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EPIDEMIOLOGY

Patterns of relapse after neoadjuvant chemotherapy in breast cancer: implications for surveillance in clinical practice

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Abstract

Purpose This study aimed to identify patterns of relapse after neoadjuvant chemotherapy (NAC) for breast cancer to refine follow-up recommendations.

Methods Retrospective analysis on 523 breast cancer patients treated with NAC at two public hospitals in Singapore between 2000 and 2014.

Results Majority of patients (71.9%) had locally advanced disease. Median follow-up was 55 months. 5-year recurrence rate was significantly higher in triple negative breast cancer (TNBC) than non-TNBC subtypes (38.4% vs. 29.5%; $p=0.042$); 85% of recurrences involved distant sites. Among TNBC and HR (hormone receptor)-/HER2+ subtypes, 97.0% and 95.0% of relapses occurred within 3 years from diagnosis respectively while 10.6% of relapses among HR+ subgroup occurred beyond 5 years. Recurrence risk in high-grade tumours decreased with time. Stage III at diagnosis (hazard ratio = 2.94; $p<0.001$), grade 3 tumours (hazard ratio = 2.87; $p=0.018$), not achieving pathologic complete response (pCR) (hazard ratio = 8.77; $p=0.003$) and not receiving adjuvant radiotherapy (hazard ratio = 3.19; $p<0.001$) were independent predictors of inferior recurrence-free survival. Serum CA 15-3 was raised in 49% of patients upon relapse; it correlated with inferior post-relapse survival (median 11 months vs. 22 months; $p=0.019$).

Conclusions While more intensive follow-up during the first 3 years may be required for patients who do not achieve pCR, especially those with TNBC and HR−/HER2+ tumours, the benefit from blood tests such as CA 15-3 appears limited, and the benefit from intensification of surveillance remains to be addressed in prospective studies on high-risk patients.

Keywords Neoadjuvant chemotherapy · Breast cancer · Recurrence · Surveillance

Background

Neoadjuvant chemotherapy (NAC) is often used to facilitate breast-conserving surgery and improve surgical outcomes for patients with locally advanced breast cancer (LABC). In addition, NAC can help to eradicate micrometastatic disease and serve as an in vivo model to test chemosensitivity while providing similar survival benefits to adjuvant chemotherapy [1–4]. Achieving pathologic complete response (pCR) after neoadjuvant chemotherapy is associated with superior survival outcomes [5, 6], with higher rates of pCR in human epidermal growth factor receptor 2 positive (HER2+) and triple negative breast cancer (TNBC) subtypes compared to hormone receptor (HR)-positive subtypes [6].

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Despite achieving pCR after NAC, studies have shown that TNBC patients have poorer survival compared to other subtypes [7, 8]. Patients who achieve pCR also remain at significant risk of relapse, with studies reporting 5-year disease-free survival (DFS) rates of 75–87% [1, 9–11]. A retrospective study of 88 Japanese patients who achieved pCR reported a recurrence rate of 13.6% and all relapses occurred within 32 months from diagnosis [12]. Several of these studies [1, 9–11] were conducted on patient cohorts who did not receive chemotherapy regimens containing both anthracycline and taxanes, or did not incorporate neoadjuvant HER2-targeted therapy.

A meta-analysis comprising 4756 patients from ten randomised trials from 1983 to 2002 found that patients who received NAC had a higher 15-year local recurrence risk compared to those who received adjuvant chemotherapy (21.4% vs. 15.9%) although there was no significant difference for distant recurrence risk, breast cancer mortality or death from any cause [4]. However, long-term outcomes in the more recent post-trastuzumab era remain relatively limited [13, 14]. Little is known about the patterns of relapse post-NAC especially in the real world, and where there is a higher proportion of locally advanced breast cancers in parts of Asia.

There are currently no specific guidelines for post-treatment follow-up of patients treated with NAC and variations in practice exist. This study aims to evaluate the relapse risks in different subgroups of breast cancers treated with NAC and identify the associated time trends and patterns of relapse in these patients, such as the sites involved, CA 15-3 levels and liver function tests at relapse. These findings may potentially lead to the development of risk-adapted surveillance strategies for patients treated with NAC.

Materials and methods

Study population

A total of 523 female breast cancer patients who received NAC between 2000 and 2014 were identified from two public healthcare institutions in Singapore, namely National Cancer Centre Singapore and KK Women's and Children's Hospital. Exclusion criteria included patients with metastatic disease at diagnosis, those who did not undergo subsequent curative intent breast surgery, those who received neoadjuvant hormonal therapy, and those who had incomplete treatment information. A total of 17 patients were excluded: 10/17 had unknown stage, 6/17 had incomplete receptor status, and 7/17 had missing treatment information. For patients with synchronous bilateral breast cancers, the clinicopathological characteristics of the tumour with the higher stage were included.

Data collection

Clinicopathological data including patient demographics, T stage, N stage, tumour grade, estrogen receptor (ER), progesterone receptor (PR), HER2 status and pathological response to NAC were collected through retrospective review of medical records. If pre-treatment biopsy tumour grade was not available, post-treatment grade was recorded. ER, PR and HER2 status were based on the diagnostic biopsy for the analyses in this study. ER and PR status were determined via immunohistochemical staining. Of note, there was a change in definition of ER and PR positivity in 2010 as recommended by American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP): positive hormonal receptor status defined as when 1% or more cells stained positive, whereas prior to that positivity was defined as when at least 10% of the lesional cells display a minimal 2+ nuclear staining pattern [15]. Tumours were classified as HR-positive if they were positive for either ER or PR, and HR-negative if they were negative for both ER and PR. HER2 status was based on fluorescence in situ hybridization (FISH) or immunohistochemistry (IHC) if FISH was not performed. HER2 positive was defined as FISH positive or IHC score of 3+, negative was defined as FISH negative or IHC scored of 0 or 1+, while equivocal was defined as IHC score of 2+ without confirmatory FISH test, or equivocal HER2 FISH result. Prior to 2013, HER2 positivity was defined as tumours with more than 30% of cells with IHC score of 3+. However, none of the patients in our study were affected by the change in definition of HER2 positivity.

All breast cancers were staged according to the 7th edition of TNM classification by American Joint Committee on Cancer (AJCC). pCR was defined as no invasive residual disease in both breast and axillary lymph nodes but allowed for in situ disease.

Patients were followed up from date of diagnosis until date of death or date of last follow-up, whichever occurred first. Survival data were gathered from hospitals' medical records. The cut-off date for the analysis was 31 July 2017.

Statistical analysis

Descriptive statistics were used to describe baseline characteristics. Patients were divided into four subtypes by receptor status of pre-treatment biopsy specimens for analyses: HR-positive/HER2-negative (HR+/HER2−), HR-positive/HER2-positive (HR+/HER2+), HR-negative/HER2-positive (HR−/HER2+) and TNBC. End points defined in this study were recurrence risk, time to local

recurrence, time to distant recurrence, recurrence-free survival (RFS), post-relapse survival (PRS) and overall survival (OS).

RFS was defined as the time from diagnosis to relapse or death, whichever occurred first. OS was defined as the time from diagnosis to death from any cause. PRS was defined as the time from relapse to death. For each endpoint, patients who had not experienced any events had their survival time censored at last follow-up. Time to relapse, OS and PRS distributions were estimated for each subtype using the Kaplan–Meier method. For each endpoint, the distributions among subtypes were compared using the log-rank test. Univariable and multivariable Cox regression analyses were performed for RFS. The proportional hazards assumption was checked for each model and hazard ratio tabulated accordingly. Where the assumption was violated, we re-fitted a model with time-varying coefficients.

All statistical analyses were done using STATA version 15.0 statistical software (StataCorp, College Station, TX), and a two-sided $p < 0.05$ was considered statistically significant.

Results

Clinicopathological features

A total of 523 patients were included in the analysed dataset. Four patients had synchronous bilateral breast cancers, none had tumours with the same stage and only the tumour with the higher stage was included. Baseline patient characteristics and treatment received are summarised in Table 1. The median age at diagnosis was 52. The distribution across ethnic groups largely reflects population demographics in Singapore with Chinese forming the majority (356/523, 68.1%), followed by Malays (91/523, 17.4%). Majority of the tumours were invasive ductal carcinoma (477/523, 91.2%). Among tumours with known histological grade, approximately half (193/384, 50.3%) were grade 3, followed by grade 2 (160/384, 41.7%) then grade 1 (31/384, 8.1%). Grade was unknown for 139/523 (26.6%) of patients as histological grade was not routinely performed on all breast biopsy specimens and hence was unknown for a subset of patients whose grade in surgical specimens could not be assessed due to post-chemotherapy effect or pathological complete response. Majority of the patients had locally advanced disease—405/523 (77.4%) were T3/T4 and 406/523 (77.6%) were node positive, with 376/523 (71.9%) being clinical stage III at diagnosis. Histologically, 257/523 (49.1%) were HR+/HER2−, 85/523 (16.3%) were HR+/HER2+, 83/523 (15.9%) were HR−/HER2+ and 91/523 (17.4%) were TNBC. Out of 523 patients, 7 (1.3%) patients had equivocal HER2 status. The higher proportion of HER2-positive and

Table 1 Clinical and pathological characteristics, including treatment details ($n = 523$)

Characteristics	Number	Percentage (%)
Median age at diagnosis (range) (years)	52 (23–78)	
Age (years)		
≤ 35	37	7.1
36–50	202	38.6
51–65	240	45.9
> 65	44	8.4
Time of diagnosis		
Before 2006	64	12.2
From 2006 onward	459	87.8
Ethnicity		
Chinese	356	68.1
Malay	91	17.4
Indian	33	6.3
Other	43	8.2
Tumour histology		
Invasive ductal carcinoma	477	91.2
Invasive lobular carcinoma	20	3.8
Mixed invasive ductal/lobular carcinoma	10	1.9
Other	16	3.1
Grade		
1	31	5.9
2	160	30.6
3	193	36.9
Unknown	139	26.6
Clinical stage (AJCC 7th edition)		
IA	4	0.8
IIA	40	7.6
IIB	103	19.7
IIIA	131	25
IIIB	191	36.5
IIIC	54	10.3
Receptor status		
HR+/HER2−	257	49.1
HR+/HER2+	85	16.3
HR−HER2+	83	15.9
TNBC	91	17.4
HER2 equivocal	7	1.3
Category of neoadjuvant chemotherapy		
Anthracycline and taxane-based	393	75.1
Anthracycline-based only	86	16.4
Taxane-based only	36	6.9
Other	8	1.5
Use of neoadjuvant HER2-directed therapy		
No	38	22.6
Yes	130	77.4
Type of breast surgery		
Mastectomy	459	87.8

Table 1 (continued)

Characteristics	Number	Percentage (%)
Breast conserving surgery	64	12.2
Adjuvant radiation therapy		
No	36	6.9
Yes	487	93.1
Achieved pCR		
No	418	79.9
Yes	105	20.1

TNBC patients in this cohort of patients treated with NAC is likely related to a higher representation of more aggressive HER2+ and TNBC subtypes among the locally advanced breast cancer patients, as well as a greater tendency for these patients to be referred for neoadjuvant chemotherapy, given the higher pCR rates with chemotherapy and anti-HER2 therapy for HER2+ patients.

Treatment received

Of the 523 patients in our entire cohort, 393 (75.1%) received both anthracycline and taxane-based chemotherapy as their neoadjuvant treatment. Among the 168 HER2-positive patients, 130 (77.4%) received neoadjuvant HER2-directed therapy—of which 123/130 (94.6%) received trastuzumab alone and 7/130 (5.4%) received dual HER2-blockade with trastuzumab and either pertuzumab or lapatinib. Out of 148 patients with HER2+ tumours diagnosed from 1 Jan 2006 onwards, 128 (86.5%) received neoadjuvant HER2-directed therapy.

Overall, 105/523 (20.1%) of patients achieved pCR. pCR rate was highest in HR−/HER2+ (35/83, 42.2%), followed by TNBC (24/91, 26.4%), HR+/HER2+ (21/85, 24.7%) and HR+/HER2− (25/257, 9.7%). These differences were statistically significant ($p < 0.001$).

Most patients underwent mastectomy (459/523, 87.8%) and 93.1% (487/523) received adjuvant radiation therapy. Most patients (428/523, 81.8%) did not receive adjuvant chemotherapy.

Patterns of recurrence

Patients were followed up for a median of 55 months. At the time of analysis, 157/523 (30.0%) of patients had relapsed, of which 146/157 (93.0%) occurred within 5 years of diagnosis. The relapsed cases subdivided by receptor status are as shown in Table 2.

By receptor status

The cumulative recurrence risk with time by subtype is as shown in Fig. 1a. At 5 years, TNBC had the highest recurrence rate at 38.4%, followed by HR+/HER2− at 31.0%, HR+/HER2+ at 28.5% and lastly HR−/HER2+ at 25.3% ($p = 0.175$). There was a statistically significant difference in recurrence risk between TNBC compared to the 3 other subtypes (5-year recurrence risk 38.4% vs. 29.5%; $p = 0.042$) as shown in Fig. 1b. TNBC and HR−/HER2+ subtypes were at risk of early relapse, with 97.0% (32/33) and 95.0% (19/20) of relapses occurring within 3 years from initial diagnosis respectively. However, recurrence risk declined sharply after the first 3 years. In contrast, HR+/HER2− and HR+/HER2+ subtypes had 65.8% (52/79) and 70.8% (17/24) of relapses occurring within 3 years from initial diagnosis respectively. Out of the 104 HR+ patients who relapsed (regardless of HER2 status), 10.6% (11/104) occurred after 5 years. Cumulative recurrence risk gradually increased with time and plateaued at 7 to 10 years from diagnosis, reflecting the potential for late relapses in HR+ subgroup regardless of HER2 status.

By pCR status

Of the 157 patients who relapsed, 4.5% had achieved pCR and 95.5% had not achieved pCR. 5-year recurrence risk was 6.8% for patients who achieved pCR versus 36.3% for

Table 2 Relapsed cases by receptor status

	All patients ($N = 523$[a])	Subtype by receptor status			
		HR+/HER2− ($n = 257$)	HR+/HER2+ ($n = 85$)	HR−/HER2+ ($n = 83$)	TNBC ($n = 91$)
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Relapsed					
No	365 (69.8)	178 (69.3)	60 (70.6)	63 (75.9)	58 (63.7)
Yes	157[b] (30.0)	79 (30.7)	24 (28.2)	20 (24.1)	33 (36.3)
Unknown	1 (0.2)	0	1 (1.2)	0	0

[a]Seven of these patients had equivocal HER2 status

[b]One of these patients had equivocal HER2 status

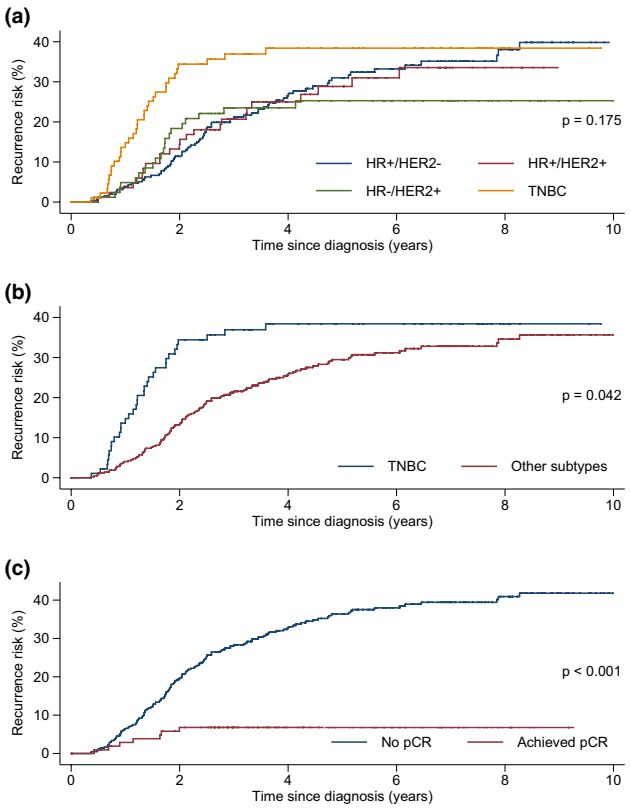

Fig. 1 Cumulative recurrence risk with time stratified by **a** receptor status, **b** TNBC versus other subtypes, **c** pCR status

those who did not ($p < 0.001$) as shown in Fig. 1c. Of the 150 patients who did not achieve pCR who relapsed, 114 (76.0%) occurred within 3 years of diagnosis. Of the seven patients who achieved pCR who relapsed, one was HR+/HER2−, three were HR+/HER2+, one was HR−/HER2+ and two were TNBC—all occurred within 2 years from diagnosis.

RFS and risk factors

Univariable and multivariable cox regression analyses were performed for RFS as shown in Table 3. Using univariable analysis, stage III at diagnosis (hazard ratio 2.99 (1.80–4.99), $p < 0.001$), grade 3 tumours (hazard ratio 2.54 (1.10–5.83), $p = 0.028$), not achieving pCR (hazard ratio 7.28 (1.80–29.45), $p = 0.005$), not receiving adjuvant radiation therapy (hazard ratio 2.75 (1.54–4.89), $p = 0.001$) and TNBC subtype (hazard ratio 1.83 (1.17–2.86), $p = 0.008$) correlated significantly with inferior RFS. Grade 2 tumours showed a non-significant trend towards inferior RFS compared to Grade 1 (hazard ratio 1.56 (0.67–3.66), $p = 0.306$), but still had a significantly better RFS compared to G3 tumours (hazard ratio 1.63 (1.12–2.35) for grade 3 versus grade 2, $p = 0.010$). Diagnosis from 2006 onward (after neoadjuvant and/or adjuvant trastuzumab, taxanes and aromatase inhibitors were routinely administered) was associated with improved RFS on univariable analysis (hazard ratio 0.59 (0.38–0.90), $p = 0.015$). On multivariable analysis, stage III at diagnosis (hazard ratio 2.94 (1.72–5.05), $p < 0.001$), not achieving pCR (hazard ratio 8.77 (2.14–35.93), $p = 0.003$) as well as not receiving adjuvant radiation therapy (hazard ratio 3.19 (1.75–5.84), $p < 0.001$) predicted for worse RFS. Importantly, although grade 3 tumours had a significantly poorer RFS in the first 5 years from diagnosis using multivariate analysis, the risk of relapse became significantly lower than Grade 1 tumours beyond 5 years.

Sites of recurrence at initial diagnosis of relapse

Out of the 157 patients who relapsed, most patients relapsed with distant metastases (85.4%). TNBC subgroup had the lowest probability of isolated local recurrence at 3% (1/33), whereas HR+/HER2− subgroup had the highest probability at 20.3% (16/79). However, there was no statistically significant difference in relapse patterns between the various subtypes overall ($p = 0.191$). Among the 134 patients who had distant metastases (either in isolation or with local recurrence), bones, lymph nodes and lung/pleura were the most common sites at initial diagnosis of relapse. Liver metastases appeared to be most common in TNBC (16/32, 50.0%) and brain metastases more common in HER2+ patients (6/17, 35.3% for HR−/HER2+ and 6/21, 28.6% for HR+/HER2+). The sites of recurrence at initial diagnosis of relapse are shown in Table 4.

Among the patients who had CA 15-3 tested at time of relapse, 49.0% (49/100) had raised levels. There was no statistically significant difference between the various subtypes ($p = 0.453$) in frequency of raised CA 15-3. Comparing patients with visceral metastases versus those who had no visceral metastases, there was also no statistically significant difference in frequency of raised CA 15-3 levels ($p = 0.729$).

Among the 138 patients who had liver function tests (LFT) done at time of relapse, 75 (54.3%) had abnormal results. Of the various components of LFT, Aspartate Aminotransferase (AST) and Alkaline Phosphatase (ALP) were the most commonly deranged at 32.5% and 28.7% respectively, followed by Alanine Aminotransferase (ALT) (15.9%), Gamma-glutamyl Transferase (GGT) (12.1%) and Bilirubin (6.4%) (Table 5). Raised ALP was positively associated with liver metastases ($p < 0.001$) although there was no association with bone metastases ($p = 0.638$).

Survival outcomes after relapse

Overall, there was no significant difference in OS from initial diagnosis among the various subtypes ($p = 0.103$), with 5-year survival rate exceeding 50% within each subtype as shown in Fig. 2a. However, there was a significant

Table 3 Univariable and multivariable cox regression analysis for relapse free survival (RFS)

Variables	Time (years)	Univariable model		Multivariable model	
		Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Age (years)					
≤ 35		1	–	1	–
36–50		0.96 (0.41–2.25)	0.92	0.82 (0.34–1.97)	0.652
51–65		1.30 (0.56–2.99)	0.541	0.75 (0.32–1.79)	0.522
> 65		1.14 (0.42–3.09)	0.794	0.76 (0.27–2.12)	0.601
Overall stage					
I, II		1	–	1	–
III		2.99 (1.80–4.99)	< 0.001	2.94 (1.72–5.05)	< 0.001
Grade[a]					
1		1	–	1	–
2		1.56 (0.67–3.66)	0.306	1.53 (0.64–3.64)	0.34
3		2.54 (1.10–5.83)	0.028		
	≤ 5			2.87 (1.20–6.88)	0.018
	> 5			0.21 (0.06–0.73)[b]	0.014
Receptor status					
HR+/HER2−		1	–	1	–
HR+/HER2+		0.88 (0.52–1.50)	0.646	0.91 (0.53–1.56)	0.72
HR−/HER2+		1.08 (0.60–1.91)	0.805	0.82 (0.45–1.48)	0.504
TNBC		1.83 (1.17–2.86)	0.008	1.32 (0.80–2.18)	0.274
Achieved pCR					
Yes		1	–	1	–
No		7.28 (1.80–29.45)	0.005	8.77 (2.14–35.93)	0.003
Adjuvant radiation therapy					
Yes		1	–	1	–
No		2.75 (1.54–4.89)	0.001	3.19 (1.75–5.84)	< 0.001
Time of diagnosis					
Before 2006		1	–	1	–
From 2006 onward		0.59 (0.38–0.90)	0.015	0.90 (0.57–1.43)	0.664

[a]Proportional hazards assumption was violated for this variable in multivariable analysis. Hence, the analysis was adjusted to time period, with a chosen cut-off of 5 years

[b]This is the interaction term between grade and time and means that the hazard ratio for grade 3 decreased by 79% (= 1 − 0.21) after 5 years, i.e. from 2.87 to 0.60

difference within the first 5 years from diagnosis with TNBC having the poorest survival ($p = 0.004$). PRS was poorest for TNBC with median PRS of 8.2 months followed by HR−/HER2+ at 9.6 months, HR+/HER2− at 20.5 months and HR+/HER2+ at 21.8 months ($p = 0.023$) as shown in Fig. 2b. Among the HR+/HER2− subgroup, patients who relapsed between 2 and 4 years and beyond 4 years had a significantly improved PRS (median PRS 24.4 months (14.2–37.2 months), hazard ratio 0.55; $p = 0.048$ and median PRS 30.1 months (15.3–undefined months), hazard ratio 0.38; $p = 0.028$ respectively) compared to patients who relapsed within 2 years from diagnosis (median PRS 9.1 months (5.4–11.9 months). Patients with raised CA- 15-3 at time of relapse had significantly worse PRS compared to those with normal CA 15-3 levels (median PRS 11 months vs. 22 months, $p = 0.019$) as shown in Fig. 2c. There was no significant difference in PRS between patients who achieved pCR versus those who did not ($p = 0.280$).

Discussion

While NAC has improved surgical outcomes for many breast cancer patients in recent decades, the risk of relapse remains high especially for patients with locally advanced breast cancer and for those who do not achieve pCR. The American Society of Clinical Oncology (ASCO) guidelines recommend surveillance by history and physical examination every 3–6 months during the first 3 years after primary therapy, every 6–12 months for the next 2 years and then

Table 4 Sites of recurrence at initial diagnosis of relapse

Sites of recurrence	All relapse patients ($N=157$[a])	HR+/HER2− ($n=79$)	HR+/HER2+ ($n=24$)	HR−/HER2+ ($n=20$)	TNBC ($n=33$)
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Local only	23 (14.6)	16 (20.3)	3 (12.5)	3 (15.0)	1 (3.0)
Distant only	96 (61.1)	43 (54.4)	17 (70.8)	14 (70.0)	21 (63.6)
Both	38 (24.2)	20 (25.3)	4 (16.7)	3 (15.0)	11 (33.3)
Sites of local recurrence	($N=61$)	($n=36$)	($n=7$)	($n=6$)	($n=12$)
Chest wall only	38 (62.3)	21 (58.3)	6 (85.7)	3 (50.0)	8 (66.7)
Ipsilateral lymph nodes	31 (50.8)	18 (50.0)	4 (57.1)	3 (50.0)	6 (50.0)
Chest wall and ipsilateral lymph nodes	11 (18.0)	5 (13.9)	3 (42.9)	0	3 (25.0)
Breast	7 (11.5)	4 (11.1)	0	1 (16.7)	2 (16.7)
Breast and ipsilateral lymph nodes	3 (4.9)	2 (5.6)	0	1 (16.7)	0
Sites of distant recurrence	($N=134$[a])	($n=63$)	($n=21$)	($n=17$)	($n=32$)
Visceral					
Lung/pleura	60 (44.8)	29 (46.0)	9 (42.9)	6 (35.3)	16 (50.0)
Liver	36 (26.9)	15 (23.8)	4 (19.0)	1 (5.9)	16 (50.0)
Brain	25 (18.7)	6 (9.5)	6 (28.6)	6 (35.3)	7 (21.9)
Leptomeningeal	2 (1.5)	1 (1.6)	0	1 (5.9)	0
Others	16 (11.9)	9 (14.3)	1 (4.8)	0	6 (18.8)
Non-visceral					
Soft tissue	15 (11.2)	10 (15.9)	1 (4.8)	0	4 (12.5)
Lymph nodes	61 (45.5)	27 (42.9)	9 (42.9)	6 (35.3)	18 (56.3)
Bone	61 (45.5)	31 (49.2)	13 (61.9)	7 (41.2)	10 (31.3)

[a]One of these patients had equivocal HER2 status

Table 5 Liver function test at relapse

	All relapse patients ($N=157$[a])	Subtype by receptor status			
		HR+/HER2−	HR+/HER2+	HR−/HER2+	TNBC
		($n=79$)	($n=24$)	($n=20$)	($n=33$)
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Abnormal LFT	75 (47.8)	36 (45.6)	8 (33.3)	10 (50.0)	20 (60.6)
ALP	45 (28.7)	22 (27.8)	3 (12.5)	3 (15.0)	16 (48.5)
GGT	19 (12.1)	7 (8.9)	3 (12.5)	6 (30.0)	3 (9.1)
AST	51 (32.5)	24 (30.4)	6 (25.0)	7 (35.0)	14 (42.4)
ALT	25 (15.9)	11 (13.9)	3 (12.5)	3 (15.0)	8 (24.2)
Bilirubin	10 (6.4)	7 (8.9)	0	1 (5.0)	2 (6.1)

[a]One of these patients had equivocal HER2 status

annually. The European Society for Medical Oncology (ESMO) recommends regular visits every 3–4 months in the first 2 years, every 6 months from years 3 to 5 and annually thereafter. Routine blood tests are not recommended and mammography is the only recommended imaging for routine breast cancer surveillance. However, variations in clinical practice exist, and it is not clear whether patients treated with NAC should be monitored post-treatment any differently.

Our results suggest that there are differences in patterns of relapse and post-relapse survival among the different subtypes and are consistent with observations seen in other study populations. A series of 956 patients treated from 1981 to 1998 [16] at a single centre in France demonstrated that at 6 months, the risk of recurrence for HR-positive patients was 74% lower compared with HR-negative group but became 30% higher at the 5 year mark and more than double at 10 years. However, data on HER2 status was

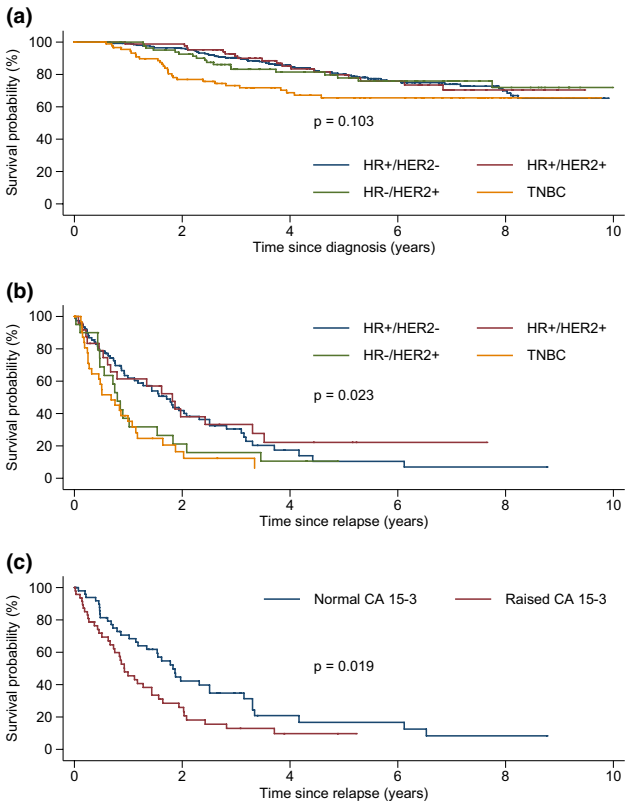

Fig. 2 **a** Overall survival stratified by receptor status; **b** post-relapse survival stratified by receptor status; **c** post-relapse survival stratified by CA 15-3 levels

not available, and outcome data from a more contemporary series receiving current standard-of-care therapies is needed. In our cohort, although patients with TNBC and HR−/HER2+ subtypes had higher rates of pCR, these patients had significantly worse post-relapse survival with a median of 8.2 months and 9.6 months, respectively (Fig. 2b). These two subgroups were also prone to early distant relapse within 3 years of diagnosis compared to HR+ patients who were at risk of late relapses beyond 5 years. Of note, Grade 3 tumours in our study cohort had significantly poorer RFS within 5 years of diagnosis using multivariate analysis although the relationship was inverted beyond 5 years. This suggests that biologically aggressive tumours are prone to early relapse, whereas relatively indolent tumours tend to relapse later.

It has been shown that pCR after NAC can be used as a surrogate marker for DFS and OS [6, 17]. In our series, we also found that patients who did not achieve pCR had a significantly higher 5-year relapse risk compared to patients with pCR (36.3% vs. 6.8%; $p < 0.001$) and 76.0% occurred within 3 years of diagnosis. Not achieving pCR also predicted for poorer RFS on multivariable analysis, consistent with findings in previous studies. Compared to older studies which report a 5-year recurrence rate of 13.6–14.1% [12, 18] or DFS rate of 75–87% [1, 9–11] among patients who achieved pCR, the 5-year recurrence risk of 6.8% among our patients who achieved pCR is generally lower in our series, likely reflecting the better survival outcomes achieved from the use of trastuzumab for HER2+ tumours and anthracyclines plus taxanes in the curative setting.

Majority of the patients in our study relapsed with distant metastases, with bones, lymph nodes and lung/pleura being the most common sites. Randomised controlled trials have failed to show any benefit of routine imaging over mammography in detecting early relapse or improving survival and are at the expense of higher healthcare costs [19–21], although none of these studies looked specifically at patients treated with NAC. A large retrospective study of 1145 patients [22] suggested that symptoms were the primary indicator of relapse in 57.6% of breast cancer patients. A French retrospective study [23] also showed that 47.2% of breast cancer recurrences detected were symptomatic, with bone and lung symptoms being the two most frequent. However, 134 (43.6%) of patients were asymptomatic at time of relapse, of which 57 patients (42.5%) had recurrence detected via raised CA 15-3.

CA 15-3 is a tumour marker commonly used to monitor treatment response in breast cancer patients in the metastatic setting. Although its use is not recommended by major guidelines such as ASCO/ESMO for routine screening purpose, clinical practice varies widely. In our cohort, CA 15-3 had limited sensitivity as it was only raised in approximately half of the patients at time of relapse. Post-relapse survival was shorter when CA 15-3 levels were raised. These findings suggest that CA 15-3 may have limited impact in surveillance, supporting previous studies which have demonstrated that there is no benefit in terms of survival, quality of life or cost–benefit with intensive follow-up with CA 15-3 [19–21]. A multicentre randomised Phase III Japanese trial (INSPIRE), which compares intensive versus standard post-operative surveillance in high-risk breast cancer patients, is currently ongoing and aims to confirm whether early detection of distant metastases by intensive follow-up incorporating cross-sectional imaging and tumour markers prolongs OS [24]. We await the results of this trial to confirm the utility of CA 15-3 monitoring in patients at higher risk of relapse, including patients who require neoadjuvant chemotherapy before surgery.

Our series also looked at liver function tests done at time of relapse; 54.3% had abnormal results, of which AST was the most commonly deranged at 32.5% followed by ALP at 28.7%. These results are surprising given that liver metastases were only seen in 27.4%, whereas bone metastases were seen in 45.9%. Even though raised ALP was found to have a significant positive correlation with liver metastases, this was not seen with bone metastases. This reflects the lack of

sensitivity and specificity of liver function tests and support current guidelines which do not recommend routine surveillance blood tests.

Strengths of this study are that it shows real-world data in patients treated with neoadjuvant chemotherapy, which differs from clinical trials that tend to focus on a particular subtype with specific neoadjuvant treatments, smaller tumours and/or fitter patients. Patients also received standard-of-care treatment and clinicopathological details were available. Limitations of this study include incomplete data pertaining to grade for some patients, the heterogeneous treatments administered as well as a relatively short median duration of follow-up for the more recent cohort of patients. Being a retrospective study, it was not possible to collect pre-set data points such as the trend of CA 15-3 trend over time, especially since CA 15-3 is not routinely monitored at our institutions as per American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guidelines [25].

Conclusion

In conclusion, breast cancer patients who receive NAC are a heterogenous population who have differing patterns of relapse as well as survival outcomes. Given the increasing use of NAC including HER2-directed therapy, the challenge is in developing the optimum surveillance strategy for this group of patients with varying risks of relapse. Based on our findings, patients with high grade tumours, higher clinical stage at diagnosis, TNBC and HR−/HER2+ subtypes, as well as those who did not achieve pCR are prone to early relapse within 3 years from diagnosis. As such, three-monthly follow-up for the first 3 years from diagnosis may be recommended for patients who do not achieve pCR, especially those with TNBC and HR−/HER2+ tumours, whereas patients with other subtypes or who achieve pCR may be followed up every 6 months. Patients who have HR+ and lower grade tumours are at risk of late relapse beyond 5 years and will need longer follow-up. The impact of surveillance methods such as CA 15-3 and liver function tests appears limited in view of suboptimal sensitivity and specificity. Given the propensity for distant metastases in patients who relapse post-NAC, whether there is a role for routine cross-sectional imaging or non-invasive biomarkers such as circulating tumour cells in addition to mammography, remains to be elucidated in future studies. Whether earlier detection of relapse with more intensive monitoring translates into better survival outcomes also remains to be investigated and may be influenced by the availability of more effective therapies.

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Data availability The datasets during and/or analysed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest Dr Yap reported consulting for and receiving honoraria, travel support from Novartis, Pfizer, Lilly, Astra Zeneca, Roche, Eisai, and research support from Novartis.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was done under approval of SingHealth Centralised Institutional Review Board (Reference Number: CIRB 2004/422/B) and was conducted according to institutional and ethical rules concerning research on patients, with waiver of consent.

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