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► **To cite this version:**

A.K. Talsma, A.M.J. Reedijk, R.A.M. Damhuis, P.J. Westenend, W.J. Vles. Re-resection rates after breast-conserving surgery as a performance indicator Introduction of a case-mix model to allow comparison between Dutch hospitals. *EJSO - European Journal of Surgical Oncology*, 2011, 37 (4), pp.357. 10.1016/j.ejso.2011.01.008 . hal-00677322

HAL Id: hal-00677322

<https://hal.science/hal-00677322>

Submitted on 8 Mar 2012

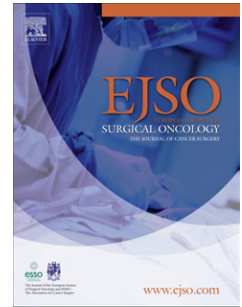
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Accepted Manuscript

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PII: S0748-7983(11)00009-6

DOI: [10.1016/j.ejso.2011.01.008](https://doi.org/10.1016/j.ejso.2011.01.008)

Reference: YEJSO 3103

To appear in: *European Journal of Surgical Oncology*

Received Date: 1 November 2010

Revised Date: 29 December 2010

Accepted Date: 6 January 2011

Please cite this article as: Talsma AK, Reedijk AMJ, Damhuis RAM, Westenend PJ, Vles WJ. Re-resection rates after breast-conserving surgery as a performance indicator Introduction of a case-mix model to allow comparison between Dutch hospitals, *European Journal of Surgical Oncology* (2011), doi: 10.1016/j.ejso.2011.01.008

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Re-resection rates after breast-conserving surgery as a performance indicator

Introduction of a case-mix model to allow comparison between Dutch hospitals

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AbstractAim:

Re-resection rate after breast conserving surgery (BCS) has been introduced as an indicator of quality of surgical treatment in international literature. The present study aims to develop a case-mix model for re-resection rates and to evaluate its performance in comparing results between hospitals.

Methods:

Electronic records of eligible patients diagnosed with in-situ and invasive breast cancer in 2006 and 2007 were derived from 16 hospitals in the Rotterdam Cancer Registry (RCR) (n=961). A model was built in which prognostic factors for re-resections after BCS were identified and expected re-resection rate could be assessed for hospitals based on their case mix. To illustrate the opportunities of monitoring re-resections over time, after risk adjustment for patient profile, a VLAD chart was drawn for patients in one hospital.

Results:

In general three out of every ten women had re-surgery; in about 50% this meant an additive mastectomy. Independent prognostic factors of re-resection after multivariate analysis were histological type, sublocalisation, tumour size, lymph node involvement and multifocal disease. After correction for case mix, one hospital was performing significantly less re-resections compared to the reference hospital. On the other hand, two were performing significantly more re-resections than was expected based on their patient mix.

Conclusions:

Our population-based study confirms earlier reports that re-resection is frequently required after an initial breast-conserving operation. Case-mix models such as the one we constructed can be used to correct for variation between hospitals performances. VLAD charts are a valuable tool to monitor quality of care within individual hospitals.

Introduction

The introduction of performance indicators in Dutch hospitals has resulted in better transparency and improved quality of hospital care. Medical consultants and hospital management are increasingly aware of the standards they have to meet. Unfortunately, the use of performance indicators can be problematic, especially when definitions and inclusion criteria differ.

In 2008 the performance indicator “Percentage of patients in whom cancer tissue was left behind after a first breast-conserving operation” was introduced for the Netherlands [1-2]. Eligibility for breast-conserving surgery (BCS) for patients with breast cancer is determined by tumour size, the ratio of tumour size to breast size, and the location of the tumour. In case of narrow or positive margins, the effect of adjuvant radiotherapy may be considered insufficient to achieve local tumour control and hence a re-excision will be required. However, a large variation in re-excision rates exists. International hospital-based studies report re-excision rates ranging from 20-50%. To reduce this variation it has been proposed to compare hospitals or surgeons in a region or country, e.g. to use re-resection rates as a performance indicator.

For performance indicators to be useful in clinical practice they have to be valid and precise, and need to stimulate interventions in case of aberrant results [3]. Therefore, case-mix adjustment is absolutely necessary to control for variation between patient series and allow comparison between hospitals [4-5]. Otherwise, for example, surgeons who only perform BCS for undemanding cases would automatically achieve superior results, and surgeons operating more difficult cases would be ‘blamed’.

The present study aims to develop a case-mix model for re-resection rates and to evaluate its performance in comparing results between hospitals. In addition, to monitor variation over time within individual hospitals the Variable Life-Adjusted Display (VLAD) chart was used.

Patients and methods

Electronic records of patients diagnosed with in-situ and invasive breast cancer in 2006 and 2007 were derived from the Rotterdam Cancer Registry (RCR) (n=4348). The RCR covers the south-western part of the Netherlands, a region with 16 hospitals and 2.4 million inhabitants. Specially trained registration clerks collect medical information on patient characteristics, tumour type (ICD-O topography and morphology), extent of disease (TNM) and treatment for all newly-diagnosed patients with cancer. The region comprises one university hospital, 5 training hospitals and 10 general hospitals. The annual number of primary operations for breast cancer ranges from 50 to 310. Eight hospitals perform less than 100 breast cancer operations per year.

Patients with clinical T3 or T4 tumours, bilateral tumours and metastasis at diagnosis were excluded from this study, since these patients were not eligible for BCS (n=930). Patients who were eligible (n=3418), but underwent mastectomy as a primary treatment or received chemotherapy in the neo-adjuvant setting (n=1495), were also excluded.

Re-resection was defined positive when the patient had to undergo at least one more operation. A total of 45 patients underwent more than 2 operations but were only counted once as a re-resection. Documented independent variables were age (< 50 years, 50-59 years, 60-69 years and \geq 70 years), tumour histology (ductal, lobular, other), tumour size (in-situ, \leq 2 cm, 2-5 cm), axillary lymph node status (negative/positive), multifocality (no/yes), oestrogen-receptor status, progesterone-receptor status and Her2/neu status (all three variables: negative/positive), Bloom-Richardson grading (1/2/3/unknown), lateralisation (left/right), sublocalisation (nipple and central portion of the breast, upper-inner quadrant, lower-inner quadrant, upper-outer quadrant, lower-outer quadrant, axillary tail, overlapping/NOS), and having a preoperative diagnosis (yes/no). This last determinant was defined as "no" when the date of incidence was the date of surgery.

Bivariate associations between these independent variables and re-resection rates were tested using the chi-squared test. To assess the association in a multivariate model, a stepwise reverse (0.2 level of significance for removal) logistic regression model was built. Only variables significantly improving prediction ($p < 0.05$) were included in the final model. Lack of preoperative diagnosis was not included in the model because this could mask poor performance of individual hospitals.

The discrimination of the model was evaluated by assessment of the area under the receiver operating curve (ROC) (c-index) [6] and the goodness of fit was tested with the Hosmer-Lemeshow statistic [7]. For this test, patients are ranked according to the estimated re-resection rate and are divided in 10 approximately equal groups (deciles). The observed and expected number of re-resections per group are compared using a chi-squared test. All analyses were performed using Stata 9.0 (StataCorp LP).

To illustrate the opportunities of monitoring re-resections over time, after risk adjustment for patient profile, a VLAD chart [8] was drawn for patients in one hospital. Within a VLAD chart, the cumulative difference between the observed and expected number of re-resections is plotted against the operation number. Around the expected number, 95% control limits were constructed using the Wald approximation for binomial proportions [9]. Monitoring of an average hospital is expected to produce a jagged curve that strides along the X-axis. Curves that cross the upper or bottom control line suggest a hospital with re-resection rates that are significantly higher or lower than average. VLAD charts can be constructed using a standard spreadsheet computer program [10].

Results

Table 1 presents the characteristics of the study population and the tumours. In this sample of women undergoing BCS, only 102 women were aged under 40 years, and 47 women were aged 80 years or older. Therefore, subdivisions for age were made as follows: under 50, 50-59, 60-69 and 70 years and older. The mean age at diagnosis was 57.9 years. Most patients were diagnosed with a ductal carcinoma. Almost 50% of the tumours were situated in the upper outer quadrant of the mamma. Two thirds of the malignant tumours were less than 2 cm, i.e. T1 tumours. Lymph node involvement was present in 441 patients. Most tumours were moderately differentiated. Differentiation grade was not mentioned for 97 tumours. Multifocal disease was seen in 317 (16.5%) of the tumours, and 10% of the population did not have a histologically confirmed preoperative diagnosis.

About 3 out of every 10 women required at least one re-resection (555/1923 = 28.9%). Of the 555 patients with a re-resection, 265 patients received a subsequent breast excision and 290 patients required a mastectomy. In Table 1, patients undergoing two or more re-resections were counted only once.

Table 2 shows the most significant univariate associations between prognostic determinants and the percentage of women who underwent a re-resection after BCS. Re-resections were more common in younger patients, lobular carcinomas, tumours located in the lower inner quadrant or central part (nipple and central portion of the breast), carcinoma in-situ, or T2 tumours and multifocal tumours. A large variation in re-resection percentages between the 16 hospitals in the RCR region was also observed ($p < 0.01$). Four hospitals performed re-resections in 10-19% of the patients, seven in 20-29% and five hospitals performed re-resections in more than 30% of the patients.

Independent prognostic factors of re-resection after multivariate analysis were histological type, sublocalisation, tumour size, lymph node involvement and multifocal disease (Table 3). The final model showed adequate discrimination (area under the ROC 0.72) and reasonable fit [Hosmer-Lemeshow test chi-square = 7.11 with 6 DF and $p = 0.31$ (8 groups)]. Compared to ductal and other histology tumours, patients with lobular tumours have a 54% higher risk for re-resection. The odds ratios (OR) for re-resection of carcinoma in-situ and T2 tumours with positive lymph nodes are 6.2 and 2.6, respectively. The OR for multifocal tumours is 3.5. Compared to tumours located in the upper quadrants of the breast, tumours in the caudal part, in the central part or overlapping parts have a 38, 48 and 56% higher risk for re-resection, respectively. The baseline probability of re-resection (15.6%) is determined by the intercept of the prediction model, and this value applies to a patient having a T1 ductal carcinoma without lymph node involvement and unifocal disease in one of the upper quadrants.

After correction for case mix, one hospital was performing significantly less re-resections compared to the reference hospital. On the other hand, two were performing significantly more re-resections than was expected based on their patient mix. There was no association between

primary mastectomy rates and adjusted re-resection rates for individual hospitals, p for trend = 0.99 (Figure 1).

As an example, Figure 2 shows a representative VLAD chart for one of the hospitals. This hospital is performing more re-resections than expected based on its case mix; 40 re-resections versus 21 expected for 74 operations. After operation number 37, the line crosses the upper 99% CI. After operation 64 the line seems to stabilize, possibly suggesting a change in the clinical management of this hospital.

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Discussion

The introduction of performance indicators in Dutch hospitals has given an important impulse to transparency and quality of care. Medical consultants and hospital management are increasingly ambitious to meet the standards. This has led to a vibrant polemic about hospital performance statistics in medical journals and newspapers. There are, of course, some reservations with respect to the influence of chance and diversity of diseases between hospitals ('case mix'), but performance indicators have at least succeeded in stimulating the discussion about definitions and case mix.

In international literature, the frequency of re-resections after BCS has been suggested as an indicator of surgical performance. The Dutch Surgical Association proposed the performance indicator "Percentage of patients in whom cancer tissue has been left behind after a first breast conserving operation", because of a general belief that results could be improved. Especially with newly-defined indicators, results may initially differ between hospitals because of differences in interpretation of coding regulations. Clinicians may be inclined to register results in their favour, especially because of the critical response of patient associations and health insurance agencies. Successfully acquired professional reputations can be destroyed in a single day after inaccurate reports in the media.

A recent Dutch study showed that the lack of a single definition and the lack of case-mix correction for patient group composition undermine the validity of the indicator[11]. Based on data from the independent Rotterdam Cancer Registry, we developed a case-mix model to appraise inter-hospital variation in re-resection rates after BCS.

Our population-based study corroborates earlier reports that re-resection is frequently required after an initial breast-conserving operation. In this sample of women, nearly 30% required re-resection (14% re-excision lumpectomy, 15% mastectomy after BCS). Independent prognostic factors of re-resection after multivariate analysis were histology type, sublocalisation, tumour size, lymph node involvement and multifocal disease. The present study also shows the importance of a pre-operative diagnosis to prevent re-resections. Lack of pre-operative diagnosis was deliberately not included in the multivariable model to ensure that inadequate diagnostics in a hospital would not be masked.

The 29% re-resection rate found in our region is much higher than the 20% standard postulated by the Dutch Health Care Inspectorate in 2008, and also higher than the percentages reported by other European studies. If the in-situ carcinomas are excluded from our study, a 24% re-resection rate remains. American studies, however, report even higher rates. Table 4 gives an overview of recent studies reporting patient, tumour and treatment-related prognostic factors associated with re-resection rates [12-18]. None of these studies were population based and all had different patient characteristics. Based on the results, a 20% standard will not be easy to accomplish in all hospitals. The question remains whether it is

indicated to set a standard based on data from literature, or to set it higher than average - as has been done in the Netherlands.

For various reasons, the results from the studies listed in Table 4 differ from each other and cannot easily be compared. Similar difficulties tend to occur when comparing re-resection rates between hospitals in the Netherlands. First, study groups vary in the proportion of ductal carcinomas in situ (DCIS) and in the proportion of patients without a preoperative diagnosis, both strong predictors of re-resection. Secondly, selection criteria for BCS may differ. Patients with a primary operable breast tumour can choose between lumpectomy and mastectomy as a surgical procedure. Despite common preoperative work-up, considerable differences in primary BCS percentages were observed in the region of the RCR; this is in accordance with an earlier study based on data from 6 other regions in the Netherlands [19]. This can introduce a selection bias; however, we cannot show this with the present data as no relation was found between primary mastectomy rates and re-resection rates for the 16 hospitals in our region.

Case-mix models (such as the one we constructed) can be used to correct for variation between hospitals. VLAD charts are a valuable tool to monitor quality of care within individual hospitals. All the present results were reported to the individual hospitals in the form of VLAD charts, to enable the hospitals to compare their results with the benchmark. After correction for case mix, one of the regional hospitals (A) was shown to perform significantly less re-resections compared to the reference base. Two other hospitals (O and P) performed significantly more re-resections than was expected based on their patient mix. However, variation may still be explained by residual confounding. Our model was developed for this particular study and cannot be used in other populations or periods without prior validation. To improve the model, additional prognostic factors could be added, such as breast size, mammographic density (which is age dependent) and size of the in-situ component.

The strength of this study lies in its sample size, its population-based nature and the independent assessments of results. Furthermore, the data are not collected by hospital staff, but by trained registration clerks who use uniform definitions and are not subject to observer bias.

During the study period, margin status was not yet scored by the cancer registry. This is unfortunate, because a positive margin after breast conservation therapy (BCT) has been the primary endpoint of several hospital-based studies over the last few years [20-22]. It is important to realize that positive margins and re-resections are not synonymous. It is evident that BCS requires clear surgical margins to minimize local recurrence. The question remains at what point margins should be considered clear, i.e. when re-resection is not indicated. Some studies consider margins > 2 mm as clear, others use a margin > 1 mm, and some even rely on radiotherapy to deal with focal irradiability. Similarly, clinicians also differ in their management of close margins. For example, in the Netherlands DCIS specimens are not considered safe until a

tumour-free margin of 10 mm or more is reached. Also, re-resection may be performed for multifocal lesions, in case of genetic disposition, or after diagnostic surgery. As a result, re-resection rates and positive margin rates cannot readily be compared.

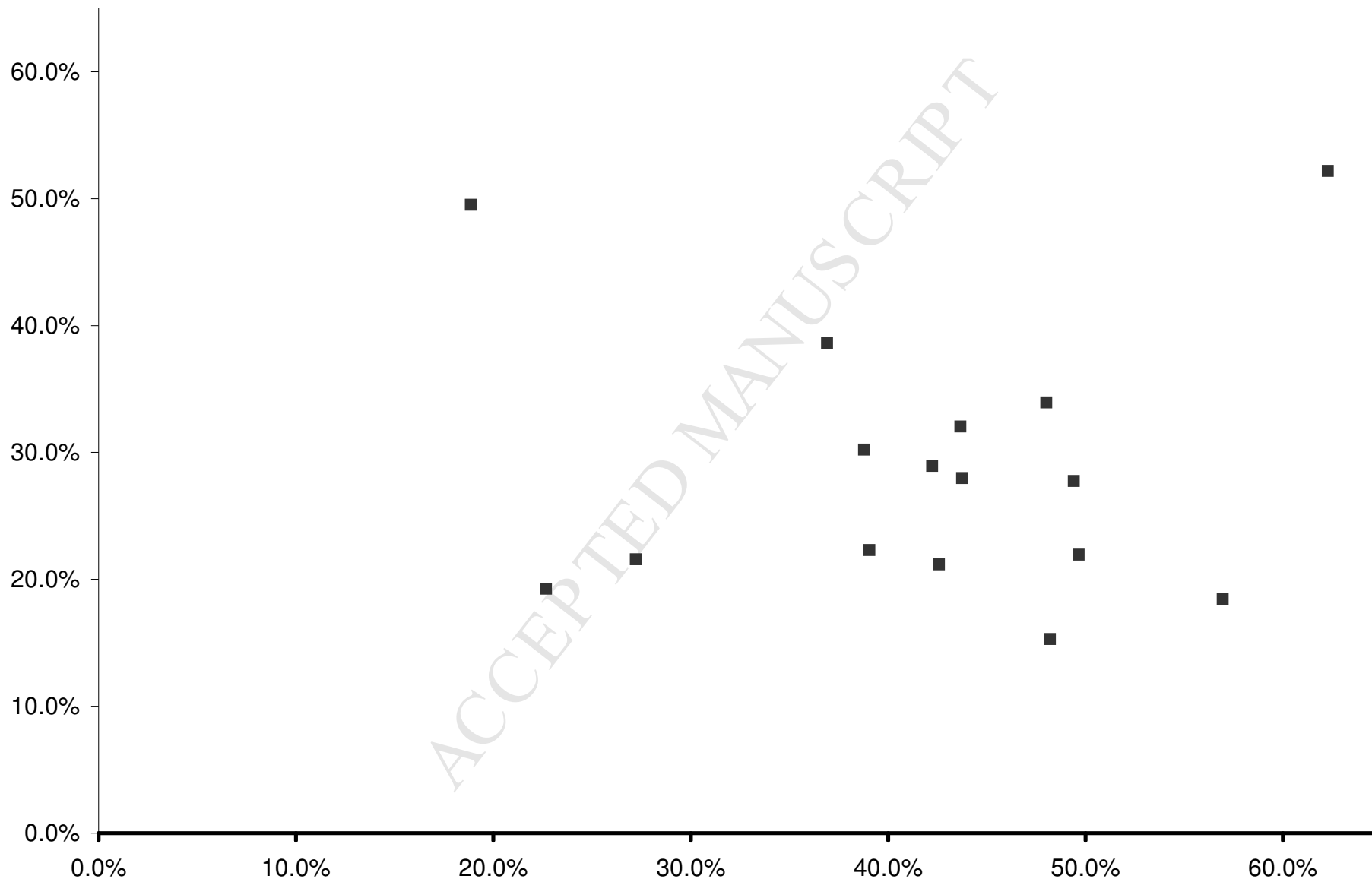
In conclusion, performance indicators have stimulated professional discussions on determinants of the quality of care. Re-resection rate can be used as a performance indicator, provided that results are interpreted critically and controlled for case mix and the clinician-related management of (focal) irradical margins. Case-mix models, based on independent registration, are powerful tools to audit and monitor hospital care resulting in more valid and reliable performance indicators.

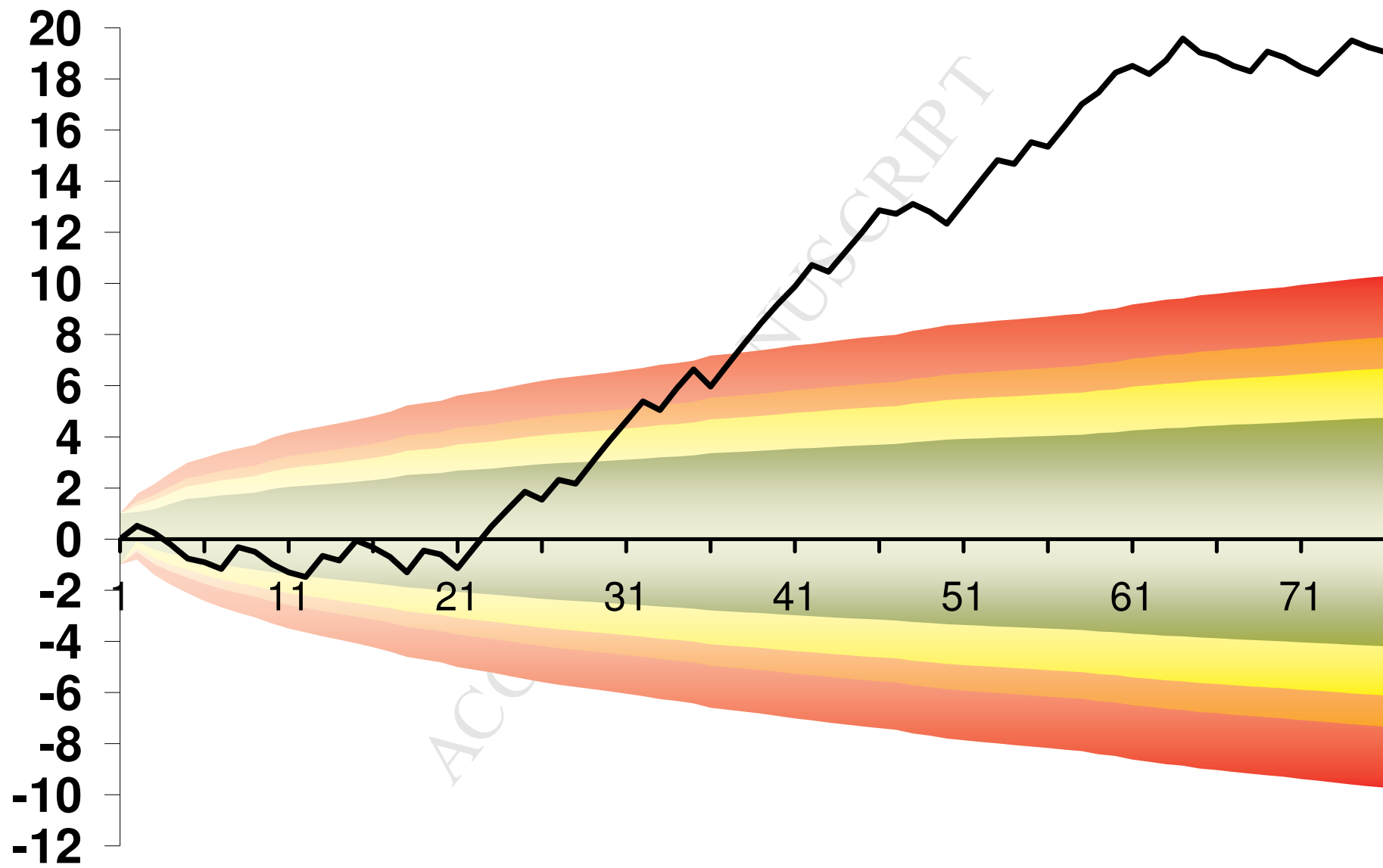
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Tables & Figures Talsma et al. Re-resection rates after BCS

Table 1 Patient and tumour characteristics of the study population.

		n	%
Age (years)	≤ 49	443	23.0
	50-59	613	31.9
	60-69	574	29.9
	≥ 70	293	15.2
Histology	ductal	1589	82.6
	lobular	225	11.7
	other	109	5.7
Tumour location in breast	Upper outer	932	48.5
	Upper inner	245	12.7
	Lower inner	195	10.1
	Lower outer	149	7.8
	Central	167	8.7
	Overlapping	235	12.2
T stage	Tis	257	13.4
	T1	1201	62.4
	T2+	150	24.2
N stage	N0/X	1482	77.1
	N+	441	22.9
Tumour grade	Low	402	20.9
	Moderate	798	41.5
	High	626	32.6
	Not specified	97	5.0
Multifocal disease	Yes	317	16.5
	No	1606	83.5
Preoperative diagnosis	Yes	1696	88.2
	No	227	11.8
Total		1923	
Re-resection	Yes	555	28.9
	No	1368	71.1
Type of re-resection	Re-excision	265	13.8
	Mastectomy	290	15.1

Table 2 Univariate analysis for re-resections after breast-conserving surgery.

		Re-resection		Total	% re-resection	p
		Yes	No			
Histology	Lobular	82	143	225	36.4%	0.01
	Ductal/NOS	473	1225	1698	27.9%	
Age (years)	<49	145	298	443	32.7%	0.02
	50-59	189	424	613	30.8%	
	60-69	150	424	574	26.1%	
	70+	71	222	293	24.2%	
Tumour location	Cranial	306	871	1177	26.0%	0.00
	Caudal	107	237	344	31.1%	
	Central	57	110	167	34.1%	
	Overlapping	85	150	235	36.2%	
T stage	Tis	147	110	257	57.2%	0.00
	T1	258	943	1201	21.5%	
	T2+	150	315	465	32.3%	
N stage	N0/X	410	1072	1482	27.7%	0.03
	N1+	145	296	441	32.9%	
Histologic grading	Grade I	98	304	402	24.4%	0.00
	Grade II	215	583	798	26.9%	
	Grade III	213	413	626	34.0%	
	Not specified	29	68	97	29.9%	
Multifocal disease	Yes	159	158	317	50.2%	0.00
	No	396	1210	1606	24.7%	
Hormonal receptor status	in-situ	146	111	257	56.8%	0.00
	Oestrogen +	289	911	1200	24.1%	
	HER2neu +	76	173	249	30.5%	
	Triple negative	44	173	217	20.3%	
Pre-operative diagnosis	Yes	426	1270	1696	25.1%	0.00
	No	129	98	227	56.8%	

4 hospitals performed 10-19% re-resections

7 hospitals performed 20-29% re-resections

5 hospitals performed $\geq 30\%$ re-resections

Table 3 Multivariate analysis of factors* associated with the risk of re-resection.

		Coefficient	Odds Ratio	95%CI	
Intercept		-1.86			
Histology	Lobular	0.43	1.54	1.13	2.11
	Ductal/NOS	ref.	1		
T & N stage	Tis	1.83	6.21	4.57	8.44
	T1N0	ref.	1		
	T1N1	0.41	1.50	1.08	2.09
	T2N0	0.42	1.52	1.10	2.09
	T2N1	0.97	2.64	1.86	3.74
Multifocal disease	Yes	1.26	3.52	2.70	4.58
	No	ref.	1		
Tumour location	Cranial	ref.	1		
	Caudal	0.32	1.38	1.04	1.83
	Central	0.39	1.48	1.02	2.14
	Overlapping	0.44	1.56	1.12	2.15

* Factor 'preoperative diagnosis' not entered into the model

Note: The probability of re-resection p for a single patient can be calculated with the formula $\ln(p / 1-p) = \text{total risk score}$. This risk score is obtained by adding the appropriate coefficients to the Intercept and this value applies to a patient having a T1 ductal carcinoma without lymph node involvement and unifocal disease in one of the upper quadrants. A patient with a ductal tumour, T2N1, multifocal disease and tumour localisation in the caudal part of her breast will have a risk score of $(0 + 0.97 + 1.26 + 0.32 - 1.86) = 0.69$, which corresponds to an expected risk of 66.6%. The baseline probability of re-resection (13.5%) is determined by the intercept of the prediction model.

Figure 1. Association* between primary mastectomy rates (X-axis) and adjusted re-resection rates (Y-axis) for individual hospitals.

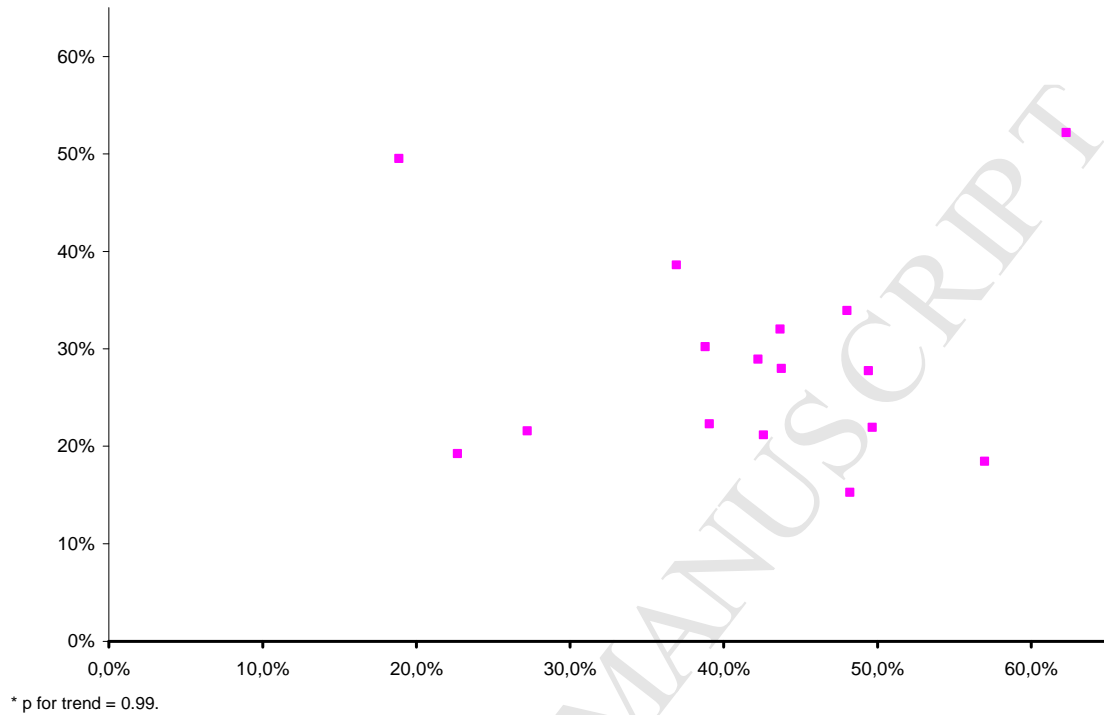
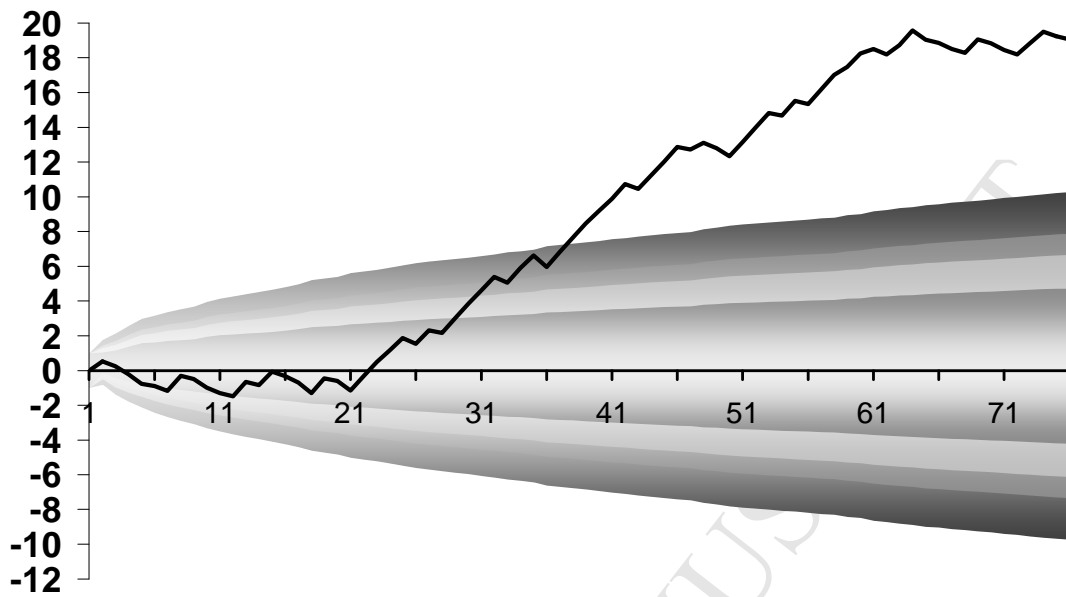


Figure 2. Example of a Variable Life-Adjusted Display chart for an individual hospital*



* This hospital performs more re-resections than expected based on its case mix. After operation number 37, the line crosses the upper 99% CI. After operation 64 the line seems to stabilize, suggesting that a change was made in the clinical management of this hospital.

Table 4. Summary of results of earlier studies reporting re-resection rates*.

First author, year of publication	No. of patients	Inclusion	Result	Aim	Prognostic factors
Smitt 2007	395	Stage I/II invasive BC 1971-1996 Hospital based USA	56% re-excision	Evaluate impact of preoperative diagnosis relative to clinico-pathologic factors in obtaining negative lumpectomy margins	
Mullenix 2004	204 (150 BCT)	Invasive BC 1998-2002 1 hospital USA	51% re-resection	Compare the number and type of surgeries required for BCT versus mastectomy	BCT, positive margins at initial excision
Waljee 2008	900	Invasive BC 2002-2006 1 hospital USA	48.6% re-resection (10.8% ablatio)	Describe patient and treatment-related factors associated with re-excision lumpectomy and mastectomy after BCS	Breast size, surgical biopsy method, timing of chemotherapy, tumour histology
Meijnen 2007	504	DCIS 1986-2005 1 hospital Netherlands	46% re-excision	Evaluate effect of different treatment modalities on the clinical outcome of patients with DCIS and identify factors associated with local recurrence	
Ramanah 2008	206	T1 invasive BC 2002-2005 1 hospital France	41% re-resection	Find predictive factors related to re-excision in this specific group	Lack of preoperative diagnosis, limited superficial or deep surgical resection, multifocal lesion, size of the in-situ carcinoma
Lovrics 2009	489	Invasive BC 2000-2002	26% positive margins	Identify technical factors predictive of negative margins after BCT	Lack of preoperative diagnosis, tumour size, histology, cavity margin dissection, volume of excision

Landheer 2004	240	DCIS and Invasive BC 1997-2002 2 hospitals Netherlands	26% re-resection (BCT + mastectomy at start)	Compare results of surgical treatment for non-palpable BC between university teaching and general teaching hospital	
Keskek 2004	301	DCIS & stage I/II invasive 1997-2002 1 hospital Great Britain	24% re-resection	Examine the incidence of residual carcinoma in total cavity margins following BCT	Tumour size, lobular histology, DCIS
Bani 2008	565	Unilateral invasive BC 2002-2006 1 hospital Germany	21% re-resection	Analyze prospectively documented data in relation to factors that may be associated with a higher rate of re- excision	Mammographic density, tumour size, multifocal, in-situ component
Gooiker 2010	762	CIS & invasive BC 2007-2008 Cancer Centre West Netherlands	21% involved margins	Determine whether surgery quality indicator 'positive margin after BCT' is independent of definition and differences in case mix.	Most hospitals fell within standard after case-mix correction
Soucy 2008	478	Invasive BC 2003-2006 1 hospital Canada	18% re-resection 21% after neoadjuvant chemotherapy	Compare margin involvement for BCT specimens from patients treated initially with operation and those after receiving neoadjuvant chemotherapy	Carcinoma type, hormonal receptor status
Kurniawan 2008	1648	CIS & invasive BC 1994-06 Screened population Australia	17.1% re-resection (diagnostic biopsy excluded)	Find factors associated with margin status. Re-excision rates were also examined.	Lack of preoperative diagnosis, tumour size, multifocal disease are related to positive margins
Boughey 2006	509 (241 BCT)	Stage I-III A invasive BC 1998-05 2 clinical trials USA	14.5% re-excision	Study the effect of preoperative versus postoperative chemotherapy on the volume and number of operations	

*BC=breast cancer; BCT/S=breast-conserving therapy/-surgery; (D)CIS= (ductal)carcinoma in situ