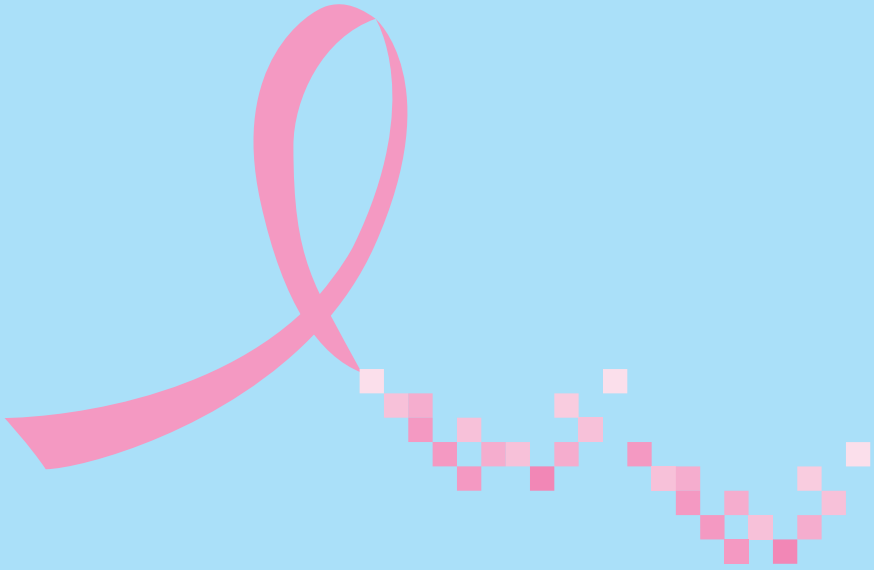

CHAPTER 2

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 20,214 breast cancer cases 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.

HIGHLIGHTS

This chapter presents the disease pattern and treatment trend of 20,214 breast cancer cases which were diagnosed between 2006 and 2018. The clinical outcome of 18,407 patients who completed at least one follow-up were also examined.

Clinical presentation

- The primary method of first cancer detection was self-detection by chance.
- While only 8.4% of self-detected cases were in situ breast cancer, 41.6% of mammography-detected cases were in situ breast cancer.
- The proportion of stages 0-I cancer was also higher among mammography-detected cases compared to self-detected cases.
- After onset of symptoms (mainly painless lumps), the majority of patients who self-detected their cancer by chance sought their first medical consultation in three months.
- A much higher proportion (12.3%) 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 (1.9%).
- The most common cancer stage at diagnosis was stage II (35.9%) followed by stage I (31.0%) and stages III-IV (16.3%). In addition, 12.8% of the patients were diagnosed with stage 0 cancer.

Cancer characteristics

- The mean size of invasive tumours was 2.2 cm, and 57.9% did not have nodal involvement. Invasive carcinoma of no specific type was the most common type. Almost all invasive cases were tested for estrogen receptor (ER) or progesterone receptor (PR) status, and more than three-quarters of them were either ER or PR positive. Also, slightly less than one-quarter of the invasive breast cancer cases were c-erbB2/HER2 positive.
- The mean size of in situ tumours was 2.0 cm. Ductal cancer was the most common type. More than two-thirds of in situ cases were tested for ER or PR status, and the majority were either ER or PR positive. In addition, 25.1% of in situ cases were HER2 positive.

Treatment

- Of the patients, 15.1% received care at private medical services, 51.1% received care at public medical services, and 33.9% received care at both private and public medical services.
- The number of treatment modalities increased with increasing cancer stage.

- Surgery
  - For patients with invasive breast cancer, nearly all (98.2%) underwent surgery as part of their treatment. About two-thirds had mastectomy, while one-third had breast-conserving surgery. Nearly all (96.7%) of the patients with invasive breast cancer received nodal surgery and among them, 37.5% required axillary dissection (AD) alone, and 16.4% required AD after sentinel node biopsy (SNB).
  - For patients with in situ breast cancer, almost all (99.2%) underwent surgery. About half had breast-conserving surgery, while 47.2% had mastectomy. In addition, 65.9% received nodal surgery and among them, 86.8% had SNB only.
  - 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.
  - SNB alone was more commonly performed on patients with negative clinical nodal status (59.0%) than those with positive clinical nodal status (16.6%), while AD alone was more commonly performed on the patients with positive clinical nodal status (68.2%) than those with negative clinical nodal status (25.8%).
- Radiotherapy
  - The majority of the patients who underwent breast-conserving surgery received radiotherapy afterwards, regardless of their cancer stage.
  - The proportion of patients who underwent mastectomy and also received radiotherapy increased significantly with progressing cancer stage, from 4.1% of stage 0 patients to 95.2% of stage III patients.
- Chemotherapy
  - Two-thirds of the patients with invasive cancer underwent chemotherapy.
  - The use of neoadjuvant chemotherapy was positively correlated with progressing cancer stage from stage I to III, while the overall use of curative intent chemotherapy also increased.
- Endocrine therapy
  - In the cohort, 67.5% of the patients were treated with endocrine therapy.
  - For patients with invasive breast cancer, about 75% or more received endocrine therapy, while for patients with in situ breast cancer, only 15.7% received endocrine therapy.
- Targeted therapy
  - Of the patients with invasive HER2-positive breast cancer, 67.2% underwent anti-HER2 targeted therapy.
  - The use of anti-HER2 targeted therapy was much lower for stage I patients, and the proportions increased with increasing cancer stage among stage II or above patients.

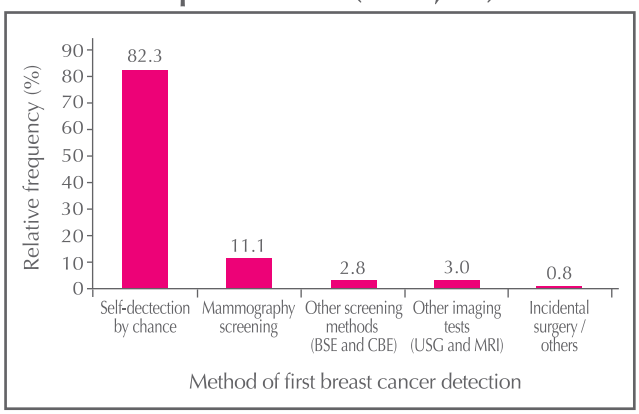
Patient status

- A total of 18,407 patients completed at least one follow-up, providing data to examine their survival aspects. The mean and median follow-up period were 6.4 and 5.7 years respectively.
- In the cohort, 2.4% experienced only locoregional recurrence, 3.2% experienced only distant recurrence, and 2.2% experienced both locoregional and distant recurrence.
- The most common sites for locoregional recurrence were breast (37.9%) and axilla (33.5%), while the top four organs involved in distant recurrence were bone (60.4%), lung (46.8%), liver (39.9%) and brain (15.8%).
- In the cohort, 1,534 patients died from breast cancer.

II. Clinical presentation

2.2 The primary method of first breast cancer detection in the patient cohort was self-detection by chance (82.3%) (Figure 2.1). Detection through healthcare service-assisted screening methods, including clinical breast examination (CBE), mammography screening (MMG), and breast ultrasound screening (USG) constituted a small proportion. Compared to Western countries, the uptake of MMG, in particular, was low. A study in the United States, for instance, found that 43% of the breast cancer cases were detected through MMG.[43]

Figure 2.1: Methods of first breast cancer detection in the patient cohort (N=19,150)



BSE: breast self-examination; CBE: clinical breast examination; USG: breast ultrasound screening; MRI: magnetic resonance imaging

2.3 In terms of the types of medical service received, the proportion of patients who self-detected their breast cancer by chance was higher among public medical service users (84.1%) or mixed public/private medical service users (83.6%) than among private medical service users (71.1%). In contrast, the proportion of the patients who first detected their breast cancer through MMG was higher among private medical service users (16.3%) than among public medical service users (11.1%) or mixed public/private medical service users (9.2%) (Table 2.1).

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.[44] In the patient cohort, only 8.4% of self-detected cases were in situ breast cancer, whereas 41.6% of MMG-detected cases were in situ breast cancer (Table 2.2). Such higher rate of in situ tumour detection rate was also reflected in Table 2.3, which shows that MMG detected a much higher proportion (83.8%) of early stage cancer cases (stages 0-I) than advanced stage cancer cases.

Table 2.1: Methods of first breast cancer detection by type of medical service users (N=19,150)

	Type of medical service users, %		
	Public (N=9,759)	Private (N=2,356)	Mixed private / public (N=7,035)
Self-detection by chance	84.1	71.1	83.6
Mammography screening	11.1	16.3	9.2
Other screening methods (BSE and CBE)	2.5	3.1	3.1
Other imaging tests (USG and MRI)	1.5	8.2	3.5
Incidental surgery / others	0.8	1.4	0.7

BSE: breast self-examination; CBE: clinical breast examination; USG: breast ultrasound screening; MRI: magnetic resonance imaging

Table 2.2: Methods of first breast cancer detection by type of cancer (N=18,996)

	Type of cancer, %	
	Invasive	In situ
Self-detection by chance (N=15,636)	91.6	8.4
Mammography screening (N=2,104)	58.4	41.6
Other screening methods (BSE and CBE) (N=522)	84.7	15.3
Other imaging tests (USG and MRI) (N=578)	70.8	29.2
Incidental surgery / others (N=156)	76.9	23.1

BSE: breast self-examination; CBE: clinical breast examination; USG: breast ultrasound screening; MRI: magnetic resonance imaging

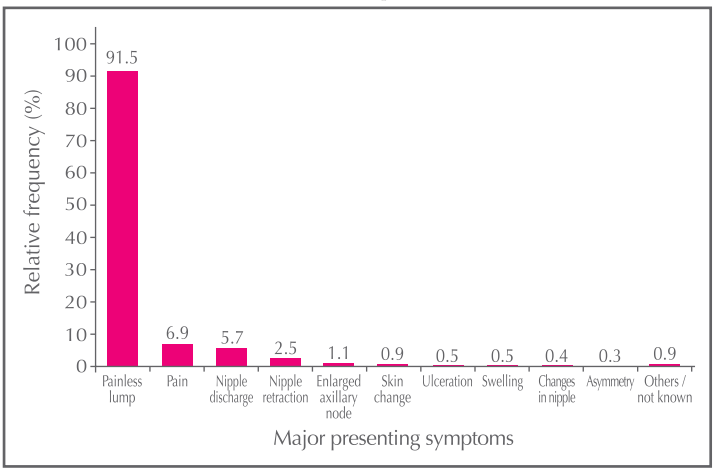
Table 2.3: Methods of first breast cancer detection by cancer stage (N=18,405)

	Cancer stage, %					
	0	I	IIA	IIB	III	IV
Self-detection by chance (N=15,102)	8.6	29.9	27.1	14.7	16.6	3.1
Mammography screening (N=2,076)	41.6	42.2	10.7	2.4	2.5	0.6
Other screening methods (BSE and CBE) (N=510)	15.7	39.2	23.3	10.2	9.8	1.8
Other imaging tests (USG and MRI) (N=567)	29.3	48.1	14.6	3.4	3.7	0.9
Incidental surgery / others (N=150)	24.0	36.0	20.7	6.0	9.3	4.0

BSE: breast self-examination; CBE: clinical breast examination; USG: breast ultrasound screening; MRI: magnetic resonance imaging

2.5 Most (91.5%) 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. Some patients (8.6%) 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=15,759)



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.[45] After the onset of symptoms, slightly more than one-third of the patients who self-detected their cancers by chance sought first medical consultation in less than one month, while about one quarter waited more than three months before seeking first medical consultation (Figure 2.3).

2.7 Within self-detected patients, the proportion of the patients who sought first medical consultation in less than one month was higher among private medical service users (43.1%) than among public medical service users (26.0%) (Table 2.4).

Figure 2.3: Time interval between onset of symptoms and first medical consultation for patients who self-detected their cancer (N=4,403)

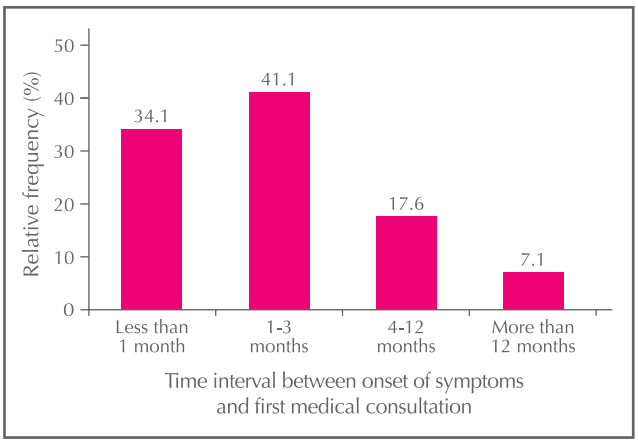


Table 2.4: Time interval between onset of symptoms and first medical consultation for patients who self-detected their cancer by type of medical service users (N=4,403)

	Type of medical service users, %		
	Public (N=2,148)	Private (N=693)	Mixed private / public (N=1,562)
Less than 1 month	26.0	43.1	41.4
1-3 months	43.0	37.1	40.4
4-12 months	22.2	14.6	12.7
More than 12 months	8.9	5.2	5.5

2.8 A much higher proportion (12.3%) 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 (1.9%) (Table 2.5).

Table 2.5: Cancer stage at diagnosis among self-detected patients by time interval between onset of symptoms and first medical consultation (N=3,883)

	Time interval between onset of symptoms and first medical consultation, %			
	Less than 1 month (N=1,340)	1-3 months (N=1,609)	4-12 months (N=674)	More than 12 months (N=260)
Stage I	36.4	30.4	26.0	23.8
Stage IIA	32.0	32.3	30.6	24.6
Stage IIB	15.6	16.5	15.7	18.1
Stage III	14.1	17.3	21.7	21.2
Stage IV	1.9	3.5	6.1	12.3

III. Cancer characteristics

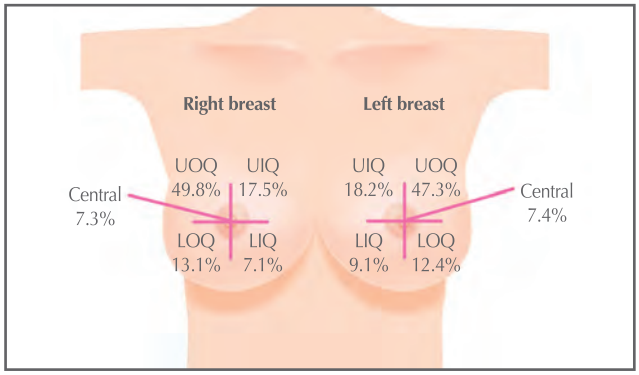
2.9 Breast cancer can occur in one (unilateral) or both (bilateral) breasts. The majority (90.7%) of the patients had unilateral breast cancer, while a small proportion (5.1%) had synchronous bilateral breast cancer at first diagnosis (Table 2.6).

Table 2.6: Laterality of breast cancer cases in the patient cohort (N=20,214)

	Number of patients	Number of cases	Time interval for metachronous cases, median (range) (years)
Unilateral	**18,330**	**18,330**	**—**
Bilateral (synchronous)	**519**	**1,038**	**—**
All bilateral (metachronous) cases	**545**	**846**	**6.9 (0.6 – 36.1)**
Bilateral (metachronous) - Initial diagnosis during 2006-2018	*301*	*602*	*4.8 (0.6 – 12.8)*
Bilateral (metachronous) - Initial diagnosis before 2006	*244*	*244*	*11.0 (1.1 – 36.1)*

2.10 As regards the locations of malignant breast tumour, about half of the breast cancer cases in either the left or the right breast (47.3% and 49.8% respectively) were detected in the upper outer quadrant (Figure 2.4).

Figure 2.4: Locations of malignant tumour on breasts within the patient cohort (N=20,214)



UOQ: upper outer quadrant UIQ: upper inner quadrant
LOQ: lower outer quadrant LIQ: lower inner quadrant
Note: Figures included 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.

2.12 For cancer diagnosis, MMG was used on 85.5% of the patients, and USG on 80.7%, while MRI was used on only 9.8% of the patients (Table 2.7). Results of imaging tests are classified into categories using 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 2.7: Sensitivity and diagnostic results of breast imaging tests (N=20,214)

	Mammography	Breast ultrasound	MRI
Proportion of patients using the test	**85.5%**	**80.7%**	**9.8%**
Overall sensitivity*	**84.7%**	**92.0%**	**97.2%**
BIRADS category, Number (%)			
Diagnostic / malignant (BIRADS 5)	5,579 (32.3)	6,005 (36.8)	1,592 (80.1)
Suspicious abnormality (BIRADS 4)	9,059 (52.4)	8,991 (55.1)	340 (17.1)
Probably benign (BIRADS 3)	857 (5.0)	803 (4.9)	27 (1.4)
Benign (BIRADS 2)	667 (3.9)	243 (1.5)	13 (0.7)
Normal (BIRADS 1)	1,011 (5.8)	254 (1.6)	15 (0.8)
Incomplete (BIRADS 0)	111 (0.6)	10 (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 65.9% of the patients with BIRADS 4 or 5 mammograms, while microcalcification was observed in 48.5% (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, 69.4% had heterogeneously dense breasts, while 6.8% 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 16.0% among patients aged between 20 and 29 to 1.6% among patients aged 70 and above (Table 2.9).

Table 2.8: Mammographic findings of patients diagnosed through mammography (N=14,638)

	Number	%
Opacity	9,640	65.9
Microcalcification	7,106	48.5
Architectural distortion	2,080	14.2
Asymmetric density	1,105	7.5
Unclassified	857	5.9

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

Figure 2.5: Mammographic density of breasts of patients diagnosed through mammography (N=10,091)

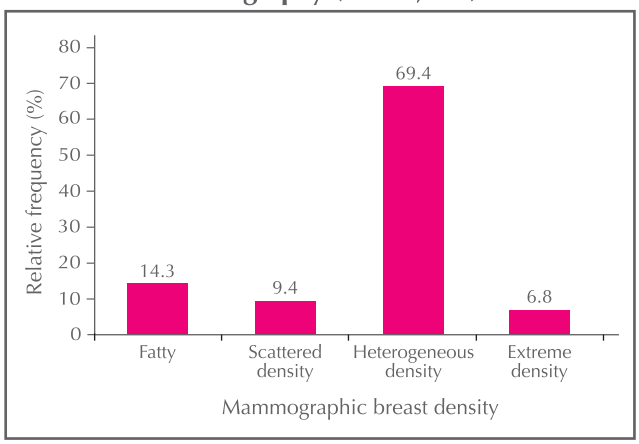


Table 2.9: Mammographic density of breasts of patients diagnosed through mammography by age group (N=9,917)

	Age group, %					
	20-29 (N=50)	30-39 (N=759)	40-49 (N=2,994)	50-59 (N=3,415)	60-69 (N=1,967)	≥70 (N=732)
Fatty	6.0	5.1	8.2	13.9	20.7	34.0
Scattered density	4.0	4.6	6.3	9.8	13.1	16.5
Heterogeneous density	74.0	77.2	75.7	70.6	62.6	47.8
Extreme density	16.0	13.0	9.8	5.8	3.6	1.6

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 86.2% of the patients in the cohort and among them, 22.6% received only FNA, 54.8% received only CNB, while 22.5% received both FNA and CNB. In addition, 9.8% of the patients had excisional biopsy. Excisional biopsy had the highest overall sensitivity of 100%, followed by CNB (99.0%) and FNA (90.6%) (Table 2.10).

Table 2.10: Sensitivity and diagnostic results of breast tissue biopsies (N=20,214)

	FNA		CNB		Excisional biopsy	
Proportion of patients using the test	**39.0%**		**66.7%**		**9.8%**	
Overall sensitivity*	**90.6%**		**99.0%**		**100.0%**	
Class, Number (%)						
Diagnostic / malignant (Class V)	5,047	(64.1)	12,923	(95.8)	1,973	(100.0)
Suspicious (Class IV)	1,198	(15.2)	224	(1.7)	—	
Atypical (Class III)	890	(11.3)	208	(1.5)	—	
Benign (Class II)	293	(3.7)	86	(0.6)	—	
Scanty benign (Class I)	326	(4.1)	39	(0.3)	—	
Incomplete (Class 0)	121	(1.5)	5	(<0.1)	—	

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 preoperatively 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 54.3%. Among those patients who had cancer staging as part of their treatment, positron emission tomography scan (PET scan) was the most common method used (Table 2.11).

2.17 According to the National Comprehensive Cancer Network (NCCN) guidelines, 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.[46] 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. However, among those patients who had cancer staging, 23.2% of stage I and 43.9% of stage IIA patients had PET scan to determine the extent of their disease (Figure 2.6).

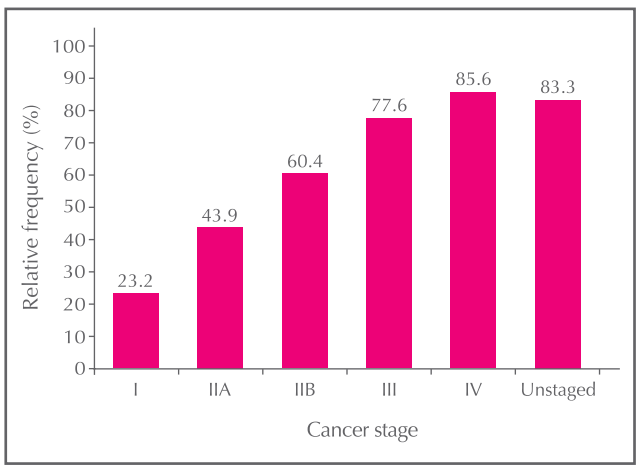
Table 2.11: Method of cancer staging among invasive breast cancer patients (N=7,963)

	Number	%
Positron emission tomography scan (PET scan)	4,179	52.5
Chest x-ray and abdominal ultrasound	2,987	37.5
Computed tomography (CT) of body parts*	558	7.0
Bone scan	240	3.0
Magnetic resonance imaging (MRI) of whole body	64	0.8
Others (e.g. bone x-ray)	477	6.0
Not known	396	5.0

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

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

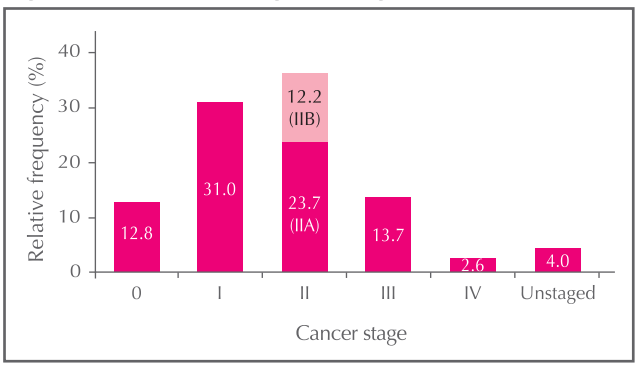
Figure 2.6: Use of PET scan among patients who had cancer staging by cancer stage (N=7,963)



2.18 The American Joint Committee on Cancer (AJCC) Anatomic Breast Cancer Staging (8th edition)[47] is used for determining cancer staging in the patient cohort. There are two stage groups according to this system: anatomic 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.

2.19 Although prognostic stage group was recommended for patient care and was used for reporting of all cancer patients in the United States starting from 2018, it was not adopted in this report. The reason was that patients in the cohort were mostly diagnosed between 2006 and 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 (35.9%) followed by stage I (31.0%) and stages III-IV (16.3%). In addition, 12.8% of the patients were diagnosed with in situ cancer (stage 0) (Figure 2.7).

Figure 2.7: Cancer stage at diagnosis (N=20,214)

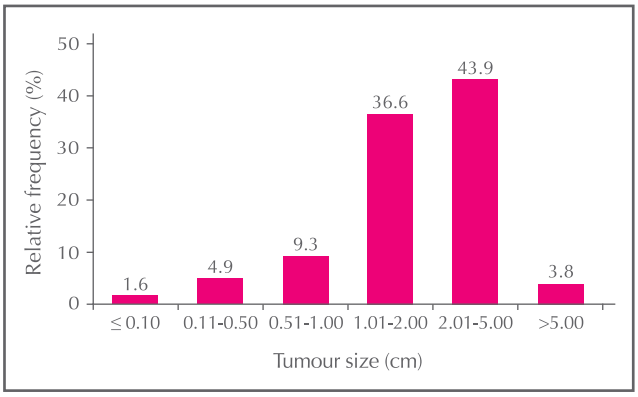


2.20 Of the 20,214 breast cancer cases analysed, data from 19,682 cases with available pathology data were used for subsequent analyses on cancer characteristics. A total of 17,079 patients were diagnosed with invasive cancer, while 2,589 patients were diagnosed with in situ cancer. In addition, 14 cases were diagnosed with occult primary breast cancer.

C. *Characteristics of invasive breast cancer*

2.21 The mean size of tumours of invasive breast cancer was 2.2 cm (range: 0.01 to 25.0 cm; standard deviation: ±1.4 cm). Tumours of one cm or less in size were found in 15.8% of the patients, while tumours of sizes 1.01 to 2.00 cm and 2.01 to 5.00 cm were respectively found in about 36.6% and 43.9% of the patients (Figure 2.8). Only a small proportion (3.8%) of patients had tumours of sizes exceeding five cm. In addition, screen-detected tumours were significantly smaller than those self-detected by chance (mean: 1.3±0.9 cm vs. 2.3±1.4 cm; p<0.001).

Figure 2.8: Distribution of tumour size (cm) of invasive breast cancer (N=14,579)



2.22 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, 57.9% had no positive axillary lymph nodes, 4.3% had isolated tumour cells (metastasis size ≤ 0.2 mm or a cluster of fewer than 200 tumour cells), 6.0% had micrometastasis (metastasis size > 0.2 mm and ≤ 2 mm), while 31.8% had at least one positive axillary lymph node with metastasis size larger than two mm (Figure 2.9).

Figure 2.9: Number of positive axillary lymph nodes among patients with invasive breast cancer (N=15,104)

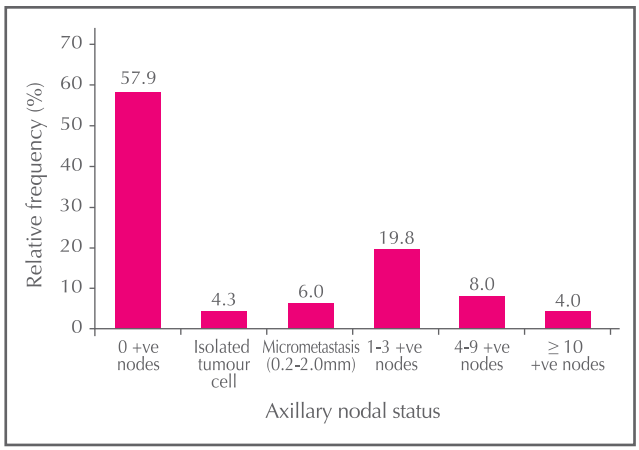
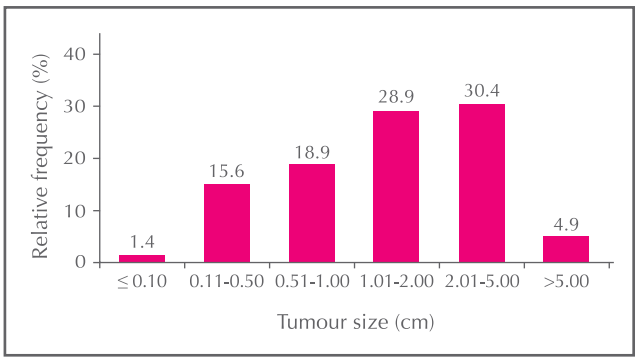


Figure 2.10: Distribution of tumour size (cm) of in situ breast cancer (N=2,113)



D. Characteristics of in situ breast cancer

2.23 The mean size of tumours of in situ breast cancer was 2.0 cm (range: 0.02 to 14.8 cm; standard deviation: ±1.6 cm). Tumours of one cm or less in size were found in 35.9% of the patients while tumours of 2.01 to 5.00 cm in size were found in 30.4% of the patients (Figure 2.10). A small proportion (4.9%) of the patients had in situ tumours larger than five cm. Of the in situ breast cancer cases where MMG was performed, 62.2% showed microcalcification.

IV. Histological and biological characteristics

2.24 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, hormone receptor status and HER2 oncogene status to help predict the likelihood of recurrence and response to treatment.

A. Invasive breast cancer

2.25 As far as histological characteristics, grading, multifocality and multicentricity of invasive breast cancer in the patient cohort are concerned, the majority (87.5%) were invasive carcinomas of no specific type (Table 2.12), and about one-third of the invasive tumours were of grade 3 (Table 2.13).

Table 2.12: Histological type of invasive breast cancer (N=17,079)

	Number	%
Invasive carcinoma of no specific type	14,945	87.5
Lobular	623	3.6
Mucinous (colloid)	561	3.3
Papillary	168	1.0
Tubular	110	0.6
Carcinoma with medullary features	87	0.5
Mixed ductal and lobular	76	0.4
Borderline / malignant phyllodes	73	0.4
Micropapillary	69	0.4
Metaplastic	63	0.4
Carcinoma with neuroendocrine features	30	0.2
Carcinoma with apocrine features	21	0.1
Adenoid cystic	18	0.1
Cribriform	8	<0.1
Tubulo-lobular	6	<0.1
Inflammatory	4	<0.1
Squamous cell	3	<0.1
Paget's disease of nipple	2	<0.1
Lipid rich	2	<0.1
Secretory	2	<0.1
Sarcoma	1	<0.1
Acinic cell	1	<0.1
Others	124	0.7
Not known	82	0.5

Table 2.13: Grading, multifocality and multicentricity of invasive breast cancer (N=17,079)

	Number	%
Grade		
Grade 1	2,802	16.4
Grade 2	6,727	39.4
Grade 3	5,449	31.9
Not known	2,101	12.3
Lymphovascular invasion	**4,348**	**25.5**
Multifocality	**1,571**	**9.2**
Number of foci		
2	859	54.7
3-4	271	17.3
5 or more	142	9.0
Not known	299	19.0
Multicentricity	**425**	**2.5**
Number of quadrants		
2	365	85.9
3	22	5.2
4	12	2.8
Not known	26	6.1

2.26 Of the patients with invasive breast cancer, almost all (97.8%) were tested for ER or PR status. Among them, 79.7% 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,[48] 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. Of the invasive breast cancer cases, 22.2% were c-erbB2/HER2 positive. The biological characteristics of invasive breast cancer are shown in Table 2.14.

Table 2.14: Biological characteristics of invasive breast cancer (N=17,079)

	Number	%
Estrogen receptor (ER) [97.7% had the test]		
Positive	13,065	78.3
Negative	3,628	21.7
Progesterone receptor (PR) [97.5% had the test]		
Positive	10,891	65.4
Negative	5,759	34.6
c-erbB2 / HER2 [96.7% had the test]		
Positive (IHC score 3)	3,275	19.8
Equivocal (IHC score 2) ISH positive	402	2.4
Equivocal (IHC score 2) ISH equivocal	170	1.0
Equivocal (IHC score 2) ISH negative	2,845	17.2
Equivocal (IHC score 2) ISH not done	1,902	11.5
Negative (IHC score 1)	3,603	21.8
Negative (IHC score 0)	3,482	21.1
Negative (IHC score not known)	838	5.1
Ki-67 index [57.3% had the test]		
<14%	3,513	35.9
≥14%	6,270	64.1

HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; ISH: in situ hybridization

2.27 Breast cancer is well known to be a heterogeneous disease and can be further classified into several biological subtypes[49] by immunohistochemical staining of several biological markers (Table 2.14). 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 are shown in Table 2.15.

Table 2.15: Biological subtypes of invasive tumours by cancer stage (N=16,010)

	Cancer stage, %				
	I (N=5,990)	IIA (N=4,625)	IIB (N=2,375)	III (N=2,624)	IV (N=396)
Luminal A	28.0	16.8	14.5	11.2	7.6
Luminal B (HER2 negative)	19.1	22.6	24.2	23.2	23.5
Luminal A/B (HER2 negative)	25.7	24.4	27.1	25.1	25.3
Luminal B (HER2 positive)	10.8	13.0	13.2	17.6	20.7
HER2 positive (HR negative)	7.4	9.0	8.5	11.9	13.9
TNBC	9.0	14.2	12.5	11.0	9.1

HR: hormone receptors (ER and PR)
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 (HR negative): ER and PR-, HER2+, and any Ki-67 index
TNBC (triple negative breast cancer): ER and PR-, HER2-, and any Ki-67 index

2.28 In the past, breast cancer patients with positive hormone receptor often underwent chemotherapy. However, it has been shown that the vast majority of these patients with early-stage breast cancer do not benefit from adjuvant chemotherapy and could be burdened by the short- and long-term side effects caused. There is therefore a change of paradigm in early breast cancer management in recent practice, i.e. considering proven chemotherapy benefit instead of assumed chemotherapy benefit. Oncotype DX Breast Recurrence Score test can classify patients into groups based on the genomic assay that is predictive of chemotherapy benefit.[50] Among the tested patients, 85.7% were found with a low or moderate risk of recurrence of breast cancer.

B. In situ breast cancer

2.29 Ductal cancer was found to be the most common type of in situ breast cancer (93.9%). Table 2.16 shows the histological characteristics, grading, multifocality and multicentricity of in situ breast cancer in the patient cohort.

Table 2.16: Histological type, grading, multifocality and multicentricity of in situ breast cancer (N=2,589)

	Number	%
Histological type		
Ductal	2,432	93.9
Mixed	51	2.0
Papillary	38	1.5
Intracystic papillary	14	0.5
Encapsulated papillary	10	0.4
Apocrine	3	0.1
Neuroendocrine	2	0.1
Cribriform	1	<0.1
Micropapillary	1	<0.1
Others	26	1.0
Not known	11	0.4
Necrosis	**828**	**32.0**
Nuclear grade		
Low	675	26.1
Intermediate	842	32.5
High	922	35.6
Not known	150	5.8
Multifocality	**295**	**11.4**
Number of foci		
2	141	47.8
3	23	7.8
4 or more	12	4.1
Not known	119	40.3
Multicentricity	**53**	**2.0**
Number of quadrants		
2	45	84.9
3	3	5.7
Not known	5	9.4

2.30 Of the patients with in situ breast cancer, more than two-thirds (68.3%) were tested for ER or PR status. Among them, the majority (82.0%) were either ER or PR positive. In addition, 25.1% of in situ breast cancer patients were HER2 positive. Table 2.17 shows the biological characteristics of in situ breast cancer in the patient cohort.

Table 2.17: Biological characteristics of in situ breast cancer (N=2,589)

	Number	%
Estrogen receptor (ER) [68.3% had the test]		
Positive	1,431	81.0
Negative	336	19.0
Progesterone receptor (PR) [66.7% had the test]		
Positive	1,245	72.1
Negative	482	27.9
c-erbB2/HER2 [61.4% had the test]		
Positive (IHC score 3)	398	25.0
Equivocal (IHC score 2) ISH positive	2	0.1
Equivocal (IHC score 2) ISH equivocal	0	0.0
Equivocal (IHC score 2) ISH negative	23	1.4
Equivocal (IHC score 2) ISH not done	533	33.5
Negative (IHC score 1)	327	20.6
Negative (IHC score 0)	267	16.8
Negative (IHC score not known)	40	2.5
Ki-67 index [41.3% had the test]		
<14%	688	64.4
≥14%	381	35.6

HER2: human epidermal growth factor receptor 2;
IHC: immunohistochemistry; ISH: in situ hybridization

V. Treatment methods

2.31 Of the patients, 15.1% received care at private medical services, 51.1% received care at public medical services, and 33.9% received care at both private and public medical services. Combinations of treatments are usually used to treat breast cancer effectively. Patients with invasive cancer are usually given multimodality treatments, which may include surgery, radiotherapy, chemotherapy, endocrine therapy, targeted therapy and immunotherapy. In contrast, patients with in situ cancer require less aggressive treatments including surgery, radiotherapy and endocrine therapy. Chemotherapy, targeted therapy and immunotherapy are generally not required for patients with in situ cancer. The non-surgical treatments may be applied in adjuvant (after surgery), neoadjuvant (before surgery) or palliative (for metastatic disease) settings according to the stage of disease at diagnosis.

2.32 Table 2.18 shows the multimodality treatment pattern of the patients. In general, the number of modalities increased with increasing cancer stage. In the cohort, the majority (90.3%) of patients with stage 0 disease received two or less treatments. On the other hand, 79.4% of the patients with stage IIA, 91.8% of those with stage IIB and 96.3% of those with stage III disease received three or more modalities.

Table 2.18: Number of treatment modalities by cancer stage (N=19,408)

	Cancer stage, %					
	0 (N=2,597)	I (N=6,265)	IIA (N=4,797)	IIB (N=2,463)	III (N=2,764)	IV (N=522)
0	0.3	0.0	0.0	0.1	<0.1	1.0
1	39.4	6.4	2.6	1.4	0.9	7.1
2	50.6	32.0	17.9	6.7	2.7	15.1
3	8.3	42.3	36.6	26.4	17.1	30.5
4	1.3	16.0	37.1	55.3	64.3	34.9
5	0.2	3.2	5.7	10.1	14.9	11.5

A. Surgical treatment

2.33 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.

2.34 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.

2.35 In the cohort, 50.3% of the patients had surgery at private medical facilities, while 49.7% had surgery at public medical facilities.

2.36 For patients with invasive breast cancer, nearly all (98.2%) underwent surgery as part of their treatment. Of the patients with invasive cancer, 64.0% had mastectomy, while 33.9% had breast-conserving surgery. Among the patients who had mastectomy, 12.1% had either immediate or delayed reconstruction. The most common type of reconstruction was TRAM flap (69.5%) (Table 2.19). Nearly all (96.7%) the patients with invasive breast cancer received nodal surgery and among them, 37.5% required AD alone, and 16.4% required AD after SNB.

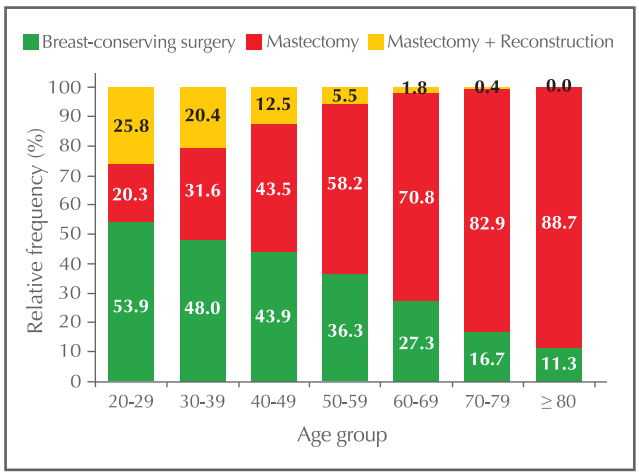
2.37 For patients with in situ breast cancer, almost all (99.2%) underwent surgery (Table 2.19). About half (51.7%) had breast-conserving surgery, while 47.2% had mastectomy. In addition, one-third (34.1%) did not receive nodal surgery, and among those who received nodal surgery, 86.8% had SNB only.

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

	Type of cancer, %	
	Invasive	**In situ**
Type of surgery (N=20,045)	**(N=17,410)**	**(N=2,635)**
No surgery	1.7	0.8
Breast-conserving surgery	33.9	51.7
Mastectomy	64.0	47.2
Nodal surgery only	0.1	<0.1
Type of surgery not known	0.1	0.3
Not known if surgery done	0.1	0.0
Type of mastectomy (N=12,386)	**(N=11,141)**	**(N=1,245)**
Total mastectomy	94.1	86.6
Skin sparing	3.9	9.3
Areolar sparing	0.1	0.3
Nipple sparing	1.7	3.6
Type not known	0.2	0.2
Type of reconstruction (N=1,619)	**(N=1,351)**	**(N=268)**
TRAM flap	69.5	61.9
Implant	16.0	29.1
LD flap	7.8	4.9
LD flap & implant	4.7	3.4
Type not known	1.9	0.7
Type of nodal surgery (N=18,577)	**(N=16,840)**	**(N=1,737)**
Sentinel node biopsy alone	45.3	86.8
Sentinel node biopsy followed by axillary dissection	16.4	2.2
Axillary dissection alone	37.5	10.0
Type not known	0.8	0.9

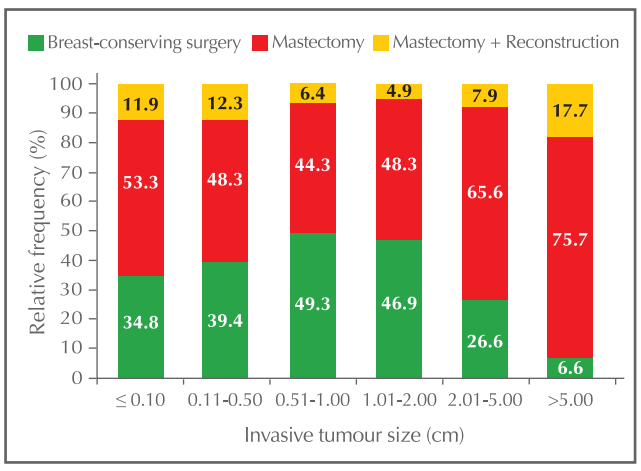
2.38 The proportion of patients who underwent mastectomy was positively correlated with increasing age, while the proportion of patients who underwent mastectomy with reconstruction was negatively correlated with increasing age (Figure 2.11).

Figure 2.11: Type of breast surgery by age group (N=19,426)



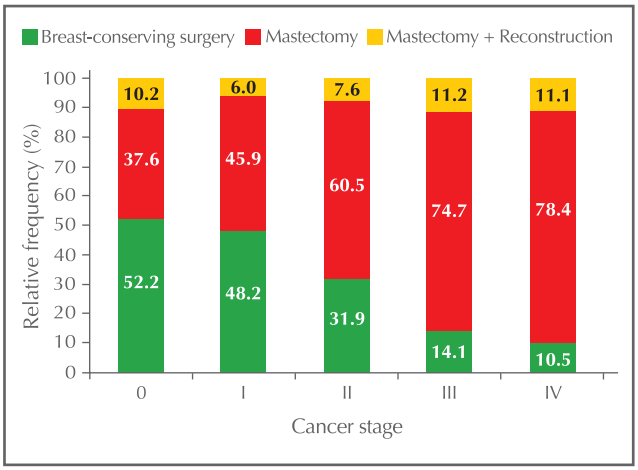
2.39 For the patients with tumours larger than 0.5 cm in size, the proportion of patients who had breast-conserving surgery was negatively correlated with increasing tumour size (Figure 2.12).

Figure 2.12: Type of breast surgery by invasive tumour size (cm) (N=14,552)



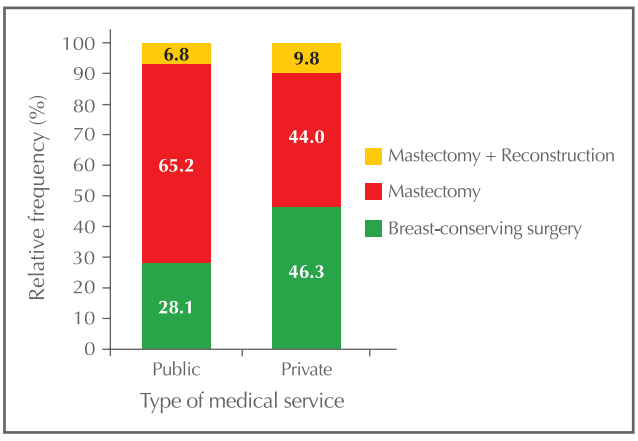
2.40 The proportion of patients who received breast-conserving surgery was negatively correlated with increasing cancer stage. The proportion of those who received mastectomy with reconstruction did not show any correlation with increasing cancer stage (Figure 2.13).

Figure 2.13: Type of breast surgery by cancer stage (N=19,127)



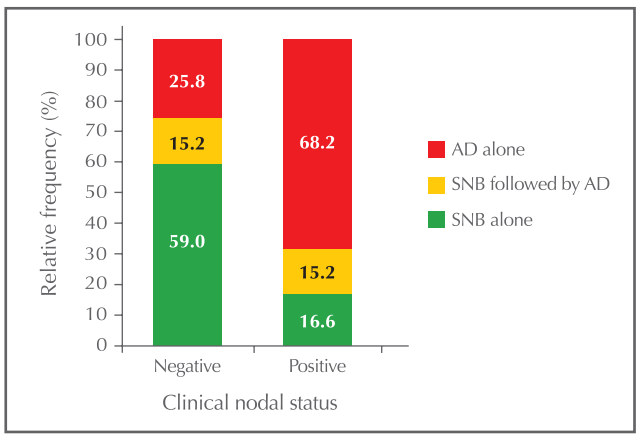
2.41 A higher proportion (46.3%) of patients who had surgery at private medical facilities underwent breast-conserving surgery than those who had surgery at public medical facilities (28.1%) (Figure 2.14).

Figure 2.14: Type of breast surgery by type of medical service (N=19,068)



2.42 SNB alone was more commonly performed on patients with negative clinical nodal status (59.0%) than those with positive clinical nodal status (16.6%). On the other hand, AD alone was more commonly performed on patients with positive clinical nodal status (68.2%) than those with negative clinical nodal status (25.8%). Figure 2.15 shows the type of nodal surgery received by patients with positive or negative clinical nodal status in the patient cohort.

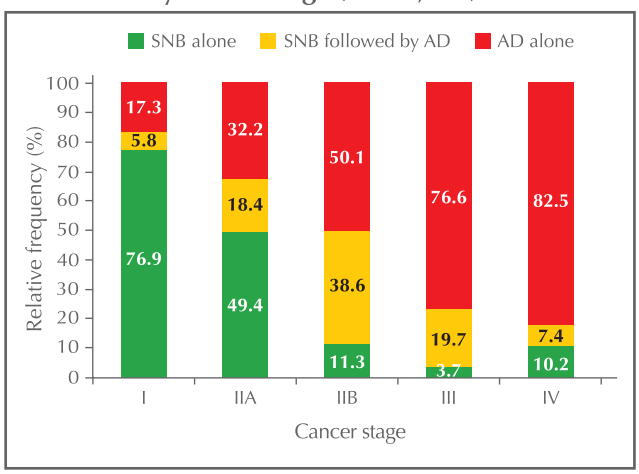
Figure 2.15: Type of nodal surgery by clinical nodal status (N=18,515)



SNB: sentinel node biopsy; AD: axillary dissection

2.43 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 2.16).

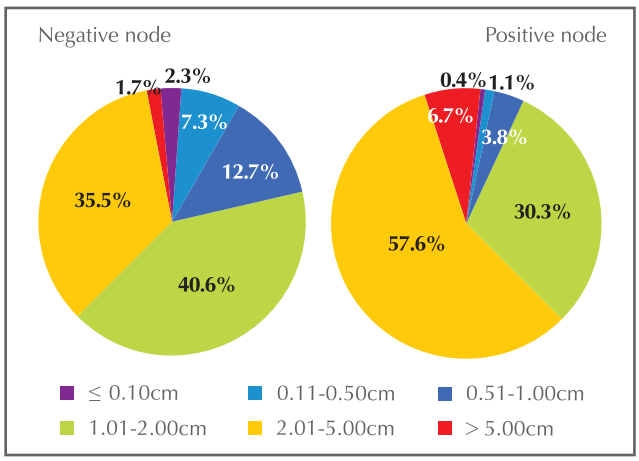
Figure 2.16: Type of nodal surgery for invasive cancer by cancer stage (N=16,285)



SNB: sentinel node biopsy; AD: axillary dissection

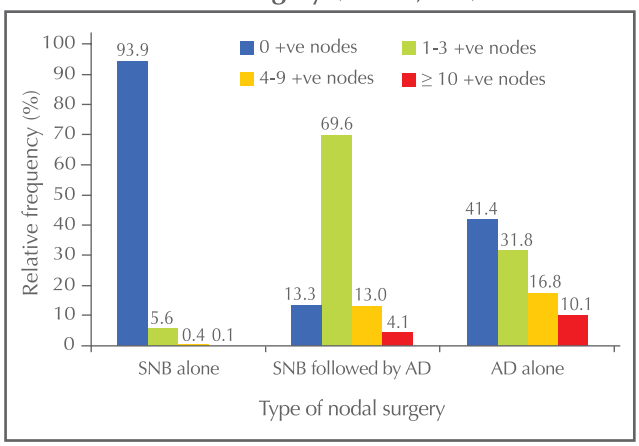
2.44 Of the patients with node positive invasive cancer, 57.6% had tumours of 2.01 to 5.00 cm in size, while a small proportion (6.7%) had tumours larger than five cm. In contrast, more patients with node negative invasive cancer (62.9%) had tumours of two cm or less, compared to patients with node positive invasive cancer (35.6%) (Figure 2.17).

Figure 2.17: Distribution of tumour size (cm) in invasive cancer with negative or positive nodal status (N=14,480)



2.45 Of the patients with invasive cancer, 93.9% who underwent only SNB had no positive lymph node, while 41.4% who underwent only AD and 13.3% who underwent AD after SNB had no positive lymph node (Figure 2.18).

Figure 2.18: Number of positive nodes by type of nodal surgery (N=16,597)



SNB: sentinel node biopsy; AD: axillary dissection

B. Radiotherapy

2.46 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

2.47 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.

2.48 In the patient cohort, 63.5% of the patients had radiotherapy as part of their treatment, with almost all (99.8%) being adjuvant. The majority (87.5%) of the patients were treated with radiotherapy at public medical facilities, while the remainder had radiotherapy at private medical facilities.

2.49 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 2.19 and 2.20 respectively. The majority (over 95%) of the invasive breast cancer patients who underwent breast-conserving surgery also received radiotherapy (Figure 2.19). On the other hand, the proportion of invasive breast cancer patients who underwent mastectomy and also received radiotherapy increased significantly with progressing cancer stage (Figure 2.20).

2.50 Of the patients with in situ cancer who had breast-conserving surgery, 93.5% received radiotherapy afterwards (Figure 2.19), while only 4.1% of the patients with in situ cancer who had mastectomy underwent radiotherapy (Figure 2.20).

Figure 2.19: Use of radiotherapy among patients who underwent breast-conserving surgery by cancer stage (N=7,047)

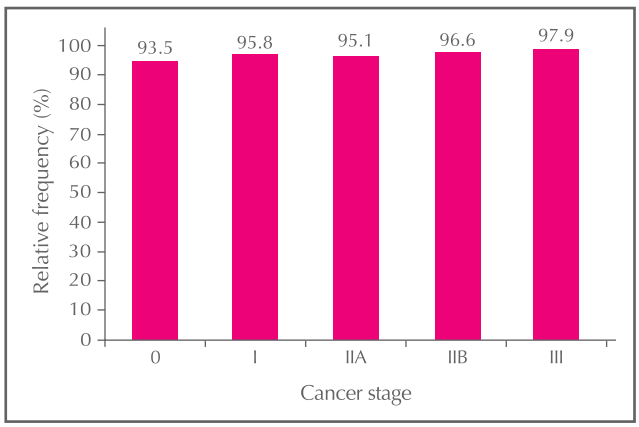
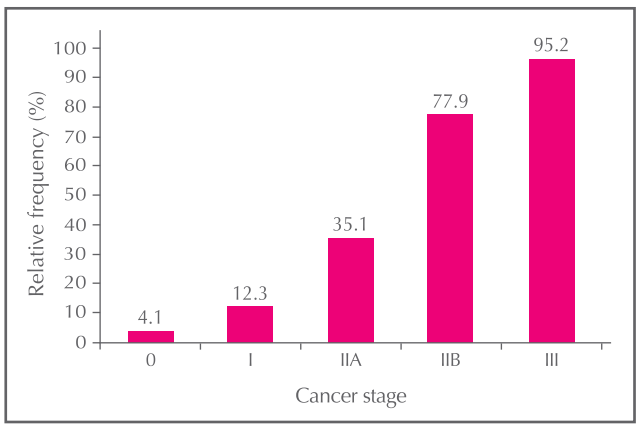


Figure 2.20: Use of radiotherapy among patients who underwent mastectomy by cancer stage (N=11,737)



2.51 Radiotherapy for breast cancer involves localised irradiation of regions such as breast and chest wall, with or without regional nodes. Table 2.20 shows the irradiated regions of adjuvant locoregional radiotherapy among the patients who received radiotherapy by the type of surgery they underwent.

Table 2.20: Coverage of regional lymph nodes by adjuvant locoregional radiotherapy (N=7,581)

	Number	%
Breast-conserving surgery (N=4,067)		
Breast alone	3,454	84.9
Breast and regional lymph nodes	613	15.1
Mastectomy (N=3,514)		
Chest wall alone	887	25.2
Chest wall and regional lymph nodes	2,627	74.8

ii. Palliative radiotherapy

2.52 Palliative radiotherapy for breast cancer is used for reducing symptoms which can be pain, pressure symptoms, airway obstruction, bleeding and secretion from metastases. Among the patients with metastatic breast cancer, 61.7% underwent palliative radiotherapy to various sites.

C. Chemotherapy

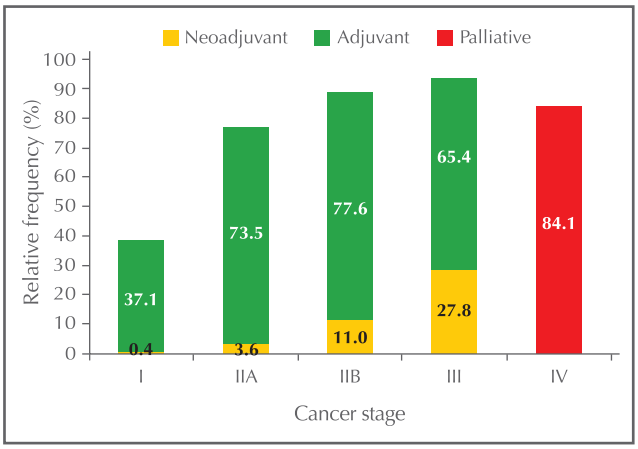
2.53 Chemotherapy is a form of systemic treatment using one or more cytotoxic drugs to kill or control cancer cell growth. The drugs destroy breast cancer cells by interfering with their ability to grow and divide. Chemotherapy is generally not required for patients with in situ tumour. Chemotherapy regimens are classified into three generations[51] 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.

2.54 Of the patients with invasive cancer, 66.5% underwent chemotherapy. Of these patients, 83.5% had adjuvant chemotherapy, 12.7% had neoadjuvant chemotherapy, and 3.8% had palliative chemotherapy. The majority (86.1%) of the patients received chemotherapy in public medical facilities, and the remainder in private medical facilities.

2.55 In the patient cohort, the use of curative intent chemotherapy was positively correlated with progressing cancer stage from stage I to III. In contrast, the majority (84.1%) of the patients with stage IV cancer underwent palliative chemotherapy (Figure 2.21).

2.56 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 in the same age group and cancer stage.

Figure 2.21: Use of chemotherapy by cancer stage (N=16,797)



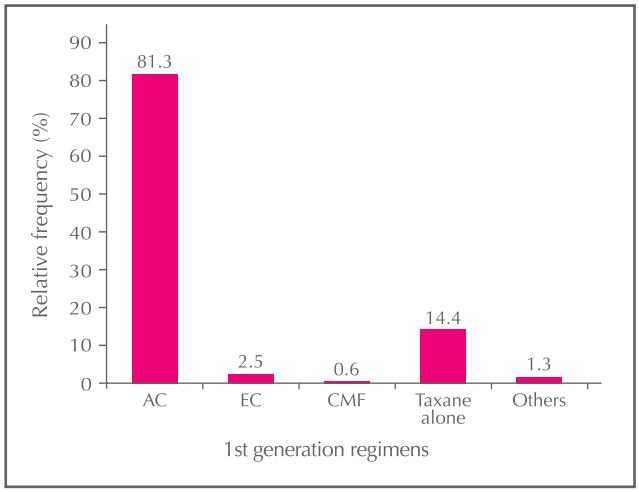
i. Neoadjuvant chemotherapy

2.57 Of the 11,581 patients who underwent chemotherapy, 12.7% received it as neoadjuvant treatment. The use of neoadjuvant chemotherapy increased substantially with progressing cancer stage (Figure 2.21). Figures 2.22, 2.23 and 2.24 show the use of chemotherapy regimens of the three generations in neoadjuvant setting among patients in the cohort. The use of HER2 regimens is shown in Figure 2.25. The types of chemotherapy regimens used by patients with different biological subtypes in the cohort are shown in Figure 2.26.

Table 2.21: Use of chemotherapy by age group and cancer stage at diagnosis (N=16,507)

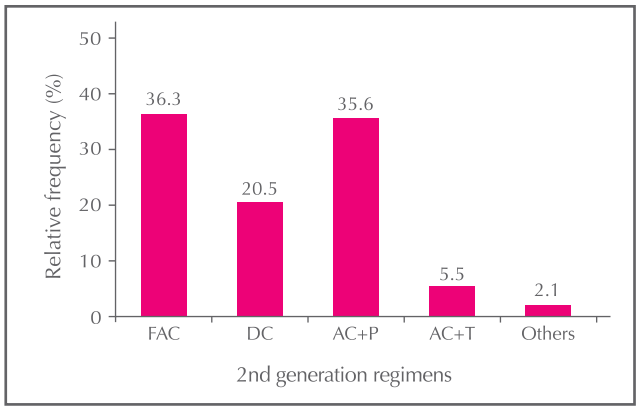
	Cancer stage, Number (% of patients in the same age group and cancer stage)									
	I		IIA		IIB		III		IV	
20-29	25	(58.1)	24	(85.7)	17	(100.0)	14	(100.0)	3	(100.0)
30-39	286	(56.2)	375	(90.6)	203	(97.6)	227	(99.1)	31	(77.5)
40-49	888	(44.3)	1,218	(87.4)	710	(95.8)	842	(98.6)	155	(95.7)
50-59	783	(39.4)	1,332	(85.5)	776	(94.2)	907	(97.2)	162	(85.7)
60-69	310	(26.8)	648	(67.9)	416	(88.5)	489	(92.8)	68	(84.0)
≥70	20	(4.5)	37	(10.3)	31	(18.9)	58	(36.3)	12	(32.4)

Figure 2.22: Type of first generation chemotherapy regimens (non-HER2) used in neoadjuvant setting (N=160)



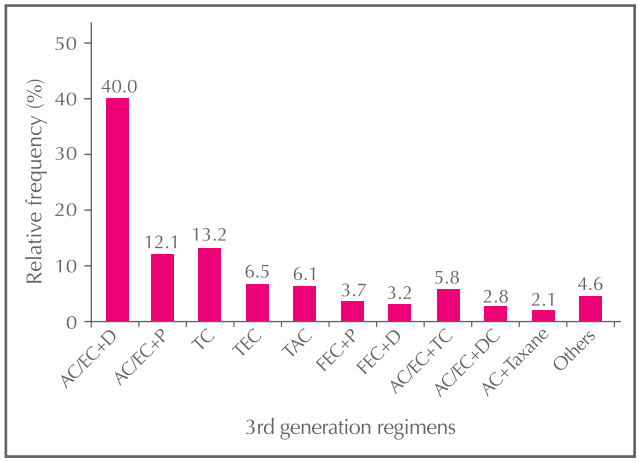
A: Adriamycin/Doxorubicin; E: Epirubicin; C: Cyclophosphamide; M: Methotrexate; F: 5FU; Taxane: Docetaxel or Paclitaxel

Figure 2.23: Type of second generation chemotherapy regimens (non-HER2) used in neoadjuvant setting (N=146)



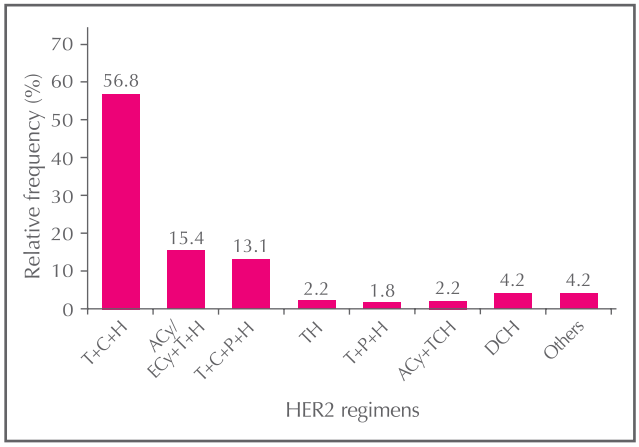
DC: Docetaxel+Cyclophosphamide; P: Paclitaxel; T: Taxane

Figure 2.24: Type of third generation chemotherapy regimens (non-HER2) used in neoadjuvant setting (N=570)



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

Figure 2.25: Type of HER2 regimens used in neoadjuvant setting (N=449)



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

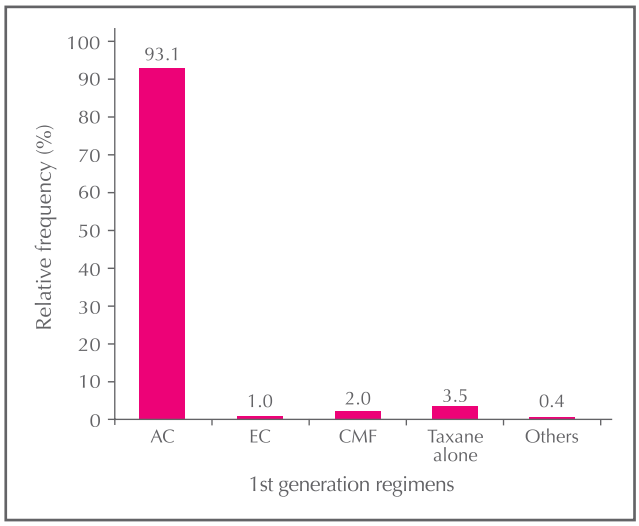
Figure 2.26: Type of chemotherapy regimens used by biological subtype in neoadjuvant setting (N=1,279)

AC+T: uncertain 2nd/3rd generation due to uncertain week intervals
* Others included any non-HER2 regimens containing Capecitabine, Gemcitabine, or Vinorelbine

ii. Adjuvant chemotherapy

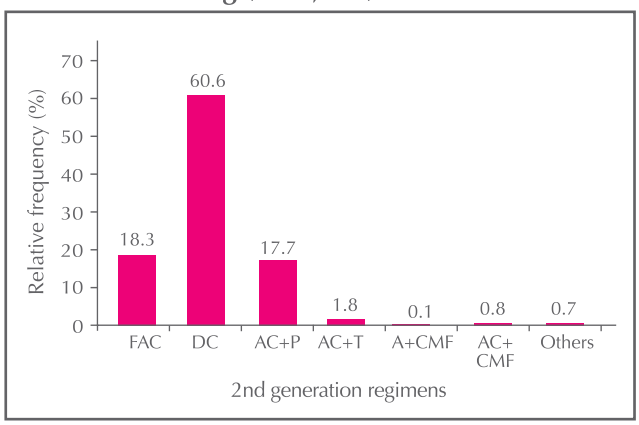
2.58 Of the 11,581 patients who underwent chemotherapy, 83.5% received it as adjuvant (stages I-III) treatment. Figures 2.27, 2.28 and 2.29 show the use of chemotherapy regimens of three generations in adjuvant setting among patients in the cohort. The use of HER2 regimens in adjuvant chemotherapy is shown in Figure 2.30. Figures 2.31 and 2.32 show the relative frequency for different types of regimens used by biological subtype and cancer stage, respectively.

Figure 2.27: Type of first generation chemotherapy regimens (non-HER2) used in adjuvant setting (N=1,662)



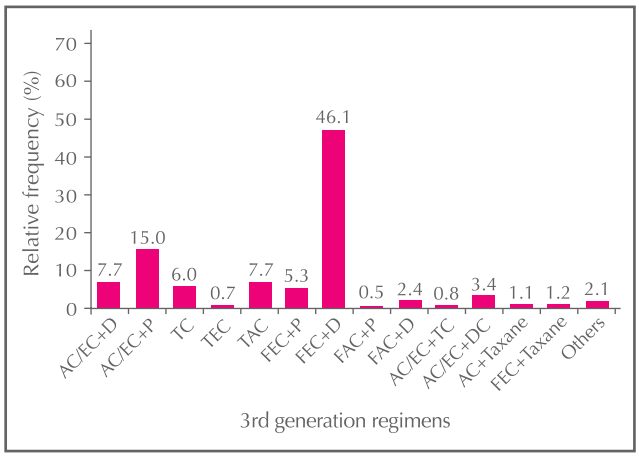
A: Adriamycin/Doxorubicin; E: Epirubicin; C: Cyclophosphamide; M: Methotrexate; F: 5FU; Taxane: Docetaxel or Paclitaxel

Figure 2.28: Type of second generation chemotherapy regimens (non-HER2) used in adjuvant setting (N=2,635)



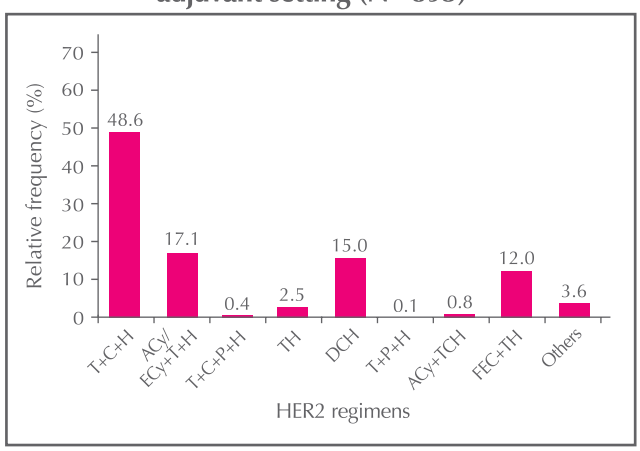
DC: Docetaxel+Cyclophosphamide; P: Paclitaxel; T: Taxane

Figure 2.29: Type of third generation chemotherapy regimens (non-HER2) used in adjuvant setting (N=2,841)



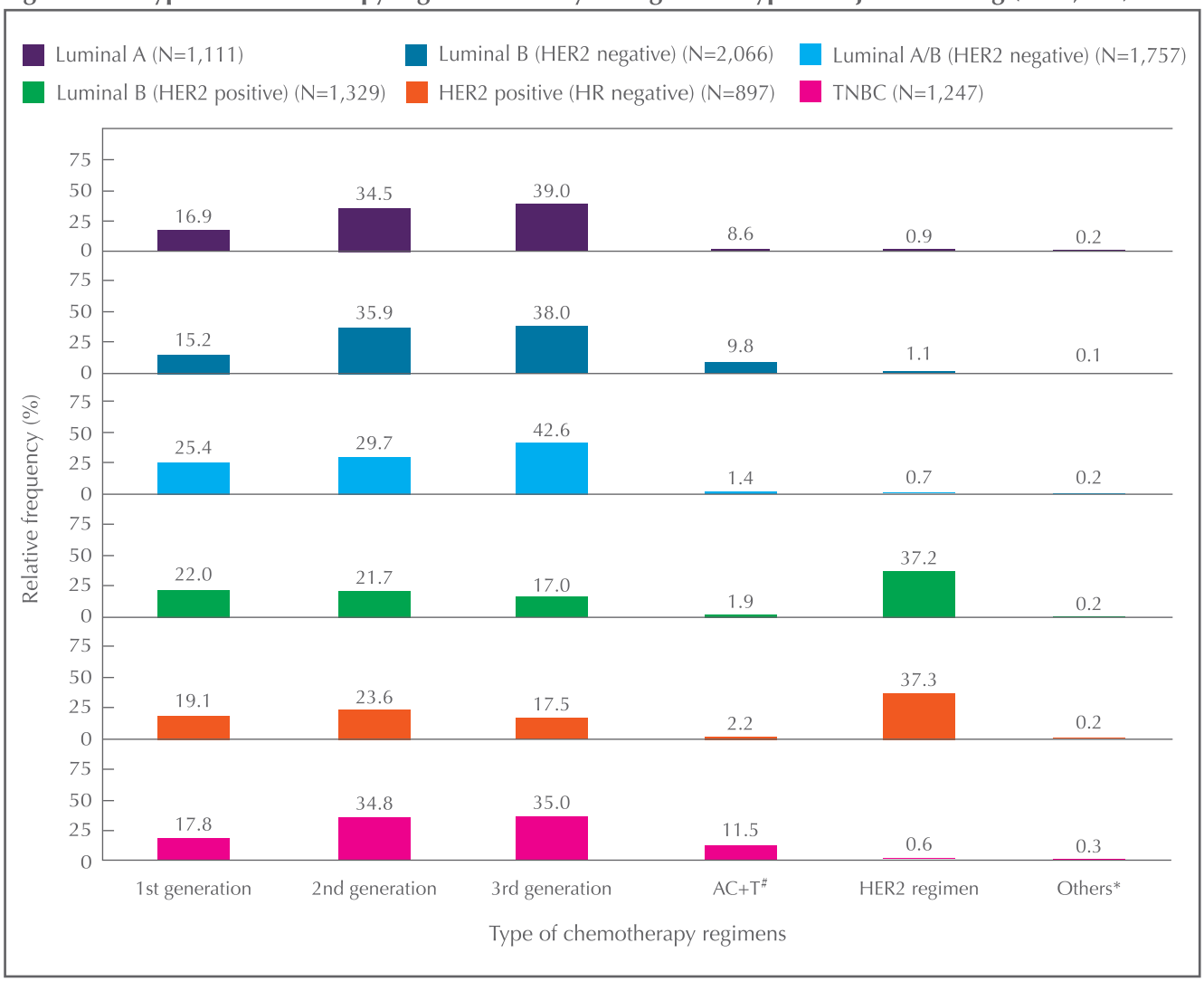
D: Docetaxel; P: Paclitaxel; TC: Paclitaxel+Carboplatin; DC: Docetaxel+Cyclophosphamide

Figure 2.30: Type of HER2 regimens used in adjuvant setting (N=895)



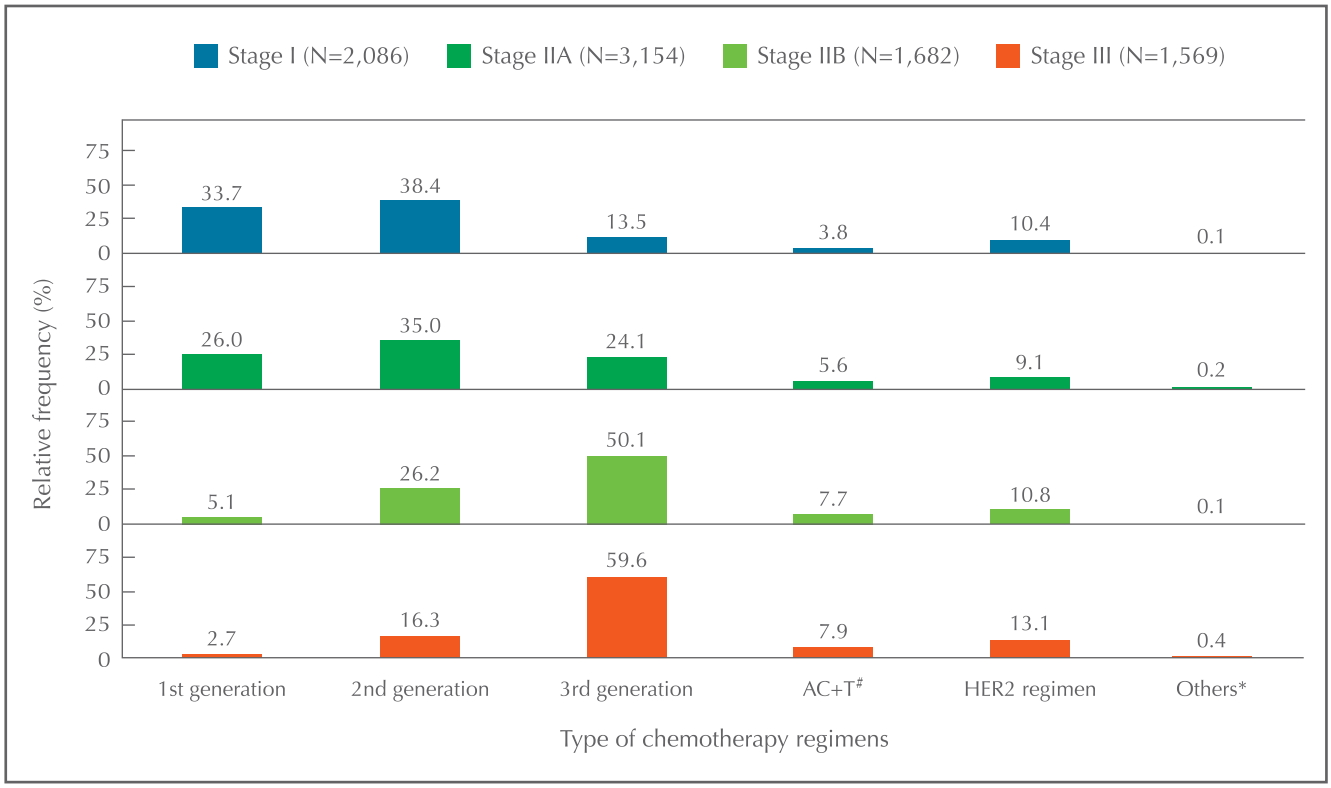
A: Anthracycline; C: Carboplatin; T: Taxane; H: Trastuzumab; P: Pertuzumab; Cy: Cyclophosphamide; DC: Docetaxel+Cyclophosphamide

Figure 2.31: Type of chemotherapy regimens used by biological subtype in adjuvant setting (N=8,407)



AC+T: uncertain 2nd/3rd generation due to uncertain week intervals
* Others included any non-HER2 regimens containing Capecitabine, Gemcitabine, or Vinorelbine

Figure 2.32: Type of chemotherapy regimens used by cancer stage in adjuvant setting (N=8,491)

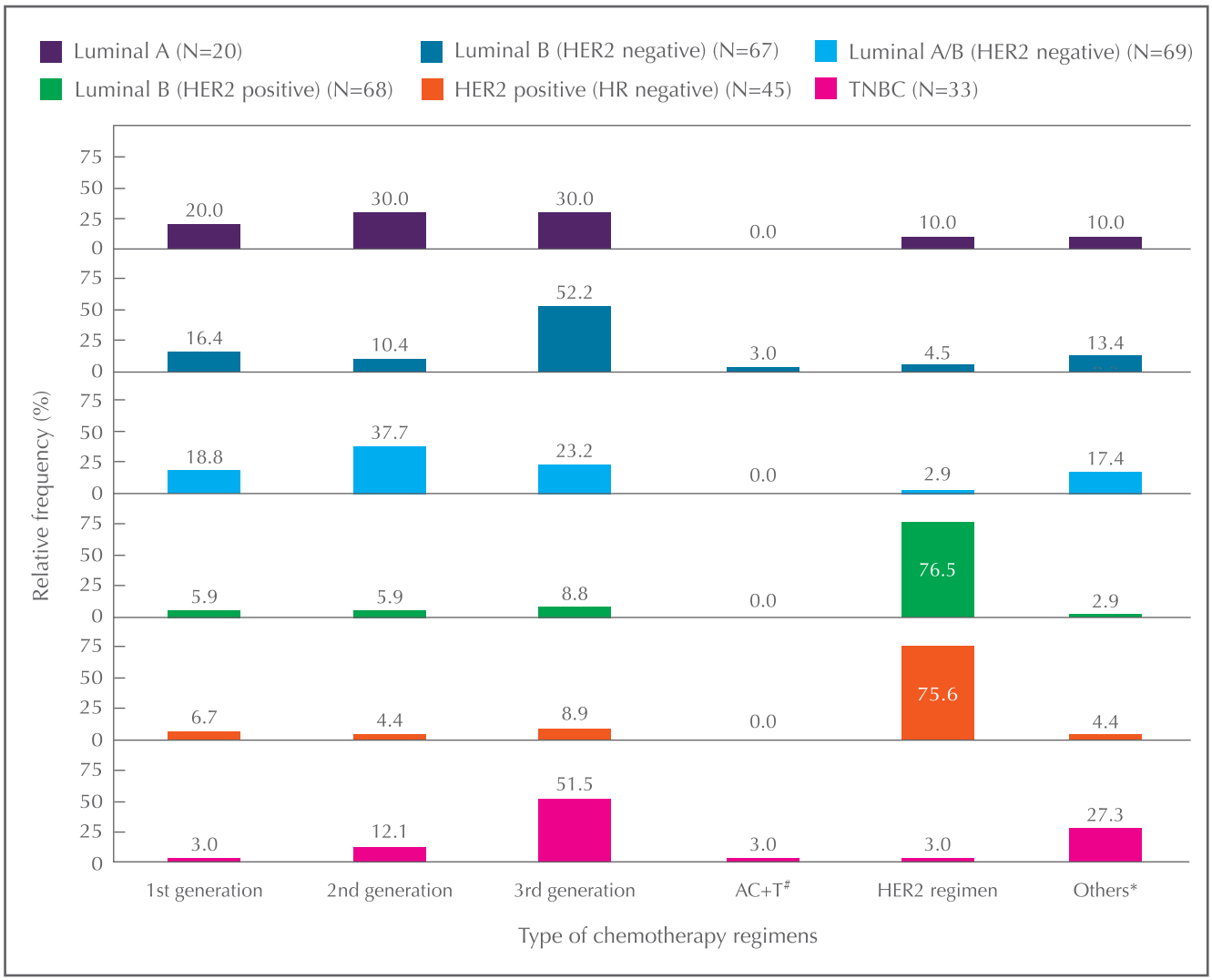


AC+T: uncertain 2nd/3rd generation due to uncertain week intervals
* Others included any non-HER2 regimens containing Capecitabine, Gemcitabine, or Vinorelbine

iii. Palliative chemotherapy

2.59 Of the 11,581 patients who underwent chemotherapy, 3.8% received it as palliative (stage IV) treatment. Figure 2.33 shows the relative frequency for different types of regimens used by biological subtype.

Figure 2.33: Type of chemotherapy regimens used by biological subtype in palliative setting (N=302)



AC+T: uncertain 2nd/3rd generation due to uncertain week intervals
* Others included any non-HER2 regimens containing Capecitabine, Gemcitabine, or Vinorelbine

D. Endocrine therapy

2.60 Endocrine therapy plays an important role in all stages of the treatment and prevention strategy for hormone receptor-positive 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.

2.61 In the cohort, 67.5% of the patients were treated with endocrine therapy. Among them, the majority (96.5%) were adjuvant, while neoadjuvant (0.4%) and palliative (3.0%) accounted for small proportions. In addition, the majority (90.0%) of the patients received endocrine therapy at public medical facilities, while the remainder received it at private medical facilities.

2.62 For patients with invasive breast cancer, about 75% or more received endocrine therapy, while for patients with in situ breast cancer, only 15.7% received endocrine therapy (Figure 2.34).

2.63 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 premenopausal and postmenopausal women. Aromatase inhibitors decrease the level of estrogen in the body. Aromatase inhibitors, including anastrozole, letrozole and exemestane, are only effective for women who are postmenopausal. Figure 2.35 shows the use of tamoxifen and aromatase inhibitors by age group in the patient cohort.

Figure 2.34: Use of endocrine therapy by cancer stage (N=19,408)

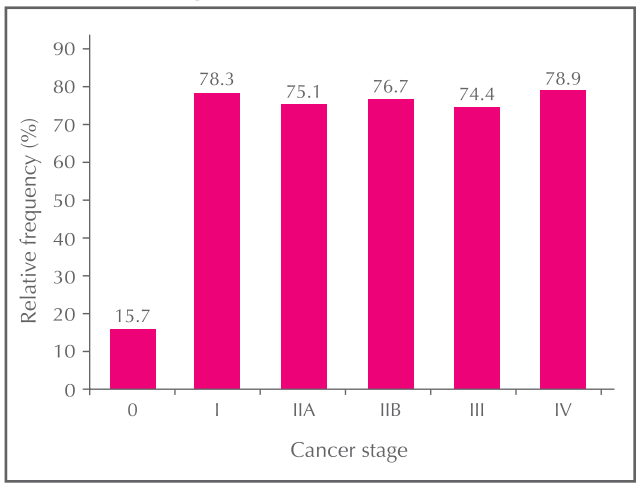
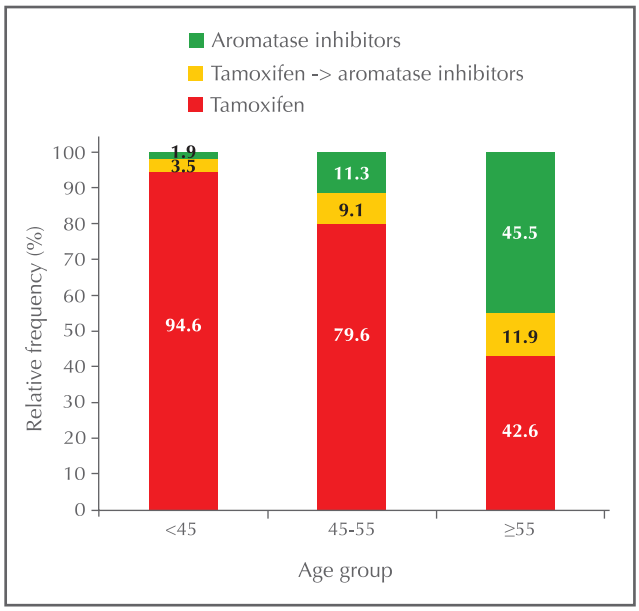


Figure 2.35: Forms of endocrine therapy by age group (N=12,510)

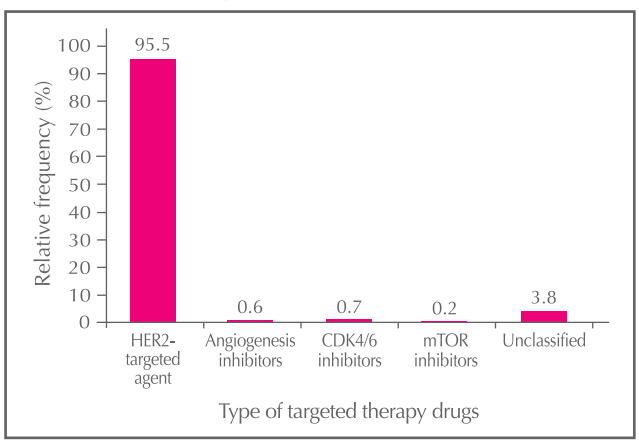


E. Targeted therapy

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

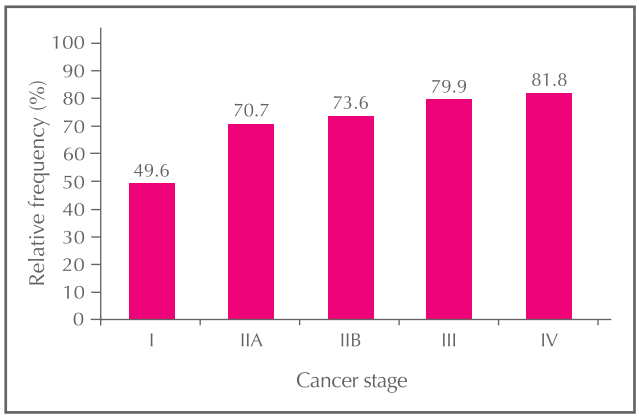
2.65 Among all patients, 14.5% received targeted therapy, particularly HER2-targeted agents (95.5%) (Figure 2.36). Of the patients with invasive HER2-positive breast cancer in the cohort, 67.2% underwent anti-HER2 targeted therapy. Among them, 79.4% were adjuvant, 16.1% were neoadjuvant and 4.5% were palliative. In addition, the majority (87.9%) of the patients received anti-HER2 targeted therapy at public medical facilities, and the remainder at private medical facilities. In the cohort, the use of anti-HER2 targeted therapy was much lower for stage I patients, and the proportions increased with increasing cancer stage among stage II or above patients (Figure 2.37).

Figure 2.36: Type of targeted therapy drugs used (N=2,924)



HER2: human epidermal growth factor receptor 2;
CDK: cyclin-dependent kinase;
mTOR: mammalian target of rapamycin
Note: The total percentages may exceed 100 as multiple types of targeted therapy drugs may be used.

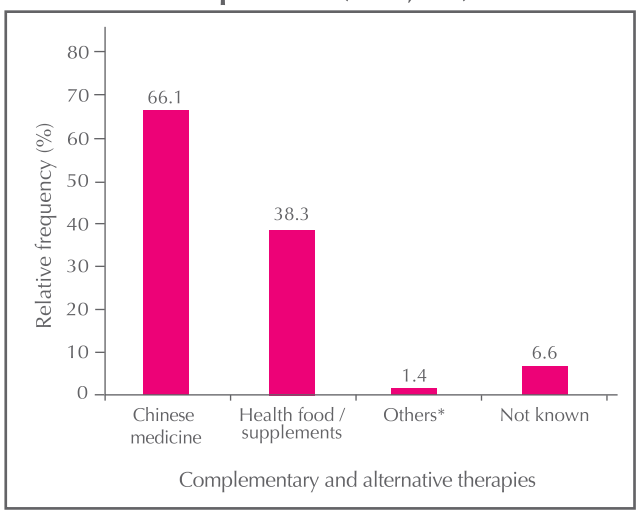
Figure 2.37: Use of anti-HER2 targeted therapy in HER2 positive patients by cancer stage (N=3,542)



F. Complementary and alternative therapies

2.66 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. A total of 7,239 (35.8%) of the patients in the cohort sought complementary and alternative therapies as part of their treatment. Two-thirds of them used traditional Chinese medicines (Figure 2.38).

Figure 2.38: Type of complementary and alternative therapies used (N=7,239)



* Others included Tai Chi, Qigong, Naturopathy, acupuncture and moxibustion, massage and yoga

Note: The total percentages may exceed 100 as multiple types of complementary and alternative therapies may be used.

VI. Patient status

2.67 Once treatment is completed, the HKBCR will follow up with the registered patients annually to ascertain the efficacy of the treatment. To date, a total of 18,407 patients completed at least one follow-up and 29.2% of them had the last follow-up within the past two years. Slightly more than half (55.3%) have been followed up for five or more years (Table 2.22). The mean and median follow-up period were 6.4 and 5.7 years respectively.

2.68 Of the patients who have been followed up, 2.4% experienced only locoregional recurrence (LRR), 3.2% experienced only distant recurrence (DR), and 2.2% experienced both locoregional and distant recurrence concurrently or sequentially. The mean and median time to recurrence are shown in Table 2.23.

Table 2.22: Follow-up of patients (N=18,407)

	Number	%
Follow-up period		
<1 year	1,337	7.3
1-2 years	1,981	10.8
2-5 years	4,892	26.6
5-10 years	5,664	30.8
≥10 years	4,512	24.5
Not known	21	0.1
Mean (95% CI)	6.4 years (6.31-6.43)	
Median (95% CI)	5.7 years (5.60-5.80)	
Mortality		
No. of deaths from breast cancer	1,534	8.3
No. of deaths from unrelated causes	690	3.7
No. of deaths with causes not known	44	0.2

CI: confidence interval

Table 2.23: Recurrence pattern of patients (N=17,764)

	Number	%
Locoregional recurrence only		
No. of locoregional recurrence only	423	2.4
Mean time (95% CI)	5.2 years (4.84-5.58)	
Median time (95% CI)	4.4 years (3.78-4.88)	
Distant recurrence only		
No. of distant recurrence only	560	3.2
Mean time (95% CI)	4.5 years (4.23-4.75)	
Median time (95% CI)	3.7 years (3.41-4.08)	
Locoregional and distant recurrence		
No. of locoregional and distant recurrence	393	2.2
Mean time (95% CI)	4.0 years (3.71-4.35)	
Median time (95% CI)	3.2 years (2.95-3.62)	

CI: confidence interval

2.69 Table 2.24 shows the number of invasive breast cancer patients with LRR in different subgroups specified by surgery type and cancer stage at diagnosis in the patient cohort. Patients who received breast-conserving surgery without radiotherapy had higher LRR rates than those who received breast-conserving surgery with radiotherapy. Similar pattern was observed among patients who received mastectomy. In addition, among patients who received mastectomy without radiotherapy, LRR rate increased with increasing cancer stage (Table 2.24). The two most common sites for LRR were breast (37.9%) and axilla (33.5%) (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	74/2,684 (2.8)	71/1,548 (4.6)	20/534 (3.7)	25/362 (6.9)	190/5,128 (3.7)
BCS without RT	7/102 (6.9)	9/74 (12.2)	2/17 (11.8)	1/7 (14.3)	19/200 (9.5)
MTX with RT	11/359 (3.1)	20/1,012 (2.0)	54/1,393 (3.9)	151/2,146 (7.0)	236/4,910 (4.8)
MTX without RT	85/2,506 (3.4)	91/1,865 (4.9)	24/385 (6.2)	17/100 (17.0)	217/4,856 (4.5)

BCS: breast-conserving surgery; MTX: mastectomy; RT: radiotherapy

Table 2.25: Sites involved in locoregional recurrence (N=816)

	Number	%
Breast	309	37.9
Axilla	273	33.5
Chest wall	227	27.8
Supraclavicular fossa	150	18.4
Internal mammary node	59	7.2
Infraclavicular fossa	8	1.0
Others	12	1.5
Unspecified	32	3.9

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

2.70 In the cohort, 953 patients experienced distant recurrence. Among them, the top four organs involved were bone (60.4%), lung (46.8%), liver (39.9%) and brain (15.8%) (Table 2.26). The median time for distant recurrence to these organs and the distribution of biological subtypes of the patients involved are shown in Table 2.27.

Table 2.26: Sites involved in distant recurrence (N=953)

	Number	%		Number	%
Bone	576	60.4	Peritoneum	27	2.8
Lung	446	46.8	Contralateral axillary node	17	1.8
Liver	380	39.9	Ovary	5	0.5
Brain	151	15.8	Spleen	5	0.5
Intrathoracic node	206	21.6	Pancreas	5	0.5
Distant lymph node	85	8.9	Thyroid gland	3	0.3
Pleura	80	8.4	Uterus	3	0.3
Neck node	78	8.2	Others	41	4.3
Adrenal gland	32	3.4	Unspecified	14	1.5

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=576)	Lung (N=446)	Liver (N=380)	Brain (N=151)
Time for metastasis, median years (range)	**3.7 (0.1-13.6)**	**3.8 (0.1-15.6)**	**3.4 (0.1-12.7)**	**2.9 (0.1-12.7)**
Biological subtype, %				
Luminal A	11.8	8.1	8.7	5.3
Luminal B (HER2 negative)	24.1	20.0	23.7	17.2
Luminal A/B (HER2 negative)	28.3	27.4	30.5	19.2
Luminal B (HER2 positive)	14.1	14.3	14.7	17.9
HER2 positive (HR negative)	6.1	7.8	7.9	15.2
TNBC	9.0	14.6	8.4	19.2
Not known	6.6	7.8	6.1	6.0

HR: hormone receptors (ER and PR)
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 (HR negative): ER and PR-, HER2+, and any Ki-67 index
TNBC (triple negative breast cancer): ER and PR-, HER2-, and any Ki-67 index

2.71 In the cohort, the proportion of patients with only LRR did not show any association with cancer stage at diagnosis. However, the proportion of the patients with only DR increased from 1.3% of stage I patients to 8.9% of stage III patients, while the proportion of the patients with both LRR and DR increased from 0.9% of stage I patients to 5.5% of stage III patients (Table 2.28).

2.72 In the cohort, 1,534 patients died from breast cancer. Slightly more than half (52.1%) of them were stage III or IV at initial diagnosis. Survival time ranged from 0.3 to 16.0 years. 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=15,121)

	Cancer stage, %			
	I (N=5,657)	IIA (N=4,503)	IIB (N=2,334)	III (N=2,627)
Locoregional recurrence only	2.2	2.3	1.2	2.0
Distant recurrence only	1.3	2.7	4.5	8.9
Locoregional and distant recurrence	0.9	1.9	3.1	5.5
No recurrence	95.5	93.1	91.3	83.6

Table 2.29: Characteristics of breast cancer-specific deaths (N=1,534)

	Cancer stage at initial diagnosis						
	0	I	IIA	IIB	III	IV	Unstaged
No. of cases (% of breast cancer death cases)	**16 (1.0)**	**144 (9.4)**	**238 (15.5)**	**213 (13.9)**	**517 (33.7)**	**283 (18.4)**	**123 (8.0)**
Survival time (range in years)	**3.7-16.0**	**1.3-15.6**	**0.3-15.4**	**1.3-13.5**	**0.8-15.3**	**0.4-14.6**	**0.3-13.1**
Time from first diagnosis of distant recurrence to death (years), mean (range)	**5.9 (2.2-12.6)**	**3.0 (0.1-10.4)**	**2.2 (0.0-10.2)**	**2.0 (0.1-7.8)**	**2.2 (0.0-11.8)**	**4.6 (0.4-14.6)**	**2.6 (0.2-5.7)**
Biological subtype, Number							
Luminal A	2	9	17	18	40	14	7
Luminal B (HER2 negative)	0	39	58	47	108	45	27
Luminal A/B (HER2 negative)	2	37	59	62	122	58	22
Luminal B (HER2 positive)	2	21	23	23	83	48	16
HER2 positive (HR negative)	2	16	21	11	50	23	5
TNBC	0	20	54	41	83	19	9
Not known	8	2	6	11	31	76	37

HR: hormone receptors (ER and PR)
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 (HR negative): ER and PR-, HER2+, and any Ki-67 index
TNBC (triple negative breast cancer): ER and PR-, HER2-, and any Ki-67 index