Prognostic factor analysis and clinical significance of HER-2-positive breast cancers with negative lymph nodes and a tumor diameter ≤1 cm

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Abstract. The 2021 National Comprehensive Cancer Network guidelines recommend that adjuvant chemotherapy combined with trastuzumab be considered for human epidermal growth factor receptor 2 (HER-2)-positive breast cancer patients with small tumors (tumor diameter ≤1 cm) and negative lymph nodes. Additionally, the prognostic factors and clinical significance of HER-2-positive breast cancer with negative lymph nodes and a tumor diameter ≤1 cm remain unclear. In the present study, the clinical data and prognostic factors of 87 patients with HER-2-positive breast cancer with negative lymph nodes and a tumor diameter ≤1 cm admitted to Guangdong Women and Children Hospital from January 2013 to December 2019 were retrospectively analyzed. The median follow-up time was 70 months, the disease-free survival (DFS) of all patients was 94.3% and the overall survival (OS) was 100%. Univariate analysis of prognosis demonstrated that patients aged ≤40 years had significantly lower DFS than those aged >40 (80.8 vs. 100.0%, P<0.001). DFS was significantly improved in patients who were hormone-receptor-positive and patients who received endocrine therapy compared with patients who were estrogen receptor negative and patients who did not receive endocrine therapy (100.0 vs. 89.6%, P=0.039; 100.0 vs. 90.0%, P=0.049). Prognostic univariate analysis demonstrated that patient age, hormone receptor status and use of endocrine therapy were significantly related to the DFS (P<0.05), while none of these were independent factors related to the DFS in the prognostic multivariate analysis (P=0.240, P=0.976 and P=0.925). The proportion of patients with a tumor diameter 0.5-1 cm receiving adjuvant anti-HER-2 treatment was significantly greater compared with patients with tumors with a diameter ≤0.5 cm (46.4 vs. 18.6%, P<0.05). There was no significance difference in the DFS of patients treated with adjuvant chemotherapy with or without anti-HER-2 therapy with tumor diameters ≤0.5 cm (P>0.05), but there was a significant difference in the DFS of patients with a tumor diameter 0.5-1 cm (P<0.05). These results suggested that adjuvant chemotherapy, with or without anti-HER-2 therapy, may affect the prognosis of HER-2-positive breast cancer patients with negative lymph nodes and a tumor diameter of 0.5-1 cm. Therefore, it could be recommended that such patients receive adjuvant chemotherapy and anti-HER-2 therapy in the future.

Introduction

Human epidermal growth factor receptor 2 (HER-2) is a gene that affects the growth and metastasis of breast cancer cells and the increased expression of this gene is an indicator of a poor prognosis for patients with invasive breast cancer (1,2) Approximately 20% of all cases of invasive breast cancer are HER-2-positive (2,3). Previous study have reported that patients with T1abN0 breast cancer have a good prognosis and the 10-year breast cancer-related mortality is 3.4%, whereas patients with HER-2-positive breast cancer have twice the risk of death compared with those with HER-2-negative breast cancer (1). Previous clinical studies have reported that postoperative adjuvant therapy with trastuzumab (an anti-HER-2 antibody) can improve the prognosis of patients with early HER-2-positive breast cancer, but these clinical studies often exclude patients with breast cancer with negative lymph nodes and a tumor diameter ≤1 cm (2-7). The Adjuvant Paclitaxel and Trastuzumab (APT) trial was the first clinical study to treat HER-2-positive breast cancer with negative lymph nodes and a tumor diameter ≤3 cm with monotherapy combined with trastuzumab (8). The study reported promising survival rates, after a median

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follow-up of 6.5 years, with a 7-year disease-free survival (DFS) rate of 93% and a 7-year overall survival (OS) rate of 95%. However, the aforementioned study was a one-arm trial and randomized studies were not considered feasible because retrospective data suggested greater than minimal risk of recurrence in this population. In addition, for patients with small node-negative HER2-positive breast cancer there was no standard treatment to define control arm, also long-term follow-up of this trial was important to better determine the true efficacy of this regimen, so additional data are required. Moreover, the factors which influence the clinical use of adjuvant chemotherapy and anti-HER-2 therapy for HER-2-positive breast cancer with negative lymph nodes and a small tumor diameter ≤1 cm remain unclear. The purpose of the present study was to evaluate the prognostic factors for patients with HER-2-positive breast cancer with negative lymph nodes and a tumor diameter ≤1 cm, as well as analyze the impact of adjuvant chemotherapy and anti-HER-2 therapy to provide further information for the future treatment of such patients.

Materials and methods

Patients. The medical records of patients with breast cancer admitted to Guangdong Women and Children Hospital from January 2013 to December 2019 were collected. The inclusion criteria for the study were as follows: i) Pathological diagnosis of invasive breast cancer, with complete data for the estrogen receptor (ER), progesterone receptor (PR), HER-2, Ki-67; ii) the patient had negative lymph nodes, tumor diameter ≤1 cm and was positive for HER-2 without distant metastasis; and iii) no neoadjuvant therapy was given before surgery. Exclusion criteria for the study were as follows: i) No surgical treatment; ii) previous breast cancer or malignant tumors of other sites; and iii) breast cancer during pregnancy or bilateral breast cancer. A total of 87 patients met the inclusion criteria, and none of them excluded for any of the reasons listed in the exclusion criteria.

Reagents. The ER (05278414001, 1 μg/ml), HER-2 (05999570001, 6 μg/ml) and Ki-67 (05278384001, 2 μg/ml) antibodies and universal secondary antibodies (05269806001, 1 mg/ml) were purchased from Roche Diagnostics. The fluorescence *in situ* hybridization (FISH) probe was provided by Beijing Jinpujia Medical Technology Co., Ltd. The HER-2 detection kit consisted of a double probe containing both the HER-2 gene and the centromeric (CEP17) sequence on chromosome 17, labeled red and green, respectively.

Immunohistochemistry for ER, and Ki-67. After routine sampling of tumor tissue, tissue specimens were fixed in 10% neutral formalin for >6 h at 54-60°C, embedded in paraffin and sliced to 4 μm thick. Immunohistochemical tests were performed using a standardized automated staining method with BenchMark XT (Ventana Medical Systems) (9), with positive and negative controls for each section. Each tissue section was independently evaluated by two senior pathologists blinded to the status of the patients. Tumors were considered to be positive for ER when ≥1% of the tumor cell nucleus demonstrated staining in the whole section, whereas samples were considered negative for ER when <1% of the tumor nucleus demonstrated staining in the whole section. A tissue sample with Ki-67 staining of <30% of the sample was considered to have low expression, whereas Ki-67 staining in ≥30% of the sample was considered to indicate high expression.

Expression of HER-2 detected by immunohistochemistry and FISH. Immunohistochemical detection of HER-2 was performed according to the aforementioned method. Infiltrating cancer cells with no staining or samples with ≤10% invasive cancer cells demonstrating incomplete and weak cell membrane staining were given a score of 0. Tissue samples with >10% of invasive cancer cells demonstrating incomplete, weak cell membrane staining were scored 1+. Samples with >10% of invasive cancer cells demonstrating weak to moderate intact cell membrane staining or ≤10% of infiltrating cancer cells demonstrating strong and intact cell membrane staining were scored 2+. Samples with >10% of the infiltrating cancer cells demonstrating strong, complete and uniform cell membrane staining were given a score of 3+. Samples with a score of 3+ were considered positive, those with a score of 0 or 1+ were considered negative and those that received a score of 2+ were subjected to subsequent FISH analyses.

The HER-2 FISH assay was performed according to the manufacturer's instructions. Briefly, slides were dewaxed, digested, dehydrated and denatured and hybridized at 42°C for 16 h. After being washed and re-stained, the hybridization signals were imaged using a fluorescence microscope. After hybridization, ≥2 representative independent areas (avoiding tissue margins and poorly treated tissues.) of invasive cancer were selected under a 100x magnification, tumor cells with uniform nuclear size, intact nuclear boundary, uniform staining of DAPI, no nuclear overlap and clear signal should be selected for interpretation. At least 20 bicolor signals (HER-2- and CEP17-positive signals) in infiltrating cancer cell nuclei were randomly counted. When observing the signal, the focal length of the microscope should be adjusted at any time according to the situation, and the signal located on different planes of the nucleus should be accurately observed to avoid omission. Interpretation criteria were as follows: When the ratio of HER-2/CEP17 was ≥2.0 and the average number of HER-2 copies/cell was ≥4.0, the sample was classed as positive. If the ratio was <4.0, the number of cells counted was increased by ≥20 to confirm the diagnosis If the result remained unchanged, the sample was classed as negative. When the ratio of HER-2/CEP17 was <2.0 and the average number of HER-2 copies/cells was ≥6.0, the number of counted cells was increased. If the result remained unchanged, the sample was classed as positive. If the HER-2/CEP17 ratio was ≥4.0 and <6.0, the values were re-counted in different fields of view and comprehensively analyzed; HER2 status in such patients should be combined with the IHC result. If the IHC result is 3+, HER2 status is judged positive. If IHC with a result of 0, 1+, or 2+, HER2 status should be judged negative). If the ratio was <4.0, the sample was classed as negative (10,11).

Patient follow-up. Outpatient or telephone follow-up was performed for all patients. The last follow-up was performed on 1st May 2023, with a follow-up rate of 100%. The DFS was defined as the time from the date of surgery to the discovery of tumor recurrence or metastasis (the first event). The OS was defined as the time from the date of surgery to the date of cancer-related death.

Statistical analysis. SPSS (version 26.0; IBM Corp.) was used for statistical analyses. Univariate analysis of prognostic factors was performed using the Log rank test following Kaplan-Meier survival analysis. Cox regression was used for multivariate analysis. The factors related to adjuvant chemotherapy and anti-HER-2 therapy were compared using the χ^2 test. Fisher's exact test was used where the expected count in >20% of cells was <5. A value of P<0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics. The 87 patients ranged in age from 23-69 years, with a median age of 45 years (Table I). The majority of the patients (72.4%; 63/87) were premenopausal, 67.8% (59/87) had a tumor diameter ≤0.5 cm, 5.7% (5/87) had grade III histology according to the WHO grading system (12) and 44.8% (39/87) were estrogen receptor-positive. Of the total number of patients, 42.5% (37/87) received endocrine therapy, 35.6% (31/87) demonstrated positive Ki-67 staining in <30% of the tumor, 58.6% (51/87) received adjuvant chemotherapy, 25.3% (22/87) received breast-conserving surgery and 20.7% (18/87) received adjuvant radiotherapy.

Prognosis of patients with HER-2-positive breast cancer with negative lymph nodes and a tumor diameter ≤1 cm. The follow-up time of the patient group ranged from 41-118 months and the median follow-up time was 70 months. The DFS and OS were 94.3 and 100.0%, respectively. There were 5 cases of recurrence reported, all of which were patients who were estrogen receptor-negative and HER-2-positive. Among these patients, one had ipsilateral axillary and supraclavicular lymph node recurrence 16 months after breast-conserving surgery and the remaining four cases had local recurrence in the ipsilateral chest wall detected at 14, 15, 16 and 26 months after mastectomy.

Univariate analysis of factors affecting the prognosis of patients with HER-2-positive breast cancer with negative lymph nodes and a tumor diameter ≤1 cm. The DFS was not significantly correlated with the menopausal status, tumor diameter (≤0.5 cm vs. 0.5-1.0 cm), histological grade, Ki-67 expression, surgical method, chemotherapy, radiotherapy or anti-HER-2 therapy (P>0.05; Table II). Compared with patients aged >40 years, patients aged ≤40 years demonstrated significantly lower DFS (80.8 vs. 100.0%, P<0.001). The DFS was significantly better in patients who were estrogen receptor-positive and patients who received endocrine therapy compared with patients who were estrogen receptor-negative and patients who did not receive endocrine therapy, respectively (100.0 vs. 89.6%, P=0.039; 100.0 vs. 90.0%, P=0.049; Fig. 1).

Multivariate prognostic analysis of patients with HER-2-positive breast cancer with negative lymph nodes and a tumor diameter ≤1 cm. Patient factors which demonstrated statistically significant differences in the univariate analysis (estrogen receptor) expression status, endocrine therapy and age) were included in a multivariate analysis of factors associated with patient prognosis. In the multivariate analysis, hormone receptor (estrogen receptor) expression, endocrine treatment and age demonstrated no significant relationship with patient prognosis (P>0.05) (Table III).

Table I. Baseline data of patients with HER-2-positive breast cancer with negative lymph nodes and a tumor diameter ≤1 cm.

Clinicopathological feature	Number of patients, n (%)
Age, years	
≤40	26 (29.9)
>40	61 (70.1)
Menopause	
No	63 (72.4)
Yes	24 (27.6)
Diameter of tumor, cm	
≤0.5	59 (67.8)
0.5-1	28 (32.2)
Histological grade	
I-II	82 (94.3)
III	5 (5.7)
Estrogen receptor status	
Negative	48 (55.2)
Positive	39 (44.8)
Ki-67, %	
<30	31 (35.6)
≥30	56 (64.4)
Surgical method	
Breast-conserving	22 (25.3)
Mastectomy	65 (74.7)
Chemotherapy	
No	36 (41.4)
Yes	51 (58.6)
Endocrine therapy	
No	50 (57.5)
Yes	37 (42.5)
Anti-HER-2 therapy	
No	63 (72.4)
Yes	24 (27.6)
Radiotherapy	
No	69 (79.3)
Yes	18 (20.7)

Endocrine therapy included Aromatase inhibitor (n=5) and Tamoxifen/Toremifene (n=32). HER-2, human epidermal growth factor receptor 2.

Adjuvant anti-HER-2 therapy in the treatment of patients with HER-2-positive breast cancer with negative lymph nodes and a tumor diameter ≤1 cm. In the patient cohort, 27.6% (24/87) of patients received anti-HER-2 treatment (Table IV). The use of adjuvant anti-HER-2 therapy demonstrated no significant association with the patient age, estrogen receptor expression, histological grade or Ki-67 expression status (P>0.05) but had a significant correlation with tumor diameter (P<0.05). The proportion of patients with a tumor diameter 0.5-1 cm who received adjuvant anti-HER-2 treatment was significantly

Table II. Univariate analysis of the factors associated with the prognosis of patients with HER-2-positive breast cancer with negative lymph nodes and a tumor diameter ≤1 cm.

Clinicopathological feature	Recurrence, n	Proportion of patients with disease-free survival, %	P-value
Age, years			<0.001
≤40	5	80.8	
>40	0	100.0	
Menopause			0.160
No	5	92.1	
Yes	0	100.0	
Diameter of tumor, cm			0.539
≤0.5	4	93.2	
0.5-1	1	96.4	
Histological grade			0.576
I-II	5	93.9	
III	0	100.0	
Estrogen receptor expression			0.039
Negative	5	89.6	
Positive	0	100.0	
Ki-67, %			0.451
<30	1	96.8	
≥30	4	92.9	
Surgical method			0.774
Breast-conserving	1	95.5	
Mastectomy	4	93.8	
Chemotherapy			0.070
No	4	88.9	
Yes	1	98.0	
Endocrine therapy			0.049
No	5	90.0	
Yes	0	100.0	
Radiotherapy			0.246
No	5	92.8	
Yes	0	100.0	
Anti-HER-2 therapy			0.692
No	4	93.7	
Yes	1	95.8	

HER-2, human epidermal growth factor receptor 2.

greater compared with the proportion of patients with a tumor diameter ≤0.5 cm (46.4 vs. 18.6%, P<0.05).

Prognostic importance of tumor diameter and chemotherapy with or without anti-HER-2 therapy. In patients with HER-2-positive breast cancer with negative lymph nodes and a tumor diameter ≤0.5 cm, the use of chemotherapy with or without anti-HER-2 treatment had no significant effect on the DFS (P>0.05) (Table V). In patients with HER-2-positive breast cancer with negative lymph nodes and a tumor diameter of 0.5-1 cm, the DFS in the group receiving chemotherapy (with or without anti-HER-2 treatment) was significantly higher compared with the group without chemotherapy and anti-HER-2 treatment for any chemotherapy group, regardless of the use of anti-HER-2 therapy (P<0.05).

Discussion

In the present study, prognostic analysis of patients with HER-2-positive breast cancer with negative lymph nodes and a tumor diameter ≤1 cm demonstrated that these patients had a better prognosis. After a median follow-up period of 70 months, the DFS rate and OS rate of these patients were 94.3 and 100%, respectively and DFS events were mainly
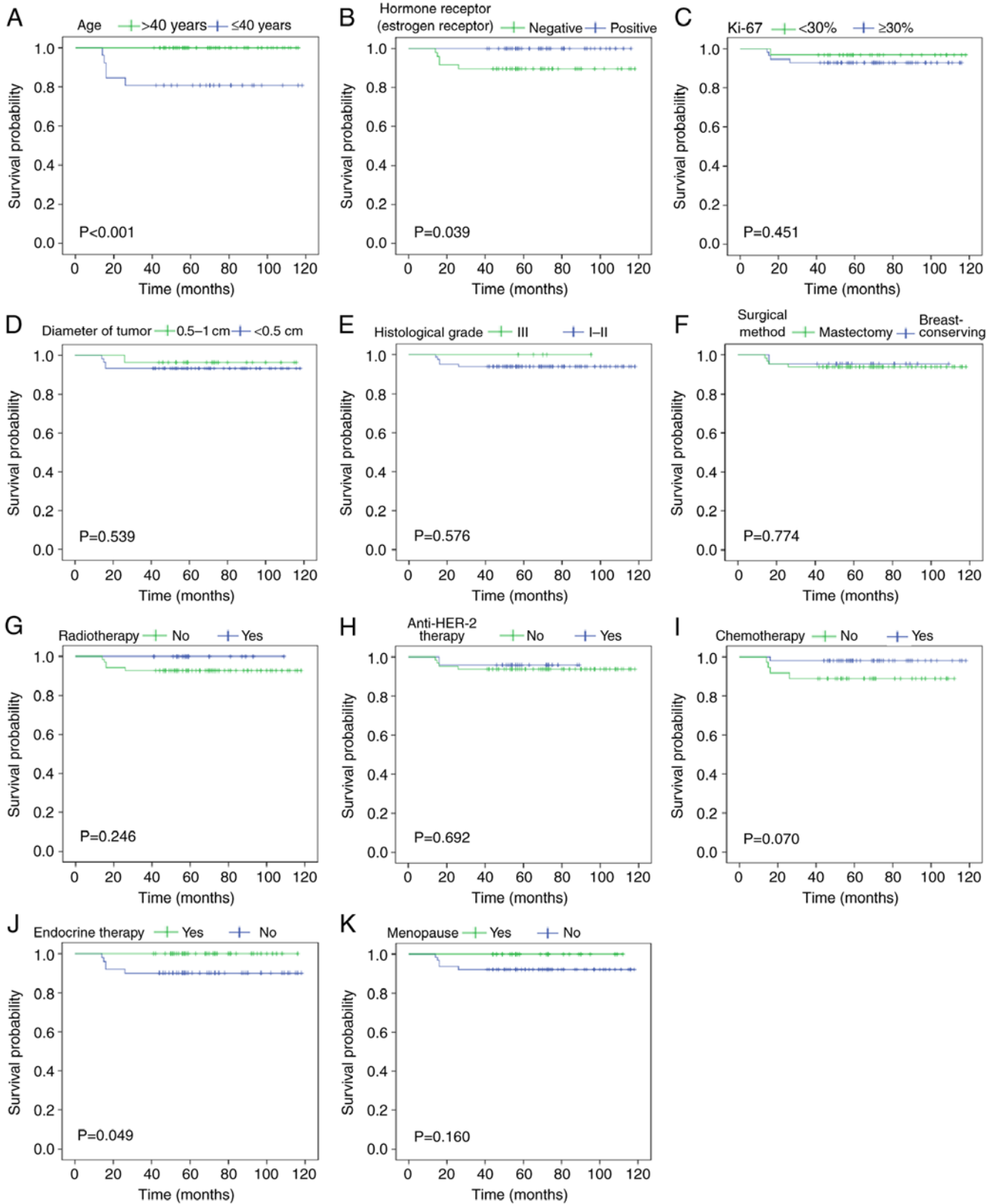
Figure 1. DFS analysis of the factors associated with the prognosis of HER-2-positive breast cancer patients with negative lymph nodes and a tumor diameter ≤1 cm. DFS analysis of (A) age, (B) estrogen receptor expression status, (C) Ki-67, (D) diameter of tumor, (E) histological grade, (F) surgical method, (G) radiotherapy, (H) anti-HER-2-therapy, (I) chemotherapy, (J) endocrine therapy and (K) menopause. DFS, disease-free survival; HER-2, human epidermal growth factor receptor 2.

recurrent events, without metastasis. The recurrence rate was ~5.7%, while a similar study previously performed in Canada reported a local recurrence rate of ~8% after a median follow-up time of 70 months (13). Although the univariate analysis demonstrated that the prognosis was related to patient age, hormone receptor (estrogen receptor) expression and use of

Table III. Multivariate analysis of factors associated with the prognosis of patients with human epidermal growth factor receptor 2-positive breast cancer with negative lymph nodes and a tumor diameter ≤1 cm.

Factors	Hazard ratio (95% CI)	P-value
Estrogen receptor expression (negative vs. positive)	$0.371 (0.000-1.981 \times 10^{27})$	0.976
Endocrine therapy (no vs. yes)	$21.648 (0.000-1.753 \times 10^{29})$	0.925
Age (≤40 vs. >40 years)	$288.042 (0.023-3.651 \times 10^{6})$	0.240

Table IV. Adjuvant anti-HER-2 therapy in patients with HER-2-positive breast cancer with negative lymph nodes and a tumor diameter ≤1 cm.

Clinicopathological characteristic	Patients, n	Patients treated with anti-HER-2 therapy, n (%)	Patients not treated with anti-HER-2 therapy, n (%)	P-value
Age, years				0.120[a]
≤40	26	4 (15.4)	22 (84.6)	
>40	61	20 (32.8)	41 (67.2)	
Diameter of tumor, cm				0.007
≤0.5	59	11 (18.6)	48 (81.4)	
0.5-1	28	13 (46.4)	15 (53.6)	
Estrogen receptor expression				0.070
Negative	48	17 (35.4)	31 (64.6)	
Positive	39	7 (17.9)	32 (82.1)	
Histological grade				0.613[a]
I-II	82	22 (26.8)	60 (73.2)	
III	5	2 (40.0)	3 (60.0)	
Ki-67, %				0.782
<30	31	8 (25.8)	23 (74.2)	
≥30	56	16 (28.6)	40 (71.4)	

[a]Data analyzed using Fisher's exact test; all other data were analyzed using the χ^2 test. HER-2, human epidermal growth factor receptor 2.

Table V. Influence of adjuvant chemotherapy and anti-HER-2 therapy on the prognosis of patients with different tumor diameters.

Clinicopathological characteristic	Patients, n	Recurrence, n	Disease-free survival, %	P-value
Tumor diameter ≤0.5 cm	59	4		0.381
No adjuvant chemotherapy and anti-HER-2 therapy	32	3	90.6	
Adjuvant chemotherapy +/-anti-HER-2 therapy	27	1	96.3	
Tumor diameter 0.5-1 cm	28	1		0.014
No adjuvant chemotherapy and anti-HER-2 therapy	4	1	75.0	
Adjuvant chemotherapy +/-anti-HER-2 therapy	24	0	100.0	

HER-2, human epidermal growth factor receptor 2.

endocrine therapy, a subsequent multivariate analysis demonstrated that the prognosis was not significantly associated with these factors. In clinical practice, adjuvant chemotherapy and anti-HER-2 therapy are often recommended for patients with HER-2-positive breast cancer with negative lymph nodes and a tumor diameter >1 cm (14). However, clinical data on whether adjuvant chemotherapy and anti-HER-2 therapy should be used for patients with breast cancer with a smaller tumor diameter

are still limited. In the present study, 27.6% of patients with breast cancer with negative lymph nodes and a tumor diameter ≤1 cm received anti-HER-2 treatment, although the proportion of patients with a tumor diameter 0.5-1 cm receiving adjuvant anti-HER-2 treatment was greater compared with patients with a tumor diameter ≤0.5 cm. Additional prognostic analysis demonstrated that adjuvant chemotherapy and anti-HER-2 treatment may affect the prognosis of patients with a tumor diameter 0.5-1.0 cm, but not those with smaller tumors.

Previous studies have reported that the prognosis of breast cancer is related to age, as a younger age is a negative prognostic factor for patients with breast cancer (15-17). Patients aged <40 years are also more likely to develop breast cancer with worse clinicopathological features and a more aggressive subtype (15-17). Multiple research studies have also reported that the estrogen receptor status may be related to the prognosis of HER-2-positive breast cancer (18,19). However, the results of large clinical trials reported that the survival benefits of HER-2 positivity in patients with breast cancer after adjuvant chemotherapy and anti-HER-2 treatment were unrelated to their age, tumor size or estrogen receptor status (20). The multivariate analysis performed in the present study also demonstrated that the patient age and estrogen receptor status were not independent prognostic factors for this type of breast cancer.

There has been debate on the tumor diameter threshold for prescribing adjuvant chemotherapy and anti-HER-2 treatment. A previous study by Parikh et al (21) suggested that T1aN0M0 and T1bN0M0 HER-2-positive breast cancer have a similar good prognosis. The potential risks and benefits of treatment should be weighed when adjuvant chemotherapy and anti-HER-2 treatment are applied for patients with this type of breast cancer. A study using the National Cancer Database reported that adjuvant chemotherapy was associated with an improved 5-years OS (96.8 vs. 92.3%) in patients with T1bN0M0 breast cancer, while no benefit was observed in patients with T1aN0M0 and T1miN0M0 breast cancer (22). However, another retrospective non-randomized study reported that anti-HER-2 therapy may benefit patients with pT1a/bN0M0 HER-2-positive malignant breast tumors (13). However, patients with T1a and T1b disease were not analyzed separately in the aforementioned study. Recently, a meta-analysis of patients with 13864 early-stage, HER-2-positive cancer in seven randomized trials reported that patients with T1a/b disease benefited from anti-HER-2 therapy, but the nodal status of this subgroup was not reported (2). The present study demonstrated that the DFS in the 0.5-1 cm tumor diameter subgroup of patients receiving adjuvant chemotherapy and anti-HER-2 therapy was improved compared with the group of patients not receiving adjuvant chemotherapy and anti-HER-2 therapy, while no such effect was observed in the patients with a tumor diameter ≤0.5 cm. This indicated that patients with a tumor diameter 0.5-1 cm may need adjuvant chemotherapy and anti-HER-2 treatment, while patients with a tumor diameter ≤0.5 cm may not benefit from adjuvant chemotherapy and anti-HER-2 treatment.

The present study has certain limitations. Firstly, the present study was a retrospective study with inherent selection bias. Secondly, the number of cases was small, the median follow-up time was short, the number of recurrences was small, with all events reported as local or local lymph node recurrence and there were no cases with distant metastasis or deaths. Further studies including a larger number of cases and with an extended follow-up time are required, especially for patients with a tumor diameter ≤0.5 cm which are rarely included in clinical studies of adjuvant therapy at present. Thirdly, the present study did not analyze the tumor-infiltrated immune cells, such as macrophages, neutrophils, MDSC, T and B cells, as a prognostic factor for patients with HER-2-positive breast cancer with negative lymph nodes and a tumor diameter ≤1 cm.

In conclusion, adjuvant chemotherapy and anti-HER-2 treatment may affect the prognosis of patients with a tumor diameter of 0.5-1 cm, but do not appear to affect the prognosis of patients with a tumor diameter ≤0.5 cm. Adjuvant chemotherapy and anti-HER-2 therapy are recommended for patients with a tumor diameter of 0.5-1 cm. However, for patients with a tumor diameter ≤0.5 cm, there does not appear to be a benefit in terms of the survival outcome. Future studies should examine whether adjuvant chemotherapy and anti-HER-2 treatment should be given to these patients.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AZ and HG conceptualized the study, and reviewed and edited the manuscript. SY, YW and YG were responsible for the data collection, cataloging and proofreading. HG acquired funding. SY and YW were responsible for data analysis and drafting the manuscript. SY, YW and YZ performed the experiments. YG was also responsible for the patient follow-up. AZ acted as project administrator. HG supervised the project. HP, HT, YL and AZ helped with data collection, cataloguing, analysis and validation. HG and AZ confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all patients and/or their legal guardian(s). All experimental protocols were approved

by the Ethics Committee of Guangdong Women and Children Hospital (approval number: 202301244).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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