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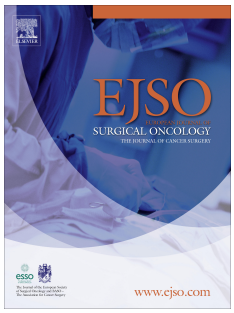

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Tailored follow-up for early breast cancer patients: a prognostic index that predicts locoregional recurrence

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ABSTRACT

Aims After treatment, early breast cancer patients undergo follow-up according to standard regimens. After the first year, the main goal is particularly to detect locoregional recurrences (LRR). Our aim was to developed a simple prognostic index to predict LRR to tailor the follow-up programme.

Methods We used data from four large international clinical randomised trials and constructed the prognostic index using Cox proportional hazards regression. The bootstrap (a resampling method) was used for internal validation.

Results A total of 6 516 patients treated according to current guidelines with complete covariable information were used for analysis. Covariables important for LRR in patients treated with breast conserving therapy were age, pathological tumour status, boost and surgical margins. The same variables were important for patients treated with a mastectomy, however, instead of the boost, the pathological nodal status was important. The index is composed to consist of three groups based on LRR risk after 10 years.

Conclusions We constructed a simple prognostic index that can be used to estimate risks of LRR in patients with early breast cancer. The prognostic index enables patients to be stratified into three subgroups with different outcomes with regard to LRR.

INTRODUCTION

Background

Early breast cancer patients are enrolled into a follow-up programme after treatment. The key elements of this programme are periodic visits for history taking, physical examination and annual surveillance mammograms.[1] This follow-up schedule is intensive and stressful for patients and the cost-effectiveness is low.[2;3] Besides, it has led to considerable workload for physicians, especially surgeons: worldwide more than 7.5 million patients are seen at outpatient clinics yearly. These problems will increase as a result of a number of trends. First, the majority of patients currently have early-stage disease and therefore more than 80% are expected to survive five years or longer.[4] Second, better survival results are obtained due to new systemic therapies and accordingly more patients will live longer. Third, only a minority of patients are discharged of follow-up; it was shown that only 15% of patients are discharged at five years and 43% at 10 years.[5]

Aims of follow-up

Follow-up of breast cancer patients has several aims. The first year is particularly important for quality of life of patients and monitoring of treatment and side-effects. After this first year, the main goal of follow-up is early detection of second primary breast tumours and locoregional recurrences (LRR) at an early stage in order to begin immediate potentially curative therapy.[6;7] Early detection of distant metastases is not an aim because these cannot be cured. It was shown that a more intensive follow-up strategy including additional investigations to detect distant metastasis did not result in a survival benefit.[8;9] Early detection of distant metastasis will only result in a poorer quality of life for patients because of the knowledge of having an incurable disease and the side effects of earlier treatment that will not result in longer lifespan.

Tailoring

In contrast to local and systemic treatment regimens, follow-up is not based on patient or tumour characteristics. All patients follow the same regimen in spite of different risk profiles. Risk of LRR

differs between patients; patients treated with breast conserving surgery (BCS) are at higher risk for LRR than patients treated with a radical mastectomy.[10] A better definition of what constitutes a patient at high or low risk of LRR would be valuable to improve follow-up. Different indices were developed that integrate combination of factors to identify high risk patients, like Adjuvantonline! and the Nottingham Prognostic Index.[11] However, these indices emphasise at overall survival, not at LRR. One of the gene-expression profiles identified subgroups of patients at increased risk of local recurrence after BCS.[12] However, to construct and validate this profile, very young breast cancer patients (80% <40 years old) were used and this does not reflect common breast cancer patients. Therefore, a prognostic index for LRR is lacking. To address this issue, we developed and validated a prognostic model for LRR. For extensive clinical use of such an index, our aim was not to derive a precise risk indicator but a simple model which can be determined without difficult calculations and which can be applied for all early breast cancer patients treated according to general guidelines. To establish this, we used clinicopathological data from four different international trials with almost 10000 patients with an adequate follow-up.

METHODS

Patients

Data of four large international trials with a long follow-up were used, the European Organisation of Research and Treatment of Cancer (EORTC) trials 10801, 10854, 10902 and 22881.

The EORTC trial 10801 included patients (n=902) from 1980 to 1986 in order to assess the safety of breast conserving treatment (BCT).[10] Eligible patients had clinical stage I or II early breast cancer and were randomised between radical mastectomy and BCS followed by radiotherapy. Radiotherapy consisted of irradiation to the breast (50 Gy), with an additional booster dose (25 Gy) directed to the lumpectomy site. For all patients of ≤55 years with pathological nodal positive disease, six cycles of

chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) were indicated. No information was available on endocrine therapy.

The EORTC trial 10854 (the so-called "Peri-operative chemotherapy, POP-trial") included patients with early breast cancer followed by surgery with curative intent from 1986 to 1991 to study whether one course of peri-operative chemotherapy yields better therapeutic results than surgery alone.[13] The patients from the surgery alone arm were included for the current analysis (n=1 395/2 793). Surgery consisted of either modified radical mastectomy or BCS, both followed by axillary clearance. Axillary lymph node positive premenopausal patients were recommended to receive five courses of CMF. Radiotherapy was given after BCS to the whole breast (50 Gy) followed by a boost on the initial tumour site (16 Gy). Besides, radiotherapy was given in all cases in which surgery was considered not to be radical. Prolonged adjuvant systemic treatment was up to the discretion of local physicians.

The EORTC trial 10902 (the so-called "Preoperative chemotherapy in operable breast cancer, POCOB-trial") included early breast cancer patients (T1c, T2, T3, T4b, N0-1 and M0) from 1991 to 1999 to evaluate the value of preoperative chemotherapy.[14] The patients from the postoperative chemotherapy arm were included (n= 348/698) for this analysis. Chemotherapy consisted of four cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC).

The EORTC trial 22881, the so-called "boost versus no boost trial", included patients (n=5569) from 1989 to 1996.[15] The aim of this trial was to evaluate the value of a boost dose after primary BCS. All patients were treated with BCS and axillary dissection, followed by irradiation of the whole breast (50 Gy). Patients with microscopically complete excisions were randomised to a boost (16 Gy) to the tumour bed and no boost. Patients with microscopically incomplete excisions were randomised to receive a boost (10 or 26 Gy) to the tumour bed versus no boost.

Statistical analysis

To use only early breast cancer patients, all patients with T3 and T4 tumours and/or with more than 10 positive nodes were excluded. Patients with preoperative chemotherapy were also excluded because of the influence on the pathological tumour and nodal status. Finally, patients treated with perioperative chemotherapy and patients treated with BCS without radiotherapy were excluded because this is not the standard anymore. In our analysis, systemic treatment (endocrine and chemotherapy) was not included as explanatory variables because the effects of such treatment are mainly on distance recurrence and these drugs and schedules have been subject to change over the last decades.

Time from randomisation to the first occurrence of local recurrence was considered. Patients were censored at time of last follow-up, distant recurrence or death. Univariable and multivariable models were fitted using Cox proportional hazards regression, stratified by the different EORTC studies. The bootstrap was used for internal validation to assess stability of prognostic variables selected.[16] The cross-validation procedure described by Verweij *et al* was used.[17] After deriving the prognostic index, cumulative incidence of LRR, accounting for distant recurrences and death as competing risk was calculated.[18] Harrell's c index was used to quantify the predictive value of the index.[19] Harrell's c index ranges from 0.5 to 1.0 with 0.5 indicating no predictive value and 1.0 perfect discrimination. However, if the index is not continuous but divided into groups, the maximum possible value of the Harrell's c index is <1.0.[20]

RESULTS

Patients, tumour and treatment characteristics are shown in Table 1. A total of 9 964 patients were included in the four EORTC trials. Exclusion of patients not treated according to current guidelines (n=2 285) and with incomplete covariable information on the covariables (n=1 163) considered left 6 516 patients for our analysis. No significant differences in LRR rates were found between the 6 516 patients considered and the 1 163 patients with incomplete covariables (p=0.86).

Constructing of the index

Since mastectomy and BCS followed by radiotherapy (BCT) constitute different (surgical) techniques with different prognostic effects, multivariable Cox regressions were first performed for mastectomy and BCT separately. The results in Table 2 show that the effect of most prognostic factors is similar for mastectomy and BCT, with two exceptions. The first is the boost, which is only defined for BCT. The second is nodal status. For BCT, the effect of nodal status was not significant, but for mastectomy it was highly significant ($p<0.0001$). The interactions between age, tumour stage and surgical margins on the one hand and type of surgery (mastectomy versus BCT) on the other were not significant ($p=0.74$, 0.79, and 0.41, respectively). The interaction between nodal status and type of surgery was highly significant ($p=0.003$), suggesting different effects of nodal status for BCT and mastectomy. Therefore, an overall model was considered with identical effects of age, tumour stage and surgical margins across types of surgery, and with separate effects of nodal status and radiotherapy/boost. The effect of nodal status for BCT was again observed to be virtually zero, so the final model was obtained by deleting the nodal status effect for BCT. The estimated regression coefficients and hazard ratios of this final model are shown in Table 2. The internal bootstrap validation showed that selection of variables was quite stable; each of the variables of the final model was selected in more than 80% of the 500 bootstrap models, with the exception of surgical margins, which was selected in 79% of the bootstrap models. A continuous index can be constructed by adding the regression coefficients, depending on the covariable values of the patient. A histogram of the values of this index in our population is given in Figure 1. The univariable hazard ratio of this continuous prognostic index was estimated as 2.72 per unit increase of the index with a 95% confidence interval from 2.31 to 3.20 ($P<0.0001$). The corresponding regression coefficient is 1 by definition. A cross-validated prognostic index was calculated for each individual following the procedure of Verweij and van Houwelingen.[17] The estimated regression coefficient of such a cross-validated prognostic index is typically <1 and can be regarded as a shrinkage factor, with values well below 1, say <0.8, indicating overfitting. Applying this procedure resulted in an estimated regression coefficient of 0.94 (standard error 0.08), indicating that the predictive value of the proposed index is almost equally good on new data as on the present data.

Different risk groups

The LRR index is to be used for tailored follow-up. We are aiming for a low-risk group, with a 10-years LRR probability of at most 7.5%, a medium-risk group, with a 10-years LRR probability between 7.5% and 12.5%, and a high-risk group with a 10-years LRR probability of at least 12.5%. The low-risk group will get less follow-up, the high-risk group more. The corresponding cut-off values of the prognostic index were found to be 1.4 and 2.1, for a 10-years LRR probability of 7.5% and 12.5%, respectively. With a low-risk group defined as having a prognostic index ≤1.4, a high-risk group defined as having a prognostic index >2.1, and the medium-risk group with a prognostic index between 1.4 and 2.1, in our study population 1 027, 4 389, and 1 100, patients were low risk, medium risk, and high risk, respectively. Figure 2 shows the estimated cumulative incidence functions for each of these three risk or follow-up intensity groups. The hazard ratios (95% confidence interval) of medium risk and high risk with respect to low risk were estimated as 2.00 (1.53 – 2.62) and 3.91 (2.94 – 5.21), respectively. The 10-years estimated probabilities of LRR (95% confidence interval) were 0.05 (0.04 – 0.07), 0.11 (0.10 – 0.12), and 0.19 (0.16 – 0.22), for low risk, medium risk and high risk groups respectively. When the index was executed in another breast cancer population (a ten year cohort of our own centre), the same distinction was seen, however, there were more patients included in the low risk group compared to the high risk group (data not shown).

Harrel's c-index was estimated as 0.61 for the continuous prognostic index and 0.59 for the three prognostic groups, indicating a moderate loss of predictive accuracy as a result of categorising the prognostic index. These values indicate only modest predictive accuracy, however, such values are quite common in the context of survival analysis. For the continuous index, Harrel's c-index was estimated as 0.65 for patients treated with a mastectomy and 0.61 for patients treated with BCT. For the three prognostic groups, Harrel's c-index was estimated as 0.60 for patients treated with a mastectomy and 0.58 for patients treated with BCT.

Prognostic index

For an individual patient, the value of the continuous prognostic index can be calculated by adding the regression coefficients of Table 2, depending on the patient's covariable values. The patient can then be assigned to a risk group, depending on whether the value of this prognostic index is below or above 1.4 and 2.1. To facilitate implementation into clinical practise, a decision tree was constructed, one for patients treated with mastectomy and one for patients treated with BCT (figure 3). The tree is stopped whenever taking further covariables into account will not change the resulting risk group. The number within brackets indicates the value of the continuous prognostic index so far.

DISCUSSION

Prognostic factors

The goal of this analysis was to develop and validate a simple prognostic index for LRR for all patients with early breast cancer who are treated according to acceptable standards. Well-defined variables were used that can be combined to produce a prognostic index. This index is simple and the decision tree can be used immediately after surgery/local therapy and gives very good discrimination, as shown by the Kaplan Meier curve.

The first distinction was local therapy: mastectomy versus BCT. The overall survival of patients treated with BCT is comparable to the one of patients treated with mastectomy. However, their chance on LRR is 4 times higher after twenty years of follow-up.[21] Radiotherapy after mastectomy and a boost in patients treated with BCT have previously shown to decrease the chance of a LRR in patients and were included in our index.[15;22] Age is the second factor in this prognostic index. Significance of age was already recognised in other studies; young age is independently associated with unfavourable outcome in patients with early breast cancer.[23;24] In the EORTC 22881 trial, disease recurrence in the ipsilateral breast or in the axilla as first event was more seen in younger patients.[15] A boost reduced the rate of LRR, however, this effect was mainly seen in younger patients (≤ 40 years) and was less prominent in older patients (≥ 51 years). Tumour stage was also an important factor. Unfortunately,

not all pathological tumours stage were known, this was especially the case in the EORTC 10854 trial, therefore, unfortunately, the majority of patients of this trial were excluded for this analysis. The pathological nodal status was only important for LRR in patients treated with mastectomy. The last factor of influence in the index are the surgical margins: positive margins are correlated with a higher chance on LRR.

Limitations

Information about histological grade was not available, this factor was not used in our analyses. Several studies investigating predictors of LRR demonstrated that grade was an important factor, other studies did not demonstrated it.[25;26] We do not have information concerning relatively new prognostic and predictive factors like ER, PgR and HER2. If we want to include these factors in the index we need information of newer studies with a shorter follow-up than the current used studies. We prefer to have a long follow-up. In the future, new factors can be included, like hormone receptor status, HER2, grade and gene expression arrays.

Several factors limit accuracy of the index to predict the exact percentage of LRR. Firstly, the trials included patients over different time periods. Over time, local therapies and administration of systemic therapies have been improved. Consequently, patients will live longer and are therefore longer exposed to risk of LRR. Secondly, treatment options differed between trials; they included different kinds of patients. Mastectomy was compared to BCT in the EORTC trial 10801 while all patients in the EORTC trial 22881 were treated with BCT. However, because this index was developed using different trials, heterogeneity in prognostic risk in early breast cancer patients was realistically reflected. And thirdly, factors considered important in our prognostic index were not routinely collected in all trials. In the EORTC trial 10854, the pathological T stage was not recorded for all patients. In spite of all differences mentioned above, an index was constructed and validated. Also, the fact that data from four different trial populations were used enabled us to study the internal validity in a natural way. This indicates that this index can be useful in different clinical settings, for example to improve the value of follow-up.

Follow-up

Doubts about the value of routine follow-up have been expressed for many years and the rationale of follow-up is still subject of discussion.[27;28] It was shown that routine follow-up confers little survival benefit and increases distress in patients.[8;29] Moreover, it was suggested that clinical examinations do not improve clinical outcome.[30] Consequently, research was performed to examine both the burden and health gains of different follow-up programmes. However, in all these studies, different risks of LRR were not taken into account. LRR are potentially curable and therefore should be detected early. When follow-up is risk based for LRR using our index, it could be more efficient.

In the Netherlands, an implementation study will be performed to evaluate a new follow-up schedule based on our index. We do not aim to modify the first year visits for any patient, as optimising quality of life after local therapy is equally relevant to all patients following treatment for breast cancer. This physical and psychosocial rehabilitation of patients will in general take one year. Therefore, we will tailor the follow-up after the first year. Patients with an intermediate risk on LRR according to the prognostic index will follow the routine follow-up programme (the second year twice and thereafter yearly, www.oncoline.nl). Patients at low risk can be seen less frequently (visit once every two years) and patients at high risk should be seen more often (visit twice every year). Mammographies will be taken yearly in every group and questionnaire will be filled in by patients and physicians to evaluate the new schedule and quality of life of patients.

In conclusion, we constructed and validated a continuous prognostic index that divided patients in three groups according to risk of LRR. We will incorporated this index in our follow-up schedule to make it (more) evidence based.

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Reference List

1. Khatcheressian JL, Wolff AC, Smith TJ, et al. American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. J Clin Oncol 2006;24: 5091-5097

2. Loprinzi CL. It is now the age to define the appropriate follow-up of primary breast cancer patients. J Clin Oncol 1994;12: 881-883

3. Renton JP, Twelves CJ, Yuille FA. Follow-up in women with breast cancer: the patients' perspective. Breast 2002;11: 257-261

4. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. CA Cancer J Clin 2005;55: 10-30

5. Maher EJ. Non-surgical management of early breast cancer in the United Kingdom: follow-up. Clinical Audit Sub-committee of the Faculty of Clinical Oncology, Royal College of Radiologists, and the Joint Council for Clinical Oncology. Clin Oncol (R Coll Radiol) 1995;7: 227-231

6. de Bock GH, Bonnema J, van der Hage JA, et al. Effectiveness of routine visits and routine tests in detecting isolated locoregional recurrences after treatment for early-stage invasive breast cancer: a meta-analysis and systematic review. J Clin Oncol 2004;22: 4010-4018

7. Rojas MP, Telaro E, Russo A, et al. Follow-up strategies for women treated for early breast cancer. Cochrane Database Syst Rev 2005; CD001768

8. The GIVIO Investigators. Impact of follow-up testing on survival and health-related quality of life in breast cancer patients. A multicenter randomized controlled trial. The GIVIO Investigators. JAMA 1994;271: 1587-1592

9. Rosselli Del Turco M, Palli D, Cariddi A, et al. Intensive diagnostic follow-up after treatment of primary breast cancer. A randomized trial. National Research Council Project on Breast Cancer follow-up. JAMA 1994;271: 1593-1597

10. van Dongen JA, Voogd AC, Fentiman IS, et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. J Natl Cancer Inst 2000;92: 1143-1150

11. Haybittle JL, Blamey RW, Elston CW, et al. A prognostic index in primary breast cancer. Br J Cancer 1982;45: 361-366

12. Nuyten DSA, Kreike B, Hart AAM, et al. Predicting a local recurrence after breast-conserving therapy by gene expression profiling. Breast Cancer Res 2006;8: R62

13. Clahsen PC, van de Velde CJH, Julien JP, et al. Improved local control and disease-free survival after perioperative chemotherapy for early-stage breast cancer. A European Organization for Research and Treatment of Cancer Breast Cancer Cooperative Group Study. J Clin Oncol 1996;14: 745-753

14. van Nes JGH, Putter H, Julien JP, et al. Preoperative chemotherapy is safe in early breast cancer, even after 10 years of follow-up; clinical and translational results from the EORTC trial 10902. Breast Cancer Res Treat 2009;115: 101-113

15. Bartelink H, Horiot JC, Poortmans PM, et al. Impact of a Higher Radiation Dose on Local Control and Survival in Breast-Conserving Therapy of Early Breast Cancer: 10-Year Results of the Randomized Boost Versus No Boost EORTC 22881-10882 Trial. J Clin Oncol 2007;25: 3259-3265

16. Sauerbrei W, Schumacher M. A bootstrap resampling procedure for model building: application to the Cox regression model. Stat Med 1992;11: 2093-2109

17. Verweij PJ, van Houwelingen HC. Cross-validation in survival analysis. Stat Med 1993;12: 2305-2314

18. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med 2007;26: 2389-2430

19. Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15: 361-387

20. Yan G, Greene T. Investigating the effects of ties on measures of concordance. Stat Med 2008;27: 4190-4206

21. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002;347: 1227-1232

22. Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet 1999;353: 1641-1648

23. Elkhuizen PHM, van de Vijver MJ, Hermans J, et al. Local recurrence after breast-conserving therapy for invasive breast cancer: high incidence in young patients and association with poor survival. Int J Radiat Oncol Biol Phys 1998;40: 859-867

24. Jobsen JJ, van der PJ, Ong F, et al. The value of a positive margin for invasive carcinoma in breast-conservative treatment in relation to local recurrence is limited to young women only. Int J Radiat Oncol Biol Phys 2003;57: 724-731

25. Clark RM, McCulloch PB, Levine MN, et al. Randomized clinical trial to assess the effectiveness of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer. J Natl Cancer Inst 1992;84: 683-689

26. Mirza NQ, Vlastos G, Meric F, et al. Predictors of locoregional recurrence among patients with early-stage breast cancer treated with breast-conserving therapy. Ann Surg Oncol 2002;9: 256-265

27. Dixon JM, Montgomery D. Follow-up after breast cancer. BMJ 2008;336: 107-108

28. Donnelly PK, Hiller L, Dunn JA. National randomised controlled trial is needed. BMJ 2008;336: 461-462

29. Del Turco RM, Palli D, Cariddi, et al. Intensive diagnostic follow-up after treatment of primary breast cancer. A randomized trial. National Research Council Project on Breast Cancer follow-up. JAMA 1994;271: 1593-1597

30. Montgomery DA, Krupa K, Jack WJ, et al. Changing pattern of the detection of locoregional relapse in breast cancer: the Edinburgh experience. Br J Cancer 2007;96: 1802-1807

Tables and figures

Table 1: Patient and tumour treatment characteristics of patients in the different EORTC trials. Data are shown in amount (grey row) and percentages (white row).

Table 2: Estimated regression coefficients and associated hazard ratios for the penalized multivariable Cox regression. Last column: deriving the simple score

Figure 1: Histogram of LRR prognostic index. On the x-axis the value of the added regression coefficients. On the y-axis, the number of patients.

Figure 2: Estimated cumulative incidences of locoregional recurrence for each of the three proposed follow-up schemes: low (Locoregional recurrence (LRR) risk after ten years of <7.5%), medium (LRR risk between 7.5 and 12.5) and high (LRR risk > 12.5%).

Figure 3. The decision tree for patients treated with breast conserving and with mastectomy. The tree is stopped whenever taking further covariables into account will not change the resulting risk group. The number within brackets indicates the value of the continuous prognostic index so far.

Table 1: Patient and tumour treatment characteristics of patients in the different EORTC trials. Data are shown in amount (grey row) and percentages (white row).

	EORTC 10801		**EORTC 10854, standard arm**		**EORTC 10902, post operative chemo arm**		**EORTC 22881**		**Total**	
	N	%	N	%	N	%	N	%	N	%
Patients in trials	902	100	1395/ 2795	100	348/ 698	100	5569	100	9964	100
Patients used in analysis	752	100	190	100	205	100	5369	100	6516	100
Age at randomisation										
<40	64	9	48	25	3913	19	453	8	604	9
40-60	479	64	141	74	144	70	3179	59	3943	61
≥60	209	28	1	1	22	11	1737	32	1969	30
Tumour stage										
pT1	363	48	91	48	82	40	4293	80	4829	74
pT2	389	52	99	52	123	60	1076	20	1687	26
Nodal stage										
pN-	455	61	190	100	79	39	4237	79	4961	76
pN+	297	39	0	0	126	61	1132	21	1555	24
Local treatment										
Mastectomy - RT	209	28	0	0	78	39	0	0	287	4
Mastectomy + RT	154	20	21	11	63	31	0	0	238	4
BCT - boost	0	0	0	0	20	10	2571	48	2591	40
BCT + boost	389	52	169	89	44	21	2798	52	3400	52
Surgical margin										
Negative	563	75	184	97	189	92	5134	96	6070	93
Positive	189	25	6	3	16	8	235	4	446	7
LRR										
No		87		80		90		89		88
Yes	96	13	38	20	20	10	611	11	765	12

Abbreviations: BCT: breast conserving therapy; LRR: locoregional recurrence; RT: radiotherapy

Table 2: Estimated regression coefficients and associated hazard ratios for the penalized multivariable Cox regression. Last column: deriving the simple score

	All patients		Mastectomy		Breast conserving therapy	
Age at randomisation	**Coefficient (SE)**	**Hazard ratio (95%CI)**	**Coefficient (SE)**	**Hazard ratio (95%CI)**	**Coefficient (SE)**	**Hazard ratio (95%CI)**
≥60		1.00		1.00		1.00
40-60	0.368 (0.092)	1.44 (1.21 – 1.73)	0.656 (0.447)	1.93 (0.80 – 4.63)	0.357 (0.094)	1.43 (1.19 – 1.72)
<40	1.062 (0.119)	2.89 (2.29 – 3.64)	1.089 (0.563)	2.97 (0.99 – 8.96)	1.062 (0.122)	2.89 (2.28 – 3.67)
Tumour stage						
pT1		1.00		1.00		1.00
pT2	0.317 (0.083)	1.37 (1.17 – 1.61)	0.412 (0.302)	1.51 (0.84 – 2.73)	0.315 (0.087)	1.37 (1.16 – 1.62)
Nodal stage						
pN-		1.00		1.00		1.00
pN+ (only Mast)	0.880 (0.310)	2.41 (1.31 – 4.43)	0.889 (0.328)	2.43 (1.28 – 4.63)	-0.080 (0.096)	0.92 (0.77 – 1.11)
Local treatment						
Mastectomy + RT		1.00		1.00		
Mastectomy - RT	0.960 (0.328)	2.61 (1.37 – 4.97)	1.019 (0.355)	2.77 (1.38 – 5.55)		
BCT + boost	1.217 (0.361)	3.38 (1.66 – 6.85)				1.00
BCT - boost	1.574 (0.366)	4.83 (2.36 – 9.90)			0.353 (0.083)	1.42 (1.21 – 1.67)
Surgical margins						
Negative		1.00				1.00
Positive	0.426 (0.145)	1.53 (1.15 – 2.03)	NA*		0.438 (0.146)	1.55 (1.16 – 2.06)

* Could not be estimated

Abbreviations: BCT: breast conserving therapy; RT: radiotherapy

Figure 1: Histogram of LRR prognostic index. On the x-axis the value of the added regression coefficients. On the y-axis, the number of patients.

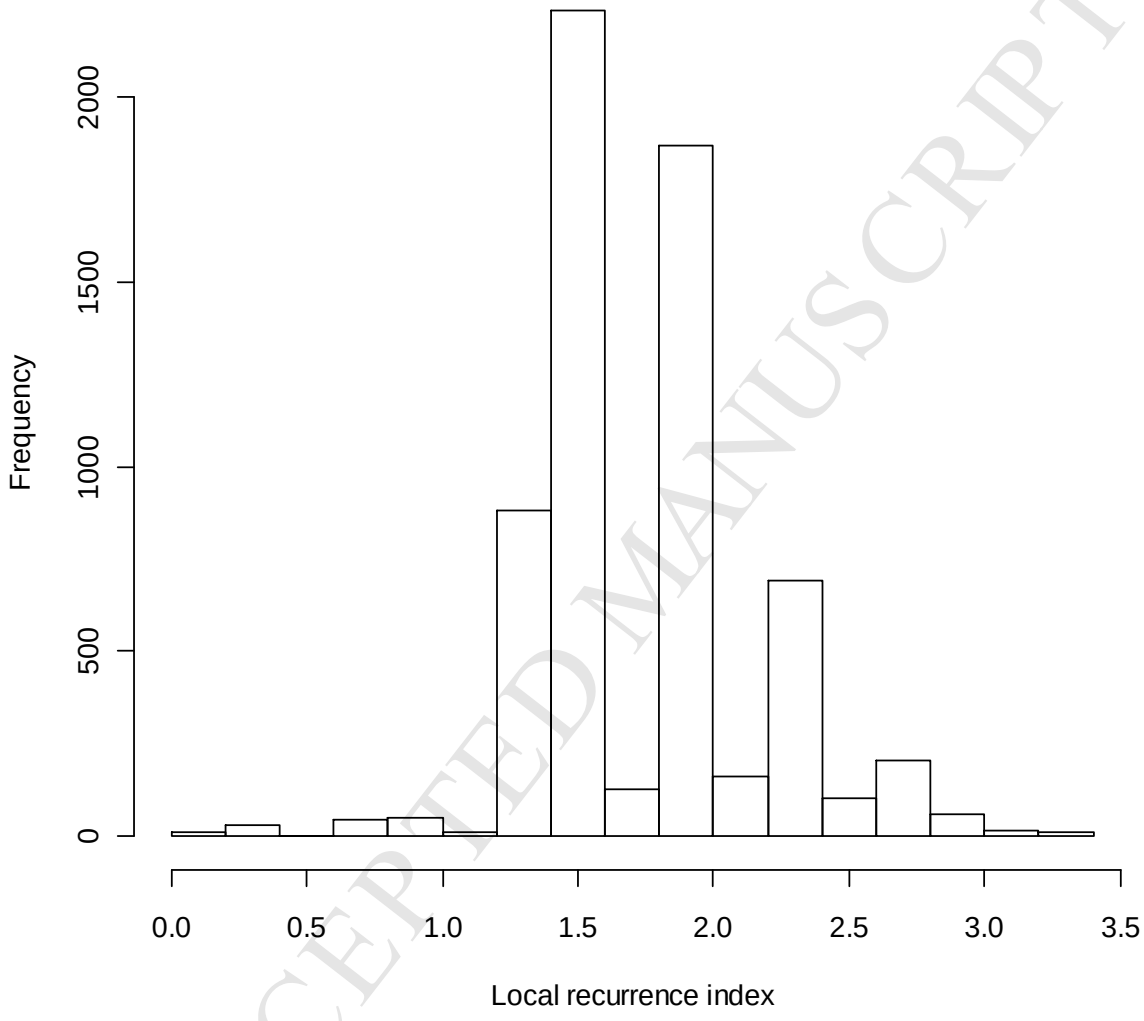
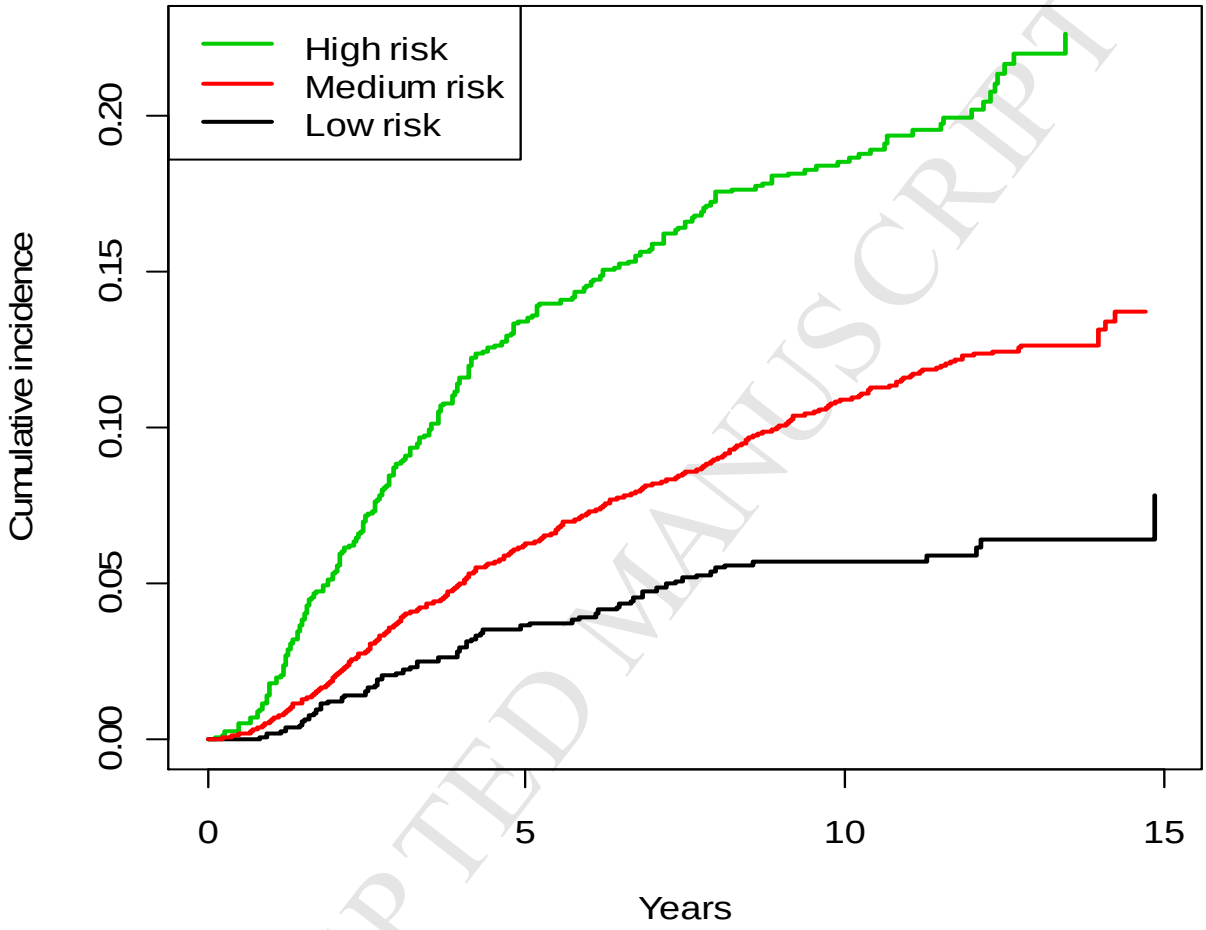
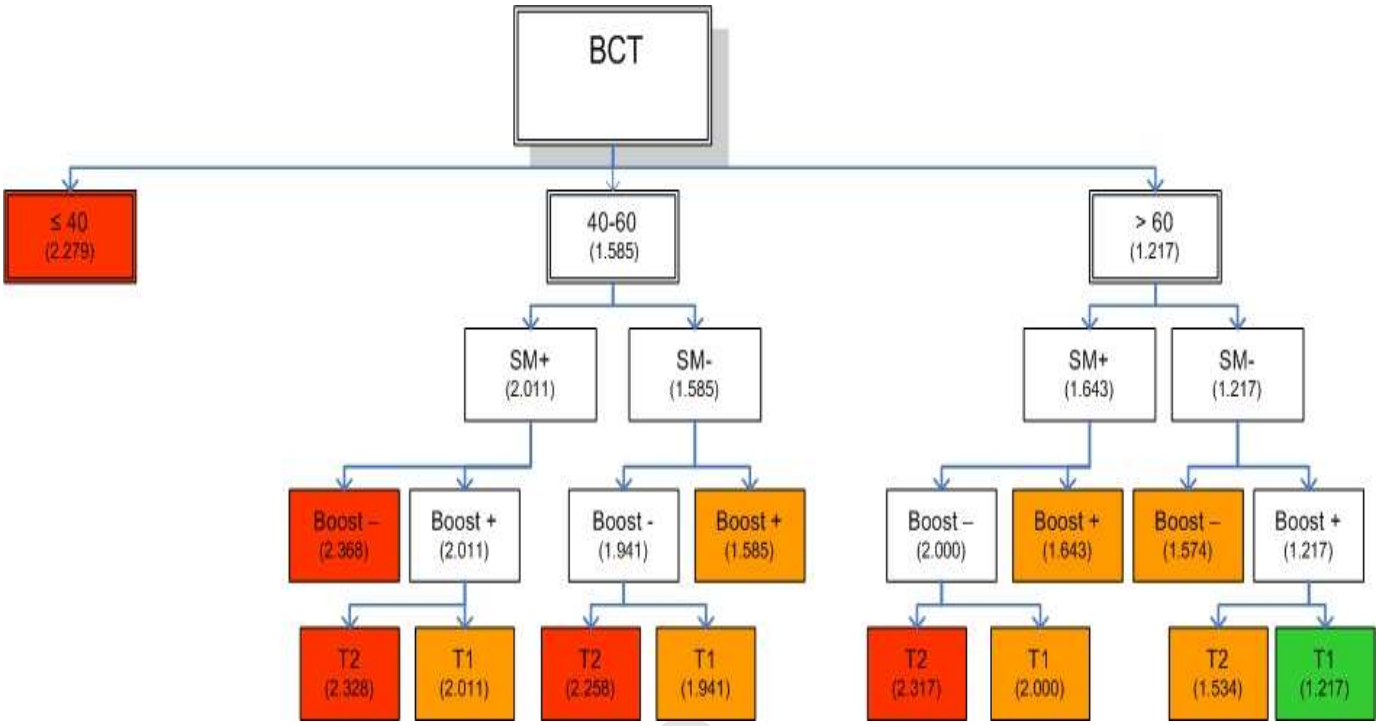


Figure 2: Estimated cumulative incidences of locoregional recurrence for each of the three proposed follow-up schemes: low (Locoregional recurrence (LRR) risk after ten years of <7.5%), medium (LRR risk between 7.5 and 12.5) and high (LRR risk > 12.5%).

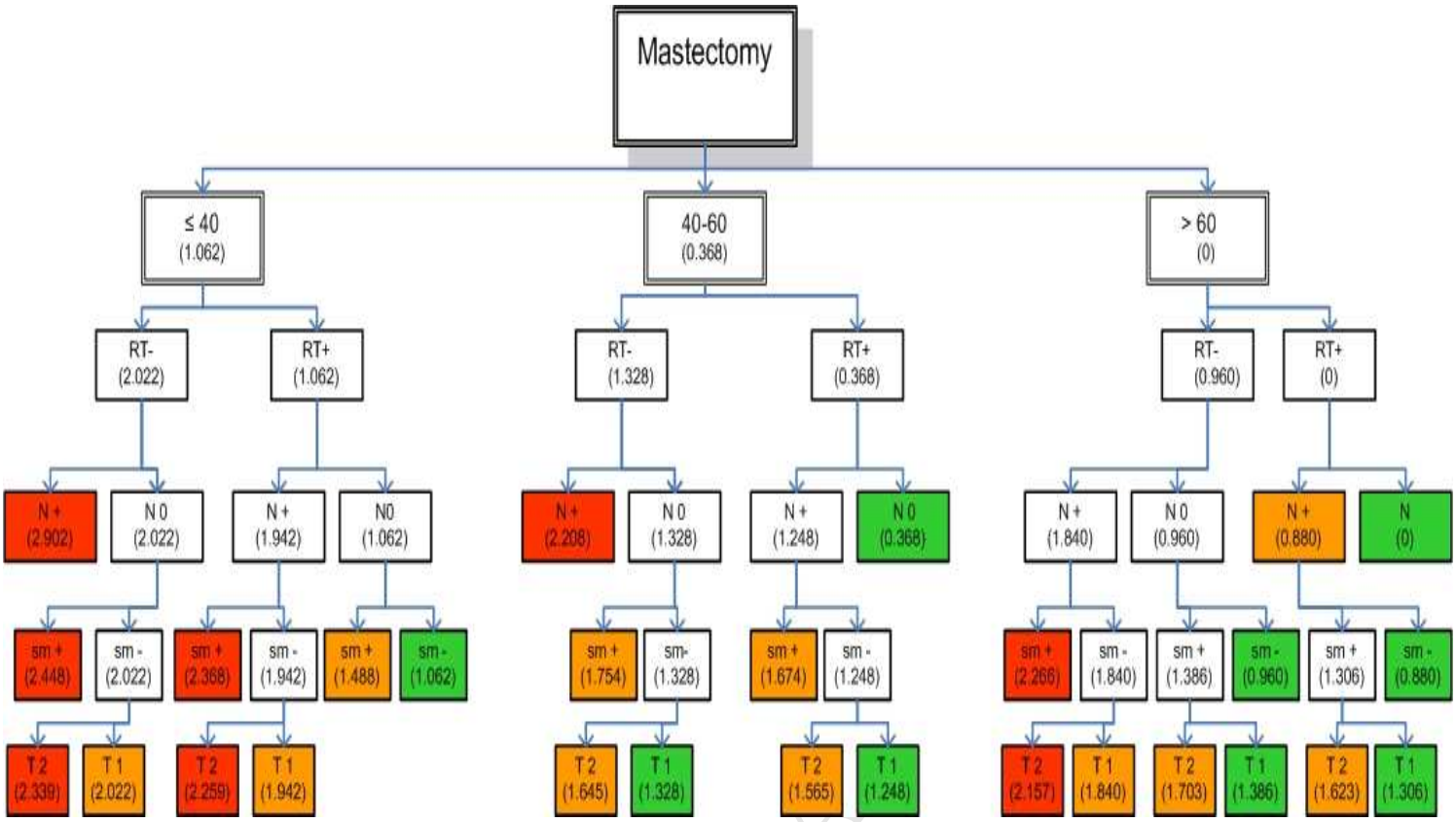


Group/year	0	2.5	5	7.5	10	12.5	15
High risk	1100	871	720	623	468	168	17
Median risk	4389	3954	3473	3078	2084	727	80
Low risk	1027	938	841	736	527	214	38

Figure 3. The decision tree for patients treated with breast conserving and with mastectomy. The tree is stopped whenever taking further covariates into account will not change the resulting risk group. The number within brackets indicates the value of the continuous prognostic index so far.



Abbreviations: BCT: breast conserving therapy; RT: radiotherapy; SM: surgical margins; T: pathological tumour stage



Abbreviations: N: pathological nodal status; RT: radiotherapy; SM: surgical margins; T: pathological tumour stage