Tailoring fellow-up in early-stage breastcancer

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Summary

INTRODUCTION

Breast cancer is the most common cancer in women in Europe, representing almost 30% of all new cancers in 2012. Thanks to early detection and better treatment, breast cancer mortality rates in Europe have decreased over the last decades with an approximate 20% decrease between 1989 and 2006 and a further 7% fall since 2009 in 2013. The increasing incidence and decreasing mortality have led to a growing number of breast cancer survivors, with a 10 year prevalence of almost a 100.000 patients in the Netherlands in 2010.

In contrast to the individualised choice of treatment based on the large variety of tumour and patient characteristics, follow-up regimens for breast cancer patients are quite uniform, and rather historical than evidence based. In many countries, current follow-up after treatment consists of frequent hospital visits and annual mammography. Over the last decades different follow-up strategies were studied, but although it is generally felt that some form of follow-up is required, no consensus on frequency or form has been reached. In this era of increased awareness of cost effectiveness and growing demands on health care professionals, the justification of frequent routine follow-up should be questioned in the absence of evidence supporting their value.

The aim of this thesis was to evaluate the feasibility of tailored follow-up for early breast cancer patients after curative treatment, based on risk of locoregional recurrence.

LOCOREGIONAL RECURRENCE

Detecting a potentially salvageable locoregional recurrence (LRR) is, besides the management of both physical and psychosocial side effects, one of the main aims of follow-up after breast cancer treatment. To estimate the need for follow-up, we evaluated the current LRR risk in a large population of postmenopausal patients, adequately treated with adjuvant endocrine therapy between 2001 and 2006 from the Tamoxifen and Exemestane Adjuvant Multinational (TEAM) trial in **Chapter 2**. This trial investigated the efficacy and safety of adjuvant endocrine therapy consisting of either exemestane or the sequence of tamoxifen followed by exemestane in postmenopausal hormone-sensitive breast cancer. The TEAM trial population represents the majority of the current breast cancer patients as 93% of all breast cancer patients are over 45 years, 58% are over 60 years, and 75% are hormone receptor positive. We evaluated whether the local therapy (breast conserving surgery plus radiotherapy (BCS+RT), mastectomy without radiotherapy (MST-only), or mastectomy plus radiotherapy (MST+RT)) was predictive for the risk of LRR, as this could have implications for LRR risk based follow-up after treatment.

The main result of the study was that with the current treatment, the risk of LRR in general is very low in this population, with a 5 year LRR rate of 1.9%-4.2%. Surprisingly, in contrast to previous studies, we found a significantly higher LRR in patients treated by MST-only compared to patients treated by BCS+RT (HR 1.53; 95%CI 1.10-2.11), while no significant difference in LRR was found between MST+RT and BCS+RT (HR 0.78; 95%CI 0.50-1.22). This suggests a beneficial effect of radiotherapy after MST. Although our findings are strengthened by multivariate analyses and a large patient population, these findings should be viewed as hypothesis-generating, as patients were not randomised between different local treatment arms. However, in postmenopausal women with early, hormone receptor positive breast cancer, LRR risk may be lower after BCS+RT than after mastectomy alone, even with optimal endocrine therapy, which should be considered when discussing treatment options and follow-up strategies.

PATIENTS

In **Chapter 3** patients' views on organisation of follow-up and their informational needs were evaluated at two timepoints after treatment, using a cross-sectional survey of 189 patients in two groups in 2005. Group A (n=89) consisted of patients operated before, and group B (n=100) after the introduction of a breast cancer unit with a central role for the NP. The response rate was 72% in group A and 84% in group B. Median time since diagnosis was 69 (54-86) and 33 (0-57) months, respectively. Aspects highly appreciated by patients in both groups were lifetime follow-up, additional investigations and information about prognosis and life style. Important discussion subjects were fatigue, pain, genetic factors, prevention and arm function and/or lymph-oedema. Less valued subjects were information about peers, conversations with psychologists or social workers, breast reconstruction, and acceptance by family members. No statistically significant differences in informational needs and preferences were found between both groups. In group B, communication with the caregiver was assessed with a higher score and more patients indicated that the caregiver took the time needed. More patients in group B indicated that they preferred follow-up by the NP (58% versus 32% (p=0.003)). Longer time since treatment correlated with a decrease in preferred frequency. Time since treatment did not correlate with informational needs in follow-up; the only factor correlated to the increase of these informational needs was young age. In conclusion, in the breast cancer unit, patients were satisfied with the follow-up in general and the role of the nurse practitioner was highly appreciated, especially by those patients for which the NP was involved from the beginning of their treatment.

PROFESSIONALS

In **Chapter 4** insight is given into professionals' opinions on breast cancer follow-up to facilitate implementation of new follow-up strategies. The study focused on current practice, purpose and perceived effects of follow-up, as well as preferred frequency and duration. A questionnaire was sent to 633 Dutch professionals in 2009 with a response rate of 31%. The available national guideline at the time was followed by

81% of respondents. All different specialists (surgeons, medical oncologists, radiation oncologists) were reported to be involved in follow-up and 69% of respondents reported NPs to be involved, underscoring their important role in cancer care. When questioned on tailored follow-up, professionals indicated more factors for increased follow-up (age <40 years, pT3-4 tumour, pN2-3, treatment related morbidity, and psychosocial support), than for reduced follow-up frequency (age >70 years and DCIS histology), compared to the guideline. Of these factors, age<40 and pN3 status were also arguments for respondents to follow patients longer than the 5 years that the national guideline recommends, where only age >70 years and DCIS histology were considered arguments for shorter follow-up. Alternative forms of follow-up (by telephone or GP) were not endorsed by >90% of respondents. Detection of a new primary tumour of the breast was considered the most important purpose of follow-up, as 98% of respondents indicated this as a goal, whereas detecting metastases was mentioned by 57%. In conclusion, professionals tend towards longer and more intensive follow-up than the current guideline for a large group of patients. Limitations of and new developments in follow-up need to be brought to the attention of these professionals to facilitate alternative follow-up strategies. Furthermore, although it was an important recommendation by the Health Care Council report in 2007, only 21% of the respondents in 2009 indicated to occasionally give their patients a written follow-up plan and in only 10% of respondents' practices a written plan was standard for all patients.

COSTS OF FOLLOW-UP

The systematic review in **Chapter 5** gives an overview of the literature on the cost-effectiveness of early breast cancer follow-up.

From the limited data available from randomised trials, it can be concluded that follow-up more frequent than every 6 months is not cost-effective and additional testing on demand only is more cost-effective than standard intensive testing (clinical level of evidence IIB, according to the Oxford centre for evidence based medicine (I-V)). Compared to standard physician follow-up, structural telephone contacts with a nurse practitioner (NP) are equally effective, but due to the need for training and the duration and number of contacts this method of follow-up may lead to higher costs

(level IB-IIB). In a more integral analysis these excess costs may well be compensated by lower travel costs and less work absence for the patients and their attendants, further study taking patients' cost in account is needed. Several other options in follow-up have been evaluated and seem promising. Patient-led, on demand follow-up by a NP is feasible and leads to fewer visits and lower costs (level IIB). Furthermore, nurse-led telephone follow-up in combination with an educational group programme is more cost-effective than hospital follow-up with or without the educational group programme (level IB). Finally, follow-up by a general practitioner (GP) is safe and leads to a decrease in costs (level IB).

As the costs of routine follow-up are increasing and retrospective data suggest that only a very limited percentage of salvageable recurrences after curative treatment for stage I-II breast cancer are detected by these standard clinical follow-up visits (level III) while alternative methods are equally effective with lower costs, reconsidering follow-up policies is more than timely.

TAILORED FOLLOW-UP

In **Chapter 6** the results of the first prospective study on the implementation of tailored follow-up are presented. In the implemented follow-up schedule the proposed number of visits per risk group was determined based on a prognostic index for LRR. Between 2007 and 2010, 180 breast cancer patients (pT1-2N0-2cM0) were included. In the second and third year of follow-up, a 22% reduction in visits per patient was seen in the low-risk group compared to the intermediate-risk group (2.8 versus 3.6). The number of visits in both groups was however significantly higher than the number of scheduled visits in this period (1 and 3 respectively). In the low-risk group a significantly higher percentage of interval visits was found compared to the intermediate-risk group (65% versus 40% $p<0.001$). The majority of interval visits in both groups was initiated by the professional. In the low-risk group the percentage of the interval visits which was initiated by the professional was significantly higher compared to the intermediate-risk group; 82% versus 65% respectively. The majority of all follow-up visits were done by the nurse practitioner both in the low- and in the intermediate-risk group in the first year (59% and 51% respectively) and the second/third year (75% and 57% respectively for low- and intermediate-risk), confirming

their important role in breast cancer follow-up care. The ratio of planned versus interval visits did not differ significantly between the various types of professionals.

No significant differences were found in attitude towards follow-up, patient satisfaction, anxiety and depression, alternative health care use or local recurrences between the risk groups after one and two years. The scores were similar to those reported previously on breast cancer survivors, indicating that patients' awareness of their risk group or the decreased number of planned follow-up visits in this study does not cause anxiety or change patients' satisfaction and attitude towards follow-up. From this study, it can be concluded that the implementation of a tailored follow-up programme with decreased number of visits for low-risk patients is feasible and acceptable to patients. As most interval visits are initiated by a professional, a further reduction of follow-up visits might be achieved if follow-up is performed by a single professional and if all professionals are educated to be more aware of the limited effect of the routine hospital visits that have been standard for many years on disease outcome and patients' wellbeing.

CONCLUSIONS AND RECOMMENDATIONS

In **Chapter 7** the main findings of this thesis are discussed and recommendations are made for clinical practice and further research. One of the main conclusions of this thesis is that patients accept less intensive follow-up schedules, as long as they are initially well informed on the purpose, the risks and limitations of follow-up. In general, implementation of minimised tailored follow-up seems feasible, but needs close monitoring as professionals tend to more frequent follow-up. Tailoring should not only be done based on LRR risk, but individually, based on the presence of treatment related side effects, either physical or psychosocial. If patients do not experience side effects, annual planned mammography and telephone contact coordinated by a single professional, preferably a specialised nurse or possibly in the future a well-trained GP, suffice in case of easily accessible on demand visits. In the first year after treatment an optional educational group program combined with telephone follow-up by a nurse practitioner could be implemented.

Specific education for professionals on the limited effect of clinical visits on psychosocial support and the limited value of early detection of metastases is needed to

decrease the number of professional-initiated interval visits. In addition, implementation of updated online prediction tools may provide more insight in actual LRR risks and convince patients and professionals of the safety of reduced follow-up frequency. To enhance coordination and adherence of all professionals to tailored follow-up schedules, a (LRR risk or side effect based) tailored follow-up schedule should be determined at the end of treatment, based on local protocols. This schedule should be entered in the patient's chart, visible for all professionals involved, and provided to the patient and their GP on paper and online as part of their personal aftercare plan. Furthermore, written information on follow-up, risk and signs of recurrence, possible treatment side effects and their treatment options, including contact information, should also be provided to all patients on paper, online or in a mobile phone application. The presence of these aftercare plans should in the Netherlands be evaluated in the NABON Breast Cancer Audit.

For training purposes, residents could join the nurse practitioner or specialised nurse in follow-up visits to see the late toxicity of their treatment. Alternatively, a special outpatient clinic to monitor late side effects can be opened in training hospitals.

Patients already included in clinical trials must adhere to follow-up schedules as specified in the protocols, but the need for frequent follow-up schedules in new trials should also be critically reviewed, dependent on the specific endpoints.

Finally, performing more adequate modelling studies with standardised outcome measures such as the incremental cost-effectiveness ratio (ICER) and quality adjusted life year (QALY), could be a good alternative to provide more insight in the cost-effectiveness of different strategies in the absence of international RCTs.