Trastuzumab翻轉HER2陽性乳癌存活格局：台北榮總五年整體與無復發存活率新證據

Trastuzumab Reshapes Survival Landscape in HER2-positive Breast Cancer: New 5-year Overall and Disease-free Survival Evidence from Taipei Veterans General Hospital

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Introduction

Over the past two decades, trastuzumab has revolutionized the management of HER2-positive breast cancer, significantly improving survival outcomes and becoming the backbone of standard therapy [1–3]. Despite these advances, disease recurrence still occurs in a subset of patients, and treatment decisions for small tumors (T1a/bN0) remain controversial, as this subgroup was excluded from pivotal randomized trials [4]. Current NCCN guidelines highlight the uncertainty of long-term benefits in these patients, raising the need for real-world evidence to guide clinical practice [5].

In parallel, the role of neoadjuvant therapy (NAC) has expanded since 2010, supported by trials demonstrating high rates of pathological complete response with dual HER2 blockade [6,7]. Accordingly, NAC is now recommended for ≥T2 or node-positive disease [5].

Using the Taipei Veterans General Hospital Cancer Registry, this study evaluates 5-year overall survival (OS) and recurrence-free survival (RFS) across stages in HER2-positive breast cancer, with special emphasis on stage IA disease and the evolving application of NAC in real-world practice.

Methodology

Patient Inclusion Criteria

We retrospectively reviewed patients diagnosed with HER2-positive breast cancer at Taipei Veterans General Hospital between 2007 and 2022. Clinical and pathological data were retrieved from the institutional Cancer Registry, which records detailed information on diagnosis date, histology, clinical and pathological TNM stage, treatment modalities, and follow-up outcomes.

A total of 1,332 patients were included after consolidating duplicated IDs according to pre-specified rules. (Figure 1) Patients with incomplete records or missing staging information were excluded.

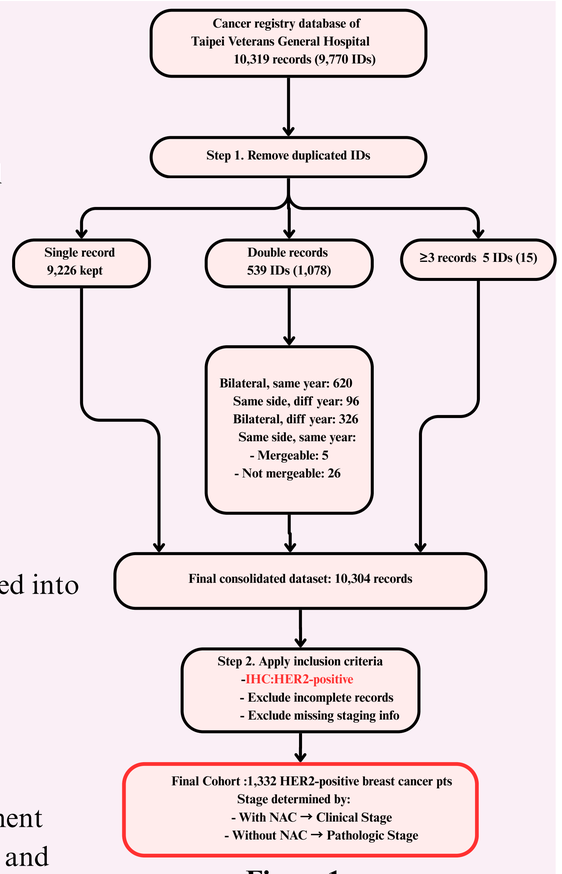

Figure 1.

Study Design

This was a retrospective cohort study. Patients were classified into four treatment groups:

- Group A: No chemotherapy, no trastuzumab
- Group B: Trastuzumab only
- Group C: Chemotherapy only
- Group D: Chemotherapy + trastuzumab

Analyses were stratified by final stage (IA–IIIC) and treatment groups (Table 1). Baseline characteristics were summarized and compared across groups (Table 2).

Endpoints

- The primary endpoint was recurrence-free survival (RFS), defined as the time from completion of primary treatment to the first recurrence (local, regional, or distant) or breast cancer–related death. Patients without an event within 5 years were censored.
- The secondary endpoint was overall survival (OS), defined as the time from diagnosis to death from any cause. Patients alive at 5 years were censored.

Table 1. Patient counts by stage and treatment group

Stage	Group A	Group B	Group C	Group D	Total
1A	191	12	30	251	484
1B	0	0	0	7	7
2A	35	5	28	287	355
2B	6	6	3	175	190
3A	2	2	4	130	138
3B	4	0	0	17	21
3C	2	5	5	125	137

Table 1. Patient counts by stage and treatment group

Statistical Analysis

Survival outcomes were estimated using the Kaplan–Meier method and compared with log-rank tests. Cox proportional hazards regression was performed to evaluate the prognostic effects of clinicopathologic variables. Each variable was first assessed in univariate models. Subsequently, multivariate models included treatment group, age, hormone receptor status, tumor grade, and stage, regardless of univariate significance.

To minimize collinearity, final stage was selected as the staging variable instead of incorporating individual T and N classifications simultaneously. Age was modeled as a continuous covariate, with the hazard ratio representing the relative risk per one-year increase. The proportional hazards assumption was verified for all Cox models. Differences were considered significant when the p-value was less than 0.05.

Characteristics	N	Group A N = 240¹	Group B N = 30¹	Group C N = 70¹	Group D N = 992¹	Overall N = 1,332¹	p-value²
Age	1,332						<0.001
Mean ± SD; Median [Min, Max]		58 ± 12; 58 [32, 89]	64 ± 16; 68 [32, 86]	55 ± 12; 57 [30, 79]	54 ± 11; 54 [20, 87]	55 ± 12; 55 [20, 89]	
Age group	1,332						0.008
< 50 y/o		57 (24%)	7 (23%)	22 (31%)	344 (35%)	430 (32%)	
≥ 50 y/o		183 (76%)	23 (77%)	48 (69%)	648 (65%)	902 (68%)	
Hormone receptor status	1,332						<0.001
HR negative		148 (62%)	9 (30%)	23 (33%)	428 (43%)	608 (46%)	
HR positive		92 (38%)	21 (70%)	47 (67%)	564 (57%)	724 (54%)	
Tumor grade	744						<0.001
I		7 (5.5%)	0 (0%)	0 (0%)	4 (0.7%)	11 (1.5%)	
II		76 (60%)	7 (44%)	27 (57%)	279 (49%)	380 (51%)	
III		44 (35%)	9 (56%)	24 (47%)	276 (50%)	353 (47%)	
Histology	1,332						0.070
IDC		224 (93%)	27 (90%)	67 (96%)	946 (95%)	1,264 (95%)	
ILC		2 (0.8%)	2 (6.7%)	0 (0%)	12 (1.2%)	16 (1.2%)	
Others		14 (5.8%)	1 (3.3%)	3 (4.3%)	34 (3.4%)	52 (3.9%)	
Endocrine therapy	1,332	89 (37%)	21 (70%)	43 (61%)	536 (54%)	689 (52%)	<0.001
Radiotherapy	1,332						
Done		240 (100%)	30 (100%)	70 (100%)	992 (100%)	1,332 (100%)	
Follow-up (months)	1,332						0.10
Mean ± SD; Median [Min, Max]		66 ± 41; 60 [0, 155]	65 ± 39; 58 [9, 147]	77 ± 42; 78 [5, 156]	75 ± 39; 71 [0, 163]	73 ± 40; 67 [0, 163]	
Final stage	1,332						<0.001
1A		191 (80%)	12 (40%)	30 (43%)	251 (25%)	484 (36%)	
1B		0 (0%)	0 (0%)	0 (0%)	7 (0.7%)	7 (0.5%)	
2A		35 (15%)	5 (17%)	28 (40%)	287 (29%)	355 (27%)	
2B		6 (2.5%)	6 (20%)	3 (4.3%)	175 (18%)	190 (14%)	
3A		2 (0.8%)	2 (6.7%)	4 (5.7%)	130 (13%)	138 (10%)	
3B		4 (1.7%)	0 (0%)	0 (0%)	17 (1.7%)	21 (1.6%)	
3C		2 (0.8%)	5 (17%)	5 (7.1%)	125 (13%)	137 (10%)	

¹n (%)

²Pearson's Chi-squared test; NA

Table 2. Clinicopathologic Characteristics

Results

Survival Analysis (Figure 2)

- Stage IA: RFS differed slightly across groups (log-rank p = 0.027), OS not significant (p = 0.59). Cox regression: trend favoring Group D vs Group A, but not significant (HR 0.49, 95% CI 0.17–1.42).
- Stage IIA: Both RFS and OS significantly improved with Group D (RFS HR 0.15, 95% CI 0.07–0.32; OS HR 0.10, 95% CI 0.04–0.30; both p < 0.001).
- Stage ≥ IIIA: Almost all patients received Group D, limiting direct comparison, but outcomes were consistently poor without it.

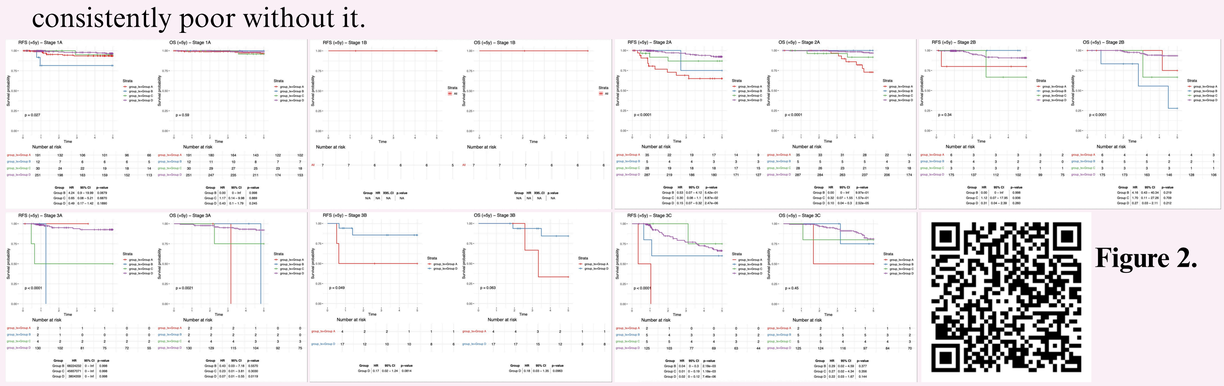

Figure 2.

Cox Regression Analysis (Table 3a–3b)

Multivariate Cox models confirmed that **chemotherapy plus anti-HER2 therapy (Group D)** was the only treatment significantly improving both OS and RFS, compared with the untreated group (Group A).

- OS: HR = 0.38 (95% CI 0.22–0.66, p = 0.001)
- RFS: HR = 0.28 (95% CI 0.15–0.54, p < 0.001). Neither trastuzumab alone (Group B) nor chemotherapy alone (Group C) conferred significant survival benefit (HR ≈ 1, p > 0.2).

Age was an independent prognostic factor for OS (HR per year = 1.05, 95% CI 1.03–1.07, p < 0.001), but not for RFS.

Stage strongly predicted outcomes, with hazard ratios rising sharply from IIA (OS HR = 3.20; RFS HR = 4.94) to IIIC (OS HR = 10.45; RFS HR = 16.91), all p < 0.001.

Table 3a. Cox Regression for Overall Survival (OS)

Variable	Level	Univariate HR (95% CI)	Univariate p	Multivariate HR (95% CI)	Multivariate p
group_tx	Group A (ref)				
group_tx	Group B	1.72 (0.71–4.14)	0.228	0.77 (0.30–1.97)	0.579
group_tx	Group C	1.10 (0.55–2.20)	0.789	0.73 (0.33–1.65)	0.451
group_tx	**Group D**	**0.66 (0.43–1.00)**	**0.052**	**0.38 (0.22–0.66)**	**0.001**
Age	**Age (per year increase)**	**1.07 (1.06–1.09)**	**0.000**	**1.05 (1.03–1.07)**	**0.000**
hr_status	HR negative (ref)				
hr_status	HR positive	0.82 (0.59–1.15)	0.255	0.79 (0.53–1.18)	0.251
grade_f	Grade I (ref)				
grade_f	II	0.56 (0.14–2.31)	0.425	0.23 (0.05–1.03)	0.055
grade_f	**III**	**0.72 (0.17–2.93)**	**0.643**	**0.19 (0.04–0.86)**	**0.031**
final_stage	Stage 1A (ref)				
final_stage	1B	0.00 (0.00–NA)	0.993	0.00 (0.00–NA)	0.994
final_stage	**2A**	**2.42 (1.34–4.38)**	**0.003**	**3.20 (1.60–6.39)**	**0.001**
final_stage	**2B**	**3.54 (1.90–6.59)**	**0.000**	**5.12 (2.34–11.22)**	**0.000**
final_stage	**3A**	**4.01 (2.10–7.65)**	**0.000**	**6.98 (3.15–15.45)**	**0.000**
final_stage	**3B**	**10.20 (4.02–25.88)**	**0.000**	**6.48 (2.21–19.02)**	**0.001**
final_stage	**3C**	**8.43 (4.77–14.90)**	**0.000**	**10.45 (4.99–21.88)**	**0.000**

Table 3a. Cox Regression for Overall Survival (OS)

Table 3b. Cox Regression for Recurrence-Free Survival (RFS)

Variable	Level	Univariate HR (95% CI)	Univariate p	Multivariate HR (95% CI)	Multivariate p
group_tx	Group A (ref)				
group_tx	Group B	1.97 (0.81–4.80)	0.134	0.62 (0.17–2.25)	0.468
group_tx	Group C	1.18 (0.58–2.38)	0.651	0.60 (0.25–1.45)	0.257
group_tx	**Group D**	**0.63 (0.40–0.97)**	**0.038**	**0.28 (0.15–0.54)**	**0.000**
Age	**Age (per year increase)**	**1.03 (1.01–1.04)**	**0.001**	**1.01 (1.00–1.03)**	**0.152**
hr_status	HR negative (ref)				
hr_status	HR positive	0.76 (0.53–1.09)	0.133	0.80 (0.51–1.24)	0.312
grade_f	Grade I (ref)				
grade_f	II	0.92 (0.13–6.70)	0.937	0.38 (0.05–2.95)	0.352
grade_f	III	0.96 (0.13–7.00)	0.970	0.27 (0.03–2.22)	0.225
final_stage	Stage 1A (ref)				
final_stage	1B	0.00 (0.00–NA)	0.994	0.00 (0.00–NA)	0.995
final_stage	**2A**	**2.24 (1.29–3.91)**	**0.004**	**4.94 (2.28–10.74)**	**0.000**
final_stage	**2B**	**1.78 (0.90–3.52)**	**0.099**	**5.01 (1.97–12.71)**	**0.001**
final_stage	**3A**	**2.05 (1.00–4.20)**	**0.049**	**6.40 (2.51–16.28)**	**0.000**
final_stage	**3B**	**7.91 (2.96–21.13)**	**0.000**	**12.57 (3.74–42.23)**	**0.000**
final_stage	**3C**	**7.11 (4.14–12.23)**	**0.000**	**16.91 (7.39–38.69)**	**0.000**

Table 3b. Cox Regression for Recurrence-Free Survival (RFS)

Neoadjuvant Therapy (NAC) Trends (Figure 3)

NAC utilization patterns revealed clear stage- and time-dependent changes. In Stage IA–IB, NAC was rarely used, consistent with guidelines that recommend upfront surgery for small tumors (T1a/bN0). Beginning in 2012, NAC adoption gradually increased in Stage IIA and IIB, stabilizing after 2017, with consistently higher rates in Stage IIB. In Stage IIIA–IIIC, NAC usage was substantially higher, reaching nearly 100% in Stage IIIC after 2020. Hormone receptor (HR) status showed limited influence, with small differences in early-stage patients that diminished in advanced stages.

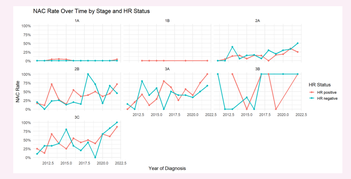

Figure 3.

Discussion & Conclusion

Discussion

Prognosis worsened with advancing stage. Trastuzumab-based chemotherapy (Group D) significantly improved OS and RFS starting at Stage IIA, consistent with landmark adjuvant trials [3,7]. NAC adoption increased markedly after 2010, especially in Stage II–III, paralleling global practice [5–7]. In Stage IA, no survival difference was observed, likely due to limited sample size and low event rate.

Conclusion

Based on our institutional data, the survival advantage of trastuzumab-based chemotherapy (Group D) became statistically significant starting from Stage IIA disease, while outcomes in Stage IA showed no clear benefit—likely limited by small sample size and few events. Notably, neoadjuvant therapy utilization has risen markedly since 2010, especially in Stage II–III, consistent with international treatment trends. These findings provide stage-specific real-world evidence to guide optimal application of anti-HER2 therapy.

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