Breast-conserving therapy is better than mastectomy

Based on registry data from Norway

PhD Thesis by
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Acknowledgments
Oslo University Hospital, Østfold Hospital and the Cancer Registry of Norway supported this work. The work was performed in the period 2011 to 2018.
Abbreviations

AC Axillary clearance
AJCC American Joint Committee on Cancer TNM system
BCT Breast-conserving treatment
CRN Cancer Registry of Norway
CTCs Circulating tumour cells
DCIS Ductal carcinoma in situ
DTCs Disseminated tumour cells
ER Estrogen receptor
EUSOMA European Society of Breast Cancer Specialists
HR Hazard ratio
HER2 Human Epidermal Growth Factor 2
LCIS Lobular carcinoma in situ
Met Metastasis
MTX Mastectomy
NBCG Norwegian Breast Cancer Group
NBCR Norwegian Breast Cancer Registry
NCCN National Comprehensive Cancer Network
pCR Pathological complete response
RT Radiation Therapy
SN Sentinel Node
TNM Tumour Node Metastasis
UICC Union for International Cancer Control (The TNM classification of Malignant Tumours)
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Paper II
Better survival after breast-conserving therapy compared to mastectomy, when axillary node status is positive in early stage breast cancer: a registry-based follow-up study of 6,387 Norwegian women participating in screening, primarily operated between 1998 and 2009.
Hartmann-Johnsen OJ, Kåresen R, Schlichting E, Nygård JF.

Paper III
Development of the Clinical Quality Registry for Breast Cancer in Norway.
Hartmann-Johnsen OJ, Kåresen R, Schlichting E, Naume B, Nygård JF.
Submitted
Introduction

Incidence and survival rates
Breast cancer is the most common cancer among women worldwide [1]. In 2012, nearly 1.7 million new cases were diagnosed. There were 521,000 deaths worldwide in 2014 [2].
Breast cancer is the most common cancer in women in Norway. In 2016, 3,371 new breast cancers were diagnosed among the Norwegian female population [3]. Figures 1 and 4 show the incidence increase during the recent decades. The Norwegian Breast Cancer Screening programme was initiated in Norway 1996 and covered the whole country for the age group 50-69 years from 2004 [4].

![Graph showing incidence rates for breast cancer by age group, from 1983-2016. National annual quality report on breast cancer 2016 [5].](image)

Over the last few decades, survival has improved. In 1980, the 5-year relative survival was 70%. In 2015, the 5-year survival rate was nearly 90%; see Figure 4.
Figure 2. Trends in survival, incidence and mortality rates. Survival is in 5-year relative survival proportions. From Cancer in Norway 2016.

The breast
Breast development happens in certain stages during a woman’s life: before birth, again at puberty, and later during the childbearing years. Changes also happen during menstrual cycle and when a woman reaches menopause. By the time a baby girl is born, nipples and the beginnings of the milk-duct system have formed. As a girl approaches her teen years, the ovaries start to produce oestrogen and causes the breast to enlarge and duct system to grow. When the menstruation begins, the secretory glands at end of milk ducts also matures. The breast are not fully mature until a woman has given birth and made milk [6]. By the fifth or sixth month of pregnancy, the breast is fully capable of producing milk. In the menopause estrogen levels dramatically decrease. The breast shrinks and loses shape [7].

Breast cancer
The breast parenchyma consists of collecting ducts and terminal duct lobular units (TDLUs). Around three-quarters of all breast cancers arise in TDLUs (Figure 3) [8]. In the WHO Classification of Breast Tumours, 4th Edition, published in 2012, the terminology for the most common type of breast cancer changed from invasive ductal carcinoma, no otherwise specified (NOS), to invasive carcinoma of no special type (NST). [9] This represents 80% of all breast cancers. Infiltrating lobular cancer is the second most common breast cancer, representing 10-15% of breast cancer cases. If the cancer is limited within the basal membrane of the ducts it is called an in situ lesion, eg ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS).
As every malignant epithelial tumour, it is characterised by the possibility of invasion to surrounding tissue and the potential to metastasise to distant sites (Figure 4). If the cancer is intraepithelial, it does not have the potential to metastasise and is considered a precursor lesion for the development of invasive breast cancer [6]. Breast cancer mainly metastasize through the lymph vascular system, but it can also spread via the bloodstream. The most common site for the spread of the disease is to the lymph nodes in the axilla. If the cancer is located in the breast and/or the regional lymph nodes, it is potentially curable and classified as loco regional breast cancer. If the cancer has spread beyond the breast and nearby lymph nodes it is advanced breast cancer, and not curable. The most common sites for the metastasis of breast cancer are the bone, lung and liver.

**Classification of breast cancer**

The commonly used classification of breast cancer is the Tumour Node Metastasis (TNM) classification from the International Union Against Cancer (UICC)[10]. The national guidelines from the Norwegian Health Department are based on the 6th edition from UICC, equal to the American Joint Committee on Cancer (AJCC) Staging Manual 6th edition [11].
Table 1. TNM staging for breast cancer. Subcategory within T1, T2, N1 etc. are not in table.

<table>
<thead>
<tr>
<th>Tumours</th>
<th>T0/Tis</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour size</td>
<td>T0: No primary tumour</td>
<td>≤2 cm</td>
<td>&gt;2 - ≤5 cm</td>
<td>&gt;5 cm</td>
<td>Tumour of any size with extension to chest wall/skin (ulceration or skin nodules)</td>
</tr>
<tr>
<td></td>
<td>Tis: tumour only in breast ducts or lobules</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodes</td>
<td>N0 lymph node metastases</td>
<td>N1 Metastases in 1-3 axillary lymph nodes</td>
<td>N2 Metastases in 4-9 axillary lymph nodes</td>
<td>N3 Metastases in infra- or supraclavicular lymph nodes or in ≥10 axillary lymph nodes</td>
<td></td>
</tr>
<tr>
<td>Metastasis</td>
<td>M0 No evidence of cancer metastasis</td>
<td>M1 Cancer found in other areas of body</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Early stage breast cancer
Early stage breast cancer, also referred to as primary operable breast cancer, is classified as T1-2N0-1M0. Most countries, including Norway, recommend surgery as the first line treatment within this classification.

Primary not operable breast cancer
If the tumour is larger than 5 centimetres it is defined as primary not operable breast cancer. Furthermore, if tumor is fixated to the chest or infiltrating the skin and/or nodes in axilla are fixated, it is also defined as primary not operable breast cancer. In this stage (locally advanced breast cancer) preoperative chemotherapy or other adjuvant treatment is recommended (neoadjuvant treatment). This treatment may shrink the tumour and/or nodal mass before surgery. Clinical definition of stage is done before surgery or neoadjuvant treatment. Tumor size measured by e.g. ultrasound can be used in the clinical definition of stage. In daily practise, all available information about tumor and nodal involvement can be used to define the clinical stage. After operation, final histological classification is done, marked with p in front of the stage definition.

Grading of breast cancer
The Nottingham Histologic Scoring System is the most commonly used [12]. Tumours are assigned a grade between 1 and 3 based on the following features: differentiation, nuclear features/polymorphism and mitotic activity. Each of the three features is assigned points between 1 and 3. The points are summed up and divided by three to arrive at the grade. Grade 3 indicates a more aggressive tumour type. In Norway, invasive carcinomas are graded with the Nottingham Histologic Scoring System and DCIS are graded after the Van Nuys Prognostic Index.
**Biomarkers**

Breast cancer is tested for biomarkers. They provide information about prognosis and also predict which type of treatment should be preferred. Four major biomarkers are routinely tested for in Norway: estrogen receptor (ER), progesterone receptor (PgR), Human Epidermal Growth Factor 2 (HER2) and the proliferation marker Ki 67. Hormone receptor positive tumours are normally sensitive to hormonal therapy and have improved prognosis. ER positive tumours are normally also progesterone receptor (PgR) positive. The cut off for ER positive status is 1% of immunostained cells irrespective of the signal intensity. The cut off for PgR is 10%. In addition to report the percentage of stained cells, it is recommended to report the staining intensity (weak, moderate or strong). Breast cancer is considered hormone receptor positive when it expresses ER and/or PgR positivity [6].

Breast cancer classification relies greatly on the histopathological features of the primary tumour (size, lymph node involvement, grade, ER, PgR, HER2 and Ki67).

**Gene expression patterns of breast cancer**

Gene expression patterns of breast cancer distinguish tumor subclasses with clinical implications [13]. Gene profile classification is not routinely used in Norway [14]. However, Oncotype Dx assay (21-gen signature), Mammaprint assay (70-gene signature), Prosigna (50-gen signature) and others [15-17] can be used in addition to the traditional histopathological parameters. The molecular profiles may divide breast cancer into four subgroups (general categories): basal-like (generally corresponds to triple-negative disease), luminal-A (generally ER positive and low grade), luminal-B (also ER positive but high grade) and HER2-positive tumours [18] [19]. However, it is not yet clear how to combine traditional histopathology, results from limited gene assays, and whole-genome profiling into a clinical useful algorithm [20].

**Breast cancer as a systemic disease**

Both circulating tumour cells (CTCs) in peripheral blood and disseminated tumour cells (DTCs) in bone marrow can be found in patients with breast cancer (Figure 5) [21]. Results from preclinical studies suggest that the majority of CTCs/DTCs will not form a clinically detectable overt metastasis. It seems that < 1% of all DTCs are capable of forming an overt tumour [22]. However, some micrometastatic foci will ultimately form overt tumours, ostensibly through their ability to recruit the necessary stroma and vasculature, whilst avoiding detection and elimination by the host immune system [23, 24].

The purpose of adjuvant therapy (chemotherapy, hormone therapy, antibody treatment and radiation therapy) is to destroy undetectable micrometastases a patient may harbour, in order to prevent future recurrent disease [25]. But, despite improvements in multidisciplinary treatment algorithms and prognosis, metastatic disease remains the cause of death in patients diagnosed with breast cancer [26].
**Figure 5.** Illustration of pT1N1M0, early stage breast cancer as a systemic disease including circulating and disseminated tumor cells in the blood and bones. The tumor is less than 2 cm and 2 of 3 sentinel nodes have metastasis. CD8 T cells are cytotoxic lymphocytes that contribute to the body’s anti-tumor immune response [27].

**Diagnosis**

More than half of women diagnosed with breast cancer observe a change in the breast themselves and are referred by their primary doctor to a breast diagnostic centre. The primary examinations are usually clinical examination, mammography and ultrasound of the axilla. Ultrasound of the breast may be needed in young patients with dense breast tissue or unclear lesions. A needle biopsy or cytology is performed when indicated. Cytology is normally taken from a lymph node in the axilla if it is enlarged on ultrasound. The case is discussed at a multidisciplinary team meeting (surgeon, radiologist, pathologist and oncologist). After the meeting, the patient usually receives an appointment with a surgeon (oncologist if neoadjuvant treatment is indicated) and receives information on diagnosis and treatment options.
The Norwegian Breast Cancer Screening Program
In 1993, the Department of Health started a mammography pilot project in four counties in Norway. In 1998, the government decided that breast cancer screening should be available for all women in Norway aged 50-69, every two years. The programme became nationwide in 2004. Figure 1 clearly shows the incidence increase of women with breast cancer aged 50-69 years from 1993. Every year, the programme detects about 1,000 cases of breast cancer or precancerous lesions. Approximately 1/3 of all women with breast cancer in Norway are detected through the Norwegian Breast Cancer Screening Program [28]. If breast cancer is detected after a normal screening and before the next scheduled screening, it is defined as an interval cancer. In one study from Norway, the proportion of interval cancer was 18% [29].

Treatment
Treatment of early stage breast cancer normally begins with surgery and is followed by chemotherapy if indicated. If hormone treatment is recommended, women normally start this treatment after chemotherapy and in parallel with radiotherapy (RT), if this is given. Treatment targeting HER2 positive cancers is given in parallel with chemotherapy and hormone therapy.

Surgical treatment
Early stage breast cancers (T1-2, N1-2, M0) usually undergo surgery as first line treatment, if there are no major contraindications to surgery. Chemotherapy can be given before surgery on tumors that are triple negative or HER2 positive with negative hormone status. Surgery is done by the removal of the tumor and some surrounding healthy tissue (breast-conserving therapy) or by removing the breast (mastectomy). Independent of the surgical procedure in the breast, an axillary operation is also performed.

Breast-conserving therapy and mastectomy
The tumour can be removed by breast-conserving therapy (BCT) or mastectomy (MTX). BCT is used to describe all operations where the approach is breast preservation, with the removal of the cancer with free margins. Several names are used for indicating BCT: biopsy, lumpectomy, partial mastectomy, segmental mastectomy and quadrantectomy.

Oncoplastic surgery
When a larger area of breast tissue needs to be removed, the breast might be distorted after surgery. To avoid a undesirable cosmetic result, surgeons use an oncoplastic surgery technique to sculpture the remaining tissue in order to realign the nipple and areola, and restore a natural breast shape appearance [30]. The opposite breast might be reduced to create symmetry.

Margins
If the margins are not clear from cancer cells, a re-excision is necessary. Reoperation rates from a study in England were 18% on women operated on using BCT (infiltrating breast cancer) [31]. The proportion of women with infiltrating breast cancer who underwent one operation in Norway in 2016 was reported to be 94% [3].

Sentinel node biopsy
A sentinel node is the hypothetical first lymph node or group of nodes draining a cancer [32]. Sentinel node biopsy is a surgical procedure to determine whether cancer has spread beyond a primary tumor into the lymphatic system. Before surgery, a radioactive
substance is injected into the affected breast. In addition to this, at surgery, it is common to inject a blue colour (blue dye) into the breast. The sentinel node is detected by being radioactive, with a device for sentinel node detection (gamma probe), and by the blue colour visually, which helps to detect the sentinel node. Normally, 1-3 sentinel lymph nodes are found.

**Axillary clearance**
Axillary clearance involves removing several or most of the lymph nodes from the armpit. Clinical lymphedema in the arm after axillary clearance are in some studies estimated to be 12-13% [33, 34]; therefore, axillary clearance operations should be kept to a minimum.

If one or more of the sentinel nodes contain cancer cells, axillary clearance might be done. This depends on how much the lymph node is affected and the number of lymph nodes affected. Furthermore, the biology of the primary tumour also influences the recommendations on axillary clearance. If potentially affected lymph nodes can be targeted well with adjuvant treatment, axillary clearance is normally not recommended. [35, 36].

**Chemotherapy**
Nowadays, chemotherapy is recommended based on the TNM stage and biomarkers. The type of surgery does not influence the choice of chemotherapy. Epirubicin and cyclofosfamid are normally given every three weeks, four times. If the tumour is high grade, negative hormone receptor and are positive for HER2, Taxans is recommended for the next 12 months after Epirubicin and cyclofosfamid [14].

**Immune treatment**
The monoclonal antibody trastuzumab targets the growth factor receptor HER2. Several randomised trials have shown benefit of treatment targeting HER 2 positive breast cancer with at last 1 year of trastuzumab combined with standard chemotherapy [37, 38]. If trastuzumab is recommended, it is given in parallel with chemotherapy [14]. On the ASCO annual meeting year 2018, a study supporting reduction of standard trastuzumab duration to 6 months was presented [39].

**Hormone therapy**
The aim of adjuvant hormonal therapy is to suppress the growth-stimulating effect of estrogen on breast cancer cells [6]. Hormone therapy is recommended for women with hormone receptor positive disease (ER-positive and/or PgR positive) with start-up after chemotherapy. The treatment is given for five to ten years. Tamoxifen is recommended for premenopausal women and aromatase inhibitors for postmenopausal women [14, 40].

**Zoledronic acid**
For women with established menopause, Zoledronic acid reduces the development of bone metastasis and improves disease outcomes [41]. In Norway, postmenopausal patients receives Zoledronic acid every six months for five years [14].

**Radiotherapy**
RT is recommended after BCT; see table 2 for the recommendations on surgery and RT from 1981 to 2017 for early stage breast cancer (T1-2 N0-1 M0) in Norway.
Changes in radiotherapy guidelines
In the first guidelines from the Norwegian Breast Cancer Group (NBCG) in 1981, before BCT was recommended, RT was believed to lead to less local and regional relapses after surgery. Prolonged survival was not documented. When BCT was introduced as a treatment option in 1988, RT was recommended because it was shown to reduce local relapse after Halsted’s radical mastectomy [42] in a Norwegian study by Høst H et al [43]. This study also showed a significant increase in the number of deaths caused by myocardial infarction in patients who had received high dose radiation. In 1996, the survival benefit of RT was still unsure. A randomised clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer published in 1996 did not show the benefit of long-term survival, only local recurrence [44]. However, in a Danish study published in 1997, reduced locoregional recurrences and prolonged survival in high-risk premenopausal women with breast cancer was found [45]. Several studies published in 1997 and later confirmed better survival among women receiving RT after both BCT and mastectomy [46-48]. In 2005, an overview of the randomised trials on the “Effects of radiotherapy and of the difference in the extent of surgery for early breast cancer on local recurrence and 15-year survival” was published in The Lancet [49]. The authors interpreted the findings of this study as follows: “Differences in local treatment that substantially affect local recurrence rates would, in the hypothetical absence of any other causes of death, avoid about one breast cancer death over the next 15 years for every four local recurrences avoided, and should reduce 15-year overall mortality.” The recommendation for axillary RT has changed in Norway during the study period (Table 4). From 1998, all women aged < 55 with N1 (1-2 lymph nodes involved) stage breast cancer were recommended radiation therapy. Women aged ≥55 years were not recommended radiation therapy towards the axilla region before 2003. From 2003, all women aged ≤70 with N1 stage breast cancer were recommended radiation therapy.

From radical mastectomy to breast-conserving therapy
In 1907, Halsted described the principles of radical mastectomy [42]. The method was based on the concept that breast cancer is a local disease before metastasis occurs, and the surgery had to be excessive (radical), involving the removal of the muscle behind the breast tissue. This operation was state-of-the-art until the 1970s, when modified radical mastectomy, which spares the muscles, gradually became more common [50]. In 1942, Geoffrey Keynes published a study where a patient with breast cancer had been treated with radium needles introduced around the tumour in the breast, in a wider area throughout the breast and axilla, without any surgery. In his study, 26 of 37 patients were alive after three years in Class 1 (no palpable glands and the tumour was clinically local)[51]. Several decades later, in 1972, Sakaria Mustakallio published a paper involving women who had undergone local excision of the tumour and postoperative radiotherapy. The cohort consisted of women with no clinical involvement of axillary nodules and where the tumour in the breast was not fixed to the chest wall and/or skin nodules. After five years, 553 of 702 women were alive [52]. The pioneering work of Umberto Veronesi in Italy and Bernard Fisher in the USA established the role of breast conserving therapy during the 1980s. They published randomized trials showing that overall survival after breast conserving plus adequate RT was similar to that following mastectomy [53, 54].
From 1973 to 1989, a total of six prospective randomised trials on BCT versus mastectomy were conducted, confirming the survival equivalence [55-60]. One of the large studies, the NSABP B-06 trial, prospectively randomised women with tumours of less than 4 cm to mastectomy, lumpectomy or lumpectomy with radiation [55]. All of the women had axillary clearance regardless of the nodal status. No difference was found in disease-free, distant-disease-free or overall survival. The data showed a significant reduction in local recurrence after BCT followed by radiation therapy. Based on these studies, the National Institute of Health in the USA issued a Consensus Conference statement in 1990 recommending BCT as the preferred surgical treatment for women with early stage breast cancer [61].

Trends in breast-conserving therapy and mastectomy

Surgery trends in the US
A nationwide study on trends in mastectomy for early stage breast cancer from the United States between 1998 and 2011 showed an increase in mastectomy rates [62]. This study included more than 1.2 million women, using the National Cancer Database in the US. In this study, 36% underwent mastectomy. They found that the odds of undergoing mastectomy in BCT-eligible women increased by 34% during the study period. The rates of breast cancer reconstruction increased from 12% to 36%. The rise in mastectomy were largely attributable to rise in bilateral mastectomy for unilateral, early stage breast cancer, from 5% of mastectomy in 1998 to 30% in 2011.

From the beginning of 2003 on, an increased use of mastectomy was reported by six single institutions from the United States [63-67].

On the other hand, some single institutes in the U.S. reported decreased mastectomy rates. One study found that mastectomy rates decreased from 41% in 2000 to 37% in 2006 [68, 69].

Overall, since 2005 there has been a falling trend of women having BCT compared with mastectomy in the U.S. [70]. Qualitative studies point to physician recommendation, patient concern about recurrence, increased use of breast magnetic resonance imaging, and desire for symmetry as the primary reasons women undergo bilateral mastectomy [71]. NCCN guidelines for breast cancer discourages prophylactic mastectomy in women other than those at high risk [14].

Surgery trends in Europe
A report from the European Society of Breast Cancer Specialists (EUSOMA), a multi-institutional European database, showed that in Europe a higher proportion of women undergo BCT than in the U.S. [72] Furthermore, an increasing rate of BCT has been found (mastectomy rates in 2005 were 38%, and in 2010, 13%).

Surgery trends in Norway
In Norway, mastectomy was the recommended choice for treatment until 1988. BCT followed with radiotherapy (RT) was introduced as a treatment option as early as in 1984 by the surgeon Johan Wiig and the oncologist Oldbjørn Klepp, in Trondheim [73]. Despite this, the introduction of BCT was delayed in Norway. This was probably based on uncertainty about whether BCT was equal to mastectomy when it came to survival [74]. In 1988, NBCG introduced BCT followed with RT as a treatment option. In the 1980s, free margins of 1-2 cm from the infiltrating tumour and DCIS were recommended, plus a
mammogram to exclude multifocal breast cancer. A good cosmetic result should be obtained and RT given to the breast (Appendix 1).

From 1988 until 2004 the number of BCT increased in Norway (Figure 6). During 2003-2006, the frequency of BCT was stable and from 2006-2009, reduced. From 2010 to today, the use of BCT has increased. However, due to different selection of pT1 and pT2, the figure has to be interpreted with caution.

**Figure 6**
Breast-conserving therapy proportion in Norway from 1998 to 2016. From 1998 to 2012 proportion undergoing BCT for infiltrating breast cancer (DCIS excluded). From 2013-2015, the proportion undergoing BCT, both infiltrating breast cancers and DCIS. From 2014, the proportion of infiltrating breast cancers and DCIS, 0-30 mm undergoing BCT [75].

In 2005, a study published in Lancet concluded that one breast cancer death could be avoided for every four local recurrences avoided [49]. In the following years, this study may have affected the proportion of women who have undergoing breast conserving treatment [49]. The opinion was that reduced use of BCT would lower the chances of local recurrence compared with mastectomy, and therefore, reduce breast cancer deaths. In 2012, a new EORTC overview with 20 years follow up, showed no difference in overall survival between BCT and mastectomy and from then, the number of BCT operations increased [76].

**The choice of surgical method**
A study on why mastectomy rates vary found that women recalled that they felt they had less autonomy and less time for decision-making when treated in a breast unit with a low proportion of mastectomies than women treated in units with a high proportion of mastectomies [77]. Conversely, women from the high and medium mastectomy rates units described the provision of more comprehensive information that felt less dictatorial in tone, together with greater support and more time for more autonomous decisions. In brief, the selection towards mastectomy seems to be the women's choice. Other studies support this finding [78-80].
Quality indicators
In 2004, the United States Federal Agency for Healthcare highlighted the need to develop validated quality measures to assess the quality of breast cancer care [81]. European guidelines for quality assurance produced under the auspices of the European Commission have listed 39 performance indicators for screening and diagnosis [82]. In 2010, a position paper from EUSOMA proposed 17 main quality indicators within breast cancer care.

Quality registries
Clinical quality registries are organisations which systematically monitor the quality of health care, within specific clinical domains, by routinely collecting, analysing and reporting health-related information. The main purpose of clinical quality registries is quality improvement and research.

A population-based study on breast cancer patients from Belgium showed that higher-volume hospitals had higher rates of multidisciplinary team meeting, diagnosis before surgery, neoadjuvant chemotherapy, BCT rate, adjuvant radiotherapy after BCT and follow up mammography [83]. Higher volume was associated with improved survival. The clinical database of the Danish Breast Cancer Cooperative Group (DBCG) has resulted in a large number of epidemiological research papers. In addition to this, 25% of the cases enrolled in the DBCG have frozen tissue, providing ideal conditions for translational research. DBCG perform large ongoing studies with aim to tailor the therapeutic intervention [84].

A large number of studies have been published based on data from the Swedish National Quality Registry for Breast Cancer (19 from publications year 2017) [85]. In the Netherlands a national breast cancer organization was established in 2011[86]. They have found that a continuous loop of registration and feedback by clinical auditing provides a powerful tool for quality monitoring and improvement [87]. Within three years' time they found several guidelines improvements and narrowing of the hospital variation for the respective QI.

In Norway several clinical registries have been established (www.kvalitetregistrene.no). Within cancer care there are eight clinical registries and the data collection is done by the Cancer Registry of Norway.

The Norwegian Breast Cancer Registry
The Norwegian Breast Cancer Registry (NBCR) was first established in 2005 as a collaboration between the Cancer Registry and members of the Norwegian Breast Cancer Group (NBCG). One of the main tasks of this collaboration was to define what information the registry should collect. Mandatory reporting forms for breast cancer were drawn up and used for breast cancer patients diagnosed from 01.01.2009. From the same date, pathology data was included in the register. In April 2011, the first form was sent by the Norwegian Health Network. The next major milestone was in February 2012, when NBCR messages became available on the Cancer Registry Reporting service (KREMT), a portal on the Norwegian Health network. In 2009, the registry received national status. The annual clinical report exists only in electronic form and the first was published in 2015 by NBCR [88]. Still, results from NBCR must be interpreted with care until more experience is achieved. The first report focused on some surgical indicators as the proportion of BCT, the proportion of resections after BC, and primary reconstruction. The selection of
quality indicators is done by the reference group for NBCR. Several of the mandatory quality indicators from EUSOMA are used as indicators, and the goal is to include the 17 which are mandatory for a Breast Centre Certification [89].

**A dynamic clinical pathway for the treatment of patients with early breast cancer**

A clinical care pathway is a methodology for mutual decision making and the organisation of care for a well-defined group of patients during a well-defined period of time [90]. The literature on clinical care pathways for breast cancer is limited [91]. In 2013, P.A. van Dame et al published “A dynamic clinical pathway for the treatment of patients with early breast cancer is a tool for better cancer care: implementation and prospective analysis between 2002–2010” [91]. They did an annual analysis of predefined clinical outcome measures, service indicators, team indicators, process indicators and financial indicators. Pathway quality control meetings were organised at least once a year. They used quality indicators defined by EUSOMA as clinical outcome measures. They found that the implementation of dynamic pathways for breast cancer improved the quality of care, patient satisfaction and outcomes.

In Norway, as mentioned under diagnosis, every new breast cancer diagnosis is discussed at a multidisciplinary team meeting.
Aim of the Thesis
The aims of the thesis is to use registry data to compare survival in women with breast cancer undergoing breast-conserving therapy with mastectomy, and highlighting the importance of using registry data for improving breast cancer health care.

Specific aims
- Compare survival among women undergoing breast-conserving therapy with those who have mastectomy for early stage breast cancer (paper I).
- Target subgroups of women who would benefit from breast-conserving therapy compared with mastectomy (paper II).
- Furthermore, describe how the mandatory quality indicators for Breast Centre Certification that are defined by EUSOMA can be calculated on a national level, and show how the data can improve survival and change guidelines. (paper III).
Material and Methods

Papers I and II are population-based studies using data from the Cancer Registry of Norway (CRN). The death registry data is collected from the Norwegian Cause of Death Registry [92]. Paper III describes the data collection, curation and presentation processes within the CRN. The registers are further described as follows:

Cancer Registry of Norway

The CRN provides almost complete incidence data on all individuals diagnosed with cancer in Norway since 1953 [93]. The reporting is based on pathology and cytology reports, clinical reports and death certificates. Variables like cancer site, date of diagnosis, histological type, basis for the diagnosis, stage or extent of the disease and date of operation are reported. These data are collected, validated and stored in the Incident Database. Breast cancer is classified after the TNM system [94]. The data in paper I is from the Incident database in CRN.

Mammography screening database

A new database in CRN was established when the Norwegian Breast Cancer Screening Programme was introduced in Norway in 1996 [95]. The programme achieved nationwide coverage in 2004. Compared to the Incident Database, the mammography screening database contains more information on items such as tumor size (in mm), number of nodes involved and hormone receptor status. However, some areas have less information; for example, it only contains information regarding the final operation. The data in paper II is from the mammography screening database.

Histology Register

The Histology Register has a record of every biopsy taken before surgery, at surgery and after surgery. The classification of the morphologic diagnosis in the Histology Register is based on the SNOMED coding system [96].

The cause of death registry

The underlying cause of death is registered, according to the International Classification of Diseases (ICD), since all deaths are reported by doctors who are required to complete a death certificate. Information about the date of death is provided to the CRN.

Study design

Paper I

Data from the Incident Database containing information on diagnosis, time of diagnosis, surgery type, surgery month, morphology, tumour grade, and TNM classification were used from the period 1998-2008. A total of 27,182 women diagnosed with invasive primary early stage breast cancer were selected. After exclusion, the cohort consisted of 13,015 women.

The cohort was divided into two main surgical cohorts, primary BCT and primary mastectomy. Primary BCT was further divided into three sub-cohorts: BCT operated once, BCT with reoperation and BCT followed by mastectomy. Primary mastectomy was further divided into two sub-cohorts: mastectomy operated once and mastectomy with reoperation. The division of the main and sub-cohorts was done three months after the primary operation.
Life tables for 5-year overall survival and breast cancer specific survival were stratified by surgical cohorts and age groups. The Cox proportional hazards method was performed to estimate the crude and adjusted hazard ratios for overall survival and breast cancer specific survival in all of the surgical cohorts. The multivariate analysis was adjusted by year of diagnosis, stage, age, histology and grade. The multivariate analysis was also performed in several strata (sub analysis) for the first three years and last three years of the study period. This was done because the proportion of BCT is different at the beginning of the study period compared to the end. Furthermore, the analysis was stratified in several age groups, mainly to compare the difference in overall and breast cancer specific survival between women undergoing BCT and mastectomy. A large difference between overall survival and breast cancer specific survival would mean a higher proportion of comorbidity. In addition to this, deterministic sensitivity analyses were performed.

**Paper II**
Data from the mammography screening database containing information on surgery, tumour size in millimetres, hormone receptor status, number of positive nodes, grade, histology, screening detection category (first screening, later screening and interval cancer) and TNM classification were used from the period 1998-2009. A total of 8,160 women with infiltrating breast cancer were selected. After exclusion, the final cohort consisted of 6,387 women.

The cohort was divided into three screening detection categories: first screening, later screening and interval cancer.

Life tables for overall survival and breast cancer specific survival were calculated for each of the screening detection categories in the following stages: pT1N0M0, pT2N0M0, pT1N1M0, and pT2N1M0, stratified by BCT and mastectomy. Kaplan-Meier survival analyses were done on BCT and mastectomy, stratified in stages. Overall death and breast cancer specific death figures were compared using the Cox proportional hazards model for estimating the hazard ratios between BCT and mastectomy in crude and multivariate analyses. The multivariate analysis was adjusted for screening detection category, year of diagnosis, screening age, T stage, nodal status by number of positive nodes involved, histology, grade and hormone status. The same multivariate analysis was also done by tumor size in mm compared to T stage. Finally, the adjusted analysis was stratified in stages.

**Paper III**
Describes the development of the Norwegian Breast Cancer Registry (NBCR). Report the development of electronic clinical forms and how data is captured, curated and presented in CRN. The main objective of the study is to assess the feasibility of using the NBCR for estimating QI individually for all hospitals diagnosing and treating breast cancer in Norway.
Summary of results

Paper I showed the benefit of BCT compared with mastectomy for women with early stage breast cancer operated on in Norway between 1998 and 2008. The adjusted analysis showed that women who underwent mastectomy had a HR of 1.64 (95% confidence interval 1.43–1.88) for breast cancer death compared to women who underwent BCT with RT. Paper II showed the survival benefit of BCT compared to mastectomy in stage T1N1N0 for women participating in the Norwegian mammography screening programme, but not for the other early stages of breast cancer. Women with T1N1N0 who underwent mastectomy had an HR of 2.91 (95% CI: 1.30–6.48) for breast cancer death compared to women who underwent BCT. This study indicates the increased survival benefit of BCT compared with mastectomy with the increasing severity of the disease. A better immune response in women undergoing BCT compared to mastectomy is discussed as a hypothesis. Paper III describes the development of the Norwegian Breast Cancer Registry and looks at how registry data can change guidelines and compliance with them. Furthermore, a summary score of Qis defined by EUSOMA was calculated for each hospital. The paper considers how a national registry can facilitate EUSOMA approval for breast cancer units on a regional level.
Discussion
The clinical trials comparing BCT with mastectomy were done decades ago [55, 57, 59, 76, 97, 98]. Since these studies were conducted, treatment and especially adjuvant therapy have changed and survival has improved [3, 36]. For more than two decades, it has been believed that early stage breast cancer outcomes were the same for women who had either mastectomy or BCT with radiotherapy. However, in 2013, Hwang et al. published a paper reporting better survival among patients undergoing BCT compared with mastectomy, challenging the notion of equality in survival between BCT and mastectomy [99].

Breast conserving therapy is better than mastectomy for early stage breast cancer
In the study from Hwang et al. they found improved disease-specific survival when women had undergone BCT compared to mastectomy among women with early stage breast cancer. Agarwal et al. published a paper in 2014 that corroborated Hwang’s study [100]. Because these two studies were not randomised trials but observational studies, more studies on this topic were needed. Paper I was the first study on this topic outside the United States. After this, several register studies have followed, showing better survival after BCT compared with mastectomy [101-103] However, in the other register studies on this topic, no subdivision of the surgical cohorts are done. In paper I, the surgical main cohorts were divided into five surgical sub cohorts. This made it possible to define the women initially treated with BCT followed by mastectomy as primary BCT (intention to treat). Without this division, these could be counted as mastectomy and give the mastectomy group a less favourable result. Other studies on this topic only describe if the operation is the first [100, 104] or final operation in the analysis [99, 102, 103, 105]. A patient undergoing BCT followed by mastectomy would not be a candidate for final BCT and this could disfavour the mastectomy group. This could be a confounding factor. However, in paper I, an adjusted analysis of the five subcohorts compared BCT operated once to mastectomy operated once and found similar results as in the two main surgical cohorts, where primary BCT had better survival than primary mastectomy. A comparable way of dividing the surgical cohorts in paper I has recently been published in a study from Denmark [106]. These researchers divided the surgical cohorts into three groups: mastectomy as the first surgical procedure, patients with breast conservation as the definitive surgical procedure and patients assigned with an initial BCT followed by mastectomy as second or later procedure. They found that patients assigned to BCT have better survival than patients assigned to mastectomy. Another confounding factor could be comorbidity, that is, that mastectomy could be preferred for women with more comorbidity than the BCT group. In paper I, a stratified adjusted analysis of all of the women under 50 years was done both for overall survival and breast cancer specific survival, showing the benefit of BCT compared with mastectomy for breast cancer specific survival. In the corresponding life tables, the difference between overall survival and breast cancer specific survival was only 1% for women undergoing BCT or mastectomy. In the age group 50-69, the difference in overall survival and breast cancer specific survival was 3% for women undergoing BCT and 4% for women undergoing mastectomy. In the age group ≥ 70, the difference increased to 7% for women undergoing BCT and 17% for women undergoing mastectomy. Therefore, comorbidity cannot explain the difference in survival between BCT and mastectomy. The proportion of women excluded from the primary cohort was large. A total of 27,182 were diagnosed with invasive, primary, early stage breast cancer during the period
January 1, 1998 to December 31, 2008. A total of 14,167 were excluded. Of these, 7,690 were excluded for the following reasons; previous cancer, more than one breast cancer, women who did not undergo surgery, missing information on the surgery, unknown size of tumour and unknown nodal status. Another 4,919 were excluded because of missing information on the metastasis status. The final cohort consists of 13,015 women, with information on surgery, TNM, stage and histology.

No information on hormone receptor status or the given adjuvant therapy were available. After all, neither of these factors determines whether a patient is recommended BCT or mastectomy. We have no information on multifocality based on preoperative diagnostic evaluation. However, BCT was only indicated if the tumor was located to one quadrant in this time period.

Observational cohort studies are prone to selection effects, but, as discussed in paper I, it is unlikely that selection effects can explain all the observed differences in survival among women undergoing BCT compared with mastectomy.

Survival benefit of BCT compared with mastectomy seems to increase with the severity of the disease

In paper II the cohort consists of women participating in the Norwegian mammography screening programme. In this paper, the survival benefit of BCT compared to mastectomy was found in stage T1N1N0. In this stage, 10-year breast cancer specific survival was 97% for women undergoing BCT and 89% for women undergoing mastectomy. No benefit was found in the other early stages of breast cancer. However, stage T2N1N0 included only 376 women of the total cohort of 6,387 women. A larger study with a larger cohort of Stage T2N10 might find a benefit of having BCT compared with mastectomy. Furthermore, node negative patients had a very good 10-year breast cancer specific survival. This was 98% in stage T1N0M0 for women undergoing BCT and 96% for women undergoing mastectomy. In Stage T2N0M0, 10 year-breast cancer specific survival was 90% for women undergoing BCT and 91% for women undergoing mastectomy. In Stage T2N1M0, 10-year breast cancer specific survival was 85% for women undergoing BCT and 84% for women undergoing mastectomy.

Triple negative cancer has worse survival than non-triple negative breast cancer [107]. In a recently publicised register study covering triple negative breast cancer, the survival benefit of BCT compared with mastectomy seems to increases with the severity of the disease [108]. In this study of 13,753 triple negative breast cancer patients, they found that BCT + RT could improve breast cancer specific survival and overall survival compared with mastectomy. Furthermore, upon stratifying the triple negative breast cancer patients according to age, grading, stage (American Joint Committee on Cancer TNM system (AJCC)), tumour size in cm, and lymph nodes status, most patients with BCT + RT presented with better survival than patients with mastectomy, except for the grade one and stage I patients, who had the same survival. Thus, they corroborated our finding that the survival benefit of BCT compared with mastectomy in some subgroups increases with the severity of the disease.

The tumour size was larger in women undergoing mastectomy compared to BCT in the main cohorts. Because of this, an analysis was also performed with T1 stage adjusted by size in mm. In the stratified adjusted analysis on stage T1N1M0, the HR for breast cancer death was 2.91 (95% CI 1.30-6.48) for women undergoing mastectomy compared with BCT. The same stage adjusted by tumour size in mm resulted in HR 3.13 (95% CI 1.32-7.45). This slight increase in HR is not significant. Anyway, it supports the increased
benefit of BCT compared with mastectomy with the increasing size of tumour, as observed in the paper on triple negative breast cancer [108]. No details on adjuvant therapy were available in our study. However, the Norwegian guidelines for hormone therapy and chemotherapy are identical in both surgical cohorts. In this study, as with other comparable register studies, only information on the final operation was known. On the other hand, paper I did not uncover any surprises regarding the surgical cohorts.

**Changing guidelines and follow treatment changes over time through registry data**

The finding of better survival when undergoing BCT compared to mastectomy is less valuable if given treatment is unknown. Therefore, a tool showing given treatment is crucial. As found in the Netherlands, a continuous loop of registration and feedback by clinical auditing provides a powerful tool for quality monitoring and improvement, e.g. increasing proportion of women undergoing BCT compared to mastectomy. Paper III describes how register data increases compliance with recommended treatment. The annual breast cancer reports reveal large differences in surgical treatment between the hospitals treating breast cancer in Norway. The proportion of women who underwent axillary clearance varied between hospitals from 6% to 20% in 2016. In 2015, new guidelines on axillary clearance came into effect, recommending that less women undergo axillary clearance. This was based on the results of the Z0011[35] study. This might have been implemented at different times in hospitals treating breast cancer. Moreover, on a national level, 786 women underwent axillary dissection in Norway in 2014. In 2016, the number was 365. This shows how a surgical procedure can change when guidelines change.

The percentage of women who underwent primary reconstruction after mastectomy in 2016 varied from 4% to 48% among hospitals treating breast cancer. Because of these large variations, a committee has been established to examine the reasons for this difference.

In 2014, the proportion of BCT in Norway was 75%, and in 2015 it was 82% [75]. The two main factors that may have influenced this change are the register studies showing the survival benefit of BCT compared with mastectomy and increased knowledge of the proportion of patients undergoing BCT at each hospital, showing the possibility for improvements.

Uptodate.com recommend BCT above mastectomy based on several register studies [109]. This guideline, in which Paper I, among other observational studies, is referred to, gives a clear indication that register studies influence guidelines. Paper III also describes how mandatory quality indicators for breast centre certification defined by EUSOMA can be calculated on a national level. This will make it possible to compare breast centres on a regional, national and international level. In the future, large register studies from several countries can be done. In paper II, where 6,387 women were included from the screening cohort, only 376 had stage T2N1M0. When cohorts are stratified, the number needed to give significant findings is rapidly reduced.

Since 1988 in Norway, BCT has been considered in the guidelines as having an equal survival benefit to mastectomy [14, 36]. Based on recommendations in the US [61, 110] and positioning European studies [53, 54], in addition to papers I and II, it is time to consider a revision of the Norwegian
guidelines. It is not so evident that BCT and mastectomy still shall be considered as equal treatment options.

Until now, it has not been shown in Norway that the introduction of quality indicators improves survival among women with breast cancer. However, several other studies have shown an improvement in survival after the introduction of quality indicators [111, 112], and there are no reasons to believe that this will not be applicable for women in Norway as well when observation time increases.

**Reporting of data to the Norwegian Breast Cancer Registry**
The yearly reports from the NBCR show that information on pathology is reported for approx. 99% of the cancer patients, and most hospitals are reporting diagnostics and surgical treatment for approx. 90%, some centres treating breast cancer do not adequately report to the NBCR. However, with pathology information coming directly from the laboratory to the NBCR, it’s straightforward to calculate the proportion of cancer cases that are missing information on e.g. surgery. Hospitals with low reporting are thus left when calculating and reporting quality indicators. The patient population might differ from hospital to hospital, e.g. some local hospitals might refer late-stage cancer to university hospitals, and some part of the country have a higher proportion of the patient with hereditary breast cancer. However, the EUSOMA criteria are precise in their specifications/data selection for the quality indicators’ minimum target, and target. These targets should be met regardless of differences between hospitals. One should therefore not do a case-mix correction, as focus is whether or not the EUSOMA criteria is meet, not if they would be meet given another set of patients. It is also quite possible that there exist structural differences between the hospitals which will be difficult to adjust for as they will not only be picked up by variables for individual patients, and that interventions designed to improve the hospitals performance and ability to meet the QI must be assessed individually at each hospital.

**Factors that can explain the survival benefit of BCT compared with mastectomy**

**Radiation therapy after BCT and immunological response**
All women undergoing BCT are recommended to have radiation therapy to reduce the local relapse of breast cancer [113]. The recommendation for RT after BCT has been quite consistent since the introduction of BCT in Norway in 1988 (Table 2).
In paper II, a survival benefit was only found in women with node positive disease; all of these women were recommended RT. A hypothesis was discussed in paper II, that RT against the remaining satellite tumours in the conserved breast, with the ensuing necrosis of tumour tissue, enhances an improved immune response against the cancer. Some studies support this hypothesis. Radiation therapy has revealed itself to be an ideal adjuvant to cancer immunotherapy, because of its ability to convert the irradiated tumour into an individualised, in situ vaccine [114]. One study using a poorly immunogenic mouse model of breast cancer found that irradiation increased the migration of CD8 T cells and impaired tumour regression following treatment with local ionising radiation to the tumour [115]. Another study showed that the transforming growth factor beta (TGFβ) receptor is a master in regulating radiation therapy-induced anti-tumour immunity. They found that the combination of
local radiation therapy with TGFβ neutralisation offers a novel individualised strategy for vaccinating patients against their tumours [116].

Chemotherapy and immunological response
Chemotherapy can improve the immune response against cancer. Doxorubicin has been shown to increase the tumour antigen-specific proliferation of CD8 T cells in mice with carcinogen-induced tumours [117]. There is accumulating evidence that some cytotoxic drugs, such as taxane, actually promote anti-tumour immunity and thereby contribute to the treatment’s therapeutic effect [118]. Women with conserved breast tissue might have an increased number of CD8 T cells that promote anti-tumour immunity compared to women with a removed breast.

The abscopal effect
The abscopal effect is a phenomenon observed during the treatment of metastatic cancer. Localised treatment of the tumour causes not only a shrinking of the treated tumour, but also a shrinking of the tumours outside the scope of localised treatment [119] [120]. Initially associated with single-tumour, localised radiation therapy, the term “abscopal” has also come to encompass other types of localised treatment [121]. It has been postulated that the abscopal effect is a result of an anti-tumour immune response induced by radiation therapy [122].

Impact of surgery on women with breast cancer
The impact of surgery on women with breast cancer is not well understood. In the early days, surgery was the only possible treatment and since then, the surgical removal of the breast cancer has always been a mandatory part of the treatment. With great improvements in adjuvant therapy, a line where adjuvant therapy is more important than surgical therapy might have been crossed for some types of breast cancer. After chemotherapy followed by surgery (neoadjuvant treatment), pathological complete response (pCR, no cancer found in the histological examination) varies from 4% to 13% [123]. We do not know if patients with pCR have any benefits or disadvantages from the surgery.

The curable effect of only doing surgery is on small tumours with low grade and no nodal involvement. In daily practise, cases where no adjuvant treatment is recommended. Surgery can activate and conduct the spread of breast cancer cells
A Norwegian study has suggested a systemic effect of surgery on occult dormant micrometastases after delayed breast reconstruction after mastectomy for breast cancer [124]. They found a peak in recurrences 18 months after reconstructive surgery. The height of the peak correlated with the extent of surgery and initial T and N stages.

Less is more
Several articles and comments regarding BCT compared to mastectomy have used headlines including the word “Less”: “less is more” [125] or “Less surgery, Longer Breast Cancer Survival” [126]. The expression is used both regarding surgery of the breast and surgery in the axilla. One of the latest articles regarding this was published online in The Breast [125]. Here, the authors claim that BCT might be even better than mastectomy in early breast cancer patients. They highlight the impact of RT as the most obvious explanation. Secondly, they speculate on a possibly depressed immune response after more extensive surgery and indeed the unknown complex relationship between surgical trauma, RT, medical treatment and immune response.
Based on recent studies, some have asked if it is appropriate to offer women suitable for BCT the choice of BCT or mastectomy [127]. Another article newly published in The Breast clearly addresses the need for less surgery by the heading “over surgery in breast cancer” [128].
Conclusions

- BCT gives a better survival benefit compared with mastectomy for early stage breast cancer. Several register studies corroborate the results from paper I [99, 100, 102-106].
- The survival benefit of BCT compared with mastectomy seems to increase with the severity of the disease. In paper II, no significant survival benefit was seen in stage T1N0M0 cancer, but in stage T1N1M0 there was a superior, significant survival benefit when women underwent BCT compared with mastectomy. The finding in paper II is comparable with a register study on triple negative breast cancer, where the benefit of BCT compared with mastectomy increases with the number of positive nodes involved [108].
- National registry on breast cancer facilitate studies that can influence guidelines and survival. Furthermore, the registry makes calculation of QIs possible.

Future perspectives

Further research is needed to understand why BCT is better than mastectomy. Does the remaining breast tissue with the remaining immune system in the conserved breast protect against the spread of cancer cells? Does chemotherapy and/or RT have an impact on the cancer in a better way when the breast tissue is conserved? Is the abscopal effect more prominent in women who have undergone BCT compared to mastectomy? Does surgery itself conduct the spread of cancer cells, and is the extent of surgery to some degree proportional to the spread of cancer cells? Should approaches to reduce the burden of surgery be implemented, e.g., doing sentinel node after removal of cancer in breast?
What is the optimal combination of surgery, chemotherapy and radiation therapy to maximise the immune response against the remaining cancer cells?
In short, how do we increase the abscopal effect in women treated for breast cancer?
## Appendix

Recommendations on surgery and RT from 1981 to 2017 for early stage breast cancer (T1-2 N0-1 M0). The guidelines are extracted from the Norwegian Breast Cancer Group [36] Group and the Norwegian Directorate of Health[14].


Colour change in background indicates a change in guidelines.

<table>
<thead>
<tr>
<th>Year</th>
<th>Breast</th>
<th>Margins</th>
<th>AC/SN</th>
<th>RT BCT</th>
<th>RT Axilla/Chest</th>
</tr>
</thead>
<tbody>
<tr>
<td>1981</td>
<td>MTX</td>
<td>Free</td>
<td>AC</td>
<td>BCT not recommended.</td>
<td>pT1 if tumour medial or central in breast. All pN1 and pT2</td>
</tr>
<tr>
<td>1988</td>
<td>MTX or BCT.</td>
<td>BCT: 1-2 cm margins</td>
<td>AC</td>
<td>50 Gy breast 10 Gy boost</td>
<td>MTX: Positive margins</td>
</tr>
<tr>
<td>1992</td>
<td>MTX or BCT.</td>
<td>BCT: 1-2 cm margins</td>
<td>AC</td>
<td>50 Gy breast 10 Gy boost</td>
<td>MTX: Positive margins</td>
</tr>
<tr>
<td>1994</td>
<td>MTX or BCT</td>
<td>BCT: 1-2 cm margins</td>
<td>AC</td>
<td>50 Gy breast 10 Gy boost</td>
<td>MTX: Positive margins</td>
</tr>
<tr>
<td>1998</td>
<td>MTX or BCT. BCT not recommended if size &lt; 3-4 cm.</td>
<td>BCT: 1-2 cm margins</td>
<td>AC</td>
<td>50 Gy breast 10 Gy boost</td>
<td>MTX: Positive margins MTX/BCT: RT if pN1 &amp; age&lt;55</td>
</tr>
<tr>
<td>2000</td>
<td>MTX or BCT. BCT not recommended if size &lt; 3-4 cm.</td>
<td>BCT: 1-2 cm margins</td>
<td>AC</td>
<td>50 Gy breast 10 Gy boost</td>
<td>MTX: Positive margins MTX/BCT: RT if pN1 &amp; age&lt;55</td>
</tr>
<tr>
<td>2003</td>
<td>MTX or BCT. BCT not rec. if size ≥ 5 cm</td>
<td>BCT: 3 mm margins to infiltrating cancer. (5mm margins to DCIS)</td>
<td>SN AC if pN1 (&gt;0.2 mm)</td>
<td>50 Gy breast 16 Gy boost age&lt;40 10 Gy boostage≥40</td>
<td>MTX: Positive margins BCT/MTX: RT if pN1 &amp; age&lt;70.</td>
</tr>
<tr>
<td>2008</td>
<td>MTX or BCT. BCT not recommended: size &gt; 4 cm; Multifocal tumours with distance more than 10 mm.</td>
<td>BCT: 3 mm margins to infiltrating cancer. (5 mm margins to DCIS)</td>
<td>SN AC if positive SN (Met&gt;0,2 mm)</td>
<td>50 Gy breast 16 Gy boost age&lt;40.</td>
<td>MTX: Positive margins MTX/BCT: RT if pN1 &amp; age&lt;70. If ≥10 nodes removed only level III, if less level I-II and III Except perinodal growth (&gt;2mm) RT to all levels</td>
</tr>
<tr>
<td>2009</td>
<td>MTX or BCT. BCT not recommended: size &gt; 4 cm; Multifocal tumours with distance more than 10 mm.</td>
<td>BCT: ≥2 mm margins to infiltrating cancer. (&gt;2 mm to DICIS)</td>
<td>SN AC if positive SN. (Met &gt;0.2mm)</td>
<td>50 Gy breast 16 Gy boost age&lt;40.</td>
<td>MTX: Positive margins MTX/BCT: RT if pN1 &amp; age&lt;70. If ≥10 nodes removed only level III, if less level I-II and III Except perinodal growth (&gt;2mm) RT to all levels</td>
</tr>
<tr>
<td>Year</td>
<td>Breast Conservation Therapy (BCT) or Mastectomy (MTX)</td>
<td>BCT recommendations</td>
<td>SN AC if positive SN. (Met &gt;0.2mm)</td>
<td>RT dosage</td>
<td>MTX recommendations</td>
</tr>
<tr>
<td>------</td>
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<td>---------------------</td>
</tr>
<tr>
<td>2010</td>
<td>MTX or BCT. BCT not recommended: size &gt; 4 cm; Multifocal tumours with distance more than 10 mm.</td>
<td>BCT: ≥2 mm margins to infiltrating cancer. (≥2 mm to DICIS)</td>
<td>SN AC if positive SN. (Met &gt;0.2mm)</td>
<td>50 Gy breast</td>
<td>MTX: Positive margins MTX/BCT: RT if pN1 &amp; age&lt;70. If ≥10 nodes removed only level III, if less level I-II and III Except perinodal growth (&gt;2mm) RT to all levels</td>
</tr>
<tr>
<td>2011</td>
<td>MTX or BCT. BCT not recommended: size &gt; 4 cm; Multifocal tumours with distance more than 10 mm.</td>
<td>BCT: ≥2 mm margins to infiltrating cancer. (≥2 mm to DICIS)</td>
<td>SN AC if positive SN. (Met &gt;0.2mm)</td>
<td>50 Gy breast</td>
<td>MTX: Positive margins MTX/BCT: RT if pN1 &amp; age&lt;70. If ≥10 nodes removed only level III, if less level I-II and III Except perinodal growth (&gt;2mm) RT to all levels</td>
</tr>
<tr>
<td>2012</td>
<td>MTX or BCT. BCT not recommended if multifocal tumours in different sectors of breast or size &gt;5 cm</td>
<td>BCT: ≥2 mm margins to infiltrating cancer. (≥2 mm to DICIS)</td>
<td>SN AC if positive SN. (Met &gt;0.2mm)</td>
<td>50 Gy breast</td>
<td>MTX: Positive margins MTX/BCT: RT if pN1 &amp; age&lt;70. If ≥10 nodes removed only level III, if less level I-II and III Except perinodal growth (&gt;2mm) RT to all levels</td>
</tr>
<tr>
<td>2013</td>
<td>MTX or BCT BCT not recommended if multifocal tumours in different sectors of breast or size &gt;5 cm</td>
<td>BCT: free margins to infiltrating cancer. (≥2 mm to DICIS)</td>
<td>SN BCT&amp;MTX: No AC if Met ≤0.2mm MTX: AC if Met&lt;0.2mm BCT: AC can be omitted if BCT and: 1-2 positive SN, PMP, ER+, PIAdjT, T1/T2, CliNegA, PRT, NoPreiGr, NoPreopChe.</td>
<td>50 Gy breast</td>
<td>MTX: Positive margins MTX/BCT: RT level III if metastasis &gt;2mm &amp; ≥10 nodes removed. If less nodes removed or perinodal growth (&gt;2mm) all levels. BCT/MTX: pN1(mic) no RT</td>
</tr>
<tr>
<td>2014</td>
<td>MTX or BCT BCT not recommended if multifocal tumours in different sectors of breast or size &gt;5 cm BCT, age&lt;50 clips in tumour bed. No size limitation on DCIS.</td>
<td>BCT: free margins to infiltrating cancer. (≥2 mm to DICIS)</td>
<td>N BCT&amp;MTX: No AC if Met ≤0.2mm MTX: AC if Met&lt;0.2mm BCT: AC can be omitted if BCT and: 1-2 positive SN, PMP, ER+, PIAdjT, T1/T2, CliNegA, PRT, NoPreiGr, NoPreopChe</td>
<td>40 Gy breast (2,67 Gy x 15) or 50Gy. 16 Gy boost</td>
<td>MTX: Positive margins MTX/BCT: RT level III if metastasis &gt;2mm &amp; ≥10 nodes removed. If less nodes removed or perinodal growth (&gt;2mm) all levels. BCT/MTX: pN1(mic) no RT</td>
</tr>
<tr>
<td>2015</td>
<td>MTX or BCT BCT not recommended if multifocal tumours in different sectors of breast or size &gt;5 cm BCT, age&lt;50 clips in tumour bed. No size limitation on DCIS.</td>
<td>BCT: free margins to infiltrating cancer. (≥2 mm to DICIS)</td>
<td>SN BCT&amp;MTX: No AC if Met ≤0.2mm MTX: AC if Met&lt;0.2mm BCT: AC can be omitted if BCT and: 1-2 positive SN, PMP, PIAdjT, T1/T2, CliNegA, PRT, NoPreiGr, NoPreopChe</td>
<td>40 Gy breast (2,67 Gy x 15) or 50Gy. 16 Gy boost</td>
<td>MTX: Positive margins MTX/BCT: RT level III if metastasis &gt;2mm &amp; ≥10 nodes removed. If less nodes removed or perinodal growth (&gt;2mm) all levels. BCT/MTX: pN1(mic) no RT</td>
</tr>
<tr>
<td>Year</td>
<td>Recommendation Details</td>
<td></td>
<td></td>
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<tr>
<td>2016</td>
<td>MTX or BCT not recommended if multifocal tumours in different sectors of breast or size &gt;5 cm. BCT, age&lt;50 clips in tumour bed. No size limitation on DCIS. BCT: free margins to infiltrating cancer. If infiltrating cancer and DCIS: Free margins. If only DCIS ≥2 mm margins. SN No AC if Met ≤2mm Met &gt;2mm AC can be omitted if1-2 positive SN, PMP, PIAJT, T1/T2, CliNegA, PRT, NoperiGr &lt;2mm, NoPreopChe 40 GY breast (2.67 Gy x 15) or 50Gy. 16 Gy boost age&lt;40 MTX: Positive margins MTX/BCT: RT level III if metastasis &gt;2mm &amp; ≥10 nodes removed. If less nodes removed or perinodal growth (&gt;2mm) all levels. BCT/MTX: pN1(mic) no RT</td>
<td>From 2016 same recommendation on AC after BCT and MTX</td>
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<td>2017</td>
<td>No changes</td>
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</table>
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Paper I
Survival is Better After Breast Conserving Therapy than Mastectomy for Early Stage Breast Cancer: A Registry-Based Follow-up Study of Norwegian Women Primary Operated Between 1998 and 2008

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1Cancer Registry of Norway, Oslo, Norway; 2University of Oslo, Oslo, Norway; 3Nesøya, Norway; 4Department of Breast and Endocrine Surgery, Oslo University Hospital, Oslo, Norway

ABSTRACT

Background. Breast-conserving therapy (BCT) and mastectomy (MTX) has been considered to have a similar long-time survival. However, better survival in women undergoing BCT compared with MTX is found in two recent register studies from the United States. The purpose of this study was to compare survival after BCT and MTX for women with early-stage breast cancer in Norway.

Methods. Women with invasive, early-stage breast cancer (1998–2008) where BCT and MTX were considered as equally beneficial treatments were included for a total of 13,015 women. Surgery was divided in two main cohorts (primary BCT, primary MTX) and five subcohorts. Analyses were stratified into T1N0M0, T2N0M0, T1N1M0, T2N1M0, and age groups (<50, 50–69, ≥70). Overall survival and breast cancer-specific survival (BCSS) were calculated in life tables, hazard ratios by Cox regression, and sensitivity analyses.

Results. Five-year BCSS for women who underwent primary BCT or primary MTX was 97 and 88 %, respectively. Women who underwent primary MTX had a hazard ratio of 1.64 (95 % confidence interval 1.43–1.88) for breast cancer death compared with women who underwent primary BCT after adjusting for the year of diagnosis, age at diagnosis, stage, histology, and grade.

Conclusions. Survival was better or equal after breast-conserving therapy than mastectomy in all early stages, surgical subcohorts, and age groups. This advantage could not only be attributed to differences in tumor biology.

INTRODUCTION

The clinical trials comparing breast-conserving therapy (BCT) with mastectomy (MTX) were done decades ago.1–6 Since these studies were conducted, treatment and especially adjuvant therapy have changed and survival improved.7,8 In 2013, Hwang et al. published a paper reporting better survival among patients undergoing BCT compared with MTX, challenging the notion of equality in survival between BCT and MTX.9 They suggested that differences in tumor biology might have contributed to survival differences between BCT and MTX. In January 2014, Agarwal et al. published a paper corroborating the results of Hwang.10 They assumed that a difference in the breast cancer-specific survival rate between BCT and MTX might be due to differences in compliance to adjuvant therapy or tumor biology. Because these two studies were not randomized trials but observational studies, more studies on this topic are needed, especially outside the United States.

In Norway, all cancer cases have to be reported to the Cancer Registry of Norway, making this a complete register for the whole population of Norway with the possibility to form a cohort where, according to national guidelines, BCT and MTX are considered as equal treatment options.11 The purpose of this study was to compare differences in survival after BCT and MTX for women with early-stage breast cancer in Norway.
MATERIALS AND METHODS

In this study, data from the Cancer Registry of Norway containing information on diagnosis, time of diagnosis, surgery type, surgery month, morphology, tumor grade, and TNM classification (done according to Union of International Cancer Control) were used.12

Cohort Selection

A total of 27,182 female residents of Norway were diagnosed with invasive, primary, early-stage breast cancer during the period January 1, 1998 to December 31, 2008. In this study, early-stage breast cancer is defined as T1–2 N0–1 M0 and stratified into T1N0M0, T2N0M0, T1N1M0, and T2N1M0 (tumor size \( \leq 5 \) cm and 0–3 ipsilateral axillary nodes with metastasis). From these women, a cohort who, according to the Norwegian Breast Cancer Group (NBCG) recommendations, could be offered either MTX or BCT was selected.7

The women excluded were as follows: women with previous cancer (2501), women diagnosed with more than one primary breast cancer in same or contralateral breast within 3 months (840), women who did not undergo surgery or information about the operation was missing (2153 of these 41 % were aged \( \geq 80 \) years), missing information about metastasis status (4919 of these 35 % underwent BCT as primary and 65 % underwent MTX as primary), unknown size of tumor or unknown nodal status (2196), final BCT (BCT operated once and BCT with reoperation) not received or missing information on RT (1073), final BCT receiving RT more than 365 days after diagnosis (62), women who received radiotherapy after MTX when nodal axillary status was negative (399), and women who died within 3 months after primary operation (24). The final cohort consists of 13,015 women.

Surgical Cohorts

Surgery was divided into two main cohorts: primary BCT and primary MTX. Primary BCT was further divided into three subcohorts: BCT operated once, BCT with reoperation, and BCT followed by MTX. Primary MTX was divided into two subcohorts: MTX operated once and MTX with reoperation. Division of surgical main and subcohorts was done 3 months after primary operation. If no further operation was done 3 months after primary operation, the operation was defined as one operation (BCT operated once and MTX operated once). If the women underwent two or more surgeries within 3 months after primary the operation, the operation was defined as several (BCT with reoperation, BCT followed by MTX, and MTX with reoperation).

Treatment Recommendations from the Norwegian Breast Cancer Group Between 1998 and 2008

NBCG criteria to accept BCT as final result of surgery was as follows: free margin should be at least 5 mm from 1998 to 2003 and 3 mm from 2003 to 2008; an acceptable cosmetic result obtained; tumor size \( < 5 \) cm from 2003; multifocal tumors were not accepted from 1998 to 2003; multifocal tumors \( < 1 \) cm apart were accepted for BCT from 2003.

Radiation therapy: all women undergoing BCT as final treatment should receive RT. Women younger than 55 years undergoing MTX with one to three positive nodes in axilla were recommended RT to chest wall and axilla from year 1998 to 2003; the age was increased to 70 years from 2003. Women undergoing MTX also were recommended RT if margins were not free. Radiation therapy was deemed given if the patient received a total dose of 47 Gy or more and start of treatment was no more than 365 days from date of diagnosis.

Neoadjuvant treatment is not recommended for early-stage breast cancer. Furthermore, choice of surgery did not influence recommendations of adjuvant chemotherapy or antiestrogen therapy.

Statistical Analyses

Life tables for 5-year overall survival (OS) and breast cancer-specific survival (BCSS) were stratified by primary BCT, primary MTX, and the following age groups: \( \leq 50 \) years, 50–69 years, and \( \geq 70 \) years. Furthermore, the surgical main cohorts were stratified in grade 1–3, ductal carcinoma, T1N0M0, T2N0M0, T1N1M0, T2N1M0, age \( < 50 \), age 50–69, and age \( \geq 70 \) years. Kaplan–Meier curves were stratified in T1N1M0, grade 3, ductal carcinoma, and age 50–69 years in the surgical main and sub cohorts.

Cox proportional hazards were performed to estimate crude and adjusted hazard ratios for OS and BCSS between BCT and MTX in the surgical main and subcohorts. Cox analyses were performed in the following strata: surgical main cohorts; surgical sub cohorts; first 3 and last 3 years of the study period; women aged \( < 50 \) years; women aged 50–69 years; women aged \( \geq 70 \) years; T1N0M0 grade1; T1-2N1M0 where primary MTX received RT and T1-2N1M0 where primary MTX did not receive RT. Furthermore, multivariate analysis was performed were all women receiving RT after MTX were excluded from the cohort. The multivariate analysis was adjusted in the surgical subcohorts for the year of diagnosis, stage, age, histology, and grade. Deterministic sensitivity analyses were performed on misclassification of surgery, selection bias, and uncontrolled confounding according to
RESULTS

Of the 13,015 women with early-stage breast cancer, 8065 (62 %) underwent primary BCT and 4950 (38 %) underwent primary MTX. Table 1 shows clinical characteristics of the patient cohort.

RT was given to 99.3 % in primary BCT and 30.7 % in primary MTX. In the subcohorts, RT was given to 100 % in BCT operated once, 100 % in BCT with reoperation, 70 % in BCT followed by MTX, 30 % in MTX operated once, and 43 % in MTX with reoperation. The proportion of women who underwent primary BCT is highest among women aged 50–69 years. Of women aged 70–79 years, 62 % were operated with primary MTX. At age 80 years and older, 88 % were operated with primary MTX.

Impact of Surgery Type on Overall and Breast Cancer-Specific Survival

A total of 2,475 deaths were identified in the cohort during the study period, including 1,132 (1,083 after 10 years) due to breast cancer. The 5-year OS was 89 %, and BCSS was 94 % (Table 2). Life tables showed better survival for women undergoing BCT compared with MTX. For women who underwent primary BCT or primary MTX, the 5-year BCSS was 97 and 88 %, respectively. In the age group 50–69 years, the 5-year BCSS for those who underwent primary BCT was 98 and 90 %, respectively.

The main and surgical subcohorts stratified in stage T1N1M0, grade 3, and ductal carcinoma showed better survival among women undergoing BCT compared with MTX (Kaplan–Meier curves in Fig. 1).

Furthermore, the two main surgical cohorts, primary BCT and primary MTX, were stratified in grade 1–3, ductal carcinoma, and stage (T1N0M0, T2N0M0, T1N1M0, T2N1M0), and none of these strata showed a significant benefit of MTX over BCT; i.e., in all these analyses, BCT was better or equal compared with MTX regarding survival (result not shown in table). Women who underwent MTX with reoperation had the worst prognosis, 79 % 5-year BCSS (Table 2).

In the adjusted Cox analysis, women who underwent primary MTX had a hazard ratio [HR] of 1.64 (95 % confidence interval [CI] 1.43–1.88) for breast cancer death compared with women who underwent primary BCT (Table 3). Adjusted analysis in the beginning of study period (1998–2001) showed HR 1.76 (95 % CI 1.02–3.05) compared with the end of study period (2006–2008) with HR 1.88 (95 % CI 1.23–2.87). Results not shown in table.

DISCUSSION

The main finding of this study is that both OS and BCSS were better in women with early-stage breast cancer undergoing BCT compared with MTX. This is contrary to the
### TABLE 1 Baseline characteristics

<table>
<thead>
<tr>
<th>Surgical main cohorts</th>
<th>Reoperateda</th>
<th>Surgical sub cohorts</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Number 13,015</td>
<td>Number 13,015</td>
</tr>
<tr>
<td></td>
<td>PrimaryBCT</td>
<td>PrimaryMTX</td>
</tr>
<tr>
<td>Number of patients</td>
<td>8065</td>
<td>4950</td>
</tr>
<tr>
<td>Proportion of patients</td>
<td>62%</td>
<td>38%</td>
</tr>
<tr>
<td>Median follow-up time</td>
<td>7.3 years</td>
<td>7.0 years</td>
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<tr>
<td>Proportion RT</td>
<td>99.3%</td>
<td>30.7%</td>
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<th>Reoperateda</th>
<th>Annual proportion (100 %)</th>
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<td></td>
<td>BCT</td>
<td>MTX</td>
<td>BCT</td>
</tr>
<tr>
<td>1998</td>
<td>34 % (264)</td>
<td>66 % (512)</td>
<td>16 %</td>
</tr>
<tr>
<td>1999</td>
<td>35 % (279)</td>
<td>65 % (520)</td>
<td>18 %</td>
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<tr>
<td>2000</td>
<td>41 % (364)</td>
<td>59 % (519)</td>
<td>14 %</td>
</tr>
<tr>
<td>2001</td>
<td>53 % (482)</td>
<td>47 % (422)</td>
<td>21 %</td>
</tr>
<tr>
<td>2002</td>
<td>63 % (736)</td>
<td>37 % (436)</td>
<td>23 %</td>
</tr>
<tr>
<td>2003</td>
<td>72 % (967)</td>
<td>28 % (384)</td>
<td>23 %</td>
</tr>
<tr>
<td>2004</td>
<td>73 % (1005)</td>
<td>26 % (368)</td>
<td>20 %</td>
</tr>
<tr>
<td>2005</td>
<td>72 % (1042)</td>
<td>28 % (407)</td>
<td>17 %</td>
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<tr>
<td>2006</td>
<td>71 % (962)</td>
<td>29 % (388)</td>
<td>18 %</td>
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<tr>
<td>2007</td>
<td>68 % (990)</td>
<td>32 % (465)</td>
<td>17 %</td>
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<tr>
<td>2008</td>
<td>65 % (974)</td>
<td>35 % (529)</td>
<td>14 %</td>
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<th>Age at diagnosis (years)</th>
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<th>Annual proportion (100 %)</th>
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<tr>
<td>&lt;30</td>
<td>61 % (31)</td>
<td>39 % (20)</td>
<td>26 %</td>
</tr>
<tr>
<td>30–39</td>
<td>56 % (287)</td>
<td>44 % (222)</td>
<td>26 %</td>
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<tr>
<td>40–49</td>
<td>66 % (1467)</td>
<td>34 % (761)</td>
<td>20 %</td>
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<tr>
<td>50–59</td>
<td>72 % (3024)</td>
<td>29 % (1203)</td>
<td>19 %</td>
</tr>
<tr>
<td>60–69</td>
<td>72 % (2515)</td>
<td>29 % (1024)</td>
<td>17 %</td>
</tr>
<tr>
<td>70–79</td>
<td>38 % (651)</td>
<td>62 % (1062)</td>
<td>16 %</td>
</tr>
<tr>
<td>≥80</td>
<td>12 % (90)</td>
<td>88 % (658)</td>
<td>13 %</td>
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<th>TNM stage</th>
<th>Annual proportion (100 %)</th>
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<th>Annual proportion (100 %)</th>
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<tr>
<td>T1N0</td>
<td>75 % (5165)</td>
<td>25 % (1686)</td>
<td>17 %</td>
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<tr>
<td>T2N0</td>
<td>44 % (888)</td>
<td>56 % (1140)</td>
<td>20 %</td>
</tr>
<tr>
<td>T1N1</td>
<td>60 % (1340)</td>
<td>40 % (893)</td>
<td>22 %</td>
</tr>
<tr>
<td>T2N1</td>
<td>35 % (672)</td>
<td>65 % (1231)</td>
<td>20 %</td>
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<table>
<thead>
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<th>Histology</th>
<th>Annual proportion (100 %)</th>
<th>Reoperateda</th>
<th>Annual proportion (100 %)</th>
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<tr>
<td>Ductal c.</td>
<td>62 % (6618)</td>
<td>38 % (3981)</td>
<td>18 %</td>
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<tr>
<td>Lobular c.</td>
<td>58 % (756)</td>
<td>42 % (549)</td>
<td>24 %</td>
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<tr>
<td>Other c.</td>
<td>62 % (691)</td>
<td>38 % (420)</td>
<td>19 %</td>
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<th>Grade</th>
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<th>Annual proportion (100 %)</th>
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<tbody>
<tr>
<td>I</td>
<td>73 % (2261)</td>
<td>27 % (844)</td>
<td>16 %</td>
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<tr>
<td>II</td>
<td>61 % (3600)</td>
<td>39 % (2259)</td>
<td>17 %</td>
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<td>III</td>
<td>54 % (1650)</td>
<td>46 % (1382)</td>
<td>23 %</td>
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<tr>
<td>Unknown</td>
<td>54 % (554)</td>
<td>46 % (465)</td>
<td>22 %</td>
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</tbody>
</table>

*BCT once* BCT operated once, *BCT reop.* BCT followed by reoperation, *BCT-MTX* BCT followed by MTX, *MTX once* MTX operated once, *MTX reop.* MTX with reoperation

a BCT reoperated is calculated by number of primary BCT undergoing BCT reoperation and BCT followed by MTX. MTX reoperated is calculated by number of primary MTX undergoing MTX with reoperation
TABLE 2 Survival by surgical main and subcohorts

<table>
<thead>
<tr>
<th>Survival</th>
<th>Median age</th>
<th>Total number at start</th>
<th>Number of overall deaths in 5-year period</th>
<th>Overall survival</th>
<th>Number of breast cancer deaths</th>
<th>Breast cancer survival</th>
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<tr>
<td>5-year</td>
<td>59.0</td>
<td>13,015</td>
<td>1334</td>
<td>89 %</td>
<td>742</td>
<td>94 %</td>
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<tr>
<td>10-year</td>
<td>59.0</td>
<td>9814</td>
<td>2260</td>
<td>78 %</td>
<td>1083</td>
<td>89 %</td>
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<tr>
<td>5-year survival BCT</td>
<td>56.9</td>
<td>8065</td>
<td>412</td>
<td>95 %</td>
<td>225</td>
<td>97 %</td>
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<td>5-year survival MTX</td>
<td>62.4</td>
<td>4950</td>
<td>922</td>
<td>80 %</td>
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<td>88 %</td>
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<td>10-year survival BCT</td>
<td>56.9</td>
<td>6370</td>
<td>796</td>
<td>86 %</td>
<td>384</td>
<td>93 %</td>
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<td>10-year survival MTX</td>
<td>62.4</td>
<td>3444</td>
<td>1464</td>
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<td>699</td>
<td>82 %</td>
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<td>5-year survival BCT</td>
<td>43.6</td>
<td>1785</td>
<td>89</td>
<td>95 %</td>
<td>72</td>
<td>96 %</td>
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<td>5-year survival MTX</td>
<td>42.7</td>
<td>1003</td>
<td>120</td>
<td>87 %</td>
<td>111</td>
<td>88 %</td>
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<td>Age 50–69 years</td>
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<td>5-year survival BCT</td>
<td>58.8</td>
<td>5539</td>
<td>232</td>
<td>95 %</td>
<td>115</td>
<td>98 %</td>
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<tr>
<td>5-year survival MTX</td>
<td>59.0</td>
<td>2227</td>
<td>296</td>
<td>86 %</td>
<td>201</td>
<td>90 %</td>
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<td>Age ≥ 70 years</td>
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<tr>
<td>5-year survival BCT</td>
<td>74.6</td>
<td>741</td>
<td>91</td>
<td>87 %</td>
<td>38</td>
<td>94 %</td>
</tr>
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<td>5-year survival MTX</td>
<td>78.3</td>
<td>1720</td>
<td>506</td>
<td>69 %</td>
<td>205</td>
<td>86 %</td>
</tr>
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<td>Surgical subcohorts, 5-year survival</td>
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</tr>
<tr>
<td>BCT operated once</td>
<td>57.0</td>
<td>6583</td>
<td>324</td>
<td>95 %</td>
<td>163</td>
<td>97 %</td>
</tr>
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<td>BCT with reoperation</td>
<td>56.2</td>
<td>1287</td>
<td>67</td>
<td>94 %</td>
<td>48</td>
<td>96 %</td>
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<tr>
<td>BCT followed by MTX</td>
<td>55.2</td>
<td>195</td>
<td>21</td>
<td>89 %</td>
<td>14</td>
<td>92 %</td>
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<tr>
<td>MTX operated once</td>
<td>62.5</td>
<td>4786</td>
<td>884</td>
<td>80 %</td>
<td>484</td>
<td>89 %</td>
</tr>
<tr>
<td>MTX with reoperation</td>
<td>59.3</td>
<td>164</td>
<td>38</td>
<td>76 %</td>
<td>33</td>
<td>79 %</td>
</tr>
</tbody>
</table>

FIG. 1 Kaplan–Meier, surgical main cohorts stratified in T1N1M0, grade 3, ductal carcinoma, and age 50–69

Breast-Conserving Therapy and Mastectomy
### TABLE 3 Crude and adjusted HR on overall and breast cancer death in women with early-stage breast cancer

<table>
<thead>
<tr>
<th></th>
<th>Crude Overall death</th>
<th>Adjusted Overall death</th>
<th>Crude Breast cancer death</th>
<th>Adjusted Breast cancer death</th>
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<tbody>
<tr>
<td></td>
<td>HR 95 % CI</td>
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<td>3.16 2.79–3.57</td>
<td>1.65 1.50–1.82</td>
<td>1.64 1.43–1.88</td>
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<td>1.00 (Reference)</td>
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<td>1.05 0.87–1.26</td>
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<td>BCT-MTX</td>
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<tr>
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<td>1.73 2.84</td>
<td>1.30 1.99</td>
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</table>

Numbers in italic are not significant ($p > 0.05$)
general consensus that MTX and BCT patients have a similar long-time survival, but corresponds well with the two studies done in the United States by Whang and Agarwal, who found better survival in women undergoing BCT compared with MTX.1,3,5,10,14–16

### Possible Selection Effects

The present study is an observational study, and several possible selection effects might explain the observed differences; i.e., the observed differences might be due to
other than the surgical procedures. In the following, we discuss the most probable selection effects that might have influenced the observed results.

**Completeness**

The Cancer Registry of Norway during the period 2001–2005 had an overall completeness on cancer estimated at 98.8%. Selection bias due to missing registration is thus unlikely. There was a higher proportion of patients undergoing primary MTX without known distant metastasis status than primary BCT, 65 versus 35%, before cohort selection. Nevertheless, information on distant metastasis status was available for all patients in the analyzed cohorts; i.e., they were metastasis-free at the time of diagnosis (M0).

**Access to Health Care**

Almost every inhabitant in Norway receives the same health care offer regardless of private insurance, and only public hospitals provide treatment of breast cancer. This might be in contrast to the United States, where women with a higher socioeconomic status are more likely to undergo BCT.

**Comorbidity**

Some of the women underwent MTX due to an overall judgment of their health situation. We have no information on comorbidity; however, the difference between OS and BCSS in women younger than aged 50 years was 1% in both the primary BCT and primary MTX strata, 3% for women undergoing BCT, and 4% for women undergoing MTX at age 50–69 years. This indicates that there are small differences in serious comorbidity in women younger than age 70 years between the two cohorts. However, comorbidity has probably influenced the choice of MTX among the older women.

**Hereditary Breast Cancer**

We are not able to stratify for women with hereditary breast cancer, because BRCA1/2 or prophylactic MTX is not recorded in the Cancer Registry. However, in a population-based incidence study in one of the counties in Norway, it was shown that 2.5% of the women studied were mutation carriers. This fraction might have a slight detrimental effect on survival in the MTX cohort.

**Patients Own Choice**

In a hospital in Norway, 14% of the women operated for breast cancer underwent MTX because of the patient’s own request, or the cancer had preoperatively been considered more prevalent than at the final histological examination. This might seem like a low proportion. However, a study from the United States regarding involvement in decision making about surgery for early-stage breast cancer showed that 9% underwent primary MTX based on patient preference.

**Tumor Biology**

When surgery is decided, results from cytology or biopsy together with mammogram and ultrasound normally give information on morphology, grade, and tumor size. Details on tumor biology, such as lymph vascular invasion, are normally not known when the decision on type of surgery is made, and therefore do not explain the difference between BCT and MTX. Furthermore, routine examination on HER2 was recommended from June 2005, late in the study period; therefore, triple-negative disease cannot explain the difference in survival between BCT and MTX.

**Radiation Therapy**

Today’s guidelines from NBCG differ from the guidelines in our study period, and today fewer patients would receive RT based on axillary node positive disease (1–3 lymph nodes). MTX with RT and MTX without RT are not directly comparable in our study, based on different recommendations for RT during the study period, but RT given to women with node-positive disease does not seem to increase the survival benefit of the MTX cohort.

Women undergoing MTX with RT likely represent a high-risk disease. Multivariate analysis where none of the patients in the MTX group received RT showed the benefit of BCT compared with MTX (HR 1.51; 95% CI 1.27–1.80).

**Adjuvant Therapy**

The Cancer Registry is incomplete when it comes to chemotherapy and antiestrogen therapy given. However, recommendations for chemo and antiestrogen therapy are identical for patients undergoing BCT and MTX. In this study it was not possible to see whether women undergoing MTX have less compliance to recommended therapy.

**Sensitivity Analysis of Misclassification, Selection Bias, and Unmeasured Confounder**

Sensitivity analyses were done under several different assumptions within the following three areas:
Breast-Conserving Therapy and Mastectomy

misclassification of surgery; selection bias, and unmeasured confounder. However, the larger the difference in the proportion of unmeasured confounding in the two cohorts, the lesser the rate ratio adjusted for unmeasured confounding. In the present study, first when assuming that as much as 90 % of women undergoing MTX had uncontrolled confounding (e.g., compliance to adjuvant therapy), and only 10 % in the BCT cohort, did we find a rate ratio of 1.0. We find it unlikely that the difference in adjuvant therapy was more than 10–30 % between the surgical groups (both surgical groups have the same recommendations to adjuvant therapy), and thus the adjusted rate ratio for unmeasured confounding was found to be 1.78, when assuming 10 and 40 % unmeasured confounding in BCT and MTX, respectively, compared with an unadjusted rate ratio of 3.31.

Proportion of Women Undergoing BCT Compared with MTX Changed During Study Period

The proportion of BCT at the beginning of study period was lower than at the end of study period, but the benefit of BCT compared with MTX did not seem to change during the study period.

Strengths and Weaknesses of the Study

The major strength of our study is that the results are based on the whole population of women diagnosed with early-stage breast cancer in Norway during the period January 1, 1998 to December 31, 2008. Dividing the surgical main cohort into five surgical subcohorts made it possible to include women initially treated with BCT followed by MTX without receiving RT. If this had not been done, women initially treated with BCT would have been regarded as BCT without RT and excluded from the cohort.

The weaknesses are that the Cancer Registry lacks information on hormone receptor status and information on given adjuvant therapy. However, neither of these factors determines whether a patient should undergo BCT or MTX. Observational studies, such as this, are prone to selection effects. However, as discussed above, we find it unlikely that this can explain all of the observed differences in survival among women undergoing BCT compared with MTX.

CONCLUSIONS

This study corroborates the findings of two studies from the United States showing better survival for women undergoing BCT compared with MTX. This advantage could not be attributed to differences in tumor biology. Further studies are necessary to determine whether this benefit is caused by variation in adjuvant therapy or by type of surgery.

ACKNOWLEDGMENT This study was supported by Oslo University Hospital by giving the first author 50 % of the working time for research.

DISCLOSURE All authors have declared: no support from any organization for the submitted work; no financial relationships with any organization for the submitted work; no financial relationships in the previous three years with any organization that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

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Paper II
Better survival after breast-conserving therapy compared to mastectomy when axillary node status is positive in early-stage breast cancer: a registry-based follow-up study of 6387 Norwegian women participating in screening, primarily operated between 1998 and 2009

Olaf Johan Hartmann-Johnsen1,2,3*, Rolf Kåresen1,4, Ellen Schlichting4 and Jan F. Nygård1

Abstract

Background: Recent registry studies on early-stage breast cancer have shown better survival rates when women underwent breast-conserving therapy (BCT) compared with mastectomy (MTX). The aim of this study is to investigate women participating in screening, in all four stages of early breast cancer (T1N0M0, T2N0M0, T1N1M0, and T2N1M0), as to whether there is a survival benefit when women undergo BCT compared to MTX.

Method: A cohort of 6387 women aged 50–69, with primary-operated breast cancer from January 1998 to December 2009, participating in screening and followed-up until the end of 2010. Life tables were calculated by stages (pT1N0M0, pT2N0M0, pT1N1M0, and pT2N1M0), surgery groups (BCT and MTX), and screening detection (first screening, later screening, or interval cancer). Cox regression was used to calculate hazard ratios (HR) between BCT and MTX in crude and adjusted analyses.

Results: In stage T1N1M0, women who underwent MTX had an HR of 2.91 (95% CI 1.30–6.48) for breast cancer death compared to women who underwent BCT, after adjusting for screening detection, years of diagnosis, age at diagnosis, histology, grade, and hormone receptor status. For all other TNM categories of early breast cancer, there was no difference in survival.

10-year breast cancer-specific survival (BCSS) in T1N0M0 was 98% for women undergoing BCT and 96% for women undergoing MTX. 10-year BCSS in T1N1M0 was 97% for women undergoing BCT and 89% for women undergoing MTX.

Conclusions: For women participating in screening, there is a benefit of BCT over MTX in stage T1N1M0. No such effects were observed in the other early stages of breast cancer.

Keywords: Breast conserving therapy, Mastectomy, Survival

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Background
Recent registry studies show better survival when women undergo breast-conserving therapy (BCT) compared to mastectomy (MTX) in early-stage breast cancer (T1-2N0-M0). In 2013, Hwang et al. found better survival among patients undergoing BCT compared with MTX [1]. They suggested that differences in tumor biology (e.g., lympho-vascular invasion or extranodal invasion) might contribute to survival differences between BCT and MTX.

In January 2014, Agarwal et al. published a paper corroborating the results of Hwang et al. [2]. They assumed that the difference in breast cancer-specific survival (BCSS) between BCT and MTX might be due to differences in adjuvant therapy regimes or tumor biology. In 2015, a Norwegian study corroborated the findings of the US studies [3].

One study has shown the benefit of BCT over MTX among women participating in screening [4]. Furthermore, interval cancers (detected between screenings) are shown to have a larger median tumor size, more affected axillary lymph nodes, higher proportion of grade 3, and fewer with positive hormone receptor status [5]. The selection of MTX rather than BCT could be more prominent in women with interval cancer and may be a confounding factor. Based on this, the cohort was divided into screening detection categories.

Previous studies, including a study with women participating in screening [4], did not examine whether there are differences in survival between BCT and MTX in early-stage breast cancer, stratified in T1N0M0, T2N0M0, T1N1M0, and T2N1M0 [1–3]. The aim of this study is to investigate, in all four stages of early breast cancer, whether there is a survival benefit when women undergo BCT compared with MTX when women participate in screening.

Methods
A database was established when mammography screening was introduced in Norway in 1996. From this database, information on women with invasive breast cancer diagnosed from January 1998 to December 2009 was selected. Information on surgery type, tumor size, hormone receptor status, grade, histology, and TNM classification (according to the Union of International Cancer Control) [6] was merged with the national death registry containing information on cause of death.

This registry study has been performed with anonymous data, and thus, no ethical approval or consent from patients were necessary.

Cohort selection
Treatment recommendations from the Norwegian Breast Cancer Group to accept BCT as the final result of surgery were as follows: the free margin should, from 1998 to 2003, be at least 5 and 3 mm from 2003 to 2009; an acceptable cosmetic result should be obtained; tumor size should be less than 5 cm from 2003; multifocal tumors were not accepted from 1998 to 2003; and multifocal tumors <1 cm apart were accepted for BCT from 2003. A cohort who, according to the Norwegian Breast Cancer Group recommendations, could have been offered either MTX or BCT was selected [7].

Contralateral prophylactic surgery was not recommended during the study period [7].

In Norway, women aged 50–69 years are invited to have a mammography every second year.

To evaluate possible differences in survival due to different screening detection categories, we divided the cohort into three groups: first screening (detected on the first screening), later screening (detected on second or later screening), and interval cancer (detected after normal screening and before the next scheduled screening).

Only women who had participated in at least one screening were selected. A total of 8160 women aged 50–69 years with primary operable breast cancer (stages T1N0M0, T2N0M0, T1N1M0, and T2N1M0) were included and followed until the end of 2010.

Women meeting one of the following criteria were excluded: more than one infiltrating breast cancer localized in breast; multifocal (217); breast cancer not primarily located in breast (169); unknown metastasis status at diagnosis (969); metastasis at diagnosis (25); not operated (4); unknown hormone status (389); unknown nodal status (0) or unknown size of tumor in mm (0). The final cohort consisted of 6387 women. Surgery was divided into BCT and MTX as the final operation.

Hormone receptor status was regarded as positive (5449) if both (3264) or one (2185) of the hormone receptor values (ER, PgrR) were positive. Hormone receptor status was regarded as intermediate (213) if: both were intermediate (82), one intermediate and one negative (131), or one intermediate and one missing (0). Hormone receptor status was regarded as negative (725) if both were negative (722) or one negative and one missing (3).

Hormone receptor status was also stratified in estrogen-receptor (ER) positive (ER 100–10%) and ER negative status (ER < 10%).

Statistical analysis
Life tables for overall survival (OS) and breast cancer-specific survival (BCSS, proportion of cohort who had not died of breast cancer within 5/10 years), were done in the following stages: pT1N0M0, pT2N0M0, pT1N1M0, and pT2N1M0, stratified by BCT and MTX.

Kaplan-Meier survival analyses were done on BCT and MTX, stratified in stages.

Overall death and breast cancer death figures were compared using the Cox proportional hazard model for
estimating hazard ratios (HR), between BCT and MTX in crude and multivariate analyses. The multivariate analysis was adjusted for screening detection category, year of diagnosis, screening age, tumor size, nodal status, histology, grade, and hormone status. Furthermore, the adjusted analysis was stratified in stages. Sub-analysis was also done on T1-2N1M0 from year 2003 (all node positive were recommended radiation therapy from year 2003, regardless of surgical treatment). This analysis did not have enough numbers to give significant results in the T1N1M0 and T2N1M0 strata.

Statistical analyses were conducted in STATA version 13.1 (StataCorp, Texas, USA).

Results
Main results
In stage T1N1M0 women participating in screening who underwent MTX had a HR of 2.91 (95% CI 1.30–6.48) for breast cancer death compared to women who underwent BCT, after adjusting for screening detection, years of diagnosis, age at diagnosis, histology, grade, and hormone receptor status. In stages T1N0M0, T2N1M0, and T2N1M0, no survival benefit of BCT compared with MTX was found after adjustment.

Baseline results
Of 6387 women diagnosed with breast cancer after participating in screening, 368 women died of all causes within 10 years of their operation. Of these, 115 died of breast cancer within 5 years. After 10 years, a total of 182 women had died of breast cancer (not in table). Median follow-up time for the whole cohort was 6.0 years (Table 1). In total, 4449 (70%) underwent BCT (Table 1) and of these 52 died of breast cancer within 5 years and a total of 88 died within 10 years of breast cancer.

Five and 10-year breast cancer-specific survival (BCSS)
Women participating in screening had 98% (95% CI 0.98–0.99) breast cancer-specific survival (BCSS) after 5 years and 96% (95% CI 0.96–0.97) after 10 years (not in table). Both surgical groups in T1-2N0M0 had no significant difference in 5- or 10-year BCSS (Table 2). Thirteen percent of the cohort had stage T1N1M0, with significantly better survival among women undergoing BCT compared to MTX. 5-year BCSS in stage T1N1M0 was 99% (95% CI 0.97–0.99) for women undergoing BCT, and 96% (95% CI 0.92–0.98) for women undergoing MTX. 10-year BCSS in stage T1N1M0 was 97% (95% CI 0.94–0.99) for women undergoing BCT and 89% (95% CI 0.83–0.93) for women undergoing MTX. BCSS in the screening detection categories: the most favorable 10-year BCSS was 98% for women undergoing BCT in stage T1N1M0 detected on first screening and stages T1N0-1M0 detected on second or later screening.

Women undergoing MTX had the following 10-year BCSS in T1N1M0 detected on first screening 93% (95% CI 74–98), 96% (95% CI 93–98) in T1N0M0 detected on second or later screening, and 91% (95% CI 82–95) in T1N1M0 detected on second or later screening. The least favorable ten-year BCSS was 64% (95% CI 0.39–0.81) in first-screening detected, stage T2N1M0 for women undergoing MTX.

Screening detection category
Screening detection of cancer was distributed as follows: first screening 20% (1251), later screening 60% (3849), and interval cancer 20% (1287) (Table 1). The highest proportion of women who underwent BCT within the screening categories was found among the later screening group (74%), and the lowest in interval cancer (58%).

Kaplan-Meier curves
Corresponding Kaplan-Meier curves show the benefit of BCT over MTX in stage T1N1M0 (Fig. 1). Furthermore, the Kaplan-Meier curves also show the benefit of BCT over MTX in stage T2N1M0 after 5 years, but at 8 years, the curves align.

Crude and adjusted analyses
Crude HR for breast cancer death for women undergoing MTX compared with BCT was 2.33 (95% CI 1.75–3.10) (Table 3). In the adjusted analysis, HR for breast cancer death for women undergoing MTX compared with BCT was 1.39 (95% CI 1.02–1.89). Adjusted analysis on breast cancer death gave interval cancer HR 1.32 (95% CI 0.87–2.00) compared with HR 1.0 detected on first screening. In the stratified adjusted analysis on stage T1N1M0, the HR for breast cancer death was 2.91 (95% CI 1.30–6.48) for women undergoing MTX compared with BCT with HR 1.0 (main result, Table 4). The same stage adjusted by tumor size in mm resulted in HR 3.13 (95% CI 1.32–7.45) for women undergoing MTX compared with BCT with HR 1.0 (result not shown in table). Furthermore, the same analysis, done with hormone receptor status divided into estrogen-receptor positive or estrogen-receptor negative status, resulted in HR for breast cancer death 2.69 (95% CI 1.21–6.00) compared with BCT with HR 1.0. In a stratified adjusted analysis on stage T1N0M0, T2N0M0, and T2N1M0, no survival benefit of BCT compared with MTX was found. Sub-analysis on stage T1N1M0 and T2N1M0 from year 2003 (women in both surgical cohorts with node positive disease were recommended radiation therapy) resulted in HR for breast cancer death 2.25 (95% CI 1.21–4.17) for women undergoing MTX compared with BCT (result not in table).
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<td>2 844 (74%)</td>
<td>747 (50%)</td>
<td>4 449 (70%)</td>
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<td>2 868 (75%)</td>
<td>637 (40%)</td>
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<tr>
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<td>62 (5%)</td>
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<td>5 449 (85%)</td>
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<td>44 (4%)</td>
<td>110 (3%)</td>
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<td>Detected on second or later screening</td>
<td>Interval cancer</td>
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**All early stages**

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**T2N1M0**

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**Hartmann-Johnsen et al. World Journal of Surgical Oncology (2017) 15:118**
Discussion
The most important finding in this study is the benefit of BCT compared with MTX in stage pT1N1M0. In all other early stages of breast cancer, there were no significant benefit of BCT over MTX when women participate in screening. In a previous study on women participating in screening, adjusted analysis revealed a 1.7 (95% CI 1.3–2.4) higher risk of breast cancer death among women who underwent MTX compared with BCT [4]. However, this study did not do the adjusted analysis in different stages of early breast cancer.

Previous registry studies have shown better survival among women undergoing BCT compared with MTX, the latest published from the Netherlands with 20 years of follow-up time [1–4, 8]. A recently published Danish study has shown better overall survival among women aged <45 undergoing MTX compared to BCT. However, women aged ≥45 had significant better overall survival when they underwent BCT compared to MTX [9]. In these studies, the adjusted analysis was done by size, nodal status, or stage [1–3, 8]. In the present study, the adjusted analysis was also done after stratifying by stage and screening detection category. The finding of better survival rates among women undergoing BCT compared with MTX when there are positive nodes in the axilla might contribute to identifying where to find the cause of the difference in survival between women undergoing BCT and MTX.

Studies on small (T ≤ 1.5 cm), lymph node-negative breast tumors show very high breast cancer survival rates at 10 years, even in the absence of chemotherapy [10]. In this study, 5-year BCSS in stage T1N0M0 is 99% in both surgical groups.

Since better survival rates among stage T1N1M0 were found, improved survival among those with a larger tumor (T2N1M0) could have been expected. Crude and adjusted analyses do not show any significant benefits of BCT over MTX in stage T2N1M0. However, the Kaplan-Meier curve shows an advantage of BCT over MTX until 8 years of follow-up. In this cohort, only 376 had T2N1M0—a study with a larger cohort might find a significant benefit of BCT over MTX within the T2N1M0 strata. Furthermore, if there had been a strong benefit from BCT compared with MTX, this would probably have been shown in earlier studies. Clinical trials comparing BCT with MTX done decades ago show similar survival benefits of BCT and MTX [11–16]. Since these studies were conducted, treatment has changed and survival improved [7, 17].

Limitations in the study
Tumor size
Tumor size was slightly larger in women undergoing MTX compared with BCT. In Hwang et al.’s and Agarwal et al.’s studies, tumor size was analyzed by size groups defined in cm. This could be a confounding factor; however, the adjusted analysis in this study on tumor size in mm, within stage T1N1M0 did not reduce the HR between MTX and BCT. Small differences in tumor size hardly explain the difference in survival between BCT and MTX in stage T1N1M0.
The number of positive nodes involved might differ between the surgical groups. For instance, a larger proportion of positive lymph nodes in women undergoing BCT compared with a low proportion of positive lymph nodes in women undergoing MTX would probably contribute to a difference in survival between BCT and MTX [18, 19]. This is the reason why the adjusted analysis was done by number of nodes involved and not by the TNM classification of nodal status (N0 or N1).

**Table 3** Overall deaths/breast cancer deaths, crude and adjusted comparing BCT to MTX

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<th>Surgery (adjusted stage)</th>
<th>Crude</th>
<th>Adjusted</th>
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<tr>
<td></td>
<td>Overall death (95% CI)</td>
<td>Breast cancer death (95% CI)</td>
</tr>
<tr>
<td>BCT</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>MTX</td>
<td>1.91 (1.56–2.33)</td>
<td>2.33 (1.75–3.10)</td>
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<table>
<thead>
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<th>Screening</th>
<th>Crude</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
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<td>Overall death (95% CI)</td>
<td>Breast cancer death (95% CI)</td>
</tr>
<tr>
<td>First screening</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Second or later</td>
<td>0.96 (0.74–1.24)</td>
<td>0.88 (0.60–1.30)</td>
</tr>
<tr>
<td>Interval cancer</td>
<td>1.65 (1.25–2.18)</td>
<td>2.39 (1.62–3.52)</td>
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<td>Breast cancer death (95% CI)</td>
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<td>1998–2004</td>
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<tr>
<td>2005–2009</td>
<td>0.58 (0.45–0.75)</td>
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<td>Breast cancer death (95% CI)</td>
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<td>1</td>
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<td>54–57</td>
<td>1.65 (1.13–2.41)</td>
<td>1.60 (1.00–2.59)</td>
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<td>58–61</td>
<td>1.80 (1.24–2.59)</td>
<td>1.45 (0.90–2.34)</td>
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<tr>
<td>62–65</td>
<td>1.94 (1.34–2.88)</td>
<td>1.26 (0.77–2.09)</td>
</tr>
<tr>
<td>66–69</td>
<td>2.29 (1.58–3.32)</td>
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<td>Breast cancer death (95% CI)</td>
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<td>T1 ≤ 2 cm</td>
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<tr>
<td>T2 &gt; 2–5 ≤ cm</td>
<td>2.27 (1.83–2.81)</td>
<td>3.86 (2.90–5.15)</td>
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<td>1.70 (1.14–2.52)</td>
<td>2.48 (1.49–4.12)</td>
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<td>3 positive nodes</td>
<td>2.39 (1.49–3.85)</td>
<td>3.68 (2.03–6.66)</td>
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<th>Histology</th>
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<tbody>
<tr>
<td></td>
<td>Overall death (95% CI)</td>
<td>Breast cancer death (95% CI)</td>
</tr>
<tr>
<td>Ductal carcinoma</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lobular carcinoma</td>
<td>0.77 (0.53–1.13)</td>
<td>0.73 (0.42–1.26)</td>
</tr>
<tr>
<td>Other carcinoma</td>
<td>0.96 (0.68–1.36)</td>
<td>0.89 (0.53–1.49)</td>
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<table>
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<tr>
<th>Grade</th>
<th>Crude</th>
<th>Adjusted</th>
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<tbody>
<tr>
<td></td>
<td>Overall death (95% CI)</td>
<td>Breast cancer death (95% CI)</td>
</tr>
<tr>
<td>Grade1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Grade2</td>
<td>1.57 (1.21–2.03)</td>
<td>2.48 (1.57–3.91)</td>
</tr>
<tr>
<td>Grade3</td>
<td>3.05 (2.31–4.04)</td>
<td>7.58 (4.81–11.93)</td>
</tr>
<tr>
<td>Unknown grade</td>
<td>1.17 (0.51–2.69)</td>
<td>4.64 (no value)</td>
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<table>
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<tr>
<th>Hormone status</th>
<th>Crude</th>
<th>Adjusted</th>
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<tbody>
<tr>
<td></td>
<td>Overall death (95% CI)</td>
<td>Breast cancer death (95% CI)</td>
</tr>
<tr>
<td>Positive</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1.66 (1.05–2.61)</td>
<td>3.61 (2.17–6.03)</td>
</tr>
<tr>
<td>Negative</td>
<td>2.83 (2.24–3.58)</td>
<td>5.01 (3.68–6.82)</td>
</tr>
</tbody>
</table>
Screening detection categories
Dividing the cohort into screening detection categories was done based on an assumption that cancer detected on first screening could have different clinicopathological features compared to later screening-detected cancer and interval cancer. Furthermore, selection toward MTX compared with BCT could be more prominent in women with interval cancer and may be a confounding factor. A study on interval cancer in Norwegian breast cancer screening done in 2001 [5] showed that interval cancer had a higher proportion of larger tumors, affected axillary lymph nodes, grade 3, and hormone-negative disease. These results are comparable with our results, where interval cancer tumors were larger and had a higher proportion of affected axillary lymph nodes, and grade 3 compared to screening-detected cancer. Crude breast cancer death is significantly higher among women with interval cancer compared to screening-detected cancer. However, in the adjusted analysis, there are no significant differences in breast cancer death between the first-screening, later-screening, and interval-screening groups. Based on this, it is unlikely that a selection toward MTX among women with interval cancer can explain the difference in survival between BCT and MTX.

Follow-up time
A high proportion of breast cancers are detected with only one mammography performed, the first screening. This is why the first screenings have the longest median follow-up time.

Grade and hormone status
Survival benefit decreases with higher-grade classification [20] and negative hormone receptor status. Both grade and hormone status are taken into account in the adjusted analysis. Furthermore, a sub-analysis on hormone receptor status divided only into estrogen-receptor positive or estrogen-receptor negative status showed no significant difference compared to the analysis with positive, intermediate, or negative hormone status.

Adjuvant therapy
Recommendations of antiestrogen therapy and chemotherapy are the same in both surgical groups and very standardized in Norway [7]. This is the first registry study showing equal survival benefit between women undergoing BCT or MTX in stage T1N0M0, T2NM0, and T2N1M. If the findings in this study were due to a difference in adjuvant therapy, differences in all stages would probably also be found. However, no details on the adjuvant therapy given were available, and studies with details on this are needed.

Choice of surgery
A study on why MTX rates vary found that women recalled less autonomy and less time for decision-making when treated in a breast unit with a low proportion of MTX than women treated in unit with a high proportion of MTX [21]. Conversely, women from the high and medium MTX rates units described provision of more comprehensive less directive information, together with greater support and time for more autonomous decision making. In brief, the selection towards MTX seems to be the women’s choice. Other studies support this finding [22–24].

One study that might have influenced the surgeon’s recommendation towards MTX in the later study period was published in 2005 [25]. Interpretation of this study was avoidance of one breast cancer death over the next 15 years for every 4 local recurrences avoided.

However, during study period, BCT and MTX were considered to give equal survival benefit when contraindications for BCT were followed [7]. This included obtaining free margins and tumor size less than 5 cm. (median tumor size in total study cohort is 14.7 mm). All women with multifocal tumors were excluded. Grade, hormonal, and nodal status (N0 or N1) did not influence guidelines regarding selection of surgery. Furthermore, if this had an influence in the clinical setting, these factors are taken into account in the adjusted analysis.

### Table 4 Overall deaths/breast cancer deaths, crude, and adjusted

<table>
<thead>
<tr>
<th></th>
<th>MTX</th>
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<th>Adjusted</th>
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<tbody>
<tr>
<td></td>
<td>Overall death (95% CI)</td>
<td>Breast cancer death (95% CI)</td>
<td>Overall death (95% CI)</td>
<td>Breast cancer death (95% CI)</td>
</tr>
<tr>
<td>T1N0M0</td>
<td>1.67 (1.27–2.21)</td>
<td>1.65 (1.04–2.62)</td>
<td>1.47 (1.11–1.96)</td>
<td>1.32 (0.83–2.12)</td>
</tr>
<tr>
<td>T2N0M0</td>
<td>1.42 (0.86–2.32)</td>
<td>1.20 (0.66–2.20)</td>
<td>1.46 (0.86–2.42)</td>
<td>1.26 (0.68–2.33)</td>
</tr>
<tr>
<td>T1N1M0</td>
<td>2.48 (1.45–4.24)</td>
<td>3.61 (1.69–7.72)</td>
<td>2.08 (1.19–3.64)</td>
<td>2.91 (1.30–6.48)</td>
</tr>
<tr>
<td>T2N1M0</td>
<td>1.09 (0.63–1.90)</td>
<td>1.39 (0.71–2.72)</td>
<td>1.19 (0.66–2.15)</td>
<td>1.40 (0.69–2.86)</td>
</tr>
</tbody>
</table>

The adjustments are done by screening detection category, years of diagnosis, screening age, nodal status, histology, grade, and hormone status (same as Table 3). BCT is base 1.0
Sentinel node biopsy (SNB) was introduced in Norway in 2000. The indications for doing SNB were the same in both surgical groups during the study period.

HER2 and Ki67
Human epidermal growth factor receptor 2 (HER2) was recommended as a routine examination in 2005, late in the study period [7]. Therefore, diagnosis year was grouped into 1998–2004 and 2005–2009. Based on this, it is unlikely that a difference in trastuzumab treatment explains the difference between the surgical groups. Furthermore, no tumor biology markers determine recommendations on surgery type [7]. The proliferation marker Ki67 was not measured during the study period.

Radiation therapy
All women undergoing BCT were recommended RT. Recommendations on radiation therapy (RT) regarding the nodal status changed during the study period. From 1998, all women aged <55, undergoing MTX with less than 4 positive lymph nodes, were not recommended radiation therapy. From 2000, all women aged <55 with 1–3 positive lymph nodes were recommended radiation therapy. From 2003, all women aged <70 years were recommended RT if 1–3 lymph nodes were positive. Sub-analysis was therefore performed on all women with stage T1-2N1M0 from 2003 (all women undergoing MTX with N1 status were recommended RT). This sub-analysis showed the benefit of BCT compared with MTX. Based on this, RT does not seem to be the main reason for the survival benefit seen in T1N1M0 in this study. It might be a combination of BCT and RT that improves survival and not RT alone. On the other hand, a meta-analysis of 8135 women published in 2014 showed the survival benefit of radiation therapy after mastectomy and axillary dissection [26]. A reduced use of RT in the MTX group might, to some degree, favor the BCT group.

Alternative explanations of findings
Surgery
Some studies have suggested that the extent of surgery can be a negative factor regarding survival. In a study by Cheng K.et al. [8], they refer to studies on animal models in which it is suggested that the surgical trauma of normal tissue promotes the implantation or growth of circulating tumor cells [27–30]. A recently published study regarding recurrence pattern following delayed breast reconstruction after MTX for breast cancer suggests a systemic effect of surgery on occult dormant micro metastases [31].

Immune response
Doxorubicin is shown to increase the tumor antigen-specific proliferation of CD8 T cells in mice with carcinogen-induced tumors [32]. There is accumulating evidence that some cytotoxic drugs, such as taxane, actually promote antitumor immunity and thereby contribute to the treatment’s therapeutic effect [33]. Women who have undergone BCT might have a better immune response against breast cancer cells compared with those who have undergone MTX. As a hypothesis, RT against remaining satellite tumors in the conserved breast with following necrosis of tumor tissue enhances an improved immune response against the cancer. A similar hypothesis might be introduced for the combination of BCT and chemotherapy and even the combination of BCT, chemotherapy, and RT. As far as we know, this hypothesis has not been tested.

Conclusions
The most important finding for women participating in screening is that there is a survival benefit of BCT compared with MTX in stage T1N1M0, but no other early stages of breast cancer.

Abbreviations
BCSS: Breast cancer-specific survival; BCT: Breast-conserving therapy; HR: Hazard ratios; MTX: Mastectomy; OS: Overall survival

Acknowledgements
None.

Funding
This study was supported by Oslo University Hospital and the Kalnes Hospital by giving the first author 50% of his working time available for research. The funding support from these hospitals had no role in study design, data collection, or data interpretation.

Availability of data and materials
The cancer registry of Norway has a special Data Delivery Unit that handles requests on deliveries from research groups and others. Data in this study were delivered by the Data Delivery Unit.

Authors’ contributions
OJHJ, JFN, and RK planned the analysis. OJHJ collected the data from the Cancer Registry of Norway. OJHJ and JFN performed the analysis. All authors have contributions in the analysis and interpretation of data and revised the work critically. All authors checked the manuscript, tables, and figures for accuracy and completeness. All authors read and approved the final manuscript.

Ethics approval and consent to participate
No ethical approval or consent to participate was necessary in this study as only registry data was used.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 21 October 2016 Accepted: 22 June 2017
Published online: 03 July 2017

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Paper III
Using clinical cancer registry data for estimation of quality indicators
Results from the Norwegian Breast Cancer Registry

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Keywords
Cancer Registry; Breast cancer; EUSOMA certification; Quality Indicators.
Abstract

**Introduction:** Increased focus on quality indicators and the use of clinical registries for breast cancer for real world studies have shown higher compliance to recommended therapy and better survival. In 2010, the European Society of Breast Cancer Specialist (EUSOMA) proposed quality indicators (QI) covering diagnosis, treatment and follow-up. To become a EUSOMA certified Breast Cancer Unit, 14 specified quality indicators, in addition to other requirements, need to be met. To evaluate the compliance and results of recommended treatment in breast cancer care in Norway and to improve the quality of epidemiological data, the Cancer Registry of Norway (CRN) in cooperation with the Norwegian Breast Cancer Group (NBCG) developed the Norwegian Breast Cancer Registry (NBCR).

The main objective of this study is to describe the NBCR and how this registry can be used to calculate QI defined by EUSOMA on a national level.

**Methods:** To provide researchers with high quality cancer data as well as for the purpose of national cancer statistics, the CRN employs a cancer registry system to 1) longitudinal capture data from all patients from all medical entities that diagnose and/or treat cancer patients (e.g., pathology, radiology and clinical departments) in Norway; 2) curate data, i.e. validate the correctness of collected data, and assemble the validated cancer data as cancer cases; 3) provide data for analytics and presentation. Estimates for 10 EUSOMA QI were calculated at national and hospital level. To compare hospitals, a summary score of QIs was defined for each hospital.

**Results:** All hospitals currently treating breast cancer patients have the technical ability to submit data to the NBCR for estimation of QIs defined by EUSOMA. Data from pathology and surgery are of high quality. However, data from oncological and radiological departments are incomplete, but improving. This currently hinders three QIs from being calculated. QI on benign to malign diagnosis needs to be calculated at the individual Breast Centre. Over time the adherence to guidelines have improved and the hospital variation for the respective QI have decreased. Two hospitals met all minimum standard on ten QIs in year 2016 and one hospital did not meet one minimum standard, but met all other targets.

**Conclusion:** The NBCR has since 2012 published annual reports on breast cancer care and for the year 2016 measured 10 of 14 QI defined by EUSOMA. Increased compliance of recommended treatment in Norway has been observed during the years the registry has been active.
1. Introduction

The complexity of breast cancer care involves several specialities where every field within diagnostic, treatment and follow-up has to adhere to the latest guidelines, and measuring the quality of care is therefore a challenging issue. Increased focus on quality indicators (QI) and clinical registries within breast cancer care shows higher compliance to recommended therapy and increased survival [1-5]. Regular audit of quality indicators for the treatment of patients with operable breast cancer proved to be important tools to improve the quality of care, patient satisfaction and outcome [5].

A clinical cancer registry offers an ideal infrastructure for estimating QIs on a regular basis, and comparison of IQs between hospitals which may facilitate changes in guidelines [6]. For example, several recent published register studies have shown better survival for women undergoing breast conserving therapy compared to mastectomy [7-11]. This new knowledge emphasizes the importance and use of clinical cancer registries.

In 2010, the European Society of Breast Cancer Specialist (EUSOMA) published a position paper with 33 QIs covering diagnosis, surgery, loco-regional treatment, systemic treatment, staging, counselling, follow-up and rehabilitation [12]. To become a EUSOMA certified specialist Breast Centre in 2016, 14 QI were mandatory [13] in addition to other requirements [14].

In Norway, breast cancer is the most common cancer in women [15]. To evaluate the compliance and results of recommended diagnostics and treatment of this disease and to improve the quality of the clinical cancer data, The Cancer Registry of Norway (CRN) in cooperation with the Norwegian Breast Cancer Group (NBCG) developed the Norwegian Breast Cancer Registry (NBCR) run by the Cancer Registry of Norway.

1.1. Aim

The main objective of this study is to assess the feasibility of using the NBCR for estimating QI individually for all hospitals diagnosing and treating breast cancer in Norway.
2. Material and methods

The Cancer Registry of Norway (CRN) is a population-based cancer research institute [16]. It is responsible for receiving data from institutions diagnosing or treating cancer patients. The reporting of these data is mandatory by law for all health personnel.

To provide researchers with high quality cancer data as well as for the purpose of national cancer statistics, the CRN employs a cancer registry system divided into three separate entities; 1) Data capture, 2) Data curation, and 3) Data analytics and statistics [17].

2.1. Description of data

The NBCR has designed and implemented the following nine electronic clinical reporting forms: diagnostics; radiotherapy; non-endocrine oncological treatment, endocrine treatment, lipofilling, follow-up, surgery, no treatment, completed trastuzumab treatment and completed endocrine treatment. Each of these forms contains only variables relevant to the reported event. These forms are used in the setting of primary breast cancer, recurrent breast cancer and metastatic breast cancer [18]. Data on pathology are submitted directly from the pathology laboratories and are (electronic) copies of the pathology report sent to the physician. 17 electronic pathology reports are implemented, include the following: mastectomy; breast conserving therapy; core biopsy of primary tumour; cytology of primary tumour; axillary clearance; sentinel node; preoperative examination of axillary lymph nodes; histology from surgery on locally relapse, core biopsy from locally relapse, cytology from locally relapse; histology on metastases from surgery; core biopsy from metastases; cytology from metastases, autopsy; hormone receptor analysis; secondary surgery with resection of primary tumour and benign breast pathology. All these forms are saved as an eXtensible Markup Language (XML) file [19].

A reference committee of specialists diagnosing and treating breast cancer from radiology, surgery and oncology originally defined the key variables. The committee regularly updates, removes and adds new variables (figure 1). Demo versions of the forms are available at the CRN webpages [20].
2.2. **Description of data capture**

The Norwegian Cancer Registry’s Electronic Reporting Service (KREMT) is established to facilitate electronic reporting thru the Norwegian Health Network [21]. There are two main options for submitting the forms, either by a portal displays the reporting forms as web-pages, or thru messaging if the forms are implemented in the local hospitals electronic health records. The message transfer uses electronic Business XML (ebXML) which ensures a secure and reliable exchange of messages between two parties within the Norwegian Health Network [22].

Reports shall be sent at time of primary diagnosis; each surgical event; primary adjuvant treatment; hormone therapy start and end of hormone therapy. Breast cancer patients are followed for 10 years after surgery. In connection with the annual follow-up, a follow-up report is sent regarding relapse status. If a recurrence is observed, a report shall be sent to specify the relapse or metastasis. Reports on pathology are sent to the CRN independently of clinical reports.

The reports from the portal are stored as an XML-file, and passed on to the data curation step, as are the XML-files received through the messages system. The data curation steps are thus independent of the data capture method.

The Norwegian Quality Registry for Breast Cancer were stepwise implemented in all hospitals in Norway. The first registration was done on local registries at Ullevål University.
hospital in 2008, and the first electronic clinical form was submitted from Østfold hospital to the CRN in 2011.

2.3. **Description of data curation**

The data curation at the CRN consists of three steps needed to ensure the necessary level of data quality, and converts multiple, independent cancer messages to a cancer case. The cancer cases are the bases for analytics and statistics [17]. The three steps are: a) *Cancer message validation* that checks the internal validity and correctness of the cancer messages. b) *Cancer case calculation* generates a cancer case, and calculates the set of variables for the cancer case, based on all cancer messages related to the cancer case. c) *Cancer case validation* checks the variables for the internal validity and correctness of the cancer case (figure 2). This process will also identify missing cancer messages, which will be requested from the hospital which failed to report the data.

**Figure 2. From cancer messages to data analytics and statistics.**

Pathology forms are reported as a mixture of structure (code data) and textual descriptions of macro, micro and diagnosis, which need coding. This is presently done manually by medical coders prior to the “cancer message validation” step.

2.4. **Data analytics and statistics**

Several reports regarding cancer are published from the CRN yearly. The main aim of the annually “Cancer in Norway” is to provide detailed cancer statistic [15]. The registration has from 1953 been considered to be close to complete, 98,8% for the registration period 2001-
The annual “Cancer in Norway” calculates incidence, prevalence, age and relative survival among several other calculations within all cancer types. In addition to “Cancer in Norway” all eight National Quality Registers publishes annually reports (breast cancer, colorectal cancer, prostate cancer, lung cancer, hereditary cancer, paediatric solid tumours, gynaecological cancer and malignant melanoma).

Upon application, data may be disclosed for research purposes from the data delivery unit at the CRN [24].

The minimum recommendation from EUSOMA is that hospitals treating breast cancer patients should have at least 150 patients diagnosed per year. For the national results we include all hospitals, while presentations on individual hospitals with less than 150 patients diagnosed per year are not shown.

For each QI, there are a minimum standard (labelled yellow in the figures), and target result (labelled green in the figures).

For testing of changes over time in QIs or differences between hospitals, binominal exact test was used, and p-value less or equal to 0.05 were considered significant. The cancer case coverage for the period 2012-2016 was estimated by the capture-recapture method using clinical forms, pathology forms, and death certificates [25]. To compare survival between counties relative survival was estimated using the Ederer2-method [26]. Analyses were performed using Stata v15 (StataCorp, Texas, USA).

2.5. **Summary score of QIs on hospital level**

For the comparison between hospitals for all QI, a score of 1 was given for reaching the target result QI, a score of 0.5 for minimum target, and 0 below minimum target. The composite score was then calculated by adding the individual scores, giving a possible range for the score of 0-10. In addition, the hospitals evaluated for all non-zero score for any of the ten QI, thus meeting at least minimum standard for all QI.
3. Quality indicators and the yearly breast cancer reports

EUSOMA have specified 14 mandatory QIs to become a EUSOMA certified specialist Breast Centre [27]. In this study, the numbering of EUSOMA criteria following the numbering from the year 2016 if not otherwise specified.

The first annual breast cancer report was published in October 2014 presenting data for 2013, and there reports have thereafter been published yearly [28]. The main parameters in the first report where: proportion of breast-conserving treatment, proportion of screening detected breast cancers, histologic type and grading. After this, the breast cancer reports have been published with increasing numbers of indicators. In this study we have presented ten QI defined by EUSOMA from NBCR year 2016, based on the 2010 EUSOMA definition of QIs (ten of 14). Missing data on oncology treatment prevents three QI to be reported, while the fourth and last QI, “The ratio of benign to malign diagnoses”, cannot be calculated using the NBCR as the CRN do not have the legal permission to collect information on benign tumours.

EUSOMA increased the number of mandatory QI for Breast Centre Certification from 14 to 17 in 2018, two have been removed and five added. One of the new QIs has already been presented in the NBCR annual report, i.e. the proportion of patients receiving immediate reconstruction [28]. Two of the new QIs can be calculated based on existing data (QI no. 11 and 14, year 2018). The QI “ratio of benign to malign diagnoses” cannot be estimated (see above). The last three new QIs needs information on oncological treatment, which today is inadequate (QI no. 8,9 and 15, year 2018). Therefore, from 2018, 13 of 17 QIs can presently be reported from the NBCR.
4. Results

In 2016, the number of breast cancer cases diagnosed in Norway was 3513. The number of hospitals which treated more than 150 patients was 12, while an additional 8 had fewer than 150, but more than 10 patients. The number of patients diagnosed with breast cancer per hospital ranged from 13 to 442 in 2016. The completeness of pathology reports was estimated to be 99%, while clinical reports covering diagnostic work-up was 90% and primary surgery 89%. Reporting of adjuvant treatment was inadequate. For instance, the number of reports on primary adjuvant chemotherapy was 709 and reports regarding start of primary hormone therapy were 529 in 2016.

4.1. National results.

The result of the 12 QIs included in the annual breast cancer report for 2016 are presented in figure 3, including 10 of the 14 mandatory QIs for EUSOMA certification in 2016. Eleven of the NBCR indicators met the target, while another three met the minimum target, and one did not meet the minimum target. For the EUSOMA QIs, eight indicators met the target, one met the minimum target, and one did not meet the minimum target.

For the EUSOMA criteria # 1, “The proportion of patients receiving a pre-operative diagnosis” in 2016 was 94% (95 % CI 93.1% - 94.8%), significantly better than both the minimum recommendation of 85 and the target of 90% (figure 3). For the EUSOMA criteria # 4, 77% of the axillary dissections resulted in removal of ≥ 10 lymph nodes, below the minimum target of 85% (figure 3).

For the EUSOMA criteria # 6, 81% of patients with invasive breast cancer ≤ 3 cm underwent BCT as primary treatment (figure 3).

For the EUSOMA criteria # 11, the proportion of women who underwent surgery once was 90% in 2014, 91% in 2015 and 94% in 2016 (figure 3).

For the EUSOMA criteria # 5, 93% of the breast cancer patients received radiation therapy after surgery, if recommended in the national guidelines. The minimum recommendation from EUSOMA is 95%.
Figure 3. The NBCR Quality Indicators for 2016.

- Cancer case coverage in the NCBCR (2012-2016): 99.9%
- Relative survival estimate based on patients living with breast cancer between 2014 and 2016: 90%
- Breast Cancer patients with preoperative histologically or cytologically confirmed diagnosis: 94%
- Registration of histological grade for cases of ductal carcinoma in situ: 99%
- Axillary dissections where > 10 lymph nodes were removed, including sentinel node: 77%
- Breast Conserving surgery for tumours ≤ 3 cm, excluding multifocal cases and neoadjuvant chemotherapy: 81%
- Patients with non-invasive breast cancer ≤ 2 cm who underwent breast conservative treatment: 91%
- Patient with ductal carcinoma in situ who were not treated with axillary dissection: 100%
- Patients (invasive cancer only) who underwent a single breast operation for the primary tumour: 94%
- Patients (DCIS only) who underwent just one operation: 95%
- Breast cancer patients without spread to axillary lymph nodes that were not treated with axillary dissection: 98%
- Postoperative radiation therapy following breast conservative surgery and appropriate axillary staging (SN and AD): 93%
4.2. **Comparison of EUSOMA QIs between hospitals**

The 5-year survival is stratified in counties, while all other QIs in figure 3 can be stratified on hospital level. We chose to use the EUSOMA QI # 6, BCT for tumours ≤ 3 cm, excluding multifocal cases and those treated neoadjuvant, for exploration of differences between the hospitals during the year 2014 to 2016. In 2016, the frequency of breast conserving surgery varied from 72 % to 92 % between hospitals with more than 150 patients treated (figure 4). No hospital was below the minimum target in 2016, and the results have improved from 2014 to 2016.

For the EUSOMA QI # 1, the proportion of patients receiving a pre-operative diagnosis varied from 54% to 100% in 2016, with two hospitals below the minimum recommendation from EUSOMA of 85 %, and another two below the target of 90 % (results not shown in figure).

For the EUSOMA criteria # 11, the proportion of women who underwent surgery once varied between hospitals from 86% to 100% in 2016 (results not shown in figure), with no hospitals below minimum target, and three hospitals below the target of 90 %.

The proportion of women receiving radiation therapy after surgery, if recommended (EUSOMA QI # 5), ranged from 87% to 99% between hospitals in 2016. One hospital was below the minimum recommendation of 90 %, and ten hospitals did not meet the target of 95%, while seven hospitals were above target.
4.3. **Non-EUSOMIA QI from the NBCR**

A marked reduction in the proportion of women undergoing axillary clearance was observed over time, as there were 786 women in Norway who underwent this surgical procedure in 2014, 535 in 2015 and 365 in 2016 (not shown in figure). In addition, there was a considerable variation was observed in the proportion of women undergoing axillary clearance at the various hospitals (6 - 20% in 2016).

Concerning histological grade, tumours classified as grade 3 ranged from 12 to 42% (mean 28%). The reported expression of the proliferation marker Ki67 also varied across the laboratories (tumours with more than 30% Ki67 positive cells ranged from 17 to 46%).

Five-year relative survival rate was 90% in 2016 for the entire group. This ranged from 86% to 94% between the hospitals.
4.4. **New EUSOMA QI**

The new mandatory EUSOMA QI from 2018, “The proportion of women who underwent primary reconstruction after mastectomy” varied markedly between hospitals (4 - 48%) in 2016. The average for the country was 25%. Minimum standard recommended by EUSOMA is 40%.

4.5. **Summary score of EUSOMA QIs on hospital level.**

In figure 5 the summary score for all the 10 EUSOMA QIs are shown. No hospitals had a perfect score of ten, but three hospitals had a score of nine. Two hospitals met all 10 minimum targets, one hospital did not meet one minimum requirement, but meet all other targets, giving a score of nine.

**Figure 5. Summary score of EUSOMA QIs in 2016.**
5. Discussion

5.1. Data structure and capture

The diagnostic and therapeutic data reporting structure of NBCR is complicated with several different forms. However, this also provides several benefits and opportunities for high quality data. Each form contains few variables and can therefore be completed and submitted online within a few minutes as each form is tailored to the specific medical task. If a patient is treated in different hospitals, which is not uncommon, the data are collected without duplication as each medical event will be reported by the hospital performing the procedure/treatment. Missing forms are easily identified, and can be requested by the national quality registry. Statistical methods are available to estimate the completeness/coverage by several independent reporting sources (i.e. capture-recapture methods) [23]. This reporting structure is adaptable and can easily be extended to incorporate new diagnostic methods and treatments, e.g., genomics, by introducing new forms. Similarly, patient reported outcomes (PROMS) can easily be incorporated as a new form [29].

The coverage of breast cancer patients in the registry was 99.9% in 2016, due to the automatic submission of pathology reports from all laboratories in Norway. There has been a gradual increase of clinical information. In 2016, all of the 19 surgical departments treating breast cancer in Norway reported to KREMT. In 2016, the coverage was 90% in diagnostics and 89% in surgical procedures [28]. However, the compliance from oncology and radiology departments is still unsatisfactory. Several initiatives have now been taken to improve reporting, including coding courses, and visits to the hospitals by the CRN coding staff.

The KREMT system will evolve, and future improvements are expected. But in the future the reporting of clinical data using the portal part of KREMT should be replaced by gathering data directly from the hospitals Electronic Health Record (EHR). This requires a structured EHR, currently not in use in Norway. However, several initiatives are ongoing introducing e.g., open EHR systems and a national initiative on archetype [30, 31]. The parameters included in NBCR should be used when designing a structured EHR system for breast diseases. One hospital in Norway used a structured EHR from 1988 to 1995, but had to end the use due to quality problems [32].

5.2. Data curation

The main product of the cancer registry is data on cancer cases. However, as all information submitted to the cancer registry is on a cancer message level, these messages needs to be validated and a cancer case with the appropriate variables needs to be created and calculated. Thus, a cancer case is an aggregate of several cancer messages related to the same cancer case for one patient. For instance, a simplified example of a cancer calculation rule would be that the date of diagnosis for a cancer case should be set as the earliest date of a
diagnostic procedure (event date), from the cancer messages that are associated with the cancer case.

The medical experts at the CRN have since 1953 defined more than 1000 cancer coding rules, which can be classified into three types (i.e., Cancer Message Validation Rules, Cancer Message Aggregation Rules and Cancer Case Validation Rules) that are employed for each task, respectively. Traditionally, all these cancer coding rules have been specified by chief medical officers at the CRN, implemented into the cancer registry system by medical programmers and applied for validation and aggregation by medical coders [17]. This management of the rules are prone to errors, especially over time as medical knowledge and thus diagnostics and treatment improves. The CRN is therefore implementing all cancer coding rules in the object constraint language (OCL), and the rules are applied in the data curation stage via a rule engine to ensure even better data quality [33].

Pathology reports are reported as a mixture of structured (coded) data and textual macro and micro descriptions and diagnosis, all which need coding. This is presently done manually by medical coders. However, a study conducted at the CRN show promising results using Natural Language Processing (NLP) to automatically extract information from pathology reports. The system also identifies reports that contain ambiguity or other content that should be reviewed by an expert. The system shows potential to encode the reports considerably faster, with less resources, and similar high quality to the manual encoding [34]. Other studies also show good results using NLP on pathology reports [35].

5.3. Definition of QIs

The definition of some QI is not completely the same in NBCR and EUSOMA. For instance, the EUSOMA QI “Proportion of patients (BRCA1 and BRCA2 patients excluded) with invasive breast cancer not greater then 3 cm (total size, including DCIS component) who underwent BCT as primary treatment” differ from the NBCR “BCT for tumours ≤ 3 cm, excluding multifocal cases and those treated neoadjuvant”. NBCR do not have information on hereditary breast cancer and can therefore not exclude these in the analysis. However, based on the Norwegian guidelines, these patients are recommended mastectomy. Furthermore, primary treatment is comparable with not treated neoadjuvant.

Regarding multifocality, these are excluded in the calculation of the QI in NBCR but not in QI defined by EUSOMA. This might have an influence when comparing the Norwegian and EUSOMA defined QI.

5.4. Comparability between hospitals

The 20 hospitals in Norway treating breast cancer surgically vary both in the number of patients treated and other parameters. One could therefore argue that the results in this study should be adjusted for case-mix (differences in the patient population) to make the comparisons valid. However, the EUSOMA criteria are precise in their specifications/data
selection for the quality indicators’ minimum target, and target. These targets should be met regardless of differences between hospitals. We therefore argue that one should not do a case-mix correction, as this study’s focus is whether or not the EUSOMA criteria is meet, not if they would be meet given another set of patients.

5.5. Some examples of the value of a breast cancer quality registry

Register studies indicate a survival benefit for patients undergoing breast conserving therapy compared to those undergoing mastectomy[7, 8, 11, 36-38]. This seems not to be due to a more advanced disease among patients treated with mastectomy, although randomized controlled trial data to support this statement is lacking. As a consequence, the proportion of women treated with breast conserving surgery has increased in Norway. Focus on oncplastic procedures has also encouraged the reduction of mastectomies.

The indicator showing proportion of women who underwent primary reconstruction after mastectomy in 2016 varied from 4% to 48%. Due to this variation, The Norwegian Breast Cancer Group has appointed a working group to address this rather unexpected variation.

The observed variations in grading and Ki67 expression between the hospitals point to the importance of understanding the cause of these differences and may help to decrease the undesirable differences. In clinical practise, both grading and Ki67 provide information of importance for decision on chemotherapy use, and a precise classification may hinder both under- and overtreatment.

In 2015, new guidelines opened for reduced use of axillary clearance based on results following the Z0011 study [39]. Therefore, one would expect less women would undergo axillary clearance. This was reflected in the NBCR, showing that the number of women who underwent axillary clearance was reduced by more than 50% from 2014 to 2016.

In addition to publish quality indicators on a yearly basis, the data in the cancer registries are being used in a multitude of medical studies. This includes both pure registry studies, clinical trials and basal molecular studies.

A population-based study on breast cancer patients from Belgium showed that higher-volume hospitals had higher rates of multidisciplinary team meeting, diagnosis before surgery, neoadjuvant chemotherapy, BCT rate, adjuvant radiotherapy after BCT and follow up mammography [40]. Higher volume was associated with improved survival.

The clinical database of the Danish Breast Cancer Cooperative Group (DBCG) has resulted in a large number of epidemiological research papers. In addition to this, 25% of the cases enrolled in the DBCG have frozen tissue, providing ideal conditions for translational research. DBCG perform large ongoing studies with aim to tailor the therapeutic intervention [41]. A large number of studies have been published based on data from the Swedish National Quality Registry for Breast Cancer (19 from publications year 2017) [42].

In the Netherlands a national breast cancer organization was established in 2011[43]. They have found that a continuous loop of registration and feedback by clinical auditing provides a
powerful tool for quality monitoring and improvement [44]. Within three years’ time they found several guidelines improvements and narrowing of the hospital variation for the respective QI.

The clinical cancer registries mentioned above are good models for our future work with NBCR and by comparing results with our neighbouring countries, the treatment of breast cancer patients will hopefully be further improved.

5.6. Conclusion

For 2016, 10 of the 14 QIs recommended from EUSOMA can be calculated on a national basis using NBCR. Missing data on oncology treatment prevents three QIs to be reported, while the fourth and last IQ, the ratio of benign to malignant diagnoses, cannot be calculated as the CRN do not have the legal permission to have information on benign tumours. The summary score of EUSOMA QIs makes it easy to compare hospitals on a national level.

The registration of treatment administered at all hospitals makes it possible to compare hospitals and follow changes after implementation of new guidelines. Publishing annual reports encourages hospitals with unsatisfactory results to improve their practice. Over time, this understanding will reduce the inequalities between hospitals, improve tailored treatment and increase compliance to national guidelines.

Authors’ contributions

OJHJ and JFN conceived the original idea. OJHJ and JFN wrote the manuscript with critical feedback from RK, ES and BN. All authors contributed to the final version of the manuscript.

Acknowledgments

We are grateful to all who have participated in the start and development of the Quality Registry for Breast Cancer in Norway. This is a large number of persons representing all specialities treating breast cancer in Norway. A special thanks to the Norwegian Breast Cancer Group who started the work and to all persons sending register information to the Cancer Registry of Norway.

Financial support

This study was supported by Kalnes Hospital by giving the first author 50% of his working time available for research. The funding support from the hospital had no role in study design, data collection, or data interpretation.

Conflict of interest statement

The authors have no conflict of interests to declare.
Summary table
What was already known before the study

- Increased focus on quality indicators and clinical registries within breast cancer care show higher compliance to recommended therapy and increases survival.
- Registry with clinical focus offers an ideal infrastructure for enrolling and following patients in clinical trials.
- 17 quality indicators defined by European Society of Breast Cancer Specialist (EUSOMA) are mandatory to become a EUSOMA certified Breast Centre.

What this study has added to the body of knowledge

- Describes the development and use of the Norwegian Quality Registry for breast cancer.
- Annual breast cancer reports increases compliance to recommended treatment.
- Simplify the approval of EUSOMA defined Quality Indicators for a breast cancer unit on a national level.
- Calculating a summary score of EUSOMA Quality Indicators makes it easy to compare hospitals.
References


[27] EUSOMA, European Society of Breast Cancer Specialist.