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Adherence to the guidelines of the CCCE in the treatment of node-positive breast cancer patients

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Abstract

Guidelines are tools to improve the quality of care in daily practice. To accomplish adherence, active implementation is needed. The effect of audit, group-oriented feedback and educational activities to increase guideline adherence were investigated in this study. Treatment according to a guideline for premenopausal node-positive breast cancer patients from 1988 to 1992 (P1) and from 1996 to 1998 (P2) was assessed using the following indicators: percentage of patients with breast-conserving surgery, secondary surgery, $\geqslant 10$ reported resected axillary lymph nodes, reported tumour differentiation grade, reported hormonal receptor status, chemotherapy received (CT), start of CT $\leqslant 28$ days after surgery, Dose Intensity (DI) $\geqslant 85\%$ and completion of CT $\leqslant 1$ week beyond the ideal duration of CT. Data were audited from patients' records. The first audit resulted in a quality programme with feedback focused on the delivery of chemotherapy and resected axillary lymph nodes and educational sessions. A Fisher's exact test was used to estimate significant differences between the two time periods. In P1, 323 patients and in P2, 155 patients were eligible for treatment according to the guideline. The percentage of patients with $\geqslant 10$ lymph nodes improved from 65.3 to 81.3% ($P=0.0004$), as did the percentage with a reported oestrogen receptor (ER) status, from 84.8 to 96.8% ($P=0.00004$), progesterone receptor (PR) status from 82.3% to 97.4% ($P<0.000001$) and with a DI $\geqslant 85\%$, from 74.9 to 93.9% ($P=0.000003$). Adherence varied between the hospitals. In conclusion, significant improvements were observed for the indicators of resected axillary lymph nodes and DI of chemotherapy, which may be attributed to the quality programme. Repeated assessment of the adherence to the guideline is important to observe changes and interhospital variations in order to remain focused on areas for improvement.

Keywords: Guideline implementation; Breast cancer; Quality improvement; Indicators

1. Introduction

Guidelines are regarded as important tools to improve the quality of care in clinical practice. They are produced to provide care based on the best evidence available. By reducing practice variation they may lead to costs savings and better quality of care [1–3]. In general, active implementation is needed to increase guideline adherence. However, which methods are the most effective is still unclear. Both randomised controlled trials and evaluation of guideline implementation programmes are needed to increase our understanding in this area. This paper reports on a regional programme aimed at improving guideline adherence for premenopausal patients with node-positive breast cancer. Audit, feedback and educational activities were part of this programme that was supported by the Comprehensive Cancer Centre East of The Netherlands (CCCE). This is one of the nine comprehensive cancer centres that cover cancer care in The Netherlands. It serves a population of approximately 1.5 million inhabitants and has 10 hospitals, including one university hospital and two teaching hospitals. In 1993, the CCCE decided to evaluate its efforts put in evidence-based guideline generation and distribution by a retrospective audit of guideline adherence. The guideline for primary breast cancer was chosen, because it was felt that every surgeon and physician should be conversant with this

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tumour. Results of this audit, which started in 1994, were published in 1999 and 2002 [4,5]. The present study compares guideline adherence between the two periods, 1988–1992 and 1996–1998 for the unchanged advices mentioned in Table 1, in order to assess the effect of the audit and feedback and educational activities between these periods.

2. Patients and methods

2.1. Design

This is a retrospective uncontrolled before-after comparison study.

2.2. Patient selection

Patients $\leqslant 56$ years old with primary breast cancer stage II to IIIa, according to the Tumour, Node, Metastases (TNM) classification of the International Union Against Cancer (UICC) as confirmed in 1978, were traced by the Dutch Cancer Registry and identified as eligible if premenopausal and treated in the CCCE.

Patients were defined as premenopausal if they had menses or were using hormonal replacement therapy or contraceptives in the last year before the histological diagnosis of breast cancer or if Follicle Stimulating Hormone (FSH) and oestradiol indicated premenopause according to local normal values when menses were absent for more than one year due to a previous hysterectomy.

Patients treated in the two periods were identified: 1988–1992 (P1) and 1996–1998 (P2).

2.3. Materials and methods

2.3.1. Development of the guideline

A draft commission was formed consisting of six surgeons, two physicians, three radiotherapists, one radiologist and one pathologist, together representing all hospitals in the region. These specialists reviewed the literature on primary breast cancer treatment using Medline and literature on the topic found by other sources and documented recommendations based on evidence. Levels of evidence were not indicated at that time, but randomised controlled trials were regarded as the 'gold standard' of evidence. These recommendations were then discussed with all the members of the CCCE treating breast cancer patients. Recommendations without a sound body of evidence were accepted when the majority agreed.

Table 1
Summary of guideline advices

Surgery:
Breast-conserving surgery unless:
Large tumours (>3–4 cm)
Multifocal tumours
Expected unsatisfactory cosmetic result
Tumour fixed to skin, pectoral muscle or fascia
Axillary lymph node clearance:
Complete removal of all axillary lymph nodes
Pathologist should report:
Largest tumour size
Histological type
Differentiation grade
Resection margins and radicality of tumour removal
Invasion of adjacent structures
Number of investigated axillary lymph nodes
Number of lymph nodes with tumour involvement
Level of tumour-involved lymph nodes
Hormonal receptor status: oestrogen and progesterone receptors
Radiotherapy should be given:
To the breast for all patients treated with breast-conserving surgery
To the axillary, infra- and supra-clavicular lymph node regions in cases of suspected residual tumour after axillary lymph node resection
To the thoracic wall in cases of suspected irradical tumour resection
Adjuvant chemotherapy:
Is indicated for all premenopausal node-positive breast cancer patients stage II-IIIa according to the TNM classification of the UICC (1978)
Should start within 28 days after surgery
Should consist of six courses CMF
Dose adjustments and delays according to international rules for toxicity

CMF, cyclophosphamide; methohexate and 5-fluorouracil; UICC, International Union Against Cancer; TNM, Tumour, Node, Metastases.

The guideline was then edited in the house-style of the guidelines from the CCCE and printed as a 48-page booklet in 1988.

2.3.2. Distribution of the guideline

The guideline was sent to all surgeons, pathologists, radiotherapists and physicians working in the CCCE and to the departments of surgery, radiotherapy, pathology and internal medicine in all of the hospitals. Five hundred copies were printed.

2.3.2.1. The guideline. The guideline described the indications for surgery, radiotherapy and chemotherapy for primary breast cancer patients (Table 1). Adequate axillary lymph node clearance was described as the complete removal of axillary fat, including interpectoral fat and the upper axilla. The inferior margin was described as the line between the axillary fat and the most lateral part of the breast gland, the superior margin as the axillary vein, the dorsal margin as the rim of the *latissimus dorsi* muscle and the ventral margin as the rim of the *pectoralis major* muscle. The upper axilla was described as located medial from the *pectoralis minor* muscle on the thoracic wall under the subclavian vein. The timing of radiotherapy, when needed, was left to the discretion of the treating physicians. The chemotherapy schedule consisted of cyclophosphamide (C) orally 100 mg/m^2 days 1–14, methotrexate (M) 40 mg/m^2 intravenously (i.v.) days 1 and 8 and 5-fluorouracil (F) 600 mg/m^2 i.v. days 1 and 8 as first described by Bonadonna and colleagues in Ref. [6]. Indications for dose reductions and delays were described according to international standards.

In 1994, a national guideline was published for the use of haematopoetic colony stimulating factors (CSF) to retain a good dose intensity of adjuvant chemotherapy.

2.3.2.2. The quality improvement programme. The quality improvement programme was intended for the breast cancer group, consisting of all specialists who treat breast cancer in the region. This group meets every 3 months to discuss various aspects of breast cancer treatment, including trials. The programme included the following activities.

2.3.2.2.1. Audit and feedback. Between 1993 and 1996, repeated feedback on the performance of the chemotherapy administration, timing and dosing was given to the breast cancer group. The feedback was given in the form of oral presentations, during three breast cancer group meetings (followed by minutes and handouts of these meetings sent to all the members). The results were also presented at two national conferences attended by most regional specialists and as a poster presentation at an international conference, which was also sent as a handout to all contributing regional specialists. The feedback consisted of a demonstration of variation in performance between the different hospitals and the region as a whole. It was a regional, but not a hospital- or specialist-specific feedback.

2.3.2.2.2. Educational activities. Important literature that became available in that period on the dose intensity of chemotherapy, sequencing of radiotherapy and the importance of adequate axillary lymph node clearance were discussed in four consecutive meetings of the breast cancer group to endorse the advice in the guideline [7–10].

2.3.2.3. Indicators. To assess indicators, the following variables were abstracted from the patients' records: menopausal state, height and weight, date of histology, date and type of surgery, date and type of secondary surgery (if applicable), tumour size, type of histology, differentiation grade, hormonal receptor status, number of examined and tumour-involved lymph nodes, dates of start and cessation of chemotherapy and type and dose and delay of each course of chemotherapy.

The following defined indicators were chosen for their potential to assess guideline adherence and for the evidence of their importance for the prognosis and quality of care of the patient: percentage of patients with breast-conserving surgery and secondary surgery, percentage of patients with more than 10 reported resected lymph nodes, with pathology reports reporting differentiation grade, with a known hormonal receptor status, receiving chemotherapy, as advised in the guideline, who started chemotherapy within the advised 28 days after completion of surgery, who completed chemotherapy within 1 week after the ideal time of completion, and with a dose intensity (DI) of chemotherapy of $\geqslant$85%. DI was defined as a percentage of the intended dose. A good DI was defined as $\geqslant$85%. For the patients who received anthracyclines in the P1 group, no doses were registered.

2.4. Statistics

A two-tailed Fisher's Exact Test (SAS Institute Inc., Cary, NC, USA) was used to estimate any significant differences in the indicators between the two treatment periods.

3. Results

The results are presented in Table 2. In the period P1, 323 patients were eligible and traceable. In the period P2, 155 patients were eligible and traceable.

3.1. Surgery

In the P1 group, 127 (39.3%) patients underwent breast-conserving surgery, 182 (56.3%) a mastectomy,

Table 2
Quality indicators in periods 1 and 2

	Period 1 1988–1992 *N* (%)	Period 2 1996–1998 *N* (%)	Period 2 Range between hospitals (%)	Significance
Number of eligible patients	323	155		
Type of surgery				
Breast-conserving	127 (39.3)	55 (35.5)	14.3-100	N.S.
Mastectomy	182 (56.3)	84 (54.2)	0-71.4	N.S
Secondary ablation	14 (4.3)	16 (10.3)	0-28.6	$P=0.015$
$\geqslant 10$ investigated lymph nodes	211 (65.3)	126 (81.3)	21.4-100	$P=0.0004$
Reporting of differentiation grade	209 (64.7)	107 (69.0)	0-93.8	N.S.
Reporting of ER	274 (84.8)	150 (96.8)	85.7-100	$P=0.00004$
Reporting of PR	266 (82.3)	151 (97.4)	86.4-100	$P<0.000001$
Receiving CT	295 (91.3)	136 (87.7)	71.4-100	N.S.
Starting CT $\leqslant 28$ days	74 (25.7)	32 (23.7)	0-46.1	N.S.
DI $\geqslant 85$	167 (74.9)	123 (93.3)	66.7-100	$P=0.000003$
Completion of CT $\leqslant$ ideal duration $+7$ days	173 (59.9)	90 (67.2)	40-100	N.S.

N.S., non-significant; ER, oestrogen receptor status; PR, progesterone receptor status; CT, chemotherapy; DI, % of intended dose.

and 14 (4.3%) a secondary ablation. In the P2 group, these figures were 55 (35.5%), 84 (54.2%), and 16 (10.3%), respectively. The variation in breast conserving surgery between hospitals in the P2 time period was large: from 14.3 to 100%. The increase in secondary ablations was significant ($P=0.015$). The number of patients with $\geqslant 10$ examined lymph nodes was 211 (65.3%) in P1 and 126 (81.3%) in P2. The increase was statistically highly significant ($P=0.0004$). However, when considering the individual hospitals in P2, a striking variation in performance was seen, with three hospitals in which less than 50% of the patients had $\geqslant 10$ lymph nodes examined, while in two hospitals all patients had $\geqslant 10$ lymph nodes examined (Fig. 1).

3.2. Pathology

In the P1 and P2 periods, reporting of the differentiation grade of the tumour was not significantly different; 209 (64.7%) of the patients in P1 and 107 (69.0%) in P2 were reported. However, the interhospital variation was large (Fig. 2).

ER reporting improved significantly, from 274 (84.8%) in P1 to 150 (96.8%) in P2 ($P=0.00004$), as did

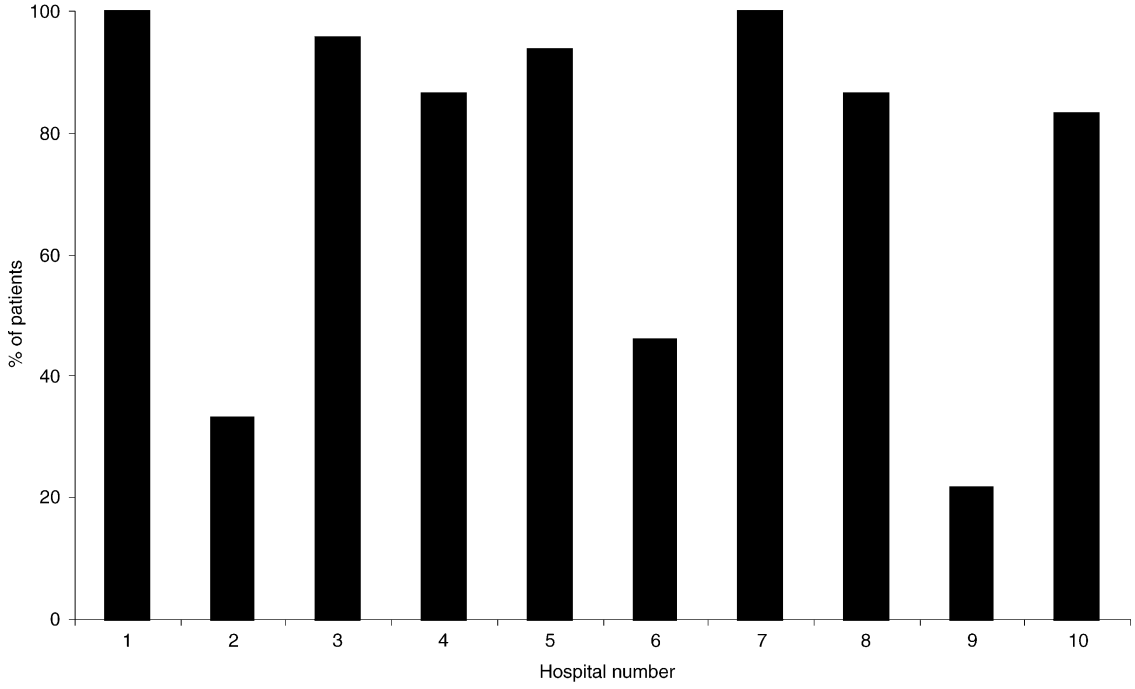

Fig. 1. Percentage of patients with 10 or more axillary lymph nodes investigated.

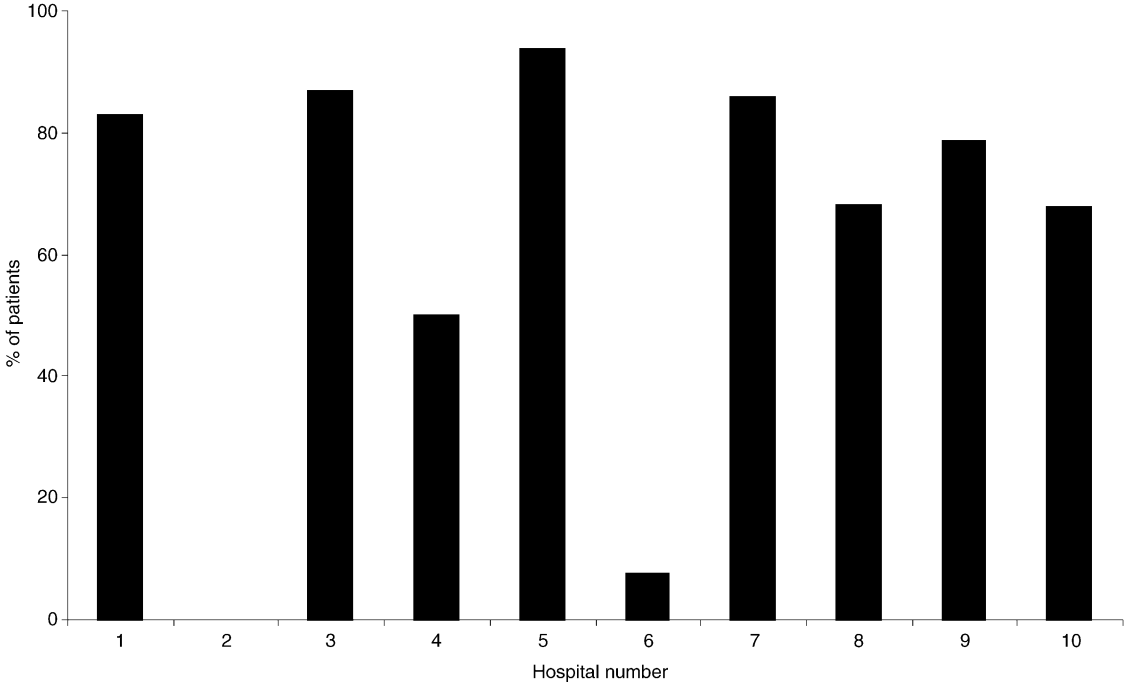

Fig. 2. Percentage of patients with a reported differentiation grade.

PR reporting, from 266 (82.3%) to 151 (97.4%) in P1 and P2, respectively ($P < 0.000001$). In the P2 time period, the ligand binding assay was replaced with immunohistochemistry.

3.3. Chemotherapy

The percentage of patients that received chemotherapy did not change significantly from 295 (91.3%) in P1 to 136 (87.7%) in P2. In P2, the most important reason for not receiving chemotherapy was an incorrect assessment of the postmenopausal state. 9 patients used contraceptives or hormone replacement therapy until surgery, 1 patient was regarded as postmenopausal by the surgeon, but had regular menses and was still premenopausal 1 year later according to her gynaecologist, 1 patient had an abdominal uterus extirpation with ovaries *in situ*, but FSH and oestradiol levels were not checked and for 3 patients no menopausal state could be assessed from their records, but according to their adjuvant therapy (no or endocrine), they were considered postmenopausal. In the periods P1 and P2 the time period between surgery and start of chemotherapy could not be calculated for 7 and 1 patient, respectively.The number of patients that started chemotherapy $\leqslant 28$ days after surgery, as desired, did not change significantly, from 74 (25.7%) in P1 to 32 (23.7%) in P2, and remained low. Again, interhospital variation was large, between approximately 50 and 100% of the patients did not start chemotherapy within the advised time frame in the P2 group.

In P1, 230 (77.7%) patients received CMF chemotherapy and 65 (22.3%), all from one hospital, received anthracycline-based chemotherapy. In P2, 113 (83.1%) patients received CMF chemotherapy and 23 (16.9%) patients (from different hospitals) received anthracycline-based chemotherapy. In P1, DI could not be calculated for 7 patients treated with CMF and 65 treated with anthracyclines. In P2, this could not be calculated for 5 treated with CMF because of missing data. The number of patients with a DI $\geqslant 85\%$ increased from 167 (74.9%) in P1 to 123 (93.9%) in P2, $P = 0.000003$. The duration of chemotherapy was known for 289 patients in P1 and for 134 in P2. The number of patients that completed their chemotherapy within the ideal duration of CT plus 1 week, did not change significantly: from 173 (59.9%) in P1 to 90 (67.2%) in P2.

CSF support was given to 7 patients: to 4 patients for one course and to 1 patient for two, four and five courses, respectively.

4. Discussion

Although performing audits of guideline adherence and providing feedback is an expensive method of quality improvement, monitoring of care by audits may be important and useful.

This report shows that adherence to different guideline advices, measured by indicators, varied depending on the advices, the quality improvement activities, the time and the hospitals. In this discussion, we will focus on reasons why adherence varies between advices and between hospitals.

In summary, improvement of adherence was found for the number of examined lymph nodes, reporting of hormonal receptor status and the DI of chemotherapy.

The number of reported examined lymph nodes depends on both the quality of the axillary dissection procedure and the examination by the pathologist of the specimen obtained. Reasons for improvement could be the longitudinal quality improvement initiatives with audit and feedback to all involved specialists that probably created an awareness among both surgeons and pathologists of the quality of their own procedures. Secondly, due to the audit, the comprehensive cancer centre consultants who became more critical of the quality of the dissection and/or examination of the axillary specimen emphasised the need for improvement. Thirdly, the publication of Overgaard and colleagues in 1997 may also have contributed to the improvement seen [10]. This randomised study showed a decrease in local recurrences after radiotherapy of the axilla. However, the publication led to an international discussion as to whether radiotherapy did not just compensate for an inadequate axillary lymph node clearance, since only 24% of the patients had more than nine axillary lymph nodes resected and the number of local recurrences in the control arm that did not receive radiotherapy was high. The reason why the change in practice in our region was more pronounced in some hospitals than in others is unknown. The hospitals with a low performance had their pathology departments located outside the comprehensive cancer centre region and this may possibly result in less involvement in these regional quality activities.

The significant improvement in the reporting of hormonal receptor status may be attributed to several factors. The ligand binding assay had, in comparison with immunohistochemistry, some major drawbacks. Firstly because it could only be assessed in two approved centres in the region. This required the local pathologists to send some tumour material to these centres. Second of all, it required a certain amount of tissue, which was not always available and, thirdly, it was a very elaborate assay. By contrast, local pathologists can perform immunohistochemistry staining on the available slides without much effort and receive financial incentives for this work. Finally, it has been increasingly acknowledged that the hormonal receptor status is important for the assignment of patients to various adjuvant treatments.

The importance of adequate dosing in chemotherapy was emphasised in the feedback. For DI, it may be hypothesised that the feedback of certain habits in dosing such as unconventional CMF chemotherapy schedules, prevention of bone marrow toxicity by under dosing and interruption of chemotherapy for holidays of patients and doctors had a positive effect [4]. Two publications on the importance of DI in adjuvant chemotherapy for breast cancer by Bonadonna and colleagues [7] and Wood and colleagues [8] in the *New England Journal of Medicine*, also probably influenced our results. Bonadonna and colleagues reported on a retrospective analysis of three categories of DI ($\geqslant 85$, 65–85 and $<65\%$) and Wood on a prospective randomised trial with three categories of DI. They both observed that survival was worse in cases of under-dosing of the chemotherapy [7,8].

Adherence to other advices in the guideline did not improve.

The number of patients who underwent breast-conserving surgery was lower than reported by others [11,12]. One reason could be that our study only reports on node-positive breast cancer patients, who, in general, will have larger tumours than node-negative patients. Another reason may be the fact that in P2 almost 20% of the patients treated in the region were treated in the university hospital, that had a very low breast-conserving surgery rate (17.2%), and this low rate was probably due to the inclusion of more complex cases, especially hereditary breast cancer patients, some of whom were referred from outside of the region. The surgeons advise these patients to have a mastectomy for two reasons: the increased chance of a second primary tumour in these patients and the difficulties in the assessment of new tumours by mammography after breast-conserving surgery and radiotherapy. Patients preferring mastectomy in a more rural area or less specialised surgeons are other possible explanations for the low rate. The number of patients who finally had a secondary ablation increased significantly from 4.3 to 10.3%. Since incomplete resections with tumour-positive margins, including *in situ* carcinoma and multifocality are the main indications for re-resections, it may be hypothesised that resection margins in breast-conserving surgery have decreased between the two time periods or that pathologists more frequently report multifocal tumours.

Differentiation grade is a prognostic factor and according to the guideline should be reported. However, it was under-reported in both time periods. Feedback on this was not given between P1 and P2. At the time of the audits, the differentiation grade was not used as a decision tool for adjuvant therapy and this may also have contributed to its under-reporting. Strikingly, the highest rates of not reporting differentiation grade were again in the pathology departments outside of the region (Fig. 2).

The interval between surgery and chemotherapy did not improve, although feedback was given. Radiotherapy, since it preceded chemotherapy in all but two of the hospitals, plays an important role in the delay of chemotherapy, but is not the only reason for a delay. The evidence that chemotherapy should start within 28 days is not firm, with just one randomised trial that investigated sequencing of chemotherapy and radiotherapy [9]. The trial resulted in only a borderline decrease in the recurrence rate of distant metastases when chemotherapy was given first.

The number of patients who did not receive chemotherapy did not change significantly and neither did the reasons. Undetermined or wrong assessment of the menopausal state was the main problem. However, the guideline was not very clear in its definition of the premenopausal state and this should be changed in the next guideline proposal.

The duration of chemotherapy did not improve significantly. The use of CSF in P2, which could have changed this, was, despite a national guideline for its use in adjuvant chemotherapy, very low. This may be attributed to several factors. Firstly, direct evidence that the use of CSF in routine adjuvant chemotherapy improves survival has not been presented [13]. Second of all, familiarity with the schedule of administration of CSF in adjuvant CMF was at that time not very high. Thirdly, the required extra administration for insurance purposes and the instruction of the patients may have refrained physicians from prescribing CSF. The second and third points, in particular, indicate that a change in behaviour that is more complex and extraneous to daily practice is less likely to be implemented, as has been reported before by Grilli and colleagues and Grol and colleagues in Refs. [14,15].

In conclusion, this study shows that improvement of guideline adherence is variable over time, for different advice and in different hospitals. The repeated feedback, in combination with discussions on the literature, may have improved the resection or examination of the axillary lymph nodes and the chemotherapy dosing. The reasons for non-adherence are now being studied in focus group interviews with all of the involved specialists, in order to develop a more specific, improved guideline implementation programme.

We emphasise the need for the continuous monitoring of the quality of the guideline, its distribution and its adherence, in order to focus on the right areas for improvement. Furthermore, the reasons for non-compliance should be explored in order to improve the quality of care.

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