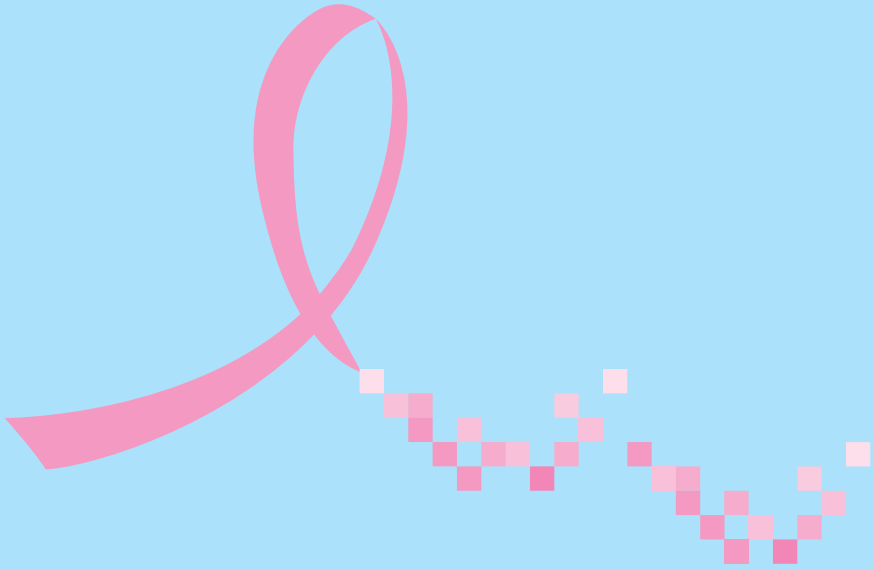

CHAPTER 2

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 16,595 breast cancer patients 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

Clinical presentation

- The primary method of first cancer detection in the patient cohort was self-detection by chance (83.3%). More stage 0 or I cancers (34.0% and 13.4% respectively) were detected by mammography screening (MMG) than stage III or IV cancers (3.0% and 1.8% respectively).
- Most (91.9%) patients who self-detected their cancers by chance found a painless lump on their breast(s). Pain is not usually a symptom of breast cancer; only 7.1% of the patients felt pain in their breast(s) at initial presentation. Some patients (8.9%) experienced changes in nipple (such as nipple discharge, nipple retraction, redness, scaliness or thickening of nipple).
- After the onset of symptoms, only one-third (36.1%) of the patients who self-detected their cancers by chance sought first medical consultation in less than one month (Table 2.4). One quarter (25.3%) waited more than three months before seeking first medical consultation.
- The majority (91.8%) of the patients had unilateral breast cancer, while 429 patients had synchronous bilateral breast cancer at first diagnosis. In addition, 350 patients developed a contralateral breast cancer subsequently after diagnosis of an initial primary breast cancer.
- Half (51.2%) of the patients with invasive breast cancer did not have any cancer staging as part of their diagnosis and treatment. Among those patients who had cancer staging as part of their treatment, the most common method used was positron emission tomography scan (45.4%), followed by a combination of chest x-ray and ultrasound of abdomen (39.5%).
- The most common cancer stage at diagnosis was stage II (37.0%) followed by stages III-IV (16.6%). In addition, 12.0% of the patients were diagnosed with in situ cancers.

Cancer characteristics

- The mean size of invasive breast cancers was 2.2 cm (standard deviation: ±1.5 cm). Tumours larger than two cm were found in 47.5% of the patients. In the patient cohort, screen-detected cancers were significantly smaller than those self-detected by chance (mean: 1.2±1.0 cm vs. 2.3±1.5 cm; $p<0.001$). In addition, 56.4% of the patients with invasive cancers had no positive lymph nodes, while 33.9% had at least one positive lymph node with metastasis size larger than two mm. The most common type was invasive carcinoma of no specific type (86.8%); 79.4% of invasive breast cancers were either estrogen receptor (ER) or progesterone receptor (PR) positive; 22.5% were c-erbB2/HER2 positive; and 11.7% were triple negative.

- The mean size of in situ breast cancers was 1.9 cm (standard deviation: ±1.5 cm). Tumours larger than two cm in size were found in 33.8% of the patients. Of the in situ breast cancer cases where MMG was performed, 61.4% showed microcalcification. Ductal cancers were the most common type of in situ breast cancers (93.1%); 81.8% of in situ breast cancers were either ER or PR positive; and 26.7% of in situ breast cancer in the cohort were c-erbB2/HER2 positive.

Treatment

- Of the 16,595 patients, 14.2% received care at private medical service, 52.1% received care at public medical services, and 33.7% received care at both private and public medical services.
- Surgery
  - The majority (97.9%) of the patients underwent surgery as part of the treatment; 47.3% of the patients had surgery at private medical facilities, while 52.7% had surgery at public medical facilities.
  - For patients with invasive tumours, about two-thirds (64.7%) had mastectomy and among them, 11.8% had reconstruction. Slightly more than half (56.5%) of the invasive patients required axillary dissection, and two-fifths (42.4%) of them required sentinel node biopsy only.
  - Slightly less than half (48.6%) of the patients with in situ tumours had mastectomy, and among them, 22.5% had reconstruction. Among those who received nodal surgery, 83.8% had sentinel node biopsy only and 11.9% had axillary dissection without sentinel node biopsy.
  - The percentage of the patients who underwent mastectomy was positively correlated with both increasing age and cancer stage.
  - Regarding nodal surgery, sentinel node biopsy without axillary dissection was more commonly used on patients with negative clinical nodal status (55.2%) than those with positive clinical nodal status (15.9%). The use of axillary dissection without sentinel node biopsy was positively correlated with increasing cancer stage.
- Radiotherapy
  - In the cohort, two-thirds (60.3%) of the patients had locoregional radiotherapy as part of their treatment. In addition, 82.5% of the patients were treated with radiotherapy at public medical facilities, while 17.5% had radiotherapy at private medical facilities.
  - Of the patients with in situ cancer who had breast-conserving surgery, 94.8% received locoregional radiotherapy afterwards, while 3.3% of the patients with in situ cancer who had mastectomy underwent locoregional radiotherapy.
  - The proportion of invasive breast cancer patients who underwent breast-conserving surgery and also received locoregional radiotherapy was high: from 85.7% in the case of stage IV patients to 98% for stage III patients. On the other hand, the proportion of invasive breast cancer patients who underwent mastectomy and also received locoregional radiotherapy increased significantly from stage I (12.5%) to stage III (94.7%), but drops sharply in stage IV (54.2%).
  - Among the patients with metastatic breast cancers, 11.7% underwent palliative radiotherapy, and of these patients, 88.1% received radiotherapy to the spine and 35.7% to the pelvis.

- Chemotherapy
  - In the cohort, 68.2% of the patients with invasive cancer underwent chemotherapy. The majority (86.9%) of the patients received chemotherapy in public medical facilities, and the remainder (13.1%) in private medical facilities.
  - In the patient cohort, the use of curative intent chemotherapy was positively correlated to increasing cancer stage from stage I to III diseases. In contrast, the majority of the patients with stage IV cancers (87.3%) underwent palliative chemotherapy. On the other hand, the use of neoadjuvant chemotherapy increased substantially with progressing cancer stage, from 0.2% of stage I patients to 26.9% of stage III patients.
- Endocrine therapy
  - In the cohort, 67.6% of the patients were treated with endocrine therapy. In addition, 90.8% of the patients received endocrine therapy at public medical facilities, while 9.2% at private medical facilities.
  - Endocrine therapy was used in only 11.6% of the in situ breast cancer cases. In contrast, over 75% of the patients with invasive cancers received endocrine therapy.
- Anti-HER2 targeted therapy
  - Of the 3,072 patients with invasive HER2-positive breast cancers, 1,878 (61.1%) patients underwent anti-HER2 targeted therapy. The majority (89.9%) of the patients received anti-HER2 targeted therapy at public medical facilities, and the remainder (10.1%) at private medical facilities.
  - The use of anti-HER2 targeted therapy was positively correlated with increasing cancer stage.
- Multimodality treatment
  - Combinations of treatments are usually used for treating breast cancer effectively. In general, the number of treatments increased with increasing cancer stage.
- Complementary and alternative therapies
  - A total of 6,378 (38.4%) patients in the cohort sought complementary and alternative therapies as part of their treatment. Among them, 64.5% of the patients used traditional Chinese medicines.

Patient status

- The mean and median follow-up period were 4.2 and 3.7 years, respectively.
  - A total of 695 (4.7%) cases in the cohort experienced recurrence, of which 1.4% experienced only locoregional recurrence, 2.1% experienced only distant recurrence, and 1.3% experienced both locoregional and distant recurrence concurrently or sequentially.
  - The common sites for locoregional recurrence were chest wall (35.2%) and breast (31.6%). The common organs involved in distant recurrence were bone (56.7%), lung (49.0%) and liver (40.1%).

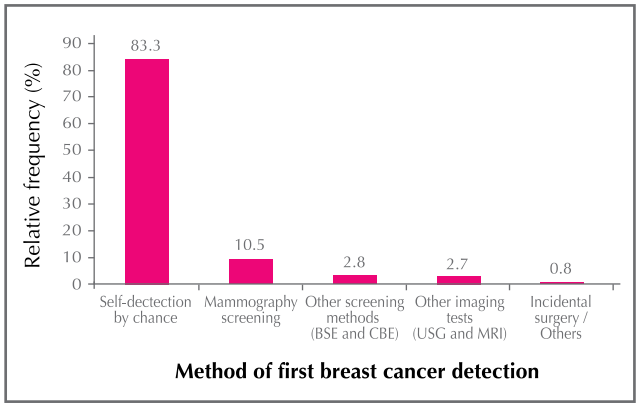
II. Clinical presentation

2.2 The primary method of first breast cancer detection in the patient cohort was self-detection by chance (83.3%) (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 (15.6%). In the United States (US), a study reported that 43% of the breast cancer cases were detected through MMG,[31] which is much higher than the 10.5% of the patient cohort.

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 or mixed private/public medical service users than among private medical service users. In contrast, the proportion of the patients who first detected their breast cancer through MMG was higher among private medical service users than among public medical service users or mixed private/public medical service users (Table 2.1).

2.4 Studies have shown that MMG is effective in detecting early cancers when there are neither signs nor symptoms that can be observed by patients or medical professionals.[32] In the patient cohort, the proportion of invasive breast cancers detected by MMG (6.8%) was much lower than that of in situ breast cancers (34.6%) (Table 2.2). In addition, more stage 0 or I cancers (34.0% and 13.4% respectively) were detected by MMG than stage III or IV cancers (3.0% and 1.8% respectively). On the other hand, over 90% of the patients with stage IIB, III or IV cancers self-detected their cancer by chance (Table 2.3).

Figure 2.1: Method of first breast cancer detection in the patient cohort (N=15,673)



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

Table 2.1: Method of first breast cancer detection by type of medical service received at cancer diagnosis and treatment (N=15,673)

	Private medical service users (N=2,215)		Public medical service users (N=8,173)		Mixed private / public medical service users (N=5,285)	
Method of first breast cancer detection	**Number**	**(%)**	**Number**	**(%)**	**Number**	**(%)**
Self-detection by chance	1,622	(73.2)	6,893	(84.3)	4,540	(85.9)
Mammography screening	340	(15.3)	900	(11.0)	399	(7.5)
Other screening methods (BSE and CBE)	80	(3.6)	205	(2.5)	158	(3.0)
Other imaging tests (USG and MRI)	148	(6.7)	114	(1.4)	156	(3.0)
Incidental surgery / Others	25	(1.1)	61	(0.7)	32	(0.6)

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

Table 2.2: Method of first breast cancer detection by type of cancer (N=15,663)

Method of first breast cancer detection	Type of cancer, Number (%)	
	In situ (N=2,072)	Invasive (N=13,591)
Self-detection by chance	1,147 (55.4)	11,900 (87.6)
Mammography screening	716 (34.6)	921 (6.8)
Other screening methods (BSE and CBE)	68 (3.3)	375 (2.8)
Other imaging tests (USG and MRI)	115 (5.6)	303 (2.2)
Incidental surgery / Others	26 (1.3)	92 (0.7)

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

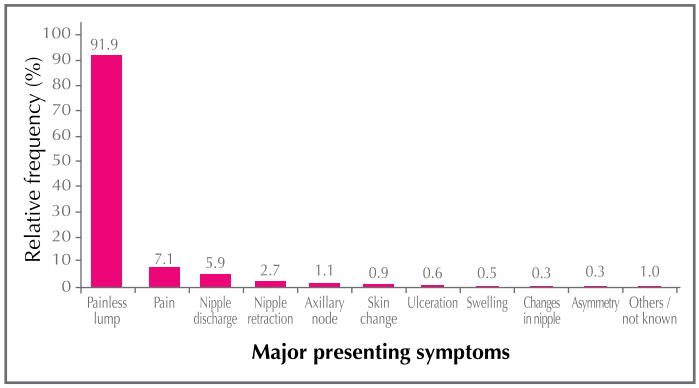
Table 2.3: Method of first breast cancer detection by cancer stage (N=15,146)

Method of first breast cancer detection	Cancer stage, Number (%)					
	0 (N=1,891)	I (N=4,840)	IIA (N=3,859)	IIB (N=1,942)	III (N=2,230)	IV (N=384)
Self-detection by chance	1,079 (57.1)	3,784 (78.2)	3,459 (89.6)	1,823 (93.9)	2,086 (93.5)	358 (93.2)
Mammography screening	643 (34.0)	649 (13.4)	201 (5.2)	45 (2.3)	67 (3.0)	7 (1.8)
Other screening methods (BSE and CBE)	63 (3.3)	171 (3.5)	104 (2.7)	40 (2.1)	38 (1.7)	11 (2.9)
Other imaging tests (USG and MRI)	89 (4.7)	197 (4.1)	73 (1.9)	26 (1.3)	19 (0.9)	5 (1.3)
Incidental surgery / Others	17 (0.9)	39 (0.8)	22 (0.6)	8 (0.4)	20 (0.9)	3 (0.8)

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

2.5 Most (91.9%) patients who self-detected their cancers by chance found a painless lump on their breast(s). Pain is not usually a symptom of breast cancer; only 7.1% of the patients felt pain in their breast(s) at initial presentation. Some (8.9%) patients 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 cancers in patient cohort (N=13,055)



*self-detection by chance only

A. *Time interval between 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.[33] After the onset of symptoms, only one-third (36.1%) of the patients who self-detected their cancers by chance sought first medical consultation in less than one month (Table 2.4). One quarter (25.3%) 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 (42.8%) than among public medical service users (30.5%) (Table 2.5).

Table 2.4: Time interval between onset of symptoms and first medical consultation for patients who self-detected* their cancers (N=3,423)

	Number	(%)
Less than 1 month	1,236	(36.1)
1-3 months	1,319	(38.5)
4-12 months	515	(15.0)
More than 12 months	353	(10.3)

*Self-detection by chance only

Table 2.5: Time interval between onset of symptoms and first medical consultation for patients who self-detected* their cancers by type of medical service (N=3,423)

	Type of medical service users, Number (%)					
	Private (N=642)		Public (N=1,634)		Mixed private / public (N=1,147)	
Less than 1 month	275	(42.8)	499	(30.5)	462	(40.3)
1-3 months	235	(36.6)	630	(38.6)	454	(39.6)
4-12 months	78	(12.1)	308	(18.8)	129	(11.2)
More than 12 months	54	(8.4)	197	(12.1)	102	(8.9)

*Self-detection by chance only

2.8 A much higher proportion (13.1%) 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 12 months (1.6%) (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=3,000)

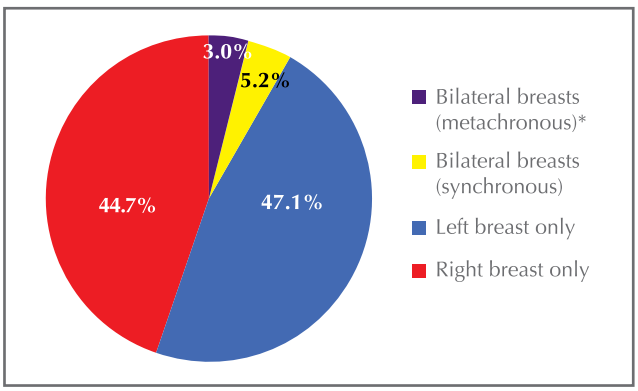
	Time interval between the onset of symptoms and first medical consultation, Number (%)			
Cancer stage at diagnosis	Less than 1 month (N=1,089)	1 – 3 months (N=1,174)	4 – 12 months (N=440)	More than 12 months (N=297)
Stage I	398 (36.5)	356 (30.3)	121 (27.5)	77 (25.9)
Stage IIA	361 (33.1)	389 (33.1)	132 (30.0)	66 (22.2)
Stage IIB	162 (14.9)	188 (16.0)	76 (17.3)	51 (17.2)
Stage III	151 (13.9)	203 (17.3)	92 (20.9)	64 (21.5)
Stage IV	17 (1.6)	38 (3.2)	19 (4.3)	39 (13.1)

*Self-detection by chance only

III. Cancer characteristics

2.9 Breast cancer can occur in one (unilateral) or both breasts (bilateral). The majority (91.8%) of the patients had unilateral breast cancer, while a small proportion (5.2%) had synchronous bilateral breast cancer at first diagnosis (Figure 2.3). A total of 151 (1.8%) patients developed contralateral breast cancer within a median of three years (range: 0.6 to 10.1 years) after diagnosis of an initial primary breast cancer (Figure 2.3). Another 199 patients also had contralateral breast cancer. However, as their initial primary breast cancer was diagnosed before 2006, only the data from their contralateral breast cancer, which was diagnosed after 2006, were included in this report.

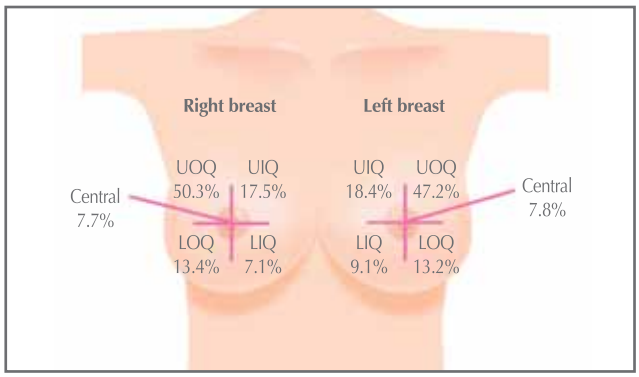
Figure 2.3: Laterality of 16,595 breast cancer cases



* Includes 199 patients who were diagnosed with initial primary breast cancer before 2006 but developed contralateral breast cancer after 2006 (only data on second diagnosis were included in this report).

2.10 As regards the locations of malignant breast tumour, about half of the breast cancers in either the right or the left breast (50.3% and 47.2% respectively) were detected in the upper outer quadrant (Figure 2.4).

Figure 2.4: Locations of malignant tumour on breasts within patient cohort (N=16,595)



UOQ: Upper outer quadrant UIQ: Upper inner quadrant
LOQ: Lower outer quadrant LIQ: Lower inner quadrant
*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 check the extent of their disease in the breast.

2.12 For cancer diagnosis, MMG was used on 85.3% of the patients, and USG on 79.8%, while MRI was used on only 9.4% of the patients (Table 2.7). 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 cancers and should be checked by further surgical tests such as biopsies.

Table 2.7: Sensitivity and diagnostic results of breast imaging tests (N=16,595)

	Mammography (N=14,158)		Breast ultrasound (N=13,236)		MRI (N=1,560)	
Proportion of patients using the diagnostic test	85.3%		79.8%		9.4%	
Overall sensitivity*	83.3%		91.1%		96.7%	
BIRADS category						
Diagnostic / malignant (BIRADS 5)	4,579	(32.3%)	4,923	(37.2%)	1,236	(79.2%)
Suspicious abnormality (BIRADS 4)	7,209	(50.9%)	7,133	(53.9%)	272	(17.4%)
Probably benign (BIRADS 3)	769	(5.4%)	721	(5.4%)	25	(1.6%)
Benign (BIRADS 2)	573	(4.0%)	210	(1.6%)	11	(0.7%)
Normal (BIRADS 1)	941	(6.6%)	241	(1.8%)	15	(1.0%)
Incomplete (BIRADS 0)	87	(0.6%)	8	(0.1%)	1	(0.1%)

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 63.9% of the patients in the cohort with BIRADS 4 or 5 mammograms, while microcalcification was observed in 50.0% (Table 2.8). 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 patient cohort, two-thirds (69.3%) had heterogeneously dense breasts, while a small proportion (6.5%) had extremely dense breasts (Figure 2.5). Mammographic density of a woman's breasts declines with increasing age. The proportion of patients with extremely dense breast decreases significantly from 14.6% among patients aged between 20 and 29 to 1.5% among patients aged 70 and above (Table 2.9).

Table 2.8: Mammographic findings of patients diagnosed through mammography (N=11,788)

	Number	(%)
Opacity	7,533	(63.9)
Microcalcification	5,890	(50.0)
Architectural distortion	1,743	(14.8)
Asymmetric density	986	(8.4)
Unclassified	526	(4.5)

Figure 2.5: Mammographic density of breasts of patients diagnosed through mammogram (N=8,463)

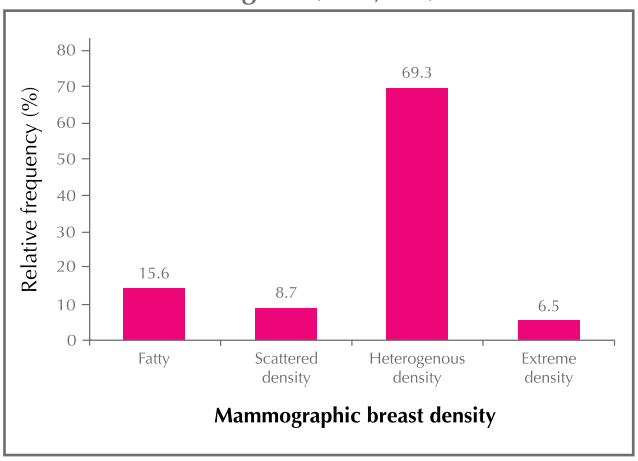


Table 2.9: Mammographic density of breasts of patients diagnosed through mammogram by age group (N=8,183)

Mammographic density	Age group, Number (%)					
	20-29 (N=48)	30-39 (N=672)	40-49 (N=2,503)	50-59 (N=2,803)	60-69 (N=1,547)	70+ (N=610)
Fatty	3 (6.3)	45 (6.7)	221 (8.8)	424 (15.1)	351 (22.7)	213 (34.9)
Scattered density	2 (4.2)	23 (3.4)	150 (6.0)	257 (9.2)	186 (12.0)	90 (14.8)
Heterogeneous density	36 (75.0)	529 (78.7)	1,908 (76.2)	1,964 (70.1)	954 (61.7)	298 (48.9)
Extreme density	7 (14.6)	75 (11.2)	224 (8.9)	158 (5.6)	56 (3.6)	9 (1.5)

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 (85.3%) of the patients in the cohort and among them, a quarter (25.2%) received only FNA, about half (52.5%) received only CNB, and about a fifth (22.3%) received both FNA and CNB. In addition, 10.8% of the patients had excisional biopsy. Excisional biopsy had the highest overall sensitivity of 100%, followed by CNB (98.9%) and FNA (91.7%) (Table 2.10).

Table 2.10: Sensitivity and diagnostic results of breast tissue biopsies (N=16,595)

	FNA (N=6,720)	CNB (N=10,596)	Excisional biopsy (N=1,797)
Proportion of patients using the diagnostic test	40.5%	63.9%	10.8%
Overall sensitivity*	91.7%	98.9%	100.0%
Class			
Diagnostic / malignant (Class V)	4,255 (63.3%)	10,110 (95.4%)	1,797 (100.0%)
Suspicious (Class IV)	1,092 (16.3%)	181 (1.7%)	—
Atypical (Class III)	815 (12.1%)	186 (1.8%)	—
Benign (Class II)	278 (4.1%)	84 (0.8%)	—
Scanty benign (Class I)	280 (4.2%)	35 (0.3%)	—
Incomplete (Class 0)	0 (0.0%)	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 usually 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 Half (51.2%) of the patients with invasive breast cancer did not have any cancer staging as part of their diagnosis and treatment. Among those patients who had cancer staging as part of their treatment, the most common method used was positron emission tomography scan (PET scan) (45.4%), followed by a combination of chest x-ray and ultrasound of abdomen (39.5%) (Table 2.11). PET scan is not recommended for patients with early breast cancer, including stage I, stage II, or operable stage III breast cancer, to determine the extent of disease. This might be due to its low sensitivity and fairly low specificity in staging of the axillary lymph nodes and poor detection of metastases in patients with apparent early-stage disease.[34] Among those patients who had cancer staging, 17.6% of stage I and 36.0% of stage IIA patients had PET scan to determine the extent of their disease (Table 2.12).

Table 2.11: Method of clinical staging in 7,016 invasive breast cancer patients

Type of cancer staging method	Number	(%)
Positron emission tomography scan (PET scan)	3,183	(45.4)
Chest X-Ray (CXR) and ultrasound abdomen (USG Abd)	2,770	(39.5)
Computed tomography of body parts*	430	(6.1)
Bone scan	218	(3.1)
Magnetic resonance imaging whole body (MRI whole body)	92	(1.3)
Others (e.g. bone x-ray)	147	(2.1)
Not known	939	(13.4)

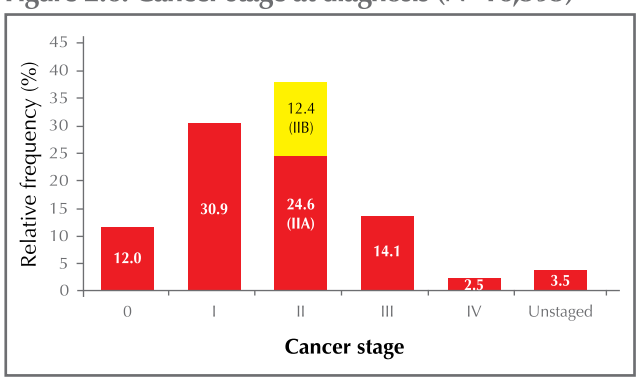
* Body parts include abdomen, thorax, pelvis, brain, or whole body

Table 2.12: Use of PET scan as a form of staging method among patients by cancer stage (N=7,016)

	Cancer stage						
	I	IIA	IIB	III	IV	Unstaged	Total
No. (%) of patients used PET scan	335 (17.6%)	618 (36.0%)	549 (50.8%)	1158 (69.0%)	326 (86.5%)	197 (76.4%)	3,183 (45.4%)

2.17 The American Joint Committee on Cancer (AJCC) Breast Cancer Staging System (8th edition 2018)[35] 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 for this was that patients in the cohort were mostly diagnosed in 2006 to 2016 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 (37.0%), followed by stages III to IV (16.6%). In addition, 12.0% of the patients were diagnosed with in situ cancers (Figure 2.6).

Figure 2.6: Cancer stage at diagnosis (N=16,595)

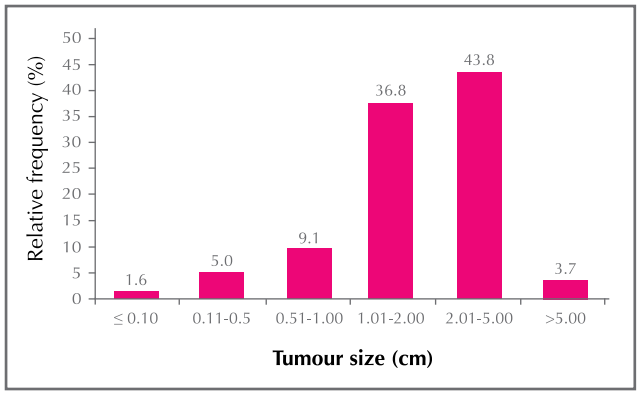


2.18 Of the 16,595 breast cancer cases analysed, data from 16,440 cases with available pathology data were used for subsequent analyses on cancer characteristics. A total of 14,234 (86.6%) patients were diagnosed with invasive cancers, while 2,194 (13.3%) patients were diagnosed with in situ cancers. In addition, 12 (0.1%) cases were diagnosed with occult primary breast cancers.

C. Characteristics of invasive breast cancer

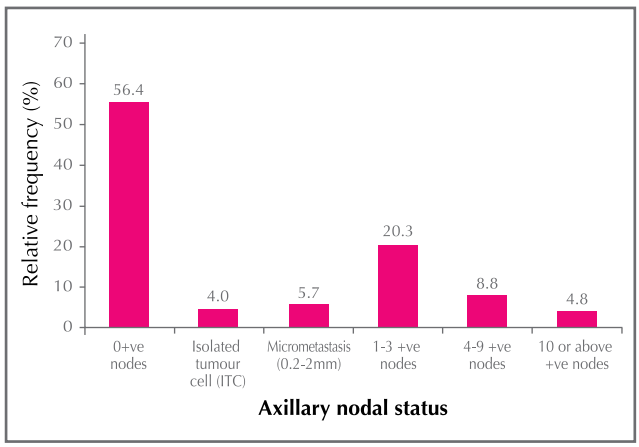
2.19 The mean size of invasive breast cancers was 2.2 cm (range: 0.01 to 23.5 cm; standard deviation: ±1.5 cm). Tumours of one cm or less in size were found in 15.7% of the patients, while tumours of sizes one to two cm and two to five cm were found in 36.8% and 43.8% of the patients respectively (Figure 2.7). Only a small proportion (3.7%) of patients had tumours of sizes exceeding five cm. In the patient cohort, screen-detected cancers were significantly smaller than those self-detected by chance (mean: 1.2±1.0 cm vs. 2.3±1.5 cm; p<0.001).

Figure 2.7: Distribution of tumour size (cm) of invasive breast cancers (N=12,213)



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 cancers, 56.4% had no positive axillary lymph nodes, 4.0% had isolated tumour cells, 5.7% had micrometastasis (metastasis size > 0.2 mm to ≤ 2 mm), while 33.9% had at least one positive axillary lymph node with metastasis size larger than two mm (Figure 2.8).

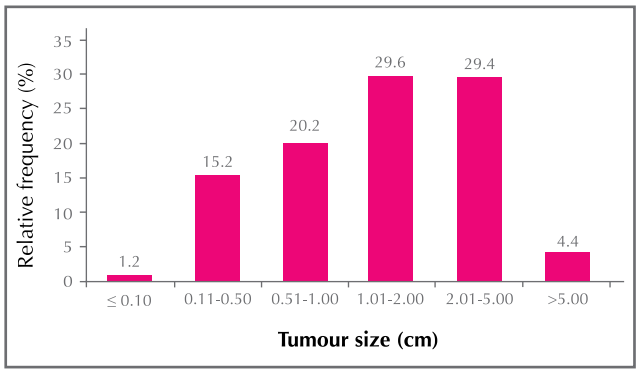
Figure 2.8: Number of positive axillary lymph nodes among patients with invasive breast cancers (N=13,904)



D. *Characteristics of in situ breast cancer*

2.21 The mean size of in situ breast cancers in the cohort was 1.9 cm (range: 0.02 to 10.0 cm; standard deviation: ±1.5 cm). Tumours of one cm or less in size were found in 36.6% of the patients while tumours of two to five cm in size were found in 29.4% of the patients (Figure 2.9). A small proportion (4.4%) of the patients had in situ tumours larger than five cm. Of the in situ breast cancer cases where MMG was performed, 61.4% showed microcalcification.

Figure 2.9: Distribution of tumour size (cm) of in situ breast cancers (N=1,781)



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 cancers in the patient cohort are concerned, the most common type was invasive carcinoma of no specific type (86.8%) (Table 2.13).

Table 2.13: Histological type, grading, multifocality and multicentricity of invasive breast cancers (N=14,234)

Histological type	Number	(%)
Invasive carcinoma of no specific type	12,351	(86.8)
Lobular	521	(3.7)
Mucinous (colloid)	480	(3.4)
Papillary	146	(1.0)
Tubular	92	(0.6)
Carcinoma with medullary features	75	(0.5)
Micropapillary	61	(0.4)
Borderline / malignant phyllodes	58	(0.4)
Mixed ductal and lobular	58	(0.4)
Metaplastic carcinoma	52	(0.4)
Carcinoma with neuroendocrine features	25	(0.2)
Adenoid cystic carcinoma	17	(0.1)
Carcinoma with apocrine features	16	(0.1)
Paget's disease of nipple	8	(0.1)
Tubulo-lobular carcinoma	7	(<0.1)
Cribriform carcinoma	5	(<0.1)
Inflammatory	4	(<0.1)
Squamous cell carcinoma	3	(<0.1)
Lipid rich carcinoma	2	(<0.1)
Sarcoma	2	(<0.1)
Secretory carcinoma	2	(<0.1)
Others (e.g. mixed types)	135	(0.9)
Not known	114	(0.8)

	Number	(%)
Grade		
Grade 1	2,301	(16.2)
Grade 2	5,645	(39.7)
Grade 3	4,560	(32.0)
Not known	1,728	(12.1)
Lymphovascular invasion	**3,968**	**(27.9)**
Multifocality	**1,384**	**(9.7)**
Number of foci		
2	710	(51.3)
3-4	238	(17.2)
≥5	129	(9.3)
Not known	306	(22.1)
Multicentricity	**418**	**(2.9)**
Number of quadrants		
2	356	(85.2)
3	23	(5.5)
4	18	(4.3)
Not known	21	(5.0)

2.24 Among the 13,843 patients with invasive breast cancers who were tested for estrogen or progesterone receptor status, more than three-quarters (79.4%) were either ER or PR positive. Amplification or over-expression of HER2 oncogene is associated with the development of certain types of breast cancer. A patient with immunohistochemistry (IHC) score 3 is considered as HER2 positive, where score 0 or 1 is considered as negative. For patients with IHC score 2, In Situ Hybridization (ISH) test will be further conducted. Patients who had positive results in ISH are also considered as HER2 positive. In the patient cohort, slightly more than one-fifth (22.5%) of invasive breast cancers were c-erbB2/HER2 positive. The biological characteristics of invasive breast cancers in the patient cohort are shown in Table 2.14.

Table 2.14: Biological characteristics of invasive breast cancers (N=14,234)

	Number	(%)
Estrogen receptor (ER) (97.2% of the patients had the test)		
Positive	10,769	(77.8)
Negative	3,069	(22.2)
Progesterone receptor (PR) (96.9% of the patients had the test)		
Positive	9,043	(65.5)
Negative	4,756	(34.5)
c-erbB2 / HER2 (96.5% of the patients had the test)		
Positive (IHC Score 3)	2,820	(20.5)
Equivocal (IHC Score 2) ISH positive	278	(2.0)
Equivocal (IHC Score 2) ISH equivocal	117	(0.9)
Equivocal (IHC Score 2) ISH negative	2,328	(17.0)
Equivocal (IHC Score 2) ISH not done	1,676	(12.2)
Negative (IHC Score 0 / 1)	6,510	(47.4)
Ki-67 index (55.7% of the patients had the test)		
<14%	2,928	(36.9)
≧14%	4,997	(63.1)

HER2: Human epidermal growth factor receptor 2
IHC: Immunohistochemistry
ISH: In Situ Hybridization

2.25 Breast cancer is not considered a single disease and can be further classified into several biological subtypes[36] by immunohistochemical staining of several biological markers (Table 2.14). Further prognostic and predictive information can be obtained by assessing these biological markers together instead of separately. The surrogate definitions of these intrinsic biological subtypes and their relative frequencies by cancer stage in the patient cohort are shown in Table 2.15.

Table 2.15: Biological subtypes of invasive tumours by cancer stage (N=13,355)

	Cancer Stage, N (%)											
Biological subtypes	**I**		**IIA**		**IIB**		**III**		**IV**		**Total**	
Luminal A*	1,323	(27.1)	653	(16.7)	297	(15.0)	263	(11.8)	32	(9.2)	2,568	(19.2)
Luminal B (HER2 negative)#	833	(17.1)	812	(20.8)	401	(20.3)	390	(17.5)	39	(11.2)	2,475	(18.5)
Luminal A/B (HER2 negative)†	1,329	(27.2)	982	(25.1)	549	(27.7)	560	(25.1)	98	(28.1)	3,518	(26.3)
Luminal B (HER2 positive)^	550	(11.3)	548	(14.0)	316	(16.0)	523	(23.4)	101	(28.9)	2,038	(15.3)
HER2 Positive❊	376	(7.7)	345	(8.8)	168	(8.5)	253	(11.3)	48	(13.8)	1,190	(8.9)
TND§	468	(9.6)	573	(14.6)	249	(12.6)	245	(11.0)	31	(8.9)	1,566	(11.7)
Total	**4,879**	**(36.5)**	**3,913**	**(29.3)**	**1,980**	**(14.8)**	**2,234**	**(16.7)**	**349**	**(2.6)**	**13,355**	**(100.0)**

* 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-positive: ER and PR-, HER2+, and any Ki-67 index

§ TND (Triple Negative Disease): ER and PR-, HER2-, and any Ki-67 index

B. In situ breast cancer

2.26 Ductal cancers were found to be the most common type of in situ breast cancers (93.1%). Table 2.16 shows the histological characteristics, grading, multifocality and multicentricity of in situ breast cancers in the patient cohort.

Table 2.16: Histological type, grading, multifocality and multicentricity of in situ breast cancers (N=2,194)

	Number	(%)
Histological type		
Ductal	2,042	(93.1)
Mixed	56	(2.6)
Papillary	40	(1.8)
Intracystic papillary	16	(0.7)
Encapsulated papillary	10	(0.5)
Apocrine	6	(0.3)
Neuroendocrine	3	(0.1)
Micropapillary	1	(<0.1)
Not known	20	(0.9)
Necrosis	**710**	**(32.4)**
Nuclear Grade		
Low	541	(24.7)
Intermediate	687	(31.3)
High	793	(36.1)
Not known	173	(7.9)
Multifocality	**251**	**(11.4)**
Number of foci		
2	113	(45.0)
3	20	(8.0)
4 or more	9	(3.6)
Not known	109	(43.4)
Multicentricity	**49**	**(2.2)**
Number of quadrants		
2	41	(83.7)
3	2	(4.1)
Not known	6	(12.2)

2.27 Among the 1,514 patients with in situ breast cancers who were tested for ER or PR status, the majority (81.8%) were either ER or PR positive (72%). Table 2.17 shows the biological characteristics of in situ breast cancers in the patient cohort. Among the 472 patients who had HER2 IHC score 2, two patients showed positive results in ISH test, which means that about a quarter (26.7%) in situ breast cancer patients in the cohort were c-erbB2/HER2 positive.

Table 2.17: Biological characteristics of in situ breast cancers (N=2,194)

	Number	(%)
Estrogen receptor (ER) (69.0% of the patients had the test)		
Positive	1,222	(80.8)
Negative	291	(19.2)
Progesterone receptor (PR) (67.5% of the patients had the test)		
Positive	1,066	(72.0)
Negative	414	(28.0)
c-erbB2/HER2 (62.3% of the patients had the test)		
Positive (IHC score 3)	363	(26.6)
Equivocal (IHC score 2)	472	(34.5)
Negative (IHC score 0/1)	532	(38.9)
Ki-67 index (38.2% of the patients had the test)		
<14%	535	(63.8)
≧14%	303	(36.2)

HER2: Human epidermal growth factor receptor 2
IHC: Immunohistochemistry

V. Treatment methods

2.28 Of the 16,595 patients, 14.2% received care at private medical service, 52.1% received care at public medical service, and 33.7% received care at both private and public medical services. Patients with invasive tumours are usually given multimodality treatments, which may include surgery, chemotherapy, anti-HER2 targeted therapy, endocrine therapy and radiotherapy. In constrast, patients with in situ tumours 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 tumour. 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 to 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 patient cohort, 47.3% had surgery at private medical facilities, while 52.7% had surgery at public medical facilities.

2.32 For patients with in situ tumour, almost all (99.1%) underwent surgery. Half (50.3%) of them had breast-conserving surgery, while about a quarter (22.5%) had reconstruction after mastectomy. In addition, about one-third (32.8%) of them did not receive nodal surgery, and among those who received nodal surgery (42.4%), the majority (83.8%) had SNB only and about a tenth (11.9%) had AD without SNB (Table 2.18).

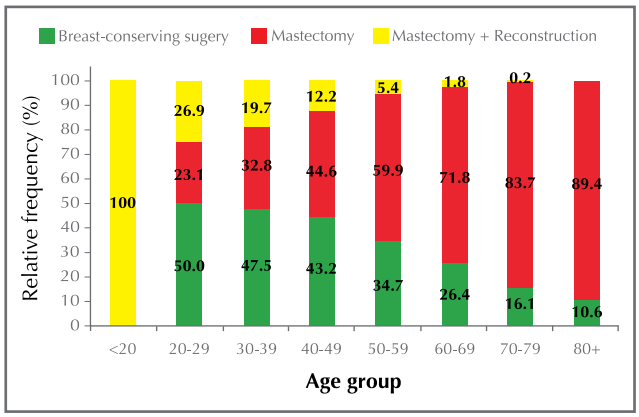
2.33 For patients with invasive tumour, the majority (97.8%) of them underwent surgery as part of their treatment. About two-thirds (64.7%) had mastectomy, while one-third (32.8%) had breast-conserving surgery. Among the patients who had mastectomy, 11.8% had either immediate or delayed reconstruction. The most common type of reconstruction was TRAM flap (69.7%) (Table 2.18). Almost all (96.3%) the patients with invasive tumours received nodal surgery and among them, 56.5% required AD, and 42.4% required SNB only (Table 2.18).

Table 2.18: Type of surgery (N=16,583)

	Patients with invasive cancer (N=14,384)		Patients with in situ cancer (N=2,199)	
	Number	(%)	Number	(%)
No surgery	280	(1.9)	19	(0.9)
Breast-conserving surgery	4,714	(32.8)	1,106	(50.3)
Mastectomy	9,309	(64.7)	1,069	(48.6)
Nodal surgery only	13	(0.1)	0	(0.0)
Type of surgery not known	25	(0.2)	4	(0.2)
Not known if surgery done	43	(0.3)	1	(<0.1)
Mastectomy (N=10,378)				
Total mastectomy	8,790	(94.4)	930	(87.0)
Skin sparing	376	(4.0)	105	(9.8)
Areolar sparing	15	(0.2)	4	(0.4)
Nipple sparing	105	(1.1)	28	(2.6)
Unknown type	23	(0.2)	2	(0.2)
Reconstruction (N=1,336)				
TRAM flap	763	(69.7)	147	(61.0)
Implant	169	(15.4)	71	(29.5)
LD flap	89	(8.1)	12	(5.0)
LD flap & implant	52	(4.7)	10	(4.1)
Unknown type	22	(2.0)	1	(0.4)
Nodal surgery (N=15,327)				
Sentinel node biopsy	5,875	(42.4)	1,237	(83.8)
Axillary dissection	5,538	(40.0)	176	(11.9)
Sentinel node biopsy & axillary dissection	2,288	(16.5)	48	(3.2)
Unknown type	149	(1.1)	16	(1.1)

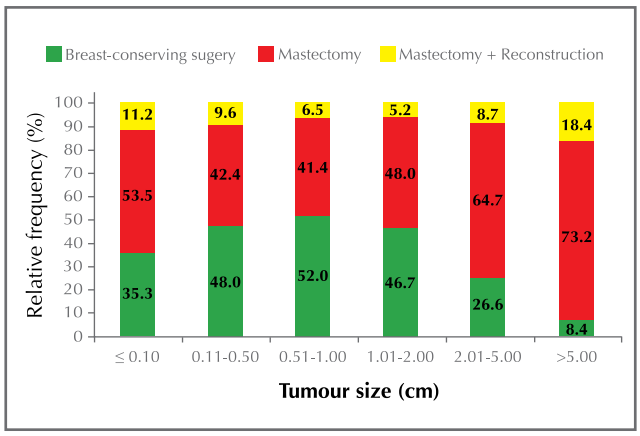
2.34 The percentage of the patients who underwent mastectomy was positively correlated with increasing age, while the percentage of the patients who underwent mastectomy with reconstruction was negatively correlated with increasing age (Figure 2.10).

Figure 2.10: Type of surgery by age group (N=15,597)



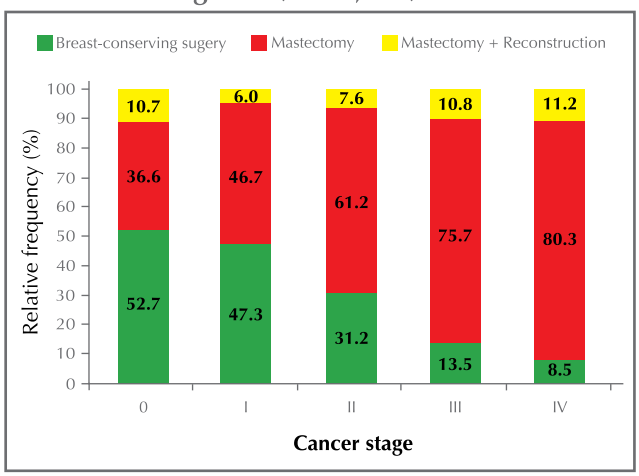
2.35 For the patients with tumours larger than one cm in size, the percentage of the patients who had breast-conserving surgery was negatively correlated with increasing tumour size (Figure 2.11).

Figure 2.11: Type of surgery by tumour size (N=13,965)



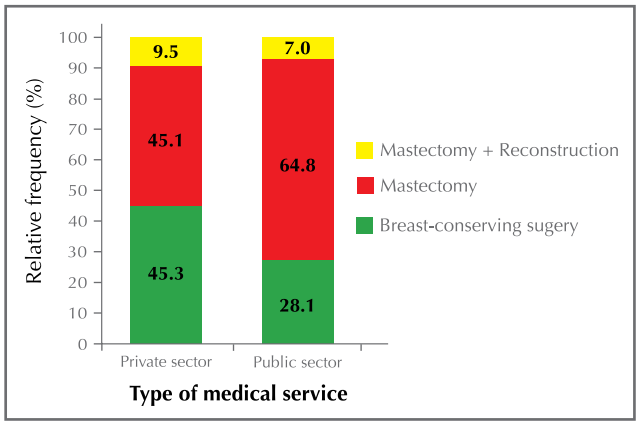
2.36 The proportion of the patients who received breast-conserving surgery was negatively correlated with increasing cancer stage. Mastectomy with reconstruction did not show any correlation with increasing cancer stage (Figure 2.12).

Figure 2.12: Type of surgery by cancer stage at diagnosis (N=15,766)



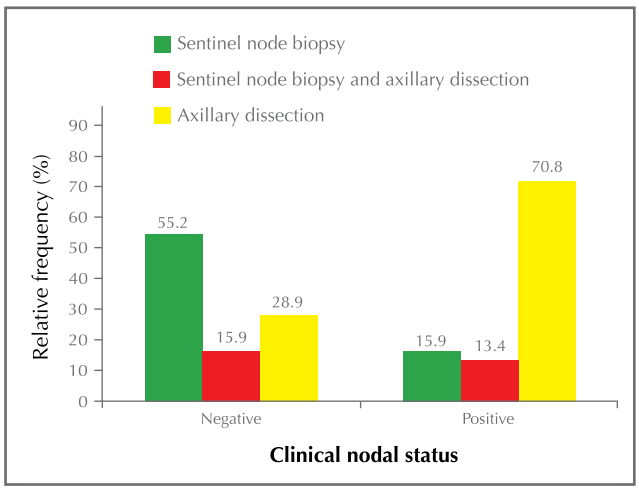
2.37 A higher proportion (45.3%) of the patients who had surgery at private medical facilities underwent breast-conserving surgery than those who had surgery at public medical facilities (28.1%) (Figure 2.13).

Figure 2.13: Type of surgery by type of medical service (N=15,668)



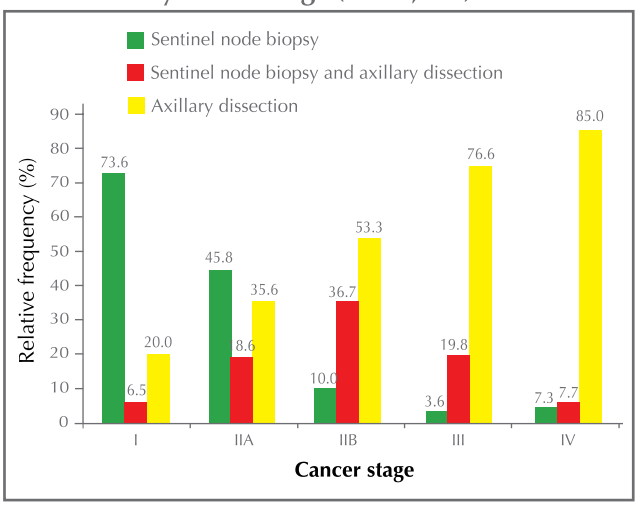
2.38 SNB without AD was more commonly performed on the patients with negative clinical nodal status (55.2%) than those with positive clinical nodal status (15.9%). On the other hand, AD without SNB was more commonly performed on the patients with positive clinical nodal status (70.8%) than those with negative clinical nodal status (28.9%). Figure 2.14 shows the type of nodal surgery received by the patients with positive or negative clinical nodal status.

Figure 2.14: Type of nodal surgery by clinical nodal status (N=15,172)



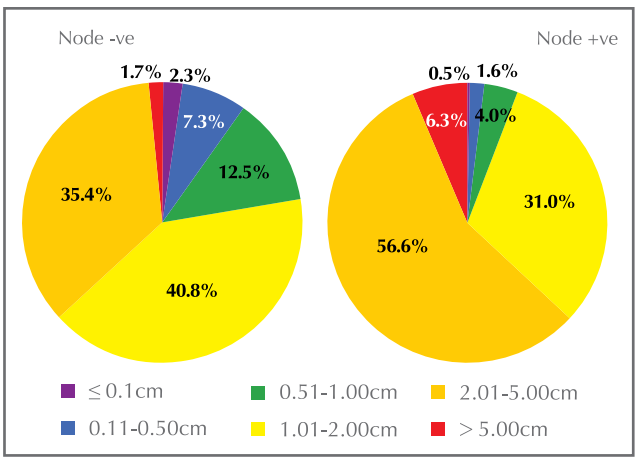
2.39 The use of AD alone was positively correlated with progressing cancer stage. In the patient cohort, the use of AD after SNB increased from stage I to II patients, but decreased for stage III or IV patients. This is because most of the patients with stage III or IV disease received AD as their first nodal surgery (Figure 2.15).

Figure 2.15: Type of nodal surgery for invasive cancer by cancer stage (N=13,376)



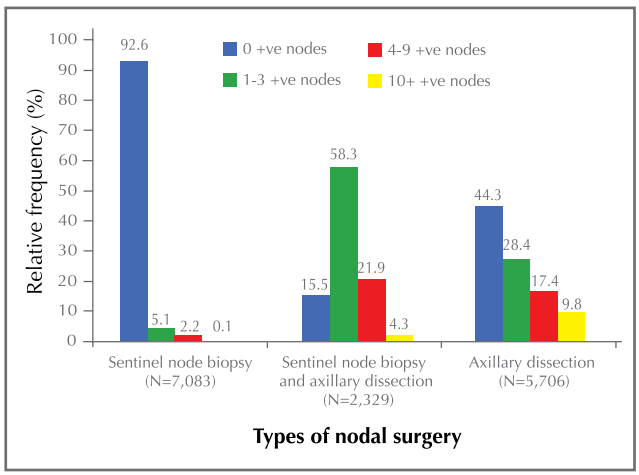
2.40 About half (56.6%) of the patients with node positive invasive cancer had tumours of two to five cm in size, while a smaller proportion (6.3%) had tumours greater than five cm. In the patient cohort, more patients with node negative invasive cancer had tumours less than two cm (62.9%) when compared to patients with node positive invasive cancer (37.1%) (Figure 2.16).

Figure 2.16: Distribution of tumour size in invasive cancer with negative or positive nodal status (N=12,147)



2.41 Of the patients in the cohort, 92.6% who underwent only SNB had no positive lymph node, while 44.3% who underwent only AD and 15.5% who underwent AD after SNB had no positive lymph node (Figure 2.17).

Figure 2.17: Number of positive nodes by types of nodal surgery (N=15,118)



B. Radiotherapy

2.42 Radiotherapy is a treatment to kill cancer cells using ionizing radiation. Radiation is capable of inflicting damage at the DNA level of a cell and can stop cells from reproducing. Radiotherapy can be administered in two settings: firstly, locoregional radiotherapy where breast, chest wall, and/or regional lymph nodes are radiated with curative intention; 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 patient cohort, two-thirds (60.3%) of the cases had locoregional radiotherapy as part of their treatment, among which 99.8% were adjuvant, and 0.2% were neoadjuvant. About four-fifths (82.5%) of the patients were treated with radiotherapy at public medical facilities, while slightly less than one-fifth (17.5%) had radiotherapy at private medical facilities.

2.45 Of the patients with in situ cancer who had breast-conserving surgery, the majority (94.8%) received locoregional radiotherapy afterwards (Figure 2.18), while only a small proportion (3.3%) of the patients with in situ cancer who had mastectomy underwent radiotherapy (Figure 2.19).

2.46 The proportions of the invasive breast cancer patients who had undergone either breast-conserving surgery or mastectomy and also received localised radiotherapy as part of their treatment by different cancer stages are shown in Figures 2.18 and 2.19 respectively. The proportion of the invasive breast cancer patients who underwent breast-conserving surgery and also received locoregional radiotherapy was high: from 85.7% in the case of stage IV patients to 98% for stage III patients. On the other hand, the proportion of the invasive breast cancer patients who underwent mastectomy and also received locoregional radiotherapy increased significantly from stage I (12.5%) to stage III (94.7%), but drops sharply in stage IV (54.2%).

Figure 2.18: Patients who underwent both breast-conserving surgery and locoregional radiotherapy by cancer stage (N=5,606)

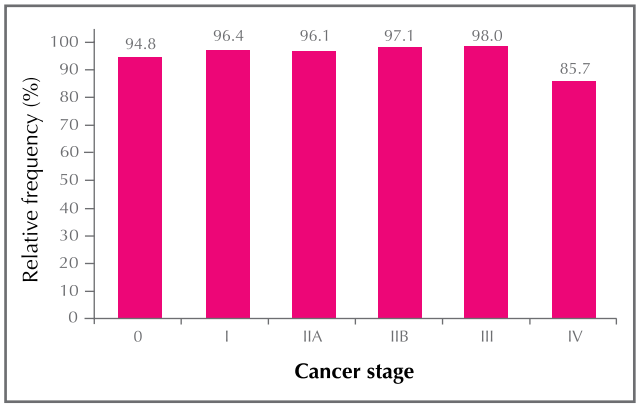
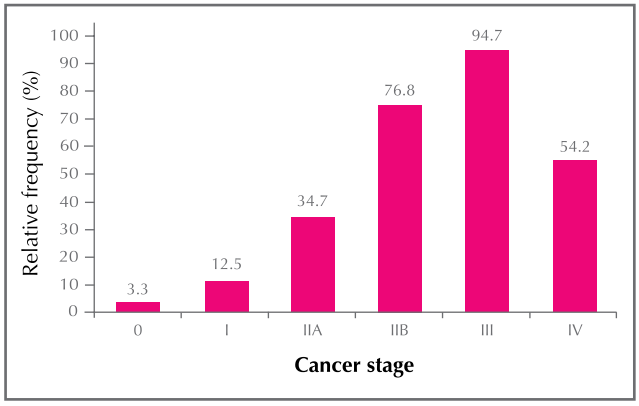


Figure 2.19: Patients who underwent both mastectomy and locoregional radiotherapy by cancer stage (N=9,871)



2.47 Radiotherapy for breast cancer involves localised irradiation of regions such as breast/chest wall, with or without regional nodes. Table 2.19 shows the irradiated regions of adjuvant radiotherapy among those patients who received radiotherapy by the type of surgery they underwent.

Table 2.19: Coverage of regional lymph nodes by adjuvant locoregional radiotherapy (N=6,478)

Type of surgery	Number	(%)
Breast-conserving surgery		
Breast alone	2,839	(84.0)
Breast and regional lymph nodes	541	(16.0)
Mastectomy		
Chest wall alone	797	(25.7)
Chest wall and regional lymph nodes	2,301	(74.3)

ii. Palliative radiotherapy

2.48 Palliative radiotherapy for breast cancer are 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 cancers, 11.7% underwent palliative radiotherapy, and of these patients, 88.1% received radiotherapy to the spine and 35.7% to the pelvis.

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 multiply. Chemotherapy is generally not required for patients with in situ tumour.

2.51 A total of 9,742 (68.2%) patients with invasive cancer in the cohort underwent chemotherapy. Of these patients, 84.5% had adjuvant chemotherapy, 11.5% had neoadjuvant chemotherapy, and 4.0% had palliative chemotherapy. The majority (86.9%) of the patients received chemotherapy in public medical facilities, and the remainder (13.1%) 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 diseases. In contrast, the majority (87.3%) of the patients with stage IV cancers underwent palliative chemotherapy (Figure 2.20).

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. For the patients with stage I or stage IIA disease, the use of chemotherapy significantly decreased with increasing age group. Table 2.20 shows the percentage of the patients who received chemotherapy by age group and cancer stage.

Figure 2.20: Chemotherapy treatment by cancer stage (N=13,732)

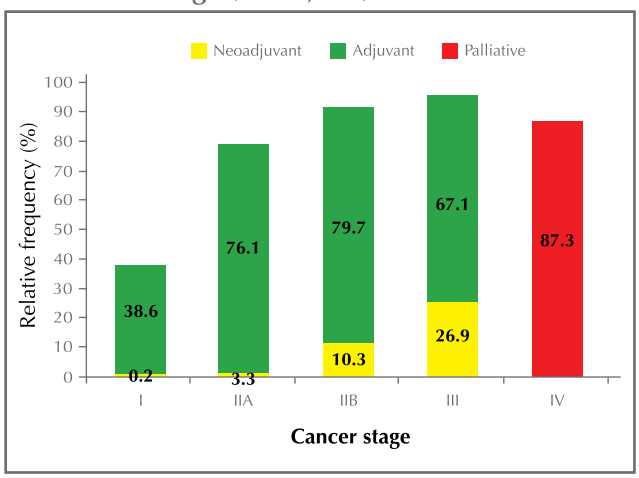


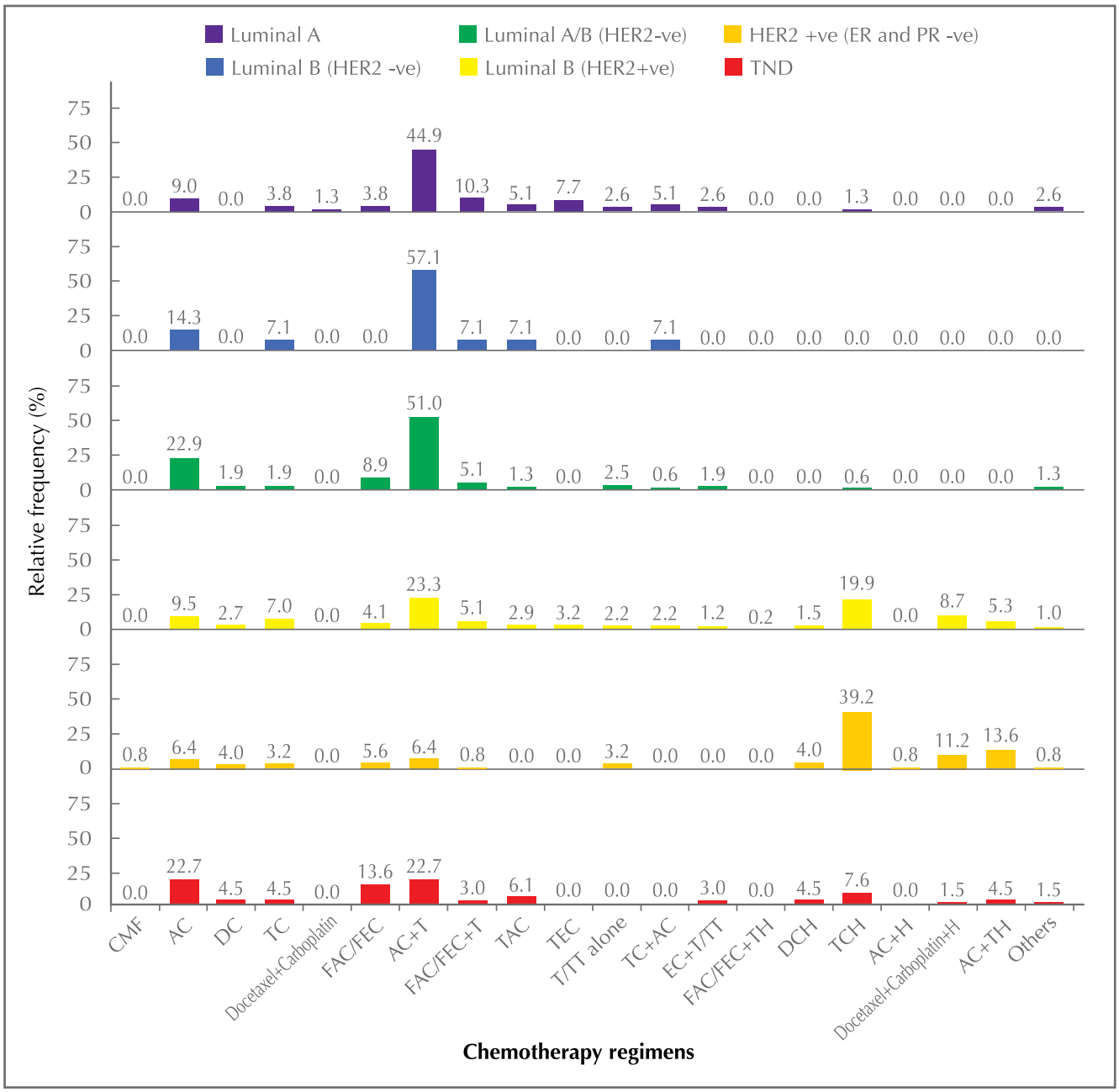
Table 2.20: Use of chemotherapy by age group and cancer stage at diagnosis (N=13,242)

	Number of patients received chemotherapy (% of patients in the same age group and cancer stage)									
Age group	Stage I		Stage IIA		Stage IIB		Stage III		Stage IV	
20-29	23	(65.7)	23	(92.0)	18	(100.0)	14	(100.0)	3	(100.0)
30-39	248	(58.2)	333	(91.2)	172	(98.9)	200	(99.0)	26	(86.7)
40-49	746	(46.3)	1,026	(89.5)	604	(96.8)	711	(98.9)	125	(96.2)
50-59	616	(39.7)	1,124	(87.9)	639	(95.9)	733	(98.0)	136	(90.7)
60-69	228	(27.0)	526	(71.4)	330	(90.7)	389	(94.4)	49	(90.7)
70-79	8	(2.8)	35	(14.9)	21	(19.1)	49	(45.4)	9	(39.1)
80+	2	(4.0)	1	(1.6)	0	(0.0)	2	(7.7)	2	(28.6)

i. Neoadjuvant chemotherapy

2.54 Of the 9,742 patients who underwent chemotherapy, 1,125 (11.5%) patients received it as neoadjuvant treatment. The use of neoadjuvant chemotherapy increased substantially with progressing cancer stage, from 0.2% of stage I patients to 26.9% of stage III patients (Figure 2.20). The regimens used by patients with different biological subtypes are shown in Figure 2.21.

Figure 2.21: Type of chemotherapy regimens in neoadjuvant setting in patients by biological subtype (N=939)



C: Cyclophosphamide;
M: Methotrexate;
F: Fluorouracil (5FU);
A: Adriamycin / Doxorubicin;
E: Epirubicin;
T: Paclitaxel / Docetaxel;
H: Trastuzumab;
DC: Docetaxel + Cyclophosphamide;
DCH: Docetaxel + Cyclophosphamide + Trastuzumab
TC: Paclitaxel + Carboplatin;
TCH: Paclitaxel + Carboplatin + Trastuzumab
Others: Capecitabine, Gemcitabine, or Vinorelbine

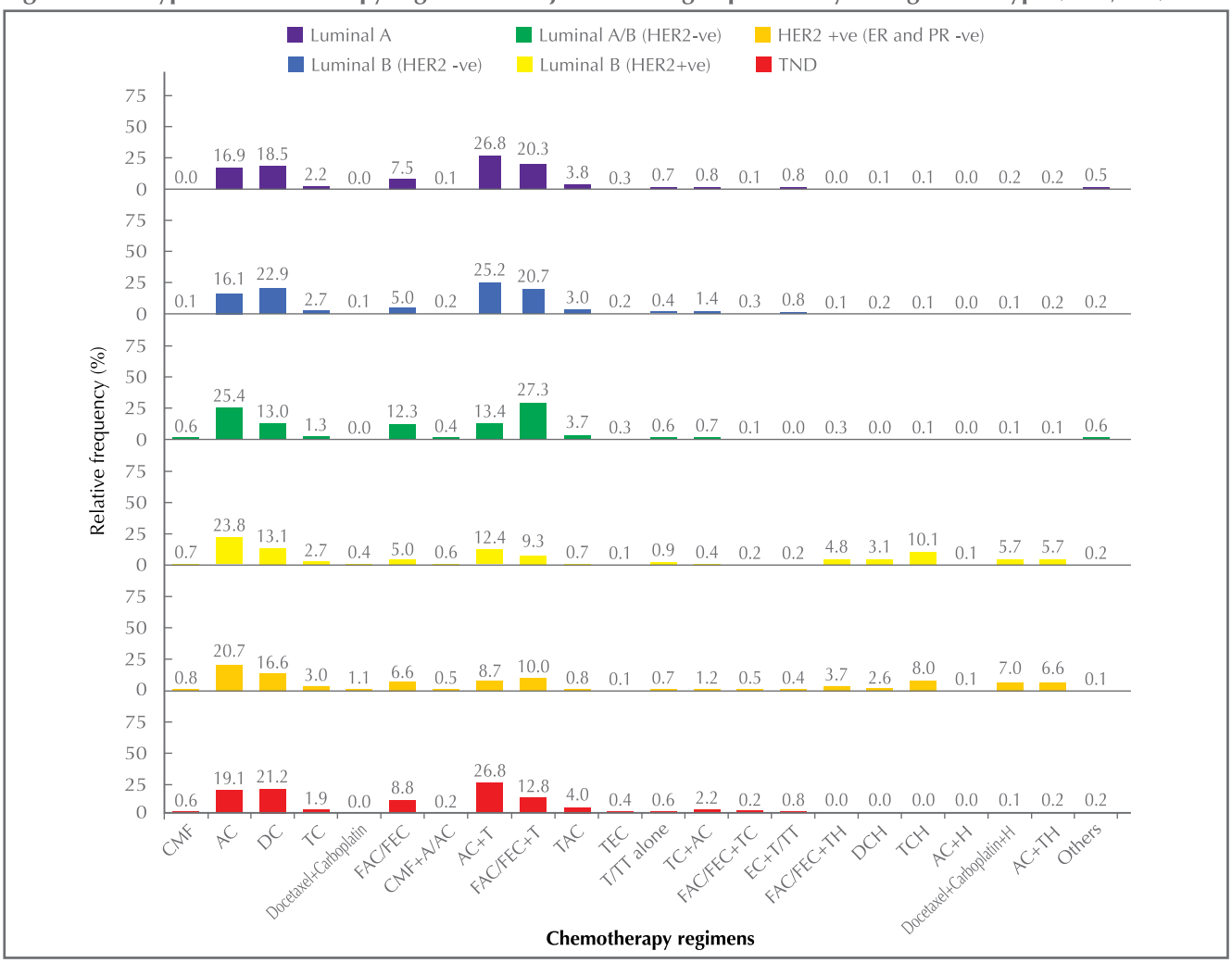
ii. Adjuvant chemotherapy

2.55 Of the 9,742 patients who underwent chemotherapy, 8,232 (84.5%) patients received it as adjuvant (Stage I-III) treatment. Figures 2.22 and 2.23 show the relative frequency for different types of chemotherapy regimen used by biological subtype and cancer stage, respectively.

iii. Palliative chemotherapy

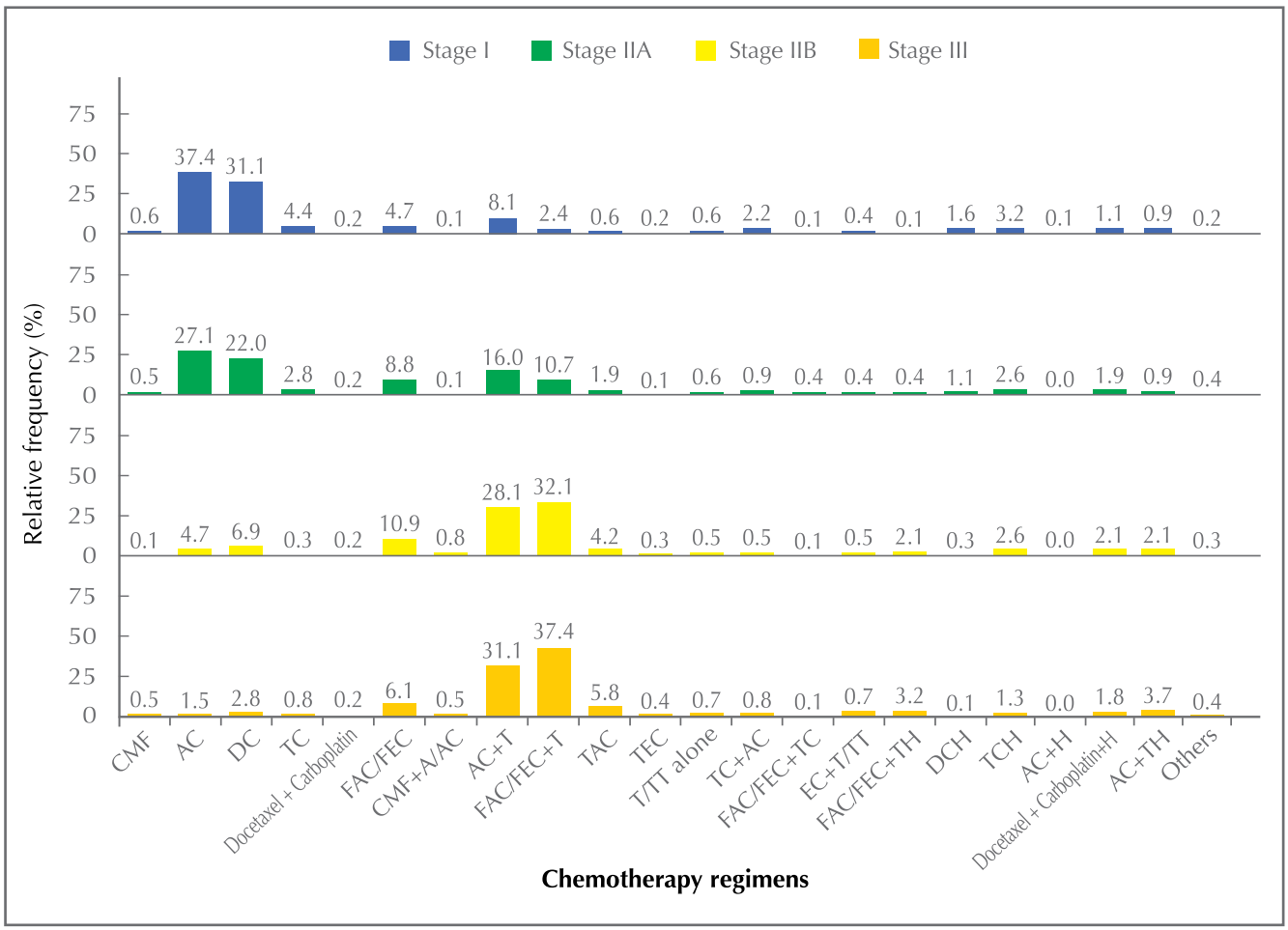
2.56 Of the 9,742 patients who underwent chemotherapy, 385 (4.0%) patients received it as palliative (Stage IV) treatment. Figure 2.24 shows the relative frequency for different types of chemotherapy regimen used by biological subtype.

Figure 2.22: Type of chemotherapy regimens in adjuvant setting in patients by biological subtype (N=7,172)



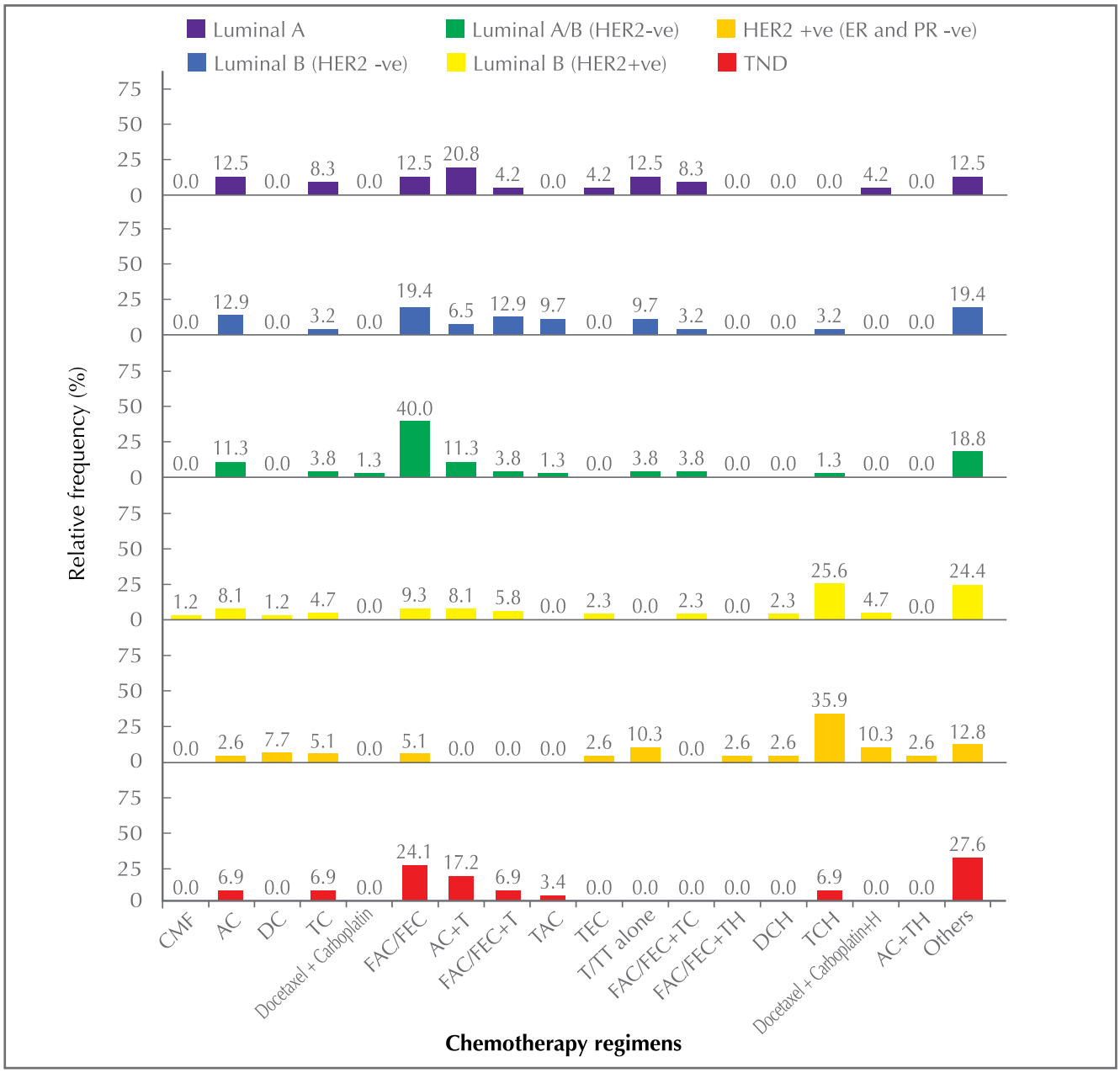
C: Cyclophosphamide;
M: Methotrexate;
F: Fluorouracil (5FU);
A: Adriamycin / Doxorubicin;
E: Epirubicin;
T: Paclitaxel / Docetaxel;
H: Trastuzumab;
DC: Docetaxel + Cyclophosphamide;
DCH: Docetaxel + Cyclophosphamide + Trastuzumab
TC: Paclitaxel + Carboplatin;
TCH: Paclitaxel + Carboplatin + Trastuzumab
Others: Capecitabine, Gemcitabine, or Vinorelbine

Figure 2.23: Type of chemotherapy regimens in adjuvant setting in patients by cancer stage (N=7,314)



C: Cyclophosphamide;
M: Methotrexate;
F: Fluorouracil (5FU);
A: Adriamycin / Doxorubicin;
E: Epirubicin;
T: Paclitaxel / Docetaxel;
H: Trastuzumab;
DC: Docetaxel + Cyclophosphamide;
DCH: Docetaxel + Cyclophosphamide + Trastuzumab
TC: Paclitaxel + Carboplatin;
TCH: Paclitaxel + Carboplatin + Trastuzumab
Others: Capecitabine, Gemcitabine, or Vinorelbine

Figure 2.24: Type of chemotherapy regimens in palliative setting in patients by biological subtype (N=289)



C: Cyclophosphamide;
M: Methotrexate;
F: Fluorouracil (5FU);
A: Adriamycin / Doxorubicin;
E: Epirubicin;
T: Paclitaxel / Docetaxel;
H: Trastuzumab;
DC: Docetaxel + Cyclophosphamide;
DCH: Docetaxel + Cyclophosphamide + Trastuzumab
TC: Paclitaxel + Carboplatin;
TCH: Paclitaxel + Carboplatin + Trastuzumab
Others: 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. All breast cancers develop from abnormal breast cells that are often sensitive to sex hormones, such as estrogen and progesterone. Endocrine therapy acts on hormone receptors of the cancer cells.

2.58 In the cohort, 11,211 (67.6%) patients were treated with endocrine therapy. Among them, 96.6% were adjuvant, 0.5% were neoadjuvant, and 2.9% were palliative. In addition, 90.8% of the patients received endocrine therapy at public medical facilities, while 9.2% at private medical facilities.

2.59 Endocrine therapy was used in only 11.6% of the in situ breast cancer cases. For the patients with invasive cancers, a high proportion, in particular stage IV patients (79.5%), received endocrine therapy (Figure 2.25).

2.60 Two types of drugs are commonly used: anti-estrogens and aromatase inhibitors. Anti-estrogen drugs slow down breast cancer growth by sticking to estrogen receptors on the 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 2.26 shows the use of Tamoxifen and Aromatase inhibitors by age group.

Figure 2.25: Endocrine therapy rates by cancer stage (N=15,829)

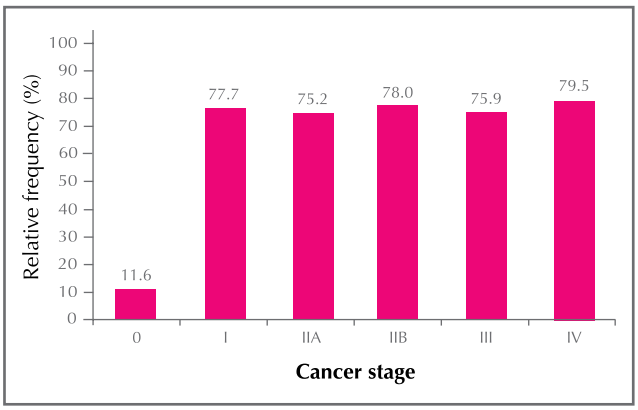
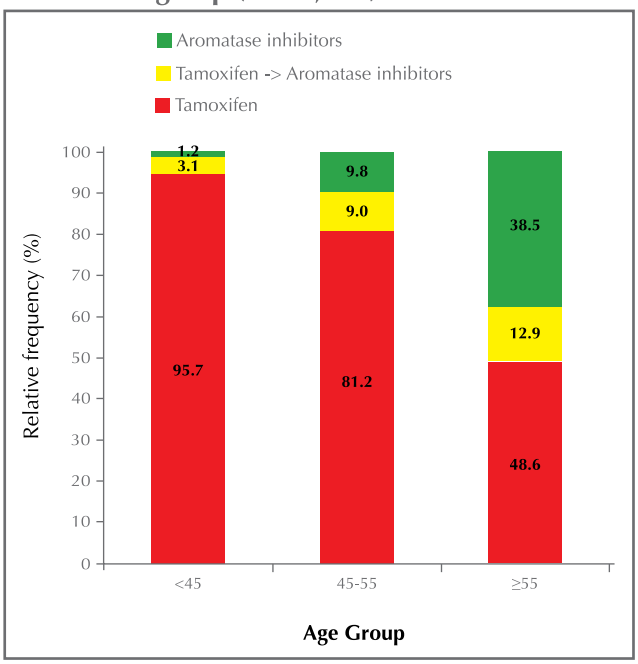


Figure 2.26: Forms of endocrine therapy by age group (N=10,095)

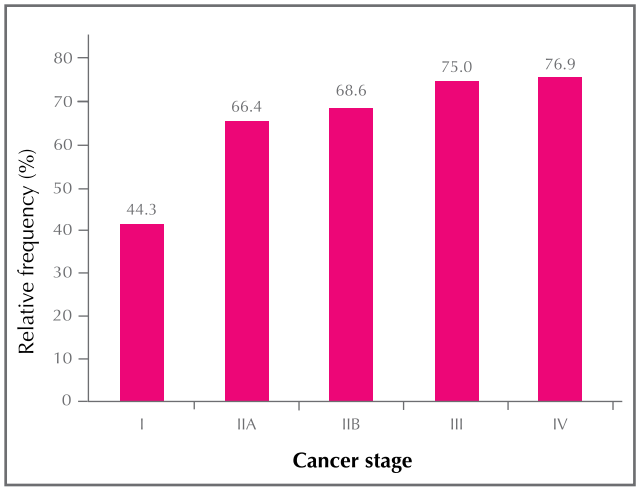


E. Anti-HER2 Targeted therapy

2.61 Targeted therapy uses a drug that specifically attacks 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 3,072 patients with invasive HER2-positive breast cancers in the cohort, 1,878 (61.1%) patients underwent anti-HER2 targeted therapy. Among them, 91.7% were adjuvant, 3.9% were neoadjuvant, and 4.4% were palliative. In addition, the majority (89.9%) of the patients received anti-HER2 targeted therapy at public medical facilities, and the remainder (10.1%) at private medical facilities. The use of anti-HER2 targeted therapy was positively correlated with increasing cancer stage (Figure 2.27).

Figure 2.27: Anti-HER2 targeted therapy rate in HER2 positive patients by cancer stage (N=2,944)



F. Multimodality treatment

2.63 Combinations of treatments, including surgery, radiotherapy, chemotherapy, endocrine therapy, and anti-HER2 targeted therapy, are usually used for treating breast cancer effectively. Table 2.21 shows the multimodality treatment pattern of the patients. In general, the number of modalities increased with increasing cancer stage. In the cohort, the majority (94.0%) of the patients with stage 0 disease received two or less modalities. More than three-quarters of the patients with stage IIA (79.9%), IIB (92.9%) or III (97.2%) disease received three or more modalities.

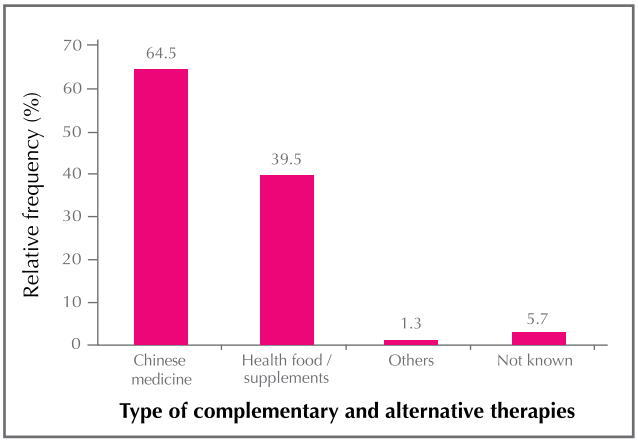
Table 2.21: Number of treatment modalities received by patients by cancer stage (N=15,654)

No. of modalities	Cancer Stage, Number (%)											
	0 (N=1,971)		I (N=5,032)		IIA (N=3,982)		IIB (N=2,013)		III (N=2,267)		IV (N=389)		Total (N=15,654)	
0	8	(0.4)	1	(<0.1)	0	(0.0)	1	(<0.1)	0	(0.0)	2	(0.5)	12	(0.1)
1	848	(43.0)	320	(6.4)	82	(2.1)	17	(0.8)	12	(0.5)	27	(6.9)	1,306	(8.3)
2	998	(50.6)	1,639	(32.6)	717	(18.0)	123	(6.1)	53	(2.3)	57	(14.7)	3,587	(22.9)
3	115	(5.8)	2,105	(41.8)	1,465	(36.8)	558	(27.7)	424	(18.7)	130	(33.4)	4,797	(30.6)
4	1	(0.1)	822	(16.3)	1,517	(38.1)	1,120	(55.6)	1,468	(64.8)	141	(36.2)	5,069	(32.4)
5	1	(0.1)	145	(2.9)	201	(5.0)	194	(9.6)	310	(13.7)	32	(8.2)	883	(5.6)

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 etc. A total of 6,378 (38.4%) patients in the cohort sought complementary and alternative therapies as part of their treatment. Among them, 95.6% were adjuvant, 3.2% were neoadjuvant, and 1.2% were palliative. About two-thirds (64.5%) of the patients used traditional Chinese medicines (Figure 2.28).

Figure 2.28: Type of complementary and alternative therapies used in 6,378 patients



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

VI. Patient Status

2.65 Once treatment is completed, the Hong Kong Breast Cancer Registry will follow up with the registered patients annually to ascertain the efficacy of the treatment. To date, there are 14,699 patients in the cohort with at least one year of follow-up. About three-fifths (58.9%) of them had the last follow-up within the past two years, and about one-third (37.4%) have been followed up for five or more years (Table 2.22). The mean and median follow-up period were 4.2 and 3.7 years, respectively (Table 2.22).

2.66 A total of 695 cases (4.7%) in the cohort experienced recurrence, of which 1.4% experienced only locoregional recurrence (LR), 2.1% experienced only distant recurrence (DR), and 1.3% experienced both locoregional and distant recurrence concurrently or sequentially. The mean and median time to recurrence are shown in Table 2.22.

Table 2.22: Follow-up of 14,699 patients

Follow-up period	Number	(%)
< 1 year	1,474	(10.0)
1-2 years	2,568	(17.5)
2-5 years	5,154	(35.1)
5-10 years	5,107	(34.7)
10+ years	396	(2.7)
Mean follow-up period		4.2 years
Median follow-up period		3.7 years
Locoregional recurrence		
No. of locoregional recurrences	201	(1.4)
Mean time to locoregional recurrence		3.0 years
Median time to locoregional recurrence		2.7 years
Distant recurrence		
No. of distant recurrences	307	(2.1)
Mean time to distant recurrence		3.1 years
Median time to distant recurrence		2.7 years
Locoregional and distant recurrence		
No. of locoregional and distant recurrences	187	(1.3)
Mean time to locoregional and distant recurrence		3.2 years
Median time to locoregional and distant recurrence		2.7 years
Mortality*		
No. of deaths from breast cancer	181	(1.2)
No. of deaths from unrelated causes	94	(0.6)
No. of deaths with causes not known	48	(0.3)

* Data as in Feb 2018 with traceable medical records only.

2.67 Table 2.23 shows the number of invasive breast cancer patients with LR in different subgroups specified by surgery type and cancer stage in the patient cohort. Patients with stage I and II disease who received breast-conserving surgery without radiotherapy had higher LR rates than those who received breast-conserving surgery with radiotherapy. Overall, patients who received mastectomy had slightly higher LR rates than those who received breast-conserving surgery without radiotherapy (Table 2.23). The common sites for LR were chest wall (35.2%) and breast (31.6%) (Table 2.24).

Table 2.23: Locoregional recurrence by type of surgery and cancer stage

	Cancer stage, Number (% in the overall patient cohort with surgeries)				
	I	IIA	IIB	III	Total
BCS with RT	26/2,086 (1.2)	39/1,236 (3.2)	6/463 (1.3)	10/332 (3.0)	81/4,117 (2.0)
BCS without RT	5/288 (1.7)	5/114 (4.4)	1/25 (4.0)	0/9 (0.0)	11/436 (2.5)
MTX	40/2,176 (1.8)	54/2,266 (2.4)	36/1,365 (2.6)	91/1,739 (5.2)	221/7,546 (2.9)

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

Table 2.24: Sites involved in locoregional recurrence (N=388)

Sites involved	Number	(%)
Chest wall	136	(35.1)
Breast	123	(31.7)
Axilla	135	(34.8)
Supraclavicular fossa	80	(20.6)
Internal mammary node	31	(8.0)
Infraclavicular fossa	4	(1.0)
Others	21	(5.4)

Note: Recurrence may involve multiple sites simultaneously, so the total percentages for recurrence sites may exceed 100.

2.68 In the cohort, 494 (3.4%) patients experienced distant recurrence. Among them, the common organs involved were bone (56.7%), followed by lung (49.0%) and liver (40.1%) (Table 2.25).

Table 2.25: Organs involved in distant recurrence (N=494)

Distant organs affected	Number	(%)	Distant organs affected	Number	(%)
Bone	280	(56.7)	Peritoneal	10	(2.0)
Lung	242	(49.0)	Thorax	10	(2.0)
Liver	198	(40.1)	Spleen	5	(1.0)
Brain	88	(17.8)	Ovary	4	(0.8)
Mediastinal nodes	80	(16.2)	Thyroid glands	3	(0.6)
Distant lymph nodes	41	(8.3)	Pancreas	2	(0.4)
Neck	39	(7.9)	Kidney	2	(0.4)
Abdomen	14	(2.8)	Uterus	1	(0.2)
Adrenal	12	(2.4)	Unspecified	21	(4.3)
Contralateral axillary nodes	12	(2.4)			

Note: Recurrence may involve multiple sites simultaneously, so the total percentages for recurrence sites may exceed 100.

2.69 Among patients with invasive breast cancer in the cohort, the proportion with only LR did not show any associations with cancer stage at diagnosis. However, the proportion of the patients with only DR increased from 0.9% of stage I patients to 6.5% of stage III patients. Stage III patients had higher rates of DR only (6.5%) and combination of LR and DR (3.5%) than those with lower cancer stages (Table 2.26).

Table 2.26: Locoregional and distant recurrence among invasive breast cancer patients by cancer stage

	Cancer stage, Number (%)				
Recurrence	I (N=4,567)	IIA (N=3,645)	IIB (N=1,865)	III (N=2,104)	Total (N=12,181)
LR only	52 (1.1)	54 (1.5)	14 (0.8)	28 (1.3)	148 (1.2)
DR only	43 (0.9)	57 (1.6)	52 (2.8)	137 (6.5)	289 (2.4)
LR and DR	18 (0.4)	44 (1.2)	29 (1.6)	73 (3.5)	164 (1.3)

2.70 In the cohort, 181 (1.2%) patients died from breast cancer. About three-fifths (58.5%) of them were stage III or IV at initial diagnosis. Survival time ranged from 0.6 to 12.1 years. Information on biological subtypes of these patients is shown in Table 2.27.

Table 2.27: Characteristics of breast cancer-specific deaths (N=181)

	Cancer stage at initial diagnosis						
	0	I	IIA	IIB	III	IV	Unstaged
No. of cases (% of breast cancer death cases)	**3 (1.7)**	**17 (9.4)**	**27 (14.9)**	**15 (8.3)**	**75 (41.4)**	**31 (17.1)**	**13 (7.2)**
Survival time (range in years)	**4.4 – 7.3**	**1.6 – 9.6**	**1.9 – 10.8**	**2.1 – 12.1**	**0.8 – 9.4**	**0.8 – 7.8**	**0.6 – 9.8**
Time from first diagnosis of DM to death (years), mean (range)	**1.2 (0.9-1.5)**	**2.1 (0.7-4.6)**	**1.3 (0.1-5.9)**	**1.4 (0.2-6.2)**	**1.0 (0.1-4.7)**	**3.0 (0.1-7.6)**	**0.6 (0.2-1.2)**
Biological subtypes							
Luminal A*	0	3	2	3	7	0	0
Luminal B (HER2 negative)#	0	4	4	2	8	2	2
Luminal A/B (HER2 negative)†	0	2	8	4	16	11	2
Luminal B (HER2 positive)^	1	2	3	1	14	9	3
HER2 Positive ❊	0	2	3	0	12	4	0
TND§	0	4	5	4	13	3	2
Not known	2	0	2	1	5	2	4

* 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 Ki67 index not known

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

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

§ TND (Triple Negative Disease): ER and PR-, HER2-, and any Ki-67 index