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Original Research

Breast cancer mortality of older patients with and without recurrence analysed by novel multi-state models

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Abstract ***Introduction:*** In older patients with breast cancer, the risk of dying from other causes than breast cancer strongly increases after the age of 70. The aim of this study was to assess contributions of breast cancer mortality versus other-cause mortality after locoregional or distant recurrence in a population-based cohort of older patients analysed by multi-state models.

Methods: Surgically treated patients ≥70 years diagnosed with stage I-III breast cancer in 2003–2009 were selected from the Netherlands Cancer Registry. A novel multi-state model with locoregional and distant recurrence that incorporates relative survival was fitted. Other-cause and breast cancer mortality were indicated as population and excess mortality.

Results: Overall, 18,419 patients were included. Ten-year cumulative incidences of locoregional and distant recurrence were 2.8% (95%CI 2.6–3.1%) and 12.5% (95%CI 11.9–13.1%). Other-cause mortality increased from 23.9% (95%CI 23.7–24.2%) in patients 70–74 years to 73.8% (95%CI 72.2–75.4%) in those ≥80 years. Ten-year probabilities of locoregional or distant recurrence with subsequent breast cancer death were 0.4–1.3% and 10.2–14.6%, respectively. For patients with a distant recurrence in the first two years after diagnosis, breast cancer death probabilities were 95.3% (95%CI 94.2–96.4%), 93.1% (95%CI 91.6–94.6%), and

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88.6% (95%CI 86.5–90.8%) in patients 70–74, 75–79, and ≥80 years.
Conclusion: In older patients without recurrence, prognosis is driven by other-cause mortality. Although locoregional recurrence is a predictor for worse outcome, given its low incidence it contributes little to breast cancer mortality after diagnosis. For patients who develop a distant recurrence, breast cancer remains the dominant cause of death, even at old age.

1. Introduction

The number of older patients with breast cancer will further increase in the upcoming years due to ageing of the population [1]. Despite having breast cancer, older patients often die from causes unrelated to breast cancer due to the shorter life expectancy and increasing co-morbidity burden with age [2–5]. Above the age of 70 years, the risk of dying from other causes strongly increases [6,7]. It is therefore essential to consider this competing mortality risk while estimating prognosis in older patients [6,8] However, the impact of competing mortality after breast cancer recurrence has not been extensively studied so far, because most studies treat recurrence as an end-point of the study and do not investigate what happens after this end-point. This is an omission since more insight in the age-dependent prognosis after recurrence can help inform treatment decisions.

Locoregional recurrence rates (LRR) have greatly diminished over the last two decades due to advances in treatment modalities and patient selection for treatments [9–11]. Recent data showed that 4% of all-aged patients diagnosed with stage II or stage III experiences a LRR [11]. Yet, LRR remains a predictor for worse overall and breast cancer survival in line with previous data, possibly because this may be associated with concurrent micrometastases [10–13]. Prognosis after developing a distant recurrence (DR) is generally poor with a median time to death of 2.0 years [14]. However, the time to death is highly variable from several months up to more than ten years, which also leaves room for improving outcome prediction by taking into account age-related mortality [14].

To our knowledge, no previous study has investigated the proportion of breast cancer versus other-cause mortality after LRR and DR [15,16]. We were capable of filling this gap thanks to our newly developed model in which we integrated relative survival techniques into a multi-state model, which enabled us to analyse observed events (recurrence and death) and unobserved events (cause of death) simultaneously. Therefore, the aim of this study was to assess all long-term outcomes in one integrated model and to compare them for different age groups. The study was performed in a nationwide population-based cohort of 18,419 older patients with stage I-III breast cancer with good quality long-term follow-up data.

2. Methods

All surgically treated patients aged 70 years or older diagnosed with stage I-III breast cancer between 2003 and 2009 were selected from the Netherlands Cancer Registry (NCR) and included in this study. The NCR is a nationwide database on cancer diagnosis and treatment, hosted by the Netherlands Comprehensive Cancer Organization. The NCR receives reports of diagnosed malignancies from the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA) which are confirmed and completed by the national hospital discharge databank. The interval 2003 to 2009 was chosen to allow sufficiently long follow-up.

Data managers from NCR collect data on diagnosis, staging and treatment from medical records using international coding rules. Breast cancer stage is defined according to the sixth edition of the TNM classification of malignant tumours [17]. Clinical T or N stage was used when the pathological stage was unknown. Oestrogen receptor and progesterone receptor status were defined positive if ≥ 10% of the tumour cells showed positive nuclear staining. The cohort consists of two separate sub-cohorts for which different follow-up information was available due to logistic reasons. Sub-cohort I contained patients diagnosed from 2003 to 2006 for which follow-up was artificially censored at 5 years, and in case of a LRR a consecutive DR was not recorded. In our analysis, these patients were censored at LRR (n = 371). Sub-cohort II contained patients diagnosed from 2007 to 2009. For this cohort follow-up was not censored at a particular time, and a DR after a LRR was recorded. Both sub-cohorts were analysed together, considering all censoring as non-informative. Vital status was available until 31 January 2017 through linkage of NCR data with the Municipal Personal Records database.

Study end-points were breast cancer mortality and other-cause mortality from diagnosis, after LRR, and after DR by age group over time. Survival time was defined as the time from diagnosis or landmark until death, with censoring of patients still alive at last follow-up visit. Breast cancer mortality was defined as death

due to breast cancer or possibly due to its treatment in patients without a recurrence, whereas other-cause mortality was mortality that the patients would also have experienced independent of their disease.

LRR was defined as breast cancer in the ipsilateral breast, ipsilateral thoracic wall or ipsilateral lymph nodes [18]. If a patient presented with a LRR and DR at the same time, the patient was classified as having a DR given the impact on prognosis.

2.1. Statistical analysis

Median follow-up duration was calculated using the reverse Kaplan–Meier method [19]. Cumulative incidences of recurrence were calculated by using competing risks methodology [20], to take into account that patients with certain 'competing' events are no longer at risk for the primary event. Death was considered a competing event for both LRR and DR. In addition, DR was considered a competing event for LRR.

Breast cancer mortality and other-cause mortality after diagnosis, after LRR, and after DR were assessed with a multi-state model with LRR and DR as intermediate events [15,21]. The novelty of this multi-state model is that cause-specific mortality outcomes are estimated separately after diagnosis, LRR and DR, thus combining observed transitions (to recurrence and death) and unobserved transitions (population and excess death). Fig. 1 shows the multi-state model. Statistical methods from the field of relative survival were used because individual data on cause of death were not available. Moreover, in older patients with early stage breast cancer, the cause of death often cannot be reliably ascertained. Using relative survival all mortality can be split in population and excess mortality. This method compares mortality in a study population to mortality in the general population matched by age, sex and year of diagnosis using country-specific life tables from the Human Mortality Database [22]. The observed (or total) death hazard is then assumed to be the sum of the population hazard and the excess hazard. In this study, excess mortality is indicated as breast cancer-related mortality. The population mortality is referred to as other-cause mortality.

The relative survival technique can be used in patient populations in which the other-cause mortality risk is equal to that in the general population [23,24]. This is a reasonable assumption for older patients with breast cancer. First, it has been demonstrated that patients with breast cancer have similar comorbidity compared to the general population [25]. Second, for women aged 65 years and older, there is no longer a disparity in breast cancer incidence by socioeconomic status [26]. Third, since our cohort is population-based, there was no selection of healthier patients in the study.

Finally, analyses were performed using landmark models describing the outcomes of patients who were alive 2 years after diagnosis and had developed a LRR or DR before. To investigate the impact of the choice of the landmark, we performed several sensitivity

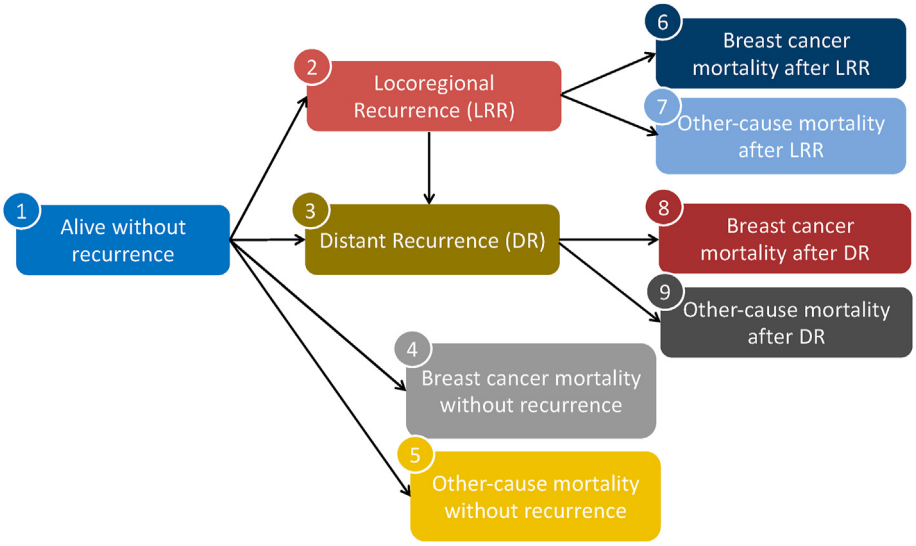

Fig. 1. The multi-state relative survival model. All patients start in the state alive without recurrence (state 1). They can progress to locoregional recurrence (state 2), distant recurrence (state 3) or death (states 4 to 9). The model separates breast cancer mortality and other-cause mortality. Each arrow indicates the transition to the next state. Locoregional recurrence and distant recurrence are intermediate states between being alive without recurrence and death, which change the hazards for breast cancer and other-cause mortality, respectively. It cannot be discerned for individual patients if they die due to breast cancer or other-cause mortality. Techniques from relative survival are used to model this distinction, assuming that the hazard of other cause mortality is equal to that in the matched general population and that the remainder (observed minus population mortality) can be considered as breast cancer mortality, i.e. excess mortality due to the disease or possibly its treatment.

analyses: different landmark times were chosen and analyses were performed in which LRR or DR was the starting point. The potential differential impact of early and late DR was investigated by separately analysing survival after early (first three years after diagnosis) and later recurrence.

All analyses were performed in R version 3.6.2 (https://cran.r-project.org/), packages 'survival', 'prodlim', 'relsurv' and 'mstate', extended with functions specifically written for this new model [20,21].

3. Results

3.1. Patients

Between 2003 and 2009, 19,748 patients aged 70 years or older diagnosed with stage I-III breast cancer underwent surgery. Of these patients, 18,419 patients with available follow-up were included. Baseline characteristics are described in Table 1. At time of diagnosis, 7793 patients (42.3%) were aged 70–74 years, 4332 patients (23.5%) were aged 75–79 years, and 6294 patients (34.2%) were aged 80 years or older. Fifty-three percent received adjuvant endocrine therapy, and 1% was treated with adjuvant chemotherapy. Baseline characteristics per age group are described in Table S1.

Table 1
Patient, disease and treatment characteristics at diagnosis of the 18,419 patients in the study.

	N (%)
Age (years)	
70–74	7793 (42)
75–79	4332 (24)
≥80	6294 (34)
No. of comorbidities	
0	2205 (29)
1–2	4008 (53)
≥3	1296 (17)
Unknown	10,910
Stage	
I	7752 (42)
II	8176 (44)
III	2463 (13)
Unknown	28
Histological grade	
1	4198 (24)
2	8390 (49)
3	4587 (27)
Unknown	1244
Hormone-receptor status	
ER and/or PR positive	15,053 (86)
ER and PR negative	2446 (14)
Unknown	920
Her2-receptor status	
Negative	11,178 (90)
Positive	1302 (10)
Unknown	5939
Type of surgery	
Mastectomy	11,111 (60)
BCS	7308 (40)
Surgical margins	
Free	17,204 (96)
Not free	807 (4)
Unknown	408
Radiotherapy after BCS	
Yes	6761 (93)
No	547 (7)
Adjuvant endocrine therapy[a]	
Yes	8026 (53)
No	7027 (47)
Adjuvant chemotherapy	
Yes	276 (1)
No	18,143 (99)

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; BCS, breast-conserving surgery.
[a] Percentage of the 15,053 hormone-receptor positive patients.

3.2. Outcomes

Of cohort I, 15 patients (0.1%) were lost to follow up before 5 years. In cohort II, median follow-up was 9.0 years (95% CI 9.0–9.1). The number of patients in follow-up is shown in Fig. S1. Outcomes stratified by age are shown in Fig. 2, and corresponding 5 and 10-year mortality outcome probabilities in Table 2. Ten-year probabilities of DR with subsequent breast cancer death were 10.2% (95%CI 9.1–11.3%), 14.6% (95%CI 13.3–15.8%), and 10.9% (95% CI 9.9–11.8%) for patients aged 70–74 years, 75–79 years, and ≥80 years respectively. For all age groups, few LRR with subsequent breast cancer death were observed (≤1.3%) or breast cancer mortality in patients without a recurrence (≤1.9%).

3.3. Locoregional recurrence

Breast cancer and other-cause mortality probabilities after LRR are shown in Table 3 and Fig. S2. For patients alive after LRR at two years after diagnosis (and without a DR in this timeframe), the 10-year other-cause mortality probabilities were 16.2% (95%CI 11.7–20.6%), 30.9% (95%CI 21.9–39.8%), and 48.3% (95%CI 27.7–68.9%) in patients aged 70–74 years, 75–79 years, and ≥80 years respectively. Overall, the 10-year probabilities of breast cancer mortality were 48.3% (95%CI 23.2–73.5%), 35.4% (95%CI 6.7–64.2%), and 41.3% (95%CI 12.6–70.0%) respectively. For patients alive after LRR at two years after diagnosis, the 10-year probabilities of DR with subsequent breast cancer death were 32.0% (95%CI 8.7–55.4%), 28.2% (95%CI 8.0–48.4%), and 12.7% (95%CI 0–28.1%), respectively. Setting the landmark at 1 year led to worse outcomes at 10 years.

3.4. Distant recurrence

Breast cancer and other-cause mortality probabilities after DR are shown in Table 4 and Fig. S3. After a DR in the first two years after diagnosis for patients still

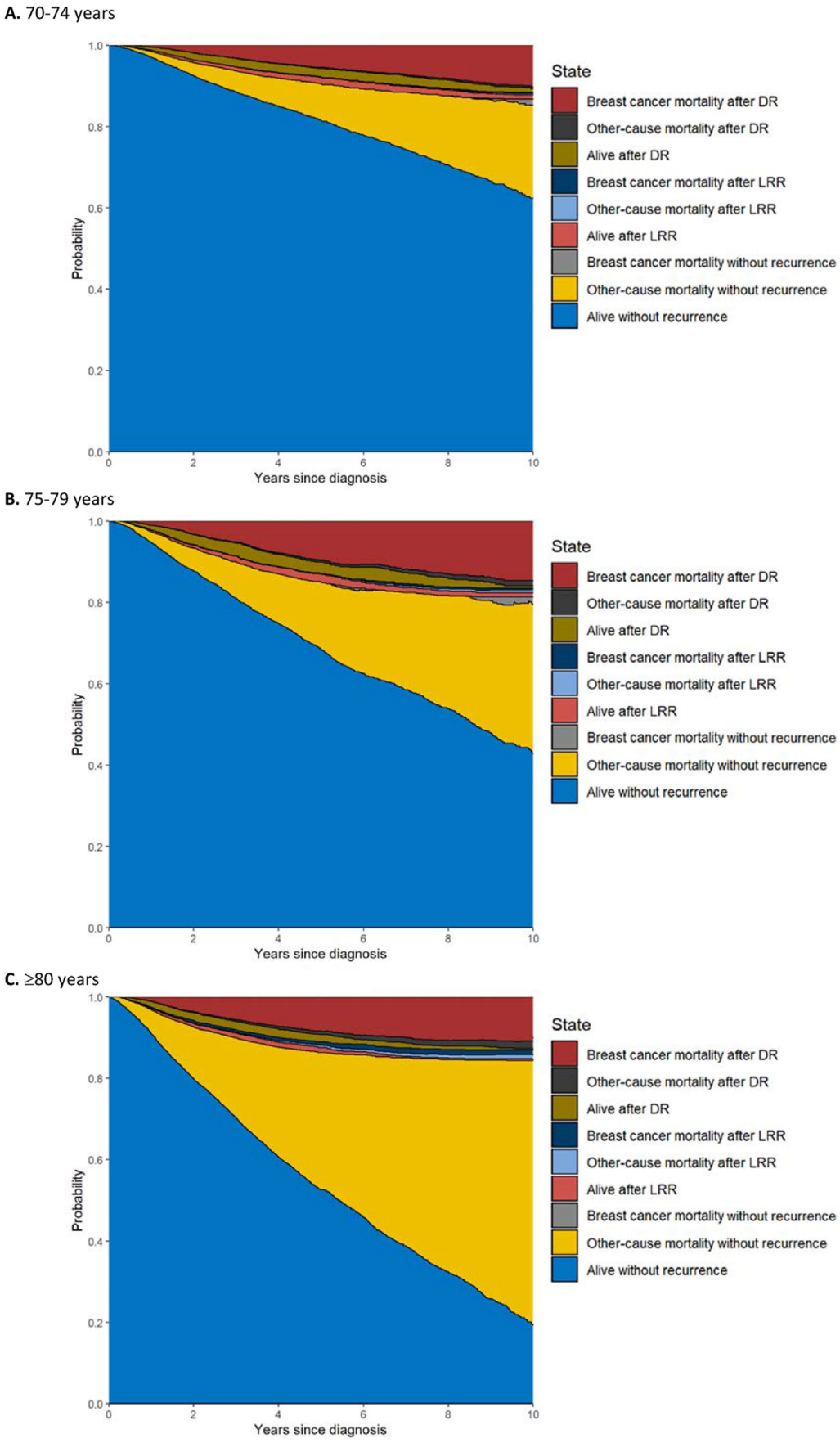

Fig. 2. Outcome probabilities since diagnosis based on the multi-state model (see Fig. 1). Curves are stacked, meaning that the probabilities of the different outcomes are indicated by the distances between the lines. Probabilities are displayed for three age groups: **A.** 70–74 years. **B.** 75–79 years. and **C.** ≥80 years. Abbreviations: DR, distant recurrence; LRR, locoregional recurrence.

Table 2
Five- and ten-year breast cancer mortality and other-cause mortality probabilities (in %) from time of first diagnosis of breast cancer according to state from where the patients died (no recurrence, locoregional recurrence, and distant recurrence) stratified by age group. 'Overall' indicates the sum of mortality from the no recurrence, locoregional and distant recurrence states (all mortality).

State	Without recurrence		Locoregional recurrence		Distant recurrence		Overall	
	Breast cancer mortality % (95% CI)	Other-cause mortality % (95% CI)	Breast cancer mortality % (95% CI)	Other-cause mortality % (95% CI)	Breast cancer mortality % (95% CI)	Other-cause mortality % (95% CI)	Breast cancer mortality % (95% CI)	Other-cause mortality % (95% CI)
At 5 years								
70–74 years	−0.9 (−0.3; 0)[a]	9.9 (9.8–10.0)	0 (0–0.3)	0.1 (0.1–0.1)	5.5 (5.0–6.0)	0.2 (0.2–0.2)	4.6 (3.8–5.4)	10.2 (9.5–14.5)
75–79 years	−0.6 (0–0.6)[a]	17.1 (16.8–17.3)	0 (0–0.3)	0.2 (0.2–0.3)	9.5 (8.8–10.3)	0.5 (0.4–0.6)	8.9 (7.3–10.5)	17.8 (17.6–18.0)
≥80 years	−6.1 (−4.7; 0)[a]	39.9 (39.3–40.5)	0.8 (0.2–1.3)	0.5 (0.3–0.8)	8.3 (7.7–9.0)	0.9 (0.8–1.0)	3.0 (1.3–4.8)	41.3 (40.6–42.0)
At 10 years								
70–74 years	1.4 (0–3.5)	23.0 (22.7–23.3)	0.4 (0–0.9)	0.3 (0.3–0.4)	10.2 (9.1–11.3)	0.5 (0.4–0.6)	12.0 (9.4–14.2)	23.9 (23.6–24.2)
75–79 years	1.9 (0–5.3)	36.7 (36.0–37.5)	0.4 (0–1.1)	0.7 (0.5–1.0)	14.6 (13.3–15.8)	1.3 (1.0–1.6)	16.8 (13.0–20.6)	38.8 (37.9–39.6)
≥80 years	−5.5 (−2.4; 0)[a]	70.5 (68.8–72.2)	1.3 (0.6–1.9)	1.0 (0.5–1.5)	10.9 (9.9–11.8)	1.7 (1.4–2.1)	6.6 (2.8–10.4)	73.3 (71.4–75.2)

Abbreviations: CI, confidence interval.
[a] Since the total and population hazard must always be positive, their difference (the excess hazard) can under rare circumstances be negative, leading to negative probabilities. Although contra-intuitive, these negative quantities can be interpreted as meaning that for certain patient groups the survival is better than that of the general population since they represent a relatively fit group.

Table 3
Five- and ten-year breast cancer mortality and other cause mortality probabilities (in %) from time of diagnosis for patients alive and in the locoregional recurrence state at the two-year landmark by age group. 'Overall' indicates the sum of mortality from the locoregional and distant recurrence states.

	Locoregional recurrence		Distant recurrence		Overall	
	Breast cancer mortality % (95% CI)	Other-cause mortality % (95% CI)	Breast cancer mortality % (95% CI)	Other-cause mortality % (95% CI)	Breast cancer mortality % (95% CI)	Other-cause mortality % (95% CI)
At 5 years						
70–74 years	3.0 (0–20.0)	5.1 (3.6–6.5)	16.5 (0–35.7)	0.7 (0–1.4)	19.5 (0–41.6)	5.7 (5.0–6.5)
75–79 years	−7.0 (0–3.4)	11.9 (9.4–14.3)	13.7 (0–29.3)	0.9 (0–1.8)	6.7 (0–27.2)	12.7 (10.7–14.8)
≥80 years	8.4 (0–35.8)	28.1 (17.5–38.7)	6.8 (0–20.6)	0.9 (0–2.8)	15.2 (0–43.3)	29.0 (19.4–38.7)
At 10 years						
70–74 years	16.3 (0–38.2)	14.4 (9.0–19.8)	32.0 (8.7–55.4)	1.7 (0.6–2.8)	48.3 (23.2–73.5)	16.2 (11.7–20.6)
75–79 years	7.2 (0–30.0)	27.6 (18.2–36.9)	28.2 (8.0–48.4)	3.3 (1.2–5.4)	35.4 (6.7–64.2)	30.9 (21.9–39.8)
≥80 years	28.6 (0–57.2)	45.5 (22.7–68.3)	12.7 (0–28.1)	2.8 (0–5.6)	41.3 (12.6–70.0)	48.3 (27.7–68.9)

Abbreviations: CI, confidence interval.

Table 4
Five- and ten-year breast cancer mortality and other-cause mortality probabilities (in %) from time of diagnosis for patients alive and in the distant recurrence state at the two-year landmark by age group.

	Breast cancer mortality % (95% CI)	Other-cause mortality % (95% CI)
At 5 years		
70–74 years	82.2 (78.3–86.0)	2.8 (2.5–3.2)
75–79 years	84.3 (80.9–87.8)	5.0 (4.4–5.6)
≥80 years	83.4 (80.0–87.2)	9.6 (8.0–11.1)
At 10 years		
70–74 years	95.3 (94.2–96.4)	3.8 (3.2–4.4)
75–79 years	93.1 (91.6–94.6)	6.3 (5.3–7.4)
≥80 years	88.6 (86.5–90.8)	11.1 (9.0–13.1)

Abbreviations: CI, confidence interval.

alive at the two-year landmark, the 5-year probabilities of breast cancer mortality were 82.2% (95%CI 78.3–86.0%), 84.3% (95%CI 80.9–87.8%), and 83.4% (95%CI 80.0–87.2%) in patients aged 70–74 years, 75–79 years, and ≥80 years respectively. Ten-year probabilities were 95.3% (95%CI 94.2–96.4%), 93.1% (95%CI 91.6–94.6%), and 88.6% (95%CI 86.5–90.8%) respectively. The 10-year other-cause mortality probabilities were 3.8% (95%CI 3.2–4.4%), 6.3% (95%CI 5.3%–7.4%), and 11.1% (95%CI 9.0%–13.1%) respectively.

Setting the landmarks at 1 or 3 years only led to minimal changes. Breast cancer mortality was the 10 year-outcome for more than 90% of patients below the age of 80. When the moment of DR was taken as starting point of the analysis, outcomes were somewhat better for patients with a recurrence later than 3 years after diagnosis (Table S2).

4. Discussion

This study showed that other-cause mortality is by far outweighed by the high breast cancer mortality following a DR. Although older patients mostly die

from other causes, after developing a DR, the prognosis seems to be only determined by breast cancer. The different sensitivity analyses showed that, although age and moment of recurrence had some impact on outcomes, in all situations and independent of the model chosen, breast cancer mortality was high in the years following the recurrence. A previous hospital-based cohort study had similar findings, however other-cause mortality was not separated and probably less pronounced since no age selection-criteria were used [14].

In line with previous literature [10–13], LRR was a predictor for worse prognosis. For patients younger than 80 years, the 10-year probability of breast cancer mortality was 12–17%, whereas after developing a LRR, 49–53% of the patients died from breast cancer. Yet, it should be emphasised that for the whole cohort the chances of dying from breast cancer after a LRR are very low with 10-year probabilities between 0.8% and 1.5%. This is a result of the very low rates of LRR in the modern era.

We hypothesise that some patients already had distant (micro) metastases at time of LRR detection as many died without developing a DR first. This is supported by recent data showing that 27% of the patients who initially presented with a LRR were found to have synchronous DR [11]. Similarly, in our own cohort, 28% of the patients with a LRR had a DR at the same time (which were classified according to the latter). Furthermore, the classification of LRR has changed since these data have been collected. Nowadays, contralateral tumours are not considered as recurrence, and a better distinction between ipsilateral second primary tumours and recurrences is possible. This implies that a modern patient with a LRR might even have a worse prognosis than the patients in the study since second primary tumours generally have a better prognosis than recurrences.

The multi-state model allows to estimate treatment-related mortality [15]. As patients with breast cancer have to develop a recurrence before dying from breast cancer, excess mortality in patients without a recurrence can be interpreted as treatment-related mortality. The treatment-related mortality at 10 years was 1–2% for patients younger than 80 years in our cohort. Since patients over 70 years were not treated with chemotherapy conform the Dutch treatment guideline, this is expected to be related to endocrine therapy such as tamoxifen-related thromboembolic events. Although breast cancer treatments are generally considered as low risk treatments, it is reassuring that our findings can confirm this for the older population in which predisposed factors related to ageing could increase the morbidity risk. Moreover, this is another indication of the quality of the data since unrecorded distant recurrences would falsely have resulted in breast cancer mortality in patients without a recurrence; the low probability of this event shows that underreporting was no serious issue.

Our finding that LRR and DR were strong predictors for breast cancer death reasons against omitting treatments in older patients with recurrent breast cancer because of the competing mortality risk. Recent population-based data showed an improvement in relative survival over time for patients aged $\geq$75 years with stage IV breast cancer, together with the increased use of CDK4/6 inhibitors [27]. Relative survival had also improved for patients aged 65–75 years with stage III breast cancer which was most likely explained by an increase in adjuvant chemotherapy [27]. These findings emphasise that at least some older patients will benefit from more extensive treatment.

This study was the first study to assess the occurrence of other-cause mortality after locoregional and distant recurrence separately which was possible thanks to the integration of methods from relative survival into a multi-state model. Furthermore, we used a large nationwide population-based cohort with detailed baseline information, long follow-up and available recurrence status. A limitation was that patients over 80 years had a better life expectancy than the matched general population (reflected in the negative breast cancer mortality probability in patients without a recurrence due to a larger expected other-cause mortality than the actual observed mortality). This indicates that the relative survival assumption that the patient population is a random subset of the general population was violated for the oldest patients. This is likely explained by the selection of surgically treated patients as frail patients may receive primary endocrine treatment instead (approximately 30% with hormone-receptor positivity) [28]. Although this might lead to a small overestimation of other-cause mortality for the oldest age group, the general patterns are not affected by this.

In conclusion, our findings indicate that other-cause mortality plays a negligible role in the outcome of older patients once they develop a DR. LRR is a predictor for worse prognosis, yet leads to a small contribution of breast cancer death after LRR for the whole cohort since the incidence of LRR is low. Future studies need to investigate how these outcomes can be accurately incorporated in clinical prediction tools that could improve individualised treatments in older patients with breast cancer.

Author contribution

Conceptualisation and methodology: AB, LW. Data acquisition: EB, LM. Formal analysis: LW. Software: DM, JS, HP, LW. Interpretation: AB, JS, NG, GL, JP, LW. Writing original draft: AB, LW. Reviewing and editing: all authors.

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Notes

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The funder had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.

Disclosures

The authors declare that there is no conflict of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author (JW) upon reasonable request.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.07.029.

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