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Distant Metastasis by Hormone Receptor Status in Initially Nonmetastatic HER2-Positive Breast Cancer Receiving Trastuzumab: A Retrospective Cohort Study

[1]Rio Nurdiansyah Batubara*, [1]Suyatno, [1]Endi Taris Pasaribu, [2]Putri Chairani Eyanoer
[1] Department of Surgery, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia*; email: rionbj91@gmail.com
[2] Department of Community and Preventive Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
*Correspondence

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Abstract
Introduction: *Hormone receptor status may influence the timing of distant relapse in human epidermal growth factor receptor 2-positive breast cancer.* ***Objective:*** *To compare documented distant metastasis by hormone receptor status among initially nonmetastatic patients receiving trastuzumab.* ***Method:*** *This retrospective cohort included 64 patients with stage I–III disease at Adam Malik Hospital. Proportions were compared using Fisher's exact test.* ***Results and Discussion:*** *Distant metastasis was documented in 13 patients (20.3%), including 7 of 40 hormone receptor-positive patients (17.5%) and 6 of 24 hormone receptor-negative patients (25.0%). The crude risk ratio was 0.70 (95% confidence interval 0.27–1.84, p = 0.530), and the crude odds ratio was 0.64 (95% confidence interval 0.19–2.18). Bone was the most frequently recorded site (7 of 13, 53.8%). In the exploratory stage comparison, metastasis was documented in 28.6% of stage III and 10.3% of stage I–II patients (p = 0.118). Later relapse may be missed when follow-up duration varies. Individual event and observation times were unavailable.* ***Conclusion:*** *The between-group difference in documented distant metastasis was statistically inconclusive, with substantial uncertainty around the estimate.*

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Introduction

Adjuvant trastuzumab reduces recurrence and breast cancer mortality by approximately one-third when added to chemotherapy for human epidermal growth factor receptor 2 (HER2)-positive early breast cancer (Early Breast Cancer Trialists' Collaborative Group, 2021). Residual risk varies with the extent of disease and tumor biology. Hormone receptor (HR) status, defined by estrogen receptor (ER) and progesterone receptor (PR) expression, identifies groups with distinct treatment options and patterns of relapse (Loibl et al., 2024; Ran et al., 2024). In tumors that coexpress ER and HER2, the two signaling pathways interact in both directions. HER2 activates intracellular pathways such as PI3K–AKT and MAPK, which can sustain proliferation and modify ER activity even in the absence of estrogen. When HER2 signaling is inhibited, some tumors can increase ER-dependent transcription and use it to sustain cell survival. These mechanisms can contribute to resistance to endocrine or HER2-directed therapy and provide a rationale for targeting both pathways in patients with receptor-positive disease (Li & Huang, 2025; Pegram et al., 2023).

The timing of relapse also differs by receptor status. In cohorts treated with adjuvant trastuzumab, relapse was more concentrated in the early years for HR-negative disease, while HR-positive disease retained a risk of later recurrence (Chumsri et al., 2019; Kang et al., 2023). A comparison based on whether metastasis was ever documented can miss later events when observation is short or differs across patients. The length and completeness of follow-up therefore affect how this comparison should be interpreted. Indonesian studies have characterized advanced-stage presentation and the association between receptor expression and neoadjuvant chemotherapy response (Indra et al., 2021; Setyawan et al., 2023). These studies leave open a different question: how often is subsequent distant metastasis documented in each receptor group after a nonmetastatic diagnosis among patients who receive adjuvant trastuzumab? A local estimate can help Adam Malik Hospital assess how recurrence is recorded and inform a registry that captures dates of recurrence, treatment, and last follow-up. This retrospective cohort study aimed to compare the proportion with documented distant metastasis between the HR-positive and HR-negative groups among patients with stage I–III HER2-positive breast cancer receiving trastuzumab at Adam Malik Hospital, and to explore differences by clinical stage.

Method

Study design and participants

This retrospective cohort study was conducted from August to December 2025 at Adam Malik Hospital, Medan, Indonesia. Hospital medical records were the source for clinical and diagnostic information, and the chemotherapy registry was used to identify trastuzumab recipients. Records were screened consecutively against the eligibility criteria. The planned minimum was 48 patients (24 per group), based on a two-proportion sample-size calculation with a two-sided significance level of 0.05 and 80% power. Eligible patients had stage I–III breast cancer at diagnosis, confirmed by histopathology, with documented HER2 positivity and receipt of adjuvant trastuzumab. Records had to support classification of HR status and distant metastasis. Exclusion criteria were stage IV disease at diagnosis, autoimmune disease, another concurrent malignancy, incomplete clinical or laboratory records, and receipt of more than eight cycles of targeted therapy.

Data sources and outcome ascertainment

HER2, ER, and PR status were abstracted as reported in pathology records. HR-positive disease was defined as ER and/or PR positivity. HR-negative disease required both markers to be reported as negative. The American Society of Clinical Oncology and College of American Pathologists guidelines define positive ER or PR staining as at least 1% of tumor nuclei and identify HER2 positivity through immunohistochemistry (3+) or an amplified result on in situ hybridization in equivocal cases, interpreted using the guideline algorithm (Allison et al., 2020; Wolff et al., 2023). These criteria provide reference standards. The analysis used the hospital's recorded interpretations, and assay platforms, antibody clones, and case-level reflex testing were not documented in the available study materials.

Clinical stage at diagnosis was abstracted from the medical record. The outcome was documented distant metastasis after a stage I–III diagnosis, defined as radiologic and/or histopathologic evidence of disease at a distant site (M1) under the American Joint Committee on Cancer eighth-edition tumor–node–metastasis framework (Giuliano et al., 2018). Clinical and diagnostic reports were reviewed for outcome and site. Cases without evidence of distant disease in the available records were classified as having no documented distant metastasis. Recorded sites were grouped as bone, lung, liver, or brain. Age, histological type, and systemic treatment regimen were also abstracted.

Statistical analysis

Age was summarized as mean and standard deviation. Categorical variables were summarized as counts and percentages. The statistical plan specified IBM SPSS Statistics version 26. Two-sided Fisher's exact tests were used for the HR group comparison and the exploratory stage III versus stage I–II comparison because of sparse event counts. Exact p values were independently checked with SciPy version 1.17.0. Crude risk ratios and odds ratios with log-scale Wald 95% confidence intervals were calculated from the 2 × 2 tables. HR-negative and stage I–II were the reference groups for their respective comparisons. Statistical significance was set at $p < 0.05$. The analysis was unadjusted and used a binary outcome because individual observation and event times were unavailable.

Result and Discussion

1. Result

Of 158 trastuzumab recipients identified in the source records, 64 patients with stage I–III disease met the eligibility criteria and were analyzed. Forty (62.5%) had HR-positive tumors and 24 (37.5%) had HR-negative tumors. Distant metastasis was documented in 13 patients (20.3%), including 7 of 40 HR-positive patients (17.5%) and 6 of 24 HR-negative patients (25.0%). Mean age was 50.6 ± 10.1 years. Stage III disease accounted for 35 patients (54.7%), and invasive ductal carcinoma of no special type accounted for 56 (87.5%). The most frequently recorded regimen was AC–TH, used in 27 patients (42.2%). Baseline characteristics are shown in Table 1.

Table 1
Baseline Characteristics by Hormone Receptor Status

Characteristic	Positive (n=40)	Negative (n=24)	Total (n=64)
Age, years, mean±SD	51.9±9.8	48.4±10.5	50.6±10.1
Age group, years			
<40	3 (7.5)	5 (20.8)	8 (12.5)
40–49	13 (32.5)	8 (33.3)	21 (32.8)
50–59	15 (37.5)	7 (29.2)	22 (34.4)
≥60	9 (22.5)	4 (16.7)	13 (20.3)
Clinical stage			
I	3 (7.5)	1 (4.2)	4 (6.3)
II	17 (42.5)	8 (33.3)	25 (39.1)
III	20 (50.0)	15 (62.5)	35 (54.7)
Histological type			
Invasive ductal carcinoma/NST	36 (90.0)	20 (83.3)	56 (87.5)
Invasive lobular carcinoma	2 (5.0)	2 (8.3)	4 (6.3)
Mixed carcinoma	1 (2.5)	2 (8.3)	3 (4.7)
Other	1 (2.5)	0 (0.0)	1 (1.6)
Treatment regimen			
AC–TH	17 (42.5)	10 (41.7)	27 (42.2)
TCH	11 (27.5)	7 (29.2)	18 (28.1)
TH	7 (17.5)	6 (25.0)	13 (20.3)
Trastuzumab monotherapy	3 (7.5)	1 (4.2)	4 (6.3)
Other regimens	2 (5.0)	0 (0.0)	2 (3.1)

Values are n (%) unless stated otherwise. SD: standard deviation; NST: no special type; AC–TH: anthracycline/cyclophosphamide followed by taxane–trastuzumab; TCH: taxane–carboplatin–trastuzumab; TH: taxane–trastuzumab. Percentages may not total 100% because of rounding.

There was no distant metastasis recorded for 51 patients (79.7%). Among the 13 patients with documented metastasis, the recorded sites were bone in seven (53.8%), lung in four (30.8%), and liver in two (15.4%). No brain metastasis was recorded (Table 2).

Table 2
Documented Distant Metastasis and Recorded Sites

Outcome/site	Positive	Negative	Total
Distant metastasis	7/40 (17.5)	6/24 (25.0)	13/64 (20.3)
No distant metastasis	33/40 (82.5)	18/24 (75.0)	51/64 (79.7)
Site among metastatic patients			
Bone	4/7 (57.1)	3/6 (50.0)	7/13 (53.8)
Lung	2/7 (28.6)	2/6 (33.3)	4/13 (30.8)
Liver	1/7 (14.3)	1/6 (16.7)	2/13 (15.4)
Brain	0/7 (0.0)	0/6 (0.0)	0/13 (0.0)

Positive and negative refer to hormone receptor status. Values are numerator/denominator (%). Metastasis status uses all patients in each group as the denominator. Recorded sites use only patients with documented distant metastasis.

The between-group difference was not statistically significant (two-sided Fisher's exact p=0.530). For hormone receptor-positive versus hormone receptor-negative disease, the crude risk ratio was 0.70 (95% CI 0.27–1.84), and the crude odds ratio was 0.64 (95% CI 0.19–2.18). Both intervals included 1 and were wide, indicating substantial uncertainty (Table 3). In the exploratory stage comparison, metastasis occurred in 10 of 35 stage III patients (28.6%) and 3 of 29 stage I–II patients (10.3%). The crude risk ratio was 2.76 (95% CI 0.84–9.10), and the crude odds ratio was 3.47 (95% CI 0.85–14.09); Fisher's exact p was 0.118. This comparison did not establish an independent association with stage.

Table 3
Crude Associations with Documented Distant Metastasis

Comparison	Metastasis	Risk ratio (95% CI)	Odds ratio (95% CI)	p
Receptor-positive vs receptor-negative	7/40 vs 6/24	0.70 (0.27–1.84)	0.64 (0.19–2.18)	0.530
Stage III vs stage I–II	10/35 vs 3/29	2.76 (0.84–9.10)	3.47 (0.85–14.09)	0.118

CI, confidence interval. Estimates are unadjusted and were calculated from the 2 × 2 counts shown. Two-sided Fisher's exact tests were used for both comparisons. The 95% CIs use log-scale Wald intervals. The stage analysis is exploratory.

2. Discussion

The proportion with documented distant metastasis was 7.5 percentage points lower in the HR-positive group. The comparison was statistically inconclusive, with a crude risk ratio of 0.70 (95% confidence interval 0.27–1.84). The interval permits clinically important differences in either direction. Stage III disease was more common in the HR-negative group (62.5% versus 50.0%), and stage was not controlled for in the receptor-group comparison. Ran et al. (2024) reported better disease-free and overall survival in HR-positive patients in a retrospective cohort of 828 patients with HER2-positive breast cancer. This is directionally consistent with the lower proportion documented in our HR-positive group. Their survival endpoints included events beyond distant metastasis, and use of HER2-directed therapy varied. The studies therefore answer related questions using different outcomes and treatment populations.

The timing of recurrence may explain why receptor-group differences vary across reports. In node-positive patients receiving adjuvant trastuzumab in two randomized-trial cohorts, Chumsri et al. (2019) found a lower hazard of relapse or death for HR-positive disease in years 0–5 (hazard ratio 0.59, 95% confidence interval 0.45–0.78). The difference was inconclusive in years 5–10. A subsequent analysis found recurrence or death between years 5 and 10 among trastuzumab-treated HR-positive patients and found limited performance of the Clinical Treatment Score Post-5 Years in that group (Chumsri et al., 2024). In a Stockholm population cohort with mixed trastuzumab exposure, Kaukonen et al. (2026) found that the interaction between ER and HER2 status for distant recurrence-free survival changed over time. Our records did not support estimation of time to distant metastasis or a common follow-up horizon. Later events could therefore be missed, and the direction and extent of any resulting bias are uncertain.

The effect of receptor status is also difficult to separate from endocrine treatment. The PERTAIN trial found longer progression-free survival when pertuzumab was added to trastuzumab plus an aromatase inhibitor in HR-positive/HER2-positive metastatic or

locally advanced disease (Arpino et al., 2023). This is evidence from a different treatment setting, and endocrine therapy use and adherence were not characterized in our cohort. The contribution of endocrine therapy to the observed proportions remains unknown. More than half of the cohort had stage III disease, and the exploratory stage comparison showed a higher proportion of documented metastasis in stage III than in stages I–II. Bonomi et al. (2025) reported 98.2% three-year distant relapse-free survival in a real-world series primarily comprising patients with stage IA disease treated with paclitaxel and trastuzumab. The long-term APT trial likewise reported favorable outcomes in patients with small, node-negative tumors (Tolaney et al., 2023). The lower-risk case mix, more uniform regimens, and defined follow-up in those studies limit direct comparison with our observed proportions.

Bone accounted for 7 of 13 recorded metastatic events. Ran et al. (2024) reported more bone metastases among HR-positive than HR-negative patients with recurrence or metastasis, and a higher frequency of lung metastases in the HR-negative group. Other cohorts also found variation in metastatic sites by tumor subtype (Fan et al., 2023; Kaukonen et al., 2026). In our cohort, the site counts were too small to estimate receptor-specific patterns reliably, and absence of a recorded brain metastasis may reflect limited observation or ascertainment. All patients received trastuzumab, but accompanying chemotherapy varied. Comparative studies of trastuzumab with different chemotherapy regimens illustrate why the treatment backbone matters when interpreting outcomes (Gao et al., 2021). The protocol's exclusion of patients who received more than eight targeted-therapy cycles limits comparison with cohorts planned for a full year of trastuzumab, such as APT (Tolaney et al., 2023). Residual invasive disease was also not characterized systematically. The final KATHERINE analysis showed that, among patients with such residual disease after neoadjuvant therapy, adjuvant trastuzumab emtansine improved invasive disease-free survival and overall survival compared with trastuzumab (Geyer et al., 2025). Those results help explain why contemporary cohorts using different post-neoadjuvant regimens can have different outcomes.

This single-center retrospective study had only 13 metastatic events. Imaging methods and surveillance frequency varied across records, and events occurring after the last documented contact or outside the hospital could have been missed. Stage, treatment duration, endocrine therapy, and other clinicopathological characteristics were not controlled for. Because all patients received trastuzumab, the study cannot estimate its treatment effect. Recording treatment start and stop dates, distant relapse dates and sites, and last patient contact would support time-to-event analyses in future multicenter studies.

Study Limitations

This study has several limitations. First, its retrospective, single-center design and small sample size (64 patients) limit generalizability and statistical power. Second, only 13 distant metastasis events were documented, resulting in wide confidence intervals and substantial uncertainty in effect estimates. Third, variable imaging methods and surveillance frequency may have led to incomplete outcome ascertainment, including missed recurrences occurring outside the hospital or after the last documented contact. Fourth, individual follow-up duration and event dates were unavailable, preventing time-to-event analysis and potentially underestimating late recurrence. Fifth, the analysis was unadjusted for potential confounders, including clinical stage, endocrine therapy,

treatment duration, and chemotherapy regimen. Finally, excluding patients who received more than eight cycles of targeted therapy may limit comparability with standard one-year trastuzumab treatment cohorts. These findings should therefore be interpreted cautiously.

Conclusion

In this cohort of patients with stage I–III HER2-positive breast cancer receiving adjuvant trastuzumab, distant metastasis was documented in 17.5% of HR-positive patients and 25.0% of HR-negative patients (crude risk ratio 0.70, 95% confidence interval 0.27–1.84, p = 0.530). The difference was statistically inconclusive. Limited precision and unavailable event and follow-up times constrain prognostic interpretation.

Ethical Considerations: The study received permission and ethical approval from the Health Research Ethics Committee of Universitas Sumatera Utara.

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