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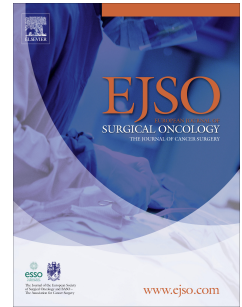
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Variation in management of early breast cancer in the Netherlands, 2003-2006

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Running head: Variation in treatment of early breast cancer in the Netherlands, 2003-2006

Key words: early breast cancer, breast conserving surgery, axillary lymph node dissection, sentinel lymph node procedure, adjuvant systemic therapy

This study was performed for the working party 'Quality of cancer care' of the Signalling Committee Cancer of the Dutch Cancer Society

Abstract

Background: To describe variation in staging and primary treatment by hospital characteristics including type and volume and region in patients with early breast cancer (BC) in the Netherlands, 2003-2006 after completion of national guidelines in 2002.

Methods: All patients newly diagnosed with invasive BC in 2003-2006 and recorded in the Netherlands Cancer Registry were included (n=51 354). Multivariable logistic regression analyses examined the influence of patient and hospital characteristics, also by region, on type of breast surgery, axillary lymph node dissection (ALND), sentinel node procedure (SNP), and adjuvant irradiation and/or systemic treatment.

Results: Patients <40 years more often underwent breast conserving surgery (BCS) in general hospitals (OR 1.4 (95%CI 1.1-1.5)) than in teaching and academic hospitals, whereas patients of 40-69 years less often received BCS in an academic hospital (OR 0.9 (95%CI 0.8-1.0)) than in teaching hospitals. Patients with pT1-2N0 cancer more often underwent primary ALND in a general hospital than in a larger teaching or academic hospital. Type of hospital did not seem to affect utilization of adjuvant systemic therapy, but patient age and tumour size and grade did. Over time, patients more often received SNP, BCS, and adjuvant systemic therapy, primary ALND being on the decline, but with substantial regional variation between geographic regions.

Conclusion: With detailed evidence-based national guidelines since 2002 the considerable regional and hospital variation in staging procedures and primary treatment among newly diagnosed patients with early breast cancer in the Netherlands decreased markedly, suggesting the presence of late adaptors rather than specific hospital characteristics.

Introduction

Breast cancer is the most frequent cancer in females in the Netherlands, with a lifetime risk of 12-13%¹. Early detection, mainly due to population-based screening, and adjuvant treatment resulted in an improved survival of patients with breast cancer and lower mortality since the mid 1990s. Breast cancer staging and treatment is evolving and, therefore, clinical practice guidelines were developed since 1999, coming into practice in 2002².

Oncological care for breast cancer is rapidly changing through surgical, pharmacological and technological innovations, thereby also becoming increasingly subspecialized. Quality increasingly becomes measurable, being considered as vital for both patients and doctors and, last but not least for health insurance companies. Important aspects are thought to be volume³⁻⁸ and type of hospital^{9, 10}, depending on the type of cancer, population density, and prosperity of region or country.

According to the Dutch clinical practice guidelines of 2002, patients with early stage (T1T2M0) breast cancer are generally eligible for breast conserving surgery (BCS), unless they are of young age or prefer otherwise. Patients who undergo BCS should receive adjuvant radiotherapy at any age². The sentinel lymph node procedure (SNP) is advised in patients with a clinically node-negative breast tumour, while a primary axillary lymph node dissection (ALND) is advised in all other patients.² Adjuvant chemotherapy, HER2-targeted therapy and hormone therapy have proven to be effective in preventing or delaying relapses and increasing survival in patients with early stage or locally advanced breast cancer.^{11, 12} Therefore, patients with a node-positive tumour or a node-negative tumour with unfavourable characteristics should receive adjuvant systemic treatment.² In the Netherlands a biannual mammography mass screening program for breast cancer in women from 50 to 70 years was gradually introduced since 1990, being fully implemented since 1997 and extended to women of 75 years since 1999.

The purpose of this nationwide study was to describe variation in staging and treatment of patients with early breast cancer by hospital characteristics including type and volume and by region. The results of this study on all patients newly diagnosed in the Netherlands in 2003-2006 will support the ongoing efforts to improve quality of care for breast cancer patients in the Netherlands and abroad.

Methods

Data collection

We used the population-based database from the Netherlands Cancer Registry (NCR), which started in 1989 and is maintained and hosted by the Comprehensive Cancer Centres (CCCs).¹ The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the national automated pathological archive (PALGA) that covers 70 laboratories. Additional sources are the national registry of hospital discharge data, which accounts for up to 8% of new cases,¹³ and regional radiotherapy institutes. Information on patient characteristics like date of birth, and tumour characteristics such as date of diagnosis, histology, stage (Tumour Lymph Node Metastasis (TNM) classification),¹⁴ grade, and primary treatment as well as staging procedures, are obtained routinely by data registration clerks from the cancer registry from the medical records about nine months after diagnosis.¹³ The quality of the data is high due to thorough training of the data managers and a variety of computerized consistency checks at regional and national level. Completeness is generally estimated to be at least 95% for all tumours but higher for breast cancer due to its high level of histological verification.¹⁵ For the current analysis, hospital characteristics including type and volume were retrieved from Prismant, an organisation which collects objective data about hospitals for e.g. quality of care assessment.¹⁶ Presence of the 21 institutes of radiotherapy was known through the Comprehensive Cancer Centres.

Patients

For the present study, all female cases with primary invasive primary breast cancer (ICD-0: C50.0) newly diagnosed in the period 2003-2006 in the Netherlands were included (n=51 354). Exclusion criteria were diagnosis by autopsy, living and treatment abroad, incomplete registration status in the NCR, clinical diagnosis only, histology of sarcoma, lymphoma, Paget's disease, neuro-endocrine tumour or carcinoid. Reported stage is postoperative, and clinical when postoperative stage was unknown. Patients who received BCS followed by mastectomy without signs of relapse were coded as having had mastectomy.

Hospitals

The categorization of hospitals was based on data from Prismant for the period 2003-2005. Hospitals with several locations, but organized as one hospital in 2003 were considered as one hospital. Patients were considered to be treated in the hospital where the tumour was diagnosed. A non-teaching hospital was categorized as a general hospital. A teaching hospital provides in-house training to surgical and/or internal medicine residents. An academic hospital was a teaching hospital uniquely affiliated with a university. The one specialized oncology centre in the Netherlands was classified as an academic hospital. Hospital volume was based on the mean number of breast cancer diagnoses per year in the

study period, and was categorized into <150 and ≥ 150 diagnoses per year. Hospital type was categorized based on teaching hospital for surgery and hospital volume, resulting in six categories. The regions were based on the areas served by one of the nine CCCs. Each CCC serves the population in an area of five to twenty hospitals. Each of the hospitals was affiliated to one CCC only.

Data were analysed by researchers of the nine CCCs in the Netherlands, supervised by experienced clinicians. The CCCs intend to improve and monitor the quality of cancer care by provision of consultancy services, implementation of national guidelines, improving organisation of cancer care, coordinating palliative care, and organising the cancer registry.

Statistical analyses

Patient, tumour, and hospital of staging and treatment characteristics as well as region were described in relation to received treatment. Surgical and radiotherapy treatment were analysed according to stage. Multivariable logistic regression analysis was performed stratified by age (<40 years, 40-69 years, and ≥ 70 years) to examine the influence of hospital type and volume on the possibility to receive BCS with adjustments for the presence of radiotherapy in a hospital, region, and year of diagnosis. Since there was significant interaction between type and volume of a hospital, these variables were merged into one variable of both type and volume of a hospital. Similarly, multivariable logistic regression analysis was performed to examine determinants of ALND, which was also done for the application of adjuvant systemic treatment. In this analysis the independent effect of hospital type and volume were analysed separately, since no interaction was found between these factors in relation to adjuvant systemic therapy and then stratified by age (<55 and ≥ 55 years). Variation in utilization of ALND and adjuvant systemic treatment was displayed as scatter plots with the average number of breast cancer patients per hospital on the X-axis and of ALNDs or adjuvant systemic treatment on the Y-axis. Hospital type was classified through symbols in the scatter plot. All analyses were done in SAS (version 9.1, SAS Institute, Cary, NC). 95% Confidence intervals were estimated and a p-value of 0.05 was considered statistically significant.

Results

In 2003, 12 460 women were diagnosed with primary invasive breast cancer in the Netherlands, which gradually increased to 13 280 in 2006, an increase of 7% in four years. Over 40% of patients were treated in a large teaching hospital, 33% in a small general hospital, and only 8% in an academic hospital (Table 1). No change in stage distribution was seen over time in the period 2003-2006 (data not shown).

Surgery

Most patients underwent BCS with radiotherapy, although this depended on the stage of disease, being 63% of patients with stage I disease, 41% in stage II, and 19% in stage III. Almost all patients who underwent BCS received radiotherapy. Mastectomy was the treatment of choice in 51% of patients with stage II disease and in 69% with stage III (Figure 1). Application of BCS in patients with T1T2 N0 disease varied from 30% to 82% among hospitals (data not shown). Patients aged <40 years were more likely to receive BCS in a general (non-teaching) hospital, whereas patients of ≥ 70 years less often received BCS in a small general or teaching hospital. Patients aged 40-69 years less often received BCS in a small hospital (Table 2a). After adjustments similar results were found, although patients aged 40-69 years were less likely to receive BCS in academic centres. The presence of radiotherapy in an – often larger - hospital positively affected the chance for BCS in patients 40-69 years. Over time, more patients underwent BCS compared to mastectomy, especially in older women, but with substantial variation between geographic regions in the Netherlands (Table 2b). When considering type of hospital alone, patients <40 years were more likely to receive BCS (OR 1.3 (95% CI 1.1-1.5)), contrasting patients ≥ 70 years (OR 0.9 (95% CI 0.8-0.9)) when treated in a general hospital compared with a teaching hospital. Academic hospitals were not different from teaching hospitals with regard to choice of BCS for patients aged <40 years or ≥ 70 years. However, patients of 40-69 years treated in academic hospitals were less likely to receive BCS (OR 0.9 (95% CI 0.8-1.0)) compared with teaching hospitals.

Axillary lymph node dissection

After a start at larger scale in 1998, the sentinel lymph node procedure (SNP) was applied in 2003 in 59% of T1T2 N0 breast cancer patients, which became 78% in 2006. Consequently, primary ALND decreased over time from 22% in 2003 to 11% in 2006. Patients with T1T2 N0 disease more often received primary ALND in a general hospital, followed by the teaching and the academic hospitals. Older age (≥ 70 years) and clinical T2 stage were positively associated with application of ALND, clearly decreasing over time. There still was large but declining variation in ALND among regions (Table 3). T1T2 N0 patients treated in a general hospital were more likely to receive ALND (OR 1.4 (95% CI 1.3-1.5)), but less in an academic hospital (OR 0.9 (95% CI 0.8-1.0)), compared to a teaching hospital. ALND in N0 patients

varied from 5% to 70% between hospitals, the proportions being higher in a general or low volume hospital than in a teaching or academic hospital (Figure 2).

Adjuvant systemic treatment

Multivariable logistic regression analyses showed that hospital factors including type and volume as well as the presence of radiotherapy in a hospital did not affect the odds of receiving adjuvant systemic therapy in T1T2 N0 patients. This decreased sharply with the rise of age, but was higher for patients with a T2 tumour or a poor differentiation grade, and also over time (Table 4). Application of adjuvant systemic treatment in T1T2 N0 breast cancer patients ranged from 20% to 45% between hospitals, being larger in low volume hospitals (Figure 3).

Discussion

In this nationwide study we have shown that breast cancer, as a very common tumour with generally accepted treatment guidelines since 2002, still exhibited considerable variation in staging and treatment across the Netherlands in the various hospitals, regardless of hospital size. Significantly more patients <40 years underwent BCS in general hospitals compared to teaching and academic hospitals, whereas women aged 40-69 years less often received BCS in an academic hospital versus teaching hospitals. Moreover, too many patients with clinically node-negative T1T2 disease diagnosed in general hospitals still received primary ALND, in the absence of a SNP compared to teaching and academic hospitals. However, almost all patients undergoing BCS received radiotherapy. The prescription of adjuvant systemic therapy did not depend on hospital type, but there was no specification according to regimen. Differences in surgical breast treatment and lymph node staging were still seen between geographic regions, but decreased over time.

Surgical breast treatment

According to the first national, Dutch clinical practice guidelines of 2002 patients with early stage breast cancer are generally eligible for BCS. There are exceptions besides the size of the tumour in relation to the size of the breast, because higher local recurrence rates have been reported in patients aged <40 years compared to those >60 years.^{17, 18} But the preference of the treating surgeon and the wish of the patient are of major importance. We found that hospital type and volume as well as region were important determinants of BCS in each age group, as also found in a French randomized trial.¹⁹ In the US, the mastectomy rate has been rising again since 2003, especially in younger patients.^{20, 21} This trend is not yet observed in the Netherlands, although patients of 40-69 years received less often BCS in academic centres than in general and teaching hospitals. This might indicate the start of a change towards an increasing mastectomy rate, also in younger women.

Lymph node analysis

Lymph node analysis is of critical importance for adequate staging of patients with early breast cancer. Since the introduction of ALND has been the standard of care for axillary lymph node staging, until long-term complications of this procedure appeared to be relatively common^{22, 23} without conferring a gain in life-expectancy. In 1996, the SNP was introduced in a few hospitals in the Netherlands with supposedly similar staging capacities^{24, 25, 26, 27} but with markedly lower morbidity.²⁸ Therefore, Dutch guidelines developed between 2000 and 2002, stated that most early stage breast cancer patients should receive SNP, for which often investments in nuclear detection equipment and training were needed. Although rapidly decreasing over time the general hospitals still performed too many ALNDs in the study period. Moreover, during the study period the indication for SNP changed with an

increase in the cut-off value of tumour size from 3 to 5 cm, but SNP seems contra-indicated due to e.g. multifocality of the tumour or disturbed lymph drainage.

Adjuvant systemic treatment

Adjuvant chemotherapy, hormonal therapy and trastuzumab have increasingly been proven to be effective in preventing or delaying relapses and increasing survival in patients with early stage breast cancer, also at older age.^{11, 12} Therefore, these therapies have become part of the treatment plan for many of these patients. Guidelines for adjuvant systemic treatment have evolved over time and strategies have become more tumour and patient-specific than ever before.^{2, 29} The rising trend in the use of adjuvant systemic treatment of breast cancer patients was described earlier in southern Netherlands and the US.^{30, 31} Our finding that patients with a large or poorly differentiated tumour more often received adjuvant systemic treatment is in line with the literature and guidelines.^{31, 32} Hospital variation in utilization of adjuvant systemic treatment in early stage node negative breast cancer patients was also found in the southern Netherlands during 2003-2006, when the proportion of adjuvant systemic treatment ranged between 26-42%.³¹

Quality of care

The large, but decreasing variation in breast cancer care for patients with early breast cancer between the various hospitals in both application of ALND and adjuvant systemic treatment cannot only be explained by patient or tumour characteristics, but is likely to result from differential fast and slow adaptors. But to what extent was the delayed introduction of the SNP or adjuvant systemic treatment in hospitals acceptable, since the SNP and adjuvant systemic treatment have proven their effectiveness in international literature since about 2005.^{11, 12, 26, 27} In medical oncology, the usual consultancy of experts in oncology meetings in the Netherlands should lead to small differences in application of adjuvant systemic treatment between academic, teaching and general hospitals. But, the consultancy structure is less common in surgical-oncological treatment, because surgical experience is generally supposed to be larger in general and teaching hospitals. Therefore, a specific consultancy structure for surgical staging and treatment of breast cancer patients should be considered. The differences in care between the regions probably reflect differences in previous academic or large teaching hospital practices transmitted by training.

The results of the analyses on intermediate outcome in this study must be interpreted carefully, not only because hospital characteristics such as type and volume, may be rough proxies for hospital characteristics like anaesthesia equipment and nurse-patient ratio. Patient factors like comorbidity and socioeconomic status could also partly explain the observed associations with outcome.^{33, 34}

In conclusion, there was considerable variation in quality of care for patients with early breast cancer in the Netherlands after, albeit limited, adjustment for case mix (only age, tumour size and grade) in the period 2003-2006, just after the first national guideline became official. The differences, especially concerning breast surgery and axillary lymph node staging could be partly explained by hospital characteristics such as presence of specialist training and volume of care, but there also seemed to be differential loco-regional practices. Variation in application of adjuvant systemic treatment seemed to be mainly caused by patient and tumour characteristics. Research of the determinants of the differences should not only focus on case-mix and hospital characteristics, but should also address often selective, referral patterns and thus provide combined regional analysis. There are certainly gains to be attained. The situation in 2010 is likely to be much better, already.

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Captions

Figure 1: Treatment of breast cancer by stage, the Netherlands 2003-2006

BCS: breast conserving surgery; RT: Radiotherapy

Figure 2: Variation in lymph node dissection in patients with N0 breast cancer per hospital by type and average number of N0 breast cancer patients per year, the Netherlands 2003-2006

Figure 3: Variation in application of adjuvant systemic treatment to T1T2 N0 breast cancer per hospital by type and average number of T1T2 N0 breast cancer patients per year, the Netherlands 2003-2006

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Table 1: Number of new cases of breast cancer in the Netherlands, 2003-2006

	N	%
Total	51 354	100
Year of diagnosis		
2003	12 460	24
2004	12 786	25
2005	12 828	25
2006	13 280	26
Age (yrs)		
<40	3421	7
40-69	33 068	64
≥70	14 865	29
Stage#		
I	20 404	40
IIA	14 525	28
IIB	6163	12
IIIA	3993	8
IIIB	1 35	2
IIIC	2082	4
IV	2524	5
Unknown	528	1
Morphology		
ductal	40 813	80
lobular	5998	12
ductal and lobular	1857	4
mucineus	854	2
medullair	408	1
tubular	576	1
other	848	2
Differentiation		
good	9319	18
moderate	19 448	38
well/undifferentiated	14 592	28
unknown	7998	16
Hospital type*		
small (<150), general	16 699	33
large (≥150), general	4636	9
small (<150), teaching	5003	10
large (≥150), teaching	20 919	41
small (<150), academic	2469	5
large (≥150), academic	1 617	3
Teaching hospital internal medicine*		
no	16 506	32
yes	30 751	60
academic centre	4086	8
Radiotherapy in hospital*		
no	41 382	81
yes	9972	19
Region of Comprehensive Cancer Center		
1	7004	14

2	4396	9
3	3882	8
4	9447	18
5	5135	10
6	7404	14
7	7293	14
8	2935	6
9	3841	8
Lymph node dissection		
none	6400	13
SNP without ALND	23 064	45
SNP with ALND	6719	13
ALND	15 171	30

BCS: breast conserving surgery; SNP: sentinel node procedure; ALND: axillary lymph node dissection

* based on hospital of first diagnosis

Table 2a: The unadjusted odds of breast conserving surgery in patients with T1T2 breast cancer, the Netherlands, 2003-2006

	<40 yrs		40-69 yrs		≥70 yrs	
	OR	95% CI	OR	95% CI	OR	95% CI
Hospital type						
small (<150), general	1.21*	1.01-1.44	0.90*	0.85-0.95	0.73*	0.67-0.80
large (≥150), general	1.54*	1.18-2.02	1.12*	1.02-1.22	0.89	0.78-1.03
small (<150), teaching	1.07	0.82-1.39	0.76*	0.70-0.83	0.58*	0.50-0.66
large (≥150), teaching	1.0		1.0		1.0	
small (<150) academic	0.95	0.70-1.29	0.80*	0.71-0.90	0.88	0.71-1.09
large (≥150), academic	0.98	0.64-1.49	0.90	0.78-1.03	1.25	0.98-1.60

* p< 0.05

Table 2b: The odds of receiving breast conserving surgery in patients with T1T2 breast cancer, the Netherlands, 2003-2006

	<40 yrs (n=2,958)		40-69 yrs (n=29,658)		≥70 yrs (n=10,645)	
	OR ^a	95% CI	OR ^a	95% CI	OR ^a	95% CI
Hospital type						
small (<150), general	1.29*	1.05-1.59	1.03	0.96-1.10	1.00	0.90-1.12
large (≥150), general	1.44*	1.07-1.92	1.02	0.93-1.13	0.94	0.81-1.10
small (<150), teaching	1.14	0.84-1.53	0.86	0.78-0.95	0.83*	0.71-0.97
large (≥150), teaching	1.0		1.0		1.0	
small (<150) academic	0.92	0.65-1.29	0.74*	0.65-0.84	0.80	0.63-1.01
large (≥150), academic	0.90	0.55-1.49	0.79*	0.68-0.93	1.04	0.78-1.39
Radiotherapy in hospital						
yes	1.19	0.91-1.56	1.20*	1.10-1.32	1.57	1.35-1.82
no	1.0		1.0		1.0	
Region						
1	0.88	0.66-1.16	0.90*	0.82-0.99	0.97	0.84-1.12
2	0.76	0.56-1.04	0.84*	0.76-0.93	1.20*	1.02-1.41
3	1.39*	1.01-1.91	1.45*	1.30-1.63	1.24*	1.04-1.47
4	1.0		1.0		1.0	
5	0.70*	0.52-0.95	1.00	0.90-1.11	0.75*	0.64-0.88
6	0.96	0.73-1.26	0.73*	0.67-0.79	0.65*	0.56-0.75

7	1.49*	1.13-1.97	1.27*	1.15-1.39	1.85*	1.59-2.15
8	0.86	0.59-1.28	0.88*	0.78-1.00	0.98	0.81-1.18
9	0.78	0.57-1.08	0.65*	0.59-0.72	1.18	0.99-1.41
Incidence year						
2003	1.0		1.0		1.0	
2004	0.89	0.73-1.09	0.96	0.90-1.03	1.01	0.90-1.13
2005	1.32*	1.07-1.63	1.14*	1.06-1.22	1.14*	1.02-1.27
2006	1.14	0.92-1.41	1.14*	1.07-1.22	1.28*	1.14-1.43

* p < 0.05

^a Adjusted for radiotherapy in hospital, region, and incidence year

Table 3: The odds of undergoing lymph node dissection by patients with pT1T2 N0 breast cancer, the Netherlands 2003-2006

	Unadjusted		Adjusted ^a	
	OR	95% CI	OR	95% CI
Hospital type				
small (<150), general	1.44*	1.34-1.55	1.52*	1.39-1.67
large (≥150), general	1.17*	1.04-1.31	1.69*	1.48-1.93
small (<150), teaching	1.06	0.95-1.19	1.15	1.00-1.31
large (≥150), teaching	1.0		1.0	
small (<150) academic	1.28*	1.10-1.50	1.20	1.00-1.43
large (≥150), academic	0.44*	0.35-0.56	0.68*	0.51-0.89
Radiotherapy in hospital				
yes			1.35	1.19-1.52
no			1.0	
Age (yrs)				
<40			1.02	0.89-1.18
40-69			1.0	
≥70			1.78*	1.65-1.91
Clinical T stage				
1			1.0	
2			2.46*	1.65-1.91
Region				
1			2.67*	2.36-3.02
2			1.05	0.90-1.22
3			1.18	1.00-1.38
4			1.0	
5			1.48*	1.29-1.70
6			1.72*	1.51-1.94
7			1.33*	1.17-1.52
8			0.58*	0.47-0.71
9			3.09*	2.68-3.55
Incidence year				
2003			1.0	
2004			0.63*	0.57-0.69
2005			0.45*	0.41-0.49
2006			0.34*	0.31-0.38

^a Adjusted for radiotherapy in hospital, age, clinical T stage, region, and incidence year

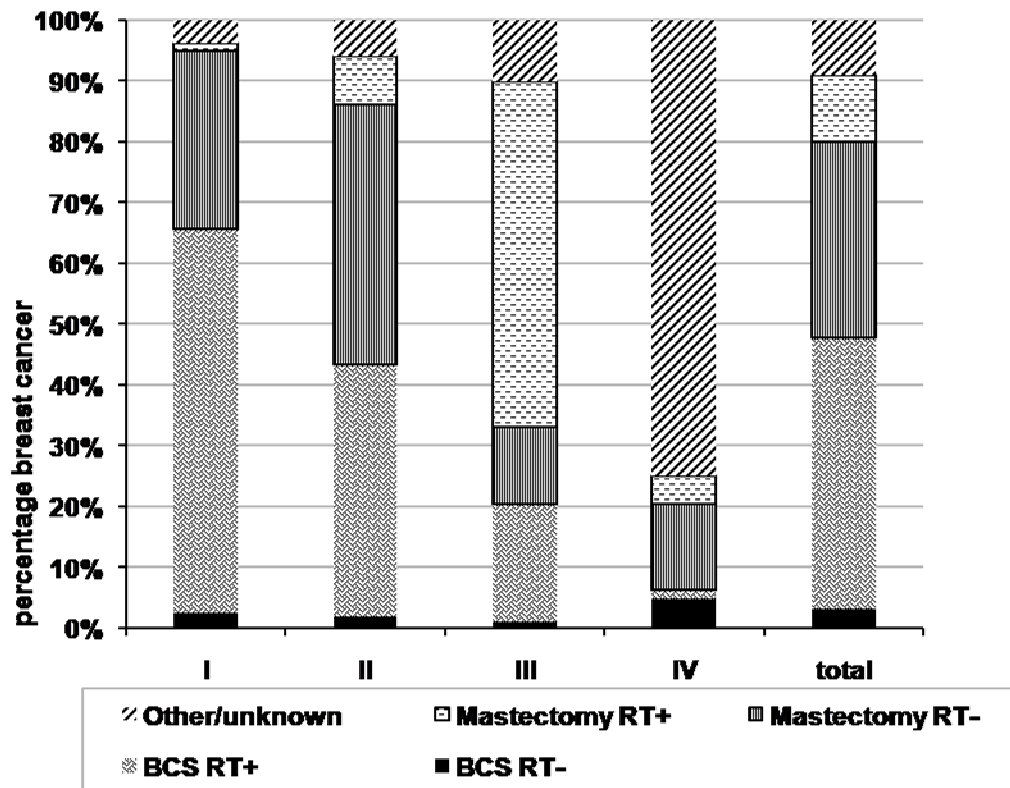
* p < 0.05

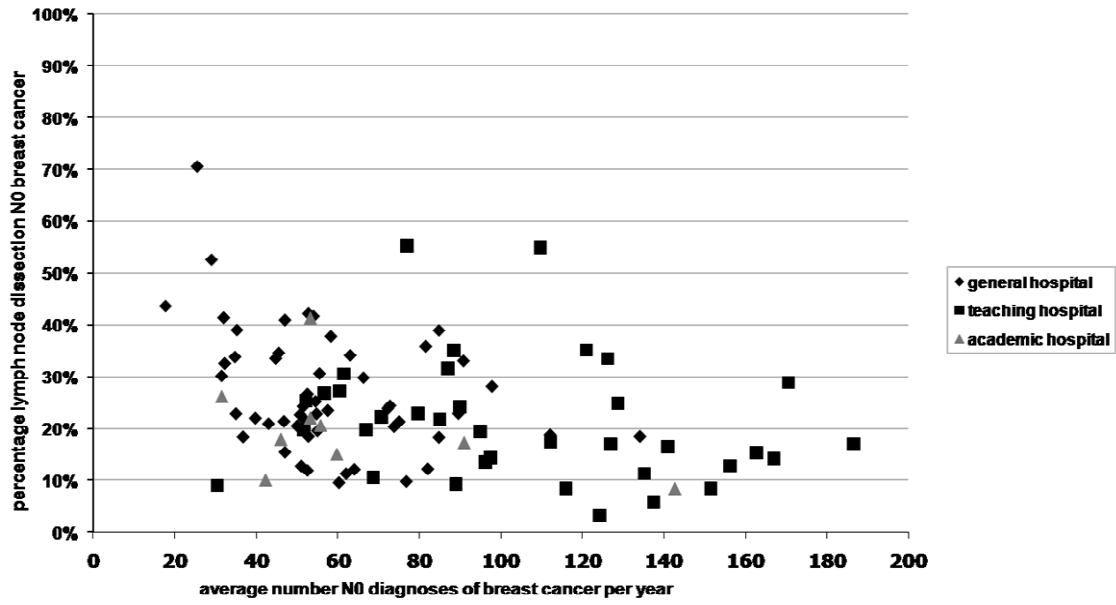
Table 4: The odds of receiving adjuvant systemic therapy by T1T2 N0 breast cancer patients in the Netherlands, 2003-2006

	OR ^a	95% CI
Type of hospital		
general	0.90	0.89-1.09
teaching (internal medicine)	1.0	
academic	1.02	0.86-1.21
Radiotherapy in hospital		
yes	1.0	
no	0.90	0.79-1.01
Hospital size		
<150	0.90	0.89-1.10
≥150	1.0	
Region		
1	0.86*	0.75-1.00
2	1.02	0.88-1.19
3	1.07	0.91-1.26
4	1.34*	1.18-1.52
5	0.93	0.80-1.80
6	0.88	0.76-1.01
7	1.0	
8	1.00	0.85-1.19
9	1.08	0.92-1.25
Incidence year		
2003	1.0	
2004	1.02	0.92-1.13
2005	1.45*	1.32-1.60
2006	1.48*	1.34-1.63
Age (yrs)		
<40	4.10*	3.54-4.75
40-69	1.0	
≥70	0.49*	0.46-0.54
T stage ^b		
1	1.0	
2	8.11*	7.51-8.75
Grade		
good	0.29*	0.26-0.33
moderate	1.0	
poor	8.84*	8.17-9.58
unknown	1.44*	1.27-1.63

^a Adjusted for radiotherapy in hospital, hospital size, region, incidence year, age, T stage, and grade

^b Pathological stage, when unknown clinical stage was used





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