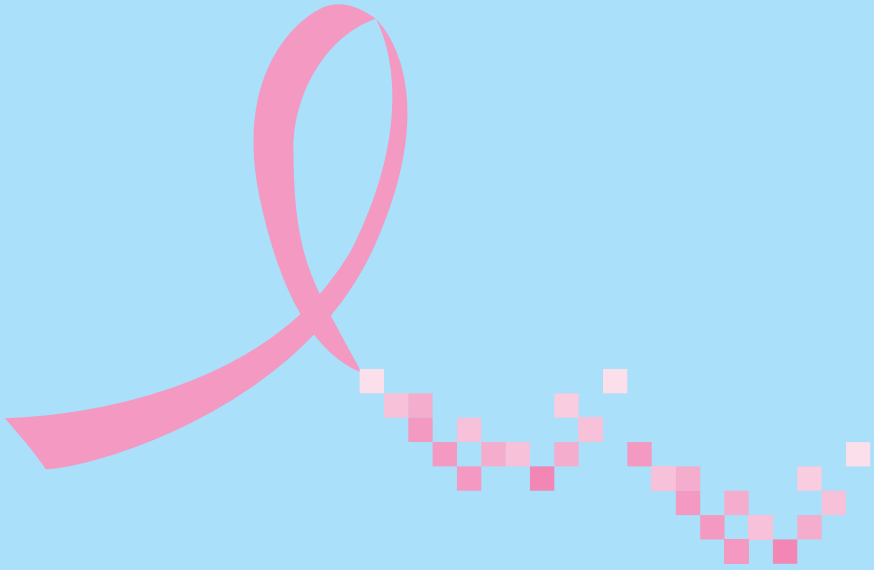

CHAPTER 2

DISEASE PATTERN, TREATMENT TREND AND CLINICAL OUTCOME OF BREAST CANCER IN HONG KONG

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I. Introduction

2.1 This chapter reviews the data collected from 3,998 breast cancer patients in the 2016-current cohort regarding their cancer's clinical presentation, cancer characteristics and treatment methods. The aim is to analyse the clinical management of breast cancer and identify the trends in disease and treatment in the local context in order to develop and improve the standard of care for breast cancer patients in Hong Kong.

KEY FINDINGS

The patients recruited in HKBCR, according to their year of cancer diagnosis, were divided into three cohorts (2006-2010, 2011-2015 and 2016-current). This report focused on analysing the data of patients diagnosed since 2016, with supplementary comparisons between the cohorts to highlight the changes over the past decade in breast cancer status, diagnosis and management. For more detailed findings in the previous two cohorts, please refer to Report 11.

Clinical presentation

- The primary method of first cancer detection was still self-detection by chance among the patients in the 2016-current cohort (80.0%), even though the proportion had slightly decreased, compared to those in the previous two cohorts (82.5%-84.2%).
- A slight increase in mammography-detected cases was observed throughout the three cohorts (from 9.6% to 13.0%). With such change, the proportion of detection of early stage cancer (stages 0-IIA) cases also increased while that of advanced stage cancer (stages III-IV) decreased.
- After onset of symptoms (mainly, painless lumps), the majority (71.3%) of patients who self-detected their cancer by chance in the 2016-current cohort sought their first medical consultation in three months. However, more patients were diagnosed with stage IV disease among those who sought medical consultation after 12 months (10.5%) than those within 12 months (2.2%-5.1%), notwithstanding that this proportion had dropped throughout the three cohorts.
- In each cohort, the most common cancer stage at diagnosis was stage II (34.9%-38.5%) followed by stage I (31.0%-31.2%) and stages III-IV (14.3%-17.7%). In addition, 11.6%-13.3% of the patients in the three cohorts were diagnosed with stage 0 – in situ cancer.

Cancer characteristics

- The mean size of tumours of invasive breast cancer in the 2016-current cohort was 2.2cm (standard deviation: ±1.4cm). The majority of the patients (43.2%) had tumours of sizes 2.01 to 5.00cm; followed by 1.01 to 2.00cm (37.0%). The proportion of patients with no positive lymph nodes slightly increased throughout the three cohorts (from 56.3% to 61.3%). The most common type was invasive carcinoma of no specific type (86.9%-87.5%). Estrogen receptor (ER) positive or progesterone receptor (PR) positive cases increased (from 76.3% to 82.8% and 63.9% to 69.4%, respectively), while there were less HER2 positive cases in the 2016-current cohort (18.1%) based on the 2018 guideline.[41]

- The mean size of tumours of in situ breast cancer in the 2016-current cohort was 1.6cm (standard deviation: ±1.4cm). Of the in situ cases where mammography was performed, 59.1% showed microcalcification. Similar to the previous two cohorts, ductal cancer (94.6%) was the most common type of in situ breast cancer. Similar to the trend observed in invasive cancer throughout the three cohorts, ER or PR positive cases increased (from 80.4% to 83.3% and 71.2% to 77.1%, respectively), whereas HER2 positive cases decreased (from 28.9% to 16.9%).

Treatment

- Of the 3,998 patients in the 2016-current cohort, 15.6% received care at private medical service, 50.9% received care at public medical service and 33.5% received care at both private and public medical services.

- Surgery
  - The proportion of patients who underwent mastectomy dropped throughout the cohorts (from 65.7% to 58.2% in invasive cancer cases and 47.6% to 39.9% in in situ cases). In contrast, more patients opted for breast-conserving surgery (from 32.5% to 39.1% in invasive cancer cases and 51.9% to 57.5% in in situ cases).
  - Such change was observed in both private and public medical facilities. In addition, more patients underwent reconstruction after mastectomy at private medical facilities than at public medical facilities.
  - The percentage of the patients who underwent mastectomy was positively correlated with both increasing age and cancer stage in all three cohorts.
  - Most (91.0%) of the patients in the 2016-current cohort underwent nodal surgery. Among patients with negative clinical nodal status, the proportion of patients who had undergone sentinel node biopsy alone increased throughout the cohorts (from 45.2% to 80.8%), whereas the use of axillary dissection alone decreased (from 41.5% to 9.0%).
  - The use of axillary dissection without sentinel node biopsy was positively correlated with increasing cancer stage in all three cohorts.

- Radiotherapy
  - In the 2016-current cohort, 63.6% of the patients had locoregional radiotherapy as part of their invasive cancer treatment. While nearly all (92.5%-94.9%) the patients who underwent breast-conserving surgery received radiotherapy, the uptake increased with progressing cancer stage among patients who had undergone mastectomy. These findings were similar to those in the previous two cohorts.

- Chemotherapy
  - In the 2016-current cohort 59.0% of the patients with invasive cancer underwent chemotherapy. The use of neoadjuvant chemotherapy increased with progressing cancer stage from stage I to III, as observed in the previous two cohorts. While the overall use of neoadjuvant chemotherapy increased, the use of adjuvant chemotherapy decreased throughout the three cohorts.
  - In adjuvant setting, first generation of chemotherapy drugs used by all biological subtypes decreased. The use of HER2 regimen in luminal B (HER2 positive) and HER2-enriched breast cancer increased throughout the cohorts.
  - While the use of the first generation of chemotherapy drugs was lower among the patients with early stage (stages I-IIA) disease, the use of second generation drugs increased in the 2016-current cohort in adjuvant setting compared to the previous cohorts.

- Endocrine therapy
  - In the 2016-current cohort, 68.9% of the patients were treated with endocrine therapy. While there was a slight decrease in the use of endocrine therapy among patients with stage 0, IIB and III cancer, an increase was found among those with stage I cancer throughout the three cohorts.
- Anti-HER2 targeted therapy
  - The use of anti-HER2 targeted therapy increased from 43.1% to 81.6% throughout the three cohorts. While the use in adjuvant setting decreased (from 94.5% to 77.1%), the use in neoadjuvant setting increased (from 3.4% to 18.6%). Overall, more patients with stages I-III disease adopted the use of anti-HER2 targeted therapy throughout the three cohorts.

Patient status

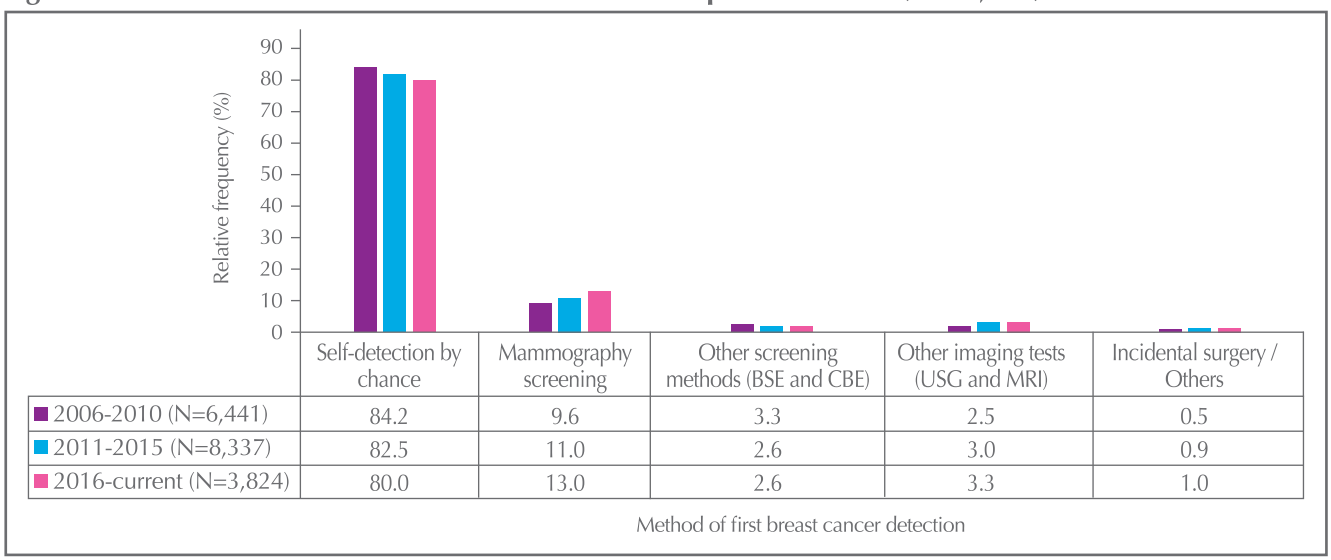
- Combining the three cohorts, a total of 17,877 patients were studied to examine the survival aspects of the patients. The mean and median follow-up period were 4.4 and 3.8 years respectively.
- Of the patients who have been followed up, 1.7% experienced only locoregional recurrence, 2.4% experienced only distant recurrence, and 1.6% experienced both locoregional and distant recurrence.
- The common sites for locoregional recurrence were chest wall (34.2%), breast (31.3%) and axilla (34.4%), while the top four organs involved in distant recurrence were bone (56.5%), lung (46.5%), liver (38.7%) and brain (18.8%).

II. Clinical presentation

2.2 The primary method of first breast cancer detection in the patient cohort was self-detection by chance (80.0%) (Figure 2.1). Detection through healthcare service-assisted screening methods, including clinical breast examination (CBE), mammography screening (MMG) and ultrasound screening (USG) constituted a small proportion (18.6%). Compared to Western countries, the uptake of MMG, in particular, was low (13.0%). A study in the United States (US), for instance, found that 43% of the breast cancer cases were detected through MMG.[42]

2.3 In terms of the types of medical service received, the proportion of the patients who self-detected their breast cancer by chance was higher among public medical service users (84.9%) or mixed private/public medical service users (79.5%) than among private medical service users (64.8%). In contrast, the proportion of the patients who first detected their breast cancer through MMG was higher among private medical service users (23.9%) than among public medical service users (9.6%) or mixed private/public medical service users (13.2%) (Table 2.1).

Figure 2.1: Method of first breast cancer detection in the patient cohorts (N=18,602)



	Self-detection by chance	Mammography screening	Other screening methods (BSE and CBE)	Other imaging tests (USG and MRI)	Incidental surgery / Others
2006-2010 (N=6,441)	84.2	9.6	3.3	2.5	0.5
2011-2015 (N=8,337)	82.5	11.0	2.6	3.0	0.9
2016-current (N=3,824)	80.0	13.0	2.6	3.3	1.0

Table 2.1: Method of first breast cancer detection by type of medical service users (N=3,824)

	Type of medical service users, Number (%)		
	Private	Public	Mixed private / public
Self-detection by chance	383 (64.8)	1,656 (84.9)	1,020 (79.5)
Mammography screening	141 (23.9)	188 (9.6)	169 (13.2)
Other screening methods (BSE and CBE)	10 (1.7)	57 (2.9)	33 (2.6)
Other imaging tests (USG and MRI)	48 (8.1)	29 (1.5)	51 (4.0)
Incidental surgery / others	9 (1.5)	20 (1.0)	10 (0.8)

BSE: Breast self-examination; CBE: Clinical breast examination; USG: Ultrasound screening; MRI: Magnetic resonance imaging

2.4 Studies have shown that MMG is effective in detecting early cancer when there are neither signs nor symptoms that can be observed by patients or medical professionals.[43] While self-detection could pick up only 8.4% of in situ breast cancer, MMG could detect 37.2% (Table 2.2). Such higher rate of in situ tumour detection rate was also reflected in Table 2.3, which showed that MMG detected a much higher proportion of early stage cancer cases than advanced stage cancer cases; 84.3% detected were stages 0-I (Table 2.3).

Table 2.2: Method of first breast cancer detection by type of cancer (N=3,796)

	Type of cancer, Number (%)	
	Invasive	In situ
Self-detection by chance	2,782 (91.6)	255 (8.4)
Mammography screening	310 (62.8)	184 (37.2)
Other screening methods (BSE and CBE)	85 (85.9)	14 (14.1)
Other imaging tests (USG and MRI)	87 (68.5)	40 (31.5)
Incidental surgery / others	27 (69.2)	12 (30.8)

BSE: Breast self-examination; CBE: Clinical breast examination; USG: Ultrasound screening; MRI: Magnetic resonance imaging

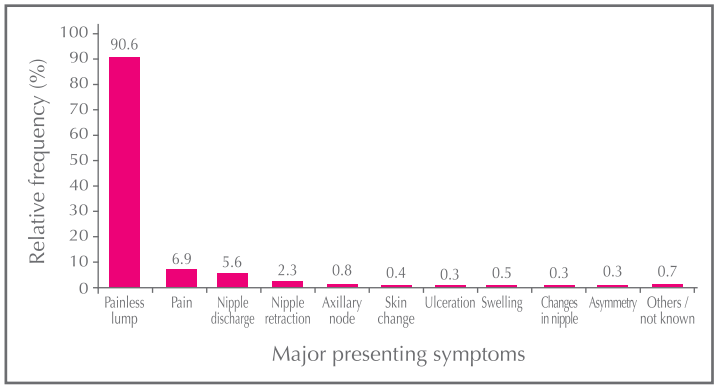
Table 2.3: Method of first breast cancer detection by cancer stage (N=3,580)

	Cancer stage, Number (%)					
	0	I	IIA	IIB	III	IV
Self-detection by chance	253 (8.9)	848 (29.9)	802 (28.2)	419 (14.8)	432 (15.2)	86 (3.0)
Mammography screening	182 (37.7)	225 (46.6)	55 (11.4)	10 (2.1)	9 (1.9)	2 (0.4)
Other screening methods (BSE and CBE)	14 (14.7)	37 (38.9)	18 (18.9)	9 (9.5)	16 (16.8)	1 (1.1)
Other imaging tests (USG and MRI)	40 (32.3)	62 (50.0)	17 (13.7)	2 (1.6)	2 (1.6)	1 (0.8)
Incidental surgery / others	11 (28.9)	13 (34.2)	7 (18.4)	2 (5.3)	4 (10.5)	1 (2.6)

BSE: Breast self-examination; CBE: Clinical breast examination; USG: Ultrasound screening; MRI: Magnetic resonance imaging

2.5 Most (90.6%) patients who self-detected their cancer by chance found a painless lump on their breast(s). Pain is not usually a symptom of breast cancer; only 6.9% of the patients felt pain in their breast(s) at initial presentation. A small proportion of patients (8.2%) experienced changes in nipple (such as nipple discharge, nipple retraction, redness, scaliness or thickening of nipple) (Figure 2.2).

Figure 2.2: Major presenting symptoms of self-detected* breast cancer in the patient cohort (N=3,059)



*Self-detection by chance only

A. *Time interval between the onset of symptoms and first medical consultation*

2.6 Longer delay in seeking medical consultation is associated with higher probability of local cancer spread or distant metastasis and poorer prognosis.[44] After the onset of symptoms, only about one-third (35.0%) of the patients who self-detected their cancer by chance sought first medical consultation in less than one month (Table 2.4). Slightly more than one-quarter (28.7%) waited more than three months before seeking first medical consultation.

2.7 The proportion of the patients who sought first medical consultation in less than one month was higher among private medical service users (46.4%) than among public medical service users (28.1%) (Table 2.5).

Table 2.4: Time interval between onset of symptoms and first medical consultation for patients who self-detected* their cancer (N=868)

	Number	%
Less than 1 month	304	35.0
1-3 months	315	36.3
4-12 months	182	21.0
More than 12 months	67	7.7

*Self-detection by chance only

Table 2.5: Time interval between onset of symptoms and first medical consultation for patients who self-detected* their cancer by type of medical service users (N=868)

	Type of medical service users, Number (%)		
	Private	Public	Mixed private / public
Less than 1 month	52 (46.4)	141 (28.1)	111 (43.7)
1-3 months	38 (33.9)	192 (38.2)	85 (33.5)
4-12 months	19 (17.0)	123 (24.5)	40 (15.7)
More than 12 months	3 (2.7)	46 (9.2)	18 (7.1)

*Self-detection by chance only

2.8 A much higher proportion (10.5%) of the patients who sought first medical consultation after 12 months of symptom onset was diagnosed with stage IV disease than those who sought first medical consultation in less than one month (2.2%) (Table 2.6).

Table 2.6: Cancer stage at diagnosis among self-detected* patients by time interval between onset of symptoms and first medical consultation (N=759)

	Time interval between onset of symptoms and first medical consultation, Number (%)			
	Less than 1 month	1-3 months	4-12 months	More than 12 months
Stage I	99 (36.5)	89 (32.4)	47 (30.1)	15 (26.3)
Stage IIA	91 (33.6)	85 (30.9)	51 (32.7)	21 (36.8)
Stage IIB	45 (16.6)	55 (20.0)	22 (14.1)	8 (14.0)
Stage III	30 (11.1)	37 (13.5)	28 (17.9)	7 (12.3)
Stage IV	6 (2.2)	9 (3.3)	8 (5.1)	6 (10.5)

*Self-detection by chance only

III. Cancer characteristics

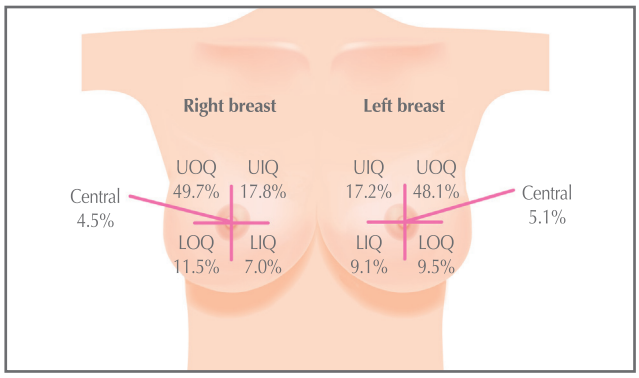
2.9 Breast cancer can occur in one (unilateral) or both breasts (bilateral). The majority (95.1%) of the patients had unilateral breast cancer, while a very small proportion (2.8%) had synchronous bilateral breast cancer at first diagnosis (Table 2.7). Another 2.1% developed contralateral breast cancer after diagnosis of an initial primary breast cancer.

Table 2.7: Number of patients and breast cancer cases in the patient cohort

	No. of patients	No. of cases	Time interval for metachronous cases, median (range) (years)
Unilateral	**3,691**	**3,691**	—
Bilateral (synchronous)	**109**	**218**	—
All bilateral (metachronous) cases	**83**	**89**	**7.8 (1.0 – 21.1)**
Bilateral (metachronous) - Initial diagnosis happened within 2016-current	*6*	*12*	*1.4 (1.0 – 2.7)*
Bilateral (metachronous) - Initial diagnosis happened within 2011-2015	*27*	*27*	*4.9 (1.4 – 8.3)*
Bilateral (metachronous) - Initial diagnosis happened within 2006-2010	*33*	*33*	*8.6 (5.5 – 12.0)*
Bilateral (metachronous) - Initial diagnosis happened before 2006	*17*	*17*	*15.6 (11.0 – 21.1)*

2.10 As regards the location of malignant breast tumour, about half of the breast cancer cases in either the left (48.1%) or the right (49.7%) breast were detected in the upper outer quadrant (Figure 2.3).

Figure 2.3: Locations of malignant tumour on breasts within the patient cohort (N=3,998)



UOQ: Upper outer quadrant UIQ: Upper inner quadrant
LOQ: Lower outer quadrant LIQ: Lower inner quadrant
Note: Figures include multicentric cancers

A. Diagnostic tests for breast cancer

2.11 There are two types of breast cancer diagnostic tests: imaging tests and biopsies. Imaging tests include diagnostic MMG, USG and magnetic resonance imaging (MRI). Diagnostic MMG is the main procedure for breast cancer diagnosis, and USG is used to distinguish a solid mass, which may be cancer, from a fluid-filled cyst, which is usually not cancer. Breast MRI is usually performed on women who have been diagnosed with breast cancer to find out the extent of the disease and also to check the other breast for cancer.

2.12 For cancer diagnosis, MMG was used on 87.7% of the patients and USG on 85.4%, while MRI was used on only 12.3% of the patients (Table 2.8). Results of imaging tests are classified into categories using a system called the Breast Imaging Reporting and Data System (BIRADS). BIRADS 4 or 5 are suspected breast cancer and should be checked by further surgical tests such as biopsies.

Table 2.8: Sensitivity and diagnostic results of breast imaging tests (N=3,998)

	Mammography	Breast ultrasound	MRI
Proportion of patients using the test	**87.7%**	**85.4%**	**12.3%**
Overall sensitivity*	**91.1%**	**95.2%**	**98.4%**
BIRADS category			
Diagnostic / malignant (BIRADS 5)	1,032 (29.4%)	1,068 (31.3%)	413 (83.8%)
Suspicious abnormality (BIRADS 4)	2,161 (61.6%)	2,181 (63.9%)	72 (14.6%)
Probably benign (BIRADS 3)	104 (3.0%)	109 (3.2%)	6 (1.2%)
Benign (BIRADS 2)	102 (2.9%)	40 (1.2%)	1 (0.2%)
Normal (BIRADS 1)	90 (2.6%)	15 (0.4%)	1 (0.2%)
Incomplete (BIRADS 0)	17 (0.5%)	1 (<0.1%)	0 (0.0%)

MRI: Magnetic resonance imaging; BIRADS: Breast Imaging Reporting and Data System
*Sensitivity: Number of true positives (BIRADS 4-5) divided by total number of patients who had the test

2.13 Opacity was observed in 71.9% of the patients with BIRADS 4 or 5 mammograms, while microcalcification was observed in 42.3% (Table 2.9). The mammographic density of a woman's breasts affects the sensitivity of mammography. Heterogeneously dense breast may obscure small masses, while extremely dense breast lowers the sensitivity of mammography. In the cohort, about three-quarters (72.7%) of the patients had heterogeneously dense breasts, while 9.0% had extremely dense breasts (Figure 2.4). Mammographic density of a woman's breasts declines with increasing age. The proportion of patients with extremely dense breast decreases significantly from 25.0% among patients aged between 20 and 29 to 3.8% among patients aged 70 and above (Table 2.10).

Table 2.9: Mammographic findings of patients diagnosed through mammography (N=3,193)

	Number	%
Opacity	2,296	71.9
Microcalcification	1,351	42.3
Architectural distortion	427	13.4
Asymmetric density	133	4.2
Unclassified	242	7.6

Note: The total percentages may exceed 100 as multiple mammographic abnormalities may be found.

Figure 2.4: Mammographic density of breasts of patients diagnosed through mammogram (N=1,869)

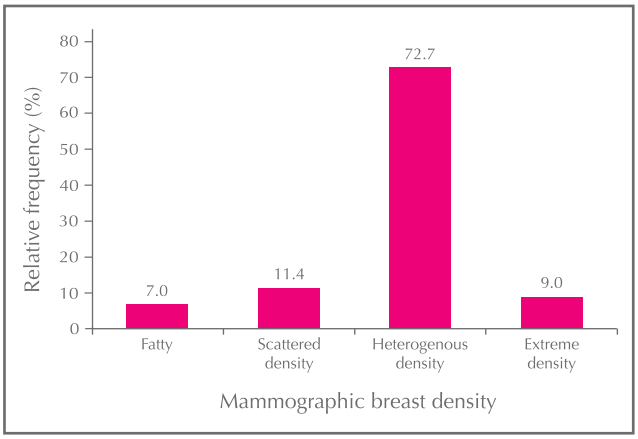


Table 2.10: Mammographic density of breasts of patients diagnosed through mammogram by age group (N=1,837)

	Age group, Number (%)					
	20-29	30-39	40-49	50-59	60-69	≥70
Fatty	0 (0.0)	1 (0.8)	19 (4.2)	30 (4.9)	49 (10.3)	28 (17.9)
Scattered density	1 (8.3)	7 (5.3)	36 (8.0)	63 (10.3)	74 (15.6)	29 (18.6)
Heterogeneous density	8 (66.7)	98 (74.8)	323 (71.8)	479 (78.0)	333 (70.3)	93 (59.6)
Extreme density	3 (25.0)	25 (19.1)	72 (16.0)	42 (6.8)	18 (3.8)	6 (3.8)

2.14 Biopsies (samplings of breast cells or tissues for examination) for breast cancer diagnosis include fine needle aspiration (FNA), core needle biopsy (CNB) and excisional biopsy. As a standard of care, biopsies are for confirming before surgery if a breast lesion is malignant. FNA and CNB are less invasive sampling methods and used more often, but sometimes an excisional biopsy, which removes a relatively larger portion of breast tissue, is necessary. FNA and/or CNB were performed in the majority (89.0%) of the patients and among them, 10.0% received only FNA; 67.6% received only CNB, while 22.4% received both FNA and CNB. In addition, 4.8% of the patients had excisional biopsy. Excisional biopsy had the highest overall sensitivity of 100%, followed by CNB (99.7%) and FNA (92.5%) (Table 2.11).

Table 2.11: Sensitivity and diagnostic results of breast tissue biopsies (N=3,998)

	FNA		CNB		Excisional biopsy	
Proportion of patients using the test	**28.8%**		**80.0%**		**4.8%**	
Overall sensitivity*	**92.5%**		**99.7%**		**100.0%**	
Class						
Diagnostic / malignant (Class V)	808	(70.1%)	3,102	(96.9%)	193	(100.0%)
Suspicious (Class IV)	149	(12.9%)	57	(1.8%)	—	
Atypical (Class III)	110	(9.5%)	31	(1.0%)	—	
Benign (Class II)	25	(2.2%)	5	(0.2%)	—	
Scanty benign (Class I)	54	(4.7%)	5	(0.2%)	—	
Incomplete (Class 0)	7	(0.6%)	0	(0.0%)	—	

FNA: Fine needle aspiration; CNB: Core needle biopsy

*Sensitivity: Number of true positives (Class III-V) divided by total number of patients who had the test

B. Methods of cancer staging

2.15 Cancer staging is the process of finding out the extent of the disease in the body pre-operatively after diagnosis of breast cancer. Cancer staging is essential for patients with clinically node positive or locally advanced disease. Patients who only had chest x-ray are considered not having adequate workup for cancer stage to be determined.

2.16 The proportion of patients with invasive breast cancer who did not have any cancer staging as part of their diagnosis and treatment was 54.7%. Among those patients who had cancer staging as part of their treatment, positron emission tomography scan (PET scan) was the most common method (73.4%), followed by a combination of chest x-ray and ultrasound of abdomen (15.3%) (Table 2.12).

Table 2.12: Method of cancer staging among invasive breast cancer patients (N=1,471)

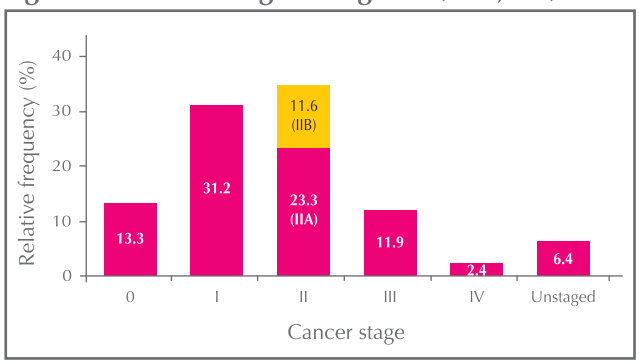
	Number	%
Positron emission tomography scan (PET scan)	1,080	73.4
Chest x-ray (CXR) and ultrasound abdomen (USG Abd)	225	15.3
Computed tomography of body parts*	133	9.0
Bone scan	30	2.0
Magnetic resonance imaging whole body (MRI whole body)	21	1.4
Others (e.g. bone x-ray)	43	2.9
Not known	12	0.8

* Body parts include thorax, abdomen, pelvis, brain, or whole body

Note: The total percentages may exceed 100 as multiple methods of cancer staging may be used.

2.17 The American Joint Committee on Cancer (AJCC) Anatomic Breast Cancer Staging (8th edition)[45] is used for determining cancer staging in the patient cohort. There are two stage groups according to this system: anatomic stage and prognostic stage groups. The anatomic stage group assigns a cancer stage based on the anatomic information on the tumour (T), regional nodes (N), and distant metastases (M) categories. The prognostic stage group, in conjunction with the aforementioned anatomic information (i.e. TNM categories), also takes into account other factors, including the tumour grade, biomarkers [human epidermal growth factor receptor 2 (HER2), estrogen receptor (ER), progesterone receptor (PR)] expression and genomic assays in assigning a stage. Although prognostic stage group was recommended for patient care and was used for reporting of all cancer patients in the US starting from 2018, it was not used in this report. The reason was that the patients in the cohort were mostly diagnosed in 2016 to 2017 and the treatment offered to patients in the cohort was based on the prevailing anatomic stage group. It is noted that there is only minimal difference in the TNM anatomic staging between the 7th and 8th edition. The most common cancer stage at diagnosis was stage II (34.9%) followed by stages III-IV (14.3%). In addition, 13.3% of the patients were diagnosed with in situ cancer (stage 0) (Figure 2.5).

Figure 2.5: Cancer stage at diagnosis (N=3,998)

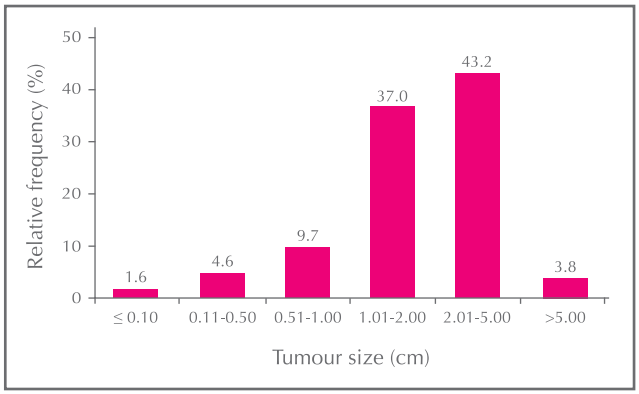


2.18 Of the 3,998 breast cancer cases analysed, data from 3,840 cases with available pathology data were used for subsequent analyses on cancer characteristics. A total of 3,318 (86.4%) patients were diagnosed with invasive cancer, while 520 (13.5%) patients were diagnosed with in situ cancer. In addition, 2 (0.1%) cases were diagnosed with occult primary breast cancer.

C. Characteristics of invasive breast cancer

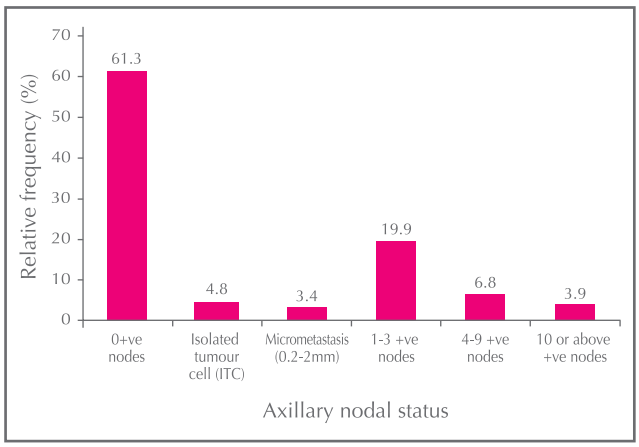
2.19 The mean size of tumours of invasive breast cancer in the patient cohort was 2.2cm (range: 0.01 to 20.0cm; standard deviation: ±1.4cm). Tumours of one cm or less in size were found in 15.9% of the patients, while tumours of sizes 1.01 to 5.0cm were found in 80.2% of the patients (Figure 2.6). Only 3.8% of the patients had tumours of sizes exceeding five cm. It was also found that tumours of screen-detected cancer were significantly smaller than those self-detected by chance (mean: 1.3±0.9cm vs. 2.4±1.5cm; p<0.001).

Figure 2.6: Distribution of tumour size (cm) of invasive breast cancer (N=2,682)



2.20 Lymph node status is one of the factors used for determining breast cancer stage. Multiple affected lymph nodes signify a higher disease stage. Of the patients with invasive breast cancer, 61.3% had no positive axillary lymph nodes, 4.8% had isolated tumour cells (metastasis size ≤ 0.2mm or a cluster of fewer than 200 tumour cells), 3.4% had micrometastasis (metastasis size > 0.2mm to ≤ 2 mm), while 30.6% had at least one positive axillary lymph node with metastasis size larger than two mm (Figure 2.7).

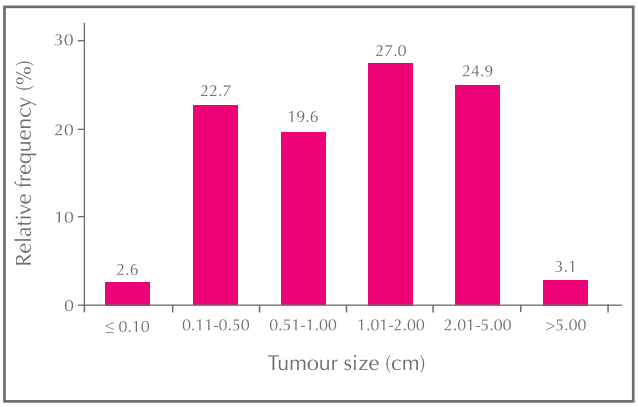
Figure 2.7: Number of positive axillary lymph nodes among patients with invasive breast cancer (N=3,064)



D. Characteristics of in situ breast cancer

2.21 The mean size of tumours of in situ breast cancer in the patient cohort was 1.6cm (range: 0.04 to 8.5cm; standard deviation: ±1.4cm). Tumours of one cm or less in size were found in 44.9% of the patients while tumours of 2.01 to 5.0cm in size were found in 24.9% of the patients (Figure 2.8). Only 3.1% of the patients had in situ tumours larger than five cm. Of the in situ breast cancer cases where MMG was performed, 59.1% showed microcalcification.

Figure 2.8: Distribution of tumour size (cm) of in situ breast cancer (N=418)



IV. Histological and biological characteristics

2.22 Breast cancer is a heterogeneous group of tumours, consisting of different histologic subtypes with diverse microscopic appearances. The histological data of breast carcinomas provide valuable prognostic information. They complement other independent parameters including size, grade, nodal status, hormonal receptor status and HER2 oncogene status to help predict the likelihood of recurrence and response to treatment.

A. Invasive breast cancer

2.23 As far as histological characteristics, grading, multifocality and multicentricity of invasive breast cancer in the patient cohort are concerned, 87.5% was invasive carcinoma of no specific type (Table 2.13) and 29.9% of the invasive tumours are of grade 3 (Table 2.14).

Table 2.13: Histological type of invasive breast cancer (N=3,318)

	Number	%
Invasive carcinoma of no specific type	2,903	87.5
Lobular	140	4.2
Mucinous (colloid)	87	2.6
Papillary	34	1.0
Mixed ductal and lobular	20	0.6
Tubular	15	0.5
Micropapillary	14	0.4
Carcinoma with medullary features	10	0.3
Metaplastic carcinoma	10	0.3
Carcinoma with apocrine features	5	0.2
Adenoid cystic carcinoma	4	0.1
Cribriform carcinoma	4	0.1
Carcinoma with neuroendocrine features	3	0.1
Tubulo-lobular	2	0.1
Lipid rich carcinoma	1	<0.1
Others (e.g. mixed types)	46	1.4
Not known	20	0.6

Table 2.14: Grading, multifocality and multicentricity of invasive breast cancer (N=3,318)

	Number	%
Grade		
Grade 1	587	17.7
Grade 2	1,259	37.9
Grade 3	991	29.9
Not known	481	14.5
Lymphovascular invasion	**718**	**21.6**
Multifocality	**319**	**9.6**
Number of foci		
2	184	57.7
3-4	57	17.9
5 or more	24	7.5
Not known	54	16.9
Multicentricity	**71**	**2.1**
Number of quadrants		
2	58	81.7
3	2	2.8
4	2	2.8
Not known	9	12.7

2.24 Among the 3,318 patients with invasive breast cancer, 97.1% were tested for ER or PR status. Among them, 83.4% were either ER or PR positive. Using immunohistochemistry (IHC), score 3 is considered as c-erbB2/HER2 positive and score 0 or 1 is considered as negative. As for score 2 (equivocal), it is also considered as HER2 positive, if the results are positive in the in situ hybridization (ISH) test. Based on the 2018 guideline[41] most of the cases classified as equivocal previously (i.e. cases with low HER2 copy number, or low HER2:CEP17 ratio) are now classified as negative. In the patient cohort, 18.1% of invasive breast cancer cases were c-erbB2/HER2 positive. The biological characteristics of invasive breast cancer in the patient cohort are shown in Table 2.15.

Table 2.15: Biological characteristics of invasive breast cancer (N=3,318)

	Number	%
Estrogen receptor (ER) [97.1% of the patients had the test]		
Positive	2,668	82.8
Negative	554	17.2
Progesterone receptor (PR) [96.7% of the patients had the test]		
Positive	2,226	69.4
Negative	982	30.6
c-erbB2 / HER2 [94.0% of the patients had the test]		
Positive (IHC Score 3)	485	15.5
Equivocal (IHC Score 2) ISH positive	81	2.6
Equivocal (IHC Score 2) ISH equivocal	52	1.7
Equivocal (IHC Score 2) ISH negative	492	15.8
Equivocal (IHC Score 2) ISH not done	303	9.7
Negative (IHC Score 0 / 1)	1,707	54.7
Ki-67 index [70.6% of the patients had the test]		
<14%	738	31.5
≥14%	1,603	68.5

HER2: Human epidermal growth factor receptor 2; IHC: Immunohistochemistry; ISH: In situ hybridization

2.25 Breast cancer is well known to be a heterogeneous disease and can be further classified into several biological subtypes[46] by immunohistochemical staining of several biological markers (Table 2.15). While amplification or over-expression of HER2 oncogene is associated with the development of certain types of breast cancer, further prognostic and predictive information can be obtained by assessing these biological markers together, rather than separately. The surrogate definitions of these intrinsic biological subtypes and their relative frequencies by cancer stage in the patient cohort are shown in Table 2.16.

Table 2.16: Biological subtypes of invasive tumours by cancer stage (N=2,945)

	Cancer stage, Number (%)									
	I		IIA		IIB		III		IV	
Luminal A*	385	(33.5)	168	(19.5)	55	(13.1)	53	(12.2)	5	(6.2)
Luminal B (HER2 negative)#	353	(30.7)	308	(35.8)	167	(39.8)	129	(29.7)	31	(38.3)
Luminal A/B (HER2 negative)†	171	(14.9)	136	(15.8)	84	(20.0)	96	(22.1)	19	(23.5)
Luminal B (HER2 positive)^	90	(7.8)	103	(12.0)	42	(10.0)	58	(13.3)	11	(13.6)
HER2-enriched❇	67	(5.8)	56	(6.5)	24	(5.7)	48	(11.0)	7	(8.6)
TNBC§	82	(7.1)	90	(10.5)	48	(11.4)	51	(11.7)	8	(9.9)

* Luminal A: ER and/or PR+, HER2-, and low Ki-67 index (<14%)

\# Luminal B (HER2 negative): ER and/or PR+, HER2-, and high Ki-67 index (≥14%)

† Luminal A/B (HER2 negative): ER and/or PR+, HER2-, and Ki-67 index not known

^ Luminal B (HER2 positive): ER and/or PR+, HER2+, and any Ki-67 index

❇ HER2-enriched: ER and PR-, HER2+, and any Ki-67 index

§ TNBC (Triple Negative Breast Cancer): ER and PR-, HER2-, and any Ki-67 index

B. *In situ breast cancer*

2.26 Ductal cancer was found to be the most common type of in situ breast cancer (94.6%). Table 2.17 shows the histological characteristics, grading, multifocality and multicentricity of in situ breast cancer in the patient cohort.

Table 2.17: Histological type, grading, multifocality and multicentricity of in situ breast cancer (N=520)

	Number	%
Histological type		
Ductal	492	94.6
Papillary	6	1.2
Mixed	5	1.0
Encapsulated papillary	5	1.0
Apocrine	2	0.4
Cribriform	2	0.4
Intracystic papillary	1	0.2
Others	3	0.6
Not known	4	0.8
Necrosis	**134**	**25.8**
Nuclear grade		
Low	150	28.8
Intermediate	184	35.4
High	151	29.0
Not known	35	6.7
Multifocality	**54**	**10.4**
Number of foci		
2	30	55.6
3	5	9.3
4 or more	0	0.0
Not known	19	35.2
Multicentricity	**7**	**1.3**
Number of quadrants		
2	6	85.7
3	0	0.0
Not known	1	14.3

2.27 Of the 520 patients with in situ breast cancer, 54.0% were tested for ER or PR status. Among them, 83.6% were either ER or PR positive. In addition, 16.9% of the in situ breast cancer patients were HER2 positive. Table 2.18 shows the biological characteristics of in situ breast cancer in the patient cohort.

Table 2.18: Biological characteristics of in situ breast cancer (N=520)

	Number	%
Estrogen receptor (ER) [54.0% of the patients had the test]		
Positive	234	83.3
Negative	47	16.7
Progesterone receptor (PR) [52.1% of the patients had the test]		
Positive	209	77.1
Negative	62	22.9
c-erbB2/HER2 [46.5% of the patients had the test]		
Positive (IHC score 3)	41	16.9
Equivocal (IHC Score 2) ISH positive	0	0.0
Equivocal (IHC Score 2) ISH equivocal	0	0.0
Equivocal (IHC Score 2) ISH negative	2	0.8
Equivocal (IHC Score 2) ISH not done	80	33.1
Negative (IHC Score 0 / 1)	119	49.2
Ki-67 index [42.5% of the patients had the test]		
<14%	124	56.1
≥14%	97	43.9

HER2: Human epidermal growth factor receptor 2;
IHC: Immunohistochemistry; ISH: In situ hybridization

V. Treatment methods

2.28 Of the 3,998 patients, 15.6% received care at private medical service, 50.9% received care at public medical service, and 33.5% received care at both private and public medical services. Patients with invasive cancer are usually given multimodality treatments, which may include surgery, chemotherapy, anti-HER2 targeted therapy, endocrine therapy and radiotherapy. In contrast, patients with in situ cancer require less aggressive treatments including surgery, endocrine therapy, and radiotherapy. Chemotherapy and anti-HER2 targeted therapy are generally not required for patients with in situ cancer. These treatments, except surgery, may be applied in adjuvant (after surgery), neoadjuvant (before surgery) or palliative (for metastatic disease) settings according to the stage of disease at diagnosis.

A. Surgical treatment

2.29 Surgery is an important consideration in the effective treatment of both in situ and invasive breast cancer. With the continuing developments in breast cancer treatment, surgery is less disfiguring nowadays. Options for local treatment include breast-conserving surgery or total mastectomy. Breast-conserving surgery followed by radiotherapy gives equivalent survival rates compared with mastectomy. Women who have a mastectomy may decide to have breast reconstruction, either at the same time or at a later stage.

2.30 Nodal surgery is usually performed together with breast surgery to ascertain the extent of disease. Lymph node surgery includes sentinel lymph node biopsy (SNB) or axillary dissection (AD). For patients with negative clinical nodal status, SNB can be conducted before AD to determine whether any lymph node is affected. This is to prevent lymphoedema which may occur when a large number of lymph nodes are removed by surgery.

2.31 In the cohort, 51.6% of the patients had surgery at private medical facilities, while 48.4% had surgery at public medical facilities.

2.32 For patients with invasive breast cancer, 97.8% underwent surgery as part of their treatment. Of the patients with invasive cancer, 58.2% had mastectomy and 39.1% had breast-conserving surgery. Among the patients who had mastectomy, 13.5% had either immediate or delayed reconstruction. The most common type of reconstruction was TRAM flap (71.1%) (Table 2.19). Almost all (95.3%) the patients with invasive breast cancer received nodal surgery and among them, 37.2% required AD, and 62.3% required SNB only.

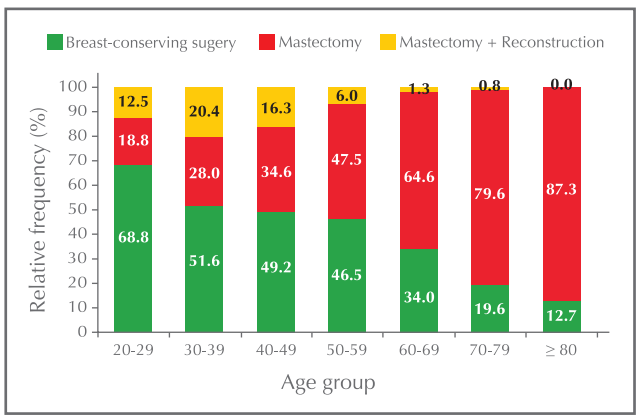
2.33 For patients with in situ breast cancer, 98.4% underwent surgery (Table 2.19). Of the patients with in situ cancer, 57.5% had breast-conserving surgery, while 22.3% had reconstruction after mastectomy. In addition, 39.1% did not receive nodal surgery, and among the 60.9% who received nodal surgery, 97.0% had SNB only and 1.7% had AD without SNB.

Table 2.19: Use of surgery for patients with invasive or in situ cancer

	Type of cancer, Number (%)			
	Invasive		In situ	
Type of surgery (N=3,971)				
No surgery	65	(1.9)	8	(1.6)
Breast-conserving surgery	1,359	(39.1)	284	(57.5)
Mastectomy	2,023	(58.2)	197	(39.9)
Nodal surgery only	11	(0.3)	1	(0.2)
Type of surgery not known	6	(0.2)	4	(0.8)
Not known if surgery done	13	(0.4)	0	(0.0)
Type of mastectomy (N=2,220)				
Total mastectomy	1,881	(93.0)	169	(85.8)
Skin sparing	48	(2.4)	12	(6.1)
Areolar sparing	0	(0.0)	0	(0.0)
Nipple sparing	86	(4.3)	16	(8.1)
Type not known	8	(0.4)	0	(0.0)
Type of reconstruction (N=317)				
TRAM flap	194	(71.1)	23	(52.3)
Implant	50	(18.3)	17	(38.6)
LD flap	16	(5.9)	3	(6.8)
LD flap & implant	8	(2.9)	0	(0.0)
Type not known	5	(1.8)	1	(2.3)
Type of nodal surgery (N=3,613)				
Sentinel node biopsy only	2,064	(62.3)	292	(97.0)
Axillary dissection only	762	(23.0)	5	(1.7)
Sentinel node biopsy followed by axillary dissection	471	(14.2)	4	(1.3)
Type not known	15	(0.5)	0	(0.0)

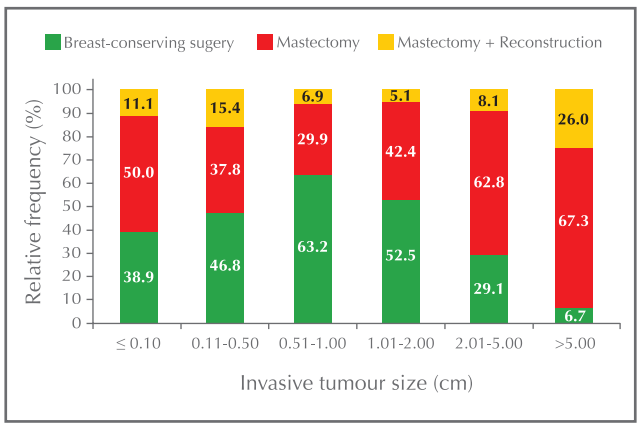
2.34 The percentage of patients who underwent mastectomy was positively correlated with increasing age, while the percentage of patients who underwent mastectomy with reconstruction was negatively correlated with increasing age (Figure 2.9).

Figure 2.9: Type of surgery by age group (N=3,798)



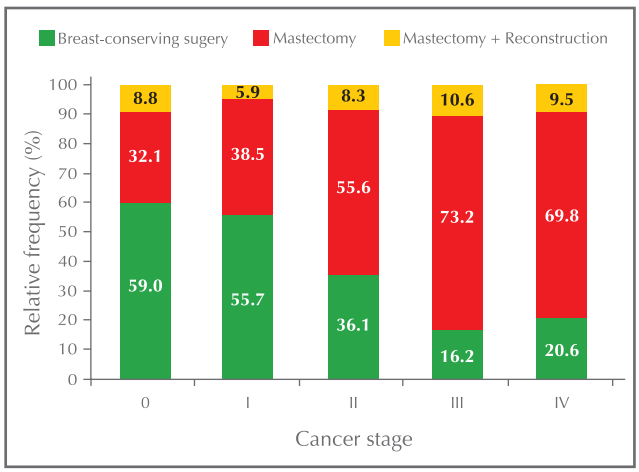
2.35 For patients with tumours larger than 0.5cm in size, the percentage of patients who had breast-conserving surgery was negatively correlated with increasing tumour size (Figure 2.10).

Figure 2.10: Type of surgery by invasive tumour size (N=2,843)



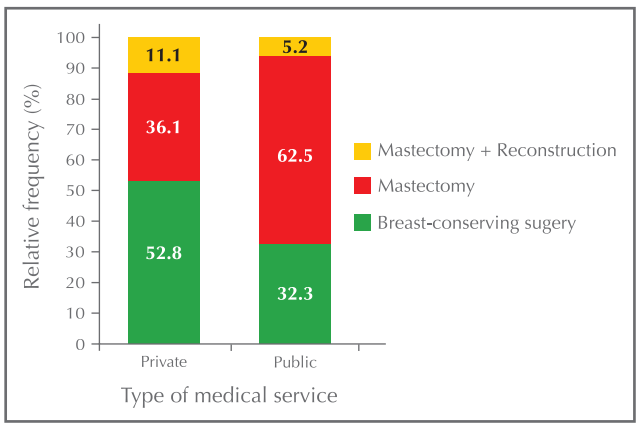
2.36 The proportion of patients who received breast-conserving surgery was negatively correlated with increasing cancer stage. Mastectomy with reconstruction did not show any correlation with increasing cancer stage (Figure 2.11).

Figure 2.11: Type of surgery by cancer stage (N=3,669)



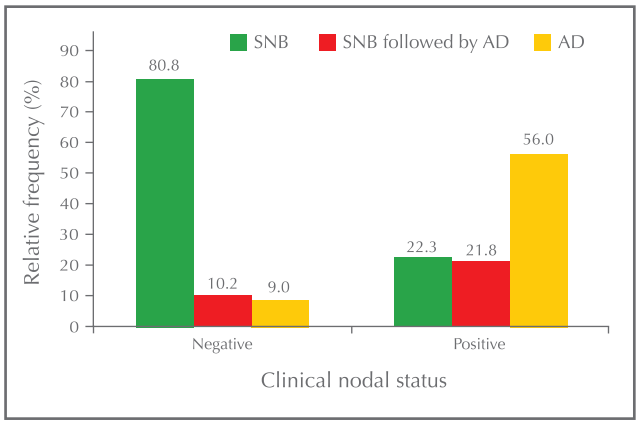
2.37 A higher proportion (52.8%) of patients who had surgery at private medical facilities underwent breast-conserving surgery than those who had surgery at public medical facilities (32.3%) (Figure 2.12).

Figure 2.12: Type of surgery by type of medical service (N=3,713)



2.38 SNB without AD was more commonly performed on patients with negative clinical nodal status (80.8%) than those with positive clinical nodal status (22.3%). On the other hand, AD without SNB was more commonly performed on patients with positive clinical nodal status (56.0%) than those with negative clinical nodal status (9.0%). Figure 2.13 shows the type of nodal surgery received by patients with positive or negative clinical nodal status in the cohort.

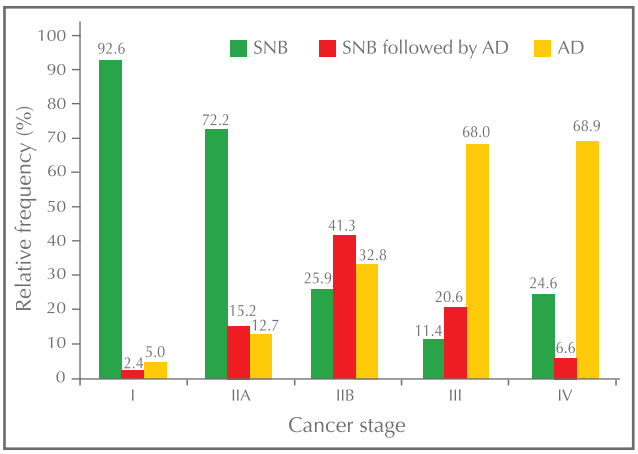
Figure 2.13: Type of nodal surgery by clinical nodal status (N=3,615)



SNB: Sentinel node biopsy; AD: Axillary dissection

2.39 The use of AD alone was positively correlated with progressing cancer stage in the cohort. The use of AD after SNB increased from stage I to II patients, but decreased for stage III or IV patients. This is because most of the patients with stage III or IV disease received AD as their first nodal surgery (Figure 2.14).

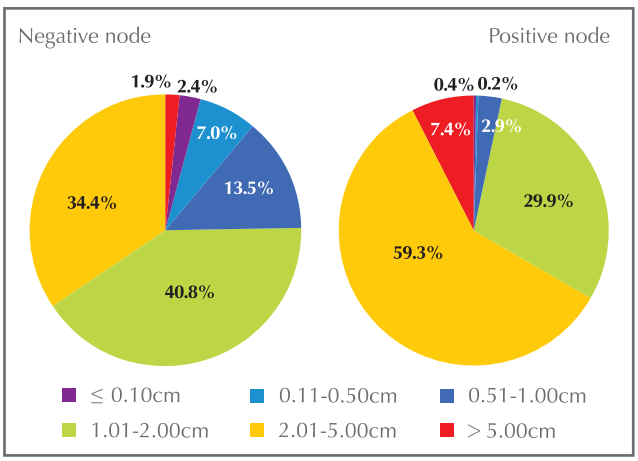
Figure 2.14: Type of nodal surgery for invasive cancer by cancer stage (N=3,132)



SNB: Sentinel node biopsy; AD: Axillary dissection

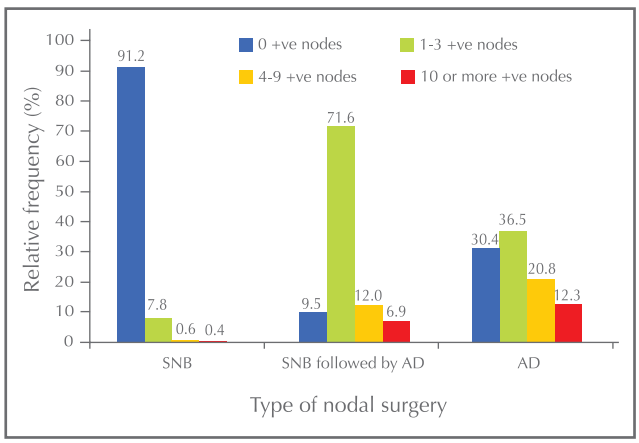
2.40 Of the patients with node positive invasive cancer, 59.3% had tumours of 2.01 to 5.00cm in size, while 7.4% had tumours larger than 5.0cm. In the cohort, more patients with node negative invasive cancer (63.7%) had tumours of 2.0cm or less, compared to patients with node positive invasive cancer (33.4%) (Figure 2.15).

Figure 2.15: Distribution of tumour size in invasive cancer with negative or positive nodal status (N=2,576)



2.41 In the cohort, 91.2% of the patients who underwent only SNB had no positive lymph node, while 30.4% who underwent only AD and 9.5% who underwent AD after SNB had no positive lymph node (Figure 2.16).

Figure 2.16: Number of positive nodes by type of nodal surgery (N=3,049)



SNB: Sentinel node biopsy; AD: Axillary dissection

B. Radiotherapy

2.42 Radiotherapy is a treatment to kill cancer cells using ionizing radiation. It is capable of inflicting damage on the DNA structure, and thus induces cell death and causes cell division failure. Radiotherapy can be administered in two settings: firstly, locoregional radiotherapy where the breast or chest wall, with or without regional lymph nodes, are irradiated with curative intent; and secondly palliative radiotherapy (e.g. to bone) is used to reduce symptoms that can be pain, pressure symptoms, airway obstruction, bleeding and secretion from metastases.

i. Locoregional radiotherapy

2.43 Locoregional radiotherapy to the breast following breast-conserving surgery is an integral part of breast-conserving therapy in order to achieve an outcome equivalent to mastectomy. This applies to all patients with invasive breast cancer and most patients with in situ cancer. Some patients whose tumour is locally advanced, or with cancer cells found in the lymphatic or blood vessels also need radiotherapy after mastectomy.

2.44 In the cohort, 63.6% of the patients had locoregional radiotherapy as part of their treatment, with almost all (99.9%) being adjuvant. The majority (84.0%) of the patients were treated with radiotherapy at public medical facilities, while the remainder (16.0%) had radiotherapy at private medical facilities.

2.45 The proportions of the invasive breast cancer patients who had undergone either breast-conserving surgery or mastectomy and received radiotherapy as part of their treatment by different cancer stages are shown in Figures 2.17 and 2.18 respectively. The majority (93.1%-94.9%) of the invasive breast cancer patients who underwent breast-conserving surgery also received locoregional radiotherapy (Figure 2.17). On the other hand, the proportion of invasive breast cancer patients who underwent mastectomy and also received locoregional radiotherapy increased significantly with progressing cancer stage (Figure 2.18).

2.46 Of the patients with in situ cancer who had breast-conserving surgery, 92.5% received locoregional radiotherapy afterwards (Figure 2.17), while 4.1% of the patients with in situ cancer who had mastectomy underwent radiotherapy (Figure 2.18).

Figure 2.17: Use of locoregional radiotherapy among patients who underwent breast-conserving surgery by cancer stage (N=1,559)

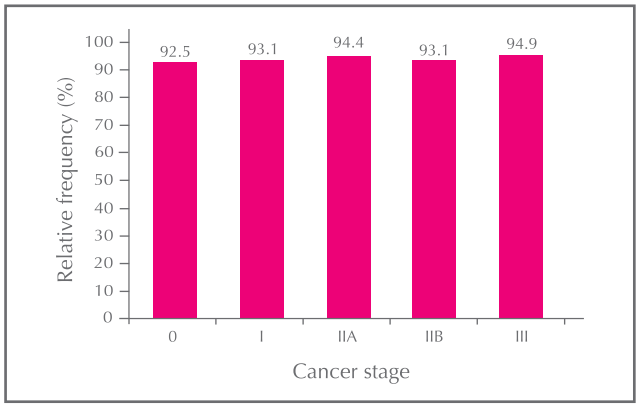
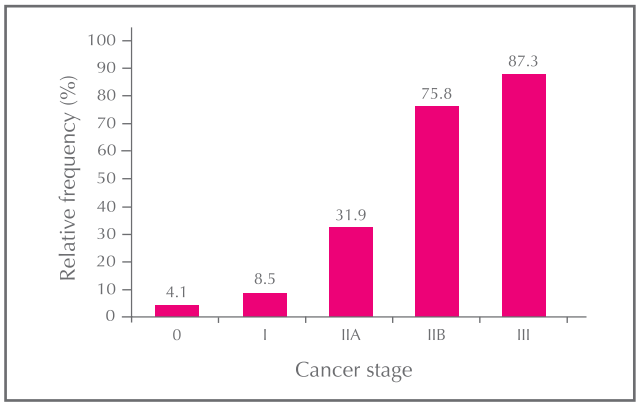


Figure 2.18: Use of locoregional radiotherapy among patients who underwent mastectomy by cancer stage (N=2,047)



2.47 Radiotherapy for breast cancer involves localised irradiation of regions such as breast/chest wall, with or without regional nodes. Table 2.20 shows the irradiated regions of adjuvant locoregional radiotherapy among those patients who received radiotherapy by the type of surgery they underwent. While the majority (90.3%) of patients undergoing breast-conserving surgery had radiotherapy to breast alone, radiotherapy to the chest wall and regional lymph nodes (75.6%) was more common among those patients undergoing mastectomy.

Table 2.20: Coverage of regional lymph nodes by adjuvant locoregional radiotherapy (N=1,184)

	Number	%
Breast-conserving surgery		
Breast alone	636	90.3
Breast and regional lymph nodes	68	9.7
Mastectomy		
Chest wall alone	117	24.4
Chest wall and regional lymph nodes	363	75.6

ii. Palliative radiotherapy

2.48 Palliative radiotherapy for breast cancer is used for reducing symptoms which can be pain, pressure symptoms, airway obstruction, bleeding and secretion from metastases.

2.49 Among the patients with metastatic breast cancer, 64.9% underwent palliative radiotherapy to various sites.

C. Chemotherapy

2.50 Chemotherapy is a form of systemic treatment using one or more cytotoxic drugs to kill or control cancer cell growth. The drugs destroy breast cancer cells by interfering with their ability to grow and divide. Chemotherapy is generally not required for patients with in situ tumour. Chemotherapy drugs are classified into three generations[47] and the number of cycles actually delivered within any regimen may vary, depending on patient factors such as bone marrow reserve and severity of side effects.

2.51 In the cohort, 2,052 (59.0%) patients with invasive cancer underwent chemotherapy. Of these patients, 75.3% had adjuvant chemotherapy, 20.6% had neoadjuvant chemotherapy and 4.0% had palliative chemotherapy. The majority (84.5%) received chemotherapy in public medical facilities, and the remainder (15.5%) in private medical facilities.

2.52 In the patient cohort, the use of curative intent chemotherapy was positively correlated to progressing cancer stage from stage I to III. In contrast, the majority (77.1%) of the patients with stage IV cancer underwent palliative chemotherapy (Figure 2.19).

2.53 In general, for all cancer stages, the use of chemotherapy among the patients aged 70 or above was much lower than that among patients aged below 70. Table 2.21 shows the percentage of the patients who received chemotherapy by age group and cancer stage.

Figure 2.19: Chemotherapy treatment by cancer stage (N=3,217)

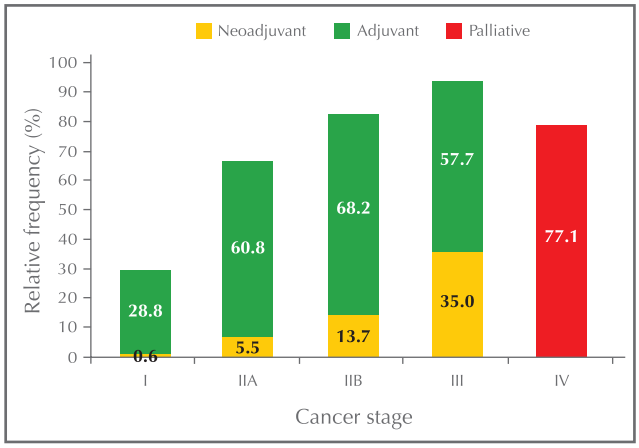


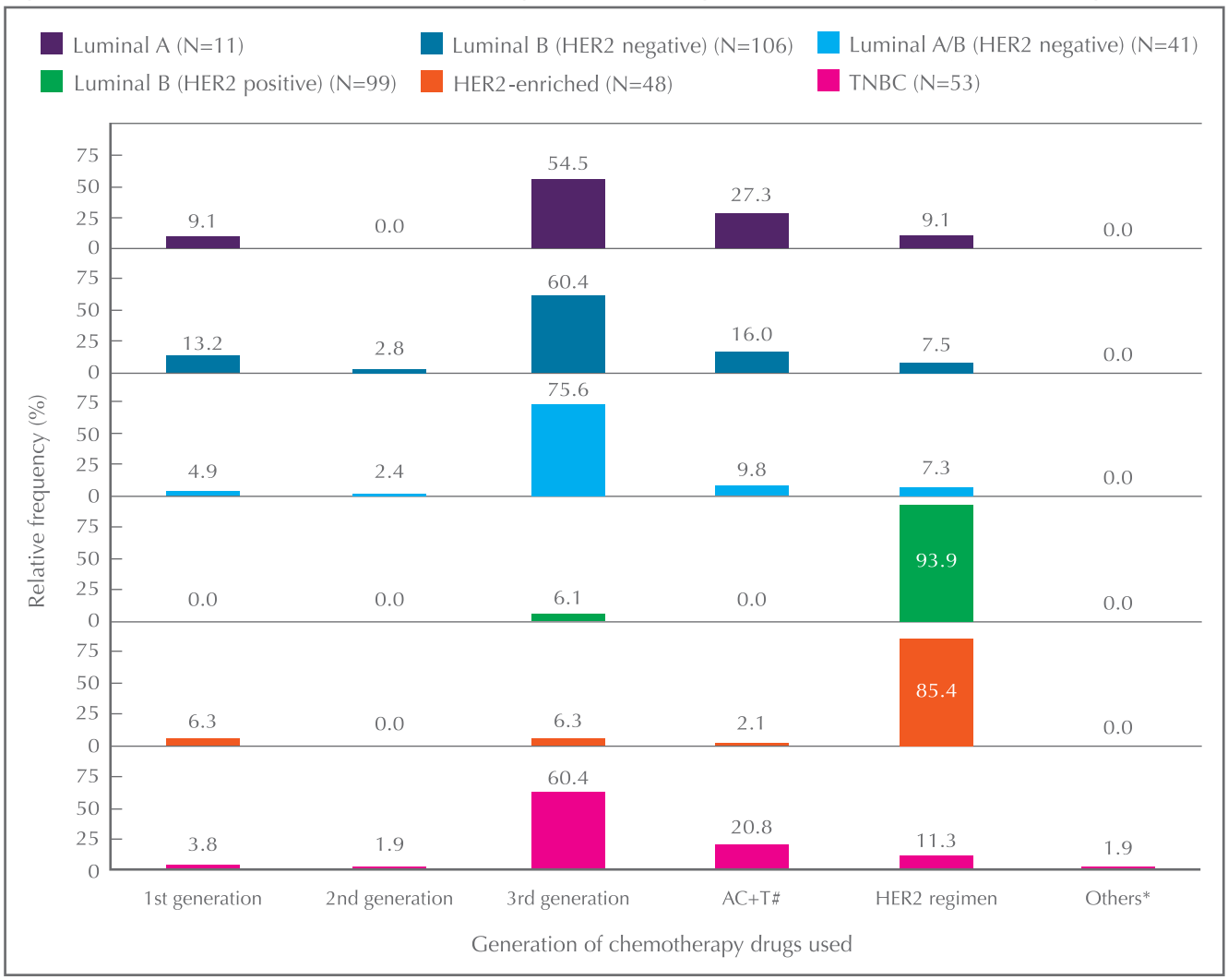
Table 2.21: Use of chemotherapy by age group and cancer stage at diagnosis (N=3,187)

	Cancer stage, Number (% of patients in the same age group and cancer stage)									
	I		IIA		IIB		III		IV	
20-29	5	(38.5)	6	(100.0)	2	(100.0)	1	(100.0)	0	(0.0)
30-39	34	(44.2)	57	(89.1)	28	(93.3)	36	(97.3)	5	(55.6)
40-49	102	(30.6)	163	(73.4)	102	(91.1)	123	(98.4)	24	(88.9)
50-59	130	(34.5)	230	(77.4)	140	(88.1)	148	(96.7)	28	(84.8)
60-69	69	(21.9)	138	(55.4)	92	(82.1)	128	(92.1)	12	(66.7)
≥70	13	(12.6)	12	(14.5)	15	(29.4)	13	(40.6)	4	(50.0)

i. Neoadjuvant chemotherapy

2.54 Of the 2,052 patients who underwent chemotherapy, 20.6% received it as neoadjuvant treatment. The use of neoadjuvant chemotherapy increased substantially with progressing cancer stage (Figure 2.19). The generations of chemotherapy drugs used by patients with different biological subtype in the cohort are shown in Figure 2.20.

Figure 2.20: Generation of chemotherapy drugs used by biological subtype in neoadjuvant setting (N=358)

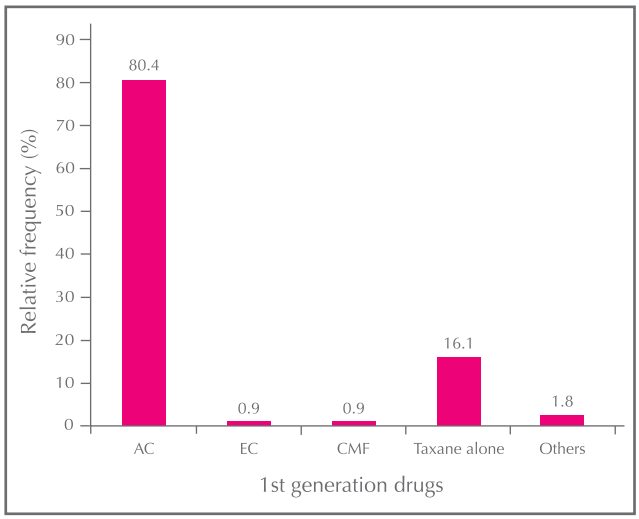


#AC+T: uncertain 2nd/3rd generation due to uncertain week intervals
*Others included any regimens containing Capecitabine, Gemcitabine, or Vinorelbine

ii. Adjuvant chemotherapy

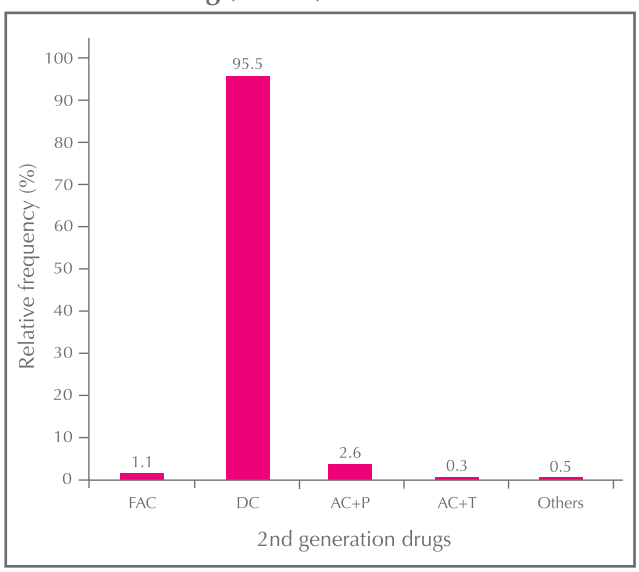
2.55 Of the 2,052 patients who underwent chemotherapy, the majority (75.3%) of patients received it as adjuvant (stages I-III) treatment. Figures 2.21, 2.22 and 2.23 show the use of chemotherapy drugs of three generations in adjuvant setting among the patients. The use of HER2 regimens in adjuvant chemotherapy is shown in Figure 2.24 below. Figures 2.25 and 2.26 show the relative frequency for different drug generations used by biological subtype and cancer stage, respectively.

Figure 2.21: Type of first generation chemotherapy drugs (non-HER2 regimen) used in adjuvant setting (N=112)



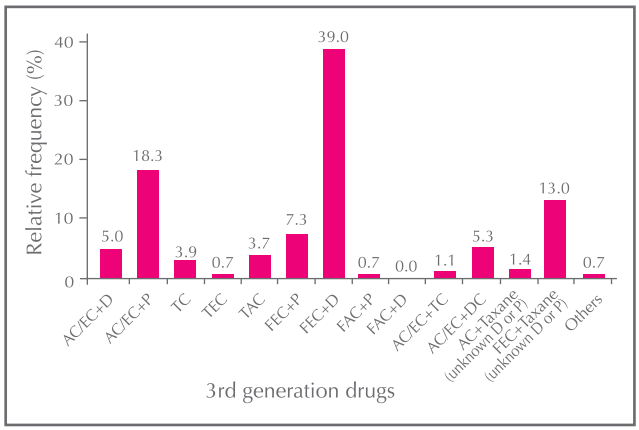
A: Adriamycin/Doxorubicin; E: Epirubicin; C: Cyclophosphamide; M: Methotrexate; F: 5FU; Taxane: Docetaxel or Paclitaxel

Figure 2.22: Type of second generation chemotherapy drugs (non-HER2 regimen) used in adjuvant setting (N=378)



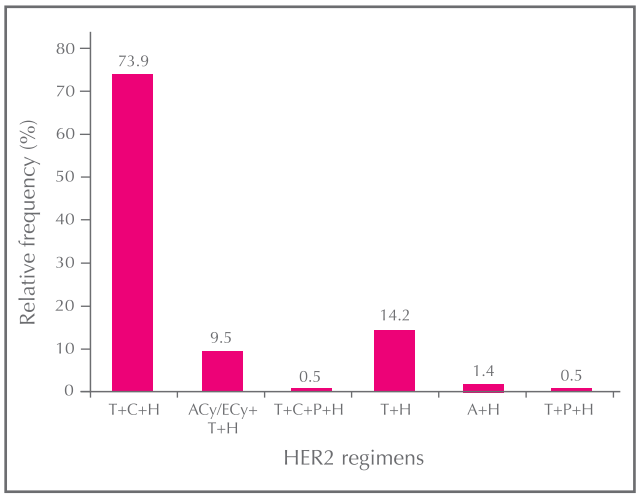
DC: Docetaxel+Cyclophosphamide; P: Paclitaxel; T: Taxane

Figure 2.23: Type of third generation chemotherapy drugs (non-HER2 regimen) used in adjuvant setting (N=438)



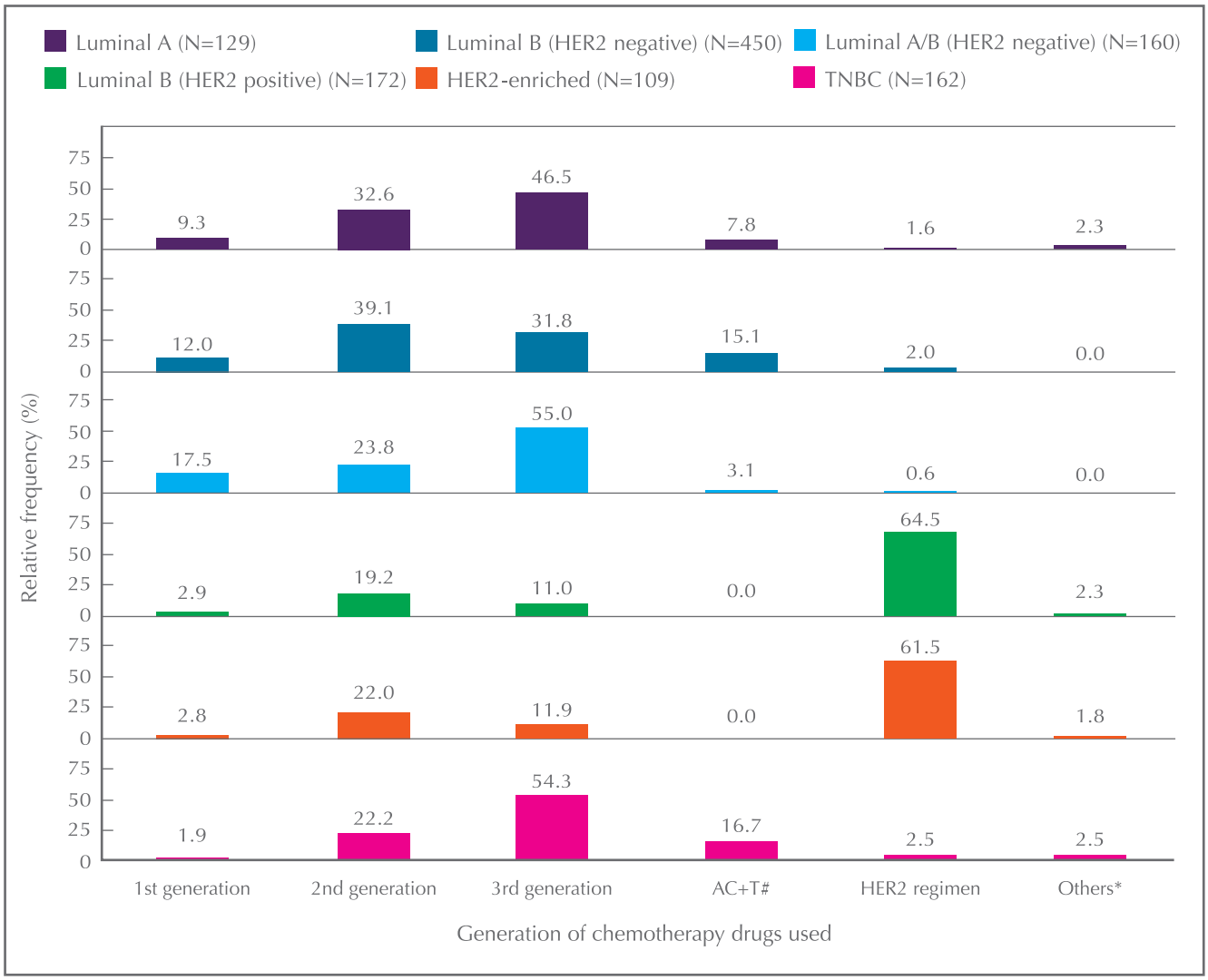
D: Docetaxel; P: Paclitaxel; TC: Paclitaxel+Carboplatin; DC: Docetaxel+Cyclophosphamide

Figure 2.24: Type of HER2 regimens used in adjuvant setting (N=211)



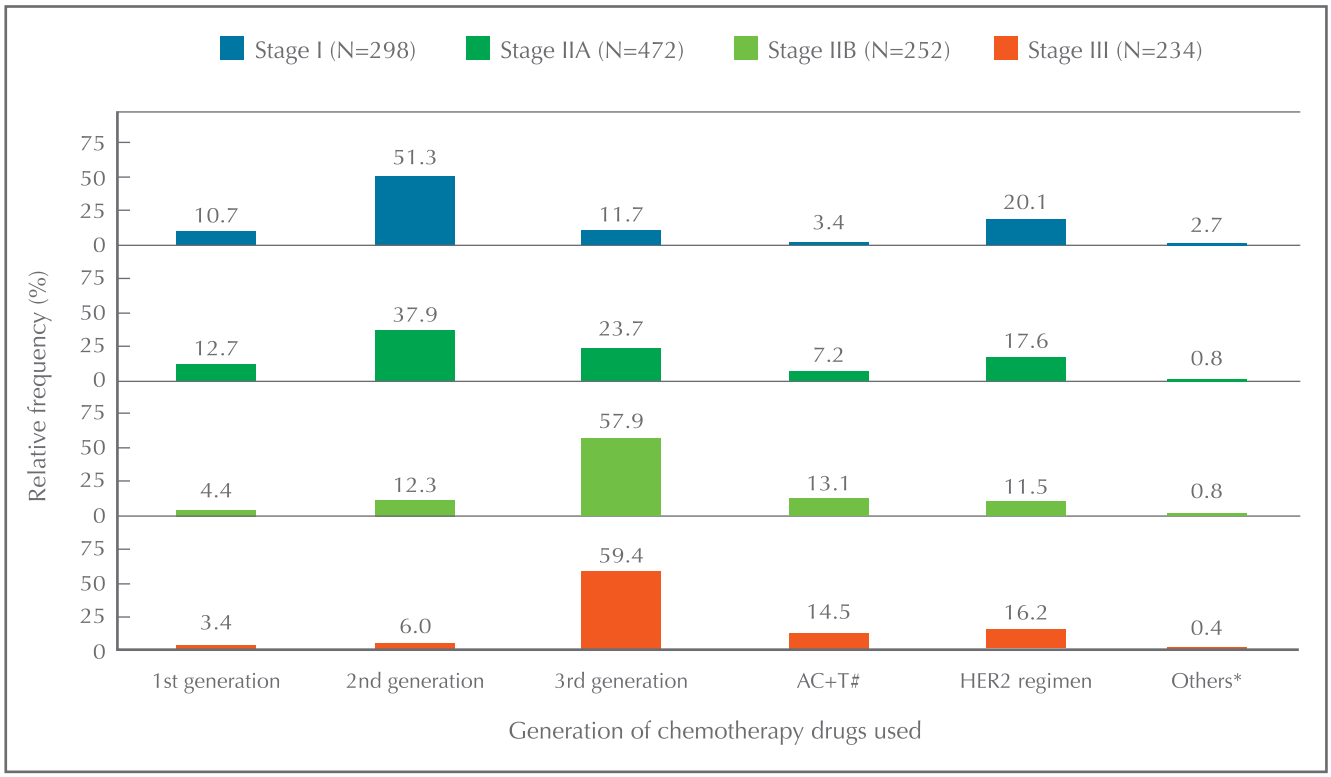
A: Anthracycline; C: Carboplatin; T: Taxane; H: Trastuzumab; P: Pertuzumab; Cy: Cyclophosphamide

Figure 2.25: Generation of chemotherapy drugs used by biological subtype in adjuvant setting (N=1,182)



#AC+T: uncertain 2nd/3rd generation due to uncertain week intervals
*Others included any regimens containing Capecitabine, Gemcitabine, or Vinorelbine

Figure 2.26: Generation of chemotherapy drugs used by cancer stage in adjuvant setting (N=1,256)

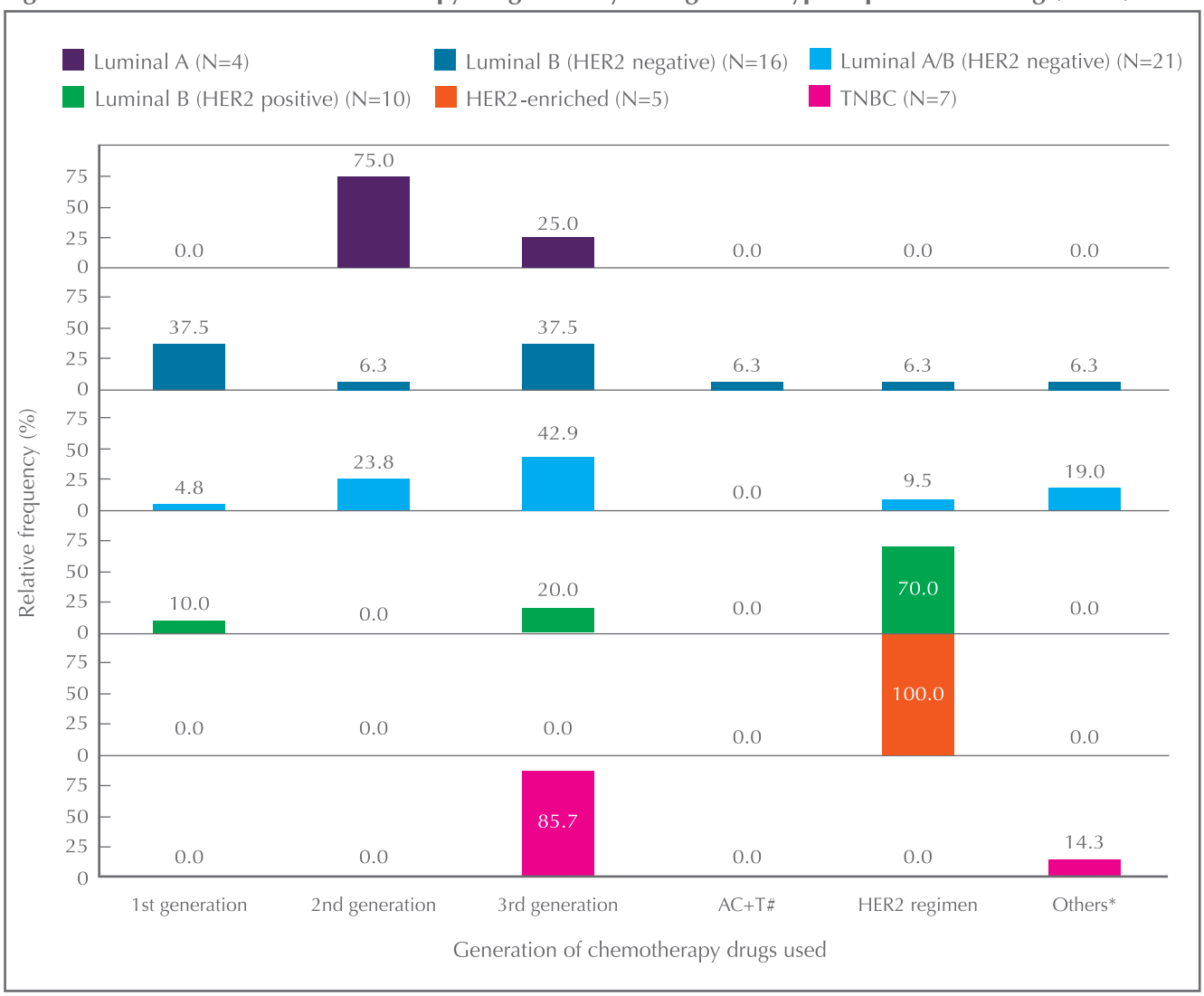


#AC+T: uncertain 2nd/3rd generation due to uncertain week intervals
*Others included any regimens containing Capecitabine, Gemcitabine, or Vinorelbine

iii. Palliative chemotherapy

2.56 Of the 2,052 patients who underwent chemotherapy, 4.0% received it as palliative (stage IV) treatment. Figure 2.27 shows the relative frequency for different generations of drugs used by biological subtype.

Figure 2.27: Generation of chemotherapy drugs used by biological subtype in palliative setting (N=63)



#AC+T: uncertain 2nd/3rd generation due to uncertain week intervals
*Others included any regimens containing Capecitabine, Gemcitabine, or Vinorelbine

D. Endocrine therapy

2.57 Endocrine therapy plays an important role in all stages of the treatment and prevention strategy for hormone receptor-positive invasive or in situ breast cancer. Breast cancer develops from abnormal breast cells that are often sensitive to sex hormones, such as estrogen and progesterone. Endocrine therapy acts on the hormone receptors of cancer cells.

2.58 In the cohort, 68.9% of the patients were treated with endocrine therapy; the majority (95.6%) being adjuvant, while neoadjuvant (0.5%) and palliative (3.9%) accounted for small proportions. In addition, the majority (87.1%) of the patients received endocrine therapy at public medical facilities, while the remainder (12.9%) at private medical facilities.

2.59 For patients with invasive breast cancer, 71.1% to 80.7% received endocrine therapy, while for patients with in situ breast cancer, only 9.2% received endocrine therapy (Figure 2.28).

2.60 Two types of drugs are commonly used: anti-estrogens and aromatase inhibitors. Anti-estrogen drugs slow down breast cancer growth by binding to ER on breast cancer cells. The most common anti-estrogen is tamoxifen which is used in both pre-menopausal and post-menopausal women. Aromatase inhibitors decreases the level of estrogen in the body. Aromatase inhibitors, including anastrozole, letrozole and exemestane, are only effective for women who are post-menopausal. Figure 2.29 shows the use of tamoxifen and aromatase inhibitors by age group in the patient cohort.

Figure 2.28: Use of endocrine therapy by cancer stage (N=3,747)

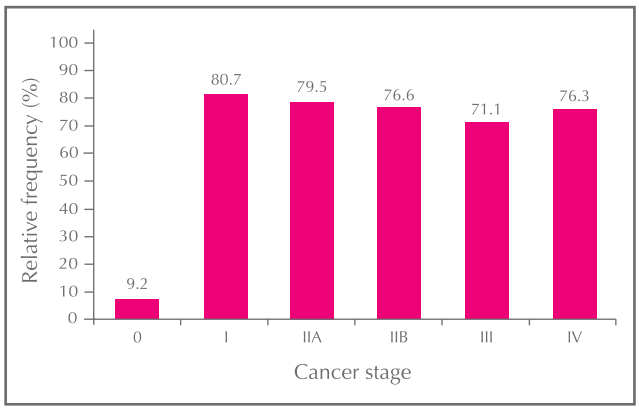
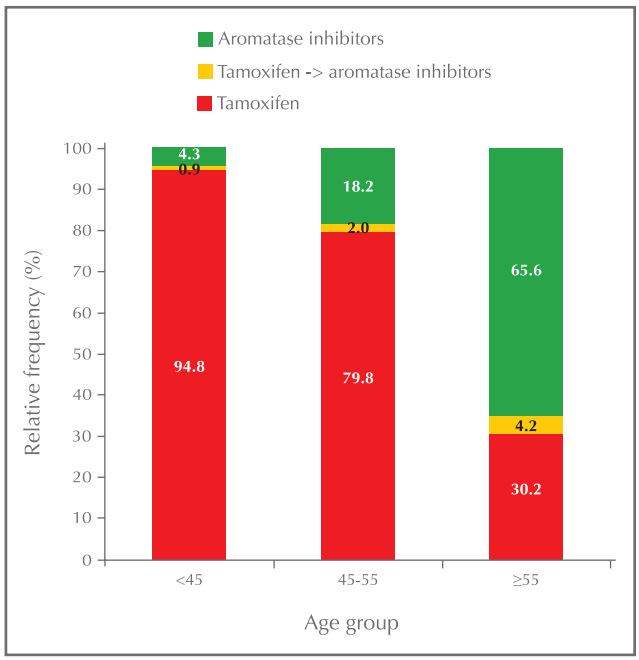


Figure 2.29: Forms of endocrine therapy by age group (N=2,360)

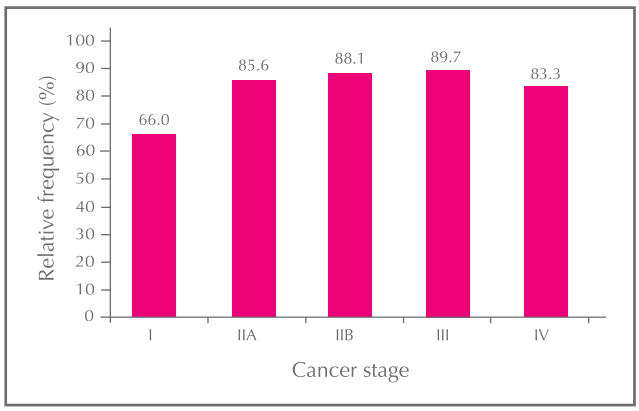


E. Anti-HER2 targeted therapy

2.61 Targeted therapy uses a drug that specifically inhibits the abnormal growth pathway of cancer cells by blocking specific molecules required for tumour growth or carcinogenesis. Anti-HER2 targeted therapy is used for treating patients with invasive breast cancer cells that over-express HER2 oncogene (HER2-positive breast cancer).

2.62 Of the 566 patients with invasive HER2-positive breast cancer, 81.6% underwent anti-HER2 targeted therapy. Among them, 77.1% were adjuvant, 18.6% were neoadjuvant and 4.3% were palliative. In addition, the majority (87.0%) of the patients received anti-HER2 targeted therapy at public medical facilities, while the remainder (13.0%) at private medical facilities. In the cohort, the use of anti-HER2 targeted therapy was much lower for stage I patients, while the proportions of stage II or above patients who had anti-HER2 targeted therapy were over 80% (Figure 2.30).

Figure 2.30: Use of anti-HER2 targeted therapy in HER2 positive patients by cancer stage (N=511)



F. Multimodality treatment

2.63 Combinations of treatment modalities, including surgery, radiotherapy, chemotherapy, endocrine therapy and anti-HER2 targeted therapy, are usually used to treat breast cancer effectively. Table 2.22 shows the multimodality treatment pattern of the patients. In general, the number of modalities increased with increasing cancer stage. In the cohort, the majority (93.9%) of the patients with stage 0 disease received two or less modalities. On the other hand, more than three-quarters of the patients with stage IIA (77.6%), stage IIB (86.4%) or stage III (92.1%) disease received three or more modalities.

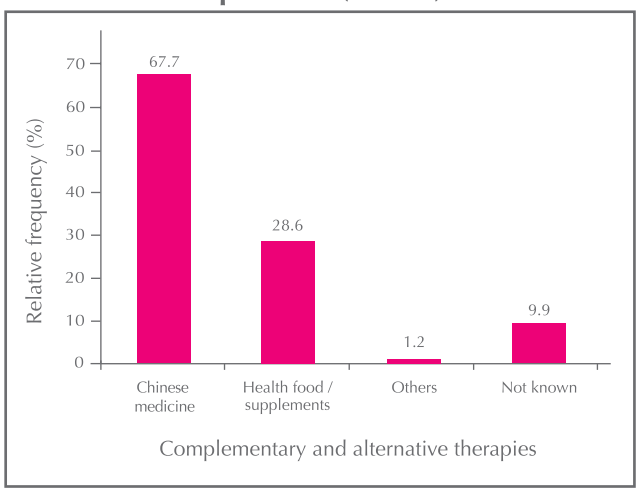
Table 2.22: Number of treatment modalities by cancer stage (N=3,747)

	Cancer stage, Number (%)											
	0		I		IIA		IIB		III		IV	
0	1	(0.2)	1	(0.1)	1	(0.1)	2	(0.4)	0	(0.0)	0	(0.0)
1	200	(40.9)	81	(6.5)	38	(4.0)	11	(2.3)	11	(2.2)	16	(16.5)
2	258	(52.8)	404	(32.3)	173	(18.3)	51	(10.9)	28	(5.7)	16	(16.5)
3	30	(6.1)	558	(44.6)	360	(38.1)	116	(24.7)	94	(19.0)	19	(19.6)
4	0	(0.0)	161	(12.9)	310	(32.8)	244	(51.9)	299	(60.4)	30	(30.9)
5	0	(0.0)	46	(3.7)	63	(6.7)	46	(9.8)	63	(12.7)	16	(16.5)

G. Complementary and alternative therapies

2.64 Apart from the standard medical treatments and care of breast cancer described in the previous sections of this chapter, patients may seek different kinds of complementary and alternative therapies, such as taking traditional Chinese medicines, health foods and supplements. In the cohort, 950 (23.8%) patients sought complementary and alternative therapies as part of their treatment. Among them, the majority (95.7%) were adjuvant, while neoadjuvant (0.6%) and palliative (3.7%) accounted for only small proportions. In addition, 67.7% of the patients used traditional Chinese medicines (Figure 2.31).

Figure 2.31: Type of complementary and alternative therapies used (N=950)



Others include: Tai Chi, Qigong, Naturopathy, acupuncture and moxibustion, massage and yoga

VI. Patient Status

2.65 Once treatment is completed, HKBCR will follow up with the registered patients annually to ascertain the efficacy of the treatment. In this section, a total of 17,877 patients were studied to examine the survival aspects of the patients who were diagnosed from 2006 onwards and completed at least one follow-up. About half (47.2%) of them had the last follow-up within the past two years and 40.4% have been followed up for five or more years (Table 2.23). The mean and median follow-up period were 4.4 and 3.8 years respectively.

2.66 Of the patients who have been followed up, 1.7% experienced only locoregional recurrence (LR), 2.4% experienced only distant recurrence (DR), and 1.6% experienced both locoregional and distant recurrence concurrently or sequentially. The mean and median time to recurrence are shown in Table 2.23.

Table 2.23: Follow-up of 17,877 patients

	Number	%
Follow-up period		
< 1 year	2,301	12.9
1-2 years	3,015	16.9
2-5 years	5,329	29.8
5-10 years	6,276	35.1
≥10 years	956	5.3
Mean (95% CI)	4.4 years (4.37-4.47)	
Median (95% CI)	3.8 years (3.71-3.87)	
Locoregional recurrence		
No. of locoregional recurrence	296	1.7
Mean time (95% CI)	3.5 years (3.16-3.75)	
Median time (95% CI)	3.0 years (2.61-3.34)	
Distant recurrence		
No. of distant recurrence	423	2.4
Mean time (95% CI)	3.3 years (3.07-3.51)	
Median time (95% CI)	2.9 years (2.64-3.15)	
Locoregional and distant recurrence		
No. of locoregional and distant recurrence	283	1.6
Mean time (95% CI)	3.3 years (3.00-3.55)	
Median time (95% CI)	2.8 years (2.50-3.05)	
Mortality*		
No. of deaths from breast cancer	226	1.3
No. of deaths from unrelated causes	111	0.6
No. of deaths with causes not known	120	0.7

*Data as of Feb 2020 with traceable medical records only.

2.67 Table 2.24 shows the number of invasive breast cancer patients with LR in different subgroups specified by surgery type and cancer stage at diagnosis in the patient cohort. The overall LR rates were similar between patients treated with breast conserving surgery and radiotherapy, and those treated with mastectomy (Table 2.24). The common sites for LR were chest wall (34.2%), breast (31.3%) and axilla (34.4%) (Table 2.25).

Table 2.24: Locoregional recurrence by type of surgery received and cancer stage at diagnosis

	Cancer stage, Number (% of patients with the same surgery type and cancer stage)				
	I	IIA	IIB	III	Total
BCS with RT	34/2,607	48/1,504	10/521	17/339	109/4,971
	(1.3)	(3.2)	(1.9)	(5.0)	(2.2)
BCS without RT	6/107	7/71	1/20	0/7	14/205
	(5.6)	(9.9)	(5.0)	(0.0)	(6.8)
MTX	58/2,848	68/2,818	48/1,704	129/2,142	303/9,512
	(2.0)	(2.4)	(2.8)	(6.0)	(3.2)

BCS: Breast-conserving surgery; MTX: Mastectomy; RT: Radiotherapy

Table 2.25: Sites involved in locoregional recurrence (N=579)

	Number	%
Chest wall	198	34.2
Breast	181	31.3
Axilla	199	34.4
Supraclavicular fossa	123	21.2
Internal mammary node	40	6.9
Infraclavicular fossa	6	1.0
Others	28	4.8

Note: The total percentages may exceed 100 as multiple sites may be involved in locoregional recurrence.

2.68 In the cohort, 706 (4.0%) patients experienced distant recurrence. Among them, the top four organs involved were bone (56.5%), lung (46.5%), liver (38.7%) and brain (18.8%) (Table 2.26). The median time for distant recurrence to bone, lung, liver and brain and the distribution of biological subtypes of the patients involved are shown in Table 2.27.

Table 2.26: Organs involved in distant recurrence (N=706)

	Number	%		Number	%
Bone	403	57.1	Peritoneum	16	2.3
Lung	331	46.9	Ovary	7	1.0
Liver	275	39.0	Spleen	4	0.6
Brain	133	18.8	Contralateral axillary node	3	0.4
Mediastinal node	123	17.4	Thyroid gland	3	0.4
Neck node	53	7.5	Kidney	3	0.4
Pleural cavity	53	7.5	Uterus	3	0.4
Distant lymph node	47	6.7	Pancreas	2	0.3
Adrenal gland	16	2.3	Unspecified	15	2.1

Note: The total percentages may exceed 100 as multiple sites may be involved in distant recurrence.

Table 2.27: Time for organ specific metastasis and distribution of the biological subtypes of patients

	Bone (N=403)	Lung (N=331)	Liver (N=275)	Brain (N=133)
Time for metastasis, median years (range)	**3.3 (0.2 - 11.2)**	**3.2 (0.2 - 11.2)**	**2.9 (0.2 - 9.9)**	**2.7 (0.2 - 10.0)**
Biological subtypes				
Luminal A*	40 (11.1)	22 (7.6)	24 (9.6)	8 (6.9)
Luminal B (HER2 negative)#	87 (24.2)	50 (17.2)	53 (21.2)	16 (13.8)
Luminal A/B (HER2 negative)†	110 (30.6)	82 (28.3)	78 (31.2)	17 (14.7)
Luminal B (HER2 positive)^	67 (18.6)	55 (19.0)	42 (16.8)	25 (21.6)
HER2-enriched❇	29 (8.1)	30 (10.3)	29 (11.6)	28 (24.1)
TNBC§	30 (8.3)	53 (18.3)	26 (10.4)	22 (19.0)
Not known	43	41	25	17

* Luminal A: ER and/or PR+, HER2-, and low Ki-67 index (<14%)

\# Luminal B (HER2 negative): ER and/or PR+, HER2-, and high Ki-67 index (≥14%)

† Luminal A/B (HER2 negative): ER and/or PR+, HER2-, and Ki-67 index not known

^ Luminal B (HER2 positive): ER and/or PR+, HER2+, and any Ki-67 index

❇ HER2-enriched: ER and PR-, HER2+, and any Ki-67 index

§ TNBC (Triple Negative Breast Cancer): ER and PR-, HER2-, and any Ki-67 index

2.69 In the cohort, the proportion of patients with only LR did not show any association with cancer stage at diagnosis. However, the proportion of the patients with only DR increased from 0.9% of stage I patients to 6.3% of stage III patients. Stage III patients also had higher rates of the combination of LR and DR (4.1%) than those with lower cancer stages (0.5%-1.8%) (Table 2.28).

2.70 In the cohort, 226 (1.3%) patients died from breast cancer, and 58.9% of them were stage III or IV at initial diagnosis. Survival time ranged from 0.6 to 11.3 years. In addition, of the four stage 0 patients who died of breast cancer, three did not receive any treatment. One had invasive cancer in the other breast prior to the in situ cancer diagnosis in the recent entry, and her death can be related to the previous invasive cancer. Information on biological subtypes of these patients is shown in Table 2.29.

Table 2.28: Locoregional and distant recurrence among invasive breast cancer patients by cancer stage (N=14,751)

	Cancer stage, Number (%)				
	I (N=5,566)	IIA (N=4,407)	IIB (N=2,255)	III (N=2,523)	Total (N=14,751)
LR only	69 (1.2)	66 (1.5)	19 (0.8)	44 (1.7)	198 (1.3)
DR only	50 (0.9)	70 (1.6)	66 (2.9)	159 (6.3)	345 (2.3)
LR and DR	29 (0.5)	58 (1.3)	40 (1.8)	104 (4.1)	231 (1.6)

LR: Locoregional recurrence; DR: Distant recurrence

Table 2.29: Characteristics of breast cancer-specific deaths (N=226)

	Cancer stage at initial diagnosis						
	0	I	IIA	IIB	III	IV	Unstaged
No. of cases (% of breast cancer death cases)	**4 (1.8)**	**22 (9.7)**	**32 (14.2)**	**23 (10.2)**	**96 (42.5)**	**37 (16.4)**	**12 (5.3)**
Survival time (range in years)	**4.5 - 7.3**	**1.6 - 9.6**	**1.6 - 11.3**	**2.1 - 11.2**	**0.8 - 9.4**	**0.6 - 8.1**	**1.1 - 6.2**
Time from first diagnosis of DM to death (years), mean (range)	**2.3 (0.9 - 4.4)**	**1.9 (0.7- 4.6)**	**1.3 (0.9 - 4.4)**	**1.6 (0.1 - 6.2)**	**1.2 (0.0 - 5.9)**	**3.2 (0.6 - 8.1)**	**1.4 (0.3 - 3.3)**
Biological subtypes							
Luminal A*	0	2	3	5	5	0	0
Luminal B (HER2 negative)#	0	5	4	3	12	2	1
Luminal A/B (HER2 negative)†	2	4	10	10	26	7	1
Luminal B (HER2 positive)^	2	2	3	1	19	7	3
HER2-enriched❊	0	4	4	0	14	7	1
TNBC§	0	5	6	3	12	4	0
Not known	0	0	2	1	8	10	6

* Luminal A: ER and/or PR+, HER2-, and low Ki-67 index (<14%)

\# Luminal B (HER2 negative): ER and/or PR+, HER2-, and high Ki-67 index (≥14%)

† Luminal A/B (HER2 negative): ER and/or PR+, HER2-, and Ki-67 index not known

^ Luminal B (HER2 positive): ER and/or PR+, HER2+, and any Ki-67 index

❊ HER2-enriched: ER and PR-, HER2+, and any Ki-67 index

§ TNBC (Triple Negative Breast Cancer): ER and PR-, HER2-, and any Ki-67 index