Breast Care

Research Article

Breast Care 2022;17:279–287
DOI: 10.1159/000520793

Received: June 10, 2021
Accepted: November 7, 2021
Published online: November 9, 2021

# Long-Term Survival Outcomes of Patients with Small (≤1 cm) Node-Negative HER2-Positive Breast Cancer Not Treated with Adjuvant Anti-HER2-Targeted Therapy: A 10-Year Follow-Up Study

Jenni S. Liikanen[a] Marjut Leidenius[a] Heikki Joensuu[b] Tuomo J. Meretoja[a]

[a]Comprehensive Cancer Center, Breast Surgery Unit, Helsinki University Hospital and University of Helsinki, Helsinki, Finland; [b]Comprehensive Cancer Center, Helsinki University Hospital and University of Helsinki, Helsinki, Finland



**Keywords**

Breast cancer · Survival · Oestrogen receptor · Human epidermal growth factor receptor 2 · HER2

**Abstract**

***Introduction:*** Human epidermal growth factor receptor 2 (HER2) expression is considered an unfavourable prognostic factor in early breast cancer when the patients are not treated with HER2-targeted therapy. However, the long-term prognostic importance of HER2 expression in small (≤1 cm, stage pT1a-b), node-negative HER2+ breast cancer is still incompletely known. ***Methods:*** A retrospective analysis was performed based on a prospectively collected database including patients with pT1 breast cancer operated at the Helsinki University Hospital, Finland, between March 2000 and April 2006. In this database, 44 patients with pT1a-bN0M0, HER2+ cancer, not treated with adjuvant anti-HER2-targeted therapy (the HER2+ group) and 291 pT1a-bN0M0, hormone receptor-positive, HER2-negative cancers (the ER+/HER2– group) were identified and included in the study. Survival outcomes were analysed using the Kaplan-Meier method. ***Results:*** The median follow-up time was 9.7 years after primary breast surgery. Ten-year distant disease-free survival (DDFS) was 84.0% in the HER2+ group and 98.2% in the ER+/HER2– group ($p < 0.001$). Ten-year overall survival was only 78.5% in the HER2+ group, but 91.7% in the ER+/HER2– group ($p = 0.09$). ***Conclusions:*** Cancer HER2 status is strongly associated with unfavourable DDFS during the first decade of follow-up in patients with small (pT1a-bN0M0) breast cancer when adjuvant anti-HER2-targeted treatment is not administered. 

## Background

Approximately 6–12% of pT1a-bN0M0 (tumour diameter ≤1 cm, node-negative) breast cancers overexpress human epidermal growth factor 2 (HER2) protein or harbour amplified *HER2* and are, therefore, considered HER2-positive cancers [1–3]. Breast cancer HER2 positivity was established as an independent factor for unfavourable prognosis in several studies that included randomized clinical trials, especially when systemic anti-HER2-targeted therapy was not administered [4–8]. However, many of these studies excluded patients with tumour size less than 1 cm, since at that time, the prognosis of small node-negative cancer was considered excellent [9–11]. However, the prognosis of small node-negative (pT1a-bN0M0) HER2-positive breast cancer remains unclear and the need of systemic adjuvant therapy in this patient group is under debate. According to the 2019 St. Gallen panel, adjuvant chemotherapy and anti-HER2 therapy for HER2-positive stage pT1bN0 breast cancer is recommended, but for pT1aN0 cancer it should be determined case by case [12].

Since adequate data about the prognosis and treatment of T1a-bN0M0 HER2-positive breast cancer is lacking [13], we investigated the prognosis and prognostic factors of pT1a-bN0M0 HER2-positive breast cancer in a retrospective study based on a prospectively collected database with a long follow-up.

karger@karger.com
www.karger.com/brc



Correspondence to:
Jenni S. Liikanen, jenni.liikanen@helsinki.fi

Karger

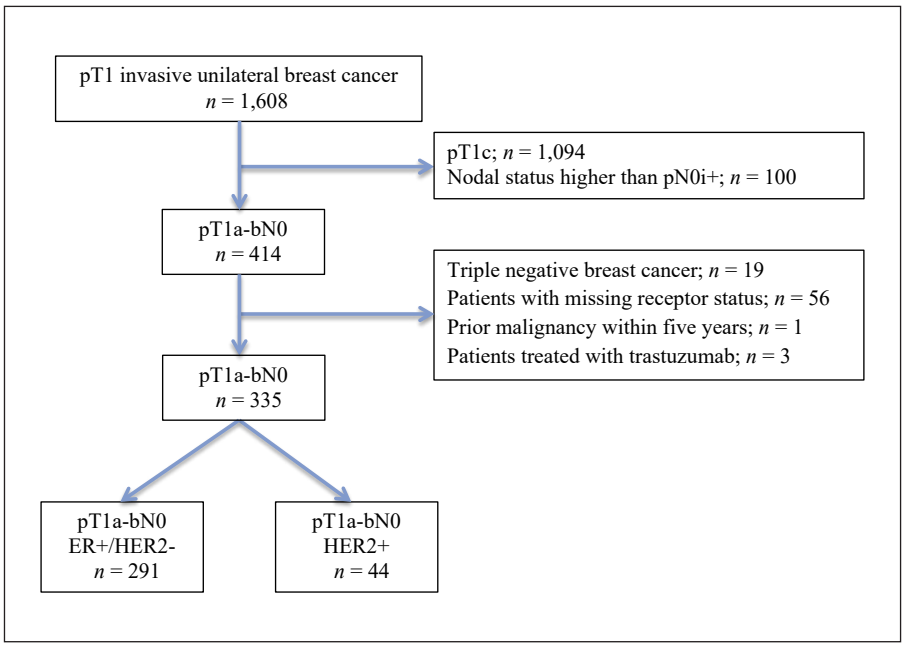


**Fig. 1.** Patient inclusion flowchart.

## Methods

*Patients*

The study is based on a prospectively collected database, including a total of 1,608 consecutive patients with pT1 breast cancer operated at the Breast Surgery Unit of the Comprehensive Cancer Center of Helsinki University Hospital, Finland, between March 2000 and April 2006. The Breast Surgery unit of the Comprehensive Cancer Center of Helsinki University Hospital, Finland, is the only dedicated breast surgery unit in the Helsinki Metropolitan area and the Uusimaa district. This area serves a population of over 1.6 million people and the Breast Surgery Unit operates nearly 100% of all breast cancers diagnosed in this area (excluding only a few patients operated at the private sector). Therefore, the data are close of being population-based.

The primary aim of collecting this comprehensive database was to evaluate the prognostic value of sentinel node isolated tumour cells (ITC) [14]. The patients had not previously been treated for invasive breast cancer or other malignancy during the last 5 years prior to the detection of breast cancer, were not treated with neoadjuvant therapy, and had a unilateral invasive breast cancer. The current study is a retrospective analysis based on this prospectively collected database with 414 patients with pT1a-bN0M0 breast cancer (shown in Fig. 1). Patients with triple-negative breast cancer (oestrogen receptor [ER]-negative, progesterone receptor [PgR]-negative, HER2–; *n = 19*), those with incomplete hormone receptor (HR) and/or HER2 status of the tumour (*n = 56*), and patients treated with trastuzumab (*n = 3*) or treated for other malignancy than breast cancer within the 5 years that preceded the diagnosis of breast cancer (*n = 1*) were excluded. The remaining 335 patients with pT1a-bN0M0 breast cancer were included in the study. Fifty-one patients had the longest tumour diameter ≤5 mm (pT1a) and 284 had a tumour diameter between 6 and 10 mm (pT1b). Twenty-four patients with ITC findings in one or more of the axillary lymph nodes were included (pN0i–, *n* = 311; pN0i+, *n* = 24) (shown in Fig. 1).

The 335 patients included in the study were categorized according to cancer HER2 status and HR status into the HER2-positive group (ER+ or ER–, HER2+, *n* = 44; hereafter referred to as the "HER2+" group) or the HER2-negative, ER-positive group (ER+, HER2–, *n* = 291; hereafter referred to as the "ER+/HER2–" group). Patients with HER2+ cancer were also investigated in subgroups formed by the tumour size (HER2+/pT1a vs. HER2+/pT1b), ER status (HER2+/ER– vs. HER2+/ER+), and the sentinel node ITC status (HER2+/pN0i– vs. HER2+/pN0i+). The patient and tumour characteristics are provided in Table 1.

An Ethics Committee at the Helsinki University Hospital approved the research protocol.

*Histopathology*

The histopathological analyses were performed in one specialist pathology laboratory and the specimens were examined by specialized breast pathologists. The breast and lymph node tissue specimens were sent to the pathology laboratory separately as fresh unfixed specimens. The tumour diameter, histological type and grade, HR status, HER2 status, and the Ki-67 proliferation index were evaluated. Immunohistochemical (IHC) methods were used to evaluate the HR status and the Ki-67 proliferation index. Over 10% of the cancer cell nuclei staining for the ER or the PgR was considered a positive staining result. Ki-67 antigen expression (the proliferation index) was determined with the MIB-1 monoclonal antibody. The patients were categorized into 3 categories according to the Ki-67 proliferation index: negative or low (0–19%), intermediate (20–30%), and high (>30%).

Cancer HER2 protein overexpression was evaluated first by IHC. The result was considered positive when the IHC staining result was 2+ or 3+ (on a scale from 0 to 3+). Cancers with a 2+ result at IHC were required to be retested using chromogen *in situ* hybridization, and whenever HER2/*neu* gene amplification was present, cancer was considered *HER2*-positive, otherwise *HER2*-negative. IHC 3+ staining was considered sufficient evidence for the presence of *HER2* amplification without chromogen *in situ* hybridization confirmation. Tumour deposits not larger than 0.2 mm in diameter found in the sentinel nodes were considered ITCs (pN0i+). The histological classification and grading are based on the World Health Organization (WHO) classification [15]. The IHC staining methods are described in detail elsewhere [16].

**Table 1.** Patient and tumour characteristics and treatments given according to cancer HER2-status

| | HER2+ | | ER+/HER2– | | All patients | | *p* |
|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | |
| Patients | 44 | 13.1 | 291 | 86.9 | 335 | 100.0 | |
| Age at diagnosis, years | | | | | | | |
| Median | 55 | | 58 | | 58 | | |
| Range | 35–83 | | 31–91 | | 31–91 | | 0.36 |
| Tumour size | | | | | | | |
| pT1a (≤5 mm) | 9 | 20.5 | 42 | 14.4 | 51 | 15.2 | |
| pT1b (6–10 mm) | 35 | 79.5 | 249 | 85.6 | 284 | 84.8 | 0.30 |
| Axillary lymph node status | | | | | | | |
| pN0i– | 40 | 90.9 | 271 | 93.1 | 311 | 92.8 | |
| pN0i+ | 4 | 9.1 | 20 | 6.9 | 24 | 7.2 | 0.54 |
| Tumour histology | | | | | | | |
| Ductal | 35 | 79.5 | 183 | 62.9 | 218 | 65.1 | |
| Lobular | 4 | 9.1 | 60 | 20.6 | 64 | 19.1 | |
| Other | 5 | 11.4 | 48 | 16.5 | 53 | 15.8 | 0.08 |
| Histological grade | | | | | | | |
| 1 | 8 | 18.2 | 173 | 59.5 | 181 | 54.0 | |
| 2 | 9 | 43.2 | 102 | 35.1 | 121 | 36.2 | |
| 3 | 15 | 34.1 | 11 | 3.8 | 26 | 7.8 | <0.001 |
| NA | 2 | 4.5 | 5 | 1.7 | 7 | 2.1 | |
| Focality | | | | | | | |
| Unifocal | 37 | 84.1 | 250 | 85.9 | 287 | 85.7 | |
| Multifocal | 7 | 15.9 | 41 | 14.1 | 48 | 14.3 | 0.75 |
| ER | | | | | | | |
| Negative (<10%) | 11 | 25.0 | 0 | 0.0 | 11 | 3.2 | |
| Positive (>10%) | 33 | 75.0 | 291 | 100.0 | 324 | 96.7 | <0.001 |
| PgR | | | | | | | |
| Negative (<10%) | 25 | 56.8 | 61 | 21.0 | 86 | 25.7 | |
| Positive (>10%) | 19 | 43.2 | 229 | 78.7 | 248 | 74.0 | <0.001 |
| NA | 0 | 0.0 | 1 | 0.3 | 1 | 0.3 | |
| Ki-67 (MIB-1) | | | | | | | |
| 0–19% | 14 | 31.8 | 240 | 82.5 | 254 | 75.8 | |
| 20–30% | 20 | 45.5 | 35 | 12.0 | 55 | 16.4 | |
| >30% | 10 | 22.7 | 15 | 5.2 | 25 | 7.5 | <0.001 |
| NA | 0 | 0.0 | 1 | 0.3 | 1 | 0.3 | |
| Breast surgery | | | | | | | |
| BCS | 33 | 75.0 | 237 | 81.4 | 270 | 80.6 | |
| Mastectomy | 11 | 25.0 | 54 | 18.6 | 65 | 19.4 | 0.31 |
| Axillary surgery | | | | | | | |
| SNB | 38 | 86.4 | 241 | 82.8 | 279 | 83.3 | |
| SNB + ALND | 3 | 6.8 | 23 | 7.9 | 26 | 7.8 | |
| ALND | 3 | 6.8 | 27 | 9.3 | 30 | 9.0 | 0.83 |
| Adjuvant endocrine therapy | | | | | | | |
| No | 29 | 65.9 | 218 | 74.9 | 247 | 73.7 | |
| Yes | 15 | 34.1 | 70 | 24.1 | 85 | 25.4 | 0.30 |
| NA | 0 | 0.0 | 3 | 1.0 | 3 | 0.9 | |
| Adjuvant chemotherapy | | | | | | | |
| No | 31 | 70.5 | 284 | 97.6 | 94 | 94.0 | |
| Yes | 13 | 29.5 | 6 | 2.1 | 19 | 5.7 | <0.001 |
| NA | 0 | 0.0 | 1 | 0.4 | 1 | 0.3 | |
| Systemic adjuvant therapy (endocrine- and/or chemotherapy) | | | | | | | |
| No | 21 | 47.7 | 220 | 75.6 | 241 | 71.9 | |
| Yes | 23 | 52.3 | 71 | 24.4 | 94 | 28.1 | <0.001 |
| Adjuvant radiation therapy | | | | | | | |
| No | 13 | 29.5 | 55 | 18.9 | 68 | 20.3 | |
| Yes | 31 | 70.5 | 235 | 80.7 | 266 | 79.4 | 0.10 |
| NA | 0 | 0.0 | 1 | 0.3 | 0 | 0.3 | |

HER2, Human epidermal growth factor 2; ER, oestrogen receptor; pN0i–/i+, isolated tumour cell negative/positive lymph node; NA, not available; PgR, progesterone receptor; Ki-67 (MIB-1), Ki-67 proliferation index determined with MIB-1 monoclonal antibody; BCS, breast conserving surgery; SNB, sentinel node biopsy; ALND, axillary lymph node dissection.

*Surgery*

Breast-conserving surgery or mastectomy was chosen according to the patient and tumour characteristics in agreement with the patient. The patients underwent either a sentinel lymph node biopsy or axillary lymph node dissection, or both (Table 1).

*Radiation Therapy and Systemic Adjuvant Therapy*

Radiation therapy was administered according to the institutional guidelines. After breast-conserving surgery, postoperative whole-breast radiotherapy was generally given to a cumulative dose of 50 Gy in 25 fractions. Tangential whole breast radiation fields were used after breast-conserving surgery. A booster dose of 10–16 Gy was given to premenopausal women to the breast tumour site. The target volume usually included the lower axilla. Separate axillary and/or supraclavicular fields were used in 2 patients. Radiotherapy was not routinely administered after mastectomy in patients with T1a-bN0 cancer, but 4 patients received it.

Chemotherapy and endocrine therapy were administered depending on the patient and disease characteristics, since systemic adjuvant therapy was not routinely recommended for patients with pT1a-bN0M0 cancer. When endocrine therapy was given, premenopausal patients were scheduled to receive tamoxifen for 5 years and postmenopausal women usually received an aromatase inhibitor for 5 years. Trastuzumab together with chemotherapy became the standard of care after May 2005 for patients with HER2+ cancer and tumour size ≥1 cm, and prior to this, adjuvant trastuzumab was administered within the context of a clinical trial [5].

*Follow-Up*

Follow-up visits after breast surgery were planned at 1, 3, and 5 years and were organized at the Department of Oncology, Helsinki University Hospital. Physical examination, blood cell counts, blood chemistry, and bilateral mammography were performed. Whenever considered necessary, breast and axillary ultrasound, bone isotope scan, and computerized tomography were also performed. An access to additional visits was readily available, whenever the patient was concerned about breast cancer recurrence.

After the first 5 years, the follow-up visits took place at the local health care centres or at private health care providers, according to the patient preference. If breast cancer recurrence was suspected, the patient was referred back to the Helsinki University Hospital for further examinations and treatment. The date of breast cancer recurrence, the cause of death, and the date of death were extracted from the hospital records. In addition, data about cancer survival were obtained from the Finnish Cancer Registry, which has a coverage exceeding 95% of the population.

*Statistical Methods*

Frequency tables were analysed with the $\chi^2$ test or Fisher's exact test (when the expected $n < 5$), and continuous variables were compared with the Mann-Whitney U test. Distant disease-free survival (DDFS) was calculated from the date of breast surgery to the date of first occurrence of breast cancer metastases outside of the breast or mastectomy area or the regional lymph nodes. Subsequent contralateral breast cancers or other second cancers were not considered as distant disease survival events. Patients who died before the detection of distant recurrence were censored on the date of death, and the patients alive without distant metastases were censored on the date of the last patient contact. Loco-regional recurrence-free survival time was calculated from the date of breast surgery to the date of first regional lymph node or ipsilateral breast recurrence censoring patients alive without loco-regional recurrence on the date of last follow-up contact and the patients who died without loco-regional recurrence on the date of death. Breast cancer-specific survival was calculated from the date of breast surgery to the date of death considered to result from breast cancer. Patients who died with distant metastases based on clinical, radiological, or autopsy evidence were considered to have died from breast cancer. Patients without such an event on the last date of contact or on the date of death from another cause were censored. Overall survival was calculated from the date of surgery to the date of death from any cause, censoring patients who were alive on the date of the last contact. When a patient was lost to follow-up, the date of death was acquired from the Finnish Cancer Registry, but if the date was not available, the patient was censored on the date when lost to follow-up.

Survival was analysed using the Kaplan-Meier method, and survival between groups was compared with the log-rank test. Two-sided $p$ values <0.05 were considered statistically significant. The statistical analyses were performed using an IBM® SPSS® Statistics Version 25 software (SPSS Inc., Chicago, IL, USA).

## Results

*Cancer Clinicopathological Characteristics and the Treatments Given*

No statistically significant differences were found between the patients with HER2+ cancer and those with ER+/HER2– tumour regarding patient age, tumour size, the axillary lymph node status (pN0i– or pN0i+), tumour histology, or tumour focality. In the HER2+ group, 33 (75%) out of the 44 cancers were ER-positive.

Patients with HER2+ cancer had more often a tumour with high histological grade and a high Ki-67 proliferation index compared to the patients with ER+/HER2– cancer ($p < 0.001$ for each comparison; Table 1).

No differences were found between HER2+ and ER+/HER2– groups regarding the breast or axillary surgery carried out. Only 94 (28.1%) of all patients received systemic adjuvant therapy (endocrine therapy or chemotherapy, or both). However, patients with HER2+ cancer were more frequently treated with adjuvant chemotherapy as compared to the ER+/HER2– group ($n = 13$ [29.5%] vs. $n = 6$ [2.1%], respectively; $p < 0.001$; Table 1).

*Follow-Up*

The median follow-up time for all patients was 9.7 years (range 0.5–12.5 years) after the date of primary breast surgery. In the subsets of patients with HER2+ cancer and those with ER+/HER2– cancer, the median follow-up times were 9.2 years (range 1.2–12 years) and 9.8 years (range 0.5–12.5 years), respectively ($p = 0.08$). Eight patients were lost to follow-up as they migrated elsewhere from the Helsinki metropolitan area. All these 8 patients were diagnosed with ER+/HER2– cancer.

*Survival Outcomes*

The survival events recorded during the follow-up are presented in Table 2. Ten-year DDFS was 84.0% in the

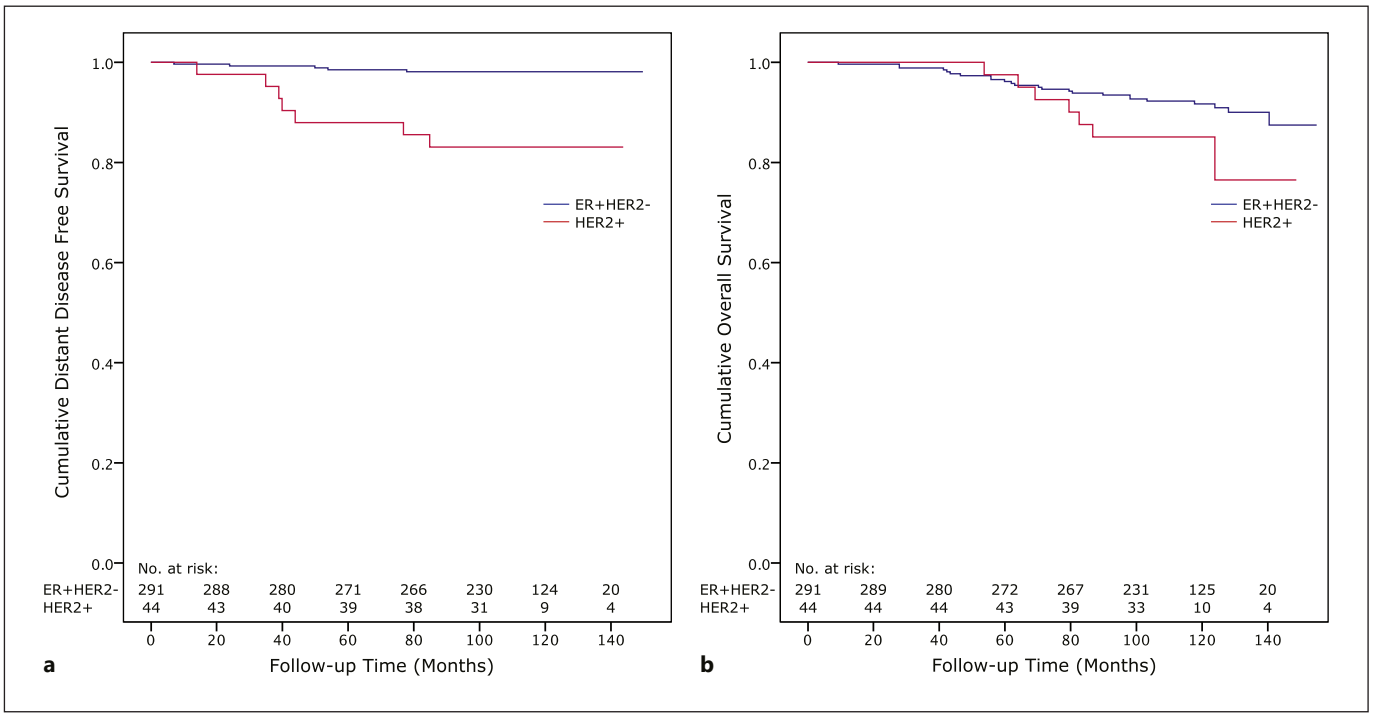


**Fig. 2.** Kaplan-Meier survival plots for distant disease-free survival ($p < 0.001$) (**a**) and overall survival ($p = 0.09$) (**b**) in the HER2+ and ER+/HER2– patient groups.

**Table 2.** Breast cancer events

| | HER2+ ($N = 44$), *n* (%) | ER+/HER2– ($N = 291$), *n* (%) | *p* |
|---|---|---|---|
| Events | | | |
| Loco-regional recurrence | 2 (4.5) | 18 (6.2) | 0.67 |
| Distant metastases | 7 (15.9) | 5 (1.7) | <0.001 |
| Breast cancer death | 5 (11.4) | 4 (1.4) | <0.001 |
| Death from any cause | 7 (15.9) | 24 (8.2) | 0.10 |

HER2, human epidermal growth factor receptor 2; ER, oestrogen receptor.

HER2+ group and 98.2% in the ER+/HER2– group ($p < 0.001$, shown in Fig. 2a). In addition to cancer HER2 status, also histological grade 3 and a high Ki-67 proliferation index were associated with an increased risk for distant recurrence (Table 3).

Ten-year loco-regional recurrence-free survival was 95.4% in the HER2+ group and 93.4% in the ER+/HER2– group ($p = 0.66$). Age over 50 years and tumour multifocality were associated with an increased risk for loco-regional recurrence (Table 3). Ten-year breast cancer-specific survival was 82.6% in the HER2+ group and 98.9% in the ER+/HER2– group ($p < 0.001$). Ten-year overall survival was 78.5% in the HER2+ group and 91.7% in the ER+/HER2– group ($p = 0.09$, shown in Fig. 2b).

None out of the 11 patients with ER–/HER2+ cancer had distant recurrence during the follow-up compared to 7 (21.2%) out of the 33 patients with ER+/HER2+ disease ($p = 0.10$, Table 4). Similarly, when tumour size (pT1a vs. pT1b), the ER status (ER+ vs. ER–), or the pN-stage (pN0i– vs. pN0i+) were compared within the subset of patients with HER2+ cancer, no significant differences were observed.

## Discussion

We found that breast cancer HER2 expression is a prognostic factor for unfavourable survival also in patients with small node-negative (pT1a-bN0) cancer. The difference in 10-year DDFS in patients with HER2+ cancer compared to patients with a ER+/HER2– tumour was rather large, 14.2 percentage points (84.0 vs. 98.2%, respectively). Similarly,

**Table 3.** Kaplan-Meier 10-year survival rate estimates

| | Loco-regional recurrence-free survival | | Distant disease-free survival | | Breast cancer-specific survival | | Overall survival | |
|---|---|---|---|---|---|---|---|---|
| | 10-year survival estimate | *p* | 10-year survival estimate | *p* | 10-year survival estimate | *p* | 10-year survival estimate | *p* |
| Age | | | | | | | | |
| <50 years | 87.2% | | 95.8% | | 98.6% | | 92.7% | |
| >50 years | 95.5% | 0.01 | 96.4% | 0.79 | 96.8% | 0.42 | 90.4% | 0.40 |
| Tumour size | | | | | | | | |
| pT1a (≤5 mm) | 87.4% | | 96.0% | | 94.0% | | 90.1% | |
| pT1b (6–10 mm) | 94.8% | 0.06 | 96.4% | 0.89 | 97.8% | 0.58 | 90.4% | 0.66 |
| pN-status | | | | | | | | |
| pN0i– | 93.2% | | 96.3% | | 97.3% | | 90.6% | |
| pN0i+ | 100.0% | 0.22 | 95.7% | 0.85 | 95.7% | 0.54 | 87.5% | 0.46 |
| HER2-status | | | | | | | | |
| ER+/HER2– | 93.4% | | 98.2% | | 98.9% | | 91.7% | |
| HER2+ | 95.4% | 0.66 | 84.0% | <0.001 | 82.6% | <0.001 | 78.5% | 0.09 |
| ER-status | | | | | | | | |
| ER– | 90.9% | | 100.0% | | 100.0% | | 100.0% | |
| ER+ | 93.8% | 0.70 | 96.2% | 0.51 | 97.7% | 0.60 | 90.0% | 0.32 |
| PgR-status | | | | | | | | |
| PgR– | 91.4% | | 94.1% | | 93.4% | | 90.0% | |
| PgR+ | 94.5% | 0.34 | 97.1% | 0.21 | 98.3% | 0.18 | 90.2% | 0.70 |
| Tumour histology | | | | | | | | |
| Other | 90.4% | | 98.0% | | 100.0% | | 91.5% | |
| Lobular | 93.2% | | 95.1% | | 94.3% | | 86.5% | |
| Ductal | 94.7% | 0.53 | 96.2% | 0.70 | 97.1% | 0.89 | 91.0% | 0.84 |
| Histological grade* | | | | | | | | |
| 1 | 94.8% | | 97.7% | | 97.6% | | 94.1% | |
| 2 | 94.6% | | 96.5% | | 96.1% | | 84.2% | |
| 3 | 84.4% | 0.09 | 84.6% | 0.01 | 88.5% | 0.01 | 88.5% | 0.12 |
| Focality | | | | | | | | |
| Unifocal | 95.6% | | 96.4% | | 97.1% | | 90.7% | |
| Multifocal | 82.3% | <0.001 | 95.6% | 0.80 | 97.7% | 0.83 | 87.2% | 0.38 |
| Ki-67 (MIB-1) | | | | | | | | |
| 0–19% | 93.8% | | 98.0% | | 99.2% | | 91.7% | |
| 20–30% | 94.4% | | 90.8% | | 90.0% | | 83.1% | |
| >30% | 90.7% | 0.9 | 91.7% | 0.02 | 91.3% | 0.01 | 91.3% | 0.40 |

pN0i–/i+, isolated tumour cell negative/positive lymph node; HER2, human epidermal growth factor receptor 2; ER, oestrogen receptor; PgR, progesterone receptor; Ki-67 (MIB-1), Ki-67 proliferation index determined with the MIB-1 monoclonal antibody. * Seven patients had missing cancer histological grade.

patients with HER2+ cancer had also inferior 10-year breast cancer-specific survival compared to those with ER+/HER2– cancer. These outcomes were worse in the HER2+ group, even though the patients with HER2+ cancer received more often systemic adjuvant chemotherapy, although none of them received adjuvant trastuzumab. However, after recurrence, advanced breast cancer was treated with trastuzumab plus chemotherapy at the centre. In general, patients with ER+/HER2– tumours had excellent 10-year survival, although only 24% of them received any type of systemic adjuvant therapy.

While cancer HER2 expression is an established prognostic factor for unfavourable survival in breast cancer in general [3, 17, 18], there is difference in opinion about whether patients with HER2+ pT1a-bN0M0 breast cancer should be routinely treated with systemic adjuvant therapy and especially with anti-HER2-targeted therapy. Several studies have come to the conclusion that also patients with subcentimetre, node-negative HER2+ tumours have unfavourable prognosis when not treated with systemic adjuvant therapy, and, therefore, could derive survival advantage from systemic treatment including trastuzumab [19–24]. Nonetheless, others consider the prognosis of subcentimetre HER2+ breast cancer to be excellent and do not advocate the routine use of systemic adjuvant therapies [25–27]. The St. Gallen consensus panel recommends adjuvant chemotherapy and anti-HER2 therapy for patients with HER2-positive stage I

**Table 4.** Distant disease-free survival in the HER2+ group patients according to the subgroups

| HER2-positive cancer (*N* = 44), subgroup | Distant disease-free survival | | | | | |
|---|---|---|---|---|---|---|
| | Patients, *n* | Events, *n* | Events, % | 5-year survival, % | 10-year survival, % | *p* |
| pT1a versus pT1b | | | | | | |
| pT1a | 9 | 1 | 11.1 | 100.0 | 88.9 | |
| pT1b | 35 | 6 | 17.1 | 85.7 | 82.9 | 0.60 |
| pN0i– versus pN0i+ | | | | | | |
| pN0i– | 40 | 6 | 15.0 | 90.0 | 84.9 | |
| pN0i+ | 4 | 1 | 25.0 | 75.0 | 75.0 | 0.50 |
| ER– versus ER+ | | | | | | |
| ER– | 11 | 0 | 0.0 | 100.0 | 100.0 | |
| ER+ | 33 | 7 | 21.1 | 84.8 | 78.7 | 0.10 |

HER2, human epidermal growth factor 2 protein; pN0i–/i+, isolated tumour cell negative/positive lymph node; ER, oestrogen receptor.

pT1bN0 breast cancer, but for patients with pT1aN0 cancer, this should be judged case by case [12]. Whether adjuvant systemic therapies should be considered for patients with pT1aN0 cancer cannot be concluded from the present study data, because there were only 9 such patients in the current series and only one DDFS event in the HER2+/pT1a patient group. Administration of anti-HER2 therapy for a duration shorter than the standard of 1 year might also be considered in these patients, but such treatments have not been evaluated in controlled trials in this patient group.

Randomized clinical trials would likely provide important information about the prognosis and the treatment effects in patients with HER2+ pT1a-bN0M0 breast cancer, but due to the relatively low incidence of such tumours and the very low numbers of survival events, it seems challenging to conduct such a trial. Therefore, meta-analyses including series like the present one seem worthwhile to perform. While further evidence is awaited, individual patient and tumour biological characteristics should be carefully taken into consideration, since a small tumour size alone may provide incomplete information for the clinical decision-making.

A long follow-up time and a setting that is close to a population-based one are strengths of the current study. The breast tumour specimens were investigated in a single pathology laboratory by specialized breast pathologists. The main limitation of the study is the small number of patients particularly in the pT1a category (tumour diameter 5 mm or less) and the low event rate, which did not allow performing a multivariable analysis, or carrying out reliable subgroup analyses in the HER2+ group. Cancer ER expression modifies the influence of HER2 expression on prognosis [28, 29], and the current treatment guidelines recommend treating even patients with small node-negative ER+/HER2+ cancer with systemic endocrine therapy [30, 31]. In the current series, all distant recurrences in the HER2+ group occurred in patients with ER+ disease, but we lacked adequate statistical power to compare the ER+/HER2+ and ER–/HER2+ subgroups. Yet, both early ER+/HER2+ breast cancer and ER–/HER2+ cancer are associated with unfavourable prognosis unless treated with adjuvant HER2-targeted therapy [28, 29].

Another limitation was the retrospective nature of the study, although the study was based on a prospectively collected database. The adjuvant treatment was not standardised throughout the study period. However, patients with HER2+ breast cancer received more systemic adjuvant treatments than the patients with ER+/HER2– cancer, and, yet, HER2 expression was strongly associated with unfavourable DDFS.

## Conclusions

Our study strengthens the view that cancer HER2 expression is an important prognostic factor for unfavourable outcome in pT1a-bN0M0 breast cancer, but more data are needed from cancers 5 mm or smaller in diameter.


## Acknowledgements

We thank Anna But, Biostatistician, PhD, Biostatistics Consulting, Department of Public Health, University of Helsinki University Hospital, Helsinki, Finland, for giving advice and consulting in biostatistics of this manuscript.


## Statement of Ethics

The project plan was approved by the Ethical Committee of Helsinki University Central Hospital (permission number 272/E6/2005) and written informed consent was obtained from all patients. The study was conducted according to the Declaration of Helsinki.

## Conflict of Interest Statement

The authors declare no relevant conflicts of interest. H.J. is the Chair of the Scientific Advisory Board at Orion Pharma and at Neutron Therapeutics Ltd.

## Funding Sources

J.S.L. was supported by an unrestricted grant from Kurt and Doris Palander foundation, Ida Montin foundation and The Finnish Medical Foundation. The funding sources did not have any role in the study design, data collection, analysis, interpretation, or writing of the report.

## Author Contributions

Study concept and design: J.S.L., M.L., H.J., T.J.M. Acquisition of data: J.S.L., M.L., H.J., T.J.M. Analysis and interpretation of data: J.S.L., M.L., H.J., T.J.M. Drafting of the manuscript: J.S.L., M.L., H.J., T.J.M. Critical revision of the manuscript for important intellectual content: J.S.L., M.L., H.J., T.J.M. Statistical analysis: J.S.L., M.L., T.J.M.

## Data Availability Statement

The datasets used and/or analysed during the current study are not publicly available to protect the privacy of the study participants but are available from the corresponding author upon reasonable request.

## References

1 Gonzalez-Angulo AM, Litton JK, Broglio KR, Meric-Bernstam F, Rakkhit R, Cardoso F, et al. High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller. J Clin Oncol. 2009 Dec;27(34):5700–6.
2 Curigliano G, Viale G, Bagnardi V, Fumagalli L, Locatelli M, Rotmensz N, et al. Clinical relevance of HER2 overexpression/amplification in patients with small tumor size and node-negative breast cancer. J Clin Oncol. 2009 Dec;27(34):5693–9.
3 Joensuu H, Isola J, Lundin M, Salminen T, Holli K, Kataja V, et al. Amplification of erbB2 and erbB2 expression are superior to estrogen receptor status as risk factors for distant recurrence in pT1N0M0 breast cancer: a nationwide population-based study. Clin Cancer Res. 2003 Mar;9(3):923–30.
4 Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005 Oct;353(16):1659–72.
5 Joensuu H, Kellokumpu-Lehtinen PL, Bono P, Alanko T, Kataja V, Asola R, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med. 2006 Feb;354(8):809–20.
6 Gianni L, Dafni U, Gelber RD, Azambuja E, Muehlbauer S, Goldhirsch A, et al. Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial. Lancet Oncol. 2011 Mar;12(3):236–44.
7 Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011 Oct;365(14):1273–83.
8 Perez EA, Romond EH, Suman VJ, Jeong JH, Sledge G, Geyer CE Jr, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J Clin Oncol. 2014 Nov;32(33):3744–52.
9 Rosen PR, Groshen S, Saigo PE, Kinne DW, Hellman S. A long-term follow-up study of survival in stage I (T1N0M0) and stage II (T1N1M0) breast carcinoma. J Clin Oncol. 1989 Mar;7(3):355–66.
10 Leitner SP, Swern AS, Weinberger D, Duncan LJ, Hutter RV. Predictors of recurrence for patients with small (one centimeter or less) localized breast cancer (T1a,b N0 M0). Cancer. 1995 Dec;76(11):2266–74.
11 Joensuu H, Pylkkänen L, Toikkanen S. Late mortality from pT1N0M0 breast carcinoma. Cancer. 1999 May;85(10):2183–9.
12 Burstein HJ, Curigliano G, Loibl S, Dubsky P, Gnant M, Poortmans P, et al. Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019. Ann Oncol. 2019 Oct;30(10):1541–57.
13 O'Sullivan CC, Bradbury I, Campbell C, Spielmann M, Perez EA, Joensuu H, et al. Efficacy of adjuvant trastuzumab for patients with human epidermal growth factor receptor 2-positive early breast cancer and tumors ≤2 cm: a meta-analysis of the randomized trastuzumab trials. J Clin Oncol. 2015 Aug;33(24):2600–8.
14 Liikanen JS, Leidenius MH, Joensuu H, Vironen JH, Meretoja TJ. Prognostic value of isolated tumour cells in sentinel lymph nodes in early-stage breast cancer: a prospective study. Br J Cancer. 2018 May;118(11):1529–35.
15 Fa T, Devilee P. Pathology and Genetics of Tumours of the Breast and Female Genital Organs. World Health Organization Classification of Tumours. WHO 2003.
16 Leidenius MH, Vironen JH, Heikkilä PS, Joensuu H. Influence of isolated tumor cells in sentinel nodes on outcome in small, node-negative (pT1N0M0) breast cancer. Ann Surg Oncol. 2010 Jan;17(1):254–62.
17 Chia S, Norris B, Speers C, Cheang M, Gilks B, Gown AM, et al. Human epidermal growth factor receptor 2 overexpression as a prognostic factor in a large tissue microarray series of node-negative breast cancers. J Clin Oncol. 2008 Dec;26(35):5697–704.
18 Rouanet P, Roger P, Rousseau E, Thibault S, Romieu G, Mathieu A, et al. HER2 overexpression a major risk factor for recurrence in pT1a-bN0M0 breast cancer: results from a French regional cohort. Cancer Med. 2014 Feb;3(1):134–42.
19 McArthur HL, Mahoney KM, Morris PG, Patil S, Jacks LM, Howard J, et al. Adjuvant trastuzumab with chemotherapy is effective in women with small, node-negative, HER2-positive breast cancer. Cancer. 2011 Dec;117(24):5461–8.
20 Rodrigues MJ, Peron J, Frenel JS, Vano YA, Wassermann J, Debled M, et al. Benefit of adjuvant trastuzumab-based chemotherapy in T1ab node-negative HER2-overexpressing breast carcinomas: a multicenter retrospective series. Ann Oncol. 2013 Apr;24(4):916–24.
21 Vici P, Pizzuti L, Natoli C, Moscetti L, Mentuccia L, Vaccaro A, et al. Outcomes of HER2-positive early breast cancer patients in the pre-trastuzumab and trastuzumab eras: a real-world multicenter observational analysis. The RETROHER study. Breast Cancer Res Treat. 2014 Oct;147(3):599–607.
22 Gori S, Inno A, Fiorio E, Foglietta J, Ferro A, Gulisano M, et al. The Promher Study: an observational Italian study on adjuvant therapy for HER2-positive, pT1a-b pN0 breast cancer. PLoS One. 2015 Sep;10(9):e0136731.
23 de Nonneville A, Goncalves A, Zemmour C, Classe JM, Cohen M, Lambaudie E, et al. Benefit of adjuvant chemotherapy with or without trastuzumab in pT1ab node-negative human epidermal growth factor receptor 2-positive breast carcinomas: results of a national multi-institutional study. Breast Cancer Res Treat. 2017 Apr;162(2):307–16.
24 Parsons BM, Uprety D, Smith AL, Borgert AJ, Dietrich LL. A US registry-based assessment of use and impact of chemotherapy in stage I HER2-positive breast cancer. J Natl Compr Canc Netw. 2018;16(11):1311–20.

25 Vaz-Luis I, Ottesen RA, Hughes ME, Mamet R, Burstein HJ, Edge SB, et al. Outcomes by tumor subtype and treatment pattern in women with small, node-negative breast cancer: a multi-institutional study. J Clin Oncol. 2014 Jul;32(20):2142–50.
26 Fehrenbacher L, Capra AM, Quesenberry CP Jr, Fulton R, Shiraz P, Habel LA. Distant invasive breast cancer recurrence risk in human epidermal growth factor receptor 2-positive T1a and T1b node-negative localized breast cancer diagnosed from 2000 to 2006: a cohort from an integrated health care delivery system. J Clin Oncol. 2014 Jul;32(20):2151–8.
27 Kolben T, Harbeck N, Wuerstlein R, Schubert-Fritschle G, Bauerfeind I, Schrodi S, et al. Endocrine sensitivity is decisive for patient outcome in small node-negative breast cancers (BC) (pT1a,b) – Results from the Munich Cancer Registry. Breast. 2015 Feb;24(1):24–31.
28 Rasmussen B, Regan M, Lykkesfeldt A, Dell'Orto P, Del Curto B, Henriksen KL, et al. Adjuvant letrozole versus tamoxifen according to centrally-assessed ERBB2 status for postmenopausal women with endocrine-responsive early breast cancer: supplementary results from the BIG 1-98 randomised trial. Lancet Oncol. 2008 Jan;9(1):23–8.
29 Kennecke H, Yerushalmi R, Woods R, Cheang MC, Voduc D, Speers CH, et al. Metastatic behavior of breast cancer subtypes. J Clin Oncol. 2010 Jul;28(20):3271–7.
30 NCCN Guidelines, Invasive Breast Cancer, version 8. 2021 [cited: 21 Oct 2021]. Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1419.
31 Cardoso F, Kyriakides S, Ohno S, Penault Llorca F, Poortmans P, Rubio IT, et al. ESMO Guidelines Committee. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019 Aug;30(8):1194–220.