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# Outcomes of a prospective cohort study of PREoperative therapy and supportive care in early & locally advanced breast cancers – PreSCella study

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The PREoperative therapy and Supportive Care in EarLy and Locally Advanced breast cancers (PreSCella) study, conducted within Singapore's SingHealth network, explored how quality of life (QOL) and supportive care needs change over the course of neoadjuvant therapy (NAT) for breast cancer. Using a longitudinal design, data were collected at three points: before NAT (T1), within two months post-surgery (T2), and at the one-year follow-up (T3). Of 241 patients enrolled, 235 were analysed. Overall QOL improved over time, especially emotional well-being. FACT-B scores rose from 113.3 at T1 to 114.3 at T2 and 120.6 at T3 (T1–T3 change: +7.3 points; 95% CI 4.7–9.8; effect size 0.47). Age-specific assessment tools were used. Women under 40 completed three additional surveys—Body Image Scale (BIS), Dyadic Assessment Scale (DAS), and Female Sexual Function Index (FSFI). They reported mild body image distress (BIS: 6.3 at T1 to 7.2 at T3), stable relationships (DAS: 16.5 to 17.0), but notable declines in sexual function (13% at T1, 75% at T2, 57% at T3). Patients over 65 completed tools like the Attitude Scale and prioritised QOL over survival length. Findings underscore the evolving nature of supportive care needs and the value of age-personalised interventions throughout cancer treatment.

Breast cancer is the most common malignancy and leading cause of cancer death in women<sup>1</sup>. In Singapore, over half of breast cancer cases are diagnosed at stages II (19%) and III (12.1%), where treatment intent is cure<sup>2</sup>. The use of neoadjuvant therapy (NAT), which is the sequencing of systemic therapies pre-operatively, has become the standard of care. Originally used to impact surgery through the downstaging of inoperable tumours or to permit breast-conserving surgery (BCS), there are now

consistent reports of the prognosticating value of responses to NAT and opportunities to tailor therapeutics based on tumour responses to improve breast cancer survival<sup>3–7</sup>. The NAT treatment strategy is employed primarily in aggressive tumour subtypes such as triple-negative, human epidermal growth factor receptor 2 (HER2)-positive (HER2+) or locally advanced high grade estrogen receptor (ER)-positive breast cancers.

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NAT is resource-intensive and requires the coordination of pre-operative investigations—including imaging of the breast primary, cancer staging, clip placement, axillary nodal biopsy, cardiac imaging, and baseline laboratory investigations—all within a short period of time. Patients are concurrently referred to a variety of specialties, including breast surgery, medical oncology, plastic surgery, clinical genetic service, obstetrics (in cases of pregnancy associated breast cancers), reproductive medicine, and psychosocial oncology. Navigating this process can be challenging; hence, several large academic cancer centers have a NAT program in place to support the required workflows.

Quality of life (QOL) is a broad, multifaceted concept, and we expect that different domains contributing to overall QOL will be impacted in various ways over time. While many existing studies focus on isolated aspects of QOL, our goal is to capture a more comprehensive picture of how QOL evolves throughout the care journey. Patients receiving NAT are often impacted as many suffer from physical symptoms related to chemotherapy. Common toxicities, including nausea and vomiting<sup>8</sup>, fatigue<sup>9</sup>, insomnia<sup>10</sup> and decline in cognitive function<sup>11,12</sup> often cause significant decline in QOL. Many patients also suffer from body-image related psychological effects<sup>13</sup> and psychiatric issues of depression and anxiety. In a meta-analysis of QOL of patients receiving NAT, influences on QOL are reflected in physical symptoms in up to 80% of patients and psychological effects in 52% of patients<sup>14</sup>. Understanding QOL outcomes in patients with breast cancer undergoing neoadjuvant treatment is critical. While much of the current literature focuses on clinical efficacy and pathological response, there is growing recognition that patient-centred outcomes, such as QOL, are equally important.

In view of the influence on QOL, newly diagnosed patients with breast cancer experience high levels of supportive care needs<sup>15,16</sup>. The types and extent of supportive care needs differ at different stages of cancer therapy. Contextual understanding of supportive care needs is crucial for effective cancer care while maintaining a patient's optimal physical, psychological, and social function throughout their cancer treatment journey. Many cross-sectional studies in breast cancer have included patients of all ages in various points in the disease trajectory; few have followed the evolution of supportive care needs of patients with breast cancer longitudinally<sup>15–18</sup>. Evidence for treatment and supportive care is particularly lacking in distinct subgroups of patients at the extremes of age. These patients have unique needs and are at high risk for disparate outcomes<sup>19–24</sup>. Findings of supportive care needs in specific subgroups of younger or older patients with breast cancer have generally been based on Caucasian populations in Western countries, whilst less is known about ethnically diverse Asian patients. Cultural perceptions and beliefs, as well as family support and dynamics are important aspects that can influence health outcomes. A specific example of differences is the close relationship and shared decision-making between the Asian patient with breast cancer and her family members. Therefore, it is essential to evaluate the quality of life and health status of patients in Asian countries, such as Singapore, who are undergoing neoadjuvant treatment. This will allow us to better understand their needs and refine the neoadjuvant program to provide more effective supportive care to help our patients navigate the challenges of treatment. With the inherent complexities of the NAT treatment approach, the NAT program—which follows patients with breast cancer from the time of the new diagnosis, treatment with intensive systemic therapy, breast surgery, through to survivorship—forms an ideal context within which to study breast cancer supportive care needs.

The NAT program at the National Cancer Centre Singapore (NCCS), a comprehensive cancer centre within Singapore's largest public healthcare cluster, was established in 2015. Singapore operates a clustered public healthcare system, and NCCS serves as the national referral centre for cancer care within the SingHealth cluster, which encompasses multiple hospitals and specialist centres across the city-state. The program employs a coordinated care model to streamline the complex treatment pathway for breast cancer patients. When breast surgical oncologists identify candidates for neoadjuvant therapy, patients are referred to a dedicated nurse practitioner who serves as a central coordinator. This specialist nurse facilitates referrals across multiple disciplines, coordinates necessary investigations

and guides patients through the intricate treatment process. This systemic approach has significantly reduced treatment delays and improved care coordination. The program now achieves same-day genetic counselling referrals for patients requiring hereditary cancer assessment, fertility specialist consultations within 48 hours for patients of reproductive age, and cardiac evaluations within one week to assess fitness for cardiotoxic therapies. These rapid turnaround times enable prompt initiation of systemic therapy which is crucial for optimal outcomes. The program also incorporates age-specific supportive care pathways. Younger patients are automatically referred to psychology services and the Adolescent and Young Adult (AYA)/Young Women with Breast Cancer (YoWo) cancer support program which addresses the unique psychosocial needs of this population. Elderly patients receive comprehensive geriatric assessments through the geriatric oncology program to optimize treatment planning for older adults with multiple co-morbidities.

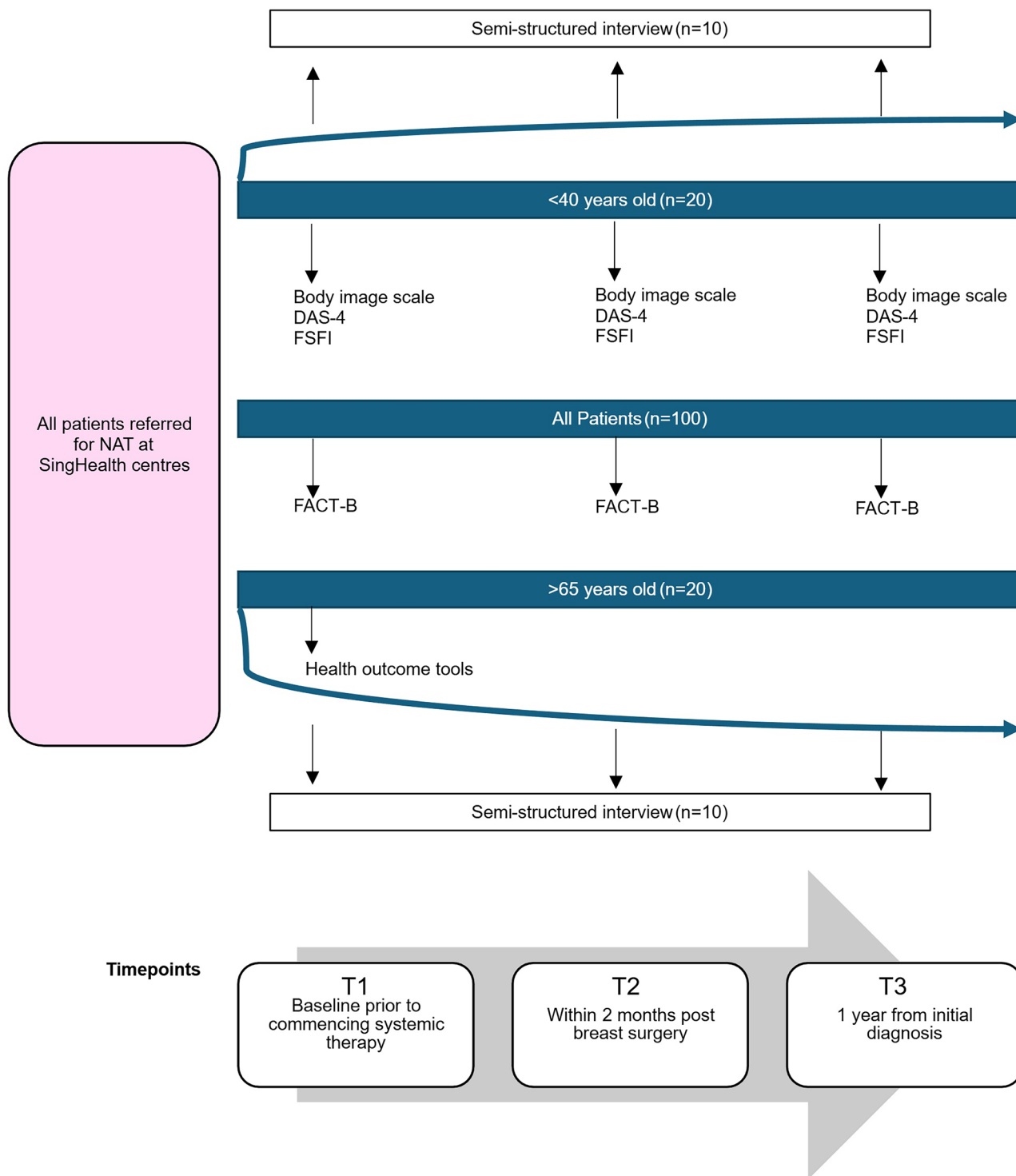
The PREoperative therapy and Supportive Care in EarLy and Locally Advanced breast cancers (PreSCella) utilises the established NAT programme within the SingHealth cluster to create a comprehensive, prospective multi-institutional registry of patients with breast cancer treated with NAT. This study employs a mixed-methods approach, combining quantitative clinical data collection with qualitative patient-reported outcome measures to provide a holistic view of the treatment experience (Fig. 1). Clinical data captured includes detailed patient characteristics, treatment protocols administered, health status indicators, and tumour response rates. Health-related quality-of-life outcomes are assessed through validated patient reported outcome measures administered at three key timepoints: at baseline diagnosis, immediately following definitive surgery, and at one-year post-diagnosis. Recognising that supportive care needs vary significantly across age groups, the study incorporates age-specific outcome assessments (Table 1). For younger patients under 40 years, particular attention is given to sexuality-related concerns and their impact on quality of life throughout treatment. For older patients over 65 years, the focus shifts to understanding treatment preferences and health outcome priorities that matter most to this population. This longitudinal design allows the study of how supportive care needs evolve throughout the treatment continuum from initial diagnosis through recovery with the ultimate goal of generating evidence that will inform the development of personalised, age-appropriate supportive care interventions that can be integrated into routine NAT protocols to optimise patient outcomes and wellbeing.

## Results

A total of 241 patients were recruited between June 2020 and July 2022 (Fig. 2). Six of these patients were confirmed to have stage IV disease after recruitment and were excluded from analysis. Of the 235 patients analysed, 33 (14%) were young women aged  $\leq 40$  years, 134 (57%) were aged 41–64 years, and 68 (29%) were older patients aged 65 years or over.

### Demographics and clinicopathological characteristics

The median age of the analysed population was 56 years old (Table 2). Most patients were ethnically Chinese (74%), followed by Indians (13.6%), Malay (8.9%) and others (3.4%)—concordant with Singapore's racial distribution. One pregnant patient was included in the study, and most patients were ECOG 0–1 (99%) at the initiation of NAT. There were expected significant differences in demographic characteristics by age groups. For example, a higher percentage of older patients were widowed, retired, post-menopausal, and had more children and comorbidities. There were no distinct differences in tumour characteristics between the 3 age groups. 27% of patients had triple negative breast cancer (TNBC), 19% had HR positive, HER2-negative breast cancers, while the remaining 53% of patients had HER2+ breast cancers. The majority of patients (95%) had stage II–III breast cancers. 29% of patients had a positive family history of breast and ovarian cancer, and genetic testing was commonly carried out amongst the younger female patients, with 88% vs 16% in the entire cohort. More than 80% of patients aged  $\leq 40$  years old were offered fertility preservation.



**Fig. 1 | Schedule of questionnaires and Comprehensive Geriatric Assessment (for the elderly subgroup) administered to study participants.** Adult female patients ( $\geq 21$  years) scheduled to receive neoadjuvant chemotherapy or endocrine therapy were enrolled in the study. Participants completed patient-reported outcome surveys at three predefined time points during treatment. All participants completed the

Functional Assessment of Cancer Therapy–Breast (FACT-B). Age-specific instruments were additionally administered: participants younger than 40 years completed the Body Image Scale, Dyadic Adjustment Scale–4 (DAS-4), and Female Sexual Function Index (FSFI), while participants older than 65 years completed health outcomes assessment tools.

**NAT characteristics and clinical outcomes**

Anthracycline-based chemotherapy regimens were more commonly received by younger patients while anthracycline-sparing chemotherapy regimens were more commonly received by older patients (Table 3). This trend was also observed amongst the subset of HER2+ patients. The

majority of HER2+ patients (92%) received dual HER2 blockade (trastuzumab and pertuzumab).

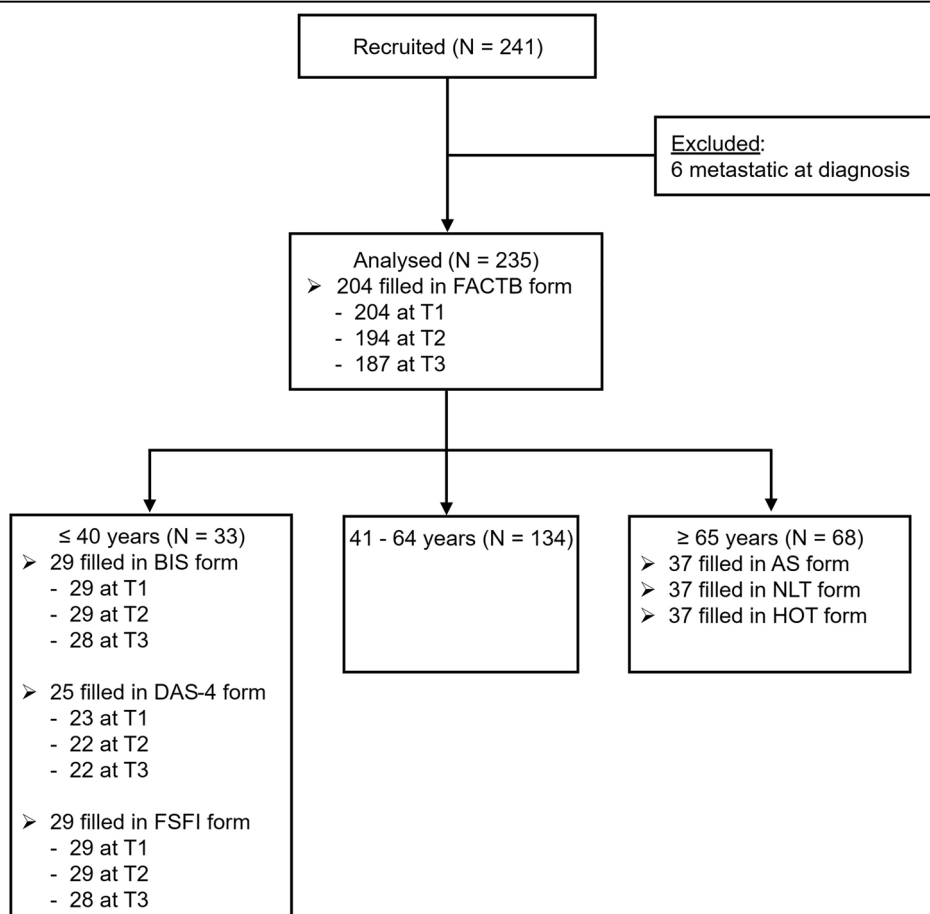
Among the patients with TNBC, 82% of younger patients received anthracycline with platinum chemotherapy—higher than the corresponding 35% among older patients. Only a minority (13%) of patients with

**Table 1 | Questionnaires and Timepoints**

Form	For	Assessed at	Outcome measure and interpretation
Functional Assessment of Cancer Therapy—Breast (FACT-B) version 4	All patients	T1: Baseline before start of NAT T2: Within 2 months post breast surgery T3: after 1 year from baseline	5 subscale scores (score range): PWB: physical well-being (0–28) SWB: social/family well-being (0–28) EWB: emotional well-being (0–24) FWB: functional well-being (0–28) BCC: breast cancer subscale (0–40) 2 total scores (score range): FACTG = PWB + SWB + EWB + FWB (0–108) FACT-B = FACTG + BCC (0–148) Higher score → better quality of life
Body Image Scale (BIS)	Young women	T1, T2, T3	Total score range: 0–30 Lower score → lower image distress
Dyadic Assessment Scale - 4 items (DAS)	Young women	T1, T2, T3	Total score range: 0–21 Higher score → lower relationship distress Total score <13 → distressed partner in relationship
Female Sexual Function Index (FSFI)	Young women	T1, T2, T3	Total score range: 2–36 Higher score → better sexual functioning Total score ≤ 26 → sexual dysfunction
Attitude Scale (AS)	Older patients	T1	2 subscale scores (score range): AS1: trade-off between quality and quantity of life (4–20) AS2: trade-off between future and present health (6–30) Higher score → greater agreement in favouring quality of life over quantity of life and present over future health
Now vs Later Tool (NLT)	Older patients	T1	Whether patient would rather have quality of life now or quality of life 1-year / 5-year from now Expected quality of life score 1-year / 5-year from now relative to quality of life score now (base = 100)
Health Outcome Tool (HOT)	Older patients	T1	Prioritisation of 4 health outcomes based on assignment of scores from 0 to 100%: - keeping you alive - maintaining independence - reducing or eliminating pain - reducing or eliminating other symptoms (dizziness, fatigue, shortness of breath). Higher score → More important outcome

<sup>a</sup>Patients were also asked to provide a rank from 1 to 4 to indicate which outcome was the most important to the least important to them. However, majority of patients did not provide their rankings in the required manner and therefore rankings were not included in this analysis.

**Fig. 2 | Diagram of patient flow through study.** A total of 241 patients were recruited, 6 were excluded due to stage IV disease diagnosed after recruitment. Of the 235 patients, 33 (15%) were young women aged ≤40 years, 134 (57%) were aged 41–64 years and 68 (29%) were older patients aged 65 years or over. All patients enrolled were requested to complete the FACT-B questionnaire at three timepoints with subgroups of patients (young women and older women) identified to complete additional questionnaires as stated in the study design.



**Table 2 | Demographics and clinicopathological characteristics by age groups**

	All patients (N = 235) (%)		≤40 year (N = 33) (%)		41–64 years (N = 134) (%)		≥65 years (N = 68) (%)		p-value
Age at start of NAT, years									
Median (IQR)	56 (47–66)		36 (33–38)		54 (48–59)		70 (68–74)		-
Race									
Chinese	174	74.0	21	63.6	93	69.4	60	88.2	0.010
Indian	32	13.6	7	21.2	19	14.2	6	8.8	
Malay	21	8.9	2	6.1	17	12.7	2	2.9	
Others	8	3.4	3	9.1	5	3.7	0	-	
Marital status									
Single	40	17.0	11	33.3	20	14.9	9	13.2	0.002
Married	160	68.1	21	63.6	98	73.1	41	60.3	
Divorced	16	6.8	1	3.0	10	7.5	5	7.4	
Widowed	19	8.1	0	-	6	4.5	13	19.1	
ECOG performance status									
0	216	91.9	32	97.0	129	96.3	55	80.9	0.004
1	16	6.8	1	3.0	4	3.0	11	16.2	
2	2	0.9	0	-	1	0.7	1	1.5	
3	1	0.4	0	-	0	-	1	1.5	
Genetic testing									
Not done <sup>1</sup>	150	63.8	4	12.1	86	64.2	60	88.2	<0.001
Yes - Positive <sup>2</sup>	16	6.8	7	21.2	8	6.0	1	1.5	
Yes - VUS detected <sup>3</sup>	35	14.9	15	45.5	19	14.2	1	1.5	
Yes - Negative	34	14.5	7	21.2	21	15.7	6	8.8	
Fertility preservation									
Yes	15	6.4	15	45.5	0	-	0	-	<0.001
No - referred but declined	13	5.5	13	39.4	0	-	0	-	
No - not referred or discussed	4	1.7	4	12.1	0	-	0	-	
Not applicable <sup>a</sup>	203	86.4	1	3.0	134	100	68	100	
Overall clinical stage									
I	12	5.1	4	12.1	4	3.0	4	5.9	0.237
II	148	63.0	21	63.6	87	64.9	40	58.8	
III	75	31.9	8	24.2	43	32.1	24	35.3	
Receptor status <sup>b</sup>									
TNBC	64	27.2	9	27.3	35	26.1	20	29.4	0.559
ER+ and/or PR +, HER2-	45	19.1	6	18.2	23	17.2	16	23.5	
ER-, PR-, HER2+	54	23.0	5	15.2	32	23.9	17	25.0	
ER+ and/or PR +, HER2+	72	30.6	13	39.3	44	32.9	15	22.1	

<sup>1</sup> Included patients who were not referred to the genetic clinic and those who were referred but declined testing.

<sup>2</sup> Positive for *BRCA1* (n = 5), *BRCA2* (n = 3), *TP53* (n = 2), *PALB2* (n = 1), *BRIPI1* (n = 1), *AIP* (n = 1), *RAD51D* (n = 1), *FANCM* (n = 1) and *FANCA* (n = 1).

<sup>3</sup> VUS included *ABRAXAS1*, *APC*, *BARD1*, *CDH1*, *CTNNA1*, *DICER1*, *ERCC4*, *MET*, *MRE11*, *MSH2*, *MSH3*, *NTHL1*, *PMS2*, *POLD1*, *POLE*, *RAD50*, *RAD51C*, *RECQL4*, *RINT1*, *SDHA*, *SDHAF2*, *SDHD*, *SMAD4* and *TSC2*.

NAT neoadjuvant therapy, IQR interquartile range, ECOG Eastern Cooperative Oncology Group, VUS variant of unknown significance, ER estrogen receptor, PR progesterone receptor, HER2 human epidermal growth factor receptor 2

<sup>a</sup> The patient aged <=40 years was found to be pregnant.

<sup>b</sup> ER- included patients with ER ≤ 10%, and PR- included patients with PR ≤ 10%.

TNBC received immunotherapy because immunotherapy had not yet received local regulatory approval during the period of recruitment and treatment. One-fifth of patients did not complete their NAT, with the commonest reason being adverse events and poor tolerance of chemotherapy. As anticipated, compared with older patients, a significantly higher proportion of younger patients successfully completed NAT (88% vs 69%,  $p = 0.006$ ) and demonstrated a higher pCR (57% vs 27%,  $p = 0.012$ ).

Seven patients did not undergo breast surgery after NAT; two patients had disease progression, two patients declined surgery, one patient defaulted surgery, one patient passed away before surgery and the last patient was lost to follow-up (returned to their home country before surgery). Most of the

young women had either BCS (30%) or a mastectomy with breast reconstruction surgery (64%), while most older patients had a mastectomy without breast reconstruction (74%).

Among the 228 patients who underwent breast surgery, 74% had their breast cancers downstaged after NAT. A total of 99 patients (43%) achieved pCR to their NAT.

**FACT-B scores**

The mean FACT-B total score was 113.3 at T1, 114.3 at T2 (T1 to T2 change: 1.0 points, 95% CI -1.6 to 3.5) and increased to 120.6 at T3 (T2 to T3 change: 6.3 points, 95% CI 3.7 to 8.9, effect size 0.48; T1 to T3 change:

**Table 3 | Neoadjuvant treatment characteristics and outcomes by age groups**

	All patients (N = 235) (%)		≤40 years (N = 33) (%)		41–64 years (N = 134) (%)		≥65 years (N = 68) (%)		p-value
<b>NAT regimen</b>									
Anthracycline only	118	50.2	17	51.5	71	53.0	30	44.1	<0.001
Anthracycline with platinum	44	18.7	7	21.2	30	22.4	7	10.3	
Taxane only	14	6.0	0	-	2	1.5	12	17.6	
Taxane with platinum	57	24.3	9	27.3	31	23.1	17	25.0	
Endocrine therapy	2	0.9	0	-	0	-	2	2.9	
<b>HER2 agent</b>									
Single blockade	8	6.3	0	-	4	5.3	4	12.5	0.438
Dual blockade	116	92.1	18	100	70	92.1	28	87.5	
No	2	1.6	0	-	2	2.6	0	-	
<b>Immunotherapy</b>									
Yes	8	12.5	0	-	7	20.0	1	5.0	0.217
No	56	87.5	9	100	28	80.0	19	95.0	
<b>NAT completion</b>									
Yes	188	80.0	29	87.9	112	83.6	47	69.1	0.006
No – adverse events	25	10.6	2	6.1	10	7.5	13	19.1	
No – disease progression	6	2.6	0	-	4	3.0	2	2.9	
No – poor tolerance	7	3.0	0	-	1	0.7	6	8.8	
No – refusal to continue	3	1.3	1	3.0	2	1.5	0	-	
No – others	6	2.6	1	3.0	5	3.7	0	-	
<b>Surgery</b>									
No	7	3.0	0	-	3	2.2	4	5.9	<0.001
Yes – Breast conservation	46	19.6	10	30.3	27	20.1	9	13.2	
Yes – Mastectomy without breast reconstruction	116	49.4	2	6.1	64	47.8	50	73.5	
Yes – Mastectomy with breast reconstruction	66	28.1	21	63.6	40	29.9	5	7.4	
<b>Axillary surgery</b>									
No	8	3.4	0	-	4	3.0	4	5.9	0.398
Yes – SLNB only	87	37.0	16	48.5	46	34.3	25	36.8	
Yes – Axillary clearance	140	59.6	17	51.5	84	62.7	39	57.4	
Among patients with surgery:	228	100	33	100	131	100	64	100	
<b>Overall stage (yp)</b>									
pCR	99	43.4	18	54.5	64	48.9	17	26.6	0.012
I	52	22.8	8	24.2	23	17.6	21	32.8	
II	50	21.9	3	9.1	29	22.1	18	28.1	
III	26	11.4	3	9.1	15	11.5	8	12.5	
III	1	0.4	1	3.0	0	-	0	-	

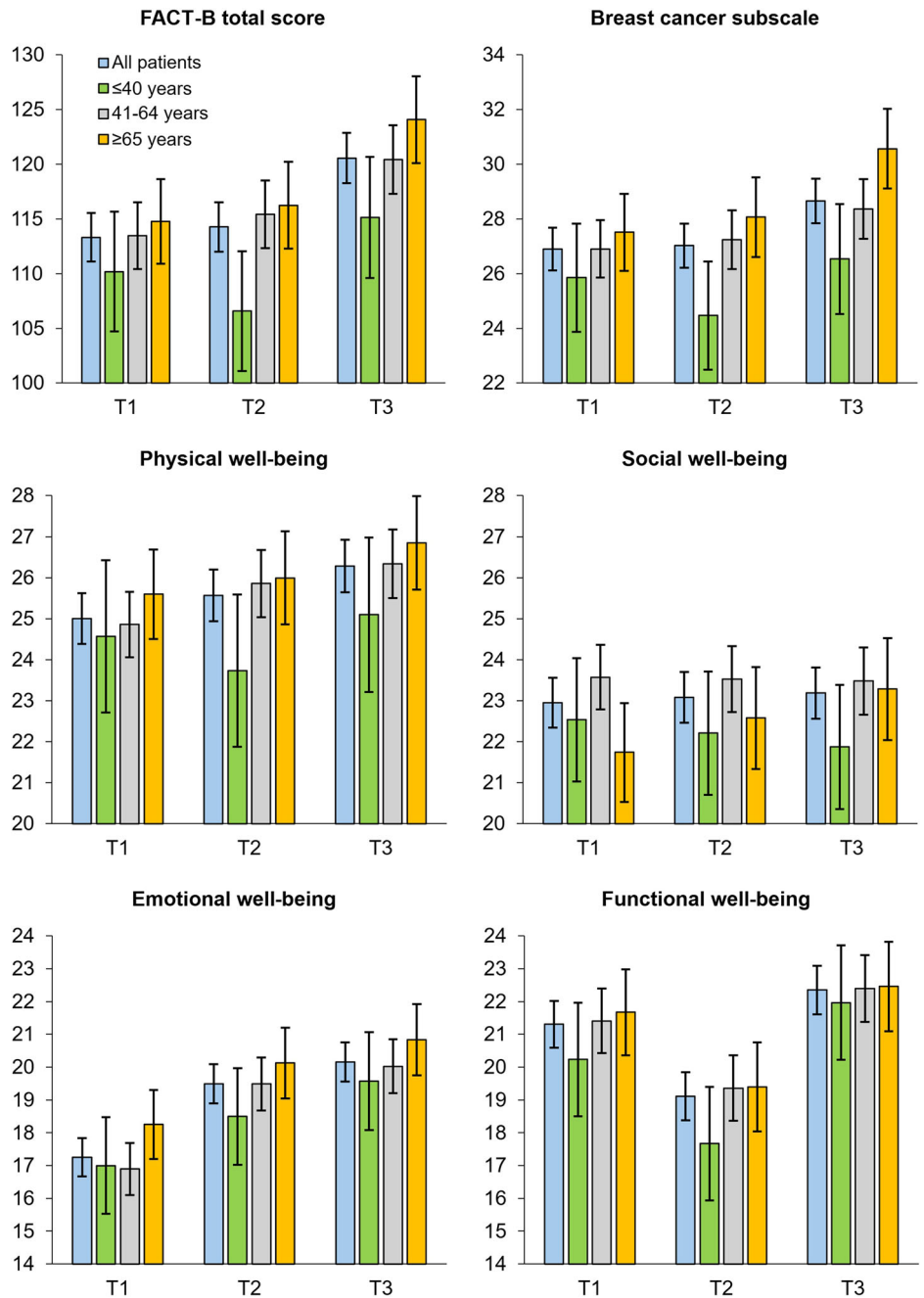
NAT neoadjuvant therapy, HER2 human epidermal growth factor receptor 2, SLNB sentinel lymph node biopsy, yp pathologic after neoadjuvant therapy, pCR pathologic complete response.

7.3 points, 95% CI 4.7 to 9.8, effect size 0.47) (Fig. 3 and Table S1). Improvements in patients’ QOL over the entire period were mainly due to emotional well-being (2.9 points), followed by their responses to items in the breast cancer subscale (1.8 points), physical well-being (1.3 points), and functional well-being (1.0 points). There were no significant changes to social/family well-being scores over time. Between T1 and T2, there was an improvement in the emotional well-being score by 2.2 points (95% CI, 1.5–3.0). However, this was negated by a corresponding deterioration in the functional well-being score. Between T2 and T3, the functional well-being score recovered to a level higher than baseline (T1). There was also a distinct improvement in the breast cancer subscale score in this period. Results of corresponding analyses by age groups were shown in Table S2 – S4.

**Young women: body image scale (BIS)—behavioural and body image symptoms**

A total of 29 (88%) young women filled up the BIS form at T1 and at T2. Only one patient was lost to follow-up and did not fill up the form at T3. Most of the patients responded “Not at all” or “A little” to each of the 10 questions on body image issues at each assessment timepoint (Fig. 4A). The mean BIS score was 6.3 at T1, 8.4 at T2 (T1 to T2 change: 2.0, 95% CI –0.4 to 4.5) and 7.2 at T3 (T2 to T3 change: –1.1, 95% CI –3.6 to 1.3; T1 to T3 change: 0.9, 95% CI –1.6 to 3.4) (Fig. 4B and Table S5). The changes in BIS score between assessment timepoints were not statistically significant. The low level of BIS scores over time (maximum score of 30) suggested that most young women were not distressed over body image issues. However, despite average numbers being low, 25.9% at T1, 40.8% at T2 and 26.6% at T3 of

**Fig. 3 | Estimated mean FACT-B total and subscale scores among all patients by age groups. Error bars indicate 95% confidence interval of the mean score at each assessment timepoint.** Mean Functional Assessment of Cancer Therapy–Breast (FACT-B) total and subscale scores over time, stratified by age group. Health-related quality of life was assessed at three time points (T1–T3). Bars represent mean scores with 95% confidence intervals. Results are shown for the overall cohort (blue) and by age group: ≤40 years (green), 41–64 years (grey), and ≥65 years (yellow). Mean FACT-B total scores increased from 113.3 at T1 to 114.3 at T2 (mean change 1.0 points; 95% CI –1.6 to 3.5), followed by a clinically meaningful improvement to 120.6 at T3. The increase from T2 to T3 was 6.3 points (95% CI 3.7 to 8.9; effect size 0.48), with an overall improvement of 7.3 points from T1 to T3 (95% CI 4.7 to 9.8; effect size 0.47). Improvements in overall quality of life were primarily driven by gains in emotional well-being, followed by improvements in the breast cancer subscale, physical well-being, and functional well-being. Social/family well-being scores remained relatively stable across all time points. Between T1 and T2, emotional well-being improved, while functional well-being declined, resulting in minimal net change in total FACT-B scores. Between T2 and T3, functional well-being recovered to levels exceeding baseline, alongside further improvements in breast cancer-specific concerns. Similar temporal trends were observed across age groups, although absolute scores differed.



young women had a BIS score of ≥10, indicating that a significant proportion of young women do experience body image difficulties.

**Young women: dyadic adjustment scale (DAS)—relationship with intimate partner**

A total of 25 (75%) patients filled up the DAS form on at least one of the assessments timepoints (23 at T1, 22 at T2, and 22 at T3). Except for the patient lost to follow-up who did not fill up the form at T3, the remaining patients did not fill up the form at an assessment timepoint because they did not have a partner at that timepoint.

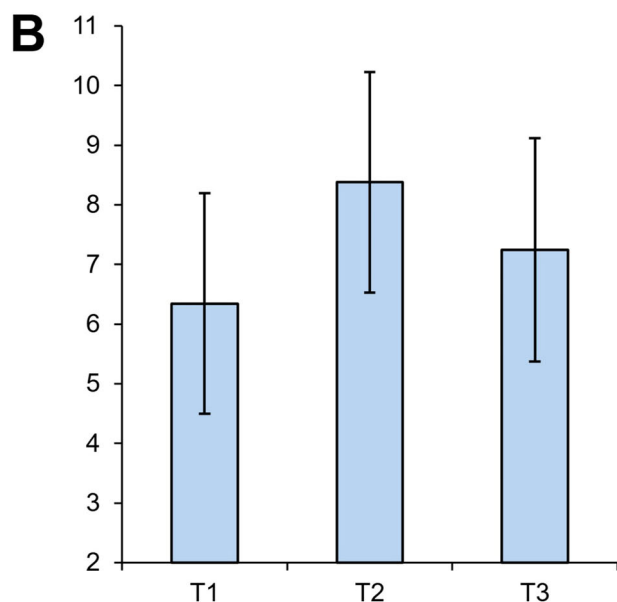
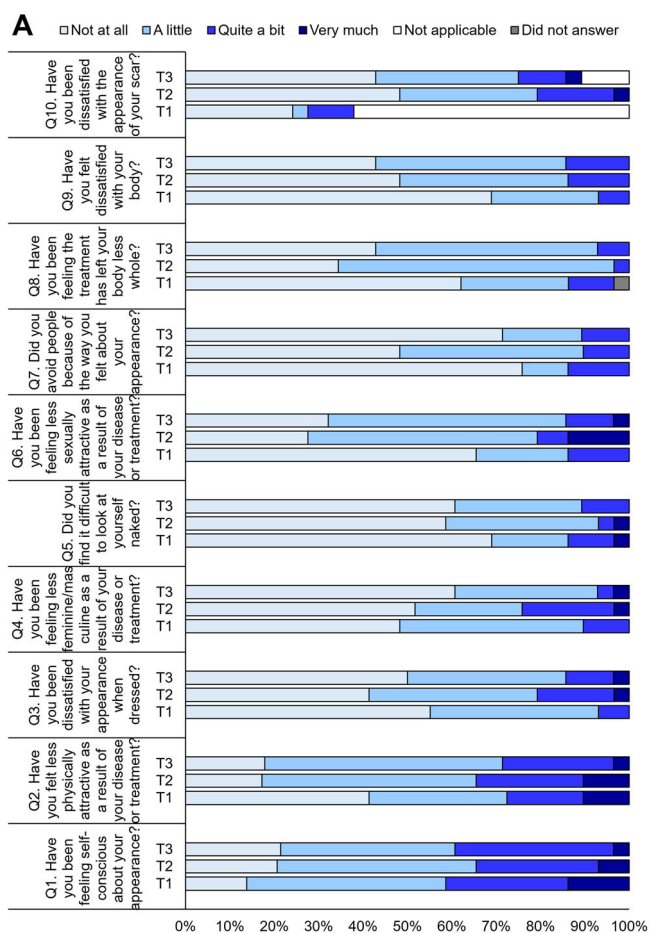
Most patients responded positively to each of the 4 questions on relationship issues at each assessment timepoint (Fig. 5A). The mean DAS score was 16.5 at T1, 16.3 at T2 (T1 to T2 change: –0.2, 95% CI –1.6 to 1.2), and 17.0 at T3 (T2 to T3 change: 0.7, 95% CI –0.7 to 2.0; T1 to T3 change: 0.5, 95% CI –0.9 to 1.8) (Fig. 5B and Table S6). The changes in DAS score between assessment timepoints were again not statistically significant. The

high level of DAS scores over time (maximum score of 21) suggested that most young women patients were not distressed over relationship issues. Only 7.5–11% of these patients were potentially experiencing relationship distress over this period.

**Young women: female sexual function index scoring (FSFI)—sexual functioning**

A total of 29 (88%) young women patients filled up the FSFI form at T1 and at T2. Only one patient was lost to follow-up and did not fill up the form at T3. The assessment of female sexual functioning using the FSFI form was applicable only for patients who had sexual activity and attempted intercourse in the last four weeks prior to interview. The number of patients who met this criterion was eight, four and seven at T1, T2 and T3 respectively.

The mean FSFI full scale score was 29.5 at T1, 21.1 at T2 (T1 to T2 change: –8.4, 95% CI –14.6 to –2.2), and 25.4 at T3 (T2 to T3 change: 4.4, 95% CI –1.9 to 10.7; T1 to T3 change: –4.0, 95% CI –9.2 to 1.2) (Fig. 6A



and Table 4). There was a reduction of scores in all FSFI domains between T1 and T2 (Fig. 6B). Except for pain, scores in all the other domains increased between T2 and T3. The change in full scale score between T1 and T2 and between T2 and T3 was mainly driven by changes of scores in the domains of satisfaction, arousal, and orgasm. In tandem with the changes in full scale score over time, the estimated percentage of patients with female sexual dysfunction increased between T1 and T2 (13% to 75%) and decreased between T2 and T3 (75% to 57%).

**Fig. 4 | Body image scale responses (A) and estimated mean body image scale scores (B) among adolescent and young adult patients.** Error bars indicate 95% confidence interval of the mean score at each assessment timepoint. Body Image Scale (BIS) responses and mean scores over time in young women ( $\leq 40$  years). Body image was assessed at three time points (T1–T3) using the 10-item Body Image Scale. Twenty-nine participants (88%) completed the BIS at T1 and T2; one participant was lost to follow-up and did not complete the assessment at T3. A Stacked bar charts show the distribution of responses for each BIS item at each time point. Response categories are colour-coded as follows: Not at all (very light blue), A little (light blue), Quite a bit (medium blue), Very much (dark blue), Not applicable (white), and Did not answer (grey). Across all items and time points, most participants reported minimal body image concerns, with the majority of responses falling within the “Not at all” or “A little” categories. B Mean BIS total scores at each time point are shown with 95% confidence intervals. The mean BIS score increased from 6.3 at T1 to 8.4 at T2 (mean change 2.0 points; 95% CI – 0.4 to 4.5), followed by a reduction to 7.2 at T3 (T2 to T3 change –1.1 points; 95% CI – 3.6 to 1.3). Overall change from T1 to T3 was small and not statistically significant (mean change 0.9 points; 95% CI – 1.6 to 3.4).

**Older patients: attitude scale—agreement with outcome related statements**

The attitude scale comprises two subscales designed to assess different aspects of health-related decision-making. Subscale 1 evaluates individuals’ preferences when faced with trade-offs between quality and quantity of life, for example, whether a person would prefer a shorter life with better health or a longer life with poorer health. Subscale 2 measures attitudes toward trade-offs between present and future health, capturing the extent to which individuals prioritize immediate well-being versus long-term health outcomes. A total of 37 (57%) older patients participated in survey questionnaires (Table 5). Half of the patients scored a total of 14 points or over (out of maximum 20 points) for subscale 1. This suggested that most patients favored QOL over quantity of life. For subscale 2, the median total score was 15 points (out of a 30-point maximum). There was no strong indication that patients were in favor of future health over their present health.

**Older patients: now vs later tool—quality-of-life at three timepoints**

Around half of the 37 older patients ( $n = 19$ ) would rather have QOL now than 1 year later (Table 6). About three-quarters of these patients ( $n = 14$ , 74%) expected their QOL to reduce in a year’s time from now. This was higher than the corresponding 67% amongst patients who would rather have QOL a year later than now. When the timeline was extended to 5 years, a lower 27% ( $n = 10$ ) would rather have QOL now than 5 years from now. Most of these patients ( $n = 8$ , 80%) expected their QOL to reduce in 5 years from now. In comparison, the corresponding percentage of patients who expected their QOL to reduce in 5 years from now was 67% amongst those who rather have QOL 5 years later than now.

**Older patients: health outcome tool—prioritization of outcomes (survival, independence, symptoms)**

Of all the outcomes, maintaining independence was given the highest scores by patients, followed by keeping alive, and then reducing/eliminating of pain and other symptoms (Table 7). Relative to the conventional outcome of survival prolongation, 86% of patients assigned either a higher or the same score to maintaining independence. The corresponding percentage of patients for the reducing/eliminating of pain and other symptoms were 65% and 54%, respectively.

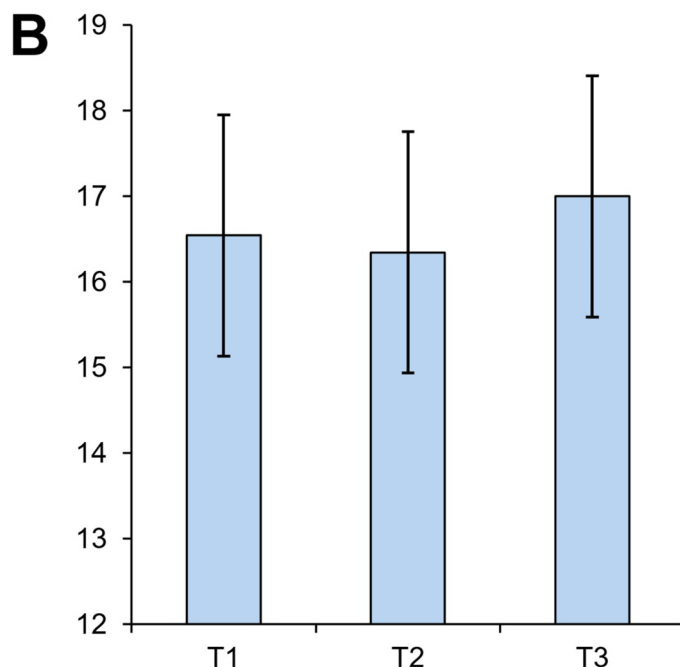
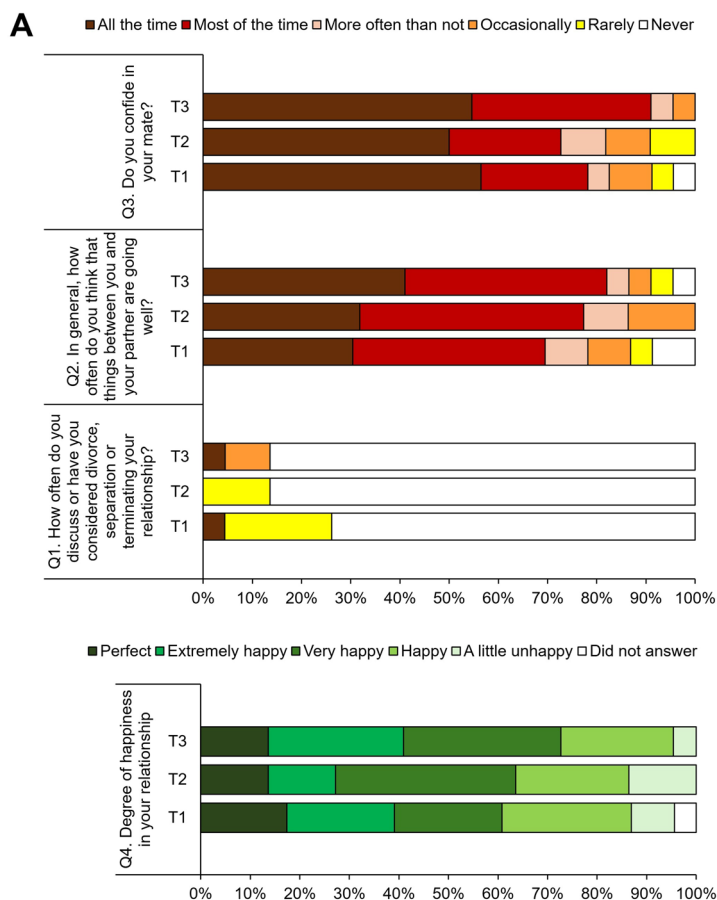
**Discussion**

We present here a contemporary overview of our institutional experience half a decade after the inception of a neoadjuvant program complete with longitudinal capture of measures of quality of life with a focus on age extremes.

**Fig. 5 | Dyadic adjustment scale-4 responses (A) and estimated mean dyadic adjustment scale-4 scores (B) among adolescent and young adult patients. Error bars indicate 95% confidence interval of the mean score at each assessment timepoint. Relationship quality was assessed at three time points (T1–T3) using the DAS-4.**

A Stacked bar charts show the distribution of responses for each DAS-4 item at each time point. Response categories for Questions 1–3 are colour-coded as follows: All the time (dark brown), Most of the time (red), More often than not (light pink), Occasionally (orange), Rarely (yellow), and Never (white). Responses to Question 4 (degree of happiness in the relationship) are colour-coded as: Perfect (dark green), Extremely happy (green), Very happy (medium green), Happy (light green), A little unhappy (very light green), and Did not answer (white). Across all four items and time points, most participants reported positive relationship experiences, with the majority of responses clustering in the higher-frequency and positive categories.

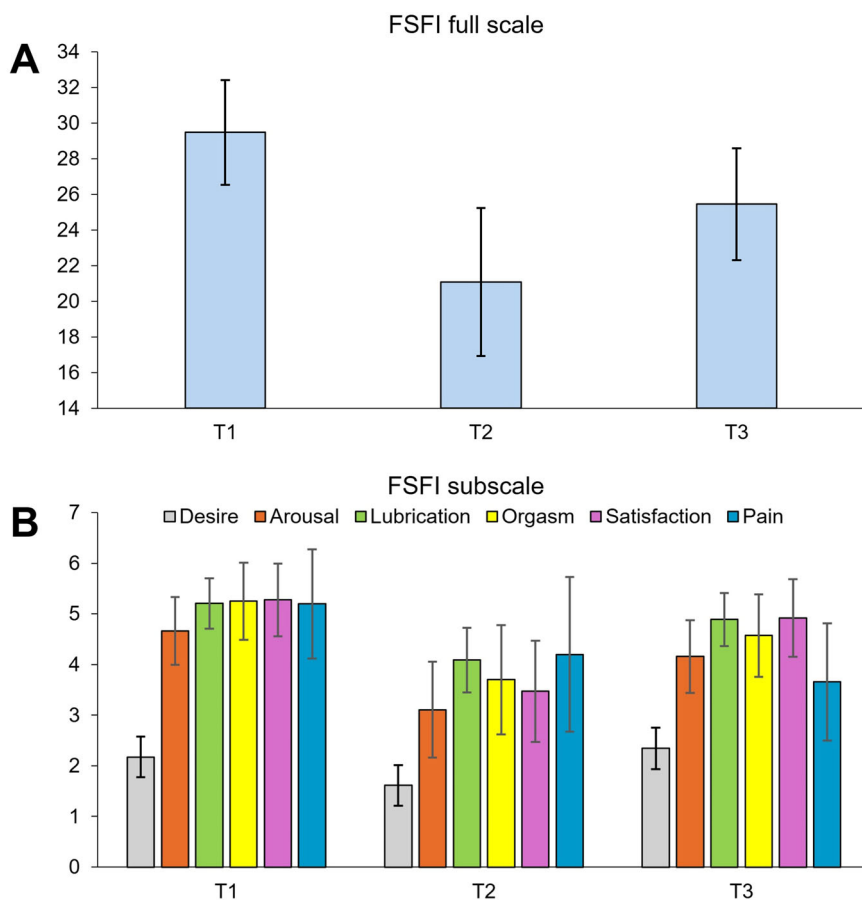
B Mean DAS-4 total scores at each time point are shown with 95% confidence intervals. The mean DAS-4 score was 16.5 at T1 and remained stable at T2 (mean 16.3; T1 to T2 change  $-0.2$ ; 95% CI  $-1.6$  to  $1.2$ ), before increasing slightly to 17.0 at T3 (T2 to T3 change  $0.7$ ; 95% CI  $-0.7$  to  $2.0$ ). The overall change from T1 to T3 was small and not statistically significant (mean change  $0.5$ ; 95% CI  $-0.9$  to  $1.8$ ), indicating generally stable relationship satisfaction over time.



A review of institutional data for this study revealed a notable trend toward the increased administration of NAT for patients with breast cancer<sup>25</sup>. Notably, fertility preservation was addressed and discussed with a significant proportion of young patients, with 85% being referred to a fertility clinic. A reassuring proportion of young patients at our institution are being offered the opportunity to make informed decisions about fertility preservation. In general, there are significant barriers reported in the

literature, both among physicians and patients, that hinder consistent discussions about fertility preservation. Referral rates to fertility specialists vary widely; in one study, only 10.7%<sup>26</sup> of patients were referred to reproductive specialist, whilst another study reported 44.7%<sup>27</sup> of breast cancer surgeons referred patients to reproductive specialists for fertility preservation counselling. For patients, common barriers include concerns about potential delays in cancer treatment and the financial cost of fertility preservation<sup>28</sup>.

**Fig. 6 | Estimated mean female sexual function index total (A) and subscale (B) scores among adolescent and young adult patients. Error bars indicate 95% confidence interval of the mean score at each assessment timepoint. Mean Female Sexual Function Index (FSFI) full-scale scores at T1, T2, and T3. A The mean FSFI score decreased from T1 to T2, followed by partial recovery at T3, although scores did not fully return to baseline levels. Bars represent mean values and error bars indicate 95% confidence intervals. B Mean FSFI domain scores for desire, arousal, lubrication, orgasm, satisfaction, and pain at T1, T2, and T3. All domain scores showed a reduction from T1 to T2, with partial recovery observed at T3 across most domains. Bars represent mean values and error bars indicate 95% confidence intervals.**



The rates of germline genetic testing were encouraging, with close to 90% of younger women undergoing genetic testing in our study. This is a significant change in the uptake compared to previous studies in Singapore where uptake was only about 35% about ten years ago<sup>29,30</sup>. This phenomenon likely indicates improvement in knowledge and understanding of the role of genetic testing and awareness of therapeutic implications in hereditary breast and ovarian cancer syndrome.

High compliance with the paper-based questionnaires, facilitated by a dedicated research team member, contributed to excellent completion rates at various treatment timepoints. This enabled us to follow patients longitudinally and generate robust results for assessing their overall quality of life (QOL). The mean FACT-B score indicated a generally acceptable QOL among our patients receiving NAT. Notably, the improvement in QOL over the course of treatment is encouraging, reflecting an objective “return to normalcy” after breast cancer treatment. The relatively stable FACT-B score is different from similar studies assessing QOL where FACT-B scores generally deteriorate following NAT<sup>31,32</sup>. While reassuring, the FACT-B score provides a quantitative analysis that enables us to examine results across large populations, identifying trends that can be further analysed for future research. The improvement in emotional well-being following neoadjuvant chemotherapy aligns with findings from a German study<sup>32</sup> assessing quality of life (QOL) in patients undergoing NAT. This positive change may be linked to the clinical response of the tumour to treatment and potentially related to relief with treatment completion. While the objective approach of assessing QOL with FACT-B helps minimise bias, it does not provide a deeper understanding of the underlying reasons nor capture all the factors that may contribute to QOL. Results from qualitative interviews with patients will be presented in a follow-up publication which may provide insights into whether the perceived return to normalcy is due to shifts in expectations or actual recovery. Hopefully, with more in-depth understanding, more can be done to support patients in their recovery.

In the young women population, the mean BIS score remained low throughout the treatment course, even after breast surgery. This may be attributed to higher rates of BCS or reconstruction among younger patients. The availability of these options is crucial in addressing body image concerns, particularly for this demographic. Studies have consistently demonstrated improvement in body image with the use of BCS or reconstruction<sup>33-36</sup>. This further supports the use of a NAT approach which facilitates BCS and allows patients and surgeons time to contemplate surgical and reconstruction options.

The DAS scores were consistently positive across treatment time points, indicating that young patients maintained healthy relationships with their partners throughout their treatment journey. Despite the DAS scores indicating relatively healthy relationships, only a small number of respondents completed the FSFI scoring. This suggests that most young women might not have been sexually active or attempted intercourse in the four weeks prior to the interview. The underlying reasons for this remain unclear, but we hypothesize that the breast cancer diagnosis and physical impact of treatment-related toxicities may have played a significant role. Multiple studies over the years have demonstrated sexual dysfunction after diagnosis and treatment of breast cancer<sup>37-39</sup>, common factors affecting sexual health include vaginal dryness and lower perceived sexual attractiveness<sup>40</sup>. Patients with breast cancer often face significantly worse sexual health than patients suffering from other cancers<sup>37,38</sup> attributed to treatment with chemotherapy, radiotherapy, and often prolonged endocrine therapy for patients with hormone-positive breast cancer. In our study, among those who are sexually active, 75% reported experiencing sexual dysfunction post-surgery, with over 50% continuing to face this issue one year after baseline. The high percentage of sexual dysfunction is concerning, and we suspect it might be under-represented, given that many patients were not sexually active. Various factors could contribute to the poor scores in sexual health, necessitating

**Table 4 | Female sexual function index scores among adolescent and young adult patients**

	Assessment timepoints (N=29)			Change in mean score ± SE (95% CI) [p-value]		
	T1	T2	T3	T1 to T2	T2 to T3	T1 to T3
No. of patients who filled up form	29	29	28	-	-	-
No. of patients who did not fill up form	0	0	1			
Lost to follow-up	-	-	1			
Among patients who have engaged in sexual activity and attempted intercourse in last 4 weeks <sup>a</sup> :	8	4	7			
Mean score (SE)						
Desire	3.8 (0.3)	2.6 (0.4)	3.3 (0.3)	-1.2±0.5 (-2.5, 0.1) [0.072]	0.7±0.5 (-0.6, 1.8) [0.377]	-0.5±0.4 (-1.6, 0.6) [0.493]
Arousal	4.7 (0.3)	3.1 (0.4)	4.2 (0.3)	-1.6±0.5 (-2.9, -0.2) [0.027]	1.1±0.5 (-0.4, 2.5) [0.162]	-0.5±0.4 (-1.7, 0.7) [0.511]
Lubrication	5.2 (0.2)	4.1 (0.3)	4.9 (0.2)	-1.1±0.3 (-2.0, -0.3) [0.010]	0.8±0.3 (-0.03, 1.6) [0.061]	-0.3±0.3 (-1.0, 0.4) [0.448]
Orgasm	5.3 (0.4)	3.7 (0.5)	4.6 (0.4)	-1.6±0.6 (-3.2, 0.1) [0.059]	0.9±0.6 (-0.8, 2.5) [0.380]	-0.7±0.5 (-2.0, 0.7) [0.421]
Satisfaction	5.3 (0.3)	3.5 (0.5)	4.9 (0.4)	-1.8±0.5 (-3.2, 0.4) [0.013]	1.4±0.6 (0.004, 2.9) [0.049]	-0.4±0.5 (-1.5, 0.8) [0.714]
Pain	5.2 (0.5)	4.2 (0.7)	3.7 (0.5)	-1.0±0.9 (-3.3, 1.3) [0.509]	-0.5±0.9 (-2.9, 1.8) [0.822]	-1.5±0.7 (-3.5, 0.4) [0.128]
Full scale	29.5 (1.4)	21.1 (2.0)	25.4 (1.5)	-8.4±2.2 (-14.6, -2.2) [0.008]	4.4±2.4 (-1.9, 10.7) [0.206]	-4.0±2.0 (-9.2, 1.2) [0.146]
Mean % of patients with female sexual dysfunction <sup>b</sup> (95% CI)	12.5 (1.5, 57.9)	75.0 (20.6, 97.2)	57.1 (20.9, 87.1)			

SE standard error, CI confidence interval.

<sup>a</sup>Did not report "No sexual activity" to question 3–14 and "Did not attempt intercourse" to question 17–19.

<sup>b</sup>Full scale score ≤26.

further follow-up or studies to identify potentially modifiable factors in this patient group. Despite the reported low levels of sexual activity, the DAS score indicating a healthy relationship suggests that the determinants of a healthy relationship in the Asian context might not be heavily influenced by sexual factors. This is seemingly consistent with other Asian studies which showed no significant influence on a patients' relationship with their partner, regardless of the impaired sexual functioning they experience<sup>41,42</sup>. In one study, patients reported symptoms such as vaginal dryness, painful intercourse, difficulty achieving orgasm, reduced sexual interest, and decreased satisfaction. However, 90.5% of patients indicated that their relationships with their partners were not negatively affected after completing cancer treatment, with some even reporting improvements in their marital relationships following diagnosis and treatment. This contrasts with Western studies demonstrating deterioration in relationship with patients' partners and a deterioration in DAS score<sup>43,44</sup>. This may be related to differences in cultural values and social bonding in the Asian population; however, this remains an area warranting further research.

In older patients, the attitude scale revealed that most prioritized QOL over quantity of life. To our knowledge, this is one of the first studies to evaluate the attitudes of older patients with breast cancer toward their life goals. These patients expressed equal concern for both present and future health. In the "Now vs Later" tool, respondents were evenly split between those who preferred QOL now and those who favoured it one year later. Among those prioritizing QOL now, many anticipated a decline in their quality over the next year, which is concerning in the context of curative breast cancer treatment. This suggests a need for enhanced supportive care

and better communication regarding treatment intentions for elderly patients. When the timeline was extended to five years, a larger proportion of patients favoured QOL at that point, but more individuals believed their QOL would diminish. This reflects potential concerns regarding the confidence of elderly patients in Singapore about healthy aging, even with curative treatment for their cancer. Moreover, older patients rated living independently and reducing or eliminating pain as more important outcomes than simply prolonging life, aligning with their desire for a fulfilling and healthy aging process. Introducing education on healthy aging earlier and focusing on maintaining overall health are likely vital to improving these patients' outlooks and should be considered in cancer survivorship programmes.

The results of the survey reflect the robust delivery of supportive care to patients with curable breast cancers within the SingHealth group of hospitals and specialist centres. We recognize that the provision of seamless and multidisciplinary care is feasible primarily within the context of a comprehensive cancer centre in a large tertiary unit. This model may not be easily applicable to single oncology practices due to the significant coordination required for the care of these patient groups.

Existing studies have typically examined individual aspects of patient well-being<sup>8–13</sup> such as sleep disturbances, fatigue, or body image concerns in isolation, and often within healthcare settings or populations that differ significantly from Singapore. In contrast, our study offers a more comprehensive assessment of psychological health in patients undergoing neoadjuvant therapy, capturing a broader spectrum of experiences within a local context. This holistic approach not only highlights unique patient needs but

**Table 5 | Baseline attitude scale outcomes among older patients**

	Total	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
Subscale 1: Tradeoffs between quality and quantity of life						
Q1. The most important thing to me is living as long as I can, no matter what my quality of life is.	37 (100)	3 (8.1)	5 (13.5)	6 (16.2)	11 (29.7)	12 (32.4)
Q2. I would rather live a shorter life than lose my ability to take care of myself (daily activities).	37 (100)	6 (16.2)	13 (35.1)	3 (8.1)	8 (21.6)	7 (18.9)
Q3. It is more important to me to maintain my thinking ability than to live as long as possible.	37 (100)	18 (48.6)	12 (32.4)	3 (8.1)	4 (10.8)	0 (-)
Q4. If I had to choose between living as long as possible or being free from pain, I would choose living as long as possible.	37 (100)	2 (5.4)	4 (10.8)	10 (27.0)	14 (37.8)	7 (18.9)
Total score						
Mean (SD)	14.5 (2.7)					
Median (IQR)	14 (12-16)					
Subscale 2: Tradeoffs between future and present health						
Q1. I am willing to have side effects right now if it means I could have a better quality of life in the future.	37 (100)	7 (18.9)	18 (48.6)	8 (21.6)	4 (10.8)	0 (-)
Q2. I would prefer to take fewer medications, even if it meant that I would not live as long.	37 (100)	1 (2.7)	5 (13.5)	13 (35.1)	16 (43.2)	2 (5.4)
Q3. I am willing to put up with more doctors' visits and dietary restrictions now if it means that in the future I will be less likely to develop a new disease.	37 (100)	9 (24.3)	14 (37.8)	13 (35.1)	1 (2.7)	0 (-)
Q4. I would prefer to have fewer medical tests and doctor visits, even if it meant that I would not live as long.	37 (100)	0 (-)	4 (10.8)	12 (32.4)	17 (45.9)	4 (10.8)
Q5. It is more important for me to feel well right now than to feel well in the future.	37 (100)	1 (2.7)	5 (13.5)	21 (56.8)	8 (21.6)	2 (5.4)
Q6. I would prefer to take fewer medications, even if it meant that my chances of dying would be higher.	37 (100)	0 (-)	4 (10.8)	14 (37.8)	17 (45.9)	2 (5.4)
Total score						
Mean (SD)	14.9 (3.1)					
Median (IQR)	15 (13-18)					

SD standard deviation, IQR interquartile range.

**Table 6 | Baseline now vs later tool outcomes among older patients**

	No. (%)	Expected QOL 1-year from now relative to QOL now (base = 100)		
		Lower	Same	Mean (SD)
<b>QOL now vs 1-year from now</b>				
Total	37 (100)	26 (70.3)	11 (29.7)	70.7 (22.4)
Rather have QOL now	19 (100)	14 (73.7)	5 (26.3)	66.3 (22.7)
Rather have QOL 1-year from now	18 (100)	12 (66.7)	6 (33.3)	75.3 (21.7)
<b>Expected QOL 5-year from now relative to QOL now (base = 100)</b>				
<b>Lower</b>				
<b>Same</b>				
<b>Mean (SD)</b>				
<b>Median (IQR)</b>				
<b>QOL now vs 5-year from now</b>				
Total	37 (100)	26 (70.3)	11 (29.7)	70.9 (21.8)
Rather have QOL now	10 (100)	8 (80.0)	2 (20.0)	64.0 (21.2)
Rather have QOL 5-year from now	27 (100)	18 (66.7)	9 (33.3)	73.5 (21.8)

SD standard deviation, IQR interquartile range.

also helps identify critical gaps in care, offering valuable insights to enhance the design and delivery of our neoadjuvant therapy program. To our knowledge, no prior study has assessed these psychosocial dimensions as broadly or within a similar patient cohort.

This survey provides valuable insights into the priorities of patients across different age groups. We recognize specific issues identified for the extremes of age can impact individuals across all age groups. However, this study was specifically designed to focus on disturbances most prevalent within age groups. In future research, we can broaden the scope to examine how these issues affect people across all age ranges, identifying similarities and differences in their impact. The field remains expansive, and further follow-up studies could offer deeper understanding and opportunities to improve outcomes and QOL for patients undergoing neoadjuvant treatment. Sexual functioning was assessed using the FSFI, which is only applicable to participants who were sexually active and had attempted intercourse within the four weeks prior to completing the questionnaire. At each assessment time point, fewer than 10 participants met this criterion. As a result, the sample size was insufficient to allow for a meaningful analysis. Areas for future research include exploring the reasons behind the lower likelihood of achieving pCR in elderly patients, conducting qualitative analyses of QOL, and investigating the role of sexual health in maintaining healthy relationships. These findings also support the need to design more targeted supportive care services for specific patient cohorts—for example, body image counselling for patients who have undergone mastectomy, and educational workshops or courses to help patients better understand their disease and manage their long-term health.

This study showcases the strength of our NAT program while identifying key areas for further development. Enhanced support during the immediate post-operative period, where patient needs are most acute, is essential. For younger women, prioritizing body image, sexual health, and relationship dynamics is crucial, while for older women, efforts should focus on boosting confidence in their long-term health following curative breast cancer treatments.

## Methods

### Study design and oversight

The PreSCella study is a prospective cohort study of patients with breast cancer treated with NAT at three centers within the SingHealth cluster's institutions. Patients completed various surveys at predefined timepoints (Fig. 1). These surveys were completed by patients using pen and paper facilitated by our study research coordinator. All patients completed the Functional Assessment of Cancer Therapy – Breast (FACT-B)<sup>45,46</sup> which is an instrument designed to measure five domains (physical, social, emotional, functional well-being, and breast cancer subscale) of QOL in patients with breast cancer. Younger patients under 40 years old completed (i) Body Image Scale (BIS)<sup>47</sup> which measured affective, behavioural and body image symptoms (10-item questionnaire), (ii) Dyadic Assessment Scale (DAS)<sup>48</sup> which measures an individual's perception of his or her relationship with an intimate partner (32-item questionnaire), and (iii) Female Sexual Function Index scoring (FSFI)<sup>49</sup> which measures the sexual functioning of women in six different domains (desire, arousal, lubrication, orgasm, satisfaction and pain) (19-item questionnaire). Older patients over 65 years old completed three validated outcome prioritization tools (i) Attitude Scale (AS) which rates agreement with outcome related statements, (ii) Now vs Later Tool (NLT) which related to the importance of QOL at three timepoints (today vs 1 or 5-year in the future) and (iii) Health Outcome Tool (HOT) which prioritizes outcomes (survival, independence, symptoms) using a visual analog scale.

This study was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, the principles of the Declaration of Helsinki and local clinical research regulations. The protocol was approved by the SingHealth Centralized Institutional Review Board (IRB Reference Number: 2020-2042). All patients provided written informed consent.

**Table 7 | Baseline health outcome tool scores among older patients**

	Mean (SD)	Median (IQR)	Compared with scores for keeping alive, scores for measure is			
			Total	Less	Same	More
Keeping alive	86.6 (15.5)	90 (80–100)	-	-	-	-
Maintaining independence	93.1 (15.1)	100 (95–100)	37 (100)	5 (13.5)	16 (43.2)	16 (43.2)
Reducing or eliminating pain	84.5 (18.4)	90 (80–100)	37 (100)	13 (35.1)	9 (24.3)	15 (40.5)
Reducing or eliminating dizziness, fatigue, shortness of breath	79.7 (16.9)	80 (70–90)	37 (100)	17 (45.9)	8 (21.6)	12 (32.4)

SD standard deviation, IQR interquartile range.

### Patients selection

Patients aged 21 and over who were diagnosed with non-metastatic breast cancers and planned for NAT at NCCS, Singapore General Hospital (SGH) and Sengkang General Hospital (SKH) were recruited into the study. Patients with bilateral breast cancers were included. For these patients, the side with the higher-stage tumour was selected for analysis. ER negative patients included patients with weak ER expression ( $\leq 10\%$ ) and progesterone receptor (PR) negative included patients with weak PR ( $\leq 10\%$ ) because of potentially limited benefit from adjuvant endocrine therapies. HER2 testing was in accordance with ASCO/CAP guidelines (updated 2018)<sup>50</sup>. Hormone receptor (HR) positive is defined as ER and/or PR positive ( $> 10\%$ ).

### Study procedures

Patients were treated with NAT according to local clinical practice. Clinical characteristics, treatment regimens, responses, and survival data were extracted from clinical records. All patients enrolled completed the FACT-B version 4 questionnaire at three timepoints: baseline before the start of NAT (T1), within two months post-breast surgery (T2) and a year from baseline (T3). Subgroups of patients (young women  $< 40$  years old and older women  $> 65$  years old) were identified to complete additional questionnaires as stated in study design (Table 1). These patients were also identified for longitudinal qualitative needs assessment study to investigate the evolution of supportive care needs throughout their breast cancer treatment journey. The qualitative needs assessment will be reported separately.

### Sample size

We expected to recruit 120 patients into the PreSCella study annually based on the number of new patient referrals to the NAT program at SingHealth. Of the 120 patients, we anticipated a 20% dropout rate and around 100 enrolled patients would have serial measures available for longitudinal evaluation. A sample of 100 patients would provide 80% power to detect an effect size of 0.28 in the mean change score of FACT-B between two timepoints with 5% significance level. Previous research suggested that effect sizes of 0.3 to 0.5 corresponded to minimally important differences for FACT-B<sup>51</sup>.

### Statistical analysis

Differences in categorical characteristics between different age groups were compared using Fisher's exact test. For continuous characteristics, comparisons between patient groups were made using the Kruskal-Wallis test.

Each questionnaire was scored according to specific scoring guidelines. Missing values in the FACT-B and the BIS form were also imputed as indicated in their scoring guideline. The mean scores in the FACT-B, BIS, DAS, and FSFI form at each assessment timepoint were estimated based on linear mixed effect models, with time-variables included as fixed factors, patient-specific random intercepts, and an unstructured covariance matrix. Each pairwise difference in the estimated mean score between assessment timepoints was tested based on an approximate t-test, and p-values were adjusted for multiple comparisons using the Tukey-Kramer method. The mean percentage of patients with body image difficulties (BIS score  $\geq 10$ ), patients who were distressed partners in their relationship (DAS score  $< 13$ ) and patients who had female sexual dysfunction (FSFI full scale score  $\leq 26$ ) at each assessment timepoint were estimated based on generalized linear

mixed effect models with a logit link function, time-variables as fixed factors, patient-specific random intercepts, and an unstructured covariance matrix. Study center effects were not accounted for in these models because SGH and SKH were satellite centers of NCCS. Patients who joined NAT program at these 3 sites would undergo the same treatment protocol and care under the same group of doctors; the only key difference being the venue where they received their doctor consultation and treatment.

All reported p-values were two-sided. A p-value  $< 0.05$  was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

### Data availability

The surveys that support the findings of this study are available from National Cancer Centre Singapore, but restrictions apply to the availability of these data, which were used under licence for the current study and so are not publicly available. The data are, however, available upon request and with the permission of the investigators.

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## Author contributions

H.Y.L, W.S.O and T.J.Y.T wrote the main manuscript text and prepared all figures and tables. W.S.O. interpreted and did statistical analysis of data.J.M, Z.Z., S.Y.T., Y.S.Y., J.J.C., R.S.Y.C.T., W.M.T., E.L., H.S., S.Y.B., L.T.S., W.Y.C., R.D., M.W, B.K.T.T, F.Y.W., K.M.V.T., T.J.T acquired patients for analysis.J.Y.T.T, G.M.J.Y., W.L.G., R.K., T.J.T. contributed to conception and

design of the study. All authors reviewed the manuscript, approved the submitted version. All authors agreed to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

### Competing interests

The authors declare no competing interests.

### Additional information

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