

# Preoperative considerations and benefits of neoadjuvant chemotherapy: insights from a 12-year review of the Hong Kong Breast Cancer Registry

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## ABSTRACT

**Introduction:** Neoadjuvant chemotherapy (NAC) was initially used for locally advanced or inoperable breast cancers. Its extension to early disease has facilitated breast-conserving surgery (BCS). This study investigated the use of NAC in patients registered with the Hong Kong Breast Cancer Registry (HKBCR); it also assessed NAC effectiveness according to rates of pathological complete response (pCR) and BCS.

**Methods:** Records were retrieved from the HKBCR regarding 13 435 women who had been diagnosed with invasive breast cancer during the period of 2006 to 2017, including 1084 patients who received NAC.

**Results:** The proportion of patients treated with NAC nearly doubled from 5.6% in 2006–2011 to 10.3% in 2012–2017. The increase was most pronounced among patients with stage II or III disease. In terms of biological subtype, substantial increases in the receipt of NAC were evident among patients with triple-negative and human epidermal growth factor receptor 2 (HER2)-positive (non-luminal) tumours. The best rates of pCR were observed in patients with HER2-positive (non-luminal) [46.0%] tumours, followed by patients with luminal B (HER2-positive) [29.4%] and triple-negative (29.3%) tumours. After NAC, the rate of BCS was 53.9% in patients with

clinical stage IIA disease, compared with 38.2% in patients with pathological stage IIA disease who did not receive NAC.

**Conclusion:** The use of NAC in Hong Kong increased from 2006 to 2017. The findings regarding rates of pCR and BCS indicate that NAC is an effective treatment; it should be considered in patients with stage  $\geq$ II disease, as well as patients with HER2-positive (non-luminal) or triple-negative breast cancers.

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### New knowledge added by this study

- The use of neoadjuvant chemotherapy (NAC) in Hong Kong increased from 2006 to 2017.
- Higher pathological complete response rates were detected in patients with human epidermal growth factor receptor 2-positive (non-luminal) and triple-negative tumours.
- After treatment with NAC, greater proportions of patients with clinical stage IIA or IIB disease underwent breast-conserving surgery.

### Implications for clinical practice or policy

- Alterations in breast cancer biomarkers after NAC suggest that reassessments of residual tumour would provide useful guidance regarding further adjuvant therapy.
- Under the care of a multidisciplinary team, patients with early breast cancer who have an appropriate indication should consider receiving NAC before surgery.

## Introduction

Neoadjuvant chemotherapy (NAC)—chemotherapy delivered before definitive breast cancer surgery—was first described in the late 1970s as treatment for locally advanced (often inoperable) breast cancers; it was intended to reduce tumour size and facilitate

surgery.<sup>1</sup> Subsequently, the use of NAC has been extended to early operable breast cancers.<sup>2–5</sup> This approach offers the advantages of down-staging the disease, potentially reducing the extent of surgery, and allowing breast-conserving surgery (BCS); in the current era of individualised treatment, it supports evaluations of therapeutic efficacy.<sup>2,6</sup>

## 前導性化療的術前考慮及好處：回顧香港乳癌資料庫12年資料所獲得的啟示

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**引言：**前導性化療起初用於局部晚期或不能動手術的乳癌，其後延伸用於早期乳癌，增加了進行乳房保留手術的機會。本研究調查了採用前導性化療並已登記加入香港乳癌資料庫的患者，以及根據病理完全反應率及乳房保留手術率評估前導性化療的效用。

**方法：**本研究從香港乳癌資料庫取得於2006至2017年期間確診浸潤性乳癌的13 435名女性的紀錄，包括接受了前導性化療的1084名患者。

**結果：**接受前導性化療的患者比例由2006-2011年的5.6%增加至2012-2017年的10.3%，增長約為兩倍，第II或第III期乳癌患者的增長尤其明顯。在生物亞型方面，接受前導性化療的三陰性及HER2陽性（非管狀）腫瘤患者人數大幅上升。在HER2陽性（非管狀）腫瘤患者觀察到最佳病理完全反應率（46.0%），其次是管狀B型（HER2陽性，29.4%）及三陰性（29.3%）腫瘤患者。進行前導性化療後，臨床第IIA期乳癌患者的乳房保留手術率為53.9%，而沒有接受前導性化療的病理學第IIA期乳癌患者則為38.2%。

**結論：**在香港採用前導性化療於2006至2017年間有所上升。有關病理完全反應率及乳房保留手術率的研究結果表明前導性化療是有效治療；應考慮在第II期或以上、HER2陽性（非管狀）或三陰性乳癌病人採用該治療。

There is evidence that NAC is equivalent to adjuvant chemotherapy in terms of preventing breast cancer recurrence.<sup>6</sup> It demonstrated equal effectiveness in terms of disease-free survival and overall survival in the National Surgical Adjuvant Breast and Bowel Project B-18 trial.<sup>7</sup> Furthermore, a recent meta-analysis by the Early Breast Cancer Trialists' Collaborative Group showed no significant differences between NAC and adjuvant chemotherapy for distant recurrence, breast cancer mortality, or death from any cause.<sup>8</sup>

Here, we hypothesised that the use of NAC would change over time among patients with breast cancer in Hong Kong, considering its increasing acceptance as a treatment approach. Thus, the objectives of this study were to investigate the use of NAC over time in patients registered with the Hong Kong Breast Cancer Registry (HKBCR), and to assess the effectiveness of NAC among patients with breast cancer in Hong Kong according to rates of pathological complete response (pCR) and BCS. This study also evaluated alterations in breast cancer biomarkers, including oestrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 proliferation index.

### Methods

Records were retrieved from the HKBCR regarding Hong Kong Chinese female patients who were

diagnosed with invasive breast cancer in the period of 2006 to 2017. Patients were excluded for the following reasons: stage 0 or stage IV disease, missing or unknown information regarding surgery, and concurrent neoadjuvant endocrine treatment or NAC received outside Hong Kong (which may involve different clinical considerations).

Breast cancer was categorised into four biological subtypes based on clinicopathological criteria, in accordance with recommendations by the St Gallen 2013 Consensus Guideline.<sup>9</sup> A cut-off of <14% reportedly has the strongest correlation with the gene-expression definition of the luminal A-like subtype; a cut-off of  $\geq 14\%$  is generally regarded as the threshold for a high Ki-67 proliferation index. Histological grade 3 was used as a surrogate indicator of the luminal B-like subtype if Ki-67 information was unavailable.<sup>10</sup> Pathological complete response was defined as no histological evidence of malignancies (ypT0) or the presence of only in-situ residuals in breast tissue (ypTis) and complete disappearance of lymph node metastasis (ypN0) after surgery.<sup>11</sup> The same definitions have been adopted by the MD Anderson Cancer Center,<sup>12</sup> as well as the Austrian Breast & Colorectal Cancer Study Group.<sup>13</sup>

Ethics approval for this study has been obtained from six relevant approving bodies. Written informed consent for data collection was obtained during patient recruitment into the HKBCR, who were from 20 hospitals and 37 clinics (online supplementary Appendix). Patient demographics, pre-chemotherapy and post-chemotherapy disease staging, tumour characteristics, and prescribed chemotherapeutic agents were evaluated. The effectiveness of neoadjuvant chemotherapy was assessed in terms of the rates of pCR and BCS. Baseline tumour characteristics were analysed, including size, nodal stage, histological grade, Ki-67 level, hormone receptor status, and HER2 status.

Descriptive statistics were used to summarise demographic and clinical characteristics of patients. Continuous variables are shown as mean, standard deviation, and range; categorical variables are reported as frequency and percentage. Means were compared between groups using independent samples *t* tests. The Pearson Chi squared test was used to evaluate differences in pCR according to biological subtype and surgical approach. Data were analysed using SPSS (Windows version 22.0; IBM Corp, Armonk [NY], United States). All *P* values were derived from two-sided statistical tests, and *P* values <0.05 were considered statistically significant.

### Results

#### Patient selection

In total, 13 990 patients with invasive breast cancer were initially screened for inclusion. After the

exclusion of 555 patients, 13 435 patients (13 625 breast cancer cases) were included in this study (Fig 1). The NAC group comprised 1084 patients (1097 breast cancer cases) and the non-NAC group comprised 12 351 patients (12 528 breast cancer cases).

### Characteristics of patients who received neoadjuvant chemotherapy

In the NAC group, the median age was 49.7 years (interquartile range, 43.5-56.7; range, 21.9-81.6), and half of the patients (53.8%) were premenopausal. The median invasive clinical tumour size was 4.0 cm (range, 0.55-20.0). The patients' clinical characteristics (eg, age, biological subtype, clinical tumour stage, nodal stage, and cancer stage) are shown in Table 1.

Among the 13 625 breast cancer cases, 13.6% of affected patients aged <40 years were treated with NAC, compared with 8.0% and 1.9% of affected patients aged 40-69 years and ≥70 years, respectively (Table 1). The administration of NAC was positively associated with cancer stage at diagnosis: the proportion increased from 0.3% in patients with stage I disease to 26.9% among patients with stage III disease (Table 1). Furthermore, greater proportions of patients with luminal B (HER2-positive), HER2-positive (non-luminal), or triple-negative subtypes of breast cancer received NAC.

### Use of neoadjuvant chemotherapy in two temporal cohorts

For the assessment of changes in NAC adoption, the 13 435 patients were divided into two groups according to the year of diagnosis: periods of 2006-2011 and 2012-2017. The proportion of patients treated with NAC nearly doubled from 5.6% in 2006-2011 to 10.3% in 2012-2017 (Table 1).

Further analysis indicated that the use of NAC was significantly increased in patients with stages II and III breast cancers, but not in patients with stage I breast cancer. It was most pronounced among patients with stages IIB (7.8% in 2006-2011 vs. 13.3% in 2012-2017) and III (20.7% vs. 32.6%) disease. An increase in the use of NAC was also observed in patients with all biological subtypes of breast cancer. In particular, substantial increases were observed among patients with triple-negative (6.4% vs. 14.3%), HER2-positive (non-luminal) [8.9% vs. 13.9%], and luminal B (HER2-positive) [8.0% vs. 18.9%] tumours (Table 1).

### Regimens of neoadjuvant chemotherapy

Among the 1084 patients who received NAC, 353 were diagnosed with HER2-positive (non-luminal) cancer. Anti-HER2 agents were added to chemotherapy in 73.7% of these patients, and the proportions increased from 57.6% in 2006-2011 to 82.5% in 2012-2017; taxane-carboplatin-trastuzumab was the most frequently used regimen.

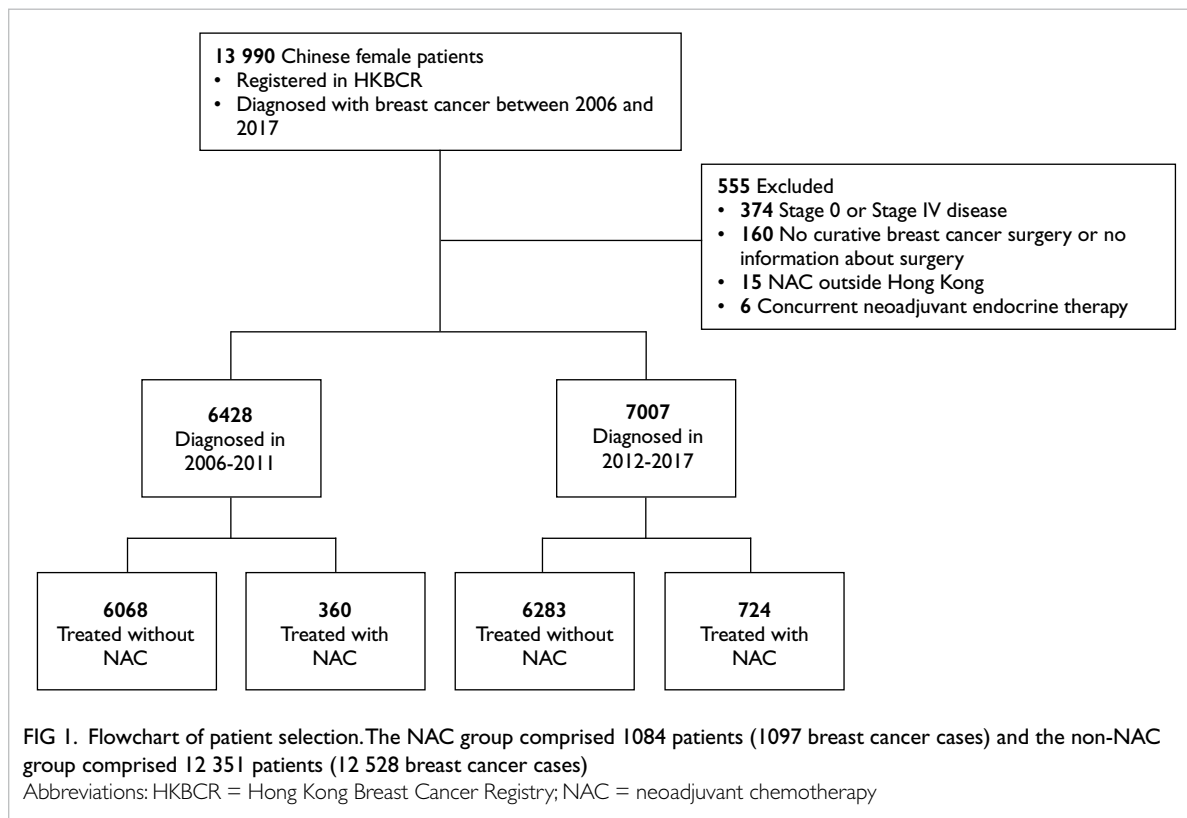


TABLE I. Clinical characteristics of non-neoadjuvant chemotherapy and neoadjuvant chemotherapy cases in each cohort\*

	Total cases		2006-2011		2012-2017	
	Non-NAC cases n=12 528	NAC cases n=1097	Non-NAC cases n=6151	NAC cases n=363	Non-NAC cases n=6377	NAC cases n=734
<b>Age-group, y</b>						
<40	1040 (8.3%)	164 (14.9%)	597 (9.7%)	53 (14.6%)	443 (6.9%)	111 (15.1%)
40-69	10 423 (83.2%)	907 (82.7%)	5081 (82.6%)	302 (83.2%)	5342 (83.8%)	605 (82.4%)
≥70	942 (7.5%)	18 (1.6%)	412 (6.7%)	7 (1.9%)	530 (8.3%)	11 (1.5%)
Unknown	123 (1.0%)	8 (0.7%)	61 (1.0%)	1 (0.3%)	62 (1.0%)	7 (1.0%)
<b>Histological type</b>						
Invasive ductal NOS	10 703 (85.4%)	932 (85.0%)	5273 (85.7%)	302 (83.2%)	5430 (85.1%)	630 (85.8%)
Invasive lobular	475 (3.8%)	19 (1.7%)	219 (3.6%)	11 (3.0%)	256 (4.0%)	8 (1.1%)
Others	1250 (10.0%)	49 (4.5%)	606 (9.9%)	16 (4.4%)	644 (10.1%)	33 (4.5%)
Unknown	100 (0.8%)	97 (8.8%)	53 (0.9%)	34 (9.4%)	47 (0.7%)	63 (8.6%)
<b>Tumour grade</b>						
1	2212 (17.7%)	24 (2.2%)	1071 (17.4%)	9 (2.5%)	1141 (17.9%)	15 (2.0%)
2	5261 (42.0%)	194 (17.7%)	2554 (41.5%)	60 (16.5%)	2707 (42.4%)	134 (18.3%)
3	4122 (32.9%)	233 (21.2%)	2058 (33.5%)	76 (20.9%)	2064 (32.4%)	157 (21.4%)
Unknown	933 (7.4%)	646 (58.9%)	468 (7.6%)	218 (60.1%)	465 (7.3%)	428 (58.3%)
<b>T stage</b>						
T1	6468 (51.6%)	58 (5.3%)	3189 (51.8%)	18 (5.0%)	3279 (51.4%)	40 (5.4%)
T2	5362 (42.8%)	375 (34.2%)	2655 (43.2%)	105 (28.9%)	2707 (42.4%)	270 (36.8%)
T3	403 (3.2%)	257 (23.4%)	200 (3.3%)	100 (27.5%)	203 (3.2%)	157 (21.4%)
T4	102 (0.8%)	285 (26.0%)	54 (0.9%)	119 (32.8%)	48 (0.8%)	166 (22.6%)
Unknown	193 (1.5%)	122 (11.1%)	53 (0.9%)	21 (5.8%)	140 (2.2%)	101 (13.8%)
<b>N stage</b>						
N0	7636 (61.0%)	229 (20.9%)	3689 (60.0%)	95 (26.2%)	3947 (61.9%)	134 (18.3%)
N1	3205 (25.6%)	391 (35.6%)	1639 (26.6%)	137 (37.7%)	1566 (24.6%)	254 (34.6%)
N2	967 (7.7%)	129 (11.8%)	515 (8.4%)	39 (10.7%)	452 (7.1%)	90 (12.3%)
N3	515 (4.1%)	198 (18.0%)	258 (4.2%)	63 (17.4%)	257 (4.0%)	135 (18.4%)
Unknown	205 (1.6%)	150 (13.7%)	50 (0.8%)	29 (8.0%)	155 (2.4%)	121 (16.5%)
<b>Cancer stage</b>						
I	4987 (39.8%)	13 (1.2%)	2403 (39.1%)	3 (0.8%)	2584 (40.5%)	10 (1.4%)
IIA	3867 (30.9%)	114 (10.4%)	1938 (31.5%)	34 (9.4%)	1929 (30.2%)	80 (10.9%)
IIB	1785 (14.2%)	213 (19.4%)	893 (14.5%)	76 (20.9%)	892 (14.0%)	137 (18.7%)
III	1639 (13.1%)	603 (55.0%)	857 (13.9%)	224 (61.7%)	782 (12.3%)	379 (51.6%)
Unknown	250 (2.0%)	154 (14.0%)	60 (1.0%)	26 (7.2%)	190 (3.0%)	128 (17.4%)
<b>Biological subtype</b>						
HR +ve, HER2 -ve	8227 (65.7%)	440 (40.1%)	3913 (63.6%)	131 (36.1%)	4314 (67.6%)	309 (42.1%)
HER2 +ve (HR +ve)	1496 (11.9%)	223 (20.3%)	859 (14.0%)	75 (20.7%)	637 (10.0%)	148 (20.2%)
HER2 +ve (HR -ve)	1012 (8.1%)	131 (11.9%)	509 (8.3%)	50 (13.8%)	503 (7.9%)	81 (11.0%)
Triple-negative	1347 (10.8%)	158 (14.4%)	678 (11.0%)	46 (12.7%)	669 (10.5%)	112 (15.3%)
Unknown	446 (3.6%)	145 (13.2%)	192 (3.1%)	61 (16.8%)	254 (4.0%)	84 (11.4%)
Median tumour size, cm (range)	2.0 (0.01-19.1)	4.0 (0.55-20.0)	2.0 (0.01-19.1)	4.1 (0.55-20.0)	2.0 (0.01-17.0)	3.8 (0.79-20.0)

Abbreviations: +ve = positive; -ve = negative; HER2 = human epidermal growth factor receptor 2; HR = hormonal receptor; NAC = neoadjuvant chemotherapy; NOS = not otherwise specified

\* Data are shown as No. (%) or median (range)

In contrast, for patients with HER2-negative tumours or unknown HER2 status, NAC regimens most commonly consisted of anthracyclines (doxorubicin or epirubicin), administered in combination or sequentially with taxanes (paclitaxel or docetaxel).

### Responses to neoadjuvant chemotherapy

#### Rates of pathological complete response

Two hundred and twenty-one (20.1%) of 1097 breast cancer cases treated with NAC achieved pCR in the breast and axillary lymph nodes. Subsequent analysis according to biological subtype revealed that outcomes were optimal in patients with HER2-positive (ER-negative and PR-negative) tumours, among which nearly half (46.0%) achieved pCR. Pathological complete response rates in luminal B (HER2-positive) and triple-negative subtypes were 29.4% and 29.3%, respectively; these were significantly higher than the rates in other hormone-positive subtypes (all  $P < 0.05$ ; Fig 2).

Factors significantly associated with pCR included ER/PR negativity and HER2 positivity. Within the HER2-positive population, pCR was more common for hormone receptor-negative tumours than for hormone receptor-positive tumours; it was also more common in patients who received trastuzumab. Other factors (eg, age, menopausal status, clinical tumour and nodal stages, ER status, and Ki-67 proliferation index) did not appear to influence the achievement of pCR.

#### Rates of breast-conserving surgery

Figure 3 shows the proportions of patients treated with NAC who subsequently underwent different

types of breast surgery, categorised according to clinical cancer stages. Patients with clinical stage IIA disease were most likely to switch from mastectomy to BCS after NAC; 53.9% underwent BCS after NAC, compared with 38.2% of patients with stage IIA disease who did not receive NAC. The second highest proportion was observed among patients with clinical stage IIB disease, 38.3% of whom underwent BCS after NAC. Even among patients with clinical stage III disease, 14.1% underwent BCS after NAC. Significant differences in the rate of BCS were also observed between the NAC and non-NAC groups in patients with stages IIA ( $P = 0.02$ ) and IIB ( $P = 0.031$ ) disease.

#### Alterations in breast cancer biomarkers

Biomarkers were compared between diagnostic core biopsies and final surgical specimens. Excluding the 221 patients who achieved pCR after NAC, 844 breast specimens with residual tumours were evaluated after final surgery. Patients without data regarding biomarkers in either pre-chemotherapy or post-chemotherapy or both were excluded from this analysis. Alterations in ER, PR, and HER2 statuses after NAC are shown in Table 2. Most patients had no change in their ER status, but 7.6% switched from positive to negative or from negative to positive. With respect to PR status, a shift occurred in 17.4% of patients, and a shift in HER2 status was detected in 10.9% of patients. More than one-fifth (21.3%) of patients with residual tumours had a change in at least one receptor status after NAC. Ki-67 proliferation index was also evaluated; among the 297 cases assessed, 131 (44.1%) showed alterations after NAC.

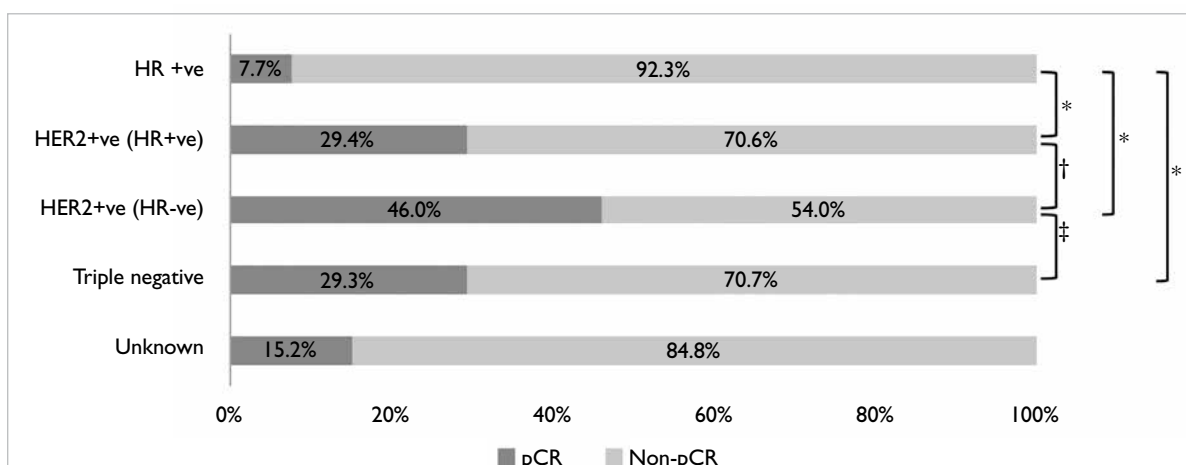


FIG 2. Proportions of breast cancer cases (n=1097) achieving pathological complete response according to biological subtype, among 1084 patients who received neoadjuvant chemotherapy

Abbreviations: +ve = positive; -ve = negative; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; pCR = pathological complete response

\*  $P < 0.001$

†  $P = 0.01$

‡  $P = 0.03$

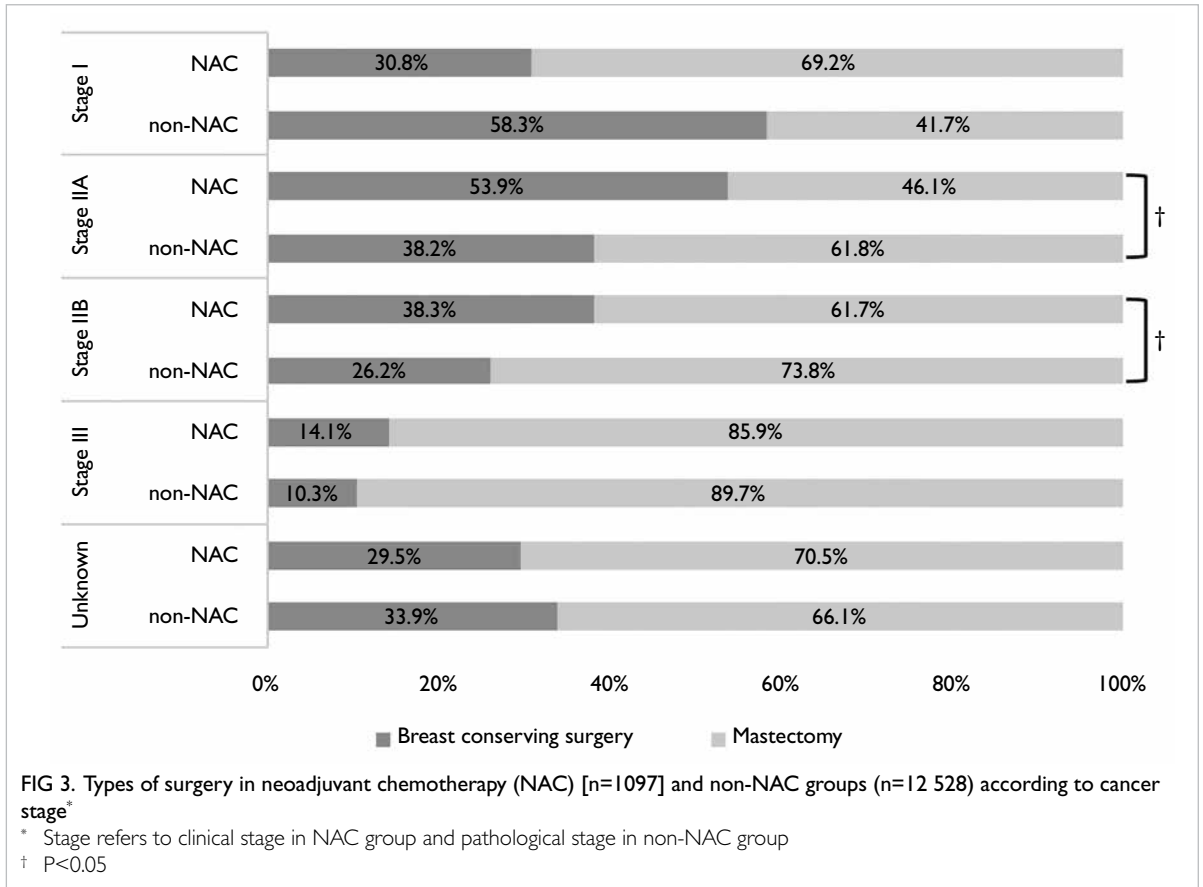


TABLE 2. Changes in breast cancer biomarkers after neoadjuvant chemotherapy\*

Biomarker status	ER (n=605)	PR (n=599)	HER2 (n=586)	Ki-67 proliferation index (n=297)
Increased	17 (2.8%)	28 (4.7%)	28 (4.8%)	3 (1.0%)
Decreased	29 (4.8%)	76 (12.7%)	36 (6.1%)	128 (43.1%)
Unchanged	559 (92.4%)	495 (82.6%)	522 (89.1%)	166 (55.9%)

Abbreviations: ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; PR = progesterone receptor

\* Data are shown as No. (%)

## Discussion

### Use of neoadjuvant chemotherapy

During the early phase of the study period, a multidisciplinary approach was not widely used for breast cancer management; thus, most treatment decisions were based on the discretion of the attending surgeon or oncologist. Nevertheless, locally advanced diseases and hormonal receptor-negative tumours were generally the targets of NAC. Over time, NAC has been increasingly accepted, as shown in updates of various national and international

guidelines (eg, National Comprehensive Cancer Network guidelines<sup>14</sup> and European Society of Medical Oncology guidelines<sup>15</sup>). This inclination clearly contributed to the substantial increase in NAC use during the periods analysed in this study: from 5.6% in 2006-2011 to 10.3% in 2012-2017.

The increased use of NAC was mainly attributed to advancements in translational research, along with new evidence from clinical trials that have led to a better understanding of breast cancer biology and the establishment of tumour biology-based targeted treatments.<sup>16</sup> After the expansion of its use in adjuvant therapy, trastuzumab was first registered for use as neoadjuvant therapy for breast cancer in 2006 under the Department of Health in Hong Kong. Its entry into the Hospital Authority Drug Formulary soon followed, and it was included in the safety net enlistment by 2009. This timeframe suggests that the drug has become accessible to a much broader spectrum of patients under the care of public sector hospitals in Hong Kong; it is also compatible with the considerable increase in use of trastuzumab over time. In our dataset, among patients with HER2-positive (non-luminal) tumours, the proportion of patients using anti-HER2 regimens in neoadjuvant therapy increased from 57.6% in 2006-2011 to 82.5% in 2012-2017.

## Pathological complete response

Neoadjuvant trials allow rapid assessment of drug efficacy; they can accelerate the development and approval of treatments for early breast cancer. Pathological complete response has been proposed as a surrogate endpoint for predictions of long-term clinical benefit.<sup>17</sup> Although it is difficult to compare outcomes among trials and individual series because of heterogeneity in terms of study design and patient populations, the results of some meta-analyses have suggested that the achievement of pCR after NAC is a predictor of overall survival, disease-free survival, and relapse-free survival.<sup>18</sup>

Our results are consistent with findings by von Minckwitz et al<sup>11</sup> and the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) meta-analysis,<sup>17</sup> which concluded that frequency of pCR was low in patients with low-grade, hormone receptor-positive tumours, whereas it was much higher among patients with more aggressive subtypes (ie, triple-negative and HER2-positive [non-luminal] tumours). Overall, these data suggest that the underlying molecular subtypes influence the rates of pathological responses. Further improvements in the rate of pCR have been observed in cases of HER2-positive (non-luminal) tumours treated with dual anti-HER2 targeted agents, as well as cases of triple-negative breast cancer treated with platinum and immunotherapy. Moreover, trials have also been done or in progress to evaluate the need for additional chemotherapy in selected patients with residual disease after NAC; the results of those trials are expected to provide further insights regarding treatments for further improving survival outcomes in neoadjuvant setting.<sup>18-20</sup>

Standard prognostic indicators, such as tumour size at the time of surgical resection or the number of involved lymph nodes, are no longer applicable in the neoadjuvant setting; systemic therapy often down-stages the disease and may lead to eradication. There is increasing evidence that the tumour response to NAC can facilitate prognostic predictions. In the multidisciplinary management of breast cancer, the identification of prognostic variables for patients receiving NAC can help to determine whether additional therapy is warranted. Given the strong support for an association between prognosis and clinicopathological features in the neoadjuvant setting, clinicians may be able to avoid additional interventions after surgery (e.g., additional chemotherapy) in patients who are otherwise considered high risk at initial presentation since pCR has been achieved. This is because although HER2-positive and triple negative breast cancers carry poor prognosis, these tumours have higher pCR rates after NAC, and pCR in HER2-positive (non-luminal) and triple-negative tumours was associated with excellent prognosis.<sup>11,17,21</sup>

## Breast-conserving surgery

Quality of life-focused research has shown that body image scores are significantly better among patients who undergo BCS than among patients who undergo mastectomy. Patients who undergo BCS are less worried about their appearance, have more freedom in their choice of clothing, feel less upset about changes in their bodies, and feel more accepted by their partners.<sup>22</sup> These findings reinforce the benefits of NAC for breast cancer in terms of down-staging the disease, increasing resectability, and enhancing BCS eligibility among patients who would otherwise require mastectomy. Furthermore, a systematic review of NAC for operable breast cancer revealed that the mastectomy rate was lower among patients who received NAC than among patients who underwent surgery prior to adjuvant chemotherapy (relative risk=0.71; 95% confidence interval [CI]=0.67-0.75); the use of NAC did not hinder local control (hazard ratio=1.12; 95% CI=0.92-1.37).<sup>23</sup> Long-term follow-up analyses also showed that preoperative chemotherapy increased rates of BCS without increasing the rates of locoregional recurrence.<sup>24,25</sup> In a previous study in Hong Kong, univariate analysis revealed that patients who achieved pCR after NAC had a higher likelihood of successful BCS (P=0.028). Pre-chemotherapy disease staging (P=0.001) and tumour size (P=0.005) were also important factors that influenced successful conversion to BCS.<sup>5</sup>

However, a recent meta-analysis by the Early Breast Cancer Trialists' Collaborative Group showed that, compared with adjuvant chemotherapy, NAC was associated with more frequent local recurrence; the 15-year rates of local recurrence were 21.4% for NAC and 15.9% for adjuvant chemotherapy (rate ratio=1.37; 95% CI=1.17-1.61; P=0.0001).<sup>8</sup> Thus, continued follow-up of patients registered in the HKBCR and updates will provide important insights with respect to NAC on long-term outcomes.

## Alterations in breast cancer biomarkers

Neoadjuvant chemotherapy can cause changes in ER, PR, and HER2 statuses, as well as the Ki-67 level, in patients with invasive breast cancer.<sup>26,27</sup> A possible explanation for this phenomenon is that chemosensitive cancer cells are destroyed by chemotherapy, whereas chemoresistant cells survive; such a change could alter the receptor status. Furthermore, because ER, PR, and HER2 are highly interdependent, a change in one receptor could lead to changes in the other receptors.<sup>28</sup> A systematic review showed that the rates of ER and/or PR discordance range from 2.5% to 51.7%; among patients who received NAC combined with trastuzumab, up to 43% exhibited a switch to HER2 negativity.<sup>29</sup>

Thus far, there are only limited data regarding the prognostic value of changes in biomarkers after NAC among patients with breast cancer.<sup>28</sup> Several groups have reported that a switch from negative to positive status (for ER, PR, or HER2) is associated with better overall survival.<sup>30,31</sup> Additionally, outcomes are better among patients with stable hormone receptor status profiles than among patients with altered profiles.<sup>32</sup> Notably, Guarneri et al<sup>33</sup> reported that patients with loss of HER2 overexpression tended to have a greater risk of relapse, compared with patients who remained HER2-positive; in contrast, a decrease in Ki-67 expression after NAC was reportedly associated with better outcomes.<sup>34</sup>

Because of the above observations, biomarkers and Ki-67 levels should be retested after NAC. Such retesting is particularly important for tumours that were ER/PR-negative and/or HER2-negative before treatment because a shift to a positive status would indicate a need for endocrine therapy and/or trastuzumab. The results of these changes may influence clinical decisions regarding subsequent treatment and help to identify patients with better outcomes after NAC.<sup>28,35</sup>

### Limitations

This study had several limitations. First, it was a retrospective analysis and the earliest records in the database were incomplete; the missing information particularly affected breast cancer biomarkers, and Ki-67 was not routinely tested in Hong Kong public hospitals. Second, selection bias may have been present because the receipt of NAC was largely dependent on surgeon assessment and patient preference. In recent years, the potential for such bias has decreased because multidisciplinary management of breast cancer is gradually becoming the preferred approach. Considering the complexities of treatment planning, monitoring, and evaluation, decisions regarding preoperative systemic therapy require input from surgeons, oncologists, radiologists, and pathologists. Of note, the comparison of rates of surgery types between NAC and non-NAC groups can only be regarded as approximation, as assignment of patients into these two groups is not randomised; furthermore, clinical stages may differ from pathological stages, thus they may not be comparable.

### Conclusion

Changes in the clinical management of breast cancer led to increased use of NAC in Hong Kong during the period of 2006 to 2017. Neoadjuvant chemotherapy was effective in tumour down-staging; one-fifth of patients subsequently achieved pCR in the breast and axillary lymph nodes. In particular, higher rates of pCR were detected in HER2-positive (non-

luminal) and triple-negative subtypes. After NAC, greater proportions of patients with clinical stage IIA or IIB disease underwent BCS. Currently, post-NAC adjustments to treatment are based on whether pCR has been achieved. In the future, alterations in breast cancer biomarkers after NAC may provide useful guidance regarding further adjuvant therapy. The indications for NAC have expanded from the treatment of locally advanced breast cancers (to facilitate surgery) to the down-staging of early disease, thereby facilitating BCS. Under the care of a multidisciplinary team, patients with early breast cancer who have an appropriate indication should consider receiving NAC before surgery. Further studies are warranted to evaluate the benefits of individual NAC regimens.

### Author contributions

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Analysis or interpretation of data: All authors.

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All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

### Conflicts of interest

All authors have disclosed no conflicts of interest.

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### Ethics approval

Ethics approval for this study has been obtained from the following six approving bodies:

1. The Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee, Hong Kong (Ref No.: CRE-2009.037)
2. Kowloon West Cluster Research Ethics Committee, Hospital Authority, Hong Kong (Ref No.: KW/EX/08-090)
3. Research Ethics Committee (Kowloon Central/ Kowloon East), Hospital Authority, Hong Kong (Ref No.: KC/KE-09-0013/ER-3)
4. Hong Kong East Cluster Research Ethics Committee,



- Hospital Authority, Hong Kong (Ref No.: HKEC-2010-004)
- New Territories West Cluster Clinical & Research Ethics Committee, Hospital Authority, Hong Kong (Ref No.: (8) in NTWC/CREC/866/10)
  - Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster, Hong Kong (Ref No.: UW 09-378)

Written consent was also obtained from all patients in the study who were recruited from the participating hospitals and clinics.

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