Breast Cancer Research and Treatment (2019) 173:465–474
https://doi.org/10.1007/s10549-018-5002-9

EPIDEMIOLOGY

Predictors of time to death after distant recurrence in breast cancer patients

Victoria Sopik[1,2] · **Ping Sun**[1] · **Steven A. Narod**[1,3]

Received: 20 September 2018 / Accepted: 8 October 2018 / Published online: 16 October 2018

Abstract

Background After experiencing a distant recurrence, breast cancer patients have a poor prognosis; fewer than 5% survive for ten or more years. However, the time to death is highly variable, ranging from a few months to many years. The purpose of this study is to identify, in a large hospital-based series of patients with early-stage breast cancer, factors which predict survival after distant recurrence.

Methods We studied a cohort of 2312 women diagnosed with invasive breast cancer at Women's College Hospital between 1987 and 2000 (stages I–III). For each patient, we abstracted information on age at diagnosis, the initial presentation of the cancer (tumour size, lymph node status, tumour grade, ER status, PR status, HER2 status), treatment (surgery, radiotherapy, chemotherapy, hormone therapy), the dates of all tumour recurrences (local, regional, distant) and the dates and causes of death. The Cox proportional hazards model was used to estimate the univariate and multivariate hazard ratios for death from breast cancer following distant recurrence associated with the various tumour features.

Results After a mean follow-up of 12.8 years from diagnosis, 523 distant recurrences were recorded among women in the cohort (23% of 2312) and 604 women (26%) died of breast cancer. For the 484 women who had a distant recurrence on record and died of breast cancer, the mean time from distant recurrence to death was 2.0 years (range 0–11.9 years). In a multivariate analysis, only two factors were significantly associated with time to death after distant recurrence: ER status (positive vs. negative, HR 0.56; 95% CI 0.43–0.71; $p < 0.0001$) and tumour grade (high vs. low, HR 1.87; 95% CI 1.16–3.01; $p = 0.01$). Among ER-negative patients ($N = 175$), high tumour grade and a short time from diagnosis to distant recurrence were associated with a rapid time to death. Among ER-positive patients ($N = 336$), there was no significant independent predictor of time from recurrence to death.

Conclusions Among ER-negative breast cancer patients, the time to death after distant recurrence was predictable to some extent; women with a short time from diagnosis to recurrence and/or with high-grade tumours were more likely to succumb to breast cancer within 3 years. Among ER-positive breast cancer patients who experience a distant recurrence, the time to death varies substantially and between patients could not be predicted by tumour factors or treatment. This suggests that for ER-positive patients, the factors that determine the time from diagnosis to distant recurrence do not predict the course of the cancer post-recurrence.

Keywords Breast cancer · Distant recurrence · Mortality · Survival · Progression

Introduction

Approximately 25% of women who are diagnosed with early-stage (non-metastatic) breast cancer will develop distant metastases and die of their disease [1]. Among women who die, the time to death is highly variable and is difficult to predict, in particular among women with ER-positive breast cancer [2]. The time from diagnosis to death can be partitioned into two periods—the time from diagnosis to distant recurrence and the time from distant recurrence to

✉ Steven A. Narod
steven.narod@wchospital.ca

[1] Women's College Research Institute, 76 Grenville Street, Toronto M5S 1B2, ON, Canada

[2] Institute of Medical Science, University of Toronto, Toronto, Canada

[3] Dalla Lana School of Public Health, University of Toronto, Toronto, Canada

death. The average time from diagnosis to distant recurrence is approximately 5 years; however, this can vary widely, with some patients relapsing a few months after operation, and others relapsing many years after [3]. For those with ER-positive breast cancer, it is relatively common to relapse after a long period of time, e.g. 10 or more years after diagnosis [3, 4]. After experiencing a distant recurrence, patient prognosis is poor, and most patients die of their disease within 2 years [5]. However, the time to death among patients following distant recurrence is also highly variable and there are some long-term survivors [5]. Most studies to date have focused on identifying risk factors for distant recurrence or for death; studies which focus on time from distant recurrence to death are relatively few. Since almost all women who die of breast cancer first develop a distant recurrence, knowledge of the relevant predictive factors may help to illuminate the dynamics of disease progression. We identified a cohort of women who developed a distant recurrence within 25 years of a diagnosis of early-stage breast cancer and we asked to what extent the variability in time to death post-recurrence can be predicted by the initial tumour features and by the time interval between diagnosis and distant recurrence.

Methods

We studied a cohort of 2312 patients who were treated at Women's College Hospital for invasive breast cancer between 1987 and 2000. For each patient, we abstracted information on the initial presentation of the cancer (age at diagnosis, tumour size, lymph node status, tumour grade, ER status, PR status, HER2 status), all treatments received at the time of diagnosis (surgery, radiotherapy, chemotherapy, hormone therapy), the dates of all tumour recurrences (local, regional, distant) and the dates and causes of death. Patients with unknown age at diagnosis, unknown tumour size or unknown cause of death were excluded.

All women were metastasis-free at the time of diagnosis, but 523 women experienced one or more distant metastases within 25 years of diagnosis. Patients were followed from the date of first distant recurrence until death from breast cancer, death from another cause, loss to follow-up or 1 January 2018. The primary endpoint was breast cancer-specific survival following distant recurrence, which we defined as the period of time between the date of distant recurrence and the date of the last follow-up or the date of the cancer-associated death. We conducted a survival analysis using Cox proportional hazards modelling to evaluate the impact of various factors on the hazard for dying of breast cancer after distant recurrence, including age at diagnosis (< 40/40–49/50–59/60 + years), grade (I/II/III), lymph node status (negative/positive), ER status (negative/positive), PR status (negative/positive), HER2 status (negative/positive), radiotherapy (no/yes), chemotherapy (no/yes), tamoxifen (no/yes), local/regional recurrence (no/yes) and time from diagnosis to distant recurrence (0–2.99/3–5.99/6 + years). We did not have information about second-line chemotherapy given at the time of recurrence. Analyses were also conducted separately for the subgroup of women with ER-positive breast cancer, and the subgroup of women with ER-negative breast cancer.

Results

Among 2312 women who were treated for non-metastatic invasive breast cancer at Women's College Hospital between 1987 and 2000, 523 developed a distant recurrence, on average 5.2 years after their initial diagnosis (range 0 to 24 years). The characteristics of these 523 women are presented in Table 1. After a mean follow-up of 2.2 years (range 0 to 17.0 years), 484 (92.5%) of the 523 women with distant recurrence had died of breast cancer. Among the women who died of breast cancer, the average time from diagnosis to death was 6.9 years (range 0.2–28.3 years) and the average time from the date of distant recurrence to death was 2.0 years (range 0–11.9 years). Thirteen women died of another cause during follow-up and 26 women were still alive at the end of follow-up.

Table 2 presents the univariate and multivariate hazard ratios for death following distant recurrence associated with the various factors for all patients in the cohort. In a univariate analysis, factors significantly associated with increased mortality after distant recurrence included large tumour size (5 + cm vs. 0–2 cm; $p = 0.03$), positive lymph nodes ($p = 0.01$), high tumour grade (vs. low grade; $p < 0.0001$), negative ER status ($p < 0.0001$), negative PR status ($p < 0.0001$) and short time from diagnosis to distant recurrence ($p < 0.0001$). However, in multivariate analysis only two factors remained significant: ER status (positive vs. negative, multivariate HR 0.56; 95% CI 0.43–0.71; $p < 1 \times 10^{-4}$) and tumour grade (high vs. low, multivariate HR 1.87; 95% CI 1.16–3.01; $p = 0.01$).

We next examined the prognostic value of the various factors in patients post-recurrence, stratified by ER status (Tables 3 and 4). Among both ER-positive and ER-negative patients, large tumour size, lymph node positivity, PR negativity, high tumour grade and a short time from diagnosis to distant recurrence were significant univariate predictors of mortality following distant recurrence. However, in multivariate analysis, the results differed significantly depending on ER status. Among ER-positive subjects, none of the variables examined were significant independent predictors of mortality following distant recurrence (Table 3). In contrast, among ER-negative subjects, both tumour grade (grade 2 or 3 vs. grade 1) and

Table 1 Characteristics of breast cancer patients in Banting database experiencing distant recurrence

Characteristic	Number of patients ($N=523$)
Year of birth	
Mean (range)	1941.3 (1899–1970)
Year of diagnosis	
Mean (range)	1993.1 (1987–2000)
Age at diagnosis (years)	
Mean (range)	51.9 (24–93)
< 40	93 (17.8%)
40–49	160 (30.6%)
50–59	136 (26.0%)
60+	134 (25.6%)
Tumour size (cm)	
Mean (range)	2.94 (0–13.0)
0–2	207 (39.6%)
2–5	264 (50.5%)
5+	52 (9.9%)
Lymph node status	
Negative	170 (34.8%)
Positive	319 (65.2%)
Missing	34
Tumour grade	
I	31 (7.2%)
II	179 (41.3%)
III	223 (51.5%)
Missing	90
ER status	
Negative	175 (34.2%)
Positive	336 (65.8%)
Missing	12
PR status	
Negative	252 (50.3%)
Positive	249 (49.7%)
Missing	22
HER2 status	
Negative	260 (68.1%)
Positive	122 (31.9%)
Missing	141
Surgery	
Lumpectomy	360 (68.8%)
Mastectomy	163 (31.2%)
Radiotherapy	
No	174 (33.9%)
Yes	339 (66.1%)
Missing	10
Chemotherapy	
No	262 (51.0%)
Yes	252 (49.0%)
Missing	9
Tamoxifen	
No	310 (60.1%)
Yes	206 (39.9%)
Missing	7
Local or regional recurrence	
No	305 (58.3%)
Yes	218 (41.7%)
Vital status	
Dead due to breast cancer	484 (92.5%)
Dead due to other cause	13 (2.5%)
Alive	26 (5.0%)
Time from dx to distant recurrence (years)	
Mean (range)	5.2 (0–24.6)
0–2.99	221 (42.3%)
3–5.99	167 (31.9%)
6+	135 (25.8%)
Time from distant recurrence to end of FU	
Mean (range)	2.2 (0–17.0)
Time from diagnosis to end of FU (years)	
Mean (range)	7.3 (0.2–28.3)

time to distant recurrence (6 + years vs. < 3 years) were significantly associated with mortality following distant recurrence in multivariate analysis (Table 4).

Figure 1 shows the distribution of times to death after distant recurrence according to ER status. Among the 306 ER-positive patients who died of breast cancer in the follow-up period, the median time to death was 1.7 years; 55.2% of patients died within 2 years of the date of distant recurrence, 33% died between 2 and 5 years and 11.8% died after five or more years (Fig. 1a). 80% of the ER-positive patients died within four years of distant recurrence.

Of the 167 ER-negative patients who died, the median time to death was 0.8 years; 76.7% of patients died within 2 years of the date of distant recurrence, 19.8% died within 2–5 years and 3.6% died after five or more years (Fig. 1b).

In the second part of the study, we sought to correlate the time from diagnosis to recurrence with the time from recurrence to death, for individual patients and for various subgroups. We estimated the annual hazard rate of distant recurrence post-diagnosis for different subgroups of patients (Fig. 2). In patients with large (2–10 cm), triple-negative, lymph node-positive breast cancer (i.e. a high overall risk of distant recurrence), the rate of distant recurrence rose sharply from the date of diagnosis, peaked at around 3 years, and dropped quickly thereafter (Fig. 2a). In this high-risk group, the annual hazard rate peaked at 17%. All distant recurrences occurred in the first six years. In contrast, among patients with ER-positive breast cancer, the hazard rate of experiencing a distant recurrence was relatively stable throughout the entire follow-up period—the annual rate

Table 2 Hazard ratios for breast cancer death after distant recurrence, all patients

Variable	Univariate HR (95%CI) *P*	Multivariate HR(95%CI) *P*
Age at diagnosis (years)		
< 40	1	1
40–49	0.81 (0.62–1.05) 0.11	0.78 (0.59–1.03) 0.08
50–59	0.87 (0.66–1.13) 0.29	0.83 (0.62–1.12) 0.22
60+	0.97 (0.74–1.28) 0.85	1.05 (0.76–1.45) 0.77
Tumour size		
0–2 cm	1	1
2–5 cm	1.17 (0.97–1.42) 0.10	1.06 (0.85–1.31) 0.62
5+ cm	1.42 (1.04–1.93) 0.03	1.10 (0.79–1.54) 0.57
Lymph node status		
Negative	1	1
Positive	1.28 (1.05–1.56) 0.01	1.13 (0.88–1.44) 0.34
Grade		
1	1	1
2	1.50 (0.97–2.33) 0.07	1.32 (0.82–2.10) 0.25
3	2.59 (1.68–3.99) $< 10^{-4}$	1.87 (1.16–3.01) 0.01
ER status		
Negative	1	1
Positive	0.54 (0.44–0.65) $< 10^{-4}$	0.56 (0.43–0.71) $< 10^{-4}$
PR status		
Negative	1	1
Positive	0.58 (0.49–0.71) $< 10^{-4}$	0.79 (0.63–1.01)0.06
HER2 status		
Negative	1	1
Positive	1.23 (0.98–1.53) 0.07	1.02 (0.80–1.30) 0.87
Radiation		
No	1	1
Yes	0.87 (0.72–1.06) 0.16	0.88 (0.71–1.09) 0.25
Chemotherapy		
No	1	1
Yes	1.25 (1.05–1.50) 0.01	1.19 (0.93–1.53) 0.17
Tamoxifen		
No	1	1
Yes	0.97 (0.81–1.17) 0.75	1.06 (0.84–1.33) 0.15
Local or regional recurrence		
No	1	1
Yes	1.05 (0.88–1.26) 0.58	1.14 (0.94–1.39) 0.20
Time diagnosis to distant recurrence		
0–2.99 years	1	1
3–5.99 years	0.74 (0.60–0.91) 0.04	0.93 (0.75–1.16) 0.54
6+ years	0.55 (0.44–0.70) $< 10^{-4}$	0.82 (0.62–1.08) 0.16

peaked at about 4% (years 2–4) and then hovered at 1–2% from years 5 to 20 (Fig. 2b).

Table 5 presents a breakdown of survival times for different subgroups of patients as a sum of the time from diagnosis to distant recurrence and the time from distant recurrence to death. On a group basis, there was a strong correlation between the two time intervals: compared to ER-negative node-positive patients, the median time from diagnosis to distant recurrence was 1.9 times longer for ER-negative node-negative cancers, was 2.2 times longer for ER-positive node-positive cancers and was 2.8 times longer for ER-positive node-negative cancers. Compared to ER-negative node-positive patients, the time from distant recurrence to end of follow-up was 1.6 times longer for ER-negative node-negative patients, was 2.1 times longer for ER-positive node-positive patients and was 2.8 times longer for ER-positive

Table 3 Hazard ratios for breast cancer death after distant recurrence, ER-positive patients

Variable	Univariate HR (95%CI) *P*	Multivariate HR (95%CI) *P*
Age at diagnosis (years)		
< 40	1	1
40–49	0.80 (0.57–1.13) 0.21	0.80 (0.56–1.15) 0.23
50–59	0.99 (0.69–1.40) 0.94	0.88 (0.58–1.32) 0.53
60+	1.11(0.78–1.57)0.57	0.99(0.63–1.53)0.95
Tumour size		
0–2 cm	1	1
2–5 cm	1.11 (0.88–1.42) 0.38	1.06 (0.81–1.38) 0.69
5+ cm	1.49 (1.00–2.22) 0.05	1.16 (0.74–1.82) 0.53
Lymph node status		
Negative	1	1
Positive	1.49 (1.14–1.96) 0.003	1.31 (0.93–1.86) 0.12
Grade		
1	1	1
2	1.24 (0.75–2.03) 0.40	1.10 (0.65–1.86) 0.73
3	1.88 (1.14–3.08) 0.01	1.37 (0.97–2.38) 0.27
PR status		
Negative	1	1
Positive	0.79 (0.62–1.00) 0.05	0.81 (0.61–1.07) 0.14
HER2 status		
Negative	1	1
Positive	1.25 (0.96–1.63) 0.10	1.13 (0.84–1.51) 0.43
Radiation		
No	1	1
Yes	0.84 (0.66–1.07) 0.16	0.85 (0.65–1.11) 0.24
Chemotherapy		
No	1	1
Yes	1.11 (0.89–1.40) 0.35	1.10 (0.78–1.55) 0.59
Tamoxifen		
No	1	1
Yes	0.84 (0.66–1.07) 0.16	1.24 (0.92–1.67) 0.15
Local or regional recurrence		
No	1	1
Yes	0.95 (0.76–1.20) 0.66	1.02 (0.79–1.31) 0.90
Time diagnosis to distant recurrence		
0–2.99 years	1	1
3–5.99 years	0.78 (0.59–1.02) 0.07	0.85 (0.63–1.13) 0.27
6+ years	0.70 (0.53–0.92) 0.01	0.82 (0.58–1.15) 0.25

node-negative patients. However, for individual patients there was very little correlation between the lengths of the two time periods. We plotted the times to distant recurrence and times from distant recurrence to end of follow-up for patients with ER-positive (Fig. 3a) and ER-negative (Fig. 3b) breast cancer. Within the subgroup of ER-positive breast cancer patients, there was no correlation between time to recurrence and time from recurrence to death (slope co-efficient = 0.03; *p* value for slope = 0.62). In contrast, among patients with ER-negative breast cancer, there was a positive correlation between the time to recurrence and the time from recurrence to death (slope co-efficient = 0.13; *p* value for slope = 0.0002).

Discussion

In nearly all cases, women who die of breast cancer will die from metastatic disease (a small number die from complications of therapy or from secondary infections) [6]. The great majority of fatal cases will experience a distant recurrence prior to death (in a small percentage of cases a

Table 4 Hazard ratio for breast cancer death after distant recurrence, ER-negative patients

Variable	Univariate RR (95%CI) *P*	Multivariate RR (95%CI) *P*
Age at diagnosis (years)		
< 40	1	1
40–49	0.82 (0.54–1.26) 0.36	0.66 (0.42–1.03) 0.07
50–59	0.64 (0.40–1.02) 0.06	0.53 (0.37–0.90) 0.02
60+	0.96 (0.60–1.54) 0.85	1.09 (0.63–1.91) 0.75
Tumour size		
0–2 cm	1	1
2–5 cm	1.54 (1.11–2.15) 0.01	1.09 (0.74–1.60) 0.68
5+ cm	1.42 (0.86–2.36) 0.17	1.14 (0.66–1.97) 0.65
Lymph node status		
Negative	1	1
Positive	1.48 (1.08–2.03) 0.02	0.99 (0.85–1.51) 0.94
Grade		
1	1	1
2	4.21 (1.24–14.3) 0.02	4.84 (1.15–20.4) 0.02
3	6.97 (2.05–23.7) 0.002	5.75 (1.34–24.6) 0.03
PR status		
Negative	1	1
Positive	0.57 (0.35–0.95) 0.03	0.89 (0.50–1.58) 0.69
HER2 status		
Negative	1	1
Positive	1.09 (0.72–1.64) 0.69	0.90 (0.57–1.44) 0.67
Radiation		
No	1	1
Yes	0.86 (0.62–1.19) 0.37	0.83(0.56–1.24) 0.36
Chemotherapy		
No	1	1
Yes	1.46 (1.06–2.10) 0.02	1.08 (0.71–1.67) 0.71
Tamoxifen		
No	1	1
Yes	0.86 (0.62–1.19) 0.37	0.66 (0.39–1.11) 0.12
Local or regional recurrence		
No	1	1
Yes	1.19 (0.88–1.62) 0.25	1.23 (0.86–1.75) 0.26
Time diagnosis to distant recurrence		
0–2.99 years	1	1
3–5.99 years	0.84 (0.60–1.20) 0.34	1.03 (0.69–1.55) 0.88
6+ years	0.36 (0.21–0.63) 0.0004	0.48 (0.24–0.93) 0.03

distant recurrence is not recorded prior to death, but these are mostly the result of inadequate data recording or lack of medical attention. In these few cases, it is presumed that the distant metastases preceded death but were not recorded). During the course of this study (1987–2000), the timing of the distant recurrence was determined from clinical symptoms, imaging studies and biopsies. That is, distant recurrence was defined as an *observable* event in the clinical course of the patient. Newer techniques such as measurement of circulating tumour cells have the potential to revise these time reference points. The distant recurrence defined in this way is an observable event; however, current theory supposes that the distant metastases were present—but *unobservable*—from the time of diagnosis to clinical recurrence, due to micro-dissemination of tumour emboli prior to surgery. In some cases, these emboli eventually proliferate and become clinically apparent. It is a currently a matter of interest if the micro-metastases assume a dormant state in the metastatic niche prior to reactivation. Because we do not now have the resolution to measure the extent of the tumour burden prior to distant recurrence, we must infer the growth characteristics of the cancer by indirect means. In the

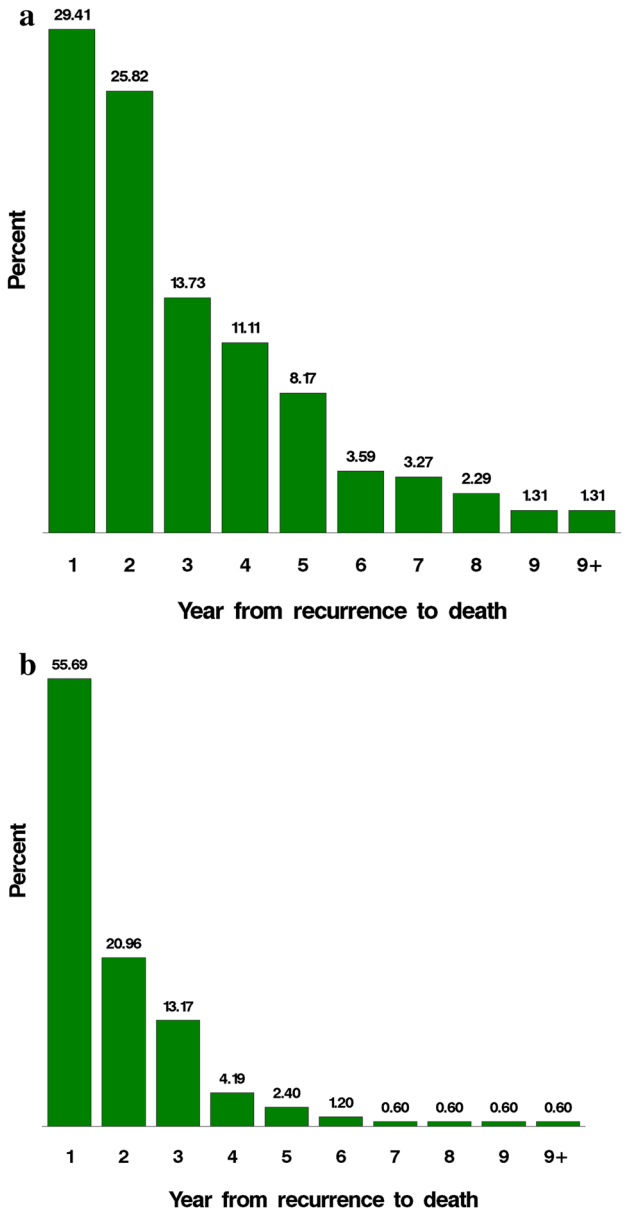

Fig. 1 **a** Distribution of times to death from breast cancer after distant recurrence, among ER-positive patients who died. **b** Distribution of times to death from breast cancer after distant recurrence, among ER-negative patients who died

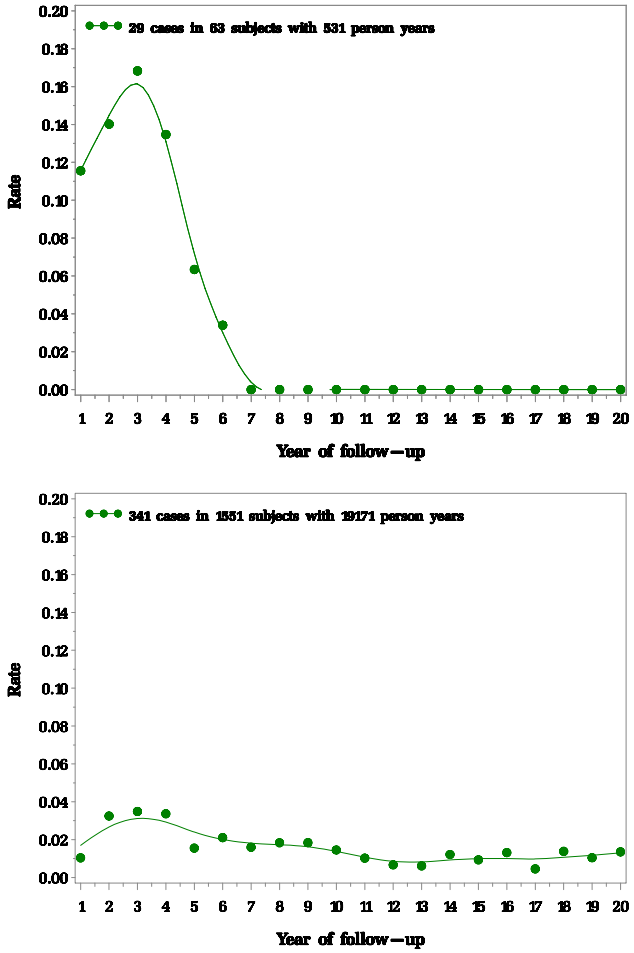

Fig. 2 **a** Annual rate of distant recurrence following diagnosis of invasive breast cancer, among patients with triple-negative (ER−/PR−/HER2−), lymph node-positive cancers 2 to 10 cm in size. **b** Annual rates of distant recurrence following a diagnosis of ER-positive invasive breast cancer

Table 5 Intervals of time (in years) between diagnosis, distant recurrence and death, in patients with distant recurrence stratified by ER and lymph node status

Subgroup	*N* patients	Diagnosis to end of FU	Diagnosis to distant recurrence	Distant recurrence to end of FU
ER− Node+	97	3.70	2.56	1.14
ER− Node−	73	6.76	4.98	1.78
ER+ Node+	217	8.08	5.72	2.36
ER+ Node−	90	10.35	7.17	3.18

approach we have taken here, we have divided the course of a patient into two time periods, from surgery to distant recurrence and from distant recurrence to death (ideally, we would also have knowledge of the time course of the cancer from inception to surgery but at this pre-clinical stage the cancer is in an unobservable state).

In the present study of 523 women who developed a distant recurrence within 20 years of diagnosis, ER status was the most significant independent predictor of mortality after distant recurrence; ER-positive patients died at approximately one-half the rate of ER-negative patients. However, among ER-positive patients with distant recurrence, the time to death was unpredictable, i.e. there was no significant independent predictor of mortality post-recurrence and in the adjusted model all of the hazard ratios were

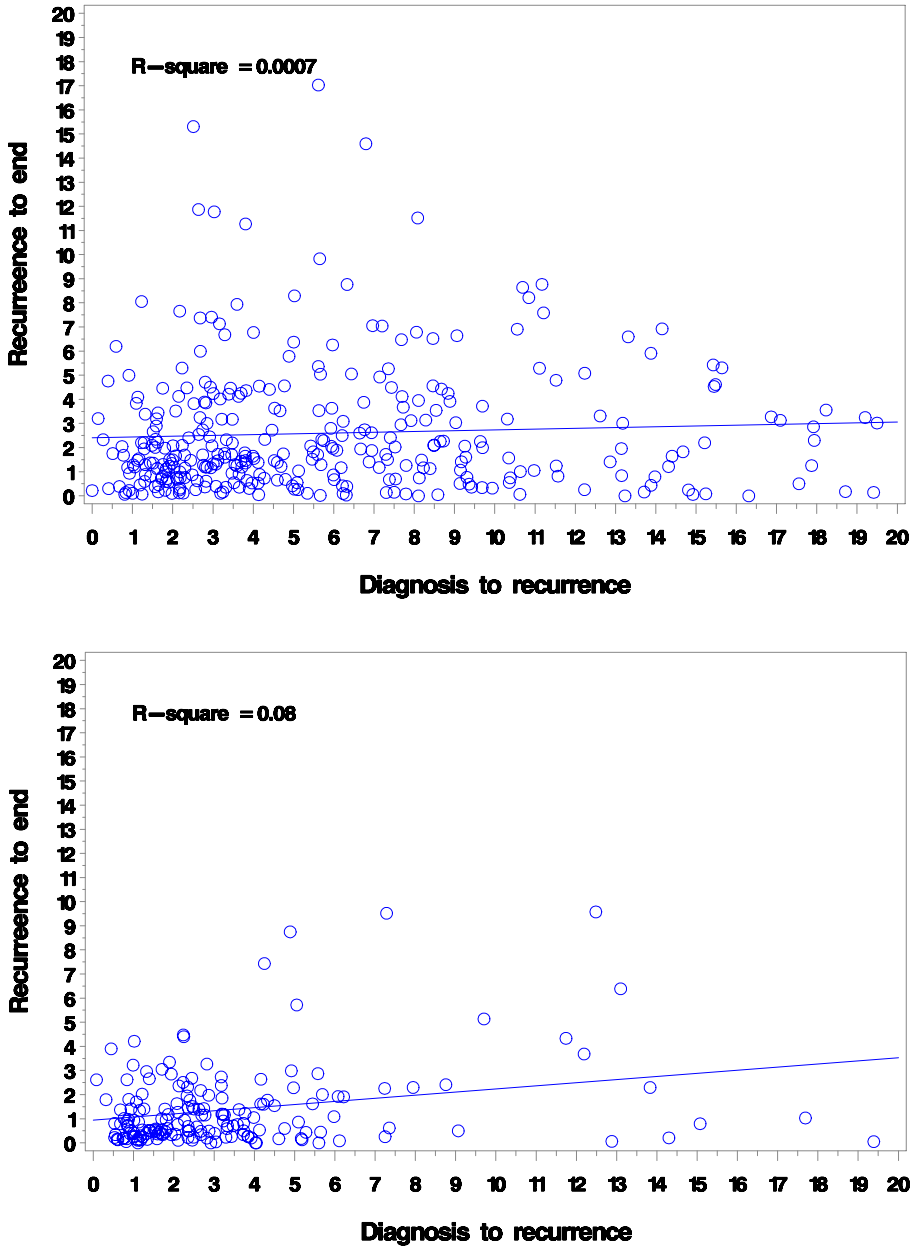

Fig. 3 **a** Relationship between time from diagnosis to recurrence and time from recurrence to death, among patients with distant recurrence following ER-positive invasive breast cancer. **b** Relationship between time from diagnosis to recurrence and time from recurrence to death, among patients with distant recurrence following ER-negative invasive breast cancer. Regression equation: time = 2.404466 + 0.032767 × distime; *p* for slope parameter = 0.62. Regression equation: time = 0.940596 + 0.129129 × distime; *p* for slope parameter = 0.0002

close to unity. In contrast, among ER-negative patients with distant recurrence, tumour grade was highly predictive of mortality in multivariate analysis. A prolonged time from diagnosis to recurrence was predictive of time from recurrence to death in ER-negative, but not in ER-positive cancer patients.

These results are in line with those of previous studies which examined prognostic factors for survival among patients with a distant recurrence. All studies to date report a significant prognostic effect for ER status on survival after distant recurrence [5, 7–13], and most studies also report a prognostic effect of tumour grade [7–10]. It is perhaps not surprising that ER status and tumour grade are predictors of the death and of time from recurrence to death as these are canonical properties of the tumour cell, and are not measures of cancer burden, such as tumour size or lymph node status. The latter two variables are highly predictive of the probability of latent metastases at diagnosis and are less predictive

of time to death [2]. Similarly, we have recently reported that the impact of early age of diagnosis on poor survival is determined by the probability of having metastases present at diagnosis and this probability is much higher for young women than for older women for cancers of equivalent size, but among patients who die of breast cancer, age of onset has no impact on the time to death [2]. This is consistent with the observation reported here that young age of onset does not hasten the time to death post-recurrence (Table 2).

Few studies have examined the prognostic value of the various factors among patients stratified by ER status [7, 13]. Kwast et al studied 2001 patients who developed metastatic disease within five years of diagnosis of early-stage breast cancer and found that, in general, the prognostic value of the initial tumour features (at diagnosis) was greater in ER-negative subjects, compared to ER-positive subjects [7]. Other significant independent factors reported in previous studies include site of metastasis (visceral vs. bone), age at diagnosis, tumour size and lymph node status [5, 7–13]. In general, studies on prognostic factors in patients with metastatic breast cancer vary considerably with respect to the selection of patients, the inclusion of various parameters and follow-up time after recurrence.

We correlated the time interval between diagnosis and distant recurrence with the time interval between distant recurrence and death. The prognostic impact of the time from diagnosis to recurrence on prognosis beyond relapse suggests that there are variables (known or hidden) which predict both time to recurrence and time from recurrence to death. ER status and tumour grade are in this category, and perhaps there are other hidden variables which are also influential in this regard.

Among ER-positive patients, the time from diagnosis to distant recurrence is not correlated with the time from distant recurrence to death across the spectrum of survival times. This complements our earlier study where we showed that for low-risk ER-positive breast cancer patients it is possible to predict the probability of death but not the time to death [2]. Together, these observations argue against the position that the survival times for ER-positive cancers are deterministic and are driven by the intrinsic biological aggressiveness of the cancer (through known variables and hidden variables); rather this lack of correlation supports the notion of a stochastic process that incorporates a random element in prognosis. It is tempting to suppose that a random element is implicated in the transition from a dormant to an active state. Alternatively a host factor (rather than a tumour characteristic) might be the primary determinant of reactivation from the dormant state. If the tumour lay dormant for a large proportion of the time from diagnosis to distant recurrence (and for none of the time from distant recurrence to death) and if reactivation were by and large stochastic (or due to tumour unrelated factors), then we would expect to see little correlation between the two phases in women with ER-positive cancers. This will be the topic of future studies.

There are several limitations to our analysis. The 523 women with distant recurrence in our study were selected from a larger cohort of breast cancer patients, all of whom were followed for a relatively long time from diagnosis (mean follow-up 12.8 years). However, sample sizes for the various subgroups (especially after stratification by ER status) were small. In making inferences regarding the underlying dynamics of metastatic progression, we are restricted to "observable" events (i.e. time points at which distant metastases were detected vs. undetected), but we do not know the extent of the metastatic tumour burden all times. There may be other (hidden) variables which may influence the time to distant recurrence and/or the time from distant recurrence to death. We did not include information on site of first metastasis (i.e. bone vs. viscera)—this has been shown to vary for patients with ER-positive versus ER-negative breast cancer and may impact upon the time to death following distant recurrence. In most studies which have included site of metastasis as a co-variate, ER status remains a significant independent predictor of mortality [7, 13]. We also did not include information on treatments received at the time of distant recurrence (i.e. chemotherapy, tamoxifen, Herceptin) and were missing information on HER2 status for many patients.

In conclusion, among breast cancer patients who experience a distant recurrence, factors which predict the time to death after distant recurrence include ER status and tumour grade. However, after stratifying by ER status, the extent to which time to death can be predicted differs widely. Among ER-negative breast cancer patients, the time to death after distant recurrence is predictable to some extent; women with a short time from diagnosis to recurrence and/or with high-grade tumours are likely to succumb to breast cancer within 3 years. Among ER-positive breast cancer patients who experience a distant recurrence, the time to death varies substantially and cannot be predicted by tumour or treatment factors. For ER-positive patients, the factors that determine the time from diagnosis to distant recurrence do not predict the course of the cancer post-recurrence.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Schairer C, Mink PJ, Carroll L, Devesa SS (2004) Probabilities of death from breast cancer and other causes among female breast cancer patients. J Natl Cancer Inst 96:1311–1321
2. Narod S, Giannakeas V, Sopik V (2018) Time to death in breast cancer patients as an indicator of treatment response. Breast Cancer Res Treat. https://doi.org/10.1007/s10549-018-4935-3
3. Dent R, Trudeau M, Pritchard KI et al (2007) Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res 13:4429–4434
4. Pan H, Gray R, Braybrooke J et al (2017) 20-year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. N Engl J Med 377:1836–1846
5. Tevaarwerk AJ, Gray RJ, Schneider BP et al (2013) Survival in patients with metastatic recurrent breast cancer after adjuvant chemotherapy: little evidence of improvement over the past 30 years. Cancer 119:1140–1148
6. Redig AJ, McAllister SS (2013) Breast cancer as a systemic disease: a view of metastasis. J Intern Med 274:113–126
7. Kwast AB, Voogd AC, Menke-Pluijmers MB et al (2014) Prognostic factors for survival in metastatic breast cancer by hormone receptor status. Breast Cancer Res Treat 145:503–511
8. Kuru B, Camlibel M, Dinc S, Gulcelik MA, Gonullu D, Alagol H (2008) Prognostic factors for survival in breast cancer patients who developed distant metastasis subsequent to definitive surgery. Singapore Med J 49:904–911
9. Planchat E, Durando X, Abrial C et al (2011) Prognostic value of initial tumor parameters after metastatic relapse. Cancer Invest 29:635–643
10. Rogoz B, Houzé de l'Aulnoit A, Duhamel A, Houzé de l'Aulnoit D (2018) Thirty-year trends of survival and time-varying effects of prognostic factors in patients with metastatic breast cancer-a single institution experience. Clin Breast Cancer 18:246–253
11. Xiong Z, Deng G, Huang X et al (2018) Score for the survival probability in metastasis breast cancer: a nomogram-based risk assessment model. Cancer Res Treat. https://doi.org/10.4143/crt.2017.443
12. Kim HJ, Ahn SG, Lee HM et al (2015) Metastasis-free interval is closely related to tumor characteristics and has prognostic value in breast cancer patients with distant relapse. J Breast Cancerm 18:371–377
13. Largillier R, Ferrero JM, Doyen J et al (2008) Prognostic factors in 1038 women with metastatic breast cancer. Ann Oncol 19:2012–2019