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High comorbidity and tumor proliferation predict survival of localized breast cancer patients after curative surgery: A retrospective analysis of real-world data in Finland

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ABSTRACT

Background: The aim of this study was to analyze the characteristics of breast cancer patients and their impact on real-world treatment and survival outcomes.

Patients and methods: We conducted a retrospective study including all patients newly diagnosed with breast cancer during 2019 in the Southwest Finland. We identified 458 patients diagnosed with either localized (n = 435, 95 %) or metastatic (n = 23, 5 %) breast cancer.

Results: In localized breast cancer, the five-year overall survival (OS) was 90.9 %, while the five-year disease-free survival (DFS) was 93.5 %. In metastatic breast cancer, the five-year progression-free survival (PFS) was 13.0 % and five-year OS 34.2 %. The median PFS was 10.9 months (95 % CI 2.5–19.4 months) and median OS was 30.6 months (lower 95 % CI 6.9 months – not reached).

In the univariate analyses, the most important tumor-specific parameters predicting decreased DFS were tumor proliferation index >20 %, low estrogen receptor expression status and tumor size >2 cm. Univariate predictors for decreased OS included Eastern Cooperative Oncology Group (ECOG) performance status ≥2 and Charlson Comorbidity Index (CCI) score ≥3. In the multivariable analyses, CCI score ≥3 and high proliferation index (21–100 % vs. 0–20 %) predicted poorer DFS, while CCI score ≥3 and increased stage (stage 2 vs. 1) predicted poorer OS. The administration of post-operative radiotherapy was significant in the multivariable analyses of both DFS (HR 4.23, 95 % CI 1.85–9.67, p = 0.0006) and OS (HR 6.84, 95 % CI 3.33–14.02, p < 0.0001).

Conclusion: Our results demonstrate that careful clinical evaluation of ECOG and comorbidities, alongside well-established tumor characteristics predict patient survival in a population where overall five-year survival in breast cancer is over 90 %.

1. Introduction

Breast cancer is the most commonly diagnosed and most mortal cancer among women worldwide, with approximately 2.3 million new cases and nearly 670,000 deaths occurring each year [1]. The global incidence and mortality of breast cancer continues to rise, with projections indicating that the number of annual cases will surpass three million and the number of deaths will reach approximately one million by 2040 [2]. Despite these alarming statistics, the five-year age-standardized net survival of breast cancer patients worldwide has steadily increased in nearly all continents from 2000 to 2014, as demonstrated by the global cancer CONCORD-3 surveillance study [3]. This upward trend has been observed in Finland, where relative breast cancer survival has improved significantly during the last 50 years to a world-class level, with relative five-year survival exceeding 90 % in 2020 [3–5].

Breast cancer is a heterogeneous disease, with a great degree of diversity of intratumor and intertumor diversity among cancer patients [6]. This heterogeneity has a significant effect on disease progression and prognosis, highlighting the importance of understanding breast cancer-specific risk and prognostic factors. Differences in incidence rates worldwide can be explained by several reproductive, hormonal and

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behavioral risk factors, including early age at menarche, later age at menopause, lower parity, use of hormone replacement therapy (HRT) and excess body weight [7–9]. Genetics also plays a role in breast cancer susceptibility. Approximately 5–10 % of breast cancer cases are hereditary, with BRCA1 and BRCA2 being the most well-understood genes associated with hereditary breast cancer [10]. Studies have shown that BRCA1/2 mutation carriers have a cumulative breast cancer risk of roughly 70 % up to 80 years of age [11].

Prognostic factors have a key role in determining whether or not a patient receives adjuvant breast cancer therapy. Established prognostic factors in breast cancer are axillary lymph node status, tumor size, tumor grade, lymphatic/vascular invasion, histological grade, histological subtypes, hormone receptor (HR) status and human epidermal growth factor receptor 2 (HER2) expression [12–14]. In addition, the commonly used proliferation marker, Ki-67, has been accepted as a prognostic marker in breast cancer, though its clinical utility remains limited due to the lack of automated scoring and possible interlaboratory variability [15]. The challenge with these traditional prognostic factors is their inability to sufficiently identify the benefit of adjuvant chemotherapy in tumors of diameter less than 2 cm with one or no affected axillary lymph nodes [13]. For this reason, multigene-expression profiles, such as Oncotype DX® and MammaPrint ®, are a growing class of prognostic tools used in breast cancer treatment planning [16]. These genomic tests are able to predict which small breast cancer tumors with limited axillary lymph node involvement benefit from adjuvant chemotherapy, thus aiding in the clinical decision-making process. However, these tests are costly and not always available for clinical use.

In addition to these tumor-specific attributes, patient-specific characteristics hold prognostic value in breast cancer. Clinical assessment tools, such as the Eastern Cooperative Oncology Group (ECOG) performance status and the Charlson Comorbidity Index (CCI), have been shown to be associated with survival in cancer, though comprehensive research regarding the effect of these parameters on specifically breast cancer survival is lacking. High ECOG performance status has been found to be a significant predictor of overall survival (OS) in solid tumor and hematological cancers [17–19]. Similarly, high comorbidity measured using the CCI has been shown to be associated with worse in-hospital outcomes after surgery, higher breast cancer-specific mortality and higher all-cause mortality [20–23]. In a Swiss study of nearly 4000 breast cancer patients, 1311 patients died during the median follow-up time of 10.9 years, with half of these patients dying due to another disease [24]. This further highlights the importance of acknowledging comorbidity in oncologic treatment planning in the highly heterogenous population of breast cancer patients. Despite this evidence supporting the use of the CCI and ECOG performance score as prognostic factors in breast cancer, these characteristics are often forgotten in clinical practice, despite their accessible nature and simplicity.

Comprehensive real-world studies investigating the characteristics and outcomes of breast cancer patients are needed to attain information on unselected patient populations with varying genetic backgrounds treated in clinical practice, outside of clinical trials. Here, we report detailed breast cancer patient characteristics and treatment outcomes in Southwest Finland.

2. Patients and Methods

2.1. Patient population

The data of this retrospective, population-based study was collected from all patients newly diagnosed with localized or metastatic breast cancer in 2019 at the Turku University Hospital in the Wellbeing Services County of Southwest Finland (population of approximately 500,000 people). This patient population was identified using Auria Clinical information services (Turku, Finland). Patients with the International Classification of Diseases, 10th edition (ICD-10) breast cancer code C50 and/or metastasis codes C77, C78, C79 present in their health records from January 1, 2019, to December 31, 2019, were included in the study. Patients diagnosed with relapse of cancer in 2019 were excluded. The final cohort was formed by manually collecting information from electronic health records to avoid the potentially erroneous nature accompanied by automated collection of data. The study cohort was followed until February 2024, thus enabling the analysis of five-year survival rates and treatment outcomes.

2.2. Study design

This was a retrospective, population-based study that collected information of all new breast cancer patients diagnosed at the Turku University Hospital in the Wellbeing Services County of Southwest Finland during the year 2019. The primary endpoints of this study were to evaluate OS and disease-free survival (DFS) of localized breast cancer patients, as well as progression-free survival (PFS) and OS of metastatic patients. The secondary endpoint of the study was to identify prognostic factors for survival in localized breast cancer.

2.3. Data collection

Data was retrospectively collected from electronic medical records of Turku University hospital. The following demographic and medical history data was extracted: age, gender, body mass index (BMI), menopausal status, postmenopausal HRT use, age at menarche, parity, family history of breast cancer, breast cancer detection method, breast cancer genetic testing results, comorbidities in the form of the Charlson Comorbidity Index (CCI) [25] and Eastern Cooperative Oncology Group (ECOG) performance status [26,27]. Family history of breast cancer was defined as having had a mother, sister or daughter diagnosed with invasive breast cancer. Genetic testing for breast cancer was performed using a gene panel consisting of the following genes, whose variants were associated with a high (over 40 %) or medium high (20–39 %) lifetime risk for breast cancer: ATM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, FANCM, MLH1, MSH2, MSH6, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11 and TP53.

The breast cancer-specific clinicopathological data collected included histological subtype, tumor size, focality, histological grade, number of metastatic sentinel lymph nodes, number of all metastatic lymph nodes, presence of micrometastases, number of lymph nodes with isolated tumor cells (ITC), lymphovascular invasion (LVI) status, estrogen receptor (ER) and progesterone receptor (PR) expression statuses [28], tumor proliferation index (measured using Ki-67 or MIB-1) [29], HER2 immunohistochemistry and in situ hybridization scores [30,31] and breast cancer stage [32]. For the tumor proliferation index, a cut-off value of 20 % was chosen due to this being the threshold value between high and low proliferation in Finnish clinical practice. HR-positivity was defined as at least $\geq$1 % of cancer cells being positive for either ER or PR.

The dates and types of breast cancer treatment were acquired, including surgeries, neoadjuvant treatments and adjuvant treatments. Surgical treatments were recorded according to the most invasive operation performed, with mastectomy and axillary lymph node dissection (ALND) defined as the most invasive types of surgery. Neoadjuvant treatments were defined as breast cancer treatments administered prior to a patient's first breast cancer surgery. Hormone therapy data included the type of hormone therapy administered and duration of hormone therapy. Types of hormone therapy included the following: selective ER modulators, aromatase inhibitors and luteinizing hormone-releasing hormone (LHRH) analogs. The administered chemotherapy and anti-HER2 therapy drugs, number of delivered cycles and dates of administration were collected. Radiation therapy (RT) target sites, dates, dosages and boosts were obtained. Disease progression was defined according to the judgment of the treating physician and their interpretation of radiological findings, laboratory results (CA15-3) and clinical status findings.

The number of metastatic cases was recorded alongside the age, biological subgroups, CCI, ECOG performance statuses and survival data of these patients. A total of 5 % (n = 23) of patients were initially diagnosed with de novo metastatic breast cancer. Patients with metastatic disease were excluded from further analyses.

2.4. Statistical analysis

Categorical variables are summarized with counts and percentages (%). Normally distributed continuous variables are presented using mean, standard deviation (SD) and 95 % confidence intervals (CI), while non-normal continuous variables are presented using median and range. First and third quartiles are presented for median times at event in the localized cohort.

For survival analyses, OS, DFS and PFS were used as endpoints. In the localized breast cancer cohort, median time at relapse or death was calculated amongst those who experienced relapse or death. For the metastatic cohort, median survival was calculated from Kaplan-Meier curves. OS was defined as the time from the first oncological appointment to the date of death from any cause. DFS referred to the duration between first oncological appointment and the date of relapse (localized recurrence or metastasis), death from any cause or last follow-up. PFS was the time from first oncological appointment to the date of disease progression or death from any cause. The end of the follow-up period, February 7th, 2024, was a censoring event in all survival analyses. Patients still alive at the end of the follow-up period were censored.

Survival curves were generated by using the Kaplan-Meier method. Univariate analyses were performed using the log-rank test and univariate Cox's proportional hazard model. The Cox model was used to examine the effect of all patient and tumor-specific variables on survival outcomes. Variables that were significant in univariate survival analyses were chosen for further analyses. Correlation analyses were performed amongst these significant variables using the chi-square test. Variables displaying strong correlation were excluded from multivariable analyses to avoid multicollinearity issues in multivariable modeling. The variables chosen for the DFS multivariable Cox proportional hazards model were CCI-score, proliferation (0–20 % vs. 21–100 %) and RT administration (no RT administered vs. RT administered). Likewise, CCI-score, stage (stage 2 vs. stage 1) and RT administration (no RT administered vs. RT administered) were the variables chosen for the multivariable Cox proportional hazards model of OS.

All statistical tests were two-sided and the alpha level for determining statistical significance was set at 0.05. All statistical analyses were performed using JMP® software (version 17.0.0. SAS Institute Inc., Cary, NC, 1989–2024.)

2.5. Ethical considerations

The study was approved by the institutional research board (License numbers T781/2023; VSSHP/2023/136140). Informed consent was waived due to retrospective design of the study according to Finnish act on Secondary Use of Social and Health Data effective from April 2019 (Act 552/2019). All data were collected, stored, and handled in a manner that meets the regulation of GDPR and the Secondary Use Act 552/2019. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions and regulations mandated by the Secondary Use Act.

3. Results

3.1. Patient characteristics

During 2019, 458 patients were newly diagnosed with breast cancer at the Turku University Hospital in the Wellbeing Services County of Southwest Finland. A majority of these patients were diagnosed with localized breast cancer (n = 435, 95 %), while the remaining 5 % (n = 23) were diagnosed with metastatic breast cancer. The demographic and clinical data of localized breast cancer patients are described in detail in Table 1.

The biological subgroups of localized breast cancer were as follows: 79 % (n = 344) were HR-positive and HER2-negative, 10 % (n = 43) HR-positive and HER2-positive, 3 % (n = 12) were HR-negative and HER2-positive, and 7 % (n = 31) were triple negative (TNBC; HR-negative and HER2-negative). In total, 13 % (n = 55) of patients were HER2-positive and 89 % (n = 387) were HR-positive. Data needed for biological subgroup classification was missing in 1 % (n = 5) of patients.

The mean patient age at diagnosis was 65 years (range 25–95 years) for localized breast cancer. Almost all patients in the study were female (n = 433, 99 %), except for two male patients with localized breast cancer.

The average BMI of patients with localized breast cancer was 27 kg/m^2 (SD 5.3, range 17–46 kg/m^2).

The performance status of 79 % of localized breast cancer patients was either similar to pre-disease performance or restricted only in physically strenuous activity (ECOG = 0–1, n = 344) at diagnosis [33]. There were 56 patients (13 %) with localized breast cancer whose ECOG performance score was 2 or greater. The average CCI-score of localized breast cancer patients was 2.7 (SD 1.8). Approximately half (n = 207, 48 %) of patients were classified as having moderate (CCI-score of 3–4) or severe (CCI-score $\geq$5) comorbidity, while 16 % (n = 69) of all patients had a severe comorbidity status.

Postmenopausal status at diagnosis was common among localized breast cancer patients (86 %, n = 374). The average age at menopause of localized breast cancer patients was 49 years (SD 5.3, range 32–61 years). History of hormone replacement therapy was reported among 41 % of localized breast cancer patients (n = 177).

Approximately 20 % (n = 89) of localized breast cancer patients had a reported family history of breast cancer. Genetic testing detected the following breast cancer mutations in 5 of the 48 (10 %) tested localized breast cancer patients: BRCA1 (c.5266dup, p.(Gln1756Profs*74)), BRCA1 (c.68_69del, p.(Glu23Valfs*17)), BRCA2 (c.6996dup, p.(Val2333Cysfs*7)), ATM (c.3153 + 14T > A) and PALB2 (c.1592del, p.(Leu531Cysfs*30)). In addition to these findings, one BRCA variant of unknown significance was found among the tested patients (2 %).

A majority of localized breast cancer cases were found via screening mammograms (n = 221, 51 %), while the remaining cases were found in symptomatic patients and through subsequent imaging (n = 189, 43 %) or in asymptomatic patients via examination by healthcare professionals (n = 24, 6 %).

Metastatic patients were excluded from detailed analyses due to low patient count. A summary of their characteristics is described in Supplementary Table 1.

3.2. Tumor characteristics of localized breast cancers

A total of 458 localized breast cancer tumors were identified, with the number of localized tumors exceeding the number of localized patients due to multifocality. A majority of localized (n = 334, 73 %) breast cancer tumors were invasive ductal carcinomas, and the second most common histological subtype was invasive lobular carcinoma (n = 76, 17 %). Over half of localized breast cancer tumors were grade 2 (n = 257, 56 %). Grade 1 (n = 100, 22 %) and 3 (n = 95, 21 %) tumors were less frequent.

The median size of localized breast cancer tumors was 15 mm (range 1–150 mm). A third (n = 151, 33 %) of tumors were T2 or greater (size >20 mm). Roughly three-quarters of localized breast cancer tumors were unifocal (n = 333, 73 %). Most localized breast cancer tumors were accompanied by zero metastatic sentinel lymph nodes (n = 291, 64 %) and zero total metastatic lymph nodes (n = 302, 66 %). Approximately one-fifth (n = 97, 21 %) of patients had one or more metastatic sentinel lymph nodes and one-third (n = 143, 31 %) had one or more total

Table 1
Demographic and clinical data of localized breast cancer patients (n = 435).

Age (years) at initial diagnosis of breast cancer	
Median (range)	66 (25–95)
Sex, n (%)	
Female	433 (100)
Male	2 (0)
BMI	
Average (SD)	27.2 (5.28)
Missing, n (%)	23 (5)
Initial ECOG performance status, n (%)	
0	164 (38)
1	180 (41)
2	45 (10)
3	10 (2)
4	1 (0)
Missing	35 (8)
CCI-score, n (%)	
0 pts	39 (9)
1–2 pts	189 (43)
3–4 pts	138 (32)
5 or more	69 (16)
Missing	0 (0)
Average (SD)	2.7 (1.75)
Menarche age (years), n (%)	
<12	49 (11)
≥ 12	299 (69)
Missing	87 (20)
Number of births, n (%)	
0 births	45 (10)
1–2 births	257 (59)
3 or more births	88 (20)
Missing	45 (10)
Menopausal status at diagnosis, n (%)	
Premenopausal	59 (14)
Postmenopausal	374 (86)
N/A because male	2 (0)
Menopause age (years), n (%)	
median (range)	50 (32–61)
Under 40	14 (3)
40-44	32 (7)
45-54	198 (46)
55 or over	36 (8)
Missing	155 (36)
History of HRT, n (%)	
Systemic HRT	50 (11)
Local HRT	45 (10)
Local and systemic HRT used	17 (4)
History of HRT use, but no information regarding delivery method	65 (15)
No history of HRT use	172 (40)
Missing	86 (20)
Family history of breast cancer[a], n (%)	
No family history	294 (68)
Family history present	89 (20)
Missing	52 (12)
Breast cancer genetic testing results, n (%)	
Genetic testing not performed	387 (89)
Genetic testing performed, but no breast cancer mutations were found	42 (10)
Genetic testing performed; breast cancer mutation found [b]	5 (1)
Genetic testing performed; mutation found that does not increase risk of breast cancer [c]	1 (0)
Missing	0 (0)
Method of breast cancer detection, n (%)	
Patient symptomatic and cancer found in subsequent imaging	189 (43)
Found in screening mammography, no prior symptoms	221 (51)
Found via examination by healthcare professional, no prior symptoms or imaging performed	24 (6)
Missing	0 (0)

Abbreviations: BMI, body mass index; SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; CCI, Charlson Comorbidity Index; HRT, hormone replacement therapy.

[a] Definition of family history: mother, sister, daughter with invasive breast cancer

[b] Genetic mutations found: BRCA1 (c.5266dup, p.(Gln1756Profs*74)), BRCA1 (c.68_69del, p.(Glu23Valfs*17)), BRCA2 (c.6996dup, p.(Val2333Cysfs*7)), ATM (c.3153 + 14T > A), PALB2 (c.1592del, p.(Leu531Cysfs*30))

[c] Genetic mutation found: BRCA variant of unknown significance

metastatic lymph nodes. Micrometastases were present in one or more lymph nodes in 11 % (n = 51) of localized breast cancer cases. LVI was present in 18 % (n = 49) of localized cases where LVI was known. Over a third (39 %, n = 178) of all localized cases lacked documentation on LVI status.

The presence of lymph node positivity in different biological subgroups was as follows: 33 % (n = 131) of HR positive tumors were lymph node positive, as were 38 % (n = 21) of HER2 positive tumors and 13 % (n = 4) of TNBC tumors. Information regarding the total number of metastatic lymph nodes was missing in 3 % (n = 13) of patients. In the HR+/HER2-subgroup, 26 % (n = 85) of patients had 1-3 metastatic lymph nodes and 7 % (n = 21) had 4 or more metastatic lymph nodes, when considering patients with known numbers of metastatic lymph nodes. Out of the 85 patients with 1–3 metastatic lymph nodes, 31 % (n = 26) had high risk tumors that were greater than or equal to 5 cm in size or gradus 3.

The median proliferation index for localized breast cancer tumors was 14 % (range 1–80 %). There were 289 tumors (63 %) with proliferation of 0–20 %, while the rest had proliferative indexes of 21–100 % (n = 143, 31 %).

There were 224 (49 %) stage I cases, 168 (37 %) stage II cases and 52 (11 %) stage III localized cases. HR positivity was enriched in stage I, with 91 % (n = 201) of them being HR positive. Regarding stage III cases, 71 % were (n = 36) HR+/HER2-, 6 % (n = 3) were HR-/HER2+, 16 % (n = 8) were HR+/HER2+ and 6 % (n = 3) were TNBC. The clinicopathological characteristics of tumors are described in further detail in Table 2.

3.3. Treatment characteristics of localized breast cancers

Nearly all patients with localized breast cancer underwent breast cancer surgery (n = 432, 99 %). Breast-conserving surgery alongside sentinel node biopsy (SNB) were the most common surgical treatment strategies among patients with localized breast cancer (n = 262, 60 %; n = 323, 74 %, respectively). Mastectomy was performed in 39 % (n = 170) of patients. The characteristics of the surgical treatments administered in localized disease are outlined in Table 3.

Neoadjuvant treatment was administered to 3 % of patients with localized disease (n = 14). The subtypes of breast cancer that received neoadjuvant treatment were the following: 64 % (n = 9) were HR+/HER2+, 21 % (n = 3) HR-/HER2+ and 14 % (n = 2) TNBC. The most frequently used neoadjuvant treatment was docetaxel-trastuzumab-pertuzumab among patients with localized breast cancer, with 87 % (n = 13) of patients receiving this regimen as part of their neoadjuvant therapy. The characteristics of neoadjuvant treatments administered in localized disease are described in Table 3.

Roughly half of patients with localized breast cancer received adjuvant chemotherapy and/or anti-HER2 therapy (n = 215, 49 %). Cyclophosphamide, epirubicin and fluorouracil (CEF) or cyclophosphamide and epirubicin (CE) was administered to 76 % (n = 164) of those who received adjuvant chemotherapy, making CEF/CE the most frequently administered adjuvant chemotherapy regimen. Among individuals who did not receive adjuvant chemotherapy, a vast majority (89 %, n = 195) were HR+/HER2-, with the remaining subtypes each comprising accounting for approximately 3–4% (n = 7–9) of patients. In addition, 69 % (n = 147) of patients who did not receive adjuvant chemotherapy were stage 1, 24 % (n = 51) were stage 2 and 7 % (n = 15) were stage 3. Only a minority (15 %, n = 32) of those who did not receive adjuvant chemotherapy were lymph node positive. Among those who received adjuvant chemotherapy, over half (64 %, n = 137) were HR+/HER2-, 16 % (n = 35) were HR+/HER2+, 10 % (n = 22) were TNBC and 6 % (n = 12) were HR-/HER2+. The distribution of stages among those who received adjuvant chemotherapy was as follows: 31 % (n = 64) were stage 1, 52 % (n = 108) stage 2 and 17 % (n = 36) stage 3. Approximately half (48 %, n = 101) of those who received adjuvant chemotherapy were lymph node positive. Out of the 180 HR+/HER-patients

Table 2
Clinicopathological characteristics of localized tumors (n = 458).

Histological subtype, n (%)	
ductal	334 (73)
lobular	76 (17)
Mixed: ductal and other[a]	27 (6)
other [b]	20 (4)
Missing/unknown	1 (0)
Tumor size, n (%)	
1–20 mm	297 (65)
> 20 mm	151 (33)
median (range)	15 (1–150)
Missing/unknown	10 (2)
Focality, n (%)	
Unifocal	333 (73)
Multifocal	118 (26)
Missing/unknown	7 (2)
Histological grade, n (%)	
1	100 (22)
2	257 (56)
3	95 (21)
Missing/unknown	6 (1)
Number of all metastatic lymph nodes, n (%)	
0	302 (66)
1	77 (17)
2	28 (6)
3-9	28 (6)
≥ 10	10 (2)
Missing/unknown	13 (3)
Number of metastatic sentinel lymph nodes, n (%)	
0	291 (64)
1	73 (16)
2	19 (4)
≥ 3	5 (1)
Missing/unknown	70 (15)
Presence of micrometastases, n (%)	
No micrometastases	394 (86)
Micrometastases present in one lymph node	44 (10)
Micrometastases present in two lymph nodes	7 (2)
Missing/unknown	13 (3)
Number of lymph nodes with ITC, n (%)	
0	406 (89)
1	37 (8)
2	2 (0)
Missing/unknown	13 (3)
LVI status, n (%)	
No LVI	231 (50)
LVI present	49 (11)
Missing/unknown	178 (39)
Hormone receptor status	
Median ER-positivity % (range)	98 (0–100)
ER-negative (0 %)	49 (11)
ER-positive (≥1 %)	407 (89)
Missing/unknown	2 (0)
Median PR-positivity % (range)	80 (0–100)
PR-negative (0 %)	92 (20)
PR-positive (≥1 %)	361 (79)
Missing/unknown	5 (1)
Proliferation[c], n (%)	
< 10 %	148 (33)
10–20 %	158 (35)
> 20 %	149 (33)
median (range)	14 (1–80)
Missing/unknown	3 (1)
HER2-status, n (%)	
HER2-negative	380 (83)
HER2-positive	58 (13)
Missing/unknown	20 (4)
Breast cancer stage, n (%)	
I	224 (49)
IIA	125 (27)
IIB	43 (9)
IIIA	39 (9)
IIIB	5 (1)
IIIC	8 (2)
Missing/unknown	14 (3)

Abbreviations: ITC, isolated tumor cells; LVI, Lymphovascular invasion; ER, estrogen receptor; PR, progesterone receptor; SD, standard deviation; HER2, human epidermal growth factor 2.

[a] Other histological subtypes appearing alongside invasive ductal: lobular, apocrine, neuroendocrine, mucinous, micropapillary, solid papillary

[b] Other histological subtypes: mucinous, tubular, solid papillary, medullary, tubulolobular, metaplastic

[c] Measured using Ki-67 or MIB-1

with either T1c N0/N1 (tumor size >10 mm and ≤20 mm; 3 or less metastatic lymph nodes) or T2N0 (tumor size >20 mm and ≤50 mm; no metastatic lymph nodes) breast cancer, 48 % (n = 86) received adjuvant chemotherapy.

A majority of localized breast cancer patients were given RT (n = 355, 82 %). RT was most often administered only to the post-resection breast (n = 203, 57 %) or post-mastectomy (n = 3, 1 %) area, with 40.05 Gy (2.67 Gy x 15) and 50 Gy (2 Gy x 25) administered nearly as frequently (n = 147, 41 %, n = 130, 37 % respectively). The following subgroups did not receive RT, despite having a clinical indication for it: 3 % (n = 8) of patients who underwent breast-conserving surgery, 100 % (n = 3) of those who did not receive any breast surgery and 8 % (n = 10) of those with lymph node-positive disease. Closer comparisons of patients who underwent RT versus those who did not revealed that the mean age of those who were not administered radiotherapy was 10.5 years greater than those who received radiotherapy. Similarly, the average CCI-score of patients who underwent radiotherapy was 2.5, while those who did not receive radiotherapy had an average CCI-score of 3.7. The percentage of patients who underwent breast-conserving surgery, or mastectomy with T3-4 (tumor size >50 mm) or lymph node positive disease was 80 % (n = 350).

Hormone therapy was administered to 71 % (n = 311) of localized breast cancer patients and 98 % (n = 307) of those who received hormone therapy were HR-positive. Aromatase inhibitors were the most prevalent type of hormone therapy administered. Out of those who were administered hormone therapy, 91 % (n = 282) received aromatase inhibitors. Letrozole was the most common type of aromatase inhibitor administered (n = 171, 61 %). Out of those who were HR-positive and did not receive hormone therapy, 73 % (n = 55) were T1a/b (tumor size 1–10 mm). The characteristics of adjuvant therapy are described in further detail in Table 3.

3.4. Survival outcomes

Follow-up data was available for all patients. In the localized breast cancer cohort, the median follow-up time was 54.7 months (range 0.4–61.1 months, mean 52.8 months), with 24 relapses and 38 deaths noted during the follow-up period. The five-year DFS and OS were 93.5 % (estimated mean survival time 55.6 months) and 90.9 % (estimated mean survival time 52.1 months), respectively (Fig. 1). Among those experiencing relapse or death, the median time at relapse was 25.6 months (Q1: 11.2 months; Q3: 37.5 months) and median time at death was 28.5 months (Q1: 20.9 months; Q3: 41.7 months).

In the metastatic breast cancer cohort, the median follow-up time was 30.5 months (range 0.2–61.2 months, mean 30.2 months). During the follow-up period, a total of 20 progressions and 15 deaths were noted. The five-year PFS was 13.0 % and five-year OS 34.2 % (Fig. 2). In reality, the five-year PFS was already achieved at approximately 4.5 years, due to all patients experiencing progression before the five-year timepoint. The median PFS was 10.9 months (95 % CI 2.5–19.4 months) and median OS was 30.6 months (lower 95 % CI 6.9 months – not reached).

3.5. Prognostic factors for survival of localized breast cancer

In the univariate regression analyses, the most significant predictors of decreased DFS were lack of RT, proliferation index >20 %, low ER

Table 3
Neoadjuvant, surgical and adjuvant therapy characteristics for localized disease (n = 435).

Neoadjuvant treatment	
Patients who received neoadjuvant treatment, n (%)	14 (3)
Neoadjuvant treatment received[a], n (%)	
Docetaxel-Trastuzumab-Pertuzumab	13 (87)
Docetaxel-Trastuzumab	1 (7)
Paclitaxel-Trastuzumab-Pertuzumab	1 (7)
Vinorelbine-Trastuzumab-Pertuzumab	1 (7)
Only Docetaxel	1 (7)
Carboplatin-Paclitaxel and CEF75	1 (7)
Surgical treatment	
Type of breast cancer surgery, n (%)[b]	
Mastectomy	170 (39)
Breast-conserving surgery	262 (60)
No breast surgery performed	3 (1)
Type of lymph node surgery, n (%)[b]	
SNB	323 (74)
ALND	68 (16)
SNB and ALND	30 (7)
No axillary surgery performed	14 (3)
Adjuvant treatment	
Patients who received adjuvant chemotherapy and/or anti-HER2 therapy, n (%)	215 (49)
Adjuvant chemotherapy and/or anti-HER2 therapy received[a], n (%)	
Docetaxel-Trastutzumab	23 (11)
Docetaxel-Trastutzumab-Pertutzumab	2 (1)
Paclitaxel-Trastutzumab	10 (5)
Capecitabine-Trastutzumab	1 (0)
Only Docetaxel [c]	97 (45)
Docetaxel-Capecitabine	3 (1)
Only Capecitabine	1 (0)
CEF or CE	164 (76)
Only Paclitaxel	1 (0)
Palbociclib	1 (0)
CMF	24 (11)
CEX	3 (1)
Maintenance anti-HER2 therapy with Trastutzumab until 1 year	42 (20)
Maintenance anti-HER2 therapy with Trastutzumab-Pertutzumab until 1 year	1 (0)
Trastutzumab-Emantasine	3 (1)
Patients who received radiation therapy, n (%)	355 (82)
Total Gy of fractionated radiotherapy given, n (%)	
40.05 (2.67 Gy x 15)	147 (41)
42.72 (2.67 Gy x 16)	58 (16)
50 (2 Gy x 25)	130 (37)
Other	20 (6)
Radiation therapy target, n (%)	
Only the post-resection breast	203 (57)
Only the post-mastectomy area	3 (1)
Breast and axillary region	146 (41)
missing	3 (1)
Boost radiation, n (%)	
Received boost radiation of the tumor bed	37 (10)
Did not receive boost radiation of the tumor bed	313 (88)
missing	3 (1)
Number (%) of patients who received hormone therapy	311 (71)
Type of hormone therapy used[a], n (%)	
Selective estrogen receptor modulator: Tamoxifen	47 (15)
Aromatase inhibitors	282 (91)
Only letrozole	171 (61)
Only anastrozole	52 (18)
Only exemestane	17 (6)
More than one type of aromatase inhibitor used	42 (15)
LHRH-analog: Leuprorelin	27 (9)

Abbreviations: CEF, cyclophosphamide, epirubicin, fluorouracil; SNB, sentinel node biopsy; ALND, axillary lymph node dissection; CE, cyclophosphamide, epirubicin; CMF, cyclophosphamide, methotrexate, and fluorouracil; CEX, capecitabine, epirubicin, cyclophosphamide; HER2, human epidermal growth factor 2; Gy, Gray; LHRH, luteinizing hormone releasing hormone.

[a] Note: some patients received more than one treatment type

[b] Defined by the most invasive operation performed

[c] Refers to patients receiving docetaxel either as single-agent chemotherapy or as part of combination chemotherapy, e.g. docetaxel followed by CEF.

expression status, tumor size >2 cm and histological grade (2 vs. 3) (Table 4). Likewise, CCI-score ≥3, ECOG performance status ≥2, mastectomy instead of breast-conserving surgery, no initial axillary surgery instead of SNB and complete lack of RT were the most significant predictors of decreased OS (Table 5). In addition, stage was a significant predictor of both DFS and OS, with the univariate analyses of both stage 2 versus stage 1 (DFS: HR 4.52, 95 % CI 1.47–13.86, $p = 0.0083$; OS: HR 2.91, 95 % CI 1.32–6.44, $p = 0.0083$) and stage 3 versus stage 1 (DFS: HR 6.93, 95 % CI 1.95–24.56, $p = 0.0027$; OS: HR 2.98, 95 % CI 1.06–8.39, $p = 0.0381$) producing significant results. Univariate analyses of DFS were also performed for BMI, menopausal status, histological subtype, local lymph node involvement (N0 versus N+), stage 2 versus stage 3, type of surgical treatment, type of axillary surgery, whether or not adjuvant chemotherapy was administered and whether or not adjuvant hormone therapy was administered, but these were not included in Table 4, since they were not significant. Similarly, univariate analyses of OS were also performed for BMI, menopausal status, histological subtype, histological grade, local lymph node involvement (N0 versus N+) and stage 2 versus stage 3, but were not included in Table 5 due to insignificance.

Multivariable regression analyses revealed that CCI-score ≥3 (HR 2.62, 95 % CI 1.06–6.49, $p = 0.0377$), proliferation index <20 % (HR 0.18, 95 % CI 0.07–0.43, $p = 0.0001$) and lack of RT (HR 4.23, 95 % CI 1.85–9.67, $p = 0.0006$) were all independent predictors of DFS (Table 4). CCI-score ≥3 (HR 5.26, 95 % CI 1.79–15.40, $p = 0.0025$) and lack of RT (HR 6.84, 95 % CI 3.33–14.02, $p < 0.0001$) were also independent predictors of OS, alongside increased stage (stage 2 vs. 1) (HR 2.31, 95 % CI 1.04–5.15, $p = 0.0405$) (Table 5).

4. Discussion

The aim of this retrospective study was to gain an understanding of the breast cancer patient population treated at the Turku University Hospital in the Wellbeing Services County of Southwest Finland by thoroughly examining patient, tumor and treatment characteristics and evaluating the effect of these characteristics on patient survival. Currently, no comprehensive cancer treatment registries exist in Finland. Here, we report retrospective real-world findings, featuring extensive data from a cohort of 458 patients who were newly diagnosed with breast cancer during 2019 in the region of Southwest Finland. Since nearly all breast cancer cases in Finland are managed within the public healthcare sector and given the excellent health registry data in Finland facilitated by Finland's national personal identity code system, this dataset is exceptionally comprehensive regarding population coverage and represents nearly 10 % of all breast cancer patients diagnosed in Finland yearly. The proportions of localized and metastatic breast cancer cases observed in our study (95 % localized and 5 % metastatic) align closely with prior research conducted within Finnish and other populations [34–36].

Our study provides novel real-world data regarding breast cancer outcomes in Finland. For localized breast cancer, the five-year DFS was 93.5 % and five-year OS was 90.9 %. Median DFS and OS at five years were not met. These survival results are consistent with previous research published in other Nordic countries [4], Europe [37], the U.S. [37,38], as well as data produced by the Finnish Cancer Registry [39]. The general characteristics of both the patient population and tumors are also in line with previous reports. Information regarding the histological subtype, grade, proliferation and hormone receptor status was exceptionally recorded in localized breast cancer, with missing data on these characteristics ranging from 0.2 to 1.3 %. The distribution of the biological subgroups of local and metastatic breast cancer were similar to previous studies. In a large French study with a cohort of 22,000 metastatic breast cancer patients, 62 % of women had HR+/HER2- disease, 18 % were HER2+ and 13 % had TNBC [40], whereas a U.S. study reported that 68 % of all breast cancer patients were HR+/HER2-, 14 % HER2+, 10 % TNBC and 8 % unknown [41]. These results are consistent with our results of 79 % HR+/HER2-, 13 % HER2+, 7 % TNBC and 1 %

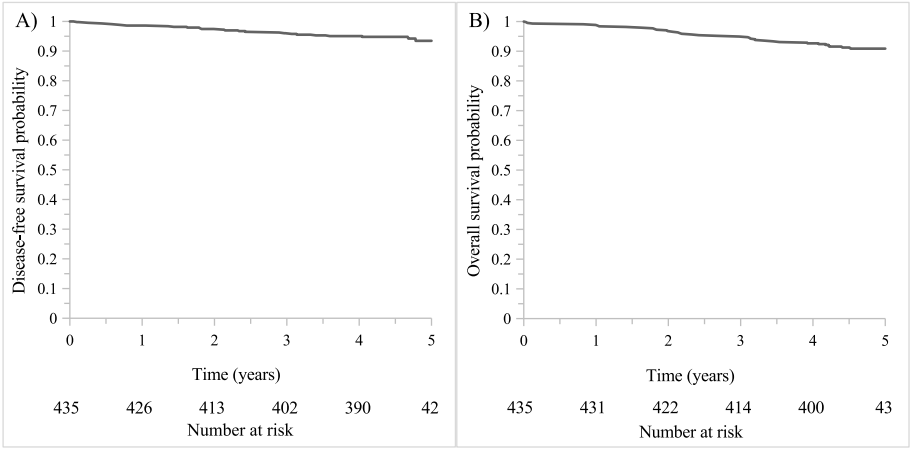

Fig. 1. A) Disease-free survival (DFS) and B) overall survival (OS) of patients with localized breast cancer. Numbers at risk reported at 0, 1, 2, 3, 4 and 5 years.

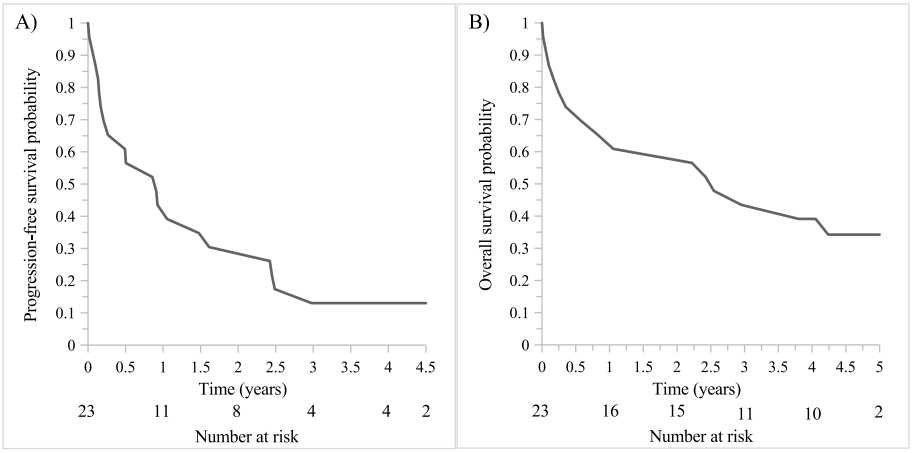

Fig. 2. A) Progression-free survival (PFS) and B) overall survival (OS) of patients with metastatic breast cancer. Number at risk reported at 0, 1, 2, 3, 4 and 4.5 years for PFS in metastatic cancer due to all patients experiencing progression before the 5-year timepoint. Number at risk reported at 0, 1, 2, 3, 4 and 5 years for OS in metastatic cancer.

Table 4
Univariate and Multivariable Cox regression analysis of disease-free survival in localized breast cancer.

Variables	Univariate Analysis		Multivariable Analysis	
	HR (95 % CI)	*P-value*	HR (95 % CI)	*P*-value
Age <65 vs. ≥ 65	2.18 (0.94–5.64)	0.0828		
CCI-score (≥3 pts vs. 0–2 pts)	2.91 (1.21–7.02)	0.0174*	2.62 (1.06–6.49)	0.0377*
ECOG performance status (2–4 vs. 0–1)	2.75 (1.07–7.03)	0.0349*		
Detection method (symptomatic vs. screening)	3.28 (1.28–8.38)	0.0131*		
Tumor size >20 mm vs. ≤ 20 mm	4.10 (1.76–9.59)	0.0011**		
ER-status (TNBC vs. ER 91–100 %)	5.41 (2.00–14.62)	0.0009**		
Histological grade (2 vs. 3)	0.27 (0.12–0.60)	0.0014**		
Proliferation (0–20 % vs. 21–100 %)	0.19 (0.08–0.47)	0.0003**	0.18 (0.07–0.43)	0.0001**
Lymph node status (≥3 vs. 1–2)	6.32 (1.58–25.28)	0.0092**		
Stage (2 vs. 1)	4.52 (1.47–13.86)	0.0083**		
Stage (3 vs. 1)	6.93 (1.95–24.56)	0.0027**		
No radiotherapy administered vs. radiotherapy administered	5.22 (2.34–11.65)	<0.0001**	4.23 (1.85–9.67)	0.0006**

Abbreviations: HR, hazard ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor.
* = $p < 0.05$, ** = $p < 0.01$.

unknown for local breast cancer and 65 % HR+/HER2-, 17 % HER2+, 9 % TNBC and 9 % unknown for metastatic breast cancers.

The most significant tumor-specific predictors of DFS in localized breast cancer were proliferation index, ER-status, tumor size and histological grade in our cohort. These findings correspond with the latest opinions and panels of breast cancer specialists [16,24]. Significant interlaboratory variability in Ki-67 staining has been described, leading to challenges regarding the clinical use of Ki-67 [15,42]. However, our data suggests excellent consistency in pathological and stage assessments. Our results also strongly support the current Finnish clinical practice of using 20 % as a cut-off value for differentiating between high and low proliferation tumors.

Table 5
Univariate and Multivariable Cox regression analysis of overall survival in localized breast cancer.

Variables	Univariate Analysis		Multivariable Analysis	
	HR (95 % CI)	*P-value*	HR (95 % CI)	*P-value*
Age <65 vs. ≥ 65	7.54 (3.01–25.26)	0.0001**		
CCI-score (≥3 pts vs. 0–2 pts)	10.01 (3.55–28.20)	<0.0001**	5.26 (1.79–15.41)	0.0025**
ECOG performance status (2–4 vs. 0–1)	10.16 (4.85–21.29)	<0.0001**		
Detection method (symptomatic vs. screening)	3.41 (1.34–8.64)	0.0098**		
Tumor size >20 mm vs. ≤ 20 mm	3.92 (1.95–7.87)	0.0001**		
Lymph node status (≥3 vs. 1–2)	5.29 (1.55–18.08)	0.0079**		
Stage (2 vs. 1)	2.91 (1.32–6.44)	0.0083**	2.31 (1.04–5.15)	0.0405*
Stage (3 vs. 1)	2.98 (1.06–8.39)	0.0381*		
Mastectomy vs. breast-conserving surgery	5.01 (2.41–10.43)	<0.0001**		
No initial axillary surgery vs. SNB	5.89 (2.51–13.82)	<0.0001**		
No chemotherapy administered vs. chemotherapy administered	5.64 (2.36–13.49)	0.0001**		
No radiotherapy administered vs. radiotherapy administered	9.60 (4.90–18.78)	<0.0001**	6.84 (3.33–14.02)	<0.0001*
No adjuvant hormone therapy administered vs. adjuvant hormone therapy administered in ER + population	2.50 (1.22–5.11)	0.0122*		

Abbreviations: HR, hazard ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; ECOG, Eastern Cooperative Oncology Group; SNB, sentinel node biopsy; ER, estrogen receptor
* = $p < 0.05$, ** = $p < 0.01$.

The use of CCI-score or ECOG performance status remains an underestimated prognostic factor in clinical practice. Our results demonstrate that these clinical assessment tools are strong predictors of both DFS and OS, with the univariate HR of both CCI-score (3+ pts vs. 0–2 pts) and ECOG performance status (2–4 vs. 0–1) being equal to 10 ($p < 0.0001$). These results are aligned with previous findings and substantiate the assertion that comorbidity is associated with survival in localized breast cancer [20,21,23]. Our results show that clinical patient characteristics, such as ECOG and CCI, are important prognostic factors in localized breast cancer, together with widely available pathological characteristics, such as tumor proliferation index, histological grade, and stage [12–15]. The predictive value of comorbidity on DFS can be in part explained by highly comorbid patients receiving modified treatment regimens. While such de-intensification may be appropriate in certain cases, it is essential to maintain a balance between undertreatment and overtreatment, carefully considering patient comorbidity. At worst, undertreatment can lead to disease relapse, yet similarly, overtreatment can lead to reduced quality of life, especially when administering novel, long-lasting adjuvant treatments in patients with chronic illnesses that shorten life expectancy.

In terms of the effect of surgical treatment options on survival in older early-stage breast cancer patients, research has demonstrated better survival for breast-conserving surgery with radiation versus mastectomy [43]. Similarly, a recent phase III, noninferiority trial studied patients with clinically node-negative primary T1 to T3 breast cancer with one or two sentinel-node macrometastases, who underwent either SNB or complete ALND [44]. The results of this phase III trial showed no significant difference in recurrence-free survival between the two trial groups, thus supporting the omittance of extensive surgery due to the long-term complications of ALND, such as lymphedema. In our study, no significant difference was observed in OS between ALND and SNB (HR 2.07, $p = 0.0773$). Nevertheless, this study was not a prospective analysis and the decision between SNB versus ALND was presumably influenced by patient selection bias, as SNB is more likely to be chosen for patients with better prognoses and ALND for those with higher risk disease. Additional randomized controlled trials comparing the effect of these methods of axillary surgery on patient survival are warranted.

We observed that the lack of adjuvant chemotherapy was significant in the univariate regression model of OS (HR 5.64, 95 % CI 2.36–13.49, $p = 0.0001$). However, this prognostic effect of chemotherapy administration is likely due to strong selection bias, meaning that patients with poor performance were not administered chemotherapy, thus providing a probable explanation for the significant survival difference between these subgroups. Furthermore, 71 % of patients were administered hormone therapy. Although 89 % of tumors were ER-positive, 17 % (n = 75) of these ER-positive patients were also T1a-b and lymph node negative. Hence, adjuvant hormone therapy was strongly indicated for approximately 72 % of patients. When compared to the 71 % that adjuvant hormone therapy was administered to, these results suggest that hormone therapy was not only appropriately administered, but also well received by patients.

The importance of guideline-adherent adjuvant therapy, such as RT, has been confirmed by several studies [45,46]. RT to the conserved breast halves breast cancer recurrence rates and decreases breast cancer mortality [47]. Studies in elderly breast cancer patients have produced similar results, with undertreatment leading to significantly lower survival rates [48,49]. In this study, 82 % of patients were administered RT. A limited number of patients did not receive RT, despite having a clinical indication for RT. However, closer analyses of the percentage of patients who had a clinical indication for RT (breast-conserving surgery, or mastectomy with T4 or high risk T3 tumor or lymph node positive disease) revealed that 80 % (n = 350) had a clear indication for RT. This proportion of patients corresponds to the proportion of patients who were administered RT, thus ruling out the possibility of significant deficiency in RT administration. Nevertheless, lack of RT administration was a significant predictor of decreased OS and DFS in the multivariable regression analyses. Our findings differ from the results of a recent phase III study, where omission of RT after breast conserving surgery in older women with HR-positive early breast cancer receiving adjuvant endocrine therapy was associated with decreased DFS, but not with OS [50]. Nevertheless, these results suggest that RT is crucial for OS and should not be omitted if the patient is not suitable for adjuvant endocrine therapy. Age bias in breast cancer treatment can be counteracted with appropriate assessment of comorbidity and performance status, as these are independent and reliable tools for elderly cancer patients [51].

This study includes several limitations. Firstly, this was a single-center study amongst a predominantly Finnish population with a European ancestry, thus further investigation among more heterogeneous populations is warranted to address the known differences in survival among various ethnic groups [37]. Also, regional differences in breast cancer incidence have been noted in Finland [38], thus exercise must be cautioned when extrapolating these results on the general Finnish population. Another limitation of the study is the plausible effect of the COVID-19 pandemic on treatment results. The majority of the patient population received their primary treatments (i.e. adjuvant chemotherapy, anti-HER2 therapy, hormone therapy and RT) before the start of the pandemic in early 2020. However, a portion of patients, notably those diagnosed with localized breast cancer at the end of 2019, may have experienced disadvantageous changes in the scheduling or

administration of their primary treatments. The pandemic may have also caused modifications to treatments used for metastatic patients. In addition, no centralized analysis of radiological imaging or uniform assessment of disease progression were performed.

Statistical modeling in cancer patients is always challenging. Many characteristics defining the biology of cancer tumors are highly correlated, which can potentially cause problems in statistical estimations. Here, we wanted to concentrate on identifying independent prognostic factors through a multivariable analysis approach, which requires for the exclusion of variables exhibiting strong correlation amongst those variables statistically significant in the univariate analysis.

It should also be taken into account that the treatment landscape of local breast cancer has evolved since 2019, for example with the addition of immunological neoadjuvant treatment, adjuvant CDK inhibitors and PARP inhibitors. For instance, only 3 % of patients with localized disease received neoadjuvant therapy in this cohort, whereas neoadjuvant therapy administration rates in Finland have significantly increased after 2019. The low rate of neoadjuvant therapy administration is also in part due to the relatively low percentage of TNBC in this study. This study also lacks evaluation of modern genomic signatures, such as Oncotype DX® and MammaPrint ®, as these were not yet used in routine breast cancer diagnostics in Finland during 2019. Moreover, recommendations for germline genetic testing have broadened since 2019 in Finland.

5. Conclusion

In this real-world retrospective study, we show that careful clinical evaluation of patients ECOG and comorbidities, as well as well-established tumor characteristics, reliably predict patient real-world survival following curative surgery in a patient population where overall five-year survival is over 90 %. Hence, it is of utmost importance to carefully assess these known prognostic factors and ensure that pathological assessments of grade and proliferation are of high quality. These patient characteristics and tumor markers are of great value in clinical decision making, even as we enter an era of novel prognostic tools in oncology. Our findings provide comprehensive, real-world data on the characteristics of breast cancer patients and the effect of these characteristics on patient outcomes in Finland.

CRediT authorship contribution statement

Milla Hollmén: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization, Validation. **Eliisa Löyttyniemi:** Writing – review & editing, Software, Resources, Methodology, Formal analysis, Visualization. **Eeva Juhanoja:** Writing – review & editing, Validation, Investigation. **Pia Vihinen:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Maria Sundvall:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Availability of data and materials

Data is available upon reasonable request to the corresponding author.

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The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

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Declaration of competing interest

MH and EL have nothing to disclose.

PV has received consulting or advisory honoraria from Merck, Bristol-Myers Squibb, Ipsen, Novartis, and Roche; speakers' bureau honoraria from Merck, Roche, and Bristol-Myers Squibb.

MS has received support to participate in educational events and conferences from Astellas, Amgen, Bayer, BMS, MSD, Novartis, Pfizer, Roche; and received lecture or consulting/advisory honoraria from Amgen, Astra Zeneca, Bayer, BMS, MSD, Novartis and Roche.

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Appendix A. Supplementary data

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