Preface

Finishing this thesis is the last hurdle before the master Health Sciences at the University of Twente is completed.

Having a background in the Technical Medicine, I was seeking for a challenging combination of both clinical- and more process related aspects of healthcare. The combination of a bachelor's degree in Technical Medicine and the master courses of Health sciences provide a good competence to perform research in this field.

In cooperation with my three supervisors, Maarten IJzerman, Ingrid Vliegen and Sabine Siesling, we were able to formulate a research topic and perform the following project:

Determining individual breast cancer recurrence risk: Towards tailored follow-up schemes

With this research, I hope to contribute to further development and implementation of the personalised medicine for breast cancer patients, to achieve improvement of health and quality of life.

Enschede, August 28, 2012
Joep Kraeima

Determining individual breast cancer recurrence risks: Towards tailored follow-up schemes

J. Kraeima[1,2], I.M.H. Vliegen, PhD[1], S. Siesling, PhD[2,3], M.J. IJzerman, PhD[2]

1 Centre for Telematics and Information Technology (CTIT), Centre for Healthcare Operations Improvement & Research (CHOIR), Enschede, the Netherlands.

2 Department Health Technology and Service Research (HTSR), MIRA institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede, the Netherlands.

3 Department of Research, Comprehensive Cancer Centre the Netherlands (IKNL), Utrecht, the Netherlands

Abstract

Background Currently, follow-up of breast cancer patients is based on clinical practice guidelines, yet they do not account for individual differences based on patient and tumour characteristics. As a consequence, the follow-up is considered a one-size-fits-all and is not differentiated in frequency and duration. In order to make efficient use of scarce resources, the aim of this study is to support the development of individualised follow-up schemes for local regional recurrences of breast cancer based on prognostic factors.

Methods [redacted]

Results [redacted]

Conclusion Based on the selected prognostic factors it is possible to determine individual probabilities for LRR, these clearly show an inter-patient variability. This study revealed that that there is a difference in detecting LRRs between patients dependent on the individual

baseline risks and follow-up strategies used. It is concluded that high risk patients will need longer or more frequent follow-up then low risk patients to end-up in the same *risk-state* after completing follow-up. Therefore it is stated that individual follow-up strategies, as part of the trend in personalised medicine, are inevitable strategies for the future of breast cancer care.

Keywords: breast cancer, follow-up, local regional recurrence, individual differences, prognostic factors, follow-up schemes

Introduction

In the Netherlands breast cancer accounts for the largest part of the total incidence of female cancer cases every year. The number of new invasive breast cancer cases is currently over 13000 per year (1), which is more than 28% of all cancer cases in females. Prevalence of the disease is increasing due to higher survival, which is an effect of earlier detection and positive treatment effects.

After primary curative treatment, most of the patients are offered at least five years of follow-up (2). This follow-up has several objectives: check the wound (healing), late treatment effects, screen the need for psycho-social support and recurrence detection. It is recognised that most psychosocial improvement can be made directly after treatment, and therefore the focus during the first year of follow-up (3). The follow-up after this first year focuses on LRR of the tumour and will therefore be the main interest of this study (2, 4). Since LRR, however still, can occur in the first year, the first year is included in this study. The detection of metastasis is no primary goal of follow-up, because earlier detection has no significant influence on the survival (4, 5).

The follow-up that patients are assigned to in the Netherlands is based on a national guideline, which does not account for individual differences based on case characteristics (6). Guidelines state that follow-up should be differentiated (6). Individualisation of the follow-up trajectory will prevent patients from returning to the hospital for years without any added value. Moreover, because of the increasing breast cancer incidence, the follow-up causes an increasing burden on healthcare budgets and hospital capacities. If follow-up schemes are adjusted to the individual patient, it will reduce an unnecessary use of valuable capacity for patients that do not need the standard five-year follow-up scheme. If patients less frequently return to the hospital it will shorten the waiting lists for diagnostics devices and other services that are required for follow-up. Moreover a reduction of follow-up time reduces the fear and discomfort that can be experienced during such a period (2, 6). Part of the LRRs is not detected during follow-up visits but by physical examination by the patient herself. The detection of recurrence by mammography (MG) is estimated at 50%, where the rest is detected by physical breast examination (PBE) during follow-up visits or reports of the patient herself (7, 8). Overall the early detection of recurrences will improve survival. The absolute reduction in mortality would be around 17-28% if all loco-regional recurrences would be detected in an early stage (9).

There are alternative schemes for follow-up, however these are not implemented structurally in the daily clinical practice (3). Several reviews and studies reveal that minimal follow-up programs are as effective as more intensive programmes (5, 10-12). A reason for not differentiating follow-up may be that medical specialists believe that patients need frequent reassurance. Another reason is that patients assume that follow-up frequency is directly related to a better prognosis (13). The outcome of this study can quantify the effect of changing follow-up schemes and thereby convince the patient to accept a

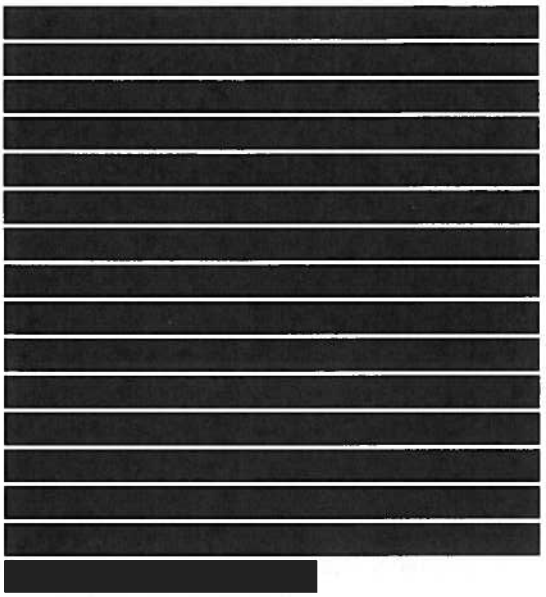
different frequency or duration. The individual follow-up is studied; the results are not pleasing at the moment. This study will provide an approach for individualising the follow-up.

For analysing different follow-up schemes on individual basis, the individual risk of a LRR must be estimated. The strategy should be adjusted to the patient profile. The calculation of individual risk, the evaluation of the possible follow-up strategies and the consequences in terms of health gain and resource use can support the shared decision for a specific follow-up strategy.

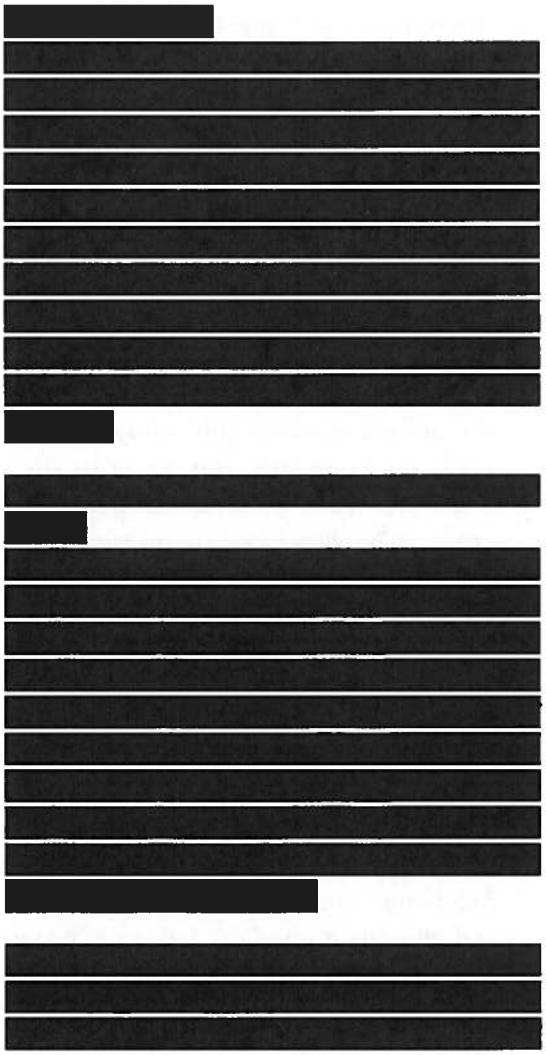
To implement the results in clinical practice, it must fit routine decision making on follow-up scenarios. When the individual follow-up schemes can be determined, the probability of implementing it in clinical practice can be increased by producing a decision support tool which can be used by every physician on for instance a smartphone or a tablet pc. Based on individual transition probabilities and follow-up method, the study will determine the number of LRRs missed if a certain follow-up scheme is chosen. The medical specialist can decide what an acceptable risk of missing LRRs is and thereby decide to adjust the follow-up scheme for the individual patient based on the results of this study.

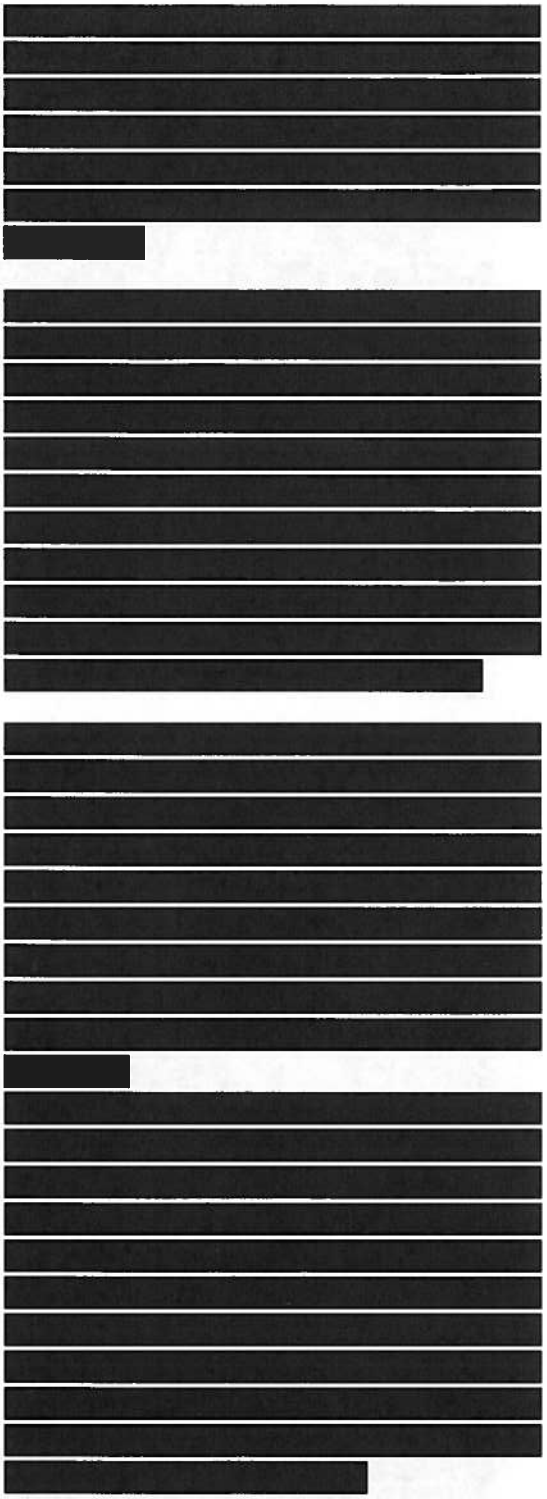
The objective of this study is to estimate individual LRR risks in six month time windows during a period of five year follow-up. The individual differences, expressed in LRR risks, and the consequence on health gain and resource use, should form the argumentation to differentiate follow-up schemes per patient. Based on the individual LRR risks per interval, different follow-up schemes are analysed with several options for distributing the focus of the chosen intervals in the schemes.

Methods



1. Selection of prognostic factors to predict individual LRR





Results

1. Selection of prognostic factors

The results of the three selection methods for selecting prognostic factors are combined and presented in Table 1.

Combining three selection methods leads to the final selection of prognostic factors for calculating the individual LRR risks. This selection is presented in the right column of Table 1.

Figure 2 presents a schematic overview of the study. The elucidation of Figure 2 shows the results of the study per step.

Expert's opinion on prognostic factors
The questionnaire showed that MG and PBE were used as follow-up methods in almost every case. Some of the experts indicated the frequent use of MRI or other methods and all excluded the use of telephone consultations.

Determination of prognostic factors using data registries
In total n=17762 patients are included. Due to incomplete registration this number might be lower for some factors. Table 2 contains the selection of case characteristics based on the combination of literature study, the expert's opinion and the chi-square test. It is attempted to produce a short but most accurate describing selection of case characteristics on which the risk on LRR can be based. The selection of case characteristics is multivariate analysis by means of a logistic regression calculation method. The result of the analysis is shown in Table 2. The final selection of prognostic factors is based on the case characteristics that are significantly prognostic according to the multivariate analysis.

Table 1: Selected prognostic factors

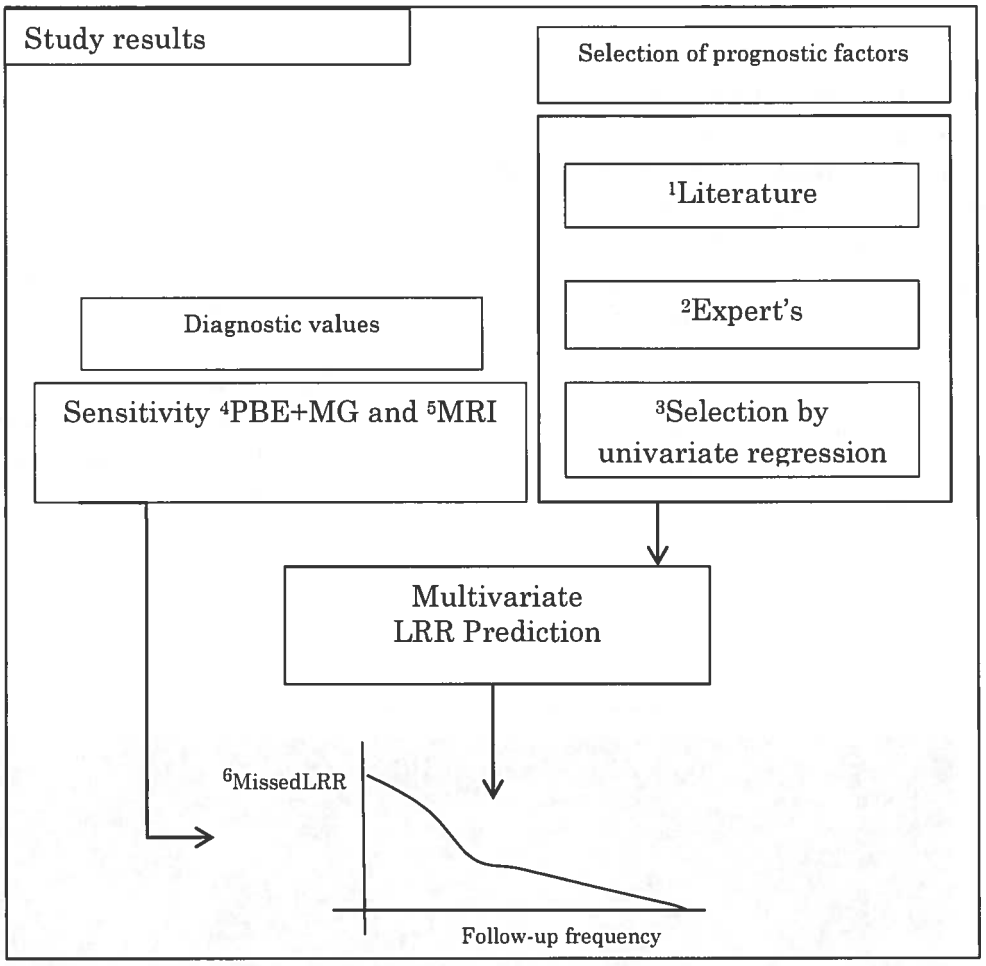


Figure 2: Graphical illustration of the study results

Figure 3 shows the LRR risk of the selected population in terms of risk per 6 month interval and cumulative risks. The LRR risk has its peak around 2.5 years after the primary treatment for the whole population (16). The risk is decreasing after this point and the shape of the curve is similar to comparable results in other studies (16). Figure 3 is based on the 2005-2006 data from the Netherlands Cancer Registry. The risk on LRR for a period longer than five years is not relevant because the probability that an LRR originates is very small after five years (16).

The patients that are registered in the selected data have different characteristics. Table 2 presents the prognostic value for each of the factors included in the selection, based on both a uni- and multivariate analysis. By using a logistic regression calculation the odds ratios, and thereby the prognostic values, are determined.

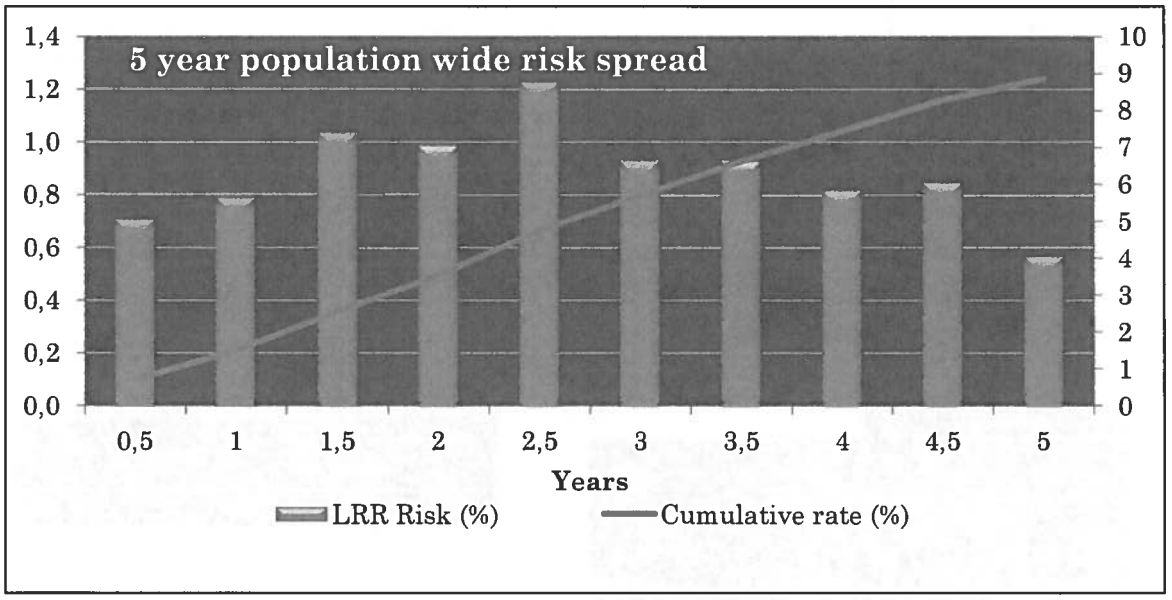


Figure 3: local regional recurrence risk per interval and cumulative risk

Table 2

Case characteristic	No. of patients	Univariate analysis OR	Univariate analysis P-value	Multivariate analysis OR	Multivariate analysis P-value	Multivariate analysis 95% CI
Age*						
<50 years	4.566	1		1		
>= 50 years	13.196	0,76	0,001	0,63	<0,001	0,51-0,78
Multifocality*						
No	14.496	1		1		
Yes	2.683	1,29	0,016	1,3	0,024	1,04-1,63
Irradicality/margin status						
No residu	16.804	1		1		
Residu	704	1,07	0,751	1,12	0,473	0,75-1,83
Adjuvant chemotherapy*						
No	11.302	1		1		
Yes	6.459	0,91	0,298	0,55	<0,001	0,44-0,70
Adjuvant radiotherapy*						
No	6.104	1		1		
Yes	11.657	0,61	<0,001	0,68	<0,001	0,57-0,82
Hormonal therapy*						
No	10.054	1		1		
Yes	7.707	0,59	<0,001	0,54	<0,001	0,43-0,69
Gradation*						
Low	3.748	1		1		
Medium	7.450	1,72	<0,001	1,83	<0,001	1,37-2,43
High	5.472	2,97	<0,001	2,98	<0,001	2,17-4,10
Tumour size*						
<2cm	11.021	1		1		
2-5cm	6.100	1,42	<0,001	1,51	<0,001	1,23-1,84
>5cm	516	1,28	0,288	1,63	0,05	1,00-2,67
Ductal/Lobular						
Ductal	14.146	1		1		
Lobular	1.918	0,85	0,245	0,93	0,05	0,86-1,00
Tumour type:						
Luminal A						
No	3607	1		1		
Yes	9.186	0,59	<0,001	1,03	0,82	0,78-1,37
Luminal B						
No	11882	1		1		
Yes	911	0,97	0,87	1	0,607	0,74-1,67
Triple Negative*						
No	10.905	1		1		
Yes	1.888	2,35	<0,001	1,56	0,012	1,1-2,21
Her2 Positive						
No	11985	1		1		
Yes	808	1,46	0,025	0,98	0,934	0,62-1,55

*Indicates significant correlation, OR: Odds ratio, CI: Confidence interval

Table 2: Result of statistical analysis of the case characteristics

[redacted]

Table 3

Prognostic factor	Low risk	High risk
Age	≥50	<50
Triple negative	No	Yes
Tumor size	2-5cm	2-5cm
Chemo therapy	Yes	Yes
Radiation therapy	Yes	Yes
Gradation	Low	High
Hormonal therapy	No	No
Multifocality	Unifocal	Multifocal

Table 3: Example of two patient groups

Table 4

Interval	Low risk	High risk
1	0,24%	0,34%
2	0,45%	1,76%
3	0,53%	0,92%
4	0,47%	2,72%
5	0,97%	1,80%
6	0,41%	0,80%
7	0,45%	0,59%
8	0,97%	1,23%
9	0,48%	1,33%
10	0,21%	0,13%
Cum	5,19%	11,61%

Table 4: LRR risk spread over 5 years for 2 patient groups

[redacted]

[redacted]

Multiple options are calculated for each frequency in the five year period. If it is chosen to perform ten interventions, there is only one option: every half year a follow-up intervention. If the number of interventions is five, there are 32 options to distribute the follow-up over the 5 years trajectory. It was chosen to evaluate three options for each frequency. This way it was possible to vary in the start, middle and end phase of the trajectory (see graph legend).

[redacted]

[redacted]

[redacted]

Discussion

Limitations of the study and recommendations for future research

This study provides the LRR risk profiles of two example patient groups in six month time windows for a five year follow-up period. With the study methods it is possible to determine such a profile for every patient type, described by the selected prognostic factors for LRR. Different follow-up schemes are analysed for these example patients, with different foci in distributing the follow-up over the five years period.

[redacted]

[redacted]

[redacted]

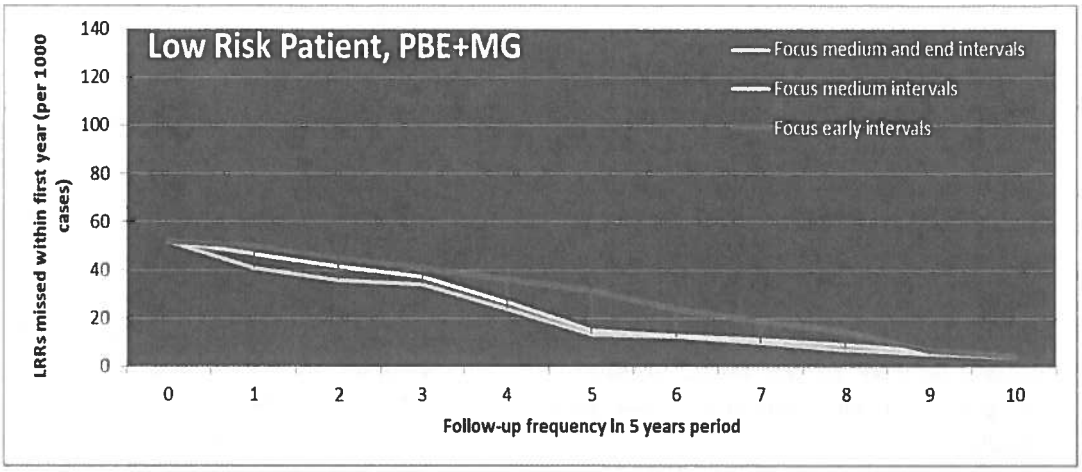


Figure 4A: The course of LRRs not detected within one year for low risk patients

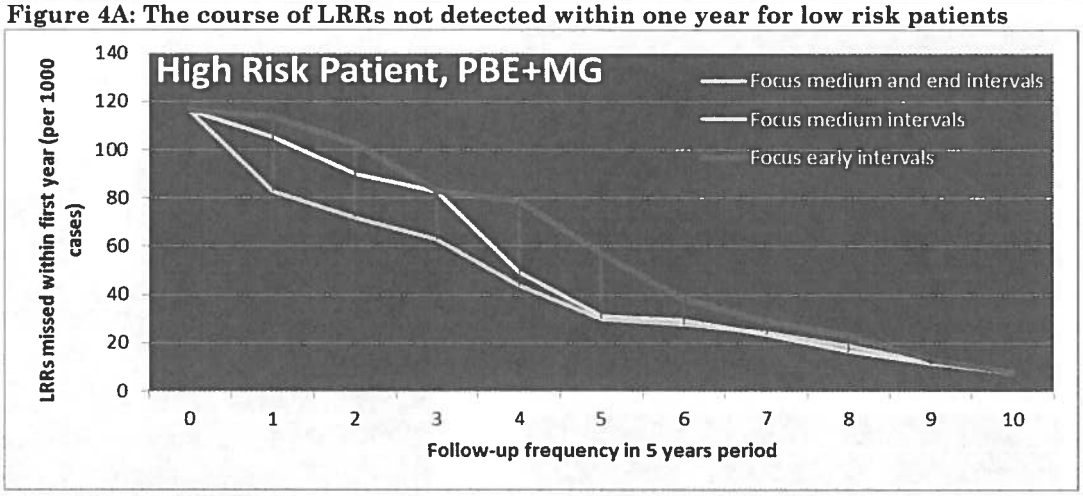


Figure 4B: The course of LRRs not detected within one year for high risk patients

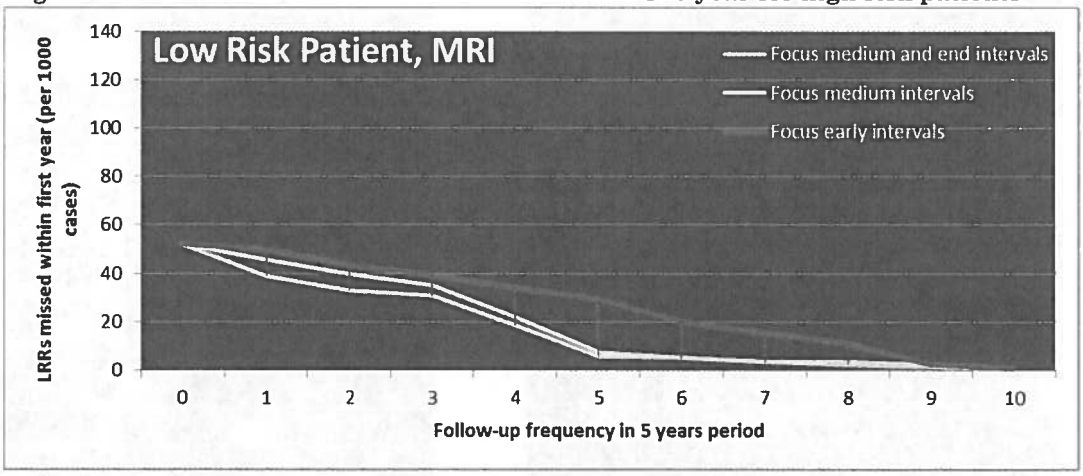


Figure 4C: The course of LRRs not detected within one year for low risk patients

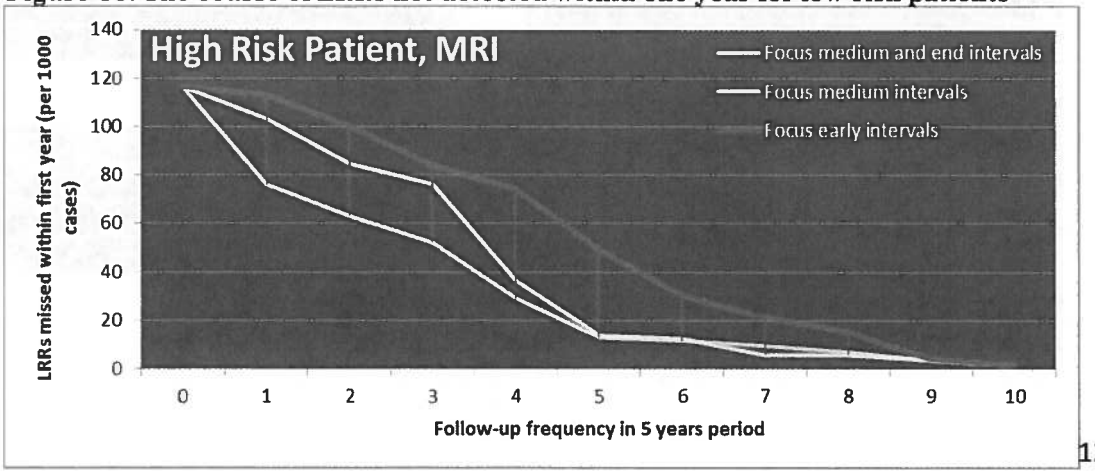


Figure 4D: The course of LRRs not detected within one year for high risk patients

[redacted]

[redacted]

Baseline risks in the selected cohort

The population selected for the risk calculation has a certain baseline risk of LRR. If patients are diagnosed with a LRR they are excluded from follow-up because treatment is started. The remaining group now has a different risk on LRR as at the interval before. It is questionable how this influences the result, because the cohort was defined retrospectively. All breast cancer patients that are registered in a certain year form the population of that year. After the follow-up is finished (five years or until loss to follow-up) the calculations were performed. An option would be to repeat the risk calculations for several populations from other periods in time. This is immediately argued by the fact that in the last year's technology has developed a, so more recurrences are detected then before.

Determination of diagnostic value of follow-up methods

[redacted]

The accuracy of these methods is derived from literature in terms of sensitivity values. These point estimates are not describing the exact diagnostic values; there is a range of values that could describe the accuracy. If progressive insights would result in different values, these could easily be changed in the calculations of this study.

The same argument is applicable to the risk calculation per six month time window. These numbers will also vary, and thereby consist of a risk range per patient type. This study uses point estimates only, but a range of values might be a more accurate description of reality. Future studies should use a range of values, or at least perform a sensitivity analysis to determine how much the results are affected by changes.

Estimation of probabilities in six month time windows

Other studies and tools online have produced comparable results for predicting recurrence risk (16, 38), however this is not based on a Dutch population, furthermore the selection of characteristics is performed with other selection methods and they do not present the risk on multiple half-year intervals (only five or 10 years as a total risk period).

Another remark is that the coefficient values of the separate case characteristics show some variation. Overall the values are in the line of expectation (for instance that the reception of chemo therapy decreases the LRR probability). However in some of the intervals the values contradict themselves, compared to other intervals. An example is the coefficient value of the triple negative factor: in most intervals it has a positive value, so increasing the LRR probability but in two intervals the value is slightly negative (decreasing the probability). This is explained by the wider confidence intervals of the coefficient values due to lower number of LRR cases for that characteristic in the population. The expectation is that these coefficient values become more consistent if a larger population is used. The registration however was only complete since 2005

because earlier not all selected factors were included in the registration. A solution is to wait for future registration data. By the end of the year 2012 the cohort of 2007 has completed its follow-up period, after which it can be included.

Determination of follow-up schemes

[redacted]

The effect of self-examination should also be included in future studies. If in the current model no follow-up is performed, a certain amount of LRRs will be missed. This number is smaller in reality because some of the LRRs can be detected because they become symptomatic or are detected by the patients' self-examination. It is difficult to quantify the effect exactly, but in a larger timeframe it should be possible to include the factor in the model.

Endpoints

[redacted]

[redacted]

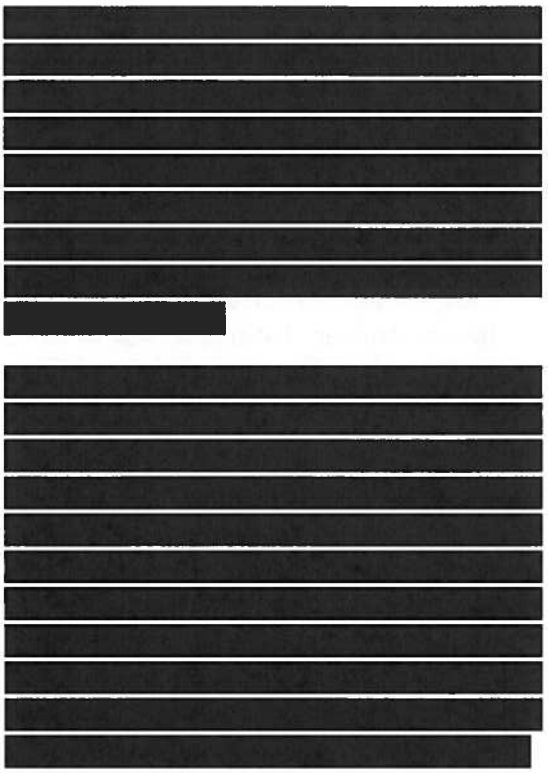
Because for this study only a limited amount of time was available, it was not possible to come entirely to a primary clinical endpoint. However the intermediate endpoint that was reached is a result that provides positive perspective for future research.

This study has produced a method to calculate individual LRR risks in six month windows. With these risks it is possible to accurately calculate the detection probabilities and the number of LRR that are not detected within a year after originating if a certain follow-up scheme is chosen for a patient. The relevance of individualising follow-up is a clear result of this study. There is serious potential to implement individual follow-up schemes in clinical practice. Future research should

extend the work of this study towards a primary clinical endpoint which expresses the results in terms of costs or QALYs.

Conclusion

This study revealed that the LRR risks based on case characteristics, for breast cancer patients can be determined on an individual basis in six-month time intervals.



All in all it is concluded that there is a difference in detecting LRRs between patients with different risks. Therefore it is stated that individual follow-up strategies, as part of the trend in personalized medicine, are inevitable strategies for the future of breast cancer care.

Acknowledgements

For this study we would like thank the Netherlands Cancer Registry (NKR) for sufficiently providing the patient data of the cancer cases in the Netherlands. In addition A.B.G. Kwast (IKNL) is thanked for her support in editing and selecting the right data before calculating individual recurrence risks.

The response of the expert panel is appreciated; especially J. Klaase, MD from the Medical Spectrum Twente hospital (MST) contributed to a successful inclusion of the professional point of view.

The calculation of the individual recurrence risk per interval was based on a logistic regression. The calculation was performed following a principle that is used more frequent. An example is the breast cancer nomogram for irradicality in surgery by R.G. Pleijhuis.

References

1. Nederland IK. Dataset Borstkanker. IKNL; 2011; Available from: http://www.cijfersoverkanker.nl/selecties/Dataset_1/img4f3ba09dec237.

2. NABON. Richtlijn Mammacarcinoom. Amsterdam2012.

3. Kimman ML, Dirksen CD, Voogd AC, Falger P, Gijsen BCM, Thuring M, et al. Economic evaluation of four follow-up strategies after curative treatment for breast cancer: Results of an RCT. European Journal of Cancer. 2011;47(8):1175-85.

4. van Nes JGH, Putter H, van Hezewijk M, Hille ETM, Bartelink H, Collette L, et al. Tailored follow-up for early breast cancer patients: A prognostic index that predicts locoregional recurrence. European Journal of Surgical Oncology (EJSO). 2010;36(7):617-24.

5. Rojas. Cochrane-follow-up-strategies, Rojas. Cochrane liberay. 2009(1).

6. Gezondheidsraad. Nacontrole in de Oncologie (Follow-up in oncology)2007.

7. Robertson C, Ragupathy SKA, Boachie C, Fraser C, Heys SD, MacLennan G, et al. Surveillance mammography for detecting ipsilateral breast tumour recurrence and metachronous contralateral breast cancer: a systematic review. European Radiology. 2011;21(12):2484-91.

8. Kolb TM, Lichy J, Newhouse JH. Comparison of the Performance of Screening Mammography, Physical Examination, and Breast US and Evaluation of Factors that Influence Them: An Analysis of 27,825 Patient Evaluations1. Radiology. 2002 October 1, 2002;225(1):165-75.

9. Lu W, Jansen L, Post W, Bonnema J, Van de Velde J, De Bock G. Impact on survival of early detection of isolated breast recurrences after the primary treatment for breast cancer: a meta-analysis. Breast Cancer Research and Treatment. 2009;114(3):403-12.

10. Collins RF, Bekker HL, Dodwell DJ. Follow-up care of patients treated for breast cancer: a structured review. Cancer Treatment Reviews. 2004;30(1):19-35.

11. Grunfeld E. Clinical practice guidelines for the care and treatment of breast cancer: follow-up after treatment for breast cancer (summary of the 2005 update). Canadian Medical Association Journal. 2005;172(10):1319-20.

12. investigators G. Impact of follow-up testing on survival and health-related quality of live in breast cancer patients. JAMA. 1994;271(20).

13. Kimman ML, Dirksen CD, Voogd AC, Falger P, Gijsen BCM, Thuring M, et al. Nurse-led telephone follow-up and an educational group programme after breast cancer treatment: Results of a randomised controlled trial. European Journal of Cancer. 2011;47(7):1027-36.

14. Abi-Raad R, Boutrus R, Wang R, Niemierko A, Macdonald S, Smith B, et al. Patterns and Risk Factors of Locoregional Recurrence in T1-T2 Node Negative Breast Cancer Patients Treated With Mastectomy: Implications for Postmastectomy Radiotherapy. International Journal of Radiation Oncology*Biology*Physics. 2011;81(3):e151-e7.

15. Touboul E, Buffat L, Belkacémi Y, Lefranc J-P, Uzan S, Lhuillier P, et al. Local recurrences and distant metastases after breast-conserving surgery and radiation therapy for early breast cancer. International Journal of Radiation Oncology*Biology*Physics. 1999;43(1):25-38.

16. Komoike Y, Akiyama F, Iino Y, Ikeda T, Akashi-Tanaka S, Ohsumi S, et al. Ipsilateral breast tumor recurrence (IBTR) after breast-conserving treatment for early breast cancer. Cancer. 2006;106(1):35-41.

17. Freedman GM. Recursive Partitioning Identifies Patients at High and Low Risk for Ipsilateral Tumor Recurrence After Breast-Conserving Surgery and Radiation. Journal of Clinical Oncology. 2002;20(19):4015-21.

18. Jobsen JJ, van der Palen J, Meerwaldt JH. The impact of age on local control in women with pT1 breast cancer treated with conservative surgery and radiation therapy. European Journal of Cancer. 2001;37(15):1820-7.

19. Arriagada R. Predictive factors for local recurrence in 2006 patients with surgically resected small breast cancer. Annals of Oncology. 2002;13(9):1404-13.

20. Horst KC, Smitt MC, Goffinet DR, Carlson RW. Predictors of Local Recurrence After Breast-Conservation Therapy. Clinical Breast Cancer. 2005;5(6):425-38.

21. Cheng SH, Horng C-F, Clarke JL, Tsou M-H, Tsai SY, Chen C-M, et al. Prognostic index score and clinical prediction model of local regional recurrence after mastectomy in breast cancer patients. International Journal of Radiation Oncology*Biology*Physics. 2006;64(5):1401-9.

22. Park B-W, Kim S-I, Kim EK, Yang W-I, Lee KS. Impact of patient age on the outcome of primary breast carcinoma. Journal of Surgical Oncology. 2002;80(1):12-8.

23. Asgeirsson KS, McCulley SJ, Pinder SE, Macmillan RD. Size of invasive breast cancer and risk of local recurrence after breast-conservation therapy. European Journal of Cancer. 2003;39(17):2462-9.

24. Hayes DF, Isaacs C, Stearns V. Prognostic factors in breast cancer: Current and new predictors of metastasis. Journal of Mammary Gland Biology and Neoplasia. 2001;6(4):375-92.

25. Huang EH, Tucker SL, Strom EA, McNeese MD, Kuerer HM, Hortobagyi GN, et al. Predictors of locoregional recurrence in patients with locally advanced breast cancer treated with neoadjuvant chemotherapy, mastectomy, and radiotherapy. International Journal of Radiation Oncology Biology Physics. 2005;62(2):351-7.

26. Clemons M, Danson S, Hamilton T, Goss P. Locoregionally recurrent breast cancer: incidence, risk factors and survival. Cancer Treatment Reviews. 2001;27(2):67-82.

27. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-Year Follow-up of a Randomized Trial Comparing Total Mastectomy, Lumpectomy, and Lumpectomy plus Irradiation for the Treatment of Invasive Breast Cancer. New England Journal of Medicine. 2002;347(16):1233-41.

28. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. The Lancet. 2000;355(9217):1757-70.

29. Griem KL. The 5-year results of a randomized trial of adjuvant radiation therapy after chemotherapy in breast cancer patients treated with mastectomy. J Clin Oncology. 1987.

30. Sismondi P, Bordon R, Arisio R, Genta F. Local recurrences after breast conserving surgery and radiotherapy: correlation of histopathological risk factors with age. The Breast. 1994;3(1):8-13.

31. Cowen D, Houvenïghel G, Jacquemier J, Resbeut M, Largillier R, Bardou VJ, et al. Récidives locales après traitement conservateur du cancer du sein: facteurs de risque et influence sur la survie. Cancer/Radiothérapie. 1998;2(5):460-8.

32. Fisher B, Dignam J, Wolmark N, Wickerham DL, Fisher ER, Mamounas E, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. The Lancet. 1999;353(9169):1993-2000.

33. Voduc KD, Cheang MCU, Tyldesley S, Gelmon K, Nielsen TO, Kennecke H. Breast Cancer Subtypes and the Risk of Local and Regional Relapse. Journal of Clinical Oncology. 2010;28(10):1684-91.

34. Jolly S, Kestin LL, Goldstein NS, Vicini FA. The impact of lobular carcinoma in situ in association with invasive breast cancer on the rate of local recurrence in patients with early-stage breast cancer treated with breast-conserving therapy. International Journal of Radiation Oncology*Biology*Physics. 2006;66(2):365-71.

35. Siesling S, Kwast ABG, Grandjean I, Ho V, van der Sangen MJC, Menke-Pluymers MBE, et al. 324 Invasive Lobular Vs. Ductal Breast Cancer – Patterns of Recurrences Are Dependent On Estrogen Receptor Status. European Journal of Cancer. 2012;48, Supplement 1(0):S137.

36. Montgomery DA, Krupa K, Jack WJL, Kerr GR, Kunkler IH, Thomas J, et al. Changing pattern of the detection of locoregional relapse in breast cancer: the Edinburgh experience. British Journal of Cancer. 2007;96(12):1802-7.

37. Litière S, Werutsky G, Fentiman IS, Rutgers E, Christiaens M-R, Van Limbergen E, et al. Breast conserving therapy versus mastectomy for stage I–II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial. The Lancet Oncology. (0).

38. inc. A. Adjuvant! online. 2011; Available from: https://www.adjuvantonline.com/index.jsp.

Supplementary material

Appendix I: Search strategy for the literature study

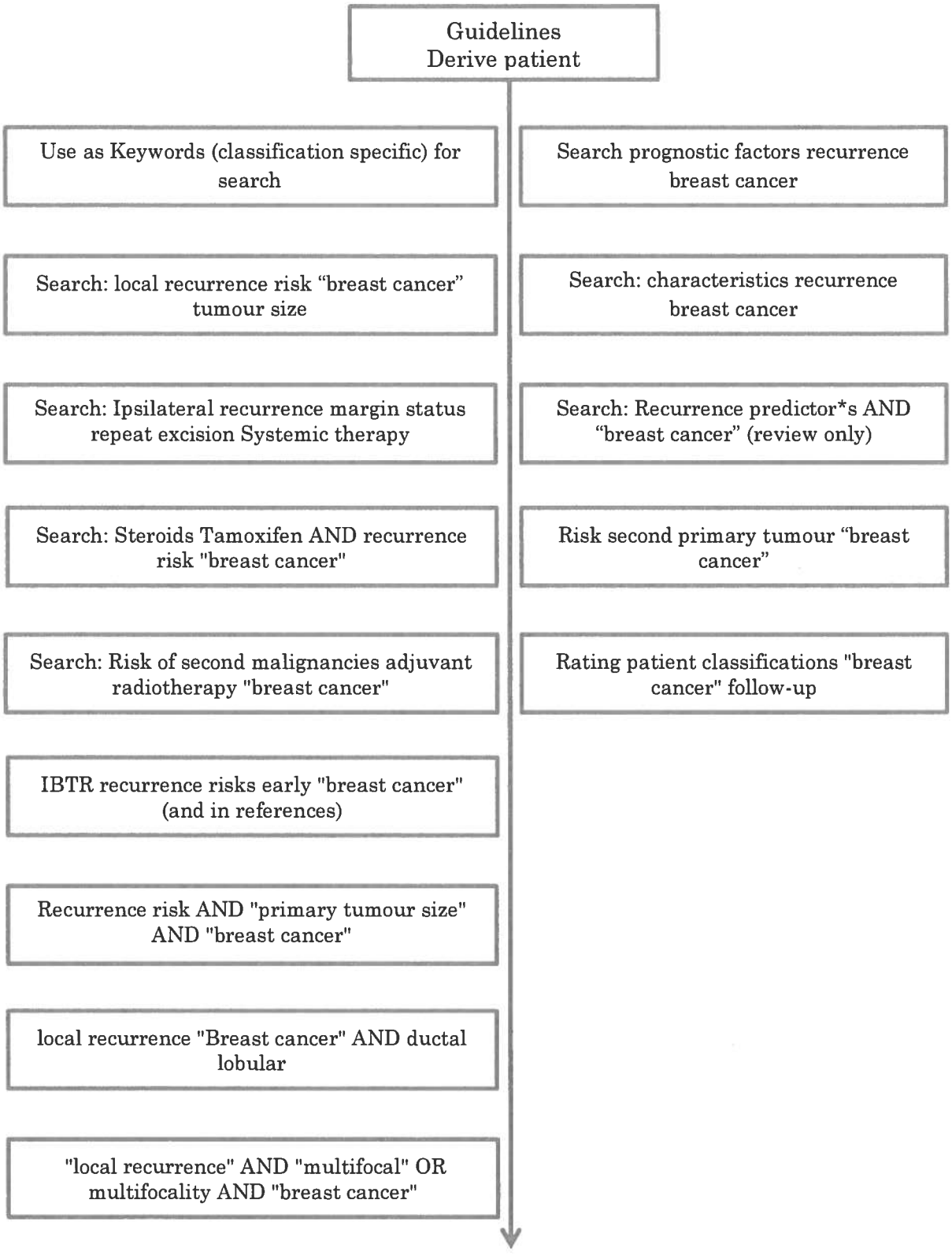
Appendix II: Questionnaire for the expert's panel

Appendix III: Follow-up strategy table

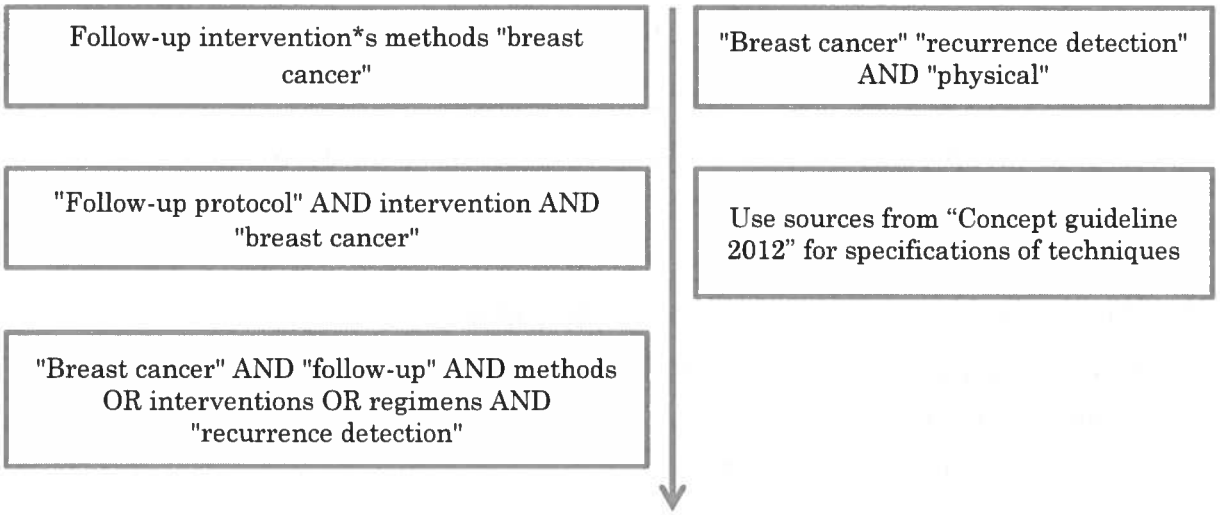
Process report

Appendix I: Search strategy

Patient classifications: Search was performed via sciencedirect.com and Scopus.
The right side in appendix I shows the search terms that are used in the search including all types of recurrence.



Search strategy for follow-up intervention types and accuracy:



Appendix II: Questionnaire

Tumour specific characteristic 1: Tumour size *Rate the importance with a mark

	1	2	3	4	5	
Not relevant	☐	☐	☐	☐	☐	Essential

Tumour specific characteristic 2: Lymph node status *Rate the importance with a mark

	1	2	3	4	5	
Not relevant	☐	☐	☐	☐	☐	Essential

Tumour specific characteristic 3: Multifocality (>1 spot in same quadrant) *Rate the importance with a mark

	1	2	3	4	5	
Not relevant	☐	☐	☐	☐	☐	Essential

Tumour specific characteristic 4: Invasiveness: DCIS or invasive *Rate the importance with a mark

	1	2	3	4	5	
Not relevant	☐	☐	☐	☐	☐	Essential

Tumour specific characteristic 5: Morphology, Ductal or Lobular *Rate the importance with a mark

1	2	3	4	5
☐	☐	☐	☐	☐

Tumour specific characteristic 6: Gradation (low, medium or high) *Rate the importance with a mark

1	2	3	4	5
☐	☐	☐	☐	☐

Tumour specific characteristic 7: Tumour type (Luminal A, B, Triple negative) *Rate the importance with a mark

1	2	3	4	5
☐	☐	☐	☐	☐

Patient specific characteristic 1: Age *Rate the importance with a mark

	1	2	3	4	5	
Not relevant	☐	☐	☐	☐	☐	Essential

Patient specific characteristic 2: menopausal status *Rate the importance with a mark

1 2 3 4 5

☐ ☐ ☐ ☐ ☐

Patient specific characteristic 3: Margin status *Rate the importance with a mark

	1	2	3	4	5	
Not relevant	☐	☐	☐	☐	☐	Essential

Therapy specific characteristics

Therapy specific characteristic 1: Adjuvant chemotherapy *Rate the importance with a mark

	1	2	3	4	5	
Not relevant	☐	☐	☐	☐	☐	Essential

Therapy specific characteristic 2: Adjuvant radiotherapy *Rate the importance with a mark

	1	2	3	4	5	
Not relevant	☐	☐	☐	☐	☐	Essential

Therapy specific characteristic 3: Hormonal therapy (only in ER+/PR+ patients) *Rate the importance with a mark

	1	2	3	4	5	
Not relevant	☐	☐	☐	☐	☐	Essential

Other characteristics: If in your opinion characteristics where missing, please name them below

Explanation Please explain the characteristics you choose in the previous question. (if nothing was choosen, skip)

General questions follow-up optimisation

What is the general content of you follow-up programmes? *Please select intervention type(s)

- ☐ Mammography
- ☐ Physical Breast Examination
- ☐ Telephone Consultations
- ☐ MRI
- ☐ Other:

If you optimise the follow-up, what is the most important criterion to base it on? *So based on what is the frequency and type of intervention determined?

- ☐ Minimisation of cost
- ☐ Maximisation of survival
- ☐ Minimisation of workload
- ☐ Minimisation of missing recurrences
- ☐ Other:

Supposed that we have a model for follow-up, what would you like it to present? *
Example1: a single optimum: treat this patient x-times during -years.
Example2: an evaluation of several options: treat the patient x-times resulting in high workload, high costs and low risk on missing. or treat y-times: lower workload and costs, but higher risk on missing.

What other specifications should the model have? For instance: compatibility with Computers, Tablets, Smartphones (application)?

End of the survey

Thank you for your participation. Please click on SUBMIT if finished. If you are interested, I can inform you when the project is finished and the results are published (please reply me by email). Joep Kraeima, Master student Health Sciences and Technical Medicine. University of Twente For questions or other remarks please contact via: j.kraeima@student.utwente.nl

Appendix III: Follow-up strategy table

Appendix Table I

	Strategy		
Follow-up frequency	bad	medium	good
0	x*	x	x
1	1	10	5
2	1, 10	2, 10	5, 10
3	1,2,10	1,3,10	2,4,10
4	1-3,10	1,3,5,10	2,4,6,10
5	1-4, 10	1,3,5,7,9	2,4, 6, 8, 10
6	1-5,10	1, 2,4, 6, 8, 10	1,3,5,7,9, 10
7	1-6,10	1-3,5,7,9,10	1,3,5,7-10
8	1-7,10	1-5,7,9,10	1,3,5-10
9	1-8,10	1-7,9,10	1,3-10
10	1-10	1-10	1-10

* the interval at which follow-up is performed

Process report

Gained skills and learning objectives:

- Search, analyse and review scientific literature
- Drawing and spreading a questionnaire (Google forms) among an expert's panel. Hereafter analysing the results of the questionnaire.
- Statistical analysis of patient data with STATA, which previously was unknown software.
- Abstract and analytical thinking for creating an evaluation model, not based on templates or examples.
- Time management and especially the sufficient use of contact moments with supervisors. This was not always optimal in the first phase of the research.
- Scientific and English writing.

Ancillary activities:

- Health Valley event (integration of innovation in healthcare)
- NABON BOOG symposium (latest developments for breast cancer)
- Paradoks Inside Out symposium (decision making in health care)
- Speaker at ORAHS conference (elevator pitch and poster session)

All in all I have seen that I developed myself during the project. It was difficult to sharply formulate the research problem in the first phase of the project, however by reading literature and debating the matter with the supervisors, the goal of the study became clear. After the plan of approach was written, the research question and thereby the focus of the project, was defined. It was however an on-going discussion until a late phase in the project, what the final outcome of the study should be.

I experienced that it was essential to prepare meetings properly to make good use of the available time of the supervisors. By preparing an agenda, send new materials in advance and summarize the meeting afterwards, the contact moments were sufficiently used.

The communication between all involved parties within the project was experienced as good, there were no obstacles worth mentioning and there was frequent consultation of all supervisors.