# MONITORING EVOLVING BREAST CANCER CARE

## RECONSTRUCTIVE SURGERY, RADIOTHERAPY AND GENE PROFILING

KAY SCHREUDER

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Monitoring evolving breast cancer care.
*Reconstructive surgery, radiotherapy and gene profiling*
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**MONITORING EVOLVING BREAST CANCER CARE**

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Dr. A. Jager

Dr. H.A. Rakhorst

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Introduction section

# Chapter 1

Introduction and outline

**Introduction**

Worldwide, breast cancer is the most common cause of cancer among women and is responsible for over one million of the approximately 10 million cancers diagnosed yearly [1]. Also in the Netherlands, breast cancer is the most frequently diagnosed cancer in women and a recent study demonstrated that 1 in 6,6 women will be diagnosed with breast cancer during lifetime [2, 3]. In 2017, 14,890 invasive breast cancers and 2,669 in ductal carcinoma in situ lesions (DCIS, a non invasive precancerous lesion) were diagnosed in the Netherlands [3].

Mastectomy and radiotherapy have been the curative treatment regimen for breast cancer patients until the 1970's [4, 5]. Breast conserving therapy (BCT), surgery which conserved the breast followed by radiotherapy, and adjuvant systemic treatment were introduced in the eighties of the 20th century to improve cosmetic outcome, locoregional and distant control of the disease. Radiotherapy after breast conserving surgery (eventually combined with a boost) was associated with a substantial decrease of locally recurrent disease and a moderate improved overall survival in low risk cases [6, 7]. Also a significant improved disease free survival and overall survival was noted after radiotherapy in high-risk and in intermediate-risk cases [8]. Meta analyses, including studies conducted between 1985 and 2000, demonstrated a substantial improved disease free survival and overall survival after adjuvant chemotherapy and hormonal therapy (in estrogen receptor positive tumours) [9]. Finally, immunotherapy was introduced in the last decade, as breast cancer was considered as not immunogenic 20 years ago [10]. Systemic therapy (chemotherapy, hormonal therapy and immunotherapy) as well as more radiotherapy contributed to excellent (still improving) local control probability [6, 11]. Due to the evolving state of the art diagnostics and treatment modalities, individualized breast cancer care is increasingly possible and has the potential to offer clear clinical benefits and cost-effective strategies [12]. Nationwide evidence based treatment guidelines were defined in 2000 [13-15] and since then, surgery, radiotherapy and systemic therapy constituted the multidisciplinary treatment trinity.

The last fifteen years are characterized by many refinements of the aforementioned treatment modalities. These refinements all aim to minimize the burden of the patient and maximize outcome in terms of locoregional control, quality of life and survival and resulted in a trend towards more individualized cancer care. In this thesis we address questions originated from clinical practice and questions that have arisen from previous studies. The evolution of three innovations is studied in this thesis; reconstructive surgery, radiotherapy and gene profiling.

*Reconstructive surgery*

For patients who undergo mastectomy, immediate breast reconstruction (IBR) was introduced in the 1960s [16] as a means to achieve a good cosmetic outcome following mutilating sur-

gery leading to a perceived better quality of life [17-19]. There is a rising desire of patients to reconstruct the contour of the breast after a mastectomy. Breast reconstruction techniques have evolved over recent years and have become more widely available. Breast reconstruction is more and more becoming an integral part of breast cancer treatment [20]. However, does the use of IBR vary between Dutch hospitals and which factors affect the use in Dutch clinical practice?

*Radiotherapy*

In the eighties of the 20th century, breast-conserving surgery was always combined with whole breast irradiation (WBI) and the use of a boost in the Netherlands. A boost dose to the tumour bed combined with WBI after breast conserving surgery aims to further reduce the risk of recurrent disease. But a growing awareness of boost-associated morbidity led to acknowledgement that the additional boost is not warranted in all patient categories [6, 21, 22]. A guideline was redefined to better identify candidates for boost treatment in the Netherlands [23]. However, how does the use of radiotherapy boost vary following adjustment of a national guideline in 2011? Moreover, we aimed to investigate the use of primary radiotherapy for all invasive breast cancer patients in the Netherlands.

*Gene profiling*

In the era of ever more systemic treatment, gene-expression profiling (GEP) was introduced to better select patients in whom adjuvant systemic treatment (chemotherapy) is effective. GEPs were developed a decade ago to better predict outcome in addition to prognostic information of conventional clinic-pathological factors (i.e tumour grade and size). Currently, there are several commercially GEPs available of which the 70-gene signature (70-GS) and the 21-recurrence score (21-RS) are used in clinical practice in the Netherlands. These tests became available in respectively 2011 and 2013 and were both validated in large randomized controlled trials [24, 25]. National guidelines suggested their use in case of 'doubt' regarding the effectiveness and indication for adjuvant chemotherapy. In clinical practice, GEPs have contributed to a trend to give less chemotherapy in breast cancer patients. We aimed to investigate use of the 70-GS and 21-RS and implications regarding chemotherapy administration in relation to clinical risk in early breast cancer patients.

These developments (IBR, breast irradiation and GEP) differ conceptually. IBR can be considered as an evolution suitable to be offered to patients undergoing mastectomy. The adjustments to boost irradiation indications aims to omit an unnecessary treatment in a selection of patients by offering clear guidelines. GEPs were introduced as a technology to better select candidates for adjuvant systemic therapy yet in the absence of a clear indication when their use is appropriate for its use. Both deployment of immediate breast reconstruction and GEPs as well

as implementation of radiotherapy guidelines into clinical practice comes with considerable institutional variation. To analyse the use and variation in developments within breast cancer care in the Netherlands, data collection on a nationwide level is necessary. The Netherlands Cancer Registry (NCR), which is hosted by the Netherlands Cancer Organisation (IKNL), collects data from all Dutch (breast) cancer patients since 1989 and therefore offers the possibility to observe evolving breast cancer care on a nationwide level.

The aim of this thesis is to analyse the variation associated with the adoption of advanced treatment modalities and the adherence to guideline changes on a national level using the three aforementioned developments in daily practice.

**Outline thesis**

**Part two** of this thesis is focussing on IBR following a mastectomy. In Dutch breast cancer guidelines, it is recommended to offer the possibility for an IBR for every patient who underwent a mastectomy [26]. Large variation in performing an IBR is observed in national and in international studies [27-29]. Therefore, the aim in **chapter two** is to investigate the variation in performing an IBR and to identify hospital organizational factors affecting the use of IBR after mastectomy for invasive breast cancer and DCIS in the Netherlands. Moreover, we aim to explore whether or not these hospital organizational factor account for the variation seen. Besides institutional factors, differences in information provision and personal opinions of surgical oncologist and plastic surgeons towards an IBR may contribute to the variation observed in performing IBR. The aim of **chapter three** is to investigate the information provision to the patients concerning an immediate breast reconstruction by surgeons and plastic surgeons and to assess their personal opinions towards contra-indications for different types of IBRs.

**Part three** addresses radiotherapy. **Chapter four** aims to explore the variation of the use of boost between radiotherapy departments in the Netherlands. Tumour, patient and department related factors are assessed that possibly are associated with the use of a boost and whether or not these factors explain the observed variation in performing boost irradiation between departments of radiation oncology in the Netherlands. **Chapter five** has a broader scope and is focussing on primary radiotherapy compliance. International studies demonstrated significant variation in the use of primary radiotherapy in the treatment of breast cancer patients and the use of radiotherapy is lower when compared with the calculated based optimum [30-37]. The aim of **chapter five** is to investigate the use of primary radiotherapy for all invasive breast cancer patients in the Netherlands focussing specifically on time trends, age effects and type of surgery.

In **part four** highlights the use of GEP to better select patients for adjuvant chemotherapy use. Nowadays, the use of GEPs is suggested in patients in whom controversy exists about the benefit

of adjuvant chemotherapy, when based on traditional clinic-pathological factors alone [38]. **Chapter six** aims to provide insight in factors associated with the use of a GEP (both 70-GS and 21-RS), inside the guideline-intended indicated area for GEP use. An interesting observation in this population-based study was the frequent use of GEP outside the guideline-intended indicated area, i.e. in patients in whom clinical guidelines state a clear recommendation to administer or withhold chemotherapy based on clinic pathological factors alone [39]. Therefore, aim of **chapter seven** is to assess the clinical implications of GEP use (70-GS) and GEP test-results when the test is used outside the guideline intended indicated area. In the final **chapter eight**, the goals were to analyse the clinical implications of 21-RS use in Dutch early stage breast cancer patients on a nation-wide level and to gain insight into factors associated with 21-RS use.

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# Part II

Reconstructive surgery

# Chapter 2

## Hospital organizational factors affect the use of immediate breast reconstruction after mastectomy for breast cancer in the Netherlands

*The Breast, 2017. 34: p. 96-102.*

K. Schreuder
A.C.M. van Bommel
K.M. de Ligt
J.H. Maduro
M.T.F.D. Vrancken Peeters
M.A.M. Mureau
S. Siesling

**Abstract**

**Objectives**

Significant hospital variation in the use of immediate breast reconstruction (IBR) after mastectomy exists in the Netherlands. Aims of this study were to identify hospital organizational factors affecting the use of IBR after mastectomy for ductal carcinoma in situ (DCIS) or invasive breast cancer (BC) and to analyze whether these factors explain the variation.

**Materials and Methods**

Patients with DCIS or primary invasive BC treated with mastectomy between 2011 and 2013 were selected from the national NABON Breast Cancer Audit. Hospital and organizational factors were collected with an online web-based survey. Regression analyses were performed to determine whether these factors accounted for the hospital variation.

**Results**

In total, 78% (n=72) of all Dutch hospitals participated in the survey. In these hospitals 16,471 female patients underwent a mastectomy for DCIS (n=1,980) or invasive BC (n=14,491) between 2011 and 2014. IBR was performed in 41% of patients with DCIS (hospital range 0-80%) and in 17% of patients with invasive BC (hospital range 0-62%). Hospital type, number of plastic surgeons available and attendance of a plastic surgeon at the MDT meeting increased IBR rates. For invasive BC, higher percentage of mastectomies and more weekly MDT meetings also significantly increased IBR rates. Adjusted data demonstrated decreased IBR rates for DCIS (average 35%, hospital range 0-49%) and invasive BC (average 15%, hospital range 0-18%).

**Conclusion**

Hospital organizational factors affect the use of IBR in the Netherlands. Although only partly explaining hospital variation, optimization of these factors could lead to less variation in IBR rates.

**Introduction**

Current surgical treatment of breast cancer patients consists of either breast conserving surgery or mastectomy. A mastectomy is performed in about 40% of invasive breast cancer patients and in approximately 33% of patients with a ductal carcinoma in situ [1-3]. An increasing number of patients desire restoration of their breast contour following mastectomy and consequently breast reconstruction has become an integral part of breast cancer treatment [4]. The breast can be reconstructed during the initial operation following mastectomy (immediate breast reconstruction (IBR)) or at a later time (delayed breast reconstruction) [2].

IBR has proven to be safe in terms of local recurrence and long-term survival rates compared to mastectomy only [5, 6]. Moreover, IBR offers women psychological benefits in terms of recovery and improved quality of life and is associated with superior aesthetic results compared to delayed breast reconstruction [5-7]. Guidelines emphasize the importance of reconstruction after mastectomy and recommend clinicians to discuss the possibility of IBR with every patient undergoing mastectomy [2, 8, 9]. Despite the benefits of IBR, the percentage of patients with DCIS or invasive breast cancer actually undergoing IBR after mastectomy is approximately 20% in the Netherlands. Large hospital variation in the use of IBR was found previously, ranging from 0 to 64% for invasive breast cancer and 0-83% for DCIS [10]. Comparable IBR rates were shown in other international studies; IBR was performed in 21% of the postmastectomy patients in the United Kingdom and 24% in the United States [2, 11, 12]. Literature has demonstrated that patient and tumor factors such as age, social economic status, multifocality, tumor type, clinical tumor stage, clinical lymph node stage, grade and previous breast surgery are predictors of the use of IBR [10, 11, 13-17]. However, these patient and tumor factors do not fully explain the large variation between hospitals in the Netherlands [10].

The aim of the present study was to investigate which hospital and hospital organizational factors affect the use of IBR after mastectomy for DCIS and invasive breast cancer in the Netherlands and whether these factors account for the variation seen.

**Material and methods**

*Data source*

Data of the NABON Breast Cancer Audit (NBCA) was used to obtain information on breast cancer patients in the Netherlands. The NBCA is a national multidisciplinary quality improvement register in which all 92 hospitals in the Netherlands participate and is supported by the Dutch Institute of Clinical Auditing (DICA) and the Netherlands Comprehensive Cancer Organisation (IKNL) [18]. Information concerning patient, tumor, diagnostics and treatment is continuously collected prospectively either by the hospitals themselves or by data managers of the Netherlands Cancer Registry (NCR).

*Study population*

All female patients diagnosed with DCIS or invasive breast cancer between January 1st, 2011 and December 31st, 2013 who underwent a mastectomy were selected.

*Hospital organizational factors based on data from the NBCA*

Hospitals were categorized as district hospitals, teaching hospital (despite educational activities, not affiliated with a medical faculty), university hospitals (hospitals having a medical faculty) and cancer specific hospitals (hospitals only treating cancer patients). According to the number of new breast cancer patients annually diagnosed in a hospital, three groups were identified (group 1: 1-150, group 2: 150-300, group 3: >300 patients per year). The percentage of mastectomies (related to all surgical excisions) were categorized in three groups (group 1: 0-30%, group 2: 30-50% and group 3: >50%).

*Survey*

All 92 hospitals were invited to complete a web-based survey regarding hospital organization factors. Questions encompassed the number of weekly MDT meetings (1, 2, >2 times per week), the presence of the various disciplines involved in breast cancer care participating the MDT meeting (e.g., nurse practitioners, pathologists, radiation oncologists, radiologists and medical oncologists), number of plastic surgeons available at institution per 100 new diagnoses of breast cancer (0-0.5, 0.5-2.5 and >2.5), number of breast surgeons available at institution per 100 new diagnoses of breast cancer (0-1.5, 1.5-2.5 and >2.5) and the presence of a plastic surgeon at weekly MDT meeting (never/incidental, structural). “Never” refers to hospitals where no plastic surgeon was attending the weekly MDT meetings and “incidental” only incidentally on request. Only patients of hospitals that responded to the survey were included for analyses. In case data were missing, we categorized them as unknown.

*Statistical Analyses*

DCIS and invasive breast cancer were analyzed separately. Factors tested for confounding were age, social economic state (SES), multifocality, clinical tumor stage, clinical lymph node stage, grade and radiation therapy. With use of logistic regression models hospital organizational factors were related to the prevalence of IBR and were presented as odds ratio’s with 95% confidence intervals (95%CIs). Factors that demonstrated to significantly affect IBR rates in univariable analyses ($p < 0.10$) were included in the multivariable analyses.

Hospital performance of IBR was visualized with the use of a funnel plot. In the funnel plots the volume is based on the number of mastectomies (and not the total number of breast cancer diagnosis treated per hospital) over 3 years. Actually, in the Netherlands, 60% of the patients are treated with breast conserving surgery, so the actual hospital volume of breast cancer patients is much higher. Data were analyzed unadjusted and adjusted for patient, tumor and hospital

organizational factors significantly affecting the use of IBR. Since the data is organized at more than one level and is clustered for the individual hospitals, multilevel analysis was performed. Not all organizational characteristics of the hospitals were known, but with use of a multilevel analysis, all hospital depending factors were taken into account in the adjusted data. All statistical analyses were performed in STATA (version 13.1 2013, Texas).



**Results**

*Study population*

Seventy-two hospitals (78.3%) responded to the survey leading to inclusion of 16,471 patients with a mastectomy for DCIS (n=1,980) and invasive breast cancer (n= 14,491) (Table 1). Almost 90% of the responding hospitals were categorized as a district or teaching hospital and most (85%) of the hospitals had 0-300 diagnosis annually. In most hospitals, one MDT meeting per week was organized and one hospital reported to have a daily MDT meeting (Table 1). All disciplines related to breast cancer care (e.g., surgeons, medical oncologists, radiation oncologists, radiologists, pathologists, nurse practitioners) structurally attended the MDT meetings. In 71% of the hospitals a plastic surgeon was structurally attending the MDT meeting. In most hospitals the geneticist, psychologist and palliative care expert were incidentally present. Eighty percent of the hospitals reported to offer plastic surgical care for breast cancer patients. In 83% of the responding hospitals, 0.5-2.5 plastic surgeons per 100 new diagnoses of breast cancer were available. For breast surgeons, most hospitals (49%) reported to have 1.5-2.5 breast surgeons per 100 new diagnoses of breast cancer (Table 1).

On average, 41% (n=809) of the patients underwent IBR after a mastectomy for DCIS. The hospital variation in performing IBR for DCIS varied between 0 and 80%. The average rate of IBR for invasive breast cancer was 17% (n=2,435) with a hospital variation ranging from 0 to 62%.

*DCIS*

Hospital organizational factors such as hospital type, hospital volume, number of weekly MDT meetings, number of plastic surgeons per 100 new diagnoses and the attendance of plastic surgeon at weekly MDT meetings significantly affected IBR rates in univariable analyses. Consequently, these variables were included in the multivariable model (Table 2). The percentage of mastectomies (related to all surgical excisions), and the number of breast surgeons available at institution per 100 new diagnoses did not affect IBR rates significantly in univariable analyses and were therefore not included in multivariable analyses.

Because age, SES and grade significantly affected IBR rates (data not shown) [10], these factors were included in the multivariable model to correct for confounding (Table 2). The multivariable model demonstrated that patients who underwent a mastectomy for DCIS at the cancer specific hospital had a higher chance of receiving IBR (OR=6.10 95%CI: 3.34-11.13) compared to patients receiving a mastectomy at a district hospital. Patients treated at a teaching (OR=1.33,

95%CI: 0.97-1.83) or university hospital (OR=0.97, 95%CI: 0.47-1.99) did not have a significant higher chance of receiving IBR compared to patients treated at a district hospital. The percentage of patients receiving IBR increased with an increasing number of plastic surgeons practicing in that specific hospital. Hospitals with more than 2.5 plastic surgeons per 100 diagnoses had a more than 3 fold higher IBR rate in comparison to hospitals with no or limited plastic surgeons available (OR=3.26, 95%CI: 1.11-9.59). The structural attendance of a plastic surgeon at the weekly MDT meeting was significantly associated with a higher IBR rate compared to MDTs with no or incidental plastic surgeon attendance (OR=1.52, 95%CI: 1.10-2.10) (Table2).
In figure 1, the variation between hospitals in the use of IBR after mastectomy for DCIS in the Netherlands is demonstrated. Case-mix adjustments for patient and tumor factors significantly affecting the use of IBR were performed. Also adjustments for hospital organizational factors were performed, due to the characteristics of a multilevel analysis. Adjusted data demonstrated a decrease in hospital variation in the use of IBR from 0-80% to 0-49%.

*Invasive breast cancer*
The hospital organizational factors (hospital type, hospital volume, percentage of mastectomies, number of weekly MDT meetings, number of plastic surgeons per 100 new diagnoses, number of breast surgeons per 100 new diagnoses and the attendance of plastic surgeon at weekly MDT meeting) demonstrated to significantly affect IBR rates in univariable analyses and were included in the multivariable model (Table 3).
Because patient (age, SES) and tumor factors (tumor and nodal stage, multifocality, grade) significantly affected IBR rates (data not shown) [10], these factors were included in the multivariable model to correct for confounding (Table 3). The multivariable model demonstrated that patients who underwent a mastectomy at a cancer specific hospital had a higher chance of receiving IBR (OR=13.39, 95%CI: 9.76-18.38) compared to patients who received a mastectomy at a district hospital. As for DCIS, invasive breast cancer patients who were treated at a teaching hospital did not have a significantly higher chance of receiving IBR (OR=0.97, 95%CI: 0.83-1.14) compared to patients treated at a district hospital. University hospitals demonstrated to perform significantly less IBRs compared to district hospitals, (OR=0.65, 95%CI:0.45-0.95).
Also the number of weekly MDT meetings positively affected the rate of IBR. Hospitals having one or two MDT meetings per week (OR=0.74, 95%CI: 0.61-0.89 and OR=0.66, 95%CI: 0.54-0.82, respectively) performed significantly less IBRs compared to hospitals that organized more than two MDT meetings per week. The percentage of patients receiving IBR increased with an increasing number of plastic surgeons practicing in that specific hospital. Hospitals with 0.5 to 2.5 plastic surgeons per 100 new diagnoses of breast cancer performed 5-fold more IBRs (OR=5.55, 95%CI: 3.04-10.11) and hospitals with more than 2.5 plastic surgeons performed twelve-fold more IBRs (OR=12.33, 95%CI: 6.03-25.21) compared to hospitals with less than 0.5 plastic surgeons per 100 diagnoses of breast cancer.

**Table 1.** *Hospital characteristics of the 72 responding hospitals in the Netherlands*

| | | Dutch hospitals (n=72) | | Number of patients | |
|---|---|---|---|---|---|
| | | Number | % | DCIS | Invasive |
| **Response** | *Non-Responding hospitals* | 20 | 21.7 | | |
| | *Responding hospitals* | 72 | 78.3 | 1,980 | 14,491 |
| **Hospital Type** | *District Hospital* | 27 | 37.5 | 499 | 4,044 |
| | *Teaching Hospital* | 37 | 51.4 | 1,106 | 8,624 |
| | *University Hospital* | 7 | 9.7 | 243 | 1,299 |
| | *Cancer specific hospital* | 1 | 1.4 | 132 | 524 |
| **Volume (# diagnosis annually)** | *Group 1 (1/150)* | 24 | 33.3 | 420 | 2,92 |
| | *Group 2 (150/300)* | 37 | 51.4 | 1,109 | 8,023 |
| | *Group 3 (>300) ub=436* | 11 | 15.3 | 451 | 3,548 |
| **% mastectomies (of all surgical excisions)** | *Group 1 (0/30)* | 4 | 5.6 | 90 | 612 |
| | *Group 2 (30/50)* | 49 | 68.1 | 1,275 | 9,505 |
| | *Group 3 (50/90)* | 19 | 26.4 | 615 | 4,374 |
| **% referrals for mastectomy** | *Group 1 (0/2.5)* | 17 | 23.6 | 691 | 4,532 |
| | *Group 2 (2.5/ 5.0)* | 26 | 36.1 | 628 | 5,054 |
| | *Group 3 (>5) ub=31* | 29 | 40.3 | 661 | 4,905 |
| **% referrals mastectomy+ reconstruction** | *Group 1 (0/2.5)* | 46 | 63.9 | 1,419 | 10,162 |
| | *Group 2 (2.5/ 5.0)* | 17 | 23.6 | 409 | 3,119 |
| | *Group 3 (> 5.0) ub=21* | 9 | 12.5 | 152 | 1,21 |
| **# of weekly MDT** | *Group 1 (1)* | 24 | 33.3 | 535 | 4,214 |
| | *Group 2 (2)* | 14 | 19.4 | 374 | 2,661 |
| | *Group 3 (>2) ub=7* | 9 | 12.5 | 265 | 2,217 |
| | *Group 4 (unknown)* | 25 | 34.7 | 806 | 5,399 |
| **# of plastic surgeons / 100 diagnoses** | *Group 1 (0/0.5)* | 4 | 5.6 | 43 | 453 |
| | *Group 2 (0.5/2.5)* | 60 | 83.3 | 1,713 | 12,791 |
| | *Group 3 (>2.5) ub=23* | 7 | 9.7 | 215 | 1,136 |
| | *Group 4 (unknown)* | 1 | 1.4 | 9 | 111 |
| **# of breast-surgeons / 100 diagnoses** | *Group 1 (0/1.5)* | 28 | 38.9 | 932 | 7,181 |
| | *Group 2 (1.5/2.5)* | 35 | 48.6 | 908 | 6,32 |
| | *Group 3 (>2.5) ub=17* | 9 | 12.5 | 140 | 990 |
| **Attendance plastic surgeon at weekly MDT** | *Never or incidental* | 13 | 18.1 | 294 | 2,404 |
| | *Yes, structural* | 51 | 70.8 | 1,381 | 10,145 |
| | *Unknown* | 8 | 11.1 | 305 | 1,942 |

ub= upper boundary MDT= multidisciplinary team meetings

**Table 2.** *Univariable and multivariable analyses of hospital organization factors affecting the use of IBR after mastectomy for 1,980 patients with DCIS*

| Immediate breast reconstruction (DCIS) (n=1,980) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Univariable | | Multivariable* | |
| | | No | % | Yes | % | Total | OR | 95% CI | OR | 95% CI |
| **Hospital Type** | *District Hospital* | 355 | 71.14 | 144 | 28.86 | 499 | ref | | ref | |
| | *Teaching Hospital* | 663 | 59.95 | 443 | 40.05 | 1,106 | 1.65 | 1.31-2.07 | 1.33 | 0.97-1.83 |
| | *University Hospital* | 127 | 52.26 | 116 | 47.74 | 243 | 2.25 | 1.64-3.09 | 0.97 | 0.47-1.99 |
| | *Cancer specific hospital* | 26 | 19.70 | 106 | 80.30 | 132 | 10.05 | 6.28-16.09 | 6.1 | 3.34-11.13 |
| **Volume (# diagnosis annually)** | *Group 1 (1/150)* | 278 | 66.19 | 142 | 33.81 | 420 | ref | | ref | |
| | *Group 2 (150/300)* | 627 | 56.54 | 482 | 43.46 | 1,109 | 1.50 | 1.19-1.90 | 1.25 | 0.88-1.78 |
| | *Group 3 (>300) ub=436* | 266 | 58.98 | 185 | 41.02 | 451 | 1.36 | 1.03-1.79 | 1.19 | 0.78-1.82 |
| **% mastectomies (of all surgical excisions)** | *Group 1 (0/30)* | 52 | 57.78 | 38 | 42.22 | 90 | ref | | | |
| | *Group 2 (30/50))* | 731 | 57.33 | 544 | 42.67 | 1,275 | 1.02 | 0.66-1.57 | | |
| | *Group 3 (50/90)* | 388 | 63.09 | 227 | 36.91 | 615 | 0.80 | 0.51-1.25 | | |
| **# of weekly MDT** | *Group 1 (1)* | 361 | 67.84 | 174 | 32.52 | 535 | 0.59 | 0.44-0.80 | 0.69 | 0.47-1.02 |
| | *Group 2 (2)* | 237 | 63.37 | 137 | 36.63 | 374 | 0.71 | 0.51-0.98 | 0.67 | 0.45-0.99 |
| | *Group 3 (>2) ub=7* | 146 | 55.09 | 119 | 44.91 | 265 | ref | | ref | |
| | *Group 4 (unknown)* | 427 | 52.98 | 379 | 47.02 | 806 | 1.09 | 0.82-1.44 | 0.71 | 0.48-1.04 |
| **# of plastic surgeons / 100 diagnoses** | *Group 1 (0/0.5)* | 33 | 76.74 | 10 | 23.26 | 43 | ref | | ref | |
| | *Group 2 (0.5/2.5)* | 1,021 | 59.60 | 692 | 40.40 | 1,713 | 2.24 | 1.10-4.57 | 1.56 | 0.70-3.47 |
| | *Group 3 (>2.5) ub=23* | 108 | 50.23 | 107 | 49.77 | 215 | 3.27 | 1.53-6.97 | 3.26 | 1.11-9.59 |
| | *Group 4 (unknown)* | 9 | 100 | 0 | 0 | 9 | omitted | | omitted | |
| **# of breast-surgeons / 100 diagnoses** | *Group 1 (0/1.5)* | 532 | 57.08 | 400 | 42.92 | 932 | ref | | | |
| | *Group 2 (1.5/2.5)* | 552 | 60.79 | 356 | 39.21 | 908 | 0.86 | 0.71-1.03 | | |
| | *Group 3 (>2.5) ub=17* | 87 | 62.14 | 53 | 37.86 | 140 | 0.81 | 0.56-1.17 | | |

| Table 2 continued. | | Immediate breast reconstruction (DCIS) (n=1,980) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Univariable | | Multivariable* | |
| | | No | % | Yes | % | Total | OR | 95% CI | OR | 95% CI |
| **Attendance plastic surgeon in weekly MDT** | Never or incidental | 209 | 71.09 | 85 | 28.91 | 294 | ref | | ref | |
| | *Yes, structural* | 798 | 57.78 | 583 | 42.22 | 1,381 | 1.80 | 1.37-2.36 | 1.52 | 1.10-2.10 |
| | *Unknown* | 164 | 53.77 | 141 | 46.23 | 305 | 2.11 | 1.51-2.96 | 2.15 | 1.39-3.34 |
| **Radiation therapy** | *No* | 1,152 | 59.20 | 794 | 40.80 | 1,946 | Ref | | | |
| | *Yes* | 19 | 55.88 | 15 | 44.12 | 34 | 1.15 | 0.58-2.27 | | |

ub= upper bound MDT= multidisciplinary team meetings

* Corrected for age, grade, social economic state, hospital type, hospital volume, % referrals for mastectomy, number of weekly MDT, number of plastic surgeons and attendance of plastic surgeon at weekly MDT

**Table 3.** *Univariable and multivariable analyses of hospital organization factors affecting the use of IBR after mastectomy for 14,491 invasive breast cancer patients*

| Immediate breast reconstruction (invasive breast cancer) (n=14,491) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Univariable | | Multivariable* | |
| | | No | % | Yes | % | Total | OR | 95% CI | OR | 95% CI |
| **Hospital Type** | *District Hospital* | 3,582 | 88.58 | 462 | 11.42 | 4,044 | ref | | ref | |
| | *Teaching Hospital* | 7,232 | 83.86 | 1,392 | 16.14 | 8,624 | 1.49 | 1.33-1.67 | 0.97 | 0.83-1.14 |
| | *University Hospital* | 1,042 | 80.22 | 257 | 19.78 | 1,299 | 1.91 | 1.62-2.26 | 0.65 | 0.45-0.95 |
| | *Cancer specific hospital* | 200 | 38.17 | 324 | 61.83 | 524 | 12.56 | 10.27-15.36 | 13.39 | 9.76-18.38 |
| **Volume (# diagnosis annually)** | *Group 1 (1/150)* | 2,579 | 88.32 | 341 | 11.68 | 2,920 | ref | | ref | |
| | *Group 2 (150/300)* | 6,596 | 82.21 | 1,427 | 17.79 | 8,023 | 1.64 | 1.44-1.86 | 1.20 | 0.97-1.48 |
| | *Group 3 (>300) ub=436* | 2,881 | 81.20 | 667 | 18.80 | 3,548 | 1.75 | 1.52-2.02 | 1.29 | 1.00-1.65 |
| **% mastectomies (of all surgical excisions)** | *Group 1 (0/30)* | 537 | 87.75 | 75 | 12.25 | 612 | ref | | ref | |
| | *Group 2 (30/50))* | 7,861 | 82.70 | 1,644 | 17.30 | 9,505 | 1.50 | 1.17-1.92 | 1.15 | 0.87-1.54 |
| | *Group 3 (50/90)* | 3,658 | 83.63 | 716 | 16.37 | 4,374 | 1.40 | 1.09-1.81 | 1.50 | 1.11-2.02 |
| **# of weekly MDT** | *Group 1 (1)* | 3,550 | 84.24 | 664 | 15.76 | 4,214 | 0.65 | 0.57-0.74 | 0.74 | 0.61-0.89 |
| | *Group 2 (2)* | 2,340 | 87.94 | 321 | 12.06 | 2,661 | 0.48 | 0.41-0.56 | 0.66 | 0.54-0.82 |
| | *Group 3 (>2) ub=7* | 1,722 | 77.67 | 495 | 22.33 | 2,217 | ref | | ref | |
| | *Group 4 (unknown)* | 4,444 | 82.31 | 955 | 17.69 | 5,399 | 0.75 | 0.66-0.84 | 0.48 | 0.39-0.59 |
| **# of plastic surgeons / 100 diagnoses** | *Group 1 (0/0.5)* | 441 | 97.35 | 12 | 2.65 | 453 | ref | | ref | |
| | *Group 2 (0.5/2.5)* | 10,606 | 82.92 | 2,185 | 17.08 | 12,791 | 7.57 | 4.26-13.46 | 5.55 | 3.04-10.11 |
| | *Group 3 (>2.5) ub=23* | 898 | 79.05 | 238 | 20.95 | 1,136 | 9.74 | 5.39-17.59 | 12.33 | 6.03-25.21 |
| | *Group 4 (unknown)* | 111 | 100 | 0 | 0 | 111 | omitted | | omitted | |

| Table 3 continued. | | Immediate breast reconstruction (invasive breast cancer) (n=14,491) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Univariable | | Multivariable* | |
| | | No | % | Yes | % | Total | OR | 95% CI | OR | 95% CI |
| **# of breast-surgeons / 100 diagnoses** | *Group 1 (0/1.5)* | 5,793 | 80.67 | 1,388 | 19.33 | 7,181 | ref | | | |
| | *Group 2 (1.5/2.5)* | *5,394* | *85.35* | *926* | *14.65* | *6,320* | *0.72* | *0.65-0.78* | *0.76* | *0.65-0.88* |
| | *Group 3 (>2.5) ub=17* | 869 | 87.78 | 121 | 12.22 | 990 | 0.58 | 0.48-0.71 | 0.64 | 0.47-0.87 |
| **Attendance plastic surgeon in weekly MDT** | *Never or incidental* | 2,227 | 92.64 | 177 | 7.36 | 2,404 | ref | | | |
| | *Yes, structural* | 8,144 | 80.28 | 2,001 | 19.72 | 10,145 | 3.09 | 2.63-3.63 | 2.91 | 2.39-3.54 |
| | *Unknown* | 1,685 | 86.77 | 257 | 13.23 | 1,942 | 1.92 | 1.57-2.35 | 2.49 | 1.91-3.24 |
| **Radiation therapy** | *No* | 8,162 | 79.96 | 2,046 | 20.04 | 10,208 | Ref | | | |
| | *Yes* | 3,894 | 90.92 | 389 | 9.08 | 4,283 | 0.4 | 0.36-0.45 | 0.45 | 0.39-0.53 |

ub= upper boundary MDT= multidisciplinary team meetings

* Corrected for age, tumor type, clinical tumor stage, clinical lymph node stage, grade, multifocality, social economic state, hospital type, hospital volume,

% mastectomies (of all surgical excisions), % referrals for mastectomy, number of weekly MDT, number of plastic surgeons, # of breast-surgeons / 100 diagnoses, attendance of plastic surgeon at weekly MDT and radiation therapy.

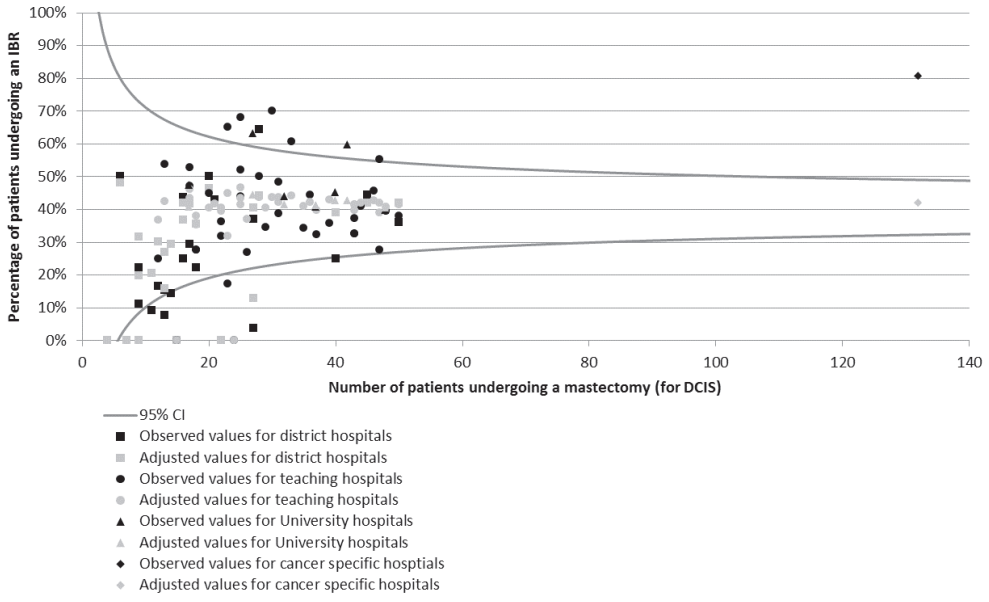


**Figure 1.** *Funnel plot demonstrating the variation in the use of IBR for DCIS between hospitals in the Netherlands with and without case-mix correction for patient and tumor factors, combined with multilevel analyses to adjust for hospital factors*

The number of breast surgeons did not affect IBR rates. The structural attendance of a plastic surgeon at the weekly MDT meeting was strongly associated with performing more IBRs compared to MDT meetings with no or incidental plastic surgeon attendance (OR=2.91 95%CI: 2.39-3.54).

In figure 2, the variation between hospitals in the use of IBR after mastectomy for invasive breast cancer in the Netherlands is demonstrated. Case-mix adjustments for patient and tumor factors, significantly affecting the use of IBR were performed. Also adjustments for hospital organizational factors were performed, due to the characteristics of a multilevel analysis. Adjusted data demonstrated a decrease in hospital variation in the use of IBR from 0-62% to 0-18%.

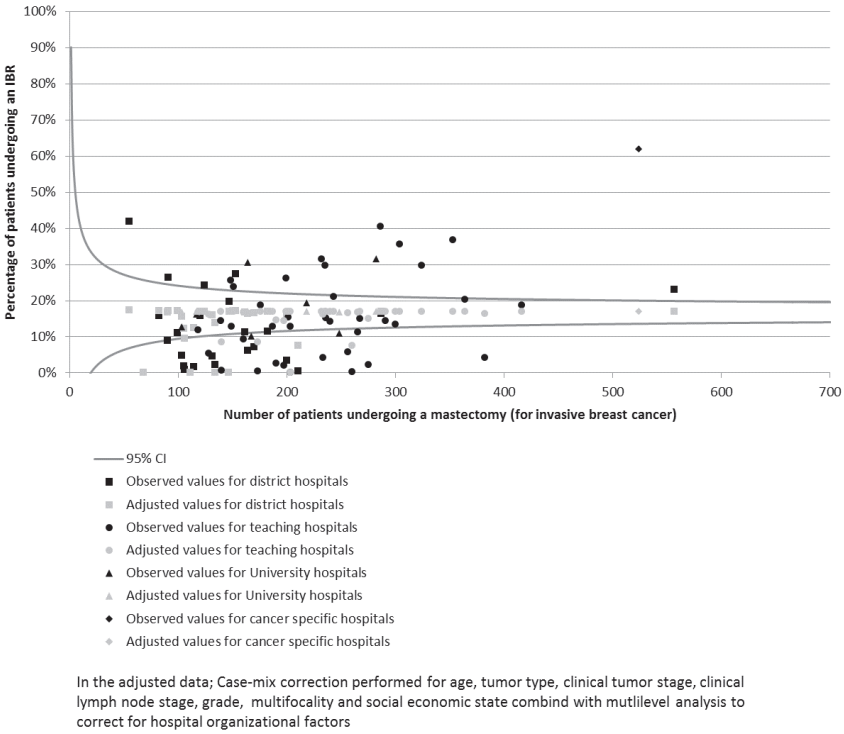


**Figure 2.** *Funnel plot demonstrating the variation in the use of IBR for invasive breast cancer between hospitals in the Netherlands with and without case-mix correction for patient and tumor factors, combined with multilevel analyses to adjust for hospital factors*

**Discussion**

It is known that various patient and tumor characteristics significantly affect IBR rates [10]. However, these characteristics were not fully responsible for the observed large hospital variation in the use of IBR following mastectomy in the current cohort [10]. Like other studies, we were able to show that hospital organizational factors such as hospital type, patient volume or presence and availability of a plastic surgery facility may additionally explain part of the hospital variation [8-12]. In previous research, Jagsi et al, demonstrated the influence of radiation therapy on the chance of receiving a reconstruction [16]. Although the focus of the current study was hospital characteristics, we performed an analysis to determine the possible influence of radiation therapy. This revealed similar results as demonstrated by Jagsi et al. Moreover, radiation therapy does not influence the effects of the hospital organizational factors in multivariable analysis.

The current population based study shows that multiple hospital organizational factors affect the use of IBR after mastectomy for DCIS and breast cancer in the Netherlands. Hospital type (cancer specific centre), the number of plastic surgeons and the structural attendance of a plastic surgeon at the MDT meeting increased IBR rates significantly for both DCIS and non-metastatic invasive breast cancer. For invasive breast cancer, also the percentage of mastectomies related to all surgical excisions (>50%), >2 weekly MDTs and number of plastic surgeons available at institution (>0.5 per 100 new diagnoses) significantly increased IBR rates.
Therefore, the use of IBR in breast cancer patients could be improved by optimization of these hospital organizational factors. Although the aim of the present study was not to stimulate performing more IBRs in clinical practice, we feel that the availability of IBR for eligible patients should be more or less comparable between hospitals and unrelated to hospital organizational factors. However, hospital variation could only be partially explained by hospital organizational factors in the present study.

A large variation was found in the use of IBR for DCIS or invasive breast cancer between hospitals that were included in the current study. The large variation is comparable with other studies; IBR was performed in 21% of the mastectomy patients in the United Kingdom and 24% in the United States [2, 11]. Our data demonstrated that some hospitals tended not to perform IBR, however, the referral rates for IBR revealed that there were collaborations between hospitals. Therefore, it is possible that hospitals referred their patients to other hospitals in case IBR was preferred. Like others, we demonstrated that collaboration between hospitals does not significantly affect IBR rates in the hospital of referral. An English national study also reported similar hospital variation in performing IBR after statistically correcting for hospital collaborations [2].

Different hospital organizational factors were investigated and appeared to be related to the use of IBR in the present study. For example, hospital type (cancer specific hospital) significantly affected IBR rates. Other nationwide studies also demonstrated the relationship between hospital type and IBR rates [11, 17]. Alderman et al. demonstrated that IBR rates were most probably higher in specialized cancer centers, because of high referrals to plastic surgeons [19]. Others revealed that high volume clinical breast hospitals extensively collaborate with plastic surgery departments, which could result in higher IBR rates [13, 19]. We were not able to demonstrate a significant association between higher volume hospital (>150 diagnoses) and higher IBR rates for invasive breast cancer.
In our study a higher number of plastic surgeons working in a hospital positively affected IBR rates. However, the number of breast surgeons working in a hospital did not. Breast Surgeons in the Netherlands differ from the Breast Surgeons in other countries, since Dutch oncologic breast surgeons only perform breast ablative surgery or breast conserving surgery and do not

carry out breast reconstructions, which is exclusively performed by plastic surgeons. In addition, the presence of a plastic surgeon at the MDT meeting positively affected the use of IBR. Alderman et al. demonstrated that a large proportion of surgeons did not refer breast cancer patients to a plastic surgeon at the time of surgical decision-making [19]. This implicates the relevance of the attendance of a plastic surgeon at the weekly MDT meeting to timely discuss the possibility of IBR. However, in Dutch clinical practice, it is quite common for patients to visit the plastic surgeon before surgery. Interestingly, Alderman et al. also concluded that surgeons who have a high referral propensity are more likely to be women [19]. Unfortunately we did not have information on gender of the (plastic) surgeon.



*Limitations*

In total, 72 of the 92 of the Dutch hospitals (78.3%) participated in this study, despite repeated invitations to the non-responding hospitals. However, the included hospitals are a good reflection of all Dutch hospitals, since representative proportions of hospital type and hospital volume were included.

Although we were able to demonstrate a significant effect of hospital type on IBR rates, it is important to realize that even *within* three out of four hospital categories variation in performing IBR existed.

DCIS and invasive breast cancer were analyzed separately, to make testing for confounding (tumor factors such as tumor and nodal stage) possible. However, due to low numbers of DCIS patients we were not able to demonstrate the same significant effect of hospital organizational factors on IBR rates as for invasive breast cancer.

To investigate the effect of hospital factors explaining variation in performing IBR, a multilevel analysis was performed to obtain the adjusted data for the funnel plot. The demonstrated reduction in variation after case-mix correction for patient and tumor factors was mainly caused by hospital factors. Other undefined hospital related factors could have contributed to this reduction, such as surgeons' attitude towards IBR, gender of surgeon, geographical location, waiting times for plastic surgery, patient preferences and loss of control of patient's management [11, 15]. Jeevan et al. demonstrated that 50% of the patients were very satisfied with the options they received about breast reconstruction but preferred no IBR [2]. Further research should identify patient preferences and surgeon's attitudes towards IBR and whether or not these factors can explain the variation in performing IBR completely; such a study is on its way.

**Conclusion**

Large hospital variation in IBR rates was observed between hospitals in the Netherlands. The current study demonstrated that the observed variation in performing IBR was significantly affected by hospital type, but also by organizational factors that could be subject for change and improvement. Although hospital variation could only be partially explained by these factors,

optimization of these factors could lead to an increased use of IBR in breast cancer patients and less variation in IBR rates between hospitals.

**Ethical approval**

According to the Central Committee on Research involving Human Subjects (CCMO), this type of study does not require approval from an ethics committee in the Netherlands. This study was approved by the Privacy Review Board of the Netherlands Cancer Registry.

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**Conflict of interest statement**

The authors declare that they have no conflict of interest.

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# Chapter 3

## Discrepancies between surgical oncologists and plastic surgeons in patient information provision and personal opinions towards immediate breast reconstruction

*Submitted*

A.C.M. van Bommel
K. Schreuder
R.K. Veenstra
K.M. de Ligt
M.T.F.D. Vrancken Peeters
J.H. Maduro
S. Siesling
M.A.M. Mureau

**Abstract**

**Background**

Immediate breast reconstruction (IBR) may improve quality of life of patients receiving mastectomy. However, a significant hospital variation exists in the use of IBR due to various reasons. To better understand this variation, the present study investigated preoperative information provision to patients and personal opinions of surgical oncologists and plastic surgeons towards potential contra-indications for IBR.

**Methods**

An online survey (35 questions) was developed including questions on respondent demographics, information provision to the patient about IBR and potential contra-indications by IBR technique.

**Results**

One-hundred-eighty-nine physicians participated: 118 surgical oncologists and 71 plastic su geons. All clinicians discussed the possibility of IBR with their patients. Complications (79% versus 100%, $p<0.001$) and aesthetic outcomes (83% versus 99%, $p=0.001$) were discussed less frequently by surgical oncologists than by plastic surgeons. Patient age >75 years, breast size >D-cup, BMI >40 kg/m2, smoking (for implant reconstruction), pulmonary/cardiac comorbidities (for autologous reconstruction) and radiotherapy were considered a contra-indication more frequently by plastic surgeons. In contrast, surgical oncologists reported tumour stage (≥cT3), nodal stage (≥cN2) and chemotherapy more frequently to be a contra-indication for IBR.

**Conclusion**

We observed that all respondents discussed the possibility of IBR with their patients, whereas patient-tailored information was given more frequently by plastic surgeons. Physicians differed in their opinions towards contra-indications for IBR, with plastic surgeons reporting patient-related risk factors for wound healing problems and surgical oncologists reporting oncological contra-indications more frequently. Consensus between physicians regarding contra-indications for IBR may optimize patient counselling and shared decision-making.

**Introduction**

In the Netherlands, about 15.000 new breast cancer patients are diagnosed annually, which makes it the most frequently diagnosed cancer in women [1]. About 40% of all surgically treated patients receive a mastectomy [2]. According to current guidelines, immediate breast reconstruction (IBR) has to be considered in every patient who is planned for mastectomy [3, 4]. IBR does not compromise the oncological outcomes [5], while resulting in improved quality of life with better psychological and functional wellbeing in the majority of patients [6-9].
In general, breast reconstruction can be performed with an implant, autologous tissue or using a combination of both. However, implant reconstructions are performed most frequently [10-13]. These different techniques vary in complexity and operation time, complication rates, recovery period and aesthetic outcomes, making not every technique suitable for every patient, depending on comorbidities, local anatomy and previous surgery/treatment, and patient preferences[14-16].



The NABON Breast Cancer Audit (NBCA) is a nationwide multidisciplinary audit measuring quality of breast cancer care in the Netherlands [17]. Current data show that the mean percentage of patients undergoing IBR in the Netherlands is rather low given every patient planned for mastectomy should be considered for IBR; 17% for invasive breast cancer and 43% for ductal carcinoma in situ (DCIS) [2, 17]. Moreover, large variation in the use of IBR between hospitals in the Netherlands was previously shown by our group; 0–64% and 0–83% for invasive breast cancer and DCIS, respectively [11]. Numerous factors are considered contra-indications for the use of IBR which may affect its current use. Patient characteristics such as older age, high Body Mass Index (BMI), smoking status, comorbidities have been reported to affect the probability to receive IBR [18, 19]. In addition, tumour factors as histology, larger tumour size and lymph node involvement also have an impact on whether or not IBR is performed as well as the need for adjuvant treatments [6, 18, 20-22]. Furthermore, differences in care processes between hospitals or physician preferences have been suggested to have a relationship with the use of IBR [18, 23, 24].

In the Netherlands, every patient diagnosed with breast cancer is discussed in a multi-disciplinary team prior to treatment. The final decision to perform IBR is predominantly made by surgical oncologists and plastic surgeons together with the patient. Physicians' personal attitudes and the weighing of possible contra-indications may affect this decision making process. Moreover, the preoperative information given to patients may affect patient preferences.

To better understand the existing large variation in the use of IBR and to ultimately improve breast cancer care, it is important to learn about the various attitudes of physicians in the decision-making process of offering patients IBR. Therefore, the aim of the current study was

to investigate the practice of preoperative information provision to patients by surgical oncologists and plastic surgeons and their personal opinion towards potential contra-indications for different types of IBR in patients with breast cancer requiring mastectomy.

**Materials and Methods**

*Respondents*

Surgical oncologists and plastic surgeons with special interest in breast cancer care were identified through clinical networks of the Netherlands Comprehensive Cancer Organisation (IKNL) and were invited to participate in a self-administered survey. The responses were collected over an 8-month period from July 2014 to February 2015. To maximize response rates, five reminders were sent approximately after 1.5 months, 3 months, 5 months, 7 months and 7.5 months.

*Questionnaire*

The survey consisted of 35 questions divided in three sections. First, the respondents' demographic information was asked. In the second section the provision of preoperative information to patients about IBR or delayed reconstruction, possible complications, expected aesthetic outcomes and reconstructive techniques was investigated. Finally, respondents were asked about their personal opinion towards contra-indications such as patient characteristics, tumour characteristics and neoadjuvant or adjuvant treatments. If one responded positively on a specific contra-indication, a drop-down menu opened asking for which specific reconstruction technique and for which subgroup of patients the contra-indication was applicable (for example, age below 35, age 35-55, age 56-75, age >75). Contra-indications were chosen based on evidence in current literature and expert-based opinions. Members of the scientific committee of the NBCA reviewed and piloted the survey. The survey was administered anonymously with the use of SurveyMonkey, an online secure web-based database [25]. None of the respondents received an offer for an incentive for completion of the survey.

*Statistical analysis*

Demographic characteristics of the respondents were analysed for surgical oncologists and plastic surgical oncologists separately. Next, the information provided to patients by surgical oncologists and plastic surgeons was evaluated. Reconstructive techniques were divided into three categories: implant reconstruction, autologous reconstruction, or combination of both implant and autologous reconstruction. The opinions about potential contra-indications per reconstructive technique reported by the respondents were categorized and results of surgical oncologists and plastic surgeons were compared.

All statistical analyses were performed using SPSS 20.0 (IBM-SPSS, Inc., Chicago, Il).

## Results

*Respondents*

In total, 41% (193/466) physicians responded. Four of the 193 surveys (2%) were excluded from analyses due to data incompleteness resulting in 118 surgical oncologists and 71 plastic surgeons participating, representing 82 of the 89 hospitals in the Netherlands. Plastic surgeons were significantly younger and on average had less working experience (Table 1).

*Preoperative information provision*

All surgical oncologists discussed the possibility of IBR and delayed reconstruction with patients undergoing a mastectomy. Surgical oncologists significantly less frequently discussed complications (79% versus 100%, p<0.001) and aesthetic outcomes (83% versus 99%, p=0.001) compared to plastic surgeons. Information provision to patients regarding the difference between IBR and delayed reconstruction did not differ significantly between surgical oncologists and plastic surgeons (97% versus 99%, respectively, p=0.594). This was also true regarding advantages and disadvantages of the timing of reconstruction (97% versus 99%, respectively, p=0.589), and consequences of other therapies such as adjuvant therapy (84% versus 91%, respectively, p=0.130). Forty-eight percent of the surgical oncologists discussed all reconstructive techniques with their patients, versus 85% of the plastic surgeons (p<0.001). The remaining surgical oncologists (52%) tended to discuss only techniques offered at their own institution (29%) or reconstructive techniques that they regarded relevant to the specific patient (23%).

**Table 1.** *Demographic characteristics of respondents (118 surgical oncologists and 71 plastic surgeons) on questionnaire regarding breast cancer management process*

| | | Surgical oncologist | | Plastic surgeon | | Total | | |
|---|---|---|---|---|---|---|---|---|
| | | n=118 | % | n=71 | % | n=189 | % | P-value*** |
| **Gender** | *Male* | 59 | 50% | 42 | 59% | 101 | 53% | 0.222 |
| | *Female* | 59 | 50% | 29 | 41% | 88 | 47% | |
| **Age** | *mean in years (range)* | 48 (35-65) | | 45 (30-64) | | 48 (30-65) | | 0.003 |
| **Working experience** | *mean in years (range)** | 13 (2-33) | | 10 (1-26) | | 12 (1-33) | | 0.002 |
| **Type of hospital**** | *District hospital* | 42 | 36% | 11 | 15% | 53 | 28% | 0.018 |
| | *Teaching hospital* | 63 | 53% | 48 | 68% | 111 | 59% | |
| | *University Hospital* | 12 | 10% | 12 | 17% | 24 | 13% | |
| **Breast cancer patients treated per year** | *0 - 50* | 20 | 17% | 47 | 66% | 67 | 35% | <0.001 |
| | *51 - 100* | 61 | 52% | 19 | 27% | 80 | 42% | |
| | *101 - 150* | 25 | 21% | 3 | 4% | 28 | 15% | |
| | *>150* | 12 | 10% | 2 | 3% | 14 | 7% | |

* Excluding time as registrar. ** One respondent left the question unanswered. *** Using Chi-square tests for categorical variables and ANOVA for numerical variables.

*Patient related contra-indications*

Table 2 provides a general overview of factors considered a contra-indication by surgical oncologists and plastic surgeons.

Age was not considered a contra-indication for any of the IBR types except age >75 years. Specifically for autologous reconstructions, a considerable percentage of the plastic surgeons (38%) reported age >75 years as contra-indication compared to 19% of the surgical oncologists. For implant reconstructions, older age was less frequently considered a contra-indication by both surgical oncologists (9%) and plastic surgeons (15%) when compared to autologous reconstructions.

Smoking was a contra-indication for IBR for surgical oncologists in 60%, 56% and 41% for autologous, combination autologous-implant and implant reconstructions, respectively. These figures were 48%, 45% and 47%, respectively, for plastic surgeons.

About 14-17% of the plastic surgeons, depending of the reconstruction technique, reported large breast size (>D-cup) to be a contra-indication compared to 7-8% of the surgical oncologists. No significant differences between reconstruction techniques were found.

Approximately 65% of the plastic surgeons and 40% of the surgical oncologists found BMI >40 $kg/m^2$ a contra-indication for IBR. A BMI <18.5 $kg/m^2$ was reported as contra-indication by approximately 13-18% of the plastic surgeons compared to approximately 3% of the surgical oncologists.

About 10% of the respondents reported that comorbidities in general should be regarded as a contra-indication for IBR, irrespective of reconstructive technique. Overall, auto-immune diseases were considered to be a contra-indication by both surgical oncologists and plastic surgeons. The most striking differences between surgical oncologists and plastic surgeons were found for autologous reconstructions. Forty-nine percent of the plastic surgeons compared to 17% of the surgical oncologists mentioned cardiac comorbidities as contra-indication for autologous reconstructions. For pulmonary comorbidities this was the case in 31% of the plastic surgeons versus 10% of the surgical oncologists (Figure 1).

*Oncological related contra-indications*

In general, surgical oncologists reported tumour T-stage and nodal N-stage more frequently as a contra-indication for IBR compared to plastic surgeons. Surgical oncologists reported tumours clinical T3 or larger for all three reconstruction techniques as a contra-indication (around 30%). Plastic surgeons had less agreement on T-stage; cT4 was reported as contra-indication for all reconstruction techniques in 12%, and also T-stages T2 and T3 were reported by 8% of the plastic surgeons, see figure 2a.

For the three reconstruction types, 39% of the surgical oncologists reported lymph node involvement ≥cN2 to be a contra-indication. Plastic surgeons showed a similar response for implant reconstructions (34%), although lower percentages were found for autologous and

autologous-implant reconstructions (Figure 2b).

Overall, surgical oncologists differed in their perspective of adjuvant treatments as contra-indication compared to plastic surgeons (Table 3).

**Table 2.** *Factors affecting the indication for immediate breast reconstruction reported by 189 surgical oncologists and plastic surgeons involved in breast cancer care*

| | | Surgical oncologist | | Plastic surgeon | | Total | | |
|---|---|---|---|---|---|---|---|---|
| **Contra-indication** | | n=118 | % | n=71 | % | n=237 | % | P-value* |
| **Age** | *Yes* | 24 | 24% | 26 | 43% | 56 | 27% | 0.015 |
| | *No* | 75 | 76% | 35 | 57% | 148 | 73% | |
| | *Missing* | 19 | | 10 | | 33 | | |
| **Smoking** | *Yes* | 67 | 66% | 36 | 58% | 130 | 61% | 0.327 |
| | *No* | 35 | 34% | 26 | 42% | 82 | 39% | |
| | *Missing* | 16 | | 9 | | 25 | | |
| **Breast Size** | *Yes* | 19 | 19% | 26 | 43% | 54 | 26% | 0.001 |
| | *No* | 83 | 81% | 35 | 57% | 154 | 74% | |
| | *Missing* | 16 | | 10 | | 29 | | |
| **Body Mass Index** | *Yes* | 63 | 63% | 52 | 85% | 142 | 69% | 0.002 |
| | *No* | 37 | 37% | 9 | 15% | 63 | 31% | |
| | *Missing* | 18 | | 10 | | 32 | | |
| **Co-morbidities** | *Yes* | 70 | 71% | 53 | 87% | 158 | 78% | 0.024 |
| | *No* | 28 | 29% | 8 | 13% | 45 | 22% | |
| | *Missing* | 20 | | 10 | | 34 | | |
| **Tumour Stage** | *Yes* | 65 | 59% | 29 | 45% | 125 | 56% | 0.064 |
| | *No* | 45 | 41% | 36 | 55% | 98 | 44% | |
| | *Missing* | 8 | | 6 | | 14 | | |
| **Nodal Stage** | *Yes* | 44 | 75% | 18 | 67% | 85 | 72% | 0.448 |
| | *No* | 15 | 25% | 9 | 33% | 33 | 28% | |
| | *Missing* | 59 | | 44 | | 119 | | |
| **Neo-adjuvant or adjuvant treatment** | *Yes* | 21 | 20% | 26 | 42% | 56 | 26% | 0.003 |
| | *No* | 82 | 80% | 36 | 58% | 157 | 74% | |
| | *Missing* | 15 | | 9 | | 24 | | |

*Using Chi-square tests to calculate differences between surgical oncologists and plastic surgeons.

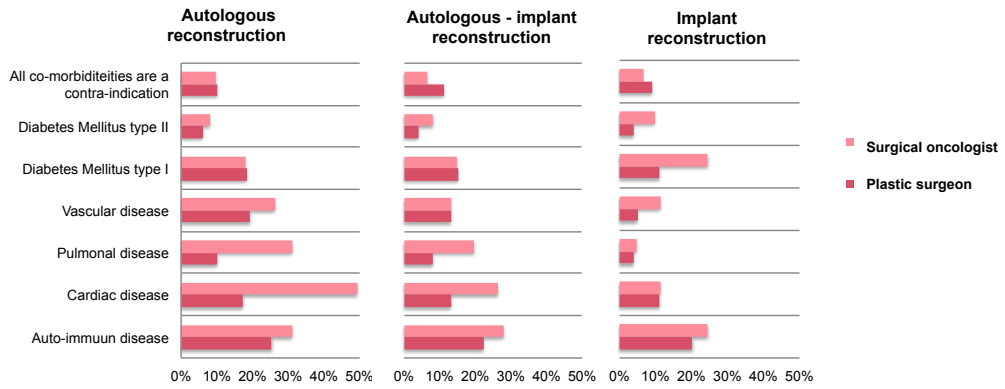


**Figure 1.** *Comorbidities indicated as contra-indication per reconstructive technique, separated for surgical oncologists and plastic surgeons*

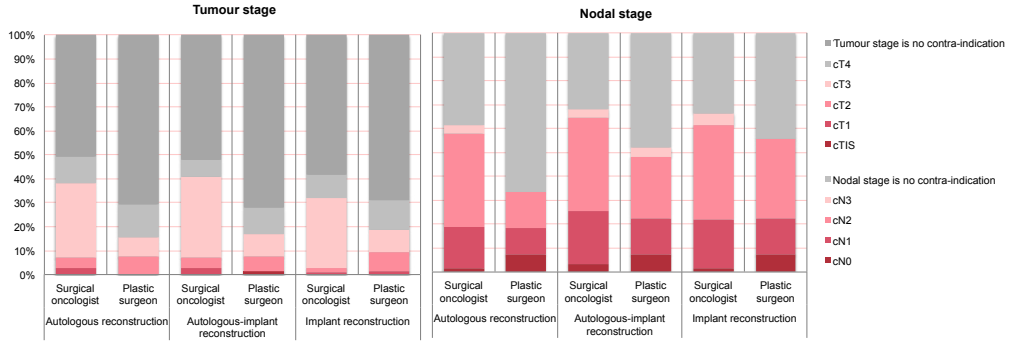


**Figure 2.** *Tumour T-stage (a) and Nodal N-stage (b) reported by clinicians as contra-indication, separated per reconstructive technique*

No difference between surgical oncologists and plastic surgeons was found for radiotherapy as contra-indication for immediate autologous reconstruction. However, in case of reconstruction using implants (either autologous-implant or implant reconstruction) radiotherapy was less often reported as contra-indication by surgical oncologists compared to plastic surgeons (Table 3). Chemotherapy, neo-adjuvant and specifically adjuvant chemotherapy were more often considered to be a contra-indication for IBR by surgical oncologists compared to plastic surgeons. Adjuvant hormonal therapy was hardly reported as a contra-indication for IBR by any of the clinicians (≤2%, Table 3).

**Table 3.** *Various treatments reported by clinicians as contra-indication, separated per reconstructive technique*

| | Autologous reconstruction | | Autologous-implant reconstruction | | Implant reconstruction | |
|---|---|---|---|---|---|---|
| | Surgical oncologist | Plastic surgeon | Surgical oncologist | Plastic surgeon | Surgical oncologist | Plastic surgeon |
| **Neo-adjuvant therapies are no contra-indication** | 7% | 15% | 7% | 8% | 6% | 2% |
| **Neo-adjuvant chemotherapy** | 4% | 6% | 4% | 2% | 4% | 0% |
| **Adjuvant therapies are no contra-indication** | 0% | 8% | 0% | 3% | 0% | 2% |
| **Adjuvant chemotherapy** | 7% | 3% | 7% | 2% | 5% | 2% |
| **Adjuvant hormonal therapy** | 1% | 2% | 1% | 0% | 1% | 0% |
| **Adjuvant radiotherapy** | 11% | 10% | 13% | 23% | 15% | 36% |



## Discussion

Hospital variation in IBR after mastectomy can partially be explained by variation in patient and tumour characteristics (i.e., case-mix factors) that cannot be altered [11]. In addition, differences in patient preferences may also be a cause of variation [6, 26]. However, variation in IBR due to hospital organisational factors [18, 24] or personal opinions towards IBR of individual physicians is undesirable [26].

As found in the present study, surgical oncologists and plastic surgeons differ in their information provision to patients about IBR. More importantly, personal opinions towards IBR differ between surgical oncologists and plastic surgeons as well. Surgical oncologists more frequently reported cancer related factors to be a contra-indication for IBR compared to plastic surgeons, whereas the latter mentioned factors affecting complications or reconstruction failure more frequently.

*Preoperative information provision*

The Dutch, evidence-based NABON breast cancer treatment guideline recommends that every patient undergoing mastectomy should be considered for IBR [3]. Interestingly, in the present study all surgical oncologists discussed the possibility of IBR with their patients, while other studies reported lower rates of information provision about IBR, ranging from 23% in Japan [27] to 74% in the United States [28]. It seems justified that surgical oncologists inform patients about the existence and possibility of IBR and delayed reconstruction, while details about the reconstructive procedures, shared decision making and patient expectations are managed by plastic surgeons, indicating that patients need to be referred to a plastic surgeon for complete and correct information on IBR.

*Patient related contra-indications*

Surgical oncologists in another study considered age (37%) as a factor affecting the decision to refer patients to the plastic surgeon for IBR [28]. Age has been described in literature as a factor

significantly affecting the prevalence of IBR [11, 13-15, 19, 26], but also as a risk factor (age>55 years) for implant loss after IBR [29]. In the current study, we found that age was not considered as a major contra-indication by both professions, except for patients aged over 75 years, which was more frequently reported by plastic surgeons compared to surgical oncologists. A possible explanation for this finding may be the assumption that older patients prefer not to undergo IBR. Another reason may be that older patients generally have more comorbidities and are therefore less eligible for IBR, specifically for more complex autologous reconstructions with potentially higher risk of complications.

Smoking was considered an important contra-indication for all types of breast reconstruction by all physicians due to associated complications. In case of autologous reconstruction smoking leads to an increased risk of fat necrosis and wound healing problems, also of the donor-site[30], and in implant reconstruction an increased risk of implant loss due to wound healing problems and infections was found [29, 31]. It is therefore recommended to stop smoking 4-6 weeks prior to surgery [32].

We presume that plastic surgeons tended to report large breast size (>cup D) more frequently as contra-indication compared to surgical oncologists, because larger breast volume is known to be associated with an increased BMI and an increased risk of complications. As expected, morbid obesity affected the decision making process for all reconstructive techniques.[18, 19, 26] It is well-known from plastic surgery literature that obesity leads to an increased risk of complications of the reconstruction itself [29, 31, 33] and therefore it was not a surprise plastic surgeons more frequently regarded obesity as a contra-indication compared to surgical oncologists.

Comorbidities have been frequently reported in literature as contra-indications for IBR [18, 19, 29, 31, 34]. Plastic surgeons specifically reported cardiac and pulmonary comorbidities as contra-indications for autologous reconstruction because of the lengthy operative procedure with prolonged general anaesthesia time leading to an increased risk of postoperative medical complications in these patients. Previous cardiac surgery has been suggested to be a predictor of major surgical complications [29].

*Oncological related contra-indications*

Consistent with previous literature [18], advanced tumour stage (cT3) and tumour positive nodes (cN2) were important contra-indications according to both groups. However, surgical oncologists reported tumour and nodal stage more frequently as contra-indication compared to plastic surgeons. Potential reason could be that in cT4 tumours the skin is involved and should be excised as well as the need for radiotherapy of the chest wall, as well as in patients diagnosed with a T3N2 tumour. A survey among breast surgical oncologists and plastic surgeons in the UK reported that 26% of the surgical oncologists would not offer IBR in patients with stage IV disease [35]. Reasons were related to poor prognosis (31%), concerns about temporary cessation of systemic treatments (21%) and recovery time (17%) [35].

In the present study, (neo)-adjuvant therapies were not considered major contra-indications while literature suggests that adjuvant therapies such as chemotherapy and radiotherapy may affect IBR rates significantly [18, 22]. The question in our survey enquiring about neo-adjuvant and adjuvant therapies may have been phrased not clearly enough, with respondents assuming that only neo-adjuvant therapies were asked for. Surgical oncologists more often regarded adjuvant chemotherapy a contra-indication for IBR compared to plastic surgeons, presumably because of fear of delay in chemotherapy administration [28]. However, a recent systematic review showed no clinically relevant delay in chemotherapy administration if a patient has undergone IBR, irrespective of type of reconstruction [36].
Of the respondents who reported (neo)-adjuvant therapies as contra-indication, radiotherapy was considered a contra-indication specifically for implant reconstructions. Use of radiotherapy leads to a significantly higher reconstruction failure rate compared to if no radiotherapy is given [37], reason for plastic surgeons not to perform IBR [38]. Radiotherapy is less detrimental to autologous reconstructions [39] and it is therefore not surprising that in this situation it was considered a less important contra-indication for this type of reconstruction. Another study showed that 19% of surgical oncologists answered they did not refer patients to a plastic surgeon if adjuvant radiotherapy was indicated [28].

Our study had respondents from nearly all hospitals in the Netherlands, resulting in a large and representative sample of clinicians. Respondent characteristics differed slightly between surgical oncologists and plastic surgeons and may have affected their opinions on contra-indications. In addition, recall bias may have occurred since the information was based on self-reports. The result that 100% of the surgical oncologists reported to preoperatively discuss the possibility of IBR with their patients may possibly be an overestimation due to socially desirable answers. One might argue the omission of other factors described in literature in this survey like socioeconomic status and ethnicity. However, we expect that these factors did not have an impact on the considerations of Dutch clinicians to offer a patient IBR. In the Netherlands, all patients have a healthcare insurance plan and postmastectomy IBR is always fully reimbursed.

Our findings suggest there are multiple opinions on selecting patients for IBR. Information provision to patients and participation in decision-making should not vary considerably between hospitals or clinicians from different specializations and ideally should not affect IBR rates. Patient selection is crucial to achieve favourable aesthetic outcomes with improved quality of life and minimal complication rates. For every individual patient a new trade-off should be made based on her patient and oncological tumour characteristics and preferences, with some contra-indications more relevant compared to others. This process could be facilitated by evidence-based guidelines, patient decision aid tools and establishment of multidisciplinary teams, ultimately leading to consistent information provision from every discipline involved

and optimization of shared decision-making. An evidence-based, multidisciplinary breast reconstruction guideline is publicly available in English since 2015 to guide the decision making process and to provide the information needed, hopefully resulting in a reduction of variation in personal opinions of physicians towards IBR [38].

**Conclusions**

Reasons whether or not to perform IBR are multifactorial, with patient and tumour factors as most examined causes. The results of the current study gained insight into personal opinions of surgical oncologists and plastic surgeons towards IBR. The final decision to offer postmastectomy IBR was affected by multiple factors weighed differently by surgical oncologists and plastic surgeons involved. Oncological characteristics (tumour size and nodal status) were reported more frequently as contra-indication by surgical oncologists, while plastic surgeons mentioned risk factors and wound-associated problems (age >75, smoking in implant reconstructions, large breast size, BMI and comorbidities) more frequently.

Reaching consensus between surgical oncologists and plastic surgeons regarding contra-indications for IBR helps improving patient counselling and optimizing shared decision-making.

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**Conflict of interest**

The authors declare that they have no conflict of interest.

**Ethical approval**

For this type of study formal consent is not required.

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# Part III

Radiotherapy

# Chapter 4

## Variation in the use of boost irradiation in breast conserving therapy in the Netherlands

*Submitted*

K. Schreuder
J.H. Maduro
P.E.R. Spronk
N. Bijker
P.M.P. Poortmans
Th. van Dalen
H. Struikmans
S. Siesling

**Abstract**

**Introduction**

The purpose of this study was to determine the variation of radiotherapy boost use in a nationwide study following adjustment of a national guideline in 2011 as well as to address the relation to patient, tumor and radiotherapy institutional factors.

**Material and methods**

All invasive breast cancers (BC) and non-invasive breast cancers (DCIS) who received external whole breast radiation between 2011 and 2016 were selected from the Netherlands Cancer Registry. Box plots were used to evaluate variation over time and logistic regression was performed to address other factors influencing the variation. Funnel plots were constructed with unadjusted and adjusted data for patient and tumor factors significantly affecting the use of a boost.

**Results**

For BC patient (n=45,207) the proportion of patients receiving a boost and its range decreased over the years from 37.3-92.7% in 2011 to 28.3-65.4% in 2016. This trend was not observed in DCIS patients (n=6,844). Young age, large tumors, high grade, and non-radical surgical resection were associated with boost use for both BC and DCIS. For BC, triple-negative tumor subtype and metastatic lymph node involvement were also associated with boost use as well. Institutional factors did not influence the use of a boost and institutional variation remained substantial after case mix adjustments.

**Conclusion**

Following adjustment of a national guideline, variation in radiotherapy boost use decreased in patients with BC but not in patients with DCIS. Several tumor and patient characteristics were associated with boost use. Substantial institutional variation could not be explained by differences in patient, tumor or predefined institutional characteristics.

**Background**

Since the introduction of breast-conserving therapy (BCT) in the Netherlands in the early eighties of the last century, radiotherapy typically consisted of whole breast irradiation (WBI; 50 Gy or equivalent dose) followed by a boost to the tumor bed (16 Gy or equivalent dose) in all cases. Breast conserving surgery (BCS) is performed in 60% of invasive breast cancer (BC) patients and in 67% of patients with a ductal carcinoma in situ (DCIS) [1].

The debate about the clinical relevance of the use of a boost has a long history. Boost was applied in almost 100% of patients during the start of breast conserving therapy during the 1980s. This endorsed the European Organization for Research and Treatment of Cancer (EORTC) to start the "Boost/No Boost" trial in 1988 of which the 5-years results were published in 2001 [2]. Thereafter, a boost was gradually given less frequently [3].

In BC, boost use improved local control in all age groups after a median follow-up period of 17.2 years [2]. Patients 40 years and younger had the most benefit in absolute figures: at 10 years follow-up the LR rate was 23.9% without a boost, compared to 13.5% when a boost was given [4, 5]. On the other hand, patients with a boost had a significantly higher risk of severe fibrosis in comparison to patients who did not have a boost (4.4% vs 1.6%) [2, 4]. In a second EORTC trial the presence (or absence) of a dose effect relationship (10 Gy vs 26 Gy) was tested for BC patients with no tumor-free resection margins. No significant differences were noted after a median follow up period of 11.3 years [6].

Various studies demonstrate an independent effect of various clinicopathological on the risk of ipsilateral breast cancer recurrence and hence suggest that a number of these factors can be used to advise on the application of a boost [4, 7-9]. For DCIS, convincing evidence about efficacy of the use of a boost in combination with WBI is lacking, while the use of a boost is associated with a worse cosmetic outcome [10]. In Dutch clinical practice, large variation in the application of boost currently exists both for BC as well as for DCIS, which was demonstrated by nationwide data from the NABON breast cancer audit (NBCA) [1].

The desirability of clear guidelines in the use of the boost was acknowledged by the National Platform Radiotherapy for Breast cancer (LPRM), which listed recommendations on when a boost can be omitted in the treatment of BC in a 2011 guideline. The LPRM recommended that the benefits of a boost should be weighed against age, co-morbidity and the risk for adverse cosmetic effects and that it may be applied when one or more of the following indications is present: age <50 years, an estimated LR risk ≥1% per year, grade 3, positive tumor margins and lymph vascular space invasion [11].

The aim of the present study was to determine the effect on additional boosting following the introduction of the new Dutch guideline concerning boost irradiation. In addition, patient, tumor, and institutional factors that could explain variation of boost use in BC and DCIS patients were evaluated.

## Material and methods

*Data source*

Patients with primary stage I-III BC or DCIS were selected from the Netherlands Cancer Registry (NCR), which registers data for the NBCA. The NBCA is a national multidisciplinary quality improvement registry in which all hospitals (n=92) and departments of radiation oncology (n=21) in the Netherlands participate. It includes information concerning the patient, tumor, work-up, treatment and outcome. The information is collected prospectively since 2011 either by the hospital registrars or by data managers of the NCR, which is hosted by the Netherlands Comprehensive Cancer Organisation (IKNL). For this study data from all radiation oncology departments were obtained through the NCR.

*Study population*

Data gathered in all departments of radiation oncology (n=21) by the NCR were used and all female patients diagnosed with non-metastatic BC or DCIS between January 1st, 2011 and December 31st, 2016 who underwent BCS followed by radiotherapy were selected. Patients could be included several times, due to multiple diagnosed and treated tumors.

*Statistical analyses*

Analyses for BC and DCIS cases were conducted separately. Analysis was performed on a tumor level, rather than on a patient level. Boxplots were constructed to demonstrate the variation in department dependent use of a boost over time. Multilevel logistic regression analyses were used to test factors influencing the use of a boost, taking patient clustering within hospitals into account. Factors that were tested were: age (<50, 50-60, 60-70, >70 years), pathological tumor size (<10, 10-20, 20-30, >30 mm), DCIS component: the presence of ductal carcinoma in situ adjacent to the invasive part of the tumor, histological type (ductal, lobular, mixed, other), tumor grade according to Bloom Richardson (grade 1, 2, 3), triple negativity (no or yes), Her2 receptor status (negative, positive), tumor resection margins (clear margins, tumor not touching ink (R0), close margins, microscopic residual disease and macroscopic residual disease, R1 and R2 respectively) and tumor involvement of lymph nodes (no, yes or unknown). Lymph vascular space invasion was not taken into account in this study, since this item was not registered systematically. We also investigated whether the type of radiation oncology department (university, independent or hospital related) and mean number of BC patients treated annually (low: <450 patients, medium: 450-650, high: >650) was associated with boost use. Patient, tumor and departmental factors in relation to the use of a boost, were presented as odds ratios for the respective categories of these factors with 95% confidence intervals (95%CIs). Factors that were significantly associated with the use of a boost in univariable analyses ($p < 0.05$) were subsequently analyzed in the multivariable analyses. Funnel plots were constructed with unadjusted and adjusted data for patient and tumor factors significantly affecting the use of a boost. All statistical analyses were performed in STATA (version 13.1 2013, Texas).

**Results**

*Study population*

During the study period, 52,051 tumors of 50,116 patients were included and treated with WBI for BC stage (n=45,207) as well as for DCIS (n=6,844) after BCS. Patient and tumor characteristics are shown in table 1. The majority of patients was aged >50 years and older and had pathologically assessed tumor sizes ranging from 0-20 mm. For BC and DCIS, most patients had a grade-2 or grade-3 tumor. More than 90% of the cases who underwent surgery for both BC and DCIS had clear margins (R0). For BC, 74.3% of the cases had no lymph node involvement. In total, 50.6% of the BC patients received a boost and 45.7% of the DCIS patients (Table 1).

*Variation*

Variation in the application of a boost between the 21 departments was observed for both BC and DCIS. Over the years 2011-2016, the proportion of patients receiving a boost and the accompanying institutional variation of boost use in BC decreased. The median annual proportion of patients who received a boost decreased from 55.3% in 2011 to 43.5% in 2016 and the institutional proportion decreased from 37.3 to 92.7% in 2011 and from 28.3 to 65.4% in 2016 (Figure 1). For DCIS, both overall use (41.9% in 2011, 40.7% in 2016) as well as institutional variation (4.6-100.0% in 2011 to 0.0-80.5% in 2016) hardly varied over time (Figure 1).

*Breast cancer*

Factors significantly influencing the use of a boost for BC in univariable analyses are listed in table 2. After multivariable logistic regression analyses, all patient- and tumor- related factors remained statistically significant, except histological type (Table 2). Patients >70 years received a boost significantly less often in comparison with patients aged <50 years. Larger tumors and tumors of higher malignancy grade were associated with more frequent use of a boost. Presence of ductal carcinoma in situ (DCIS) adjacent to the invasive tumor was also positively associated with the use of a boost. In patients with unfavorable molecular subtype tumors (triple-negative and Her2-positive tumors) a boost was also administered more often and microscopic incomplete tumor resection margins were also strongly associated with the use of a boost. Finally, involved lymph nodes were also positively related with the use of a boost compared to no lymph involvement. Departmental patient volume and hospital type did not affect the proportion of patients who received a boost.

Age, DCIS component, grade, triple negativity, tumor resection margin and lymph node involvement, were positively associated with the use of a boost in 2011 as well as in 2016, but the association was more pronounced in 2016. In 2016, tumor size was significantly influencing the use of boost that was not the case in 2011. For Her2-positive tumors a significant positive association in the use of a boost was found in 2011 only.

Figure 2 displays the variation between the departments of radiation oncology for the use of

**Table 1.** *Baseline characteristics of all 52,051 invasive BC or DCIS lesions included in this study*

| | | Study population (n=52,051) | | | |
|---|---|---|---|---|---|
| | | Invasive BC (n=45,207) | | DCIS (n=6,844) | |
| | | number | % | number | % |
| **Boost** | *no* | 22,337 | 49.4% | 3,718 | 54.3% |
| | *yes* | 22,870 | 50.6% | 3,126 | 45.7% |
| **Age (years)** | *0-50* | 9,680 | 21.4% | 1,058 | 15.5% |
| | *50-60* | 12,557 | 27.8% | 2,363 | 34.5% |
| | *60-70* | 15,088 | 33.4% | 2,471 | 36.1% |
| | *>70* | 7,882 | 17.4% | 952 | 13.9% |
| **Size (mm)** | *0-10* | 14,949 | 33.1% | 1,387 | 20.3% |
| | *10-20* | 21,366 | 47.3% | 1,067 | 15.6% |
| | *20-30* | 6,735 | 14.9% | 519 | 7.6% |
| | *>30* | 1,527 | 3.4% | 329 | 4.8% |
| | *Unknown* | 630 | 1.4% | 3,542 | 51.8% |
| **DCIS component** | *No* | 23,019 | 50.9% | - | - |
| | *Yes* | 22,148 | 49.0% | - | - |
| | *Unknown* | 40 | 0.1% | - | - |
| **Histological type** | *Ductal* | 38,268 | 84.7% | - | - |
| | *Lobular* | 3,852 | 8.5% | - | - |
| | *Mixed* | 981 | 2.2% | - | - |
| | *Other* | 2,106 | 4.7% | - | - |
| **Grade** | *1* | 12,541 | 27.7% | 840 | 12.3% |
| | *2* | 19,243 | 42.6% | 2,595 | 37.9% |
| | *3* | 10,064 | 22.3% | 3,131 | 45.7% |
| | *Unknown* | 3,359 | 7.4% | 278 | 4.1% |
| **Triple negative** | *No* | 40,656 | 89.9% | - | - |
| | *Yes* | 4,551 | 10.1% | - | - |
| **Her2** | *Negative* | 39,477 | 87.3% | - | - |
| | *Positive* | 4,766 | 10.5% | - | - |
| | *Dubious* | 141 | 0.3% | - | - |
| | *Unknown* | 823 | 1.8% | - | - |
| **Tumor resection margin** | *R0* | 42,475 | 94.0% | 6,264 | 91.9% |
| | *R1* | 2,364 | 5.2% | 474 | 6.9% |
| | *R2* | 160 | 0.4% | 36 | 0.5% |
| | *Unknown* | 208 | 0.5% | 70 | 1.0% |
| **Involved lymph nodes** | *No* | 33,590 | 74.3% | - | - |
| | *Yes* | 10,652 | 23.6% | - | - |
| | *Unknown* | 965 | 2.1% | - | - |

a boost for BC. Following case-mix adjustments for patient and tumor factors (age, tumor size, DCIS component, grade, triple negativity, Her2-positive tumor, tumor resection margin, pathological lymph node involvement) institutional variation remained significant (40.0–68.2%).

*DCIS*

Factors significantly influencing the use of a boost for DCIS in univariable analyses are displayed in table 3. In the multivariable logistic regression analyses, most significant univariable factors remained statistically significant (Table 3). Patients >70 years had a significantly lower chance to receive a boost in comparison with patients <50 years. The probability of receiving a boost decreased with increasing age. Patients with a pathologically assessed size of DCIS >1 cm had an increased risk of receiving a boost compared to patients with a lesion <1 cm. The probability of receiving a boost increased as tumor size increased. Grade-3 lesions were strongly associated with an increased use of a boost compared to grade-1 lesions. Microscopic positive tumor resection margins were strongly positively associated with the use of a boost compared to tumor-free resection margins.

All lesions and patient related factors were positively related with the use of a boost from 2011 throughout 2016, but for almost all factors these associations were higher in 2016. As for BC, case-mix adjustments for patient and lesion factors (age, tumor size, grade, tumor resection margin) decreased the variation between departments in the use of a boost for DCIS only marginally (data not shown).

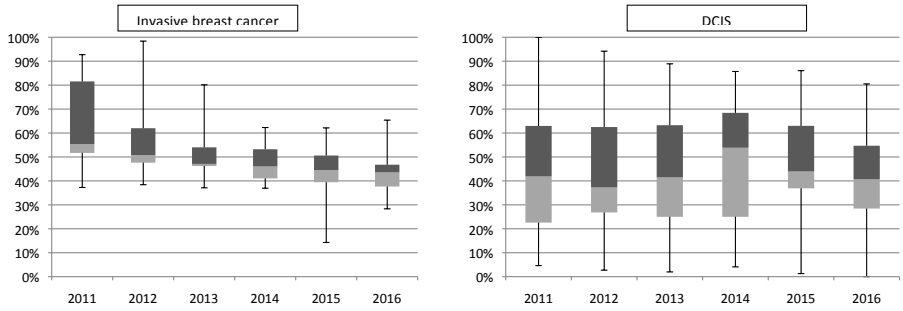


**Figure 1.** *Variation in the use of boost irradiation over the period 2011-2016 after breast conserving therapy for non-metastatic invasive breast cancer (left) and DCIS (right)*

**Table 2.** *Patient and tumor related factors determining the use of boost irradiation for non-metastatic invasive breast cancers lesions (n=45,207) for the whole period 2011-2016 and 2011 and 2016 separately*

| Boost irradiation for non-metastatic invasive breast cancer | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 2011-2016 (n=45,207) | | | | 2011 (n=7,048) | | 2016 (n=7,697) | |
| | | | | | Univariable | | Multivariable | | Multivariable | | Multivariable | |
| | | Boost | % | Total | OR | 95% CI | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| *Patient/tumor characteristics* | | | | | | | | | | | | |
| **Age (years)** | *0-50* | 8,232 | 85.0% | 9,680 | ref | | ref | | ref | | ref | |
| | *50-60* | 6,439 | 51.3% | 12,557 | 0.18 | 0.16-0.19 | **0.17** | 0.16-0.18 | **0.30** | 0.25-0.36 | **0.11** | 0.10-0.14 |
| | *60-70* | 5,912 | 39.2% | 15,088 | 0.10 | 0.10-0.11 | **0.10** | 0.09-0.11 | **0.17** | 0.14-0.21 | **0.07** | 0.06-0.08 |
| | *>70* | 2,287 | 29.0% | 7,882 | 0.07 | 0.06-0.07 | **0.05** | 0.05-0.06 | **0.06** | 0.05-0.08 | **0.05** | 0.04-0.06 |
| **Size (mm)** | *0-10* | 6,553 | 43.8% | 14,949 | ref | | ref | | ref | | ref | |
| | *10-20* | 10,777 | 50.4% | 21,366 | 1.28 | 1.23-1.34 | **1.16** | 1.10-1.22 | 0.97 | 0.84-1.11 | **1.37** | 1.19-1.58 |
| | *20-30* | 4,185 | 62.1% | 6,735 | 2.04 | 1.92-2.17 | **1.33** | 1.24-1.44 | 1.05 | 0.86-1.28 | **1.56** | 1.28-1.90 |
| | *>30* | 1,018 | 66.7% | 1527 | 2.53 | 2.26-2.84 | **1.62** | 1.41-1.87 | 0.99 | 0.67-1.45 | **2.66** | 1.87-3.78 |
| | *Unknown* | 337 | 53.5% | 630 | 1.53 | 1.31-1.80 | 0.95 | 0.77-1.16 | **0.55** | 0.33-0.92 | 1.68 | 0.90-3.11 |
| **DCIS component** | *No* | 10,581 | 46.0% | 23,019 | ref | | ref | | ref | | ref | |
| | *Yes* | 12,273 | 55.4% | 22,148 | 1.47 | 1.41-1.52 | **1.66** | 1.58-1.74 | **1.45** | 1.28-1.64 | **1.95** | 1.72-2.22 |
| | *Unknown* | 16 | 40.0% | 40 | 0.92 | 0.49-1.75 | 0.48 | 0.22-1.07 | **0.18** | 0.05-0.59 | | |
| **Histological type** | *Ductal* | 19,917 | 52.0% | 38,268 | ref | | ref | | ref | | ref | |
| | *Lobular* | 1,539 | 40.0% | 3,852 | 0.61 | 0.57-0.65 | 0.92 | 0.84-1.00 | 1.10 | 0.88-1.38 | 0.93 | 0.74-1.15 |
| | *Mixed* | 462 | 47.1% | 981 | 0.85 | 0.75-0.97 | 0.99 | 0.85-1.16 | 1.05 | 0.71-1.54 | 0.88 | 0.59-1.32 |
| | *Other* | 952 | 45.2% | 2,106 | 0.76 | 0.69-0.83 | 1.06 | 0.95-1.18 | 1.08 | 0.81-1.44 | 0.94 | 0.71-1.26 |
| **Grade** | *1* | 4,387 | 35.0% | 12,541 | ref | | ref | | ref | | ref | |
| | *2* | 8,163 | 42.4% | 19,243 | 1.36 | 1.30-1.43 | **1.25** | 1.18-1.32 | 1.13 | 0.98-1.31 | **1.28** | 1.10-1.49 |
| | *3* | 8,200 | 81.5% | 10,064 | 8.54 | 8.01-9.10 | **8.21** | 7.59-8.88 | **3.68** | 3.00-4.50 | **13.42** | 10.96-16.44 |
| | *Unknown* | 2,120 | 63.1% | 3,359 | 3.27 | 3.02-3.55 | **2.43** | 2.20-2.68 | **1.73** | 1.33-2.25 | **2.26** | 1.63-3.15 |

| Table 2 continued. | | Boost irradiation for non-metastatic invasive breast cancer | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 2011-2016 (n=45,207) | | | | 2011 (n=7,048) | | 2016 (n=7,697) | |
| | | | | | Univariable | | Multivariable | | Multivariable | | Multivariable | |
| | | Boost | % | Total | OR | 95% CI | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| **Triple negative** | No | 19,480 | 47.9% | 40,656 | ref | | ref | | ref | | ref | |
| | *Yes* | 3,390 | 74.5% | 4,551 | 3.28 | 3.05-3.51 | **1.41** | 1.28-1.54 | **1.36** | 1.07-1.73 | **1.81** | 1.43-2.27 |
| **Her2** | *Negative* | 19,350 | 49.0% | 39,477 | | | | | ref | | ref | |
| | *Positive* | 3,164 | 66.4% | 4,766 | 2.08 | 1.95-2.22 | **1.14** | 1.05-1.24 | **1.65** | 1.33-2.04 | 0.96 | 0.78-1.18 |
| | *Dubious* | 61 | 43.3% | 141 | 0.88 | 0.63-1.24 | 1.09 | 0.72-1.65 | 1.77 | 0.60-5.23 | 0.99 | 0.28-3.45 |
| | *Unknown* | 295 | 35.8% | 823 | 0.55 | 0.47-0.64 | **0.77** | 0.64-0.91 | 0.91 | 0.58-1.43 | **0.52** | 0.31-0.87 |
| **Tumor resection margin** | *R0* | 20,447 | 48.1% | 42,475 | ref | | ref | | ref | | ref | |
| | *R1* | 2,159 | 91.3% | 2,364 | 11.86 | 10.25-13.71 | **21.54** | 18.45-25.15 | **12.17** | 8.12-18.25 | **51.74** | 34-52-77.55 |
| | *R2* | 129 | 80.6% | 160 | 5.09 | 3.43-7.56 | **8.98** | 5.80-13.90 | **4.52** | 1.65-12.34 | **13.28** | 4.88-36.12 |
| | *Unknown* | 135 | 64.9% | 208 | 1.99 | 1.49-2.65 | **1.63** | 1.15-2.29 | 1.75 | 0.68-4.51 | 1.39 | 0.44-4.32 |
| **Involved lymph nodes** | *No* | 15,905 | 47.4% | 33,590 | ref | | ref | | ref | | ref | |
| | *Yes* | 6,508 | 61.1% | 10,652 | 1.75 | 1.67-1.83 | **1.42** | 1.34-1.50 | **1.28** | 1.11-1.48 | **1.40** | 1.21-1.62 |
| | *Unknown* | 457 | 47.4% | 965 | 1.04 | 0.91-1.19 | **1.25** | 1.07-1.46 | **2.02** | 1.15-3.55 | **1.55** | 1.13-2.14 |
| *Department characteristics* | | | | | | | | | | | | |
| **Department of radiation oncology type** | *University* | 11,565 | 50.9% | 22,705 | ref | | | | | | | |
| | *Independent* | 7,641 | 51.3% | 14,884 | 1.12 | 0.80-1.56 | | | | | | |
| | *Hospital related* | 3,664 | 48.1% | 7,618 | 0.86 | 0.62-1.20 | | | | | | |
| **Department of radiation oncology volume (patients treated yearly)** | *Low* | 8,237 | 51.3% | 16,061 | ref | | | | | | | |
| | *Medium* | 7,546 | 50.3% | 15,001 | 1.02 | 0.73-1.42 | | | | | | |
| | *High* | 7,087 | 50.1% | 14,145 | 1.01 | 0.69-1.48 | | | | | | |

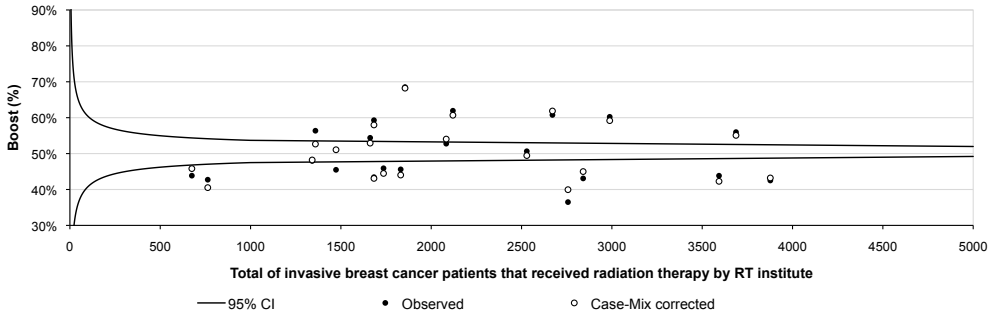


**Figure 2.** *Variation in the use of boost irradiation after breast conserving therapy for invasive breast cancer in the Netherlands over the years 2011-2016, with and without case-mix adjustment (for age, tumor size, DCIS component, grade, triple negativity, Her2-positive tumor, tumor resection margin, pathological lymph node involvement) (n=45,207)*

**Discussion**

In the present study considerable variation was observed in the use of a radiation boost after BCT for both BC and DCIS between the 21 departments of radiation oncology in the Netherlands and was not attributable to patient or tumor characteristics. Following the implementation of a national guideline for boost use in patients with invasive cancers, the use and variation of administered boost decreased for BC, but remained unchanged for DCIS.

Guidelines suggest using a boost for patients for whom a substantial decrease in the local recurrence rate is expected and a boost should only be offered to high-risk patients [7, 11]. Various factors are known to be associated with the risk of local recurrences, including young age and grade-3 disease [12]. Moreover, previous studies demonstrated that tumor size and lymph node involvement are significantly related to local recurrence rates and could be predictors of distant metastases [16, 18]. Also the width of the tumor-free margins significantly influence the ipsilateral breast tumor recurrence (IBTR) rate [13,14]. The observed variation illustrates that clinicians do not agree when clinically meaningful reductions can be expected.

We demonstrated that young age and grade-2 and 3 disease were related with an increased use of a boost. For both DCIS and BC, patients aged younger than 51 years received a boost significantly more often. We also demonstrated for both DCIS and BC that grade-3 and grade-2 tumors, when compared to grade-1 tumors, were related with the use of a boost.

**Table 3.** Patient and tumor related factors determining the use of boost irradiation for DCIS (n=6,844) for the whole period 2011-2016 and 2011 and 2016 separately

| | | Boost irradiation for DCIS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 2011-2016 (n=6,844) | | | | 2011 (n=1,004) | | 2016 (n=1,153) | |
| | | | | | Univariable | | Multivariable | | Multivariable | | Multivariable | |
| | | Boost | % | Total | OR | 95% CI | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| *Patient/tumor characteristics* | | | | | | | | | | | | |
| **Age (years)** | *0-50* | 595 | 56.2% | 1,058 | ref | | ref | | ref | | | |
| | *50-60* | 1,190 | 50.4% | 2,363 | 0.76 | 0.64-0.90 | **0.63** | 0.52-0.75 | **0.63** | 0.48-0.82 | **0.77** | 0.49-1.20 |
| | *60-70* | 1,048 | 42.4% | 2,471 | 0.51 | 0.43-0.60 | **0.39** | 0.32-0.46 | **0.45** | 0.35-0.59 | **0.34** | 0.22-0.54 |
| | *>70* | 293 | 30.8% | 952 | 0.26 | 0.21-0.32 | **0.16** | 0.13-0.21 | **0.18** | 0.13-0.26 | **0.19** | 0.11-0.33 |
| **Size (mm)** | *0-10* | 520 | 37.5% | 1,387 | ref | | ref | | ref | | ref | |
| | *10-20* | 504 | 47.2% | 1,067 | 1.74 | 1.45-2.09 | **1.63** | 1.34-1.99 | | | **1.80** | 1.23-2.64 |
| | *20-30* | 290 | 55.9% | 519 | 2.71 | 2.15-3.42 | **2.20** | 1.70-2.85 | | | **2.23** | 1.40-3.57 |
| | *>30* | 192 | 58.4% | 329 | 3.11 | 2.36-4.10 | **2.45** | 1.81-3.33 | | | **2.41** | 1.38-4.20 |
| | *Unknown* | 1,620 | 45.7% | 3,542 | 1.48 | 1.28-1.71 | **1.34** | 1.15-1.57 | | | 1.08 | 0.65-1.81 |
| **Grade** | *1* | 279 | 33.2% | 840 | ref | | ref | | ref | | ref | |
| | *2* | 1,101 | 42.4% | 2,595 | 1.50 | 1.25-1.80 | **1.72** | 1.40-2.10 | 1.32 | 0.80-2.18 | **3.01** | 1.66-5.44 |
| | *3* | 1,666 | 53.2% | 3,131 | 2.81 | 2.35-3.37 | **3.46** | 2.83-4.23 | **2.50** | 1.53-4.10 | **7.25** | 4.00-13.15 |
| | *Unknown* | 80 | 28.8% | 278 | 0.79 | 0.57-1.10 | 1.07 | 0.75-1.53 | 1.03 | 0.43-2.45 | 1.29 | 0.36-4.57 |
| **Tumor resection margin** | *R0* | 2,624 | 41.9% | 6,264 | ref | | ref | | ref | | ref | |
| | *R1* | 431 | 90.9% | 474 | 19.18 | 13.59-27.07 | **26.47** | 18.42-38.04 | **26.22** | 9.79-70.18 | **37.79** | 10.84-83.40 |
| | *R2* | 31 | 86.1% | 36 | 8.72 | 3.28-23.17 | **11.90** | 4.25-33.36 | **11.30** | 1.07-118.99 | omitted | |
| | *Unknown* | 40 | 57.1% | 70 | 1.98 | 1.15-3.41 | **2.24** | 1.28-3.93 | 1.61 | 0.27-9.78 | **17.31** | 2.86-104.85 |

| Table 3 continued. | | Boost irradiation for DCIS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 2011-2016 (n=6,844) | | | | 2011 (n=1,004) | | 2016 (n=1,153) | |
| | | | | | Univariable | | Multivariable | | Multivariable | | Multivariable | |
| | | Boost | % | Total | OR | 95% CI | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| *Department characteristics* | | | | | | | | | | | | |
| **Department of radiation oncology type** | University | 1,485 | 42.2% | 3,515 | ref | | ref | | | | | |
| | *Independent* | 1,109 | 51.4% | 2,157 | 1.58 | 0.50-5.05 | | | | | | |
| | *Hospital related* | 532 | 45.4% | 1,172 | 1.33 | 0.42-4.27 | | | | | | |
| **Department of radiation oncology volume (patients treated yearly)** | *Low* | 1,052 | 43.5% | 2,421 | ref | | ref | | | | | |
| | *Medium* | 873 | 37.8% | 2,310 | 0.69 | 0.23-2.08 | | | | | | |
| | *High* | 1,201 | 56.8% | 2,113 | 1.61 | 0.46-5.68 | | | | | | |

Our study showed a significant positive association between larger tumor sizes and the use of a boost for both BC and DCIS. For BC, we also demonstrated a positive association between positive lymph nodes and the application of a boost. In the current study we also demonstrated an almost 22- and 26-fold higher use of a boost in patients with microscopically positive resection margins for BC or DCIS, respectively. In Dutch clinical practice a re-excision is replaced by a radiotherapy boost after a microscopically (R1) focally involved tumor-positive resection margin.

Following case-mix correction for the aforementioned clinicopathological factors, considerable variation remained in BC patients that was neither explained by institutional characteristics such as patient volume and academic orientation of a particular institute. Some patient and tumor factors may have impacted boost use such as comorbidity, precluding extension of the radiotherapy treatment and lymph vascular, but information regarding these factors were not available.



Apparently, institutional differences exist regarding what is considered a clinically meaningful reductions in risk of local recurrences. Departmental policies, (non-) adherence to risk prediction tools and doctor's preferences likely contribute to the observed variation between the departments, albeit that data to support this are not available. Surgery-associated considerations could have contributed as well, e.g. the individually-based omission of the boost if the target volume could not be reconstructed reliably following extensive surgery or in the presence of a large seroma of hematoma [17].

Over time, we observed an overall decrease of boost administration and a decrease in the departmental variation. Factors that constitute an indication for applying a boost based on the new guidelines introduced in 2011 were associated more strongly with the use of a boost in 2016 compared to 2011, illustrating the adherence to newly introduced guidelines and the waning hypothesized influence of departmental policies.

The absence of phase-III trials concerning the efficacy of a boost dose for DCIS probably explains why the observed large variation remained unchanged over the years and the implemented guideline did not take contain guidelines for boost use in DCIS.

Uniform risk prediction tools could possibly contribute to a further reduction in the variation in the use of boost between the departments. A recent study demonstrating decreasing IBTR rates from 3.2 to 2.4 in 5 years (2003-2008) accompanying the increased use of systemic treatment [18] might lead to a reconsideration of risk factors in particular appreciating the role of molecular subtype. This systemic treatment associated relative 30 percent risk reduction casts doubt on the additional benefit of using a boost in breast cancer patients. On the other hand,

patient factors such as severe co-morbidity and different approaches in involving the patient in the process of shared decision making may be associated with persisting variation that may be to some extent desirable. Bartelink et al. already propagated that the expected gain in local control and the negative cosmetic effects should be discussed with the patients on an individual base [4].

The population-based character of the present study is unique and provides insight in the overall use of a boost in daily practice in all 21 departments of radiation oncology in the Netherlands after the introduction of the guideline. However, we have to mention some drawbacks of the study. We were not able to avoid the risk of confounding by severity. Due to incomplete registration of tumor sizes for DCIS in certain years, we had to deal with missing tumor sizes in especially 2011.

The NBCA dataset offered a unique opportunity to monitor the use of boost radiation in the upcoming years. Based on this data it was possible to examine whether or not the factors demonstrated in this study indeed fully explained the variation on longer term. Further research should identify doctors' attitudes towards and patients' preferences regarding the use of a boost and whether these factors explain the variation.

**Conclusion**

In the Netherlands, a substantial variation between departments of radiation oncology was found for the use of a boost to the primary tumor bed in the framework of BCT in patients bearing BC and DCIS. This variation could not completely be explained by patient- , tumor- or department-related characteristics. For BC, we found that the use of a boost decreased (further) over time.

**Ethics approval and consent to participate**

According to the Central Committee on Research involving Human Subjects (CCMO), this type of study does not require the approval from an ethics committee in the Netherlands. This study was approved by the Privacy Review Board of the Netherlands Cancer Registry.

**Availability of data and materials**

The data that support the findings of this study are available from Netherlands Comprehensive Cancer Organisation but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Netherlands Comprehensive Cancer Organisation.

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**Competing interests**
The authors do not declare any conflicts of interest.

**Authors contribution**
KS analyzed the data. All authors interpreted the results. All authors were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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# Chapter 5

An actualised population-based study on the use of primary radiation therapy in breast cancer patients in the Netherlands

*Submitted*

K. Schreuder
J.G. Middelburg
M.J. Aarts
J.W.S. Merkus
P.M.P. Poortmans
J.J. Jobsen
S. Siesling
H. Struikmans

**Abstract**

**Purpose**

Radiation therapy (RT) is an important component of primary treatment of breast cancer patients. We investigated the use of primary RT for all invasive breast cancer patients in the Netherlands focussing specifically on time trends, age effects and type of surgery.

**Methods**

Data of all primary invasive non-metastatic breast cancers patients diagnosed between 2011 and 2015 were selected from the Netherlands Cancer Registry. Trends over time in the use of RT were described. Logistic regression was performed to determine factors associated with the use of RT after breast-conserving surgery (BCS) and mastectomy.

**Results**

Over the period 2011-2015 the utilization rate of RT increased from 64.4% to 70.3% for all patients and from 26.6% to 34.9% for patients aged over 75 years. After BCS and mastectomy, 97.3% and 26.1% of the patients received RT, respectively. For patients undergoing BCS, younger age, screen detection and ER+ tumours, diagnoses in 2011 and in specific regions were positively associated with higher RT utilisation rates. After mastectomy, younger age, larger tumour sizes, lymph node involvement, grade-2 and 3 tumours, ER+ tumours, diagnosis in more recent years, diagnosis in specific regions and higher hospital specific lump rates, were associated with higher RT utilization rates.

**Conclusion**

From 2011 till 2015 an increase in the use of RT was observed and was specifically associated by the finding that more patients underwent RT after mastectomy. An even stronger increase was observed for patients aged over 75 years.

**Introduction**

Radiation therapy (RT) is an important part in the treatment of breast cancer patients. The Dutch treatment guidelines, initially published in 2002, advice to deliver whole breast irradiation for all patients after breast-conserving surgery (BCS) and in stage III after mastectomy [1, 2].

International population-based data demonstrated significant variation in the use of RT in breast cancer patients and underutilization of RT is observed worldwide [3-10]. Also in studies focussing specifically on European countries, for example Belgium and Sweden, variation in the use of RT is observed and the utilization rate of RT is lower when compared with the reported calculated optimum [3, 8].

In the period 1997-2008 the use of RT for breast cancer in the Netherlands increased, regionally ranging from 55–61% in 1997 to 58–68% in 2008 and was associated with an increased use of BCS [11]. In this period, a decrease in the variation in utilization rates of RT between the various regions was observed, both after BCS and after mastectomy [11]. The authors attributed their findings to the implementation of the nationwide evidence-based breast cancer treatment guidelines in 2002 [1]. However, the current situation in The Netherlands is unknown and in 2008 a revision of the nationwide guidelines was published [1].



We, therefore, decided to investigate the use of RT for all invasive breast cancer patients in the Netherlands focussing particularly on time trends, age effects and type of surgery. Now it was possible to include all Dutch breast cancer patients, whereas in the former study about 50% of the Dutch (breast cancer) population were included [11].

**Material and methods**

*Data source*

Patients with primary invasive breast cancer were selected from the Netherlands Cancer Registry, covering all hospitals (n=92) and departments of radiation oncology in the Netherlands. It includes information concerning the patient, tumour, diagnostics and treatment. Trained data managers of the Netherlands Comprehensive Cancer Organisation (IKNL) collect the data prospectively.

*Study population*

All female patients diagnosed with first primary non-metastatic invasive breast cancer between January 1$^{st}$, 2011 and December 31$^{st}$, 2015 were included. The following five regions were identified based on the locations of former Dutch Comprehensive cancer centres and comparable breast cancer patient numbers; North-East, South, Amsterdam, West, Central. Patients were assigned a region according to the hospital of diagnosis.

*Statistical Analyses*

Trends over time in the use of different treatment combinations were analysed separately for all ages combined and those aged >75. The cut-off of >75 years was chosen, since patients aged 50-75 are invited for the nationwide breast cancer screening programme. Utilisation rates of RT were assessed for four different patients groups; patients treated with BCS (with and without primary systemic therapy (PST)) and for those treated with mastectomy (with and without PST).

Mastectomy was defined as a modified radical mastectomy, a simple mastectomy or any type of mastectomy primarily or directly following BCS. BCS and mastectomy included also axillary lymph node staging using either the sentinel node procedure (SNB) or axillary lymph node dissection (ALND) in the presence of lymph node metastases or when the SNB was not feasible [12].

Logistic regression analyses were performed separately for BCS and mastectomy to test which of the variables significantly influenced the use of RT. Patients who were treated with chemotherapy prior to surgical treatment were excluded from logistic regression analysis as PST influences pathologically assessed tumour characteristics. Variables that were tested were; age (0-49, 50-65, 66-75, 76-85, >85), socio economic status (SES; high, medium, low [13]), screen-detected tumours (diagnosis as a consequence of the breast cancer screening programme: no, yes, not applicable (for patients aged <50 and >75) or unknown), pathological tumour size (<11mm, 11-20 mm, 21-30 mm, >30 mm or unknown), number of positive lymph nodes (0, 1-3, >3), tumour grade according to Bloom Richardson (grade 1, 2 or 3), Her2, oestrogen (ER), progesterone (PR) receptor status (negative, positive or unknown), year of diagnosis (2011 - 2015), hospitals of diagnosis were clustered into anonymized regions (A, B, C, D and E) and hospital specific ratio of BCS (lump rate) defined by the number of BCS cases divided by the total number of BCS and mastectomy added together and categorized (<40%, 40-50%, 51-60%, >60%). We used pathologically assessed tumour sizes and lymph node involvement (if unknown, clinical tumour size was used). Factors that were significantly associated with the use of RT in univariable analyses ($p<0.05$) were subsequently included in the multivariable model. Analyses were performed in STATA (version 13.1 2013, Texas).

**Results**

*Study population*

The number of breast cancer patients increased from 13,443 in 2011 to 13,671 in 2015 (total n=68,271, Table 1). Mean age at diagnosis was 61.2 years. Most patients (81.3%) received no PST. Of all patients, 46.7% underwent a combination of surgery, RT and systemic therapy, varying over the regions between 44.4-51.0%. Most patients underwent BCS, varying over the regions between 52.1– 60.4% (mean 56.0%) (Table 1).

*Breast conserving surgery (BCS) and mastectomy (with and without PST)*

Over the years, an overall increase in utilization rate of RT was observed; from 64.4% in 2011 to 70.3% in 2015 (Figure 1). This increase consisted of 2.3% more patients receiving surgery in combination with RT and 3.6% more patients receiving surgery, RT and systemic therapy. The utilization rate of RT increased in particularly for patients >75 years: with 8.3% (from 26.6% in 2011 to 34.9% in 2015). For these patients, the increase was composed by 3.6% more patients undergoing surgery and RT and 4.2% undergoing surgery, RT and systemic therapy (residual increase caused by 0.5% more patients treated with RT only) (Figure 2).

From 2011 till 2015, a decrease of 0.6% was observed in the utilization rate of RT for patients treated with BCS (with or without PST) and an increase of 8.4% for patients treated with mastectomy (with or without PST).

Over the same period, for patients >75 years, an increase in the utilization rate of RT of 3.4% was observed after BCS (with or without PST) and of 7.7% after mastectomy (with or without PST).

After BCS, comparable utilization rates were observed for patients who did or did not receive PST (Table 2). For patients treated with mastectomy without PST an increase in the use of RT was observed from 23.5% in 2011 to 29.1% in 2015. For patients who received PST prior to mastectomy, a decrease in the use of RT was observed from 80.0% in 2011 to 67.1% in 2015 (Table 2).



*Breast conserving surgery (BCS) without primary systemic therapy (PST)*

In total 34,286 patients underwent BCS (without PST) and a mean utilization rate of 97.3% RT was observed over the years 2011 and 2015. Univariable analysis demonstrated that lower age (≤75 years); screen detected breast cancers; small tumour sizes (ranging from 0-10 mm); no lymph node involvement, grade-1 tumours, ER+/PR+ tumours; diagnosis in 2011 and region A were associated with a higher use of RT over the period 2011 to 2015 (Table 3).

Multivariable logistic regression, table 3, demonstrated that elderly patients aged 76-85 years (RT use: 90.7%, odds ratio (OR)= 0.31, 95%CI: 0.24-0.39) and >85 years (RT use: 50.9%, OR= 0.04, 95%CI: 0.03-0.06) were significantly less likely to undergo RT than patients aged <50 years (RT use: 97.4%). Patients bearing screen detected breast cancers were more likely to be treated with RT compared to those diagnosed with non-screen breast cancers (OR= 2.10, 95%CI: 1.72-2.56). Those with ER+ tumours were associated with higher utilization rates (OR= 1.38, 95%CI: 1.05-1.81) compared to those with ER- tumours. A significant lower utilization rate is found in 2015 (OR= 0.72, 95%CI: 0.58-0.90) compared to 2011 (96.7% versus 97.4%). For the other years, no significant association is found. One region in the Netherlands was characterized with significant lower RT rates (96.8% versus 97.8%); region D (OR= 0.79, 95%CI: 0.64-0.99), compared to region A. The other factors, number of positive lymph nodes, grade and PR status did not show statistical significance anymore in multivariable analyses (Table 3).

**Table 1.** *Patient, tumour and treatment characteristics of patients diagnosed with breast cancer per region over the years 2011-2015 (n=68,271)*

| | | Region | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Region A (n=14,498) | Region B (n=13,465) | Region C (n=12,930) | Region D (n=15,554) | Region E (n=11,824) | Total (n=68,271) | p-value |
| **Primary systemic therapy** | *no* | 84.4% | 78.9% | 75.2% | 83.7% | 83.6% | 81.3% | |
| | *yes* | 9.1% | 14.5% | 18.0% | 10.4% | 11.2% | 12.5% | |
| | *no surgery* | 6.5% | 6.7% | 6.9% | 5.9% | 5.2% | 6.2% | p<0.05 |
| **Age (in years)** | *mean* | 61.80 | 61.80 | 60.6 | 61.4 | 60.5 | 61.2 | |
| | *0-49* | 20.3% | 19.4% | 22.4% | 20.9% | 22.7% | 21.1% | |
| | *50-65* | 39.6% | 41.1% | 41.1% | 40.4% | 41.2% | 40.7% | |
| | *66-75* | 24.4% | 23.8% | 22.4% | 23.2% | 22.1% | 23.2% | |
| | *76-85* | 10.3% | 11.1% | 9.5% | 10.3% | 9.6% | 10.2% | |
| | *>85* | 5.4% | 4.5% | 4.6% | 5.2% | 4.4% | 4.9% | p<0.05 |
| **Socio economic status** | *High* | 13.3% | 21.6% | 45.2% | 36.3% | 35.5% | 30.1% | |
| | *Medium* | 42.3% | 48.0% | 32.9% | 34.8% | 42.5% | 40.0% | |
| | *Low* | 44.4% | 30.5% | 21.9% | 28.8% | 22.0% | 30.0% | p<0.05 |
| **Diagnosed after screening** | *No* | 24.5% | 26.3% | 26.2% | 26.4% | 26.5% | 25.9% | |
| | *Yes* | 39.4% | 38.4% | 34.4% | 35.5% | 36.6% | 76.4% | |
| | *NA^* | 36.0% | 35.1% | 36.5% | 36.4% | 36.7% | 36.1% | |
| | *Unknown* | 0.1% | 0.3% | 2.9% | 1.7% | 0.2% | 1.1% | p<0.05 |
| **Tumor size (in mm)** | *0-10* | 24.3% | 33.6% | 33.6% | 25.6% | 28.7% | 29.0% | |
| | *11-20* | 38.5% | 37.0% | 35.5% | 36.7% | 38.0% | 37.1% | |
| | *21-30* | 19.7% | 15.5% | 14.5% | 19.3% | 17.1% | 17.4% | |
| | *>30* | 12.6% | 8.7% | 8.0% | 12.2% | 10.9% | 10.6% | |
| | *Unknown* | 5.0% | 5.2% | 8.4% | 6.1% | 5.2% | 6.0% | p<0.05 |
| **Number of positive lymph nodes** | *0* | 59.7% | 62.4% | 62.2% | 60.9% | 61.7% | 61.3% | |
| | *1-3* | 27.0% | 25.3% | 26.6% | 26.2% | 27.0% | 26.4% | |
| | *>3* | 7.9% | 6.4% | 5.4% | 7.8% | 6.5% | 6.9% | p<0.05 |
| | *Unknown* | 5.5% | 5.8% | 5.7% | 5.1% | 4.8% | 5.4% | |
| **Grade** | *1* | 20.5% | 26.7% | 19.1% | 19.4% | 21.3% | 21.4% | |
| | *2* | 41.6% | 40.0% | 42.2% | 38.8% | 36.3% | 39.8% | |
| | *3* | 24.2% | 20.7% | 21.4% | 27.4% | 24.4% | 23.7% | |
| | *Unknown* | 13.7% | 12.6% | 17.3% | 14.4% | 18.0% | 15.1% | p<0.05 |
| **Her2** | *Her2-* | 83.0% | 83.8% | 80.4% | 81.7% | 81.3% | 82.1% | |
| | *Her2+* | 12.3% | 12.3% | 11.9% | 13.2% | 12.3% | 12.5% | |
| | *Doubtful* | 0.2% | 0.6% | 0.4% | 0.5% | 0.2% | 0.4% | |
| | *Unknown* | 4.5% | 3.3% | 7.3% | 4.5% | 6.1% | 5.1% | p<0.05 |

| Table 1 continued. | | Region | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Region A (n=14,498) | Region B (n=13,465) | Region C (n=12,930) | Region D (n=15,554) | Region E (n=11,824) | Total (n=68,271) | p-value |
| **Estrogen receptor** | *ER-* | 14.9% | 15.2% | 14.6% | 16.8% | 13.6% | 15.1% | |
| | *ER+* | 84.2% | 83.7% | 80.0% | 81.2% | 85.3% | 82.8% | |
| | *Unknown* | 0.9% | 1.1% | 5.4% | 2.0% | 1.0% | 2.1% | p<0.05 |
| **Progesterone receptor** | *PR-* | 28.3% | 29.2% | 30.1% | 33.3% | 30.4% | 30.3% | |
| | *PR+* | 70.5% | 69.6% | 64.4% | 64.3% | 68.5% | 67.4% | |
| | *Unknown* | 1.2% | 1.2% | 5.5% | 2.4% | 1.1% | 2.3% | p<0.05 |
| **Year of diagnosis** | *2011* | 19.9% | 20.1% | 19.5% | 19.9% | 18.9% | 19.7% | |
| | *2012* | 19.9% | 19.8% | 20.3% | 19.6% | 20.4% | 20.0% | |
| | *2013* | 19.7% | 20.4% | 20.6% | 20.2% | 19.1% | 20.0% | |
| | *2014* | 20.0% | 20.2% | 19.5% | 20.2% | 21.6% | 20.3% | |
| | *2015* | 20.5% | 19.5% | 20.1% | 20.1% | 19.9% | 20.0% | p<0.05 |
| **Therapy** | *S* | 8.2% | 8.0% | 7.3% | 8.7% | 7.7% | 8.0% | |
| | *S + RT* | 18.5% | 24.2% | 20.3% | 18.7% | 22.2% | 20.6% | |
| | *S + SYSTM* | 20.5% | 15.9% | 14.6% | 22.4% | 17.7% | 18.4% | |
| | *S+RT+SYSTM* | 46.3% | 45.2% | 51.0% | 44.4% | 47.2% | 46.7% | |
| | *SYSTM* | 6.0% | 6.3% | 6.4% | 5.4% | 4.9% | 5.8% | |
| | *other* | 0.5% | 0.4% | 0.5% | 0.5% | 0.3% | 0.4% | p<0.05 |
| **Type of surgery** | *none* | 6.6% | 6.9% | 7.0% | 6.0% | 5.4% | 6.4% | |
| | *BCS* | 52.1% | 58.2% | 60.4% | 52.7% | 57.8% | 56.0% | |
| | *Mastectomy* | 41.2% | 34.9% | 32.5% | 41.1% | 36.8% | 37.5% | |
| | *other* | 0.1% | 0.0% | 0.1% | 0.1% | 0.1% | 0.1% | p<0.05 |
| **Department of radiation oncology type** | *University* | 19.2% | 22.2% | 54.7% | 33.3% | 48.7% | 34.8% | |
| | *Independent* | 25.7% | 26.2% | 2.3% | 12.2% | 19.9% | 17.3% | |
| | *Hospital dpt** | 20.2% | 21.1% | 1.2% | 17.6% | 0.8% | 12.8% | |
| | *Other* | 34.9% | 30.5% | 41.8% | 36.9% | 30.6% | 35.1% | p<0.05 |
| **Department of radiation oncology volume (patients treated yearly)** | *0-449* | 80.7% | 32.6% | 66.5% | 78.8% | 47.8% | 62.4% | |
| | *450-649* | 18.9% | 41.0% | 2.3% | 19.5% | 20.6% | 20.6% | |
| | *>649* | 0.4% | 26.4% | 31.2% | 1.7% | 31.5% | 17.0% | p<0.05 |

*S = Surgery, RT= Radiation therapy, SYSTM= Systemic therapy, ^NA= not applicable, * dpt= department*

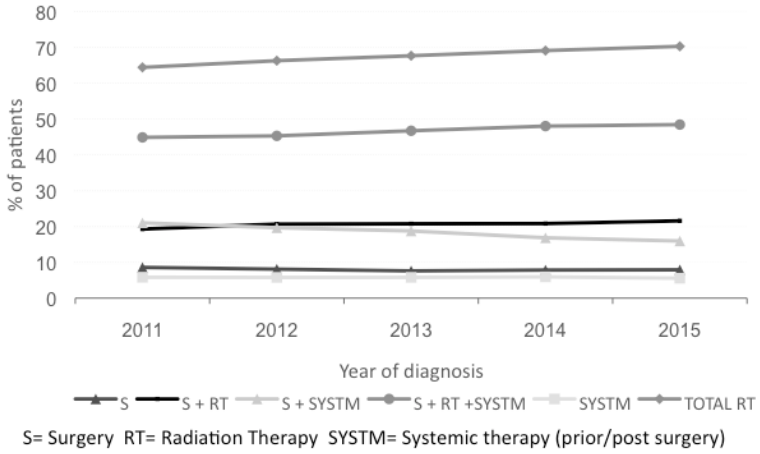


**Figure 1.** *Trends in treatment of breast cancer in the Netherlands for all ages over the period 2011-2015 (n=68,271)*

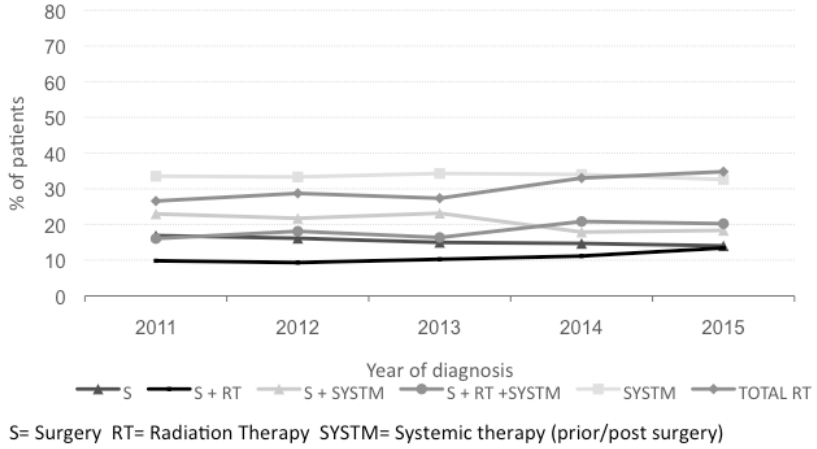


**Figure 2.** *Trends in treatment of breast cancer in the Netherlands for patients aged over 75 years over the period 2011-2015 (n=10,283)*

**Table 2.** *Utilization rate of RT over the years for different surgery related treatment groups (n=63,857)*

| Trend in use of radiation therapy | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **BCS (without PST)** (n=34,286) *Radiation therapy:* | | | | **Mastectomy (without PST)** (n=21,048) *Radiation therapy:* | | | | **PST + BCS** (n=3,954) *Radiation therapy:* | | | | **PST + mastectomy** (n=4,569) *Radiation therapy:* | | | |
| | *No* | | *Yes* | | *No* | | *Yes* | | *No* | | *Yes* | | *No* | | *Yes* | |
| **Years** | *n* | *%* | *n* | *%* | *n* | *%* | *n* | *%* | *n* | *%* | *n* | *%* | *n* | *%* | *n* | *%* |
| *2011* | 178 | 2.6% | 6,543 | 97.4% | 3,617 | 76.5% | 1,113 | 23.5% | 4 | 0.9% | 439 | 99.1% | 173 | 20.0% | 694 | 80.0% |
| *2012* | 150 | 2.1% | 6,872 | 97.9% | 3,384 | 75.7% | 1,086 | 24.3% | 16 | 3.2% | 489 | 96.8% | 235 | 30.6% | 533 | 69.4% |
| *2013* | 172 | 2.5% | 6,764 | 97.5% | 3,124 | 74.2% | 1,084 | 25.8% | 15 | 2.0% | 751 | 98.0% | 280 | 31.4% | 611 | 68.6% |
| *2014* | 216 | 3.1% | 6,752 | 96.9% | 2,831 | 71.1% | 1,151 | 28.9% | 25 | 2.6% | 920 | 97.4% | 329 | 32.4% | 686 | 67.6% |
| *2015* | 217 | 3.3% | 6,422 | 96.7% | 2,594 | 70.9% | 1,064 | 29.1% | 34 | 2.1% | 1621 | 97.9% | 395 | 32.9% | 806 | 67.1% |

*Mastectomy without primary systemic therapy (PST)*

In total 21,048 patients underwent mastectomy (without PST) and of these patients a mean of 26.1% (n=5,498) underwent RT. Univariable analyses demonstrated that lower age (<50 years); not screen detected breast cancers, tumour sizes over 10 mm, positive lymph nodes, grade-2 and 3 tumours, Her2+/ER- tumours, incidence years 2013, 2014 or 2015 and treatment in a hospital with a higher lump rate (>60%) were associated with a higher use of RT over the period 2011 to 2015 (Table 3). Diagnosis in region B and region D were significantly associated with less RT use compared to region A.

Multivariable analyses, table 3, demonstrated that patients aged 50-65 years (RT use: 25.3%, OR= 0.71, 95%CI: 0.63-0.80), 66-75 years (RT use: 24.7%, OR= 0.69, 95%CI: 0.61-0.79), 76-85 years (RT use: 25.8%, OR= 0.43, 95%CI: 0.37-0.49) and >85 (RT use: 11.1%, OR= 0.08, 95%CI: 0.06-0.10) were less likely to receive RT compared to those aged ≤ 49 years (RT use: 32.1%). Increasing tumour size, number of positive lymph nodes and grade were associated with increasing odds of receiving RT (≥30 mm vs ≤10 mm (OR= 3.82, 95%CI: 3.25-4.48); 1-3 vs 0 positive lymph nodes (OR= 7.91, 95%CI: 7.20-8.70) and >3 vs 0 positive lymph nodes (OR= 94.21, 95% CI: 81.42-109.01); grade 2 vs grade 1 (OR= 1.19, 95%CI: 1.05-1.35) and grade 3 vs 1 (OR= 1.73, 95%CI: 1.50-1.99)). Over the years, RT utilization rates significantly increased (OR 2015 vs 2011= 2.54, 95%CI: 2.23-2.90). One region, when compared to the other regions, was characterized with significant lower RT rates; region D (OR= 0.66, 95%CI: 0.58-0.74), compared to region A. However, two other regions demonstrated higher RT use, region B (OR= 1.20, 95%CI: 1.05-1.37) and region C (OR= 1.39, 95%CI: 1.21-1.60), compared to region A. For hospitals with higher lump rates (> 60%) we noted an increased use of RT. Hospitals performing a BCS in more than 60% of all surgical excision significantly more RT were administered (OR= 1.41, 95% CI: 1.13-1.75) compared to hospitals with low lump rates (<40%) (Table 3).

**Table 3.** *Factors associated with RT after breast conserving surgery (n=34,286) or mastectomy (n=21,048)*

| | | Factors associated with radiation therapy after surgery | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | After breast conserving surgery (n=34,286) | | | | | | | After mastectomy (n=21,048) | | | | | | |
| | | Total | No RT | RT | | | | | Total | No RT | RT | | | | |
| | | (n=34,286) | (n=933) | (n=33,353) | | | | | (n=21,048) | (n=15,550) | (n=5,498) | | | | |
| | | | | | Univariable | | Multivariable | | | | | Univariable | | Multivariable | |
| | | *n* | *%* | *%* | *OR* | *95% CI* | *OR* | *95% CI* | *n* | *%* | *%* | *OR* | *95% CI* | *OR* | *95% CI* |
| **Age (in years)** | *0-49* | 5,227 | 2.6% | 97.4% | ref | | ref | | 4,700 | 67.9% | 32.1% | ref | | ref | |
| | *50-65* | 16,543 | 1.6% | 98.4% | 1.68 | 1.36-2.07 | 1.19 | 0.93-1.51 | 7,374 | 74.8% | 25.3% | 0.71 | 0.66-0.77 | 0.71* | 0.63-0.80 |
| | *66-75* | 10,231 | 2.0% | 98.0% | 1.29 | 1.03-1.60 | 0.85 | 0.66-1.09 | 4,616 | 75.3% | 24.7% | 0.69 | 0.63-0.76 | 0.69* | 0.61--0.79 |
| | *76-85* | 1,990 | 9.3% | 90.7% | 0.26 | 0.21-0.33 | 0.31* | 0.24-0.39 | 3,428 | 74.2% | 25.8% | 0.73 | 0.67-0.81 | 0.43* | 0.37-0.49 |
| | *>85* | 295 | 49.2% | 50.9% | 0.03 | 0.02-0.04 | 0.04* | 0.03-0.06 | 930 | 88.9% | 11.1% | 0.26 | 0.21-0.33 | 0.08* | 0.06-0.10 |
| **Socio economic status** | *High* | 10,576 | 2.8% | 97.2% | ref | | ref | | 5,914 | 73.6% | 26.4% | ref | | ref | |
| | *Medium* | 13,892 | 2.5% | 97.5% | 1.11 | 0.95-1.31 | | | 8,261 | 73.8% | 26.2% | 0.99 | 0.92-1.07 | | |
| | *Low* | 9,818 | 3.0% | 97.0% | 0.91 | 0.78-1.08 | | | 6,873 | 74.2% | 25.8% | 0.97 | 0.89-1.05 | | |
| **Diagnosed after screening** | *No* | 8,127 | 2.5% | 97.5% | ref | | ref | | 6,167 | 70.6% | 29.4% | ref | | ref | |
| | *Yes* | 18,267 | 1.2% | 98.8% | 2.02 | 1.67-2.45 | 2.10* | 1.72-2.56 | 5,674 | 79.6% | 20.4% | 0.62 | 0.57-0.67 | 1.00 | 0.90-1.12 |
| | *NA^* | 7,512 | 6.2% | 93.8% | 0.38 | 0.32-0.45 | omitted | | 9,058 | 72.4% | 27.6% | 0.92 | 0.85-0.98 | omitted | |
| | *Unknown* | 380 | 11.1% | 89.0% | 0.20 | 0.14-0.29 | 1.16 | 0.67-2.02 | 149 | 79.2% | 20.8% | 0.63 | 0.42-0.94 | 2.33* | 1.33-4.07 |
| **Tumor size (in mm)** | *0-10* | 9,911 | 2.1% | 97.9% | ref | | ref | | 3,062 | 89.3% | 10.7% | ref | | ref | |
| | *11-20* | 17,103 | 2.3% | 97.8% | 0.92 | 0.78-1.09 | 1.04 | 0.86-1.26 | 6,851 | 83.2% | 16.8% | 1.68 | 1.47-1.91 | 1.20* | 1.03-1.41 |
| | *21-30* | 5,420 | 3.7% | 96.4% | 0.56 | 0.46-0.68 | 0.85 | 0.67-1.07 | 5,535 | 73.4% | 26.6% | 3.02 | 2.66-3.44 | 1.52* | 1.30-1.79 |
| | *>30* | 1,145 | 5.6% | 94.4% | 0.36 | 0.27-0.48 | 0.71 | 0.51-1.00 | 5,091 | 52.1% | 47.9% | 7.67 | 6.76-8.71 | 3.82* | 3.25-4.48 |
| | *Unknown* | 707 | 11.3% | 88.7% | 0.17 | 0.13-0.22 | 0.59* | 0.37-0.94 | 509 | 78.6% | 21.4% | 2.27 | 1.79-2.89 | 1.57* | 1.13-2.20 |

| Table 3 continued. | | Factors associated with radiation therapy after surgery | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | After breast conserving surgery (n=34,286) | | | | | | | After mastectomy (n=21,048) | | | | | |
| | | Total | No RT | RT | | | | | Total | No RT | RT | | | |
| | | (n=34,286) | (n=933) | (n=33,353) | | | | | (n=21,048) | (n=15,550) | (n=5,498) | | | |
| | | | | | Univariable | | Multivariable | | | | | Univariable | | Multivariable | |
| | | *n* | *%* | *%* | *OR* | *95% CI* | *OR* | *95% CI* | *n* | *%* | *%* | *OR* | *95% CI* | *OR* | *95% CI* |
| **Number of positive lymph nodes** | *0* | 26,056 | 2.3% | 97.8% | ref | | ref | | 11,436 | 93.3% | 6.7% | ref | | ref | |
| | *1-3* | 6,892 | 2.1% | 97.9% | 1.05 | 0.88-1.27 | 1.15 | 0.95-1.39 | 6,618 | 63.1% | 36.9% | 8.15 | 7.45-8.90 | 7.91* | 7.20-8.70 |
| | *>3* | 819 | 3.7% | 96.3% | 0.60 | 0.42-0.88 | 0.68 | 0.46-1.02 | 2,666 | 14.9% | 85.2% | 79.96 | 70.25-91.02 | 94.21* | 81.42-109.01 |
| | *Unknown* | 519 | 33.0% | 67.1% | 0.05 | 0.04-0.06 | 0.10* | 0.08-0.13 | 328 | 93.0% | 7.0% | 1.05 | 0.68-1.62 | 1.44 | 0.92-2.25 |
| **Grade** | *1* | 10,241 | 2.3% | 97.7% | ref | | ref | | 3,662 | 84.9% | 15.1% | ref | | ref | |
| | *2* | 14,852 | 2.6% | 97.5% | 0.89 | 0.76-1.05 | 1.05 | 0.87-1.25 | 9,843 | 74.8% | 25.2% | 1.89 | 1.71-2.10 | 1.19* | 1.05-1.35 |
| | *3* | 7,843 | 2.8% | 97.2% | 0.81 | 0.67-0.97 | 1.18 | 0.94-1.49 | 6,421 | 65.9% | 34.1% | 2.91 | 2.63-3.23 | 1.73* | 1.50-1.99 |
| | *Unknown* | 1,350 | 7.3% | 92.7% | 0.30 | 0.23-0.38 | 0.60* | 0.44-0.81 | 1,122 | 75.7% | 24.3% | 1.81 | 1.53-2.13 | 1.92* | 1.54-2.39 |
| **Her2** | *Her2-* | 30,014 | 2.4% | 97.6% | ref | | ref | | 17,127 | 74.3% | 25.7% | ref | | ref | |
| | *Her2+* | 3,064 | 2.7% | 97.3% | 0.89 | 0.71-1.13 | | | 3,066 | 68.9% | 31.1% | 1.30 | 1.20-1.42 | 0.98 | 0.87-1.10 |
| | *Doubtful* | 107 | 1.9% | 98.1% | 1.31 | 0.32-5.31 | | | 87 | 81.6% | 18.4% | 0.65 | 0.38-1.12 | 0.71 | 0.35-1.45 |
| | *Unknown* | 1,101 | 10.8% | 89.2% | 0.21 | 0.17-0.25 | | | 768 | 84.2% | 15.8% | 0.54 | 0.44-0.66 | 0.89 | 0.64-1.23 |
| **Estrogen receptor** | *ER-* | 4,085 | 3.7% | 96.3% | ref | | ref | | 3,457 | 72.0% | 28.0% | ref | | ref | |
| | *ER+* | 29,566 | 2.4% | 97.6% | 1.59 | 1.33-1.90 | 1.38* | 1.05-1.81 | 17,221 | 74.0% | 26.0% | 0.91 | 0.83-0.98 | 1.15* | 1.01-1.29 |
| | *Unknown* | 635 | 13.1% | 86.9% | 0.26 | 0.19-0.34 | 0.65 | 0.18-2.36 | 370 | 87.6% | 12.4% | 0.37 | 0.27-0.50 | 0.58 | 0.33-1.02 |
| **Progesterone receptor** | *PR-* | 9,123 | 2.9% | 97.1% | ref | | ref | | 6,737 | 72.9% | 27.1% | ref | | ref | |
| | *PR+* | 24,480 | 2.4% | 97.6% | 1.23 | 1.06-1.43 | 0.99 | 0.80-1.22 | 13,910 | 74.0% | 26.0% | 0.95 | 0.89-1.01 | | |
| | *Unknown* | 683 | 12.5% | 87.6% | 0.21 | 0.16-0.27 | 0.77 | 0.22-2.64 | 401 | 86.5% | 13.5% | 0.42 | 0.31-0.56 | | |

| Table 3 continued. | | Factors associated with radiation therapy after surgery | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | After breast conserving surgery (n=34,286) | | | | | | | After mastectomy (n=21,048) | | | | | |
| | | Total | No RT | RT | | | | | Total | No RT | RT | | | |
| | | (n=34,286) | (n=933) | (n=33,353) | | | | | (n=21,048) | (n=15,550) | (n=5,498) | | | |
| | | | | | Univariable | | Multivariable | | | | | Univariable | | Multivariable | |
| | | *n* | *%* | *%* | *OR* | *95% CI* | *OR* | *95% CI* | *n* | *%* | *%* | *OR* | *95% CI* | *OR* | *95% CI* |
| **Year of diagnosis** | *2011* | 6,721 | 2.7% | 97.4% | ref | | ref | | 4,730 | 76.5% | 23.5% | ref | | ref | |
| | *2012* | 7,022 | 2.1% | 97.9% | 1.25 | 1.00-1.55 | 1.26 | 0.99-1.60 | 4,470 | 75.7% | 24.3% | 1.04 | 0.95-1.15 | 1.14 | 1.00-1.30 |
| | *2013* | 6,936 | 2.5% | 97.5% | 1.07 | 0.87-1.32 | 1.05 | 0.83-1.33 | 4,208 | 74.2% | 25.8% | 1.13 | 1.02-1.24 | 1.41* | 1.24-1.61 |
| | *2014* | 6,968 | 3.1% | 96.9% | 0.85 | 0.70-1.04 | 0.83 | 0.66-1.03 | 3,982 | 71.1% | 28.9% | 1.32 | 1.20-1.45 | 2.08* | 1.83-2.37 |
| | *2015* | 6,639 | 3.3% | 96.7% | 0.81 | 0.66-0.98 | 0.72* | 0.58-0.90 | 3,658 | 70.9% | 29.1% | 1.33 | 1.21-1.47 | 2.54* | 2.23-2.90 |
| **Region** | *Region A* | 6,844 | 2.2% | 97.8% | ref | | ref | | 5,206 | 72.3% | 27.7% | ref | | ref | |
| | *Region B* | 6,795 | 2.4% | 97.6% | 0.93 | 0.75-1.16 | 1.11 | 0.87-1.40 | 3,624 | 74.4% | 25.6% | 0.90 | 0.82-0.99 | 1.20* | 1.05-1.37 |
| | *Region C* | 6,423 | 3.0% | 97.0% | 0.75 | 0.60-0.92 | 0.89 | 0.70-1.12 | 3,074 | 72.7% | 27.3% | 0.98 | 0.89-1.08 | 1.39* | 1.21-1.60 |
| | *Region D* | 7,275 | 3.2% | 96.8% | 0.69 | 0.56-0.84 | 0.79* | 0.64-0.99 | 5,464 | 76.9% | 23.1% | 0.79 | 0.72-0.86 | 0.67* | 0.59-0.76 |
| | *Region E* | 6,016 | 2.7% | 97.3% | 0.82 | 0.66-1.02 | 0.84 | 0.66-1.06 | 3,680 | 72.2% | 27.9% | 1.01 | 0.92-1.11 | 1.08 | 0.95-1.23 |
| **Lump rate** | *<40%* | 623 | 3.2% | 96.8% | ref | | ref | | 961 | 76.0% | 24.0% | ref | | ref | |
| | *40-50%* | 4,120 | 3.1% | 96.9% | 1.05 | 0.65-1.70 | | | 4,494 | 78.5% | 21.5% | 0.87 | 0.74-1.02 | 0.83 | 0.66-1.04 |
| | *51-60%,* | 8,251 | 2.7% | 97.3% | 1.19 | 0.75-1.89 | | | 6,096 | 73.9% | 26.1% | 1.12 | 0.95-1.31 | 1.23 | 0.99-1.54 |
| | *> 60%* | 21,292 | 2.6% | 97.4% | 1.22 | 0.78-1.92 | | | 9,497 | 71.5% | 28.5% | 1.26 | 1.08-1.47 | 1.41* | 1.13-1.75 |

** Significant OR*

*^ NA= not applicable*

**Discussion**

In the current population-based study, we analysed 68,271 patients and assessed the use of primary RT for invasive breast cancer patients in the Netherlands focussing specifically on time trends and age effects. The comparison of the results of this study with that of the former study [11], however, is to some degree biased by the (increased) use of PST during the last period.

*Breast conserving surgery (BCS) and mastectomy*

We demonstrated an increase in utilization rate of RT of 5.9% for all ages together and of 8.2% for patients aged over 75 years. This increased utilization rate of RT was specifically associated by the finding that more patients underwent RT after mastectomy. The overall increase was in line with the expected increase in the number of radiotherapy treatment courses as reported by Borras et al [14].

Patients who were diagnosed with breast cancer as a result of attending the Dutch screening programme who underwent BCS were more likely to be treated with RT compared to those who did not attend. Whereas, after mastectomy, this association was absent. Most probably, this is due to the fact the screening programme results in an increased number of diagnoses of small, "low risk" early stage breast cancers, which are more suitable to undergo BCS (and, hence, RT). In both groups (BCS and mastectomy), increasing age was associated with lower RT utilization rates. Age has been shown to be a powerful prognostic factor of the risks of both recurrence and distant metastases [15-19]. Since women diagnosed with breast cancer at young age have more aggressive disease and, hence, increased risk of recurrence, the higher utilization rates of RT for younger patients was anticipated [15]. For patients treated with BCS and mastectomy, variation in utilization rates of RT over time and between regions was observed. In one specific region (D) we noted significantly lower utilisation rates after RT after BCS as well as after mastectomy. No explanation was found. Similar findings were seen in the previous study [11]. Besides, also differences in variables influencing the use of RT between patients treated with BCS and mastectomy were observed.

*Breast conserving surgery (BCS)*

RT is an integral component of breast conserving therapy based on the reported substantial improvements in local control rates and the (limited) gain in survival [20]. For patients treated with BCS, no further increase in RT use was expected, since almost all patients already received RT after BCS in Dutch breast cancer patients. For patients undergoing BCS, younger age, screen detection and ER+ tumours, diagnosis in 2011 and in specific regions were positively associated with RT. In a previous study performed by Struikmans et al, a similar increase of approximately 5.5% was observed over the period 1997-2008 [11]. No significant association was found between year of diagnosis and RT compliance after BCS, due the fact almost all patients already received RT after BCS over all these years (mean 97.3%).

*Mastectomy*

For patients treated with mastectomy significantly reduced recurrence rates, improved disease-specific survival and improved overall survival notably in high-risk women with early-stage breast cancer and in more advanced cancer stages were noted [21]. Later the same pattern was noted for patients with intermediate risk breast cancer [22-25].

Because of these findings, higher utilization rates of RT were expected in more recent years in patients treated with mastectomy. In the present study, we observed that patients with positive lymph nodes were much more likely to receive RT compared to patients with negative lymph nodes after mastectomy. Also younger age, larger tumour sizes, grade-2 and 3 tumours, ER+ tumours, diagnosis in most recent years, diagnosis in specific regions and higher hospital specific ratio of BCS. Over the years 2011-2015, increased utilization rates of RT after mastectomy were observed, hereby following the reported positive effects of post mastectomy RT [22].

A drawback of the present study is that we could not find an explanation for all observed differences in the use of RT in breast cancer patients, because differences may be attributed to variables we could not retrieve. Departmental or hospital related factors (e.g. policy/personal preference of radiation oncologist concerning RT prescription, weighing the relevance of treatment efficacy versus worsening of the cosmetic result after boost radiotherapy and co-morbidity of the patient may have influenced the use of RT. The possibility that policy/personal preference of radiation oncologist did influence RT prescription is another possibility. Moreover, active involvement in clinical decision making by the patient herself may have influenced the use of RT. Further research should identify doctors' attitudes and patients' preferences towards the use of RT in breast cancer management.

Finally, the population-based character of the present study is unique and provides insight in the overall use in daily practice of RT in all 21 departments of radiation oncology in the Netherlands.

**Conclusion**

A substantial increase in the use of RT was observed over the years. The utilization rate of RT increased; particularly for patients aged over 75 years. Different factors were associated with the utilization rate of RT, differing between BCS and mastectomy.

**Conflict of interest**

The authors do not declare any conflicts of interest.

**Ethical considerations**

According to the Central Committee on Research involving Human Subjects (CCMO), this type of study does not require approval from an ethics committee in the Netherlands. The Privacy Review Board of the Netherlands Cancer Registry approved this study.

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# Part IV

Gene profling

# Chapter 6

Factors associated with the use of gene-expression profiles in estrogen-receptor positive early-stage breast cancer patients: a nation-wide study

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A. Kuijer
K. Schreuder
S.G. Elias
C. Smorenburg
E. J. Th. Rutgers
S. Siesling
Th. van Dalen

**Abstract**

**Background**

Breast cancer guidelines suggest the use of gene-expression profiles (GEPs) in estrogen-receptor positive (ER+) breast cancer patients in whom controversy exists regarding adjuvant chemotherapy benefit based on traditional prognostic factors alone. We evaluated current use of GEPs in these patients in the Netherlands.

**Patients and methods**

Primary breast cancer patients treated between 2011-2014 eligible for GEP use according to Dutch guideline were identified in the Netherlands Cancer Registry: ER+ patients <70 years with grade 1 > 2cm; or grade 2 1-2 cm tumors without overt lymph node metastases (pN0-Nmi). Mixed-effect logistic regression analysis was performed to associate characteristics of patients, tumors and hospitals with GEP use.

**Results**

GEPs were increasingly deployed: 12% of eligible patients received a GEP in 2011 vs. 46% in 2014. Lobular vs. ductal morphology (OR 0.58 95%CI 0.47 – 0.72), pN1mi status (vs. pN0 OR 0.52 95%CI 0.40 – 0.68), tumor size (>3 cm vs. >2 cm OR 0.33 95%CI 0.14 – 0.88) were inversely associated with GEP use. High socioeconomic status (OR 1.32 95%CI 1.06 – 1.64) and younger age (OR 0.96/year increasing age 95%CI 0.95 – 0.96) were positively associated with GEP use. GEP use per hospital did vary, but no predefined institutional factors remained independently associated with GEP use.

**Conclusion**

GEP use increased over time and was influenced by patient- and tumor associated factors, as well as by socioeconomic status.

**Introduction**

Breast cancer prognosis has improved over the last two decades for an important part due to the administration of adjuvant systemic therapy (AST) [1]. The indication area for AST has gradually expanded, now recommending adjuvant chemotherapy (CT) and/or endocrine therapy in the majority of all breast cancer patients. Then again, there is a growing awareness that this is associated with a considerable risk of CT overtreatment.

Especially in estrogen-receptor positive (ER+) early-stage breast cancer patients controversy exists regarding the benefit of adjuvant CT. Several gene-expression profiles (GEPs) were developed and validated to improve prognosis prediction and hereby reduce CT overtreatment in these patients [2-5]. Currently, both national [6] and international [7,8] treatment guidelines suggest the use of a GEP as an adjunct to clinicopathological factors to guide decisions on adjuvant CT for ER+ early-stage breast cancer.

The Dutch national breast cancer guideline (2012) suggests the use of a validated GEP in ER+ breast cancer patients in whom controversy exists regarding the benefit of administering adjuvant CT based on traditional prognostic factors alone [6]. In 2011 the 70-GS became available in Dutch clinical practice followed by the 21-recurrence score which became available in the Netherlands in 2013. GEPs are available for every Dutch ER+ breast cancer patient since health insurance is mandatory and practically all health insurance companies fully reimburse GEPs. We have recently reported that using GEPs leads to a decrease in CT administration in Dutch ER+ early-stage breast cancer patients. In this study we noticed that only a modest proportion of Dutch breast cancer patients for whom GEP is considered worthwhile actually received a GEP [9].

Therefore, the aim of the present study is to gain insight in factors associated with the use of a GEP in daily practice in patients with ER+ early breast cancer in the Netherlands.

**Patients and methods**

*Study-population*

The Dutch national guideline (2012) suggests the use of a GEP in ER+ breast cancer patients in whom controversy exists regarding the benefit of adjuvant CT based on traditional prognostic factors alone [6]. According to the directives in the Dutch guidelines this category consists of patients 35-70 year of age with either grade 1 ER+ invasive breast cancer > 2 cm or grade 2 ER+ invasive breast cancer 1-2 cm with no or limited axillary lymph-node involvement (pN0 or pN1mi). In the absence of GEP use national guidelines would advocate the administration of CT for this category of patients. Patients within this guideline-directed indicated area for GEP use who were surgically treated between January 1, 2011, and December 31, 2014, were identified

in the Netherlands Cancer Registry (NCR). Patients with a prior malignancy and those receiving neo-adjuvant systemic treatment were excluded.

*Data collection and variable categorization*

The NCR prospectively registers demographic and clinicopathological information of all cancer patients treated in the Netherlands since 1989 [10]. Demographic information included age and postal code. The postal code at the time of diagnosis was used to determine socio-economic status (SES). This SES-indicator uses individual fiscal data based on a combination of the mean value of the home and mean house-hold income and is provided at an aggregated level for each postal code (covering an average of 17 households). Postal codes were categorized to one of three predefined socio-economic status categories: low (first to third decile), medium (fourth to seventh decile) and high (eight to tenth decile). Patients living in a care-providing institution were categorized into a fourth category that was not included in the present analysis. Furthermore, common clinicopathological variables on all Dutch cancer patients are prospectively collected by the NCR. The NCR started registering use of a GEP since 2011 of both the 70-gene signature (70-GS) and the 21-recurrence score (21-RS). Information obtained on hospital characteristics consisted of type of hospital, hospital localization and volume of delivered breast cancer care. Institutional patient volume was categorized based on the annual number of patients treated for primary breast cancer (<100, 100-200, > 200 breast cancer patients per year), hospital localization as a location in the North, Middle or South of the Netherlands). There are currently 26 top clinical hospitals in the Netherlands. These hospitals, without an academic affiliation, focus on improvement of quality of care, education and medical research and are inspected every 5-year on strict quality criteria to obtain or preserve this quality mark. Hospital type was categorized as teaching hospital for surgical and/or internal medicine residents (yes/no) and as district hospitals, university hospitals or top clinical hospitals (not affiliated with a medical university).

*Statistical analysis*

The distributions of patient-, tumor- and hospital characteristics were compared between patients who did or did not receive a GEP with a Chi-square test for categorical variables and a Wilcoxon rank sum test for the non-normal distributed continuous variables age, volume of breast cancer care and tumor size. To assess the increase in GEP use over time, percentages of patients within the guideline directed-indicated area for GEP use actually receiving a GEP, categorized according to SES, was plotted against calendar year.

A mixed-effect logistic regression analysis was performed to assess the association between patient-/tumor- and hospital characteristics and GEP use, taking into account patient clustering within hospitals. For this purpose, we included a random intercept per hospital (thus taking baseline differences in GEP use among hospitals into account). We adjusted for age and tumor

size (continuously) and tumor morphology, invasive tumor grade, PR receptor status, axillary status, incidence year, socio-economic status, volume of breast cancer care in treating hospital and type of hospital and region (categorically).
A p-value < 0.05 was considered to be statistically significant. All analyses were performed by using STATA ©, version 12.0, and in R version 3.1.3 using the lme4 package for the mixed-effect model.

**Results**

Based on the guideline advocated use of GEPs 5110 patients were eligible for GEP use during our study period and 1360 of them (27%) received a GEP. In most patients (1321) the 70-gene signature was used whereas 39 patients (3%) received the 21-recurrence score. Over time, GEPs were increasingly used: in 2011, 12% of all eligible patients received a GEP, compared to 13%, 33% and 46% in 2012, 2013 and 2014, respectively. Of patients who received a GEP 66% were assigned to the low-risk and 29% to the high-risk category by the 70-GS. In 5% of patients who received the 70-GS no risk profile was recorded. The 21-recurrence score assigned 67% of patients to the low-, 15% to the intermediate and 18% of patients to the high-risk category. The test result was adhered to (i.e. no administration of CT in case of a low-risk profile and administration of CT in case of a high-risk profile) in 89% of all patients.

*Factors associated with GEP use*

Characteristics of patients, tumor and hospital according to the use of GEP are depicted in Table 1. Tumor characteristics significantly associated in univariable analysis with the use of a GEP were invasive ductal carcinoma as opposed to lobular carcinoma, the absence of axillary micro-metastases (pN0), small tumor size and intermediate malignancy grade (as opposed to low malignancy grade). Patients who received a GEP were on average younger and of higher socio-economic status compared to patients who did not receive a GEP. In addition, GEP testing was more frequent in patients treated in district hospitals, in hospitals with a higher volume of breast cancer care and in hospitals situated in the Northern part of the Netherlands (Table 1).
We plotted the proportion of patients receiving a GEP for the three different SES categories over time to assess whether there was a relation between time since reimbursement of GEPs and the association between SES and GEP use (Figure 1). Patients of lower SES had similar tumor- and patient characteristics as patients of medium or high SES. However, patients of high SES were slightly more often treated in hospitals with a large volume of breast cancer care, top clinical hospitals and hospitals situated in the Northern part of the Netherlands (Suppl. Table 1). Before reimbursement (2011), there was no significant difference in GEP use between the SES categories (11%; 13% vs. 12%, of patients received a GEP in the low-, medium and high SES category in 2011, p=0.589). After reimbursement GEPs were more frequently deployed in patients of high SES compared to low- or medium SES (Figure 1).

**Table 1**. *Patient-, tumor- and hospital characteristics of patients within the guideline-directed indicated area for gene-expression profile (GEP) use (ER+/Her2- disease without axillary lymph-node involvement and grade I tumours > 2 cm or grade II tumours 1-2 cm)*

| | | Odds Ratio | 95% CI | p-value |
|---|---|---|---|---|
| *Tumor characteristics* | | | | |
| **Morpholgy** | *Ductal* | 1 (ref) | | |
| | *Lobular* | 0.58 | 0.47 – 0.72 | < 0.001 |
| | *Mixed* | 0.93 | 0.60 – 1.43 | 0.735 |
| | *Other* | 0.52 | 0.30 – 0.88 | 0.015 |
| **Tumorsize** | *< 2 cm* | 1 (ref) | | |
| | *2 – 3 cm* | 0.93 | 0.60 – 1.45 | 0.752 |
| | *> 3 cm* | 0.33 | 0.14 – 0.80 | 0.013 |
| **Invasive tumor grade** | *Grade I* | 1 (ref) | | |
| | *Grade II* | 1.31 | 0.78 – 2.21 | 0.302 |
| **Progesterone receptor status** | *Negative* | 1 (ref) | | |
| | *Positive* | 0.83 | 0.67 – 1.03 | 0.09 |
| **pN status** | *pN0* | 1 (ref) | | |
| | *pN1mi* | 0.52 | 0.40 – 0.68 | < 0.001 |
| Patient characteristics | | | | |
| **Age** | *in years* | 0.96 | 0.95 – 0.97 | < 0.001 |
| **Incidence year** | *2011* | 1 (ref) | | |
| | *2012* | 1.06 | 0.82 – 1.37 | 0.674 |
| | *2013* | 4.34 | 3.45 – 5.47 | < 0.001 |
| | *2014* | 8.27 | 6.56 – 10.43 | < 0.001 |
| **Socioeconomic status** | *Low* | 1 (ref) | | |
| | *Medium* | 1.02 | 0.83 – 1.25 | 0.857 |
| | *High* | 1.32 | 1.06 – 1.64 | 0.012 |
| Hospital characteristics | | | | |
| **Volume of breast cancer care per year** | *< 100 patients* | 1 (ref) | | |
| | *100 - 200 patients* | 0.33 | 0.88 – 2.19 | 0.153 |
| | *> 200 patients* | 0.68 | 0.95– 4.08 | 0.068 |
| **Type of hospital** | *District* | 1 (ref) | | |
| | *Top clinical* | 0.82 | 0.44 – 1.51 | 0.519 |
| | *University* | 0.47 | 0.19 – 1.15 | 0.099 |
| **Teaching hospital** | *No* | 1 (ref) | | |
| | *Yes* | 0.75 | 0.46 – 1.22 | 0.242 |
| **Region** | *North* | 1 (ref) | | |
| | *Middle* | 0.90 | 0.57 – 1.42 | 0.648 |
| | *South* | 0.67 | 0.39 – 1.17 | 0.162 |

*Mixed-effect logistic regression analysis*

Mixed-effect logistic regression analysis, including a random intercept per hospital to correct for patient clustering at a hospital level (thus taking baseline difference in GEP use between individual hospitals into account), demonstrated an independently decreased probability of GEP use for patients with invasive lobular carcinomas (vs. ductal OR 0.58, 95%CI 0.47 – 0.72), larger tumor size (>3cm vs. <2cm OR 0.33 95%CI 0.14 – 0.80) and presence of axillary lymph node micro-metastasis (vs. pN0 OR 0.52 95%CI 0.40 – 0.68). Patient characteristics independently associated with GEP use were younger age (OR 0.96/year increase in age 95%CI 0.95 – 0.97), high SES (vs. low SES OR 1.32 95%CI 1.06 – 1.64) and diagnosis in a more recent year (2014 vs. 2011 OR 8.27 95%CI 6.56 – 10.43). In the mixed-effect analysis none of the aforementioned institutional characteristics remained independently associated with GEP use (Table 2). An interaction term for SES at a patient level and percentage of patients of high SES per hospital was added to the model to assess whether there was a difference in the association between SES and GEP use in hospitals with a high SES patient population but this interaction term was not statistically significant.

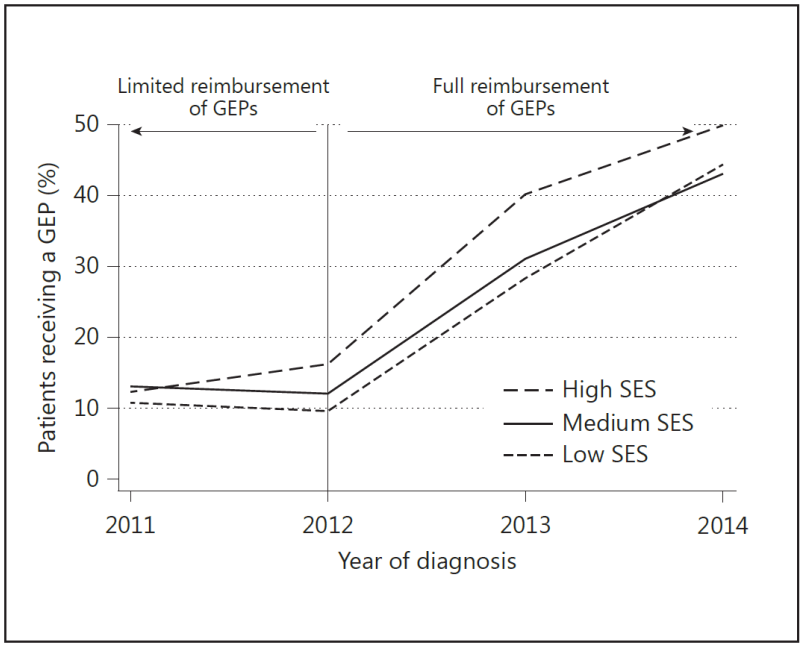


**Figure 1.** *Use of gene-expression profiles (GEP) in Dutch breast cancer patients within the guideline-directed indication area for GEP use over time stratified for socio-economic status (SES) category*

**Discussion**

In this population based study in a country where GEPs are available for every ER+ breast cancer patient, we observed an increase in GEP use over time with considerable variation in GEP use in eligible patients. In 2014 46% of eligible patients according to the Dutch breast cancer treatment guideline received a GEP. As expected, tumor factors pertaining to an intermediate clinical risk profile were independently associated with GEP use. Surprisingly, we observed a lower probability of GEP deployment in patients of low SES. Furthermore, the proportion of eligible patients receiving a GEP differed between individual hospitals. However, this inter-hospital variation could not be explained by hospital size, - type, - region or presence of an educational program.

In accordance with previous reports we observed a higher probability of GEP testing in patients with an intermediate clinical risk profile: smaller tumors of low or intermediate grade without axillary lymph-node involvement [11-15]. This finding is in itself not surprising since in these patients most controversy exists regarding CT benefit. GEP use in this category can lead to the decision to omit CT while national guidelines would otherwise advocate administration of CT. We observed lower percentages of patients with axillary micro-metastasis receiving a GEP, reflecting a reluctant attitude of clinicians to consider patients with axillary micro-metastasis as clinical intermediate risk. Furthermore, patients with an invasive ductal carcinoma were more likely to receive GEP testing compared to patients with tumors of lobular pathology which coheres to the knowledge that GEP validation studies did not include analysis of histologic subtypes and controversy exists regarding the deployment of GEPs in tumors other than of ductal morphology.

Considerable inter-hospital variation in GEP use was observed. In univariable analysis, GEPs were more frequently deployed in regional hospitals with a large patient volume situated in the Northern part of the Netherlands. However, this association between institutional factors and GEP use did not remain significant after correction for baseline difference among hospitals in GEP use in a mixed effect logistic regression model, thus taking patient clustering at a hospital level into account. This finding indicates that the chance of receiving a GEP depends on the hospital in which a patient is diagnosed but this difference is not attributable to the type of hospital, the volume of breast cancer care per hospital or the region. Until date, there are limited reports on inter-hospital variation regarding deployment of a GEP. Enewold et al. reported no association between hospital ownership, presence of a residency program or hospital bed size and 21-RS use in the United states [13]. Based on the present data we conclude that baseline attitudes of hospitals towards GEPs vary but this attitude is not associated with hospital type, size, region or presence of an educational program.

**Table 2.** *Patient-, tumor and hospital characteristics associated with GEP use in patients within the guideline-directed indication area for GEP in a multilevel logistic regression model including a random intercept per hospital*

| | | Odds Ratio | 95% CI | p-value |
|---|---|---|---|---|
| *Tumor characteristics* | | | | |
| **Morpholgy** | *Ductal* | 1 (ref) | | |
| | *Lobular* | 0.58 | 0.47 – 0.72 | < 0.001 |
| | *Mixed* | 0.93 | 0.60 – 1.43 | 0.735 |
| | *Other* | 0.52 | 0.30 – 0.88 | 0.015 |
| **Tumorsize** | *< 2 cm* | 1 (ref) | | |
| | *2 – 3 cm* | 0.93 | 0.60 – 1.45 | 0.752 |
| | *> 3 cm* | 0.33 | 0.14 – 0.80 | 0.013 |
| **Invasive tumor grade** | *Grade I* | 1 (ref) | | |
| | *Grade II* | 1.31 | 0.78 – 2.21 | 0.302 |
| **Progesterone receptor status** | *Negative* | 1 (ref) | | |
| | *Positive* | 0.83 | 0.67 – 1.03 | 0.09 |
| **pN status** | *pN0* | 1 (ref) | | |
| | *pN1mi* | 0.52 | 0.40 – 0.68 | < 0.001 |
| *Patient characteristics* | | | | |
| **Age** | *in years* | 0.96 | 0.95 – 0.97 | < 0.001 |
| **Incidence year** | *2011* | 1 (ref) | | |
| | *2012* | 1.06 | 0.82 – 1.37 | 0.674 |
| | *2013* | 4.34 | 3.45 – 5.47 | < 0.001 |
| | *2014* | 8.27 | 6.56 – 10.43 | < 0.001 |
| **Socioeconomic status** | *Low* | 1 (ref) | | |
| | *Medium* | 1.02 | 0.83 – 1.25 | 0.857 |
| | *High* | 1.32 | 1.06 – 1.64 | 0.012 |
| *Hospital characteristics* | | | | |
| **Volume of breast cancer care per year** | *< 100 patients* | 1 (ref) | | |
| | *100 - 200 patients* | 0.33 | 0.88 – 2.19 | 0.153 |
| | *> 200 patients* | 0.68 | 0.95– 4.08 | 0.068 |
| **Type of hospital** | *District* | 1 (ref) | | |
| | *Top clinical* | 0.82 | 0.44 – 1.51 | 0.519 |
| | *University* | 0.47 | 0.19 – 1.15 | 0.099 |
| **Teaching hospital** | *No* | 1 (ref) | | |
| | *Yes* | 0.75 | 0.46 – 1.22 | 0.242 |
| **Region** | *North* | 1 (ref) | | |
| | *Middle* | 0.90 | 0.57 – 1.42 | 0.648 |
| | *South* | 0.67 | 0.39 – 1.17 | 0.162 |

Some patient factors were independently associated with the receipt of a GEP in the current study. We observed a higher incidence of GEP use in younger patients. Several reports endorse this finding [13,14,16] whereas others report an increased use of GEPs in patients between 50-69 years of age [11,15]. Since the added value of CT is inversely related with age, it is possible that the observed preferential GEP use in younger women is explained by the fact that GEPs are mainly used to seek reassurance in withholding CT in these women in whom guidelines advocate administration of CT [17]. In a previous study, conducted by this research group, we observed a higher baseline propensity to administer CT in younger women eligible for GEP use compared to patients of older age. In the latter study GEP use was independently associated with a decreased probability of receiving CT in younger patients whereas in older patients a reverse relationship was observed [9]. The conceivably more aggressive attitude in younger women might explain the increased use of GEPs in order to come to a substantiated decision to omit CT in younger women.

Noteworthy, Dutch patients with lower SES were less likely to receive GEP testing in the current study compared to patients of high SES. Previous studies, mainly conducted in a US health care setting, report contradictory results on the association between race, median income or educational status and GEP use. Some observed disparities [13,15,18] whereas others found no differences in GEP uptake [11,12]. In a US health-care setting disparities in GEP uptake between different socio-economic classes may well be explained by financial inequalities. In a Dutch health care setting these financial motives cannot explain difference in GEP uptake as GEPs are fully reimbursed for every breast cancer patient. The fact that only a limited proportion of patients received a GEP illustrates that GEP use within the guideline-directed indicated area is not yet self-evident and one can hypothesize that GEP use is driven by patient request to some extent. DeFrank et al. [12] report higher incidence of GEP use in patients who played an active role in their treatment decision-making style; these patients commonly are younger patients and of a higher educational level [19]. The retrospective observational design of the present study precludes firm conclusions.

The population-based character of the current study makes this work unique and enables us to give an overview of GEP use in the Dutch health care setting. Both 21-RS use and 70-GS use were incorporated into the current study in contrast to other reports on GEP uptake. Data on income or education on an individual level was not available and we therefore used mean value of the home and household income on an aggregated level as a proxy for SES. Although this method is adapted by others and has shown to give a fair estimation of SES on an individual level [20], care must be taken when interpreting the association between SES and GEP use. Furthermore, the current study design precludes detailed analysis on possible explanations for the observed disparities in GEP use uptake between different SES categories and therefore our findings merit further study.

In conclusion, substantial variation was observed in the deployment of GEPs in breast cancer patients eligible for GEP use in the Dutch health-care setting. In 2014 nearly half of all patients for whom GEPs are considered worthwhile received a GEP. Tumor characteristics pertaining to an intermediate clinical risk-profile were associated with the use of GEP. Older patients and patients of low SES were less likely to receive GEP testing, the latter coming as a surprise. As GEP use within this guideline-directed indicated area for GEP use has been shown to decrease the proportion of patients receiving CT and hence prevents overtreatment and two-thirds of the tests come out as low risk, efforts should be made to diminish the disparities in GEP use.

**Suppl. Table 1.** *Patient-, tumor and treatment characteristics of patients within the guideline-directed indicated area for gene-expression profile (GEP) use stratified for the three socioeconomic status categories*

| | | Low SES (n = 1,383) | Medium SES (n = 2,083) | High SES (n = 1,644) | |
|---|---|---|---|---|---|
| | | n (%) | n (%) | n (%) | p-value |
| *Tumor characteristics* | | | | | |
| **Morpholgy** | *Ductal* | 1,086 (79%) | 1,603 (80%) | 1,245 (76%) | |
| | *Lobular* | 208 (15%) | 338 (16%) | 295 (18%) | |
| | *Mixed* | 41 (3%) | 83 (4%) | 61 (4%) | |
| | *Other* | 48 (4%) | 59 (3%) | 43 (3%) | 0.164 |
| **Tumorsize in mm** | *mean** | 20.5 | 21 | 23.8 | 0.421 |
| **Invasive tumor grade** | *Grade I* | 175 (13%) | 216 (10%) | 176 (11%) | |
| | *Grade II* | 1,208 (87%) | 1,867 (90%) | 1,468 (89%) | 0.092 |
| **PR-status** | *Negative* | 208 (15%) | 309 (15%) | 256 (16%) | |
| | *Positive* | 1,174 (85%) | 1,771 (85%) | 1,379 (84%) | 0.788 |
| | *Missing* | 1 | 3 | 9 | |
| **pN status** | *pN0* | 1,245 (90%) | 1,865 (90%) | 1,450 (88%) | |
| | *pN1mi* | 138 (10%) | 218 (10%) | 194 (12%) | 0.232 |
| **GEP use** | *No* | 1,055 (76%) | 1,561 (75%) | 1,134 (69%) | |
| | *Yes* | 328 (24%) | 522 (25%) | 510 (31%) | <0.001 |
| *Patient characteristics* | | | | | |
| **Age in years** | *mean** | 57.1 | 57 | 56.5 | 0.105 |
| | *< 35* | 2 (0%) | 2 (0%) | 2 (0%) | |
| | *35 - 50* | 335 (24%) | 517 (25%) | 452 (28%) | |
| | *51 - 69* | 1,046 (76%) | 1,564 (75%) | 1,190 (72%) | 0.257 |

| Suppl. Table 1 continued. | | Low SES (n = 1,383) | Medium SES (n = 2,083) | High SES (n = 1,644) | |
|---|---|---|---|---|---|
| | | n (%) | n (%) | n (%) | p-value |
| **Incidence year** | *2011* | 336 (24%) | 497 (23%) | 372 (23%) | |
| | *2012* | 315 (23%) | 492 (24%) | 388 (24%) | |
| | *2013* | 336 (24%) | 509 (24%) | 388 (24%) | |
| | *2014* | 309 (22%) | 464 (22%) | 403 (25%) | 0.808 |
| *Hospital characteristics* | | | | | |
| **Volume of breast cancer care p/y** | *mean** | 134.3 | 141.5 | 143.8 | < 0.001 |
| | *<100 patients* | 402 (29%) | 517 (25%) | 401 (24%) | |
| | *100-200 patients* | 789 (57%) | 1,183 (57%) | 936 (57%) | |
| | *>200 patients* | 192 (14%) | 383 (18%) | 307 (19%) | < 0.001 |
| **Type of hospital** | *District* | 475 (34%) | 647 (31%) | 367 (22%) | |
| | *Top clinical* | 801 (58%) | 1,336 (64%) | 1,159 (71%) | |
| | *University* | 107 (8%) | 100 (5%) | 118 (7%) | < 0.001 |
| **Teaching hospital** | *No* | 505 (37%) | 725 (35%) | 548 (33%) | |
| | *Yes* | 878 (63%) | 1,358 (65%) | 1,096 (67%) | 0.187 |
| **Region** | *North* | 630 (46%) | 720 (35%) | 602 (37%) | |
| | *Middle* | 424 (31%) | 763 (37%) | 793 (48%) | |
| | *South* | 328 (24%) | 599 (29%) | 248 (15%) | < 0.001 |

* One-way ANOVA, other values represent Chi-square values.

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# Chapter 7

Impact of gene-expression profiling in patients with early breast cancer when applied outside the guideline directed indication area

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K. Schreuder
A. Kuijer
E. J. Th. Rutgers
C.H. Smorenburg
Th. van Dalen
S. Siesling

**Abstract**

**Purpose**

In Dutch guidelines gene expression profiles (GEP) are indicated in estrogen receptor positive early breast cancer patients in whom benefit of chemotherapy (CT) is uncertain based on traditional prognostic factors alone. Aim of the current study is to assess the use and impact of GEP on administration of adjuvant CT in breast cancer patients who have according to national guidelines a clear indication to either use or withhold adjuvant chemotherapy (clinical high or low risk).

**Methods**

Clinical low- and high risk patients, according to Dutch breast cancer guidelines, diagnosed between 2011-2014 were selected from the Netherlands Cancer Registry (NCR). Influence of GEP use and GEP test result on CT administration was assessed with logistic regression.

**Results**

Overall, 26,425 patients were identified; 4.8% of patients with clinical low- risk (444/ 9,354), 7.5% of the patients with a clinical high-risk (1,281/ 17,071) received a GEP. GEP use was associated with a significantly increased odds of CT administration in clinical low-risk patients (OR=2.12 95%CI: 1.44-3.11). In clinical high-risk patients GEP use was associated with a decreased frequency of CT administration (OR=0.55, 95%CI: 0.48-0.63). Adherence to the GEP result was higher in clinical high-risk patients with a discordant GEP result as compared to clinical low-risk patients with a discordant GEP result: 71.7% vs. 52.2%, respectively.

**Conclusion**

GEP is frequently used outside the indicated area and significantly influenced the administration of adjuvant CT, although adherence to the test-result was limited.

**Introduction**

The use of adjuvant systemic therapy has considerably improved the prognosis of patients with breast cancer over the last two decades [1]. However, there is also a growing awareness that this broad application of adjuvant chemotherapy (CT) increases the risk of overtreatment as the threshold to use CT is difficult to determine [2]. Different biologic and clinical clues suggest that not all patients derive substantial benefit from CT [3]. Especially in estrogen-receptor (ER) positive (+) early-stage breast cancer patients doubt exists regarding the benefit of adjuvant CT. Because of negative side effects of systemic therapies, effective use is important [4].

Gene expression profiles (GEPs) were developed a decade ago to enable a prediction of prognosis in addition to the prognostic information of conventional clinicopathological factors. Although the predictive value of GEPs in terms of a quantified benefit of administering CT is still disputed, national and international treatment guidelines currently suggest the use of a GEP complementary to clinicopathological factors in ER+ early stage breast cancer patients [3, 5-9]. The Dutch guideline (2012) suggests the use of a validated GEP in early breast cancer patients, in whom benefit of CT is uncertain based on traditional prognostic factors alone [3, 9]. In a previous study it was demonstrated that this category, in which GEP use is highest, consists of patients with estrogen receptor (ER) positive (+)/HER2-Neu negative (-) disease without overt lymph-node metastasis (pT1c-2N0-1mi)[10] .

Since all insurance companies fully reimburse GEP use in the Netherlands, and health-care insurance is mandatory, GEPs are available for every Dutch breast cancer patient. Within the guideline directed indicated area an increase in GEP use over recent years and high adherence rates to the GEP test-result were observed [11]. An unexpected observation in a previous population-based study was the frequent use of GEPs outside the guideline-intended indicated area, i.e. in patients in whom clinical guidelines state a clear recommendation to administer or withhold CT based on clinicopathological factors alone [12]. GEP use in this patient group raises the question whether the GEP test results influenced CT administration in these patients.

The aim of the current study is to evaluate the clinical implications (CT administration) of GEP use (MammaPrint™ 70-gene signature) and GEP test results when used outside the guideline intended GEP indication area. In this group, clinical risk estimation and the GEP test-result was compared and adherence rates to the test-result were determined in case of discordance between the clinical and genomic risk assessment.

## Material and methods

*Data source*

Data was derived from the Netherlands Cancer Registry (NCR) database. Since 1989, the NCR registers data on patient-, tumour-, diagnostic- and treatment characteristics of all Dutch cancer patients, obtained by data-managers directly from patient records. All surgically treated female patients diagnosed with primary non-metastatic invasive breast cancer between January 1st 2011 and December 31st 2014 were identified.

*Study population*

Patients with a prior history of malignancy or initially treated with CT or endocrine therapy prior to surgical treatment were excluded from the analysis. Patients >70 years of age were excluded since guidelines are inconclusive about the benefit of adjuvant CT advice in these patients. For the present study, patients were excluded for whom the current guideline advises to use a GEP as an adjunct to clinicopathological factors to guide adjuvant CT decision-making, i.e. patients with ER positive /HER2-Neu negative (-) disease without overt lymph-node metastasis (pT1c-2N0-1mi). The 70-GS is accountable for 97% of all deployed GEPs in the Netherlands, and we therefore decided to focus on the MammaPrint™ 70-gene signature only.

Patients for whom the current Dutch treatment guidelines states a clear advice to administer or withhold CT, so without an indication to perform a GEP, were included in the study. This includes patients ≤70 years of age, regarded as clinical low- risk, for which adjuvant CT is not recommended or high-risk based with recommendation to administer CT according to the Dutch breast cancer treatment guideline (Supplementary Table 1) [13] .

*Statistical Analyses*

Clinical low- and high-risk group were identified and further classified into different subcategories according to the Dutch guidelines based on grade, tumor size and lymph-node involvement. For both the clinical low- and high-risk group patient and tumor characteristics as well as hospital type (district, teaching and university) were compared between patients who did and did not received GEP testing by chi-square tests and an independent t-test for the normally distributed continuous variables age and size. Proportions of patients receiving a GEP in relation to the frequencies of the listed low- and high risk categories are summarized and listed with the respective GEP test results and proportions of patients receiving adjuvant CT. Implications of GEP use, in terms of discordance between the clinical and genomic risk estimate and adherence to the test-result reflected in adjuvant CT administration were evaluated in both the clinical low- and high-risk patients and the various subcategories. Subsequently, logistic regression analysis was performed to assess if GEP use was independently associated with the administration of adjuvant CT in clinical low- or high-risk patients after correction for confounders. The same approach was used to assess whether the GEP test result was independently associated

with CT administration in clinical low- or high-risk patients who received GEP testing. Results are presented as Odds Ratio's (OR) and 95% confidence intervals (95% CI). A p-value of <0.05 was considered to be statistically significant. All statistical analyses were performed in STATA (version 13.1 2013, Texas).

**Results**

*Study population*

A total of 26,425 patients were identified in the NCR database: 35.4% of these patients were considered as clinical low-risk and 64.6% as clinical high-risk according to the guideline (Figure 1). Overall, 3.9% patients in the clinical low-risk group received CT and 79.7% of clinical high-risk patients. A total of 1,725 GEPs (6.5%) were deployed in the study-population: in 4.8% (n=444) of the patients in the clinical low-risk group and in 7.5% (n=1,281) of patients in the clinical high-risk group received a GEP. Overall, 68.5% of patients with a discordant clinical and genomic risk estimation were treated in line with the GEP test result.

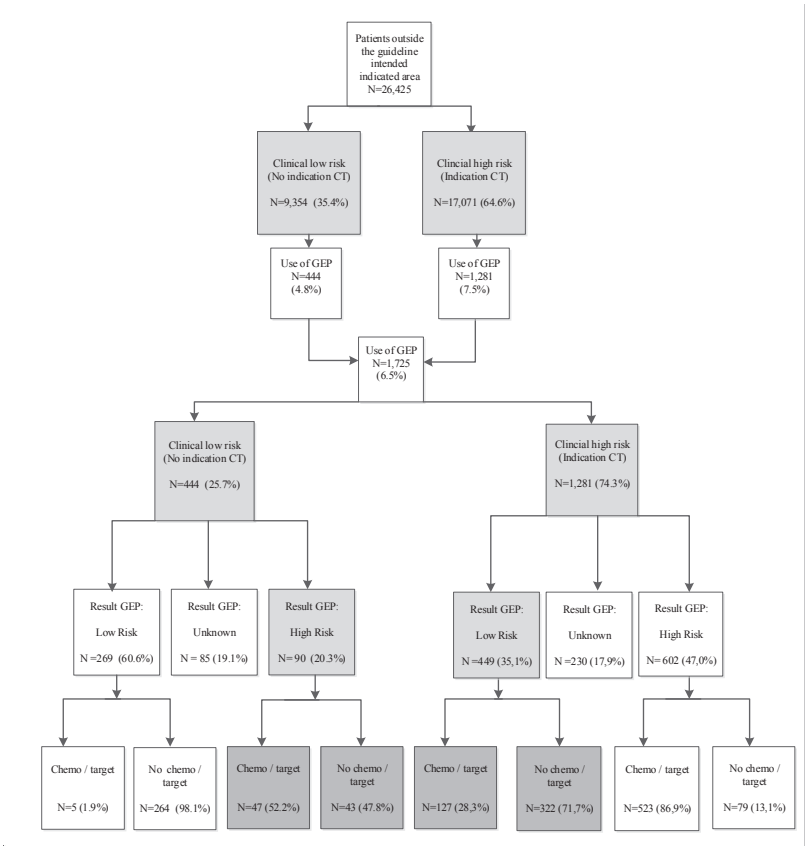


**Figure 1.** *Flowchart describing discordance between the clinical and genomic risk estimation and adherence to the genomic test-result reflected in adjuvant CT administration*

*GEP use in clinical low-risk patients*

GEPs assigned 20.3% of the clinical low-risk patients to a high genomic risk category. GEPs were more frequently deployed in patients under 35 years of age, with ER+/HER2- tumors of limited size without axillary lymph-node involvement. Furthermore, GEPs were more often deployed in patients treated in teaching hospitals (Table 1). GEP use was highest (32.2%) in the clinical low-risk patients <35 years of age with HER2-negative, grade 1 tumours ≤ 1cm without axillary lymph-node involvement (group 1, Supplementary Table 2).

Overall, in 15.5% of clinical low-risk patients who underwent CT a GEP was deployed compared to 4.3% who did not receive CT ($p<0.05$) (Table 1). GEP use was independently associated with an increased risk of receiving CT in clinical low-risk patients on multivariate logistic regression analysis (OR=2.12, 95%CI: 1.44-3.11, data not shown). The presence of axillary micro-metastases was the only clinicopathological factor that remained independently associated with CT administration in clinical low-risk patients who received GEP testing (pNmi vs. pN0, OR=10.75 95%CI: 3.29-35.13, Table 2). In the subset of clinical low risk patients with discordance between clinical and genomic risk assessment (n=90; i.e. the GEP assigned patients to the high-risk category) CT was administered in 52.2% of patients (Figure 1).

*GEP use in clinical high-risk patients*

The GEP assigned 449 patients to a low genomic risk category (35%). GEPs were more frequently deployed in clinical high-risk patients who were slightly older and more often had ER+/Her2- tumors <3 cm without axillary node involvement (Table 1). In 6.1% of clinical high-risk patients who received CT a GEP was deployed compared to 12.8% of patients who did not receive CT ($p<0.001$, Table 1). GEP use in clinical high-risk patients remained independently associated with a decreased risk of CT administration in multivariate logistic regression analysis (OR=0.55 95%CI: 0.48-0.63, data not shown).

In clinical high-risk patients who received a GEP, a low-risk GEP result was strongly associated with a decreased risk of CT administration (OR=0.05, 95%CI: 0.03-0.07). In 71.7% (n = 322) of these discordant patients the administration of adjuvant CT was in line with the low-risk GEP test-result (i.e. no CT was administered, Figure 1). Young age, larger tumor size, higher grade, Her2+ disease and (micro-)metastatic lymph-node involvement remained independently associated with an increased risk of CT administration in these patients (Table 3).

**Table 1.** *Patient and tumour characteristics as well as hospital type were compared between patients who did and did not received GEP testing for both the clinical low- and high-risk group*

| | | Clinical low risk (n=9,354) | | | | | Clinical high risk (n=17,071) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No GEP received (n=8,910) | | GEP received (n=444) | | p-value* | No GEP received (n=15,790) | | GEP received (n=1,281) | | p-value* |
| **Age in years (mean, SD)** | | 57.74 | 7.82 | 54.29 | 8.37 | | 53.69 | 9.87 | 54.32 | 9.22 | |
| | *<35* | 12 | 70.6% | 5 | 29.4% | | 637 | 95.2% | 32 | 4.8% | |
| | *35-50* | 1,812 | 92.5% | 147 | 7.5% | | 5,368 | 92.6% | 429 | 7.4% | |
| | *50-75* | 7,086 | 96.0% | 292 | 4.0% | <0.05 | 9,785 | 92.3% | 820 | 7.7% | <0.05 |
| **Tumour Size in mm (mean, SD)** | | 9.15 | 4.05 | 11.46 | 4.41 | | 23.3 | 13.07 | 20.67 | 9.6 | |
| | *<10* | 6,147 | 96.5% | 221 | 3.5% | | 977 | 94.9% | 52 | 5.1% | |
| | *10-20* | 2,763 | 92.5% | 223 | 7.5% | | 6,283 | 91.1% | 614 | 8.9% | |
| | *21-30* | 0 | 0.0% | 0 | 0.0% | | 5,315 | 91.8% | 473 | 8.2% | |
| | *> 31* | 0 | 0.0% | 0 | 0.0% | | 2,800 | 95.6% | 130 | 4.4% | |
| | *Unknown* | 0 | 0.0% | 0 | 0.0% | <0.05 | 415 | 97.2% | 12 | 2.8% | <0.05 |
| **Estrogene receptor** | *ER-* | 576 | 96.5% | 21 | 3.5% | | 3,756 | 95.2% | 188 | 4.8% | |
| | *ER+* | 8,245 | 95.1% | 422 | 4.9% | | 11,793 | 91.5% | 1,092 | 8.5% | |
| | *Unknown* | 89 | 98.9% | 1 | 1.1% | <0.05 | 241 | 99.6% | 1 | 0.4% | <0.05 |
| **Progesterone receptor** | *PR-* | 1,870 | 96.3% | 71 | 3.7% | | 5,979 | 94.1% | 375 | 5.9% | |
| | *PR+* | 6,945 | 94.9% | 372 | 5.1% | | 9,550 | 91.4% | 904 | 8.6% | |
| | *Unknown* | 95 | 99.0% | 1 | 1.0% | <0.05 | 261 | 99.2% | 2 | 0.8% | <0.05 |
| **Her2 Neu** | *Her2-* | 8,450 | 95.1% | 434 | 4.9% | | 11,862 | 91.7% | 1,068 | 8.3% | |
| | *Her2+* | 268 | 97.8% | 6 | 2.2% | | 3,613 | 94.7% | 203 | 5.3% | |
| | *Unknown* | 192 | 98.0% | 4 | 2.0% | <0.05 | 315 | 96.9% | 10 | 3.1% | <0.05 |

| Table 1 continued. | | Clinical low risk (n=9,354) | | | | | Clinical high risk (n=17,071) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No GEP received (n=8,910) | | GEP received (n=444) | | p-value* | No GEP received (n=15,790) | | GEP received (n=1,281) | | p-value* |
| **Node state** | *Negative* | 8,177 | 95.9% | 347 | 4.1% | | 7,129 | 89.7% | 821 | 10.3% | |
| | *Mi*** | 540 | 85.2% | 94 | 14.8% | | 1,127 | 92.3% | 94 | 7.7% | |
| | *N1* | 0 | 0.0% | 0 | 0.0% | | 5,358 | 94.9% | 285 | 5.1% | |
| | *N2* | 0 | 0.0% | 0 | 0.0% | | 1,283 | 96.5% | 47 | 3.5% | |
| | *N3* | 0 | 0.0% | 0 | 0.0% | | 712 | 96.7% | 24 | 3.3% | |
| | *Unknown* | 193 | 98.5% | 3 | 1.5% | <0.05 | 181 | 94.8% | 10 | 5.2% | <0.05 |
| **Grade** | *1* | 5,703 | 95.1% | 297 | 5.0% | | 1,417 | 92.3% | 118 | 7.7% | |
| | *2* | 2,481 | 95.9% | 105 | 4.1% | | 6,383 | 91.8% | 567 | 8.2% | |
| | *3* | 660 | 94.0% | 42 | 6.0% | | 7,663 | 92.9% | 587 | 7.1% | |
| | *Unknown* | 66 | 100.0% | 0 | 0.0% | <0.05 | 327 | 97.3% | 9 | 2.7% | 0.05 |
| **Multifocality** | *No* | 7,867 | 95.3% | 388 | 4.7% | | 12,595 | 92.0% | 1,096 | 8.0% | |
| | *Yes* | 989 | 94.6% | 56 | 5.4% | | 2,934 | 94.1% | 184 | 5.9% | |
| | *Unknown* | 54 | 100.0% | 0 | 0.0% | 0.17 | 261 | 99.6% | 1 | 0.4% | <0.05 |
| **Hospital of surgery** | *District* | 2,992 | 95.7% | 133 | 4.3% | | 5,377 | 93.3% | 388 | 6.7% | |
| | *Teaching* | 5,108 | 94.6% | 293 | 5.4% | | 9,081 | 91.4% | 850 | 8.6% | |
| | *University* | 810 | 97.8% | 18 | 2.2% | <0.05 | 1,332 | 96.9% | 43 | 3.1% | <0.05 |
| **Chemo/Targeted therapy** | *No* | 8,604 | 95.7% | 388 | 4.3% | | 3,028 | 87.2% | 445 | 12.8% | |
| | *Yes* | 306 | 84.5% | 56 | 15.5% | <0.05 | 12,762 | 93.9% | 836 | 6.1% | <0.05 |

** Chi-square test*

*** Micrometastasis*

**Table 2.** *Association between known GEP test result and the administration of adjuvant CT in clinical low- risk patients. ^ Patients with an unknown GEP test results (n=85) were excluded from this analyses*

| Factors associated with adjuvant chemotherapy administration in clinical low-risk patient who received a GEP (n=359) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | No Chemo / Targeted (n=307) | | Chemo / Targeted (n=52) | | | | | |
| | | | | | | Univariable | | Multivariate | |
| | | *n* | *%* | *n* | *%* | *OR* | *95% CI* | *OR* | *95% CI* |
| **GEP result** | *Low Risk* | 264 | 86.0% | 5 | 9.6% | ref | | ref | |
| | High Risk | 43 | 14.0% | 47 | 90.4% | 57.71 | 21.73-153.26 | 90.95* | 26.19-315.81 |
| **Age in years** | *<35* | 3 | 1.0% | 2 | 3.8% | ref | | ref | |
| | *35-50* | 108 | 35.2% | 23 | 44.2% | 0.32 | 0.05-2.02 | | |
| | *50-75* | 196 | 63.8% | 27 | 51.9% | 0.21 | 0.03-1.29 | | |
| **Tumour size in mm** | *<10* | 136 | 44.3% | 32 | 61.5% | ref | | ref | |
| | *11-20* | 171 | 55.7% | 20 | 38.5% | 0.50 | 0.27-0.91 | 0.82 | 0.20-3.33 |
| **Estrogene receptor** | *ER-* | 9 | 2.9% | 7 | 13.5% | ref | | ref | |
| | *ER+* | 298 | 97.1% | 45 | 86.5% | 0.19 | 0.07-0.55 | 1.37 | 0.27-7.05 |
| | Unknown | 0 | 0.0% | 0 | 0.0% | | | | |
| **Progesterone receptor** | *PR-* | 40 | 13.0% | 16 | 30.8% | ref | | ref | |
| | *PR+* | 267 | 87.0% | 36 | 69.2% | 0.34 | 0.17-0.66 | 0.52 | 0.16-1.65 |
| | *Unknown* | 0 | 0.0% | 0 | 0.0% | | | | |
| **Her2 Neu** | *Her2-* | 302 | 98.4% | 51 | 98.1% | ref | | ref | |
| | *Her2+* | 2 | 0.7% | 1 | 1.9% | 2.96 | 0.26-33.25 | | |
| | *Unknown* | 3 | 1.0% | 0 | 0.0% | omitted | | | |

| **Table 2 continued.** | **Factors associated with adjuvant chemotherapy administration in clinical low-risk patient who received a GEP (n=359)** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | No Chemo / Targeted (n=307) | | Chemo / Targeted (n=52) | | | | | |
| | | | | | | Univariable | | Multivariate | |
| | | *n* | *%* | *n* | *%* | *OR* | *95% CI* | *OR* | *95% CI* |
| **Node state** | *Negative* | 236 | 76.9% | 32 | 61.5% | ref | | ref | |
| | *Mi*** | 69 | 22.5% | 20 | 38.5% | 2.14 | 1.15-3.97 | 10.75* | 3.29-35.13 |
| | *Unknown* | 2 | 0.7% | 0 | 0.0% | omitted | | | |
| **Grade** | *1* | 224 | 73.0% | 24 | 46.2% | ref | | ref | |
| | *2* | 63 | 20.5% | 12 | 23.1% | 1.78 | 0.84-3.75 | 1.09 | 0.23-5.16 |
| | *3* | 20 | 6.5% | 16 | 30.8% | 7.47 | 3.42-16.30 | 3.13 | 0.62-15.65 |
| | *Unknown* | 0 | 0.0% | 0 | 0.0% | omitted | | | |
| **Multifocality** | *No* | 267 | 87.0% | 41 | 78.8% | ref | | ref | |
| | *Yes* | 40 | 13.0% | 11 | 21.2% | 1.79 | 0.85-3.77 | | |
| | *Unknown* | 0 | 0.0% | 0 | 0.0% | | | | |
| **Hospital of surgery** | *District* | 93 | 30.3% | 17 | 32.7% | ref | | ref | |
| | *Teaching* | 201 | 65.5% | 31 | 59.6% | 0.84 | 0.44-1.60 | | |
| | *University* | 13 | 4.2% | 4 | 7.7% | 1.68 | 0.49-5.78 | | |

** Significant OR*

*** Micrometastasis*

**Table 3.** *Association between known GEP test result and the administration of adjuvant CT in clinical high-risk patients. ^ Patients with an unknown GEP test results (n=230) were excluded from this analyses*

| Factors associated with adjuvant chemotherapy administration in clinical high-risk patient who received a GEP (n = 1,051) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | No Chemo / Targeted (n=401) | | Chemo / Targeted (n=650) | | | | | |
| | | | | | | Univariable | | Multivariate | |
| | | *n* | *%* | *n* | *%* | *OR* | *95% CI* | *OR* | *95% CI* |
| **GEP result** | *Low Risk* | 322 | 80.3% | 127 | 19.5% | 0.06 | 0.04-0.08 | 0.05* | 0.03-0.07 |
| | High Risk | 79 | 19.7% | 523 | 80.5% | ref | | ref | |
| **Age in years** | *<35* | 4 | 1.0% | 19 | 2.9% | ref | | ref | |
| | *35-50* | 91 | 22.7% | 248 | 38.2% | 0.57 | 0.19-1.73 | 0.31 | 0.07-1.40 |
| | *50-75* | 306 | 76.3% | 383 | 58.9% | 0.26 | 0.09-0.78 | 0.12* | 0.03-0.54 |
| **Tumour size in mm** | *<10* | 22 | 5.5% | 20 | 3.1% | ref | | ref | |
| | *11-20* | 165 | 41.1% | 356 | 54.8% | 2.37 | 1.26-4.47 | 2.82* | 1.11-7.16 |
| | *21-30* | 184 | 45.9% | 204 | 31.4% | 1.22 | 0.64-2.31 | 3.10* | 1.17-8.25 |
| | *> 31* | 26 | 6.5% | 65 | 10.0% | 2.75 | 1.29-5.86 | 6.84* | 2.21-21.23 |
| | *Unknown* | 4 | 1.0% | 5 | 0.8% | 1.38 | 0.32-5.85 | 5.25 | 0.73-37.74 |
| **Estrogene receptor** | *ER-* | 14 | 3.5% | 124 | 19.1% | ref | | ref | |
| | *ER+* | 387 | 96.5% | 525 | 80.8% | 0.15 | 0.09-0.27 | 0.54 | 0.25-1.16 |
| | Unknown | 0 | 0.0% | 1 | 0.2% | omitted | | | |
| **Progesterone receptor** | *PR-* | 59 | 14.7% | 227 | 34.9% | ref | | ref | |
| | *PR+* | 342 | 85.3% | 421 | 64.8% | 0.32 | 0.23-0.44 | 0.78 | 0.48-1.29 |
| | *Unknown* | 0 | 0.0% | 2 | 0.3% | omitted | | | |

| Table 3 continued. | Factors associated with adjuvant chemotherapy administration in clinical high-risk patient who received a GEP (n=1,051) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | No Chemo / Targeted (n=401) | | Chemo / Targeted (n=650) | | | | | |
| | | | | | | Univariable | | Multivariate | |
| | | *n* | *%* | *n* | *%* | *OR* | *95% CI* | *OR* | *95% CI* |
| **Her2 Neu** | *Her2-* | 365 | 91.0% | 535 | 82.3% | ref | | ref | |
| | *Her2+* | 28 | 7.0% | 113 | 17.4% | 2.75 | 1.78-4.25 | 3.30* | 1.68-6.52 |
| | *Unknown* | 8 | 2.0% | 2 | 0.3% | 0.17 | 0.04-0.81 | 0.3 | 0.02-5.11 |
| **Node state** | *Negative* | 286 | 71.3% | 430 | 66.2% | ref | | ref | |
| | *Mi*** | 34 | 8.5% | 40 | 6.2% | 0.78 | 0.48-1.27 | 1.85 | 0.95-3.60 |
| | *N1* | 77 | 19.2% | 139 | 21.4% | 1.20 | 0.88-1.65 | 7.48* | 4.27-13.13 |
| | *N2* | 0 | 0.0% | 22 | 3.4% | omitted | | omitted | |
| | *N3* | 1 | 0.2% | 12 | 1.8% | 7.98 | 1.03-61.72 | 28.01* | 3.15-249.41 |
| | *Unknown* | 3 | 0.7% | 7 | 1.1% | 1.55 | 0.40-6.05 | 1.17 | 0.23-5.95 |
| **Grade** | *1* | 55 | 13.7% | 42 | 6.5% | ref | | ref | |
| | *2* | 232 | 57.9% | 240 | 36.9% | 1.35 | 0.87-2.10 | 2.19* | 1.17-4.10 |
| | *3* | 113 | 28.2% | 361 | 55.5% | 4.18 | 2.66-6.59 | 3.93* | 1.94-7.96 |
| | *Unknown* | 1 | 0.2% | 7 | 1.1% | 9.17 | 1.09-77.40 | 2.97 | 0.24-36.72 |
| **Multifocality** | *No* | 350 | 87.3% | 551 | 84.8% | ref | | ref | |
| | *Yes* | 51 | 12.7% | 98 | 15.1% | 1.22 | 0.85-1.76 | | |
| | *Unknown* | 0 | 0.0% | 1 | 0.2% | omitted | | | |
| **Hospital of surgery** | *District* | 135 | 33.7% | 187 | 28.8% | ref | | ref | |
| | *Teaching* | 246 | 61.3% | 444 | 68.3% | 1.30 | 0.99-1.71 | | |
| | *University* | 20 | 5.0% | 19 | 2.9% | 0.69 | 0.35-1.33 | | |

** Significant OR*

*** Micrometastasis*

**Discussion**

While the Dutch guideline suggests the use of a validated GEP in ER+ early breast cancer patients, in whom benefit of CT is uncertain based on traditional prognostic factors alone [3, 9], in the present population based study GEPs were used in 4.7% and 7.5% of patients who were considered as clinical low-risk and high-risk respectively. In these groups a discordance between the clinical and genomic risk-estimation was observed in 20.3% and 35.1% respectively and GEP use significantly influenced CT administration in these patients.

To our knowledge this is the first report on the clinical impact of GEP use in patients in whom a GEP should be superfluous as the recommendation to administer or withhold CT is clear based on clinicopathological factors. The observed frequency of 6.5% in the present group is remarkable and compares to a 15% deployment of GEPs in the category of patients in whom GEPs were advocated [10]. The relatively high incidence of GEP use in the present study and the apparent impact of GEP use on CT administration in these patients, suggests limited support among clinicians and patients for the current clinical guideline recommendations. The mere frequency of 'unintended' GEP use underscores that clinicians need reproducible and objective measures for the decision to administer CT. In both clinical low- as high-risk patients GEP use was more frequent in patients with ER+/Her2- intermediate grade tumors of limited size, indicating uncertainty regarding CT administration especially in these subgroups of patients. Patients with micro-metastatic axillary lymph-node involvement were more likely to receive a GEP in the clinical low-risk group while GEPs were deployed mere frequently in node-negative patients in the clinical high-risk group.

When a GEP was deployed we observed an overall discordance between clinical and genomic risk estimation in 31,3% of patients assigned to the clinical low- or high-risk category. One out of three clinical high-risk patients were assigned to the low-risk category by GEPs which led to omission of CT, despite a guideline indication to administer CT, in approximately 72% of these patients. The results of the MINDACT trial support the omission of adjuvant CT in stage I-III early stage clinical high-risk breast cancer patients with up to three axillary lymph-node metastasis when the GEP categorizes these patients as having a low genomic risk [14]. On the other hand, in the MINDACT trial clinical utility of 70-gene signature use was not demonstrated for clinical low-risk patients as clinical low-risk patients assigned to the genomic high-risk profile who did not receive CT had similar 5-year disease free survival rates as patients who did receive CT. Therefore, the indication area for GEP use as stated in current clinical practice guidelines will probably be further broadened to clinical high-risk patients in coming years while its use will be discommended in clinical low-risk patients.

Overall, 68.5% of patients with a discordant clinical and genomic risk estimation were treated in line with the GEP test result (52.2% in low and 71.7% in high). This is substantially lower as compared to patients within the guideline intended area for GEP use, in whom adherence rates to the GEP result of up to 89% have been reported [10]. This observation is on the one hand not surprising since the level of evidence for GEP use in clinical low- or high risk patients was modest during our study-period. On the other hand it remains strange that the test was deployed for 'some' reason and subsequently not adhered to in 47.8% of patients with a low and 28.3% of patients with a high risk test result. This may be explained by deployment of a GEP on a patients' request. Interestingly, GEP use was observed in 3-4% of N2/N3 high-risk patients. The use of GEPs in these patients can possibly be explained by patients' preferences to avoid CT. However, further qualitative psycho-oncological research is necessary to determine the influence of patients' preferences in undergoing CT in clinical low and high risk patients with (dis)cordant GEP results. On the other hand physicians may seek more support for the recommendation or avoidance of CT instead of being in true doubt when deploying a GEP in the guideline intended indication area. The results of the MINDACT trial will probably strengthen the motivation for GEP use in clinical high-risk patients, and may lead to a higher adherence to the low-risk GEP result. The observed higher adherence to the GEP result in clinical high risk patients assigned to the low-risk GEP category (71.7%) in comparison to clinical low risk patients assigned to the high GEP category (52.2%) is in line with previous studies which also report on GEPs being mainly used for a substantiated decision to withhold CT.

The population-based character of the present study makes our work unique and enables us to provide a nation-wide overview of GEP use (MammaPrint™ 70-gene signature). Implications of GEP use in ER+/Her2- early stage breast cancer patients in whom uncertainty exists regarding CT benefit based on traditional prognostic factors alone are increasingly studied. Reports on implications of GEP testing at a nation-wide level or in patients outside this guideline intended indication area are scarce. The strength of the population based design is the weakness of the study as well. Although we assessed the association between GEP use and CT administration in multivariable logistic regression analysis correcting for all known clinicopathological characteristics, confounding by indication cannot be ruled out completely.

**Conclusion**

GEPs are relatively quite frequently used to aid adjuvant CT decision-making in patients with a clear clinical guideline recommendation to administer or withhold CT in the Netherlands. Although adherence to the test result is limited in the categories of patients who are considered as having a low- or high clinical risk of developing metastases, GEP use significantly influenced CT decision-making in these patients illustrating the clinicians need for reproducible and objective measures for the decision to administer CT.

**Conflict of interest**

The authors do not declare any conflicts of interest.

**Ethics approval and consent to participate**

According to the Central Committee on Research involving Human Subjects (CCMO), this type of study does not require approval from an ethics committee in the Netherlands. This study was approved by the Privacy Review Board of the Netherlands Cancer Registry.

**Availability of data and materials**

The data that support the findings of this study are available from Netherlands Comprehensive Cancer Organization but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Netherlands Comprehensive Cancer Organization.

**Suppl. Table 1.** *Patients outside the guideline intended GEP indicated area: distinction between clinical low- or high-risk early stage breast cancer patients based on established prognostic factors according to the Dutch breast cancer treatment guideline. This guideline recommends to withhold chemotherapy in patients considered as clinical low-risk and administer chemotherapy in clinical high-risk patients*

| Clinical low-risk: | Clinical high-risk*: |
|---|---|
| No axillary lymph-node involvement (pN0 or pN1mi), > 35 years of age, Her2- disease and: | All patients with metastatic axillary lymph-node involvement (≥pN1a) (Group I) |
| Tumour size < 1 cm (Group 2)<br>o ER+<br>o ER-<br>o Grade III<br>o Grade I/II | All patients <35 years of age with tumours > 1cm |
| Grade I and tumour size 1 - 2 cm (Group 3) | All patients with Her2+ disease (except for tumours 0 – 0.5 cm) |
| Or: | Patients without metastatic axillary lymph-node involvement (pN0 or pN1mi) and: |
| <35 years of age, grade I, 0 - 1 cm (Group I) | Tumour size > 2 cm |
| Her2+, tumour size 0 - 0.5 cm (Group 4) | Grade II or III tumours > 1 cm |

*Note: adjuvant chemotherapy is only recommended in clinical high-risk patients <70 years of age.

**Suppl. Table 2.** *Proportions of patients receiving a GEP in relation to the frequencies of the listed low- and high risk categories are summarized and listed with the respective GEP test results and proportions of patients receiving adjuvant CT*

| Clinical Low risk (n=9,354) | Total | GEP test | | GEP result | | | | | | Adjuvant CT administration | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | n | % | Low Risk | | High Risk | | Un-known | | Patients with no GEP | | GEP Low Risk | | GEP high risk | |
| **Group 1** | | | | n | % | n | % | n | % | n | % | n | % | n | % |
| p1N0, MS or 1M, age <35, grade 1, size <11 mm and her2 negative disease | 16 | 5 | 32.3% | 4 | 80.0% | 1 | 20.0% | 0 | 0.0% | 1 | 9.1% | 1 | 25.0% | 1 | 100.0% |
| **Group 2** | | | | | | | | | | | | | | | |
| p1N0, MS or 1M, age >34, grade 1, 2 or 3, size <11 mm and her2 negative disease | 643 | 42 | 6.5% | 13 | 31.0% | 23 | 54.8% | 6 | 14.3% | 90 | 15.0% | 1 | 8.0% | 15 | 65.2% |
| **Group 3** | | | | | | | | | | | | | | | |
| p1N0, MS or 1M, age >35, grade 1, size <21 mm and her2 negative disease | 2,986 | 223 | 7.5% | 154 | 69.1% | 37 | 16.6% | 32 | 14.4% | 93 | 3.4% | 2 | 1.0% | 18 | 48.7% |
| **Group 4** | | | | | | | | | | | | | | | |
| p1N0, MS or 1M, age >35, grade 1 or 2, size <11 mm and her2 negative disease | 5,435 | 168 | 3.1% | 97 | 57.7% | 27 | 16.1% | 44 | 26.2% | 77 | 1.5% | 1 | 1.0% | 12 | 44.4% |
| **Group 5** | | | | | | | | | | | | | | | |
| p1N0, MS or 1M, >34 , size <6 mm and her2 disease | 273 | 6 | 2.2% | 1 | 16.7% | 2 | 33.3% | 3 | 3.0% | 44 | 16.5% | 0 | 0.0% | 1 | 50.0% |
| **Group 6** | | | | | | | | | | | | | | | |
| p1N0, MS or 1M, age <35, grade 1, size <11 mm | 1 | 0 | 0.0% | 0 | 0.0% | 90 | 0.0% | 85 | 0.0% | 1 | 100.0% | | | | |

**Suppl. Table 2 continued.** *Proportions of patients receiving a GEP in relation to the frequencies of the listed low- and high risk categories are summarized and listed with the respective GEP test results and proportions of patients receiving adjuvant CT*

| **Clinical High risk (n=17,071)** | **Total** | **GEP test** | | **GEP result** | | | | | | **Adjuvant CT administration** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | n | % | Low Risk | | High Risk | | Un-known | | Patients with no GEP | | GEP Low Risk | | GEP high risk | |
| **Group 1** | | | | n | % | n | % | n | % | n | % | n | % | n | % |
| All patients with metastatic axillary lymph-node involvement (≥pN1a) | 7,709 | 356 | 4.6% | 144 | 40.5% | 107 | 30.1% | 105 | 29.5% | 6,382 | 86.8% | 74 | 51.4% | 99 | 95.5% |
| **Group 2** | | | | | | | | | | | | | | | |
| p1N0, MS or 1M, grade I or II, size > 10 mm | 6,341 | 733 | 11.6% | 263 | 35.9% | 393 | 53.6% | 77 | 10.5% | 4,126 | 73.6% | 40 | 15.2% | 333 | 84.7% |
| **Group3** | | | | | | | | | | | | | | | |
| p1N0, MS or 1M, age >35, grade 1, size > 20mm | 169 | 13 | 7.7% | 8 | 61.5% | 3 | 23.1% | 2 | 15.4% | 56 | 35.9% | 0 | 0.0% | 2 | 66.7% |
| **Group 4** | | | | | | | | | | | | | | | |
| p1N0, MS or 1M, size > 0.5 mm and her2 positive disease | 2,378 | 152 | 6.4% | 28 | 18.4% | 84 | 55.3% | 40 | 26.3% | 1,797 | 80.7% | 9 | 32.1% | 76 | 90.8% |
| **Group 5** | | | | | | | | | | | | | | | |
| p1N0, MS or 1M, < 35 years | 474 | 27 | 5.7% | 6 | 22.2% | 15 | 55.6% | 6 | 22.2% | 401 | 89.7% | 4 | 66.7% | 13 | 86.7% |

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# Chapter 8

Use and impact of the 21-gene recurrence score in relation to the clinical risk of developing metastases in early breast cancer patients in the Netherlands

*Submitted*

K. Schreuder
A. Kuijer
S. Bentum
Th. van Dalen
S. Siesling

**Abstract**

**Background**

The use of the 21-gene recurrence score (21-RS) and implications regarding chemotherapy administration in relation to clinical risk in early breast cancer patients is investigated.

**Methods**

Breast cancer patients surgically treated between 2014-2016 were selected from the Netherlands Cancer Registry and categorized as having a clinical low, intermediate or high risk of developing metastases. The use and impact of 21-RS test result on chemotherapy administration was assessed in relation to clinical risk, patient- and tumor characteristics and analyzed with chi-square tests.

**Results**

Of all patients, 20,488 were considered as clinical low-, 4,309 as intermediate- and 15,266 as high-risk patients. The 21-RS was deployed in 0.1% (n=23), 3.2% (n=137) and 0.6% (n=90), respectively. In the clinical intermediate-risk group the 21-RS assigned 73.7%, 13.1% and 13.1% of patients to the genomic low-, intermediate- or high-risk category, respectively. Adherence to the 21-RS was 95.6% in these patients.

**Conclusion**

In the Netherlands, the 21-RS test is applied both inside and outside the guideline directed area. In case of discordance between the genomic and clinical risk, patients were treated in line with the result of the 21-RS.

**Introduction**

The use of adjuvant systemic therapy has considerably improved outcome of breast cancer patients over the last two decades [1]. There is growing awareness that the selection of patients in whom the benefit of adjuvant chemotherapy (CT) outweighs the side effects of adjuvant CT can be optimized [2]. In addition to prognostic clinical factors, gene-expression profiles (GEPs) have found their way in recent years into clinical practice to more accurately distinguish between patients at low or high risk of disease recurrence [3].

Since 2012, the Dutch national breast cancer guideline (NABON) advocates the use of a GEP in patients in whom controversy exists about the benefit of adjuvant CT [3]. The latter group consists of patients with estrogen receptor (ER) positive (+)/HER2-Neu negative (-) disease of limited size and of low or intermediate malignance grade without overt lymph-node metastasis (pT1c-2N0-1mi) [4]. There are several GEPs commercially available of which the 70-gene signature (70-GS) and the 21-recurrence score (21-RS) are available in the Netherlands. The 70-GS and the 21-RS were both validated in large prospective trials [5, 6] and their prognostic value has been confirmed in ER+ breast cancer patients in a number of studies [7-11].

In a previous population based study, we observed an increase of 70-GS use in Dutch breast cancer patients within the aforementioned guideline directed indicated area in recent years [12]. When the 70-GS was used in accordance with the Dutch guideline, high adherence rates to the 70-GS test result were observed [13]. Remarkably, the 70-GS was frequently used in patients in whom the guideline was clear about the recommendation to administer or withhold CT. Although lower adherence rates to the GEP result were observed in these patients, use of a GEP significantly influenced CT decision-making [14].

The aim of the current study is to evaluate the use and clinical implications of 21-RS use in Dutch early stage breast cancer patients on a nation-wide level.

**Material and methods**

*Data Collection*

Data was derived from the Netherlands Cancer Registry (NCR). Since 1989, the NCR registers data on patient, tumour, diagnostic and treatment characteristics of all Dutch cancer patients. The information is collected by trained data managers and obtained directly from the patient records. Data concerning GEP use is available since 2011. The 21-gene recurrence score became available for clinical use in the Netherlands in 2013.

*Study Population*

From the NCR, all patients surgically treated for primary non-metastatic breast cancer between January 1st 2014 and December 31st 2016 were identified. Patients who were treated with CT or endocrine therapy prior to surgical treatment were excluded from the analysis. Since 2012, the Dutch national breast cancer guideline (NABON) suggests the selective use of a GEP in ER+ breast cancer patients in whom controversy exists about the indication for adjuvant CT since they are considered to have an intermediate risk of developing distant metastases. Following these Dutch breast cancer guideline directives, patients were categorized into clinical low, intermediate or high risk of recurrence or distant metastases which corresponded with the recommendation to omit or administer CT, respectively [3] (Table 1). The 70-GS and the 21-RS became available in Dutch clinical practice in 2011 and 2013 respectively. Patients in whom the 70-GS was deployed were excluded from the study population.

The deployment of the 21-RS in relation to the clinical risk profile was assessed as well as adherence to the test result for the respective clinical risk categories. Discordance was defined as a disagreement between clinical risk estimation and genomic test result (i.e., either high clinical risk and low genomic risk or low clinical risk and high genomic risk). Adherence to the test result was defined as treating the patient in line with the 21-RS test result. (i.e., CT administration or omission in patients with a genomic high or a genomic low risk, respectively). For patients with a genomic intermediate risk the omission of CT was seen as in line with the test result.

In addition, the clinical impact of the 21-RS was evaluated in the group of patients with an intermediate clinical risk of developing metastases in terms of the proportion of patients who received CT or not in relation with 21-RS deployment.

*Statistical Analysis*

A flowchart was created to visualize the implications of the use of the 21-RS, in terms of discordance between clinical and genomic risk estimate and adherence to the test result reflected in adjuvant CT use. To analyse trends in 21-RS use over time, the percentage of eligible patients actually receiving 21-RS, was set out against year of breast cancer diagnosis. Chi-square tests were performed and a p-value of $<0.05$ was considered to be statistically significant. Results are presented as actual numbers and (column) percentages. A Cohens kappa coefficient (k) was calculated to determine the agreement in clinical risk determination and 21-RS test result. Adherence to the 21-RS score was calculated per clinical risk category by dividing the number of patients assigned to the low-risk 21-RS result who did not receive CT plus the number of patients assigned to the high-risk 21-RS result who did receive CT by the total number of patients assigned to a 21-RS low or high-risk test result. All analyses were performed using STATA © version 14.1.

**Results**

A total of 40,887 patients surgically treated for primary non-metastatic breast cancer were identified during the study period, 50.1% were categorized as having a high clinical risk profile, 37.3% as having a low-risk profile and the remaining 4,309 patients had an intermediate risk. CT was administered in 52.2% of the clinical high-risk category, 3.7% of the low-risk category and 21.2% of the intermediate clinical risk category. During the study period a GEP was deployed in 3,921 patients. Of the patients in whom a GEP was used, the 21-RS was deployed in 254 patients (6.5%), while the remaining (majority of) patients received a 70-GS. Approximately half of the patients in whom the 21-RS was deployed (n=137) had an intermediate clinical risk profile. The 21-RS was deployed in 0.6%, 1.2% and 0.7% of the patients in the study population (n=29,935) in 2014, 2015 and 2016 respectively. The patient and tumour characteristics in relation to the clinical risk profile and 21-RS deployment are demonstrated in table 2.

Of the 254 patients in whom the 21-RS was deployed, 53.9% (n=137) were considered to have a clinical intermediate risk, 9.1% were considered as having a clinical low risk and 35.4% as having a clinical high risk. In four patients the clinical risk determination was not possible due to missing data (Figure 1). The 21-RS assigned 64.2% (n=163) of patients to a genetic low-risk profile, 19.3% (n=49) to an intermediate-risk result and 16.5% (n=42) to a high-risk test result. The 21-RS test result was in line with the clinical risk determination in 21.2% (n=53) of patients, which reflects a poor agreement (Cohens kappa: -0.01 (95%CI: -0.07-0.05)) (Table 3).

**Table 1.** *Study population: surgically treated patients between 2014-2016 divided by the guideline described clinical risk profiles*

| **Clinical high risk (chemotherapy indicated) n=20,488:** | **Intermediate risk (doubtful indication for chemotherapy) n=4,309:** | **Clinical low risk (chemotherapy not indicated) n=15,266:** |
|---|---|---|
| a. All patients with lymph node metastases (≥N1a), < 70 year of age. | a. Patients < 70 year of age, without lymph node metastases (N0), met grade I tumours, tumour size > 2 cm. | a. All patients who do not meet the earlier mentioned criteria: |
| b. Patients < 70 year of age, without lymph node metastases (N0 of N1mi) | b. Patients < 70 year of age, without lymph node metastases (N0), met grade II tumours, tumour size 1-2 cm. | i. ≥ 35 year of age, N0, grade I, tumour size < 2 cm. |
| and adverse prognostic factors: | c. Patients < 70 year of age, with lymph node metastases (N1mi), grade I of II, tumour size up to 2 cm. | ii. ≥ 35 year of age, N0, grade II of III, tumour size < 1 cm |
| i. Grade II tumours > 2 cm | | iii. Her2+ tumour, tumour size < 0.5 cm, without other unfavourable characteristics. |
| ii. Grade III tumours > 1 cm | | iv. Patients ≥ 70 year of age |
| iii. Her2+ tumour (> 0.5 cm). | | |
| iv. < 35 year of age, regardless of other tumour characteristics (excl. grade I tumour < 1 cm). | | |

**Table 2.** *Patient and tumour characteristics in relation to the clinical risk profile and 21-RS deployment (n=29,935)*

| | | Clinical low risk | | | | | Clinical intermediate risk | | | | | Clinical high risk | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 21-RS use (n=23) | | No 21-RS use (n=17,075) | | | 21-RS use (n=137) | | No 21-RS use (n=2,369) | | | 21-RS use (n=90) | | No 21-RS use (n= 9,644) | | |
| | | n | % | n | % | p-value | n | % | n | % | p-value | n | % | n | % | p-value |
| **Incidence per year** | *2014* | 6 | 26.1% | 5,709 | 33.4% | | 34 | 24.8% | 762 | 32.2% | | 19 | 21.1% | 3,831 | 39.7% | |
| | *2015* | 10 | 43.5% | 5,700 | 33.4% | | 75 | 54.7% | 784 | 33.1% | | 38 | 42.2% | 3,208 | 33.3% | |
| | *2016* | 7 | 30.4% | 5,666 | 33.2% | 0.57 | 28 | 20.4% | 823 | 34.7% | <0.05 | 33 | 36.7% | 2,605 | 27.0% | <0.05 |
| **Age in year** | *<35* | 0 | 0.0% | 11 | 0.1% | | 0 | 0.0% | 2 | 0.1% | | 2 | 2.2% | 317 | 3.3% | |
| | *35-50* | 2 | 8.7% | 1,000 | 5.9% | | 27 | 19.7% | 353 | 14.9% | | 23 | 25.6% | 2,328 | 24.1% | |
| | *50-70* | 13 | 56.5% | 6,532 | 38.3% | | 110 | 80.3% | 2,014 | 85.0% | | 65 | 72.2% | 6,999 | 72.6% | |
| | *>70* | 8 | 34.8% | 9,532 | 55.8% | 0.25 | 0 | 0.0% | 0 | 0.0% | 0.30 | 0 | 0.0% | 0 | 0.0% | 0.83 |
| **Size in mm** | *0-10* | 5 | 21.7% | 7,238 | 42.4% | | 0 | 0.0% | 0 | 0.0% | | 6 | 6.7% | 726 | 7.5% | |
| | *11-20* | 14 | 60.9% | 6,011 | 35.2% | | 125 | 91.2% | 2,110 | 89.1% | | 32 | 35.6% | 3,899 | 40.4% | |
| | *21-30* | 3 | 13.0% | 2,157 | 12.6% | | 10 | 7.3% | 172 | 7.3% | | 42 | 46.7% | 3,101 | 32.2% | |
| | *>30* | 1 | 4.3% | 1,567 | 9.2% | | 2 | 1.5% | 61 | 2.6% | | 10 | 11.1% | 1,743 | 18.1% | |
| | *Unknown* | 0 | 0.0% | 102 | 0.6% | 0.12 | 0 | 0.0% | 26 | 1.1% | 0.53 | 0 | 0.0% | 175 | 1.8% | <0.05 |
| **Estrogene receptor** | *Negative* | 1 | 4.3% | 1,729 | 10.1% | | 0 | 0.0% | 0 | 0.0% | | 2 | 2.2% | 2,304 | 23.9% | |
| | *Positive* | 22 | 95.7% | 15,255 | 89.3% | | 137 | 100.0% | 2,369 | 100.0% | | 88 | 97.8% | 7,292 | 75.6% | |
| | *Unknown* | 0 | 0.0% | 91 | 0.5% | 0.61 | 0 | 0.0% | 0 | 0.0% | na | 0 | 0.0% | 48 | 0.5% | <0.05 |
| **Progesterone receptor** | *Negative* | 6 | 26.1% | 4,350 | 25.5% | | 20 | 14.6% | 368 | 15.5% | | 18 | 20.0% | 3,697 | 38.3% | |
| | *Positive* | 17 | 73.9% | 12,631 | 74.0% | | 117 | 85.4% | 2,001 | 84.5% | | 72 | 80.0% | 5,892 | 61.1% | |
| | *Unknown* | 0 | 0.0% | 94 | 0.6% | 0.94 | 0 | 0.0% | 0 | 0.0% | 0.77 | 0 | 0.0% | 55 | 0.6% | <0.05 |

| Table 2 continued. | | Clinical low risk | | | | | Clinical intermediate risk | | | | | Clinical high risk | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 21-RS use | | No 21-RS use | | | 21-RS use | | No 21-RS use | | | 21-RS use | | No 21-RS use | | |
| | | (n=23) | | (n=17,075) | | | (n=137) | | (n=2,369) | | | (n=90) | | (n= 9,644) | | |
| | | n | % | n | % | p-value | n | % | n | % | p-value | n | % | n | % | p-value |
| **Her2 Neu** | *Negative* | 20 | 87.0% | 15,352 | 89.9% | | 137 | 100.0% | 2,369 | 100.0% | | 88 | 97.8% | 7,262 | 75.3% | |
| | *Positive* | 2 | 8.7% | 967 | 5.7% | | 0 | 0.0% | 0 | 0.0% | | 2 | 2.2% | 2,293 | 23.8% | |
| | *Unknown* | 1 | 4.3% | 756 | 4.4% | 0.82 | 0 | 0.0% | 0 | 0.0% | na | 0 | 0.0% | 89 | 0.9% | <0.05 |
| **Grade** | *1* | 11 | 47.8% | 7,122 | 41.7% | | 12 | 8.8% | 260 | 11.0% | | 11 | 12.2% | 829 | 8.6% | |
| | *2* | 8 | 34.8% | 6,894 | 40.4% | | 125 | 91.2% | 2,109 | 89.0% | | 56 | 62.2% | 4,158 | 43.1% | |
| | *3* | 4 | 17.4% | 2,763 | 16.2% | | 0 | 0.0% | 0 | 0.0% | | 23 | 25.6% | 4,524 | 46.9% | |
| | *Unknown* | 0 | 0.0% | 296 | 1.7% | 0.85 | 0 | 0.0% | 0 | 0.0% | 0.42 | 0 | 0.0% | 133 | 1.4% | <0.05 |
| **Multifocality** | *No* | 20 | 87.0% | 15,170 | 88.8% | | 115 | 83.9% | 1,988 | 83.9% | | 77 | 85.6% | 7,792 | 80.8% | |
| | *Yes* | 3 | 13.0% | 1,875 | 11.0% | | 22 | 16.1% | 378 | 16.0% | | 13 | 14.4% | 1,807 | 18.7% | |
| | *Unknown* | 0 | 0.0% | 30 | 0.2% | 0.93 | 0 | 0.0% | 3 | 0.1% | 0.92 | 0 | 0.0% | 45 | 0.5% | <0.05 |

**Table 3.** *Clinical risk profile by result of 21-RS test result*

| | Clinical risk profile | | | | |
|---|---|---|---|---|---|
| | **Low** | **Intermediate** | **High** | **Unknown** | **Total** |
| **21-RS Low risk** | 15 (9.2) | 101 (62.0) | 46 (28.2) | 1 (0.6) | 163 (100.0) |
| **21-RS Intermediate** | 4 (8.2) | 18 (36.7) | 24 (49.0) | 3 (6.1) | 49 (100.0) |
| **21-RS High risk** | 4 (9.5) | 18 (42.9) | 20 (47.6) | 0 (0.0) | 42 (100.0) |

*Pearson chi2(6) = 20,3918, Pr = 0.002, k <0 (clinical unknown risk category was excluded for kappa coefficient determination)*

*Use of the 21-RS in Patients in whom Controversy Exists about CT Benefit*

In the clinical intermediate-risk category, the 21-RS assigned 73.7%, 13.1% and 13.1% of the 137 patients to the genomic low-, intermediate- and high-risk category, respectively (Figure 1). Considering the omission of CT in patients with a genomic intermediate risk to be in line with the test result, overall adherence to the test result of the 21-RS was 95.6% in this category of patients. Adherence to the 21-RS was higher in patients assigned to the genomic low-risk profile (98.0% did not receive CT) as compared to patients assigned to the genomic high-risk profile (88.9% of patients received CT). Twenty patients (14.6%) of the clinical intermediate-risk category received CT when a GEP was used, compared to 21.2% of all patients who received CT in the intermediate-risk category irrespective of GEP-use. In patients assigned to the genomic intermediate-risk category 11.1% (n=2) received adjuvant CT (Figure 1).

*Use of the 21-RS in Patients in Clinical Low- and High-risk Patients*

In the 23 clinical low-risk patients who received a 21-RS, 65.2%, 17.4% and 17.4% of patients were assigned to the low, intermediate and high 21-RS test result, respectively (Figure 1). Overall adherence to the 21-RS was 91.3% in these patients, considering the four patients who were assigned to the genomic intermediate-risk category and who did not receive adjuvant CT as being treated in line with the rest result. Four of the 23 clinical low-risk patients in whom the 21-RS was used received CT (17.4%), compared to 3.7% of all patients in the clinical low-risk category irrespective of GEP-use.

In the 90 patients categorized as clinical high risk, the 21-RS assigned 51.1%, 26.7% and 26.6% of patients to the genomic low-, intermediate- and high-risk category, respectively (Figure 1). Overall, CT administration was in line with the genomic risk in 81.1% of the patients in the clinical high-risk category, considering the administration of CT in patients with a genomic intermediate risk to be in line with the test result. Twenty-nine of these patients received CT (32.2%), compared to 52.2% of all patients in the high-risk category received CT irrespective of GEP-use.

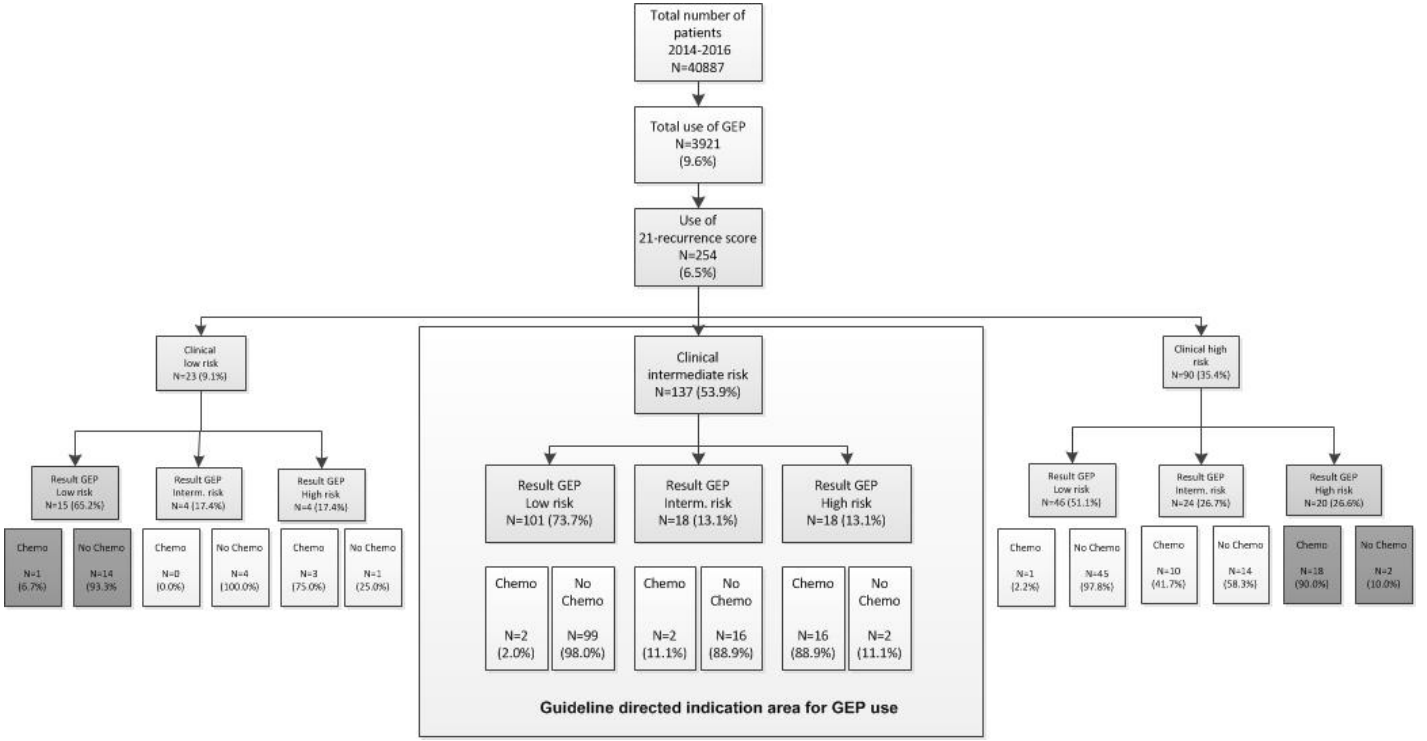


**Figure 1.** *Number of included patients grouped by the clinical risk, GEP (21-recurrence score) result and admittance of chemotherapy*

**Discussion**

In this study, we aimed to gain insight in the use and impact of the 21-RS test in Dutch early stage breast cancer patients following its introduction in Dutch clinical practice in 2013. The test was deployed in a limited number of patients, comprising less than 10 percent of the GEPs that were used during the study period [12]. Approximately half of the tests were used outside the intended indication area. The 21-RS test was in line with the clinical risk determination in 21.2% of all patients, and the test result was adhered to in over 90% of the patients irrespective of the deployment in relation to the indication area and a high or low clinical risk. Within the intended indication area, 15% received chemotherapy when the 21-RS was deployed.

While Dutch guidelines suggest the selective use of a GEP in ER+ breast cancer patients in whom controversy exists about the indication for adjuvant CT, we observed the use of the 21-RS test both inside and outside the guideline directed area: half of the 21-RS tests (53.9%) were applied in patients who were considered candidates for gene expression profiling according to the current Dutch guideline based on doubt regarding CT benefit. This observation is in line with previous studies on the 70-GS where a similar frequent use of the 70-GS outside the guideline directed area was observed [4, 14].

In the clinical intermediate-risk group of patients, adherence to the 21-RS was high (95%). In a previous study, focussing on the 70-GS, lower adherence rates to the genomic test result, varying between 83% and 89%, were observed [4]. We observed that in case of an intermediate genomic risk, patients were treated as having a clinical low risk, resulting in the omission of CT. A low and intermediate risk resulted in omission of CT in 85% of these clinical intermediate-risk patients. This compares to a proportion of 66% who did not receive CT following 70-GS use in the same proportion of patients [4]. Then again, an independent trend towards more restrictive use of CT was observed over time, since in the latter study, conducted between 2011 and 2013, 45% of the clinical intermediate-risk patients received CT without the use of a GEP compared to 21% in the present study. The present study confirms that the genomic test result yields to lower implementation of CT, a finding that was also supported by a study where patients reported to be more reluctant to undergo CT when a genomic test indicated low recurrence risk [15].

When the 21-RS was deployed outside the indication area, the majority of patients was treated in line with the genomic risk, in both the clinical low- and the clinical high-risk group of patients. The adherence to the 21-RS test result was higher in the clinical high-risk group with a discordant GEP result than in the clinical low-risk patients and this was in line with previous population based studies into the 70-GS use [14]. In clinical high-risk patients this led to a 20% absolute reduction of administered chemotherapy when the 21-RS was applied and this obser-

vation supports the observation by other studies that GEPs are mainly used for a substantiated decision to withhold CT in clinical high-risk patients [4, 14]. This partly explains why a high genomic risk in clinical low-risk patients is frequently disregarded and in doing so, clinicians and patients may feel supported by the recent outcome results from the EORTC 10041/BIG 3-04 MINDACT trial [16]. Clinical low-risk patients had excellent outcomes irrespective of their genomic risk and the administration of chemotherapy.

The population-based character of this study enables us to provide an overview of the 21-RS use in all Dutch hospitals. The 21-RS is, in contrast to 70-GS, not so much applied in the Dutch health care setting, what resulted in a small study population. However, this study design gives a detailed analysis of 21-RS use and administration of CT in relation to the clinical risk of developing metastases in early breast cancer patients in the Netherlands. Despite the small patient number, this study can support further implementation of the 21-RS and implementation of innovations developed in future.

**Conclusion**

In the Netherlands, the 21-RS test is applied both inside and outside the guideline directed area. In all clinical risk categories, the majority of patients were assigned to the genomic low- and intermediate-risk category and adherence to the 21-RS was high. In case of discordance between the genomic and clinical risk, patients were treated in line with the result of 21-RS and a clinically relevant decrease in CT administration was observed after 21-RS use in clinical intermediate- and high-risk patients.

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**Ethical approval and consent to participate**

According to the Central Committee on Research involving Human Subjects (CCMO), this type of study does not require the approval from an ethics committee in the Netherlands. This study was approved by the Privacy Review Board of the Netherlands Cancer Registry.

**Conflict of interest statement**

The authors do not declare any conflicts of interest.

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None

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# Part V

Closing section

# Chapter 9

Discussion and future perspectives

# General discussion

In this thesis the current use of immediate breast reconstruction, radiotherapy and gene-expression profiling in breast cancer patients in the Netherlands was evaluated. The practice of immediate breast reconstruction, administration of radiotherapy and deployment of genetic profiling differed conceptually in a number of ways. Immediate breast reconstruction still is a gradually involving surgical technique that has become available for more patients as it is being performed ever more often over the last decades. Radiotherapy is the mainstay of breast conserving therapy for forty years albeit that the routine use of additional boosting is disputed as the local recurrence rates have decreased over recent years. Gene-expression profiling is a technique to predict outcome more accurately and as such it was recently introduced into clinical practice in the absence of clear guidelines when to use it. Variation in immediate breast reconstruction and a radiation boost was studied between institutions (hospitals or radiation oncology departments). Variation over time was addressed when evaluating the use of radiotherapy and additional radiation boost. Variation in relation to a prevailing guideline was evaluated for the use of a gene-expression profiling. Insight in the variation in breast cancer care between Dutch hospitals and the identification of unintended variation is important. Transparency regarding existing variance may help to reduce the bandwidth of the variation and ultimately improve breast cancer care.

**Theory of variation**

In order for variation to exist, at least two entities must be present. For example; a defined group of patients can be compared to another group of patients or to a standard. It is natural that persons or groups of patients differ in condition, typically with certain limits. Based on a definition of Altman (1991), variation is synonymous with dispersion and as such variation can be quantified by statistics (e.g. to determine a range, and calculate a standard deviation or inter-quartile range) [1]. Variation can be categorized as intended or unintended variation.

*Intended variation*

In health care intended variation is when a medical clinician makes a planned and deliberate (patient-centred) choice in the setting of well-organized health care [2]. Intended variation can be associated with differences in tumour or patient characteristics, as guidelines may recommend different care based on these characteristics. Moreover, intended variation can be the result of choices made by patients, preferably after appropriate shared-decision making giving information on all treatment options and possible outcomes, e.g. to neglect a (limited) advantage of a specific treatment in order to avoid the risk of treatment associated toxicity (Figure 1). Clinical guidelines are “systematically developed statements to assist practitioner and patients decision about appropriate health care for specific circumstances” [3], and support decision

making based on as much scientific evidence as possible to obtain the best outcome, in which "specific circumstances" refer to patient and clinical characteristics. The word "assist" implies a certain degree of flexibility in adherence to guidelines. Therefore, guideline compliance is not a requirement in itself and can be affected by doctors and patients 'educated' preferences. While clear recommendations in guidelines aim to reduce variation [3], the intended variation reflects the extent of patients' and doctors' ambiguity towards an existent guideline. A relation between the level of evidence for a guideline recommendation and the extent to which adherence to a guideline varies is conceivable. Recommendations are based on consensus if the level of evidence is low. Registering the variation in case of low-evidence based recommendations offers an opportunity to obtain relevant information and might contribute to evidence for future guidelines by comparing the corresponding outcomes (including side effects) between the different care options given. Finally, also institutional-related policies and regulations may be associated with intended variation, on condition that the institute is aware of this association (Figure 1).

*Unintended variation*

Unintended variation is the result of unplanned or misguided changes in the healthcare process [2]. Unintended variation results from a lack of knowledge, whereas intended variation stems from 'educated' choices based on clinical and/or personal differences between patients. Unintended variation can be subdivided into common-cause and special-cause variation (Figure 1) [4]. Common-cause variation is caused by unidentified factors leading to a steady but random distribution of output around the average of the data and cannot be eliminated [5]. Special-cause variation, on the other hand, is the result of a cause outside the core processes [4]. Common-cause variation is the variation that remains after eliminating special causes and intended variation.

For example, a specific breast conserving surgery takes normally between 45 and 75 minutes, with an average of 60 minutes. This variation (+/- 15 minutes) is normal and can be the result of different common causes, for example how easily the tumour can be localized and removed under different circumstances. Using oncoplastic surgical techniques, an institutional policy to perform surgery together with a plastic surgeon, or to supervise surgical trainees may be factors that lead to more intended variation in operation times. On the contrary, prolonged operation times can be the results of performing unnecessary lymph node dissections ignoring the results of the Z0011 and AMAROS-trial [6, 7] and due to the surgeon associated. Prolonged operation times due to ignoring the results of trials is an example of special-cause variation, while the dexterity and experience of individual surgeons will influence operation times but as a variation inducing factor is hard to influence (i.e. common-cause variation).

*Distinction*

Making a distinction between intended and unintended variation is not always easy. Sometimes, the same cause can result in intended or in unintended variation. The implementation of new guidelines, for example, can be associated with intended variation over time and between institutes, as not all institutes are able to fully adapt the new guidelines at the same moment in time with the same time frame. However, when an institute is not adequately adopting the new guideline due to lack of knowledge or awareness, this will result in unintended special-cause variation.

Furthermore, it is not possible to adjust for all intended variation, which should be kept in mind in case of comparisons. Intended variation in treatment can be caused by differences in the underlying patient population and in the way that clinicians work and make choices. Identifying unintended variation is a substantial challenge too. Walter A. Shewart (also known as the founder of statistical control, 1891-1967) focused his research on unintended variation and had the opinion that reducing this type of variation is an important means to improved health care outcomes and reduced costs [2].

To reduce this unintended variation the two types need different approaches. For common-cause variation it is necessary to change the whole process, since the common-causes are scattered through the complete process [5]. Special-cause variation can be influenced for example by the implementation of departmental policies or national guidelines [4]. Hence, the ability to differentiate between common- and special-cause variation is essential to determine in the best approach and make improvements in healthcare possible. Then, to reduce special-cause variation it is necessary to first identify the cause and subsequently act accordingly. Figure 1 provides an overview of the different types of variation and their impact on influence on the process.

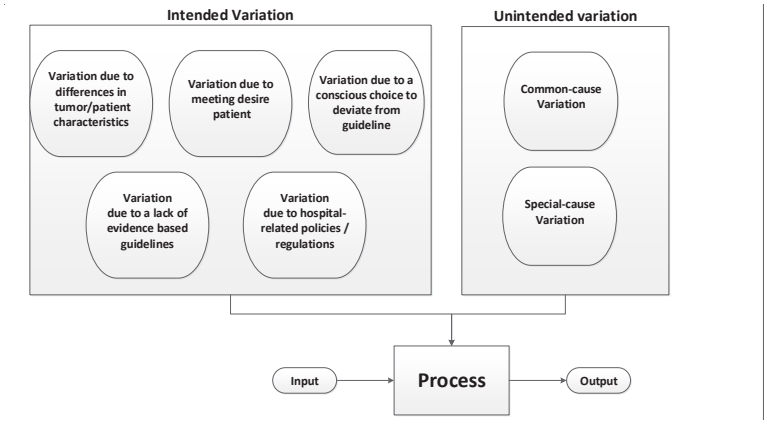


**Figure 1.** *Distinction between intended and unintended variation (K. Schreuder, 2018)*

Special-cause variation can be more easily identified when a large part of the intended variation is already controlled [4]. To address special-cause variation in a certain health care process, case-mix adjustments should be performed in order to make patient groups comparable regarding clinical and patient related characteristics [8]. Case-mix correction helps to identify and exclude the effect of intended variation due to differences based on both clinical as personal characteristics of the studied subjects.

Although it is not possible to adjust for all intended variation it is, by default, assumed that after eliminating the intended variation by case-mix correction, the remaining variation is unintended variation. Subsequently, in order to distinguish between special-cause and common-cause variation, Shewhart developed a control chart (Figure 2). The control chart consists of three important lines; the first line represents the mean or median value, while the upper and lower lines are termed the control limits. When a certain observation is below the lower line or above the upper line, it indicates the existence of special-cause variation, while values within these limits (due to common-cause variation) are in the confidence interval of what is to be expected as a normal value. The example concerning the duration of the surgery demonstrated before is used as an example in this figure, illustrating the special-cause (e.g. prolonged operation times due to performing unnecessary lymph node dissections) above the upper control limit line. In this thesis, we will use funnel plots to objectify variation and these graphs have great similarities with Shewharts chart [9]. A funnel plot assesses the variation and heterogeneity of a certain outcome within a study population and aims to explore significant deviation from the observed mean with use of confidence intervals (lower and upper control limit).

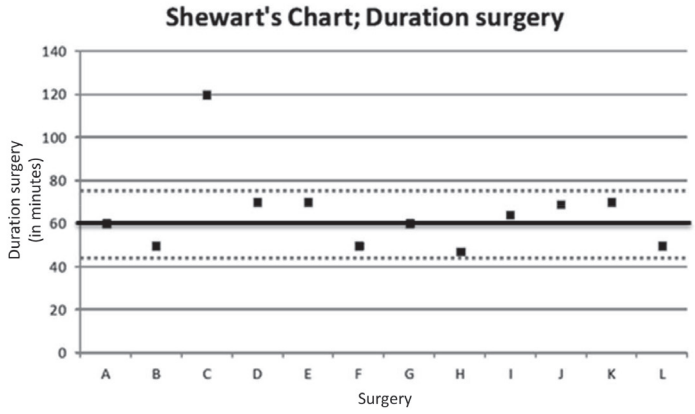


**Figure 2.** *Shewart's chart [9]*

Once variation is identified as cause-related unintended variation, reflection on these measurements can initiate the process of 'improvement'. The final aim in 'variation management' is to achieve a condition under which the remaining unintended variation is attributable to common causes only. In line with the idea of Shewart, when this state is achieved it is in "statistical control". A phenomenon or system is controlled when, through the use of past experience, we can predict, at least within limits, how the phenomenon may be expected to vary in the future. Prediction within limits means that we can state, at least approximately, 'the probability that the observed phenomenon will fall within the given limits" [10]. Despite Shewart is largely focussing on identifying and reducing the unintended variation, we feel the need to emphasize that identifying and reducing the unintended variation is not the only relevant improvement strategy. In case a process is in statistical control (as defined by Shewart), but characterized by a mean that is lower than a set standard, adjustments are necessary to improve the whole process.

Monitoring and studying variation around a certain mean value is important for several stakeholders: clinicians, patients, employees of the quality department of a hospital (quality employees), researchers, insurance companies and the health care inspectorate. These stakeholders may and will manage observed variation of care in different ways with different reasons and in different time frames [4]. Clinicians will seek for factors influencing the variation in health care related outcome parameters and they may use external peer review, such as clinical auditing [11]. Moreover, for patients the causes of variation between hospitals are of interest. This may be helpful in selecting a hospital that better meets the needs of the patient. Quality employees feel responsible for appropriate quality results used for external justification and aim to find methods to improve these results. Moreover, quality employees will seek for variance that reflects 'insufficient' quality (special-case unintended variation) and will dichotomize observed values in good or bad. Researchers may think in terms of various experimental settings and the limitations of 'normal dispersion', i.e. considering observed variation of outcomes by default as common-cause unintended variation, unless [4]. As mentioned before, this information might contribute to evidence for future guidelines by comparing the corresponding outcomes (including side effects) between the different care options given. Insurance companies and health care inspectorate are especially interested in hospital related causes of variation when the observed quality is lower compared to a benchmark or the established standard. For all stakeholders it is important to understand the nuances of variation in health care and to minimize unintended variation as much as possible.

The relevant time frames for assessing variation differs for the respective stakeholders as well. For clinicians and quality employees, real time monitoring of outcomes and variation is desirable in order to make timely adjustments to improve or maintain the quality of the provided

care. Real time monitoring tools are important and find their way in practice (for example, NKR-online). With their use a "PDCA (plan–do–check–act) management method" can be supported [12], providing a solid means to *C*heck ones' institutional or individual results enhancing the possibilities to *A*ct accordingly. For insurance companies and health care inspectorate, real-time assessment of health care related outcomes and variation is less important. Obtaining long-term results periodically based on robust data are necessary to base their conclusions.

In this thesis the use of immediate breast reconstruction, radiotherapy and gene-expression profiling in breast cancer patients in the Netherlands was studied using high-quality nation-wide data, as obtained from the Netherlands Cancer Registry. The observed variation of the use and administration of the aforementioned diagnostic and treatment modalities has been described.

**Variation in immediate breast reconstructions**

In **chapter two and three**, we analysed and discussed variation in the practice of immediate breast reconstruction in the Netherlands. Combining a mastectomy with an immediate breast reconstruction is associated with better aesthetic results and psychosocial effects than performing a simple mastectomy with or without delayed breast reconstruction. Notwithstanding these evident advantages, the risk of surgical complications is relative high [13]. Moreover, surgical practices differ in the availability of plastic surgeons and the technical possibilities on offer and patient preferences contribute as well. Furthermore, use of radiotherapy leads to a significantly higher reconstruction failure rate compared to if no radiotherapy is given [14]. The latter may be a reason for plastic surgeons not to perform an immediate breast reconstruction, since delay of radiotherapy is considered to be associated with worsening of treatment efficacy. Certain choices made in multidisciplinary team meetings may result in the recommendation to omit an immediate breast reconstruction, but perform a delayed breast reconstruction instead. Therefore, it is propagated that patients who are planned for breast amputation are counselled about reconstructive options and a large proportion of patients undergoing immediate breast reconstruction. In **chapter two** we demonstrated that hospital organizational factors affect the use of an immediate breast reconstruction and partly explain the variation observed between Dutch hospitals. Case-mix correction explained part of the variation in performing an immediate breast reconstruction between hospitals in the Netherlands. After annihilating the intended variation by this case-mix correction, remaining unintended variation could be attributed to hospital factors such as the number of plastic surgeons available in the hospital (common-cause) and the attendance of a plastic surgeon at the multidisciplinary team meeting (special-cause). Data adjusted for case-mix and certain hospital organizational factors demonstrated a decrease in hospital variation in the use of an immediate breast reconstruction from 0-80% to 0-49% for patients bearing invasive breast cancer. Despite this substantial

decrease of variation, considerable unexplained variation persisted. In **chapter three** we observed that surgical oncologists and plastic surgeons differ in personal opinions towards an immediate breast reconstruction and in their information provision to patients. Hence, these significant differences in information provision and personal opinions towards an immediate breast reconstruction contributed to the unintended special-cause (and as well to hitherto undiscovered intended) variation seen between hospitals. As of now undefined hospital related factors may have contributed to the observed variation (intended and untended) in immediate breast reconstructions, such as gender of surgeon, the availability of proficient plastic surgeons, the propensity to offer or desire delayed reconstructive surgery, geographical location and waiting times for plastic surgery [15, 16]. Most probably, differences in patient preferences contributed importantly too [17, 18]. Jeevan et al. demonstrated that 50% of the patients were very satisfied with the options they received about breast reconstruction, but preferred not to undergo an immediate breast reconstruction [19]. Further research into patient preferences towards immediate breast reconstruction may shed light on the way that these factors explain variation in performing immediate breast reconstructions; such a study is on its way.

A small portion of patients underwent an immediate breast reconstruction in a hospital different from the hospital were the patient was diagnosed with breast cancer. When a certain hospital was identified as a hospital performing no immediate breast reconstructions, it is possible that this hospital refers patients for an immediate breast reconstruction to another hospital, which is to be considered as appropriate care. This may have impacted the validity of the results. Regarding methodology, it is also of note that we used self-reports in **chapter three** to detect special causes of the observed variation and we have to take into account that recall bias may have played a role [20]. The fact that 100% of the surgical oncologists reported that the possibility of an immediate breast reconstruction was discussed with the patients testifies to that.

**Variation in radiotherapy**

In the eighties of the 20th century, breast-conserving surgery became standard of care in the Netherlands comprising whole breast irradiation and the routine use of a boost dose. A boost directed to the lumpectomy cavity walls aims to further improve local control [21, 22]. In 2001 a decrease from 7.3% to 4.3% in the 5-years rates of local recurrences was observed after using a boost [23]. Throughout the years a growing awareness of boost (and whole breast irradiation) associated morbidity developed [24]. Also compelling data showed that the 5-years ipsilateral breast tumour recurrences rates decreased even further to 3.2%-2.4% for patients treated between 2003-2008 in the Netherlands [25]. A boost dose was not used in all cases whereas adjuvant systemic treatment was given more frequently. All this led to the acknowledgement that an additional boost is not always warranted. In a nationwide study (**chapter four**), large

variation in the use of a boost between the 21 departments of radiation oncology in the Netherlands was demonstrated for patients with invasive as well as for those with non-invasive breast tumours (DCIS). Following adjustment of a national guideline with respect to the usage of a boost in patients with invasive tumours, variation in the usage of boost decreased significantly. Several tumour and patient characteristics were associated with the decreased boost use. Intended variation apparently played a minor role in this study, given the limited effect of case-mix correction. Other than the studied factors may have led to intended variation too, such as comorbidity, lymph vascular space invasion and the patients' expectation of cosmetic outcome [24, 26]. Regarding the variation that persisted after the guideline implementation, logistic regression analysis revealed that substantial institutional variation remained that could not be explained by differences in patient, tumour or predefined institutional characteristics. We assumed that department related factors explain for most of the unintended variation between the departments. Departmental policies and clinicians' preferences likely contributed to the variation of boost use and this variation is labelled as unintended on condition that the institutes are not aware of this association. Further research should identify doctors' attitudes and patients' preferences towards boost and whether these factors may explain the variation in the use of a boost.

For DCIS patients, the aforementioned guideline provided no directives. In this group the large variation persisted. As phase-3 trials dealing with the clinical relevance of administering "boost no boost" in DCIS patients are lacking, it is not possible to adequately value the observed variation as unintended or intended. Doctors' preferences in the absence of a guideline may be considered as intended while others may regard the intervention in the absence of robust proof but with potential side-effects as special-cause unintended. All in all, this study demonstrates that the observations are as much the *C*heck part of the *P*lanned uniformity of radiotherapy boosting (for invasive cancer) as it feeds the need to draw a *P*lan to come to a more uniform treatment (for DCIS).

In **chapter five** the use of external beam radiotherapy was addressed. Radiotherapy after breast conserving surgery is an integral part of breast conserving therapy and is associated with substantial improvements in ipsilateral breast tumour recurrence rates as well as (limited) improvements in survival rates [27]. A recent meta-analysis (2014) also demonstrated substantial decreased locoregional recurrence rates and increased survival rates following adjuvant (locoregional) radiotherapy after total mastectomy in N1-3 and N>3 disease [28]. These findings led to the recommendation of administering adjuvant (locoregional) radiotherapy after mastectomy [29]. An increase in the utilization rate of radiotherapy was observed in the current study merely attributable to the fact that more patients underwent radiotherapy after total mastectomy. The latter illustrates the effect of the recent recommendations of administering adjuvant radiotherapy after mastectomy. No (further) increase in radiotherapy was

observed in patients receiving breast-conserving surgery, as it was already around 97%. After both breast conserving surgery and mastectomy, we found lower utilization rates of radiotherapy in elderly patients. For patients aged over 85 years, a radiotherapy utilization rate of 50.9% was observed, compared to 97.4% in patients aged under 50 years. Overall, we found an increase of 8.6% in radiotherapy use in elderly patients (aged >75 years), from 26.6% in 2011 to 34.9% in 2015. These adoption rates in BCS patients compare favourable to international data, as underutilization of radiotherapy is observed worldwide [30-36]. Variation in the use of radiotherapy was analysed over time (2011-2015), between Dutch regions. After breast conserving surgery, limited variation in the use of radiotherapy was analysed between regions (mean 97.3%, SD: 0.4). However, after mastectomy more variation in the use of radiotherapy between the regions was observed (mean 33.8%, SD: 3.0). The variation in radiotherapy use over time and between regions for patients treated with a mastectomy can be the result of the implementation time of the new recommendations.

**Variation in gene-expression profile use**

Gene-expression profiling was introduced into clinical practice to better guide clinical decision-making regarding adjuvant chemotherapy. A gene-expression profiling test can enhance the prognostication of breast cancer patients and thereby better identifies patient groups that should receive chemotherapy or not. Dutch national guidelines suggested a role for the use of GEPs in 2012 [37]. The indication area comprised patient categories for which the benefit of adjuvant chemotherapy was disputable when based on clinic pathological factors alone. In common practice in the Netherlands the 70-GS and the 21-RS are since 2012 used in patients with ER+, Her2 negative breast cancers of intermediate malignancy grade who have no or limited metastatic lymph node involvement. The implementation and use of gene-expression profiling and implications regarding chemotherapy administration in relation to clinical risk in early breast cancer patients were investigated.

We demonstrated in **chapter six** that the chance of deploying a gene-expression profile, albeit that the guideline has been at no time crystal clear about the delineation of the patient groups for whom an gene-expression profile is recommended, depends on tumour characteristics pertaining to an intermediate clinical risk-profile, as described above. Nonetheless a significant of these tests were deployed in patients who had a well defined low or high risk of developing metastases, i.e. approximately half of the tests were deployed in patients for whom the 'imaginary' guideline discommended the use of the test because clinic pathological factors in itself guided the advice to administer chemotherapy or not. As mentioned before, variation due to consciously deviating from the guidelines based on the desire of the patient may be labelled as intended. Unfortunately, no information concerning the desire of the patients in deploying a gene-expression profile outside the guideline indicated area was available, but we expect only

a minor contribution of this type of intended variation. By default, variation in the deployment of gene-expression profiles outside the guideline intended indication area is to be considered as collective special-cause unintended variation. The hospital in which a patient was diagnosed was associated with this unintended variation, although this was not attributable to the pre-defined and studied type of hospital, volume of breast cancer care per hospital or region. We observed in **chapter seven** and **chapter eight** variations in the use of gene-expression profiling both for the 70-GS and 21-RS in and outside the guideline intended indication area. Different patient and tumour related factors were associated with the use of a gene-expression profile outside the guideline indicated indication area. The genomic test result yielded lower implementation of chemotherapy in- and outside the guideline indicated area, which can be clarified by findings of a previous study where patients were also more reluctant to undergo chemotherapy when a genomic test indicated low recurrence risk [38]. Hence, part of the unintended variation (use of a gene-expression profile while the present guideline recommends the administration of chemotherapy) served as a justification to withhold chemotherapy will lead to intended variation of chemotherapy use in relation to existing guidelines. The focus in these studies was not so much to assess intended and unintended variation, but the results so far offer material to further explore the different forms of variation in the deployment of gene-expression profiles.

There is, at present, on-going discussion concerning the clinical utility and the level of evidence for gene-expression profiling. The National Health Care Institute (ZIN) claims that results of the MINDACT trial were not able to significantly illustrate the benefit of the deployment a gene-expression profile in clinical low- and high-risk patients with a discordant genomic test result. In the MINDACT trial it was noted that the 5-year rate of distant metastasis free survival was not impaired after the withdrawal of chemotherapy in clinically assessed high-risk patients who have a low-risk gene-expression profile (DMFS) [39]. At the same time patients with a low risk clinical profile have good outcome, irrespective of gene-expression profile and adjuvant chemotherapy use. Apart from the more conceptual disputes implies that the boundaries of the indication area for gene-expression use ought to shift.

**Variation: good or bad?**

In 2014 the Dutch Cancer Society published a report concluding that cancer care in the Netherlands is of high quality, but the signalling committee noted that the bandwidth of the variation between the hospitals should be reduced [40]. We feel that this thesis also demonstrates that merely aiming to reduce variation does not do justice to the present collective efforts to improve health care in the Netherlands. In addition, addressing variation considering in terms of intended 'good' versus unintended 'bad' variation is an oversimplification of today's clinical practice.

Immediate breast reconstruction is increasingly performed in patients who undergo a breast mastectomy, but large variation in the practice of immediate breast reconstruction still persists. Although the final aim of the studies in this thesis was not to stimulate performing more immediate breast reconstructions in clinical practice, we feel that the availability of an immediate breast reconstruction for eligible patients should be more or less comparable between hospitals and unrelated to special-causes of unintended variation. Dutch guidelines emphasize the importance of reconstruction after mastectomy and recommend clinicians to discuss the possibility of an immediate breast reconstruction with every patient undergoing mastectomy [41]. The increasing use over time is in itself not an undesirable development but it is hard to believe that merely discussing this treatment option has led to the increased use of an immediate breast reconstruction over recent years. Institutional availability of surgical technical options, cooperation between surgeons and plastic surgeons, evolving radiotherapy indications, the frequency of devastating local complications and the institutional policy towards neo-adjuvant systemic treatment are just a number of interrelated institutional factors that play a role for the multidisciplinary team to develop expertise with and confidence in this treatment strategy. As observed in a recent study into the increasing use of all efforts to pertain the breast contour (van Bommel et al. submitted), the 'intended' increasing use of this novel surgical treatment strategy is accompanied by increasing variation. Conversely, in addressing variation in a context of an on-going evolving treatment strategy, it may well be sensible to encourage increasing variation as it will move the mean into the desired direction and for that matter it makes sense that intended and unintended variation are not further discerned.

The radiotherapy studies did confirm the vision of the Dutch Cancer Society to strive for less variation between hospitals in the Netherlands. In patients with invasive breast cancer who underwent breast-conserving surgery a recent literature-based guideline adjustment resulted in decreased boost use and less variation. In the same category of patients, the outcome of breast conserving therapy was assured by the observation that radiotherapy was nationwide uniformly administered in over 97% of the patients. The evolving role for radiotherapy in mastectomy patients was illustrated by higher utilization rates of radiotherapy over time. This trend was accompanied by substantial variation over time between departments, in line with the similar observation in the proportions of patients who underwent immediate breast reconstruction.

Finally, the studies focusing on the deployment of gene-expression profiles in relation to the 'intended' indication area merely demonstrate that variation is nearly impossible to interpret when it is unclear what the limits, i.e. the indication area, for its usefulness are. The studies also demonstrate that unintended use of gene-expression profiles, i.e. when used outside the assumed indication area, may still lead to the intentional net effect of giving less chemotherapy

since the test result was adhered to in many genomic low risk patients. Randomized trials will help clarifying the role of this test by more clearly defining in which patients this test ought to be deployed aiming for the least burden with the best possible outcome, thereby delineating the limits of intended variation.

In this thesis we tried to make clinicians and other stakeholders aware of the different origins and circumstances that may lead to variation in the frequency of deployment of a test or treatment modality. In particular for evolving techniques it is difficult to discern between intended and unintended use. While case-mix correction elucidates a part of the intended variation, institutional policies and availabilities of technical possibilities will lead to variation that is regarded as intended dependent on the direction of the variation and of the unintended special-cause type when the variation is observed in the other direction. Unintended variation may be converted into intended variation, when clinicians take the observed special causes of variation into account in making deliberate choices regarding their treatment policies. Many of the factors that characterize an institution by its variation, as a forerunner or best practice are not easily identified neither simply copied by others. Then again, awareness of this variation and transparency regarding its presence may well be the best incentive to improve.

*"Variation, not per se good or bad,*
*yet for achieving better and for preventing worse"*

Kay Schreuder

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# Summary

**Monitoring evolving breast cancer care**

*Reconstructive surgery, radiotherapy and gene profiling*

Breast cancer is the most common cause of cancer among women worldwide and is responsible for over one million of the approximately 10 million cancers diagnosed yearly.
The last fifteen years are characterized by many refinements of diagnostic test and treatment modalities. These refinements all aim to minimize the burden for the patient and maximize outcome in terms of locoregional control, quality of life and survival and resulted in a trend towards more individualized cancer care. In this thesis, variation in the use of three novel test or treatment modalities and the adherence to changed recommendations in the guideline were assessed in daily practice on a national level. Data from the Netherlands Cancer Registry (NCR) was used. Additionally, data was collected by self-administered web-based surveys. The NCR is hosted by the Netherlands Cancer Organisation (IKNL) and collects data from all Dutch (breast) cancer patients since 1989 and therefore offers the possibility to observe evolving breast cancer care on a nationwide level. In this thesis we addressed the use of immediate breast reconstruction, radiotherapy and gene profiling in breast cancer patients in the Netherlands.

**Part II: Reconstructive Surgery**

In **part two**, the focus was on the use of an immediate breast reconstruction in Dutch clinical practice. For patients who undergo mastectomy, immediate breast reconstruction was introduced in the 1960s to achieve a good cosmetic outcome following mutilating surgery leading to a perceived better quality of life. In **chapter two** significant hospital variation in the use of immediate breast reconstruction after mastectomy was described in the Netherlands. Patient- and tumour-related factors explained part of the variation in performing an immediate breast reconstruction between hospitals in the Netherlands. After annihilating the intended variation by case-mix correction for these factors, remaining unintended variation could be attributed to hospital factors such as hospital type, number of plastic surgeons available in the hospital of surgery and the attendance of a plastic surgeon at the pre-operative multidisciplinary team meeting. Adjustment for case-mix and the hospital organizational factors resulted in a decrease in hospital variation in the use of an immediate breast reconstruction from 0-80% to 0-49% for patients with invasive breast cancer. Despite this substantial decrease of variation after adjusting for case-mix and some hospital organizational factors, considerable unexplained variation persisted. Although hospital organizational factors only partly explain the

hospital variation, optimization of these factors could lead to less variation in immediate breast reconstruction rates. In **chapter three** we described, based on self-administered web-based survey, that both the surgical oncologists and the plastic surgeons discuss the possibility of an immediate breast reconstruction with their patients, whereas patient-tailored information was given more frequently by plastic surgeons. The decision to offer an immediate breast reconstruction is affected by multiple factors weighed differently by surgical oncologists and plastic surgeons involved. Oncological characteristics (tumour size and nodal status) were reported more frequently as contra-indication by surgical oncologists, while plastic surgeons mentioned risk factors and wound-associated problems (age >75, smoking in implant reconstructions, large breast size, BMI and comorbidities) more frequently. Hence, the observed significant differences in information provision and personal opinions towards an immediate breast reconstruction contributed to the unintended special-cause (and as well to hitherto undiscovered intended) variation seen between hospitals.

**Part III: Radiotherapy**

**Part three** addressed radiotherapy. In the 1980s, breast-conserving surgery was always combined with whole breast irradiation and the use of a boost in the Netherlands. A boost dose to the tumour bed combined with whole breast irradiation after breast conserving surgery aims to further reduce the risk of recurrent disease. But a growing awareness of boost-associated morbidity led to acknowledgement that the additional boost is not warranted in all patient categories. In **chapter four** we demonstrated large variation in the use of a radiation boost after breast conserving therapy for both invasive breast cancer and Ductal Carcinoma in Situ (DCIS) between the 21 departments of radiation oncology in the Netherlands. Different patient- and tumour- related factors affected the use of a boost and logistic regression analysis revealed that substantial institutional variation remained that could not be explained by differences in patient, tumour or predefined institutional characteristics. Intended variation apparently played a minor role in the use of a boost, given the limited effect of case-mix correction. Following the implementation of a national guideline for boost use in patients with invasive cancers, the use and variation of administered boost decreased for invasive breast cancer, but remained unchanged for DCIS. In **chapter five** we looked at the general use of radiotherapy in Dutch clinical practice. We demonstrated an increase in utilization rate of radiotherapy. This increased utilization rate of radiotherapy was specifically associated by the finding that more patients underwent radiotherapy after mastectomy. No increase in radiotherapy was observed in patients receiving breast-conserving surgery, as it was already around 97%. After both breast conserving surgery and mastectomy, we found lower utilization rates of radiotherapy in elderly

patients. Variation in the use of radiotherapy was analysed over time (2011-2015), between Dutch regions. After breast conserving surgery, limited variation in the use of radiotherapy was analysed between regions (mean 97.3%, SD: 0.4). However, after mastectomy more variation in the use of radiotherapy between the regions was observed (mean 33.8%, SD: 3.0). The variation in radiotherapy use over time and between regions for patients treated with a mastectomy can be the result of the implementation time of the new recommendations to use radiotherapy after a mastectomy.

**Part IV: Gene profiling**

In **part four** the use of gene-expression profiles was assessed. In the era of ever more systemic treatment, gene-expression profiling was introduced to better select patients in whom adjuvant systemic treatment (chemotherapy) is effective. The Dutch guidelines recommend the use of gene-expression profile in patients with an intermediate risk of developing metastases. This is the group where 'doubt' exists about the effectiveness of adjuvant chemotherapy. In patients with a clinical low or high risk of developing metastases, there is already a recommendation to withhold or administer chemotherapy, respectively. A gene-expression profile is therefore not indicated in these groups. In **chapter six** substantial variation was observed in the deployment of gene-expression profiles in breast cancer patients eligible for gene-expression profile use in the Dutch health-care setting. In 2014 nearly half of all patients for whom gene-expression profiles are considered worthwhile received a gene-expression profile. Tumour characteristics pertaining to an intermediate clinical risk-profile were associated with the use of gene-expression profile. Older patients and patients of low socio-economic status were less likely to receive gene-expression profile testing. In **chapter seven**, frequent use of a 70-gene signature (70-GS) in patients with a clear clinical guideline recommendation to administer or withhold chemotherapy in the Netherlands was seen. 70-GS use was associated with a significantly increased odds of chemotherapy administration in clinical low-risk patients. In clinical high-risk patients 70-GS use was associated with a decreased frequency of chemotherapy administration. Although adherence to the test result is limited in the categories of patients who are considered as having a low or high clinical risk of developing metastases, gene-expression use significantly influenced chemotherapy decision-making in these patients. In **chapter eight**, the focus was on another gene-expression profile: 21-gene recurrence score (21-RS). In the Netherlands, the 21-RS was applied both inside and outside the guideline directed area. In all clinical risk categories, the majority of patients were assigned to the genomic low- and intermediate-risk category and adherence to the 21-RS was high. In case of discordance between the genomic and clinical risk, patients were treated in line with the result of 21-RS. In patients with a clinical

intermediate or high risk and a low genomic test result, a clinically relevant decrease in chemotherapy administration was observed. In general, **part four** confirmed that the gene-expression profile test result yields to lower use of chemotherapy. Furthermore, part of the unintended variation (use of a gene-expression profile while the present guideline clearly recommends the administration of chemotherapy based on the clinical risk profile) served as a justification to withhold chemotherapy will lead to intended variation of chemotherapy use in relation to existing guidelines.

In conclusion, this thesis provides an overview of different sources of variation in the use of an immediate breast reconstruction, radiotherapy and gene-expression profile. The practice of these test and treatment modalities differed conceptually in a number of ways. Variation in immediate breast reconstruction and a radiation boost was studied between institutions (hospitals or radiation oncology departments). Variation over time was addressed when evaluating the use of radiotherapy and additional radiation boost. Variation in relation to a prevailing guideline was evaluated for the use of a gene-expression profiling. Insight in the variation in breast cancer care between Dutch hospitals and the identification of unintended variation is important. Transparency regarding existing variance may help to reduce the bandwidth of the variation and ultimately improve breast cancer care. However, reducing variation is not a primary goal. Variation due to consciously deviating from the guidelines (for example based on the desire of the patient), can possibly result in a clinically less optimal treatment and may be labelled as intended, as long as clinicians and patients are aware of the deviation and possible induced variation. For example, a patient can choose to neglect a (limited) advantage of a specific treatment in order to avoid the risk of treatment associated toxicity. Due to implementation times and possibly limited evidence, it is in particular for evolving techniques and novel technologies difficult to discern between intended and unintended use. While case-mix correction elucidates a part of the intended variation, differences in institutional policies and resources will lead to variation that is regarded as intended or unintended dependent on the direction and the circumstances of the variation.

# Samenvatting

**Monitoren van ontwikkelingen in de borstkankerzorg**

*Reconstructieve chirurgie, radiotherapie en genexpressieprofielen*

Borstkanker is onder vrouwen wereldwijd de meest voorkomende vorm van kanker en is verantwoordelijk voor meer dan een miljoen, van de in totaal 10 miljoen, jaarlijks gestelde diagnoses kanker. De laatste vijftien jaar worden gekenmerkt door veel verfijningen in diagnostiek en de behandeling. Deze aanpassingen zijn allemaal gericht op het reduceren van de belasting voor de patiënt en het maximaliseren van de uitkomst in termen van locoregionale controle, kwaliteit van leven en overleving. Deze ontwikkelingen laten een trend zien richting meer gepersonaliseerde kankerzorg. Dit proefschrift beschrijft de geobserveerde variatie van drie verschillende test en behandelingsmodaliteiten. Ook is er gekeken naar de naleving van recente aanbevelingen in de Nederlandse richtlijnen op nationaal niveau. Data uit de Nederlandse Kankerregistratie (NKR) is gebruikt en is aangevuld met data afkomstig van verschillende vragenlijsten die zijn uitgezet binnen de Nederlandse ziekenhuizen. De NKR wordt beheerd door Integraal Kankercentrum Nederland (IKNL) en hierin wordt data verzameld van alle Nederlandse kankerpatiënten vanaf 1989. Hiermee wordt er unieke mogelijkheid gecreëerd om de ontwikkeling van borstkankerzorg op een nationaal niveau te bestuderen. In dit proefschrift hebben we het gebruik van een directe borstreconstructie, radiotherapie en genexpressieprofielen bij borstkankerpatiënten geëvalueerd.

**Deel II: Reconstructieve chirurgie**

In **deel twee** van dit proefschrift lag de focus op het gebruik van een directe borstreconstructie in de Nederlandse ziekenhuizen. De mogelijkheid tot een directe borstreconstructie voor patiënten die een niet-borstsparende chirurgie ondergaan is geïntroduceerd in de jaren 60 van de vorige eeuw om het cosmetisch resultaat van de behandeling te verbeteren. Dit resulteerde op zijn beurt tot een betere kwaliteit van leven voor de patiënt. In **hoofdstuk twee** werd er significante ziekenhuisvariatie geobserveerd in het gebruik van een directe borstreconstructie na een niet-besparende operatie. Verschillende patiënt- en tumorkarakteristieken bleken geassocieerd te zijn met het gebruik van een directe reconstructie. Aangetoond werd dat deze karakteristieken een verklaring zijn voor een deel van de geobserveerde variatie in de toepassing van een directe borstreconstructie tussen de Nederlandse ziekenhuizen. Na het elimineren van de bedoelde variatie door de toepassing van case-mix correctie, waarbij gecorrigeerd werd voor patiënt- en tumorkarakteristieken, bleef er een deel van de variatie over, welke

gezien kon worden als onbedoelde variatie. Deze onbedoelde variatie was toe te schrijven aan verschillen in ziekenhuisfactoren, zoals bijvoorbeeld ziekenhuistype, aantal plastisch chirurgen werkzaam in het ziekenhuis en de aanwezigheid van een plastisch chirurg bij het preoperatieve multidisciplinaire overleg. Na correctie voor case-mix en organisatorische ziekenhuisfactoren werd er een reductie gezien in de variatie in de toepassing van een directe borstreconstructie voor patiënten met invasieve borstkanker van 0-80% naar 0-49%. Ondanks deze substantiële afname bleef er variatie bestaan die we niet hebben kunnen verklaren met de gegevens die beschikbaar waren voor deze studie. Ondanks dat ziekenhuisfactoren slechts gedeeltelijk de variatie verklaren, kan het optimaliseren van de ziekenhuisfactoren resulteren in een verdere reductie in de geobserveerde variatie tussen de Nederlandse ziekenhuizen. In **hoofdstuk drie** concludeerden we, gebaseerd op een online vragenlijst, dat zowel de oncologische chirurgen als de plastisch chirurgen de mogelijkheid tot het ondergaan van een directe borstreconstructie bespraken met hun patiënten. Echter, meer gedetailleerde geïndividualiseerde informatie betreffende de reconstructie werd vaker gegeven door plastisch chirurgen. De keuze om een directe borstreconstructie aan te bieden werd beïnvloed door verschillende factoren en oncologisch chirurgen en plastisch chirurgen beoordeelde de relevantie van deze factoren verschillend. Oncologische kenmerken (tumorgrootte en klierstatus) werden vaker gemeld als contra-indicatie door oncologische chirurgen, terwijl plastisch chirurgen met name risicofactoren en wond-geassocieerde problemen bestempelde als een contra-indicatie (hogere leeftijd >75 jaar, roken, grote borstomvang, hoge BMI en onderliggende ziekten). De waargenomen substantiële verschillen in informatievoorziening en persoonlijke meningen ten aanzien van een directe borstreconstructie hebben bijgedragen aan de onbedoelde (en ook tot de tot nu toe onbekende, bedoelde) variatie die geobserveerd is tussen ziekenhuizen.

**Deel III: Radiotherapie**

In **deel drie** van het proefschrift werd het gebruik van radiotherapie geëvalueerd. In de jaren tachtig werd borstsparende chirurgie in Nederland altijd gecombineerd met volledige borstbestraling in combinatie met een boost. Een boost dosis op het tumor bed in combinatie met volledige borstbestraling na borstsparende chirurgie heeft tot doel om het risico van terugkerende ziekte te verminderen. Echter, een toename in het bewustzijn van boost-geassocieerde morbiditeit leidde tot de erkenning dat de extra boost niet in alle patiëntencategorieën gerechtvaardigd is. In **hoofdstuk vier** lieten we een grote variatie zien in het gebruik van een boost na borstsparende therapie voor zowel invasieve borstkanker als Ductaal Carcinoom in Situ (DCIS) tussen de 21 radiotherapie afdelingen of instellingen in Nederland. Uit de logistische regressieanalyse bleek dat verschillende patiënt en tumor gerelateerde factoren het gebruik

van een boost beïnvloedden. Hieruit bleek dat er nog aanzienlijke institutionele variatie was die niet kon worden verklaard door verschillen in patiënt-, tumor- of vooraf gedefinieerde institutionele kenmerken. Bedoelde variatie speelde blijkbaar een ondergeschikte rol in het gebruik van een boost, gezien het beperkte effect van case-mix correctie. Na de implementatie van een nationale richtlijn voor het gebruik van een boost bij patiënten met invasieve borstkanker daalde de toepassing van een boost en reduceerde de variatie van de boost voor invasieve borstkanker. Voor DCIS bleef de variatie onveranderd. In **hoofdstuk vijf** hebben we gekeken naar het algemene gebruik van radiotherapie in de Nederlandse klinische praktijk. Er werd een toename van het gebruik van radiotherapie aangetoond. Deze toename in het gebruik van radiotherapie was geassocieerd met een toename van het gebruik van radiotherapie na niet-borstsparende chirurgie tot 70%. In het gebruik van radiotherapie bij patiënten die een borstsparende operatie ondergingen werd geen toename gezien, aangezien voor deze groep patiënten weinig ruimte voor een toename is (gebruik was reeds 97%). Bij zowel borstsparende als niet-borstsparende operatie vonden we een lager gebruik van radiotherapie bij oudere patiënten. Variatie in het gebruik van radiotherapie werd geanalyseerd tussen Nederlandse regio's (tussen 2011 en 2015). Na een borstsparende operatie werd een beperkte variatie in het gebruik van radiotherapie geanalyseerd tussen de regio's (gemiddeld 97,3%, SD: 0,4). Na niet-borstsparende chirurgie werd echter meer variatie in het gebruik van radiotherapie tussen de regio's waargenomen (gemiddeld 33,8%, SD: 3,0). De variatie in gebruik van radiotherapie in de tijd en tussen regio's voor patiënten die werden behandeld met een niet-borstsparende behandeling kan het gevolg zijn van de implementatietijd van de nieuwe aanbevelingen voor het gebruik van radiotherapie na een niet-borstsparende operatie.

**Deel IV: Genexpressieprofielen**

In **deel vier** werd het gebruik van een genexpressieprofiel onder de loep genomen. In het tijdperk van steeds meer systemische behandelen werd genexpressieprofilering geïntroduceerd om een betere selectie te kunnen maken van patiënten bij wie adjuvante systemische behandeling (chemotherapie) effectief is. De Nederlandse richtlijnen bevelen het gebruik van een genexpressie aan in patiënten met een intermediair risico op het ontwikkelen van metastases. Dit is de groep waar 'twijfel' bestaat over de effectiviteit van adjuvante chemotherapie. In patiënten met een klinisch laag of hoog risico op het ontwikkelen van metastases bestaat reeds een aanbeveling om chemotherapie te onthouden of voor te schrijven, respectievelijk. Een genexpressie profiel is in deze groepen daarom niet geïndiceerd. In **hoofdstuk zes** werd een aanzienlijke variatie waargenomen in de inzet van genexpressieprofielen bij borstkankerpatiënten die volgens de Nederlandse richtlijnen in aanmerking komen voor het gebruik van

een genexpressieprofiel. In 2014 ontving bijna de helft van alle patiënten voor wie, gebaseerd op de Nederlandse richtlijn, een genexpressieprofiel geïndiceerd was een genexpressieprofiel. Tumorkenmerken gerelateerd aan een klinisch intermediair risicoprofiel waren geassocieerd met het gebruik van een genexpressieprofiel. Oudere patiënten en patiënten met een lage sociaaleconomische status hadden minder kans op de inzet van een genexpressieprofiel. In **hoofdstuk zeven** werd een frequent gebruik waargenomen van een 70-genen expressie profiel (70-GS) bij patiënten met een duidelijke klinische richtlijnaanbeveling om chemotherapie toe te dienen of te onthouden. Hoewel de naleving van het testresultaat beperkt is in de categorieën van patiënten die een laag of hoog klinisch risico hebben om metastasen te ontwikkelen, heeft het gebruik van de 70-GS de besluitvorming omtrent toediening van chemotherapie bij deze patiënten significant beïnvloed. De toepassing van een 70-GS was geassocieerd met een significant verhoogde kans op chemotherapie gebruik bij klinische laag risico patiënten. Bij klinische hoog risico patiënten was de toepassing van een 70-GS geassocieerd met een verminderde kans op het gebruik van chemotherapie. In **hoofdstuk acht** lag de focus op een ander genexpressieprofiel: 21-gene recidief-score (21-RS). In Nederland werd de 21-RS, net als de 70-GS, zowel binnen als buiten het indicatiegebied toegepast. In alle klinische risicocategorieën werd de meerderheid van de patiënten ingedeeld in een genomisch laag en intermediair risicoprofiel en de naleving van het 21-RS test resultaat was hoog. In geval van een discrepantie in het genomisch en klinisch risico werden de patiënten behandeld in overeenstemming met het 21-RS test resultaat. In klinisch intermediair en hoog risico patiënten met een laag genomisch test resultaat, werd er een klinisch relevante afname in chemotherapie toediening waargenomen. In het algemeen bevestigde **deel vier** dat het testresultaat van het genexpressieprofiel resulteerde in een afname van het gebruik van chemotherapie. Een deel van de onbedoelde variatie (gebruik van een genexpressieprofiel terwijl de huidige richtlijn duidelijk de toediening van chemotherapie op basis van het klinische risicoprofiel aanbeveelt) lijkt het gevolg te zijn van het zoeken naar een rechtvaardiging om chemotherapie te kunnen onthouden. Dit, op zijn beurt, resulteert in een mogelijke oorzaak tot het introduceren van bedoelde variatie in chemotherapie gebruik, aangezien er bewust afgeweken wordt van de huidige richtlijnen omtrent chemotherapie.

Concluderend; dit proefschrift geeft een overzicht van verschillende oorzaken van variatie in het gebruik van een directe borstreconstructie, radiotherapie en een genexpressieprofiel. De context van deze test- en behandelingsmodaliteiten verschilde op een aantal manieren. Variatie in een directe borstreconstructie en een boost werd bestudeerd tussen instellingen (ziekenhuizen of radiotherapie instellingen). Variatie over de tijd kwam aan de orde bij het

evalueren van het gebruik van radiotherapie en de aanvullende boost. Variatie in relatie tot een bestaande richtlijn werd geëvalueerd voor het gebruik van een genexpressieprofiel. Inzicht in de variatie in borstkankerzorg tussen Nederlandse ziekenhuizen en de identificatie van onbedoelde variatie is belangrijk. Transparantie met betrekking tot bestaande variatie kan de bandbreedte van de variatie helpen verminderen en uiteindelijk de zorg voor borstkankerpatiënten verbeteren. Het verminderen van variatie is echter geen primair doel op zich. Variatie door bewust af te wijken van de richtlijnen (bijvoorbeeld op basis van de wens van de patiënt), wat mogelijk resulteert in een klinisch minder optimale behandeling, kan worden beschouwd als bedoelde variatie, zolang clinici zich bewust zijn van de afwijking en de mogelijk geïntroduceerde variatie. Een patiënt kan er bijvoorbeeld voor kiezen om een (beperkt) gunstig effect van een specifieke behandeling te negeren om een mogelijk risico van behandeling te vermijden. Door de implementatietijd en mogelijk gebrek aan bewijs, is het met name voor evoluerende technieken moeilijk om onderscheid te maken tussen bedoeld en onbedoeld gebruik. Hoewel case-mix correctie een deel van de bedoelde variatie verklaart, zullen verschillen in instelling en in beleid leiden tot variatie die als bedoeld of onbedoeld kan worden beschouwd, afhankelijk van de richting en de omstandigheden van de variatie.

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## Curriculum Vitae

Kay Schreuder was born on the 5th of June 1987 as part of an identical twin. Together with his twin brother and an older sister, he grew up in Hengelo in a household of 5 persons. He completed Atheneum at the De Grundel (Hengelo) in 2006 and started the same year with his bachelor Technical Medicine at the University of Twente (Enschede). In 2009 he started with his master Technical Medicine and he combined this master with the master Industrial Engineering and Management (track name: health care and technology management). During his bachelor and master Kay successfully completed the different medical internships in different hospitals (Deventer Ziekenhuis, Medisch Spectrum Twente Enschede, Gelderse Vallei Ede, Antoni Van Leeuwenhoek Amsterdam and AMC Amsterdam). During his study, he was chair of the “student representation committee”. In this committee he was responsible to evaluate all courses related to the bachelor and master program of Technical Medicine. In 2013 he defended successfully his master thesis named: Early estimation of the potential effects of the CTC trap on health care”. After working a couple of months at the University of Twente to further elaborate his master thesis, he went for 5 months to Austria for one of his biggest passions: to become a certified ski instructor. After coming home in the spring of 2014, he started as a Junior Researcher at Netherlands Comprehensive Cancer Organisation where he started as a member of the scientific committee of the NABON breast cancer audit. A year later he officially started his PhD research and the result of it after three years is in front of you.

# Publications

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**K. Schreuder**, A. C. M. van Bommel, K. M. de Ligt, J. H. Maduro, M. Vrancken Peeters, M. A. M. Mureau and S. Siesling, *Hospital organizational factors affect the use of immediate breast reconstruction after mastectomy for breast cancer in the Netherlands*. Breast, 2017. **34**: 96-102.

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