Defining the quality of surgical breast cancer care

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Defining the quality of surgical breast cancer care

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Chapter 1

General introduction

A total of 13,257 primary breast cancers and 1,996 carcinoma in situ were diagnosed in the Netherlands in 2010. The 10-year overall survival for breast cancer is 76% but is largely defined by the stage at diagnosis. It is estimated that on January 1st, 2011, 99,372 women in The Netherlands were alive who had breast cancer diagnosed in the past ten years.[1] These numbers make the quality of breast cancer care a major healthcare issue; for patients, physicians and the health care system in general.

Surgical breast cancer care

Breast cancer diagnosis and treatment focus on three basic elements: optimal local control, examining lymph node involvement and assessment of the risk of potential distant metastases.

Optimal local control

Adequate removal of the primary tumour is the basis for treatment of breast cancer. Breast conserving surgery (BCS) was introduced as an alternative to mastectomy. Major benefit of BCS is a better cosmetic outcome, resulting in higher patient satisfaction. BCS became commonly used in the 1980s for patients with tumours up to 2 cm.[2,3] Efficacy in tumours up to 5 cm was later demonstrated and led to further implementation of BCS.[4–7] To obtain the same cosmetic results for patients with larger tumours, neo-adjuvant systemic therapy before surgery is increasingly used to reduce the size of the lesion. BCS has become a treatment option for even more patients. In 2011, 63% of patients with early breast cancer (pT1-2, any N, M0) underwent BCS (non published data NCR). Radiotherapy is standard after BCS.

To optimise local control, adequate removal of the tumour is assessed through meticulous examination of tumour margins. In case of positive margins, re-excision or additional radiotherapy on the tumour bed is required.

Lymph node involvement

Examination of the axilla is of major importance in staging breast cancer, for nodal involvement is associated with poorer prognosis. Staging entails removal of all axillary lymph nodes for pathological examination.

A major change in lymph node staging was the introduction of the sentinel node biopsy (SNB) in the late 1990s.[8–10] SNB replaces the complete axillary lymph node dissection, which can lead to substantial morbidity, such as lymphedema. SNB builds on the hypothesis of an orderly pattern of lymphogenic tumour cell dissemination; if the sentinel node is free of tumour, remaining axillary nodes are also likely to be tumour negative. Sentinel nodes are identified through lymphatic mapping with radioactive colloid and intra-operative patent blue dye injection (Figure 1). The surgeon locates and removes the sentinel node(s) for histopathological examination by the pathologist. Based on results of the SNB, additional axillary clearance is considered.

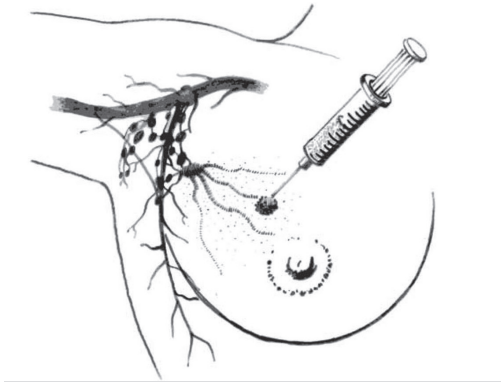

Figure 1. Sentinel node biopsy

Risk assessment of distant metastases

Adjuvant systemic therapies, such as chemotherapy and hormonal treatment, aim to prevent distant metastases. Given the therapy side effects and costs, accurate patient selection is essential. Decisions are based on data on the primary tumour, axillary status and patient characteristics. Thorough deliberation by a multidisciplinary breast cancer team is required.

Quality of care

Quality of care is often defined as '… the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge'.[11] The desired health outcomes can be characterised by several dimensions, e.g. safe care, effective care, appropriate care, patient-centred care, timely care and equitable care (accessible to all).[12] Conclusions on the quality of care are based on the perspective chosen. During the past decade, measuring the quality of care gained growing interest. Various reports were made public, in some cases even with contradicting conclusions on the quality of care in the same hospital.[13] This reflects the complexity of the concept as was already stated by Donabedian in 1966 by saying: '… the quality of care is a remarkably difficult notion to define'.[14] However, as stated in the fore mentioned definition, care has to be consistent with current professional knowledge. Tools to measure quality of care are called performance indicators. Many performance indicators are derived from professional knowledge.

Clinical practice guidelines

Current professional knowledge is readily available in clinical practice guidelines that support physicians treating breast cancer patients. The Dutch breast cancer guideline is developed by the National Breast cancer Organization Netherlands (NABON), a multidisciplinary working group facilitated by Comprehensive Cancer Centre the Netherlands (CCCNL).[15] The guideline includes all important aspects of breast cancer care, i.e. screening, diagnosis, treatment

(surgery, radiotherapy and systemic treatment), rehabilitation and follow up. The most recent guideline was published on February 13, 2012.
Complementary to the diagnosis and treatment guideline is the so-called 'NABON nota'; a manual about the organisation of breast cancer care.[16] The NABON nota is based on the European standard and the Dutch breast cancer guideline.[15,17] It describes the basic elements to enable adequate care by health care providers and sets basic standards to be achieved by all breast cancer teams.

Performance indicators in breast cancer care

Currently, a number of indicators in breast cancer care are obligatory for all hospitals in the Netherlands (Table 1). Results are monitored and made public by the Dutch health care inspectorate. The health care inspectorate uses these data to identify hospitals with potential risks to the quality of care. Others use these data after publication for their own purposes, e.g. insurance companies for debating the contracts with the hospitals which care will be reimbursed and patient groups to inform patients about the quality of care of different hospitals.

Table 1. Breast cancer indicators Dutch health care inspectorate 2012

Number of patients operated with primary breast cancer (or DCIS)
Percentage of patients with more than focal tumour residue after first breast conserving surgery for invasive breast cancer
Percentage of patients with unknown tumour residue after first breast conserving surgery for invasive breast cancer
Percentage of patients with focal or more than focal tumour residue after first breast conserving surgery for DCIS
Percentage of patients with unknown tumour residue after first breast conserving surgery for DCIS
Percentage of patients who undergo first surgery within 5 weeks after diagnosis
Percentage of patients who received first neo adjuvant treatment within 5 weeks after diagnosis
Percentage of patients discussed in a multidisciplinary team before treatment started
Percentage of patients discussed in a multidisciplinary team after surgery
Percentage of local recurrences within 5 year after diagnoses for patients with breast conserving surgery as final surgery
Percentage of local recurrences within 5 year after diagnoses for patients with mastectomy as final surgery

Outline of this thesis

In **Part 1** of this thesis, we focus on various aspects of the implementation of SNB as an innovative method in axillary staging. The Dutch national guideline on SNB was released in 1999.[8] **Chapter 2** provides an overview of SNB implementation over the period 1998 – 2003 in the Netherlands. Patient and tumour characteristics that are associated with the procedure of SNB are described, and region-specific patterns of introduction are visualised.
To aid the implementation, seven hospitals in the Utrecht region (formerly known as CCCMN) jointly developed local sentinel node protocols. Not all hospitals had a nuclear department

and pathology laboratory on site, so tailored procedures were needed. Treatment results for all hospitals were monitored through a registration study coordinated by CCCMN. The results are presented in **Chapter 3**.
Sentinel nodes generally are more thoroughly examined than lymph nodes from a complete axillary dissection. As pathologists receive only a few lymph nodes for investigation, standard dissection of nodes evolved into serial sectioning with immunohistochemistry staining, with potential increase of diagnosing small deposits of tumour metastases (between 0.2 and 2 mm) or even isolated tumour cells (single cells or small clusters of cells <0.2 mm). In **Chapter 4**, we examine whether the introduction of the sentinel node biopsy led to more patients being diagnosed with tumour positive lymph nodes.
With the possible detection of more and smaller nodal metastases, the relevance of minimal lymph node involvement in breast cancer becomes increasingly important. **Chapter 5** examines the prognosis of breast cancer patients with minimal lymph node involvement and studies the effect of adjuvant systemic therapy in these patients.

In **Part 2** of this thesis, we present studies in which performance indicators are used to provide insight in the quality of care and variations between hospitals.
The most important outcomes in breast cancer care are disease free and overall survival. Since 2009, hospitals are obliged to report the 5-year local recurrence rate after breast cancer surgery. The Netherlands Cancer Registry (NCR) aided in uniform and complete registration of this indicator. **Chapter 6** describes the results of the local recurrence rates of patients diagnosed in 2003 of all Dutch hospitals. The value of the indicator is discussed and recommendations are made for future use. **Chapter 7** reports on the same indicator of local recurrences, but combines data on four consecutive years. This study aims to determine whether extra data can add to the value of the indicator.
A more timely indicator used by the Dutch health care inspectorate is on the adequate surgical removal of tumour tissue during the first BCS. **Chapter 8** describes the variation between hospitals in surgical margins after first breast conserving surgery.

In the general discussion (**Chapter 9**) we focus on the process of improving the quality of care and on the measurement of this concept. We also discuss opportunities and pitfalls in comparing hospitals based on performance indicators.

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Part 1

Implementation of sentinel node biopsy

Chapter 2

Implementation of sentinel node biopsy in breast cancer patients in the Netherlands

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Abstract

Background

This population-based study describes the implementation of the sentinel node biopsy (SNB) in breast cancer patients in The Netherlands. We examined the extent of use over time of SNB in women who were considered eligible for SNB on the basis of their clinical status.

Methods

The study included a total of 35,465 breast cancer patients who were diagnosed with T1–2 tumours (≤5.0 cm), negative axillary lymph node status and no distant metastases upon clinical examination between January 1, 1998, and December 31, 2003 in six Comprehensive Cancer Centre regions in The Netherlands. Information on axillary surgery was classified as SNB alone, SNB + axillary lymph node dissection (ALND), ALND alone, or none. Patterns of use of axillary surgery were summarized as the proportion of patients receiving each surgery type.

Results

Overall, 25.7% of patients underwent SNB alone, 19.1% underwent SNB + ALND, 50.0% had ALND alone, and 5.2% did not have axillary surgery. SNB was more common in women who had breast-conserving surgery: 50.5% of patients who received breast-conserving surgery underwent SNB compared to 40.7% of patients who had mastectomy ($p<0.0001$). Among patients receiving breast-conserving treatment, 31.7% had SNB as final axillary surgery, while 20.5% of patients who had mastectomy had SNB alone ($p<0.0001$). The proportion of women who underwent a SNB alone or in combination with ALND increased over the period 1998 to 2003, from 2.1% to 45.8% and from 6.7% to 24.8%, respectively. There were marked differences in patterns of dissemination of the use of SNB between regions: by 2003, the difference between the regions with the highest and lowest proportion of use was 25%.

Conclusions

SNB has become standard-of-care for the treatment of breast cancer patients clinically diagnosed with T1–2 tumours, clinically negative lymph nodes and without distant metastases. In 2003, 70.6% of patients with early breast cancer in The Netherlands received SNB, and within this group, 64.9% of patients had SNB as final axillary treatment. Implementation of SNB may depend on factors associated with regional organization of care.

Introduction

The sentinel node biopsy (SNB) was introduced almost 15 years ago as an intraoperative lymph node staging method for breast cancer patients.[1,2] The SNB had already been described as a staging method for patients with penile cancer in 1977[3], and the procedure was then further developed for detection of non palpable lymph node metastases of melanoma.[4] SNB may also be applied in other solid malignancies.[5]

Axillary lymph node status is the most important prognostic factor for breast cancer, and it affects the choice of adjuvant systemic therapy and radiotherapy. Histopathologic examination of lymph nodes requires axillary-specific surgery as a critical component of breast cancer care. Until recently, axillary surgery consisted of axillary lymph node dissection (ALND). Although ALND is considered a safe procedure resulting in optimal regional control after local treatment and additional prognostic information, dissection of all lymph nodes lacks clinical value if the nodes are tumour negative, as is the case in about 70% of breast cancer patients in countries with mammographic screening programs. Moreover, post-ALND morbidity, which include upper arm paresthesias, shoulder and arm pain, restriction of shoulder mobility and permanent and potentially disabling lymph oedema, have a significant impact on patients' quality of life.[6–11] The technique of SNB allows for a selective method of staging, thus enabling lymph node assessment without the use of ALND: as a result, use of ALND should be restricted to patients with lymph node metastases. Indeed, the risks of short-term morbidity and lymph oedema are markedly lower with SNB.[12–14] Also, SNB shows a similar sensitivity for detecting patients with positive lymph nodes.[15]

SNB is based on the by now confirmed hypothesis of an orderly pattern of lymphogenic tumour cell dissemination. Sentinel lymph nodes should be at the greatest risk of bearing cancer metastases, and if these nodes prove to be negative, the remaining axillary lymph nodes are also likely to be negative. The sentinel nodes are located by lymphatic mapping with preoperative lymphoscintigraphy alone or the most frequently used combined technique, lymphoscintigraphy with ^{99m}technetium-labeled nanocolloid and patent blue dye. As the colloidal material accumulates in the draining sentinel lymph nodes, the nodes may be identified at surgery, visually and by gamma probe if required, and removed for histopathologic examination. Ideally, sentinel nodes are examined during breast surgery, and if the pathologist then identifies cancer metastases, e.g. by frozen section analysis[16], ALND may be performed in the same surgery. SNBs require adequate cooperation between departments of surgery, nuclear medicine, and pathology. Since community hospitals may not be equipped with a pathology laboratory, SNBs often require cooperation between hospitals as well.

SNBs are suitable for breast cancer patients with primary tumours with a maximum size of 5 cm or less (T1–2), with no multiple lesions, no previous breast surgery or axillary surgery, and no signs of malignancy in axillary lymph nodes.[17] The reliability of the procedure in these patients is considered adequately tested after several studies of SNB with concomitant ALND: experienced surgeons are able to locate sentinel nodes in more than 90% of cases, while

the prediction of lymph node status assessed by SNB is accurate in 95% (range 84–100%) of cases.[18,19] The false-negative rate has been estimated at 3.2% (range 0–15%), but follow-up of patients with a negative sentinel lymph node seldom detected axillary metastases.[20–23] A recent study showed a false-negative rate of 9.8%, with higher percentages for patients who had excisional biopsy and patients with a tumour in the upper outer quadrant of the breast.[24] In The Netherlands, the procedure for SNB was first described in Dutch national guidelines for staging of breast cancer in 2000[25], but regional implementation had by then already started. This study examines the implementation of SNB in The Netherlands from 1998 through 2003, a time period during which SNB entered clinical practice.

Patients and Methods

Data sources

Information on women with newly diagnosed breast cancer was extracted from the regional cancer registries of six out of nine Dutch Comprehensive Cancer Centres (CCCs, Figure 1).

A. CCC East
B. CCC Limburg
C. CCC Middle Netherlands
D. CCC North Netherlands
E. CCC Rotterdam
F. CCC South

Figure 1. The regions of six Dutch Comprehensive Cancer Centres (in dark grey)

These six registries cover around 10,350,000 inhabitants in 2006, or approximately 60% of the total Dutch population. The CCCs form a network of health care professionals and institutions for cancer care and palliative care in The Netherlands. The CCC regions cover between five and twenty hospitals. The CCCs do not treat patients, but foster expertise and multidisciplinary cohesion in (regional) cancer care. Among other activities, they host the Netherlands Cancer

Registry (NCR), a nationwide population-based cancer registry established in 1989.

The NCR provides incidence data on a national level. It is composed of the Regional Cancer Registries (RCRs) of the nine CCCs in The Netherlands. PALGA, the Dutch network and registry of histo- and cytopathology, notifies the RCRs of all newly diagnosed malignancies. Following this notification, trained registry personnel from the RCRs collect data on diagnosis, staging, and treatment from hospital records, including pathology and surgery reports. Primary treatment is coded in sequence of administration, and patients are staged according to the TNM system of the International Union Against Cancer (UICC).[26,27] Case ascertainment is provided by the national hospital discharge database, which receives discharge diagnoses of patients admitted from all hospitals in The Netherlands. The study design, data abstraction process and storage protocols have been approved by the national supervisory committee of the NCR.

Study population and eligibility criteria

The data of the NCR distinguishes clinical tumour stages (cTNM) from pathologic stages (pTNM), which enabled us to accurately identify the larger part of patients who should have undergone SNB on the basis of their clinical tumour status (cTNM) according to the Dutch guideline for the treatment of breast cancer.[17] The clinical status of patients was based on physical examination, biopsies, imaging techniques and other diagnostic information retrieved prior to therapeutic intervention; this information was supplemented with post-surgical histopathological examination to determine the pathological tumour status (pTNM). In case the clinical extent of the primary tumour was unknown (cTX), patient information was supplemented by the pathologic extent of the tumour (pT); this was the case for 19.2% of the population. Patients were eligible for this study if they were clinically diagnosed with T1–2 tumours (≤ 5.0 cm), negative axillary lymph node status and no (signs of) distant metastases.

Patients had to be presented in one of the six regions participating in the study between January 1, 1998, and December 31, 2003. For the study period, the data from the remaining three CCCs could not be used to identify SNB implementation patterns as these centres only register the most extensive axillary surgery for each patient. In these regions, SNB was not registered if the procedure was followed by ALND.

Classification of axillary and definitive breast surgery

The type of axillary surgery was classified into one of four categories for each patient: no axillary surgery (None); SNB without further axillary surgery (SNB alone); SNB followed by complete ALND (SNB + ALND); or ALND without SNB (ALND alone). Patients were considered as lymph node positive if any axillary lymph node contained histologically proven metastases (whether assessed by SNB or otherwise). Axillary surgery was coded as SNB alone if SNB was performed and the patient had no other axillary surgery at any time during initial treatment of the primary cancer. Axillary surgery was classified as ALND alone if axillary dissection was performed and the patient had no prior or concomitant SNB.

The type of definitive breast surgery was classified into one of three categories for each patient: no breast surgery (None); breast-conserving surgery; and mastectomy. Patients who were initially treated with breast-conserving surgery but had subsequent mastectomy were included in the latter category.

Statistical analysis

Descriptive statistics were used to describe the patient population. We summarized the patterns of use of definitive breast surgery as the proportion of patients receiving each surgery type (i.e., None, Breast-conserving surgery, or Mastectomy). The same was done for patterns of use of axillary surgery (i.e., None, SNB alone, SNB + ALND, or ALND alone). The type of axillary surgery was also linked with type of definitive breast surgery. Since our study population consisted mainly of breast cancer patients with small primary tumours, we expected to observe a large group of women who underwent breast-conserving therapy, especially when a SNB had indicated a negative axillary lymph node status in these patients. The chi-square test was applied to test associations of axillary surgery with type of breast surgery. The type of axillary surgery was also analyzed according to patient age, clinical and pathological tumour size, and pathological tumour stage. A p-value below 0.05 (two-sided) was considered statistically significant.

To describe the implementation of SNB during the study period, we examined the time trends of axillary surgery among women who may be considered eligible for SNB on the basis of their clinical status from January 1998 through December 2003. Time trends were also studied for the separate regions.

Results

Patient characteristics

Between January 1, 1998, and December 31, 2003, 35,904 women were diagnosed with clinically small breast tumours (≤5.0 cm), clinically negative axillary lymph node status and no signs of distant metastases in the six CCC regions under study. Of these patients, we excluded 439 (1.2%) for lack of reliable and unambiguous information on definitive breast surgery, leaving 35,465 women (98.8%) in our study. 4,825 (13.6%) Patients were diagnosed or treated in the region of CCC East (Figure 1: A); 3,141 (8.9%) in CCC Limburg (B); 4,122 (11.6%) in CCC Middle Netherlands (C); 7,888 (22.2%) in CCC North Netherlands (D); 7,652 (21.6%) in CCC Rotterdam (E); and 7,837 (22.1%) in CCC South (F).

The median age of patients was 59 years (Table 1); 27.1% of all patients was aged 50 years or younger. The clinical tumour size was 2 cm or less for 68.6% of patients, and 52.7% of these patients received breast-conserving surgery. Overall, 48.8% of patients underwent breast-conserving surgery, 49.1% had mastectomy, and 2.1% did not have definitive breast surgery. With respect to axillary surgery, 25.7% of all patients had SNB alone, 19.1% had SNB with concomitant ALND, and 50.0% had ALND alone; 5.2% of the patients did not have axillary surgery performed.

The patient selection concerns a population which would be considered eligible for SNB on

the basis of clinical tumour status (cTNM). As for the pathological staging of patients (pTNM), which is determined postoperatively and therefore does not affect the indication for SNB, 48.5% of patients were diagnosed with stage I breast cancer, 33.9% with stage IIA, and 14.5% with IIB. Furthermore, 2.9% of the patients were diagnosed with stage III and 0.2% with stage IV breast cancer. Four (<0.0%) patients had unknown stage, and five (<0.0%) patients were pathologically diagnosed with in situ breast malignancy.

Table 1. Patient characteristics for 35,465 patients with breast cancer who presented with a clinical T1–2 tumour (tumour size ≤5.0 cm), clinically negative lymph nodes and without distant metastases in six Dutch Comprehensive Cancer Centre regions in 1998–2003

	N	%
Age at diagnosis (years)		
Median (interquartile range)	59	(50-71)
< 40	2,043	5.8%
40–49	6,375	18.0%
50–59	9,332	26.3%
60–69	7,769	21.9%
70–79	6,815	19.2%
≥ 80	3,131	8.8%
Tumour size (cT), cm		
0–2.0	24,326	68.6%
> 2.0–5.0	11,139	31.4%
Type of definitive surgery		
None	757	2.1%
Breast-conserving surgery	17,303	48.8%
Mastectomy	17,405	49.1%
Breast-conserving surgery within tumour size, cm		
0–2.0 (n = 24,326)	12,827	52.7%
> 2.0–5.0 (n = 11,139)	4,476	40.2%
Type of axillary surgery		
None	1,847	5.2%
SNB alone	9,111	25.7%
SNB + ALND	6,780	19.1%
ALND alone	17,727	50.0%

[a] SNB: sentinel node biopsy, ALND: axillary lymph node dissection

Patterns of axillary surgery according to definitive surgery type

Use of SNB (SNB alone or with concomitant ALND) was statistically significantly associated with breast-conserving surgery (Table 2). Among patients who received breast-conserving surgical treatment 50.6% had SNB, while this proportion was 40.7% for patients who underwent mastectomy (p<0.0001). Also, SNB was more often the only axillary surgery in women who were treated with breast-conserving surgery than in women who had mastectomy: 31.7% vs. 20.5%, respectively (p<0.0001).

Table 2. Definitive breast surgery stratified by type of axillary surgery for 35,465 breast cancer patients

	None, no. (%)	SNB alone, no. (%)	SNB + ALND, no. (%)	ALND alone, no. (%)
	n = 1,847 (5.2)	n = 9,111 (25.7)	n = 6,780 (19.1)	n = 17,727 (50.0)
Type of definitive breast surgery				
None	684 (90.4)	47 (6.2)	11 (1.5)	15 (2.0)
Breast-conserving surgery	639 (3.7)	5,490 (31.7)	3,258 (18.8)	7,916 (45.7)
Mastectomy	524 (3.0)	3,574 (20.5)	3,511(20.2)	9,796 (56.3)

[a] SNB: sentinel node biopsy, ALND: axillary lymph node dissection

Patterns of axillary surgery according to patient and tumour characteristics

Overall, the proportion of patients who received SNB alone was 26%, while 20% had SNB with concomitant ALND, and 50% had ALND alone (Table 3). For women in age groups under 80, the type of axillary surgery was not associated with age. Women aged 80 years or over were most likely not to undergo axillary surgery, and they had the highest proportion of ALND alone when patients who did not undergo axillary surgery are excluded.

SNB alone was more common in patients with smaller tumours, i.e. clinically assessed tumour sizes of 2.0 cm or less (cT1): 29.3% of these patients had SNB as final axillary treatment, while this was the case for 17.7% of patients with a tumour between 2 and 5 cm (cT2). The same pattern was observed in lower tumour stages compared to higher stages.

ALND was most commonly used in almost all pathological tumour sizes and tumour stages.

Time trends of axillary surgery among patients who were eligible for SNB on the basis of their clinical tumour status

Overall, the use of SNB increased from 8.8% in 1998 to 70.6% in 2003. The proportion of women who received SNB as final axillary treatment (= SNB alone) increased from 2.1% to 45.8% (Figure 2). In the study period, the proportion of patients who had SNB followed by ALND (SNB+ALND) also shows a temporal trend, with an overall increase from 6.7% to 24.8%. In 2001, the proportion of patients treated with SNB alone exceeded the proportion of patients treated with SNB and concomitant ALND for the first time. The use of ALND alone gradually decreased from 84.5% in 1998 to 24.3% in 2003.

Region-specific patterns in types of axillary surgery

In all six regions, we observed an increase in the use of SNB over the period 1998–2003 (Figure 3). Patients in several regions already received SNB in 1998 (A, B and F), while the procedure was still minimally applied in other regions (C, D and E). Over the whole study period, the proportion of women who received SNB was highest in region B (the smallest region): here, the proportion rose from 28.0% in 1998 to 84.0% in 2003, with a sharp increase in 1999–2000 (40.0% to 73.4%). The difference between the regions with the highest (B: 84.0%) and lowest (E: 58.8%) proportion of use of SNB at the end of the study period was still 25.2% and statistically significant ($p<0.0001$).

Table 3. Type of axillary surgery by clinical tumour size, pathological tumour stage, and age groups for 35,465 breast cancer patients

	None	SNB alone	SNB + ALND	ALND alone
	no. (%)	no. (%)	no. (%)	no. (%)
	n = 1,847 (5.2)	n = 9,111 (25.7)	n = 6,780 (19.1)	n = 17,727 (50.0)
Age, years				
< 40 (n = 2,043)	33 (1.6)	491 (24.0)	498 (24.4)	1,021 (50.0)
40–49 (n = 6,375)	141 (2.2)	1,624 (25.5)	1,507 (23.6)	3,103 (48.7)
50–59 (n = 9,332)	233 (2.5)	2,631 (28.2)	2,007 (21.5)	4,461 (47.8)
60–69 (n = 7,769)	206 (2.7)	2,241 (28.8)	1,432 (18.4)	3,890 (50.1)
70–79 (n = 6,815)	382 (5.6)	1,635 (24.0)	1,023 (15.0)	3,775 (55.4)
≥ 80 (n = 3,131)	852 (27.2)	489 (15.6)	313 (10.0)	1,477 (47.2)
Tumour size (cT), cm				
cT1: 0–2.0 (n = 24,326)	1,106 (4.5)	7,137 (29.3)	4,511 (18.5)	11,572 (47.6)
cT2: > 2.0–5.0 (n = 11,139)	741 (6.7)	1,974 (17.7)	2,269 (20.4)	6,155 (55.3)
Tumour size (pT), cm				
pTis: in situ (n = 5)	1 (20.0)	3 (60.0)	1 (20.0)	0 (0.0)
pT1: 0–2.0 (n = 22,527)	1,086 (4.8)	6,703 (29.8)	3,913 (17.4)	10,825 (48.1)
pT2: > 2.0–5.0 (n = 12,169)	726 (6.0)	2,333 (19.2)	2,707 (22.2)	6,403 (52.6)
> pT2: > 5.0 (n = 764)	34 (4.5)	72 (9.4)	159 (20.8)	499 (65.3)
Tumour stage				
In situ (n = 5)	1 (20.0)	3 (60.0)	1 (20.0)	0 (0.0)
In situ (n = 5)	1 (20.0)	3 (60.0)	1 (20.0)	0 (0.0)
I (n = 17,193)	1,042 (6.1)	6,102 (35.5)	1,573 (9.1)	8,476 (49.3)
IIA (n = 12,009)	713 (5.9)	2,453 (20.4)	2,923 (24.3)	5,920 (49.3)
IIB (n = 5,151)	56 (1.1)	434 (8.4)	1,925 (37.4)	2,736 (53.1)
IIIA (n = 599)	7 (1.2)	62 (10.4)	233 (38.9)	297 (49.6)
IIIB (n = 290)	20 (6.9)	30 (10.3)	48 (16.6)	192 (66.2)
IIIC (n = 146)	4 (2.7)	26 (17.8)	67 (45.9)	49 (33.6)
IV (n = 68)	4 (5.9)	0 (0.0)	10 (14.7)	54 (79.4)
Unknown (n = 4)	0 (0.0)	1 (25.0)	0 (0.0)	3 (75.0)

[a] SNB: sentinel node biopsy, ALND: axillary lymph node dissection

The increase in the use of SNB alone was also most profound in region (B): from 5.5% in 1998 to 70.7% in 2003 (Figure 4). The difference between the regions with the highest (B: 70.7%) and lowest (E: 35.9%) proportion of use of SNB alone in 2003 was also statistically significant ($p<0.0001$). Two regions (C and D) showed a clear increase during the period 2000–2002.
The use of ALND alone steadily declined in all regions, with region B having the lowest levels of use over the whole study period.

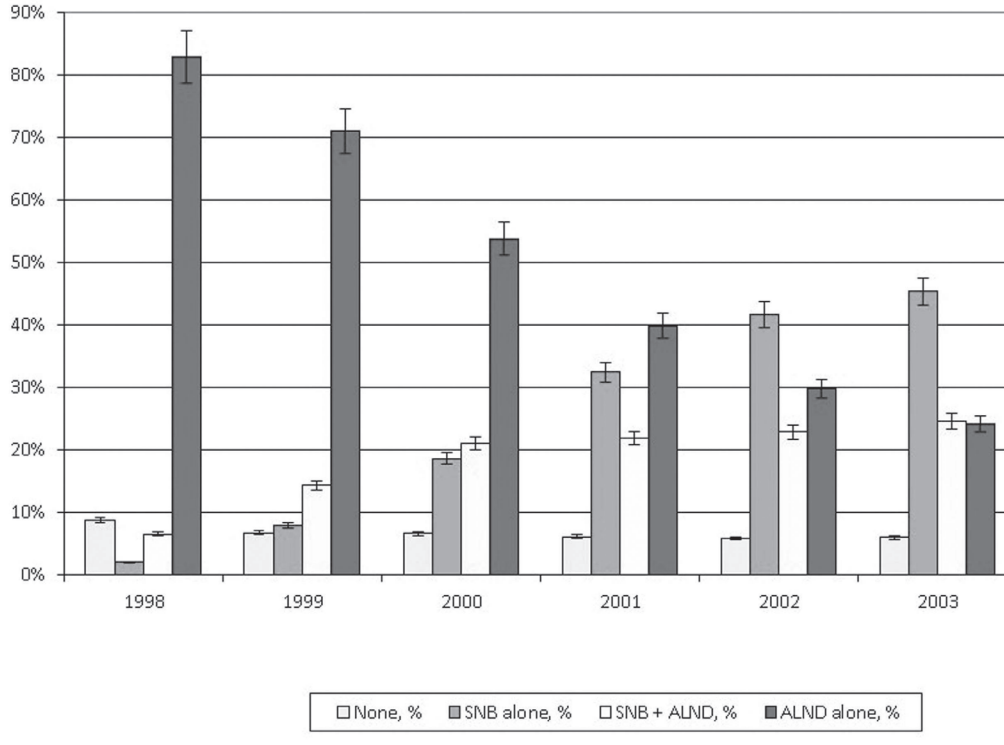

Figure 2. Type of axillary surgery for 35,465 breast cancer patients in 1998–2003

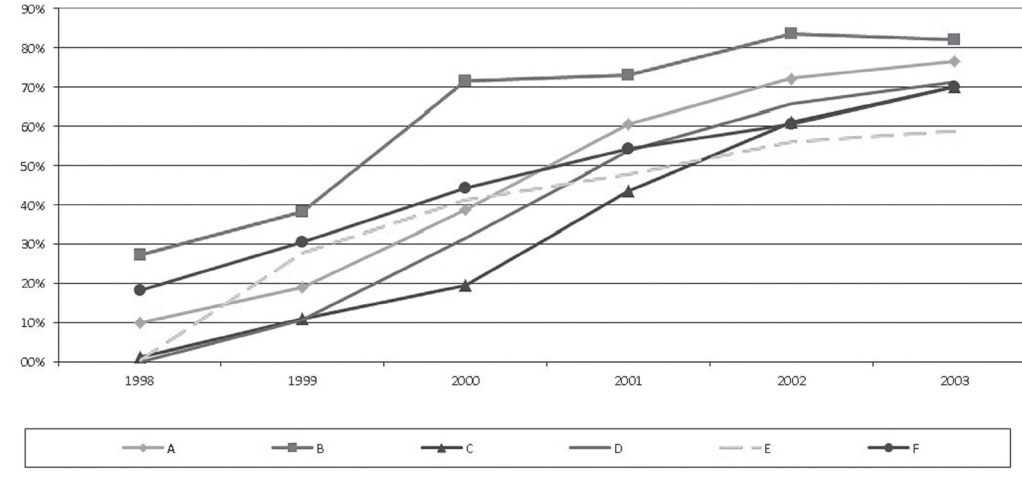

Figure 3. Use of SNB in the regions of six Dutch Comprehensive Cancer Centres

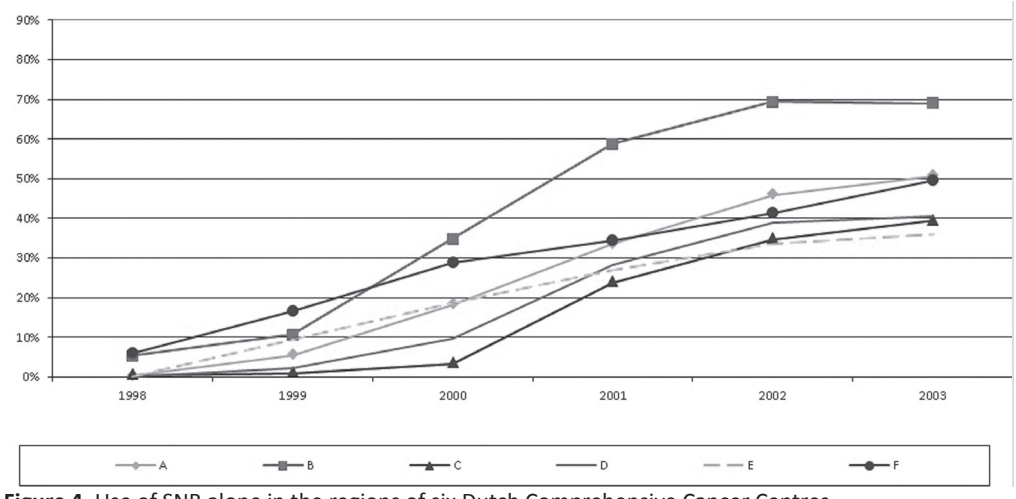

Figure 4. Use of SNB alone in the regions of six Dutch Comprehensive Cancer Centres

Discussion

In the period 1998–2003, 44.8% of breast cancer patients clinically diagnosed with T1–2 tumours, negative axillary lymph node status and no signs of distant metastases, received SNB as axillary staging method. The proportion increased from 8.8% in 1998 to 70.6% in 2003. SNB was the final axillary treatment for 25.7% of patients, 2.1% in 1998 to 45.8% in 2003. Overall, SNB was most common in women who had breast-conserving surgery. The CCC regions show different patterns of use of SNB, with or without concomitant ALND.

The database of the NCR allowed for a unique population-based study, entailing a large number of patients. As the data of the NCR distinguishes between clinical (cTNM) and pathological tumour stages (pTNM), we were able to include women on the basis of clinical eligibility. This provided insight in patients' upstaging after surgical treatment (even to stage III and IV breast cancer), as the pathological tumour stage is determined through histopathological examination. Patients with higher pathological tumour stages would generally be excluded from other studies.[28]

Apparently, despite their clinical tumour size (cT1–2), approximately half of all patients underwent mastectomy as definitive surgery. By 2003, 24.3% of women still had ALND alone, even though SNB was indicated given their clinical tumour status. Of course, this is in part explained by the relatively high proportion of elderly patients undergoing ALND alone. The pathological presentation of the cancer during breast surgery may also represent a partial explanation, as is indicated by the higher tumour stages (IIB and over) in our patient population. However, we lacked further information to determine patient eligibility more accurately: patients may have had multiple lesions, or they may have had previous breast surgery or axillary surgery. Furthermore, some women may well have preferred one surgery type over

another, and the same may be true for their physicians.

The implementation of SNB showed different time trends in the separate regions of the CCCs. Each region's relative proportion of community hospitals, university hospitals and teaching hospitals may explain these trends. Differences in availability of nuclear medicine departments and pathology laboratories may in addition influence the introduction. Also, the region-specific time trends show that some regions adopted SNB earlier than others. Overall, region B, the smallest in size and covering approximately 5.2% of the total Dutch population was able to achieve the highest proportion of SNB use. The high proportion of use was maintained during the study period, and by 2003, the difference between this region (83.9%) and the region with the lowest proportion of SNB use (58.8%) was still 25%. The region's relative small geographic size may form an explanation, as new surgical procedures would be able to have spread more rapidly from one hospital to another. In fact, one community hospital had been actively adopting the SNB as standard-of-care prior to and during the study period.[29]
The difference between the regions with the highest (B: 70.7%) and lowest (E: 35.9%) proportion of use of SNB alone in 2003 was also statistically significant ($p<0.0001$). The low proportion of use in region E may be partly explained by incomplete registration in some hospitals at the start of the study period. More importantly, two large medical centres in this region just implemented the SNB in the course of 2003. Two regions (C and D) showed a clear increase during the period 2000–2002.

Like any new surgical procedure, SNB is associated with a learning curve. During the learning curve, surgeons are trained in locating sentinel nodes, and lymph node status is affirmed by concomitant ALND. Hence, SNB would often be followed by ALND in the first years of introduction, after which a negative SNB result would not be followed by ALND due to sufficient training and increased confidence in the procedure.
Limitations of our study include the fact that our data do not permit description of the learning curve associated with introduction of the SNB. Hence, we are not able to identify a shift from an early learning phase during which results of SNB were confirmed by ALND, toward a later stage in which ALND was performed only if the sentinel lymph node was found to be positive. Although our study provides information on patterns of axillary surgery in only six regions of the CCCs, we consider the data representative for the Dutch population.

The study results show that implementation of SNB in The Netherlands did not necessarily start with description and recommendation of the procedure in national clinical practice guidelines in 1999. The study period does coincide with publication of literature supporting the use of SNB, and this may well have stimulated acceptance of SNB by physicians. Acceptance was not hampered by the absence of definitive data from clinical trials addressing the accuracy and safety of the new procedure. Some have pointed out that the widespread use of SNB in the routine care setting may affect accrual and generalisability of ongoing trials.[28]

Preliminary results of current clinical trials show that use of SNB alone resulted in fewer complications (wound infections, axillary seromas, and paresthesias) compared to the use of SNB + ALND.[30] Pending definitive trial results, application of SNB already allowed for a selective approach to ALND.[31,32] Some have suggested that ALND may be omitted even in the presence of metastasized tumour cells in the sentinel lymph node, since a relatively high proportion of patients with positive sentinel nodes do not show metastases in the remaining axillary lymph nodes. A wait-and-see policy may be acceptable in women who have a low expected risk of positive lymph nodes.[33,34] The low risk appears to be associated with particular tumour characteristics[35–37], but additional research is needed. The optimal timing of SNB in relation to neoadjuvant chemotherapy also requires further investigation.[38]

With SNB, sentinel lymph nodes are subjected to extensive examination including serial sectioning and immunohistochemistry. Improved survival of breast cancer patients with a negative lymph node status assessed by SNB as compared to node negative patients determined by ALND has been cautiously attributed to this examination[39–40], but long-term survival data are still lacking. Concurrently, SNB is held responsible by some for the phenomenon of stage migration in breast cancer patients.[41] Sentinel node examination would leave these patients more often diagnosed with small axillary metastases where they would previously have been classified as node negative. The present study does not examine stage migration or changes in therapy due to introduction of the SNB, although we reported stage migration in the region of Middle Netherlands (region C) for the incidence years 1997–2002.[42] Since the update of the TNM staging system in 2002, a distinction is made between isolated tumour cells (ITCs) for metastases not exceeding 0.2 mm (pN0(i+)), and micrometastases for metastases between 0.2 mm and 2.0 mm in size (pN1mi). In a study in 360 patients, we observed that the introduction of SNB led to detection of more ITCs due to the intensified work-up of the sentinel node by the pathologist, but stage migration did not occur when ITCs were categorized as node-negative disease, in agreement with the 2002 TNM classification (data not shown). Overall, the prognostic value and clinical significance of both types of minimal metastases have been subject for debate, and their implications have remained unclear. Some have argued that micrometastases do not affect survival of patients when compared to node negative women[43–46], while others stated that their survival is worse.[47–49]

In conclusion, Dutch physicians have accepted SNB as standard of care for the treatment of breast cancer patients who are clinically diagnosed with T1–2 tumours, clinically negative lymph nodes and who do not show signs of distant metastases. Approximately 70% of patients received SNB as the first axillary procedure in 2003, and for 46% of patients, SNB was the final axillary treatment.

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Chapter 3

Axillary recurrence rate after tumour negative and micrometastatic positive sentinel node procedures in breast cancer patients

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Abstract

Background

The sentinel lymph node procedure is a widely accepted method for staging of patients with early breast cancer. This study evaluates the incidence of axillary relapse after negative sentinel node biopsy in the seven hospitals in the central part of the Netherlands.

Methods

This study concerns all patients with a T1-2 breast carcinoma who were staged with a sentinel lymph node biopsy in one of the hospitals in the region. Patients with a tumour-free sentinel node without additional axillary lymph node dissection and patients with a sentinel node containing micrometastases were prospectively included and data concerning tumour and primary treatment were recorded. After a median follow-up period of 46 months supplementary data were collected of all patients.

Results

Between January 2002 and December 2003, 541 patients underwent a sentinel node biopsy of which the sentinel node was negative for metastatic disease. During the follow-up period three patients were diagnosed with an axillary recurrence. The incidence of axillary relapse after tumour negative sentinel node biopsy in this study is 0.6% (3/541). In 23 patients a distant metastasis developed. An event occurred in 11% of the patients with a micrometastasis in the sentinel node. This was not significantly different from the patients with a tumour-free sentinel node.

Conclusion

The results suggest that the sentinel lymph node procedure as performed in the region Middle Netherlands is a reliable and accurate instrument for staging of patients with early breast cancer. In our study we observed a non-significant different risk of distant disease in case of micrometastases compared to a tumour negative sentinel node.

Introduction

The sentinel lymph node procedure is a widely accepted method for staging of patients with early breast cancer. This procedure is based on the concept that the lymph node upon which the carcinoma drains directly is also the first to be infiltrated by tumour cells. Many studies, mainly single-centre studies, have shown that the sentinel node provides a reliable and valid image of the tumour status of the remaining axillary lymph nodes.[1-3] The number of axillary relapses varies in most studies between 0-1.4% after a median follow-up of 24-79 months.[4,5] These favourable figures have led to the routine use of the sentinel node biopsy in patients with T1-2 breast cancer. This procedure saves the patient from the possible morbidity of an axillary lymph node dissection, provided that the sentinel node is free from tumour.[6]

The tumour status of the axillary lymph nodes is an important prognostic factor in breast cancer and helps to determine the appropriate adjuvant therapy. The pathological work-up of the sentinel nodes consists of serial sectioning of the lymph node and also involves immunohistochemistry using antibodies against cytokeratines which makes it possible to recognize micrometastases (diameter 0.2-2 mm) and isolated tumour cells (diameter < 0.2 mm) as well. The upstaging of breast cancer observed with the introduction of the sentinel lymph node procedure is due to the detection of more micrometastases.[7] This has raised questions concerning treatment of the axilla with a micrometastasis positive sentinel lymph node as well as questions concerning the clinical relevance of these observations. Van Deurzen et al. concluded that as it is impossible to predict the involvement of the remaining lymph nodes it is justified to perform axillary lymph node dissections in patients with tumour positive sentinel lymph nodes.[8] Others state that axillary lymph node dissection can safely be omitted in patients with submicrometastases.[9] Several studies concerning the biological significance of micrometastases have resulted in opposing conclusions.[8-11] The prognostic and therapeutic implications remain unclear, however, present day protocols usually do not consider micrometastatic disease a N+ classification.

In the Surgical Oncology Group of the Comprehensive Cancer Centre Middle Netherlands (CCCMN) all seven hospitals of the central region in the Netherlands collaborate in developing treatment protocols and in analysing treatment results. The Surgical Oncology Group developed the protocol for sentinel node staging of patients with early breast cancer and passed it through the CCCMN's Advisory Board for Scientific Research. This protocol has been uniformly used for the validation period for all hospitals. It required informed consent and consisted of an axillary lymph node dissection for every patient after sentinel node biopsy had been performed. As results in this validation period varied remarkably between hospitals (not published data) the Group agreed to prospectively collect and analyse the data of the first two-year cohorts of patients staged solely by the sentinel node procedure in order to identify and analyse the axillary recurrence rate and possible clinical implications of micrometastases in the sentinel node.

Patients and methods

This population based study concerns all patients with a T1-2 breast carcinoma who were staged with a sentinel node procedure between January 2002 and December 2003 in one of the hospitals in the region. Exclusion criteria were the presence of only in situ carcinomas, tumours larger than 5 cm, presence of lymph nodes suspected of malignancy by clinical examination, patients with multifocal disease and patients after neoadjuvant therapy or axillary lymph node dissection. Patients with a tumour-free sentinel node or a sentinel node containing micrometastases were prospectively included and data concerning tumour and primary treatment were recorded.
After a median follow-up of 46 months supplementary data were collected of all patients. The primary endpoint was defined as the occurrence of an axillary relapse after a tumour negative sentinel node without complementary axillary dissection. Secondary endpoints were local recurrence, distant metastasis and death.

Diagnosis, primary and adjuvant therapy

With a palpable lesion the diagnosis of breast cancer was based on clinical examination, radiological imaging and pathological investigation. In case of a non-palpable lesion a stereotactically or ultrasound guided core needle biopsy was performed to confirm the diagnosis.
Treatment of patients with breast conserving surgery was completed with radiotherapy consisting of total breast irradiation up to a dose of 50 Gy and a boost when indicated.
Additional adjuvant radiotherapy, chemotherapy and hormonal therapy was considered for every patient according to national guidelines based on conventional criteria such as SLN status, hormone receptor status, age (pre-/postmenopausal), tumour size and Scarff-Bloome-Richardson (SBR) tumour grade.[12] Patients with a sentinel node containing micrometastases were assessed individually for necessary adjuvant therapy.
In the first year after the primary surgery patients were followed-up every three months by means of clinical examination, the second and next years check-up were performed every six months. A mammography was obtained every year, and additional diagnostic procedures were performed when indicated.

Sentinel lymph node procedure

The technique introduced for visualizing the sentinel node and its identification during surgery has been according to accepted standards as extensively described by Uren et al. and others.[13,14,4] With palpable tumours in addition to the Technetium^{99} colloid, patent blue was injected at arrival in the operating room. With non-palpable lesions the dye was injected guided by ultrasound or stereotactically. The procedure used to visualize the axillary and retrosternal sentinel node differed only in minor aspects between hospitals depending on the local resources. During the first part of the study one hospital used a two-day protocol. In order to obtain a possible indication for radiotherapy on a parasternal field, the protocol advised to biopsy retrosternally located sentinel nodes. Details are summarized in Table 2. If the axillary sentinel node(s) seen on lymphoscintigraphy could not be identified intraoperatively

an axillary lymph node dissection was performed. All removed lymph nodes were sectioned at 500-micron distance, with at least three sections for each node. At each level two parallel sections were prepared and examined using hematoxylin-eosin and anti-cytokeratin staining to prove or exclude the presence of tumour.

Data collection

Each collaborating surgeon was responsible for the analysis and the contribution of the data for the patients he managed. The Regional Cancer Registry audited the completeness of the two-year cohorts that have been analyzed. If no data could be retrieved patients were considered 'lost-to-follow-up'.

Results

Between January 2002 and December 2003, 595 patients underwent a sentinel node biopsy of which the sentinel node was negative for metastatic disease. The sentinel node procedure failed in 1.0% (6/595) of cases. In one patient the sentinel node was not visualized and in five patients the sentinel node was not identified intraoperatively. The axillary node dissection revealed axillary lymph nodes without metastatic tumour but these patients were excluded from further analysis. Twenty-seven patients were excluded because of the presence of a ductal carcinoma in situ without invasive growth, 11 were excluded because histologic examination revealed no invasive carcinoma and 10 patients were lost-to-follow-up. A total of 541 sentinel lymph node procedures were analyzed. The median follow-up was 46 months (range 11-64 months).

Patient characteristics

Data concerning the patient characteristics are summarized in Table 1, and Table 2 gives details concerning the sentinel node biopsies. In 38 patients micrometastases were located in the sentinel node. In 70 patients both axillary and retrosternal sentinel nodes were visualized on lymphoscintigraphy. A total of 73 retrosternal lymph nodes were removed. In three patients the retrosternal lymph node could not be identified intraoperatively. None of these three patients developed a local or regional recurrence or distant metastasis.

Axillary recurrences

During the follow-up period three patients were diagnosed with an axillary recurrence. The first patient, a 74-year-old female underwent a total mastectomy because of a pleomorphic carcinoma with a negative hormone receptor status. The axillary sentinel node contained no metastatic tumour. No adjuvant treatment was indicated. Three months after the initial treatment she developed a palpable lymph node in the axilla, which turned out to be a metastasis. She underwent an axillary dissection and radiotherapy. Histology demonstrated nine tumour positive lymph nodes. In view of her age and as systemic disease could not be proven chemotherapy was not considered indicated. Two years after this a CT-scan showed multiple liver metastasis and the patient died 32 months after the initial treatment.

Table 1. Patient and tumour characteristics (n=541)

	N	%
Age (years)		
Mean (range)	58	(29-92)
Palpable tumour		
Yes	406	75%
No	135	25%
Localisation tumour		
Lateral upper quadrant	241	44%
Lateral lower quadrant	48	9%
Medial upper quadrant	96	18%
Medial lower quadrant	42	8%
Central	110	20%
Unknown	4	1%
Biopsy method		
Needle biopsy	492	91%
Excision biopsy	39	7%
Unknown	10	2%
Surgical procedure		
Lumpectomy	390	72%
Total mastectomy	108	20%
Both	43	8%
Tumour size in millimetres		
0-10	117	21%
11-20	271	50%
21-30	112	21%
31-40	19	4%
41-50	4	1%
Unknown	18	3%
Tumour histology		
Invasive ductal	413	76%
Invasive lobular	51	9%
Invasive ductulolobular	37	7%
Tubular	11	2%
Mucineus	5	1%
Papillar	5	1%
Other	19	4%
Hormone receptor status		
ER+/PgR+	327	60%
ER+/PgR-	90	17%
ER-/PgR-	88	16%
ER-/PgR+	4	1%
Unknown	32	6%

table 1 continued

Adjuvant chemotherapy		
Yes	113	21%
No	424	78%
Unknown	4	1%
Adjuvant hormonal therapy		
Yes	124	23%
No	410	76%
Unknown	7	1%
Radiotherapy		
After breast conserving surgery	388	72%
Thorax	3	1%
Supraclavicular	8	2%
Infraclavicular	3	1%
Parasternal	10	2%
Axilla	4	1%
No radiotherapy	148	27%

A 76-year-old female presented with an invasive ductal carcinoma with a positive hormone receptor status. She underwent a total mastectomy and intraoperatively one radioactive and blue and one radioactive sentinel node were removed. Histological examination showed no lymph node metastases. No adjuvant treatment was indicated considering tumour size and SBR tumour grade I. During the follow-up period she presented after 30 months with pulmonary and liver metastasis. A CT-scan also revealed pathological lymph nodes in both axillae. Hormonal therapy was started; no chemotherapy was given considering age and physical condition. Thirty-seven months after the initial treatment the patient died.

A 40-year-old female was diagnosed with an invasive ductal carcinoma with a positive hormone receptor status. She underwent breast-conserving therapy. The axillary sentinel node contained no metastasis. No further adjuvant therapy was indicated considering tumour size and SBR tumour grade I. After 51 months the patient presented with a palpable lesion in the right axilla, which turned out to be a metastasis. Further investigation also revealed bone metastases. Hormonal therapy was started and this patient continues to do well.

Local recurrences and distant metastases

All events are summarized in Table 3. The mean time in which patients presented with a local or axillary recurrence or a distant metastasis was 27 months (range 1-58 months). Twenty-seven patients died, 14 of these deaths were related to metastatic disease. Twenty-three patients developed distant metastasis in bone (n=8), lung (n=3), brain (n=1), intra-abdominal (n=1) or at multiple localisations (n=10). Looking at the subgroup of patients with micrometastases (n=38) an event occurred in 11% of these patients: three patients developed distant metastases and one patient had a local recurrence. In the group with a tumour-free sentinel node local recurrence and distant metastases was observed in 5% of the patients. These figures are not significantly different (Chi-square p=0.128).

Table 2. Sentinel node procedure (n=541)

	N	%
Technique		
Technetium	13	2%
Patent blue	2	1%
Combined	526	97%
Dosage technetium (n=539)		
One day protocol	418	78%
Mean (range)	74 Mbq (52-100)	
Two-day protocol	37	7%
Mean (range)	208 Mbq (140-314)	
Unknown	84	15%
Site of injection technetium (n=539)		
Peritumoral	502	93%
Intratumoral	8	1%
Subareolar	3	1%
Unknown	26	5%
Site of injection patent blue (n=528)		
Peritumoral	268	51%
Intradermal	222	42%
Subareolar	7	1%
Unknown	31	6%
Number of removed sentinel nodes		
Mean (range)		1.6 (1-5)
Number of removed remaining lymph nodes		
Mean (range)		0.3 (0-3)
Number of patients with micrometastasis (n=38)		
Adjuvant axillary dissection	18	47%
Adjuvant radiotherapy	3	8%
Both	1	3%
No adjuvant therapy	16	42%

Table 3. Patterns of relapse in patients with negative sentinel node or sentinel node with micrometastases

	Local recurrence	Regional recurrence	Distant recurrence	Local and regional	Regional and distant
	N (%)	N (%)	N (%)	N (%)	N (%)
Negative SN (n = 503)	5 (1.0)	0 (0.0)	17 (3.4)	1 (0.2)	3 (0.6)
Micrometastasis SN (n = 38)	1 (2.6)	0 (0.0)	3 (7.9)	0 (0.0)	0 (0.0)

SN: sentinel lymph node(s)

Discussion

Axillary recurrence after sentinel node biopsy in our study

The axillary tumour status provides the physician and the patient with important information concerning postoperative treatment and prognosis about T1-2 breast carcinoma. Burak et al. showed that an axillary dissection is an accurate procedure but with considerable morbidity.[6] Considering these facts the aim of this study in the seven hospitals of the Middle Netherlands was to assess the sentinel node biopsy as minimal invasive procedure for staging of the remaining lymph nodes. The results of this study show that the sentinel node biopsy is a valid and safe instrument in T1-2 breast cancer patients with an axillary recurrence rate of 0.6% based on a median follow-up of 46 months. These results are in accordance with the results of follow-up studies showing relapse rates of 0-1.4% after a median follow-up of 22-79 months.[4,5,15-17] It is noteworthy that in the first patient developing an axillary recurrence this event occurs three months after the initial treatment. Histology of the axillary lymph node dissection proved nine tumour-containing lymph nodes. This patient underwent an axillary dissection and radiotherapy. This heavy axillary tumour load makes re-routing of the flow of lymph due to blocking of the sentinel node by metastatic tumour a likely explanation. This case illustrates the importance of removing palpably suspicious lymph nodes as well as hot and/or blue sentinel nodes. Furthermore, inappropriate selection of patients for the sentinel node procedure can be avoided if in selected cases clinical examination of the axilla is completed with ultrasound and Fine Needle Aspiration.[18] This patient underwent an axillary dissection and radiotherapy. As systemic disease could not be proven at that time chemotherapy was not considered indicated. In the other two patients the axillary recurrence was observed after 30 and 51 months together with distant disease. Treatment focused mainly on the distant metastasis, therefore, the axillary recurrence had no clinical implications. The majority of events in our study are distant metastases without signs of local or regional recurrence (Table 3). The fact that these metastases occurred in patients with a tumour negative sentinel node signifies that tumour status of the sentinel node is not the only important factor predicting recurrence, but other prognostic factors need to be considered as well.

Data from the literature

The sentinel node biopsy has been accepted as a staging procedure only a few years ago, so no long-term data are currently available. In 2003, Veronesi et al.[17] published a randomised trial comparing patients undergoing a sentinel node biopsy followed by an axillary lymph node dissection with patients undergoing a sentinel node biopsy only followed by an axillary lymph dissection if the sentinel node contained metastatic cells. This latter group consisted of 167 sentinel node-negative patients. An update of this study was published in 2006.[5] After a median follow-up of 78 months one patient was diagnosed with an axillary recurrence, therefore, the axillary relapse rate was 0.6%. Naik et al. analyzed in an impressive single-centre study 4008 out of 6278 consecutive sentinel node procedures after a median follow-up of 31 months.[1] Final pathologic examination required serial sectioning and anti-cytokeratin staining. In 2340 patients with tumour-free sentinel nodes and no axillary lymph node dissection three axillary recurrences were observed: one as first event, one coincident with local relapse and one

coincident with distant disease, at an axillary relapse rate of 0.1%. These results are achieved in renown centres. In our population based study after a median follow-up of 46 months an axillary recurrence rate of 0.6% was observed. Our results compared well.

Micrometastases and the risk of tumour in non-sentinel nodes

In our study the sentinel node of 38 patients contained micrometastases. In 18 of them an axillary dissection was performed, no positive lymph nodes were obtained. There is an ongoing debate concerning the clinical implications of micrometastases in the sentinel node. Many observational studies have been published but results do not justify uniform conclusions. In 1999, Chu et al. showed that if the sentinel node contained micrometastases there was a 6% chance that the remaining lymph nodes also contained metastases.[19] Others found comparable or higher figures.[8,20,21] No subgroup with regard to size and grade was identified that did not have non-sentinel lymph node metastases. In a large study Van Rijk et al. observed in a subgroup of patients that underwent an axillary clearance subsequent to micrometastasis in the sentinel node in 4% a macrometastasis in non-sentinel nodes.[9] However, in none of these patients this finding indicated additional treatment.

Recently, Noguchi reviewed the literature concerning management of the axilla after a tumour positive sentinel node. He concluded that for the group of patients with macrometastases as well as for the group with micrometastases in the sentinel node it is impossible to identify a subset of patients in whom axillary dissection can be omitted.[22] As there is no significant difference in the risk of metastases in non-sentinel nodes when comparing patients with isolated tumour cells in the sentinel node with those with true micrometastases, some investigators have argued for axillary clearance for patients with isolated tumour cells in the sentinel node as well.

Micrometastases and disease-free survival

In our study we observed a non-significantly different risk of distant disease in case of micrometastasis compared to a tumour negative sentinel node. However, the small number of patients might misrepresent this result. Bettelheim et al. performed serial sectioning of ipsilateral lymph nodes judged to be disease-free after routine histological examination.[23] Their study revealed micrometastases in 9% of 921 patients. These patients had a significantly poorer disease-free and overall survival of five years. Querzoli et al. also re-evaluated the lymph nodes of 377 patients without nodal disease by step-sectioning and immunohistochemistry, out of 702 with an eight year median followup.[10] Cumulative incidence curves for metastatic relapse were significantly different for patients with micrometastatic nodal disease compared to true tumour negative axillary status. Kahn et al. studied a cohort of 214 consecutive histologically node-negative breast cancer patients with a median follow-up of eight years.[11] Two 4 µm sections were cut from all the nodes in formalin-fixed paraffin-embedded blocks, one for H&E and one for anti-cytokeratin-8 staining. Twenty-seven patients had micrometastases and two had isolated tumor cells. Micrometastases were not significantly associated with disease-free or overall survival.

There is a difference in the pathology protocol used in this study compared to the studies mentioned earlier that must be taken into account when comparing these studies. But the

results of a recent prospective trial have demonstrated that micrometastases have no prognostic implication when there are no further signs of axillary metastases.[24] It appears that the observational studies present opposing results. Studies with cohorts of patients with longer follow-up often lack elaborate histological work-up and their results cannot easily be compared with present day cohorts with micrometastatic nodal disease.[25,26]
At present several large prospective multicentre trials that address surgical and management aspects subsequent to sentinel node staging of breast cancer are ongoing.[27-29] It is expected that these studies will provide definitive answers with regard to the clinical relevance of nodal micrometastatic disease in breast cancer, their results must be awaited.

Conclusion

With our study we aimed to investigate the axillary recurrence rate in patients with a tumour negative sentinel node. The results are obtained after a period of midterm follow- up, this may pose a limitation to our study but studies that provided data after 4-5 years follow-up have shown that the majority of the axillary relapses occur within five years of the initial treatment.[30]
An important feature of our study is its population-based design.
In conclusion, our results show that the sentinel node procedure in the region Middle Netherlands is a reliable and accurate instrument for staging of patients with early breast cancer. Our results also reflect the current incomplete comprehension of the significance of micrometastatic nodal disease in breast cancer.

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Chapter 4

Introduction of sentinel node biopsy and stage migration of breast cancer

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Abstract

Aim

The purpose of this study was to examine in a large population based group of breast cancer patients treated in a regular care setting whether the introduction of the Sentinel Node Biopsy (SNB) led to detection of a higher percentage of patients with positive regional lymph nodes.

Methods

The study includes 3665 early breast cancer patients, aged 30-85 years, diagnosed in the period 1997-2002 and registered at the Regional Cancer Registry of the Comprehensive Cancer Centre Middle Netherlands. During this period the SNB was introduced. The outcome of staging was compared for groups staged with or without SNB. A logistic regression model was used to adjust for age, calendar period and tumour size.

Results

Overall a quarter of all patients over the period 1997-2002 underwent a SNB as method of lymphatic staging. The use of SNB clearly increased over time: from 2% in 1998 to 65% in 2002. The percentage node positive patients also rose significantly; before introduction of the SNB 30% of all patients were diagnosed with positive lymph nodes, and after SNB introduction this percentage was 40%. The increase is largely explained by the increase of patients diagnosed with only micrometastases. Adjustment did not change the results.

Conclusion

In conclusion, introduction of the SNB in early breast cancer led to significant upstaging of breast cancer patients treated in a regular care setting, due to the detection of more micrometastases. Since the relevance of micrometastases for long term survival is not yet known, this upstaging potentially led to over treatment of patients. On the other side, for some patients axillary lymph node dissection was prevented by the SNB procedure, preventing comorbidity.

Introduction

In the Netherlands over 11,000 women are newly diagnosed with breast cancer every year (Netherlands Cancer Registry; data at www.iKCnet.nl). About 90% is diagnosed with a small tumour (<5 cm). An important prognostic factor for these patients is the tumour status of the regional lymph nodes, which is the main determinant of adjuvant therapy. To establish the regional lymph node status, patients formerly underwent an axillary lymph node dissection (ALND) after (local) tumour resection. Removal of the axillary lymph nodes often causes negative side effects, such as neuropathy (63-78%), functional restriction of the shoulder (1-21%) and oedema (2-20%).[1]

In the 1990's a new technique for intra operative lymphatic mapping was developed, the sentinel node biopsy (SNB).[2-5] This procedure identifies the first lymph node(s) draining the site of the primary tumour. This is the most likely first site of metastasis and therefore only the SN(s) is (are) initially removed and examined for the presence of tumour tissue. Several reviews have concluded that the SNB is a valid method of lymphatic staging.[6-8] As a result of the development and introduction of the SNB, patients with a tumour negative sentinel node no longer undergo standard ALND. For these patients the new procedure means they undergo a less aggressive staging procedure with considerable reduction of morbidity. In the Netherlands, guidelines for the application of SNB for staging of breast cancer patients were published in 1999.[9]

It has been hypothesised that the introduction of the SNB leads to a shift in staging of early breast cancer. The more thorough pathological examination of the lymph nodes due to the use of serial sectioning and immunohistochemistry, leads to the more frequent detection of (micro) metastases.[10] This increase could have an important effect on the treatment of patients.[11,12] Based on the Dutch treatment guidelines, most patients with small tumours and negative nodes will not be treated with adjuvant therapy, while patients staged with metastases will receive adjuvant treatment. It is not yet clear whether patients with micrometastases should be treated as node positive or negative.[13]

Aim of this study was to investigate in a large, population based patient group treated within a regular clinical setting, whether the introduction of the SNB indeed led to upstaging of breast cancer patients.

Patients and methods

Data were collected from the Regional Cancer Registry (RCR) of the Comprehensive Cancer Centre Middle Netherlands (CCCMN), which collects data on all new cancer cases in the central part of The Netherlands. The region has over 1.3 million inhabitants. It comprehends 7 hospitals, 3 of which are community hospitals, 1 is a university hospital and 3 are teaching hospitals. The latter four have their own nuclear medicine department and pathology laboratory.

The community hospitals use the facilities of these hospitals. Almost all early breast cancer patients living in the central part of The Netherlands are diagnosed and treated at these 7 hospitals. After being notified by pathologists and medical registration offices, specially trained registration clerks from the RCR collect data from the hospital files.
We retrospectively identified all patients with breast carcinoma stage T1/T2, aged 30-85 years, diagnosed from 1997-2002 and registered at the RCR (n = 4,319). Patients with clinically diagnosed metastases in regional lymph nodes or distant metastases were excluded, as well as patients who did not undergo surgical treatment or lymphatic staging (n = 654).
For the remaining patients (n = 3,665) we extracted information from the cancer registry concerning the method of lymphatic staging and the clinical and pathological TNM stage (including the outcome of lymphatic staging).
We describe the introduction of the SNB over time by comparing percentage of lymph node involvement in three groups of patients: patients who underwent only an ALND, a SNB and an ALND or only a SNB. Also the outcome of lymphatic staging over time is described in three groups: patients with negative nodes, micrometastasis and macrometastases (coded according to the TNM classification of the UICC).[14,15] To determine whether a stage migration occurred, we compared the outcome of the lymphatic staging before and after the introduction of the SNB. Therefore we compared patients who underwent staging through only ALND with patients staged through SNB. In this last group we joined the groups SNB only and SNB in combination with ALND.
In further analyses we constructed a logistic regression model with lymphatic stage (negative versus positive) as outcome of the method of staging (ALND versus SNB). In this model we adjusted for three possible confounders: year of diagnosis, age at diagnosis and tumour size (defined as T1-T2). Analyses were conducted with the Statistical Package for Social Sciences (SPSS 12.0.1).

Results

Table 1 shows the characteristics of included patients. Almost three quarter of all patients were diagnosed with a tumour smaller than 2 centimetres. Women in the age 50-70 were more often diagnosed with a smaller tumour than women in the age groups 30-50 and 70-85 (77% vs. 69% and 64%, Chi^2-test, df = 2; $P < 0.001$).

Over the whole period more than a quarter of all included patients underwent a SNB for lymphatic staging. Half of this group received only a SNB, the other half underwent a SNB in combination with an ALND. SNB was more frequent in younger patients. The percentage decreases from 29% within patients aged 30-50 to 26% in patients aged 50-70 and 21% in patients aged 70-85 (Chi^2-test, df = 2; $P < 0.001$). Younger patients were more frequently diagnosed with positive nodes than older patients (40% vs. 30% and 29%, Chi^2-test, df = 2; $P < 0.001$). The use of a SNB for staging patients was not determined by the size of the tumour, defined as T1 versus T2 (26% vs. 25%, Chi^2-test, df = 1; $P = 0.658$).

Table 1. Characteristics of early breast cancer patients from a cancer registry

	N
Age (years)	
Mean (range)	57 (30-84)
30-50	1,159
50-70	1,760
70-85	746
Tumour stage	
T1	2,639
T2	1,026
Method of lymphatic staging	
Only ALND	2,721
SNB and ALND	502
Only SNB	442
Outcome of lymphatic staging	
Negative node(s)	2,473
Positive node(s), only micrometastases	113
Positive node(s), macrometastases	1,079

In Table 2 the method of lymphatic staging is presented according to year. In 1997 SNB was not yet used as method of staging in the region Middle Netherlands. The introduction started in 1998, and its use increased from 2% in 1998 to 21% in 2000 and 65% in 2002. Most patients who underwent a SNB in the period 1998-2000 also received an ALND. The number of patients with only SNB rose quickly after 2000 and in 2002 37% of all patients were staged by a SNB only.

Table 2. Method of lymphatic staging over the period 1997-2002 in 3665 breast cancer patients from a cancer registry

	1997	1998	1999	2000	2001	2002	Total
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Only ALND	545 (100)	518 (99)	566 (88)	515 (79)	364 (52)	213 (35)	2,721 (74)
ALND + SNB	0 (0)	5 (1)	69 (11)	113 (17)	145 (21)	170 (28)	502 (14)
Only SNB	0 (0)	3 (1)	7 (1)	25 (4)	184 (27)	223 (37)	442 (12)
Total	545	526	642	653	693	606	3,665

Table 3. Percentage of lymph node involvement in 3665 breast cancer patients from a cancer registry over the period 1997-2002

	1997	1998	1999	2000	2001	2002	Total
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Negative	389 (72)	360 (68)	452(70)	440 (67)	457 (66)	375 (62)	2,473 (68)
Micro	2 (0)	5 (1)	3 (1)	12 (2)	31 (5)	60 (10)	113 (3)
Macro	154 (28)	161 (31)	187 (29)	201 (31)	205 (29)	171 (28)	1,079 (29)
Total	545	526	642	653	693	606	3,665

Table 4. Percentage of lymph node involvement in 3665 breast cancer patients from a cancer registry according to method of staging

	ALND	SNB*	Total
	N (%)	N (%)	N (%)
Negative	1,906 (70)	567 (60)	2,473 (68)
Micro	35 (1)	78 (8)	113 (3)
Macro	780 (29)	299 (32)	1,079 (29)
Total	2,721	944	3,665

* including all patients with SNB, with or without a following ALND

Table 3 shows the outcome of lymphatic staging according to the year of incidence. Over time the percentage of lymph node positive patients rose significantly from 28% in 1997 to 38% in 2002 (Chi^2-test for trend; $P < 0.001$).

Table 4 shows the outcome of lymphatic staging according to staging method dichotomised as ALND and SNB (with or without additional ALND). Data show that 30% of patients staged through ALND were found lymph node positive versus 40% of patients staged through SNB. This is a significant increase in detection of positive nodes after the introduction of the SNB (Chi^2-test, df = 1; $P < 0.001$). The increase in positive lymph nodes found when diagnosed through a SNB is largely explained by the increase in the detection of micrometastases. The increase of micrometastases was significant (1% to 8%, Chi^2-test, df = 1; $P < 0.001$), the increase of macrometastases was not significant (29% to 32%, Chi^2-test, df = 1; $P = 0.08$).
To adjust for possible confounders, we estimated the odds having positive lymph nodes by the method of staging (ALND versus SNB). In our logistic regression model the crude odds ratio was 1.5 (95% CI: 1.3-1.8). Adjusted for age at diagnosis, tumour size and year of incidence, the odds ratio decreased to 1.4 (95% CI: 1.1-1.7), which was still significant.

Discussion

Our analyses using data from the RCR of the central region of the Netherlands showed that the introduction of the SNB for staging of early breast cancer patients increased the percentage of patients who were diagnosed with positive lymph nodes. The proportion of patients with positive nodes increased from 30% before introduction to 40% after introduction of the SNB. This increase is for the larger part explained by the increase of patients diagnosed with only micrometastases.

The advantage of using data from a cancer registry is that this represents a geographical population and it therefore produces non-selected, population based data. The region of the CCCMN includes 3 community hospitals, as well as 3 teaching hospitals and a university hospital. It represents the actual situation in diagnosing and staging breast cancer patients in The Netherlands.

In our analyses we used data collected during the period of introduction of the SNB in the region (1997-2002). In 2002 65% of selected patients underwent a SNB as method of lymphatic staging. We expect this percentage to rise in later years. Furthermore, we expect the percentage of patients who undergo an ALND after the SNB to drop. During the introduction of the new treatment protocol, hospitals were advised to validate the technique in their local setting. During this learning curve (almost) all SNB's were followed by an ALND in order to confirm an acceptable percentage false-negative rate (under 5%).[9,16] Now that the procedure has become standard, a larger group of patients will be saved an ALND and the possible negative side effects such as neuropathy, functional restriction and oedema that go with it.

In 1995 Giuliano estimated the possible stage shift in a prospective study with 296 patients. It was shown that 29% of the ALND group was node positive and 42% of the SNB group. The percentage of micrometastasis was 3% of the ALND group and 16% of the SNB group.[10] A study by Cserni et al reported the increase in lymph node positive patients to be 9-47% higher after diagnosing through immunohistochemistry, depending on the exact technique used.[17] The increase of lymph node positive patients in our study from 30 to 40% is in line with these reported earlier findings. The percentage of micrometastases found however is on the low end of the spectrum described by Cserni et al. This might be explained by the fact that our study describes the implementation of the procedure in the regular care setting. Our data also suggest that over time sentinel node biopsies are more extensively examined, resulting over time in an increase of the percentage of patients with micrometastasis of all patients undergoing a SNB: the percentage of micrometastasis of all SNB was 4% in 1999, 9% in 2000 and 15% in 2002. The reason for this increase is not clear.

The status of the regional lymph nodes is still one of the most important prognostic factors for breast cancer patients. However, the importance of micrometastases is more and more discussed. One important question is whether patients with only micrometastases in a SN need ALND. Several studies have tried to predict the outcome of the ALND after SNB.[5,18-22] Determinants of the outcome of the ALND are the number of positive SNs, the size of the metastasis in the SN, the size of the primary tumour and the receptor status of the primary tumour. Based on a combination of these characteristics subgroups have been described in which the chances of further metastases in the ALND is under 10%. However, none of the authors of these studies advised to replace the ALND by axillary surveillance. They all refer to ongoing randomised trials with large groups of patients, like trial Z0011 of the American College of Surgeons Oncology Group, in which patients with a small tumour-positive SN are randomized to ALND or no additional axillary therapy. A second relevant question is whether patients with only micrometastasis need adjuvant treatment, such as chemotherapy. The current Dutch treatment guideline states that it is not clear whether patients with only micrometastasis (and no other indications for metastasis) should be considered for chemotherapy.[13] In our study patients with only micrometastasis were often treated with adjuvant chemotherapy: 13% of node negative patients, 58% of patients with only micrometastasis and 63% of patients with macrometastasis received chemotherapy.

Our study shows that the introduction of SNB in the regular treatment setting of patients with early breast cancer has led to an increase in patients with (micro) metastases in regional lymph nodes. These findings emphasize the importance of gaining knowledge on the relevance of micrometastases found through immunohistochemistry for the long term survival of patients. These data are expected to come from large ongoing randomised trials. Meanwhile, the debate on optimal staging and treatment of this group of patients will continue. Based on cancer registry data, it is possible to examine over time the treatment of patients with only micrometastases. Also, differences in treatment between hospitals can be studied. This would give more insight in the actual impact of the introduction of the SNB on the regular treatment of early breast cancer patients.

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Chapter 5

Outcomes of a population based series of early breast cancer patients with micrometastases and isolated tumour cells in axillary lymph nodes

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Summary

Background

Axillary lymph node staging is traditionally important to provide prognostic information to guide further treatment. However, the relevance of isolated tumour cells (ITC) or micrometastases in axillary nodes and the need for adjuvant treatment remains uncertain.

Patients and methods

Data from 18,748 patients with pT1-2 breast cancer with pN0, pN0i+ or pN1mi were analysed. The primary endpoint was 5-year disease-free survival (locoregional recurrence, distant metastases or contralateral breast cancer).

Results

Five-year disease-free survival was 89.9% (95% CI 89.5–90.4); and did not differ significantly between groups. After adjusting for prognostic factors (including treatment), patients with ITC had comparable risk (HR=1.12) as patients with node negative disease, whilst patients with micrometastases had 38% higher risk of recurrence.

Conclusions

Patients with ITC and node negative breast cancer appear to have similar prognosis, and patients with micrometastases have a 38% higher risk of tumour recurrence. However, considering that disease-free survival is already high, we are reluctant to advise chemotherapy in all patients with ITC or micrometastases. In future, genomic tumour characteristics might predict the propensity of dissemination from the primary cancer better than the status of the axillary lymph nodes.

Introduction

Axillary lymph node staging is traditionally important to provide prognostic information to guide adjuvant radiotherapy and systemic treatment. Sentinel node biopsy (SNB) is generally accepted as a safe method for predicting axillary lymph node involvement, which prevents an invasive complete axillary lymph node dissection (ALND) in patients with a negative SNB biopsy.[1-6] Further lymph node involvement is a strong indicator for the prognosis of the patient. With the introduction of the SNB and immunohistochemical staining, the detection of isolated tumour cells (ITC, pN0i+) and micrometastases (pN1mi) has increased.[7,8]
This additional knowledge has led to some uncertainties and debates: in case of ITC or micrometastases, what is the risk of further nodal involvement of the axilla? Does this information have any prognostic relevance, and, if yes, to what extent? And finally, is standard adjuvant treatment required?

Some studies report that minimal lymph node involvement is associated with poorer prognosis.[9-12] Other studies do not find differences in disease-free and overall survival of patients with ITC or micrometastases versus node negative patients.[13-15] Subsequently, implications for further treatment of patients with ITC or micrometastases vary between studies (e.g. complete axillary lymph node dissection and/or adjuvant systemic therapy). A large cohort study (MIRROR) reported that patients with ITC or micrometastases had a significantly worse 5-year disease-free survival, and patients with ITC or micrometastases who were treated with adjuvant systemic therapy had better survival rates.[16] Another study, based on data from 7 hospitals (partially the same cohort as the MIRROR study), reported no significant impact of micrometastases on overall survival during the first five years after diagnosis. These authors postulate that micrometastic disease itself should not be an indication for adjuvant systemic therapy.[15]

The Netherlands Cancer Registry (NCR) records all new cancers occurring in the Netherlands. The current study, which uses NCR data on breast cancer patients diagnosed between 2003 and 2006 with the completion of 5-year follow-up, aims to add valuable data to guide the before mentioned discussion.

Aim of this study is to examine the prognosis of breast cancer patients with ITC or micrometastases while thoroughly accounting for all other prognostically relevant clinical variables and to study the effect of adjuvant systemic therapy in an unselected population based cohort of patients.

Patients and methods

The NCR is a nationwide, population based cancer registry with information on tumour characteristics and treatment. PALGA, the Dutch network and registry of all pathological diagnoses, notifies the NCR of all newly diagnosed malignancies. Following this notification,

trained registrars actively record data on diagnosis, staging, and treatment directly from the patient's medical records, including pathology and surgery reports. Primary treatment is coded in sequence of administration, and patients are staged according to the TNM system of the International Union Against Cancer.[17]

From the NCR all female breast cancer patients diagnosed between January 1, 2003 and December 31, 2006 who had a pT1-2 tumour, no macrometastases in axillary nodes (thus including pN0, pN0i+ and pN1mi) and no distant metastases, who had no history of cancer and no bilateral breast cancer were selected. Patient and tumour characteristics (age at diagnosis, pathological tumour size (pT), nodal status (pN), histological grade, histological subtype, multifocality, hormone receptor status (ER and PgR) and her2 status), information on treatment (type of breast surgery, method of axillary staging, radiotherapy, chemotherapy, hormonal therapy and trastuzumab) were extracted. Clinical follow up data (recurrence of disease, occurrence of other cancer and vital status) was collected for all patients five years after diagnosis.

We excluded patients who received neo-adjuvant therapy or were not treated with curative intent (no surgery, no axillary staging (SNB and/or ALND) or had macroscopic tumour residue after final surgery). Finally, we excluded patients with unfavourable tumour characteristics (grade 3 tumours sized > 1cm) and patients without follow-up data.

Classification of axillary lymph node involvement

From the 6th edition of TNM staging system onwards ITC are included in the IUCC coding system.[17] ITC are defined as 'single cells or small clusters of cells (≤ 0.2 mm)' that are usually detected with IHC staining. Axillary nodes with ITC are considered to be cancer-negative and coded as pN0i+. Micrometastases are slightly larger with a diameter between 0.2 and 2.0 mm, and are considered node positive and coded as pN1mi.

Endpoints

The primary endpoint was 5-year disease-free survival, using a composite endpoint (locoregional recurrence, distant metastases or contralateral breast cancer). Secondary endpoint was a composite endpoint consisting of either locoregional recurrence or distant metastases. Patients were censored at date of death or date of diagnosis of a second malignancy other than breast cancer. Survival time was defined as time between date of diagnosis up to any of the above endpoints whichever occurred first, or the date until a patient was lost to follow-up.

Statistical analysis

Patient and tumour characteristics are presented as means (continuous data) or percentages. The X^2 test was used to evaluate differences in categorical variables.

Multivariate Cox proportional hazards regression was used to assess the prognostic significance of ITC and micrometastases on disease-free survival, independent of other prognostic factors which were selected based on significance in univariate analyses ($p<0.1$). The prognostic factors included were age (continuous), tumour size (pT1mi, pT1A, pT1B, pT1C, pT2), grade (I, II, III, unknown), receptor status (ER or PgR positive, ER and PgR negative), type of final surgery (breast conserving surgery, mastectomy), SNB (yes, no), ALND (yes, no) radiotherapy

(yes, no), chemotherapy (yes, no), hormonal therapy (yes, no) and her2 status combined with treatment (her2 negative, her2 positive without trastuzumab, her2 positive with trastuzumab, her2 unknown).
We imputed missing values (grade 1,645 missings, 9.0%; receptor status 4,166 missings, 22.7%; multifocality 5,145 missings, 28.0%; SNB 1,458 missings, 7.9%) with a multiple imputation procedure in which each missing value was imputed 20 times. We did not impute her2 status and tumour residue after the final surgery (her2 was not routinely assessed during our study period and tumour residue was not significant in univariate analyses). Values were imputed based on the predictive distribution in an imputation model which included risk factors and outcome. This procedure resulted in 20 complete datasets. All analyses were performed on both the complete case dataset and the multiple imputation sets. Results reported are based on the multiple imputed data.
We compared disease-free survival between node negative patients, and patients with ITC or micrometastases. We also examined whether chemo- and hormonal treatment were effective after adjustment for other patient and tumour characteristics that are associated with disease-free survival. We also tested for interaction between adjuvant treatment and nodal status.
All analyses were performed using STATA (version 12.0; StataCorp, College Station, TX, U.S.A.).

Results

A total of 18,748 patients were diagnosed with pT1-2, pN0-pN1mi, M0 breast cancer over the period 2003 to 2006 and met our inclusion criteria. Of these patients 378 (2.0%) were excluded due to incomplete of follow-up data, leaving 18,370 patients who were included in our analyses.

Patient and tumour characteristics are shown in Table 1. Node negative patients generally had smaller and more often well differentiated tumours, compared to patients with ITC or micrometastases. Patients with ITC more often had lobular carcinoma.
Treatment varied substantially between the groups: node negative patients were treated with breast conserving surgery (combined with radiotherapy) more frequently. Complete ALND occurred more in patients with ITC or micrometastases than in node negative patients (50%, 81% and 23%, respectively). The proportion of patients with complete ALND following a SNB procedure remained stable over time for patients with micrometastases, but decreased for patients with node negative disease and ITC (from 35% to 14% in node negative disease and from 69% to 38% in ITC in 2003 and 2006, respectively). The proportion of patients receiving systemic adjuvant treatment is related to nodal stage: hormonal therapy was administered to 15%, 32% and 62% of the patients with node negative, ITC and micrometastases, respectively. Chemotherapy was administered to 7%, 14% and 32% of these patients, respectively.
The median follow-up was five years (mean 4.3 years, range 0.1 – 5.0 years; total 81,399 years of observation).

Table 1. Patient and tumour characteristics according to axillary status in 18,370 pT1-2 breast cancer patients diagnosed between 2003-2006

	Node negative (n=16,011)	ITC (n=703)	Micrometastase (n=1,656)	
	N (%)	N (%)	N (%)	P value
Age, median (range)	60 (20 - 98)	59 (22 - 92)	26 (28 - 92)	
Age				
<35	166 (1)	8 (1)	22 (1)	
35-50	2,832 (18)	154 (22)	446 (27)	
50-70	8,896 (56)	400 (57)	909 (55)	
>=70	4,117 (26)	141 (20)	279 (17)	<0.001
pT				
1mi	145 (1)	5 (1)	5 (0)	
1A	909 (6)	34 (5)	50 (3)	
1B	4,201 (26)	115 (16)	271 (16)	
1C	7,505 (47)	337 (48)	846 (51)	
2	3,251 (20)	212 (30)	484 (29)	<0.001
Grade				
well differentiated	5,108 (35)	175 (28)	444 (29)	
moderately differentiated	8,730 (60)	432 (68)	1,017 (66)	
poorly differentiated	725 (5)	25 (4)	69 (5)	<0.001
unknown	1,448	71	126	
Subtype				
ductal	12,818 (80)	491 (70)	1,396 (84)	
lobular	1,894 (12)	137 (19)	173 (10)	
ductal + lobular	704 (4)	55 (8)	71 (4)	
other [a]	595 (4)	20 (3)	16 (1)	<0.001
Multifocality				
no	10,042 (87)	450 (82)	1,002 (85)	
yes	1,454 (13)	96 (18)	179 (15)	<0.001
unknown [b]	4,515	157	475	
Receptor status				
ER or PgR positive	11,169 (91)	551 (92)	1,248 (94)	
ER and PgR negative	1,103 (9)	48 (8)	85 (6)	0.005
unknown [b]	3,739	104	323	
Final surgery [c]				
breast conserving surgery	10,605 (66)	423 (60)	1,010 (61)	
mastectomy	5,406 (34)	280 (40)	646 (39)	<0.001

table 1 continued

Residue				
no	15,157 (97)	670 (97)	1,585 (97)	
yes (microscopic) [d]	497 (3)	18 (3)	48 (3)	
Unknown	357	15	23	0.638
Sentinel node biopsy				
yes	13,412 (90)	621 (96)	1,228 (95)	
no	1,554 (10)	26 (4)	71 (5)	<0.001
unknown	1,045	56	357	
Axillary lymph node dissection				
yes	3,609 (23)	349 (50)	1,345 (81)	
no	12,402 (77)	354 (50)	311 (19)	<0.001
Radiotherapy				
yes	10,588 (66)	437 (62)	1,057 (64)	
no	5,423 (34)	266 (38)	599 (36)	0.021
Chemotherapy				
yes	1,150 (7)	96 (14)	530 (32)	
no	14,861 (93)	607 (86)	1,126 (68)	<0.001
Hormonal treatment				
yes	2,407 (15)	228 (32)	1,034 (62)	
no	13,604 (85)	475 (68)	622 (38)	<0.001
Her2 and trastuzumab				
her2 negative, no trastuzumab	6,196 (39)	334 (47)	676 (41)	
her2 positive, no trastuzumab	491 (3)	20 (3)	39 (2)	
her2 positive, trastuzumab	83 (1)	8 (1)	33 (2)	
her2 unknown [e]	9,241 (57)	341 (49)	908 (55)	<0.001

Records with missing values that were imputed: grade: 1,645 (9.0%); multifocality 5,145 (28.0%); expression of receptors 4,166 (22.7%); sentinel node biopsy 1,458 (7.9%).

[a] Subtype 'other': e.g. mucinous adenocarcinoma, medullary carcinoma, metaplastic carcinoma

[b] Category 'unknown' consists largely of unknown due to missing in registration in earlier years

[c] In case of re excision after breast conserving surgery, the final surgery is presented (BCS or mastectomy)

[d] Resection margins after final surgery contain microscopic tumour foci without further surgery. Patients with macroscopic tumour residu after final surgery were excluded in this study

[e] Her2 testing and treatment with trastuzumab were implemented as standard care in September 2005. Missing data largely in earlier years.

Table 2. Number of events and crude 5-year survival rates according to axillary lymph node status in 18,370 pT1-2 breast cancer patients diagnosed 2003-2006

	Node negative (n=16,011)		Isolated tumour cells (n=703)		Micrometastases (n=1,656)	
	N	rate (%)[c]	*N*	rate (%)	*N*	rate (%)
First events						
Locoregional recurrence	368	2.6%	21	3.4%	34	2.2%
Local recurrence	*270*	*2.0%*	*14*	*2.3%*	*30*	*2.0%*
Regional recurrence	*98*	*0.7%*	*7*	*1.1%*	*4*	*0.3%*
Distant metastases	622	4.4%	32	5.2%	89	5.9%
Contralateral breast cancer	465	3.4%	16	2.6%	36	2.4%
Primary endpoint[a]	1,455	90.0%	69	89.2%	159	89.7%
Secondary endpoint[b]	990	93.1%	53	91.6%	123	92.0%

[a] Composite endpoint including locoregional recurrence, distant metastases, contralateral breast cancer

[b] Composite endpoint including locoregional recurrence, distant metastases

[c] Rates using Kaplan Meier estimates

Table 3. Adjusted Hazard rates for primary endpoint (locoregional, distant metastasis or contralateral breast cancer) and secondary endpoint (locoregional, distant metastasis) according to axillary status

	Primary endpoint		Secondary endpoint	
	HR (95% CI)	P	HR (95% CI)	P
Node negative	1.00		1.00	
Isolated tumour cells	1.12 (0.87 - 1.43)	0.384	1.20 (0.90 - 1.60)	0.216
Micrometastases	1.38 (1.13 - 1.69)	0.002	1.50 (1.19 - 1.89)	0.001

Adjusted for age (continuous), year of diagnosis, pT, grade, multifocality, final surgery, sentinel node biopsy, axillary lymph node dissection, radiotherapy, chemotherapy hormonal therapy and her2/trastuzumab. Year of diagnosis was included as a time varying covariate.

Table 2 shows the number of events according to nodal status. Five-year primary endpoint for all women was 89.9% (95% CI 89.5 – 90.4); it was 90.0%, 89.2% and 89.7% for patients with node negative disease, ITC and micrometastases, respectively. The crude, unadjusted risk for disease-free survival did not differ between these three groups; the Hazard Ratio (HR) was 1.09 (95% CI 0.86 – 1.39) and 1.04 (95% CI 0.88 – 1.22) for patients with ITC or micrometastases versus node negative patients, respectively.

After adjusting for prognostic factors (including treatment), patients with ITC had comparable risks as node negative patients (HR=1.12, n.s. and HR=1.20, n.s. for primary and secondary endpoint respectively; Table 3). Patients with micrometastases had a 38% to 50% higher risk (HR=1.38, sign and HR=1.50, sign, respectively). In separate analyses of patients who did not receive any kind of systemic therapy comparable results were seen (data not shown).
Other tumour characteristics with prognostic value are larger tumour size, higher grade, multifocality and negative receptor status, with comparable results for primary and secondary

endpoints (Figure 1a and Figure 1b).
Chemotherapy reduced the primary event risk for all patients (HR 0.74; 95% CI 0.60-0.92). The effect of hormonal treatment was determined by nodal status. The reduction of the event risk in case of hormonal therapy was 66% in patients with micrometastases (HR 0.34; 95% CI 0.23 – 0.51) and 46% and 54% patients with node negative disease or ITC (HR 0.54; 95% CI 0.45 - 0.65 and HR 0.46; 95% CI 0.25 – 0.86 respectively). These results were comparable in analyses of the secondary endpoint. No interaction was found between nodal status and chemotherapy.

Discussion

We found that the prognosis of patients with ITC did not differ significantly from that of patients with node negative disease in a large unselected population. Patients with micrometastases, however, had a significantly worse prognosis, with a 38% higher risk of locoregional recurrence, distant metastases or contralateral breast cancer within five years after diagnosis. Furthermore, we demonstrated that all patients benefitted from adjuvant systemic treatment (chemotherapy and hormonal treatment), and patients with micrometastases seemed to derive more benefit from hormonal therapy than patients with ITC or node-negative disease.

The results of our study differ from the findings of the Dutch MIRROR study that found that the prognostic significance of ITC is comparable to micrometastases (HR 1.50 and 1.56 for ITC versus node negative and micrometastases versus node negative respectively). The MIRROR study selected the node negative cohort from patients diagnosed over the period 2000 to 2001 and the ITC and micrometastases cohorts over 1997 to 2005. Apart from the fact that our study concerns more recent years of diagnosis for all patients (2003 – 2006), we have no explanation for the difference in findings. However, other studies have reported no worse overall or disease-free survival for patients with micrometastases.[13-15] The number of events in these studies was relatively small, thus possibly obscuring a small effect. The results from the large NSABP trial B-32 are comparable to our findings, with HR of 1.18 and 1.38 for ITC and micrometastases on disease-free survival.[12] Data from the SEER database also show similar results on overall survival for patients with micrometastases.[10]

Complete axillary lymph node dissection following Sentinel Node Biopsy

Recent large studies show that complete ALND after SNB has no additional benefit on regional control and overall survival for patients with ITC or patients with micrometastases who receive adjuvant systemic therapy.[18-23] Data from the National Cancer Database show in the United States 45% of patients with micrometastases did not undergo ALND in 2005.[24] In our study, the percentage of ALND is 80% for patients with micrometastases, and this did not drop over the study period up to 2006. Further analyses on more recent data will give more insight in current practice, as it is expected that this percentage will drop for patients with micrometastases, as it did for ITC.

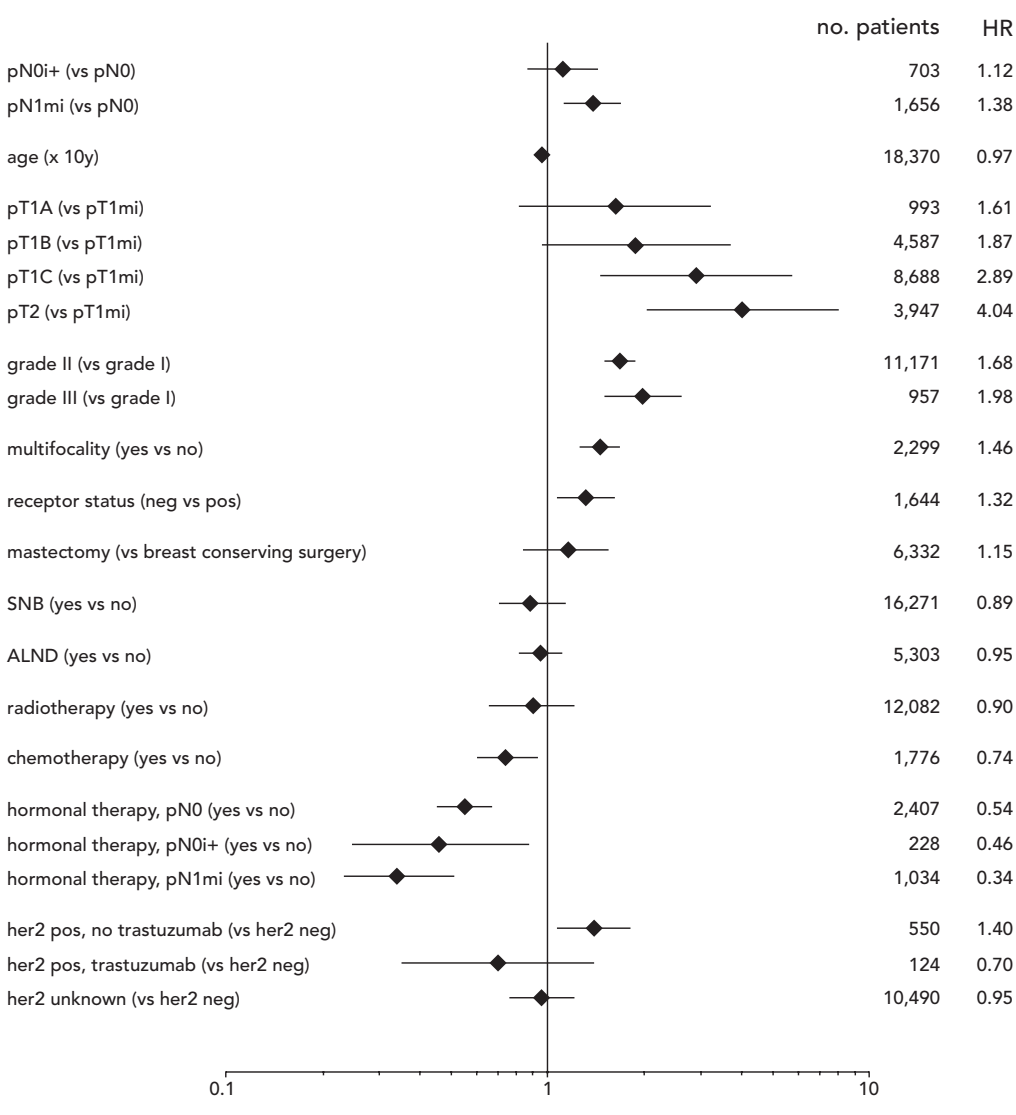

Figure 1a. Forest plot for primary endpoint (locoregional, distant metastasis or contralateral breast cancer)based on multivariate Cox proportional hazard model[a]

[a] Year of diagnosis was included as a time varying covariate. All reported hazard ratios are adjusted for all variables included in the analyses. Patient numbers in imputed variables (grade, multifocality, receptor status, sentinel node biopsy) are estimated proportions from 20 datasets.

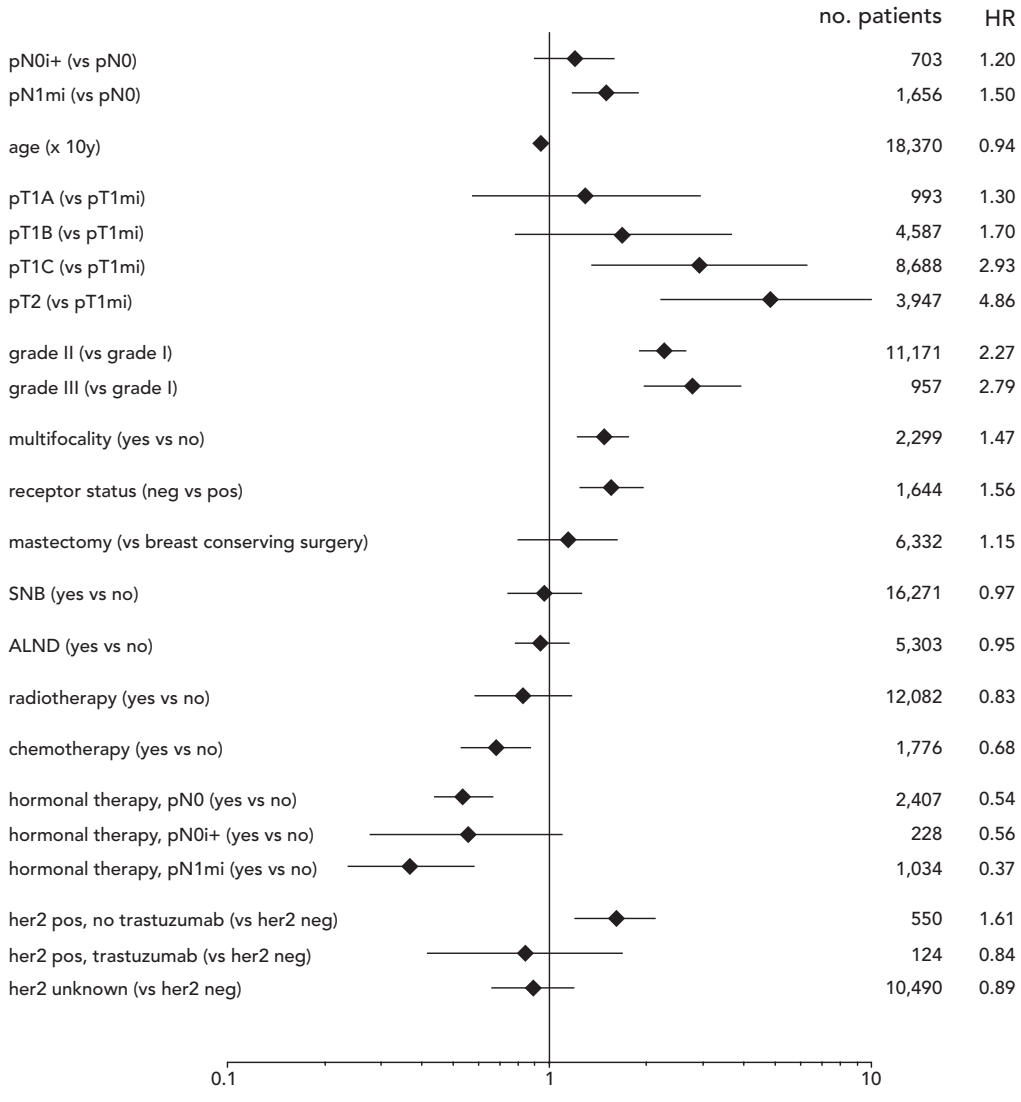

Figure 1b. Forest plot for secondary endpoint (locoregional, distant metastasis) based on multivariate Cox proportional hazard model[a]

[a] Year of diagnosis was included as a time varying covariate. All reported hazard ratios are adjusted for all variables included in the analyses. Patient numbers in imputed variables (grade, multifocality, receptor status, sentinel node biopsy) are estimated proportions from 20 datasets.

Adjuvant treatment

Debate currently focuses on the benefits of adjuvant therapy in patients with micrometastases in axillary lymph nodes. The MIRROR study reported a lower 5-year disease-free survival rate of nearly ten percent in patients with ITC or micrometastases when receiving systemic adjuvant chemotherapy, with adjusted HR of 0.66 (95% CI 0.46 – 0.95) and 0.50 (95% CI 0.35 – 0.72), respectively. Our study differentiates between adjuvant chemotherapy and hormonal treatment. All patients benefit from additional adjuvant treatment. We observed that patients with micrometastases benefit to a larger extent from hormonal therapy than patients with node negative disease.

The MIRROR study has pleaded to consider adjuvant chemotherapy based only on the presence of ITC or micrometastases in the axilla. However, we are reluctant to advise chemotherapy in all patients with ITC or micrometastases, especially in those who have no aggressive tumour characteristics. The disease-free survival is already good, which makes the potential benefit from chemotherapy small; while side effects of chemotherapy are considerable. Furthermore, it is likely that genomic primary tumour characteristics will tell more about the propensity of dissemination from the primary cancer rather than the status of the axillary lymph nodes. Reported HRs on 5-year distant metastases free survival for three genetic signatures (high versus low risk) vary from 3.4 to 7.1.[25] Treatment decisions in these patients require thorough deliberation taking into account all primary tumour characteristics and findings in the lymph nodes.

As all observational cohort studies our study has it strengths and weaknesses. The main drawback of this study is that the allocation of treatment was not random. Patients in our cohort have been treated according to their tumour and patient characteristics, thus introducing the possibility of treatment bias (or 'bias by indication') that is unsolvable in this study design.[26] Our major strength is the large size, the population based character and the fact that we have included all breast cancer patients with axillary node negative disease, isolated tumour cells or micrometastases in our cohort, reflecting the actual diagnosis, treatment and prognosis of breast cancer patients in the Netherlands. All patients were staged according to the 6th edition of the TNM and treated according to the Dutch national guidelines. Most studies to date have reported on minimal lymph node involvement, combining ITC and micrometastases in their analyses, while in this study we could disentangle the effects of ITC and micrometastases on prognosis.

Based on the results of this study, it appears that patients with ITC and node negative breast cancer have similar prognosis, while patients with micrometastases have a 38% higher risk of locoregional recurrence, distant metastases or contralateral breast cancer. Considering the already high disease-free survival in patients with pT1-2 breast cancer without axillary macrometastases, and the subsequent smaller potential benefit from chemotherapy, we do not advise standard chemotherapy for patients with ITC or micrometastases.

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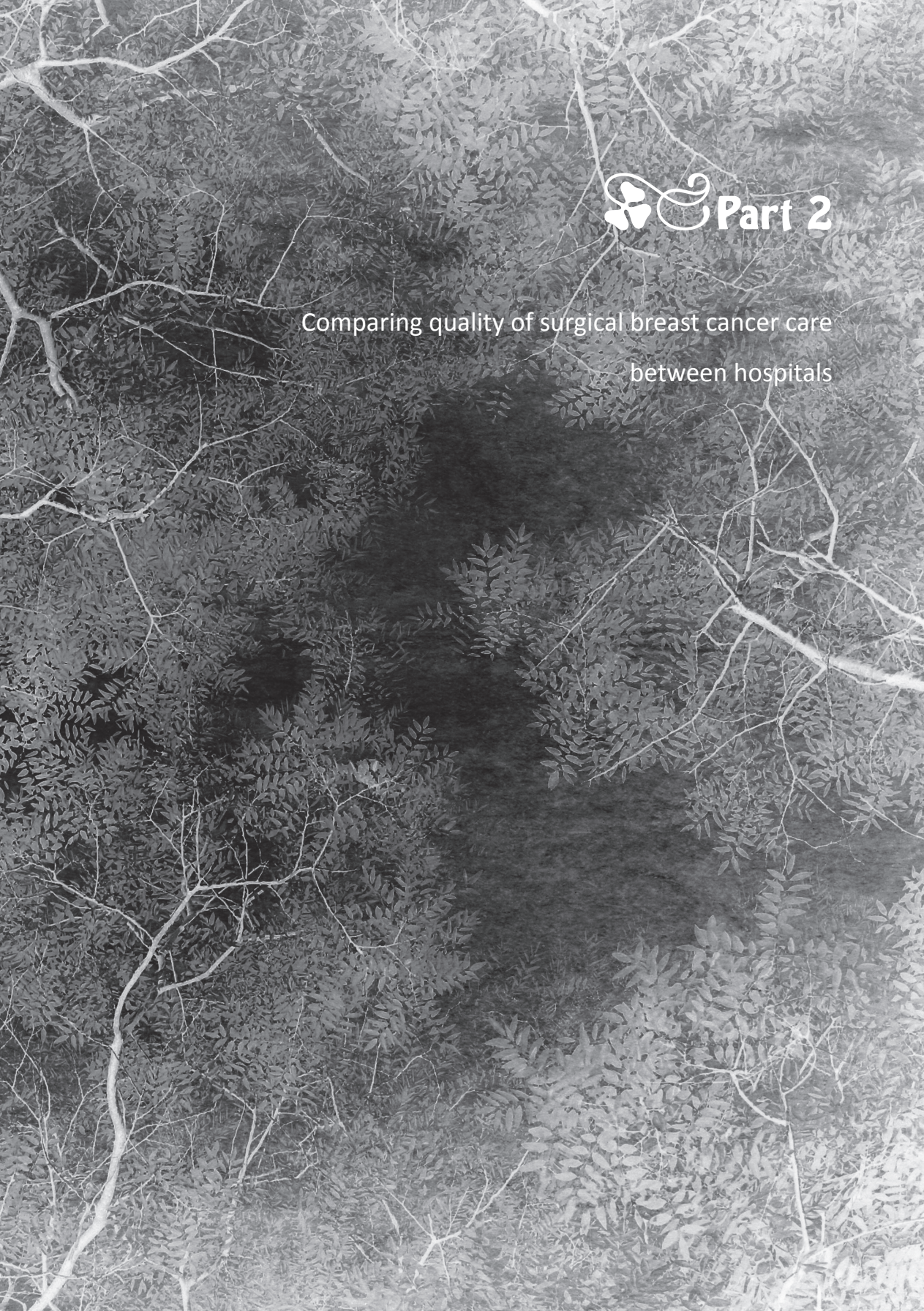

Part 2

Comparing quality of surgical breast cancer care between hospitals

Chapter 6

Weinig lokaal recidieven na mammachirurgie: goede kwaliteit van de Nederlandse borstkankerzorg

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Abstract

Doel
Het beschrijven van het percentage lokaal recidief binnen 5 jaar na operatie van mammacarcinoom als prestatieindicator van de Nederlandse ziekenhuizen.

Opzet
Beschrijvend, cohortonderzoek.

Methode
Alle vrouwen bij wie in 2003 een eerste invasief mammacarcinoom was gediagnosticeerd en die in opzet curatief waren geopereerd (met of zonder radiotherapie), werden geselecteerd uit de Nederlandse kankerregistratie (NKR). Registratiemedewerkers van de NKR verzamelden gegevens over het optreden van recidieven binnen 5 jaar bij deze patiënten aan de hand van een gestandaardiseerd protocol. Recidiefpercentages werden bepaald per ziekenhuis met de Kaplan Meier methode en weergegeven in 'forest'-plots en 'funnel'-plots.

Resultaten
In 2003 werden 9898 patiënten in 99 Nederlandse ziekenhuizen gediagnosticeerd en curatief behandeld voor een eerste mammacarcinoom. 266 patiënten kregen een lokaal recidief binnen 5 jaar. Het 5-jaarsrecidiefpercentage was 3,03 (95% BI: 2,69-3,41). Na een borstsparende operatie was het 5-jaarsrecidiefpercentage 2,63 (95% BI: 2,21-3,12); na borstamputatie was dit 3,50% (95% BI: 2,97-4,13). Er was een grote variatie in recidiefpercentage tussen ziekenhuizen (0-17%). De aantallen behandelde patiënten waren in de meeste ziekenhuizen echter te laag om betrouwbare schattingen te geven.

Conclusie
Het percentage lokaal recidieven na chirurgische behandeling voor mammacarcinoom lag in Nederland onder de norm van 5% binnen 5 jaar. Het is niet mogelijk om op basis van deze indicator een uitspraak te doen over verschillen in de kwaliteit van zorg tussen ziekenhuizen door de lage gemiddelde recidiefkans en het relatief lage aantal patiënten met een lokaal recidief per ziekenhuis.

Introductie

Prestatie-indicatoren hebben tot doel de kwaliteit van zorg inzichtelijk te maken, zodat deze verbeterd kan worden. In 2006 is een aantal indicatorensets opgesteld binnen het ZonMw project 'Kwaliteit van zorg in de etalage', waaronder de indicatorenset mammacarcinoom.[1] Deze set is in 2008 overgenomen door Zichtbare Zorg Ziekenhuizen met verplichting tot rapportage door alle ziekenhuizen. Eén van de belangrijkste indicatoren voor mammacarcinoom betreft het percentage lokaal recidieven binnen 5 jaar na chirurgische behandeling.

Adequate behandeling van patiënten met een operabel mammacarcinoom resulteert in een hoge ziektevrije overleving. De lokale controle van de tumor is hierbij van belang, aangezien lokaal recidieven meestal ontstaan door uitgroei van resttumor.[2] De primaire locoregionale behandeling heeft daarom in de eerste plaats tot doel de primaire tumor radicaal te verwijderen, in combinatie met adequate lokale en/of regionale bestraling.[3] Binnen de beroepsgroep bestaat consensus over het streven naar een maximaal percentage lokaal recidieven van 10% binnen 10 jaar, ofwel 5% binnen 5 jaar.[4;5] Daarbij geldt dat bij borstsparende behandeling het percentage lokaal recidieven en de overlevingskans vergelijkbaar moet zijn met de resultaten na amputatie. Met het oog hierop maakt de indicatorenset onderscheid tussen patiënten die sparend zijn behandeld en patiënten die een amputatie hebben ondergaan.

De gegevens die voor deze indicator benodigd zijn, zijn niet beschikbaar in geautomatiseerde ziekenhuisinformatiesystemen. Daarom hebben we gebruik gemaakt van de database van de Nederlandse Kankerregistratie (NKR), waarin de integrale kankercentra sinds 1989 alle nieuwe gevallen van kanker registreren. Eind 2008 besloten de kankercentra tot een aanvullend registratieproject teneinde de follow-up gegevens voor de hier beschreven indicator te verzamelen. De uitkomsten werden medio mei 2009 ter beschikking gesteld aan de ziekenhuizen, die deze zodoende konden gebruiken voor aanlevering aan Zichtbare Zorg.

In dit artikel beschrijven we de uitkomsten op de indicator 'Percentage lokaal recidief binnen vijf jaar na operatieve behandeling van mammacarcinoom' van alle ziekenhuizen in Nederland.

Methode

Onderzoekspopulatie

Alle vrouwen die in 2003 werden gediagnosticeerd met een eerste invasief mammacarcinoom zonder metastasen die hiervoor in opzet curatief werden behandeld, werden geselecteerd uit de NKR. Patiënten met een carcinoom met ingroei in de huid of de thoraxwand en patiënten bij wie na de laatste operatie nog macroscopische tumorrest aanwezig was, werden geëxcludeerd, evenals patiënten die in het buitenland werden geopereerd.
Cases werden toegewezen aan het ziekenhuis van chirurgische behandeling. De chirurgische behandeling werd gecodeerd als 'mammasparende operatie' of 'amputatie'. Patiënten die een mammasparende operatie hadden ondergaan, gevolgd door een amputatie, werden ingedeeld

in de groep 'amputatie'. In totaal werden 10.284 patiënten geïncludeerd.

Dataverzameling

In de periode januari-april 2009 werden aanvullende gegevens verzameld door registratiemedewerkers van de NKR volgens een gestandaardiseerde handleiding. Bij patiënten die tumorvrij bleven, werd de laatste datum van contact in het ziekenhuis vastgelegd. In geval van terugkeer van de borstkanker, werd de datum van diagnose en de lokalisatie van het recidief vastgelegd: een lokaal recidief (in de borst of de huid), een regionaal recidief (in het omliggend okselklierweefsel) of een metastase op afstand. Bij twijfel over de wijze van coderen werd overlegd met de projectgroep, dan wel de behandelaar.
Na dataverzameling werden 384 patiënten (3,7%) alsnog geëxcludeerd. Van 162 patiënten (1,6%) waren geen follow-up gegevens beschikbaar. Van de overige 222 patiënten was de follow-up korter dan 6 maanden (2,1%) door het ontbreken van recente informatie in het medisch dossier, doordat de patiënt was overleden of vanwege het optreden van een (lokaal of regionaal) recidief of metastase op afstand. Volgens de instructies van de indicator dienden deze patiënten niet meegenomen te worden in de analyses.

Analyse

De uitkomstmaat was het optreden van een lokaal recidief tussen 6 maanden en 5 jaar na pathologische bevestiging van mammacarcinoom. Voor het onderscheid tussen een lokaal recidief en een tweede primaire tumor, gingen wij uit van de codeerregels van de NKR. Een tumor van een andere morfologisch type werd beschouwd als een nieuwe primaire tumor. Een tumor van hetzelfde type werd beschouwd als een recidief, tenzij de behandelaar deze expliciet had aangeduid als nieuwe tumor.
De recidiefkans werd berekend middels de Kaplan Meier methode. Hierbij wordt rekening gehouden met patiënten die niet de volledige follow-upperiode 'at risk' waren (omdat ze eerder overleden waren, er over hen geen informatie meer beschikbaar was in het medisch dossier of omdat de ziekte zich regionaal of op afstand manifesteerde zonder lokaal recidief).
De recidiefpercentages en bijbehorende betrouwbaarheidsintervallen werden per ziekenhuis weergegeven in een 'forest'-plot.[6] De horizontale lijn toont de norm voor het recidiefpercentage van 5%. In een 'funnel'-plot werden de percentages lokaal recidief uitgezet tegen het aantal patiënten dat in een ziekenhuis was geopereerd.[6] De horizontale lijn in de 'funnel'-plot is de norm van de indicator, met daar omheen de bijbehorende 95%- en 99,8%- betrouwbaarheidsintervallen.[7]

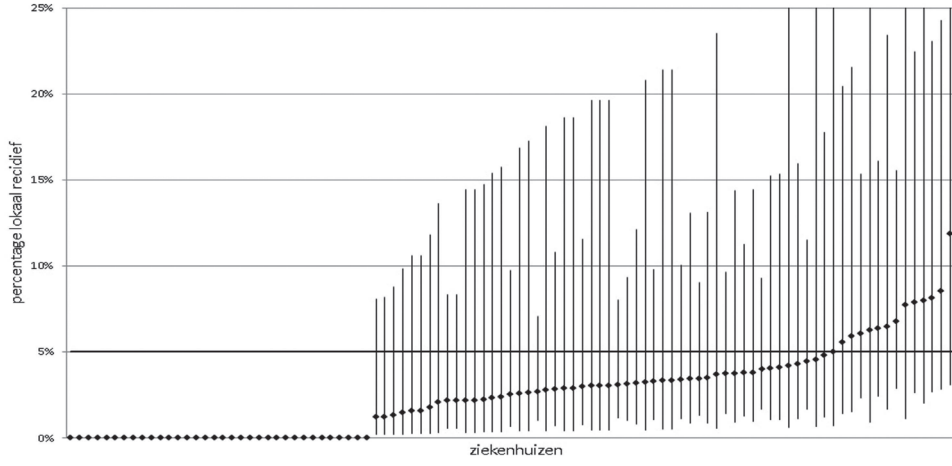
Resultaten

De 9.898 patiënten die in 2003 werden gediagnosticeerd met primair mammacarcinoom, werden in 99 (locaties van) ziekenhuizen behandeld. Het aantal geopereerde vrouwen per ziekenhuis lag tussen de 15 en 275 patiënten, met een gemiddelde van 100 vrouwen per ziekenhuis. In 14 ziekenhuizen werden minder dan 50 patiënten met een primair mammacarcinoom geopereerd.

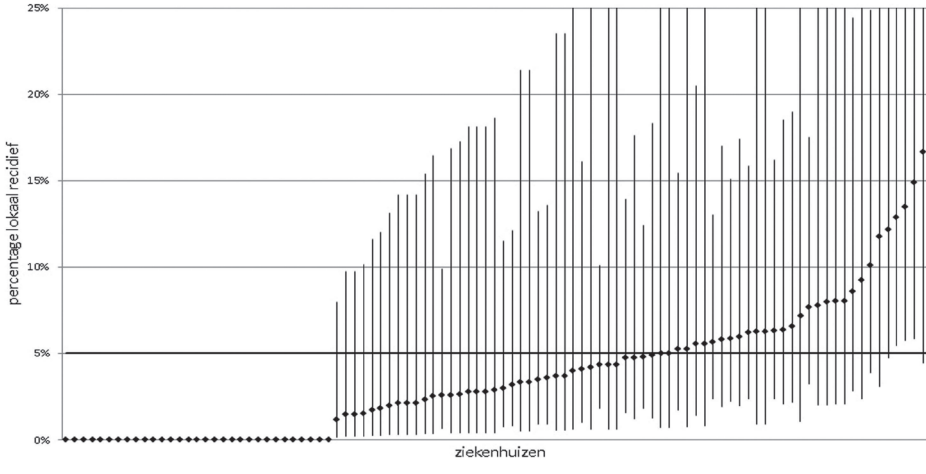
Tabel 1. Kenmerken van 9.898 vrouwen met een mammacarcinoom die daar in 2003 voor geopereerd werden, opgesplitst naar het type van de laatste operatie

	borstsparend	amputatie
	N (%)	N (%)
leeftijdscategorie		
< 35	91 (2)	126 (3)
35-50	1.229 (23)	1.135 (25)
50-70	3.118 (59)	1.887 (41)
>=70	876 (16)	1.436 (31)
T-stadium		
T1	3.871 (73)	1.977 (43)
T2	1.408 (26)	2.227 (49)
T3	19 (0)	343 (7)
TX	16 (0)	37 (1)
N-stadium		
N0	3.746 (70)	2.321 (51)
N+	1.568 (30)	2.263 (49)
stadium		
1	2.962 (56)	1.292 (28)
2A	1.548 (29)	1.452 (32)
2B	477 (9)	876 (19)
3	311 (6)	936 (20)
X	16 (0)	28 (1)
histologisch type		
ductaal	4.325 (81)	3.463 (76)
lobulair	455 (9)	659 (14)
gemengd ductaal en lobulair	192 (4)	200 (4)
tubulair	119 (2)	34 (1)
mucineus	91 (2)	84 (2)
overig	132 (2)	144 (3)

Tabel 1 geeft een overzicht van de kenmerken van de patiëntengroep. De helft van de patiënten was tussen 50 en 70 jaar oud. De gemiddelde leeftijd was 57 jaar voor de sparend geopereerde vrouwen en 60 jaar voor vrouwen die een amputatie ondergingen.
In totaal werd 54% van de vrouwen (5.314 patiënten) sparend behandeld. Het percentage sparend geopereerde vrouwen in 2003 verschilde aanzienlijk tussen de verschillende ziekenhuizen, met een de spreiding van 20%-90%.



a.



b.

Figuur 1. Lokaal recidiefpercentage binnen 5 jaar na (a) borstsparende operatie en (b) amputatie, geanalyseerd per ziekenhuis. Voor ieder ziekenhuis is de uitkomst is weergegeven met het bijbehorend 95%-betrouwbaarheidsinterval in een 'forest'-plot. De horizontale lijn geeft de norm van 5% aan.

Bij 266 patiënten werd binnen 5 jaar een lokaal recidief vastgesteld. Het lokaal recidiefpercentage was voor de totale groep 3,03% (95% BI: 2,69%-3,41%). Na mammasparende operatie was het lokaal recidiefpercentage 2,63% (95% BI: 2,21%-3,12%). De uitkomsten werden per ziekenhuis weergegeven in een 'forest'-plot (figuur 1a). Het 5-jaars lokaal recidiefpercentage na mammasparende operatie varieerde tussen ziekenhuizen van 0-11,9%. 34 ziekenhuizen hadden een lokaal recidiefpercentage van 0%. Opvallend voor alle ziekenhuizen waren de brede

betrouwbaarheidsintervallen als gevolg van de kleine aantallen. Geen van de ziekenhuizen had een significant hoger lokaal recidiefpercentage dan 5%.

Na amputatie was het lokaal recidiefpercentage 3,50% (95% BI: 2,97%-4,13%). Figuur 1b geeft de uitkomst per ziekenhuis weer. Het 5-jaars lokaal recidiefpercentage varieert van 0-16,7%. 31 ziekenhuizen hebben een lokaal recidiefpercentage van 0%. Ook hier zijn brede betrouwbaarheidsintervallen zichtbaar. In 3 ziekenhuizen lag het 5-jaars lokaal recidiefpercentage na amputatie significant hoger dan de norm van 5 procent. In deze ziekenhuizen ondergingen 51, 49 en 29 patiënten een amputatie, waarna respectievelijk 5, 5 en 4 patiënten een lokaal recidief ontwikkelden. Een 4e ziekenhuis kende een recidiefpercentage van 16,7%, maar dit was niet significant hoger dan de norm: van 12 patiënten ontwikkelden 2 patiënten een lokaal recidief (95% BI: 4,5-51,8%).

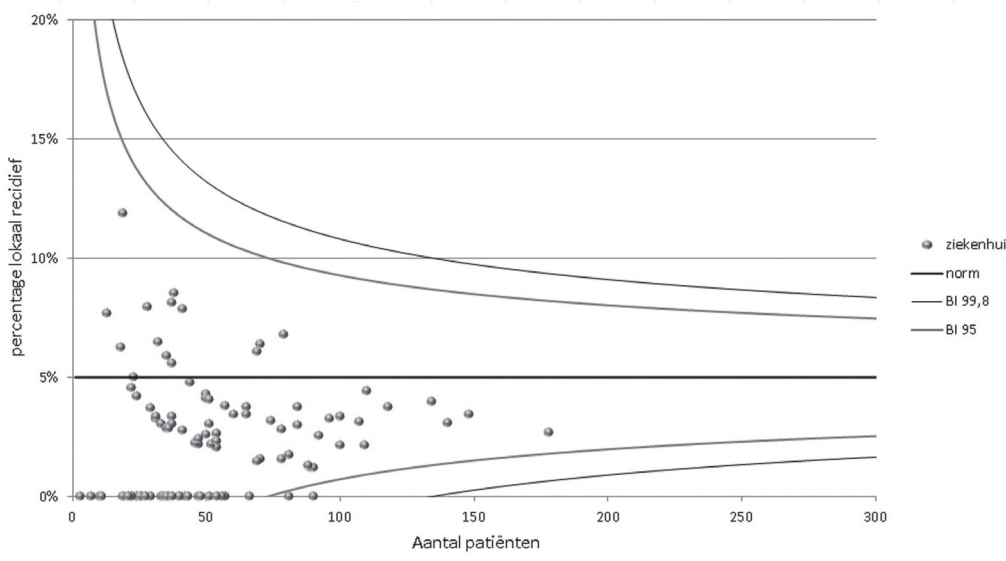
De 'funnel'-plots (figuren 2a en 2b) laten grafisch zien dat hoge en lage recidiefkansen voorkomen in ziekenhuizen waar minder dan 100, en voornamelijk minder dan 50 patiënten werden behandeld. De weergegeven betrouwbaarheidsintervallen (voor de norm van 5%) maken zichtbaar dat de invloed van het toeval fors toeneemt bij kleiner wordende aantallen.

Beschouwing

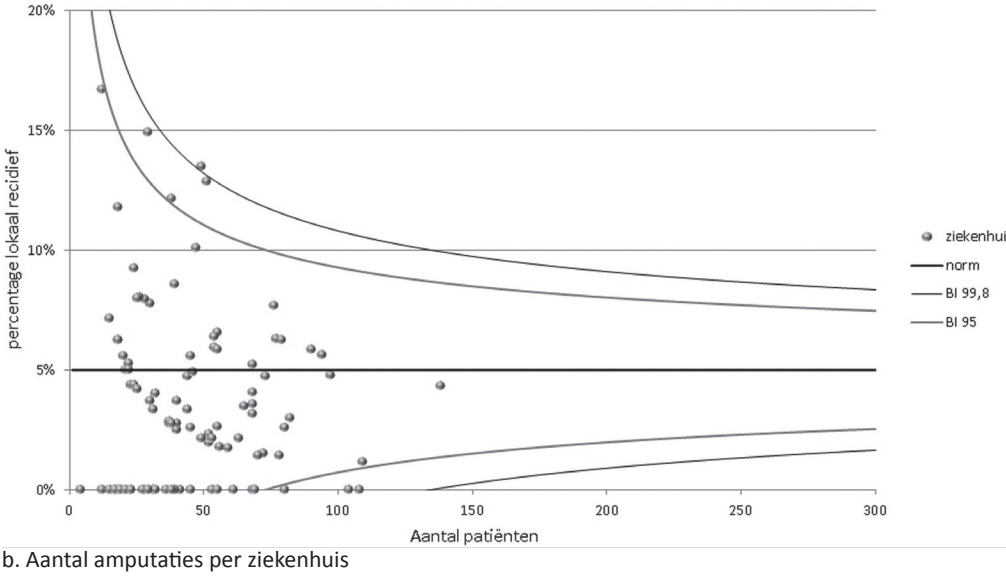
In deze studie maakten wij de uitkomsten van alle Nederlandse ziekenhuizen op de indicator 'Percentage lokaal recidief binnen vijf jaar na operatieve behandeling van mammacarcinoom' inzichtelijk. Het 5-jaars lokaal recidiefpercentage was 2,63% (95% BI: 2,21%-3,12%) na mammasparende operatie en 3,50% (95% BI: 2,97%-4,13%) na amputatie. Deze percentages waren significant lager dan de in de indicator beschreven norm van 5% binnen 5 jaar.

Een belangrijke voorwaarde voor valide kwaliteitsbepaling middels indicatoren is een uniforme dataverzameling. Eerder ontstond veel onrust na de publicatie van uitkomsten op aan andere prestatie-indicator, het 'percentage patiënten bij wie kankerweefsel is achtergebleven na een eerste borstsparende operatie'.[8,9] Hierbij bleek dat definities niet eenduidig waren, waardoor interpretatieverschillen tussen ziekenhuizen leidden tot verschillende wijzen van registratie en daarmee minder betrouwbare en onvergelijkbare uitkomsten.

In onze studie was uniforme dataverzameling gewaarborgd middels gebruik van de Nederlandse Kankerregistratie (NKR), die een vrijwel complete registratie heeft van patiënten met kanker.[10] Registratie van de follow-up door NKR-medewerkers vond plaats volgens gestandaardiseerde protocollen. Hierdoor konden wij de uitkomsten berekenen zonder dat verschillen in codering en interpretatie tussen ziekenhuizen een rol speelde.
Kanttekening bij deze studie is dat patiënten die tijdens de follow-up periode overgingen naar een ander ziekenhuis zonder vermelding in de status, niet verder konden worden gevolgd. Deze patiënten werden alleen meegeteld tot het laatste contactmoment in het ziekenhuis. Hoewel met de uitval rekening wordt gehouden in de Kaplan Meier methode, bestaat de kans dat dit



a. Aantal borstsparende operaties per ziekenhuis



b. Aantal amputaties per ziekenhuis

Figuur 2. Lokaal recidiefpercentage binnen 5 jaar na (a) borstsparende operatie en (b) amputatie, geanalyseerd per ziekenhuis. Elke stip in deze 'funnel'-plot vertegenwoordigt een ziekenhuis. De horizontale lijn geeft de norm van 5% aan. De curves geven de grenzen van het 95% BI (grijs) en het 99,8% BI (zwart) rond de norm. Deze weergave maakt het verband tussen de uitkomsten en het ziekenhuisvolume inzichtelijk. Ziekenhuizen buiten de curves scoren significant beter of slechter dan de norm van 5%

selectief patiënten betrof met een lokaal recidief en dan zou het werkelijk recidiefpercentage hoger liggen. Dit probleem zal overigens ook spelen als gegevens door de ziekenhuizen zelf worden verzameld, in plaats van door de NKR.
Voorts kan men ter discussie stellen of het terecht is dat lokaal recidieven die binnen 6 maanden optreden, werden uitgesloten. De werkgroep oordeelde destijds dat dit veelal bijzondere gevallen betrof, zoals bijvoorbeeld een tijdens de diagnostiek gemiste lymfangitis carcinomatosa. De grens van 6 maanden is arbitrair en het zou logischer zijn deze tijdslimiet te laten vervallen. Overigens zal het waarschijnlijk om kleine aantallen patiënten gaan.

Kwaliteitsverschillen niet te beoordelen

Het is niet mogelijk op basis van deze indicator verschillen in kwaliteit van zorg tussen ziekenhuizen te beoordelen. Ten eerste was de invloed van het toeval groot door de relatief lage aantallen patiënten per ziekenhuis en het lage aantal lokale recidieven. De helft van de ziekenhuizen kwam in 2003 tot niet meer dan 40 amputaties per jaar voor een primair mammacarcinoom. Bij deze aantallen operaties kan 1 lokaal recidief meer of minder leiden tot grote variaties: bij 2, 3 of 4 patiënten met een lokaal recidief wordt het percentage respectievelijk 5, 7,5 of 10. De invloed van toeval bij kleine aantallen wordt grafisch inzichtelijk gemaakt door de brede betrouwbaarheidsintervallen in de funnelplots (zie de figuren 2a en 2b). Het samenvoegen van gegevens uit meerdere jaren per ziekenhuis kan dit probleem overigens gedeeltelijk oplossen.
Een tweede aandachtspunt bij deze indicator is de mogelijkheid om de zorg te verbeteren naar aanleiding van de uitkomsten. De uitkomsten op de indicator weerspiegelen niet de actualiteit. Het betreft de kwaliteit van de behandeling van 5 jaar geleden. De kans is reëel dat de huidige kwaliteit van zorg anders is dan de indicator aangaf. Immers, de samenstelling van het mammateam kan veranderd zijn of er kan verdere expertise verkregen zijn. De indicator is per definitie niet goed in staat om veranderingen in de zorg op korte termijn te monitoren.
Een derde punt van kritiek bij de kwaliteit van de indicator heeft te maken met de inhoudelijke veronderstelling waarop de indicator is gebaseerd. Lokale recidieven ontstaan vanuit resttumor die is achtergebleven na eerdere lokale behandeling, namelijk chirurgische excisie en eventueel aanvullende bestraling. Het is echter bekend dat niet alle patiënten die resttumor hebben, een lokaal recidief krijgen. Verschillende studies tonen na 5 tot 10 jaar follow-up recidiefpercentages van 2-8% bij tumorvrije snijvlakken en 9-27% bij tumorpositieve snijvlakken.[11]

De kans op het optreden van een lokaal recidief wordt naast de volledigheid van excisie mede bepaald door patiënt- en tumorkenmerken, zoals de leeftijd van de patiënt, de tumorgrootte en tumorpositieve lymfeklieren, en door andere behandelkenmerken, zoals de tumorvrije marge en aanvullende therapieën.[12] Ook is bekend dat het optreden van een lokaal recidief niet altijd leidt tot verdere progressie van de ziekte en uiteindelijk het overlijden van de patiënt. Voor elke 4 patiënten bij wie men een lokaal recidief voorkomt, is 1 patiënt méér na 15 jaar nog in leven.[13]

Een uitkomstindicator houdt idealiter rekening met de factoren die de uitkomst beïnvloeden. Correctie voor heterogeniteit in de patiëntengroep (‘case mix’) is echter niet mogelijk in de

huidige methode van gegevensverzameling op ziekenhuisniveau, waarbij de instellingen alleen tellers en noemers aanleveren.

Indicatoren op kritische beslispunten

Hoewel de onderzochte indicator weinig waarde heeft voor het evalueren van verschillen in kwaliteit van zorg tussen instellingen op korte termijn, is de informatie op populatieniveau waardevol. De gegevens kunnen in vervolgonderzoek bijdragen aan het inzicht in het optreden van lokaal recidieven na behandeling van borstkanker. Het evalueren van kwaliteit van zorg tussen instellingen lukt beter op kritische beslispunten in de behandeling. Dat soort indicatoren geeft op korte termijn inzicht in eventuele lacunes in de zorg in ziekenhuizen, zonder dat correctie voor de heterogeniteit in de patiëntengroep nodig is.

Conclusie

Op basis van de uitkomsten van deze studie concluderen wij dat het 5-jaarslokaal-recidiefpercentage na operatieve behandeling van borstkanker in Nederland niet geschikt is om de kwaliteit van zorg tussen ziekenhuizen te vergelijken. Dit recidiefpercentage ligt in Nederland lager dan de gestelde norm van 5%. De kwaliteit van borstkankerzorg lijkt daarmee meer dan voldoende. Voor een definitief oordeel zijn ook de recidiefkansen en overlevingscijfers na 10 jaar belangrijk.

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Chapter 7

Measuring the quality of breast cancer care in the Netherlands: hospital variation in ipsilateral breast tumour recurrence rates

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Submitted

Abstract

Background

As a means of quality assurance, all Dutch hospitals are obliged to report their 5-year ipsilateral breast tumour recurrence (IBTR) rate after breast cancer surgery to the Dutch Health Care Inspectorate. This study assessed IBTR rates in patients with early breast cancer in the Netherlands over the period 2003-2006.

Methods

All female breast cancer patients with primary operable breast cancer (pT1-3, anyN, M0) who underwent breast cancer surgery in the period January 1, 2003 to December 31, 2006 from 80 Dutch hospitals were selected from the Netherlands Cancer Registry. Patients were excluded in case of previous cancer, neo-adjuvant chemotherapy, or if treatment did not have a curative intent. Data on 5-year recurrences were retrieved from hospital records. IBTR rates were calculated using Kaplan Meier estimates and presented for BCS and mastectomy separately. Hospital variation was presented in funnel plots with a maximum acceptable upper limit value of 5%.

Findings

A total of 31,992 breast cancer patients were selected. The proportion of BCS varied substantially between hospitals (16% to 80%). The overall 5-year IBTR rate was 2·51% (95%CI 2·23 – 2·71), which was significantly lower for BCS than for mastectomy (1·96% and 3·23%, respectively). A decrease of IBTR rates over time was seen in both groups; in 2006 1·49% and 2·71%, for BCS and mastectomy, respectively. IBTR rates varied from 0·82% to 5·40% between hospitals. In one hospital the IBTR rate after mastectomy was significantly higher than the 5% limit.

Interpretation

Our population-based findings show that IBTR rates in the Netherlands are low and rates have improved during recent years. The IBTR indicator is not suitable for comparing quality between hospitals since the number of patients treated per hospital and the number of recurrences are small, causing wide CI's.

Introduction

In society today, the call for transparency in the quality of care delivered by individual providers has led to continuous attempts to develop valid quality indicators. Quality indicators give insight in specific aspects of care and are used to measure and evaluate care in order to enable improvement. Generally, three types of indicators are recognized: those measuring 1) the organisation of care (structural indicators), 2) the care provided (process indicators) and 3) clinical outcome of care (outcome indicators).[1–3] To enable health care improvement, indicators need to measure aspects of care which can be influenced by care providers; by improving their skills, altering care processes or making structural adjustments. Outcome indicators are often considered the most appropriate instruments to evaluate quality of care. However, defining and assessing appropriate outcome indicators has proven to be difficult. If outcome indicators are used to compare clinical care on hospital level, a strict definition, uniform collection of clinical data and case mix adjustment are required.[3,5]

In the Netherlands, over 13,000 women are annually diagnosed with breast cancer.[4] To evaluate quality of breast cancer care, several indicators have been developed in recent years.[6,7] Optimal local disease control with low relapse rates is one of the main objectives of breast cancer treatment. Therefore, one of the outcome measures defined is the ipsilateral breast tumour recurrence (IBTR) rate at five years after breast surgery. In the Netherlands, based on consensus of experts in the field, the maximum acceptable upper limit value for IBTR within five years after breast conserving surgery (BCS) and mastectomy was set at 5%.[7,8] Since 2009, all Dutch hospitals are obliged to report the 5-year IBTR rate to the Dutch Health Care Inspectorate.[9]

Detailed clinical data concerning diagnosis, treatment and survival of breast cancer patients are registered in the Netherlands Cancer Registry (NCR). In a previous study on IBTR, based on data from patients diagnosed in 2003, we revealed that overall results were below the upper limit of 5%: 5-year IBTR rates were 2·6% and 3·5% for BCS and mastectomy, respectively.[10] However, the indicator was not able to discriminate between high and low quality hospitals in the Netherlands (n=99), due to the relatively low number of patients treated per hospital, and the relatively low IBTR rate. Currently, data on 5-year follow-up of four consecutive years are available, which enables further analysis of the relevance of this indicator.

Aim of this study is to determine the value of IBTR as an indicator to compare quality of care between individual hospitals. To meet this objective, we evaluate treatment patterns, time-trends as well as hospital variation in IBTR rates for patients diagnosed with early breast cancer in the Netherlands over the period 2003-2006.

Methods

Study design and patients

The NCR is a population-based cancer registry, collecting data on all new malignancies in the Netherlands. Specially trained registrars collect data on diagnosis, staging and treatment from hospital records, including pathology and surgery reports. Primary treatment is coded in sequence of administration. Stage is coded according to the TNM system of the International Union Against Cancer.[11] Data on recurrence five years after diagnosis was retrieved from the hospital patients files in retrospect for 80 out of 91 hospitals, all located in the region of Comprehensive Cancer Centre the Netherlands (CCCNL). Patients without tumour recurrence were coded as tumour-free on the last date of contact in the hospital, with a maximum follow-up of five years. If breast cancer re-occurred, date of diagnosis and the localization of recurrence was recorded categorized as: local (in breast or skin), regional (ipsilateral lymphatic tissue) or distant (metastases), or a combination of these. In case of doubt, registrars were instructed to consult a NCR coding expert or the treating physician. Data on new primary tumours (including new ipsilateral breast tumours) are routinely collected in the NCR. Information on vital status is available through annual linkage with the Municipal Personal Records Database, which has complete information on all deceased and emigrated residents of the Netherlands.

All female breast cancer patients with primary operable breast cancer (pT1-3, anyN, M0) who underwent BCS or mastectomy in the period January 1, 2003 to December 31, 2006 from 80 hospitals were selected. Patients with previous cancer were excluded, as well as patients who received neo-adjuvant chemotherapy, and patients who were not treated with curative intent (macroscopic tumour residue after final surgery or no axillary staging). Patients who underwent more than one operation were classified according to the final surgery. Patients were assigned to the hospital of final surgery.

Statistical Analysis

The endpoint of this study is defined as ipsilateral invasive breast tumour recurrence (IBTR) occurring within five years of diagnosis, irrespective of the localization or histological subtype (i.e. both true recurrences and second primary tumours are included). IBTR is reported irrespective of synchronous regional or distant metastases, whilst the indicator focusses on IBTR as a measure for the quality of local treatment of breast cancer.

Recurrence rates were calculated using Kaplan Meier estimates over the total period 2003-2006 and for every year separately, censoring patients no longer at risk (death, lost to follow up or with regional or distant metastases as first event without local recurrence). The upper limit for the indicator was defined at 5%. Hospitals scored higher than 5% when the observed IBTR rate exceeded the upper limit of the 95% confidence interval of 5% (which increases when the number of patients operated is lower).

The use of adjuvant treatment (e.g. radiotherapy, chemotherapy and hormonal treatment) over time was described. Observed trends in rates over time were evaluated by X^2 for trend tests. Results of individual hospitals are presented in funnel plots for BCS and mastectomy separately.[12]

All analyses were conducted using STATA (version 12·0; StataCorp, College Station, TX, U.S.A.).

Table 1. Patient and tumour characteristics according to final surgery in 31,992 breast cancer patients treated in 80 hospitals between 2003-2006 in the Netherlands

	BCS (n=17,642)	mastectomy (n=14,350)
	N (%)	N (%)
Age		
<35	278 (1)	367 (2)
35-50	4,234 (24)	3,418 (24)
50-70	10,348 (59)	6,030 (42)
>=70	2,782 (16)	4,535 (32)
pT		
<= 0·5 cm (T1A)	644 (4)	559 (4)
>0·5 to 1 cm (T1B)	3,410 (19)	1,187 (8)
1 to 2 cm (T1C)	8,982 (51)	4,730 (33)
2 to 5 cm (T2)	4,554 (26)	6,931 (48)
>5 cm (T3)	52 (0)	943 (7)
pN		
0	12,391 (70)	7,126 (50)
1	4,216 (24)	4,620 (32)
2	742 (4)	1,646 (11)
3	293 (2)	958 (7)
Grade		
well differentiated	4,262 (26)	2,061 (16)
moderately differentiated	7,409 (44)	6,191 (46)
poorly differentiated	4,982 (30)	5,084 (38)
unknown	989	1,014
Subtype		
ductal	14,993 (85)	11,111 (78)
lobular	1,445 (8)	2,050 (14)
ductal + lobular	603 (3)	729 (5)
other [a]	601 (3)	460 (3)
Multifocality		
no	12,267 (93)	8,121 (74)
yes	932 (7)	2,863 (26)
unknown [b]	4,443	3,366
Expression of receptors		
ER or PR positive	11,768 (83)	9,166 (79)
ER and PR negative	2,427 (17)	2,395 (21)
unknown [b]	3,447	2,789
Her2		
no	7,370 (88)	5,304 (83)
yes	986 (12)	1,093 (17)
unknown [c]	9,286	7,953

table 1 continued		
Residue		
no	16,428 (95)	13,412 (97)
yes (microscopic)	783 (5)	450 (3)
unknown [b]	431	488

[a] Subtype 'other': e.g. mucinous adenocarcinoma, medullary carcinoma, metaplastic carcinoma

[b] Category unknown consists largely of unknown due to missing in registration in earlier years

[c] Her2 testing was implemented as standard care in September 2005 and registered in the Netherlands Cancer Registry since 2005. Category unknown consists largely of missing data in earlier years

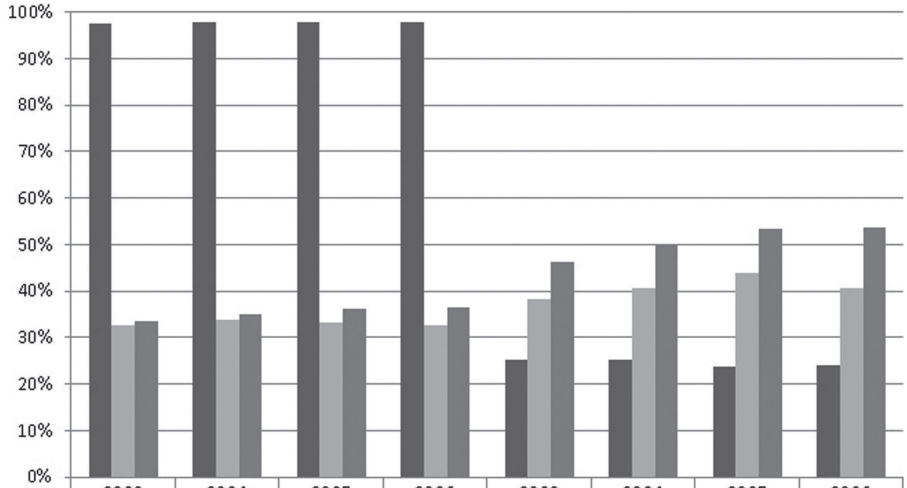
Results

A total of 31,992 breast cancer patients diagnosed over the period 2003 to 2006 were treated in 80 Dutch hospitals. Over 80 percent of tumours were of ductal type and most patients (61%) had node negative disease at diagnosis (70% and 50% in patients with BCS and mastectomy, respectively; Table 1).

The number of patients per hospital per year varied from 12 to 269, with an average of 99. Overall, 55% of all patients underwent BCS as final surgery and 45% had mastectomy. The proportion BCS as final surgery increased from 53% in 2003 to 56% in 2006 (p for trend<0·0001). The proportion BCS varied substantially between hospitals (16% to 80%; data not shown).

The percentage of patients with radiotherapy after BCS was high (98%) and stable over time (Figure 1). After mastectomy, a quarter of patients received radiotherapy. The use of chemotherapy was stable for patients with BCS, and showed a significant increase only for patients with mastectomy (from 38% to 41%; p for trend<0·001). Hormonal treatment also increased moderately over time in both groups (p for trend=0·022 and p for trend<0·001 for BCS and mastectomy, respectively).

In 694 patients an IBTR occurred within five years after diagnosis (Table 2). In 140 (20%) of these patients concurrent regional (n=37) or distant disease (n=103) was diagnosed. The overall 5-year IBTR rate was 2·51% (95%CI 2·23 – 2·71). This IBTR rate was significantly lower for BCS than for mastectomy (1·96 versus 3·23% respectively; p<0.0001). IBTR dropped significantly over time (Table 2; p for trend<0.001), but was only significant for BCS (p for trend=0.001) and not for mastectomy (p for trend=0.098). In 2006, the 5-year IBTR rate was 1·49% and 2·71% for patients with BCS and mastectomy, respectively.



	BCS				mastectomy			
	2003	2004	2005	2006	2003	2004	2005	2006
radiotherapy	98%	98%	98%	98%	25%	25%	24%	24%
chemotherapy	33%	34%	33%	33%	38%	41%	44%	41%
hormonal treatment	34%	35%	36%	36%	46%	50%	53%	54%

Figure 1. Percentage of patients receiving adjuvant treatment per year according to final surgery

Table 2. Ipsilateral breast tumour recurrence rates of 80 Dutch hospitals according to final surgery, and number of hospitals who scored statistically significantly over 5%

	no. patients	follow-up (years)	no. events	IBTR (95% CI)	no. hospitals sign> 5% (%)
breast conserving surgery					
2003	4,159	18,669	93	2·54 % (2·07 - 3·10)	1 (1%)
2004	4,334	19,269	84	2·21 % (1·79 - 2·74)	2 (3%)
2005	4,551	20,541	68	1·68 % (1·33 - 2·13)	0 (0%)
2006	4,598	20,768	61	1·49 % (1·16 - 1·92)	0 (0%)
Total, 2003-2006	17,642	79,248	306	1·96 % (1·76 - 2·20)	0 (0%)
mastectomy					
2003	3,646	14,767	106	3·48 % (2·88 - 4·20)	3 (4%)
2004	3,642	14,536	110	3·71 % (3·08 - 4·46)	3 (4%)
2005	3,461	14,133	88	3·03 % (2·46 - 3·72)	2 (3%)
2006	3,601	15,003	84	2·71 % (2·19 - 3·35)	1 (1%)
Total, 2003-2006	14,350	58,442	388	3·23 % (2·92 - 3·56)	1 (1%)

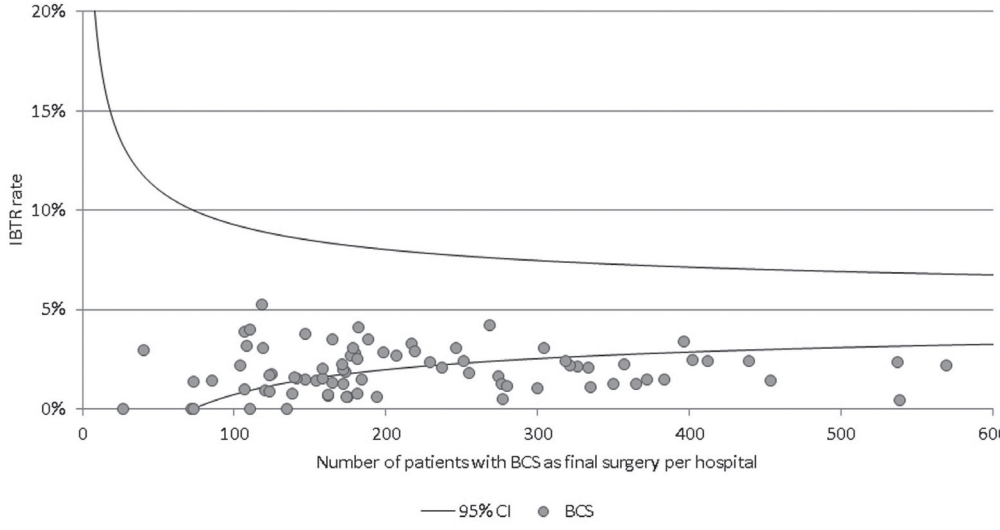


Figure 2a BCS: Funnel plot with IBTR rates for BCS in 2003-2006 by hospital

The results per hospital over the period 2003 – 2006 combined are shown in funnel plots (Figure 2a and Figure 2b). The overall IBTR rates varied between hospitals from 0.82% to 5.40% and split for type of surgery from 0 to 5.2% and 0 to 11.6% for BCS and mastectomy, respectively. In patients with BCS, no hospital had significantly higher IBTR rates than the target value of 5%. In patients with mastectomy, in one hospital a significantly higher IBTR rate was observed. This hospital treated a total of 70 patients with mastectomy over the period of 4 years, and a significantly higher IBTR rate was observed in a combined analysis of these 4 years (11·6%, while the upper limit of 5% with that number of patients was 10·1%), but statistically significant only in the first two years (16·6% (sign) in 2003; 16·9% (sign) in 2004; 0·0% in 2005, and 8·3% in 2006). In this hospital, 64% of patients received BCS as final surgery and the IBTR rate for BCS was 0·9%.

Discussion

This study shows that the quality of local control in breast cancer patients in the Netherlands is high, and even improved the last 5 years. The variation between hospitals in ipsilateral breast tumour recurrence is modest, only one hospital performed significantly worse with a 5-year IBTR rate significantly higher than the 5% upper limit. IBTR rates were higher and showed larger variation between hospitals for mastectomy than for BCS. This suggests that there still is room for improvement.

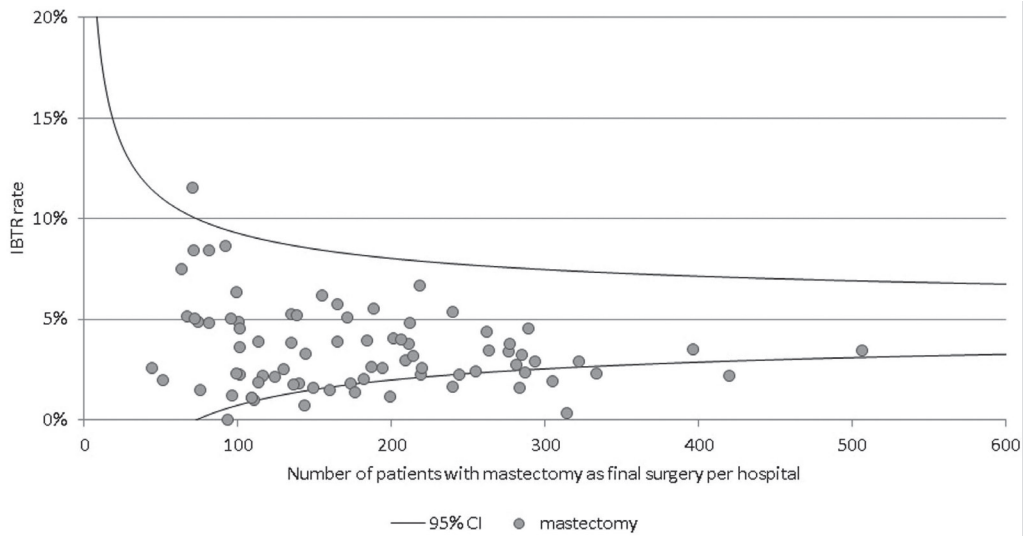


Figure 2b Mastectomy: Funnel plot with IBTR rates for mastectomy in 2003-2006 by hospital

Overall IBTR rates in the Netherlands were significantly lower than the upper limit of 5% within five years and were also lower than reported in large meta analyses, such as the EBCTCG overview that reports on data from over 42,000 patients in 78 trials that began by 1995. In this review, five-year isolated breast recurrence rates of 2·3% and 6·3% in patients node negative disease were reported for mastectomy with or without radiotherapy. For node positive patients, these rates were higher: up to 5·8% and 22·8% for mastectomy with or without radiotherapy, respectively. In our study, IBTR was 3·23% in patients with mastectomy (half of them having node negative disease and 25% receiving radiotherapy).
For BCS, the EBCTCG overview reported 5-year isolated breast recurrence rates of 6·7% for node negative patients with radiotherapy, and 11·0% in patients with node positive disease.[14] In our patients, the IBTR rate was 1·96% with 98% of patients receiving radiotherapy. The authors of the EBCTCG overview already stated that it is reasonable to assume that future patients might have lower recurrence rates than recorded in these trials, due to advancements in screening, surgery, pathology, radiotherapy, and systemic therapy.[15] This is confirmed by our results and might also explain the decreasing trend in IBTR that we found, although we were not able to examine the effects of treatment on IBTR.

Hospitals varied in overall IBTR rates from 0.82% to 5.40%. Hospital variation was considerably higher for mastectomy than for BCT (0 to11.6% and 0 to 5.2%, respectively). The upper limit for acceptable IBTR (5% 5 years after diagnosis) as defined by a working committee in 2006 and derived from EUSOMA guidelines published in 2001 was achieved in our study by almost all hospitals.[8,13] Studying the IBTR rate per hospital by using funnel plots, we accounted for the role of chance by visualising 95% confidence intervals around the target value of 5%. The influence of chance is still considerable given the wide confidence intervals, especially in low

volume hospitals. We conclude that this outcome indicator is not suitable for comparing results between hospitals, for the numerators and denominators are too low, even when data on four consecutive years are available.

A limitation of this study lies in the limited follow up period of five years. This can be viewed as to short to detect all IBTR. Approximately three-quarters of all IBTR are diagnosed within five years after initial diagnosis[14]. Late recurrences (after five years) are more often new primary tumours that are associated with better prognosis[19,20]. However, the indicator aims to measure the optimal local control of the diagnosed cancer, so true recurrences (mostly within five years) are of more interest than second primary breast cancers. Furthermore, we did not adjust for confounding by patient and tumour characteristics. Case mix correction is of importance when interpreting hospital variation in outcome indicators[12,21]. However, with the small numbers of patients and a low IBTR rate, case mix correction is problematic, especially given the multiple predictors needed, each with low or moderate predictive values. The major strength of our study is the large, population based cohort including all breast cancer patients diagnosed over a period of four consecutive years in 80 hospitals within the Netherlands. Furthermore, registration by NCR registrars based on a strict coding manual minimizes registration bias.

In concluding IBTR rate is not a suitable outcome indicator for comparing care between hospitals, the question rises how the quality of care should be compared. Process indicators hold major advantages over outcome based monitoring; process indicators 1) focus on violation of agreed standards in specific subgroups of patients, minimizing the need for case mix adjustment, 2) are measured close to the point of delivery of care, and therefore enable quick responses to improve care and 3) pinpoint the target for action as action is inherent in the measurement itself.[6,16] A possible process indicator to be inspected in more detail is the proportion of patients receiving BCS in early breast cancer. We observed substantial variation between hospitals from 16% up 80% of patients with BCS as final surgery. Comparable variation (from 30% up to 80% BCS) has been described earlier for patients with node negative breast cancers up to five cm in the Netherlands over the same period.[17] This variation is higher than previously described variation in the UK, varying from 55% up to 75%.[18] And although the choice between BCS or mastectomy is not based on the efficacy of treatment, variation can be considered as undesirable from other perspectives of quality of care (e.g. least invasive treatment or best cosmetic result). The large variation suggests there might be room for improvement and calls for further research to elucidate underlying causes.

Our findings show that ipsilateral breast tumour recurrence rates are low and still improving. This outcome indicator is of interest on a national level for international comparison, but is not suitable for comparing hospital quality of care within the Netherlands.

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Chapter 8

Variation between hospitals in surgical margins after first breast-conserving surgery in the Netherlands

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Abstract

Background

Surgical margin status after first breast conserving surgery (BCS) is used as a quality indicator of breast cancer care in The Netherlands. The aim is to describe the variation in surgical margin status between hospitals.

Patients and methods

7,345 patients with DCIS or invasive cancer (T1-2,N0-1,M0) diagnosed between July 1, 2008 and June 30, 2009, who underwent BCS as first surgery, were selected from the Netherlands Cancer Registry. Patients were treated in 96 hospitals. Maximum target values were 30% 'focally positive' or 'more than focally positive' for DCIS and 10% 'more than focally positive' for invasive carcinoma. Results per hospital are presented in funnel plots. For invasive carcinoma, multivariate logistic regression was used to adjust for case mix.

Results

Overall 28.5% (95% CI: 25.5-31.4%) of DCIS and 9.1% (95% CI: 8.4-9.8%) of invasive carcinoma had positive margins. Variation between hospitals was substantial. 6 and 10 hospitals respectively for DCIS and invasive cancer showed percentages above the upper limit of agreement. Case mix correction led to significant different conclusions for 5 hospitals. After case mix correction, 10 hospitals showed significant higher rates, while 7 hospitals showed significant lower rates. Rates were not related to breast cancer patient volume or type of hospital (teaching versus non-teaching). Higher rates were related to hospitals where the policy is to aim for BCS instead of mastectomy.

Conclusion

The overall percentage of positive margins in the Netherlands is within the predefined targets. The variation between hospitals is substantial, but can be largely explained by coincidence. Case mix correction leads to relevant shifts.

Introduction

Breast conserving surgery (BCS) is common practice in the treatment of early breast cancer patients. BCS with additional radiotherapy leads to better cosmetic results with equal long term disease free and overall survival compared to mastectomy. In The Netherlands over the period 2003-2006 over 21,000 patients with early breast cancer underwent BCS (63% of stage I and 41% stage II breast cancer).[1]

Surgeons aim to obtain a radical excision of the tumor in BCS, since so called tumor-free margins result in the best local control. The size of the lump is a balance between cosmetic aspects and completeness of surgery: a wider excision than needed leads to a worse cosmetic result, but a too narrow excision may leave residual tumor tissue. Incomplete resections lead to additional surgical procedures (either BCS or mastectomy), which implicate extra burden on the patient and extra costs.
The surgical margins of the excised lump of BCS are examined by a pathologist according to protocols. The amount of cancer that could have been left in the breast is estimated. Based on Dutch breast cancer treatment guidelines, the pathologist distinguishes 'clear' margins (tumor not touching the inked surface of the lump), 'focally positive' margins (one or two foci of tumor touching ink; less than 4 mm) and 'more than focally positive' margins. Margin status determines the further steps needed in adequate local treatment. All patients with BCS (DCIS and invasive cancer) receive additional radiotherapy, but the indication for re-excision varies for patients with DCIS or invasive cancer. Patients with DCIS undergo re-excision in case of 'focally positive' or 'more than focally positive' margins, while patients with invasive cancer undergo re-excision only in case of 'more than focally positive' margins. In case of 'focally positive' margins, local control is (in most cases) supposed to be achieved by more radiotherapy including a boost dose on the tumor bed.[2]

The percentage of patients with positive margins is used as a quality indicator of breast cancer care that all hospitals have to report to the Dutch Health Care Inspectorate annually since 2007.[3] The target value to be achieved is 10% for DCIS and invasive carcinoma combined. The current Dutch breast cancer treatment guidelines state that surgeons should strive for a maximum of 20% 'more than focally positive' margins in patients with invasive carcinoma and 30% 'focally positive' or 'more than focally positive' margins in patients with DCIS.[2]
Apart from the discussion on the agreed target value, there is the issue of comparability of data provided by hospitals due to registration artifacts (such as case selection and the multi-interpretability of 'positive margin' when combining DCIS and invasive tumors) and case mix differences between hospitals.[4,5]

In 2008 the Netherlands Cancer Registry (NCR) started the collection of information on margin status after the first BCS aiming to provide comparable and population-based data on all breast cancer patients in The Netherlands, including information on case-mix. This study describes the variation between hospitals in surgical margins after first breast conserving surgery (BCS) in patients with DCIS or early breast cancer in The Netherlands.

Methods

Study population

All female early breast cancer patients (DCIS and invasive carcinoma T1-2, N0-1, M0; LCIS not included) who underwent BCS in the period July 1, 2008 to June 30, 2009 were selected from the Netherlands Cancer Registry (NCR). Patients who received neo adjuvant systemic therapy were excluded.

The NCR is a population based cancer registry, collecting incidence data on a national level. PALGA, the Dutch network and registry of pathology, notifies the NCR of all newly diagnosed malignancies. Following this notification, trained NCR personnel collect data on diagnosis, staging and treatment from hospital records, including pathology and surgery reports. Primary treatment is coded in sequence of administration, and patients are staged according to the TNM system of the International Union Against Cancer.[6]

We extracted information on patient characteristics (age), tumor characteristics (histological subtype, grade, localization, multifocality, TNM stage, tumor size) and treatment characteristics (neo adjuvant treatment, surgical treatment, radiotherapy, surgical margin status after first BCS and hospital of treatment).

Classification of surgical margins

Coding of the surgical margin status was based on the most recent Dutch diagnostic and treatment guideline for breast cancer.[2] The guideline defines how pathologists should assess surgical margin status after breast conserving surgery (BCS) and subsequently what information should be included in their report. The classification of surgical margins in the Dutch breast cancer guideline defines 3 categories: clear surgical margins (no tumor cells in the inked surface of the resection), 'focally positive' margins (tumor in a limited area of the inked surface, i.e. one or two foci of tumor, maximum of 4mm) and 'more than focally positive' margins. In records with unclear or missing information, the margin status was coded as 'unknown'. The assessment of tissue from following procedures was not used in the classification of the margin status after the first BCS.

Classification of hospitals

Classification of hospitals was based on the hospital where surgery was performed. All Dutch hospitals (96) were included. Two types of hospitals were defined: 42 non-teaching hospitals, 54 teaching or academic hospitals (including one specialized oncology centre). Hospital volume was based on the number of breast cancer patients with BCS as the first surgery, and two groups were defined: less than 50 BCS/y (33 hospitals), 50 BCS/y or more (63 hospitals). The percentage of BCS in a hospital was calculated by dividing the number of patients who underwent a BCS as first surgery, by the total number of patients with DCIS or invasive carcinoma T1-2,N0-1,M0 who received surgery in that hospital. Hospitals were categorized into two groups; less than 70% BCS (66 hospitals) and 70% BCS or more (30 hospitals).

Quality indicator targets

All results are presented separately for DCIS and invasive breast cancer. Patients with invasive tumor and DCIS component(s) are included in the invasive group. For invasive cancer positive margins were those classified as 'more than focally positive' with a target value of 10%, based on the targets set by the Dutch Health Care Inspectorate. For DCIS we defined positive margins as margins that were classified by pathologists as 'focally positive' or 'more than focally positive' with a target value of 30% based on the breast cancer guideline.

Statistical analyses

The proportions of positive margins per hospital are presented in funnel plots. The funnel plot presents the target with its 95% confidence limit that varies in relation to the population size.[7] We also computed the number of hospitals with percentage of positive margins outside the limits of agreement at various target values (10%, 20% and 30% for DCIS; 10% and 20% for invasive cancer). Patients with unknown surgical margins (2.7%) were excluded in univariate and multivariate analysis.

For case mix correction in invasive cancer, we first selected risk factors of positive margins using univariate logistic regression. These factors were based on literature and included: age, tumor size, nodal status, multifocality and histological subtype.[8-11] Significant factors were included in a multivariate logistic regression model to determine the mutually independent factors. Subsequently, the obtained coefficients were used to predict for each individual the risk of positive margins based on her set of risk factors. Next, for each hospital the expected percentage of patients with positive margins was assessed based on their specific case mix (E). Then, the observed percentage (O) was divided by the expected value (E) and multiplied by the overall mean (9.1% for invasive cancer, O/E * mean) to obtain the case mix adjusted percentages. These for case mix adjusted percentages of patients with positive margins are presented per hospital in a funnel plot.

To explore characteristics of hospitals with percentages above and under the limits of 10% positive margins, these hospitals were compared to the others on type of hospital, the number of breast cancer patients with BCS as first surgery per year, and the percentage of breast cancer patients who received BCS as first surgery. Differences were tested using Fisher's Exact test.

Analyses were performed in STATA and SPSS (multivariate logistic regression).

Table 1. Patient and tumor characteristics of 7345 early breast cancer patients with BCS as first surgery

	DCIS	Invasive (+/- DCIS)	Total
	N (%)	N (%)	N (%)
Age			
< 50	151 (16.0)	1,302 (20.3)	1,453 (19.8)
50-69	649 (68.7)	3,917 (61.2)	4,566 (62.1)
>=70	145 (15.3)	1,181 (18.5)	1,326 (18.1)
Invasive tumor size			
<=10 mm	n.a.	1,807 (28.2)	
10-20 mm		3,220 (50.3)	
20-30 mm		1,131 (17.7)	
30-40 mm		202 (3.2)	
40-50 mm		40 (0.6)	
Nodal status			
N0	940 (99.5)	4,697 (73.4)	5,637 (76.7)
N ITC	5 (0.5)	240 (3.8)	245 (3.3)
N micro	0 (0.0)	438 (6.8)	438 (6.0)
N+	0 (0.0)	1,025 (16.0)	1,025 (14.0)
Stage			
0	945 (100)	0 (0.0)	945 (12.9)
1	0 (0.0)	4,071 (63.6)	4,071 (55.4)
2A	0 (0.0)	1,819 (28.4)	1,819 (24.8)
2B	0 (0.0)	510 (8.0)	510 (6.9)
Multifocality			
Unifocal	823 (87.1)	5,712 (89.3)	6,535 (89.0)
Multifocal	65 (6.9)	636 (9.9)	701 (9.5)
Unknown	57 (6.0)	52 (0.8)	109 (1.5)
Histology			
Ductal	817 (86.5)	5,238 (81.8)	6,055 (82.4)
Lobular	excluded	581 (9.1)	581 (7.9)
Mixed ductal/lobular	19 (2.0)	186 (2.9)	205 (2.8)
Tubular	0 (0.0)	93 (1.5)	93 (1.3)
Mucinous	0 (0.0)	117 (1.8)	117 (1.6)
Medulary	0 (0.0)	62 (1.0)	62 (0.8)
Papillary	73 (7.7)	69 (1.1)	142 (1.9)
Paget's disease	15 (1.6)	8 (0.1)	23 (0.3)
Other	21 (2.2)	46 (0.7)	67 (0.9)

Results

A total of 7,345 patients who underwent BCS were identified in the period July 1, 2008 and June 30, 2009 in the Netherlands. BCS was performed in all 96 hospitals. Mean age at diagnosis was 59 years. 945 patients were diagnosed with DCIS (12.9%). 82% of all lesions were of ductal type, and over 75% of women had lymph node negative disease (table 1).

The surgical margin status was known for 7,146 patients (97.3%) (table 2). Overall, 9.5% of all resections margins were classified as 'focally positive' while another 10.0% showed 'more than focally positive' margins. These percentages were higher in patients diagnosed with DCIS than in patients with invasive cancer (table 2). The percentage of women with 'unknown' margin status varied substantially between hospitals (0 - 9.4%, data not shown).

Table 2. Surgical margin status after initial BCS for 7,345 breast cancer patients

	DCIS	Invasive (+/- DCIS)	Total
	N (%)	N (%)	N (%)
Clear margins	641 (67.8)	5,075 (79.3)	5,716 (77.8)
Focally positive margins	108 (11.4)	591 (9.2)	699 (9.5)
More than focally positive margins	147 (15.6)	584 (9.1)	731 (10.0)
Unknown or inconclusive	49 (5.2)	150 (2.4)	199 (2.7)

The proportion of patients with positive margins varied substantially by hospital. For DCIS the mean proportion 'focally positive' or 'more than focally positive' margins was 27% and ranged between 0 and 100%. Most of this variation could be due to coincidence as a result of the low number of DCIS in each hospital (1 to 34 patients). The results of 88 hospitals (92%) fit within the limits of agreement of the proposed 30% target (figure 1): 6 hospitals showed higher, and 2 lower percentages of positive margins. If a target of 20% or 10% is used, 17 and 43 hospitals respectively would fall outside the agreement limits (all too high).

For invasive tumors the mean proportion of 'more than focally positive' margins was 9.1%, with less variation between hospitals (0% to 30%), due to more stable estimates based on larger numbers of cases operated per hospital (between 10 and 173 patients). For 80 hospitals (87%) results fit within the limits of agreement at the proposed target of 10% 'more than focally positive' margins. 10 hospitals showed statistical significant higher percentages, while 6 hospitals showed statistical significant lower percentages (figure 2). When the target of 20% was applied, no hospitals had higher proportions than the limits of agreement around this target, and 50 hospitals (52%) had significant lower percentages.
None of the hospitals had higher proportions of positive margins for both DCIS and invasive tumors.

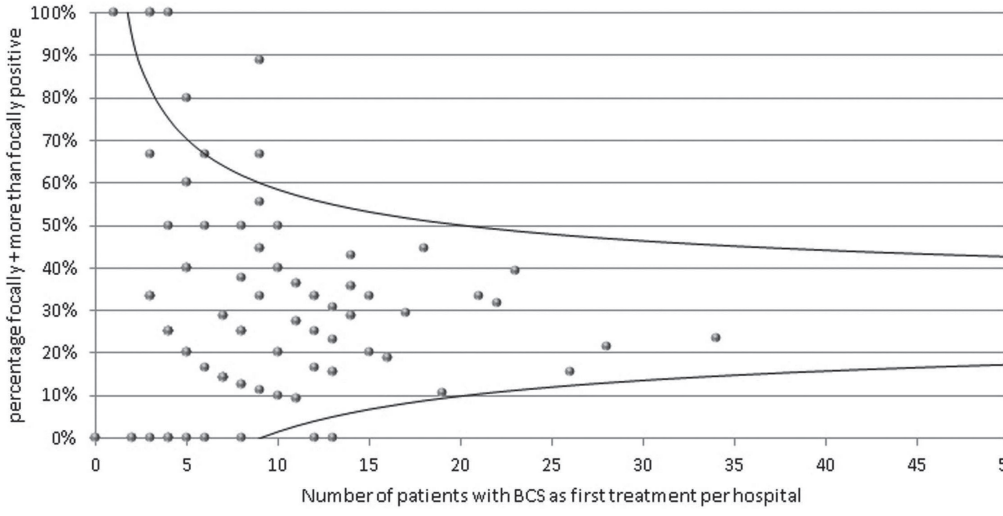

Figure 1. Funnel plot with proportion 'focally positive' or 'more than focally positive' margins after initial BCS by hospital for DCIS

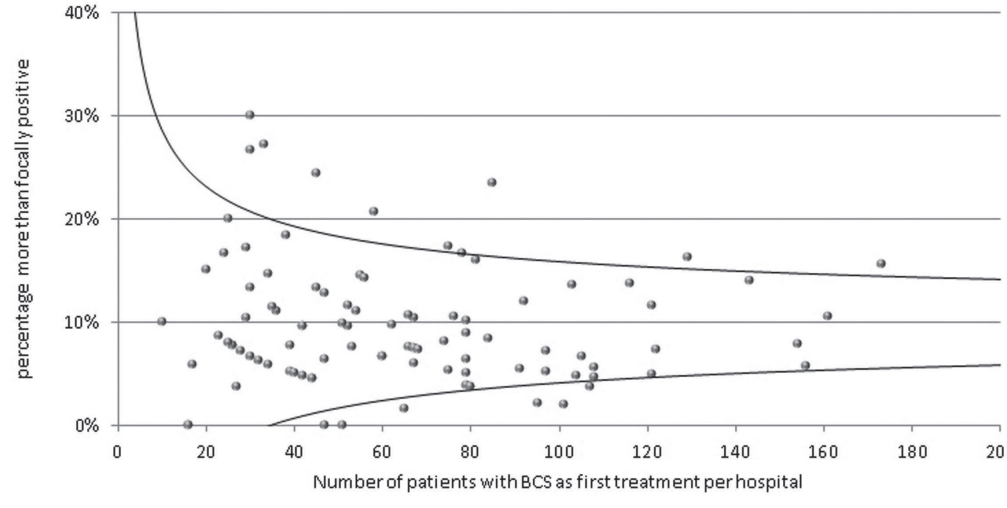

Figure 2. Funnel plot with proportion 'focally positive' or 'more than focally positive' margins after initial BCS by hospital for invasive tumors

Risk factors for positive margins and correction for case mix

For DCIS, multifocality was associated with a significant higher rate of positive margins (52% versus 26%) (table 3). Case mix correction for the percentage of positive margins in DCIS treatment was not possible due to limited numbers per hospital.

For invasive tumors, characteristics that were associated with higher rates of positive margins in univariate analyses were younger age, larger tumors, nodal involvement, multifocality, and a

Table 3. Univariate analyses with risk factors for positive margins after initial BCS

	DCIS			Invasive (+/- DCIS)		
	N	focally positive + more than focally positive (%)	P	N	more than focally positive (%)	P
Age						
< 50	141	46 (32)		1,274	138 (11)	
50-69	618	172 (28)		3,816	354 (9)	
>=70	137	37 (27)	0.481	1,160	92 (8)	0.048
Invasive tumor size						
<=10 mm		n.a.		1,760	181 (10)	
10-20 mm				3,153	242 (8)	
20-30 mm				1,101	117 (11)	
30-40 mm				197	37 (19)	
40-50 mm				39	7 (18)	0.000
Nodal status						
N0	891	253 (28)		4,590	385 (8)	
N ITC	5	2 (40)		236	33 (14)	
N micro				433	53 (12)	
N+			0.566	991	113 (11)	0.000
Multifocality						
Unifocal	783	203 (26)		5,597	454 (8)	
Multifocal	63	33 (52)		612	123 (20)	
Unknown	50	19 (38)	0.000	47	7 (15)	0.000
Histology						
Ductal	778	229 (29)		5,123	439 (9)	
Lobular		excluded		557	79 (14)	
Mixed ductal/lobular	18	5 (28)		182	29 (16)	
Other	100	21 (21)	0.212	388	37 (10)	0.000
Tumor grade						
1		n.a.		1,740	143 (8)	
2				2,686	249 (9)	
3				1,582	146 (9)	0.442

lobular or ductolobular histological type (table 3). Multivariate results are shown in Table 4. The obtained coefficients from the multivariate analyses were used to perform case mix correction for invasive cancers. This slightly affected the observed estimates. In 5 hospitals (8.3%) case mix correction altered the conclusion on whether the proportion of positive margin status was outside the limits of agreement. For 3 hospitals the adjusted percentage was lower than the uncorrected (two hospitals into and one under the limits of agreement) and for 2 hospitals the adjusted percentage was higher after case mix correction (both above the limit of agreement) (figure 3). The net result is that 10 hospitals showed positive margin rates significant higher than 10%, while 7 hospitals showed significant lower rates.

Hospitals with significant higher positive margin rates frequently had a high percentage first BCS (6 hospitals out of 33 compared to 6 out of 66; p=0.05), but did not differ on other hospital characteristics (type of hospital and number of BCS per year). Hospitals with significant lower positive margin rates treated more often over 50 patients with BCS per year (7 hospitals out of 63 compared to 0 out of 33; p=0.05), and did not differ on other characteristics.

Table 4. Multivariate analyses with risk factors for 'more than focally positive margins' in invasive tumors after initial BCS

	OR (95% CI)	
Age		
<50	1.0 (ref)	
50-70	0.88 (0.71-1.09)	
>=70	0.74 (0.55-0.98)	*
Size		
<=10 mm	1.0 (ref)	
11 - 20 mm	0.68 (0.55-0.83)	*
21 - 30 mm	0.94 (0.72-1.21)	
31 - 40 mm	1.71 (1.14-2.57)	*
41 - 50 mm	1.50 (0.64-3.54)	
Nodal status		
N0	1.0 (ref)	
N ITC	1.61 (1.09-2.38)	*
N micro	1.48 (1.08-2.02)	*
N+	1.28 (1.02-1.62)	*
Multifocality		
Unifocal	1.0 (ref)	
Multifocal	2.72 (2.18-3.40)	*
Unknown	1.92 (0.85-4.33)	
Histologic subtype		
Ductal	1.0 (ref)	
Lobular	1.72 (1.32-2.24)	*
Ductal + lobular	1.74 (1.14-2.65)	*
Other	1.16 (0.81-1.66)	

* statistically significant (P<0.05)

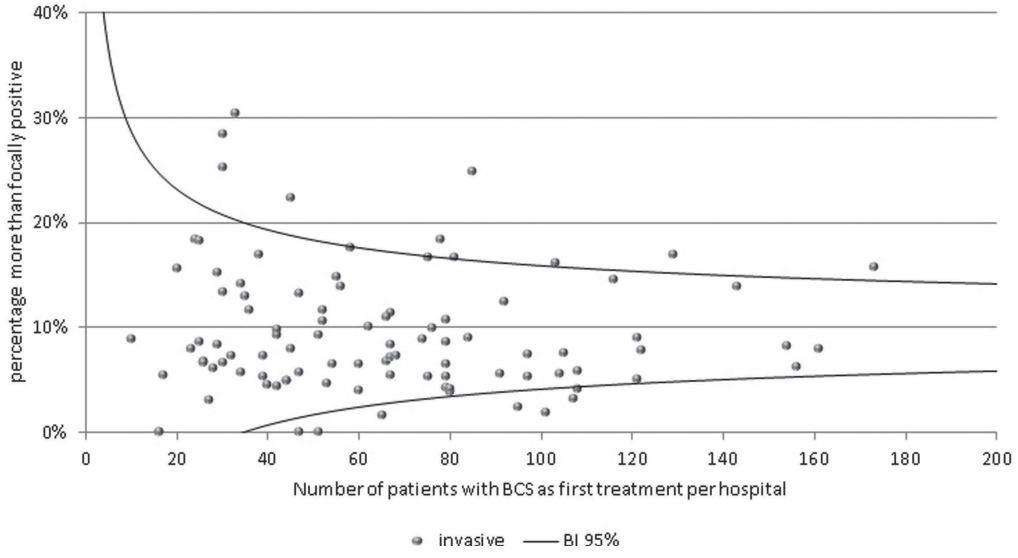

Figure 3. Funnelplot with proportion 'more than focally positive margins' after initial BCS for invasive tumors by hospital, after correction for age, tumor size, nodal status, multifocality and histological subtype

Discussion

The percentage of breast cancer patients with positive surgical margins after a first breast conserving surgery in the Netherlands is approximately 30% for women with DCIS and 10% for early invasive cancers. These patients need a second surgical intervention, leading to additional costs, extra burden on the patient and a poorer cosmetic result. We found substantial differences between hospitals that were larger for DCIS than for invasive cancer. The differences were largely attributed to coincidence due to relatively low numbers of breast cancer cases treated in each hospital. However, taken into account random variation and case mix correction for invasive cancer, the percentages of positive margins were above 30% for DCIS and 10% for invasive cancers for 6 and 10 hospitals, respectively. None of the hospitals had a percentage of positive margins above the limit of agreement for both DCIS and invasive cancers.

Questions have been raised about the comparability of data on surgical margins after BCS between hospitals.[3-5] Our study has the advantage that data were collected by trained personnel of the cancer registry directly from the medical records of patients. Personnel was instructed on coding, following the Dutch diagnosis and treatment guidelines for breast cancer, with clear instructions on how to code in case of inconsistent information, additional information from re-excisions and the in- and exclusion of cases such as LCIS. However, if the source information is not comparable, for example due to differences in scoring by pathologists, this cannot be solved by trained data collectors. We observed considerable variation in percentage of cases

with missing data on margin status between hospitals, ranging from 0 up to 9.5%. Unknown margin status was coded for various reasons; 'true unknown' (tissue could not be assessed, for instance because it was presented in various lumps, without adequate marking) or unclear definition by the pathologist. All cases with unknown margin status were excluded in further analyses. However, this information would be of additional value when assessing the quality of care of a hospital.

In our study we lack information on the presence of a DCIS component in the case of invasive breast cancer. Our study showed that DCIS leads more often to incomplete resections than invasive tumors. Therefore, adding this information to the case mix adjustment could improve the comparability of hospitals. Furthermore, a recent study showed that prediction models for margin status in DCIS had very large unexplained differences between surgeons, whilst controlling for detailed clinical and nonclinical factors.[12] In our study, we were not able to assess outcome on the level of individual surgeons.

Definition of margin status

Comparing data between hospitals asks for unambiguous definitions. Firstly, the definition used by the Dutch Health Care Inspectorate is problematic because it combines DCIS and invasive tumors. Complete resection rates of these lesions differ considerably even in highly qualified surgeons, and this is due to the specific biological behavior of DCIS. The observed result on hospital level would be highly determined by the proportion of DCIS diagnosed and treated in that hospital. The quality indicator should therefore be computed separately for invasive and non-invasive lesions.

Secondly, the definition of 'positive margins' differs between DCIS and invasive tumors. The focus of this quality indicator is the proportion of patients that needs to undergo further surgery after a first BCS. The clinical significance of the need for re-excision lies in the subsequent local recurrence and mortality rates, which is also influenced by tumor and patient characteristics.[13] The criteria determining the indication for re-excision differ between DCIS and invasive cancer. For invasive cancer, the clinical importance of re-excising tumors with only focally involved margins in invasive breast cancer is disputable.[11,13-17] The Dutch treatment guideline (2008) advises only re-excision in patients with 'more than focally positive' margins. Hence the latter definition was used to classify the proportion of patients with invasive cancer having a 'positive margin'. In contrast, for DCIS 'focally positive margins' are not acceptable and associated with a risk of local recurrence. In current literature, the most accepted definition for true clear margins for DCIS is a margin threshold of 2 mm between the lesion and the inked surface.[11,18] The Dutch treatment guideline advises to re-excise all patients with tumor in the inked surface and to strive for a macroscopic margin threshold of 10 mm at surgery. In our study, we did not collect data on the margin threshold, but used the presence of tumor in the resection surface (either focally or more than focally) as the quality indicator 'positive margin'.

Funnel plots in interpreting hospital data

The funnel plots clearly show the large influence of randomness on the estimates when these are based on small numbers of patients: the confidence interval around the target value

becomes very wide. In case of small numbers, only extreme deviations of the target will be detected as 'abnormal', and a large variation of measured values will fit within the confidence intervals. As such, in itself surprising values have to be accepted as 'in agreement with the target value'. Conversely, funnel plots also show the inappropriateness of using a crude value of 10, 20 or even 30 % as a quality parameter, for a lot of incorrect accusations to hospitals will be the consequence if the 95% limits of agreement are not taken into account. This may cause hospitals and individual surgeons taking wider excisions or conducting more mastectomies to strive for much lower percentages, which would be an undesired side effect of a quality indicator that focuses on optimizing the current use of BCS.

Risk factors for positive margins and case mix correction

When comparing surgical care between hospitals, case mix correction is important to improve the comparability of data. Hospitals with less favorable patient populations improve after case mix adjustment. Univariate logistic regression showed that age, tumor size, nodal status, multifocality and histological subtype influence the risk of positive margins. We adjusted for these characteristics through case mix correction for invasive tumors.

In 5 hospitals, the case mix adjustment led to a different conclusion on whether the observed outcome was within the limits of agreement. This demonstrates the relevance of adjustment for case mix factors. However, case mix correction requires data analysis on record level for all hospitals combined. With current methods of generating data for quality indicators by hospitals themselves, it is not possible to introduce case mix correction in the Dutch system. This calls for an independent organization, like the cancer registry, to collect and analyze these data and adjust for case-mix.

The hospitals scoring above the limit of agreement had more frequent a high percentage of first BCS (>=70%). This might indicate differences in technical approach of surgeons in these hospitals. Hospitals scoring under the limit of agreement were all hospitals treating more than 50 patients with BCS per year. Both findings were borderline significant (p=0.05). Further research is needed, in which information on the level of individual surgeons may add valuable information.

Combining quality indicators

The clinical relevance of this quality indicator lies in optimizing the quality of BCS by minimizing additional costs due to re-operation, minimizing burden on the patient and improving cosmetic result. Others have suggested using re-resection rates or the number of operations needed for removal of the tumor as a quality indicator.[19,20] Also, for understanding the treatment results on hospital level, we should have insight in the additional treatment for patients with positive margins.[12,21] Combining these indicators would give a more comprehensive insight in adequate treatment.

We conclude that quality of care outcomes on hospital level should be interpreted separately for DCIS and invasive tumors. In addition, the limits of agreement should be taken into consideration for example by using funnel plots. Lastly, results without case mix correction should be interpreted with caution.

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Chapter 9

General discussion

The studies presented in this thesis show that in the Netherlands the overall quality of surgical breast cancer care is high. Ipsilateral breast tumour recurrence rates are low (1.96% and 3.23% for breast conserving surgery (BCS) and mastectomy, respectively; chapter 7), and disease free survival in early breast cancer is high (89.9% 5-year disease free survival; chapter 5). These conclusions are in line with earlier reports on the quality care and guideline adherence in breast cancer.[1-4]
Measuring the quality of care comes with several challenges in defining criteria, designing adequate tools for measuring and interpreting the results.

Defining performance indicators

Tools to measure quality of care are called performance indicators. An adequate performance indicator is preferably based on scientific evidence. An indicator has to be reliable, valid and it needs to yield meaningful information.[5] Performance indicators are often classified as (a) 'health care structure'-related (b) process related or (c) patient-related health outcome.[6]

(a) Structure related indicators focus on the presence of adequate facilities, equipment and qualified personnel. Structure indicators are usually easy to measure. They are based on the assumption that given the proper setting of care, good medical care will follow as a consequence. However, although they are a prerequisite for high quality of care, it is not self-evident that adequate facilities automatically imply high quality of care.

(b) Process related indicators measure elements of the process of care. They focus on violation of agreed standards. There are three types of process indicators:[7]
- Those that are 'Problem solving'- process indicators: they relate to the strategy that needs to be followed to obtain adequate results, e.g. is all pathological information available?
- Those that are 'Procedural'- process indicators: they refer to the actual steps taken in order to achieve the result aimed for, e.g. were all therapies given as planned?
- Interim result indicators: they refer to intermediate results during the diagnosis or treatment process, an example is: was all tumour tissue removed during the first breast conserving surgery?

Process indicators are often easily accepted by professionals, because they focus on clearly defined aspects of care. An additional benefit is the short period of time between the delivery of care and the measurement of the indicator, making quick changes possible to improve care. This is not possible for several health related outcome indicators such as 5-year overall survival rate. A drawback to process indicators is that they are very specific and need extensive standardized registration. This may interfere with daily practice and become cumbersome.

(c) Outcome indicators measure an important health status in the treated patient, such as survival, disease recurrence or functional restrictions. Outcome indicators are rarely questioned as a valid tool to measure quality of care and measurement appears unambiguous and fairly easy. However, using outcome indicators to compare hospitals is complex. The observed

variation between hospitals is not only a result of differences in quality of care, but differences also result due to differences in patient characteristics, registration and random variation (variations in case-mix).[8]

In breast cancer care, numerous performance indicators have been proposed.[9-14] In 2010, the National Breast cancer Organisation the Netherlands (NABON) formulated a set of multidisciplinary breast cancer care indicators for the Dutch care setting. The set includes already wide-accepted indicators (e.g. tumour recurrence and incomplete tumour resections), and newer, less accepted indicators, such as percentage of patients receiving neo-adjuvant therapy in early stage breast cancer. The set entails mainly process indicators focussing on problem solving strategies, procedures and interim results. Most indicators measure aspects of appropriate and effective care, but patient-orientated indicators were added as well (such as waiting times between various treatments) and indicators that measure possible overtreatment (complete axillary lymph node dissection in patients without nodal metastases).
With the development of this well-considered set of indicators, the basis for assessing the quality of care has been set. But not all difficulties concerning measuring and judging the quality of care are solved. Whether a performance indicator can be qualified as 'appropriate' often cannot be predicted based only on theory and existing knowledge. The indicator has to be evaluated based on actual data with respect to feasibility to be measured, reliability of data and the value of the indicator in actual care settings.

Interpreting results

Using indicators to compare care between hospitals and thus judging hospital performance sets additional requirements for the indicators used. Indicators must truly reflect underlying differences in quality of care. And, as stated earlier, variation between hospitals reflects not only differences in the clinical quality of care, but is also caused by random variation, patient characteristics and registration bias. The effect of these aspects has to be taken into account when comparing hospital performance.

Random variation

Measurements will always be affected by the influence of random processes. The amount of uncertainty in the analysis of hospital performance indicators may be especially high if the number of patients is limited and the indicator refers to a relatively rare outcome in these patients. It is important to take this random variation into account when presenting hospital based indicators. A way of doing this is by presenting results in funnel plots, in which the impact of chance can directly be observed.[15] A funnel plot presents the performance indicator for each hospital, ranked according to the volume of the hospital. The funnel lines show the 95% confidence limits at the value of the indicator that is accepted as the target of optimal care. Hospitals that lie outside the confidence interval can be marked as outliers, although multiple testing at a confidence interval of 95% also has its restrictions; when testing 20 providers, one will be identified as 'outlier' based on chance alone.[16,17] The impact of chance is high

when comparing the local recurrence rates after breast conserving surgery and mastectomy (chapters 6 and 7). As an example: half of all Dutch hospitals treated less than 40 patients with mastectomy in 2003. In case of 2, 3 or 4 events, the corresponding recurrence rates are 5.0%, 7.5% or 10.0%. These values may all still represent an underlying true recurrence rate of 5%. We concluded that this indicator is not suitable for hospital comparison due to the low local recurrence rates and the relatively low number of patients per hospital.
The use of funnel plots has also been adopted by the Dutch Institute for Clinical Auditing.[4]

Patient characteristics

Observed variation between hospitals is partly determined by patient and tumour characteristics (case-mix). Patient populations vary between hospitals. It is possible to adjust for differences in patient or tumour characteristics if adequate determinants are known and registered. Case-mix correction should always be considered when comparing outcome indicators.[15] The importance of case mix correction has been demonstrated in measuring cancer care before.[18-21] One of the indicators in breast cancer care is the time between definitive diagnosis of breast cancer and the date of the first surgery. In the Netherlands, one high volume clinic is an important outlier with apparently long waiting times. However, in depth analyses showed that this hospital has many secondary referrals of relatively young patients. Consequently, the use of MRI is high, there are a lot of requests for rapid testing for BRCA-1 and BRCA-2 mutations, measures are taken to preserve fertility, and a large proportion of direct reconstructions takes place. All these factors lead to longer intervals and case-mix correction would improve the comparability of the results between hospitals.[4]
It should be recognized that residual confounding may still be responsible for a part of the observed differences between hospitals, even when case mix adjustment is performed.[7]

Registration bias

Registration bias occurs when different definitions of a performance indicator are used or in case of an incomplete or unreliable data registration. Registration bias can be minimized by a clear and generally accepted definition and by using a detailed (and regularly updated) coding manual. The use of objective and qualified registrars further improve uniform registration.[12]
The introduction of the performance indicator measuring the proportion of patients with incomplete tumour resections at the first breast conserving surgery is a good example of a poorly defined indicator. This seemingly clear-cut indicator was first requested by the Dutch health care inspectorate in 2007, and it led to substantial commotion. First, the selection criteria were ambiguous: the introduction of the indicator stated that the indicator should be computed for patients with DCIS and for patients with invasive carcinoma. But in the specifications, the denominator included ‘all malignant breast tumours’ (which by definition does not include patients who had DCIS only). Second, the definition of ‘incomplete resection’ used in the indicator was not in line with the professional guideline at that time. The indicator defined ‘incomplete resection’ as ‘inked resection surface not clear of tumour and/or excision not radical according to the pathologist’. The relevance of the indicator was seen as a measurement for preventing unwanted re-excisions. However, the guideline at the time distinguished ‘focal’ from ‘more than focal’ tumour in the inked surface, only advising re-excision in patients with

more than focal tumour residue.
The comparability of hospital data to estimate this indicator was openly questioned[22], and it resulted in an in-depth investigation by the health care inspectorate. The report that followed in 2010 concluded that surgical breast cancer care in all hospitals was in line with the requirements set by the health care inspectorate.[3] And although the health care inspectorate concluded that this process demonstrated the usefulness of measuring hospital performance, it also shows the potential harm an indicator can do. These results were made public: hospitals were unfairly blamed by third parties (e.g. health insurance companies) and patients might have been misled by this information while making health care decisions.

The indicator on incomplete tumour resections is still viewed as an important indicator of the quality of surgical breast cancer care by professionals. Since the abovementioned discussion, it has further evolved and the indicator has been split up for patients with only DCIS and patients with invasive breast cancer (with or without concomitant DCIS), with different definitions of incomplete resections for these two groups (in line with treatment guidelines). By doing so, the indicator has reached a level of sophistication that needs continuous explaining on 'how and why' the selections and definitions are made, even for professionals.

Sometimes indicators show substantially larger variation by hospital or by region than can by explained by the performed case-mix correction and chance alone. This phenomenon is called 'over-dispersion' of an indicator. Published results show a large variation between hospitals in the percentage of patients undergoing BCS as first surgery.[23] The percentages vary between hospitals from 30% to 80%. A clear explanation and understanding of this variation is lacking. Currently, this indicator is not included in the NABON set of indicators. This is one way of dealing with over-dispersion (disregarding the indicator). Others are: improving case-mix correction if refinement is possible or analysing results through benchmarking within more homogenous groups.[24] Further research might add valuable information on the quality of care.

Creating meaningful information

In society today, we are used to simplify complex matters. The question 'which hospital provides the best breast cancer care' should preferably result in a clear and seemingly objective list with all hospitals ranked from best to worst, or valued by adding tags showing 'best hospital' or 'reasonable, nearby alternative'.
But ranking of hospitals based on their performance is generally considered inappropriate.[7,25-27] As discussed earlier, results on a single indicator can at best distinguish so-called outliers. Ranking presumes that the hospital ranked 7th is better than the hospital ranked 8th or 10th.
If information on several indicators is combined, this becomes even more troublesome. It is an illusion to presume that it is possible to compute a combined measure with a clear meaning based on various indicators like waiting times, the percentage of incomplete resections and the number of patients operated in a hospital. The results of each indicator need to be quantified and weighed to construct a single end score. The underlying assumptions and calculations that

are set in this process are arbitrary (e.g. are complete resections and waiting times equally important, or is one of more importance?). The relative importance of the indicators will vary for various users of the information created (e.g. the distance to a specialized clinic might be of less importance to young patients).

Recommendations

The observation of Donabedian, as stated in the introduction of this thesis, is still valid: '… the quality of care is a remarkably difficult notion to define'.[6]
The quality of breast cancer care in the Netherlands is generally considered to be high. However, there are and always will be differences in the care delivered, especially regarding more patient-oriented performance indicators. Performance measurement can add valuable information in the continuing process of improving all aspects of care.

NABON breast cancer audit: adding valuable knowledge

The performance indicators that were developed by NABON in 2010 hold great expectations. In 2011, Comprehensive Cancer Centre The Netherlands (CCCNL) and the Dutch Institute of Clinical Auditing (DICA) have jointly started data collection under the umbrella 'NABON breast cancer audit (NBCA)'. This audit will produce substantial new information on the quality of breast cancer care in the Netherlands, as it will give insight in guideline adherence and hospital variation. Continuous feedback systems including benchmarks will aid health care professionals to regularly evaluate processes and treatment decisions. On a national level, the NBCA might show potential areas of quality improvement, gaps in knowledge implementation or identify late adapters. The 2012 analysis on the first 7,000 registered patients showed excellent rates of preoperative diagnosis (in >95% of patients) and complete resections at first surgery for breast conservation (94%) for invasive cancers. Large disparities were identified as well: the use of MRI in invasive breast cancer (3-96%), the use of neo-adjuvant chemotherapy in stage II and III breast cancers (0-60%) and the use of immediate breast reconstruction in mastectomy patients (0-30%). These first data set a good example how this new, complete, well accepted dynamic registry may help to improve breast cancer care.[4]
The use of the data that are currently being generated needs to be well considered. Information will often be taken at face value. As we discussed, not all indicators are suitable for hospital comparison. The responsibility to ensure appropriate use lies with all parties involved.

Keep on moving

Registration of indicators is costly and time-consuming, and it should be deployed wisely. Redundant indicators should be disregarded. Dropping indicators that were accepted by the majority of hospitals will be challenging, for there will always be 'late adapters'. However, many factors influence the implementation of changes in care. If feedback-information has not yet resulted in the required changes, it is unlikely that repeating the same message will lead to improvement. If changes are needed (i.e. because the quality of care is not optimal), other incentives might be more effective. Professionals need to find a way to convince the so called

'late adapters'. And while doing so, the majority of hospitals and professionals should move, and focus on a new horizon to keep on improving breast cancer care.

Keep on improving

The process of improvement can be visualised as a continuous cycle, often visualised as the plan–do–study–act cycle.[28,29] New evidence incorporated in guidelines needs to be implemented and new perspectives on existing care should be explored.

The most recent update of the breast cancer treatment guideline was published in February 2012. The update has not yet resulted in a definition of new indicators by NABON. However, new recommendations in the guideline (e.g. on the use of MRI in diagnosis or the treatment of the axilla in patients with only ITC or micrometastases in sentinel nodes) can provide the basis for new performance indicators in near future.

An example of changing perspectives on existing care was recently published by Krekel et al.[30] Instead of focussing on the percentage of incomplete resections after first breast conserving surgery, they evaluated the size of the lump that was removed by the surgeon. The authors concluded that on average a 2 to 4-fold amount of excessive breast tissue was removed in breast conserving procedures, whilst still one out of five resections was not complete. The authors stated that introducing ultrasound-guided surgery for non-palpable breast cancer can improve both the proportion of complete resections and the volume of the excisions.

By repeating the continuous cycle of improvement and making full use of the potential of the NBCA, breast cancer care can be further improved over the coming years.

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Summary

Breast cancer is the most common cancer in women. It is a major healthcare issue; for patients, physicians and the health care system in general. The quality of breast cancer care is of great importance to all involved. Measuring the quality of care is complex. Tools for measuring quality of care are called indicators and many indicators are derived from professional knowledge on the best treatment. Breast cancer treatment focusses on optimal local control, examining lymph node involvement and assessment of the risk of distant metastases.

Part 1 of this thesis focusses on the implementation of sentinel node biopsy (SNB) as an innovation in examining lymph node involvement in breast cancer patients. The Dutch national guideline for the use of SNB was published in 1999. In **Chapter 2** an overview is given on the implementation of SNB in early breast cancer in The Netherlands based on data from the Netherlands Cancer Registry (NCR). Overall, 25.7% of patients underwent SNB alone, 19.1% underwent SNB and ALND, 50.0% had ALND alone and 5.2% had no axillary surgery. SNB was more common in women who underwent breast-conserving surgery (BCS) than in patients who underwent mastectomy ($p < 0.0001$). The proportion of women who received SNB alone or in combination with ALND increased over the period 1998–2003, from 2.1% to 45.8% and from 6.7% to 24.8%, respectively. In 2003, 70.6% of early breast cancer patients in the Netherlands received SNB, and within this group, 64.9% of patients underwent SNB as the final axillary surgery. We showed marked differences in the patterns of dissemination of the use of SNB between regions: by 2003, the difference between the regions with the highest and lowest proportion of use was 25%.

One critical element in introducing SNB is the cooperation between departments of surgery, nuclear medicine and pathology. Seven hospitals in the Utrecht region jointly developed local SNB protocols. Treatment results for all hospitals were monitored in a registration study, in which all patients with a tumour-free sentinel node or a sentinel node containing only micrometastases were included. **Chapter 3** presents the results from this study. Between January 2002 and December 2003, 541 patients were included (503 and 38 with node negative and micrometastatic axilla, respectively). During the follow-up period three patients were diagnosed with axillary recurrence, and one patient had a combined local and regional recurrence. Distant metastases occurred in 23 patients. Results were not significantly different for patients with node negative and micrometastatic sentinel nodes. Results were in line with findings in other studies. It was concluded that SNB was a reliable method of staging in the Utrecht region.

With the introduction of SNB, pathologists started to receive only a couple of lymph nodes for investigation. **Chapter 4** examines whether the use of SNB as staging method led to upstaging of patients with respect to their final axillary status. For this study, we used population based data extracted from the Utrecht region of the NCR. Overall, a quarter of all patients over the period 1997-2002 underwent SNB as method of lymphatic staging. The use of SNB in the Utrecht region increased rapidly over time: from 2% in 1998 to 65% in 2002. The percentage

node positive patients also rose significantly; before introduction of the SNB, 30% of all patients were diagnosed with positive lymph nodes. After SNB introduction this percentage was 40%. The increase was largely explained by the increase of patients diagnosed with only micrometastases (1% and 8% in ALND and SNB, respectively). Adjustment for year of diagnosis, age at diagnosis and tumour size did not change the results. We concluded that the introduction of SNB as axillary staging method led to significant upstaging of breast cancer patients.

Chapter 5 examines the prognosis of patients with isolated tumour cells (ITC) and micrometastases and studies the effect of adjuvant systemic therapy in these patients. Data from 18,748 patients with node negative disease, ITC or micrometastases were analysed. The primary endpoint was 5-year disease-free survival (locoregional recurrence, distant metastases or contralateral breast cancer).
Five-year disease-free survival was 89.9% (95% CI 89.5–90.4). After adjusting for prognostic factors (including treatment), patients with ITC had comparable risks as node negative patients (HR=1.12; 95% CI 0.87–1.43), whilst patients with micrometastases had a 38% higher risk (HR=1.38; 95% CI 1.13–1.69). Considering the already high disease-free survival in these patients, we were reluctant to advise chemotherapy in all patients with micrometastases. In future, it is likely that genomic primary tumour characteristics will tell more about the propensity of dissemination from the primary cancer rather than the status of the axillary lymph nodes.

In **Part 2**, studies are presented in which indicators are used to compare surgical breast cancer care between hospitals. As a means of quality assurance, all Dutch hospitals are obliged to report their 5-year ipsilateral breast tumour recurrence (IBTR) rate after breast cancer surgery to the Dutch Health Care Inspectorate since 2009. In **Chapter 6**, we present the outcome of this indicator for all patients diagnosed in 2003 based on data collected by the NCR. IBTR rates were calculated by Kaplan Meier estimates and presented for all 99 hospitals in forest and funnel plots. Of 9,898 patients, 266 patients had IBTR within the first 5 years after diagnosis. The overall 5-year IBTR rate was 3.03 (95% CI: 2.69-3.41); and 2.63 (95% CI: 2.21-3.12) and 3.50% (95% CI: 2.97-4.13) after BCS and mastectomy, respectively. Large hospital variation was observed (0-17%). In not one hospital an IBTR rate over 5% was found after BCS, and in three hospitals we observed a significantly higher IBTR rate after mastectomy. We concluded that the overall IBTR rate was below the target value of 5% within 5 years. We concluded that this performance indicator is not suitable to detect differences between hospitals with respect to quality of breast cancer care, due to the low average recurrence rate per hospital and the small number of cases treated in each hospital.

Chapter 7 describes the results on the same performance indicator, but now based on data on four consecutive years. We included early breast cancer patients over the period 2003-2006. A total of 31,992 breast cancer patients were treated in 80 Dutch hospitals. The overall 5-year IBTR rate was 2.51% (95%CI 2.23 – 2.71). The IBTR rate was significantly lower for BCS than for mastectomy (1.96 versus 3.23% respectively) and dropped significantly for both groups over time. In 2006 the 5-year IBTR rates were 1.49% and 2.71%, for BCS and mastectomy respectively.

In only one hospital an IBTR rate over 5% was found after mastectomy. The proportion of BCS varied substantially between hospitals (16% to 80%). We concluded that IBTR rates in the Netherlands are low. The indicator is not suitable for comparing quality between hospitals, because of small numbers and the long period of time between treatment and measurement of the indicator. For further quality improvement, we need to focus on more actionable process indicators measuring guideline adherence.

Chapter 8 describes the overall results and hospital variation on the indicator 'irradical excisions after BCS'. We selected 7,345 patients with DCIS or invasive cancer diagnosed between July 1, 2008 and June 30, 2009 and with BCS as first surgery from the Netherlands Cancer Registry. Maximum target values were 30% 'focally positive' or 'more than focally positive' for DCIS and 10% 'more than focally positive' for invasive carcinoma. Results per hospital were presented in funnel plots. For invasive carcinoma, multivariate logistic regression was used to adjust for case mix. Overall 28.5% (95%CI: 25.5 – 31.4%) of DCIS and 9.1% (95%CI: 8.4 – 9.8%) of invasive carcinoma had positive margins. Variation between hospitals was substantial. Six and 10 hospitals for DCIS and invasive cancer respectively showed percentages above the upper limit of agreement. Case mix correction led to significant different conclusions for five hospitals. After case mix correction, 10 hospitals showed significant higher rates, while seven hospitals showed significant lower rates. Rates were not related to breast cancer patient volume or type of hospital (teaching versus non-teaching). Higher rates were related to hospitals where the policy is to aim for BCS instead of mastectomy. We concluded that the overall percentage of positive margins in the Netherlands is within the predefined targets. The variation between hospitals is substantial, but can be largely explained by coincidence. Case mix correction led to relevant shifts.

Chapter 9, the general discussion, addresses the complexity of measuring the quality of breast cancer care, which comes with challenges in defining criteria, designing adequate tools and interpreting the results. With the development of a well-considered set of indicators by the National Breast cancer Organisation the Netherlands (NABON) in 2010, a solid basis for assessing the quality of care has been set. In interpreting the results, it is of importance to realize that variation between hospitals reflects not only differences in the clinical quality of care, but is also caused by random variation, patient characteristics and registration bias. The effect of these aspects has to be taken into account, by using funnel plots, case mix correction and ensuring objective registration based on detailed (and regularly updated) coding manuals. We recommend thorough evaluation on these aspects of all indicators.
Data collection on the indicators developed by NABON started in 2011. By making full use of the potential of the data generated, breast cancer care can be further improved over coming years.

Samenvatting

Borstkanker is de meest voorkomende kanker bij vrouwen. De kwaliteit van zorg is van groot belang voor patiënten, artsen en het gezondheidszorgsysteem in het algemeen. Het meten van de kwaliteit van zorg is complex. Om de kwaliteit te meten wordt gebruik gemaakt van indicatoren die veelal worden afgeleid van professionele standaarden. De behandeling van borstkanker richt zich op optimale lokale controle, het vaststellen van verspreiding van de ziekte naar de regionale lymfeklieren en het maken van een risicoschatting van metastasering op afstand.

Deel 1 van dit proefschrift richt zich op de introductie van de schildwachtklierprocedure (SWK-procedure) als innovatieve methode voor het vaststellen van de verspreiding van de ziekte naar de lymfeklieren in de oksel. In 1999 werd de Nederlandse richtlijn hierover gepubliceerd. **Hoofdstuk 2** geeft een overzicht van de implementatie van de SWK-procedure in Nederland op basis van gegevens uit de Nederlandse kankerregistratie (NKR) over de jaren 1998–2003. Bij 25,7% van de patiënten was de SWK-procedure de enige stageringsmethode, 19.1% onderging een SWK in combinatie met een complete oksel dissectie (OKD) en 50,0% onderging alleen een OKD. Van de patiënten onderging 5,2% geen okselstadiering. Vrouwen kregen eerder een SWK-procedure na een borstsparende operatie dan na een amputatie ($p < 0,0001$). De toepassing van de SWK-procedure nam toe over de tijd. In 2003 onderging ruim 70% van de borstkankerpatiënten met een tumor tot 5 centimeter een SWK-procedure en voor 64,9% was het de enige ingreep in de oksel. Er waren aanzienlijke verschillen in invoering van de SWK-procedure tussen regio's: in 2003 was het verschil tussen de regio met het hoogste en laagste invoeringspercentage 25%.

De samenwerking tussen chirurg, nucleair geneeskundige en patholoog is van essentieel belang bij de invoering van de SWK-procedure. In de regio Utrecht hebben zeven ziekenhuizen de landelijke richtlijn vertaald naar lokale invoeringsprotocollen. Na invoering zijn de behandelresultaten vastgelegd in een registratiestudie. In **Hoofdstuk 3** worden de resultaten van deze studie gepresenteerd. In 2002 en 2003 zijn 541 patiënten geïncludeerd (503 met een tumorvrije SWK en 38 met micrometastases in de SWK). Gedurende de follow-up is bij drie patiënten een recidief in de oksel opgetreden en bij één patiënt een gecombineerd recidief in de borst en de oksel. Bij 23 patiënten werd een metastase op afstand gediagnosticeerd. De resultaten verschilden niet tussen patiënten met een tumorvrije SWK of een SWK met alleen micrometastasen, en kwamen overeen met andere studies. Op basis van deze studie is geconcludeerd dat de SWK-procedure een betrouwbare manier van stagering was in de regio Utrecht.

Met de introductie van de SWK-procedure worden nog slechts enkele okselklieren door de patholoog onderzocht op de aanwezigheid van tumorcellen. In **Hoofdstuk 4** hebben we bekeken of de introductie van de SWK-procedure heeft geleid tot het vaker afgeven van een hoger stadium. We gebruikte gegevens uit de Utrechtse regio van de NKR. In totaal onderging een kwart van de patiënten over de periode 1997-2002 een SWK-procedure als methode van

okselstadiering. De toepassing steeg snel van 2% in 1998 tot 65% in 2002. Het percentage patiënten met positieve okselklieren steeg van 30% naar 40%. Deze toename was grotendeels toe te schrijven aan de patiëntengroep met alleen micrometastasen (1% bij OKD en 8% bij SWK-procedure). De uitkomsten veranderden niet na correctie voor het jaar van diagnose, de leeftijd van de patiënt en de afmeting van de tumor. De conclusie was dat door de invoering van de SWK-procedure bij meer patiënten positieve okselklieren worden gevonden.

Hoofdstuk 5 bestudeert de prognose van patiënten met geïsoleerde tumorcellen (ITC) en micrometastasen, en het effect van adjuvante systemische therapie. Gegevens van 18.748 patiënten met tumorvrije okselklieren of klieren met ITC of micrometastasen werden geanalyseerd. Het primaire eindpunt van de studie was 5-jaars ziektevrije overleving (locoregionale terugkeer, metastasering op afstand of contralaterale borstkanker). De 5-jaars ziektevrije overleving was 89,9% (95% BI 89,5–90,4). Na correctie voor prognostische factoren (inclusief behandeling) hadden patiënten met ITC een vergelijkbare prognose als patiënten met tumorvrije okselklieren (HR=1,12; 95% BI 0,87–1,43), terwijl patiënten met micrometastasen een 38% hoger risico hadden op terugkeer van de ziekte (HR=1,38; 95% BI 1,13–1,69). Gezien de reeds hoge ziektevrije overleving in deze patiënten, zijn we terughoudend in het adviseren van standaard chemotherapie voor alle patiënten met micrometastasen. Het is te verwachten dat in de toekomst de genetische kenmerken van de primaire tumor meer informatie zullen geven over het risico op metastasering van de ziekte dan de okselklierstatus.

In **Deel 2** worden studies gepresenteerd waarin indicatoren worden gebruikt om de kwaliteit van chirurgische borstkankerzorg in ziekenhuizen met elkaar te vergelijken. Sinds 2009 zijn ziekenhuizen verplicht om het percentage lokaal recidieven na operatie voor borstkanker te rapporteren aan de Inspectie voor de Gezondheidszorg (IGZ). **Hoofdstuk 6** presenteert de uitkomst van deze indicator voor alle patiënten die in 2003 zijn gediagnosticeerd. Het percentage lokaal recidieven werd berekend voor 99 ziekenhuizen op basis van gegevens uit de NKR. Bij 266 van 9898 patiënten trad een lokaal recidief op binnen 5 jaar na diagnose. Het overall 5-jaars lokaal recidief percentage was 3,03% (95% BI 2,69 - 3,41), en was na borstsparende operatie 2,63% (95% BI: 2,21-3,12) en na amputatie 3,50% (95% BI: 2,97-4,13). De variatie tussen ziekenhuizen was groot (0-17%). Op ziekenhuisniveau werd bij geen van de instellingen een significant hoger percentage lokaal recidieven waargenomen na borstsparende operatie, en bij drie ziekenhuizen een significant hoger percentage na amputatie. Op basis van deze gegevens hebben we geconcludeerd dat het overall percentage lokaal recidieven in Nederland onder de gestelde norm van 5% binnen vijf jaar lag. Omdat het percentage lokaal recidieven laag is en het aantal patiënten per ziekenhuis beperkt, is de indicator niet geschikt om verschillen in de kwaliteit van zorg tussen ziekenhuizen te meten.

Hoofdstuk 7 beschrijft de resultaten van de indicator over het percentage lokaal recidieven na operatie voor borstkanker op basis van gegevens van vier opeenvolgende jaren. Gegevens van 31.992 patiënten met laag stadium borstkanker die behandeld werden in 80 ziekenhuizen over de periode 2003-2006 werden geïncludeerd. Het overall 5-jaars lokaal recidief percentage was 2,51% (95% BI 2,23 – 2,71). Het lokaal recidief percentage was significant lager voor sparend

geopereerde patiënten dan voor patiënten met een amputatie (1,96% en 3,23%) en daalde significant voor beide groepen over de tijd. In 2006 waren de 5-jaars lokaal recidief percentages 1,49% en 2,71% voor sparende operatie en amputatie. In slechts één ziekenhuis werd een lokaal recidief percentage na amputatie significant boven de norm van 5% gezien. De proportie sparend geopereerde patiënten varieerde substantieel tussen ziekenhuizen (16% tot 80%). Op basis van deze studie hebben we geconcludeerd dat het percentage lokaal recidief na operatie voor borstkanker in Nederland laag is. De indicator is niet geschikt voor het vergelijken van de kwaliteit van zorg tussen ziekenhuizen, omdat het zeer kleine aantallen betreft en de periode tussen de behandeling en het meten van de indicator te lang is. Dus om de kwaliteit van zorg verder te verbeteren, zijn indicatoren die sneller meetbaar zijn en die zich bijvoorbeeld richten op het handelen conform de richtlijn meer geschikt.

In **Hoofdstuk 8** wordt de variatie tussen ziekenhuizen beschreven aan de hand van de indicator 'irradicaliteit na eerste borstsparende operatie'. Voor deze studie werden 7.345 patiënten geselecteerd uit de NKR die gediagnosticeerd waren tussen 1 juli 2008 en 30 juni 2009. De norm was voor patiënten met DCIS maximaal 30% irradicale resecties (gedefinieerd als 'focaal irradicaal' of 'meer dan focaal irradicaal') en voor patiënten met invasief carcinoom maximaal 10% (gedefinieerd als meer dan 'focaal irradicaal'). Voor invasief carcinoom werden de resultaten gecorrigeerd voor case-mix. Overall was het percentage irradicale resecties voor DCIS 28,5% (95% BI:25,5 – 31,4%) en voor invasief carcinoom 9,1% (95% BI: 8,4 – 9,8%). De variatie tussen ziekenhuizen was aanzienlijk. Zes ziekenhuizen scoorden voor DCIS significant hoger dan de norm en 10 ziekenhuizen voor invasief carcinoom. Case-mix correctie leidde voor vijf ziekenhuizen tot een andere conclusie. Een significant hoger percentage irradicale resecties was niet gerelateerd aan het volume van het ziekenhuis of het type ziekenhuis (algemeen ziekenhuis versus opleidings- of academisch ziekenhuis). Een hoger percentage was wel gerelateerd aan ziekenhuizen die relatief veel patiënten in opzet sparend opereren. We hebben geconcludeerd dat overall het percentage irradicale resecties in Nederland onder de gestelde normen ligt. De variatie tussen ziekenhuizen is substantieel, maar kan grotendeels verklaard worden door toeval. Case-mix correctie leidt tot relevante verschuivingen in het oordeel over de kwaliteit van zorg in individuele ziekenhuizen.

Hoofdstuk 9, de algemene discussie, richt zich op de complexiteit van het meten van de kwaliteit van zorg, met uitdagingen ten aanzien van het definiëring van criteria, het ontwikkelen van indicatoren en het interpreteren van resultaten. Met de ontwikkeling van een weloverwogen set indicatoren door het Nationaal Borstkankeroverleg Nederland (NABON) in 2010, is een solide basis gelegd voor het bepalen van de kwaliteit van zorg. Bij de interpretatie van de resultaten dient rekening te worden gehouden met het feit dat de variatie tussen ziekenhuizen niet alleen verschillen in de kwaliteit van zorg betreft, maar tevens wordt veroorzaakt door toevalsvariatie, patiëntkenmerken en registratie-artefacten. Met deze aspecten dient rekening te worden gehouden door middel van het gebruik van funnelplots, case mix correctie en het waarborgen van objectieve registratie op basis van gedetailleerde en actuele handleidingen. Wij adviseren dat alle NABON indicatoren worden geëvalueerd op de bruikbaarheid van de informatie.

De dataverzameling ten behoeve van de NABON indicatoren is gestart in 2011. Door optimaal gebruik te maken van de mogelijkheden van deze data kan de kwaliteit van borstkanker zorg in de komende jaren verder worden verbeterd.

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Curriculum Vitae

Margriet van der Heiden-van der Loo was born on August 21st, 1974, in Waddinxveen, the Netherlands. After graduating from high school at Coenecoop College in Waddinxveen in 1993, she studied Health Sciences at Maastricht University in Maastricht, the Netherlands. In 1998 she obtained her Master of Public Health (Health Economics, Policy and Management).
From 1999 to 2000, she worked as a researcher at VU Medical Center on an implementation study on extramural treatment of patients with deep venous thrombosis. In 2000, she started to work at the Comprehensive Cancer Center Middle Netherlands (CCCMN) on various projects. In 2006, she graduated as a Master of Epidemiology at the EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam, the Netherlands. She coordinated the registration and research department of CCCMN from 2006 to 2010.
In 2009, she officially started her PhD research described in this thesis at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands under supervision of prof.dr.P.H.M. Peeters and prof.dr. E.J.Th. Rutgers (department of surgery, Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands). Since the merging of CCCMN into Comprehensive Cancer Center the Netherlands (CCCNL) in 2011, she has been working as a researcher. She will continue to work at CCCNL, mainly focussing on breast cancer and the NABON breast cancer audit.

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