

Locoregional recurrence after neoadjuvant versus adjuvant chemotherapy based on tumor subtypes in patients with early-stage breast cancer: A multi-institutional retrospective cohort study

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ABSTRACT

Background: Neoadjuvant chemotherapy (NACT) for early-stage breast cancer is associated with an increased risk of locoregional recurrence (LRR). We investigated whether the risk of LRR after NACT varies across tumor subtypes.

Methods: We retrospectively reviewed the medical records of women who underwent breast-conserving surgery for breast cancer at three institutions between January 1, 2004, and December 31, 2018. Patients received either NACT or adjuvant chemotherapy (ACT), followed by radiotherapy. LRR was analyzed according to the hormone receptor (HR) and human epidermal growth factor receptor-2 (HER2) status using propensity score matching, log-rank test, and Cox regression analysis.

Results: Among 10,328 patients, 2479 (24.0 %) received NACT. Within the median follow-up of 84.5 (IQR, 35.1–118.5) months, the 10-year LRR-free survival rates were 94.5 % and 90.7 % for the ACT and NACT groups, respectively (hazard ratio: 2.04, 95 % confidence interval [CI]: 1.68–2.46, $p < 0.0001$). NACT was significantly associated with higher LRR in the HR+/HER2– (hazard ratio: 2.52, 95 % CI: 1.83–3.46, $p < 0.0001$) and HR–/HER2– (hazard ratio: 1.85, 95 % CI: 1.37–2.50, $p < 0.0001$) subtypes. In the HR+/HER2– subtype, the elevated risk remained significant after propensity-score matching and Cox-regression analysis. However, NACT was not associated with LRR in the HR–/HER2– subtype after adjusting for other variables. Annual LRR pattern among the HR+/HER2– subtype showed the highest incidence in the early period of treatment.

Conclusion: Patients with the HR+/HER2– subtype showed an increased risk of LRR after NACT, while those with other subtypes showed comparable LRR-free survival.

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1. Introduction

Neoadjuvant chemotherapy (NACT) is now widely accepted as a standard treatment option for breast cancer, and its use has increased over time, especially in patients with advanced stages [1,2]. NACT provides several advantages over upfront surgery, as it enables breast-conserving surgery (BCS) for patients who are not initially ineligible, avoids the need for axillary node dissection by reducing disease burden, eradicates micrometastatic disease early, and serves as an excellent *in vivo* test for assessing response to systemic treatments [3–8].

Several previous studies have demonstrated the oncologic safety of NACT compared to adjuvant chemotherapy (ACT) [9–12]. Especially, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis [11] reported the long-term outcomes of maintaining oncologic safety of NACT. However, NACT was significantly associated with a higher incidence of local recurrence, and this difference persisted even after excluding patients who did not undergo surgery. Nevertheless, the results of this meta-analysis should be interpreted with caution. Only a small number of patients received anthracycline with a taxane, and none of the patients were treated with trastuzumab [13,14]. Moreover, since NACT increased the rate of BCS, the analysis including those who underwent total mastectomy led to critical selection bias.

Interestingly, few studies have compared the recurrence rate between NACT and ACT in the aspect of the different molecular subtypes. The locoregional recurrence (LRR) rates and incidence patterns differ according to the hormone receptor (HR) and human epidermal growth factor receptor-2 (HER2) status [15]. Moreover, as different subtypes have varying tumor responses [16] and distinct shrinkage patterns after chemotherapy [17], we assumed that the impact of NACT on LRR would be different depending on the specific tumor subtypes.

Thus, we aimed to investigate whether the impact of NACT compared with that of ACT on LRR differs according to tumor subtype in patients with early-stage breast cancer. To mitigate potential bias, we only included patients who underwent BCS followed by radiotherapy [18].

2. Methods

2.1. Patients

We reviewed the clinicopathological records of female patients who underwent BCS for breast cancer between January 1, 2004 and December 31, 2018 at the three leading hospitals in South Korea. Patients who did not receive systemic chemotherapy or radiotherapy were excluded. We also excluded patients with carcinoma in situ lesions, recurrent breast cancer, male breast cancer, and synchronous or metachronous malignancies in other organs. This study was approved by the institutional review board (IRB) of each institution (IRB number: Seoul National University Hospital, 2204-074-1316; Samsung Medical Center, 2023-09-076-001; Boramae Medical center, 10-2023-73). All procedures were conducted in accordance with the Declaration of Helsinki [19], and the requirement for informed consent was waived owing to the retrospective nature of the study. This study was retrospectively registered at <https://clinicaltrials.gov/> (NCT ID: NCT06299930). The study was reported according to the Strengthening of Reporting of Observational Studies in Epidemiology guidelines (STROBE, [Supplementary Table 1](#)) [20].

Age was categorized using a cutoff of 40 years because the number of women aged <35 years, which is a generally accepted threshold for high recurrence risk [21,22], was too few for the analysis. The year of diagnosis was categorized based on the median year of all included patients.

2.2. Treatments

NACT was administered preoperatively with or without additional postoperative chemotherapy, while ACT was administered

postoperatively. Chemotherapy regimens were selected by the medical oncologists based on the most appropriate treatment options available at the time of treatment. Breast magnetic resonance imaging was periodically performed to evaluate the patient's response to chemotherapy and determine the extent of surgery. Based on each clinician's judgment, clip insertion at the tumor site was performed before or during NACT, in patients who were expected to experience significant tumor size reduction or achieve pCR. Each patient received either conventional whole-breast radiation or hypo-fractionated radiation, with most patients also receiving boost radiation based on the judgement of each radiologist ([Supplementary Table 2](#)).

2.3. Pathologic assessment

A positive HR (estrogen and/or progesterone receptors) status was defined as $\geq 1\%$ of stained cells or an Allred score of >2 on the immunohistochemistry assay. The HER2 status was evaluated according to the American Society of Clinical Oncology and College of American Pathologists guidelines [23]. If equivocal results were obtained on immunohistochemical (IHC) tests, the tumors were subsequently reevaluated using fluorescence in situ hybridization (FISH) or silver-enhanced in situ hybridization (SISH) tests; the HER2 status was considered positive when the HER2/chromosome enumeration probe 17 ratio was >2.0 . The subtype of the NACT group was evaluated using the initial biopsy tissue, as the IHC profile of some tumors changed after chemotherapy [24]. Notably, this study focused on investigating the different outcomes according to the tumor subtypes; we excluded patients who were not diagnosed with any breast cancer molecular subtype or who obtained an IHC score of 2+ but did not undergo FISH or SISH tests. The Ki-67 expression level was classified as high or low based on the cutoff value of each institution. The tumors of the NACT and ACT groups were clinically and pathologically staged, respectively, according to the American Joint Committee on Cancer Staging Manual, Eighth Edition [25]. Pathological complete regression (pCR) was defined as the absence of residual invasive cells in both breast and axillary lymph nodes.

2.4. Definition of recurrence

The primary endpoint of our study was LRR events, which included both local and regional recurrences. LRR was defined as the first recurrence of cancer in the ipsilateral breast, skin, incision sites, or regional lymph nodes, including the ipsilateral axillary, supraclavicular, infraclavicular, and internal mammary lymph nodes. Ipsilateral breast tumor recurrence (IBTR) was defined as the recurrence "in" the ipsilateral breast. Distant metastasis (DM) was defined as any recurrences at any sites outside the breast and regional lymph nodes. LRR-free survival was defined as the time interval between the date of initial administration of chemotherapy and the date of pathological or radiological confirmation of LRR or the last follow-up date. DM-free survival referred to the time interval until the date of DM confirmation or the last follow-up date. Regarding the competing risk, DM events prior to LRR was treated as censored at the time of occurrence.

2.5. Statistical analyses

Categorical variables were compared using Pearson's chi-square test. Mann-Whitney *U* and Kruskal-Wallis tests were used to compare continuous variables. Cox proportional hazards regression analysis was performed to adjust for related clinicopathological variables and estimate hazard ratios. Variables with a two-sided p-value of <0.05 in the univariate analysis were included in the multivariate analysis, and those that showed a variance inflation factor of >4.0 in the multicollinearity test were excluded. The model's goodness of fit was evaluated using the Hosmer-Lemeshow test, and a two-sided p-value of >0.05 indicated an appropriate model.

The study was consistent with reporting guidelines for propensity-score matched analyses [26]. The propensity scores were estimated using a logistic regression model that included the variables that were differently distributed between the two groups and were used for matching analysis: age at diagnosis, year of diagnosis, tumor size, axillary lymph node status, HR and HER2 status, Ki-67 level, histologic grade, and adjuvant treatment. We performed 1:1 propensity score matching using the greedy nearest-neighbor method without replacement using a caliper width of 0.10 standard deviation of the logit of the propensity scores [27]. The standardized mean differences were calculated for each covariate to evaluate the balance between the two groups before and after matching. A standardized mean difference value of less than 0.1 was considered adequate balance. Missing data were treated using a complete case analysis approach.

Analyses were conducted using SPSS (version 26.0; SPSS Inc., IBM, Armonk, NY, USA) or R Statistical software (version 3.6.3; R Foundation for Statistical Computing, Vienna, Austria). Kaplan-Meier curves were drawn using GraphPad Prism (version 10.0; GraphPad Software, San Diego, USA). The patterns of annual recurrence incidence were smoothed using the kernel smoothing method with the *ksmooth* function in R. A two-sided p-value of <0.05 was considered significant.

3. Results

3.1. Patient's demographics

In total, 10,328 female patients met the inclusion criteria and were included in the study (Supplementary Fig. 1). The median age at the time of diagnosis was 48.0 (interquartile range [IQR]: 42.0–55.0) years, and more than half of the patients were treated after 2013 (54.9 %) (Table 1). Approximately 51.1 %, 24.8 %, 13.6 %, and 10.5 % of the patients had the HR+/HER2-, HR-/HER2-, HR+/HER2+, and HR-/HER2+ subtypes, respectively. Detailed information on the clinicopathological features according to tumor subtype is listed in Supplementary Table 3.

Of the total study participants, 2479 (24.0 %) underwent NACT, while 7849 (76.0 %) underwent upfront surgery. Patients in the NACT group were younger and had more aggressive pathological features, including T/N stage, Ki-67 levels, histological grade, and HR negativity (Table 1). The most frequently administered chemotherapy regimen in the NACT group was anthracycline with taxane (80.7 %), while anthracycline without taxane was the most frequently administered regimen in the ACT group (43.1 %). After NACT, 843 (34.6 %) patients achieved pCR, and those with the HR-/HER2+ and HR-/HER2- subtypes achieved pCR rates of 59.8 % and 38.7 %, respectively (Supplementary Table 4).

3.2. LRR after NACT versus ACT according to the tumor subtype

Within the median follow-up of 84.5 (IQR: 35.1–118.50) months, the 10-year LRR-free survival rate for all patients was 93.6 %. As shown in Fig. 1A, the NACT group showed significantly poorer LRR-free survival than the ACT group (hazard ratio: 2.04, 95 % confidence interval [CI]: 1.68–2.46, log-rank $p < 0.0001$). As the observed difference in survival could be due to the uneven distribution of well-known risk factors between the two groups, we conducted a 1:1 propensity score matching analysis incorporating age at diagnosis, year of diagnosis, tumor size, axillary lymph node status, HR and HER2 status, Ki-67 level, histologic grade, and adjuvant treatment (Table 2). A total of 2880 patients were included in the propensity-score matching analysis, and the LRR-free survival was significantly poorer in the NACT group than in the ACT group (hazard ratio: 1.87, 95 % CI: 1.35–2.57, log-rank $p = 0.0001$; Fig. 1B).

Next, we investigated the impact of the NACT versus the ACT on LRR according to tumor subtypes. Patients with the HR-/HER2- subtype had the worst LRR-free survival, followed by those with the HR-/

Table 1

Demographic and clinicopathological characteristics of patients.

	All patients (n = 10328)	Neoadjuvant chemotherapy (n = 2479)	Adjuvant chemotherapy (n = 7849)
Age at diagnosis, years	48.0 (42.0–55.0)	47.0 (40.0–54.0)	48.0 (43.0–55.0)
≤40	2124 (20.6 %)	661 (26.7 %)	1463 (18.6 %)
>40	8204 (79.4 %)	1818 (73.3 %)	6386 (81.4 %)
Year of diagnosis			
2000–2012	4662 (45.1 %)	688 (27.8 %)	3974 (50.6 %)
2013–2018	5666 (54.9 %)	1791 (72.2 %)	3875 (49.4 %)
Institution			
Institution A	5032 (48.7 %)	1471 (59.3 %)	3561 (45.4 %)
Institution B	4990 (48.3 %)	997 (40.2 %)	3993 (50.9 %)
Institution C	306 (3.0 %)	11 (0.4 %)	295 (3.8 %)
Axilla surgery			
Sentinel lymph node biopsy	6151 (59.6 %)	1257 (50.7 %)	4894 (62.4 %)
Axillary lymph node dissection	4169 (40.4 %)	1219 (49.2 %)	2950 (37.6 %)
Unknown	8 (0.1 %)	3 (0.1 %)	5 (0.1 %)
T stage ^a			
T1	4283 (41.5 %)	191 (7.7 %)	4092 (52.1 %)
T2	5392 (52.2 %)	1741 (70.2 %)	3651 (46.5 %)
T3–4	553 (5.4 %)	449 (18.1 %)	104 (1.3 %)
Unknown	100 (1.0 %)	98 (4.0 %)	2 (0.0 %)
N stage ^a			
N0	4834 (46.8 %)	204 (8.2 %)	4630 (59.0 %)
N1	3622 (35.1 %)	1084 (43.7 %)	2538 (32.3 %)
N2	1265 (12.2 %)	777 (31.3 %)	488 (6.2 %)
N3	488 (4.7 %)	301 (12.1 %)	187 (2.4 %)
Unknown	119 (1.2 %)	113 (4.6 %)	6 (0.1 %)
Ki-67 index			
Low	5515 (53.4 %)	1090 (44.0 %)	4425 (56.4 %)
High	4719 (45.7 %)	1357 (54.7 %)	3362 (42.8 %)
Unknown	94 (0.9 %)	32 (1.3 %)	62 (0.8 %)
Histologic grade			
I–II	5054 (48.9 %)	1144 (46.1 %)	3910 (49.8 %)
III	4668 (45.2 %)	924 (37.3 %)	3744 (47.7 %)
Unknown	606 (5.9 %)	411 (16.6 %)	195 (2.5 %)
Tumor subtypes			
HR+/HER2-	5275 (51.1 %)	858 (34.6 %)	4417 (56.3 %)
HR+/HER2+	1407 (13.6 %)	437 (17.6 %)	970 (12.4 %)
HR-/HER2+	1080 (10.5 %)	430 (17.3 %)	650 (8.3 %)
HR-/HER2-	2566 (24.8 %)	754 (30.4 %)	1812 (23.1 %)
Chemotherapy regimen			
Both	4792 (46.4 %)	2001 (80.7 %)	2791 (35.6 %)
anthracycline and taxane			
Anthracycline- based, no taxane	3455 (33.5 %)	72 (2.9 %)	3383 (43.1 %)
Taxane-based, no anthracycline	646 (6.3 %)	320 (12.9 %)	326 (4.2 %)
Others	1122 (10.9 %)	53 (2.1 %)	1069 (13.6 %)
Unknown	313 (3.0 %)	33 (1.3 %)	280 (3.6 %)
Adjuvant hormonal treatment			
Administered	6654 (64.4 %)	1303 (52.6 %)	5351 (68.2 %)
Not administered	3641 (35.3 %)	1174 (47.4 %)	2467 (31.4 %)
Unknown	33 (0.3 %)	2 (0.1 %)	31 (0.4 %)
HER2-targeted treatment			
Administered	1771 (17.1 %)	786 (31.7 %)	985 (12.5 %)
Not administered	8337 (80.7 %)	1676 (67.6 %)	6661 (84.9 %)
Unknown	220 (2.1 %)	17 (0.7 %)	203 (2.6 %)

Data are presented as the median (IQR) or number (%).

Abbreviations: HR, hormone receptor; HER2, human epidermal growth factor receptor-2.

^a Stratified according to the American Joint Committee on Cancer (AJCC) 8th TNM stage. Patients in the neoadjuvant chemotherapy group were evaluated clinically.

HER2+, HR+/HER2+, and HR+/HER2- subtypes (Supplementary Fig. 2). As shown in Fig. 1C–F, the subgroup analysis demonstrated a significant difference in the LRR-free survival of patients with the HR+/HER2- and HR-/HER2- subtypes between the NACT and ACT groups (HR+/HER2-, hazard ratio: 2.52, 95 % CI: 1.83–3.46, log-rank $p <$

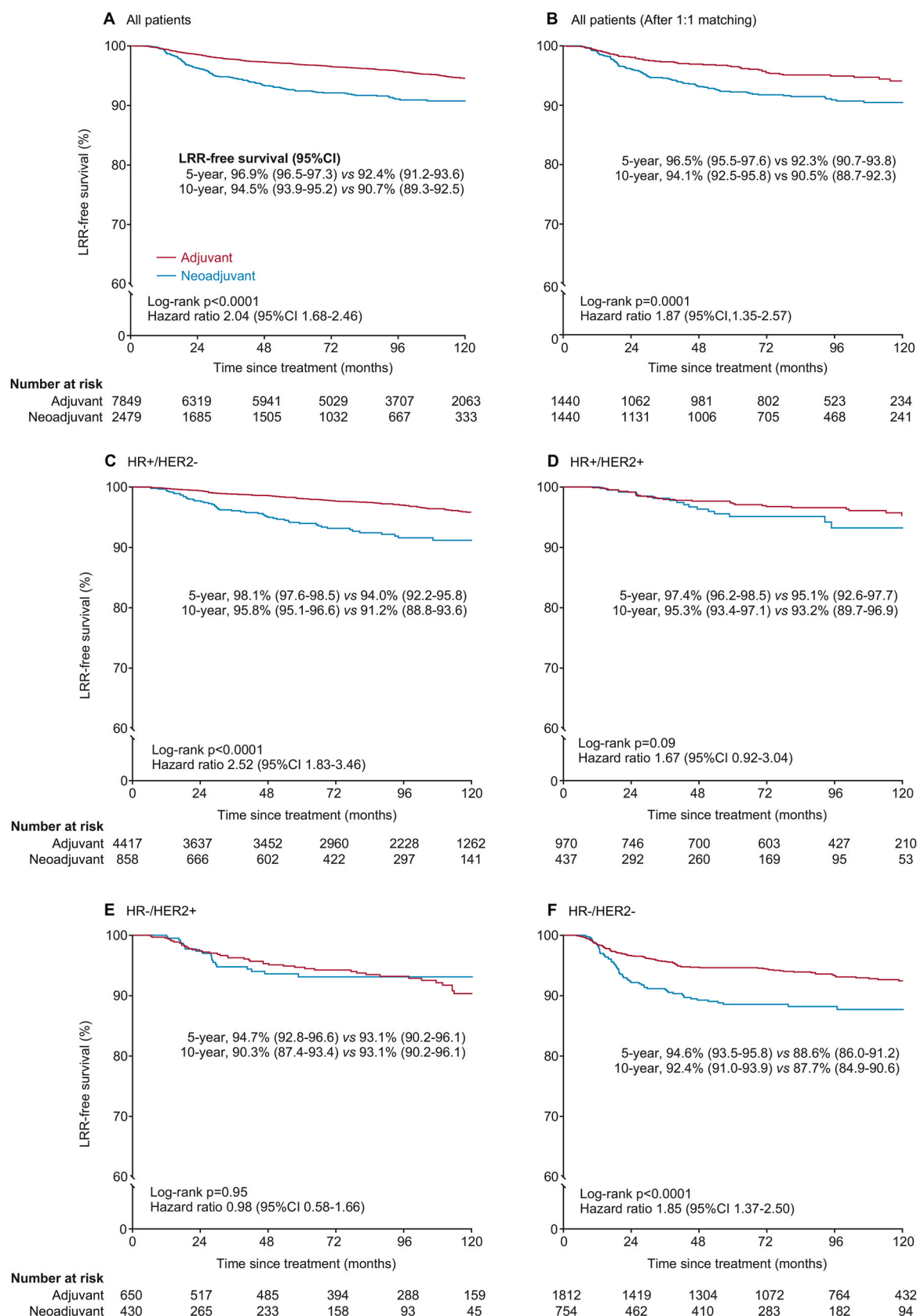


Fig. 1. Kaplan-Meier curves of the locoregional recurrence-free survival of all patients (A) after 1:1 propensity score matching (B) and according to tumor subtypes (C-F). The p-value was calculated using a log-rank test, and the hazard ratio was calculated using univariable Cox regression analyses. Abbreviations: HER2, human epidermal growth factor 2; HR, hormone receptor; LRR, locoregional recurrence.

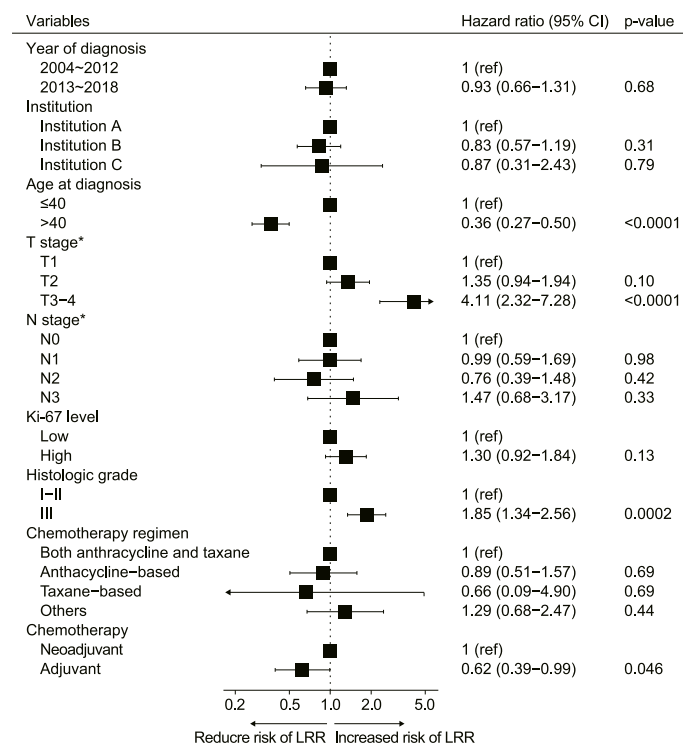
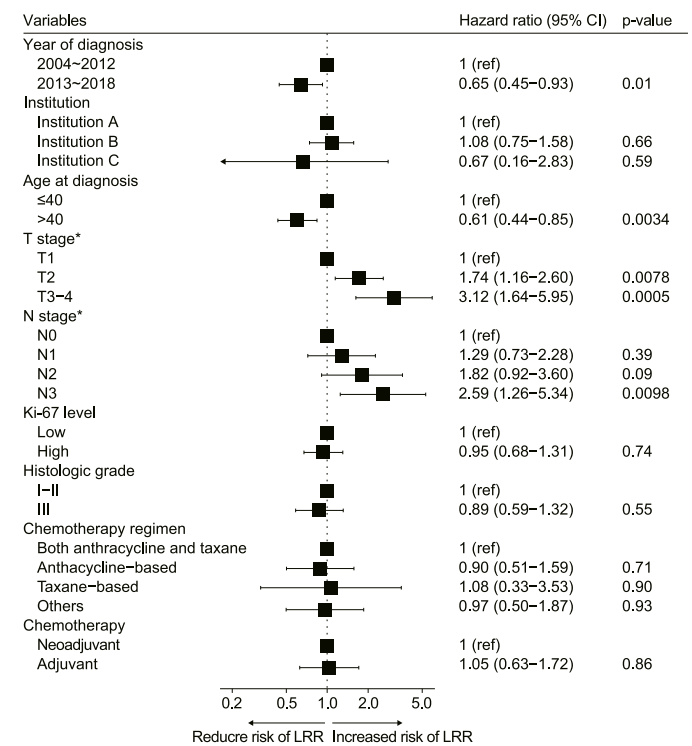
Table 2

Baseline characteristics before and after propensity score matching.

	Before propensity score matching			After propensity score matching		
	Neoadjuvant chemotherapy	Adjuvant chemotherapy	SMD	Neoadjuvant chemotherapy	Adjuvant chemotherapy	SMD
All patients	n = 1965	n = 7374		n = 1440	n = 1440	
Age at diagnosis, years	47.2 (10.0)	48.7 (7.2)	−0.16	47.4 (9.9)	47.7 (9.1)	−0.03
Year of diagnosis, 2013–2018	1791 (72.2 %)	3875 (49.4 %)	0.49	952 (66.1 %)	972 (67.5 %)	−0.03
Tumor size < 2 cm ^a	191 (7.7 %)	4092 (52.1 %)	1.66	152 (10.6 %)	146 (10.1 %)	−0.02
ALN metastasis, absent ^a	2162 (87.2 %)	3213 (40.9 %)	1.77	176 (12.2 %)	183 (12.7 %)	0.02
HR status (+) ^a	1295 (52.2 %)	5387 (68.6 %)	0.23	960 (66.7 %)	1020 (70.8 %)	0.08
HER2 status (+) ^a	867 (35.0 %)	1620 (20.6 %)	−0.26	324 (22.5 %)	309 (21.5 %)	−0.02
High Ki-67 index	1357 (54.7 %)	3362 (42.8 %)	0.14	679 (47.2 %)	619 (4.0 %)	0.08
Histologic grade, III	924 (37.3 %)	3744 (47.7 %)	−0.10	657 (45.6 %)	620 (43.1 %)	0.05
Hormone treatment, yes	1303 (52.6 %)	5351 (68.2 %)	0.22	956 (66.4 %)	1016 (70.6 %)	0.08
HER2-targeted treatment, yes	786 (31.7 %)	985 (12.5 %)	−0.38	267 (18.5 %)	254 (17.6 %)	−0.02
HR+/HER2- subtype^b	n = 858	n = 4417		n = 734	n = 734	
Age at diagnosis, years	46.2 (9.8)	48.2 (8.8)	−0.19	46.4 (9.6)	46.7 (8.9)	−0.036
Year of diagnosis, 2013–2018	597 (69.6 %)	2121 (48.0 %)	0.47	521 (71.0 %)	522 (71.1 %)	−0.003
Tumor size < 2 cm ^a	78 (9.1 %)	2255 (51.1 %)	1.42	70 (9.5 %)	74 (10.1 %)	0.019
ALN metastasis, absent ^a	81 (9.4 %)	2149 (48.7 %)	1.25	74 (10.1 %)	69 (9.4 %)	−0.023
High Ki-67 index	313 (36.5 %)	1493 (33.8 %)	−0.03	244 (33.2 %)	225 (30.7 %)	0.055
Histologic grade, III	241 (28.1 %)	1265 (28.6 %)	−0.00	214 (29.2 %)	190 (25.9 %)	0.072
HR-/HER2- subtype	n = 754	n = 1812		n = 319	n = 319	
Age at diagnosis, years	46.3 (10.3)	48.8 (10.1)	−0.26	48.0 (10.5)	47.8 (10.1)	0.021
Year of diagnosis, 2013–2018	531 (70.4 %)	882 (48.7 %)	0.32	521 (71.0 %)	522 (71.1 %)	−0.019
Tumor size < 2 cm ^a	63 (8.4 %)	912 (50.3 %)	1.59	70 (9.5 %)	74 (10.1 %)	0.024
ALN metastasis, absent ^a	62 (8.2 %)	1398 (77.2 %)	2.45	74 (10.1 %)	69 (9.4 %)	0.045
High Ki-67 index	522 (69.2 %)	1082 (59.7 %)	0.14	244 (33.2 %)	225 (30.7 %)	0.027
Histologic grade, III	386 (51.2 %)	1484 (81.9 %)	−0.41	214 (29.2 %)	190 (25.9 %)	−0.046

Data are presented as the mean (standard deviation) or number (%).

Abbreviations: SMD, standardized mean difference; ALN, axillary lymph nodes; HR, hormone receptor; HER2, human epidermal growth factor receptor-2.

^a Patients in the neoadjuvant chemotherapy group were evaluated clinically.^b Among patients who administered hormone treatments.**A HR+/HER2- subtype****B HR-/HER2- subtype****Fig. 2.** Forest plot for the multivariable Cox regression analyses of factors associated with locoregional recurrence-free survival. Hosmer-Lemeshow goodness-of-fit test results: HR+/HER2-: χ^2 , 13.88; p-value = 0.09; HR-/HER2-: χ^2 , 3.23; p-value = 0.92. Adjuvant hormonal treatment showed multicollinearity for locoregional recurrence; hence, it was excluded from the multivariate analysis.

Abbreviations: HR, hormone receptor; HER2, human epidermal growth factor 2; LRR, locoregional recurrence.

0.0001; HR+/HER2-, hazard ratio: 1.85, 95 % CI: 1.37–2.50, log-rank $p < 0.0001$). However, the LRR-free survival rates between the two groups were comparable in patients with the HER2+ subtype.

Thus, we conducted further analysis for the HR+/HER2- and HR-/HER2- subtypes. Among patients with the HR+/HER2- subtype, NACT remained significantly associated with poor LRR after adjusting for related clinicopathologic variables affecting recurrence in their univariate analysis (hazard ratio: 1.61, 95 % CI: 1.01–2.56, adjusted $p = 0.046$; Fig. 2A, Supplementary Table 5). Additionally, the 1:1 propensity score matching analysis also revealed that the NACT group had a significantly poorer LRR-free survival (hazard ratio: 1.96, 95 % CI: 1.19–3.21, log-rank $p = 0.007$; Table 2, Fig. 3A). Among patients with the HR-/HER2- subtype, the timing of chemotherapy was not associated with LRR after Cox proportional hazards regression analysis (hazard ratio: 0.95, 95 % CI: 0.58–1.59, adjusted $p = 0.86$, Fig. 2B) and propensity score matching analysis (hazard ratio: 1.01, 95 % CI: 0.61–1.69, log-rank $p = 0.96$, Fig. 3B).

3.3. Annual recurrence pattern between NACT and ACT

To investigate the reason for the difference in LRR between the NACT and ACT groups, we performed a post-hoc analysis to determine the annual incidence of LRR after the completion of chemotherapy. The recurrence patterns of patients with the HR-/HER2- subtype were similar in the NACT and ACT groups, with the highest peak in the second year of treatment, followed by a dramatic decrease (Fig. 4B). In patients with HR+/HER2- subtype, the ACT group showed an increasing pattern for years without indistinguishable peak. However, the NACT group showed a higher recurrence rate during the first two years of treatment, which then gradually decreased (Fig. 4A).

3.4. DM-free survival and overall survival

The 10-year DM-free survival rate of the NACT and the ACT groups was 84.3 % and 92.9 %, respectively. The NACT group showed significantly poorer DM-free survival than the ACT group (hazard ratio: 2.43, 95 % CI: 2.09–2.82, log-rank $p < 0.0001$), and subgroup analysis according to tumor subtypes revealed the similar results (Supplementary

Fig. 3). In addition, patients after NACT showed worse overall survival than after ACT, especially for patients with the HR+/HER2- subtype (hazard ratio: 2.17, 95 % CI: 1.61–2.94, log-rank $p < 0.0001$) and the HR-/HER2- subtype (hazard ratio: 2.21, 95 % CI: 1.72–2.85, log-rank $p < 0.0001$) (Supplementary Fig. 4). However, NACT or ACT was not remained to be associated with DM or overall survival after Cox proportional hazards regression analysis for each tumor subtype.

3.5. Sensitivity analysis

Treating distant metastasis as a censored event can lead to the underestimation of LRR and overestimation of survival outcomes, especially for aggressive tumors. Thus, we conducted a post-hoc sensitivity analysis without considering distant metastasis as a competing event and included all LRR events that occurred after distant metastasis. This analysis showed similar results; that is, patients with the HR+/HER2- subtype in the NACT group showed poorer LRR-free survival (before matching, hazard ratio: 2.45, 95 % CI: 1.80–3.32, log-rank $p < 0.0001$; after matching, hazard ratio: 1.80, 95 % CI: 1.13–2.87, log-rank $p = 0.012$), while no difference was found in the LRR rate among those with other subtypes between the two groups (Supplementary Fig. 5).

In addition, with regard to the different pCR rates between tumor subtypes, we conducted an additional post-hoc analysis after excluding patients who achieved pCR in the NACT group (Fig. 5). The LRR-free survival of the non-pCR group was poorer than that of the ACT group for all subtypes, although the difference was not statistically significant among the HR+/HER2+ and HR-/HER2+ subtypes. Next, we conducted subgroup analysis according to the axillary surgery methods. Among those who underwent sentinel lymph node biopsy or omitted axillary surgery, the poorer LRR-free survival of the NACT compared to that of the ACT was shown in only the HR+/HER2- subtype (hazard ratio: 2.40, 95 % CI: 1.43–4.03, log-rank $p < 0.0001$) (Supplementary Fig. 6). After axillary lymph node dissection, LRR-free survival rate was significantly different among the HR+/HER2- (hazard ratio: 2.55, 95 % CI: 1.68–3.85, log-rank $p < 0.0001$) and the HR-/HER2- subtypes (hazard ratio: 1.92, 95 % CI: 1.26–2.94, log-rank $p = 0.002$) (Supplementary Fig. 7).

Lastly, the different periods of chemotherapy regimens can increase

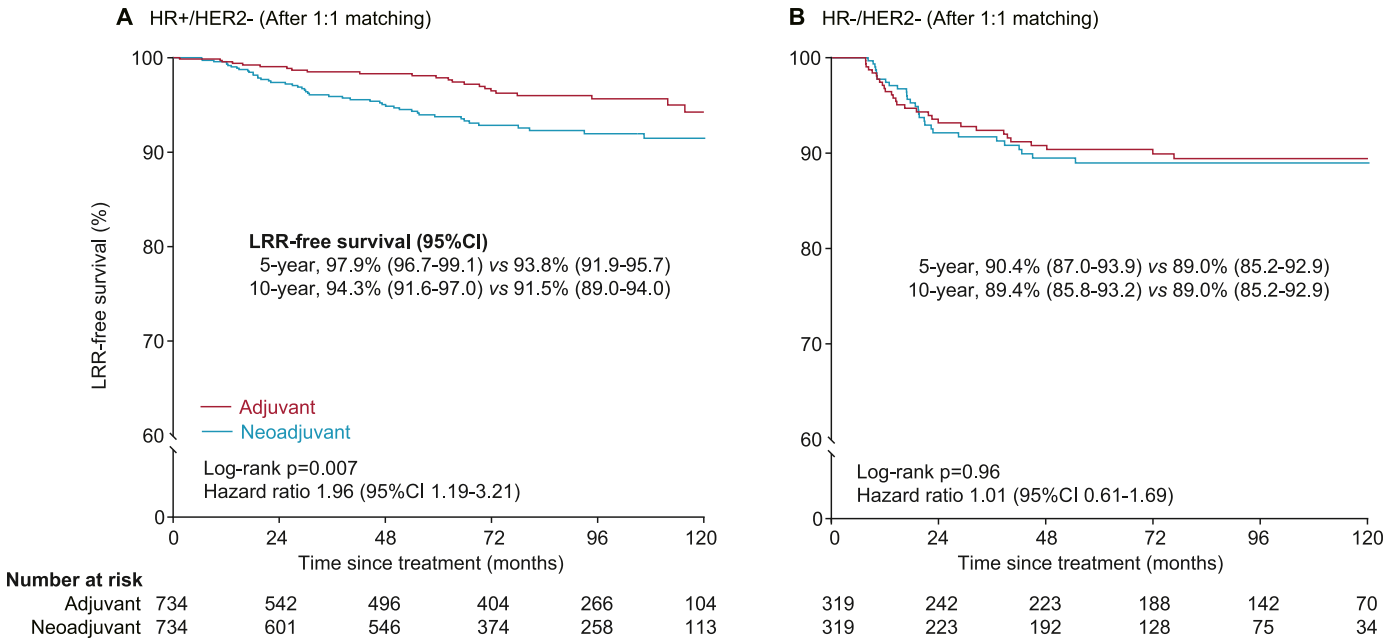


Fig. 3. Kaplan-Meier curves for locoregional recurrence-free survival after 1:1 propensity score matching among patients with the HR+/HER2- (A) and HR-/HER2- (B) subtypes
Abbreviations: HER2, human epidermal growth factor 2; HR, hormone receptor; LRR, locoregional recurrence.

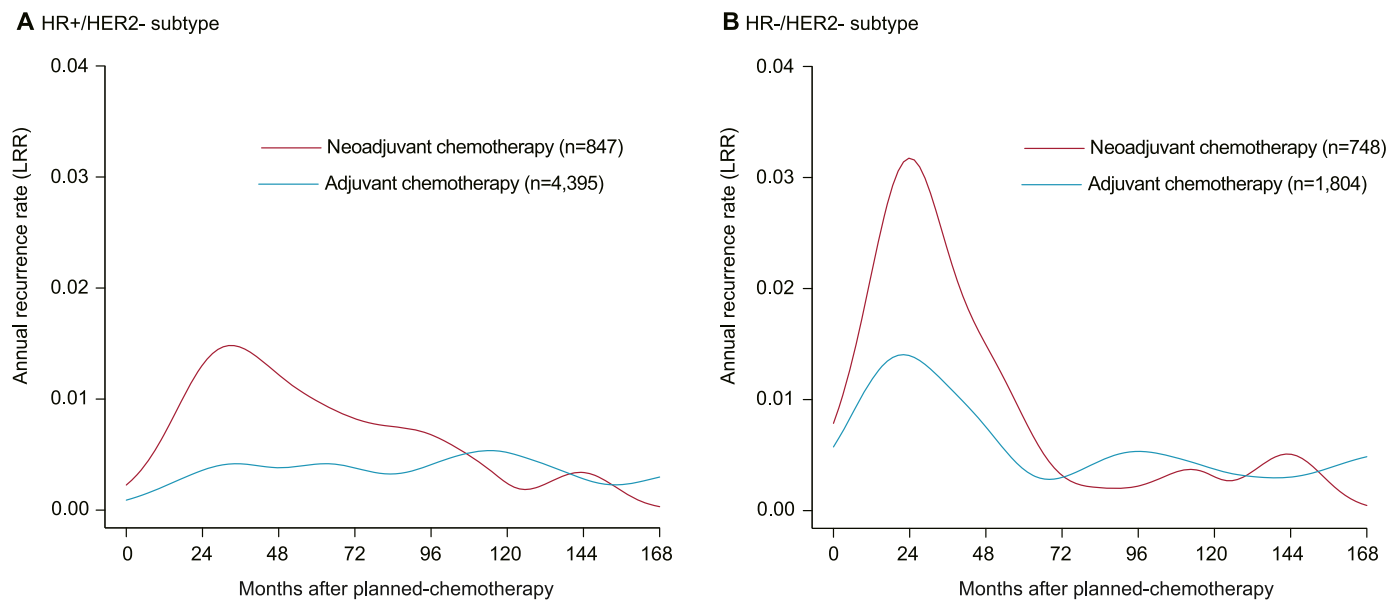


Fig. 4. Patterns of annual recurrence incidence per 1000 patients for patients with the HR+/HER2- (A) and HR-/HER2- (B) subtypes. Abbreviations: HER2, human epidermal growth factor 2; HR, hormone receptor; LRR, locoregional recurrence.

lead time bias. To minimize this potential bias, LRR-free survival was analyzed based on the period after the completion of the pre-planned chemotherapy. Results showed that ACT had better LRR-free survival than NACT in patients with the HR+/HER2- subtype, before and after new 1:1 propensity score matching analysis (Supplementary Fig. 8).

4. Discussion

In early-stage breast cancer, NACT has been widely accepted as a common treatment option [1,2], and its long-term oncological safety has been reported in previous studies [10,11]. The current study demonstrated that NACT was associated with a higher frequency of LRR than ACT. However, this difference was only observed in patients with the HR+/HER2- subtype, while those with other subtypes showed comparable outcomes between the two groups.

Previously, three meta-analyses investigating several randomized controlled trials compared the survival outcomes of NACT and those of ACT [9–11]. The meta-analysis conducted by the EBCTCG [11] demonstrated no significant differences in the distant metastasis and mortality rates but showed a higher LRR incidence in patients after NACT (risk ratio: 1.28, 95 % CI: 1.06–1.55, log-rank $p = 0.010$). Mauri et al. [10] also found no difference in the overall survival, disease progression, or distant metastasis rates between the NACT and ACT groups, although NACT was significantly associated with higher LRR incidence (risk ratio: 1.22, 95 % CI: 1.04–1.43, $p = 0.015$), which was more significant when surgery was omitted (risk ratio: 1.53, 95 % CI: 1.11–2.10, $p = 0.009$). Although these studies provided the most reliable evidence, their results should be interpreted with caution. For instance, the chemotherapy regimens were outdated, as the included trials were conducted decades ago. Additionally, trials included patients who underwent mastectomy, which is associated with lower LRR than BCS [28]. These situations increase the critical bias when LRR is compared as an endpoint because patients in the NACT group were more likely to undergo BCS than those in the ACT group, as noted in the EBCTCG study. Finally, owing to the nature of the meta-analysis, patient-level information was unavailable, and subgroup analysis according to tumor subtypes could not be performed.

Several retrospective studies also reported the impact of NACT compared with that of ACT on LRR incidence in patients who underwent BCS. Cho et al. [29] retrospectively investigated 1687 patients recruited

from a single institution and found a significant difference in the IBTR and LRR-free survival rates between NACT and ACT. Conversely, Yang et al. [30] showed no difference in the IBTR rate after propensity score matching; other studies [31,32] also reported no difference in survival outcomes after tumor stage-wise comparison. However, these studies had short median follow-up periods and only included a limited number of patients. The current study has some strengths in that we reported the results of a substantial number of cohorts from multiple institutions with a prolonged follow-up time. To the best of our knowledge, this study is the first to investigate whether the impact of NACT compared with that of ACT on LRR incidence differs among tumor subtypes.

Several factors can contribute to the higher LRR after NACT, which was observed exclusively in patients with the HR+/HER2- subtype. First, the shrinkage patterns during NACT differed according to subtype: the HR+/HER2- subtype usually shrinks with a multifocal pattern, while the HR-/HER2+ subtype shrinks with a concentric pattern [33, 34]. Moreover, preoperative magnetic resonance imaging had a lower sensitivity in evaluating residual tumors after NACT in patients with the HR+/HER2- subtype than in those with other subtypes [35]. These findings imply that tumor islands or residual intraductal components that were assumed to be completely regressed at the tumor site would have made it challenging to secure adequate margins during surgery, especially in those with the HR+/HER2- subtype. This hypothesis is supported by our findings, which demonstrated a high annual LRR incidence in the early period of NACT treatment for the HR+/HER2- subtype, which was not observed after ACT. Furthermore, additional post-hoc analysis revealed that the IBTR-free survival of patients with the HR+/HER2- subtype significantly differed between the two groups, and the difference was greater than that of the LRR incidence (hazard ratio: 2.71, 95 % CI: 1.77–4.14; log-rank $p < 0.0001$; Supplementary Fig. 9). However, patients with other subtypes showed comparable IBTR-free survival rates between the NACT and ACT groups. Thus, the high LRR incidence observed in patients with the HR+/HER2- subtype after NACT could be attributed to the increased risk of surgical failure.

Another possible explanation could be the different chemotherapy responses of various tumor subtypes [16,36]. Data from the combined analysis of the National Surgical Adjuvant Breast and Bowel Projects B-18 and B-27 [35] and European Organization for Research and Treatment of Cancer 10994/BIG 1-00 study [37] reported that improved tumor response was an independent predictor of lower LRR risk. Several

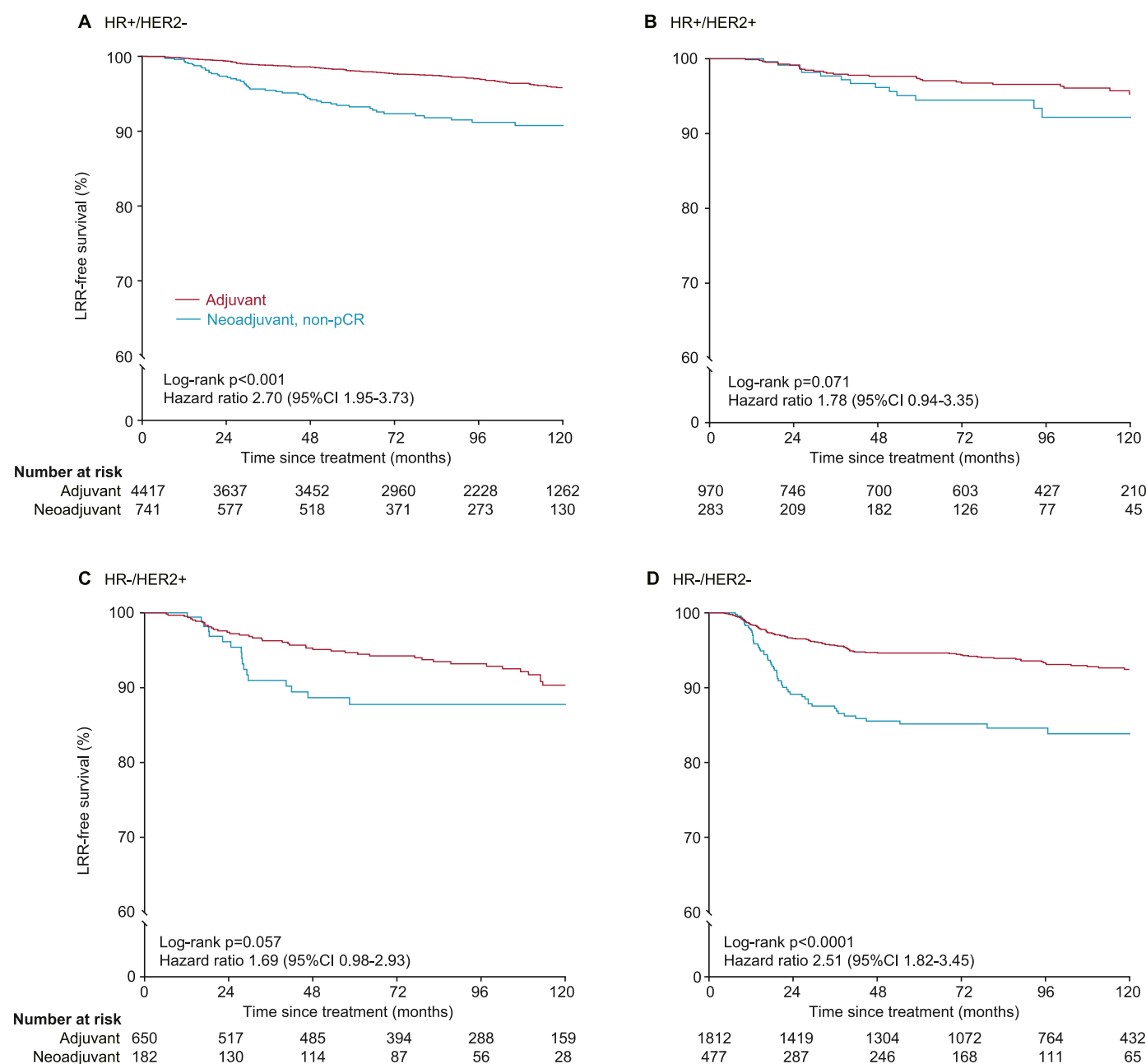


Fig. 5. Kaplan-Meier curves for LRR-free survival after excluding patients who achieved pCR

Abbreviations: pCR, pathologic complete regression; HR, hormone receptor; HER2, human epidermal growth factor 2; LRR, locoregional recurrence.

other retrospective studies have also demonstrated similar results [38, 39]. Our findings of subgroup analysis imply that the low pCR rate and poor response to chemotherapy could have resulted in higher LRR in the NACT group, especially in patients with the HR+/HER2- subtype. Conversely, the high pCR rate in patients with other subtypes may explain the lack of a difference in the LRR risk between the two groups.

The use of NACT in patients with the HR+/HER2- subtype has remained controversial for years. Although NACT offers several benefits, it also has several drawbacks: 1) NACT enables cancer cells to proliferate and metastasize [40]; 2) the tumor burden targeted by NACT would surpass that encountered in ACT after surgery, potentially leading to more treatment-resistant clones [41]; and 3) patients are compelled to harbor anxiety and distress for several months, especially when pCR is not achieved [42]. These disadvantages are accentuated in those with the HR+/HER2- subtype, with a relatively low rate of reduction in surgical extent [43] and higher LRR rates after NACT. Considering the

risk-benefit balance of NACT, a multidisciplinary strategy is recommended for treating HR+/HER2- breast cancer.

Although our study is the first to provide patient-level evidence supporting the high LRR incidence after NACT for different tumor subtypes, it has some limitations. First, the inherent nature of the retrospective study introduced hidden biases. Discordant chemotherapy and radiation treatment regimens over the long-term period require cautious interpretation when applying the results to the current real-world practice. Moreover, we did not consider physician-related factors or various treatment and surveillance strategies across multiple institutions. Second, patients in the NACT group were assessed using core needle biopsy and clinical staging, whereas those in the ACT group were assessed based on the pathological reports from the resected specimens. This discrepancy in the methods used to evaluate patient characteristics between the two groups makes it challenging to compare the two groups. Furthermore, we could not adjust for several pathological

variables, such as lymphovascular invasion, because core needle biopsy does not provide sufficient information. Lastly, the assessment of patients' eligibility for BCS before NACT could not be performed owing to the limitations of the retrospective design. Notably, tumors that are downsized by NACT are consistently associated with higher LRR after surgery [11]. To address this issue, we additionally compared patients with T2 or smaller tumors in the NACT group and all patients in the ACT group, and the results were not significantly different from those of previous analyses (Supplementary Fig. 10). Similarly, patients with large tumors after NACT may opt for total mastectomy, which could potentially affect the results of those with subtypes other than the HR+/HER2- subtype.

5. Conclusion

In conclusion, although NACT shows comparable DM-free survival and overall survival compared to ACT, it is significantly associated with an elevated risk of LRR. However, this risk was only observed in patients with the HR+/HER2- subtype, especially in the early period after treatment; meanwhile, those with the other subtypes did not show a significant difference between the two treatments. When administering NACT for patients with HR+/HER- breast cancer, comprehensive evaluations, including preoperative radiologic exams, accurate tumor localization, and detailed pathologic reports on margin status, along with appropriate radiation treatments and intensive surveillance, should be performed to minimize the LRR risk. Moreover, among patients with HR + subtypes, a multigene assay using core-needle biopsy specimens would help identify those who may benefit from NACT. Additional prospective studies with a larger sample size are also required to validate our findings.

Ethical approval and informed consent

The study was performed in accordance with the Declaration of Helsinki or comparable ethical standards. Approval was granted by the ethics committee or institutional review board at the participating sites. Requirement for informed consent was waived for all patient because this was a retrospective study.

CRediT authorship contribution statement

Jong-Ho Cheun: Writing – review & editing, Writing – original draft, Validation, Investigation, Formal analysis, Data curation, Conceptualization. **Youngji Kwak:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Eunhye Kang:** Data curation. **Ji-Jung Jung:** Data curation. **Hong-Kyu Kim:** Writing – review & editing. **Han-Byoel Lee:** Writing – review & editing, Funding acquisition. **Kyung-Hun Lee:** Writing – review & editing. **Hyeong-Gon Moon:** Writing – review & editing. **Ki-Tae Hwang:** Writing – review & editing. **Yeon Hee Park:** Writing – review & editing. **Jeong Eon Lee:** Writing – review & editing, Project administration, Formal analysis, Conceptualization. **Wonshik Han:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Consent to publication

All authors have read the paper and consent to its publication.

Conflicts of interest

Han-Byoel Lee and Wonshik Han report being a member on the board of directors of and holding stock and ownership interests at DCGen, Co., Ltd., not relevant to this study. Other authors declare no competing interests.

Access to data and data analysis

Jong-Ho Cheun had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Summary statistical data will be available from the Jong-Ho Cheun (chun89aaa@naver.com) on reasonable request after approval of a proposal.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.breast.2024.103828>.

References

- [1] Mougalian SS, Soulos PR, Killelea BK, Lannin DR, Abu-Khalaf MM, DiGiovanna MP, et al. Use of neoadjuvant chemotherapy for patients with stage I to III breast cancer in the United States. *Cancer* 2015;121:2544–52. <https://doi.org/10.1002/cncr.29348>.
- [2] Aquina CT, Ejaz A, Tsung A, Pawlik TM, Cloyd JM. National trends in the use of neoadjuvant therapy before cancer surgery in the US from 2004 to 2016. *JAMA Netw Open* 2021;4:e211031. <https://doi.org/10.1001/jamanetworkopen.2021.1031>.
- [3] Schott AF, Hayes DF. Defining the benefits of neoadjuvant chemotherapy for breast cancer. *J Clin Oncol* 2012;30:1747–9. <https://doi.org/10.1200/JCO.2011.41.3161>.
- [4] Mougalian SS, Hernandez M, Lei X, Lynch S, Kuerer HM, Symmans WF, et al. Ten-year outcomes of patients with breast cancer with cytologically confirmed axillary lymph node metastases and pathologic complete response after primary systemic chemotherapy. *JAMA Oncol* 2016;2:508. <https://doi.org/10.1001/jamaoncol.2015.4935>.
- [5] Mieog JSD, van der Hage JA, van de Velde CJH. Neoadjuvant chemotherapy for operable breast cancer. *Br J Surg* 2007;94:1189–200. <https://doi.org/10.1002/bjs.5894>.
- [6] Golshan M, Loibl S, Wong SM, Huober JB, O'Shaughnessy J, Rugo HS, et al. Breast conservation after neoadjuvant chemotherapy for triple-negative breast cancer. *JAMA Surg* 2020;155:e195410. <https://doi.org/10.1001/jamasurg.2019.5410>.
- [7] Bear HD, Anderson S, Brown A, Smith R, Mamounas EP, Fisher B, et al. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from national surgical adjuvant breast and Bowel Project protocol B-27. *J Clin Oncol* 2003;21:4165–74. <https://doi.org/10.1200/JCO.2003.12.005>.
- [8] Fisher B, Brown A, Mamounas E, Wieand S, Robidoux A, Margolese RG, et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J Clin Oncol* 1997;15:2483–93. <https://doi.org/10.1200/JCO.1997.15.7.2483>.
- [9] van der Hage JH, van de Velde CJ, Mieog SJ, Charehbil A. Preoperative chemotherapy for women with operable breast cancer. *Cochrane Database Syst Rev* 2007;2021. <https://doi.org/10.1002/14651858.CD005002.pub2>.
- [10] Mauri D, Pavlidis N, Ioannidis JPA. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. *JNCI J Natl Cancer Inst* 2005;97:188–94. <https://doi.org/10.1093/jnci/dji021>.
- [11] Asselain B, Barlow W, Bartlett J, Bergh J, Bergsten-Nordström E, Bliss J, et al. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. *Lancet Oncol* 2018;19:27–39. [https://doi.org/10.1016/S1470-2045\(17\)30777-5](https://doi.org/10.1016/S1470-2045(17)30777-5).
- [12] Deo SVS, Bhutani M, Shukla NK, Raina V, Rath GK, Purkayasth J. Randomized trial comparing neo-adjuvant versus adjuvant chemotherapy in operable locally advanced breast cancer (T4b N0-2 M0). *J Surg Oncol* 2003;84:192–7. <https://doi.org/10.1002/jso.10323>.
- [13] Braybrooke J, Bradley R, Gray R, Hills RK, Pan H, Peto R, et al. Anthracycline-containing and taxane-containing chemotherapy for early-stage operable breast cancer: a patient-level meta-analysis of 100 000 women from 86 randomised trials. *Lancet* 2023;401:1277–92. [https://doi.org/10.1016/S0140-6736\(23\)00285-4](https://doi.org/10.1016/S0140-6736(23)00285-4).

- [14] 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;353:1659–72. <https://doi.org/10.1056/NEJMoa052306>.
- [15] Cheun J-H, Kim H-K, Moon H-G, Han W, Lee H-B. Locoregional recurrence patterns in patients with different molecular subtypes of breast cancer. *JAMA Surg* 2023; 158:841. <https://doi.org/10.1001/jamasurg.2023.2150>.
- [16] Houssami N, Macaskill P, von Minckwitz G, Marinovich ML, Mamounas E. Meta-analysis of the association of breast cancer subtype and pathologic complete response to neoadjuvant chemotherapy. *Eur J Cancer* 2012;48:3342–54. <https://doi.org/10.1016/j.ejca.2012.05.023>.
- [17] Pastorello RG, Laws A, Grossmith S, King C, McGrath M, Mittendorf EA, et al. Clinico-pathologic predictors of patterns of residual disease following neoadjuvant chemotherapy for breast cancer. *Mod Pathol* 2021;34:875–82. <https://doi.org/10.1038/s41379-020-00714-5>.
- [18] Veronesi U, Cascinelli N, Mariani L, Greco M, Saccocci R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002;347:1227–32. <https://doi.org/10.1056/NEJMoa020989>.
- [19] World Medical Association Declaration of Helsinki. *JAMA* 2013;310:2191. <https://doi.org/10.1001/jama.2013.281053>.
- [20] Elm E von, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007;335:806–8. <https://doi.org/10.1136/bmj.39335.541782.AD>.
- [21] Kim HJ, Kim S, Freedman RA, Partridge AH. The impact of young age at diagnosis (age <40 years) on prognosis varies by breast cancer subtype: a U.S. SEER database analysis. *Breast* 2022;61:77–83. <https://doi.org/10.1016/j.breast.2021.12.006>.
- [22] Han W, Kim SW, Ae Park I, Kang D, Kim S-W, Youn Y-K, et al. Young age: an independent risk factor for disease-free survival in women with operable breast cancer. *BMC Cancer* 2004;4:82. <https://doi.org/10.1186/1471-2407-4-82>.
- [23] Wolff AC, Hammond MEH, Allison KH, Harvey BE, Mangu PB, Bartlett JMS, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American society of clinical oncology/college of American Pathologists clinical practice guideline focused update. *J Clin Oncol* 2018;36:2105–22. <https://doi.org/10.1200/JCO.2018.77.8738>.
- [24] De La Cruz LM, Harhay MO, Zhang P, Ugras S. Impact of neoadjuvant chemotherapy on breast cancer subtype: does subtype change and, if so, how? *Ann Surg Oncol* 2018;25:3535–40. <https://doi.org/10.1245/s10434-018-6608-1>.
- [25] Hortobagyi GN, Connolly JL, D'Orsi CJ, Edge SB, Mittendorf EA, Rugo HS, et al. Breast. *AJCC cancer staging man*, vol. 36. Cham: Springer International Publishing; 2017. p. 589–636. https://doi.org/10.1007/978-3-319-40618-3_48.
- [26] Yao XI, Wang X, Speicher PJ, Hwang ES, Cheng P, Harpole DH, et al. Reporting and guidelines in propensity score analysis: a systematic review of cancer and cancer surgical studies, vol. 109. *JNCI J Natl Cancer Inst*; 2017. <https://doi.org/10.1093/jnci/djw323>.
- [27] Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011;46:399–424. <https://doi.org/10.1080/00273171.2011.568786>.
- [28] Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;366: 2087–106. [https://doi.org/10.1016/S0140-6736\(05\)67887-7](https://doi.org/10.1016/S0140-6736(05)67887-7).
- [29] Cho JH, Park JM, Park HS, Park S, Kim S II, Park B-W. Oncologic safety of breast-conserving surgery compared to mastectomy in patients receiving neoadjuvant chemotherapy for locally advanced breast cancer. *J Surg Oncol* 2013;108:531–6. <https://doi.org/10.1002/jso.23439>.
- [30] Yang F, Wu S-Y, Mo M, Xiao Q, Yang X, Liu Y-Y, et al. Neoadjuvant systemic therapy does not compromise local control after breast-conserving surgery: a single-center, propensity score matching study in China. *Transl Cancer Res* 2020;9: 155–65. <https://doi.org/10.21037/tcr.2019.11.23>.
- [31] Mittendorf EA, Buchholz TA, Tucker SL, Meric-Bernstam F, Kuerer HM, Gonzalez-Angulo AM, et al. Impact of chemotherapy sequencing on local-regional failure risk in breast cancer patients undergoing breast-conserving therapy. *Ann Surg* 2013; 257:173–9. <https://doi.org/10.1097/SLA.0b013e3182805c4a>.
- [32] Agarwal G, Sonthineni C, Mayilvaganan S, Mishra A, Lal P, Agrawal V. Surgical outcomes of primary versus post-neoadjuvant chemotherapy breast conservation surgery: a comparative study from a developing country. *World J Surg* 2018;42: 1364–74. <https://doi.org/10.1007/s00268-018-4466-4>.
- [33] Ballesio L, Gigli S, Di Pastena F, Giraldo G, Manganaro L, Anastasi E, et al. Magnetic resonance imaging tumor regression shrinkage patterns after neoadjuvant chemotherapy in patients with locally advanced breast cancer: correlation with tumor biological subtypes and pathological response after therapy. *Tumor Biol* 2017;39:101042831769454. <https://doi.org/10.1177/1010428317694540>.
- [34] Pastorello RG, Laws A, Grossmith S, King C, McGrath M, Mittendorf EA, et al. Clinico-pathologic predictors of patterns of residual disease following neoadjuvant chemotherapy for breast cancer. *Mod Pathol* 2020;5–8. <https://doi.org/10.1038/s41379-020-00714-5>.
- [35] Janssen LM, den Dekker BM, Gilhuijs KGA, van Diest PJ, van der Wall E, Elias SG. MRI to assess response after neoadjuvant chemotherapy in breast cancer subtypes: a systematic review and meta-analysis. *Npj Breast Cancer* 2022;8:107. <https://doi.org/10.1038/s41523-022-00475-1>.
- [36] Choi JE, Kim Z, Park CS, Park EH, Lee SB, Lee SK, et al. Breast cancer statistics in Korea, 2019. *J Breast Cancer* 2023;26:207. <https://doi.org/10.4048/jbc.2023.26.e27>.
- [37] Gillon P, Touati N, Breton-Callu C, Slaets L, Cameron D, Bonnefoi H. Factors predictive of locoregional recurrence following neoadjuvant chemotherapy in patients with large operable or locally advanced breast cancer: an analysis of the EORTC 10994/BIG 1-00 study. *Eur J Cancer* 2017;79:226–34. <https://doi.org/10.1016/j.ejca.2017.04.012>.
- [38] Swisher SK, Vila J, Tucker SL, Bedrosian I, Shaitelman SF, Litton JK, et al. Locoregional control according to breast cancer subtype and response to neoadjuvant chemotherapy in breast cancer patients undergoing breast-conserving therapy. *Ann Surg Oncol* 2016;23:749–56. <https://doi.org/10.1245/s10434-015-4921-5>.
- [39] Yang TJ, Morrow M, Modi S, Zhang Z, Krause K, Siu C, et al. The effect of molecular subtype and residual disease on locoregional recurrence in breast cancer patients treated with neoadjuvant chemotherapy and postmastectomy radiation. *Ann Surg Oncol* 2015;22:495–501. <https://doi.org/10.1245/s10434-015-4697-7>.
- [40] Karagiannis GS, Pastoriza JM, Wang Y, Harnay AS, Entenberg D, Pignatelli J, et al. Neoadjuvant chemotherapy induces breast cancer metastasis through a TMEM-mediated mechanism. *Sci Transl Med* 2017;9. <https://doi.org/10.1126/scitranslmed.aan0026>.
- [41] Cowan R, Chi D, Kehoe S, Nankivell M, Leary A. Primary surgery or neoadjuvant chemotherapy in advanced ovarian cancer: the debate continues. *Am Soc Clin Oncol Educ B* 2016:153–62. <https://doi.org/10.1200/EDBK.160624>.
- [42] Rodrigues J, Sá A, Fontes R, Barbosa A, Barbosa-Martins J, Oliveira C, et al. Anxiety and depression screening during neoadjuvant chemotherapy treatment in early breast cancer patients: a multicenter longitudinal observational study. *Eur J Cancer* 2022;175:S36. [https://doi.org/10.1016/S0959-8049\(22\)01446-0](https://doi.org/10.1016/S0959-8049(22)01446-0).
- [43] Boughey JC, McCall LM, Ballman KV, Mittendorf EA, Ahrendt GM, Wilke LG, et al. Tumor biology correlates with rates of breast-conserving surgery and pathologic complete response after neoadjuvant chemotherapy for breast cancer. *Ann Surg* 2014;260:608–16. <https://doi.org/10.1097/SLA.0000000000000924>.