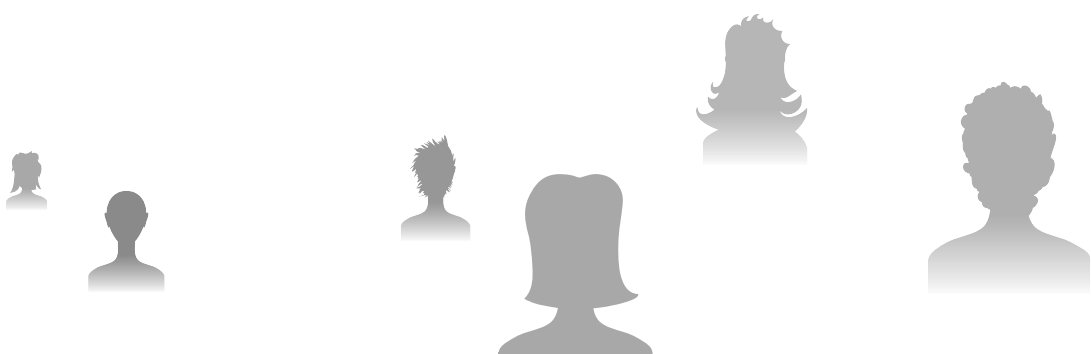
chapter 1

Introduction



1.1 EPIDEMIOLOGY

Breast cancer is the most common cancer in women in Europe, representing almost 30% of all new cancers in 2012. In the Netherlands alone, almost 14.000 women were diagnosed with breast cancer in 2011, and one in eight women will be diagnosed with breast cancer in her lifetime[1] (www.cijfersoverkanker.nl). The majority of these breast cancer patients are postmenopausal woman (93% >45 years and 58% >60 years), and 60-84% have stage I-II disease, according to the 7th TNM classification.[2-4] Incidence has increased over the last decades in western Europe, due to better screening and the increased prevalence of risk factors for breast cancer. These risk factors include childlessness or having a first child after the age of 35 years, having no period of breast feeding, the use of alcohol, oral contraceptives or oestrogen replacement and obesity after menopause.[5]

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[6] and a further 7% fall since 2009 in 2013, resulting in an Age Standardized mortality Rate of 14,6/100.000 in 2013.[7] 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.

1.2 TREATMENT

Treatment of patients with breast cancer depends on tumour and patient characteristics such as TNM stage, grade, oestrogen and progesterone receptor expression, Her 2 receptor status, age and comorbidity. In the Netherlands, each breast cancer patient is discussed in a multidisciplinary meeting with a radiologist, a pathologist, a surgeon, a medical oncologist and a radiation oncologist to determine an individual treatment plan.

Local treatment

Surgical treatment can consist of breast-conserving surgery (BCS) or amputation of the entire breast (mastectomy). If breast cancer is detected at an early stage (stage I or II), or in the case of limited pre-malignant ductal carcinoma in situ (DCIS), BCS is as effective as mastectomy if this surgery is followed by irradiation of the entire breast and, in the case of adverse characteristics, an additional boost on the original tumour bed.[8-10] The combination of these treatments is referred to as breast-conserving therapy (BCT). In recent years, as local recurrence and mortality rates have decreased, the focus on quality of life has increased and an oncoplastic reconstruction of the breast after wide excision has become more common. This allows patients with centrally located or large tumours to be treated with breast conserving surgery with sufficient margins and a good cosmetic result without increased risk of recurrence,[11,12] where traditionally mastectomy would have been the only treatment option for these patients. An adverse effect of these reconstructive techniques might be that it hampers the localisation of the original tumour bed for the planning of the radiation boost, leading to possible geographical misses or larger boost volumes which may deteriorate cosmetic outcome.[13] If the tumour, or DCIS is too large to reconstruct the breast after excision or if is there more than one tumour in the same breast, a mastectomy is usually performed. Other reasons to perform a mastectomy could be recurrent tumour, the presence of a BRCA mutation or patients' preference.

After mastectomy, according to our national guidelines, additional irradiation to the thoracic wall is given after irradical resection, in case of a cT4 tumour, or a pT3 tumour in combination with at least one risk factor (age $\leq$=40, lymphangioinvasion, grade 3). At the moment, it can be considered in the case of 1-3 positive lymph nodes and the presence of one or more risk factor (tumour $\geq$3 cm, age $\leq$40, lymphangioin-

vasion, grade 3), or pNo and the presence of three or more of these risk factors. The SUPREMO trial, which recently finished accrual, will hopefully provide more insight in the effect of irradiation of the chest wall in this intermediate risk group.[14]

Regional treatment

Historically all patients underwent an axillary lymph node dissection (ALND), for staging and as axillary treatment. In the last 10-15 years this has changed to a sentinel lymph node (SN) biopsy for all clinically node negative patients, with far less morbidity than the ALND. This sentinel node procedure provides a 95% accurate estimation of lymph node involvement and, in case of negative SN, a $<$1% risk of axillary recurrence.[15-19] Up to 2011, an ALND was still performed for all SN positive patients and locoregional radiation was only given when more than 4 axillary lymph nodes were affected in the ALND. However, in recent years regional treatment for clinically node negative patients with a positive SN has shifted from axillary dissection towards irradiation. This shift is based on the accumulating evidence on the effects of regional treatment such as the long term results of the NSABP-04 trial reporting equal locoregional control and less morbidity with regional radiation compared to ALND.[9,20,21] In the American College of Surgeons Oncology Group (ACOSOG) Z-11 study 856 breast cancer patients (cT1-2No) with $<$3 tumour positive nodes found during the sentinel node procedure, were treated with BCS, local radiation therapy and adjuvant systemic therapy (96%).[22] Patients were randomised between ALND or no further axillary treatment, although possibly level I and II of the axilla were incorporated in the irradiation of the breast. In both arms the regional recurrence rates were low: 0.9% (SN alone) and 0.5% (SN + ALND). Prognostic factors for the occurrence of loco regional recurrence were a grade 3 tumour and age $\leq$ 50 years. Survival was similar in both arms: 92.5% and 91.8%. The results of the recent AMAROS trial, randomising between ALND and regional radiation therapy after positive SN, also showed low regional recurrence rates in both arms and less morbidity in the patients treated with regional radiation therapy.[23] Based on these data, the current consensus in the Netherlands is that clinically node negative patients with micrometastases (0.2-2 mm) in the sentinel node without risk factors (grade 3, $>$3 cm, lymphangioinvasion) receive no axillary treatment, in the presence of 1 risk factor level I/II of the axilla are included in the radiation fields. In case of $\leq$2 macrometastases ($\geq$2 mm) in the sentinel node, level I/II are irradiated, in the case of macrometastases in the presence of

risk factors, also level III and the supraclavicular lymph node region are advised to be incorporated in the radiation field. The absence of information regarding the extent of nodal involvement in the radiotherapy arm appears to have no major impact on determining the indication for adjuvant chemotherapy.[24]

Systemic treatment

In addition to local treatment, systemic therapy (endocrine therapy, chemotherapy, targeted therapy or a combination of these) may be used to reduce the risk of both local and distant recurrence. For the past decades, the selection of early stage breast cancer patients who are at a high risk of recurrence and eligible to receive adjuvant systemic treatment (AST) has been based on clinicopathological factors, such as age, tumour size, nodal status, histological grade, and hormone-receptor status. These factors can be used in specific algorithms for risk estimations such as Adjuvant! Online (AOL) and the Nottingham Prognostic Index (NPI), and in guidelines for AST recommendations such as the Sankt Gallen expert panel recommendations of 2013, and the Dutch national guidelines of 2004 and 2012.[25-28] Over the years these guidelines have recommended the additional use of AST in a growing percentage of patients, as also high risk node negative patients with tumours >1 cm and older patients also seem to benefit. A relatively new online tool for outcome prediction in breast cancer patients is PREDICT plus.[29] This tool not only uses the clinicopathological factors mentioned above, but also incorporates HER2 status and method of detection. Each of these clinical risk prediction algorithms may define a slightly different group of patients at a low or high risk, so individual risk assessment remains challenging.[30] In addition to these clinical risk predictors, gene-expression classifiers have been developed and validated on historical data to refine clinical risk estimations and related adjuvant chemotherapy recommendations.[31,32] One of these classifiers is the 70-gene signature (MammaPrintTM®, Agendia Inc., Amsterdam, the Netherlands).[33,34] Between 2004 and 2006, the 70-gene signature has been assessed in the first prospective study (RASTER) to determine the need for chemotherapy in node negative patients. A considerable discrepancy in risk estimations between different clinical guidelines and the 70-gene signature was observed,[35,36] with more patients assessed to be low risk based on the 70-gene signature than based on commonly used prediction tools such as Adjuvant! Online. Patients with a low risk 70-gene signature have an excellent overall survival, independent of their clinical risk estima-

tion. Adding the 70-gene signature to clinical risk prediction algorithms improves risk estimations and therefore might improve the identification of early stage node-negative breast cancer patients for whom chemotherapy has limited value.[30] The recently closed large multicentre prospective randomised MINDACT trial will further validate the prognostic value of this tool for pN0-1 patients.[37]

Systemic treatment was usually given after local therapy, but in present practice, in the case of a large tumour or a clear indication for systemic treatment, it is more often given prior to the operation (neo-adjuvant). This may facilitate BCT by reducing tumour size and enables response monitoring. Consequences of good radiologic and pathological response to the neo-adjuvant treatment for locoregional treatment such as surgical axillary treatment and indications for radiation of the regional lymph nodes, are yet to be determined. The RAPCHEM study, a Dutch prospective multicentre cohort study evaluates current practice and will hopefully answer this question in the future.

1.3 LOCOREGIONAL RECURRENCE

A locoregional recurrence (LRR) of breast cancer is defined as a return of the disease in the breast, the thoracic wall, or in the axillary, infraclavicular or supraclavicular lymph node area after intended curative treatment. A comprehensive literature review of papers published before 2001 on invasive breast cancer showed an overall ten-year LRR rate of 13% after mastectomy and 12% after BCT.[38] Three quarters of these recurrences are true local recurrence and one quarter regional recurrences. The risk of LRR after invasive breast cancer has decreased over the last decades and even further over the last decade. Several factors may contribute to this decrease; local treatment may be better as patients are diagnosed at an earlier stage by the introduction of screening. In addition, the pre-surgery imaging of the extent of the tumour has improved by digital mammography and the use of MRI, thereby enabling the surgeon to plan an adequate excision and achieve negative resection margins. Furthermore, a larger percentage of patients are treated with more effective systemic treatment, reducing LRR.[39] Currently, a 10-year LRR rate of 6% after both BCT and mastectomy is found in general,[10,40] but 10 year LRR risk after BCT in a low risk population of older women, adequately treated by endocrine therapy may be as low as 2%.[41] In ductal carcinoma

in situ DCIS) the ten-year local recurrence rate is 10-15% after BSC and 0-4% after mastectomy. Half of these recurrences are invasive.[42,43]

In invasive carcinoma factors such as increasing primary tumour size, axillary lymph node positivity, a multifocal primary tumour, the presence of extensive intraductal component, positive tumour margins, age, family history of breast cancer, gene mutation status, radiation therapy, adjuvant endocrine therapy and chemotherapy have all been found to be associated with the risk of LRR.[38,44,45] Other factors such as histological type, lymphatic invasion, peritumoural vascular invasion, oestrogen receptor negativity, P53 positivity and overexpression of HER-2 neu have all variably been found to be associated with the risk of LRR. Gene-expression classifiers, such as the 70-gene signature, which discriminates risk groups for distant metastases and overall survival have not been validated for risk of LRR. Biological subtypes based on immunohistochemical markers (Luminal A, Luminal B, Basal like and Her 2 enriched) do seem to have a prognostic value for predicting LRR.[46]

Although LRR in breast cancer can be treated with curative intention, patients after LRR have a worse prognosis than after primary treatment. It is unclear whether this is caused by the LRR, or whether the LRR is a sign of a worse biological behaviour.[47] Large studies on local treatment that showed marked difference in LRR, failed to show a significant difference in overall survival,[9,48] possibly thanks to good salvage treatment, the small absolute number of recurrences or insufficient follow-up duration. In two large meta-analyses by the European Breast Cancer Trialists' Collaborative Group, the prevention locoregional recurrences by adequate local treatment, did seem to prevent breast cancer death after 15-20 years,[49,50] underscoring the importance of optimal local treatment.

1.4 FOLLOW-UP

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. The randomised clinical trial by Palli et al. in 1999[51] and the review published by Rojas et al. in 2005[52] were a turning point in many guidelines internationally to end intensive routine additional testing in follow-up as this showed no impact on overall survival. By that time, these

additional tests in breast cancer follow-up had already been abandoned the Netherlands following publications of Zwaveling et al. and Rutgers et al. in the eighties that showed the very low detection rate of these tests.[53-55] In the following years, different follow-up strategies were compared in randomised trials: routine physical examination and annual mammograms versus intensive follow-up (with routine blood test, liver ultrasound, chest X-rays and bone scans),[51,56,57] general practitioner (GP) versus hospital follow-up,[58,59] patient initiated nurse-led follow-up versus routine physician follow-up[60] and telephone versus clinical follow-up.[61,62] All were found to be equally effective in detecting local recurrence, overall survival, patient satisfaction and quality of life. Three reviews of the literature on the effectiveness of different follow-up strategies were published,[52,63,64] but although it is generally felt that some form of follow-up is required, no consensus on frequency or form has been reached.[65-68]

Historically, follow-up of breast cancer patients has several aims. Given that recurrences are unlikely to occur in the first year, follow-up during this period mainly focused on monitoring treatment-related side-effects and offering psychosocial support to patients after a serious life event, although we know that follow-up visits may paradoxally also induce stress.[69-71] After this first year, a shift occurs towards detection of second primary tumours and loco regional recurrences at an early stage in order to initiate potentially curative therapy in time.[52,72] Of course, patients' support needs and detection of late side-effects are ongoing. In contrast to the expectations of most patients, early detection of distant metastases is not regarded as important, because cure can unfortunately no longer be offered in this situation. This has been confirmed in several studies, showing that a more intensive follow-up strategy including additional investigations to detect distant metastases did not result in a survival benefit.[51,56,57] As a result, early detection of asymptomatic distant metastases will only result in a decreased quality of life in patients due to the awareness of having an incurable disease, whereas treatment will only start when symptoms occur.

Concerning the components of follow-up, the value of physical examination has recently been questioned,[73,74] although it is still standard practice in most follow-up programmes. For detection of local recurrences, annual mammography has been the only measure with proven impact on patient outcome.[75] About half of locoregional recurrences are found by annual mammography (40%), whereas the other half is detected by patients themselves (40-50%).[52,64,72]

Despite these limitations of follow-up, the routine schedule until 2011 in the Netherlands consisted of: a standard follow-up schedule of hospital visits every 3 months the first year after treatment, every 6 months in the second year and then

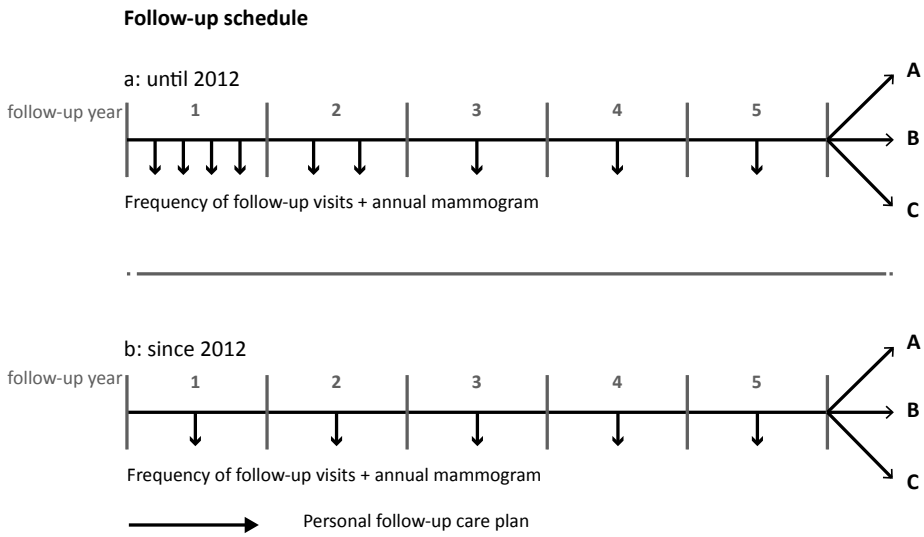
annually until 5 years after treatment. During these visits, a medical history and physical examination were performed and mammograms were made annually (see figure 1). The current, recently revised American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO) guidelines on follow-up still recommend a similar standard schedule for all patients.[76,77]

In the Netherlands, with increased awareness of cost effectiveness and growing demands on health care professionals, the justification of this strategy has recently been questioned.[73,78]

The Dutch Healthcare Council advised in 2007 on re-evaluating standard follow-up in cancer care, which resulted in a new national guideline on "Aftercare after cancer treatment" in 2011. This guideline advises only to check for disease recurrence after cancer treatment if it improves life-expectancy or has a positive impact on the quality of life of the patient. In addition, it emphasises the importance of information on and the treatment of the physical and psychosocial side effects of the initial treatment. The use of a written personal aftercare plan for each individual patient was strongly recommended.

Based on these recommendations and the accumulating evidence of the limited value of frequent routine physical examination, the Dutch national guideline for breast cancer follow-up has been recently updated (see figure 1). Since November 2012 the guideline advises a minimum of 1 hospital visit a year for medical history and physical examination and annual mammograms up to five years after treatment. If needed, additional visits can be planned by the patient and the treating professional to address physical or psychological complaints due to treatment.

Different follow-up strategies are advised after 5 years of follow-up based on to age (Figure 1). This subdivision is controversial as the cut-off age is not evidence based and other factors should be taken into account. In other types of cancer it has been suggested that follow-up might be most efficient if it is tailored according to the risk of developing a recurrence that is amenable to curative treatment.[79] For breast cancer patients with few treatment side effects, it might be effective to determine which patients are at low risk of developing a locoregional recurrence. In this group, follow-up frequency and duration could perhaps safely be reduced, leading to a more efficient use of both time and resources from physicians and patients around the world.



A: < 60 years of age annual visit and mammogram continue

B: 60 - 75 years of age patients are referred to the general practitioner (biennial mammogram in hospital) or national screening programme

C: > 75 years of age consider to end follow-up care

Figure 1.1: Courtesy of A.B.G. Kwast (2014), Follow-up and risk of relapse after breast cancer treatment (thesis).

Patients' perspective

Policy makers and clinicians increasingly aim to take the patients' perspective into account in medical decision making, as patients may comply better to guidelines when they are satisfied with their care and treatment setting.[80-82] In this light, evaluation of patients' preferences and their opinion on current practice is important to implement new follow-up schedules. In general, patient satisfaction reflects the patients' personal perception of the actual care received in light of the patients' personal preference and expectations. Satisfaction can be measured in different aspects of cancer care using the Ware's Patient Satisfaction Questionnaire III (PSQ III).[83] This

questionnaire (43 items) was designed to measure technical competence, interpersonal manner, and access to care. More specifically, patients' attitude towards follow-up can be assessed using a validated questionnaire developed by Stiggelbout et al..[84] This questionnaire consists of four subscales: communication (with the physician), reassurance, nervous anticipation, and specific perceived disadvantages of follow-up. Patients' anxiety and depression can be assessed using the Dutch version of the Hospital Anxiety and Depression Scale (HADS).[85] To analyse patients' information needs and medical technical preferences with respect to breast cancer follow-up, de Bock et al. developed a questionnaire.[86] Results of the studies on patients' opinions in breast cancer follow-up using these questionnaires are described below.

Organisation of follow-up

Not much is known about patients' preference for frequency and duration of follow-up. Many patients find follow-up visits anxiety-provoking, fearing the detection of recurrent disease. Other studies confirm that this anxiety exists, but that patients will ultimately be reassured by follow-up visits.[70,87] De Bock et al. showed a preference for life-long follow-up, twice a year by a hospital doctor in patients after a median follow-up of 3 years.[86] Kwast et al. recently confirmed patients' preference for longer follow-up than the guideline prescribes.[88] On the other hand, a British study compared the experiences of patients with breast cancer who underwent the standard follow-up procedure with those in whom routine follow-up was restricted to the mammography.[89] Results of this study showed that patients seemed willing to pursue a less frequent follow-up and patients with less intensive follow-up did not have more telephone appointments or visits to the general practitioner. Factors influencing patients' preferred follow-up duration and frequency have not been studied, nor is much known about the change in preference and informational needs over the years after treatment.

Professionals involved in follow-up

Follow-up is traditionally performed by the treating physician in the hospital. In the case of breast cancer treatment this will in most hospitals primarily be the surgeon and, if involved in the treatment of the patient, also the medical oncologist and radiation oncologist.

The possibility of the participation of other professionals than hospital specialists in follow-up has been studied. In a large multicentre trial, patients with early-stage breast cancer who completed adjuvant treatment (n=968) were randomised to

follow-up in the cancer centre according to usual practice or follow-up from their own general practitioners.[59] Patients' anxiety, quality of life or satisfaction with care did not differ significantly, although most women preferred general practitioners to care by a specialist in a hospital. Moreover, several studies demonstrate that general practitioners would prefer a more active role in follow-up of breast cancer patients.[90,91] Over the last twenty years specialized nurses, or nurse practitioners (NP)have been introduced in cancer care. They now play a central role in the pre- and postoperative patient care, giving information on surgery and adjuvant systemic treatment, and performing follow-up. Few studies have investigated the role of specialised nurses within follow-up of breast cancer; a Swedish group randomised 264 patients with stage I or II breast cancer to routine medical follow-up by physicians or to on demand follow-up by a specialist nurse.[60] Endpoints were patients' quality of life and satisfaction; no differences could be detected between the two arms. Patients' preference on who should be involved in their follow-up and the influence of NPs on patients' specific information needs and preferences is unclear.

Professionals' perspective

Although many professionals spend much time performing follow-up, little research has been performed on their opinion on the subject.

In the United Kingdom, a 20-point questionnaire was sent to 562 specialists with items on case-load, perceptions of follow-up, local policy and opinions on greater primary care involvement. A remarkable result concerning the duration of follow-up was that the majority of specialists favour a risk-based adjusted discharge strategy.[92] Another survey among specialist in Canada showed no clear consensus on follow-up regarding the adoption of less interventional programs.[93] A recent qualitative interview study by Kwast et al. showed that half of the health care professionals in breast cancer indicated that follow-up could be tailored to patient and tumour characteristics, with a decreased frequency or duration for low risk older patients. On the other hand, one third of professionals thought follow-up should be prolonged based on patients' expectations, the ongoing risk of a secondary tumour, management of hormonal treatment and the financial incentive.[88] So although the scarce evidence seems to suggest the professionals have a preference for a more risk-based approach to breast cancer follow-up, the effect of different risk factors is not known and the implementation of a risk-based regiment has not been addressed.

Costs of breast cancer follow-up

In the Netherlands, the annual incidence of 14.000 new breast cancer patients, with a 5 year overall survival of 85% (www.cijfersoverkanker.nl), and on average 2,6 follow-up visits per year during the first 5 years,[73] leads to an estimate of 155.000 outpatient visits a year. At 75 euro a visit, this cumulates to an annual burden of approximately 11.6 million euro on health care costs.

In an era of expanding health care costs, objective data about cost and cost-effectiveness are nowadays required to determine the optimal follow-up strategy. Three reviews of the literature showed equal effectiveness of different follow-up strategies,[52,63,64] but costs are not often taken into account.

1.5 AIM OF THE THESIS

The aim of this thesis is to evaluate the feasibility of tailored follow-up for early breast cancer patients after curative treatment, based on risk of locoregional recurrence. In order to do so, we first determined the risk of locoregional recurrence dependent on local treatment in a large cohort of low-risk breast cancer patients, treated with adequate modern systemic therapy. In the second part we evaluated both patients' and professionals' needs and preferences for breast cancer follow-up and we reviewed the literature on cost effectiveness of known follow-up schedules. Finally we prospectively examined whether the implementation of a tailored follow-up programme, based on a prognostic index for LRR, is feasible and acceptable to patients and professionals. We hypothesise that the patients in the 'low' risk group can do with fewer visits than patients in the 'intermediate' risk group, without loss of patient satisfaction or increased anxiety, thereby decreasing the burden on health care costs.

1.6 OUTLINE OF THE THESIS

As detecting a local recurrence is the main purpose of follow-up in breast cancer, in **Chapter 2** the current differences in locoregional recurrence (LRR) patterns between type of local treatment in postmenopausal patients treated with adequate adjuvant

endocrine therapy in the large database of postmenopausal women of the Tamoxifen and Exemestane Adjuvant Multinational (TEAM)[94] trial are examined.**Chapter 3** is a cross-sectional study which describes patients' information needs and preferences regarding organisation of follow-up care and evaluates their satisfaction with care after treatment. The determinants of these needs and preferences are evaluated and furthermore the results between patients treated before and after the introduction of the nurse practitioner at the breast cancer unit are compared. In **Chapter 4** the opinion of Dutch health care professionals on common clinical practice and their perception of the purpose of breast cancer follow-up is evaluated. Furthermore the influence of individual risk factors on follow-up preference is surveyed to facilitate the implementation of tailored follow-up. In **Chapter 5**, the costs of the different follow-up strategies are evaluated in a review of the literature, so that in light of equal effectiveness, the least cost consuming strategy could be identified. **Chapter 6** describes the results of a prospective trial on the feasibility of tailored follow-up, based on a prognostic index for LRR, with reduced number of visits for low-risk patients. The number and reason of visits as well as patients' anxiety, needs and preference are examined. In **Chapter 7** the main findings of this thesis are discussed and recommendations are made for future research and the implementation of tailored follow-up.

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