Risk Evaluation of Early-stage Hormone Receptor-positive and Human Epidermal Growth Factor Receptor 2-negative Breast Cancer Patients: a Population-based Study From Taiwan

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Research Article

Abstract

PURPOSE:

To assess the prognostic value of the Dutch criteria for patients with early-stage hormone receptor-positive and human epidermal growth factor receptor 2-negative breast cancer from the Taiwan Cancer Database.

PATIENTS AND METHODS:

We included 8,295 patients with early-stage node-negative breast cancer who underwent surgery during January 2008–December 2012. Patients were stratified into low- and high-risk groups based on the Dutch criteria. The Kaplan–Meier method and log-rank test were used to estimate the difference in breast cancer-specific survival (BCSS) and overall survival (OS) between groups. Multivariable analysis was used to evaluate the prognostic value of the Dutch criteria.

RESULTS:

Overall, the low-risk and high-risk groups comprised 5,375 and 2,920 patients, respectively. In the low- and high-risk groups, the 5-year BCSS rate was 99.6% and 98.2% (P<0.0001) and the 5-year OS rate was 98.3% and 96.8% (P<0.0001), respectively. The hazard ratio for BCSS was 4.18 (95% confidence interval [CI], 2.63–6.63, P<0.0001), and the hazard ratio for OS was 1.94 (95% CI, 1.48–2.55); both were significantly poorer in the high-risk group than in the low-risk group. In the low-risk group, the 5-year BCSS and OS of patients who did and did not receive adjuvant chemotherapy were similar (99.5% versus 99.6% [P=0.927] and 98.8% and 98.1% [P=0.0683], respectively).

CONCLUSIONS:

The prognosis of low-risk patients as classified using the Dutch criteria is excellent with or without adjuvant chemotherapy. The benefit of multi-gene testing for chemotherapy decision-making might be minimal in these patients.

Introduction

Breast cancer is the most common malignant disease in women, causing approximately 630,000 deaths worldwide in 2018 [2]. Hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2−) breast cancer is the most common subtype of breast cancer, accounting for approximately 60% of all breast cancer cases [7]. The biological nature of and postsurgical treatment strategies for early-stage HR + and HER2− breast cancer are very different from those of other breast cancer subtypes. HR + and HER2− breast cancer has a sustained risk of disease recurrence and death for at least 15 years after diagnosis, and most patients are treated with long-term endocrine therapy following adjuvant chemotherapy [6].

One of the biggest challenges in treating patients with early stage HR + and HER2− breast cancer is identifying high-risk patients who could benefit from adjuvant chemotherapy [15]. Numerous commercial multi-gene prediction models have been developed to guide decision-making for adjuvant chemotherapy in low-risk patients without medical concerns [4, 10, 13, 14, 18]. Despite the superior risk prediction performance of genomic-level models, clinicopathological factors still play an important role; for instance, the 70-gene signature (MammaPrint) in the MINDACT trial divided patients into clinical low- and high-risk groups (Dutch criteria) and demonstrated that clinically low-risk patients would not benefit from genomic testing [4]. Recently, the value of clinical risk criteria was examined in the well-known 21-gene test (Oncotype DX) in the TAILORx trial [19] in which only 8.9% (589/6616) of clinically low-risk patients had a recurrence score > 25. Although the authoritative guideline endorses the Oncotype DX test to guide adjuvant therapy decision-making for patients with early stage HR + and HER2− breast cancer [8], the clinical criterion to undergo this testing is tumor size greater than 0.5 cm. Consequently, excessive testing might be performed. Moreover, this kind of testing is related to a patient's income (patients with a higher income would have a higher testing rate; the current estimated cost is ~$4,000) and is available to about one-third of eligible patients in the United States [16]. Furthermore, a recent study using the Connecticut Tumor Registry revealed that the Oncotype DX was not cost effective for patients with low-risk breast cancer [21]. In Asian countries, these global commercial multi-gene models are desperately needed but are unavailable for many reasons, including racial differences in tumor biology and survival [9, 11]. health beliefs, insurance coverage, and limited quality control of available tests [1]. Therefore, using clinical risk scales to identify patients with early-stage HR + and HER2− breast cancer who may have excellent survival after surgery and may not benefit from adjuvant chemotherapy is still worthwhile, especially in resource-constrained areas.

The prognostic value of the clinical risk scale (Dutch criteria) initially was adapted from Dutch CBO guidelines in 2004; it had a 70% concordance with MammaPrint [3]. These criteria were then used in the TAILORx and MINDACT trials, but they have not been examined in a large cohort of patients with breast cancer. We assume that if the Dutch criteria could help identify a subgroup of patients with breast cancer who had excellent outcomes, then expensive multi-gene tests could be omitted for these low-risk patients. Therefore, we conducted a retrospective study to evaluate the prognostic value of the Dutch criteria using a cancer database in Taiwan.

Materials And Methods

Eligibility

We retrospectively evaluated patients with lymph node-negative, HR+, and HER2− invasive breast cancer initially treated with primary surgery and registered in the Taiwan Cancer Database (TCDB) between January 2008 and December 2012. The included patients with breast cancer met the following criteria: (1) pathologic stage T1–2 and node-negative disease, (2) HR positive, (3) HER2 negative, and (4) complete data on tumor grade and tumor size. Patients who had undergone preoperative chemotherapy and those with node-positive, pT3–4, cM1, or synchronous bilateral breast cancers were excluded.

This study was reviewed and approved by the Institutional Review Board of National Taiwan University Hospital (NTUH-REC No.: 201910027W). The requirement for informed consent was waived because the data in the cancer registry were deidentified. Information acquired from the national database included age at diagnosis, histological grade, tumor stage, nodal stage, metastasis, ER/PR/HER2 status, and adjuvant therapies. The Consolidated Standards of Reporting Trials diagram is shown in Fig. 1. We included patients who underwent primary surgery in the form of either mastectomy or breast-conserving surgery and received adjuvant systemic therapy according to the routine clinical practice during that period. Adjuvant systemic therapy included endocrine therapy, chemotherapy, and radiotherapy.

Risk classification and survival endpoints

We used the binary clinical risk classification system based on the modified Adjuvant! algorithm used in the MINDACT and TAILORx trials [4][17]. The clinical low-risk scale (Dutch criteria) was defined as follows: age > 35 years and grade 1 tumor measuring ≤ 3 cm, grade 2 tumor measuring ≤ 2 cm, or grade 3 tumor measuring ≤ 1 cm; all other patients were categorized as high risk [3]. The primary study endpoint was breast cancer-specific survival (BCSS), which was defined as the interval from breast cancer surgery until death owing to breast cancer. The secondary endpoint was overall survival (OS), which was defined as the interval from breast cancer surgery until death owing to any cause. The last follow-up information was obtained from the TCDB and national death certification system in December 2019.

Statistical analysis

Statistical analysis was conducted using R (v.3.6.1) [20]. Differences in continuous data were calculated using the chi-square test, and P values < 0.05 were considered statistically significant. The 5-year BCSS and 5-year OS rates were defined as survival endpoints for survival analysis, and differences in survival between the low- and high-risk groups were calculated using the Kaplan–Meier method and log-rank test. Univariate and multivariate analyses of the prognostic value of the Dutch criteria were performed using Cox proportional hazards analysis.

Results

Patient characteristics

There were 90,837 patients newly diagnosed with primary invasive breast cancer during the study periods in the TCDB registries. Among them, 8,295 (9.1%) patients having pT1−2, node-negative, HR+, and HER2− breast cancer were included in this study (Fig. 1). The baseline characteristics of all patients are listed in Table 1. The median age of patients with a high risk was less than that of patients with a low risk (52 years vs. 55 years, P < 0.001). Compared with high-risk patients, low-risk patients were less likely to have T2 tumors, grade 3 tumors, and stage II disease (all P < 0.001). They were also less likely to have received adjuvant chemotherapy and radiotherapy but were more likely to have undergone endocrine therapy (all P < 0.001).

Table 1
Baseline information of patients in the conservative cohort

Variable	High-Risk (N = 2,920) No. (%)	Low-Risk (N = 5,375) No. (%)	P Value
Age (years), median (IQR*)	52 (43−62)	55 (46−62)	< .001
Tumor size			
T1a	43 (1.5)	678 (12.6)	< .001
T1b	52 (1.8)	1,243 (23.1)	
T1c	665 (22.8)	3,043 (56.6)	
T2	2160 (73.9)	411 (7.7)	
Tumor grade			
1	208 (7.1)	2,241 (41.7)	< .001
2	1,548 (53.0)	3,024 (56.3)	
3	1,164 (39.9)	110 (2.0)	
Pathological stage			
I	760 (26.0)	4,964 (92.4)	< .001
II	2,160 (74.0)	411 (7.6)	
Chemotherapy			
Yes	1,764 (60.4)	1,276 (23.7)	< .001
No	1,156 (39.6)	4,099 (76.3)	
Radiotherapy			
Yes	1,335 (45.7)	2,924 (54.4)	< .001
No	1,585 (54.3)	2,451 (45.6)	
Hormone therapy			
Yes	2,667 (91.3)	5,211 (96.9)	< .001
No	253 (8.7)	164 (3.1)	
*IQR: interquartile range			

Survival analyses

The median follow-up interval of the entire cohort was 4.2 years (range: 0.1–7 years). In the low-risk and high-risk groups, the 5-year BCSS rates were 99.6% (95% CI, 99.4–99.8%) and 98.2% (95% CI, 97.7–98.7%), respectively ($P< 0.0001$), and the 5-year OS rates were 98.3% (95% CI, 98.0–98.6%) and 96.8% (95% CI, 96.2–97.4%), respectively ($P< 0.0001$) (Figs. 2A-2B).

In the low-risk group, the 5-year BCSS rates of patients who did and did not receive adjuvant chemotherapy were 99.5% (95% CI, 99.1–99.9%) and 99.6% (95% CI, 99.4–99.8%), respectively ($P= 0.8927$); the 5-year OS rates were 98.8% (95% CI, 98.2–99.4%) and 98.1% (95% CI, 97.7–98.5%), respectively ($P= 0.0676$) (Figs. 3 and 4).

In the high-risk group, the 5-year BCSS rates of patients with and without adjuvant chemotherapy were 98.4% (95% CI, 97.8–99.0%) and 97.8% (95% CI, 97.0–98.6%), respectively ($P= 0.257$). The absolute difference was 0.6% ($P= 0.257$); the magnified figure shows a trend toward significance (Fig. 3). The 5-year OS rates of patients with or without chemotherapy were 97.6% (95% CI, 96.9–98.3%) and 95.5% (95% CI, 94.3–96.7%), respectively ($P= 0.0027$). The absolute difference in the OS rate at 5 years was 2.1% (Fig. 4, magnified figure).

Considering low-risk patients who received chemotherapy as a reference, hazard ratios for the 5-year breast cancer-specific mortality in high-risk patients with or without adjuvant chemotherapy were 3.527 ($P= 0.0025$) and 4.781 ($P= 0.0002$), respectively, and those for 5-year overall mortality were 2.175 ($P= 0.0046$) and 3.892 ($P< 0.0001$), respectively (Table 2). The hazard ratios for overall mortality in low-risk patients with and without chemotherapy were 1.606 ($P= 0.068$) and 1.791 ($P= 0.0027$) in high-risk patients.

Table 2
Low- and high-risk groups defined using the Dutch criteria with and without adjuvant chemotherapy

Endpoint and risk group	Patient #	Event	Hazard ratio	P value	Hazard ratio	P value
Breast cancer-specific survival						
Low risk, chemo	1276	7	1		1	
Low risk, no chemo	4099	16	0.9421	0.8927	0.96	0.927
High risk, chemo	1764	28	3.5271	0.0025	1	
High risk, no chemo	1156	25	4.7812	0.0002	1.349	0.257
Overall survival						
Low risk, chemo	1276	15	1		1	
Low risk, no chemo	4099	76	1.608	0.0676	1.606	0.0683
High risk, chemo	1764	42	2.175	0.0046	1	
High risk, no chemo	1156	52	3.892	< 0.0001	1.791	0.0027

Multivariate survival analysis

Univariate analysis revealed that age at diagnosis, tumor size, and histology grade were significant prognostic factors. After adjusting these clinical risk factors and adjuvant treatments, the multivariate survival analysis (Model I) showed that high risk as defined using the Dutch criteria was the only independent negative predictor of both BCSS (hazard ratio 4.18 [2.63–6.63], $P < 0.0001$) and OS (1.94 [1.48–2.55], $P < 0.0001$); the concordance index to predict outcomes was 0.76 and 0.63, respectively (Table 3). If we did not include the Dutch criteria in the model, age at diagnosis, tumor size, and histology grade (Model II) were significantly associated with BCSS and OS (Table 3). Patients aged ≤ 35 years had a poorer BCSS (hazard ratio 2.44, 1.22–4.87, $P = 0.0117$) but not OS (hazard ratio 0.96, 0.49–1.87, $P = 0.9027$). The hazard ratios for tumor size (per cm increment) with respect to BCSS and OS were 1.05 and 1.04, $P = 0.0006$ and < 0.0001, respectively. Using grade 1 as a reference, grade 2 and grade 3 were also independent prognostic factors of BCSS and OS (Table 3).

Table 3
Multivariate survival analyses for the entire cohort

	Breast cancer-specific survival		Overall survival	
	Model I			
Variable	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Low risk	1		1	
High risk	4.18 (2.63–6.63)	< 0.0001	1.94 (1.48–2.55)	< 0.0001
C-index	0.68		0.58	
	Model II			
Age				
>35 years	1		1	
≤ 35 years	2.44 (1.22–4.87)	0.0117	0.96 (0.49–1.87)	0.9027
Size (cm)	1.05 (1.03–1.07)	< 0.0001	1.04 (1.03–1.05)	< 0.0001
Grade				
Grade 1	1		1	
Grade 2	2.61 (1.23–5.54)	0.0129	1.44 (1.00–2.08)	0.0477
Grade 3	5.60 (2.58–12.17)	< 0.0001	2.00 (1.32–3.05)	0.0011
C-index	0.75		0.63	
CI: confidence interval				

Discussion

In the era of multi-gene expression panel-guided adjuvant systemic therapy, the use of conventional clinical and pathological risk factors to predict response to therapy should not be dismissed for patients with early stage HR + and HER2− breast cancer. In this study, we affirmed the prognostic value of the clinical risk scale (Dutch criteria) adopted in previous clinical trials in a real-world study of a node-negative breast cancer population in Taiwan. The Dutch criteria defined a subset of patients with node-negative, HR+, and HER2− breast cancer whose 5-year BCSS was greater than 99% (Fig. 2). Additionally, the 5-year OS of those patients was above 98%, which is very similar to the released data of patients with a recurrence score ≤ 25 by the Oncotype DX test in the TAILORx trial [17]. In the low-risk group, no significant survival benefit was observed with adjuvant chemotherapy after a minimum 5-year follow-up period. The independent prognostic value of the Dutch criteria was also confirmed in the multivariate analysis (Table 3). Finally, though there was a significant difference in survival based on the administration of chemotherapy in the entire cohort, the survival benefit in the clinically high-risk setting was minimal, reflecting the lack of predictive value of the Dutch criteria for guiding adjuvant chemotherapy. Altogether, our findings suggest that the National Comprehensive Cancer Network (NCCN) guidelines should supersede the recommendation of the Oncotype DX test only for clinically high-risk patients for cost considerations. This recommendation is especially meaningful for medical care in low- or medium-income areas.

Though the 21-gene signature is widely accepted for adjuvant chemotherapy decision-making for all patients with early stage HR + and HER2− breast cancer, the latest NCCN guideline recommends its use for women with tumors measuring > 0.5 cm. However, for tumors with low-grade histology and no lymphovascular invasion, physicians can decide whether to perform gene signature testing [8]. Another commercial and widely approved multi-gene expression test is the 70-gene test. Though this test has different genomic algorithms than the Oncotype DX, it was originally used for clinical risk evaluation and has proven that clinically low-risk patients did not benefit from adjuvant chemotherapy, regardless of whether they had a high genomic risk [5]; thus, it is more rational based on our results that only clinically high-risk patients would potentially benefit from genomic testing because clinically low-risk patients had favorable outcomes. Data supporting the value of clinical risk evaluation beyond genomic testing in the TAILORx trial were recently released and revealed that clinically low-risk patients were mainly genomically low-risk [19]. Though the application of genomic testing for patients with lymph node-positive breast cancer is currently being examined in clinical trials [5] [12], our data confirm that among lymph node-negative patients, those who could benefit from expensive multi-gene expression signature tests should be prioritized.

Some limitations and cautions regarding this study need to be discussed. First, this was a retrospective population-based study, and our conclusion could have some uncontrolled biases. The broad application of systemic therapy makes it difficult to obtain information on patients who did not receive such therapies. Second, having recurrence-related endpoints in addition to BCSS and OS would have improved the survival analysis in our study. Unfortunately, we were restrained by preserved documents in this labor-

intensive established national database search. Therefore, we focused on BCSS because understanding the risk of BCSS is the first step in clinical practice to make an informed treatment decision. Third, information on comorbid conditions was not included in the national registry; patients without chemotherapy might have poorer performance. Therefore, there was a small difference in the OS of low-risk patients with and without chemotherapy (98.8% versus 98.1%, Fig. 4); however, this difference was not observed in BCSS (99.5% versus 99.6%, Fig. 3). Additionally, the potential relatively long-term survival of patients with HR + and HER2− breast cancer and the competing risk of death might dilute the prognostic value of OS. Our inclusion of BCSS as an endpoint is therefore vital. Finally, age-specific differences in survival should be examined. We examined the effect of age in the low-risk subgroup and observed a significant difference based on age (< 50 vs. ≥50 years) in OS (98.7% versus 95.9%, P = 0.0009) but not in BCSS (99.1% versus 98.9%, P = 0.7578). This conclusion is understandable, as older patients would have worse OS than younger patients.

Conclusion

The benefit of chemotherapy in low-risk patients as defined using the Dutch criteria might be minimal because breast cancer mortality was < 1% with a minimum 5-year follow-up. Therefore, we do not recommend multi-gene testing for these patients, as it would not be cost effective. High risk as defined using the Dutch criteria was an independent negative factor in survival analysis. More data are warranted to confirm our conclusion.

Declarations

Conflicts of interest/Competing interests

The authors declare that they have no conflict of interest.

Availability of data and material

Data is available in Taiwan Cancer Registry: http://tcr.cph.ntu.edu.tw/main.php?Page=A1

Code availability

Source codes are available on the website of Taiwan Cancer Registry: http://tcr.cph.ntu.edu.tw/main.php?Page=A1

Authors' contributions

Data Access, Responsibility, and Analysis: HC and SHC had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: LL and SHC.

Acquisition, analysis, or interpretation of data: HC, TP, and SHC

Drafting of the manuscript: LL and SHC

Critical revision of the manuscript for important intellectual content: LL, TP and SHC

Statistical analysis: HC and TP

Obtained funding: LL and SHC

Ethics approval

Institutional Review Board of National Taiwan University Hospital (NTUH-REC No.: 201910027W).

Consent to participate

This study was exempted from an informed consent by the review board.

Consent for publication

Not applicable

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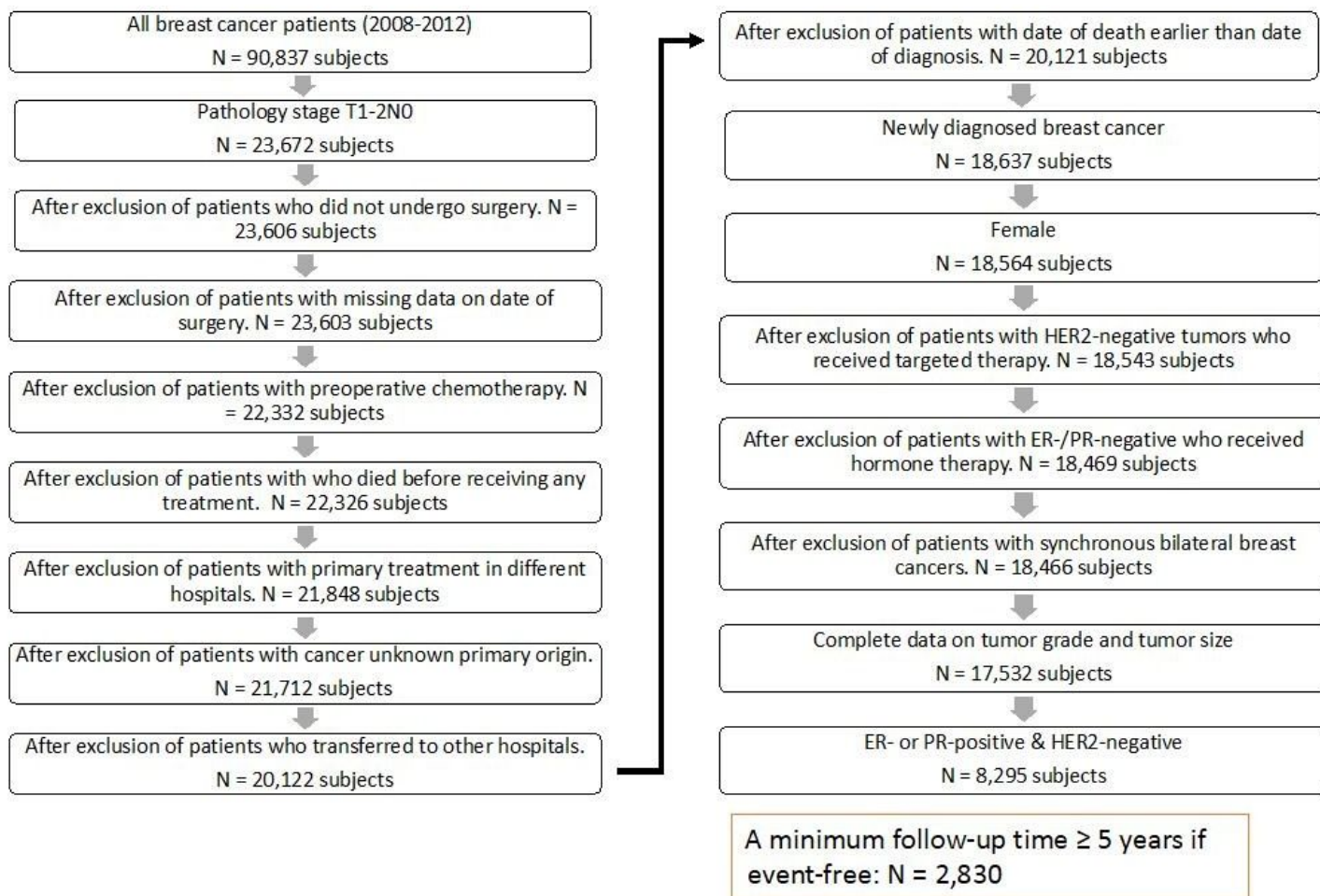
Figures

Figure 1

Study flow of patient selection. Subjects were selected from the Taiwan Cancer Database between 2008 and 2012. There were 8295 patients included in this study; the last follow-up information was obtained in December 2019. (Abbreviation: HER2: human epidermal growth factor receptor 2; ER: estrogen receptor; PR: progesterone receptor)
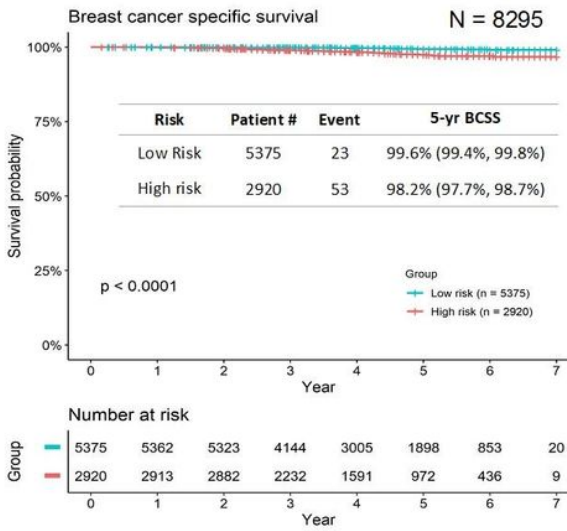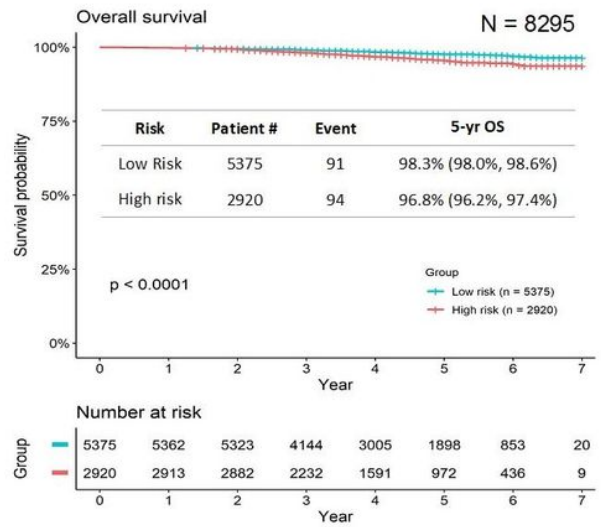
Figure 2

Breast cancer-specific survival (2A) and overall survival (2B) of low- and high-risk patients according to the Dutch criteria

Figure 3

Dutch definition: low risk and high risk with or without chemotherapy
Breast Cancer-Specific Survival

Risk	Patient #	Adjuvant chemo	Event	5-yr BCSS	P value
Low Risk	1276	Yes	7 (7)	99.5% (99.1%, 99.9%)	0.927
	4099	No	16 (19)	99.6% (99.4%, 99.8%)	
High Risk	1764	Yes	28 (32)	98.4% (97.8%, 99.0%)	0.257
	1156	No	25 (26)	97.8% (97.0%, 98.6%)	

Group
- Low risk Chemo = No
- Low risk Chemo = Yes
- High risk Chemo = No
- High risk Chemo = Yes

$p < 0.0001$

Number at risk

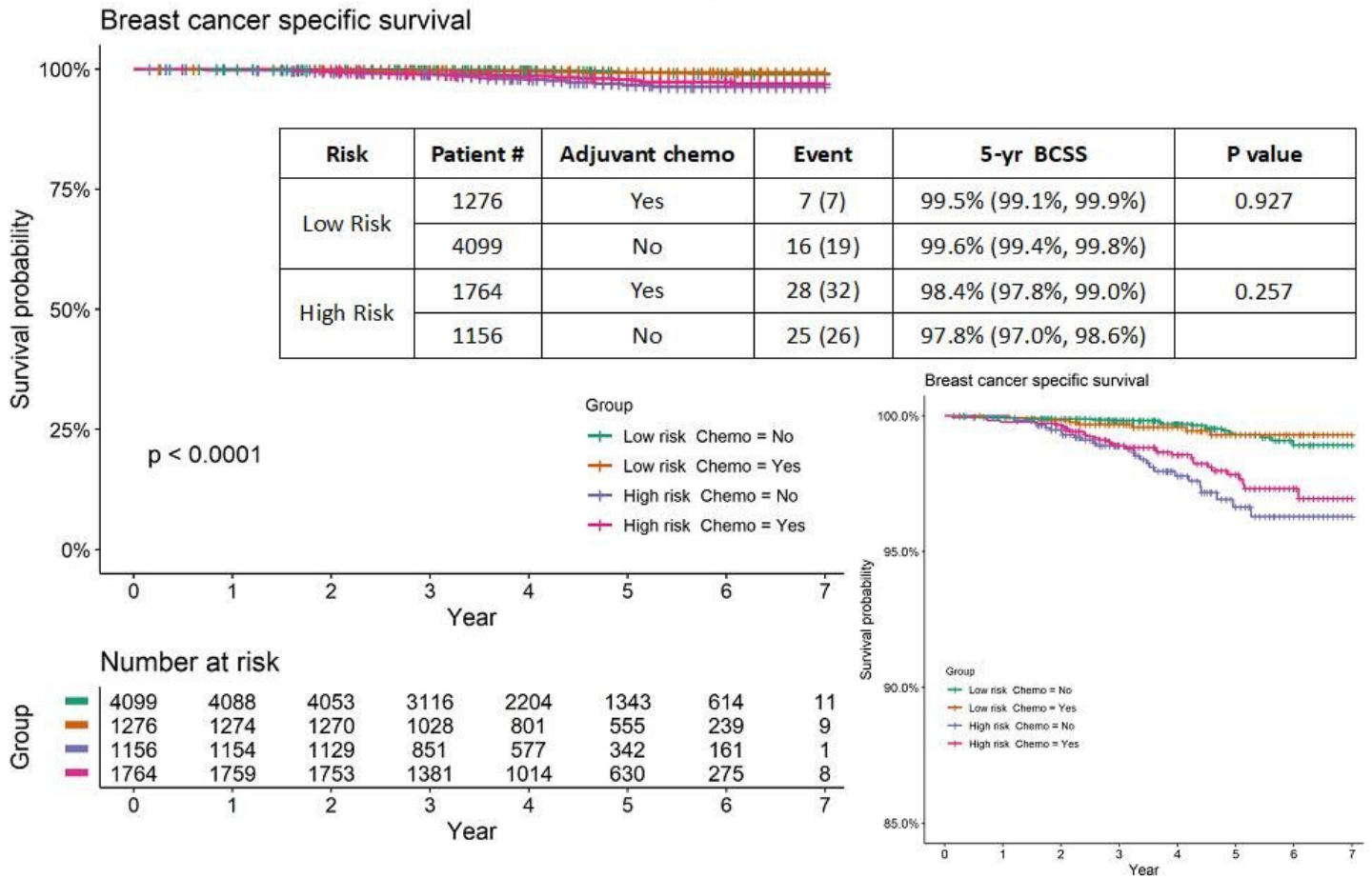| Group	0	1	2	3	4	5	6	7
	4099	4088	4053	3116	2204	1343	614	11
	1276	1274	1270	1028	801	555	239	9
	1156	1154	1129	851	577	342	161	1
	1764	1759	1753	1381	1014	630	275	8

Figure 3

Breast cancer-specific survival of low- and high-risk patients based on the administration of adjuvant chemotherapy. There is no significant difference in breast cancer-specific survival between low-risk patients with or without chemotherapy. The magnified figure shows a small difference in breast cancer-specific survival between high-risk patients with or without chemotherapy; the p value was 0.257.

Figure 4

Dutch definition: low risk and high risk with or without chemotherapy
Overall Survival

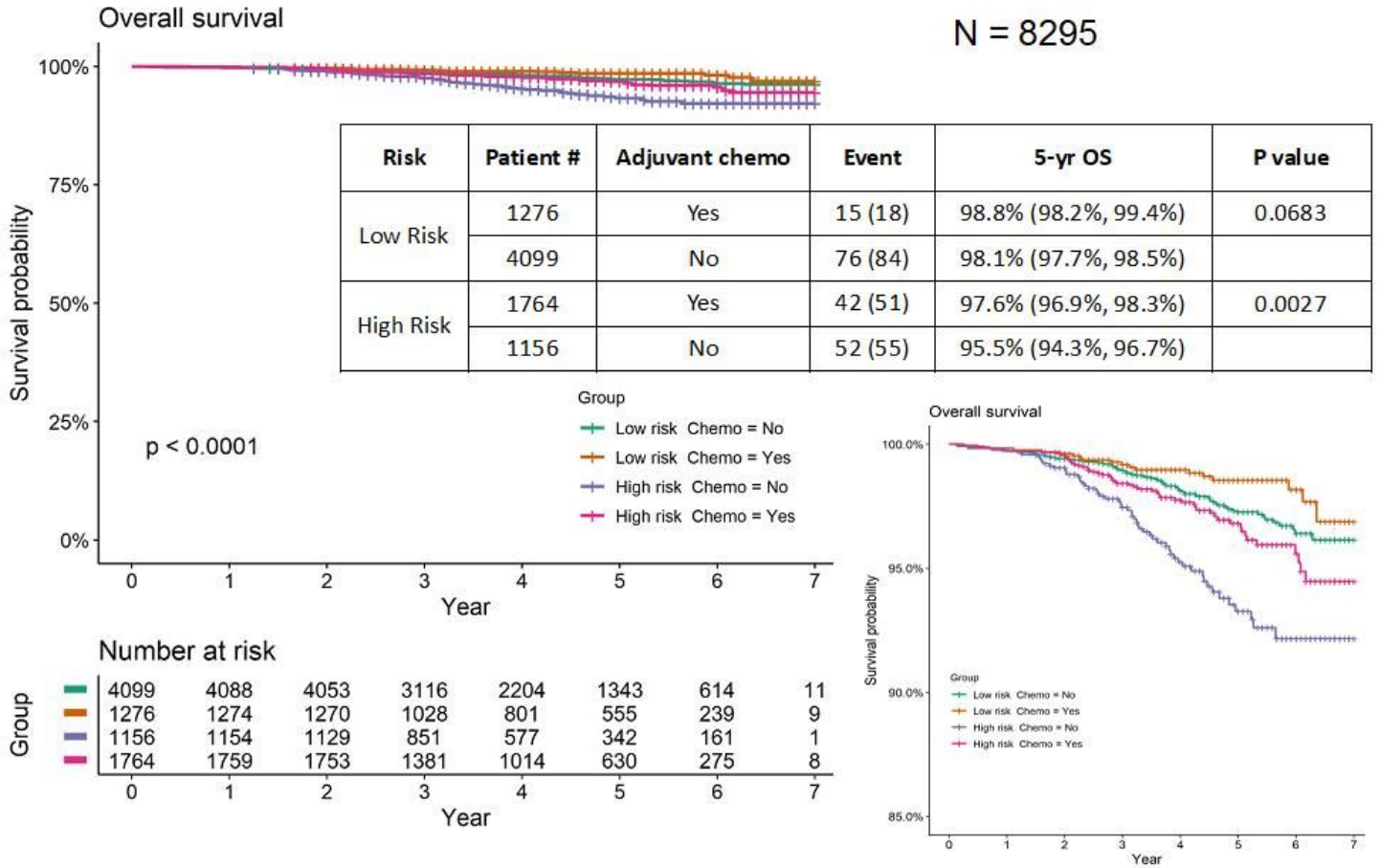| Risk	Patient #	Adjuvant chemo	Event	5-yr OS	P value
Low Risk	1276	Yes	15 (18)	98.8% (98.2%, 99.4%)	0.0683
	4099	No	76 (84)	98.1% (97.7%, 98.5%)	
High Risk	1764	Yes	42 (51)	97.6% (96.9%, 98.3%)	0.0027
	1156	No	52 (55)	95.5% (94.3%, 96.7%)	

Figure 4

Overall survival of both low- and high-risk patients based on the administration of adjuvant chemotherapy. A trend of survival difference between low-risk patients with or without chemotherapy is observed (P = 0.0683). The difference in the overall survival of high-risk patients with or without chemotherapy is significant (P = 0.0027).