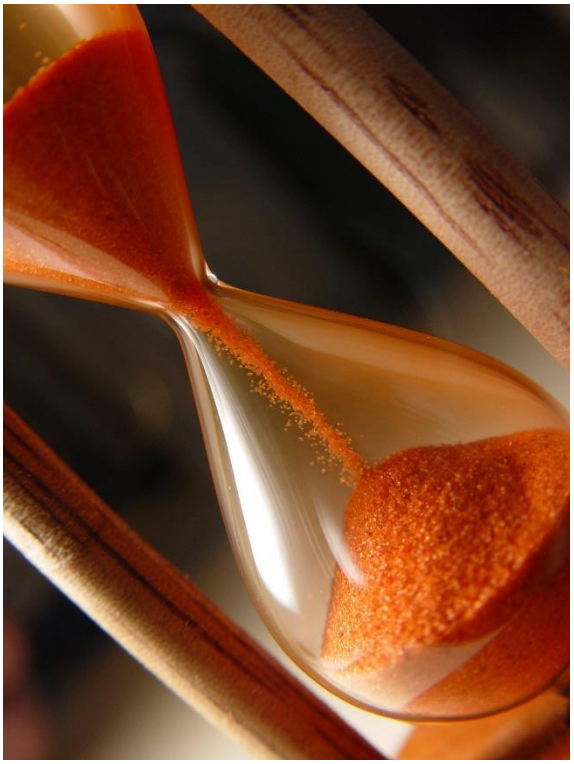

Article

Does preoperative breast MRI lead to an improvement of survival of breast cancer patients in the Netherlands?

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1 Abstract

Purpose

Breast magnetic resonance imaging (MRI) is used in patients with breast cancer for the evaluation of tumor diameter, multifocality, and potential presence of contralateral breast cancer, and therefore aims to optimize the extent of surgery and radiotherapy. This may result in improved local control, fewer metastasis, and an improved overall survival (OS). Previous studies show no statistically significant differences for these outcomes, however some do state that it has a tendency towards better OS. The purpose of this retrospective population-based study was to evaluate the effect of preoperative breast MRI on OS for invasive breast cancer patients in the Netherlands.

Methods

In this study we selected all women from the Netherlands Cancer Registry diagnosed with invasive breast cancer between 2011 and 2013. Patients without surgical treatment, with distant metastases, and/or treated with neoadjuvant therapies were excluded. The study population was divided into a MRI and non-MRI group, according to preoperative use of breast MRI. Subsequently, the study population was assigned to one of the following subgroups: invasive carcinoma of no special type (NST) or the invasive lobular carcinoma (ILC). The OS with and without MRI was calculated with the Kaplan-Meier method and was compared with the log-rank test. A Cox proportional hazard regression analysis was performed to estimate the hazard ratio (HR) for OS with a 95% confidence interval (CI). To account for missing data multiple imputation was performed.

Results

Of the 31,756 included patients, 9,632 (30.3%) received preoperative breast MRI and 22,124 (69.7%) did not. The subgroup invasive carcinoma NST consisted of 27,752 patients (26.6% MRI vs 56.1% non-MRI) and the subgroup ILC consisted of 4,004 patients (56.1% MRI vs 43.9% non-MRI). The mean follow-up period was 5.3 years. In both the total study population and both subgroups, the Kaplan-Meier, log-rank, and univariable Cox regression analysis showed that breast MRI was significantly associated with improved OS compared to non-MRI (p<0.0001). After stratification by age categories of the log-rank test, it was only significant for patients older than 60 years in the total study population, and patients older than 70 in both subgroups. The calculated HR for breast MRI per age category in the multivariable Cox regression analysis showed that preoperative breast MRI had a tendency towards better OS, however not always statistically significant. In the total study population the association between breast MRI and OS was only significant for the age categories 50-59 (HR 0.80, 95%-CI 0.66-0.97), 60-69 (HR 0.80, 95%-CI 0.68-0.94), and older than 70 (HR 0.66, 95%-CI 0.57-0.76). For the invasive carcinoma NST significant differences were only found for the age categories 60-69 (HR 0.80, 95%-CI 0.67-0.96) and older than 70 (HR 0.67, 95%-CI 0.56-0.79). And for the ILC subgroup it was only significant for patients older than 70 years (HR 0.59, 95%-CI 0.46-0.76). Also noteworthy, the upper endpoint of the 95%-CI of patients aged 50-59 in the invasive carcinoma NST subgroup (HR 0.82, 95%-CI 0.67-1.01) and the HR of patients aged <50 in the ILC subgroup, which was the lowest of all, but with a large 95%-CI (HR 0.54, 95%-CI 0.23-1.24).

Conclusion

The calculated HR for breast MRI per age category showed that preoperative breast MRI tended to be associated with a better OS, but this association was only statistically significant for patients aged >50 in the total study population, patients aged >60 in the invasive carcinoma NST subgroup, and patients aged

>70 in the ILC subgroup. In addition, the HR for patients aged 50-59 in the invasive carcinoma NST subgroup was almost statistically significant and for patients aged <50 in the ILC subgroup, the HR was low but with a large 95%-CI. These results suggest that the indication for preoperative breast MRI use in ILC patients, and in particular young woman, is correct. However, in order to provide a better recommendation for preoperative breast MRI in general use, it is recommended to evaluate the effect of preoperative breast MRI on disease free survival and to perform a cost-effectiveness analysis.

2 Introduction

Breast Cancer is the second most common cancer-type in the world (2.09 million cases) and for women it is the most common cancer-type[1]. Within the Netherlands, more than 14,000 woman are diagnosed with invasive breast cancer and more than 2,500 are diagnosed with non-invasive breast cancer each year[2].

Conventional imaging techniques for early detection and diagnosis of breast cancer are full-field digital mammography (FFDM) and ultrasound, in combination with tissue sampling of suspicious lesions[3]. In the last decades, there is an increased use of preoperative breast Magnetic Resonance Imaging (MRI) as an additional diagnostic imaging technique. However, the use of breast MRI has been a subject of debate since the additional value is questionable. Theoretically, breast MRI could have beneficial effects, because of its high sensitivity in the evaluation of tumor diameter, multifocality, and potential presence of contralateral breast cancer[4,5]. Therefore, breast MRI could be used for optimizing the extent of surgery and radiotherapy, which may reduce the rates of positive surgical margins and re-excision, but moreover may result in improved local control[6], fewer metastasis, and an improved OS. On the other hand, due to its high sensitivity, the possibility of overdiagnosis exists and consequently the lacking specificity may result in higher false-positive results[3]. Both may lead to (unnecessary) extensive resections, treatment delay, and higher costs[7,8].

Regarding short-term effects of the use of preoperative breast MRI, previous studies have shown that mastectomy rates increased, and that surgical margins and reduced re-excision rates were not or slightly improved [3,7,9]. However, for some subgroups, such as the invasive lobular carcinoma (ILC), preoperative breast MRI could lead to beneficial short-term effects, but results are contradictory[3,7,9]. Regarding the long-term effects of preoperative breast MRI, previous studies have shown that there were no statistically significant differences in local and distant recurrences, contralateral breast cancer development, and disease free and overall survival[6,8,10–14]. However, some research stated that preoperative breast MRI has a tendency towards improved survival[11,14]. Hence, there are still some uncertainties about whether preoperative breast MRI is beneficial for long-term effects. The purpose of this retrospective population-based study was to evaluate the effect of preoperative breast MRI on OS for invasive breast cancer patients in the Netherlands.

3 Methods

3.1 Data collection

This retrospective study includes all female patients treated with surgery for invasive carcinoma of no special type (NST) and ILC, diagnosed in the period of 2011-2013 in the Netherlands. The OS had a maximum follow up of seven years. There was no age-limitation and patients treated with adjuvant radio, chemo, hormonal, and/or target therapies were included. Patients without surgical treatment, with distant metastases at baseline, and/or treated with neoadjuvant therapies were excluded. Data was obtained from the Netherlands Cancer Registry (NCR) and was registered by specially trained registrars based on notification by the automated pathology laboratory archive (PALGA). The 7th edition of the TNM-classification was used[15]. According to the national guideline, routine use of preoperative breast MRI was not advised but limited to some indications: (a) patients with ILC, (b) patients with invasive carcinoma who wanted a breast conserving surgery but there were discrepancies between physical examination and conventional imaging, and (c) patients with ductal carcinoma in situ (DCIS) who wanted a breast conserving surgery but there was a high-grade DCIS with uncertainty about the tumor size or there was DCIS with a suspicion of (micro)invasion. These recommendations applied in particular to young women[16].

The following variables were selected for the present study: age at diagnosis (<50, 50-59, 60-69, ≥70 years), tumor size, nodal status, molecular subtypes (luminal A: estrogen receptor (ER) and/or progesterone receptor (PR) positive, HER2 negative; luminal B: ER and/or PR positive, HER2 positive; HER2 enriched: ER and PR negative, HER2 positive; and triple negative: ER, PR, and HER2 negative), histological grade (low, medium, or high), multifocality (yes or no), tumor location (lateral, medial, or other), use of breast MRI (yes or no), surgical margin status after surgery (negative margin (NM) <0 mm, focal positive margin (FPM) <4 mm, or more than focal positive margin (MFPM) >4mm), type of final surgery (mastectomy or lumpectomy), adjuvant therapy (radio, chemo, hormonal, or target), and vital status (dead or alive). Period till death or last contact was linked with the database of the municipality, and was updated until the first of February 2018.

3.2 Statistical analysis

The study population was divided into a MRI and non-MRI group, according to preoperative use of breast MRI. Subsequently, the study population was stratified into one of the following subgroups: invasive carcinoma NST or ILC. General characteristics between the groups were tested using the chi-square test for categorical variables and the Mann-Whitney U test for continuous variables. The OS was calculated with the Kaplan-Meier method and survival curves were compared with the log-rank test, and was stratified by age categories. Possible confounders were examined using univariable and multivariable Cox proportional hazard regression analysis, with hazard ratio (HR) and corresponding 95% confidence interval (CI). In the multivariable model the interaction term MRI and age per category was used. Multiple imputation by the chained equations, with 50 iterations and 20 imputations, was used to account for missing data. The pooled results were used based on Rubin's rule. Variables in the multivariable model, that were not statistically significant, were excluded based on the Akaike's information criterion (AIC) selection method. Proportional hazards assumption were tested by the Schoenfeld test and by plotting the scaled Schoenfeld residuals. Statistical analyses were performed by using Stata/SE 14.2 for Windows. *P*-Values (two-sided) less than 0.05 were considered statistically significant.

4 Results

4.1 General characteristics

The database of the NCR included 31,877 records. Records with no follow-up data (n=80), unknown surgery (n=20), and unknown treated therapy (n=21) were excluded. The final study population included 31,756 (99.6%) records, of which 22,124 (69.7%) did not had a breast MRI and 9,632 (30.3%) had a breast MRI. Of the final study population 27,752 (87.4%) were invasive carcinomas NST (73.4% non-MRI and 26.6% MRI) and 4,004 (12.6%) were ILC (43.9% non-MRI and 56.1% MRI).

Table 1 shows the patient, tumor, and treatment characteristics for the total study population and per subgroup according to the use of breast MRI. Patients in the non-MRI group were older compared to the MRI group (62.9 vs 56.1 year respectively), had slightly higher histological grades, and were less often treated with adjuvant chemo, hormonal, and/or target therapies. The MRI group had slightly higher tumor sizes and nodal status, had more multifocal tumors (23.9 vs 10.5%), and had more mastectomies as final operation (49 vs 36.1%). The subgroups had relatively the same patients characteristics, except for the ILC subgroup wherein the distribution of the final operation within the non-MRI and MRI groups were relatively the same and more mastectomies were done. In addition, ILC had less triple negative and more luminal A type of patients compared with the invasive carcinoma NST subgroup.

4.2 Survival analysis

There were 2,939 (9.25%) incomplete cases for which multiple imputation was used after the assumption that the data were missing at random. The imputed data were compared with the original data, which showed that some proportions differed slightly (Appendix 1, Table 4 and 5). After further examination of these deviations, these results could be explained.

Within the total study population, 19,186 (87%) of 22,124 patients in the non-MRI group survived compared to 8,889 (92%) of 9,632 patients in the MRI group, after a median follow-up of 5.3 years (range 0.1-7.1 years). In the invasive carcinoma NST subgroup 17,751 (87%) of 20,366 patients in the non-MRI group survived compared to 6,819 (92%) of 7,386 patients in the MRI group, after a median follow-up of 5.3 years (range 0.1-7.1 years). In the ILC subgroup 1,435 (82%) of 1,758 patients in the non-MRI group survived compared to 2,070 (92%) of 2,246 patients in the MRI group, after a median follow-up of 5.3 years (range 0.1-7.1 years). See Appendix 2, Table 6 for the events of deaths per subgroups, stratified by age categories, where it can be seen that most deaths occur in the age category of >70 years.

The Kaplan-Meier analysis and the log-rank test showed that having a breast MRI was significantly associated with improved OS, compared to not having a breast MRI (7 year survival function 0.89 (95%-CI 0.87-0.90) vs 0.83 (95%-CI 0.82-0.83), respectively). However, after stratification in the total study population it was only statistically significant for the age groups 60-69 (p=0.036) and >70 (p<0.000). In both the invasive carcinoma NST as the ILC subgroups, it was only significant for the age group >70 (p<0.000). In Figure 2 and 3 the Kaplan-Meier curves are shown per subgroup and stratified by age category. See Appendix 2 Table 7 for the survival function per year and Table 8 for the results of the log-rank test.

Table 2 shows the results of the univariable and multivariable Cox proportional hazard regression analysis for the total study population and the subgroups. The univariable analysis of the total study

population and invasive carcinoma NST subgroup showed that all variables were significant indicators for the overall survival (p<0.05). For the ILC subgroup, multifocality, tumor location, and both hormonal as target therapies were not significant indicators (p>0.15).

The multivariable analysis showed that radiotherapy (HR 0.45, 95%-CI 0.40-0.50), chemotherapy (HR 0.63, 95%-CI 0.57-0.70), hormonal therapy (HR 0.74, 95%-CI 0.67-0.81), and target therapy (HR 0.50, 95%-CI 0.41-0.62) were significantly associated with a better OS. Significant predictors for a worse OS were older age (>50 years), higher tumor sizes, higher nodal status, and higher histological grades. In addition, the molecular subtypes luminal B (HR 1.23, 95%-CI 1.06-1.42), HER2 enriched (HR 1.41, 95%-CI 1.17-1.69), and triple negative (HR 1.74, 95%-CI 1.54-1.96), the focally positive margins (HR 1.19, 95%-CI 1.02-1.38) and more than focally positive margins (HR 1.85, 95%-CI 1.43-2.40), and a lumpectomy as final operation (HR 1.20, 95%-CI 1.07-1.34) were indicators for a worse OS. After calculating the HR of breast MRI with the interaction term, the HR for breast MRI was only significant for the age categories 50-59 (HR 0.80, 95%-CI 0.66-0.97), 60-69 (HR 0.80, 95%-CI 0.68-0.94), and older than 70 (HR 0.66, 95%-CI 0.57-0.76) (Table 3).

Within the subgroup of patients with invasive carcinoma NST the results of the multivariable model for OS were largely similar to the results of the total study population. The calculated HR of breast MRI with the interaction term, breast MRI was only statistically significant for the age categories 60-69 (HR 0.80, 95%-CI 0.67-0.96) and older than 70 (HR 0.67, 95%-CI 0.56-0.79). For the ILC subgroup, significant indicators for a better OS were radiotherapy (HR 0.54, 95%-CI 0.45-0.66), chemotherapy (HR 0.56, 95%-CI 0.41-0.76), and hormonal therapy (HR 0.73, 95%-CI 0.57-0.94). Significant indicators for a worse OS were older age (>70 years), higher tumor sizes, and higher nodal status. In addition, the molecular subtype triple negative (HR 1.85, 95%-CI 1.20-2.86) and histological grade high (HR 1.92, 95%-CI 1.32-2.78) were significant indicators for a worse OS. The calculated HR for breast MRI with the interaction term, breast MRI was only significant for the age category older than 70 (HR 0.59, 95%-CI 0.46-0.76).

5 Discussion

After stratification of the total study population by age categories, the Kaplan-Meier and Log-rank test showed that breast MRI was significantly associated with improved OS, compared to non-MRI, for patients older than 60 years. In both the invasive carcinoma NST as the ILC subgroups, this was only significantly associated for patients older than 70 years. In both the total study population and both subgroups, the univariable Cox regression analysis showed that breast MRI was significantly associated with improved OS compared to non-MRI. In the multivariable analysis, the calculated HR for breast MRI with the interaction term per age category, showed that preoperative breast MRI had a tendency towards better OS, however not always statistically significant. In the total study population, it was statistically significant for patients older than 50 years. For invasive carcinoma NST patients it was significantly associated for patients older than 60 years. Lastly, for the ILC subgroup it was only significant for patients older than 70 years. Moreover, not statistically significant but worth mentioning, the upper endpoint of the 95%-CI of the breast MRI HR for patients aged 50-59 years in the invasive carcinoma NST subgroup exceeds the HR towards a worse OS minimally, namely 1.01 with a HR of 0.82. In addition, for the ILC subgroup patients aged <50 the HR was the lowest of all, but with a large 95%-CI (HR 0.54, 95%-CI 0.23-1.24).

The positive association of breast MRI use on OS was also seen in previous studies, however this association was not statistically significant[6,11–14]. Ryu and colleagues indicated in a study of T1-2 breast cancer patients that breast MRI was not associated with a better OS (HR 1.18 95%-CI 0.27-5.08)[12]. In this study the follow-up was not equivalent (median MRI 64.5 months vs non-MRI 78.5 months) and patient characteristics were not completely balanced, the non-MRI group was older and had less hormone therapy. Solin and colleagues indicated in a non-randomized retrospective analysis, that there were no differences between the two groups for OS (univariable HR 0.84, 95%-CI 0.50-1.41, p=0.51)[13]. Unfortunately they did not showed the results of the multivariable model. In a non-randomized retrospective study towards early stage invasive carcinomas treated with breast conservation treatment (BCT), with a median follow-up of 13.8 years, Vapiwala and colleagues indicated that breast MRI had no significant impact on the 15 year OS (MRI group 77% vs 71% non-MRI group, p=0.24)[6]. Choi and colleagues indicated that the MRI group had a tendency towards better survival, however insignificant (univariable HR 0.79, 95%-CI 0.48-1.31, p=0.362)[11]. Unfortunately, they did not include the breast MRI in the multivariable model, so we do not know the adjusted HR. Ha and colleagues studied the effect of preoperative breast MRI solely on ILC patients. Its results showed that the MRI group had a tendency towards better OS, however not statistically significant (HR 0.485, 95%-CI 0.149-1.585, p=0.231)[14]. During this study period the breast MRI protocols were non-uniform. Of the previously mentioned studies, three focused solely on patients undergoing BCT[6,12,13] and two studies included both patients with lumpectomy as mastectomy[11,14]. All studies were based on patients cohorts from single institutions, which may limit the generalizability of their findings[6,11–14]. In addition, the study populations were significant smaller than our study population (range 287-2441) and patient characteristics were not completely balanced, the MRI group were younger and had slightly more favorable tumor characteristics[6,13,14]. The patient characteristics and treatment characteristics within our observational study were not well balanced as well. After further examination of the treatment characteristics, it was somewhat noticeable that patients in the total study population and in the age categories >60 treated with amputation, were slightly more treated with adjuvant radiotherapy in the MRI group, compared to the non-MRI group. Patients in the age category of >70 and treated with lumpectomy, were slightly less treated with adjuvant radiotherapy in the non-MRI group, compared to the MRI group. In both the

invasive carcinoma NST subgroup and the ILC subgroup the same results applied, however in the invasive carcinoma NST subgroup this was less noticeable. In addition, in the ILC subgroup patients in the age category of <50 and treated with lumpectomy, were slightly less treated with adjuvant radiotherapy in the non-MRI group, compared to the MRI group. Although we corrected for the unbalanced patient and treatment characteristics in our multivariable analysis, we still cannot exclude residual confounding.

All the univariable Cox regressions analysis were graphically compared with the Kaplan-Meier curve. Summarized it could be said that the HRs of tumor size 3-4, nodal status 4, molecular subtype HER2 enriched and triple negative, surgical margin more than focal positive, and adjuvant hormonal therapy were not in line with the Kaplan-Meier curves. A cause could be the smaller sample sizes of the categorical subgroup. For the ILC subgroup the adjuvant target therapy was also not in line with the Kaplan-Meier curves. Hence, the HR of all these variables must be interpreted with caution, since the proportional hazard assumption for these seems to be violated. Regarding the multivariable model, the Schoenfeld test showed that the proportional hazard assumption was violated. However, since the sample size is large, the 95% confidence interval will be smaller and therefor minuscule deviations become statistically significant[17]. The plotted scaled Schoenfeld residuals met the appropriate conditions. Some who slightly deviated could be explained by clinical trends. Hence, the proportional hazard assumption of the multivariable model does not seem to be violated.

This study has several strengths and limitations. One strength is the use of a nationwide population-based cancer registry, which increases the generalizability of the results. This also led to a large sample size, which made stratification on the subgroups invasive carcinoma NST and ILC, and the age categories possible, while still having sufficient statistical power. However, since the sample size was large, the confidence intervals were relatively small. It is important to take this in consideration while interpreting the results. Another strength of this study is that it includes several other prospective factors which may influence and adjust the HR of breast MRI, such as the tumor location and type of operation.

A limitation of this study is its retrospective and observational design. An important limitation is that the reasons for performing a MRI were unknown, which leaves room for confounding by indication. Although we corrected for several confounders, other possible confounders, such as comorbidity, were not included. Another limitation of this study is that no information was available on loco-regional and distant recurrences. The disease free survival is important in the diagnostics and treatment of breast cancer patients, so this is a major loss in this study. Another limitation is the maximum follow-up of seven years, which resulted in a mean follow-up of 5.3 years. A longer follow-up would have given more insight into the possible long-term impact of preoperative breast MRI on the OS and would have increased the statistical power to detect clinically relevant differences.

Preoperative breast MRI could be used for optimizing the extent of surgery and radiotherapy, which may lead to improved local control, fewer metastases, and an improved OS. Previous studies have shown that there were no statistically significant differences in OS, however some stated that preoperative breast MRI has a tendency towards improved survival. The purpose of this retrospective population-based study was to evaluate the effect of preoperative breast MRI on OS for invasive breast cancer patients in the Netherlands. Summarized, preoperative breast MRI was significantly associated with a better OS. After adjustment for possible confounders, preoperative breast MRI has still a tendency towards better OS but this was only significant for patients aged >50 in the total study

population, patients aged >60 in the invasive carcinoma NST subgroup, and patients aged >70 in the ILC subgroup. In addition, the HR for patients aged 50-59 in the invasive carcinoma NST subgroup was almost statistically significant and for patients aged <50 in the ILC subgroup, the HR was low but with a large 95%-CI. These results suggest that the indication for preoperative breast MRI use in ILC patients, and in particular young woman, is correct. However, in order to provide a better recommendation for preoperative breast MRI in general use, it is recommended that a next study should focus on the disease free survival with a longer follow-up period. It is also recommended to perform a cost-effectiveness analysis to justify the use of preoperative breast MRI.

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7 Tables and figures

Table 1: Patient, tumor, and treatment characteristics total study population and per subgroup, according to use of breast MRI

	Total study population				Invasive carcinoma NST				ILC			
	non-MRI (n=22,124)		MRI (n=9,632)		non-MRI (n=20,366)		MRI (n=7,386)		non-MRI (n=1,758)		MRI (n=2,246)	
Characteristic	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Age												
Mean (range)	62.9	(19-97)	56.1	(21-94)	62.5	(19-97)	54.8	(21-94)	66.9	(28-93)	60.3	(24-88)
<50	3,092	(14)	2,976	(30.9)	2,936	(14.4)	2,557	(34.6)	156	(8.9)	419	(18.7)
50-59	5,375	(24.3)	2,821	(29.3)	5,083	(25)	2,168	(29.4)	292	(16.6)	653	(29.1)
60-69	7,078	(32)	2,534	(26.3)	6,529	(32.1)	1,834	(24.8)	549	(31.2)	700	(31.2)
>70	6,579	(29.7)	1,301	(13.5)	5,818	(28.6)	827	(11.2)	761	(43.3)	474	(21.1)
Tumor size												
1	15,366	(69.8)	6,223	(65)	14,444	(71.2)	5,072	(69.1)	922	(52.7)	1,151	(51.5)
2	6,115	(27.8)	2,919	(30.5)	5,446	(26.9)	2,074	(28.2)	669	(38.2)	845	(37.8)
3-4	547	(2.5)	436	(4.6)	388	(1.9)	199	(2.7)	159	(9.1)	237	(10.6)
Unknown	96		54		88		41		8		13	
Nodal status												
0	14,831	(68.5)	6,168	(64.7)	13,748	(69)	4,736	(64.8)	1,083	(63.5)	1,432	(64.5)
1	5,313	(24.6)	2,547	(26.7)	4,886	(24.5)	1,989	(27.2)	427	(25)	558	(25.1)
2	928	(4.3)	527	(5.5)	842	(4.2)	396	(5.4)	86	(5)	131	(5.9)
3	566	(2.6)	288	(3)	456	(2.3)	188	(2.6)	110	(6.4)	100	(4.5)
Unknown	486		102		434		77		52		25	
Histological grade												
Low	5,417	(25.3)	2,112	(22.8)	5,167	(26.2)	1,726	(24.2)	250	(14.9)	386	(18)
Medium	9,690	(45.2)	4,614	(49.8)	8,423	(42.7)	3,023	(42.4)	1,267	(75.3)	1,591	(74.1)
High	6,316	(29.5)	2,547	(27.5)	6,150	(31.2)	2,378	(33.4)	166	(9.9)	169	(7.9)
Unknown	701		359		626		259		75		100	
Multifocal												
No	19,579	(89.5)	7,305	(76.1)	18,118	(89.9)	5,630	(76.5)	1,461	(84.8)	1,675	(74.9)
Yes	2,300	(10.5)	2,289	(23.9)	2,039	(10.1)	1,728	(23.5)	261	(15.2)	561	(25.1)
Unknown	245		38		209		28		36		10	
Molecular subtype												
Luminal A	16,531	(77.3)	7,376	(78.3)	14,976	(76)	5,300	(73.3)	1,555	(93)	2,076	(94.4)
Luminal B	1,707	(8)	836	(8.9)	1,651	(8.4)	757	(10.5)	56	(3.3)	79	(3.6)
HER2 enriched	808	(3.8)	372	(3.9)	801	(4.1)	359	(5)	7	(0.4)	13	(0.6)
Triple negative	2,327	(10.9)	842	(8.9)	2,273	(11.5)	811	(11.2)	54	(3.2)	31	(1.4)
Unknown	751		206		665		159		86		47	
Tumor location												
Lateral	10,708	(49.0)	4,302	(45.2)	9,863	(49.0)	3,340	(45.7)	845	(48.9)	962	(43.4)
Medial	4,693	(21.5)	1,830	(19.2)	4,410	(21.9)	1,455	(19.9)	283	(16.4)	375	(16.9)
Other	6,462	(29.6)	3,389	(35.6)	5,861	(29.1)	2,510	(34.4)	601	(34.8)	879	(39.7)
Unknown	261		111		232		81		29		30	
Final operation												
Mastectomy	7,987	(36.1)	4,717	(49)	6,981	(34.3)	3,441	(46.6)	1,006	(57.2)	1,276	(56.8)
Lumpectomy	14,137	(63.9)	4,915	(51)	13,385	(65.7)	3,945	(53.4)	752	(42.8)	970	(43.2)
Surgical margin												
NM	20,207	(93.2)	8,955	(93.7)	18,650	(93.4)	6,899	(94.1)	1,557	(91.7)	2,056	(92.4)
FPM	1,286	(5.9)	530	(5.5)	1,174	(5.9)	391	(5.3)	112	(6.6)	139	(6.3)
MFPM	178	(0.8)	73	(0.8)	149	(0.7)	44	(0.6)	29	(1.7)	29	(1.3)
Unknown	453		74		393		52		60		22	
Adjuvant therapy												
Radio - no	6,668	(30.1)	3,503	(36.4)	5,914	(29)	2,658	(36)	754	(42.9)	845	(37.6)
Radio - yes	15,456	(69.9)	6,129	(63.6)	14,452	(71)	4,728	(64)	1,004	(57.1)	1,401	(62.4)
Chemo - no	14,658	(66.3)	4,872	(50.6)	13,335	(65.5)	3,590	(48.6)	1,323	(75.3)	1,282	(57.1)
Chemo - yes	7,466	(33.7)	4,760	(49.4)	7,031	(34.5)	3,796	(51.4)	435	(24.7)	964	(42.9)
Hormonal - no	10,178	(46)	3,637	(37.8)	9,688	(47.6)	3,119	(42.2)	490	(27.9)	518	(23.1)
Hormonal - yes	11,946	(54)	5,995	(62.2)	10,678	(52.4)	4,267	(57.8)	1,268	(72.1)	1,728	(76.9)
Target - no	20,481	(92.6)	8,663	(89.9)	18,761	(92.1)	6,484	(87.8)	1,720	(97.8)	2,179	(97)
Target - yes	1,643	(7.4)	969	(10.1)	1,605	(7.9)	902	(12.2)	38	(2.2)	67	(3)

Table 2: Results of uni- and multivariable cox proportional hazard regression analysis

	Total study population				Invasive carcinoma NST				ILC			
	Univariable		Multivariable		Univariable		Multivariable		Univariable		Multivariable	
Variable	HR	95%-CI	HR	95%-CI	HR	95%-CI	HR	95%-CI	HR	95%-CI	HR	95%-CI
MRI												
Yes	**0.57	(0.52-0.61)	0.91	(0.74-1.11)	**0.58	(0.53-0.64)	0.96	(0.78-1.19)	**0.41	(0.34-0.50)	0.54	(0.23-1.24)
Age												
<50	**1	-	1	-	**1	-	1	-	**1	-	1	-
50-59	1.04	(0.91-1.19)	*1.25	(1.05-1.49)	1.03	(0.90-1.19)	*1.28	(1.06-1.53)	1.22	(0.74-2.01)	0.92	(0.40-2.10)
60-69	**1.53	(1.35-1.73)	**1.76	(1.49-2.08)	**1.49	(1.31-1.70)	**1.79	(1.51-2.13)	*2.19	(1.39-3.45)	1.45	(0.71-2.98)
>70	**4.83	(4.31-5.40)	**3.52	(2.98-4.16)	**4.62	(4.11-5.19)	**3.49	(2.94-4.15)	**7.69	(5.04-11.74)	**3.72	(1.83-7.56)
MRI#age												
<50	-	-	1	-	-	-	1	-	-	-	1	-
50-59	-	-	0.88	(0.67-1.17)	-	-	0.85	(0.63-1.14)	-	-	1.67	(0.59-4.74)
60-69	-	-	0.88	(0.68-1.15)	-	-	0.83	(0.63-1.10)	-	-	1.67	(0.66-4.19)
>70	-	-	*0.73	(0.57-0.93)	-	-	*0.69	(0.53-0.91)	-	-	1.10	(0.46-2.64)
Tumor size												
1	**1	-	1	-	**1	-	1	-	**1	-	1	-
2	**2.54	(2.37-2.72)	**1.69	(1.56-1.83)	**2.62	(2.44-2.82)	**1.74	(1.60-1.89)	**2.18	(1.78-2.66)	*1.39	(1.10-1.75)
3-4	**4.69	(4.15-5.30)	**2.30	(1.99-2.66)	**5.38	(4.65-6.23)	**2.33	(1.97-2.76)	**3.86	(3.01-4.95)	**2.02	(1.50-2.72)
Nodal status												
0	**1	-	1	-	**1	-	1	-	**1	-	1	-
1	**1.54	(1.43-1.66)	**1.66	(1.52-1.80)	**1.53	(1.41-1.66)	**1.66	(1.52-1.81)	**1.59	(1.28-1.97)	**1.67	(1.33-2.11)
2	**2.93	(2.61-3.28)	**3.46	(3.03-3.95)	**3.06	(2.71-3.45)	**3.55	(3.08-4.10)	**2.21	(1.58-3.09)	**3.01	(2.09-4.36)
3	**5.45	(4.86-6.11)	**6.01	(5.22-6.92)	**5.17	(4.53-5.91)	**5.98	(5.09-7.03)	**6.39	(5.04-8.12)	**6.11	(4.59-8.13)
Hist. grade												
Low	**1	-	1	-	**1	-	1	-	**1	-	1	-
Medium	**1.49	(1.35-1.64)	**1.27	(1.14-1.41)	**1.43	(1.29-1.60)	**1.26	(1.13-1.41)	*1.51	(1.14-2.00)	1.28	(0.95-1.71)
High	**2.70	(2.45-2.98)	**1.97	(1.75-2.21)	**2.74	(2.47-3.04)	**1.97	(1.74-2.23)	**2.56	(1.80-3.64)	*1.92	(1.32-2.78)
Multifocal												
Yes	*1.10	(1.01-1.21)	£	-	*1.11	(1.01-1.23)	£	-	1.03	(0.83-1.27)	£	-
Mol. subtype												
Luminal A	**1	-	1	-	**1	-	1	-	**1	-	1	-
Luminal B	1.00	(0.88-1.13)	*1.23	(1.06-1.42)	1.02	(0.89-1.16)	*1.26	(1.08-1.47)	1.02	(0.62-1.69)	1.10	(0.66-1.84)
HER2 enriched	**1.75	(1.51-2.02)	**1.41	(1.17-1.69)	**1.78	(1.54-2.06)	**1.43	(1.18-1.73)	*2.69	(1.20-6.02)	1.59	(0.67-3.78)
Triple negative	**2.52	(2.32-2.74)	**1.74	(1.54-1.96)	**2.55	(2.34-2.77)	**1.71	(1.50-1.94)	**4.23	(2.97-6.02)	*1.85	(1.20-2.86)
Tumor location												
Lateral	**1	-	1	-	*1	-	1	-	1	-	£	-
Medial	1.00	(0.91-1.09)	*1.10	(1.01-1.21)	1.01	(0.92-1.11)	*1.12	(1.02-1.23)	0.93	(0.71-1.22)	-	-
Other	**1.18	(1.09-1.26)	1.07	(1.00-1.16)	**1.18	(1.09-1.28)	*1.11	(1.02-1.20)	1.14	(0.94-1.38)	-	-
Final operation												
Lumpectomy	**0.41	(0.38-0.44)	*1.20	(1.07-1.34)	**0.41	(0.39-0.44)	**1.27	(1.12-1.43)	**0.33	(0.27-0.41)	£	-
Surg. marg.												
NM	**1	-	1	-	**1	-	1	-	*1	-	£	-
FPM	0.90	(0.77-1.04)	*1.19	(1.02-1.38)	0.92	(0.79-1.08)	*1.23	(1.05-1.45)	0.76	(0.51-1.15)	-	-
MFPM	**2.16	(1.67-2.80)	**1.85	(1.43-2.40)	**2.01	(1.49-2.72)	**1.88	(1.38-2.56)	**2.63	(1.60-4.33)	-	-
Adj. therapy												
Radio - yes	**0.48	(0.45-0.51)	**0.45	(0.40-0.50)	**0.47	(0.44-0.50)	**0.43	(0.38-0.48)	**0.59	(0.49-0.70)	**0.54	(0.45-0.66)
Chemo - yes	**0.56	(0.52-0.61)	**0.63	(0.57-0.70)	**0.59	(0.55-0.64)	**0.65	(0.58-0.73)	**0.39	(0.31-0.49)	**0.56	(0.41-0.76)
Hormonal - yes	**0.84	(0.78-0.89)	**0.74	(0.67-0.81)	**0.82	(0.77-0.88)	**0.74	(0.67-0.82)	0.87	(0.71-1.05)	*0.73	(0.57-0.94)
Target - yes	**0.50	(0.42-0.58)	**0.50	(0.41-0.62)	**0.48	(0.40-0.56)	**0.45	(0.37-0.56)	1.00	(0.57-1.73)	£	-

Abbreviations (new): MRI#age = interaction term MRI and age per category; Hist. grade = Histological grade; Mol. Subtype = Molecular subtype; Adj. therapy = Adjuvant therapy

* p<0.05

** p<0.000

£ excluded due to AIC selection method

Table 3: Calculated HR breast MRI per subgroup and age category, based on the multivariable model.

	Total study-population [a]			Invasive carcinoma NST [a]			ILC [b]		
Age category	HR	95%-CI	*p*-value	HR	95%-CI	*p*-value	HR	95%-CI	*p*-value
<50	0.91	(0.74-1.11)	0.346	0.96	(0.78-1.19)	0.728	0.54	(0.23-1.24)	0.146
50-59	0.80	(0.66-0.97)	0.020	0.82	(0.67-1.01)	0.055	0.90	(0.49-1.66)	0.731
60-69	0.80	(0.68-0.94)	0.007	0.80	(0.67-0.96)	0.016	0.89	(0.61-1.31)	0.567
>70	0.66	(0.57-0.76)	0.000	0.67	(0.56-0.79)	0.000	0.59	(0.46-0.76)	0.000

a : adjusted for the variables tumor size, nodal status, histological grade, molecular subtype, tumor location, final operation, surgical margin, radiotherapy, chemotherapy, hormonal therapy, and target therapy.

b : adjusted for the variables tumor size, nodal status, histological grade, molecular subtype, radiotherapy, chemotherapy, and hormonal therapy.

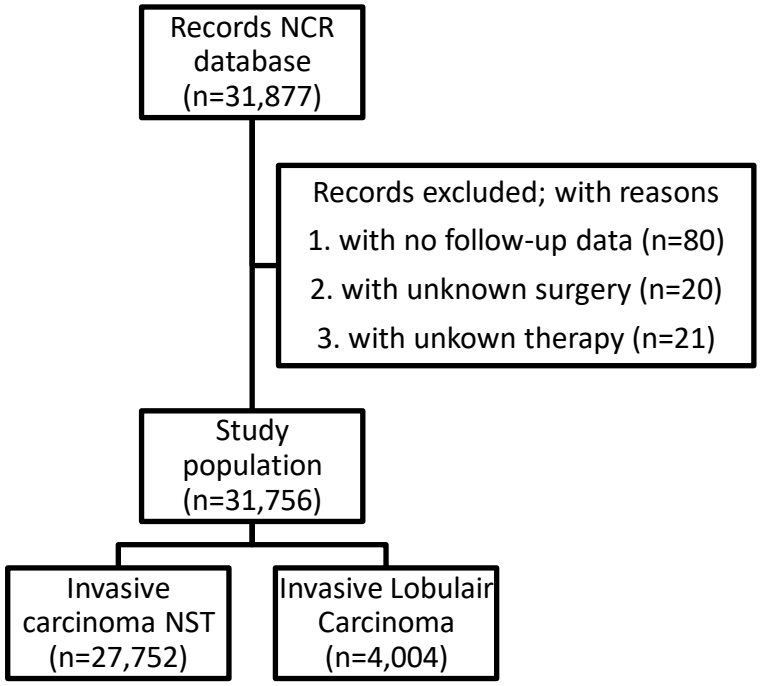
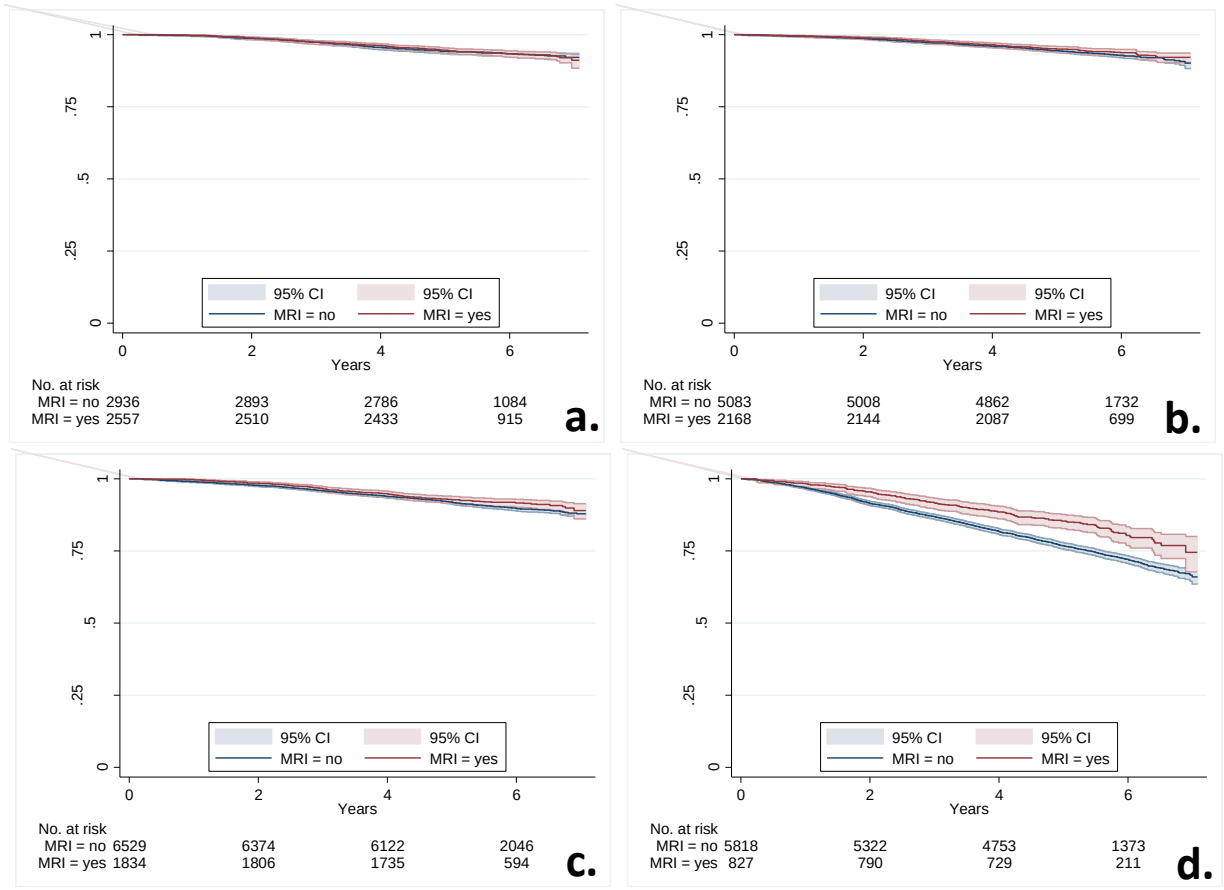
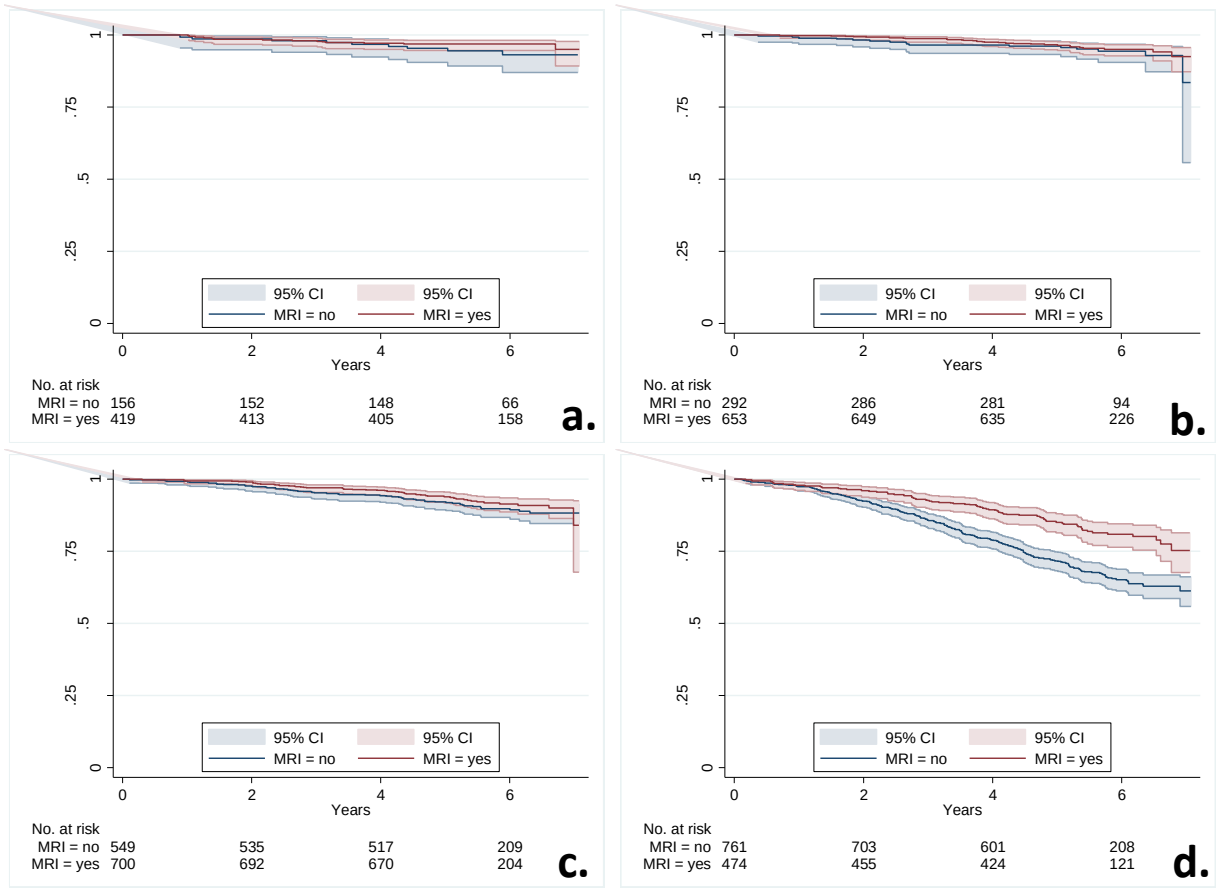


Figure 1: Flowchart exclusion study population



a. age <50 years. b. age 50-59 years. c. age 60-69 years. d. age >70 years.

Figure 2: Kaplan-Meier curve of survival function subgroup invasive carcinoma NST, stratified per age category



a. age <50 years. b. age 50-59 years. c. age 60-69 years. d. age >70 years.

Figure 3: Kaplan-Meier curve of survival function subgroup ILC, stratified per age category

8 Appendix

8.1 Comparison imputed data

Table 4: Comparison proportions original data vs imputed data

Variable		Original	Imputed	Difference
Tumor size	1	68.3	68.9	0.6
	2	28.6	28.1	-0.5
	3	2.6	2.8	0.2
	4	0.5	0.2	-0.3
Nodal status	0	67.4	78.7	11.3
	1	25.2	17.9	-7.4
	2	4.7	2.3	-2.4
	3	2.7	1.2	-1.5
Histological grade	Low	24.5	32.9	8.4
	Medium	46.6	44.4	-2.2
	High	28.9	22.7	-6.1
Multifocal	Yes	85.4	88.8	3.3
	No	14.6	11.2	-3.3
Molecular subtype	Luminal A	77.6	82.7	5.0
	Luminal B	8.3	5.3	-3.0
	HER2 enriched	3.8	3.8	-0.1
	Triple negative	10.3	8.3	-2.0
Tumor location	Lateral	47.8	47.7	-0.2
	Medial	20.8	20.5	-0.3
	Other	31.4	31.8	0.4
Surgical margin	NM	93.4	93.1	-0.3
	FPM	5.8	6.1	0.2
	MFPM	0.8	0.9	0.1

Table 5: Comparison means original data vs imputed data

Variable	Original	imputation
Tumor size	1.35	1.35
Nodal status	1.43	1.42
Histological grade	2.04	2.04
Multifocal	0.15	0.15
Molecular subtype	1.47	1.47
Tumor location	1.84	1.84
Surgical margin	1.07	1.07

8.2 Events per subgroup, stratified by age categories

Table 6: Events of death stratified by age categories

	Total study population		Invasive carcinoma NST		ILC	
	Non-MRI	MRI	Non-MRI	MRI	Non-MRI	MRI
Age categories	n (%)*	n (%)*	n (%)*	n (%)*	n (%)*	n (%)*
<50	193 (6.2)	169 (5.7)	184 (6.3)	155 (6.1)	9 (5.8)	14 (3.3)
50-59	349 (6.5)	153 (5.4)	333 (6.6)	124 (5.7)	16 (5.5)	29 (4.4)
60-69	651 (9.2)	197 (7.8)	598 (9.2)	145 (7.9)	53 (9.7)	52 (7.4)
>70	1,745 (26.5)	224 (17.2)	1,500 (25.8)	143 (17.3)	245 (32.2)	81 (17.1)

* Percentage of deaths within whole age category

8.3 Survival function and log-rank test

Table 7: Overview total study population survival function per year, non-MRI vs MRI

	Non-MRI				MRI			
Year	Beginning total	Fail	Survivor function	95%-CI	Beginning total	Fail	Survivor function	95%-CI
0	0	0	1.00	.	0	0	1.00	.
1	21813	299	0.99	(0.98-0.99)	9580	45	1.00	(0.99-1.00)
2	21277	516	0.96	(0.96-0.97)	9460	107	0.98	(0.98-0.99)
3	20691	569	0.94	(0.93-0.94)	9278	168	0.97	(0.96-0.97)
4	20070	599	0.91	(0.91-0.91)	9119	145	0.95	(0.95-0.96)
5	13661	521	0.88	(0.88-0.89)	6110	153	0.93	(0.93-0.94)
6	6836	314	0.86	(0.85-0.86)	3139	86	0.92	(0.91-0.92)
7	535	120	0.83	(0.82-0.83)	223	39	0.89	(0.87-0.90)

Table 8: Overview results Log-rank test per subgroup and age category

	Total study population	Invasive carcinoma NST	ILC
Age group	*p*-value	*p*-value	*p*-value
<50	0.43	0.85	0.20
50-59	0.08	0.24	0.51
60-69	0.04	0.09	0.26
>70	<0.0000	<0.0000	<0.0000