The Breast 41 (2018) 151–158

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Impact of subtypes and comorbidities on breast cancer relapse and survival in population-based studies

Silvia M. Ess [a, *], Christian Herrmann [a, b], Christine Bouchardy [c], Isabelle Neyroud [c], Elisabetta Rapiti [c], Isabelle Konzelmann [d], Andrea Bordoni [d], Laura Ortelli [e], Sabine Rohrmann [f], Harald Frick [a, g], Mohsen Mousavi [a], Beat Thürlimann [h]

[a] Cancer Registry St. Gallen-Appenzell, Cancer League Eastern Switzerland, St. Gallen, Krebsregister St.Gallen - Appenzell. Flurhofstr. 7, 9001 St. Gallen, Switzerland
[b] Swiss Tropical and Public Health Institute, Basel, Krebsregister St.Gallen - Appenzell. Flurhofstr. 7, 9001 St. Gallen, Switzerland
[c] Geneva Cancer Registry, University of Geneva, Magnin Registre genevois de tumeurs Rue Michel Servet 1, 1211 Geneve, Switzerland
[d] Valais Cancer Registry, Observatoire valaisan de la santé, Sion, Registre valaisan de tumeurs, Avenue Grand-Champsec 64, 1950 Sion, Switzerland
[e] Ticino Cancer Registry, Registro tumori del Ticino Via in Selva 24, 6601, Locarno, Switzerland
[f] Cancer Registry of the Canton Zurich and Zug, University of Zurich, Krebsregister der Kantone Zürich und Zug Vogelsangstr. 10, 8091 Zürich, Switzerland
[g] Institute for Pathology, Kantonsspital St. Gallen, Institut für Pathologie. Rorschacher Strasse 95, 9007 St.Gallen, Switzerland
[h] Breast Cancer Centre, Kantonsspital St. Gallen, Brustzentrum St. Gallen. Rorschacher Strasse 95, 9007 St.Gallen, Switzerland

ARTICLE INFO

Article history:
Received 19 May 2018
Received in revised form
11 July 2018
Accepted 29 July 2018
Available online 30 July 2018

Keywords:
Breast cancer subtypes
Distant relapse
Locoregional relapse
Breast cancer survival
Population-based study
Switzerland

ABSTRACT

Objective: To study the impact of subtypes and comorbidities on breast cancer (BC) relapse and survival in the heterogeneous patients of the real world.
Methods: We identified patients diagnosed with BC between January 2003 and December 2005 from six population-based Swiss cancer registries. Clinicopathologic data was completed with information on locoregional and distant relapse and date and cause of death for over 10-years. We approximated BC subtypes using grade and the immunohistochemical panel for oestrogen, progesterone and human epidermal growth factor 2 (HER2) receptor status. We studied factors affecting relapse and survival.
Results: Luminal A-like subtype represented 46% of all newly diagnosed BC (N = 1831), followed by luminal B-like (N = 1504, 38%), triple negative (N = 436, 11%) and HER2 enriched (N = 204, 5%). We observed regional disparities in subtype prevalence that contribute to explain regional differences in survival formerly described. Disease relapse and BC specific mortality differed by subtype and were lower for luminal A like tumours than for other subtypes for any stage at diagnosis. After a median follow-up of 10.9 years, 1311 (33%) had died, half of them 647 (16%) due to another disease, showing the importance of comorbidities. Omission of systemic therapies in selected patients was not associated with poorer BC specific survival, BC subtype and life expectancy playing a role.
Conclusions: Information on tumour subtype is necessary for an adequate interpretation of population-based BC studies. Measures of comorbidity or frailty help in the evaluation of quality of care in the highly heterogeneous patients of the real world.

1. Introduction

Nowadays, breast cancer (BC) is recognized as a heterogeneous disease, both on a molecular basis and in terms of clinical behaviour. Microarray analysis has identified BC subtypes with distinct gene expression profiles [1]. Numerous subsequent studies have further shown that these molecular (intrinsic) subtypes predict recurrence and contribute additional prognostic value to standard clinicopathologic factors like tumour size and extent of nodal

* Corresponding author. Cancer Registry St. Gallen-Appenzell, Cancer League Eastern Switzerland. Flurhofstr. 7, CH-9000 St.Gallen, Switzerland.
E-mail addresses: Silvia.ess@kssg.ch (S.M. Ess), Christian.herrmann@kssg.ch (C. Herrmann), Christine.BouchardyMagnin@unige.ch (C. Bouchardy), isabelle.neyroud-caspar@unige.ch (I. Neyroud), Elisabetta.Rapiti@unige.ch (E. Rapiti), isabelle.konzelmann@ovs.ch (I. Konzelmann), andrea.bordoni@ti.ch (A. Bordoni), laura.ortelli@ti.ch (L. Ortelli), sabine.rohrmann@usz.ch (S. Rohrmann), Harald.Frick@kssg.ch (H. Frick), Mohsen.Mousavi@kssg.ch (M. Mousavi), beat.thuerlimann@kssg.ch (B. Thürlimann).

https://doi.org/10.1016/j.breast.2018.07.011
0960-9776/

involvement [2–4]. As gene expression signatures are not universally used, the prevalence and impact of intrinsic subtypes on survival in the general population of BC patients is less well characterised. In clinical practice subtypes are often approximated by immunohistochemistry (IHC) using the oestrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor 2 (HER2) receptor status and a marker of proliferation (Ki67 and/or grading) [5].

Epidemiologic data on BC outcomes by subtypes are scarce and highly needed for defining policies to reduce the burden of disease in the real world. Trials are often conducted in unrepresentative patient populations, patients that are younger and with less comorbidity than average clinical populations. Management strategies in real life practice require taking into account not only tumour biology and risk, but also host biology and patient preferences [6]. Variations on functional status, cognition and comorbidity may influence tolerance to cancer therapy as well as the overall risk-benefit ratio of cancer therapies [7]. Surveillance, Epidemiology and End Results (SEER) registries collect ER, PR and HER2 receptor status since 2010 allowing for tumour biology specific cancer incidence statistics. Hormone receptor (HR) positive and HER2 negative tumours had highest incidence rates among local stage cases and low poverty areas and were strongly positively correlated with mammography use [8]. More recently, Chavez-MacGregor et al. [9] showed the importance of incorporating subtypes to the anatomical stage system for patients of the California Cancer Registry when analysing BC specific survival (BCSS) and overall survival (OS). However, big epidemiological studies documenting survival differences of women with BC across European countries [10,11] and worldwide [12] have failed to adjust for BC subtypes. In Switzerland, regional disparities in 5-year stage-corrected survival rates [13] and in patterns of care [14,15] have been described, but the impact of BC subtypes on regional disparities in survival remained unclear so far.

The aim of the present study is to investigate the long-term (10-year) impact of tumour subtype, substandard therapies and comorbidities on disease relapse and BC specific mortality in the heterogeneous patients of the real world.

2. Methods

2.1. Study population and variables

The present study is a follow-up of patients recruited for the "Patterns of Care in Breast Cancer in Switzerland Study". The methodology for this study has been described elsewhere [14]. In short, female patients diagnosed with invasive BC between January 2003 and December 2005 and living in the catchment area of six population based cancer registries in Switzerland (Geneva, Valais, Ticino, Zürich, St. Gallen-Appenzell and Grisons-Glarus) were included in the study. These registries are regular and long-time contributors to the International Agency for Research on Cancer (IARC). Cases diagnosed solely on autopsy or death certificate were excluded from the study as well as patients with non-epithelial neoplasia ($N = 16$) and patients with previous BC ($N = 192$). We ascertained clinicopathologic and patient demographic data including patient age and place of residence at the time of diagnosis, clinical presentation of disease, tumour size, number of examined and positive lymph nodes and tumour grade. Type of surgery, administration of radiotherapy and systemic therapies and the regimens used were assessed. Patients were followed for vital status, date and type of disease relapse, treatments at first relapse, cause and date of death. Cause of death was ascertained by medical chart review and from the cause of death statistic of the Federal Statistical Office. Patients that moved outside the catchment area of the registry and for whom no information on vital status and disease relapse was available were considered lost to follow up at the date of last contact. Comorbidities were extracted from medical reports and evaluated using the Charlson comorbidity index.

Primary endpoints of this study were BC specific outcomes: BC death, distant recurrence and isolated locoregional recurrence (LRR). Isolated local recurrence was defined as disease relapse within the breast after breast-sparing surgery or within the ipsilateral chest wall after mastectomy or in the ipsilateral axillary, supraclavicular or internal mammary lymph nodes in the absence of distant relapse. A breast carcinoma developing in the contralateral breast was viewed as a new primary tumour and not as relapse. Distant recurrence was defined as metastasis to other sites. The secondary endpoint of this study was overall survival (OS), defined as the time elapsed from date of first diagnosis to death of any cause; while BC specific survival was defined as the time elapsed from date of first diagnosis to death with progression of BC. Follow − up duration was calculated in the subgroup of living patients as the time elapsed between the date of diagnosis and the date of end of follow-up.

Subtype approximation was performed based on IHC biomarkers including expression of ER, PR, HER2 status and grade as a proxy for proliferation according to the St Gallen Consensus Conference 2017 [5] and the Cancer Genome Atlas Network [16]. We used histological grade, as marker for proliferation because information on Ki67 was not always available. HER2 unknown status was considered as negative. We classified tumours as luminal A like (lumA-like) if they presented high (>50%) ER/PR expression, HER2 negative status and low-intermediate histological grade (grade 1 and 2). We included in the luminal B like (lumB-like) category those tumours with ER and/or PR expression not qualifying for lumA-like category. We classified as HER2 enriched those tumours with no expression of ER and PR receptors and HER2 over-expressed or amplified. We included in the TN group those tumours with no expression of ER, PR and non-amplified HER2 status. We excluded 126 women (3%) that could not be classified within one of these subtypes because of unknown ER, PR and HER2 status.

2.1.1. Statistical analyses

We compared categorical variables using the chi-square test. To analyse factors influencing disease relapse, BC death and overall survival we used time-to-event methods that accounted for censoring and follow-up time. Kaplan-Meier methods were used to analyse rates of disease relapse or survival, whereas we used Cox proportional hazards regression analysis to estimate hazard ratios (HRs) and 95% confidence intervals (CI) of the outcome of interest in multivariate analysis. The proportional hazard assumption was checked. All models included subtype, age and stage at diagnosis, received therapies, comorbidities, and canton of residence. Patients not experiencing the outcome of interest, i.e. disease relapse or BC death, were censored at the date of the last contact. In order to study the effect of censoring of patients dying from other causes on the hazard of dying from BC we performed for BCSS a competing risk regression according to the method of Fine and Gray [17] using the stcrreg function from Stata. Results from Cox and competing risk regression were similar.

We used margin estimations (performed by the "margins" command) to estimate and visualize adjusted predictions of BC specific mortality for the different subtypes at different stages at diagnosis after fitting a model including stage, age at diagnosis and subtype.

All tests of significance were two sided; $P < 0.05$ was considered to be significant. All statistical analyses were carried out using STATA 14.1 software (STATA Corp., College Station, TX).

2.2. Ethics

The study was approved by the Ethics Committee St Gallen (EKSG 13/074) where the study centre was located. Patient consent for registration and further research was obtained at the time of registration from treating physician according to Swiss legislation.

3. Results

The final cohort consisted of 3975 women diagnosed for the first time with invasive BC between January 2003 and December 2005 and followed-up for a median of 10.9 years. The most frequent subtype, representing half of all tumours was the lumA-like one (1831, 46%) followed by lumB-like (1504, 38%) and TN-subtype (436, 11%) while the HER2 enriched group included only 5% ($N = 204$) of all patients. Within the lumB-like group, 365 (24%) had HER2 positive status.

Table 1 presents baseline characteristics of patients and tumours according to immunohistochemically-defined subtypes. Compared with the lumA-like subtype, patients with other subtypes and especially those with HER2+ or TN disease were more likely to be younger, present with higher stage and were less likely to be detected by screening (all $P < 0.01$). We observed important regional differences in the subtype's distribution. LumA-like tumours represented 57% of all tumours diagnosed in Geneva, but only 34% of those diagnosed in Grisons-Glarus ($P < 0.001$). These regional differences in subtype distribution among regions were biggest for stage I, decreased with increasing stage and were non-statistical significant for stage IV (Supplement, Table 1s).

Endocrine therapy was seldom omitted in patients with endocrine responsive disease, but chemotherapy was omitted in 25% of patients with HR- BC, especially those presenting with stage I or stage IV disease. Anti-HER2 therapy was administered to only 34% of patients with HER-enriched subtype, more frequently to patients with advanced HER2 positive disease (stage III and IV) (Supplement, Table 2s).

Table 2 displays outcomes by subtypes. After a median time of 10.9 years of follow-up, 1311 patients (33%) had died, 663 (17%) of them due to BC. All BC specific outcomes (disease relapse and BCS death) were less frequent in patients with lumA-like tumours. Only 9% of patients with lumA-like tumours died from BC vs. 30% of those with HER2-enriched and 27% of those with TN tumours. Median time to distant or locoregional failure was highest in lumA-like tumours, intermediate in lumB-like tumours and shortest in the HR negative subtypes. Moreover, after diagnosis of metastatic disease (relapse or stage IV disease) survival differed considerable

Table 1
Clinical and demographic characteristics according to subtypes.

	Luminal A like	Luminal B like	HER2 enriched	Triple negative	*P*-value
Numbers	1831 (46%)	1504 (38%)	204 (5%)	436 (11%)	
Age					
median (range)	62 (26–100)	61 (25–94)	59 (32–98)	57 (25–97)	$P < 0.001$
Age group					
<40 years	60 (3%)	80 (5%)	22 (11%)	58 (13%)	$P < 0.001$
40–49 years	289 (16%)	255 (17%)	38 (19%)	79 (18%)	
50–69 years	893 (49%)	743 (49%)	109 (53%)	209 (48%)	
70–79 years	358 (20%)	263 (17%)	20 (10%)	59 (14%)	
80 and older	231 (13%)	163 (11%)	15 (7%)	31 (7%)	
TNM category					
IA	812 (44%)	517 (34%)	46 (23%)	121 (28%)	P < 0.001
IB	51 (3%)	32 (2%)	3 (1%)	5 (1%)	
IIA	500 (27%)	365 (24%)	49 (24%)	120 (28%)	
II B	196 (11%)	198 (13%)	25 (12%)	67 (15%)	
III A	126 (7%)	140 (9%)	24 (12%)	51 (12%)	
III B	46 (3%)	62 (4%)	19 (9%)	20 (5%)	
III C	48 (3%)	82 (5%)	22 (11%)	26 (6%)	
IV	48 (3%)	103 (7%)	16 (8%)	25 (6%)	
X	4 (<1%)	5 (<1%)	0 (0%)	1 (<1%)	
Grade					
G1	590 (32%)	210 (14%)	2 (1%)	17 (4%)	$P < 0.001$
G2	1241 (68%)	630 (42%)	59 (29%)	101 (23%)	
G3	0 (0%)	556 (36%)	130 (64%)	298 (68%)	
GX	0 (0%)	108 (7%)	13 (6%)	20 (5%)	
Histological type					
ductal	1423 (78%)	1194 (79%)	187 (92%)	365 (84%)	$P < 0.001$
lobular	275 (15%)	193 (13%)	2 (1%)	20 (5%)	
other	133 (7%)	117 (8%)	15 (7%)	51 (12%)	
Comorbidities					
Score 0-1	1681 (92%)	1363 (91%)	192 (94%)	413 (95%)	$P = 0.03$
Score 2 or more	149 (8%)	140 (9%)	12 (6%)	23 (5%)	
Detection					
Screening	455 (25%)	267 (18%)	29 (14%)	59 (13%)	$P < 0.001$
Symptoms	834 (46%)	828 (55%)	121 (59%)	276 (63%)	
Incidental	238 (13%)	174 (12%)	19 (9%)	52 (12%)	
Other/unknown	304 (17%)	235 (16%)	35 (17%)	49 (11%)	
Place of residence[a]					
Geneva	588 (57%)	300 (29%)	39 (4%)	110 (11%)	$P < 0.001$
Valais	239 (45%)	198 (37%)	15 (3%)	78 (15%)	
Ticino	345 (48%)	253 (35%)	44 (6%)	71 (10%)	
Zurich	189 (39%)	218 (46%)	21 (4%)	51 (11%)	
St. Gallen-Appenzell	324 (41%)	318 (40%)	56 (7%)	92 (12%)	
Grisons-Glarus	146 (34%)	217 (51%)	29 (7%)	34 (8%)	

[a] Percentages refer to row.

Table 2
Outcomes according to subtypes.

	Luminal A like (n = 1831)	Luminal B like (n = 1504)	HER2 enriched (n = 204)	Triple negative (n = 436)	p-value
Status at end of follow up					P < 0.001
Alive disease free	1118 (61%)	768 (51%)	93 (46%)	234 (54%)	
Alive with relapse	87 (5%)	102 (7%)	19 (9%)	26 (6%)	
Died from BC	170 (9%)	314 (21%)	62 (30%)	117 (27%)	
Died from another disease	348 (19%)	242 (16%)	16 (8%)	42 (10%)	
Lost to follow-up w.o. relapse	108 (6%)	78 (5%)	14 (7%)	17 (4%)	
Relapses	237 (13%)	344 (23%)	67 (33%)	119 (27%)	P < 0.001
Distant (w. or w.o. LRR)	171 (9%)	269 (18%)	46 (23%)	89 (20%)	
Isolated LRR	66 (4%)	75 (6%)	21 (13%)	30 (9%)	
Median (IQR) time to distant failure in mths [a]	55 (34–90)	41 (23–69)	25 (14–40)	18 (11–35)	P = 0.002
Median (IQR) time to isolated LLR in mths [a]	70 (41–109)	57 (31–92)	31 (13–49)	33 (18–98)	P = 0.002
Median (IQR) BC specific survival time in mths	71 (43–98)	53 (33–81)	41 (20–63)	27 (13–47)	P = 0.002
Median (IQR) survival time from diagnosis of metastatic disease (relapsed or de novo) in mths	27 (9–53)	22 (8–40)	18 (6–51)	10 (3–22)	P < 0.001
Metastatic site					P < 0.001
At first diagnosis of metastatic disease (de novo or relapsed)					
Bone	106 (6%)	205 (14%)	17 (8%)	27 (6%)	
Visceral	92 (5%)	176 (12%)	35 (17%)	56 (13%)	
Brain	0 (0%)	15 (1%)	8 (4%)	13 (3%)	
At any time in course of disease					
Bone	116 (6%)	222 (15%)	21 (10%)	42 (10%)	
Visceral	123 (7%)	224 (15%)	38 (19%)	74 (17%)	
Brain	17 (1%)	60 (4%)	25 (12%)	26 (6%)	

Abbreviations: w.: with, w.o.: without; mths: months, LRR: locoregional relapse.
[a] When failure occurred.

among subtypes, reflecting biology and differences in frequency and site of metastases.

BC specific mortality as well as relapse rates increased with stage at diagnosis and differed greatly among subtypes, even within the same stage. Fig. 1 shows the predicted probability of BC death by subtype at different stages of disease corrected by age at diagnosis. At all stages, lumA-like tumours show lower risk than other subtypes, and the difference increases with stage at diagnosis. Fig. 2 shows cumulative hazard for distant relapse according to subtypes. The curves have different shapes: For both HR positive subtypes the hazard of relapse continued to increase during the whole observation period.

The determinants of BCSS and OS were examined in a multivariable Cox proportional hazards model (Table 3). While stage is the strongest predictor of outcome, subtypes are as well independently associated with the outcomes. High histologic grade, used as criterion for defining subtype in hormone receptor positive tumours, was not independently associated with outcome. Omission of endocrine therapy and radiotherapy were independently associated with poorer OS even after accounting for comorbidities. Table 4 analyses the determinants for distant and isolated LRR. Interestingly, age at diagnosis is associated with higher hazard of BC death but not of distant relapse. Patients older than 80 years have very poor survival after diagnosis of metastatic disease (de novo or

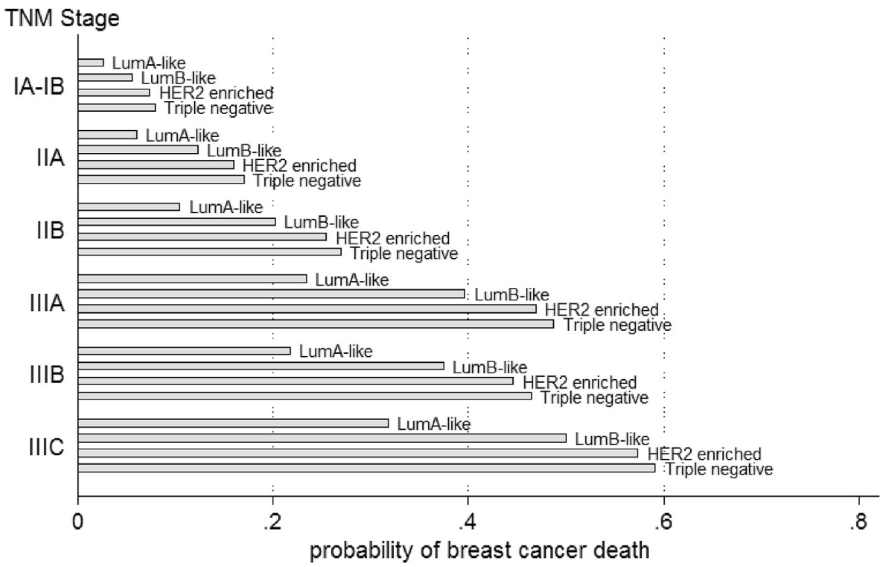

Fig. 1. Predicted probability of breast cancer death by subtype and tumour stage corrected by age. Risk of BC death differs by subtype and is distinctly lower for lumA-like tumours at any stage of the disease.

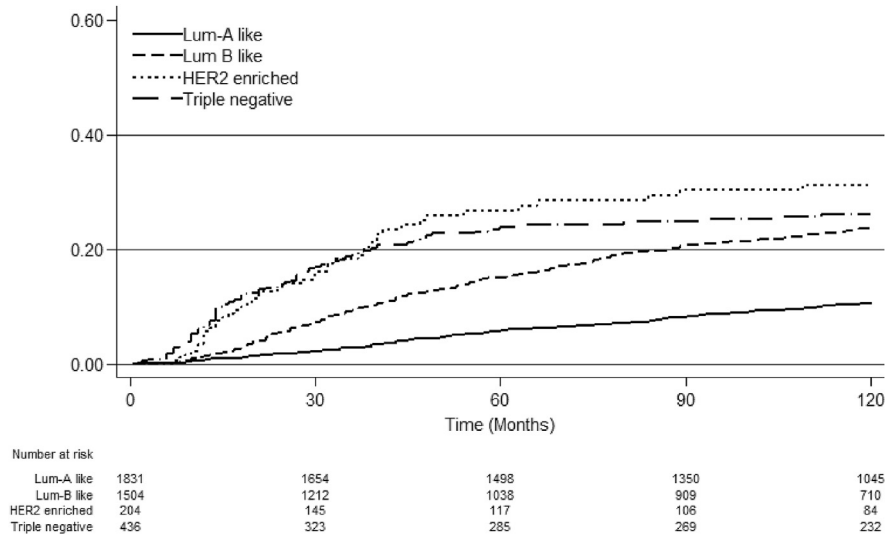

Fig. 2. Cumulative hazard for distant relapse. The risk of distant relapse differs considerably according to subtypes: for triple negative and HER2-enriched subtypes, the risk increases rapidly in the first 40 months and remains stable thereafter, while for the two HR positive subtypes the risk continues to increase till the end of the observation period.

relapsed) (Supplement, Fig. 1s). Median survival for patients aged 80 or older after diagnosis of metastatic disease was 6 months (IQR 1–17 months) versus 23 months (IQR 9–44 months) ($P > 0.01$) for patients younger than 80. This may account for the differential influence of age on distant relapse and BCSS. After controlling for other factors, regional differences were small and non-significant for BCSS and OS but present for distant and LRR (Table 4).

Isolated LRR, documented in 192 patients (5%) diagnosed with stage I–III disease, was independently associated with TN subtype, age (higher in those <40 or older than 70), place of residence and omission of radiotherapy or anti-HER2 therapy, but not with stage at diagnosis (Table 4). Omission of radiotherapy when indicated (after breast conserving surgery or after mastectomy in T3-T4/N3 tumours) increased with age. Among 274 patients aged 80 + for which radiotherapy was required, it was omitted in 198 (72%) but only in 320 out of 2813 (11%) of those younger than 80. Isolated LRR rates were, however, similar: 8% (25 out of 320) for those younger than 80 and 10% (19 out of 198) for patients 80 or older ($P = 0.5$).

4. Discussion

This population-based study highlights the importance of integrating biological features along with extent of the disease for the adequate interpretation of outcomes in population-based studies. Distant and locoregional relapse add important information that overall or even BC specific survival rates alone cannot provide. Older age at diagnosis of de novo metastatic or relapsed disease is associated with very poor survival, especially for HR negative subtypes. This suggests the need of more research on management approaches of older patients with advanced BC. Omission of radiotherapy when indicated, very frequent in older women, resulted in an increased hazard of locoregional relapse, with important regional disparities.

The prevalence of subtypes in our study differed by geographic region, similarly to what has been described in the United States [8]. These differences may possibly explain, at least in part, regional variations in survival corrected for stage shown by Fisch et al. [13]. They described higher survival rates in those regions where we found higher prevalence of less aggressive, low-grade lumA-like tumours. This may be associated with screening practices together with differential use of hormone replacement treatment [18].

In our real-world heterogeneous cohort, the influence of comorbidities and age (or frailty) on the risk of death without recurrence was considerable for patients with early BC and especially for elderly patients with lumA-like tumours. About half of the patients who died in our study, died from another condition than BC. The interaction of BC and non BC-related health conditions might be considerable but is not well characterised. The diagnosis of BC, even if not advanced, may reduce the willingness to treat aggressively or even adequately other conditions, which may contribute to the poorer relative survival rates observed in older women [19].

We observed frequent departures from state-of-the-art management especially in patients treated outside specialised centres and by teams not involved in clinical research [15]. The omission of systemic adjuvant therapies in selected patients has not lead to an increase in the hazard of BC mortality but is associated with an increased hazard of overall mortality, suggesting that omission has occurred in patients with poor health condition and reduced life expectancy. This supports the opinion of the expert panel at the 15th St. Gallen Consensus Conference, that therapeutic decisions have to be patient tailored and that de-escalation (less therapy) is possible and justified in selected patients [5]. A specialised multidisciplinary team is best suited to assure optimum care for the patient.

In our study, patients with HER2 positive tumours and especially those with endocrine insensitive disease showed very poor prognosis. This may be explained by the low proportion of women that received trastuzumab, which was approved in the adjuvant setting only in 2005. Similar findings have been described in patients with HER2 positive disease that have not received trastuzumab in historic or older cohorts [20,21]. Because of the use nowadays of targeted therapies, HER2 expression is no longer considered a risk factor [22].

Limitations of the study include the use of standard immunohistochemical panel (ER, PR and HER2 status together with grading) for determining BC subtypes and the lack of central pathological review. Discrepancies between intrinsic (gene expression based) subtypes and its approximations using a standard immunohistochemical panel are well documented [17]. Even if such an approximation may be insufficient for therapeutic decisions in individual cases, these data, readily available from pathology reports for

Table 3
Cox proportional hazard models evaluating determinants of BCSS and OS among 3975 patients by patient and tumour characteristics (all stages).

Characteristic	Number of patients (n = 3975)	Number of breast cancer deaths (%)	Number of deaths from any cause (%)	BCSS Hazard ratio (95% CI)	OS Hazard ratio (95% CI))
Subtype					
LumA-like	1831	170 (9%)	518 (28%)	1.0 (base)	1.0 (base)
LumB-like	1504	314 (21%)	556 (37%)	**1.77 (1.32–2.37)**	**1.39 (1.11–1.74)**
HER2 enriched	204	62 (30%)	78 (38%)	**4.35 (1.60–11.87)**	**3.48 (1.47–8.21)**
Triple negative	436	117 (27%)	159 (36%)	**4.18 (2.18–7.99)**	**3.06 (1.80–5.19)**
Stage					
IA	1496	58 (4%)	276 (19%)	1.0 (base)	1.0 (base)
IB	91	5 (5%)	10 (11%)	0.45 (0.06–3.31)	0.44 (0.18–1.07)
IIA	1034	103 (10%)	302 (29%)	**2.80 (1.91–4.11)**	**1.42 (1.18–1.70)**
IIB	486	84 (17%)	176 (36%)	**4.91 (3.29–7.35)**	**1.81 (1.46–2.24)**
IIIA	341	118 (35%)	157 (46%)	**10.23 (6.90–15.17)**	**2.94 (2.32–3.72)**
IIIB	147	56 (38%)	98 (67%)	**10.94 (6.74–17.76)**	**2.37 (1.75–3.20)**
IIIC	178	83 (47%)	106 (60%)	**16.71 (11.01–25.35)**	**4.05 (3.10–5.28)**
IV	192	155 (81%)	179 (93%)	**61.55 (41.21–91.93)**	**12.43 (9.69–15.95)**
X	10	1 (10%)	7 (70%)	0.00	**5.60 (1.37–22.83)**
Age at diagnosis					
<40 years	220	40 (18%)	43 (20%)	1.0 (base)	1.0 (base)
40–49 years	661	94 (14%)	112 (17%)	0.91 (0.53–1.55)	0.93 (0.57–1.51)
50–69 years	1954	276 (14%)	427 (22%)	1.15 (0.70–1.90)	1.52 (0.97–2.38)
70–79 years	700	147 (21%)	346 (49%)	**1.86 (1.09–3.17)**	**3.76 (2.38–5.95)**
80 and older	440	106 (24%)	383 (87%)	**3.18 (1.80–5.63)**	**9.47 (5.91–15.16)**
Tumour grade					
G1-G2	2850	337 (12%)	836 (29%)	1.0 (base)	1.0 (base)
G3	984	276 (28%)	394 (40%)	1.22 (0.95–1.55)	1.12 (0.93–1.35)
Comorbidities					
Score 0-1	3649	597 (16%)	1066 (29%)	1.0 (base)	1.0 (base)
Score 2 or higher	324	66 (20%)	243 (75%)	1.08 (0.77–1.51)	**1.91 (1.60–2.28)**
Endocrine therapy [a]					
Given	2934	433 (15%)	891 (30%)	1.0 (base)	1.0 (base)
Omitted	293	35 (12%)	146 (50%)	1.07 (0.73–1.58)	**1.60 (1.31–1.95)**
Chemotherapy [b]					
Given	1144	295 (26%)	365 (32%)	1.0 (base)	1.0 (base)
Omitted	1000	198 (21%)	428 (43%)	1.09 (0.83–1.44)	0.98 (0.79–1.21)
Herceptin therapy [c]					
Administered	146	39 (27%)	44 (30%)	1.0 (base)	1.0 (base)
Omitted	423	96 (23%)	158 (37%)	0.99 (0.72–1.36)	1.01 (0.80–1.27)
Radiotherapy [d]					
Performed	2512	313 (12%)	576 (22%)	1.0 (base)	1.0 (base)
Omitted	518	191 (37%)	365 (70%)	**1.29 (1.01–1.65)**	**1.29 (1.10–1.53)**
Place of residence					
Geneva	1037	120 (12%)	271 (26%)	1.0 (base)	1.0 (base)
Valais	530	81 (15%)	169 (32%)	1.21 (0.85–1.71)	1.16 (0.93–1.45)
Ticino	713	105 (15%)	211 (30%)	0.97 (0.71–1.33)	0.97 (0.79–1.20)
Zurich	479	86 (18%)	161 (34%)	0.88 (0.61–1.25)	1.02 (0.81–1.30)
St. Gallen-Appenzell	790	177 (22%)	327 (41%)	1.26 (0.95–1.66)	1.21 (0.99–1.46)
Grisons-Glarus	426	94 (22%)	172 (40%)	1.02 (0.72–1.42)	1.11 (0.88–1.40)

Abbreviations: BCCS: breast cancer specific survival, OS: overall survival.
Values in bold indicate statistically significant results.
[a] In hormone receptor positive tumours.
[b] In lumB-like, HER2 enriched and TN subtypes.
[c] In HER2 positive tumours.
[d] After breast conserving surgery or after mastectomy of locally advanced (T3/T4 or N2/N3) tumours.

cancer registries, were useful to identify subgroups with prognostic significance and reduce misinterpretation of survival results and patterns of care in this observational, population-based study.

We have not been able to capture poor function in daily life or frailty adequately. A proxy might be omission of endocrine therapy, which was independently associated with overall mortality after adjusting for age and comorbidities but not with BC specific mortality, suggesting poor health conditions.

An important strength of this study is its population-based approach. Thanks to identification of cases through cancer registries, we have been able to study patients in the community setting, in all types of practices, of any age and presenting with other health-impairing conditions. Swiss cancer registries are characterised by a high level of data completeness [23], assuring good reflection of everyday practices, even outside specialised centres. Furthermore, the broad range of outcomes studied has allowed the identification of factors related to disease relapse, seldom found in population-based studies, but very relevant for patients.

5. Conclusion

In order to refine prognosis and adequately interpret population-based studies on BC incidence, relapse, survival and quality of care, the addition of tumour biology to the anatomical extension of disease is necessary. Measures of comorbidity or frailty may help in the evaluation of quality of care in the highly heterogeneous patients of the real world.

Table 4
Cox proportional hazard models evaluating determinants of distant and isolated locoregional relapse among 3764 patients with stage I–III disease by patient and tumour characteristics.

Characteristic	Number of patients (n = 3764	Number of patients with distant relapse (%)	Number of patients with isolated LRR[a](%)	Hazard ratio of distant relapse (95% CI	Hazard ratio of isolated LRR (95% CI))
Subtype					
LumA-like	1773	170 (10%)	66 (4%)	1.0 (base)	1.0 (base)
LumB-like	1395	269 (19%)	75 (5%)	**1.36 (1.00–1.83)**	1.16 (0.64–2.10)
HER2 enriched	188	46 (24%)	21 (11%)	2.21 (0.81–6.09)	3.72 (0.76–18.28)
Triple negative	408	88 (22%)	29 (7%)	**2.30 (1.11–4.75)**	2.64 (0.75–9.23)
Stage					
IA	1496	73 (5%)	68 (5%)	1.0 (base)	1.0 (base)
IB	91	10 (11%)	6 (7%)	1.91 (0.82–4.44)	1.34 (0.47–3.79)
IIA	1034	129 (13%)	56 (5%)	**2.90 (2.07–4.04)**	1.04 (0.68–1.60)
IIB	486	95 (20%)	23 (5%)	**4.73 (3.30–6.80)**	1.16 (0.67–2.00)
IIIA	341	124 (36%)	20 (6%)	**9.62 (6.76–13.70)**	0.95 (0.48–1.89)
IIIB	147	51 (35%)	10 (7%)	**10.01 (6.22–16.10)**	1.50 (0.63–3.57)
IIIC	178	91 (51%)	8 (4%)	**17.19 (11.75–25.15)**	0.88 (0.30–2.58)
Age at diagnosis					
<40 years	215	47 (22%)	27 (13%)	1.0 (base)	**3.63 (2.03–6.52)**
40–49 years	638	90 (14%)	32 (5%)	0.73 (0.46–1.16)	1.23 (0.73–2.08)
50–69 years	1862	253 (14%)	67 (4%)	0.84 (0.55–1.29)	1.0 (base)
70–79 years	650	110 (17%)	36 (6%)	1.01 (0.63–1.63)	**1.73 (1.07–2.79)**
80 and older	399	73 (18%)	29 (7%)	1.36 (0.80–2.32)	**2.18 (1.19–3.98)**
Tumour grade					
G1-G2	2743	327 (12%)	119 (4%)	1.0 (base)	1.0 (base)
G3	920	227 (25%)	68 (7%)	**1.34 (1.04–1.73)**	1.25 (0.76–2.05)
Comorbidities					
Score 0-1	3472	525 (15%)	179 (5%)	1.0 (base)	1.0 (base)
Score 2 or higher	290	48 (17%)	12 (4%)	0.99 (0.69–1.42)	1.00 (0.49–2.06)
Endocrine therapy [b]					
Given	2798	398 (14%)	113 (4%)	1.0 (base)	1.0 (base)
Omitted	270	25 (9%)	21 (8%)	0.83 (0.54–1.28)	1.50 (0.88–2.54)
Chemotherapy [c]					
Given	1066	252 (24%)	68 (6%)	1.0 (base)	1.0 (base)
Omitted	925	151 (16%)	57 (6%)	**1.41 (1.05–1.89)**	0.93 (0.53–1.63)
Herceptin therapy [d]					
Administered	124	22 (18%)	13 (10%)	1.0 (base)	1.0 (base)
Omitted	408	91 (22%)	35 (9%)	1.18 (0.86–1.62)	**1.90 (1.13–3.22)**
Radiotherapy [e]					
Performed	2531	360 (14%)	100 (4%)	1.0 (base)	1.0 (base)
Omitted	374	81 (22%)	41 (11%)	1.23 (0.91–1.66)	**2.74 (1.70–4.43)**
Place of residence					
Geneva	995	107 (11%)	29 (3%)	1.0 (base)	1.0 (base)
Valais	515	78 (15%)	20 (4%)	1.34 (0.95–1.89)	1.47 (0.72–2.97)
Ticino	670	82 (12%)	55 (8%)	0.84 (0.60–1.16)	**2.33 (1.34–4.05)**
Zurich	457	78 (17%)	27 (6%)	0.96 (0.67–1.37)	**2.31 (1.22–4.37)**
St. Gallen-Appenzell	730	152 (21%)	37 (5%)	**1.42 (1.07–1.89)**	**1.89 (1.06–3.36)**
Grisons-Glarus	397	76 (19%)	23 (6%)	1.23 (0.86–1.75)	1.78 (0.87–3.63)

Values in bold indicate statistically significant results.
[a] In the absence of distant relapse.
[b] In hormone receptor positive tumours.
[c] In lumB-like, HER2 enriched and TN subtypes.
[d] In HER2 positive tumours.
[e] After breast conserving surgery or after mastectomy of locally advanced (T3/T4 or N2/N3) tumours.

Funding

This work was supported by Swiss Cancer Research (grant number KFS-3381-02-2014).

Conflicts of interest

The authors have declared no conflicts of interest.

Acknowledgements

This work was supported by Swiss Cancer Research (grant number KFS-3381-02-2014). The funding source was not involved in either study design; data collection, analysis and interpretation of data; writing of the report or decision to submit the article for publication.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.breast.2018.07.011.

References

[1] Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours. Nature 2000;406(6797):747–52.
[2] Sotiriou C, Wirapati P, Loi S, et al. Gene expression profiling in breast cancer: understanding the molecular basis of histologic grade to improve prognosis. J Natl Cancer Inst 2006;98(4):262–72.
[3] Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen treated node negative breast cancer. N Engl J Med 2004;351:2817–26.

[4] Solin LJ, Gray R, Goldstein LJ, et al. Prognostic value of biologic subtype and the 21-gene recurrence score relative to local recurrence after breast conservation treatment with radiation for early stage breast carcinoma: results from the Eastern Cooperative Oncology Group E2197 study. Breast Canc Res Treat 2012;134(2):683–92.
[5] Curigliano G, Burstein HJ, Winer EP, et al. De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen international expert Consensus conference on the primary therapy of early breast cancer 2017. Ann Oncol 2017;28(8):1700–12.
[6] Gnant M, Harbeck N, Thomssen C. St. Gallen 2011: summary of the Consensus discussion. Breast Care 2011;6(2):136–41.
[7] Pal SK, Katheria V, Hurria A. Evaluating the older patient with cancer: understanding frailty and the geriatric assessment. CA Cancer J Clin 2010;60(2):120–32.
[8] Kohler BA, Sherman RL, Howlader N, et al. Annual report to the nation on the status of cancer, 1975-2011, featuring incidence of breast cancer subtypes by race/ethnicity, poverty, and state. J Natl Cancer Inst 2015;107(6). djv048.
[9] Chavez-MacGregor M, Mittendorf EA, Clarke CA, et al. Incorporating tumor characteristics to the american joint committee on cancer breast cancer staging system. Oncologist 2017;22(11):1292–300.
[10] Sant M, Chirlaque Lopez MD, Agresti R, et al. Survival of women with cancers of the breast and genital organs in Europe 1999–2007. Results of the EUROCARE-5 Study. Eur J Cancer 2015;51(15):2191–205.
[11] Crocetti E, Roche L, Buzonni C et al. Trends in net survival from breast cancer in six European Latin countries: results from the SUDCAN population-based study. Eur J cancer prev 2017 trends in cancer survival in six European Latin countries: the SUDCAN study S85–S91 http:dx.doi.org/10.1097/CEJ.0000000000000291.
[12] Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37513025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet 2018;391:1023–75.
[13] Fisch T, Pury P, Probst N, et al. Variation in survival after diagnosis of breast cancer in Switzerland. Ann Oncol 2005;16(12):1882–8.
[14] Ess S, Savidan A, Frick H, et al. Geographic variation in breast cancer care in Switzerland. Cancer Epidemiol 2010;34(2):116–21.
[15] Ess S, Joerger M, Frick H, et al. Predictors of state-of-the-art management of early breast cancer in Switzerland. Ann Oncol 2011;22(3):618–24.
[16] The Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumors. Nature 2012;490:61–70.
[17] Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509.
[18] Verkooijen HM, Koot VC, Fioretta G, et al. Hormone replacement therapy, mammography screening and changing age-specific incidence rates of breast cancer: an ecological study comparing two European populations. Breast Canc Res Treat 2008;107(3):389–95.
[19] Bouchardy C, Lorez M. Arndt V and the NICER working group Effects of age and stage on breast cancer survival in Switzerland. Schweizer Krebsbulletin 2015;35(2):152–328.
[20] Engstrøm MJ, Opdahl S, Hagen AI, et al. Molecular subtypes, histopathological grade and survival in a historic cohort of breast cancer patients. Breast Canc Res Treat 2013;140(3):463–73.
[21] Yi M, Mittendorf EA, Cormier JN, et al. Novel staging system for predicting disease-specific survival in patients with breast cancer treated with surgery as the first intervention: time to modify the current American Joint Committee on Cancer staging system. J Clin Oncol 2011;29(35):4654–61.
[22] Giuliano AE, Connolly JL, Edge SB, et al. Breast Cancer-Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017;67(4):290–303.
[23] Bray F, Colombet M, Mery L, Piñeros M, Znaor A, Zanetti R, Ferlay J, editors. Cancer incidence in five continents. XI (electronic version). Lyon: International Agency for Research on Cancer; 2017. Available from: http://ci5.iarc.fr. [Accessed 20 September 2017].