Individualized breast cancer follow-up

Cost-effectiveness for various follow-up scenarios

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MANAGEMENT SUMMARY

This study investigates the follow-up of breast cancer and took place from September 2007 until February 2008. One of the main goals of follow-up is to improve the survival of patients. Follow-up influences survival by detecting local recurrences and second primary tumors in an early stage, thereby reducing the risk of metastases.

Breast cancer occurs in about one in eight women in the Netherlands. Every year, 11000 new cases are registered and about 3500 women die of breast cancer. Prognosis after primary treatment for patients with breast cancer is improving. This leads to an increased number of patients in follow-up, which leads to increased workload. All patients are currently assigned the same follow-up: five years long, with a frequency of two consults per year, as national guidelines prescribe. This study wants to determine a more individualized follow-up in order to give women the follow-up they need and reduce workload in hospitals.

We classify various patient groups, according to age, tumor size and lymph node status. We choose follow-up scenarios based on their type of consult (surgeon face-to-face, nurse practitioner face-to-face, nurse practitioner telephone), frequency (once, twice per year) and length (one, three, five years), and determine the most appropriate follow-up scenario for each patient group.

To investigate the cost-effectiveness scenarios, we model the process of breast cancer in a discrete-event state-transition model and measure the cost-effectiveness of all scenarios for all patient groups.

Primary recommendations flowing from the research are the following:

- This study illustrates the possibility and potential for individualized follow-up in various types of cancer.
- Implementing individualized follow-up can lead to savings of up to 89% of the number of consults needed.
- We have come to the insight that in general, patients younger than 50 require a more intensive follow-up than patients older than 70. Older patients have a lower life expectancy, and therefore there are less QALYs to be gained and the effectiveness of follow-up is lower. Specific results are:
    - Patients older than 70 and with favorable tumor characteristics) are served best with a minimal follow-up of one year.
    - Patients younger than 40 and patients with unfavorable tumor characteristics (>3 lymph nodes, tumor size > 2.0 cm) can benefit from a more intensive follow-up of five or possibly ten years.
    - Patients with age older than 40 but younger than 70 sometimes benefit from a more intensive follow-up, e.g. when younger than 50 and tumor size >2,0 cm.

CONTENTS

PREFACE

I am very pleased to have finished the thesis within six months time. Although it was sometimes a struggle, the graduation has been a pleasant one. To come in close contact with the field of health care has been a rewarding experience. With a meaningful and interesting subject I have enjoyed the various phases of the study. The continuing interest from friends, tutors and the media has continued my drive to deliver a sound study.

I want to thank Dr. Joost Klaase and Ms. Caroline Bandel from the Centre for Mammacare. They were most helpful with determining the course of the research and I enjoyed our meetings. I also thank Dr. Ir. Erwin Hans and Dr. Ir. Leo Van der Wegen from the University of Twente for their constructive feedback and suggestions. They have made the study much more valuable. Also a word of thanks goes to Timon Sibma, who executed another part of the study at MST. It was nice to team up with another student and share ideas and suggestions. Final thanks to Dr. Sabine Siesling from IKST for helping out with actual data on the population.

I hope our study has improved the ability of the Centre for Mammacare to offer their patients an individual, cost-effective follow-up.

Enschede, February 2008,

Jesse van Elteren

1 INTRODUCTION

About 12000 women are diagnosed with breast cancer annually, making up for more than 33% of female cancer patients in the Netherlands (Visser and Van Noord 2005). About one in every eight women will be diagnosed with breast cancer in her lifetime (Kankerbestrijding 2007), making this a very relevant point of interest in the Dutch healthcare. The MST (Medisch Spectrum Twente) wants to offer an individualized follow-up, leading to more appropriate follow-up for patients and possibly to a decrease of costs.

The effectiveness of breast cancer follow-up has been debated for a long time. One of the most important questions in these debates is: If breast cancer follow-up is not medically effective, why do we still offer follow-up as we do now? This is a crucial question in this study.

This study took place from September 2007 until March 2008. Initiator of the study is Dr. Joost Klaase, surgeon, MST (Medisch Spectrum Twente) hospital in Enschede, The Netherlands. Medisch Spectrum Twente is a conglomeration of various hospitals in the Eastern part of The Netherlands. A special division of the MST is the Centre for Mammacare, where (suspected) breast cancer patients from the Twente region are treated.

This chapter gives a short introduction to the subject, describes the problem, research questions and the scientific importance of this study.

1.1 BACKGROUND

The Centre for Mammacare annually receives about 500 patients with suspected breast cancer. Of these, approximately 250 patients are diagnosed positively. After the diagnosis has been established, the clinical part of the treatment starts in which a mastectomy (removal of the breast) or breast conserving therapy is performed, together with optional radiotherapy and/or chemotherapy, depending on the diagnosis. After these primary treatments, a surveillance strategy called follow-up starts, provided by the health care institution where the patient received treatment. The patient annually returns to the hospital for a check-up. Follow-up is defined as the subsequent examination of a patient for the purpose of monitoring earlier relapses. Follow-up has five aims: detection of recurrence, detection of second primary cancers (Jacobs, Dijck et al. 2001), evaluation of primary and adjuvant therapies, psychosocial support (Wiggers 2001), and collecting data for research (Hiramanek 2004). These aims are outlined in Chapter 2.

The visits vary in frequency, time span and type of consultation, depending on national and/or local guidelines. In The Netherlands, the recommended procedures for breast cancer follow-up are described by the Institute of Quality in Health Care. In addition to these guidelines, the Centre for Mammacare follows locally agreed guidelines, which are more extensive in time span and frequency per year than the national guidelines. Further information on the guidelines can be found in Section 2.2.

1.2 EFFECTIVENESS OF FOLLOW-UP

Breast cancer patients frequently return to the hospital for their follow-up visits, mostly performed by the surgeon. These follow-up services can be divided into two groups. Limited follow-up includes annual history taking, physical examination and an annual mammography. In addition to these operations, intensive follow-up includes also chest X-ray, blood analysis and bone scintigraphy (bone scan). In the Netherlands, limited follow-up is usually offered.

Patients die from breast cancer because of the occurrence of distant metastases, e.g. bone-, lung-, or liver metastases. When distant metastases are detected, no cure can be given (Schapira 1993). Figure 1-1 shows two types of metastases. Distant metastases are caused either by the primary tumor (option 1) or by a form of recurrence (option 2) (Engel, Eckel et al., 2003). Follow-up visits after primary treatment do not influence the risk of primary metastases, they only detect them and no cure can be given at that point. Follow-up visits only influence survival when a recurrence (option 2) is detected at an earlier time, so the recurrence has no chance to grow further and hence the risk of secondary metastases is lowered. Because the risk of primary metastases cannot be influenced by follow-up, the effectiveness of follow-up is lower than one would expect initially.

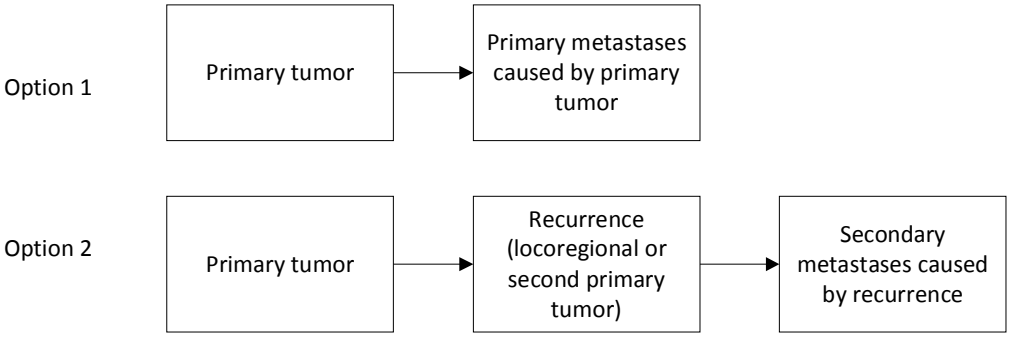

Figure 1-1 Two different types of distant metastases are possible

In the past twenty years many studies have been performed that study the effectiveness of follow-up services. Collins, Bekker et al. employ a systematic review of these studies. They included all studies that report empirical data of patients attending a routine follow-up service after treatment for breast cancer (in English from 1989 to 2001), and frequency tables are used to summarize the study characteristics. From the selected studies, they perform a systematic review of 38 articles that met previous defined conditions about the effectiveness of follow-up services (Collins, Bekker et al. 2004). After reviewing these 38 studies, Collins, Bekker et al. conclude that no scientific evidence exists that justifies intensive follow-up for patients who have been treated for breast cancer. A minimal approach is as effective as intensive follow-up in terms of survival, timeliness of recurrences detection, and quality of life.

A study that shows similar results, and was not included in the review of Collins et al, is a study by Jacobs et al. (Jacobs, Dijck et al. 2001). In this study Jacobs, Bijck et al. apply a simulation model to evaluate the impact of different follow-up strategies, using a five-state Markov chain model. Medical aspects such as life expectancy and the percentage of the patients who died from breast cancer are

studied. In the simulation, standard follow-up is defined as physical examination and history taking (three-monthly in the first year, six-monthly in the second to sixth year and annually thereafter) and annual mammography. They compare standard follow-up to no follow-up, in four different age cohorts: 40, 50, 60 and 70 years. The conclusion of this study reaches even further than the conclusion of Collins et al., saying that in the most beneficial situation the gain in years of life for a woman aged 40 is only 73 days, and even less for a woman aged 60: 37 days.

Two studies that are reviewed by Collins et al. and are considered definite proof that intensive follow-up is unnecessary (te Boekhorst, Peer et al., 2001), are the studies of Roselli Del Turco et al, and the GIVIO-investigators, both published in the Journal of the American Medical Association. In the latter study a randomized clinical trial is performed of 1320 women who were assigned to one of two groups of follow-up that varied in intensity The conclusion is that routine use of intensive follow-up methods should be discouraged (Roselli Del Turco, Palli et al. 271; GIVIO-Investigators 1994).

The conclusion that earlier detection of a recurrence does not have an effect on prognosis or on survival not only questions the effectiveness of intensive follow-up, but also the effectiveness of limited follow-up. This conclusion corresponds to the conclusion of the earlier discussed study of Jacobs et al., and the conclusion of Loong et al., who review 490 patients and also conclude that detection and treatment of local recurrence in the asymptomatic stage do not have beneficial effects on overall survival (Loong, M. et al. 1998).

Summarizing can be concluded that two reasons exist why even limited follow-up is not medically efficient: only a minority of the recurrences is found in the asymptomatic stage, and the life expectancy of those women who do get diagnosed earlier during a follow-up visit does not increase significantly. Many more studies conclude the same (e.g. (Jacobs, Dijck et al. 2001; Collins, Bekker et al. 2004; Rojas, Telaro et al. 2007; Tolaney and Winer 2007; Tondini, Fenaroli et al. 2007; Kimman, Voogd et al. 2007a).

One wonders, if for so many years studies have come up with the same conclusions over and over again, assigning little medical effectiveness to neither extensive nor limited follow-up, why are the follow-up schemes still as long and intensive as they are today? Although the national guidelines show a trend of decrease of length and frequency, the Centre for Mammacare wants to cut through this tradition by introducing a more individual approach, with the underlying goal to increase the efficiency and effectiveness of follow-up. Although studies assign little medical effectiveness of follow-up in general, these conclusions do not apply to the whole patient population, since all patients have different characteristics. The current follow-up leaves little room for individualizing follow-up scenarios. A more individualistic approach only assigns an intensive follow-up to patients who actually need it, e.g. because of medical or psychosocial circumstances. This not only improves the quality of life for the patients in the follow-up (Allen 2002), but also for new patients, since more time becomes available for this group of patients

1.3 PROBLEM FORMULATION

In this study the focus lies on offering more individualistic follow-up, corresponding to the needs of patients. Consequently, fewer visits are needed for patients who do not need this and more time becomes available for those who do. As Wheeler (1999) mentions "The ideal follow-up for patients with cancer should be sensitive to the likelihood of relapse". We look at the frequency of the consults, the time span, and the type of consult. Investigation of the operations within the consult (history taking, physical examination and mammography) is beyond the scope of the project.

The Centre for Mammacare experiences a high workload resulting from follow-up patients. Because the follow-up period is long (ten years), follow-up patients consume much time of the staff. The costs in terms of time are high because early stage breast cancer patients have a good prognosis and recurrences can be observed several years after primary treatment. The total patient follow-up workload therefore increases every year. However, many treated breast cancer patients will never experience a recurrence (Mould, Asselain et al. 2004). At this moment, according to one surgeon of the Centre for Mammacare, consulting follow-up patients takes so much time that it starts to affect the ability of surgeons to treat new patients. Therefore a point of interest of this research is the workload. Workload is part of quality of care, as well as other aspects we discuss next. An aim of the study is to lower the amount of time the staff of the Centre for Mammacare is treating follow-up patients, while respecting patient's preferences.

The costs that are made for current follow-up are significant (Grunfeld, Fitzpatrick et al. 1999), especially time invested. Medical procedures are designed to prolong the length of live, thus lengthening life expectancy (LE). A more accurate target is to lengthen Quality Adjusted Life Years (QALY), taking quality of life of the years lived into account. From a societal perspective, increases in life expectancy and QALY need to be balanced with the costs of the medical treatment. In other words, medical treatments need to be cost-effective. If lengthening life expectancy with one year costs a thousand surgeon's hours, the cost-effectiveness is obviously low. On the other hand, if lengthening life expectancy with one year costs one surgeon's hour, the cost-effectiveness is high. The threshold, somewhere in the middle, is subjective. Because some patients have more risk of recurrence than others, a follow-up scenario that is cost-effective for one patient is not necessarily cost-effective for the other patient. The point of interest of this study is the cost-effectiveness of various scenarios for follow-up.

These facts taken into account, the problem formulation is:

Workload and costs for performing follow-up at the Centre for Mammacare are high because of an increasing number of patients, who all receive the same follow-up.

The main goal is to offer more individualistic follow-up, which results in a decrease in input of the patients into the follow-up (which has already been scientifically proven to not change quality of life and therefore considered to be feasible). Our approach is to divide the patient population in groups based on age, tumor size and number of positive lymph nodes (see Section 3.1). By dividing patients into groups, patients with good prognoses will receive less intensive follow-up, resulting in a decrease of input of patients into the follow-up population.

1.4 GENERAL RESEARCH QUESTIONS AND METHODOLOGY

We derive the central research question from the problem formulation:

How cost-effective are various scenarios for follow-up and what is their workload impact for the Centre for Mammacare?

1.4.1 RESEARCH QUESTIONS AND METHODOLOGY

The cost-effectiveness domain discusses the cost-effectiveness of the defined scenarios, and their impact on the workload of the staff in the Centre for Mammacare. The sub-questions that help answering the main question are:

1. *What is the cost-effectiveness of these scenarios?*

To evaluate various scenarios for cost-effectiveness we simulate the usage of various follow-up strategies with a discrete event state transition model. The model shows states for patients and transition rates to other states. Cost-effectiveness is a concept that has two parts in it: costs and effectiveness. Therefore, we are able to make a division into two sub questions:

1.1 What are the costs of these scenarios?

To calculate the cost of the scenarios, we break down the scenarios in activities per year. We add up the costs for all activities for all patients. We focus on costs from a surgeons' perspective.

1.2 What is the effectiveness of these scenarios?

Effectiveness is a somewhat vague term and needs to be operationalized. We use Quality Adjusted Life Years (QALYs).

To compute the cost effectiveness we compute the incremental cost-effectiveness ratio (ICER). It is defined as the ratio of the change in costs of a therapeutic intervention, compared to the alternative. The alternative can be defined in various ways e.g. as a very minimal follow-up, or as the current follow-up scenario.

2. *How do the scenarios influence the workload in the Centre for Mammacare?*

In this step of the study, we inspect the viability of the scenarios for implementation. The Centre for Mammacare has limited personnel and different scenarios will change their workload.

1.5 SCIENTIFIC IMPORTANCE

Our goal is to create follow-up schemes, for different risk groups. To individualize this follow-up, we propose several categories of patients which are medically based, depending on their tumor size and number of positive lymph nodes. The proposed scenario can then be individualized to categories of patients, making the scheme more appropriate for that patient. This might increase patient

satisfaction and quality of life, since the proposed follow-up is more corresponding to the patients' needs.

The added value of the cost-effectiveness part of the study lies in the combination of using a state transition model together with a cost analysis. This combination has yielded interesting results in studies considering other types of cancer follow-up (Borie, Combescure et al. 2004; Spermon, Hoffmann et al. 2005). Also we individualize follow-up, by modeling patient groups.

Summarized, the scientific contribution of this research is that we classify the patients into risk groups, and propose individualized follow-up scenarios for these groups.

SUMMARY

- The Centre for Mammacare is experiencing more and more follow-up visits from breast cancer patients. This leads to increased workload.
- All patients currently receive the same follow-up. The Centre for Mammacare wants to determine a more individualized follow-up.
- We determine patient groups, study different follow-up scenario's, and determine the most appropriate follow-up scenario for each patient group.
- We focus on the cost-effectiveness of follow-up scenarios

2 CONTEXT: FOLLOW-UP AFTER PRIMARY TREATMENT

This chapter describes the reasons for follow-up (2.1), guidelines for follow-up (2.2), possible events related to recurrence of breast cancer (2.3) and the influence of follow-up on the disease (2.4).

2.1 REASONS FOR FOLLOW-UP

Follow-up for patients treated for breast cancer has five reasons (Jacobs, Dijck et al. 2001; Wiggers 2001; Hiramanek 2004; Kimman, Voogd et al. 2007a):

1. *Detection of loco-regional recurrence*

Breast cancer patients have a certain risk of a recurrence. A loco-regional recurrence is a tumor that occurs in the same breast or in the same site as the first primary tumor. Some patients have higher risk of a recurrence than other patients. The risk depends on various factors, such as age, tumor size and nodal status (Saphner, Tormey et al. 1996). When a local recurrence has been diagnosed a patient is first checked for metastases. When metastases are not present, curative treatment is possible.

2. *Detection of second primary tumors*

Women with breast cancer have a higher risk of a second primary tumor than women who have not experienced breast cancer. A second primary tumor is a tumor that occurs in the other breast than the first tumor. Because of this higher risk, surgeons perform follow-up in order to detect second primary tumors at an earlier stage.

3. *Evaluation of primary and adjuvant therapies*

During follow-up, the surgeon inspects the results of the therapy. Especially in the first year after primary treatment, postoperative morbidities exist that need to be treated, such as monitoring the healing of the wound and possible psychosocial problems.

4. *Psychosocial support*

Breast cancer has great physical, psychological and social impact (Ferrell, Hassey-Dow et al. 1995), and many women experience anxiety and distress (Fallowfield and Baum (1989). The follow-up helps to relieve this distress. A follow-up consult gives women reassurance no recurrence or new primary tumor has developed and some women appreciate this reassurance (Allen 2002). At the same time, it is a cause of stress. 70% of women experience distress at follow-up (Paradiso, Nitti et al. 1995).

5. *Collect data for research*

Medical research often takes place in the form of clinical trials. These trails need data to measure variables. Follow-up provides an opportunity to record data for research (Hiramanek, 2004).

It is important to realize that patients who develop distant metastases are essentially incurable (Shapira 1993). Distant metastases are metastases that occur mostly in the bones, lungs and liver. Cancer that occurs in the lymph nodes, however, can be treated. It is important to understand this difference. Because of the incurable character of distant metastases, diagnosing these distant metastases is not one of the aims of follow-up. Discovering these incurable metastases when the

patients have not yet developed symptoms has a large psychological impact and leads to a decreased quality of life.

2.2 CURRENT GUIDELINES FOR FOLLOW-UP

In the Netherlands, the Institute of Quality in Healthcare (Kwaliteitsinstituut voor de Gezondheidszorg, CBO) publishes national guidelines for the follow-up for breast cancer patients. The CBO tries to improve patient care in the Dutch health care system, focusing on less complications, shorter waiting times for surgeries, and better cooperation between patient and health care provider, disciplines, departments and hospitals(http://www.cbo.nl/algemeen/default_view).

In its 2005 report, in cooperation with the Vereniging van Integrale Kankercentra, CBO recommends to have consults that include history taking and physical examination 4 times in the first year of follow-up, twice in the next year, and once a year thereafter. No particular time span is recommended, but under normal circumstances it should not be longer than 5 years, unless the patient has the BRCA 1/2 gene mutation, which increases the chance for breast cancer. Further recommendations include a mammography once a year until the age of 60, and once in 2 years thereafter. Patients and their general practitioner should know whom to contact when complaints arise.

In addition to the national guidelines, regional guidelines exist that apply to the Centre for Mammacare. These guidelines are formulated by ONCON, the Oncological Network Surgeons East Netherlands (Oncologisch Netwerk Chirurgen Oost Nederland). Their guidelines can be consulted in Table 2-1. The main goal of this network is to optimize the oncological surgery for cancer patients (http://www.ikcnet.nl/IKST/werkgroepen/oncologisch_netwerk_chirurgie_oost_nederland/index.php). The differences between the national and local guidelines can be found in the frequency and time span of the consults. Since the Centre for Mammacare follows the local guidelines, we take these guidelines as a basis for this study.

Women < 60 years	Years 0-5	Years 6-10	Years >10*
History + PE Mammography	2 1	1 1	1 1
Women ≥ 60 years			
History + PE Mammography	2 Once in 2 years	1 Once in 2 years	1 Once in two years
PE = Physical Examination * = Optional when considered appropriate			

Table 2-1 Current follow-up scheme MST frequency per year (source: MST)

2.3 POSSIBLE EVENTS IN THE PROCESS OF BREAST CANCER

When patients are diagnosed with breast cancer, they are treated with curative intent only if no distant metastases are present. Normally, a breast conserving treatment or a mastectomy is performed. Patients who have received initial curative treatment, regardless of breast conserving

therapy or mastectomy, all enter the same process of follow-up in the current situation. Figure 2-1 shows a flowchart of the process.

After the primary treatment (surgery and adjuvant treatment if necessary), patients are essentially healthy and reside in box "after primary treatment [1,0]. The numbers between brackets indicate the status of the patients' two breasts. They receive follow-up according to the schedule decided by the surgeon. If no recurrence takes place, patients will eventually die from another cause. This event is modeled by the dashed arrow to box "death from other causes".

Of course, the possibility exists that patients do experience a recurrence. This event is modeled by the arrows within the large box "disease process". The possibility of recurrence is influenced by many prognostic factors. Examples of these are the size of the primary tumor, the number of affected lymph nodes (lymph node status), the invasiveness of the tumor (tumor grade), the degree to which the tumor was fully removed during surgery (margin status) and the age of the patient. Other prognostic factors are the use of chemo- or radiotherapy as adjuvant treatment (Saphner, Tormey et al. 1996; Wheeler 1999; Park, Kim et al. 2002; Bollet, Sigal-Zafrani et al. 2007; Sanghani, Balk et al. 2007).

There are three types of recurrence. The first is locoregional recurrence, when breast cancer returns in the same breast or in the same site as where the primary tumor was located. The second type of recurrence is a second primary tumor. This means that a second tumor has developed in the other breast than the first tumor. This second primary tumor has no causal relation to the first primary tumor, hence the term second *primary* tumor. There is a possibility a recurrence happens in a second primary tumor. The third type of recurrence is the occurrence of distant metastases. Examples are metastases in bone, lung or liver. Local recurrence and second primary tumors are always treated if no distant metastases are apparent. In the case of distant metastases no cure can be given (Schapira 1993).

When a curative treatment is given, the patient is essentially healthy again, although risk of metastases is much higher. Local recurrence serves as an indicator as well as a cause of metastases (Engel, Eckel et al. 2003). Research shows the risk factor for distant metastases is approximately 3 (Engel, Eckel et al. 2003) for patients with local recurrence compared to patients without local recurrence. This means that patients who develop local recurrence run a risk of distant metastases three times as large as the risk of metastases for patients who do not develop a local recurrence. When distant metastases are detected, patients will eventually die of breast cancer.

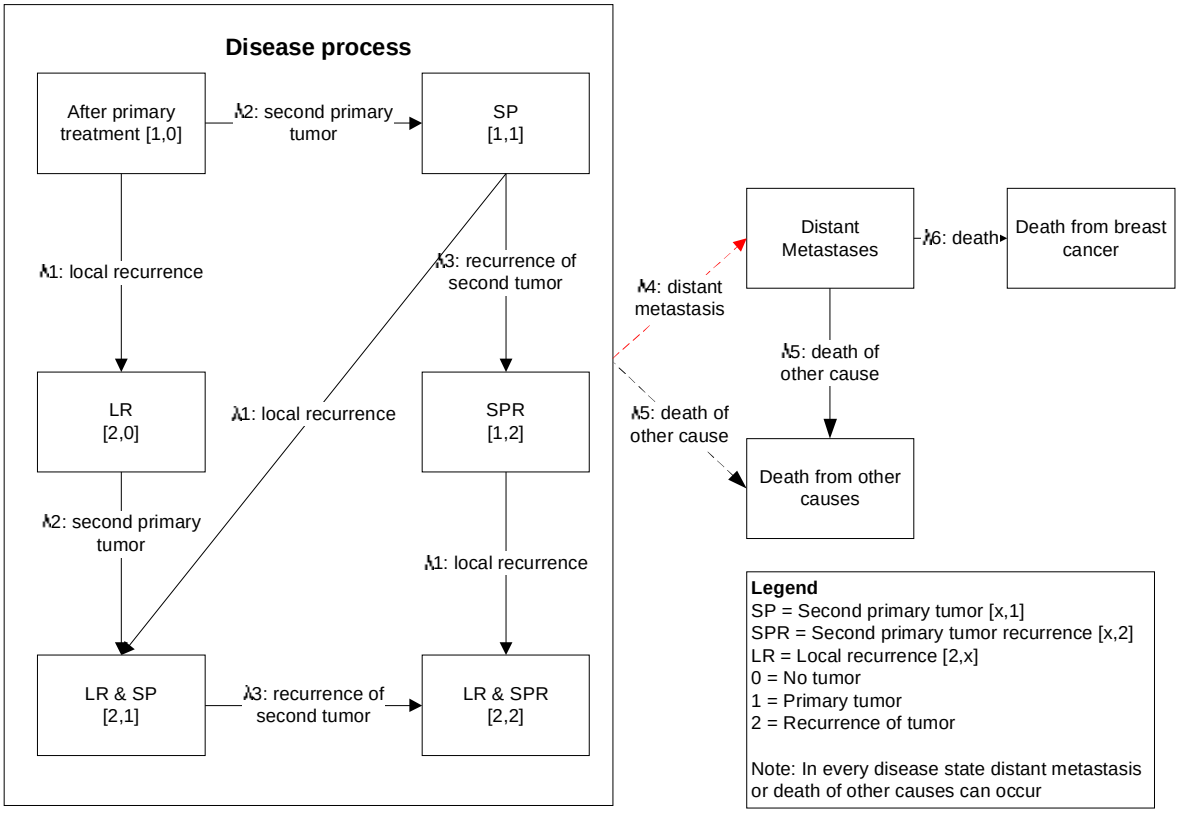

Figure 2-1 Flowchart of process of breast-cancer

Concluding it can be said that while every event in the disease process can be treated, it does heighten the patients' risk of distant metastases (depicted by the red arrow).

Figure 2-1 is a generalized view of the states in follow-up, but it serves as a good framework to understand other aspects of the problem that are discussed.

2.4 INFLUENCE OF FOLLOW-UP: THE PROCESS OF METASTASISATION

Where in Figure 2-1 does follow-up play a role? To answer this question we need to know more about the process of metastasisation. The process of metastasisation can be illustrated as in Figure 2-2. Figure 2-2 shows that distant metastases can originate from the first primary tumor, but also from a local recurrence or a second primary tumor. Engel, Eckel et al. (2003) have coined the term 'primary metastases' and 'secondary metastases'. The term indicated which tumor caused the distant metastases, secondary referring to a locoregional tumor or a second primary tumor.

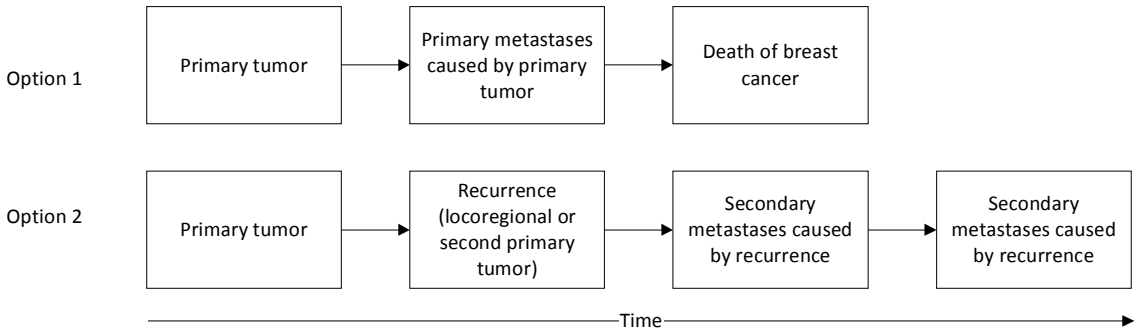

Figure 2-2 Primary as well as secondary metastases are possible.

Follow-up is only useful for early detection of locoregional recurrences and second primary tumors. When they are detected early, the recurrence does not have the chance to grow any further. Hence, the risk of secondary metastasisation is reduced. Important is the notion that follow-up does not prevent primary metastases from occurring. A certain fraction of the population of breast cancer patients will die of distant metastases no matter how intensive the follow-up scenario has been defined. About the growth of metastases, Engel et al. estimate "(…) it takes approximately one to 2 years for a tumour to double in diameter (from 14 to 28 mm) or for the tumour volume to increase 8-fold".

Finally, not all recurrences are detected during follow-up. As mentioned, te Boekhorst et al. found that only 37% of the recurrences were found during the asymptomatic stage. The authors conclude that the medical impact of the current follow-up is low, and "follow-up visits after treatment for breast cancer are hardly warranted" (te Boekhorst, Peer et al. 2001). This confirms the results of another study that reviewed 490 patients and concludes that the detection and treatment of local recurrence in the asymptomatic stage do not have beneficial effects on overall survival (Loong, M. et al. 1998). The mentioned studies also conclude that most recurrences present at unscheduled appointments.

SUMMARY

- The reasons for follow-up are fivefold: Detection of loco-regional recurrence, detection of second primary tumors, evaluation of primary and adjuvant therapies, psychosocial support, collecting data for research.
- Current National guidelines advise a follow-up of at least five years. The Centre for Mammacare follows ONCON guidelines with a follow-up of ten years.
- Three types of recurrence are possible: a second primary tumor in the contralateral breast, a local recurrence and distant metastases. The latter is not curable, the first two are. However, a local recurrence does indicate a heightened risk of distant metastases.
- Follow-up can influence survival by detecting local recurrences and second primary tumors in an early stage, thereby reducing the risk these patients run of metastases caused by the recurrence.

3 THEORY

This chapter discusses the theory needed to answer our research questions. Section 3.1 discusses the patient classification and patient population. Section 3.2 inspects scenarios to test for cost-effectiveness. Section 3.3 studies the concept of quality of life in order to be able to measure in QALYs. Section 3.4 explains the theory behind cost-effectiveness analyses and Section 3.5 discusses models to calculate cost-effectiveness.

3.1 PATIENT CLASSIFICATION

In this part of the paper, we classify patients into groups according to certain characteristics. Each group has a different risk of a recurrence, which influences the cost-effectiveness of scenarios. We also illustrate the total number of new patients annually and its division into the groups. The population consists of all patients diagnosed with breast cancer that underwent breast conserving treatment or mastectomy with curative intent. By doing this, we exclude patients who have no chance of curative treatment for they will not enter the follow-up trajectory. Furthermore, we only include patients in which the margin status is negative, meaning that the tumor was fully removed during surgery. Patients who have a positive margin status have a high and variable risk of a recurrence. Decisions about their follow-up are needed to be made by their surgeon.

3.1.1 DEFINITION OF GROUPS

Cost-effectiveness includes two aspects: costs and effectiveness. Costs are determined by the followed scenario. Effectiveness is influenced the follow-up scenario and by patient and disease characteristics. We use three patient characteristics: lymph node status, tumor size and age (Saphner, Tormey et al. 1996). These characteristics influence the risk of a recurrence. When a patient has high risk of locoregional recurrence, effectiveness of an intensive scenario will be higher. When a patient has low risk of a recurrence, an intensive scenario is probably not needed.

The first variable is lymph node status. When diagnosing the patient with breast cancer, the number of affected lymph nodes is determined. The more lymph nodes are positive, the worse the patients' prognosis. A regular division of patients into lymph node status groups is 0 nodes positive, 1-3 nodes positive and >3 nodes positive (Saphner, Tormey et al. 1996).

The second variable that is a major determinant of risk of a recurrence is tumor size. The tumor size is also determined during diagnosis. A regular division of patients in tumor size groups is 0.1-1.0 cm, 1.1-3.0 cm and >3.0 cm (Saphner, Tormey et al. 1996).

The third variable is age. Age is not a very strong predictor of recurrence of breast cancer, except with patients younger than 35, where it significantly increases risk of a locoregional recurrence (Bollet, Sigal-Zafrani et al. 2007). Elderly women have a higher risk of dying from other causes, which makes a successful detection and curative treatment of recurrence less effective because they have a lower life expectancy than younger women.

3.1.2 NUMBER OF PATIENTS IN THE NETHERLANDS

As mentioned, about 12000 females are diagnosed with cancer annually, making up for more than 33% of female cancer patients in the Netherlands (Visser and Van Noord 2005). About one in every eight women will be diagnosed with breast cancer in her lifetime (Kankerbestrijding 2007). Figure 3-1 shows the age distribution for the total yearly population of new breast cancer patients.

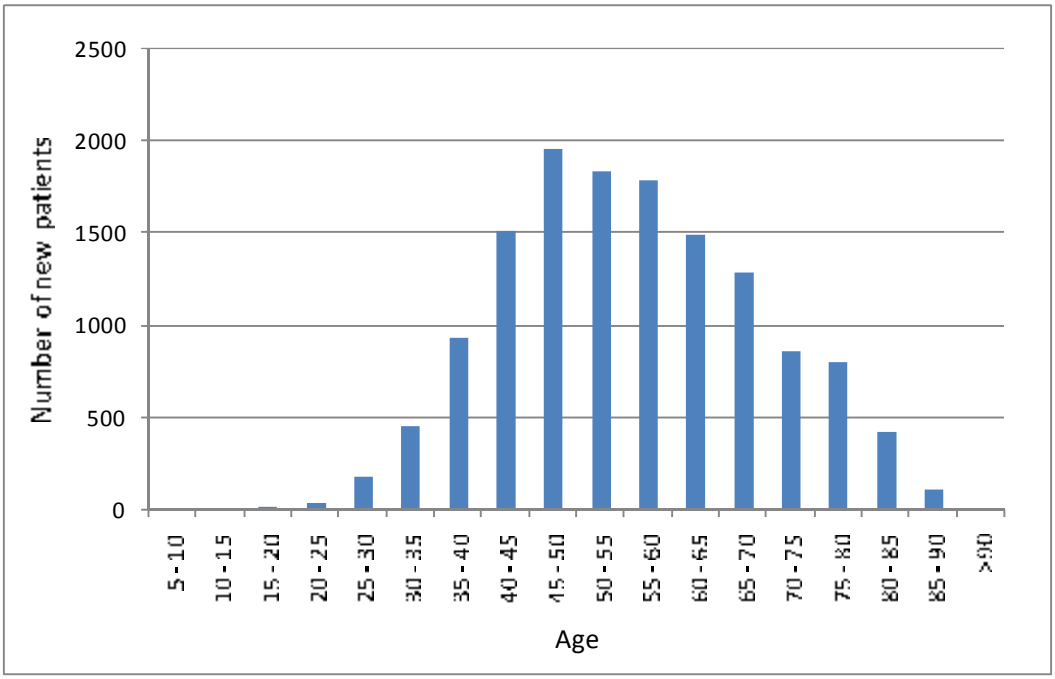

Figure 3-1 New breast cancer patients in the Netherlands 2006 (source: CBS, 2007)

3.1.3 NUMBER OF PATIENTS IN MST

We obtained the population of breast cancer patients in MST from IKST. Every year about 180 new patients undergo surgery and enter the follow-up process. Appendix II shows statistics about the patient population.

3.2 SCENARIOS FOR FOLLOW-UP

Follow-up consults in the first year have more applications than in the years thereafter. The quality of the surgery and post-morbidity (e.g. psychosocial problems, chronic fatigue) are monitored in the first year (Wiggers 2001; Hiramanek 2004). However, after the first year everything is close to normal and the next years of follow-up start. Although the first year is part of the whole follow-up scheme, this year is unquestioned because of the extra applications and reasons for the consults in this year. Therefore, when proposing follow-up scenarios for different groups of breast cancer patients, we take the first year for granted and focus on the years thereafter.

The national guidelines recommend a consult 4 times in the first year of follow-up, twice in the next year, and once a year thereafter. Since this research' domain is the follow-up after year 1, we include only "once" and "twice" a year as attribute levels. When we propose a scenario with a frequency of once a year, this means that there is one consult per year in which the results of the mammography are discussed and the history taking and physical examination is performed. When we propose a scenario with a frequency of twice a year, in only one of these consults the results of the mammography is discussed; in both physical examination and history taking is taking place. When a woman is over 60 years old, the current guidelines are followed, e.g. a mammography once in two years. The variance of the attribute 'frequency per year' lies in the frequency of the consult (history taking and physical examination); we do not propose different frequencies for the mammography.

Although the current time span for follow-up in the Centre for Mammacare is 10 years, according to the local guidelines, we only investigate follow-up scenarios with a time-span of maximum 5 years, according to the national guidelines. Another reason for this is that by doing so we reduce the total number of possible scenarios. This choice is also based on previous studies that indicate that less intensive follow-up is as medically effective as more intensive follow-up, as discussed in 1.2. When we propose scenarios of no more than 5 years this limitation is for the consult (i.e. history taking, physical examination) as well for the mammography. When the women are done with their follow-up scheme, they are recommended to take part in the national breast cancer prevention program, which means that a mammography is taken once in two years for women with the age starting from 50 until and included 75.

When focusing on type of consult, we selected 3 attribute levels: Surgeon face-to-face, NP face-to-face, NP telephone. An NP is a Nurse Practitioner, a nurse who has completed an advanced nursing education, mostly a master's degree. These levels are a combination of type of physician (surgeon or NP) and type of consult (face-to-face or telephone), in which the combinations are chosen according to plausibility. Because of a lack of time and due to financial reasons, the combination "Surgeon telephone" is not plausible. Only when the prognosis and information the health care provider has to provide to the patient is good, the telephone is a suitable alternative. In such a case the Nurse Practitioner is as capable as the surgeon, but cheaper for the hospital. Therefore the combination "Surgeon telephone" is not plausible.

The attributes and their corresponding levels are summarized in Table 3-1.

Attribute	Attribute levels
Frequency per year	Once, twice
Total length of follow-up	1, 3, 5 years
Type of consult	Surgeon face-to-face, NP face-to-face, NP telephone

*NP = Nurse Practitioner

Table 3-1 Attributes and corresponding attribute levels

3.3 QUALITY OF LIFE

As mentioned we are not only interested in the number of years a patient lives with certain follow-up scenarios, but also in the quality of life of these years. Therefore we use Quality Adjusted Life Years (QALYs) as an output measurement in the cost-effectiveness analysis. QALYs form a mathematical expression of a certain medical intervention. QALYs are recommended when performing a cost-effectiveness analysis (Mauskopf, Sullivan et al. 2007).

QALYs are obtained by multiplying each year lived with a weight indicating the quality of life of these years. These weights are constructed by measurement of the Health Related Quality of Life. The weights range from 0 (dead) to 1 (fully healthy). There are three main methods to determine these weights: the rating scale, the time trade-off and the standard gamble (Lidgren, Wilking et al. 2007). A questionnaire is normally used with the rating scale method. Time trade-off lets the patient make a tradeoff between living a number of years in their current health state, or living a reduced number of years in full health. In a standard gamble, respondents are asked to choose between remaining in a state of ill health for a period of time, or choosing a medical intervention which has a chance of either restoring them to perfect health, or killing them. Neither of these methods is considered clearly the best (Petrou 2001).

Patients diagnosed with breast cancer enter a process with health states. We describe this process in 2.3 "process of follow-up". Health states are most appropriate when there is a set of states for which the transitions are clear and which are indicative of QoL valuations (Glasziou, Cole et al. 1998). (Lidgren, Wilking et al. 2007) distinguish between four states:

- First year after primary breast cancer (State P)
- First year after recurrence (State R)
- Second and following years after primary breast cancer or recurrence (State S)
- Metastatic disease (State M)

They collect trade-off weights for the health states defined above. The weights are averages of the weights of all respondents in a certain health state, so in reality the QoL will differ among patients in a certain health state. We can use these weights, since our health states as defined in 2.3 correspond to their defined health states. Furthermore, time trade-off method is a reliable and practical method to measure quality of life (Petrou 2001).

3.4 COST-EFFECTIVENESS ANALYSIS

Cost-effectiveness analysis is the standard tool for the assessment of health technologies (Siebert 2003). A cost-effectiveness analysis is an analytic tool, that calculates the costs and effectiveness of an intervention designed to prevent, diagnose, or treat disease (Mandelblatt, Fryback et al. 1997). Many experts and consensus groups have recommended a cost-effectiveness analysis as the best way to conduct economic evaluations (Brauer, Rosen et al. 2006). Cost-effectiveness analysis is designed to maximize the health of the patient population, given limited financial resources. It differs from a cost-benefit analysis because it does not measure the outcomes of intervention in monetary terms, but in health outcomes.

Many cost-effectiveness analyses have been conducted in various fields of oncology (Borie, Combescure et al. 2004; Spermon, Hoffmann et al. 2005; Guadagnalo, Punglia et al. 2006). Regarding breast cancer follow-up, only a comparison has been executed between follow-up performed by the medical specialist and follow-up performed by the general practitioner (Grunfeld, Fitzpatrick et al. 1999). Their study takes only costs into account without specifically looking at quality-adjusted life-years. Research about follow-up indicates the need for a cost-effectiveness analysis of follow-up scenarios (Tolaney and Winer 2007; Kimman, Voogd et al. 2007a).

Apart from the advantages, cost-effectiveness analysis does have its drawbacks. A cost-effective intervention might be perceived as the perfect one by decision makers. However, cost-effectiveness is not the only aspect to consider when making a medical policy decision. Other aspects to be considered are acceptability and feasibility (Mandelblatt, Fryback et al. 1997). Acceptability is the degree to which the suggested policy is perceived acceptable by all stakeholders. Feasibility is also an important aspect, since scenarios with a very favorable cost effectiveness ratio might be totally unfeasible.

Another drawback of cost-effectiveness analyses are ethical objections. Cost-effectiveness analysis regards every patient case as equal (Sulmasy 2007). He gives an example of a woman who wants to see her grandchild born and needs an expensive treatment that will prolong her life with two months. Cost-effectiveness analysis would regard this treatment equal to one where thirty patients live two days longer. He argues that there are differences between patient cases and every case is a unique one. We agree that the medical specialist should decide on the follow-up given to the patient, but argue that cost-effectiveness analysis should be incorporated in his decision. We propose guidelines, tailored to the individual patient. The medical specialist can further individualize his prescribed follow-up for each patient.

The Panel on Cost Effectiveness (Phillips and Chen 2002) has three important guidelines when conducting cost-effectiveness analysis:

- Use of QALYs
- Calculation of incremental cost-effectiveness ratios, in order to be able to successfully compare scenarios.
- Use of a 3% discount factor for costs as well as QALYs, in order to take the future value of money and life into account.

3.5 MODELS FOR CALCULATING COST-EFFECTIVENESS

Mathematical models are well suited for cost-effectiveness analysis. Models do not have many of the issues associated with real-life randomized controlled trails. When using a mathematical model for cost-effectiveness analysis, designers need to make decisions on three dimensions (Mandelblatt, Fryback et al. 1997). These dimensions are the analytic methodology, the handling of the population and the method of calculation. We discuss every dimension and use information from (Mandelblatt, Fryback et al. 1997).

3.5.1 TYPE OF MODEL

We first discuss the type of model. Two mathematical options are frequently used within cost-effectiveness analysis: Decision tree models and state-transition models. Decision tree models represent chance events and decisions over time. Each path in the decision tree represents a possible sequence of event. The analysis of a decision tree works well when analyzing events with limited recursion and a limited fixed time horizon (Siebert 2003). A drawback of decision tree models is that they are not suitable for representing events that occur multiple times (recursion). The problem with follow-up is that a patient can theoretically experience a very large number of recurrences, thereby enlarging the decision tree greatly.

State-transition models are able to represent these kinds of events. In a state transition model, one allocates the population to certain states and, as a result of probabilities, reallocates fractions of the population to other states.

A Markov model is a special type of state-transition model. In a Markov model, transition probabilities are dependent only on the current state. A small example to clarify is useful. One could develop a Markov model of the weather. This model would consist of several states representing different types of weather, e.g. sun, rain and clouds. All these states would have a possibility to transfer into another state. In our model, the chance to go from sunny to rainy is 20%. In a Markov model, this chance is *independent* of previous states. It does not matter if it was raining of cloudy before, because right now it is sunny. Maybe a couple of days later the sun shines again, in that case the chance it will rain is still 20%.

This property of Markov chains is useful for modeling the follow-up scenarios. An example would be the state "death from breast cancer". Indifferent of the state before "death", the possibility to exit the "death" state is always 0. Another example is in case of metastatic recurrence, the probability for curative treatment is always 0. We describe our exact data and choices in Chapter 4.

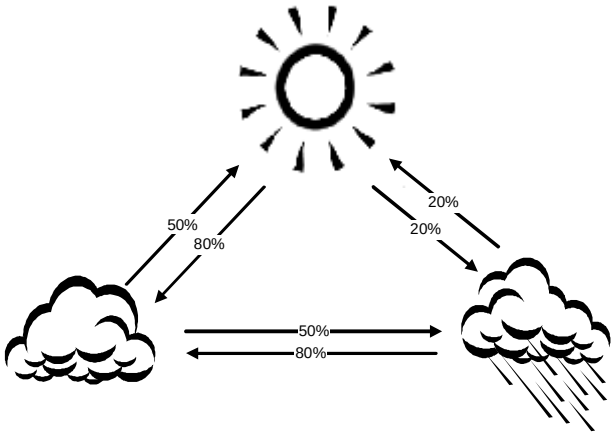

Figure 3-4 Example of Markov model

Markov chains are extensively used in medical decision making and in cost-effectiveness analyses of cancer treatments (Chen, Thurfjell et al. 1998; Jacobs, Dijck et al. 2001; Borie, Combescure et al.

2004; Spermon, Hoffmann et al. 2005). These Markov chains are a helpful tool for decision makers. One study investigates the effectiveness of a regular follow-up scenario with breast cancer compared with no follow-up at all (Jacobs, Dijck et al. 2001). However, this model does not take quality of life into account. It also only analyses effectiveness, rather than cost-effectiveness. Finally, it regards all patients as the same, while patients have different characteristics. Therefore, they are not able to recommend an individualized approach.

3.5.2 TYPE OF POPULATION

The second dimension describes the use of a longitudinal or a cross-sectional model. Models always make use of a population, in our case breast cancer patients. A longitudinal study calculates outcomes for typical patients or cohorts and follows them in order to evaluate health outcomes. Results of these models are usually expressed in QALYs.

The other possibility for modeling the population is by using a cross-sectional model. A cross-sectional model divides the population into subclasses and follows them through a specified period. The difference between cross-sectional models and longitudinal models is that cross-sectional models measure at a certain point in time whereas longitudinal models consist of multiple measurements in time.

3.5.3 TYPE OF CALCULATION

In the model, transitions from one health state to the next health state are made. These transitions can be calculated in two ways: deterministic and stochastic. The first option is to use a deterministic approach. This approach uses an average value to determine the fraction of the population that changes to the next state. We could for example want to know how many sunny days change into a rainy day. From a population of one hundred days, we would calculate that 20 days change into the rainy state. Stochastic calculation uses another approach. Every day is treated separately and using randomization with a 20% chance it is determined whether the days changes into a rainy day. When we would execute this simulation many times the actual days changing into the rainy state would approach 20%. Summarizing deterministic models determine the transition of the entire population in a certain state whereas stochastic models determine the transition of every instance separately, given the transition rate.

3.5.4 CALCULATING COST-EFFECTIVENESS OF FOLLOW-UP SCENARIO'S IN RECURRENT DISEASES

Cost-effectiveness analyses have been performed in many studies. Figure 3-5 presents a robust model for measuring cost-effectiveness in recurrent diseased. All mentioned factors influence cost-effectiveness in follow-up scenarios.

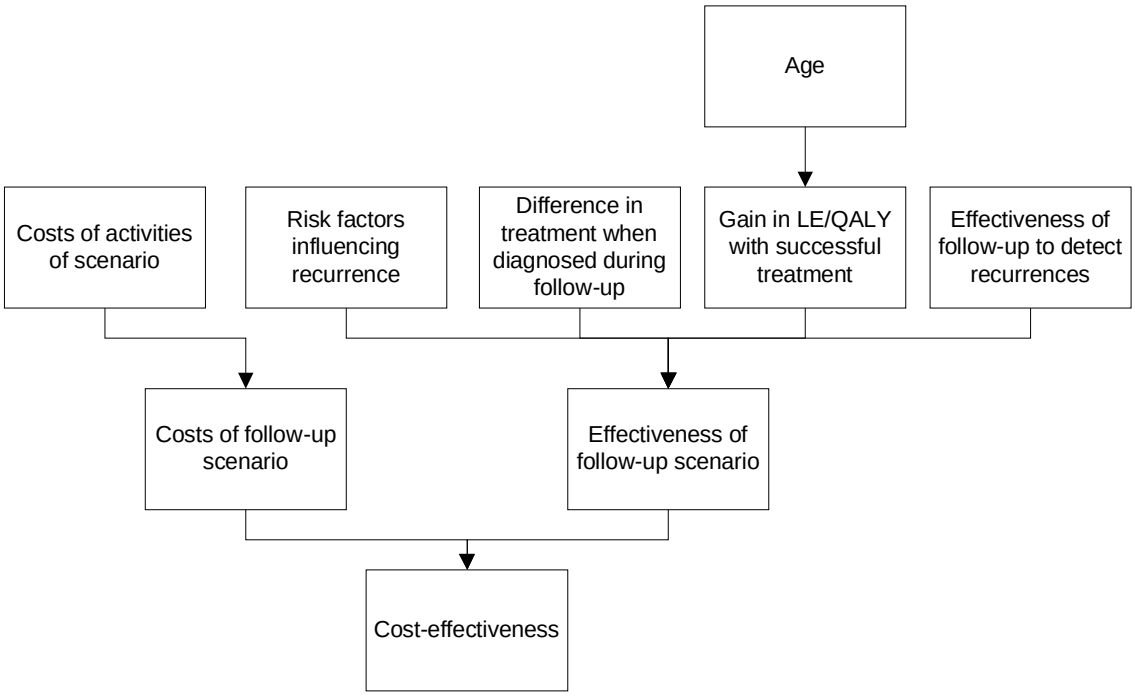

Figure 3-5 Factors influencing cost-effectiveness of follow-up scenarios in recurrent diseases

- Cost-effectiveness itself is a somewhat abstract term and it is useful to make a distinction into various aspects all influencing cost-effectiveness. Costs are determined in a straightforward manner, by aggregating the costs of activities of scenarios into total costs. Effectiveness is more difficult. It is influenced by:
- Risk factors: when there is a very low risk of a recurrence, usefulness of scenarios is bound to be low.
- Difference in treatment when diagnosed during follow-up: when it does not matter when a recurrent disease is detected, follow-up does not need to be performed.
- Gain in LE/QALY with successful treatment: when a patient is successfully treated for recurrent disease and dies immediately after because of another cause, the effectiveness of treatment is low. This factor is influenced by age.
- Effectiveness of follow-up to detect recurrences: when a scenario discovers no recurrences whatsoever, effectiveness will be lower

This model can also be used with other types of cancer or recurrent diseases in general.

SUMMARY

- Patients are classified by age, tumor size and lymph node status.
- The Centre for Mammacare annually treats about 200 new breast cancer patients. This number is expected to grow.
- We choose scenarios based on their type of consult (surgeon face-to-face, nurse practitioner face-to-face, nurse practitioner telephone), frequency (once, twice per year) and length (one, three, five years).
- Quality-adjusted life years discount the number of years lived by the quality of those years. It is the recommended measure to use in cost-effectiveness analyses.
- Cost-effectiveness is influenced by costs and effectiveness of a follow-up scenario. These factors can be further divided into sub factors.
- A mathematical state-transition model is a good tool to simulate the events that occur with breast cancer patients in real life.

4 AN APPROACH FOR CALCULATING COST-EFFECTIVENESS

In this Chapter, we describe the objective of the approach and describe the model. We go into depth to inspect the used data and transition rates the model uses. We end with a validation of the model and sensitivity analysis. Finally we note the assumptions our model is build upon.

4.1 OBJECTIVE OF APPROACH

The objective of the approach is to measure outcomes of the follow-up process, while varying follow-up scenario and patient group. An appropriate outcome to measure is the years of life gained by the average patient. We further refine this outcome by taking into account the quality of life. Doing so, outcomes are measured in quality-adjusted life-years (QALY). We also approximate the number of consults these patients incur during their follow up. When the effectiveness and costs of the scenarios are known, we compute a cost-effectiveness ratio, e.g. number of extra consults per additional life year. This ratio will be different per patient group, because of differences in risk of a recurrence and differences in mortality rates influence effectiveness. The ratio will be different per scenario because of differences in occurrence of secondary metastases and differences in number of consults. With all cost-effectiveness ratios known, we finally make a recommendation about every patient group's most cost-effective follow-up scenario.

4.2 MODEL DESCRIPTION

To fulfill the objective, we construct a state-transition diagram (Figure 2.1). We use a large group of hypothetical patients as population. For every patient, an age, tumor size and lymph node status is specified. These characteristics determine the risk of the various types of recurrence (local recurrence, second primary tumor and distant metastases). Using discrete event simulation, we determine whether and when a patient experiences a certain type of recurrence by using these risk rates. We use a longitudinal model because for the measurement of QALYs we need to measure each period the quality of life of a patient in order to derive the QALY. Every year, the patients' quality of life is measured and costs for follow-up are determined. When a recurrence occurs, the model determines the patient's chances at other events in the process of breast cancer. When distant metastases are detected, the patient will die from breast cancer after a certain period. Each year, patients also have the possibility of dying from another cause that is not related to breast cancer. We run our model until all patients have died, either from breast cancer or from other causes.

For our model we use stochastic modeling. We make this choice because deterministic models require computations for the whole population for every state. This is not very efficient, since the number of periods (years) is quite large and this means the number of computations would be very large. With stochastic modeling, in every period, changes in health state will be determined for every patient by drawing randomly from the given distributions. The drawback of stochastic modeling is that it is not exact. To compensate for this shortcoming, we need to make multiple simulation runs.

Figure 4-1 demonstrates the operating procedure of model. The model creates 1000 patients when a run starts. Age, lymph node status and tumor size are assigned to the patient and the model continues with the generation of a disease process. Depending on the patient group of the patient,

local recurrence, second primary tumor, primary metastases are generated. When a second primary tumor will occur, the model also calculates if a local recurrence of the second primary tumor will occur. Next, the model increases time in steps of one year. Every year, costs and quality of life are recorded. Also, every year all patients run a risk to die of other causes, depending on their age. Finally, this model moves patients to another health state, depending on the disease process that was generated earlier. When an event occurs (e.g. local recurrence), the model computes the risk of secondary metastases. Appendix VIII shows the procedure for this step. Finally, when enough time has passed, all patients have died, either from breast cancer or from other causes. Then the model saves relevant information about the patients and continues with the next run.

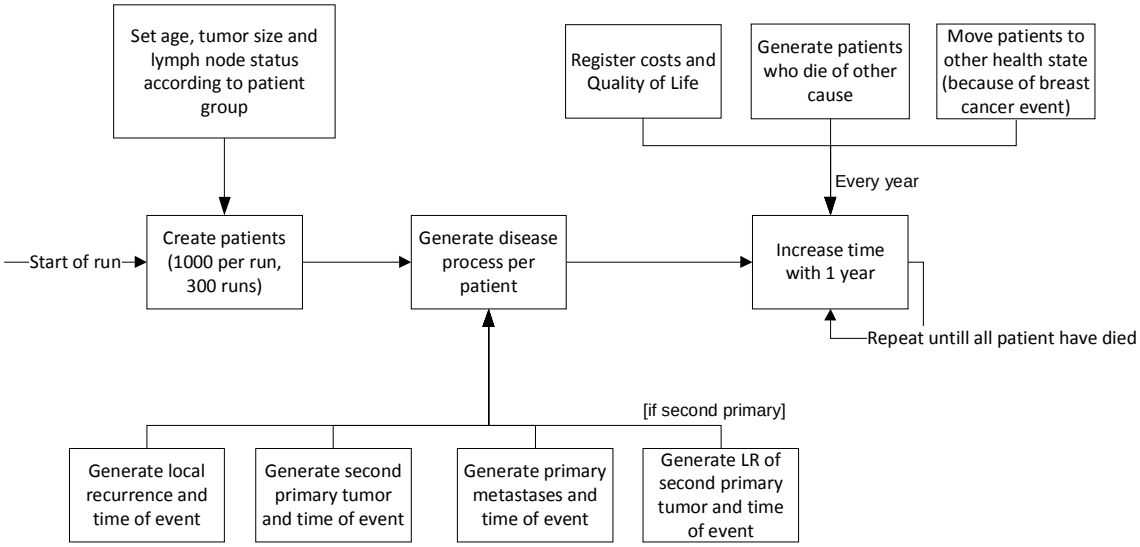

Figure 4-1 Operating procedure of model

4.3 DATA FOR COMPUTING COST-EFFECTIVENESS

In this section we describe the data for the model. We make a distinction in patient groups, determine transition rates, select Quality of Life weights and determine costs per follow-up scenario.

4.3.1 PATIENT GROUPS

In Section 3.1.1 we discuss variables to divide the population into separate smaller groups. For lymph node status we use the theoretical classification (see Section 3.1.1). For tumor size we also use the theoretical classification. However, we do separate the tumor size group 1.1 – 3.0 cm (see Section 3.1.1) into a group of 1.1-2.0 cm and a group of 2.1-3.0 cm because of the data we use to predict risk of locoregional recurrence (see Section 4.4.1). Finally we separate patients by 5-year age groups to inspect the influence of mortality rates per age group. Table 4.1 shows the values we use to classify patient groups.

Variable	Possible values
Lymph node status	0 nodes positive 1-3 nodes positive >3 nodes positive
Tumor size	0.1 – 1.0 cm 1.1 – 2.0 cm 2.1 – 3.0 cm > 3 cm
Age group	0 – 35 years 36 - 40 years 41 45 years 46 50 years 51 55 years 56 60 years 61 65 years 66 – 70 years 71 – 75 years > 75 years

Table 4-1 Possible values of three main variables

Altogether, we obtain 120 groups (lymph node status, tumor size, age group).

4.3.2 USE OF ADJUVANT TREATMENT

We do not include the use of adjuvant treatment in the classification of patient groups, but we do include its use in the calculation of risk rates for patient groups. Patients are treated by Oncoline-guidelines (Oncoline 2007). When adjuvant treatment is used for a certain patient group, we include its use in the parameters for calculation of risk rates.

Oncoline distinguishes between patients with positive or negative hormonal receptor status ER and PgR. Since most patients have positive receptor status, we use the adjuvant treatment for this group for all patient groups. Furthermore, Oncoline distinguishes between tumor grade as a measure of invasiveness (grade I, II or III). We use the adjuvant treatment for tumor grade II on all patient groups as an 'average' adjuvant treatment.

QUALITY OF LIFE

Table 4-2 shows the health states used in our study, the corresponding QoL weights we use and reference to the states of Lidgren, Wilking et al. where we obtained the QoL data (see Section 2.6, also for a more detailed description of QoL). In the model, every year a patient lives, we record the QoL of the patient during that year. The QoL of the patient depends only at the health state of the patient and whether it is the first year for the patient to be in that state or not. In this study, QoL is not dependent from the type of treatment a patient undergoes or other specific patient variables.

When a patient has died, we add up all the QoL weights recorded during her lifetime, starting after primary treatment, in order to obtain the QALY for that patient.

Health state	Quality of Life (95% confidence interval)	Source state
After primary treatment	First year: 0,901 (0,848-0,935) Following years: 0,889 (0,860-0,913)	(P) (S)
Recurrence (all types)	First year: 0,842 (0,733-0,926) Following years: 0,889 (0,860-0,913)	(R) (S)
Metastatic disease	0,820 (0,760-0,874)	(M)
Death from other causes	0 per definition	
Death from breast cancer	0 per definition	

Table 4-2 Quality of Life weights for various health states

COSTS OF FOLLOW-UP

We model the direct costs associated with the medical care given and discard indirect costs. This way we adopt a surgeon's perspective. Some studies adopt a societal perspective and also give an economic value other aspects, e.g. patient time, gasoline costs while driving to the hospital. There are however some problems with this approach. It is not clear whether nonproductive leisure time of patients has an economic value. If it has no value, it should be omitted. Otherwise, questions about the time of the patients life lost due to disease should also be prized (Ernst 2006). This introduces such difficulties that we omit it from this study and only focus on direct costs. We discount the follow-up by an annual factor of 3%, as advised by (Phillips and Chen 2002).

Type of scenario	Time per consult
Surgeon face-to-face	10 minutes
Nurse Practitioner face-to-face	20 minutes
Nurse Practitioner telephone	10 minutes

Table 4-3 Time per consult for different scenarios

We assume a consult with a surgeon takes five minutes with an additional five minutes for administrative tasks. A face-to-face consult with a nurse practitioner takes fifteen minutes with an additional five minutes for administrative tasks. A telephonic consult takes five minutes with again five minutes for administrative tasks. Table 4-3 shows the times of the various consults. Note that we interpret costs in a broad sense by using the duration of a consult. We choose to focus on the duration of a consult, because this will give a clear cost-effectiveness tradeoff: a patient has to visit the surgeon a number of times in order to gain one QALY. Assigning a monetary value to these consults is possible, but we find a tradeoff between time and QALY more practical instead of a tradeoff between costs and time.

4.4 TRANSITION RATES

We gathered data for all transition rates of the model. Since we measure the difference in effectiveness between scenarios, we need to estimate the probabilities of all events that occur as a

consequence of the follow-up (Mandelblatt, Fryback et al. 1997). For every transition rate we mention the source of the data.

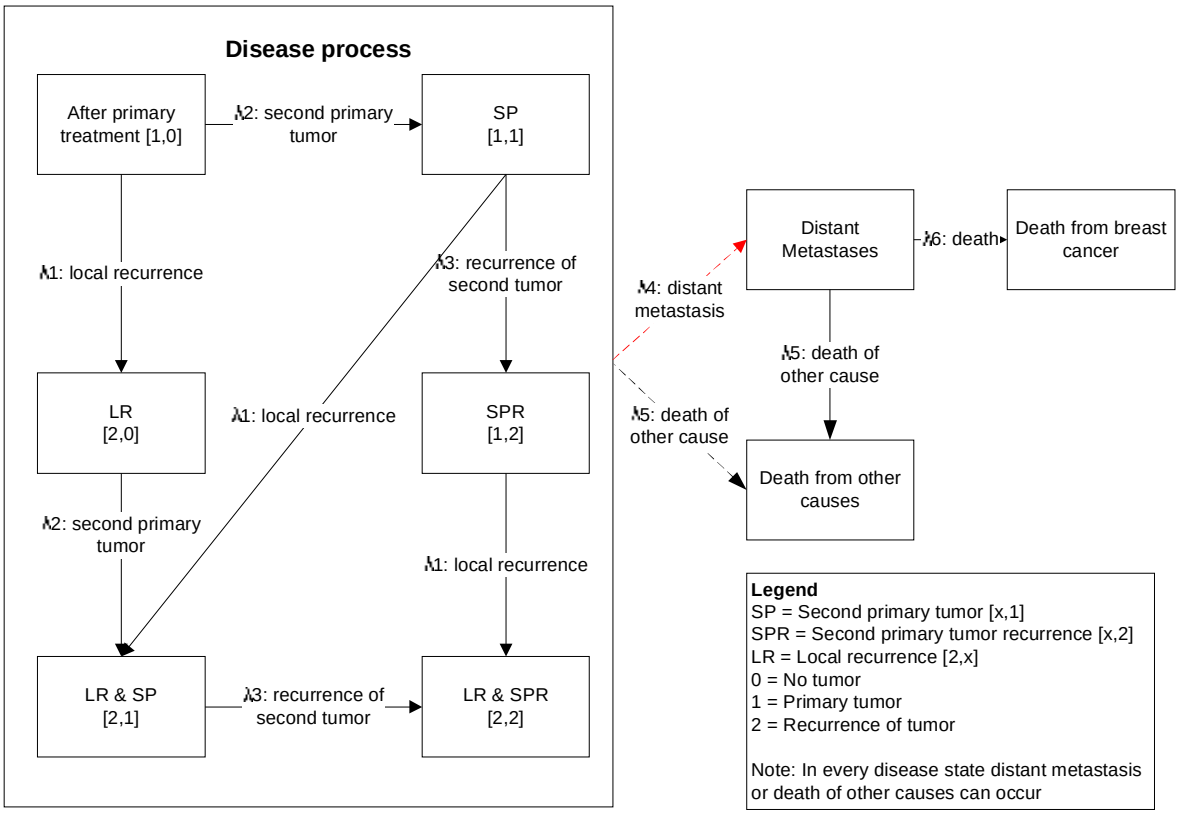

Figure 4-2 State-transition diagram of follow-up process

4.4.1 RISK OF A RECURRENCE (λ1, λ2, λ3)

These transition rates have been obtained from Adjuvant! for Breast Cancer Standard Version 8.0 (http://www.adjuvantonline.com) and IBTR! Breast Cancer Model (http://www.nemc.org/ibtr).

IBTR! is a new tool to estimate the risk of locoregional recurrence (λ1). It has recently been developed with data from a systematic literature study and randomized controlled trials. However, it has not yet been independently validated with large clinical data. IBTR! computes a risk of locoregional recurrence using risk factors for prognostic factors (e.g. tumor size <1 cm = risk factor 0.8, size 1.1 - 2.0 cm = risk factor 1, size > 2.0cm = risk factor 1.36). IBTR! is intended for use with patients who have had a breast-conserving treatment. Because we make no distinction between patients who have been treated with breast conserving treatment or mastectomy, we use estimates from IBTR! for all patient groups. More extensive information about IBTR! as well as a preliminary validation is available in Sanghani, Balk et al. (2007). For the exact procedure we use to obtain risk of local recurrence, see Appendix III.

Next, we obtain the risk of second primary tumor (λ2). Technically speaking, a second primary tumor is no real recurrence, because it is unrelated to the first primary tumor. Because follow-up scenarios

do detect them, we still include second primary tumors in the model. The risk of second primary breast cancer is constant over the years, with about 0,6% risk per year (Gao, Fisher et al. 2003). For the exact numbers, see Appendix IV.

For risk of a recurrence of second primary tumors (λ3) we use the risk of locoregional recurrence (λ1). Because second primary tumors are not very large, we assume the recurrence of the second primary tumor has a diameter between 1 and 2 cm and no positive lymph nodes. One exception is when the patient had more than 3 positive lymph nodes after primary treatment. In this case we assume the tumor has a diameter between 1 and 2 cm. and 1-3 positive lymph nodes.

Now we only need to estimate the risk of metastases (λ4). For this we use Adjuvant! Adjuvant! is useful to calculate total risk of a recurrence in breast cancer patients (so λ1, λ2 and λ 3 together). To obtain the risk of metastases we subtract the risk of locoregional recurrence from the total risk of a recurrence. Further information about the validation of Adjuvant! can be found at https://www.adjuvantonline.com/breasthelp0306/breastindex.html. Adjuvant has been validated for use with the Dutch population (Fiets, Chabot et al. 2006). Appendix V shows the procedure to obtain the risk of metastases.

4.4.2 RISK OF DISTANT METASTASES WHEN LOCOREGIONAL RECURRENCE OR SECOND PRIMARY TUMOR IS DETECTED

As described in Section 2.4 we make a distinction between primary metastases, caused by the primary tumor and secondary metastases, caused by a locoregional recurrence (denoted as LR) or a second primary tumor (denoted as SP). We make the same distinction for the average risk of metastases computed in Section 4.4.1.

- The risk of primary metastases for patients who do not experience a LR or SP = P(p,no)
- The risk of primary metastases for patients who do experience a LR or SP = P(p, yes)
- The risk of secondary metastases for patients who do experience a LR or SP = P(s)

The following three formulas make it possible to compute P(p,no), P(p, yes) and P(s):

1. *P(p,yes) + P(s) = 3,0 *P(p,no)* (source: Eckel et al., 2003)
2. *0,63 P(s) = 0,37 P(p,yes)* (source: Engel, Eckel et al., 2003)
3. *P(average) = X(no)*P(p,no) + X(yes) * (P(p,yes) + P(s))*

Notes: *"P(p)"* denotes the risk of primary metastases
"P(s)" denotes the risk of secondary metastases
"yes" denotes a patient experiences a LR or SP
"no" denotes a patient does not experience a LR or SP
"P(average)" denotes the risk of metastases for the average patient

As described in Section 2.3 the risk of metastases is three times higher when a locoregional recurrence or a second primary tumor is detected. Patients with a recurrence will experience distant metastases 3,0 times as often as patients who do not experience a LR or SP (equation 1). We also know that for patients who experience a LR or SP, the fraction of metastases caused by the primary

tumor compared to the fraction of metastases caused by LR is about 0,63 : 0,37 (equation 2). Finally we know that the total risk of metastases for an average patient is equal to (the fraction of the population that does not experiences a LR or SP * the risk of patients without a LR or SP to experience metastases) + (the fraction of the population that experiences a LR or SP * the risk of patients with a LR or SP to experience metastases) (equation 3).

Three formulas with three unknown variables can be easily solved mathematically.

4.4.3 MORTALITY RATES

When patients are diagnosed with distant metastases, they will most likely die from breast cancer ($\lambda 4$), although death from another cause is still possible. Although women with metastatic breast cancer have a highly variable clinical course and outcome, we will regard all cases as the same since it does not has a large effect on cost-effectiveness. (Engel, Eckel et al. 2003) find a median survival time from diagnosis of distant metastases of 27.6 months (no 95% CI specified), while (Kato, Severson et al. 2001) find a median survival time from diagnosis of distant metastases of 18 months (95% CI: 17-18). Both studies had more than 10000 patients in their population, so the difference is striking. But, when diagnostic examinations are only conducted on patients with symptoms, survival time might appear shorter (Engel, Eckel et al. 2003). This is the case in the Netherlands, where it is not a primary goal to search for metastases during follow-up. We therefore use 18 months for survival time with metastases.

Patients can also die from other causes in each health state (i.e. except death). We obtain a mortality rate from other causes from Statistics Netherlands (Centraal Bureau voor de Statistiek, CBS). Statistics Netherlands is responsible for collecting, processing and publishing statistics to be used in practice, by policymakers and for scientific research (Statline 2008). Appendix VI describes our procedure to obtain mortality rates.

4.4.4 TIME OF RECURRENCE

Because the occurrence of a recurrence varies from year to year, we need a function that describes the incidence of a recurrence. From (Engel, Eckel et al. 2003) we obtain cumulative distributions of local recurrence and cumulative distributions of metastases. The distributions for locoregional recurrence are further specified by tumor size. The annual rate of second primary tumors is constant (Gao, Fisher et al. 2003).

To generate the time that a recurrence occurs, we use the inverse transform sampling method. In this method, the cumulative probability function is inversed and by generating random numbers, sampling can be performed. Appendix VII describes our procedure to calculate the time of recurrence.

4.4.5 INFLUENCE OF FOLLOW-UP SCENARIO ON SECONDARY METASTASES

The risk of secondary metastases for patients who experience a local recurrence or second primary tumor, P(s) is influenced by the rate of follow-up, because when a locoregional recurrence or second

primary tumor is detected later, it has more time to grow and will cause more cases of distant metastases. Figure 4-3 shows the cumulative distribution for incidence of local recurrence. The cutoff point for follow-up divides the patients who experience local recurrence into two groups: one that experiences a locoregional recurrence before the follow-up ends and one that experiences a locoregional recurrence after the follow-up ends.

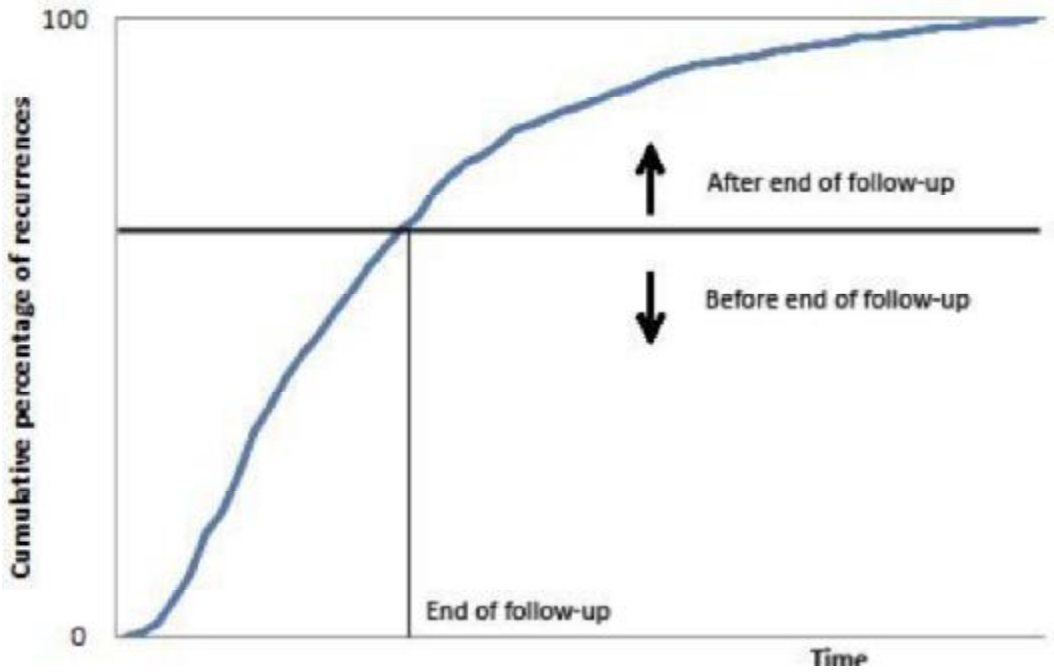

Figure 4-3 Two groups influenced in a different way by follow-up scenario (example)

The frequency of the follow-up scenario influences the time a recurrence can grow in patients who experience a recurrence before the end the follow-up. We decide that twice a year is the default follow-up. The average detection time of .25 year is average for current data. When follow-up is performed yearly, the average detection time will be .5 year. This allows the tumor to grow for an additional 91 days. This would allow the tumor to double in volume at maximum growth rate (but it would not double the diameter of the tumor). As Engel et al. (2003) mentions: "A 10-mm tumour can double in volume in 4 months (120 days) making a 12.6-mm diameter tumour. In this time, further metastases may be initiated in 2.6% of these concerned (1%/mm)". Therefore, if a scenario only has follow-up once per year, we add 0,026 to P(s).

The length of the follow-up influences the time a recurrence can grow in patients who experience a recurrence after the end of follow-up. We assume that P(s) for these patients will grow to P(p,yes). In other words, when no follow-up is performed, recurrences grow to the same size as their primary tumor had when discovered.

These assumptions are mostly made in favor of a more intensive follow-up. We do not take into account that early recurrences mostly have more unfavorable factors compared to late recurrences (Courdi, Largillier et al. 2007). This is known as length time bias (Jacobs, Dijck et al. 2001). Also patients will probably detect a recurrence earlier due to self-examination. We do not take these

arguments into account, because they are hard to quantify. Because we do not take these two phenomena into account, we overestimate the importance of follow-up. Table 4-4 displays the influence of follow-up on secondary metastasisation. Appendix VIII demonstrates how the model computes the risk of secondary metastases when local recurrence, a second primary tumor or recurrence of a second primary tumor is found.

Type of scenario	Local recurrence is found during follow-up	Local recurrence is found after end of follow up
Frequency: twice per year	P(s)	No influence
Frequency: once per year	P(s) + 2,6%	No influence
Length: five years	No influence	P(p,yes)
Length: three years	No influence	P(p,yes)
Length: one year	No influence	P(p,yes)

Table 4-4 Influence of type of scenario on risk on secondary metastasisation

Finally, the third variable that builds the scenario is the mode of follow-up. The surgeon and nurse practitioner have the same ability in detecting recurrences. This means the model will advise to choose scenarios with the mode of nurse practitioner, since this is a cheaper option with the same effectiveness. Finally, the nurse practitioner on the phone has no ability to detect a recurrence. Therefore this mode will automatically have no effectiveness.

4.5 COMPUTATION OF REQUIRED NUMBER OF PATIENTS TO SIMULATE

Using a sequential procedure (Law and Kelton 2000) we obtain the number of runs necessary to run the simulation model with a standard error of 0,05 and a relative error of 0,05. Using populations of 1000 patients, 150 runs are necessary for the desired error margin. To lower the error margin even more, we use 300 runs. Appendix IX shows the actual data with the used formulas.

4.6 VALIDATION OF THE APPROACH

We validate the model in two different ways. First we compare our risk rates with the rates of (Engel, Eckel et al. 2003). Second, we run the model and compare 10-year survival rates with data on Dutch breast cancer patients.

4.6.1 RISK RATE COMPARISON

Engel, Eckel et al. (2003) in "The process of metastasisation for breast cancer" inspect a population of 12423 patients. We compare their risk rates to our computed risk rates. We compute our risk rates in pT groups by averaging the risk rates all patient groups with the same attributes as the pT classification. Table 4-5 shows risk of different types of recurrence for different tumor sizes. The shown values are rounded from the actual values, so the value in the column "difference" sometimes seems incorrect, but this is not the case. Differences are present, but are acceptable. One exception is the overestimation of the percentage of local recurrence patients where metastases also occur. A

possible explanation for this overestimation is the fact that in reality, some patient groups will be overrepresented, other underrepresented.

	Engel, Eckel et al.	This article	Difference
Local recurrence (LR)			
pT1 (0-2 cm)	0,08	0,08	0,00
pT2 (2-5 cm)	0,10	0,10	0,00
pT3 (>5 cm)	0,15	0,13	-0,02
Metastases (MET)			
pT1 (0-2 cm)	0,11	0,12	0,02
pT2 (2-5 cm)	0,21	0,20	-0,02
pT3 (>5 cm)	0,30	0,28	-0,01
(LR and MET) / total LR			
pT1 (0-2 cm)	0,36	0,32	-0,04
pT2 (2-5 cm)	0,53	0,51	-0,02
pT3 (>5 cm)	0,56	0,70	0,14

Table 4-5 Comparison of risk rates between Engel, Eckel et al. (2003) and this article

4.6.2 TEN-YEAR SURVIVAL COMPARISON

We compare our data with Adjuvant! Online predictions of ten-year survival. The model shows a tendency to overestimate the ten-year survival of patients. This tendency is especially apparent for young patients and patient with >3 positive lymph nodes in combination with a tumor larger than 2.0 cm. We will use caution when making recommendations for the patient groups that have a difference larger than 10 percent. Appendix X presents the difference between the two sets of information.

4.7 SENSITIVITY ANALYSIS

To investigate the robustness of the model, we vary all parameters that influence the cost-effectiveness of follow-up in our model. Table 4-6 shows the adjusted parameters. We differentiate between a setting where the parameters are adjusted so they will lead to an underestimation of effectiveness of follow-up and a setting where the parameters are adjusted so they will lead to an overestimation of the effectiveness of follow-up.

	Follow-up effect underestimated	Normal parameters	Follow-up effect overestimated
Adjuvant: Total recurrence risk	0,9x	x	1,1x
IBTR: Local recurrence risk	0,9x	x	1,1x
Second primary risk	0,5	0,6	0,8
Penalty for risk of secondary metastases when follow-up once per year	0,02	0,026	0,05
Ratio of metastases LR or SP patients : metastases patients without LR or SP	2,5	3	3,5
Time of (all types of) recurrence	x + 2 months	x	x - 2 months
Time from diagnosis metastases to death	20 months	18 months	16 months

Table 4-6 Adjusted parameters for sensitivity analysis

4.8 ASSUMPTIONS

When making a model, making assumptions is inevitable. We note the assumptions and their impact on our results. Risk rates provided by Adjuvant! and IBTR! are based on many different sources. All these sources obtain their data from clinical trials, where a certain follow-up scenario is followed. Because follow-up itself influences the occurrence of metastases, the data these models provide is influenced by follow-up. We assume the data is obtained while patients are under intensive follow-up. This way, we can penalize less intensive follow-up scenarios in our model.

We assume that the risk of metastases is equal to the total risk of a recurrence, adjusted for second primary tumors, minus the risk of a locoregional recurrence. Errors in Adjuvant! and IBTR! may reinforce each other, thus leading to an increased error margin in the risk of metastases.

We use the same risk multiplier (3,0) for the risk of metastases when locoregional recurrence is detected for all patient groups. This may not be the case in reality, but no literature is available on this subject. We also use the relationship of 0,67 : 0,33 for metastases causes by the primary tumor: metastases caused by the secondary tumor.

SUMMARY

- The objective of the approach is to measure outcomes of the follow-up process, while varying follow-up scenario and patient group.
- To fulfill the objective, we construct a state-transition model. We use a large group of hypothetical patients as population.
- We use information about risk of a recurrence from Adjuvant! Online and IBTR! two online tools, we use information about the time of recurrence from Engel, Eckel et al. (2003)
- Patients who experience a recurrence during a follow-up scenario of once a year have a 2,6% higher risk of secondary metastases. Patients experience a recurrence after the follow-up have a risk of secondary metastases equal to the risk of primary metastases
- Validation showed that the model overestimated ten-year survival. This is probably caused by the method of calculating metastases. When either IBTR! or Adjuvant! makes no difference between patient groups and the other one does, the risk of metastases changes.

5 RESULTS

In this section we discuss the computational results we obtain from the simulation model. We start with the results per patient group. Here, we inspect the risk rates obtained from Adjuvant! and IBTR! We continue with the results per scenario, where we come to a cost-effective scenario per patient group. We end Chapter 5 with the results of a sensitivity analysis and compute the workload impact of various follow-up scenarios.

5.1 PATIENT GROUP RESULTS

We inspect the influence of the three variables (age, lymph node status and tumor size) on the risk rates.

Adjuvant! and IBTR! do sometimes not distinguish between different categories of variables we use to distinguish patient groups. An example is the difference between 1-3 positive lymph nodes and ≥4 positive lymph nodes in IBTR! (IBTR! only distinguishes between negative and positive status). Therefore, our model uses the same numbers for two categories.

The data shows elder patients have a lower risk of locoregional recurrence, but a higher risk of distant metastases. This can be explained because the total risk obtained from Adjuvant! does not change with age. The IBTR! model does, and the way we compute risk of metastases (total risk – risk of second primary risk of local recurrence) results in an inverse risk of metastases compared to locoregional recurrence. Figure 5-1 shows an example of this phenomenon. Appendix XI shows all data for all patient groups.

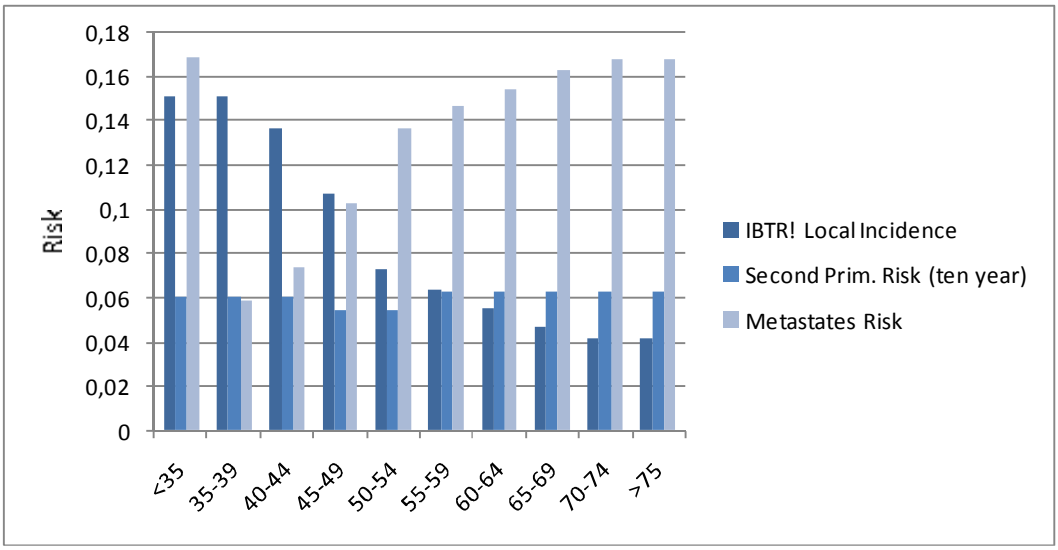

Figure 5-1 Risk of a recurrence by age (lymph node status: 0; tumor size: 1,1-2,0 cm)

When we inspect the lymph node status, Figure 5-2 is obtained. Risk of second primary tumor remains equal. Adjuvant treatment dampens the difference in locoregional recurrence between negative and positive lymph node status. The graph shows a slight increase with more positive lymph

nodes. Finally, the risk of distant metastases is much higher when more lymph nodes have a positive status.

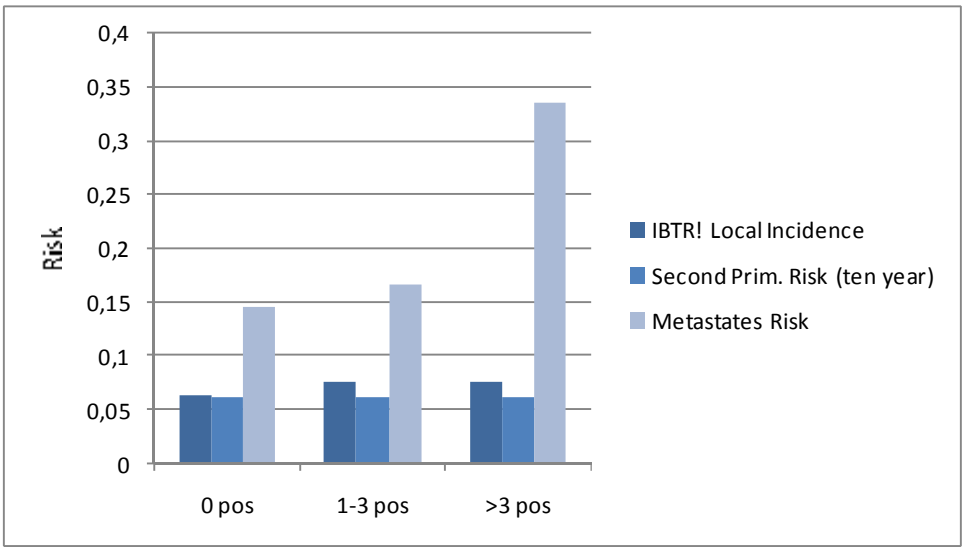

Figure 5-2 Risk of a recurrence by lymph node status (age: 55-59, tumor size 1,1-2.0 cm)

Tumor size also primarily influences the risk of metastases (Figure 5-3), while risk of a second primary tumor remains equal. Risk of a locoregional recurrence remains about equal. Very interesting is the marginal decrease in risk of locoregional recurrence between 1,1-2,0 cm and 2,1-3.0 cm. This is caused by adjuvant treatment that is not yet administered to patients with tumor size 1,1-2,0 cm but is to patients with tumor size 2,1-3,0 cm.

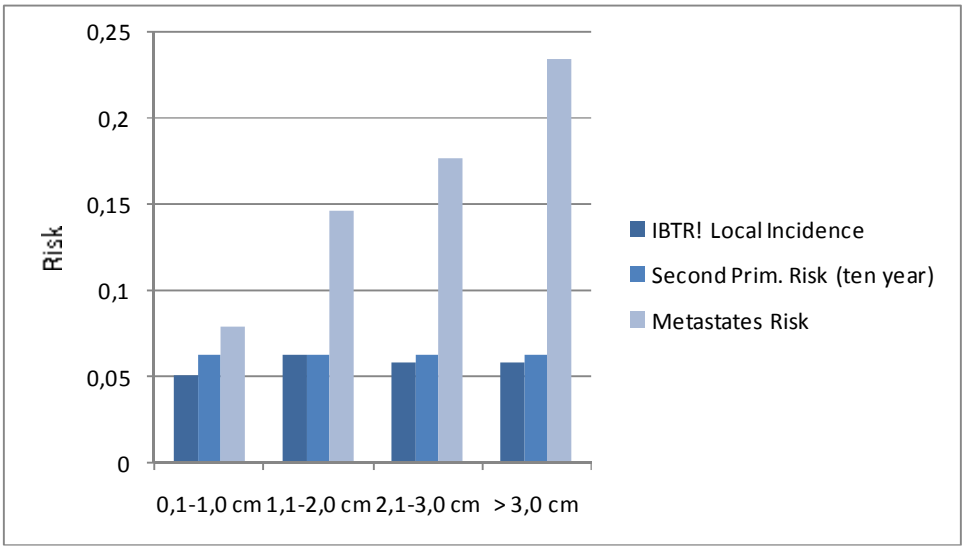

Figure 5-3 Risk of a recurrence by tumor size (age: 55-59; lymph node status: 0 positive)

With changing tumor size or lymph node status, a decrease in locoregional risk or risk of metastases is sometimes seen between two categories. One would expect this not to be the case, since worse characteristics mean increasing risk. This phenomenon has two explanations.

The first explanation is a natural one. Adjuvant treatment is only given from a certain threshold value. The adjuvant treatment accounts for a larger decrease of risk than the worse prognostic factor account for an increase of risk.

The second explanation is a limitation of the method and can be found in the way risk of metastases is calculated. If IBTR! computes a higher increase of the risk of locoregional recurrence than the increase of total risk that Adjuvant! computes, a decrease of distant metastases will be the result.

5.2 SCENARIO RESULTS

We assume the effectiveness of a surgeon and a nurse practitioner of detecting a recurrence to be equal. Therefore, follow-up scenarios with a nurse practitioner are always more cost-effective compared to scenarios with a surgeon.

We assume the effectiveness of scenarios involving a nurse-practitioner making a telephone call to be 0. From a cost-effectiveness viewpoint these follow-up scenarios are therefore judged as a waste of time and money.

These two straightforward arguments make the nurse practitioner face-to-face superior to the other scenarios. We therefore focus on the impact of frequency and length of the follow-up scenarios.

SAMPLE PATIENT GROUP: AGE 50-54, LYMPH NODE STATUS 0, TUMOR SIZE 0,1-1,0CM.

Scenario	QALY	Life Expectancy	# Consults	Death BC	Secondary Metastases	10year survival	Δconsult	ΔQALY	CE-ratio
1y: 1x	14,67	24,18	1,1	0,080	0,014	0,871	0,0	0,00	none
3y: 1x	14,68	24,18	3,1	0,080	0,013	0,871	2,0	0,00	666
5y: 1x	14,69	24,19	5,0	0,079	0,013	0,871	4,0	0,01	343
1y: 2x	14,67	24,18	2,2	0,080	0,014	0,871	1,1	0,00	1029
3y: 2x	14,69	24,20	6,2	0,079	0,012	0,872	5,2	0,02	334
5y: 2x	14,69	24,21	10,1	0,078	0,011	0,872	9,0	0,02	486

Table 5-1 Results for sample patient group (age: 50-54, lymph node status: 0, tumor size: 0,1-1,0cm

Scenario	Follow-up scenario, number of years (y) and annual frequency (x)
QALY	Quality of Life, discounted with 3% per year
Life Expectancy	From year of primary treatment
# Consults	Average number of consults per patient during follow-up
Death BC	Percentage of patients who die from breast cancer (as a result of primary and secondary metastases)
Secondary Metastases	Percentage of patients who die from secondary metastases
10year survival	Percentage of patients alive after 10 years
Δconsult	Difference in #consults between scenario and minimal scenario (1y,1x)
ΔQALY	Difference in QALY between scenario and minimal scenario (1y, 1x)

CE-ratio	Cost-effectiveness ratio, computed by ΔConsults/ΔQALY. Number of consults that is needed in addition to the minimal scenario (1y, 1x) per patient to gain 1 QALY

As can be seen in Table 5-1, longer follow-up scenarios lead to a marginally larger life expectancy and QALY. Discounting of QALYs explains the difference between QALY and life expectancy. The number of consults is approximately what we expected by multiplying frequency and length of the scenarios (leading to respectively 1, 3, 5, 2, 6 and 10 consult). Variability from this number is accounted for by patients not fulfilling their follow-up by dying; they have a lower number of consults. Also patients who enter follow-up again, because diagnosis of a local recurrence or second primary tumor, have a higher number of consults. The percentage of patients is increasing with a less intensive follow-up, as well as the percentage of patients that get secondary metastases. The most intensive scenario leads to 1,1% death of secondary metastases, while the minimal follow-up leads to 1,4% death of secondary metastases. Finally, the 10 year survival is marginally lower for patients with a less intensive follow-up.

In this example, follow-up hardly matters. We now inspect the cost-effectiveness of the scenarios and to do this, we inspect the final three columns. First we compute the difference in number of consults and the difference in QALY of the scenarios compared to the minimal scenario. Next, we compute the cost-effectiveness ratio, which shows how many consults a patient has to go through in order to gain one additional QALY (ΔConsult / ΔQALY). For example, the value of 334 means that when a surgeon has fulfilled 334 additional consults compared to the minimal follow-up scenario, that patient has gained one QALY extra compared to the minimal follow-up scenario. The lower the CE-ratio, the better this is for the cost effectiveness of a scenario. A negative CE-ratio shows that the scenario actually has a lower QALY but extra consults.

SAMPLE PATIENT GROUP: AGE 40-44, LYMPH NODE STATUS 1-3, TUMOR SIZE 2,1-3,0CM.

Scenario	QALY	Life Expectancy	# Consults	Death BC	Secondary Metastases	10year survival	Δconsult	ΔQALY	CE-ratio
1y: 1x	16,99	32,61	1,2	0,21	0,065	0,813	0,00	0,00	none
3y: 1x	17,11	32,88	3,3	0,20	0,057	0,820	2,09	0,12	17
5y: 1x	17,19	33,05	5,2	0,20	0,051	0,824	3,98	0,20	20
1y: 2x	17,00	32,64	2,4	0,21	0,064	0,814	1,18	0,02	74
3y: 2x	17,16	32,97	6,5	0,20	0,054	0,822	5,37	0,17	32
5y: 2x	17,24	33,17	10,3	0,19	0,047	0,827	9,16	0,26	36

Table 5-2 Results for sample patient group (age: 40-44, lymph node status: 1-3, tumor size: 2,1-3,0cm

In the example patient group shown in Table 5-2, follow-up does matter. The difference in life expectancy between 1y: 1x and 5y: 2x is a notable six months. Because this patient group has worse tumor characteristics than the patient group of Table 5-1, the number of consults is somewhat higher. This occurs because patients will have more recurrence and will start follow-up again. The percentage of patients who die from breast cancer, the percentage of patients who die from secondary metastases and ten-year survival all demonstrate that follow-up matters. The most

intensive scenario leads to 4,7% of patient that die of secondary metastases, while the minimal scenario leads to 6,5% death of secondary metastases. For this patient group, the follow-up of 5y: 2x leads to the largest increase in QALY and still has a low CE-ratio. If we would take a threshold of 40 for a cost-effective follow-up scenario, a CE-ratio of 36 would be lower than the threshold of 40, and the preferred follow-up for this patient group would be five years long with two consults annually.

For all 120 patient groups, we compute tables similar to Table 5-1 and Table 5-2. Next, we choose a cost-effectiveness threshold of 40 extra visits per QALY. Note that this is an arbitrary threshold. With this threshold, we choose the most intensive follow-up that is still below the threshold. Table 5-3 shows the selected follow-up scenario per patient group. Patient groups colored green have the minimal follow-up scenario assigned to then, patient groups colored red have the most intensive follow-up assigned to them.

	lymph node status: 0 pos									
0 pos	< 35	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	> 74
0.1 - 1.0 cm	1y: 1x	1y: 1x	1y: 1x	1y: 1x	1y: 1x	1y: 1x	1y: 1x	1y: 1x	1y: 1x	1y: 1x
1.1 - 2.0 cm	5y: 2x	1y: 1x	1y: 1x	1y: 1x	1y: 1x	1y: 1x	1y: 1x	1y: 1x	1y: 1x	1y: 1x
2.1 - 3.0 cm	5y: 1x	3y: 1x	3y: 1x	5y: 1x	5y: 1x	3y: 1x	1y: 1x	1y: 1x	1y: 1x	1y: 1x
> 3 cm	5y: 2x	5y: 2x	5y: 2x	5y: 1x	5y: 1x	5y: 1x	3y: 1x	3y: 1x	1y: 1x	1y: 1x

	lymph node status: 1-3 pos									
1-3 pos	< 35	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	> 74
0.1 - 1.0 cm	5y: 1x	1y: 1x	1y: 1x	1y: 1x	3y: 1x	1y: 1x	1y: 1x	1y: 1x	1y: 1x	1y: 1x
1.1 - 2.0 cm	1y: 1x	1y: 1x	1y: 1x	1y: 1x	1y: 1x	3y: 1x	1y: 1x	1y: 1x	1y: 1x	1y: 1x
2.1 - 3.0 cm	5y: 2x	5y: 2x	5y: 2x	5y: 2x	5y: 2x	5y: 2x	5y: 1x	5y: 1x	1y: 1x	1y: 1x
> 3 cm	5y: 2x	5y: 2x	5y: 2x	5y: 2x	5y: 2x	5y: 2x	5y: 1x	5y: 1x	3y: 1x	1y: 1x

	lymph node status: > 3 pos									
> 3 pos	< 35	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	> 74
0.1 - 1.0 cm	5y: 2x	5y: 2x	5y: 2x	5y: 2x	5y: 1x	1y: 1x	1y: 1x	1y: 1x	1y: 1x	1y: 1x
1.1 - 2.0 cm	5y: 2x	5y: 2x	5y: 2x	5y: 2x	5y: 1x	5y: 1x	1y: 1x	1y: 1x	1y: 1x	1y: 1x
2.1 - 3.0 cm	5y: 2x	5y: 2x	5y: 2x	5y: 2x	1y: 1x	1y: 1x	5y: 1x	3y: 1x	1y: 1x	1y: 1x
> 3 cm	5y: 2x	5y: 2x	5y: 2x	5y: 2x	1y: 1x	1y: 1x	5y: 1x	3y: 1x	1y: 1x	1y: 1x

Table 5-3 Assigned follow-up scenarios per patient group

We discuss the interpretation of these results in Chapter 6: Conclusions.

5.3 SENSITIVITY ANALYSIS

To inspect the stability of the model, we perform a sensitivity analysis. Table 5-4 displays the maximum difference for all measured variables for two settings. In the first setting, we adjust all variables so the effect of follow-up is underestimated; in the second setting we adjust all the parameters so the effect of follow-up is overestimated. The two runs produce results in range with our expectations. Some notable results are the decrease in number of consults in both settings. This can be explained because in the setting where follow-up effect is underestimated, the patients will experience fewer recurrences, thus leading to fewer patients who will have to restart their follow-up.

In this setting where the follow-up effect is overestimated, the risk of metastases is higher, leading to a higher death rate of patients, which leads to more patients dropping out of follow-up.

Another interesting result is the great relative increase of secondary metastases in the setting where the follow-up effect is overestimated. When we look at the absolute increase, it becomes clear that 70% did not translate in a high absolute difference, because the number of patients that die from secondary metastases was low initially. Also a difference in the number of patients that dies from secondary metastases does not always translate into a difference in the number of patients that die from breast cancer. This is due to patients where secondary metastases occurs, but would otherwise also have died from primary metastases or vice versa.

Variable	Follow-up effect underestimated		Follow-up effect overestimated	
	Absolute	Relative	Absolute	Relative
QALY (discounted)	+0,8 year	+7%	-0,7 year	-4%
Life Expectancy	+1,7 year	+8%	-1,6 year	-5%
# Consults	-0,8 consult	-8%	-0,8 consult	-8%
Death BC	-6%	-15%	+4%	+25%
Secondary Metastases	-2%	-18%	+4%	+70%
10year survival	+5%	+9%	-3%	-4%

Table 5-4 Maximum differences per variables compared to normal setting

We also analyze if the "underestimation" and "overestimation" setting would impact recommended follow-up scenarios. When we choose the threshold of 40 extra consults per QALY, the model only recommends other scenario's for 13 out of 120 patient groups in the "underestimation" setting. When we inspect the "overestimation" setting, the model recommends other scenarios for 31 out of 120 patient groups. Recommendations for patients <40 and patients > 70 rarely change. Appendix XII displays the data for sample patients groups of Table 5-1 and Table 5-2.

5.4 WORKLOAD IMPACT

In this section we discuss the impact on the Centre for Mammacare when new scenarios are followed as opposed to the regular follow-up scenario.

Follow-up-according to	NL	Reduction	MST	Reduction
Oncoline guidelines (5y, 2x for all patients)	78700		1500	
Individualized approach CE-threshold: 100 extra consults/QALY	49000	38%	925	38%
Individualized approach CE-threshold: 70 extra consults/QALY	37700	52%	668	55%
Individualized approach CE-threshold: 40 extra consults/QALY	24000	70%	410	73%
Individualized approach CE-threshold: 10 extra consults/QALY	8700	89%	172	89%
Oncoline guidelines & patients > 70 years: 1y: 1x	61550	22%	1240	17%
Oncoline guidelines & patients with tumor size: 0,1-1,0 & 0 positive lymph nodes: 1y: 1x	72300	8%	1330	11%

Table 5-5 Annual number of consults, resulting from guidelines (NL: 8200 new cases annually, MST: 160 new cases annually)

Table 5-5 presents interesting values for the resulting workload. For the Dutch population, the Oncoline guidelines result in a baseline number of consults of 78700, which is about equal with (the number of patients per year [8200] * the number of years follow-up [5] * the frequency per year [2] = 82000). The extra consults are explained by patients who undergo less consults because they are diagnosed with metastases or die from another cause. The number of patients yearly is in reality about 32% higher, but we only used cases where all information was available. Appendix II shows an in-depth view of the population of the Netherlands and MST.

When we use a high CE-threshold of 100 extra visits per additional QALY to determine the best follow-up scenarios, savings are significant (38%). When we lower this threshold, savings increase up to 89%.

We also test two specific settings. A policy where patients older than 70 years receive minimal follow-up results in large savings of 22%. This number is lower for MST, because this population is younger (see Appendix II). Giving minimal follow-up to patients >35, tumor size 0,1-1,0 cm and lymph node status 0 result in savings of 8%. This number is higher for MST (11%).

SUMMARY

- Locoregional recurrence and distant metastases show an inverse relation with changing age.
- Lymph node status and tumor size both lead to increasing risk of metastases with worse prognostic factors.
- Adjuvant treatment dampens the difference is risk of types of recurrence between categories.
- The effectiveness of a surgeon and a nurse practitioner of detecting a recurrence is assumed equal. Therefore follow-up scenarios with a nurse practitioner are always more cost-effective compared to scenarios with a surgeon.
- The effectiveness of scenarios involving a nurse-practitioner making a telephone call is assumed 0. Therefore these follow-up scenarios are judged from a cost-effectiveness viewpoint as a waste of time and money.
- For most young patients follow-up seems cost-effective, for most old patients it does not seem cost-effective.
- Savings in the number of consults ranging from 10 to 80 percent can be achieved by individualizing follow-up. The amount of savings depends on the threshold for cost-effective scenarios.

6 CONCLUSIONS

In this chapter we discuss the conclusions we draw from the results and answer the last research question: which follow-up scheme do we recommend for each breast cancer patient group? Before we discuss if follow-up what follow-up scenario is most cost-effective, we discuss the differences between patient groups.

In general, we can conclude that young patients (<50) require a more intensive follow-up than older patients (>70). Older patients have a lower life expectancy, and therefore there are less QALYs to be gained and the effectiveness of follow-up is lower.

With regard to tumor characteristics as tumor size and lymph node status, a patient with a very small tumor size (0,1-1,0 cm) and 0 positive lymph nodes needs fewer follow-up visits than a patient with a average tumor size (1,1-3,0 cm) and 1-3 lymph nodes positive. This is an intuitive conclusion, because worse tumor characteristics mean higher risk of (secondary) metastases. On the other hand, one could also expect patients with unfavorable tumor characteristics to need less follow-up, because when a locoregional recurrence or second primary tumor is found, the patient will probably already be metastasized. The results show this is not the case. Many patients with unfavorable tumor characteristics will metastasize and will not benefit from follow-up. However, for the patients that have not metastasized but do have a locoregional recurrence or second primary tumor, the benefit is higher than for patients with favorable tumor characteristics.

We have computed cost-effectiveness ratios; the extra number of consults needed to gain one QALY. The point of view to take is a difficult issue. We could imagine, hypothetically, that a patient would probably prefer to have 30 follow-up visits in order to gain one QALY: one month of visits to the hospital, and eleven months extra to live. From the viewpoint of the hospital, this policy is not very attractive: a surgeon could possibly save more QALYs in the five hours these extra visits would take.

Where to draw the line? For the computation of workload impact we have calculated workload with difference cost-effectiveness thresholds. For the interpretation of the results, we have taken the number of 30 extra visits to gain 1 QALY as limit for a cost-effective policy. Finally, this decision has to be taken by the decision makers in the MST on local level and by policy makers on national level.

By changing the follow-up only for certain patients, quite large savings can be realized. Even a policy with the large number of 70 extra visits per QALY as threshold is able to reduce the number of consults by 33%.

SUMMARY

- Age does not impact the total risk of a recurrence, but does impact the effectiveness of follow-up. Because life expectancy of older patients is lower, less QALY are saved.
- Patients with (very) unfavorable tumor characteristics still benefit from follow-up.
- The number of consults can be reduced dramatically by switching to an individualized follow-up.
- Policy makers have to decide on the threshold for a cost-effective follow-up.

7 DISCUSSION

In this chapter we discuss the recommendations flowing from the study. We also discuss future research and reflect upon the study.

7.1 RECOMMENDATIONS

This study makes the first step from "one follow-up for all" to a more individualized approach. We show that for breast cancer, there are major differences between patients and the risk of recurrence in the consecutive follow-up process.

Previous research shows that intensive follow-up has a very low added value for patients. It also suggested that no follow-up (one time in the first year) could be as effective as a "normal follow-up (length > one year). The results agree with that suggestion when we talk about patients with certain characteristics (>70, favorable tumor characteristics). These patients are served best with a minimal follow-up of one year. The results disagree with the suggestion when we discuss other patients (<50, unfavorable tumor characteristics). These patients should receive a follow-up of five years and possibly even ten years.

Individualized follow-up will lower current workload and could provide each patient with a follow-up scenario that is cost-effective. We recommend that policy makers should incorporate the results of this study in their guidelines for follow-up after breast cancer.

With the number of elderly people growing, the need for medical personnel is also growing in the Netherlands. The transition from surgeons to nurse practitioners as caregivers who execute the follow-up enables surgeons to invest their time in activities that are more beneficial for patients. Furthermore, adjusting the follow-up guidelines will result in significant savings of up to 80% of number of consults needed for follow-up patients.

This model cannot be used directly for other types of cancer, since it was developed for the specific process of breast cancer. However, the ideas behind it are robust, because all recurrent diseases have the same building blocks. Figure 3-5 shows the building blocks of such a model.

7.2 REFLECTION

Reflection on this study enables us to give useful advice on researchers who will construct an individualized model for follow-up for a recurrent disease. The following points will be useful:

- Make a conceptual framework and reach consensus about it before building the model. This will save time, whereas having to update the model every time the team changes the framework will cost much time.
- Initially, make the model simple. Keep the number of patient groups small, by choosing a small number of variables and a small number of values for these variables. After preliminary experiments and correcting, expand the model. This iterative process keeps the complexity of the data under control.
- Another timesaver is the validation of the model before interpreting results. Choose information to validate the model, preferably from randomized controlled trials. In our study we questioned the correctness of the Adjuvant! Online predictions.

- Specify the functionality of the software and choose accordingly. Flexible software that is easy to use provides many advantages. Also the possibility to visualize results is an advantage. Popular software (e.g. Microsoft Excel) might already be able to do the job in an acceptable way.

Follow-up data in the literature is always influenced by the follow-up that is already used. This introduces uncertainty in the model. We decided to interpret the available data as recorded under frequent follow-up (twice annually, during the complete course of the disease). Next, we penalize late detection of recurrences. Also we assumed that all recurrences are found during follow-up visits and patients do not discover recurrences themselves. This produces a bias in the research: more distant metastases are simulated than occur in reality.

However, the validation of the model with Adjuvant! data on ten-year survival shows a general overestimation of the ten- year survival chance by our model. This is probably caused by some assumptions that we generalize for all patient groups but are actually patient group-specific. An example is the risk rate of metastases of 3.0 for patients who develop recurrence compared to patients who do not develop recurrence. Also, the different categories used by Adjuvant! and IBTR! introduce uncertainty in the risk of metastases. Results for patient groups with a large difference in ten-year survival should be used cautiously.

Positive about the usability of the results of the study is that the patient groups that have a large difference with Adjuvant! ten-year survival are also the patient groups to which the model assigns an intensive follow-up. Thus policy makers only run the risk of assigning patients with a follow-up that is too intensive and not the risk of assigning patients with a scenario that is not intensive enough.

7.3 FUTURE RESEARCH

As mentioned, much research can be done on individualizing follow-up for other types of disease. Types of cancer with a high prevalence (e.g. lung, colon cancer, prostate) are perfect candidates for this because they have a large impact on the quality of life of patients. Furthermore, much time and money is invested by society in the follow-up of these diseases and this should be allocated in the best way possible.

To make the model of follow-up after breast cancer more reliable, additional research is needed. Especially some of the assumptions of the model need to be refined:

- The applicability of the model of secondary metastasisation on all patient groups.
- The risk rate of metastases of 3.0 for patients who develop recurrence compared to patients who do not develop recurrence. This risk rate may be different for different patient groups
- Validation of the inverse relation between (local) recurrence and metastases. This effect can reflect reality, but can also be caused by the method we use to calculate metastases. A tool to estimate risk of metastases is needed.
- Impact of self-examination on follow-up. In this study we assume all recurrences are found during follow-up. However this is not the case and there will always be patients who visit the hospital between consecutive follow-up consults.

This study has made a step towards individualization of follow-up for patients with breast cancer, but age, tumor size and lymph node status are not the only variables that play a role. The model can be further refined by adding variables as tumor grade, ER status and co morbidity.

SUMMARY

- Minimal follow-up of one year is not detrimental to the QALY of patients with certain characteristics (age >70, favorable tumor characteristics)
- Young patients (<40) and patients with unfavorable tumor characteristics (>3 lymph nodes, tumor size > 2.0 cm) can benefit from a more intensive follow-up of five or possibly even ten years.
- Implementing individualized follow-up can lead to savings of up to 80% of the number of consults needed.
- This study shows the possibility and potential for individualized follow-up for patients with cancer.
- The study made some assumptions need further research

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APPENDIX I: GLOSSARY	
Adjuvant therapy	Use of chemotherapy or radiotherapy in addition to surgical procedures in the treatment of cancer
BRCA 1/2 gene mutation	Breast cancer gene, indication of breast cancer
Co morbidity	Non lethal complications of primary treatment
Contralateral tumor	Second primary tumor
Cost-effectiveness ratio	Number of extra consults needed to gain one extra QALY
Distant metastases	Metastases, occur with breast cancer mostly in the bones, lungs and liver, incurable
ER status	Oestrogen receptor status, indicator for responsivity of cancer to hormone therapy
Follow-up	Consults after primary treatment
Loco-regional recurrence	Tumor that occurs in the same breast or same site as the first primary tumor
Lymph node status	Important parameter for patient prognosis. Refers to the number of positive lymph nodes (adjuvant! 2005).
Metastases	Transfer of cancer from one organ or part of the body to another not directly connected with it
ONCON	Oncological Network Surgeons East Netherlands (Oncologisch Netwerk Chirurgen Oost Nederland
Patient age	Chronological age, used to make estimates of competing mortality by other causes than breast cancer (Adjuvant! 2005).
Patient group	Group of patient with the same age, tumor size and lymph node status
Primary metastases	Distant metastases caused by the primary tumor
Primary treatment	Treatment related to surgical removal of primary tumor
Primary tumor	Tumor marked as origin of breast cancer
QALY	Quality Adjusted Life Years, used to discount for loss of quality of life
Second primary tumor	Occurs in the contralateral (=opposite) breast than the first primary tumor, unrelated to primary tumor
Secondary metastases	Distant metastases caused by a locoregional recurrence or a second primary tumor
Tumor grade	Classification of invasiveness of tumor
Tumor size	Important parameter for patient prognosis. Maximum diameter of invasive component of tumor (adjuvant! 2005).

APPENDIX II-A: DESCRIPTIVES OF THE DUTCH BREAST CANCER POPULATION

The next three figures give a description of the breast cancer population in the Netherlands. In 2002, there were 10854 registered cases, in 2003 there were 10953 registered cases. Non-invasive cases (2069 totally) are not included in these numbers. Most of the patients have zero positive lymph nodes. About 24% of the cases have an unknown lymph node status. Tumor size of 1,1-3,0 is most common (76%) and patients older than 70 years make up for >25% of the population.

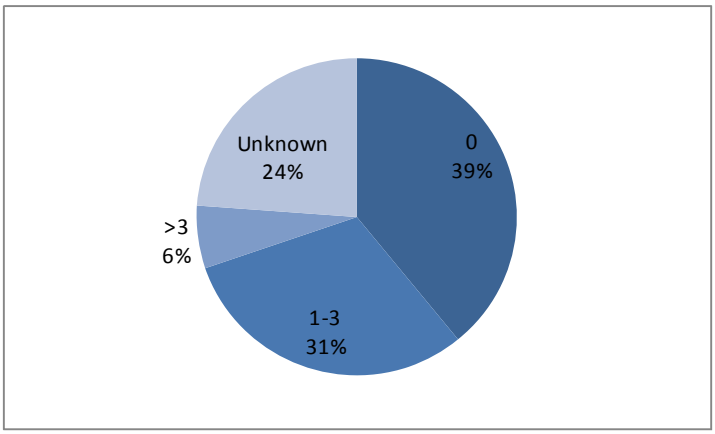

Figure II-1 Division of NL population by lymph node status

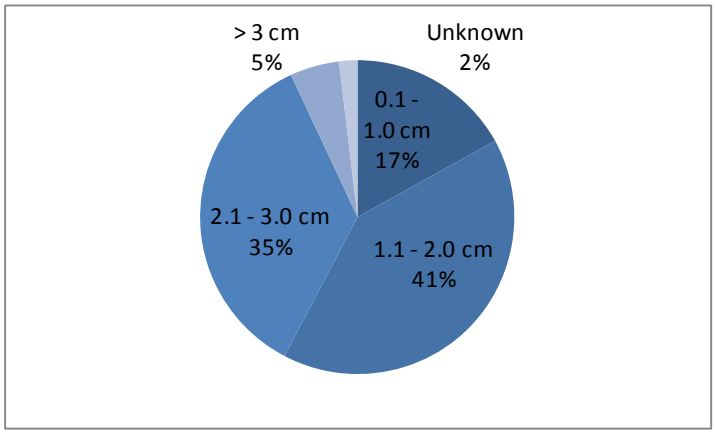

Figure II-2 Division of NL population by tumor size

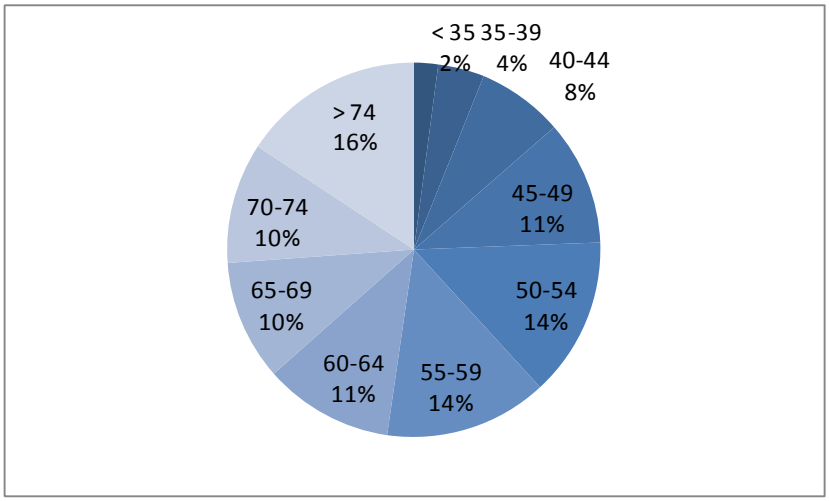

Figure II-3 Division of NL population by age group

APPENDIX II B DESCRIPTIVES OF MST BREAST CANCER POPULATION

The next three figures give a description of the breast cancer population at the Centre for Mammacare of MST. In 2004, there were 158 registered cases, in 2005 140 and in 2006 202. Non invasive cases (62 totally) are not included. Compared to the Dutch population, the population of MST is somewhat younger.

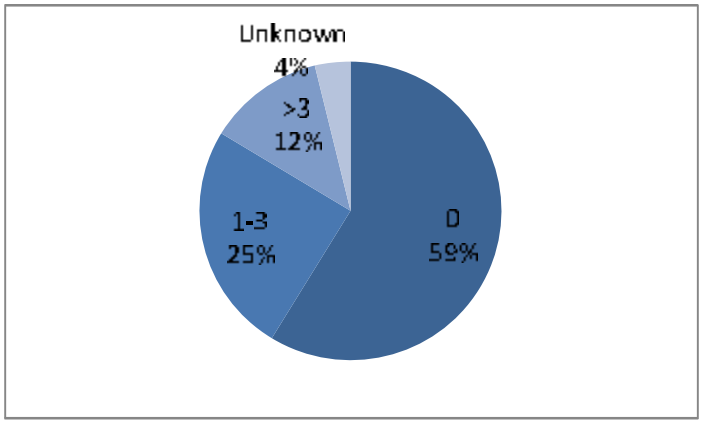

Figure II-4 Division of MST population by lymph node status

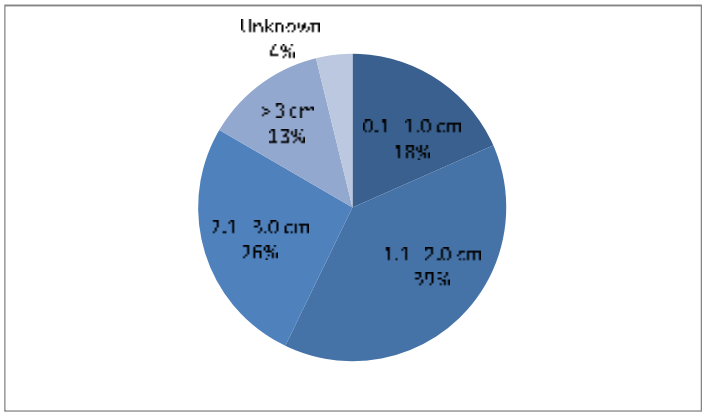

Figure II-5 Division of MST population by tumor size

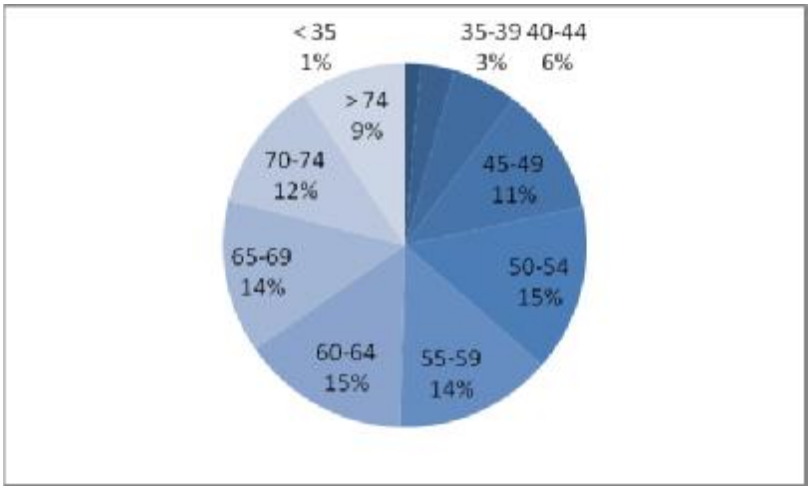

Figure II-6 Division of MST population by age group

APPENDIX III RISK OF LOCAL RECURRENCE

When we had no information about the parameter used in IBTR!, we entered the parameter with risk factor 1. This meant that we entered for every patient group: the age group, tumor size of the group, tumor grade intermediate, margin status >2 mm and lymph node status of the group. We use the risk rates for adjuvant therapy from Adjuvant! since Adjuvant! has a more accurate description of different adjuvant treatments

The highest tumor size group IBTR! distinguishes is >2.0 cm. Therefore, for patients in the 2.1-3.0 cm and >3.0 cm group, we used the same values. Furthermore, IBTR! distinguishes only positive and negative lymph node status. Therefore, for patients with 1-3 and >3 nodes positive, we used the same value (positive). Finally, we used the same value for patients with age group ≤35 and patient with age group 36-40. We calculated the 10-year risk of locoregional recurrence including radiotherapy.

An example for calculation of the risk of local recurrence for the patient group (age = 51-55, lymph node status = 0, tumor size = 1,1-2,0) leads to a 10-year risk of 7,3%.

APPENDIX IV RISK OF SECOND PRIMARY BREAST CANCER

Gao, Fisher et al. (2003) mention that literature finds the rates of second primary breast cancer limited and inconsistent. Annual rates between 0,5% and 1,0% are reported. We use their data because their study follows a total of 134,501 women with breast cancer, the largest study available. Table IV-1 shows their rates per 5, 10, 15 and 20 years. We computed an annual rate by averaging the four values. The annual value for women >55 shows that their risk to develop a second primary tumor is 0,63% in every additional year lived. Because second primary tumors after ten years do not influence effectiveness of follow-up, we stop simulation of second primary tumors after ten years.

Age	5 years	10 years	15 years	20 years	Annual
<45	3,1	6,2	8,8	11,3	0,60 %
45-55	2,6	5,3	8,3	11,3	0,54 %
>55	3,0	6,3	9,6	12,8	0,63 %

Table IV-1 Rates of second primary breast cancer (source: Gao, Fisher et al., 2003). Last column computed for this study

APPENDIX V RISK OF DISTANT METASTASES

For every patient group, we entered an average age (e.g. 53 when inquiring the 51-55 group), average for age co morbidity, undefined ER status, undefined tumor grade, the tumor size of the group and the number of positive lymph nodes. For patient groups with tumor size group > 3.0 cm, we chose the value of 3.1-5.0 cm in Adjuvant, because tumors larger than 5.0 cm are quite rare. The proportion of patients in patient groups with tumor size > 3.0 cm will therefore be small. For patient groups with lymph node status > 3, we chose the value of 4-9 nodes positive in Adjuvant, because values > 9 are quite rare. For patient groups that received chemotherapy, we substracted the influence of chemotherapy from total risk. Finally we calculated for 10-year recurrence risk. As said, this is the total risk of all recurrences and does not tell us anything about when a recurrence is going to take place.

Adjuvant! documentation mentions that its total risk rate is influenced by second primary tumors. "If one wants to make estimates of the improvement in recurrence rates unconfounded by effects on contralateral breast cancer (=second primary tumor), you should subtract (the approximate risk of contralateral breast cancer) from the estimates of recurrence in the "10 Year Risk:" scroll box." The number to subtract is shown in Table V-1. Please note that these are not the actual risks at second primary tumors per year, but an estimation of how many patients will get a second primary tumor.

Base Line Recurrence Risk	Subtract Contralateral Risk
15 - 25 %	6 %
26 - 45 %	5%
46 - 55 %	4%
56 - 65 %	3%
> 65 %	2%

Table V-1 Subtraction of risk of second primary tumor (source: https://www.adjuvantonline.com/breasthelp0306/breastindex.html)

The following formula sums up our calculation of the risk of metastases: *Risk of metastases = Adjuvant! total risk – contralateral risk influence IBTR! locoregional risk.*

An example for calculation of the risk of metastases for the patient group (age = 51-55, lymph node status = 0, tumor size = 1,1-2,0) leads to a 10-year risk of metastases of 26% (adjuvant) -5% (contralateral risk influence) 7,3 (IBTR) = 13,7%.

APPENDIX VI MORTALITY RATE FROM OTHER CAUSES

We extracted mortality rates per age from the year 2006. Because we are interested in the total mortality rate minus the breast cancer related mortality rate we performed a correction. We obtained the fraction of death not related to breast cancer and multiplied this fraction with mortality rates. The data on actual deaths was only available in 5-year cohorts, whereas the data on mortality was available per year. We multiplied each mortality rate each 5-year cohort with the corresponding 5-year cohort fraction of non-breast cancer related deaths.

Age	Risk	Age	Risk	Age	Risk	Age	Risk
0	0,003	26	0,000	52	0,003	78	0,035
1	0,001	27	0,000	53	0,003	79	0,040
2	0,000	28	0,000	54	0,004	80	0,046
3	0,000	29	0,000	55	0,004	81	0,050
4	0,000	30	0,000	56	0,004	82	0,059
5	0,000	31	0,000	57	0,004	83	0,071
6	0,000	32	0,000	58	0,005	84	0,078
7	0,000	33	0,000	59	0,005	85	0,086
8	0,000	34	0,001	60	0,006	86	0,103
9	0,000	35	0,001	61	0,006	87	0,111
10	0,000	36	0,001	62	0,007	88	0,125
11	0,000	37	0,001	63	0,007	89	0,145
12	0,000	38	0,001	64	0,008	90	0,163
13	0,000	39	0,001	65	0,008	91	0,181
14	0,000	40	0,001	66	0,009	92	0,209
15	0,000	41	0,001	67	0,010	93	0,227
16	0,000	42	0,001	68	0,011	94	0,257
17	0,000	43	0,001	69	0,013	95	0,270
18	0,000	44	0,001	70	0,014	96	0,312
19	0,000	45	0,002	71	0,016	97	0,330
20	0,000	46	0,002	72	0,018	98	0,379
21	0,000	47	0,002	73	0,020	99	0,439
22	0,000	48	0,002	74	0,022	100	0,439
23	0,000	49	0,003	75	0,024	101	0,439
24	0,000	50	0,003	76	0,027	102	0,439
25	0,000	51	0,003	77	0,031	103	0,439

Table VI-1 Annual mortality risk per age

APPENDIX VII CALCULATION OF TIME OF RECURRENCE

Table VII-1 shows the formulas and their fit with the data. Values for x depict random generated numbers between 0 and 1. Values for t depict the time of the event in years. The value of 0,006 for second primary tumor is the value for the group of patients younger than 45 years. For the other values, see Appendix VII. The R^2 values indicate the ability of the formula to generate the cumulative curves of Engel, Eckel et al. (2003). For second primary tumors the fit is perfect, assuming that the annual risk is constant.

Event	Formula	Fit with data (R^2)
Local recurrence, tumor size group ≤ 2.0 cm (pT1)	$t = 333{,}3x^6 - 659{,}8x^5 + 518{,}8x^4 - 138{,}3x^3 - 7{,}593x^2 + 11{,}7x$	0,999
Local recurrence, tumor size group > 2.0 cm (pT2)	$t = 449{,}7x^6 - 1001{,}x^5 + 918{,}2x^4 - 354{,}4x^3 + 46{,}63x^2 + 5{,}134x$	0,998
Distant metastases (without local recurrence)	$t = -2334{,}x^5 + 2343{,}x^4 - 1057{,}x^3 + 201{,}9x^2 - 6{,}505x$	0,992
Distant metastases (with local recurrence)	$t = -1183{,}x^5 + 1049{,}x^4 - 380{,}6x^3 + 41{,}48x^2 + 8{,}264x$	0,996
Second primary tumor	$t = -\ln(x)/0{,}006$	1

Table VII-1 Formula used for sampling of events

APPENDIX VIII COMPUTATION OF RISK OF SECONDARY METASTASES

Figure VIII-1 shows the way the model computes the risk of secondary metastases. The decision tree is split into three branches: recurrence during follow-up (annual frequency = 1x), recurrence during follow-up (annual frequency = 2x) and recurrence after follow-up. When a second primary tumor is diagnosed, the risk of local recurrence of the second primary tumor is also computed.

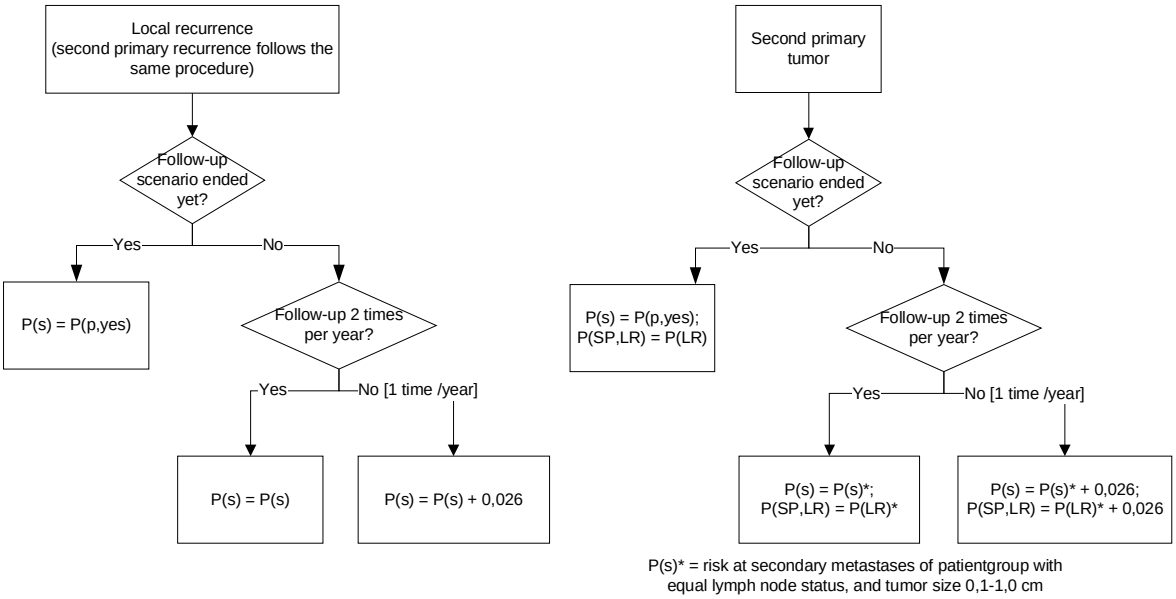

Figure VIII-1 Computation of risk of secondary metastases

Notes: "P(p)" denotes the risk of primary metastases
"P(s)" denotes the risk of secondary metastases
"yes" denotes a patient experiences a locoregional recurrence or second primary tumor
"no" denotes a patient does not experience a locoregional recurrence or second primary tumor

APPENDIX IX DETERMINATION OF REQUIRED NUMBER OF RUNS

We use the following formula from Law, Kelton (2000):

$$\delta(n,\alpha) = t_{n-1,1-\frac{\alpha}{2}}\sqrt{\frac{S_n^2}{n}}, with \ \propto = 0{,}05 \ and \ \gamma = 0{,}05$$

This formula calculates the possible deviation $\delta(n,\alpha)$ from the mean $\bar{X}_n$ for a certain standard error α. Next, we compute the relative error for a certain number of runs n:

$$\frac{\delta(n,\alpha)}{\bar{X}_n} < \gamma', with\ \gamma' = \frac{\gamma}{1-\gamma}$$

When the relative error is not below threshold γ', we adjust n so the formula is satisfied. This led to 150 required runs of 1000 patients. Using the following formula, we compute the confidence interval

$$95\%\ C.I. = [\bar{X}_n - \delta(n,\alpha), \bar{X}_n + \delta(n,\alpha)]$$

Since the measure for the number of secondary metastases was the most unstable, we choose to perform the calculation for this variable. We take patient group (51 55 year, 0 positive lymph nodes, tumor size 1.1-2.0) and scenario (nurse practitioner, 5 years, 2x a year) as sample.

No. Runs n (x1000 women)	$\frac{\delta(n,\alpha)}{\bar{X}_n}$	γ'	$\delta(n,\alpha)$	95% C.I.	
5	0,1310	0,0309	0,0025	0,0169	0,0219
10	0,1186	0,0309	0,0023	0,0172	0,0218
50	0,0761	0,0309	0,0015	0,0180	0,0209
100	0,0528	0,0309	0,0010	0,0183	0,0203
150	0,0413	0,0309	0,00079	0,0183	0,0199
170	0,0393	0,0309	0,00076	0,0185	0,0200
200	0,0315	0,0309	0,00059	0,0181	0,0193
300	0,0302	0,0309	0,00059	0,0188	0,0200
400	0,0256	0,0309	0,00050	0,0190	0,0200
500	0,0230	0,0309	0,00044	0,0189	0,0198

Table IX-1 Computation of required number of patients

This leads to the following δ(n,α) for other measured variables:

Variable	δ(n,α) (300 runs)
Life expectancy	0,0778
QALY	0,0698
Percentage death from breast cancer	0,0013
#consults	0,0139
Ten year survival	0,0012

Table IX-2 δ(n, α) for measured variables (runs = 300)

APPENDIX X COMPARISON WITH ADJUVANT! TEN-YEAR SURVIVAL

Table X-1 shows the comparison between Adjutants' ten-year survival data and this article's ten-year survival data. Patient groups are marked red when the difference is larger than 10%.

	lymph node status: 0 pos									
	< 35	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	> 74
0.1 - 1.0 cm	0,02	-0,04	-0,03	-0,01	0,00	-0,01	-0,01	-0,01	0,00	0,04
1.1 - 2.0 cm	-0,01	-0,05	-0,04	-0,02	0,01	0,00	0,00	0,00	0,01	0,04
2.1 - 3.0 cm	-0,14	-0,05	-0,04	-0,02	-0,02	-0,02	-0,07	-0,06	-0,04	-0,01
> 3 cm	-0,10	-0,04	-0,03	-0,01	-0,01	-0,01	-0,07	-0,06	-0,04	-0,01

	lymph node status: 1-3 pos									
	< 35	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	> 74
0.1 - 1.0 cm	-0,08	-0,06	-0,04	-0,02	-0,02	-0,02	-0,07	-0,06	-0,04	-0,01
1.1 - 2.0 cm	-0,10	-0,09	-0,07	-0,04	-0,04	-0,04	-0,08	-0,07	-0,05	-0,01
2.1 - 3.0 cm	-0,20	-0,13	-0,11	-0,07	-0,06	-0,05	-0,11	-0,09	-0,07	-0,03
> 3 cm	-0,20	-0,13	-0,11	-0,06	-0,06	-0,05	-0,11	-0,09	-0,07	-0,03

	lymph node status: > 3 pos									
	< 35	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	> 74
0.1 - 1.0 cm	-0,14	-0,03	-0,02	0,00	-0,01	-0,01	-0,10	-0,10	-0,06	-0,02
1.1 - 2.0 cm	-0,17	-0,07	-0,05	-0,02	-0,03	-0,03	-0,11	-0,10	-0,06	-0,03
2.1 - 3.0 cm	-0,30	-0,14	-0,12	-0,08	-0,08	-0,08	-0,16	-0,15	-0,10	-0,06
> 3 cm	-0,30	-0,14	-0,12	-0,08	-0,08	-0,07	-0,16	-0,15	-0,10	-0,06

Table X-1 Comparison of ten-year survival data of Adjuvant and this article

APPENDIX XI RISK OF ALL PATIENT GROUPS

The legend shows the codes used in the green column of table XI-1.

Code	Age	Lymph node status	Tumor size
0	<35		
1	35-39	0 pos	0,1-1,0 cm
2	40-44	1-3 pos	1,1-2,0 cm
3	45-49	>3 pos	2,1-3,0 cm
4	50-54		> 3,0 cm
5	55-59		
6	60-64		
7	65-69		
8	70-74		
9	>75		

Age Group	Lymph Nodes	Tumor Size	Adjuvant Total	IBTR! Local Incidence	Second Prim. Risk (yearly)	Metastases Risk	P(p,no)	P(p,yes)	P(s)
0	1	1	0,220	0,121	0,006	0,099	0,072	0,136	0,080
1	1	1	0,130	0,121	0,006	0,009	0,003	0,005	0,003
2	1	1	0,130	0,109	0,006	0,021	0,012	0,023	0,013
3	1	1	0,130	0,086	0,005	0,044	0,032	0,060	0,035
4	1	1	0,130	0,058	0,005	0,072	0,057	0,108	0,063
5	1	1	0,130	0,051	0,006	0,079	0,064	0,122	0,072
6	1	1	0,130	0,044	0,006	0,086	0,071	0,134	0,079
7	1	1	0,130	0,037	0,006	0,093	0,078	0,148	0,087
8	1	1	0,130	0,033	0,006	0,097	0,083	0,156	0,092
9	1	1	0,130	0,033	0,006	0,097	0,083	0,156	0,092
0	1	2	0,320	0,151	0,006	0,169	0,126	0,239	0,140
1	1	2	0,210	0,151	0,006	0,059	0,044	0,083	0,049
2	1	2	0,210	0,137	0,006	0,073	0,056	0,107	0,063
3	1	2	0,210	0,107	0,005	0,103	0,083	0,157	0,092
4	1	2	0,210	0,073	0,005	0,137	0,118	0,223	0,131
5	1	2	0,210	0,064	0,006	0,146	0,128	0,243	0,142
6	1	2	0,210	0,055	0,006	0,155	0,138	0,260	0,153
7	1	2	0,210	0,047	0,006	0,163	0,148	0,280	0,164
8	1	2	0,210	0,042	0,006	0,168	0,154	0,291	0,171
9	1	2	0,210	0,042	0,006	0,168	0,154	0,291	0,171
0	1	3	0,250	0,103	0,006	0,147	0,118	0,223	0,131
1	1	3	0,236	0,140	0,006	0,096	0,076	0,143	0,084
2	1	3	0,236	0,126	0,006	0,109	0,089	0,167	0,098
3	1	3	0,236	0,099	0,005	0,136	0,115	0,217	0,127
4	1	3	0,236	0,068	0,005	0,168	0,149	0,282	0,166
5	1	3	0,236	0,059	0,006	0,177	0,159	0,301	0,177
6	1	3	0,210	0,047	0,006	0,164	0,149	0,282	0,166
7	1	3	0,210	0,039	0,006	0,171	0,158	0,299	0,175
8	1	3	0,210	0,035	0,006	0,175	0,163	0,309	0,181
9	1	3	0,210	0,035	0,006	0,175	0,163	0,309	0,181
0	1	4	0,290	0,103	0,006	0,187	0,154	0,291	0,171
1	1	4	0,293	0,140	0,006	0,153	0,125	0,236	0,139
2	1	4	0,293	0,126	0,006	0,167	0,138	0,262	0,154
3	1	4	0,293	0,099	0,005	0,194	0,167	0,316	0,186
4	1	4	0,293	0,068	0,005	0,226	0,205	0,387	0,227
5	1	4	0,293	0,059	0,006	0,234	0,216	0,408	0,240
6	1	4	0,264	0,047	0,006	0,217	0,203	0,383	0,225
7	1	4	0,264	0,039	0,006	0,224	0,213	0,402	0,236
8	1	4	0,264	0,035	0,006	0,229	0,218	0,413	0,242
9	1	4	0,264	0,035	0,006	0,229	0,218	0,413	0,242
0	2	1	0,255	0,106	0,006	0,149	0,118	0,224	0,131
1	2	1	0,242	0,145	0,006	0,098	0,077	0,145	0,085
2	2	1	0,242	0,131	0,006	0,112	0,090	0,170	0,100
3	2	1	0,242	0,103	0,005	0,140	0,117	0,221	0,130
4	2	1	0,242	0,070	0,005	0,173	0,153	0,289	0,170
5	2	1	0,242	0,061	0,006	0,182	0,163	0,309	0,181
6	2	1	0,217	0,048	0,006	0,168	0,153	0,290	0,170

7	2	1	0,217	0,041	0,006	0,176	0,162	0,307	0,180
8	2	1	0,217	0,036	0,006	0,180	0,168	0,318	0,187
9	2	1	0,217	0,036	0,006	0,180	0,168	0,318	0,187
0	2	2	0,255	0,133	0,006	0,122	0,090	0,170	0,100
1	2	2	0,242	0,181	0,006	0,062	0,044	0,083	0,049
2	2	2	0,242	0,163	0,006	0,079	0,058	0,110	0,065
3	2	2	0,242	0,128	0,005	0,114	0,090	0,169	0,100
4	2	2	0,242	0,087	0,005	0,155	0,132	0,249	0,146
5	2	2	0,242	0,076	0,006	0,166	0,144	0,273	0,160
6	2	2	0,217	0,061	0,006	0,156	0,138	0,260	0,153
7	2	2	0,217	0,051	0,006	0,166	0,149	0,282	0,165
8	2	2	0,217	0,045	0,006	0,171	0,156	0,294	0,173
9	2	2	0,217	0,045	0,006	0,171	0,156	0,294	0,173
0	2	3	0,365	0,181	0,006	0,184	0,133	0,251	0,147
1	2	3	0,392	0,246	0,006	0,146	0,100	0,190	0,111
2	2	3	0,392	0,222	0,006	0,169	0,121	0,228	0,134
3	2	3	0,392	0,175	0,005	0,217	0,165	0,313	0,184
4	2	3	0,392	0,119	0,005	0,273	0,228	0,430	0,253
5	2	3	0,392	0,103	0,006	0,288	0,247	0,467	0,274
6	2	3	0,354	0,082	0,006	0,272	0,241	0,456	0,268
7	2	3	0,354	0,069	0,006	0,285	0,259	0,489	0,287
8	2	3	0,354	0,062	0,006	0,293	0,269	0,509	0,299
9	2	3	0,354	0,062	0,006	0,293	0,269	0,509	0,299
0	2	4	0,365	0,181	0,006	0,184	0,133	0,251	0,147
1	2	4	0,392	0,246	0,006	0,146	0,100	0,190	0,111
2	2	4	0,392	0,222	0,006	0,169	0,121	0,228	0,134
3	2	4	0,392	0,175	0,005	0,217	0,165	0,313	0,184
4	2	4	0,392	0,119	0,005	0,273	0,228	0,430	0,253
5	2	4	0,392	0,103	0,006	0,288	0,247	0,467	0,274
6	2	4	0,354	0,082	0,006	0,272	0,241	0,456	0,268
7	2	4	0,354	0,069	0,006	0,285	0,259	0,489	0,287
8	2	4	0,354	0,062	0,006	0,293	0,269	0,509	0,299
9	2	4	0,354	0,062	0,006	0,293	0,269	0,509	0,299
0	3	1	0,380	0,106	0,006	0,274	0,235	0,444	0,261
1	3	1	0,412	0,145	0,006	0,267	0,220	0,415	0,244
2	3	1	0,412	0,131	0,006	0,281	0,235	0,445	0,261
3	3	1	0,412	0,103	0,005	0,309	0,269	0,509	0,299
4	3	1	0,412	0,070	0,005	0,342	0,314	0,594	0,349
5	3	1	0,412	0,061	0,006	0,351	0,327	0,619	0,363
6	3	1	0,243	0,033	0,006	0,210	0,202	0,381	0,224
7	3	1	0,243	0,028	0,006	0,215	0,208	0,393	0,231
8	3	1	0,373	0,036	0,006	0,337	0,328	0,620	0,364
9	3	1	0,373	0,036	0,006	0,337	0,328	0,620	0,364
0	3	2	0,380	0,133	0,006	0,247	0,201	0,381	0,224
1	3	2	0,412	0,181	0,006	0,231	0,178	0,336	0,197
2	3	2	0,412	0,163	0,006	0,249	0,196	0,371	0,218
3	3	2	0,412	0,128	0,005	0,284	0,235	0,445	0,261
4	3	2	0,412	0,087	0,005	0,325	0,288	0,544	0,319
5	3	2	0,412	0,076	0,006	0,336	0,304	0,574	0,337
6	3	2	0,243	0,041	0,006	0,202	0,190	0,359	0,211
7	3	2	0,243	0,035	0,006	0,208	0,198	0,374	0,220
8	3	2	0,373	0,045	0,006	0,328	0,313	0,592	0,348
9	3	2	0,373	0,045	0,006	0,328	0,313	0,592	0,348
0	3	3	0,435	0,181	0,006	0,254	0,192	0,362	0,213
1	3	3	0,510	0,246	0,006	0,264	0,186	0,351	0,206
2	3	3	0,510	0,222	0,006	0,288	0,209	0,394	0,231
3	3	3	0,510	0,175	0,005	0,336	0,260	0,491	0,288
4	3	3	0,510	0,119	0,005	0,392	0,331	0,625	0,367
5	3	3	0,510	0,103	0,006	0,407	0,360	0,681	0,400
6	3	3	0,308	0,056	0,006	0,252	0,234	0,441	0,259
7	3	3	0,308	0,047	0,006	0,261	0,245	0,463	0,272
8	3	3	0,464	0,062	0,006	0,402	0,385	0,728	0,428
9	3	3	0,464	0,062	0,006	0,402	0,385	0,728	0,428
0	3	4	0,435	0,181	0,006	0,254	0,192	0,362	0,213
1	3	4	0,510	0,246	0,006	0,264	0,186	0,351	0,206
2	3	4	0,510	0,222	0,006	0,288	0,209	0,394	0,231
3	3	4	0,510	0,175	0,005	0,336	0,260	0,491	0,288
4	3	4	0,510	0,119	0,005	0,392	0,331	0,625	0,367
5	3	4	0,510	0,103	0,006	0,407	0,360	0,681	0,400
6	3	4	0,308	0,056	0,006	0,252	0,234	0,441	0,259
7	3	4	0,308	0,047	0,006	0,261	0,245	0,463	0,272
8	3	4	0,464	0,062	0,006	0,402	0,385	0,728	0,428
9	3	4	0,464	0,062	0,006	0,402	0,385	0,728	0,428

Table XI-1 Risk of different types of recurrence

APPENDIX XII SENSITIVITY ANALYSIS FOR TWO SAMPLE PATIENT GROUPS

Table XII-1 and Table XII-2 display the data obtained by the sensitivity analysis for two sample patient groups.

	ΔQALY		ΔLife Expectancy		Δ# Consults		ΔDeath BC		ΔSecondary Metastasis		Δ10year survival	
Scenario	min	max	min	max	min	max	min	max	min	max	min	max
1y: 1x	0,00	-0,28	-0,01	-0,52	-0,02	0,00	0,000	0,025	0,000	0,010	0,000	-0,019
3y: 1x	0,00	-0,28	0,00	-0,51	-0,15	-0,12	0,000	0,025	-0,001	0,010	0,000	-0,019
5y: 1x	0,00	-0,28	0,00	-0,50	-0,37	-0,36	0,000	0,025	-0,001	0,009	0,000	-0,019
1y: 2x	0,00	-0,28	-0,01	-0,50	-0,05	-0,01	0,001	0,025	0,000	0,009	0,000	-0,019
3y: 2x	0,00	-0,26	-0,01	-0,48	-0,30	-0,24	0,000	0,024	0,000	0,008	0,000	-0,017
5y: 2x	0,00	-0,25	0,00	-0,46	-0,74	-0,71	0,001	0,023	0,000	0,008	-0,001	-0,016

Table XII-1 Sample patient group: age 50-54, lymph node status 0, tumor size 0,1-1,0 cm: Absolute differences with normal setting

Note: "min" denotes the setting where the follow-up effect is underestimated
"max" denotes the setting where the follow-up effect is overestimated

	ΔQALY		ΔLife Expectancy		Δ# Consults		ΔDeath BC		ΔSecondary Metastasis		Δ10year survival	
Scenario	min	max	min	max	min	max	min	max	min	max	min	max
1y: 1x	0,42	-0,37	0,89	-0,81	-0,03	-0,01	-0,025	0,025	-0,008	0,019	0,021	-0,017
3y: 1x	0,41	-0,37	0,88	-0,81	-0,15	-0,14	-0,025	0,025	-0,007	0,019	0,021	-0,017
5y: 1x	0,41	-0,36	0,87	-0,80	-0,34	-0,38	-0,025	0,025	-0,007	0,018	0,021	-0,016
1y: 2x	0,40	-0,36	0,86	-0,79	-0,07	-0,02	-0,025	0,024	-0,008	0,018	0,020	-0,017
3y: 2x	0,39	-0,32	0,84	-0,72	-0,30	-0,28	-0,024	0,022	-0,006	0,015	0,020	-0,015
5y: 2x	0,39	-0,29	0,83	-0,65	-0,69	-0,75	-0,023	0,021	-0,005	0,014	0,020	-0,013

Table XII-2 Sample patient group: age 40-44, lymph node status 1-3, tumor size 2,1-3,0cm: Absolute differences with normal setting

Note: "min" denotes the setting where the follow-up effect is underestimated
"max" denotes the setting where the follow-up effect is overestimated