of whom 13,185 (72.5%) underwent BCS and 5,003 (27.5%) OPS. Patients who had BCS were older than those who had OPS (mean (s.d.) 62.1 (11.5) versus 59.9 (11.5) years; p<0.001) (Table 8.1). Patients who underwent OPS had a lower co-morbidity score than those who had BCS (p<0.001), but poorer prognostic tumor factors, including higher differentiation grade (p<0.001), larger tumor size (p<0.001) and more lymph node involvement (p<0.001). The use of OPS decreased significantly from 30.3% in 2012 to 26.4% in 2018 (p<0.001).
OPS was performed with volume displacement in 4,171 patients (83.4%), volume reduction in 679 (13.6%) and volume replacement in 153 (3.1%). Patients who underwent OPS with volume reduction or replacement had lower co-morbidity scores (p=0.020), larger tumors (p<0.001) and more lymph node involvement (p<0.001) than those who had volume displacement (Table 8.2). Baseline characteristics of patients who underwent the three types of OPS are provided in Table 8.2.
In total, 2,763 patients (15.2%) underwent re-excision, in whom the final surgical treatment was BCS in 2,108 patients (76.3%) and mastectomy in 655 (23.7%). The re-excision rate was 15.6% for patients who underwent BCS and 14.1% among those who had OPS (p=0.012). Re-excision rates varied according to OPS technique: 14.5% for volume displacement, 10.3% for volume reduction and 20.9% for volume replacement (Table 8.3). The unadjusted re-excision rate did not change significantly over time (p=0.438).
Multivariable analysis showed that patients who underwent OPS were less likely to undergo re-excision than those who had BCS (adjusted OR 0.80, 95%-CI 0.72-0.88). Subsequent analyses showed that patients who underwent OPS with volume displacement (OR 0.83, 95%-CI 0.75-0·92) or volume reduction (OR 0.50, 95%-CI 0.39-0.65) were less likely to undergo re-excision than those who had BCS (Table 8.3). Patients who underwent OPS with volume replacement had the same likelihood of re-excision as the BCS group (OR 1.16, 95%-CI 0.78-1.73).
Other characteristics associated with re-excision were lobular or other histological subtype, higher differentiation grade, unknown estrogen receptor status, positive HER2 status, larger tumor size and lymph node involvement (Table 8.3). Re-excisions were less likely with increasing age. Year of surgery and co-morbidity were not associated with re-excision.

Table 8.1. Baseline characteristics of patients who underwent breast-conserving surgery or oncoplastic surgery.

	All patients (n=18,88)	BCS (n=13,185)	BCS with OPS (n=5,003)	p-value†
Year of operation				<0.001
2012	2,667 (14.7)	1,858 (14.1)	809 (16.2)	
2013	2,733 (15.0)	2,052 (15.6)	681 (13.6)	
2014	2,751 (15.1)	1,933 (14.7)	818 (16.4)	
2015	2,626 (14.4)	1,909 (14.5)	717 (14.3)	
2016	2,533 (13.9)	1,852 (14.0)	681 (13.6)	
2017	2,476 (13.6)	1,813 (13.8)	663 (13.3)	
2018	2,402 (13.2)	1,768 (13.4)	634 (12.7)	
Age (years)*	61.5 (11.5)	62.1 (11.5)	59.9 (11.5)	<0.001‡
Charlson Co-morbidity				<0.001
Index Score				
0	13,987 (76.9)	9,942 (75.4)	4,045 (80.9)	
1	2,500 (13.7)	1,910 (14.5)	590 (11.8)	
2	1,118 (6.1)	868 (6.6)	250 (5.0)	
≥3	583 (3.2)	465 (3.5)	118 (2.4)	
Histological finding				<0.001
ductal	14,777 (81.2)	10,669 (80.9)	4,108 (82.1)	
lobular	1,888 (10.4)	1,339 (10.2)	549 (11.0)	
other	1,505 (8.3)	1,161 (8.8)	344 (6.9)	
unknown	18 (0.1)	16 (0.1)	2 (0.0)	
Differentiation grade				<0.001
I	4,809 (26.4)	3,683 (27.9)	1,126 (22.5)	
II	7,958 (43.8)	5,700 (43.2)	2,258 (45.1)	
III	3,747 (20.6)	2,496 (18.9)	1,251 (25)	
not determined	1,505 (8.3)	1,161 (8.8)	344 (6.9)	
unknown	169 (0.9)	145 (1.1)	24 (0.5)	
Oestrogen receptor (%)				<0.001
<10	2,272 (12.5)	1,562 (11.8)	710 (14.2)	
≥10	15,867 (87.2)	11,583 (87.8)	4,284 (85.6)	
unknown	49 (0.3)	40 (0.3)	9 (0.2)	
HER2 status				<0.001
negative	16,086 (88.4)	11,751 (89.1)	4,335 (86.6)	
positive	1,916 (10.5)	1,281 (9.7)	635 (12.7)	
unknown	186 (1.0)	153 (1.2)	33 (0.7)	
T category				<0.001
T1	14,302 (78.6)	10,854 (82.3)	3,448 (68.9)	
T2	3,790 (20.8)	2,264 (17.2)	1,526 (30.5)	
T3	85 (0.5)	57 (0.4)	28 (0.6)	
Unknown	11 (0.1)	10 (0.1)	1 (0.0)	
N category				<0.001
N0	12,649 (69.5)	9,397 (71.3)	3,252 (65.0)	
N1	4,220 (23.2)	2,818 (21.4)	1,402 (28.0)	
N2	673 (3.7)	436 (3.3)	237 (4.7)	
N3	313 (1.7)	226 (1.7)	87 (1.7)	
Unknown	333 (1.8)	308 (2.3)	25 (0.5)	

Values in parentheses are percentages unless indicated otherwise; *values are mean (s.d.). BCS, breast-conserving surgery; OPS, oncoplastic surgery; HER2, human epidermal growth factor receptor 2. † χ^2 test, except; ‡ Mann–Whitney *U* test.

Table 8.2 Baseline characteristics according to type of oncoplastic surgery.

	Volume displacement (n=4,171)	Volume reduction (n=679)	Volume replacement (n=153)	p-value†
Year of operation				<0.001
2012	658 (15.8)	113 (16.6)	38 (24.8)	
2013	536 (12.9)	119 (17.5)	26 (17.0)	
2014	680 (16.3)	111 (16.3)	27 (17.6)	
2015	609 (14.6)	88 (13.0)	20 (13.1)	
2016	561 (13.5)	97 (14.3)	23 (15.0)	
2017	583 (14.0)	72 (10.6)	8 (5.2)	
2018	544 (13.0)	79 (11.6)	11 (7.2)	
Age (years)*	60.1 (11.5)	58·9 (11.2)	57·4 (10.3)	<0.001‡
Charlson Co-morbidity				0.020
Index score				
0	3,355 (80.4)	557 (82)	133 (86.9)	
1	515 (12.3)	63 (9.3)	12 (7.8)	
2	198 (4.7)	44 (6.5)	8 (5.2)	
≥3	103 (2.5)	15 (2.2)	0 (0)	
Histological finding				0.909
ductal	3,418 (81.9)	563 (82.9)	127 (83.0)	
lobular	456 (10.9)	75 (11.0)	18 (11.8)	
other	295 (7.1)	41 (6.0)	8 (5.2)	
unknown	2 (0)	0 (0)	0 (0)	
Differentiation grade				0.071
I	963 (23.1)	131 (19.3)	32 (20.9)	
II	1,884 (45.2)	299 (44.0)	75 (49.0)	
III	1,010 (24.2)	204 (30.0)	37 (24.2)	
not determined	295 (7.1)	41 (6.0)	8 (5.2)	
unknown	19 (0.5)	4 (0.6)	1 (0.7)	
Oestrogen receptor (%)				0.752
<10	592 (14.2)	95 (14.0)	23 (15.0)	
≥10	3,570 (85.6)	584 (86.0)	130 (85.0)	
unknown	9 (0.2)	0 (0)	0 (0)	
HER2 status				0.721
negative	3,620 (86.8)	581 (85.6)	134 (87.6)	
positive	522 (12.5)	94 (13.8)	19 (12.4)	
unknown	29 (0.7)	4 (0.6)	0 (0)	
T category				<0.001
T1	3000 (71.9)	370 (54.5)	78 (51.0)	
T2	1152 (27.6)	300 (44.2)	74 (48.4)	
T3	18 (0.4)	9 (1.3)	1 (0.7)	
unknown	1 (0)	0 (0)	0 (0)	
N category				0.006
N0	2749 (65.9)	417 (61.4)	86 (56.2)	
N1	1,134 (27.2)	215 (31.7)	53 (34.6)	
N2	190 (4.6)	39 (5.7)	8 (5.2)	
N3	74 (1.8)	7 (1.0)	6 (3.9)	
unknown	24 (0.6)	1 (0.1)	0 (0)	

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). HER2, human epidermal growth factor receptor 2. † $\chi 2$ test, except; ‡ Kruskal–Wallis test.

A shift from an imbalance in characteristics before propensity score matching to a balance after matching was observed when the BCS group was matched with the OPS group as a whole, and by type of OPS (Tables S8.1–S8.4, supporting information). In the matched cohort with OPS as a whole, re-excision was less likely after OPS than BCS (OR 0.79, 95%-CI 0·71-0·88), similar to the results of multivariable analysis of the unmatched study population. Matched patients who underwent OPS with volume displacement (OR 0.80, 95%-CI 0.71-0.90) or volume reduction (OR 0.46, 95%-CI 0.34-0.63) were less likely to undergo re-excision than the BCS group, whereas patients who underwent OPS with volume replacement had the same likelihood of re-excision as patients who had BCS (OR 1.13, 95%-CI 0.65-1.98).

Further analyses showed similar use of secondary interventions in patients older than 50 years undergoing BCS or OPS (16.4 versus 15.9%; p=0.430). However, among patients who had secondary interventions, boost radiation was used less often in patients who underwent BCS compared with those who had OPS (14.7 versus 21.2%; p<0·001).

In total, conversion to mastectomy was performed in 655 patients (3.6%). The CMR was 3.7 and 3.2% after BCS and OPS respectively (p=0.105). Different CMRs were observed among the OPS techniques: 3.2% for volume displacement, 2.9% for volume reduction and 5.9% for volume replacement. Over time, the unadjusted CMR decreased significantly from 4.3 to 2.7% (p=0.003) (Table S8.5, supporting information).

Table 8.3. Univariable and multivariable logistic regression analyses of characteristics predictive of re-excision.

	Re-excision		Odds ratio† Univariable analysis	Odds ratio† Multivariable analysis	
	No (n=15,425)	Yes (n=2,763)	(n=18,188)	(n=18,188)	p-value‡
Type of surgery					<0.001
BCS	11,128 (84.4)	2,057 (15.6)	1.00 (reference)	1.00 (reference)	
volume displacement	3,567 (85.5)	604 (14.5)	0.92 (0.83-1.01)	0.83 (0.75-0.92)	
volume reduction	609 (89.7)	70 (10.3)	0.62 (0.48-0.80)	0.50 (0.39-0.65)	
volume replacement	121 (79.1)	32 (20.9)	1.43 (0.97-2.12)	1.16 (0.78-1.73)	
Year of operation					0.202
2012	2,295 (86.1)	372 (13.9)	1.00 (reference)	1.00 (reference)	0.202
2013	2,332 (85.3)	401 (14.7)	1.06 (0.91-1.24)	1.07 (0.92-1.25)	
2014	2,330 (84.7)	421 (15.3)	1.12 (0.96-1.30)	1.12 (0.96-1.31)	
2015	2,208 (84.1)	418 (15.9)	1.17 (1.00-1.36)	1.19 (1.02-1.39)	
2016	2,144 (84.6)	389 (15.4)	1.12 (0.96-1.31)	1.13 (0.97-1.33)	
2017	2,083 (84.1)	393 (15.9)	1.16 (1.00-1.36)	1.21 (1.04-1.42)	
2018	2,033 (84.6)	369 (15.4)	1.12 (0.96-1.31)	1.19 (1.01-1.39)	
Age (years)*	61.8 (11.6)	59.9 (11.2)	0.99 (0.98-0.99)	0.99 (0.98-0.99)	<0.001
Charlson Co-morbidity Index score					0.061
0	11 790 (84·3)	2,197 (15.7)	1.00 (reference)	1.00 (reference)	
1	2148 (85·9)	352 (14.1)	0.88 (0.78-0.99)	0.94 (0.83-1.07)	
2	962 (86·0)	156 (14.0)	0.87 (0.73-1.04)	0.96 (0.81-1.15)	
≥3	525 (90·1)	58 (9.9)	0.59 (0.45-0.78)	0.69 (0.52-0.91)	

Table 8.3. (continued)

	Re-excision		Odds ratio† Univariable analysis	Multivariable analysis	
	No (n=15,425)	Yes (n=2,763)	(n=18,188)	(n=18,188)	p-value‡
Histological finding					<0.001
ductal	12,614 (85.4)	2,163 (14.6)	1.00 (reference)	1.00 (reference)	
lobular	1,527 (80.9)	361 (19.1)	1.38 (1.22-1.56)	1.40 (1.23-1.59)	
other	1,269 (84.3)	236 (15.7)	1.09 (0.94-1.26)	1.45 (1.22-1.71)	
unknown	15 (83.3)	3 (16.7)	1.17 (0.34-4.03)	0.18 (0.04-0.78)	
Differentiation grade					<0.001
I	4,246 (88.3)	563 (11.7)	1.00 (reference)	1.00 (reference)	
II	6,658 (83.7)	1,300 (16.3)	1.35 (1.23-1.48)	1.32 (1.19-1.47)	
III	3,141 (83.8)	606 (16.2)	1.33 (1.19-1.49)	1.18 (1.03-1.36)	
not determined	1,269 (84.3)	236 (15.7)	-	-	
unknown	111 (65.7)	58 (34.3)	3.61 (2.60-5.00)	3.69 (2.57-5.3)	
Oestrogen receptor (%)					0.005
<10	1,902 (83.7)	370 (16.3)	1.10 (0.98-1.24)	0.97 (0.85-1.12)	
≥10	13,490 (85.0)	2,377 (15.0)	1.00 (reference)	1.00 (reference)	
unknown	33 (67.3)	16 (32.7)	2.75 (1.51-5.01)	3.69 (1.66-8.21)	
HER2 status					<0.001
negative	13,775 (85.6)	2,311 (14.4)	1.00 (reference)	1.00 (reference)	
positive	1,496 (78.1)	420 (21.9)	1.67 (1.49-1.88)	1.60 (1.42-1.81)	
unknown	154 (82.8)	32 (17.2)	1.24 (0.84-1.82)	0.85 (0.52-1.38)	
T category					<0.001
T1	12,284 (85.9)	2,018 (14.1)	1.00 (reference)	1.00 (reference)	
T2	3,097 (81.7)	693 (18.3)	1.36 (1.24-1.50)	1.33 (1.20-1.48)	
T3	37 (43.5)	48 (56.5)	7.90 (5.13-12.16)	7.16 (4.58-11.18)	
Unknown	7 (63.6)	4 (36.4)	3.48 (1.02-11.89)	2.58 (0.64-10.37)	
N category					<0.001
N0	10,865 (85.9)	1,784 (14.1)	1.00 (reference)	1.00 (reference)	
N1	3,501 (83.0)	719 (17.0)	1.25 (1.14-1.38)	1.20 (1.09-1.33)	
N2	521 (77.4)	152 (22.6)	1.78 (1.47-2.14)	1.51 (1.24-1.84)	
N3	243 (77.6)	70 (22.4)	1.75 (1.34-2.30)	1.39 (1.05-1.84)	
Unknown	295 (88.6)	38 (11.4)	0.79 (0.59-1.10)	0.75 (0.52-1.09)	

Values in parentheses are percentages unless indicated otherwise. BCS, breast-conserving surgery; HER2, human epidermal growth factor receptor 2. * Values are mean(s.d.) and † values in parentheses are 95%-CIs; † Adjusted for type of surgery, year of operation, age, histological finding, differentiation grade, estrogen receptor, HER2 status, T and N category; ‡ Wald test.

Multivariable analysis showed that patients who underwent OPS were less likely to undergo conversion to mastectomy than those who had BCS (OR 0.69, 95%-CI 0.58-0.84). Similar results were found for subgroups who had OPS with volume displacement (OR 0.71, 95%-CI 0.58-0.87) or volume reduction (OR 0.53, 95%-CI 0.33-0.84) (Table S8.5, supporting information). There was no difference in CMR between OPS with volume replacement and BCS (OR 1.07, 95%-CI 0.53-2.13). Conversion to mastectomy was more likely in patients with poor prognostic characteristics, including lobular histology (p<0.001), larger tumor (p<0·001) and more lymph node involvement (p<0.001). In the matched cohorts (Tables S8.1-S8.4, supporting information), results of multivariable analyses were similar to those for the unmatched groups, in comparisons of OPS as a whole versus BCS (OR 0.70, 95%-CI 0.57-0.86), and OPS with volume

displacement (OR 0.67, 95%-CI 0.54-0.84), volume reduction (OR 0.51, 95%-CI 0.30-0.89) or volume replacement (OR 1.13, 95%-CI 0.43-3.02) versus BCS.

Discussion

In this population-based cohort study, re-excision or conversion to mastectomy was less likely among patients who underwent OPS than BCS, although differences were modest. The re-excision rate and CMR were lower among patients who underwent OPS using volume displacement and reduction techniques, but both rates were similar after BCS and OPS with volume replacement, although numbers in the latter group were small. This large population-based study adjusted for confounders, and limited confounding by indication bias by means of propensity score matching.

Although no long-term differences in recurrence rates and survival between BCS and OPS have been reported,[13,19,22,43-45] current evidence regarding the impact of OPS on the re-excision rate is limited because the data are from single-center studies with relatively few patients undergoing OPS (ranging from 31 to 1177), and in most studies the methodology was weak.[11,13,44,46-48] The present results are in line with a meta-analysis[19] from 2018 that found a significantly lower risk of re-excision in patients who underwent OPS compared with those who had BCS (relative risk 0.66, 95%-CI 0.48-0.90). However, more recently, comparable re-excision rates after BCS and OPS were reported in two studies from Finland[13] and Iceland.[11] In contrast to the present study, only relatively small numbers of patients were included, without extensive adjustment for confounders.

Since 2011, Danish guidelines[31] have stated that OPS should be considered when, for example, tumor size and location do not allow a satisfactory cosmetic result with BCS. In the present study, use of OPS among patients who underwent BCS decreased between 2012 and 2018 (from 30.3 to 26.4%), specifically in volume reduction and replacement techniques. A large multicenter study[10] from the USA showed a significant rise in the OPS rate from 4.3 to 9.0% between 2005 and 2016. Among those who underwent OPS, the percentage who had volume displacement was similar to that in the present study (85.2 and 83.4% respectively). Nonetheless, the overall use of OPS here was still substantially higher than in most previous studies.[18,19]

Boost radiation is associated with serious side-effects such as fibrosis, radiation heart disease and second non-breast cancer,[49,50] and so re-excision may have been preferred over boost radiation, specifically in patients with a tumor bed in front of the heart.[51] Nonetheless, in the present study, the rate of secondary interventions among patients older than 50 years was similar in those undergoing BCS and OPS, although boost

radiation was preferred to re-excision in the event of insufficient margins for those who underwent OPS. This was slightly surprising, as radiotherapy planning is challenging after OPS, because identification of the tumor bed can be difficult.[52] These findings highlight the challenge in balancing morbidity from re-excision with that of boost radiation, and the importance of close collaboration between surgeons and radiation oncologists. Any decision regarding re-excision or boost radiation should be made at a multidisciplinary team meeting.

Heterogeneous definitions of insufficient margins, ranging from 'tumor within 10mm from the ink margin' to 'tumor on ink', may partly explain the difference between the findings here and those of other studies.[18,19] The present overall re-excision rate of 15.2% is within the range (0-15.7%) reported in other studies that used the same definition of 'tumor on ink'.[13,53-55] The associations between poor prognostic factors, such as larger tumor or lymph node involvement, and re-excision and conversion to mastectomy are in line with previous findings.[18,53,55] Future guidelines may highlight the additional risk when considering OPS in these patients.

The overall CMR of 3.6% in this analysis is well below the mean of 6.2% and within the range of 0-34.2% reported in previous studies, and a systematic review of 55 studies.[18] However, it is not in line with the results of a meta-analysis from 2014,[17] which found a higher CMR for OPS with volume reduction and volume replacement compared with BCS. This may be explained partly by the fact that most included studies did not adjust for confounders and did not exclude patients diagnosed with *in situ* disease alone, because such patients are less likely to have a re-excision rate similar to that for invasive breast cancer.[56]

The differing rates of re-excision between OPS techniques might be explained by the small absolute numbers, and consequently wide confidence intervals. Another explanation could be differences in patient or tumor factors used for surgical procedure selection. Breast and tumor size, tumor location and glandular density are, among other factors, used in selection of the preferred OPS technique,[16,57] but also affect the likelihood of having a secondary mastectomy. For instance, patients with smaller breasts who require OPS with volume replacement may be less eligible for a secondary BCS, and may therefore undergo a secondary mastectomy when indicated.

The present data support the theory that OPS is associated with fewer re-excisions, although other explanations are possible. Patients and surgeons might be less willing to accept re-excisions following OPS because of the primary focus on the cosmetic result. Unfortunately, tumor margin data for the primary procedure are incomplete in the DBCG database for the early years of the present study and could therefore not be included.

Future studies should evaluate whether the effect of OPS on re-excision is similar in patients treated with and with- out neoadjuvant therapy, as patients who are considered candidates for neoadjuvant therapy, such as those with locally advanced tumors,[58] are also candidates for OPS. Neoadjuvant chemotherapy can be used for tumor downstaging, making more patients eligible for BCS without OPS. It could therefore be argued that there might be less need for OPS in the future as use of neoadjuvant chemotherapy in most high-income countries has been increasing in recent years.[8,57] Neoadjuvant chemotherapy has only been used for breast cancer downstaging in Denmark more recently,[59,60] and patients receiving such treatment were not included in the present study. The increasing use of neoadjuvant chemotherapy might, however, explain the slight decrease in OPS in more recent years in this study.

The changing paradigm from primary BCS to more mastectomy seen in, for instance, the USA could also have influenced the present findings.[61] Earlier reports from the DBCG database, however, showed that the proportion of patients undergoing primary mastectomy remained stable at around 25% in Denmark during the inclusion period of the present study.[59,60]

This study has several limitations. Several factors, such as breast size,[22] smoking status[11] and surgeons' preference,[62] are known to affect both the choice of surgery and outcomes. Likewise, local resources (such as operating times) and level of experience among staff members can affect both the use of OPS and re-excision rates. Unfortunately, information on these potential confounders was not available. Moreover, the rationale behind the choice of a specific surgical technique (such as racket mammoplasty or reduction with superior pedicle flap) is not registered by the DBCG. Residual confounding by indication could have been present as the matched analyses could only include available variables.

The present findings do not support the use of OPS in all patients undergoing BCS, but rather highlight the safety of OPS for those in whom a satisfactory cosmetic result could not be achieved with BCS alone. This study does not encourage the use of OPS in every patient, but emphasizes its appropriate use in selected patients who otherwise would not be eligible for breast conservation.

Supporting information

Table S8.1. Baseline characteristics of patients who underwent BCS and oncoplastic surgery before and after matching.

	Before matching			After matching [a]		
	BCS (n=13,185)	OPS (n=5,003)	Standardized difference	BCS (n=5,003)	OPS (n=5,003)	Standardized difference
Year of operation						
2012	1,858 (14.1)	809 (16.2)	0.058	829 (16.6)	809 (16.2)	0.011
2013	2,052 (15.6)	681 (13.6)	0.055	655 (13.1)	681 (16.4)	0.015
2014	1,933 (14.7)	818 (16.4)	0.047	773 (15.5)	818 (16.4)	0.025
2015	1,909 (14.5)	717 (14.3)	0.004	735 (14.7)	717 (14.3)	0.010
2016	1,852 (14.0)	681 (13.6)	0.013	673 (13.5)	681 (13.6)	0.005
2017	1,813 (13.8)	663 (13.3)	0.015	701 (14.0)	663 (13.3)	0.022
2018	1,768 (13.4)	634 (12.7)	0.022	637 (12.7)	634 (12.7)	0.002
Age, mean (SD)	62.1 (11.5)	59.9 (11.5)	0.190	59.8 (11.8)	59.9 (11.5)	0.008
CCI						
0	9,942 (75.4)	4,045 (80.9)	0.132	4,081 (81.6)	4,045 (80.9)	0.018
1	1,910 (14.5)	590 (11.8)	0.080	572 (11.4)	590 (11.8)	0.011
2	868 (6.6)	250 (5.0)	0.068	237 (4.7)	250 (5.0)	0.012
≥3	465 (3.5)	118 (2.4)	0.069	113 (2.3)	118 (2.4)	0.007
Histological finding						
ductal	10,669 (80.9)	4,108 (82.1)	0.031	4,144 (82.8)	4,108 (82.1)	0.019
lobular	1,339 (10.2)	549 (11.0)	0.027	532 (10.6)	549 (11.0)	0.011
other	1,161 (8.8)	344 (6.9)	0.072	325 (6.5)	344 (6.9)	0.015
unknown	16 (0.1)	2 (0.0)	0.029	2 (0.0)	2 (0.0)	<0.001
Differentiation grade						
I	3,683 (27.9)	1,126 (22.5)	0.125	1,148 (22.9)	1,126 (22.5)	0.010
II	5,700 (43.2)	2,258 (45.1)	0.038	2,303 (46.0)	2,258 (45.1)	0.018
III	2,496 (18.9)	1,251 (25)	0.147	1,202 (24.0)	1,251 (25.0)	0.023
ND	1,161 (8.8)	344 (6.9)	0.072	325 (6.5)	344 (6.9)	0.015
unknown	145 (1.1)	24 (0.5)	0.070	25 (0.5)	24 (0.5)	0.003
Oestrogen receptor (%)						
<10	1,562 (11.8)	710 (14.2)	0.070	662 (13.2)	710 (14.2)	0.028
≥10	11,583 (87.8)	4,284 (85.6)	0.066	4,334 (86.6)	4,284 (85.6)	0.029
unknown	40 (0.3)	9 (0.2)	0.025	7 (0.1)	9 (0.2)	0.010
HER2 status						
negative	11,751 (89.1)	4,335 (86.6)	0.076	4,399 (87.9)	4,335 (86.6)	0.038
positive	1,281 (9.7)	635 (12.7)	0.094	577 (11.5)	634 (12.7)	0.036
unknown	153 (1.2)	33 (0.7)	0.053	27 (0.5)	33 (0.7)	0.016
T category						
T1	10,854 (82.3)	3,448 (68.9)	0.316	3,458 (69.1)	3,448 (68.9)	0.004
T2	2,264 (17.2)	1,526 (30.5)	0.317	1,512 (30.2)	1,526 (30.5)	0.006
T3	57 (0.4)	28 (0.6)	0.018	32 (0.6)	28 (0.6)	0.010
unknown	10 (0.1)	1 (0.0)	0.026	1 (0.0)	1 (0.0)	<0.001
N category						
N0	9,397 (71.3)	3,252 (65.0)	0.135	3,290 (65.8)	3,252 (65.0)	0.016
N1	2,818 (21.4)	1,402 (28.0)	0.155	1,397 (27.9)	1,402 (28.0)	0.002
N2	436 (3.3)	237 (4.7)	0.073	218 (4.4)	237(4.7)	0.018
N3	226 (1.7)	87 (1.7)	0.002	75 (1.5)	87 (1.7)	0.019
unknown	308 (2.3)	25 (0.5)	0.156	23 (0.5)	25 (0.5)	0.006

Values are the number of patients followed by column percentages between parentheses. Note: Standardized difference of 10% or more reflects an imbalance. Abbreviations: breast-conserving surgery, BCS; Charlson Co-morbidity Index, CCI; standard deviation, SD; Not determined, ND. [a] Patients were matched on the likelihood of undergoing OPS as a whole using the following covariates: year of operation, age, CCI, histological finding, differentiation grade, oestrogen receptor, HER2 status, T-stage and N-status.

Table S8.2. Baseline characteristics of patients who underwent BCS and oncoplastic surgery with volume displacement before and after matching.

	Before matching			After matching [a]		
	BCS (n=13,185)	OPS (n=4,171)	Standardized difference	BCS (n=4,171)	OPS (n=4,171)	Standardized difference
Year of operation						
2012	1,858 (14.1)	658 (15.8)	0,047	693 (16.6)	658 (15.8)	0.023
2013	2,052 (15.6)	536 (12.9)	0,078	515 (12.3)	536 (12.9)	0.015
2014	1,933 (14.7)	680 (16.3)	0,045	629 (15.1)	680 (16.3)	0.034
2015	1,909 (14.5)	609 (14.6)	0.003	621 (14.9)	609 (14.6)	0.008
2016	1,852 (14.0)	561 (13.5)	0.017	554 (13.3)	561 (13.5)	0.005
2017	1,813 (13.8)	583 (14.0)	0.007	600 (14.4)	583 (14.0)	0.012
2018	1,768 (13.4)	544 (13.0)	0.011	559 (13.4)	544 (13.0)	0.011
Age, mean (SD)	62.1 (11.5)	60.1 (11.5)	0.168	60.0 (11.6)	60.1 (11.5)	0.016
CCI						
0	9,942 (75.4)	3,355 (80.4)	0.122	3,394 (81.4)	3,355 (80.4)	0.024
1	1,910 (14.5)	515 (12.3)	0.063	514 (12.3)	515 (12.3)	0.001
2	868 (6.6)	198 (4.7)	0.079	166 (4.0)	198 (4.7)	0.038
≥3	465 (3.5)	103 (2.5)	0.062	97 (2.3)	103 (2.5)	0.009
Histological finding						
ductal	10,669 (80.9)	3,418 (81.9)	0.026	3,478 (83.4)	3,418 (81.9)	0.038
lobular	1,339 (10.2)	456 (10.9)	0.025	413 (9.9)	456 (10.9)	0.034
other	1,161 (8.8)	295 (7.1)	0.064	278 (6.7)	295 (7.1)	0.016
unknown	16 (0.1)	2 (0)	0.025	2 (0.0)	2 (0.0)	<0.001
Differentiation grade						
I	3,683 (27.9)	963 (23.1)	0.111	943 (22.6)	963 (23.1)	0.011
II	5,700 (43.2)	1,884 (45.2)	0.039	1,9367 (46.4)	1,884 (45.2)	0.026
III	2,496 (18.9)	1,010 (24.2)	0.129	996 (23.9)	1,010 (24.2)	0.008
ND	1,161 (8.8)	295 (7.1)	0.064	278 (6.7)	295 (7.1)	0.016
unknown	145 (1.1)	19 (0.5)	0.073	17 (0.4)	19 (0.5)	0.007
Oestrogen receptor (%)						
<10	1,562 (11.8)	592 (14.2)	0.070	573 (13.7)	592 (14.2)	0.013
≥10	11,583 (87.8)	3,570 (85.6)	0.067	3,587 (86.0)	3,570 (85.6)	0.012
unknown	40 (0.3)	9 (0.2)	0.017	11 (0.3)	9 (0.2)	0.010
HER2 status						
negative	11,751 (89.1)	3,620 (86.8)	0.072	3,647 (87.4)	3,620 (86.8)	0.019
positive	1,281 (9.7)	522 (12.5)	0.089	501 (12.0)	522 (12.5)	0.015
unknown	153 (1.2)	29 (0.7)	0.049	23 (0.6)	29 (0.7)	0.018
T category						
T1	10,854 (82.3)	3,000 (71.9)	0.249	3,050 (73.1)	3,000 (71.9)	0.027
T2	2,264 (17.2)	1,152 (27.6)	0.253	1,105 (26.5)	1,152 (27.6)	0.025
T3	57 (0.4)	18 (0.4)	<0.001	14 (0.3)	18 (0.4)	0.016
unknown	10 (0.1)	1 (0)	0.023	2 (0.0)	1 (0.0)	0.013
N category						
N0	9,397 (71.3)	2,749 (65.9)	0.116	2,786 (66.8)	2,749 (65.9)	0.019
N1	2,818 (21.4)	1,134 (27.2)	0.136	1,123 (26.9)	1,134 (27.2)	0.006
N2	436 (3.3)	190 (4.6)	0.064	174 (4.2)	190 (4.6)	0.019
N3	226 (1.7)	74 (1.8)	0.005	69 (1.7)	74 (1.8)	0.009
unknown	308 (2.3)	24 (0.6)	0.147	19 (0.5)	23 (0.6)	0.017

Values are the number of patients followed by column percentages between parentheses. Note: Standardized difference of 10% or more reflects an imbalance. Abbreviations: breast-conserving surgery, BCS; Charlson Co-morbidity Index, CCI; standard deviation, SD; Not determined, ND. [a] Patients were matched on the likelihood of undergoing OPS with volume displacement using the following covariates: year of operation, age, CCI, histological finding, differentiation grade, oestrogen receptor, HER2 status, T-stage and N-status.

Table S8.3. Baseline characteristics of patients who underwent BCS and oncoplastic surgery with volume reduction before and after matching.

	Before matching			After matching [a]		
	BCS (n=13,185)	OPS (n=679)	Standardized difference	BCS (n=679)	OPS (n=679)	Standardized difference
Year of operation						
2012	1,858 (14.1)	113 (16.6)	0.071	109 (16.1)	113 (16.6)	0.016
2013	2,052 (15.6)	119 (17.5)	0.053	113 (16.6)	119 (17.5)	0.023
2014	1,933 (14.7)	111 (16.3)	0.047	104 (15.3)	111 (16.3)	0.028
2015	1,909 (14.5)	88 (13.0)	0.044	92 (13.5)	88 (13.0)	0.017
2016	1,852 (14.0)	97 (14.3)	0.007	103 (15.2)	97 (14.3)	0.025
2017	1,813 (13.8)	72 (10.6)	0.096	71 (10.5)	72 (10.6)	0.005
2018	1,768 (13.4)	79 (11.6)	0.054	87 (12.8)	79 (11.6)	0.036
Age, mean (SD)	62.1 (11.5)	58.9 (11.2)	0.277	59.5 (12.0)	58.9 (11.2)	0.045
CCI						
0	9,942 (75.4)	557 (82)	0.162	576 (84.8)	557 (82.0)	0.075
1	1,910 (14.5)	63 (9.3)	0.161	42 (6.2)	63 (9.3)	0.116
2	868 (6.6)	44 (6.5)	0.004	48 (7.1)	44 (6.5)	0.023
≥3	465 (3.5)	15 (2.2)	0.079	13 (1.9)	15 (2.2)	0.021
Histological finding						
ductal	10,669 (80.9)	563 (82.9)	0.052	575 (84.7)	563 (82.9)	0.048
lobular	1,339 (10.2)	75 (11.0)	0.029	75 (11.0)	75 (11.0)	<0.001
other	1,161 (8.8)	41 (6.0)	0.106	29 (4.3)	41 (6.0)	0.080
unknown	16 (0.1)	0 (0)	0.049	-	-	-
Differentiation grade						
I	3,683 (27.9)	131 (19.3)	0.205	133 (19.6)	131 (19.3)	0.007
II	5,700 (43.2)	299 (44.0)	0.016	313 (46.1)	299 (44.0)	0.041
III	2,496 (18.9)	204 (30.0)	0.261	201 (29.6)	204 (30.0)	0.010
ND	1,161 (8.8)	41 (6.0)	0.106	29 (4.3)	41 (6.0)	0.080
unknown	145 (1.1)	4 (0.6)	0.056	3 (0.4)	4 (0.6)	0.021
Oestrogen receptor (%)						
<10	1,562 (11.8)	95 (14.0)	0.064	100 (14.7)	95 (14.0)	0.021
≥10	11,583 (87.8)	584 (86.0)	0.055	579 (85.3)	584 (86.0)	0.021
unknown	40 (0.3)	0 (0)	0.078	-	-	-
HER2 status						
negative	11,751 (89.1)	581 (85.6)	0.107	597 (87.9)	581 (85.6)	0.070
positive	1,281 (9.7)	94 (13.8)	0.128	79 (11.6)	94 (13.8)	0.066
unknown	153 (1.2)	4 (0.6)	0.061	3 (0.4)	4 (0.6)	0.021
T category						
T1	10,854 (82.3)	370 (54.5)	0.627	370 (54.5)	370 (54.5)	<0.001
T2	2,264 (17.2)	300 (44.2)	0.613	300 (44.2)	300 (44.2)	<0.001
T3	57 (0.4)	9 (1.3)	0.096	9 (1.3)	9 (1.3)	<0.001
unknown	10 (0.1)	0 (0)	0.039	-	-	-
N category						
N0	9,397 (71.3)	417 (61.4)	0.210	428 (63.0)	417 (61.4)	0.033
N1	2,818 (21.4)	215 (31.7)	0.235	210 (30.9)	215 (31.7)	0.016
N2	436 (3.3)	39 (5.7)	0.117	37 (5.4)	39 (5.7)	0.013
N3	226 (1.7)	7 (1.0)	0.059	3 (0.4)	7 (1.0)	0.069
unknown	308 (2.3)	1 (0.1)	0.199	1 (0.1)	1 (0.1)	<0.001

Values are the number of patients followed by column percentages between parentheses. Note: Standardized difference of 10% or more reflects an imbalance. Abbreviations: breast-conserving surgery, BCS; Charlson Co-morbidity Index, CCI; standard deviation, SD; Not determined, ND. [a] Patients were matched on the likelihood of undergoing OPS with volume reduction using the following covariates: year of operation, age, CCI, histological finding, differentiation grade, oestrogen receptor, HER2 status, T-stage and N-status.

Table S8.4. Baseline characteristics of patients who underwent BCS and oncoplastic surgery with volume replacement before and after matching.

	Before matching			After matching [a]		
	BCS (n=13,185)	OPS (n=153)	Standardized difference	BCS (n=153)	OPS (n=153)	Standardized difference
Year of operation						
2012	1,858 (14.1)	38 (24.8)	0.274	37 (24.2)	38 (24.8)	0.015
2013	2,052 (15.6)	26 (17.0)	0.039	29 (19.0)	26 (17.0)	0.051
2014	1,933 (14.7)	27 (17.6)	0.081	22 (14.4)	27 (17.6)	0.089
2015	1,909 (14.5)	20 (13.1)	0.041	22 (14.4)	20 (13.1)	0.038
2016	1,852 (14.0)	23 (15.0)	0.028	28 (18.3)	23 (15.0)	0.088
2017	1,813 (13.8)	8 (5.2)	0.294	4 (2.6)	8 (5.2)	0.135
2018	1,768 (13.4)	11 (7.2)	0.206	11 (7.2)	11 (7.2)	<0.001
Age, mean (SD)	62.1 (11.5)	57.4 (10.3)	0.432	57.3 (13.3)	57.4 (10.3)	<0.001
CCI						
0	9,942 (75.4)	133 (86.9)	0.298	134 (87.6)	133 (86.9)	0.020
1	1,910 (14.5)	12 (7.8)	0.212	11 (7.2)	12 (7.8)	0.025
2	868 (6.6)	8 (5.2)	0.057	8 (5.2)	8 (5.2)	<0.001
≥3	465 (3.5)	0 (0)	0.270	-	-	-
Histological finding						
ductal	10,669 (80.9)	127 (83.0)	0.054	125 (81.7)	127 (83.0)	0.034
lobular	1,339 (10.2)	18 (11.8)	0.052	21 (13.7)	18 (11.8)	0.059
other	1,161 (8.8)	8 (5.2)	0.140	7 (4.6)	8 (5.2)	0.030
unknown	16 (0.1)	0 (0)	0.049	-	-	-
Differentiation grade						
I	3,683 (27.9)	32 (20.9)	0.164	25 (16.3)	32 (20.9)	0.118
II	5,700 (43.2)	75 (49.0)	0.116	86 (56.2)	75 (49.0)	0.144
III	2,496 (18.9)	37 (24.2)	0.128	34 (22.2)	37 (24.2)	0.046
ND	1,161 (8.8)	8 (5.2)	0.140	7 (4.6)	8 (5.2)	0.030
unknown	145 (1.1)	1 (0.7)	0.048	1 (0.7)	1 (0.7)	<0.001
Oestrogen receptor (%)						
<10	1,562 (11.8)	23 (15.0)	0.094	23 (15.0)	23 (15.0)	<0.001
≥10	11,583 (87.8)	130 (85.0)	0.084	130 (85.0)	130 (85.0)	<0.001
unknown	40 (0.3)	0 (0)	0.078	-	-	-
HER2 status						
negative	11,751 (89.1)	134 (87.6)	0.048	136 (88.9)	134 (87.6)	0.041
positive	1,281 (9.7)	19 (12.4)	0.086	17 (11.1)	19 (12.4)	0.041
unknown	153 (1.2)	0 (0)	0.153	-	-	-
T category						
T1	10,854 (82.3)	78 (51.0)	0.705	80 (52.3)	78 (51.0)	0.026
T2	2,264 (17.2)	74 (48.4)	0.705	72 (47.1)	74 (48.4)	0.026
T3	57 (0.4)	1 (0.7)	0.030	1 (0.7)	1 (0.7)	<0.001
unknown	10 (0.1)	0 (0)	0.040	-	-	-
N category						
N0	9,397 (71.3)	86 (56.2)	0.317	92 (60.1)	86 (56.2)	0.080
N1	2,818 (21.4)	53 (34.6)	0.299	39)25.5)	53 (34.6)	0.201
N2	436 (3.3)	8 (5.2)	0.095	10 (6.5)	8 (5.2)	0.056
N3	226 (1.7)	6 (3.9)	0.134	12 (7.8)	6 (3.9)	0.167
unknown	308 (2.3)	0 (0)	0.219	-	-	-

Values are the number of patients followed by column percentages between parentheses. Note: Standardized difference of 10% or more reflects an imbalance. Abbreviations: breast-conserving surgery, BCS; Charlson Co-morbidity Index, CCI; standard deviation, SD; Not determined, ND. [a] Patients were matched on the likelihood of undergoing OPS with volume replacement using the following covariates: year of operation, age, CCI, histological finding, differentiation grade, oestrogen receptor, HER2 status, T-stage and N-status.

Table S8.5. Univariable and multivariable analyses of characteristics predictive of conversion to mastectomy.

	Conversion to mastectomy [a]		Odds ratio (95%-CI)		
	No (n=17,533)	Yes (n=655)	Univariable (n=18,188)	Multivariable [b] (n=18,188)	p-value[‡]
Type of surgery					0.001
BCS	12,692 (96.3)	493 (3.7)	1.00 (reference)	1.00 (reference)	
volume displacement	4,038 (96.8)	133 (3.2)	0.85 (0.70-1.03)	0.71 (0.58-0.87)	
volume reduction	659 (97.1)	20 (2.9)	0.78 (0.50-1.23)	0.53 (0.33-0.84)	
volume replacement	144 (94.1)	9 (5.9)	1.61 (0.82-3.17)	1.07 (0.53-2.13)	
Year of operation					0.200
2012	2,551 (95.7)	116 (4.3)	1.00 (reference)	1·00 (reference)	
2013	2,626 (96.1)	107 (3.9)	0.9 (0.69-1.17)	0·92 (0.70-1.21)	
2014	2,646 (96.2)	105 (3.8)	0.87 (0.67-1.14)	0·89 (0.68-1.18)	
2015	2,539 (96.7)	87 (3.3)	0.75 (0.57-1.00)	0·78 (0.58-1.04)	
2016	2,447 (96.6)	86 (3.4)	0.77 (0.58-1.03)	0·79 (0.59-1.06)	
2017	2,386 (96.4)	90 (3.6)	0.83 (0.63-1.10)	0·90 (0.68-1.21)	
2018	2,338 (97.3)	64 (2.7)	0.60 (0.44-0.82)	0·66 (0.48-0.91)	
Age, mean (SD)	61.6 (11.5)	59.2 (12.4)	0.98 (0.98-0.99)	0·98 (0.97-0.99)	<0.001
CCI					0.550
0	13,468 (96.3)	519 (3.7)	1.00 (reference)	1.00 (reference)	
1	2,421 (96.8)	79 (3.2)	0.85 (0.67-1.08)	0.93 (0.73-1.20)	
2	1,075 (96.2)	43 (3.8)	1.04 (0.76-1.43)	1.20 (0.86-1.66)	
≥3	569 (97.6)	14 (2.4)	0.64 (0.37-1.09)	0.82 (0.48-1.42)	
Histological finding					<0.001
ductal	14,312 (96.9)	465 (3.1)	1.00 (reference)	1.00 (reference)	
lobular	1,753 (92.8)	135 (7.2)	2.37 (1.95-2.89)	2.34 (1.89-2.90)	
other	1,451 (96.4)	54 (3.6)	1.15 (0.86-1.53)	1.58 (1.12-2.38)	
unknown	17 (94.4)	1 (5.6)	1.81 (0.24-13.63)	0.12 (0.01-1.44)	
Differentiation grade					<0.001
I	4,696 (97.7)	113 (2.3)	1.00 (reference)	1.00 (reference)	
II	7,631 (95.9)	327 (4.1)	1.58 (1.31-1.91)	1.42 (1.13-1.77)	
III	3,604 (96.2)	143 (3.8)	1.46 (1.16-1.83)	1.15 (0.87-1.54)	
not determined	1,451 (96.4)	54 (3.6)	-	-	
unknown	151 (89.3)	18 (10.7)	4.39 (2.63-7.32)	3.87 (2.13-7.05)	
Oestrogen receptor (%)					0.120
<10	2,179 (95.9)	93 (4.1)	1.18 (0.94-1.47)	1.07 (0.83-1.39)	
≥10	15,311 (96.5)	556 (3.5)	1.00 (reference)	1.00 (reference)	
unknown	43 (87.8)	6 (12.2)	3.84 (1.63-9.07)	3.24 (1.03-10.19)	
HER2					<0.001
negative	15,548 (96.7)	538 (3.3)	1.00 (reference)	1.00 (reference)	
positive	1,812 (94.6)	104 (5.4)	1.66 (1.34-2.06)	1.63 (1.29-2.05)	
unknown	173 (93.0)	13 (7.0)	2.17 (1.23-3.84)	1.38 (0.66-2.88)	
T-stage					<0.001
T1	13,895 (97.2)	407 (2.8)	1.00 (reference)	1.00 (reference)	
T2	3,579 (94.4)	211 (5.6)	2.01 (1.70-2.39)	1.84 (1.52-2.22)	
T3	51 (60.0)	34 (40.0)	22.76 (14.59-35.52)	15.77 (9.72-25.59)	
unknown	8 (72.7)	3 (27.3)	12.80 (3.38-48.43)	7.48 (1.61-34.82)	
N-stage					<0.001
N0	12,292 (97.2)	357 (2.8)	1.00 (reference)	1.00 (reference)	
N1	4,027 (95.4)	193 (4.6)	1.65 (1.38-1.97)	1.49 (1.24-1.80)	
N2	609 (90.5)	64 (9.5)	3.62 (2.74-4.78)	2.54 (1.88-3.42)	
N3	283 (90.4)	30 (9.6)	3.65 (2.47-5.40)	2.29 (1.51-3.49)	
unknown	322 (96.7)	11 (3.3)	1.18 (0.64-2.17)	0.92 (0.47-1.80)	

Values in parentheses are 95 percent confidence intervals unless indicated otherwise. Abbreviations: breast-conserving surgery, BCS; standard deviation, SD; odds ratio, OR; confidence interval, CI. [a] Values are numbers and row percentages in parentheses. [b] Multivariable analyses were adjusted for type of surgery, year of operation, age, histological finding, differentiation grade, oestrogen receptor, HER2 status, T-stage and N-stage; [‡]Wald test.

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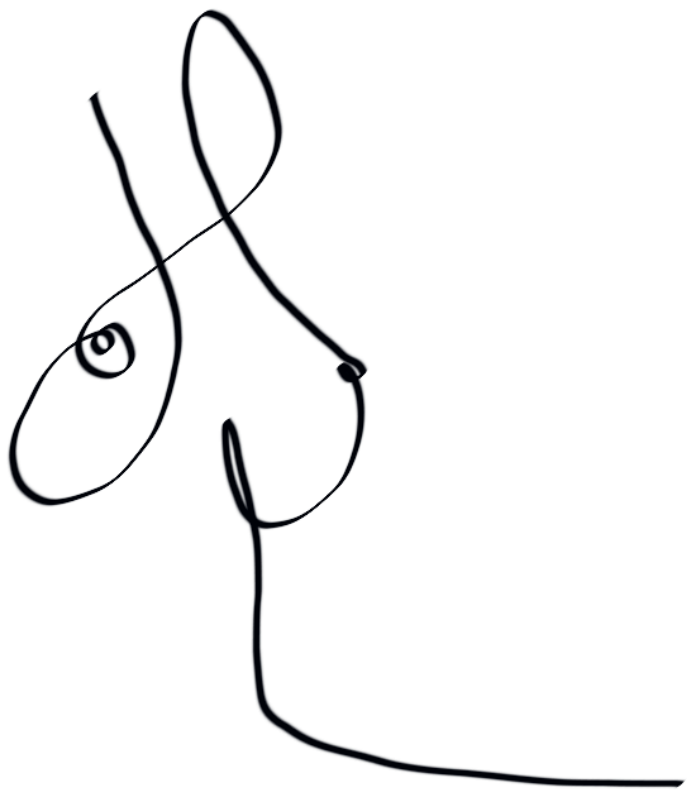
Chapter 9

General discussion and future perspectives



General discussion and future perspectives

Assessing and improving quality of breast cancer care has received an increasing attention in the last decades due to several reasons. Among these reasons are the increase in different treatment options and efficacy, but also the increased patients' autonomy and own responsibility due to the rising popularity of the concept of 'shared decision making'.[1,2] In this thesis, the six dimensions of healthcare quality (Table 9.1) according to the definition of the Institute of Medicine (IOM) were used to assess and improve the quality of breast cancer care.[3] For this purpose, data from different nationwide clinical breast cancer registries were compared and analyzed. In summary, quality aspects of hospital transfers, the continuity of the adjuvant chemotherapy pathway and several breast reconstruction strategies were assessed by addressing one or more of the six quality dimensions.

Table 9.1. Six dimensions of quality of healthcare defined by the Institute of Medicine

Dimension	Definition
Safety	Not harming or limiting the harm and risks for patients as a consequence of provided care
Effectiveness	Using care resources that have proven to result in the most superior clinical and non-clinical outcomes
Patient-centeredness	Providing care that considers patients' preferences after assuring patients are well-informed
Timeliness	Providing care that is timely without unnecessary delays considering time consuming factors
Efficiency	Maximizing resource use and limiting waste of care and resources
Equity	Limiting unintentional disparities in quality of care among patients with differences such as gender, race, intelligence, social-economic status, sexual orientation, insurance or location of residence

PART I: Hospital transfer in breast cancer care

The extent and impact of hospital transfers in breast cancer care

Delay of treatment is a frequent expressed concern of breast cancer patients. Analyzing potential delaying factors and components is emphasized for sufficient patient-counselling and improvement of the quality dimension *timeliness*. Various treatment delaying factors have been identified by previous studies,[4-7] but literature focusing on patients changing hospital after a breast cancer diagnosis (defined as a hospital transfer) and its impact on the continuity of breast cancer care is sparse. In **Chapter 2** we demonstrate that hospital transfers after diagnosis occurred in 24% of breast cancer

patients in the Netherlands, most commonly when patients were treated with neoadjuvant chemotherapy (NAC).[8] Primary treatment was significantly delayed for patients who transferred hospital,[8] especially in those who underwent primary surgery. Optimizing hospital transfers seems most warranted for patients who undergo mastectomy followed by immediate breast reconstruction (IBR) as the longest delay in primary treatment was observed in these patients. While the extent of hospital transfers is smaller compared to findings in the US, the treatment delaying impact is comparable.[5,6]

This thesis does not propagate that primary breast cancer treatment should be rushed as diagnostics, patient-counselling and commonly multidisciplinary treatment requires time. Moreover, modest treatment delay is not per se associated with decreased survival of breast cancer patients. However, a critical approach towards treatment delay seems defensible as several studies have shown an association between increased time from diagnosis to treatment and decreased outcomes.[9-11]

Hospital transfers seem inevitable in the Netherlands and several other European countries since healthcare systems and health insurances allow patient-initiated transfers and free choice of hospital. Furthermore, the call for centralization of high-expertise care will force certain patients to change hospital. The findings in this chapter may be useful for optimization the quality of care dimension *timeliness* as patients and physicians may not be aware of the delaying impact of breast cancer hospital transfers.

Current findings did not include whether treatment delay originated at the hospital of diagnosis or the treating hospital. Therefore, with the current level of evidence, both hospitals should analyze their care process aiming to minimize potential treatment delay due to a hospital transfer. Collaboration of breast cancer care between hospitals and formal referral agreements might allow optimization of the care pathway and thereby decreasing the delaying impact of a hospital transfer.

Second opinions in breast cancer care: waste of resources or added medical value?

Most of the hospital transfers in the Netherlands may have resulted from patients seeking a second opinion rather than a hospital transfer initiated by the medical specialist. Currently, there is a continuous discussion regarding the medical value with respect to the diagnosis and treatment of breast cancer second opinions. Evaluating breast cancer second opinions and the discrepancy of diagnosis and treatment between first and second opinions allows answering this question. Moreover, defining and categorizing discrepancy will allow quantification and comparison of the findings with future studies. Thereby *effectiveness* and *efficiency* of this part of breast cancer care

can be assessed. **Chapter 3** demonstrated a considerable discrepancy between first and second opinions, especially in primary treatment. Although part of these findings might be explained by the high-expertise character of the hospital of second opinion and consequently deviation from national guidelines, the findings in this chapter are in concordance with previous literature.[12-18] Moreover, we are first to describe breast cancer care discrepancy between first and second opinions in a multidisciplinary manner using a well-defined categorization as opposed to discrepancy within one medical discipline without clear definitions of discrepancy as seen in previous literature.[13,15,17-21]

The surprisingly high number of missing information in referral letters is in concordance with previous literature,[12-14] although part of the missing information might be explained by unfinished diagnostics at first opinion. The suggested lack of consensus regarding indications for certain primary breast cancer treatment modalities, such as use of NAC and IBR is in concordance with previous Dutch studies focusing on variation in the use of treatment modalities between hospitals.[22-25] Although national and international guidelines clearly state which patients are eligible for NAC,[26,27] the type of surgery after NAC is a challenging outcome of balancing tumor biology and size, tumor-to-breast ratio, patient characteristics[28] and preferences, the physicians' experience with for instance NAC or extensive reconstructive techniques, and to some degree organizational factors.[29] Although a certain degree of variation between physicians in weighing these factors might be inevitable, the high discrepancy found in this chapter, together with previous literature suggesting unwanted variation,[22,23,29,30] emphasizes the need for more consensus among physicians on indications of these breast cancer treatment modalities.

Altogether, the findings in this chapter demonstrate a considerable added value of second opinions after breast cancer diagnosis, and they highlight room for improvement in *effectiveness* (e.g. use of NAC or breast conservation) and *efficiency* of care (e.g. resource utilization such as repeated or additional imaging and biopsies).

PART II: Continuity of the adjuvant chemotherapy pathway

Is timely initiation of adjuvant chemotherapy compromised by immediate breast reconstruction after mastectomy?

Mastectomy followed by IBR has been associated with delayed adjuvant chemotherapy, although reviewing previous literature demonstrated various limitations and biases.[31] Therefore, high-quality evidence focusing on the *timeliness* of the postoperative breast

cancer care is warranted. **Chapter 4** demonstrated a modest delay in initiating adjuvant chemotherapy in patients that were treated with mastectomy plus IBR in the Netherlands, though most likely without clinical relevance in the majority of breast cancer patients.[32] Therefore, IBR after mastectomy should not be considered a contra-indication for the majority of patients with an indication for adjuvant chemotherapy. The findings in this chapter are in line with a recently published large multicenter study from the United Kingdom.[33] Interestingly, they furthermore demonstrated that major complications resulted in significant delay, irrespective of type of surgery that was performed. This latter conclusion supports our finding that axillary surgery is associated with delay in initiating adjuvant chemotherapy, as mastectomy plus IBR in combination with axillary surgery is a known risk factor for postoperative complications.[32]

In line with **chapter 3**, the study in **chapter 4** showed that hospital transfers were associated with delayed care as patients with hospital transfers between surgery and chemotherapy were less likely to receive chemotherapy within 6 weeks after surgery.

The findings in this chapter can be used to improve the quality of breast cancer care for patients who undergo mastectomy plus IBR by optimizing *timeliness* in the postoperative care setting. Patient counselling can be improved as physicians can use this information to inform their patients. Hereby, the dimension *patient-centeredness* can be enhanced.

What is the time-survival relationship when using adjuvant chemotherapy for patients with triple-negative breast cancer?

Despite that chemotherapy will most likely be initiated in the neoadjuvant setting for most TNBC patients in the future as this is recommend by national guidelines[34,35], currently use of chemotherapy is still in the adjuvant setting and of these patients up to 74% receive chemotherapy beyond 30 days after surgery.[36-40] Therefore, we will focus first on the time-survival relationship in the adjuvant setting of TNBC patients. Reliable conclusions regarding the time-survival relationship in the neoadjuvant setting are difficult to make, since NAC is only administered to a small number of TNBC patients and follow-up is short since introduction and nationwide use of NAC in the Netherlands.[41]

The increased risk of death due to initiation of adjuvant chemotherapy beyond 30 days after BCS in TNBC patients presented in **chapter 5** is within the range of previous literature.[36,38-40] It could be suggested that the more aggressive biology of TNBC requires earlier initiation of chemotherapy after BCS. Interestingly, a different time-survival relationship between BCS and mastectomy was observed. Unfortunately,

comparing this latter finding to previous literature is not possible as previous studies did not stratify analysis for type of surgery.

Residual confounding after propensity score matching may explain part of the association. However, previous studies reported that the toxicological effect of chemotherapy seems to be reduced in delayed time from surgery to chemotherapy as residual tumor and micrometastases have more time to grow.[42-44] It has been suggested that there even might be a decreased sensitivity of the tumor cells to chemotherapy due to delayed time from surgery to chemotherapy, although this was only shown in mouse models.[45] The different time-survival relationship between BCS and mastectomy may partly be explained by a reduced toxicologic effect of chemotherapy on potential remaining cancer cells which in theory are more at risk of being present in those undergoing BCS compared to mastectomy. This theory requires additional future high-quality evidence.

Interestingly, it has been hypothesized that the delay-survival relationship might even be different among TNBC patients,[38] as evidence is growing suggesting that TNBC is a heterogenous disease which in the future should be treated accordingly.[46] The current definition of TNBC is a diagnosis of exclusion and is characterized by lacking expression of molecular targets of hormone receptors and an absence of HER2 overexpression.[47] Subtypes of TNBC have been described using protein, gene and mRNA expression which may have different treatment sensitivity and a time-survival relationship.[46] Moreover, other promising prognostic factors of TNBC such tumor-stroma ratio might be imbalanced in current analyses.[48] Current findings were not adjusted for potential unbalanced distribution of previous mentioned potential subtypes within TNBC as these are still under debate and had not been routinely registered. However, as the heterogeneity of TNBC is currently poorly understood, equal distribution among the time intervals could be expected in the cohort of this chapter.

The findings in this chapter should raise awareness among physicians and patients regarding the importance of timely initiation of chemotherapy in TNBC patients. The findings in this chapter can be used to improve the quality dimension *safety*, *effectiveness* and *timeliness*. Guidelines should highlight timely initiation of chemotherapy for TNBC patients, specifically if physicians deviate from the guidelines by initiating chemotherapy in the adjuvant instead of the neo-adjuvant setting.

In **chapters 4** and **5**, the focus was on *safety*, *effectiveness* and *timeliness* of breast cancer care. Continuous evaluation of these dimensions of care is essential as organizational factors or systemic treatment protocols, and the understanding of disease heterogeneity may change over time.

PART III: Quality assessment of breast reconstruction strategies

Direct-to-implant *versus* two-stage implant-based breast reconstruction

There is no golden standard for the optimal breast reconstruction strategy since it depends on various factors. While immediate reconstructions are increasingly popular in most countries, the vast majority of these reconstructions is an implant-based breast reconstruction (IBBR), either direct or in two-stages.[41,49-51] Current literature is contradictory regarding *safety* outcomes of direct-to-implant and two-stage IBBR.[52-54] **Chapter 6** demonstrated the revision incidence of both IBBR approaches in the Netherlands. Both short- and long-term revision rate was lower in patient with a direct-to-impact IBBR compared to patient that obtained two stage IBBR. Comparing these findings to previous literature is problematic due to heterogeneity in outcome definitions and duration of follow-up.[53-55] Furthermore, the majority of previous studies were conducted in a single-center setting while including only a small number of revisions.[53-55] The findings of this chapter do not support the direct-to-implant approach in all patients undergoing IBBR, but rather provide high-quality evidence regarding revision indications and rates of both approaches. Current findings may also reflect optimized patient selection for the two types of IBBR in the Netherlands.

The final choice of IBBR approach and additional techniques should be a shared-decision balancing all factors, risks and preferences. Therefore, the findings of our current study may be useful during patient-counselling concerning breast reconstruction strategies.

The observed revision indications in this chapter suggest that short-term revision rates of both approaches could be reduced by focusing on mastectomy skin flap quality and strategies preventing seroma and deep wound infection. The risk of seroma and potentially a deep wound infection may be reduced by minimizing the dead space using for instance quilting sutures or an axillary drain.[56] Long-term revision rates may be reduced by focusing on optimizing implant and patient selection, because the majority of these revisions after both approaches was due to complaints about asymmetry and pain in the reconstructed breast. Furthermore, optimizing both expectation management regarding the risk of asymmetry and volume, and the risk of postoperative pain and malposition may result in better clinical and patient-reported outcomes (PROs).

Improving breast-contour preserving strategies: why not look beyond our own borders?

There is a vast body of literature reporting on outcome of single breast cancer treatment modalities and recently one study in the Netherlands reported on comprehensive breast-contour preserving (BCP) strategies (Figure 9.1) using multiple treatment modalities [22-24,30,51,57,58] . Breast contour preservation is a quality aspect that gained an increase in popularity.

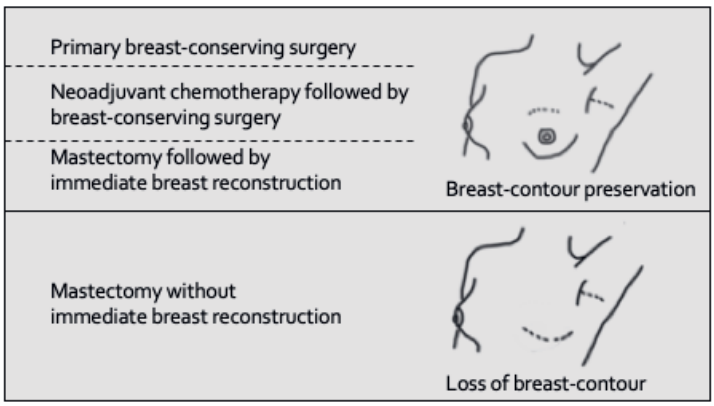


Figure 9.1. Breast-contour preserving procedures.

However, no literature exists comparing the different strategies enabling breast contour preservation on an international level. The findings in **chapter 7** provide insight into the comprehensive treatment of early-stage breast cancer patients in Denmark and the Netherlands with a focus on breast contour preservation.[59] An interesting finding was the difference in BCP strategies specifically in patients younger than 50 years. Although in both countries the proportion of BCP achieved with NAC followed by BCS and mastectomy followed by IBR was highest in patients younger than 50 years, the use of these two BCP modalities was considerable higher in the Netherlands. In addition, while in Denmark a stable high BCP rate over time was achieved predominantly by using primary BCS, a steady increase in BCP rate over time was observed in the Netherlands. The increase in BCP rate in the Netherlands was specifically achieved by an increasing use of NAC followed by BCS and IBR following mastectomy. Part of the increase in BCP rate in the Netherlands over time may reflect the incentive of hospitals to improve their BCP rate as the BCP rates of each Dutch hospitals is published annually.

These findings may be used by future studies focusing on modifiable factors to improve the percentage of patients that will receive a BCP strategy. In 2016, Tan *et al.* suggested several approaches for modification of factors that could be used to increase BCP.[60] He categorized factors into patient, disease, surgeon, and treatment units.[60] Modifiable patient factors could among other things be an unrealistic fear of recurrence,[61] lack of information regarding reconstructive options,[62] or having an unrealistic perception of survival benefit from mastectomy.[63,64] These factors may be improved by optimizing the accuracy of perceived information and information transmission.[65] Regarding surgeon and treatment unit factors, previous studies showed that factors such as study participation, type of hospital, plastic surgeon attendance in multidisciplinary meeting were associated with increased use of NAC and postmastectomy IBR in the Netherlands.[22,25,29]

Together with previous literature demonstrating substantial variation in the use of treatment modalities[22,30,57,58,66], this chapter highlights room for improvement in BCP strategies and raises the question what to do with (un)wanted variation between hospitals in achieving BCP. This may among other things be achieved by improving consensus on (contra)indications on the treatment modalities and breast reconstructive strategies, specifically for early-stage breast cancer. However, a certain degree of variation between physicians is justified allowing patient-tailored care considering personal wishes, preferences and circumstances.

What is the impact of oncoplastic surgery on re-excision rates and breast conservation?

In reviewing literature, the combination of oncological and reconstructive plastic surgery during BCS, defined as oncoplastic breast surgery (OPS), shows promising results compared to BCS or mastectomy.[67-70] The question remains whether OPS results in fewer re-excisions and conversions to mastectomy due to insufficient tumor margins after primary BCS. This is an interesting scientific question as OPS has been associated with wider excisions compared to BCS alone.[71-73] Not surprisingly, excision of a larger proportion of the breast without OPS is associated with poorer patient satisfaction.[74]

Chapter 8 demonstrated a modest decrease in re-excision rates and less frequent conversion to mastectomy after OPS compared to BCS while adjusting for a wide set of confounders using nationwide data,[75] opposed to most previous studies.[69,71,76-78] These findings, together with previous literature,[69,71,73,77] support the safe use of OPS. OPS may be considered more often in the future, especially for those women who otherwise would not be eligible for BCS. Increasing the use of OPS in those eligible may consequently increase the BCP rate as described in **chapter 7**. Interestingly, among

patients older than 50 years who underwent a secondary intervention (re-excision or boost) boost radiation was more frequently used in patients who underwent OPS compared to BCS. This finding may reflect the challenging patient-tailored care required in those with insufficient margins. Physicians have to balance potential morbidity of a re-excision and side effects of boost radiation,[79-81] challenges in identification of the tumor bed after primary surgery,[82] preservation of remaining breast volume, together with patients' preferences. By increasing the proportion of patients eligible for BCP using OPS, *safety* and *effectiveness* of breast cancer care may be improved. These findings may be useful for future studies focusing on how to improve BCP as described in **chapter 7**.

Methodological strengths and limitations

The prospectively registered data in nationwide population-based databases used in this thesis was essential in answering important clinical questions which would have been nearly impossible to answer with conventional research such as a retrospective analysis or in a randomized controlled trial (RCT). Nationwide population-based databases allow insight into treatment effects in a real-world breast cancer population on the condition that these findings are interpreted carefully. It is important to note that the results described in all chapters merely show associations and are not necessarily causal due to the observational setting. However, well-designed observational studies using strong methodology show comparable effect estimates compared to RCTs.[83,84] And, in the current era where shared decision making plays an important role in the tailored breast cancer treatment it is becoming more difficult to include patients in randomized trials. Quality of breast cancer care is most likely improved by using both the methodology from conventional research and nationwide observational studies.

Besides the limitations that are already mentioned in the different chapters, some other shortcomings should be noted. Although we were able to adjust for an extensive set of confounders and limit confounding by indication, several unknown and not-registered confounders should ideally have been included, which may (partly) change our findings in each previous chapter. Furthermore, it remains unknown what part of hospital transfers in **chapter 2** was due to second opinions as these are not registered in the Dutch nationwide database. The second opinions in **chapter 3** may reflect discrepancy between secondary and tertiary care as discrepancy might be less substantial between hospitals with similar expertise. Also, the cause of delayed initiation of adjuvant chemotherapy was not registered in **chapter 4**, leaving a blind spot regarding the association with IBR. The current unknown completeness of revision

surgery registration limits the implications of **chapter 7**. Finally, the findings of **chapter 8** are limited as the rationale of using specific OPS techniques remains unknown, although it would be difficult to include this on a large scale.
Although the aspects and components identified in this thesis may contribute to optimizing different dimensions of quality of breast cancer care, they may only be useful when taking all dimensions into account as they are highly overlapping, linked to and dependent on each other. In addition, the priority of end-points used in this thesis may not reflect the most optimal care pathway for all stakeholders as the priority of the dimensions of quality of care differ as described in **chapter 1** of this thesis.

Future perspectives and suggestions for future research

Although it seems like the quality dimensions *safety, effectiveness*, *timeliness* and *efficiency* have the largest share in this thesis, *patient-centeredness* and *equity* are strongly connected and hinge on insight into the first four dimensions. These latter two are not less important and future studies should focus on the relationship between the six dimensions.
The quality and completeness of national clinical audit databases are essential for continuous improvement of breast cancer care. They may be improved by optimizing source data. Automatic digital data extraction with clear definitions of for instance radiological findings, surgery and systemic treatment regiments would allow insight into clinical practice and moreover significantly reduce the administrative burden. Standardized synoptic reports may facilitate this and improve data completeness as literature showed that synoptic reporting compared to narrative reporting improved completeness of pathology reports.[85] It could be expected that the success of standardized synoptic surgery reports depends on a well thought out implementation and the support of the national physician societies.
Increasing the attention for the continuity of breast cancer care, such as hospital transfers and SOs may result in less repeated diagnostics, biopsies and consultations, and treatment delay. Improved *timeliness* of the postoperative care process might be achieved by future studies focusing on the combination of IBR and axillary surgery such as sentinel node biopsy or ALND as this combination was specifically associated with treatment delay.[32] Future studies focusing on the time-survival relationship should also include characteristics surrogate for patient frailty to adjust for potential imbalances. Better understanding heterogeneity of TNBC might alter the time-survival relationship found in this thesis. Furthermore, breast cancer survival may be improved by awareness among physicians and patients of the clinical impact of the treatment

continuity in the future. Further optimization of modifiable factors may increase BCP rate and reduce unwanted variation between hospitals. Future studies focusing on the *safety* of OPS may include more detailed information regarding the type of OPS as the categorization used in this thesis was rather robust.

Current breast cancer registrations such as the NBCA and DBCG allow insight during introduction of new diagnostics and therapies on a nationwide level. Together with recently started registration of PROMs, these databases might be used during patient consultation in the future. This real-world data would allow patients together with their physician to select 'patients like me'. Selecting patients with for example the same tumor- and patient characteristics and treatment, but also preoperative PROs could provide insight into various expected symptoms such as pain, numbness, confidence, but also outcomes such as complications, recurrence and survival rate. This type of information has shown to be an attribute for patients with various diseases.[86,87] It might be useful during patient consultation regarding breast reconstructive strategies, but also in self-assessment of patients, 'am I recovering as to be expected?'. Moreover, physicians could hereby focus more on outliers as these patients could be detected automatically. However, the accuracy of information of 'patients like me' remains dependent of the number of 'patients like me' and should only be seen as an attribute to the current shared-decision making. Currently, evidence-based guidelines and the experience of physicians form the basis for patient-counselling since 'patients like me' has only been introduced recently in breast cancer care in the Netherlands. Altogether, combining PRO and clinical breast cancer registrations have the potential to substantially improve all dimensions of quality.

Achieving quality improvement of breast cancer care may require several changes. First, the findings in this thesis could be considered when formatting new guidelines. Second, the structure of current local care pathways should be re-evaluated when new insights into treatment delaying factors or their clinical impact are demonstrated. A clear breast cancer care pathway allows mapping of different factors and modification if necessary. Third, (inter)national governance and transparent publication of structure, process and outcome indicators allow benchmarking, comparison and identification of outliers which can be used to identify room for improvement.

Conclusions

Assessing and improving quality of breast cancer care relies on having high-quality evidence of all dimensions of quality of healthcare. Based on the findings presented in this thesis, together with previous literature, several associations and points of

improvements addressing these dimensions were identified, specifically regarding the dimension's *safety*, *effectiveness, timeliness and efficiency*.

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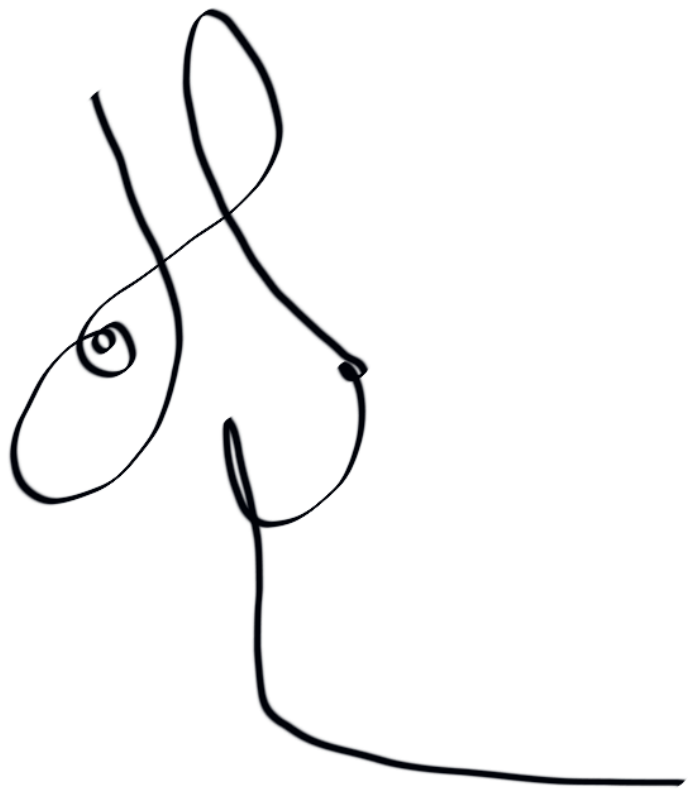
Chapter 10

Summary



Summary

In **Chapter 1**, a general introduction into different dimensions of quality of breast cancer care, and the outline of this thesis is presented. The primary aim of this thesis was to contribute to the improvement of the quality of breast cancer care on an individual and population-based level by using data from multiple nationwide databases. The chapters in this thesis address one or more of the six dimensions of quality of care according to the definition of the Institute of Medicine (*safety*, *effectiveness, patients-centeredness, timeliness, efficiency, and equity*) in each of the chapters.[1] In the first part of this thesis, we analyze the *effectiveness, timeliness* and *efficiency* of preoperative breast cancer care. In the second part, the *safety* and *timeliness* of the adjuvant breast cancer care is investigated and in the concluding part we room for improvement regarding *safety*, *effectiveness* and *efficiency* of different breast reconstructive strategies. Although it seems like the quality dimensions *safety, effectiveness*, *timeliness* and *efficiency* have the largest share in this thesis, *patient-centeredness* and *equity* are strongly connected and hinge on insight into the first four dimensions.

The following conclusions were drawn based on the findings described in the previous chapters of this thesis:

1. A hospital transfer after breast cancer diagnosis is a delaying factor for primary treatment, specifically for those who undergo surgery in the Netherlands.[2]
2. Second opinions in breast cancer care can have a significant impact on diagnostics and primary treatment strategies in certain patients.[3]
3. Immediate breast reconstruction (IBR) after mastectomy is not contra-indicated for the majority of patients who have an indication for adjuvant chemotherapy.[4]
4. Initiation of adjuvant chemotherapy beyond 30 days after surgery is associated with decreased 10-years overall survival in patients with triple-negative breast cancer who undergo breast-conserving surgery (BCS).[5]
5. Direct-to-implant immediate implant-based breast reconstruction (IBBR) compared to two-stage IBBR is associated with a lower unplanned revision incidence.
6. The Netherlands and Denmark have a comparable breast-contour preservation rate around 75%, despite a more frequent use of neoadjuvant chemotherapy and postmastectomy immediate reconstruction in the Netherlands.[6]
7. BCS using oncoplastic techniques is a safe option regarding re-excision and conversion to mastectomy rate.[7]

Part I: Hospital transfer in breast cancer care

There is a large body of literature focusing on factors that influence the continuity of breast cancer treatment.[8-12] Focusing on potential treatment delaying factors may have the potential to improve the quality dimension *timeliness*. A relatively unknown factor in breast cancer care is patients changing hospital after diagnosis,[13] from now on referred to as hospital transfers. **Chapter 2** demonstrated that on a national level almost 5% of the breast cancer patients undergoing primary surgery and almost 25% of those undergoing NAC transferred hospital after diagnosis in the Netherlands.[2] The extent of hospital transfers for both types of treatment decreased between 2014 and 2016. Hospital transfers were more likely in young (aged <40 years) patients and those who underwent a mastectomy with IBR. Time from diagnosis to primary treatment was significantly prolonged up to 9 days after a hospital transfer, specifically for patients undergoing primary surgery. Hospital transfers most commonly occurred if breast cancer had been diagnosed in a district hospital regardless of the primary treatment. While a hospital transfer among patients undergoing primary surgery most commonly occurred towards a teaching hospital, those receiving NAC most commonly changed to another district hospital. Although the extent of hospital transfers among patients who underwent primary surgery was modest, the treatment delaying impact seems substantial.

Part of the extent of hospital transfers may be caused by patients who change hospital due to a second opinion after diagnosis. Evaluating the medical value of breast cancer second opinions could facilitate improvement in *effectiveness* and *efficiency* of the preoperative breast cancer phase. We composed a breast cancer second opinion (BCSO) classification system to quantify the degree of discrepancy in diagnostical findings and treatment proposal between a first and second opinion in a reproducible manner for future studies. **Chapter 3** demonstrated that in more than 45% of breast cancer patients who had not received treatment prior to the consultation a second opinion resulted in at least one minor or major discrepancy in diagnostic findings or treatment proposal.[3] Interestingly, major discrepancies occurred in more than 29% of patients, specifically in the primary treatment proposal (e.g. NAC instead of primary surgery, BCS instead of mastectomy, and in using IBR). Physician and patient initiated second opinions demonstrated to have comparable discrepancy rates. Discrepancy was more common in patients who at the second opinion received additional diagnostics such as imaging or biopsy. The majority of patients did not return to the hospital of first opinion. These findings showed a substantial clinical impact of second opinions and support its use among breast cancer patients. The high-expertise character of the

hospital of second opinion might have influenced our results. Future studies using our classification system are required to answer that question. Improving consensus regarding primary treatment between hospitals might reduce variation between first and second opinion.

Overall, **Part I** of this thesis provided insight into breast cancer patients changing hospital after diagnosis on a nationwide level and on a local level. Moreover, identifying prognostic factors and quantifying the impact of a hospital change on breast cancer care provided insight into the potential room for improvement of *efficiency*, *effectiveness* and *timeliness* of preoperative breast cancer care.

Part II: Continuity of the adjuvant chemotherapy pathway

Despite the vast body of literature, there is an ongoing discussion about the impact of IBR on time from surgery to initiation of adjuvant chemotherapy[14-17] and the time-survival relationship after breast cancer.[15,18-20] While Dutch and European guidelines recommend initiation of adjuvant chemotherapy within 6 weeks after surgery,[21-23] literature shows that the clinical acceptable maximum time between surgery and adjuvant chemotherapy lays between 7 and 12 weeks.[18,20,24] **Chapter 4** demonstrated that while in the Netherlands more than two-third of all patients who received adjuvant chemotherapy after mastectomy received systemic treatment within 6 weeks after surgery, the vast majority within 9 weeks and almost all patients within 12 weeks.[4] Patients undergoing IBR after mastectomy compared to mastectomy alone had a reduced likelihood of receiving adjuvant chemotherapy within 6 weeks, but not within 9 and 12 weeks after limiting confounding by indication by means of propensity score matching. Based on these results, IBR most likely does not delay adjuvant chemotherapy to a clinically relevant extent, suggesting that IBR is not necessarily a contra-indication for patients who undergo a mastectomy and have an indication for adjuvant chemotherapy.

Recent studies suggest that the relationship between time from surgery to adjuvant chemotherapy and survival might be breast cancer sub-type dependent.[20,25-28] Is has been suggested that the clinical acceptable maximum time from surgery to adjuvant chemotherapy might be shorter for more aggressive high-risk tumors, such as triple-negative breast cancer (TNBC). Chapter 5 demonstrated that TNBC patients who underwent BCS and received adjuvant chemotherapy beyond 30 days after surgery had a 69% increased risk of death within 10-years compared to those who received adjuvant chemotherapy within 30 days.[5] No difference in 10-years overall survival (OS)

was observed between the two time-interval groups for patients who underwent mastectomy. Similar associations were observed after stratifying analysis for the use of radiotherapy. Although part of the findings might be explained by residual confounding, these findings support the idea that if chemotherapy is administered in the adjuvant setting, a more timely initiation of chemotherapy in TNBC patients seems warranted after BCS.

After adjusting for confounders, **Part II** of this thesis demonstrated a relatively limited delaying impact of postmastectomy IBR on the continuity of the adjuvant chemotherapy pathway and it highlights the importance of timely initiation of adjuvant chemotherapy in patients diagnosed with TNBC. These findings might be useful for initiatives to improve *timeliness* and *safety* of the quality of adjuvant breast cancer care.

Part III: Quality assessment of breast reconstruction strategies

Previous contradicting studies comparing cosmetic outcomes and complications after immediate IBBR using direct-to-implant and two-stage techniques (tissue expander first) may contribute to unwanted variation in practice among healthcare providers.[29-32] Providing insight into the unplanned revision surgery incidence after both techniques using nationwide data may be used to improve *safety* and *patients-centeredness* of breast reconstruction strategies. **Chapter 6** demonstrated that short- and long-term revision surgery occurred less often after direct-to-implant IBBR compared to two-stage IBBR, although the crude cumulative revision incidence of a long-term revision was comparable after limiting confounding by indication. The majority of revision surgery after two-stage IBBR occurred during the tissue-expander phase. The observed indications for short-term revisions suggest that the rate of revision surgery of both techniques could potentially be improved specifically by optimizing the quality of the mastectomy skin flap and prevention of infections.

Although there is no current golden strategy for the most optimal breast-contour preservation strategy, preservation of the breast mound seems nowadays possible for most early stage breast cancer patients. Breast-contour preservation can be defined using either primary BCS, NAC followed by BCS, or mastectomy followed by IBR.[33] A comparison of these strategies between countries which are comparable regarding their wealth, culture and healthcare organization could provide insight into potential room for improvement of breast cancer care in both countries. In Chapter 7, a substantial difference in breast-contour preservation strategies between Denmark and

the Netherlands was observed, specifically in more common use of NAC followed by BCS and mastectomy followed by IBR in the Netherlands.[6] While the overall breast-contour preservation rate was stable in Denmark between 2012-2017 (75.8% to 76.8%), a significant increase was observed in the Netherlands (69.5% to 78.5%). We observed a decrease in variation between hospitals in breast-contour preservation rates in both countries between 2012 and 2017. Interestingly, a relatively high hospital volume was observed in Denmark compared to the Netherlands. Together with previous chapters, these findings raise the question whether more consensus is warranted among physicians on the different treatment strategies not only on a national, but also on an international level.

Part of the surgical de-escalation and increase in the breast-contour preservation rate might be achieved by optimizing systemic therapies, such as that NAC seems to make some patients eligible for BCS.[34,35] In addition, surgical techniques such as oncoplastic surgery (OPS) during BCS are thought to contribute as well.[36] OPS has the potential to reduce re-excision and conversion to mastectomy rates as OPS has been associated with larger resections while achieving good clinical and patient-reported outcomes.[37-44] Re-excision and conversion to mastectomy after primary BCS are associated with poorer outcomes and additional healthcare costs.[45-47] Chapter 8 demonstrated that patients who underwent primary BCS with OPS compared to BCS only were less likely to undergo re-excision or conversion to mastectomy.[7] Re-excision rates were significantly lower after OPS compared to BCS, although differences were modest. Similar results were found when accounting for the use of boost radiation in patients older than 50 years. Together with previous literature,[38-41,44] these findings support the safe use of OPS, specifically in patients in whom otherwise BCS with a satisfactory cosmetic result would most likely not have been possible.

Part III of this thesis evaluated breast-contour preservation and oncoplastic strategies on a national and international level. The findings can be used to improve quality of breast cancer care, specifically *safety*, *effectiveness* and *efficiency*. The outcomes and identified prognostic factors could be used by physicians during patient-counselling, but also by healthcare policymakers seeking potential room for improvement in current breast reconstructive strategies.

In **chapter 9**, we present a general discussion of the findings of each chapter in which we explore the interpretations, implications, limitations and critically put them in a broader perspective. In conclusion, we elaborate on recommendations for the future perspectives of breast cancer care.

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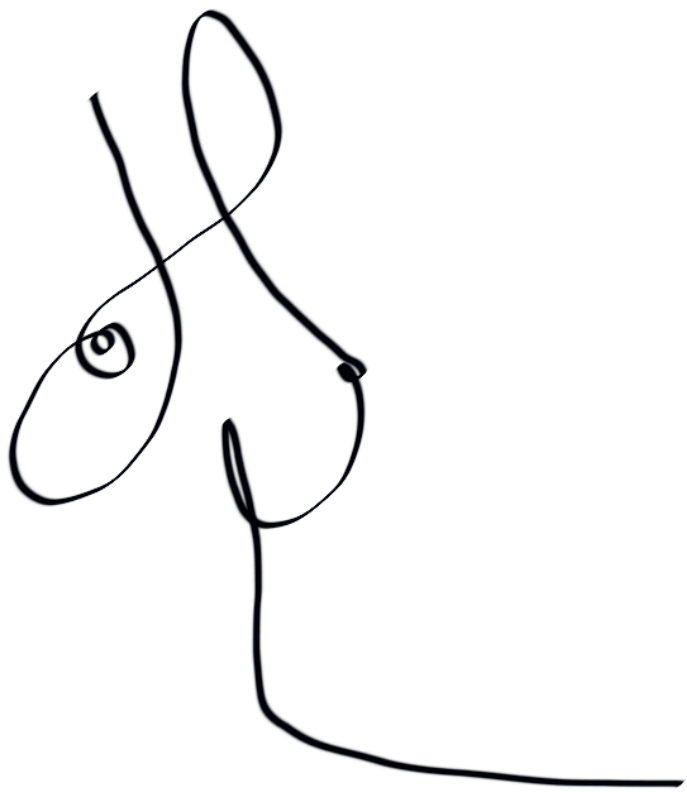
Samenvatting



Samenvatting

In **hoofdstuk 1** wordt een algemene introductie gegeven omtrent de verschillende dimensies van kwaliteit van borstkankerzorg en de verschillende hoofdstukken worden uiteengezet. Het primaire doel van dit proefschrift is een bijdrage te leveren aan het verbeteren van de kwaliteit van de borstkankerzorg op individueel en bevolkingsniveau door gebruik te maken van meerdere landelijke databases. De hoofdstukken in dit proefschrift adresseren een of meer van de zes dimensies van kwaliteit van zorg volgens de definitie van het Institute of Medicine (*veiligheid, effectiviteit, patiëntgerichtheid, tijdigheid, efficiëntie* en *gelijkheid*) in elk van de hoofdstukken.[1] In het eerste deel van dit proefschrift analyseren we de *effectiviteit, tijdigheid en efficiëntie* van de preoperatieve borstkankerzorg. In het tweede deel bestuderen we de *veiligheid* en *tijdigheid* van de adjuvante borstkankerzorg en in het laatste deel beschouwen we de *veiligheid, effectiviteit* en de *efficiëntie* van verschillende borst reconstructieve strategieën.

De volgende conclusies zijn getrokken op basis van de bevindingen in de hoofdstukken in dit proefschrift:

1. Een ziekenhuiswissel na de diagnose borstkanker is een vertragende factor voor de primaire behandeling in Nederland, met name voor de patiënten die primair geopereerd worden.[2]
2. Second opinions kunnen een significante impact hebben op de diagnostiek en primaire behandel strategie voor een selectie van de borstkanker patiënten.[3]
3. Een directe borstreconstructie na een mastectomie is geen contra-indicatie voor het merendeel van de patiënten die een indicatie hebben voor adjuvante chemotherapie.[4]
4. Het starten van adjuvante chemotherapie in meer dan 30 dagen na de operatie is geassocieerd met een slechtere algemene 10-jaars overleving bij patiënten met triple-negatief borstkanker die een borstsparende operatie ondergaan.[5]
5. Een directe borstreconstructie met een definitieve prothese is geassocieerd met een lagere niet-geplande revisie incidentie in vergelijking met een directe borstreconstructie in 2-etappen.
6. In Nederland en Denemarken wordt een vergelijkbaar percentage rond de 75% behaald op het borst-contour behoud, ondanks frequenter gebruik van neoadjuvante chemotherapie en een directe borstreconstructie in Nederland.[6]
7. Een borstsparende operatie waarbij oncoplastische technieken worden gebruikt is een veilige optie wat betreft het aantal re-excisies en conversies naar een mastectomie.[7]

Deel I: Ziekenhuiswissels in de borstkankerzorg

Er is reeds veel onderzoek verricht naar welke factoren de continuïteit van de behandeling van borstkanker beïnvloeden.[8-12] De focus op potentieel vertragende factoren heeft de potentie om de dimensie van kwaliteit *tijdigheid* te verbeteren. Een relatief onbekende factor in de borstkankerzorg zijn patiënten die van ziekenhuis wisselen na de diagnose borstkanker.[13] We refereren vanaf nu naar deze factor als een ziekenhuiswissel. In **hoofdstuk 2** tonen we aan dat bijna 5% van de Nederlandse borstkanker patiënten die een primaire operatie ondergaan van ziekenhuis wisselt na diagnose, en dat dit bijna 25% is onder patiënten die met neoadjuvante chemotherapie worden behandeld.[2] De mate van ziekenhuis wissels in Nederland lijkt af te nemen tussen 2014 en 2016. Een ziekenhuiswissel is geassocieerd met een jongere patiënten leeftijd (<40 jaar) en met een directe borstreconstructie na een mastectomie. De tijd tussen diagnose en primaire behandeling was bij een ziekenhuiswissel significant vertraagt met 9 dagen en dan met name onder patiënten die een primaire operatie ondergingen. Ziekenhuiswissels lijken vaker voor te komen als de diagnose borstkanker wordt gesteld in een regionaal ziekenhuis, onafhankelijk van het type primaire behandeling. Terwijl een ziekenhuiswissel het vaakst voorkwam richting een niet-academisch opleidingsziekenhuis onder patiënten die een primaire operatie ondergingen, bleek dat onder patiënten die een neoadjuvante chemotherapie behandeling ondergingen een ziekenhuiswissel het vaakst richting een ander regionaal ziekenhuis voorkwam. Alhoewel de mate van ziekenhuiswissels onder patiënten die een primaire operatie ondergaan in Nederland relatief beperkt is lijkt de vertragende impact op de behandeling substantieel.

Een deel van de ziekenhuiswissels wordt mogelijk veroorzaakt door patiënten die van ziekenhuis wisselen in verband met een second opinion na de diagnose borstkanker. Een evaluatie van de medische impact van second opinions in de borstkankerzorg kan voor verbetering zorgen van de *effectiviteit* en de *efficiëntie* van de preoperatieve borstkanker fase. Om dit te bewerkstelligen hebben we een borstkanker second opinion classificatie ontwikkeld om de discrepantie in diagnostische bevindingen en het behandelvoorstel tussen de 'first' en 'second' opinion te kwantificeren en daarnaast reproduceerbaar te maken voor toekomstige studies. **Hoofdstuk 3** liet zien dat in meer dan 45% van de onbehandelde borstkanker patiënten een second opinion resulteerde in minimaal één kleine of grote discrepantie in diagnostische bevindingen of het behandelvoorstel.[3] Opvallend was dat in 29% van de patiënten een grote discrepantie plaats vond, met name in het primaire behandelvoorstel (bijv. neoadjuvante chemotherapie i.p.v. primaire chirurgie, borstsparende operatie i.p.v. een mastectomie

en in het gebruik van een directe borstreconstructie na mastectomie). We zagen geen verschil in het percentage discrepanties tussen second opinions welke waren geïnitieerd door de behandelaar en patiënten. Patiënten die bij de second opinion aanvullende diagnostiek ondergingen, zoals beeldvorming of biopsieën, hadden een hoger discrepantie percentage in vergelijking met patiënten die geen aanvullende diagnostiek ondergingen. Het merendeel van de patiënten ging na de second opinion niet retour naar het ziekenhuis van de first opinion. Deze resultaten laten een substantiële klinische impact zien van second opinions en onderstrepen daarmee het gebruik onder borstkanker patiënten. Toekomstige studies die ons classificatiesysteem gebruiken kunnen uitwijzen in hoeverre onze resultaten zijn beïnvloed door het hoge-expertise karakter van het ziekenhuis van de second opinion. Het bereiken van een betere consensus tussen ziekenhuizen omtrent de primaire behandeling zal mogelijk de variatie tussen de first en second opinion in de toekomst kleiner maken.

Samenvattend**, deel I** van dit proefschrift biedt op een landelijk en lokaal niveau inzicht in borstkanker patiënten die van ziekenhuis wisselen na diagnose. Bovendien wordt er een voorstelling gemaakt over potentiele ruimte voor verbetering in *effectiviteit*, *tijdigheid* en *efficiëntie* van de preoperatieve borstkankerzorg door het identificeren van prognostische factoren en het kwantificeren van de impact van een ziekenhuiswissel op de borstkankerzorg.

Deel II: Continuïteit van het adjuvante chemotherapie behandeltraject

Ondanks het uitgebreide aanbod aan literatuur bestaat er een voortdurende discussie over de impact van een directe borstreconstructie op de tijd van operatie tot adjuvante chemotherapie[14-17] en de relatie tussen deze tijdsperiode en overleving na borstkanker.[15,18-20] Terwijl Nederlandse en Europese richtlijnen adviseren om te starten met adjuvante chemotherapie binnen 6 weken na de operatie,[21-23] laat onderzoek zien dat de klinisch acceptabele maximale tijd tussen de operatie en starten met adjuvante chemotherapie waarschijnlijk tussen de 7 en 12 weken ligt.[18,20,24] **Hoofdstuk 4** liet zien dat bij meer dan twee derde van de Nederlandse patiënten binnen 6 weken na de een mastectomie met adjuvante chemotherapie is gestart.[4] Bij het grote merendeel van de patiënten was gestart binnen 9 weken en bijna alle patiënten binnen 12 weken. Een mastectomie met een directe borstreconstructie was in vergelijking met patiënten zonder directe borstreconstructie geassocieerd met het niet ontvangen van adjuvante chemotherapie binnen 6 weken, maar deze associatie werd niet gevonden met een 9 en 12 weken limiet wanneer confounding werd beperkt doormiddel van propensity-score matching. Deze resultaten suggereren dat een directe borstreconstructie de start

van adjuvante chemotherapie niet lijkt te verlengen tot een klinisch relevante omvang. Daarmee lijkt een directe borstreconstructie niet een contra-indicatie voor patiënten die een mastectomie ondergaan en een indicatie hebben voor adjuvante chemotherapie.

Recente studies laten zien dat de relatie tussen de tijd van operatie en adjuvante chemotherapie en de overleving na borstkanker mogelijk afhankelijk is van het subtype borstkanker.[20,25-28] Er wordt gesuggereerd dat de klinisch acceptabele maximale tijd tussen operatie en adjuvante chemotherapie korter is voor hoog-risico tumoren, zoals triple-negatief borstkanker (TNBC). **Hoofdstuk 5** liet zien dat patiënten met TNBC behandeld met een borstsparende operatie en adjuvante chemotherapie een 69% hogere kans op overlijden hadden binnen 10 jaar wanneer de chemotherapie werd gestart in meer dan 30 dagen na de operatie in vergelijking met een start binnen 30 dagen.[5] Er werd geen verschil in de 10-jaars algehele overleving gezien tussen de twee tijdsintervallen voor patiënten die een mastectomie ondergingen. Nadat de analyses waren gestratificeerd voor het gebruik van adjuvante radiotherapie bleven beide bevindingen ongewijzigd. Alhoewel een deel van de bevindingen in dit hoofdstuk mogelijk verklaard worden door ongemeten confounding, ondersteunen deze resultaten wel de opvatting dat tijdig starten met adjuvante chemotherapie van belang is bij patiënten met TNBC die een borstsparende operatie ondergaan.

Deel II van dit proefschrift liet zien dat na het beperken van de impact van gemeten confounders een directe borstreconstructie een relatief beperkte vertragende impact heeft van op de continuïteit van het adjuvante chemotherapie behandeltraject. Daarnaast wordt het belang van tijdig starten van adjuvante chemotherapie belicht bij patiënten met TNBC. Deze resultaten kunnen mogelijk gebruikt worden om de *veiligheid* en *tijdigheid* van de adjuvante borstkankerzorg te verbeteren.

Deel III: Kwaliteitsbeoordeling van borst reconstructieve strategieën

Eerdere tegenstrijdige studies die het optreden van complicaties en de cosmetische resultaten vergeleken na een directe borstreconstructie middels een definitieve prothese en een 2-etappen techniek (eerst een tissue expander) dragen mogelijk bij aan ongewenst variatie onder zorgverleners in het gebruik van beide technieken.[29-32] Inzicht in de incidentie van niet-geplande revisie chirurgie van beide technieken waarbij gebruik wordt gemaakt van landelijke data kan de *veiligheid* en *patiëntgerichtheid* van borst reconstructieve strategieën verbeteren. **Hoofdstuk 6** laat zien dat korte en lange termijn revisie chirurgie minder vaak voor kwam na een directe borstreconstructie

middels een directe prothese in vergelijking met een 2-etappen techniek, alhoewel de ruwe cumulatieve revisie incidentie van lange termijn revisie chirurgie vergelijkbaar was na het beperken van potentiele confounding op indicatie. Het merendeel van de revisie chirurgie na de 2-etappen techniek vond plaats tijdens de periode van de tissue-expander. De geobserveerde revisie indicaties voor de korte termijn suggereren dat het aantal revisies na beide technieken potentieel kan worden verlaagd door specifiek de kwaliteit van de overgebleven huidenvelop en infectiepreventie te optimaliseren.

Ondanks dat er momenteel geen gouden strategie is voor de meest optimale borst-contour preserverende strategie, lijkt het mogelijk om van de borst-contour voor de meeste patiënten met vroeg-stadium borstkanker te behouden. Er is sprake van borst-contour preservatie wanneer er gebruik wordt gemaakt van een primaire borstsparende operatie, neoadjuvante chemotherapie gevolgd door een borstsparende operatie, of een mastectomie gevolgd door een directe borstreconstructie.[33] Een vergelijking van borst-contour preservatie strategieën tussen landen met een vergelijkbare welvaart, cultuur en opzet van de gezondheidszorg kan potentieel inzicht bieden in ruimte voor verbetering van de borstkankerzorg in beide landen. **Hoofdstuk 7** laat een vergelijkbaar borst-contour behoud zien van rond de 75% in Nederland en Denemarken. Echter wordt er ook een substantieel verschil zien in het gebruik van de verschillende strategieën, specifiek in het frequentere gebruik van neoadjuvante chemotherapie gevolg door een borstsparende operatie en een directe borstreconstructie na mastectomie in Nederland.[6] Terwijl het algemene percentage borst-contour behoud in Denemarken stabiel bleef tussen 2012 en 2017 (75.8% naar 76.8%), was er een significante stijging te zien in Nederland (69.5% naar 78.5%). We observeerden een afname in de variatie tussen ziekenhuizen in het algemene percentage borstcontour behoud in beide landen tussen 2012 en 2017. Opvallend was het relatief hoge patiënten volume per ziekenhuis in Denemarken in vergelijking met Nederland. Samen met de vorige hoofdstukken roepen deze bevindingen de vraag op of er niet meer consensus nodig is omtrent de verschillende behandelstrategieën op niet alleen een nationaal, maar ook op een internationaal niveau.

Een de-escalatie van de chirurgische behandeling en een verbetering van het percentage patiënten die haar borst-contour behoudt is wellicht gedeeltelijk te bereiken door het optimaliseren van het gebruik van systemische therapieën. Eerdere studies suggereren dat meer patiënten in aanmerking komen voor een borstsparende behandeling bij het gebruik van neoadjuvante chemotherapie.[34,35] Daarnaast bestaat de opvatting dat het percentage borst-contour behoud kan worden verhoogd door ontwikkeling van chirurgische technieken, zoals oncoplastische chirurgie tijdens een

borstsparende behandeling.[36] Oncoplastische chirurgie heeft de potentie om het percentage re-excisies en conversie naar een mastectomie te verlagen, doordat een borstsparende behandeling met oncoplastische chirurgie is geassocieerd met grotere resecties met behoud van goede klinische en patiënt gerapporteerde uitkomsten.[37-44] Een re-excisie en conversie naar een mastectomie na een primaire borstsparende operatie zijn geassocieerd met slechtere uitkomsten en hogere kosten voor de gezondheidszorg.[45-47] **Hoofdstuk 8** liet zien dat een primaire borstsparende operatie met oncoplastische chirurgie geassocieerd was met minder re-excisies en conversie naar een mastectomie.[7] Het percentage re-excisies was significant lager na een primaire borstsparende operatie met oncoplastische chirurgie in vergelijking met de operatie zonder oncoplastische chirurgie, alhoewel de verschillen klein waren. Vergelijkbare resultaten werden gevonden wanneer er werd gecorrigeerd voor het gebruik van boost radiatie bij patiënten ouder dan 50 jaar. De analyses in dit hoofdstuk waren ongewijzigd na het beperken van confounding door indicatie. Samen met eerdere literatuur ondersteunen deze resultaten het veilige gebruik van oncoplastische chirurgie,[38-41,44] specifiek voor patiënten waarbij een borstsparende operatie met een bevredigend cosmetisch resultaat zonder oncoplastische chirurgie waarschijnlijk niet mogelijk is.

Deel III van dit proefschrift evalueert de borst-contour preservatie en oncoplastische strategieën op een nationaal en internationaal niveau. De bevindingen in dit deel van het proefschrift kunnen mogelijk gebruikt worden om de kwaliteit van de borstkankerzorg te verbeteren, en dan met name de *veiligheid, effectiviteit* en de *efficiëntie.* De uitkomsten en geïdentificeerde prognostische factoren kunnen door behandelaars gebruikt worden tijdens een behandeladvies aan een patiënt, maar ook door beleidsmakers in de zorg die op zoek zijn naar potentiele ruimte voor verbetering in hedendaagse reconstructieve strategieën.

In **hoofdstuk 9** worden de verschillende hoofdstukken bediscussieerd, waarbij we de interpretatie, implicatie, limitatie van de bevindingen uiteenzetten, maar ook kritisch in een brede perspectief plaatsen. Afsluitend wijden we uit met aanbevelingen over het toekomstperspectief van de borstkankerzorg. Alhoewel het lijkt dat de dimensies van kwaliteit *veiligheid, effectiviteit, tijdigheid* en *efficiëntie* het leeuwendeel van dit proefschrift beslaan zijn *patiëntgerichtheid* en *gelijkheid* sterk verbonden en afhankelijk van inzicht in de eerste vier dimensies.

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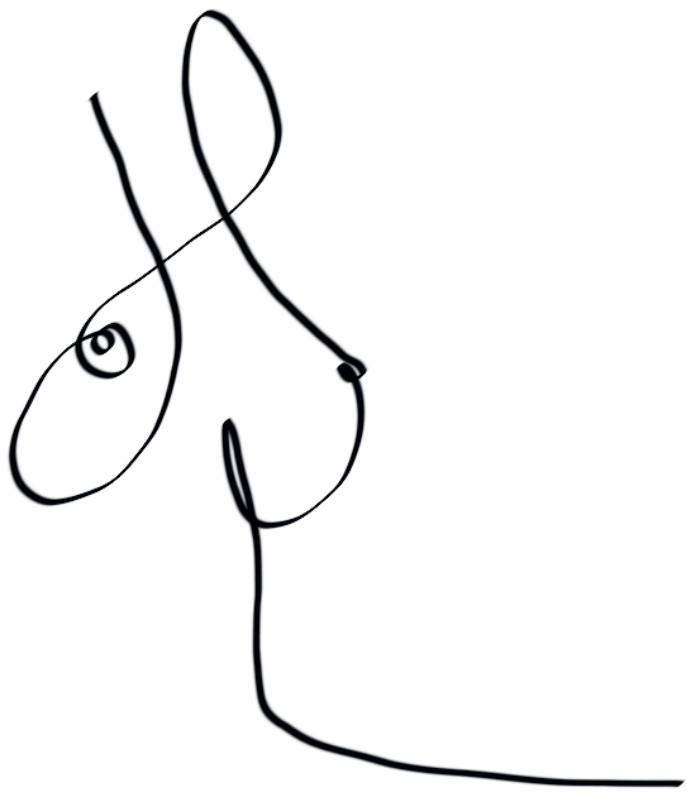

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2016

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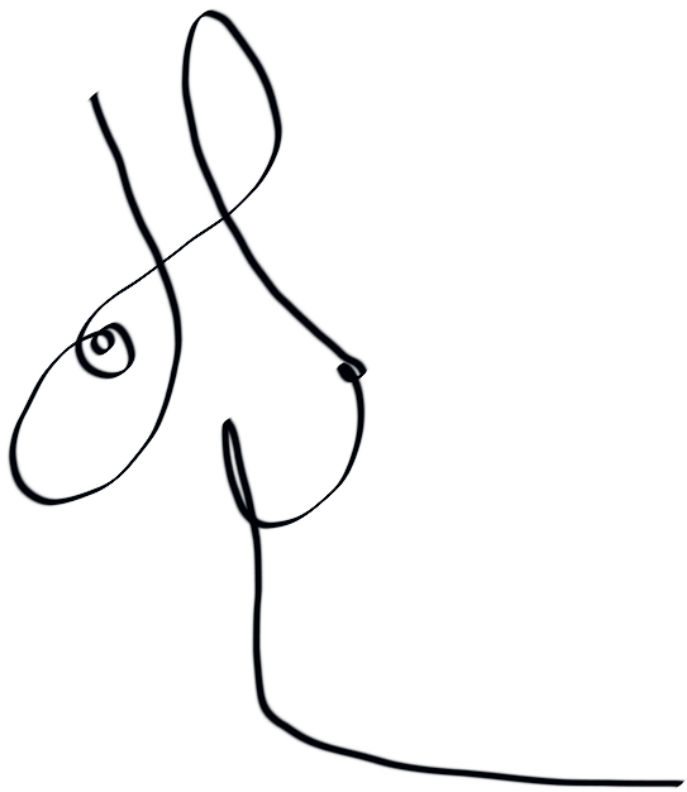
Joint Space Narrowing in Patients With Pisotriquetral Osteoarthritis.
HAND (NY) 2016; 10:1-3.

Dankwoord (acknowledgements)



Dankwoord (acknowledgements)

I would like to thank all the people who advised, guided, supported and sometimes pushed me in the right direction. Some of you I would like to thank in particular.

Mijn promotor prof. dr. Tollenaar, beste Rob, onze vergaderingen waren naast gezellig, zeer waardevol doordat je snel tot de kern van een dilemma kwam, waarbij je me verbaasde met interessant perspectieven.
Mijn promotor prof. dr. Mureau, beste Marc, vanaf dag 1 scherp, efficiënt en doelgericht in onze samenwerking. Naast dat je mij inspireerde tijdens alle vergaderingen en in de kliniek, ben ik je zeer dankbaar voor je vertrouwen en rol als mentor, ook buiten mijn werk als promovendus.
Mijn copromotor prof. dr. Vrancken Peeters, beste Marie-Jeanne, vanaf het eerste onderzoek de basis van mijn PhD. Als ik mij verloor in details bracht jouw helicopterview het weer op de juiste koers. Ik ben je zeer dankbaar voor je vastberadenheid, prettige samenwerking en nimmer aflatende vertrouwen.

Ik bedank mijn coauteurs voor de prettige en constructieve samenwerking: Sabine Siesling, Kay Schreuder, Marissa van Maanen, Jan Oosterwijk, Monique Bos, Yasmin Civil, Marij Hillen, Carolien Smorenburg, Leonie Woerdeman, Ellen Groen, Xavier Harmeling, Pauline Spronk en Gonneke Winter-Warnars.
In het bijzonder, dr. Marang-van de Mheen, jouw kritische kijk en wil om de bol wol, waar mijn onderzoek soms op leek, te ontrafelen bracht de methodiek die dit proefschrift nodig had.

Special thanks to dr. Jensen, dear Maj-Britt, you made me feel at home at the DBCG from day one as your door was always open for a scientific discussion or a casual chat. Your patience and extensive knowledge was priceless to our research. Prof. Ejlertsen and Prof. Christiansen, dear Peer and Bent, thank you both for the pleasant collaboration and opportunity to work at the DBCG. For the constructive collaboration at the DBCG: prof. Holmich, prof. Lænkholm, prof. Offersen and dr. Bodilsen. Ann, Brian, Michael, Lise, Rasoul, Tobias and Iben: Jeg kunne ikke have fået en bedre modtagelse, mange tak. I miss our Wednesday fish lunch!

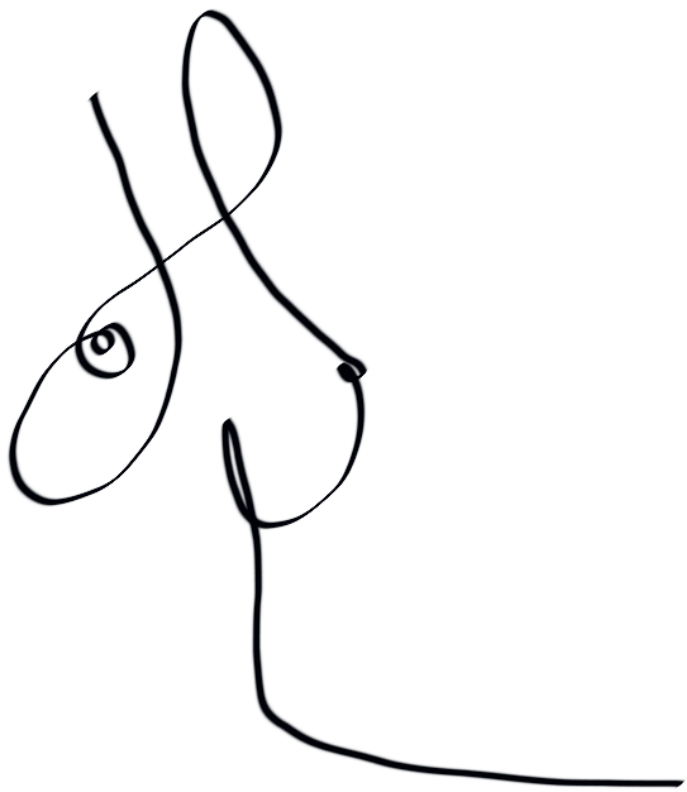
Mijn dank voor de prettige samenwerking met het bestuur en de wetenschappelijke commissie van de NBCA.
Enkele DICA collega's in het bijzonder: Pauline, Michael, Niels, Leonie, Laurien, Stijn, Fieke, Nishita, Robin en Jacqueline, en natuurlijk Cunera, de steunpilaar van DICA.

Dr. Verbeek en dr. In ’t Hof uit het Flevoziekenhuis, jullie enthousiasme inspireerde mijn promotietraject.

Babette Becherer, mijn paranimf, al sinds ons eerste jaar in Groningen fijn om met jou over serieuze, luchtige, ambitieuze en mooie dingen te praten. Sjoerd Meijer, mijn paranimf, al 30 jaar bijna hetzelfde avontuurlijke pad belopen. Mooi om te zien dat je de rol van ‘Sam’ zo serieus op je neemt. Ik ben trots dat je vandaag naast me staat en koester onze vriendschap.
Lieve Anna, tegelijkertijd aan een PhD avontuur begonnen, maar uiteraard was jij mij sneller af. Je geeft mij het gevoel dat alles in het leven mogelijk is en je inspireerde mij zelfs om je achterna te reizen naar Kopenhagen. Afgelopen jaren waren hopelijk slechts een proloog van ons leven samen. Alles is leuker samen met jou!

Mijn ouders, jullie geduld, vertrouwen en liefde heb ik altijd gevoeld. Dit proefschrift is voor jullie.

Curriculum Vitae



Curriculum Vitae

Erik Heeg was born on April 28th 1989, in Groningen, The Netherlands. Together with his 3 brothers and 3 stepsisters, he grew up in Zwolle in a large household. He completed high school at Thorbecke scholengemeenschap in Zwolle in 2008 and started the same year studying medicine at the University Medical Center in Groningen.

During the first two years of his studies, he worked in the liver transplantation team in an assistant role. In these first years, his interest for surgery took root. The elective and scientific internship during his studies at the department of Plastic, Reconstructive and Hand surgery in the Amsterdam University Medical Center (UMC) further stimulated his interest for science and (plastic) surgery. After obtaining his medical degree at the University of Groningen in 2016, he obtained clinical experience as a resident not in training at the department of Surgery at Flevoziekenhuis in Almere.

In 2017, Erik enrolled in a fulltime PhD program at the Leiden UMC, stationed at the Dutch Institute for Clinical Auditing (DICA) under supervision of prof. R.A.E.M. Tollenaar, prof. M.A.M. Mureau, and prof. M.T.F.D. Vrancken Peeters which led to this thesis. A substantial part of his work at DICA consisted of the daily management of the multidisciplinary NABON Breast Cancer Audit (NBCA). After receiving several scholarships and grants, Erik started a study collaboration in Denmark, Copenhagen for ten months as a visiting PhD at the Danish Breast Cancer Group (DBCG).

In 2020, he was accepted to start as a resident in training at the department of Plastic, Reconstructive and Hand surgery in the Amsterdam UMC.