CHAPTER 2

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

CHAPTER 2
DISEASE PATTERN, TREATMENT TREND AND CLINICAL OUTCOME OF BREAST CANCER IN HONG KONG

This chapter reviews the clinical presentation, cancer characteristics and treatment methods using data collected from 12,023 breast cancer patients. Through analysis of these data, it provides insight into the current methods of clinical management of breast cancer and cancer characteristics and identifies potential areas of concern for the local community.

KEY FINDINGS

Clinical presentations

► 9,536 patients were diagnosed with invasive cancers and 1,492 were diagnosed with in situ cancers.

► 84.6% of patients discovered their first breast cancer by self-detection by chance. More invasive breast cancers were self-detected by chance (88.4%) than in situ breast cancers (58.0%).

► The most common self-detected presenting symptom was a painless lump (92.1%).

► After the onset of symptoms, only 19.4% of patients sought first medical consultation in less than three months.

► 4.5% of patients had synchronous bilateral breast cancer at first diagnosis, and 4.0% developed a contralateral breast cancer subsequently (metachronous cancer).

► Cancer staging was not conducted in 23.5% of the patients. The most common staging method used was Chest X-ray (73.8%). Positron emission tomography scan (PET scan) was used in 23.6% of patients. 5.6% and 9.0% of stage 0 and stage I patients, respectively, used PET scan and 18-30% of the patients with stages IIA or IIB diseases used PET scan.

► At diagnosis, the most common cancer stage was stage II (39.7%). Advanced cancer (stages III-IV) constituted to 15.3%. 11.3% of patients were diagnosed with in situ cancer.

► The mean invasive tumour size was 2.2cm (standard deviation: 1.4cm) and median of 1.9cm. The mean invasive tumour size in self-detected cancers by chance (2.2cm) was significantly larger than those screen-detected cancers (1.3cm) (p<0.001). 60.4% of invasive breast cancers had no positive lymph nodes. 77.0% of invasive breast cancers were either ER or PR positive. 21.8% of invasive breast cancers were c-erbB2/HER2 positive.

► The mean size of in situ breast cancer was 2.0cm (standard deviation: 1.5cm), and median of 1.6cm. Of the in situ breast cancers where mammography screening (MMG) was performed, 62.5% showed microcalcification by MMG. IHC study of biological characteristics of in situ breast cancer showed that 59.1% were either ER or PR positive and 29.1% were c-erbB2/HER2 positive.

Treatment

► 17.1% of patients were treated at solely private medical facilities, 48.9% solely used public medical facilities, and 34.0% used a mix of both private and public medical facilities.

► Number of treatments received by patients increased with increasing cancer stage, with the exception of those with stage IV breast cancer.

► 98.3% of patients had surgery. 52.9% had surgery at a private medical facility, while 47.1% had surgery at public medical facilities. 63.1% had mastectomy, while 35.1% had breast-conserving surgery. Of the patients that had reconstruction, 65.6% of patients had TRAM flap reconstruction surgery, while 19.5% had breast implants. Patients who had mastectomy increased with increasing age, while patients who had mastectomy and reconstruction or breast-conserving surgery reduced with increasing age. Use of breast-conserving surgery reduced with increasing cancer stage. Breast-conserving surgery was conducted in more private health care patients (44.8%) than public health care patients (26.2%).

► Axillary dissection (AD) was conducted in 43.4% of patients with negative clinical nodal status, while sentinel node biopsy was conducted in 9.4% of patients with positive clinical nodal status. The use of AD was positively correlated with increasing cancer stage.

► 60.5% patients had chemotherapy. Of the patients that underwent chemotherapy, 953 (13.1%) of patients also received targeted therapy.

► 62.2% of patients had radiotherapy as part of their treatment. 93.2% of patient who had breast-conserving surgery had radiotherapy.

► 66.7% of patients had endocrine therapy. The frequency of use of tamoxifen was negatively correlated with growing age, while the use of Aromatase inhibitors was positively correlated with growing age.

► 8% of patients had targeted therapy. The use of targeted therapy was positively correlated with increasing cancer stage. The most commonly used targeted therapy was Trastuzumab (94.7%), which is used to treat HER2 positive cancers.

► 39.9% of patients used complementary and alternative treatments.

Patient status

► 46.8% of the patient cohort had the last follow-up data within the last 2 years. The mean follow-up period was 4.9 years and median follow-up period was 4 years.

► 6.4% of the patient cohort experienced recurrence (either locoregional or distant recurrence, or both).

► The most common organ involved in distant recurrence was bone (52.9%), followed by lung (39.4%).

2.1 Clinical presentation

Self-detection by chance was the most frequent mode of first breast cancer detection (84.6%) (Figure 2.1). A recent study found that although 70-90% of Hong Kong Chinese women had heard of breast self-examination (BSE), clinical breast examination (CBE) and mammography screening (MMG), only half or less practiced regular screening[26]. The detection of breast cancer by health care service assisted screening methods (CBE, MMG and ultrasound screening (USG)) was very low in Hong Kong.

The proportion of patients who self-detected their first breast cancer by chance was lower in private medical service users in comparison to public medical service users and mixed health care users (Table 2.1). This highlights the importance of increased awareness of BSE, and the need for increased MMG screening in public health care facilities.
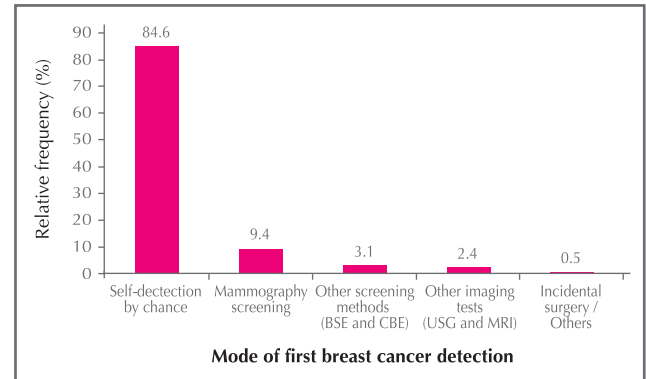

Figure 2.1 Mode of first breast cancer detection in the patient cohort (N=11,093)

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

Table 2.1 Mode of first breast cancer detection by type of medical service received at diagnosis (N=11,093)

	Private medical service users (N=1,857)		Public medical service users (N=5,413)		Mixed private / public medical service users (N=3,823)	
Mode of first breast cancer detection	Number	(%)	Number	(%)	Number	(%)
Self-detection by chance	1,420	(76.5)	4,630	(85.5)	3,330	(87.1)
Mammography screening	244	(13.1)	544	(10.0)	256	(6.7)
Other screening methods (BSE and CBE)	81	(4.4)	131	(2.4)	137	(3.6)
Other imaging tests (USG and MRI)	97	(5.2)	81	(1.5)	86	(2.2)
Incidental surgery / Others	15	(0.8)	27	(0.5)	14	(0.4)

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

The proportion of invasive breast cancers first self-detected by chance (88.4%) was much higher than in situ breast cancers (58.0%) (Table 2.2).

Table 2.2 Mode of first breast cancer detection by type of cancer (N=11,001)

|	Type of cancer, Number (%)	
Mode of first breast cancer detection	**In situ (N=1,392)**	**Invasive (N=9,609)**
Self-detection by chance	807 (58.0)	8,493 (88.4)
Mammography screening	455 (32.7)	585 (6.1)
Other screening methods (BSE and CBE)	46 (3.3)	298 (3.1)
Other imaging tests (USG and MRI)	73 (5.2)	190 (2.0)
Incidental surgery / Others	11 (0.8)	43 (0.4)

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

Higher proportions of stages 0 or I cancers (32.3% and 11.6% respectively) were detected by mammography screening compared to that in stages III or IV cancers (2.9% and 1.7% respectively) (Table 2.3).

Table 2.3 Mode of first breast cancer detection by cancer stage (N=10,769)

	Cancer stage, Number (%)					
Mode of first breast cancer detection	**0 (N=1,262)**	**I (N=3,385)**	**IIA (N=2,980)**	**IIB (N=1,437)**	**III (N=1,470)**	**IV (N=235)**
Self-detection by chance	750 (59.4)	2,719 (80.3)	2,685 (90.1)	1,341 (93.3)	1,388 (94.4)	215 (91.5)
Mammography screening	407 (32.3)	393 (11.6)	141 (4.7)	38 (2.6)	42 (2.9)	4 (1.7)
Other screening methods (BSE and CBE)	40 (3.2)	131 (3.9)	97 (3.3)	33 (2.3)	25 (1.7)	10 (4.3)
Other imaging tests (USG and MRI)	57 (4.5)	128 (3.8)	43 (1.4)	19 (1.3)	9 (0.6)	4 (1.7)
Incidental surgery / Others	8 (0.6)	14 (0.4)	14 (0.5)	6 (0.4)	6 (0.4)	2 (0.9)

BSE: Breast self-examination; CBE: Clinical breast examination; USG: Ultrasound screening; MRI: Magnetic resonance imaging
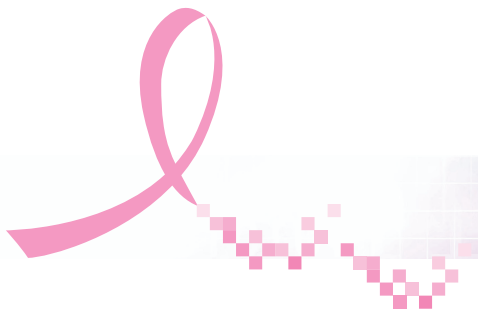
The most common presenting symptom on self-detected breast cancers by chance was a painless lump (92.1%) (Figure 2.2) .
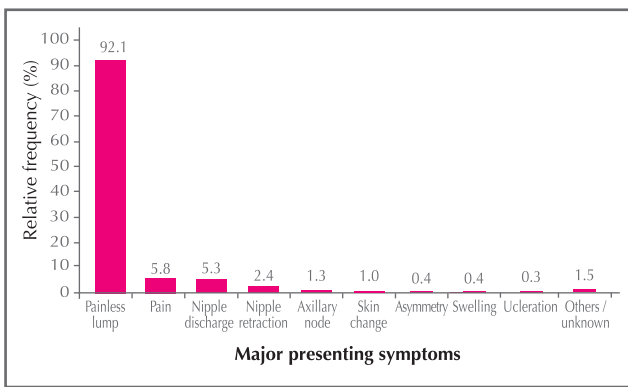

Relative frequency (%)

Major presenting symptoms

Figure 2.2 Major presenting symptoms of self-detected breast cancers (N=9,380)

2.1.1 Duration from onset of symptoms to first medical consultation

Of the self-detected breast cancers, after the onset of symptoms, only 19.4% of patients sought first medical consultation in less than three months. (Table 2.4).

Table 2.4 Duration from onset of symptoms to first medical consultation for patients who self-detected* their cancers (N=9,380)

	Number	(%)
Less than 1 month	909	(9.7)
1-3 months	908	(9.7)
4-12 months	318	(3.4)
More than 12 months	280	(3.0)
Not known	6,965	(74.3)

*self-detection by chance only

A higher proportion of patients who were private medical service users sought medical consultation in less than a month (21.6%) than public medical service users (5.6%) and mixed medical sevice users (10.3%) (Table 2.5).

Table 2.5 Duration from onset of symptoms to first medical consultation for patients who self-detected* their cancers by type of medical service (N=9,380)

	Private medical service users (N=1,420)		Public medical service users (N=4,630)		Mixed private / public medical service users (N=3,330)	
	Number	(%)	Number	(%)	Number	(%)
< 1 month	307	(21.6)	260	(5.6)	342	(10.3)
1-3 months	230	(16.2)	357	(7.7)	321	(9.6)
4-12 months	83	(5.8)	151	(3.3)	84	(2.5)
> 12 months	61	(4.3)	146	(3.2)	73	(2.2)
Not known	739	(52.0)	3,716	(80.3)	2,510	(75.4)

*self-detection by chance only

Higher proportions of stages III and IV patients took more than 12 months to seek first medical consultation than the patients who were diagnosed with early stage cancer (Stages I, IIA or IIB) (Table 2.6).

Table 2.6 Duration from onset of symptoms to first medical consultation for patients who self-detected* their cancers by cancer stage at diagnosis (N=8,348)

	Cancer stage, Number (%)				
	Stage I (N=2,719)	Stage IIA (N=2,685)	Stage IIB (N=1,341)	Stage III (N=1,388)	Stage IV (N=215)
<1 month	298 (11.0)	275 (10.2)	119 (8.9)	99 (7.1)	13 (6.0)
1-3 months	244 (9.0)	281 (10.5)	133 (9.9)	139 (10.0)	14 (6.5)
4-12 months	87 (3.2)	84 (3.1)	36 (2.7)	60 (4.3)	12 (5.6)
>12 months	62 (2.3)	56 (2.1)	44 (3.3)	53 (3.8)	25 (11.6)
Not known	2,028 (74.6)	1,989 (74.1)	1,009 (75.2)	1,037 (74.7)	151 (70.2)

*self-detection by chance only

2.2 Cancer characteristics

Of the 12,023 patients, 271 patients had synchronous bilateral breast cancer at first diagnosis, and 241 developed a contralateral breast cancer within, on average, 7.9 years (range: 0.5 – 34.5 years, median: 5.9 years) after diagnosis of an initial primary breast cancer (Figure 2.3).
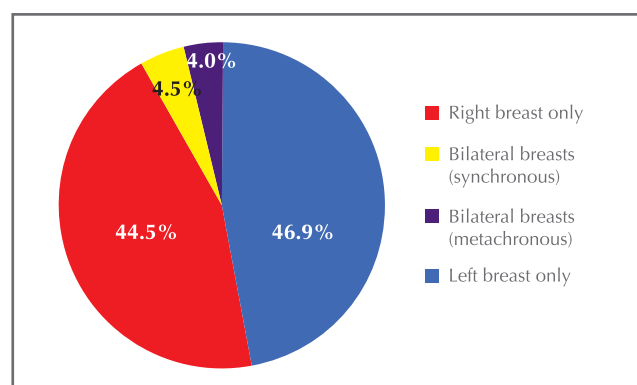
Majority of the breast cancers were detected in the left upper outer or right upper outer quadrant of the breasts (45.9 and 49.4% respectively) (Figure 2.4).
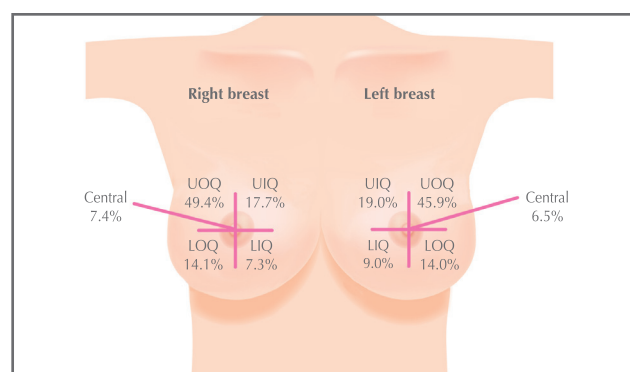

Figure 2.3 Laterality of 12,023 breast cancer cases

Right breast only — 44.5%
Left breast only — 46.9%
Bilateral breasts (synchronous) — 4.5%
Bilateral breasts (metachronous) — 4.0%

Figure 2.4 Locations of breast cancers (N=12,023)

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

Right breast — UOQ 49.4%, UIQ 17.7%, LOQ 14.1%, LIQ 7.3%, Central 7.4%
Left breast — UIQ 19.0%, UOQ 45.9%, LIQ 9.0%, LOQ 14.0%, Central 6.5%

2.2.1 Diagnostic tests for breast cancer

Malignant breast cancer is diagnosed using diagnostic imaging and cytohistochemical biopsies. MMG is currently the most important imaging tool used during breast cancer diagnosis. USG and MRI are used for further investigation. Fine needle biopsy (FNA) and core needle biopsies (CNB) are used to confirm the breast lesion is malignant. 80.6% of patients were diagnosed using MMG, while 74.0% were diagnosed using USG and 6.7% were diagnosed using MRI.

Breast Imaging Reporting and Data System (BIRADS) is a classification system used by radiologists to determine likelihood of malignancy in the breast. The overall sensitivity of MMG was 80.5%, while the sensitivity of USG was 88.9% and MRI was 96.5% (Table 2.7).

Table 2.7 Sensitivity and diagnostic results of breast imaging tests (N=12,023)

	Mammography (N=9,696)		Breast ultrasound (N=8,900)		MRI (N=811)	
Proportion of subjects using the diagnostic test	80.6%		74.0%		6.7%	
Overall sensitivity*	80.5%		88.9%		96.5%	
BIRADS category						
Diagnostic / malignant (BIRADS 5)	2,897	(29.9%)	3,225	(36.2%)	615	(75.8%)
Suspicious abnormality (BIRADS 4)	4,905	(50.6%)	4,686	(52.7%)	168	(20.7%)
Probably benign (BIRADS 3)	626	(6.5%)	574	(6.4%)	11	(1.4%)
Benign (BIRADS 2)	435	(4.5%)	192	(2.2%)	6	(0.7%
Normal (BIRADS 1)	793	(8.2%)	216	(2.4%)	11	(1.4%)
Incomplete (BIRADS 0)	40	(0.4%)	7	(0.1%)	0	(0.0%)

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

FNA was used in 45.3% of patients; CNB was used in 51.0% of patients while excisional biopsy was used in 14.8% of patients. The overall sensitivity of FNA was 90.2%, while CNB had an overall sensitivity of 98.7% and excisional biopsy had a sensitivity of 100% (Table 2.8). As a standard of care, biopsy (sampling of breast cells or tissues for examination) was usually done before surgery to confirm the presence of cancer cells, in our patient cohort, 88.6% of the patients have biopsies done before surgery. Among them, 3,520 (36.5%) patients used FNA solely, 4,208 (43.6%) used CNB solely, while 1,924 (19.9%) patients used both FNA and CNB.

Table 2.8 Sensitivity and diagnostic results of breast tissue biopsies (N=12,023)

	FNA (N=5,444)		CNB (N=6,132)		Excisional biopsy (N=1,778)	
Proportion of subjects using the diagnostic test	45.3%		51.0%		14.8%	
Overall sensitivity*	90.2%		98.7%		100.0%	
Class						
Diagnostic / malignant (Class V)	3,278	(60.2%)	5,813	(94.8%)	1,778	(100.0%)
Suspicious (Class IV)	1,026	(18.8%)	137	(2.2%)	—	
Atypical (Class III)	608	(11.2%)	101	(1.6%)	—	
Benign (Class II)	261	(4.8%)	51	(0.8%)	—	
Scanty benign (Class I)	182	(3.3%)	28	(0.5%)	—	
Incomplete (Class 0)	89	(1.6%)	2	(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 have taken the test

Of the 7,802 patients diagnosed with MMG, opacity was observed in 59.2%, while microcalcification was observed in 50.7% of patients (Table 2.9).

Table 2.9 Mammographic findings of patient cohort who were diagnosed through mammography (N=7,802)

	Number	(%)
Opacity	4,617	(59.2%)
Microcalcifications	3,955	(50.7%)
Architectural distortion	1,034	(13.3%)
Asymmetric density	783	(10.0%)
Unclassified	378	(4.8%)

Majority of the patients (67.5%) had heterogeneous mammographic density of the breasts. 5.8% had extremely dense breasts (Figure 2.5).
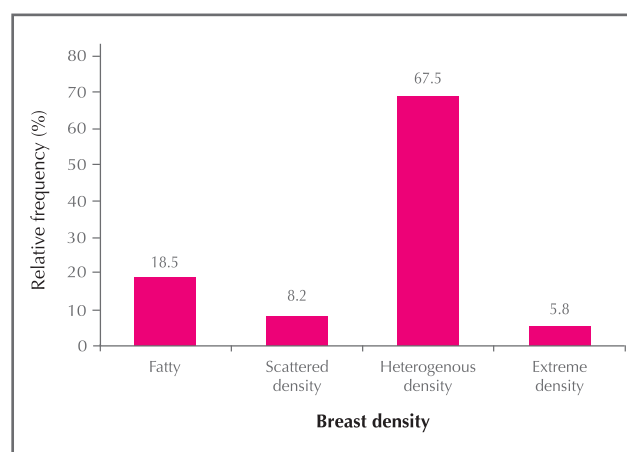
Figure 2.5 Mammographic density of breasts of breast cancer patients with diagnostic mammography (N=5,514)

2.2.2 Methods of cancer staging

After diagnosis of breast cancer, extent of disease is studied by further imaging. About a quarter (23.5%) of the patients did not have cancer staging while among those who had cancer staging, the most common method used for cancer staging was Chest X-ray (73.8%), USG of the abdomen (40.8%) and Positron emission tomography scan (PET scan) (23.6%) (Table 2.10). According to the 2010 practice guidelines of the National Comprehensive Cancer Network (NCCN), patients with early breast cancer, including stage I, stage II, or operable stage III breast cancer, are not recommended to use PET scan to determine the extent of disease [27]. However, among the patient cohort, 5.6% and 9.0% of stage 0 and stage I patients, respectively, used PET scan and 18-30% of the patients with stages IIA or IIB used PET scan to determine the extent of their disease (Table 2.11).

Table 2.10 Cancer staging in 10,531 breast cancer patients

Type of cancer staging method	Number	(%)
No cancer staging	2,477	(23.5)
Chest X-Ray (CXR)	5,942	(73.8)
Ultrasound abdomen (USG Abd)	3,284	(40.8)
Positron emission tomography scan (PET scan)	1,897	(23.6)
Bone scan	301	(3.7)
Computed tomography of body parts*	246	(3.1)
Magnetic resonance imaging whole body (MRI whole body)	35	(0.4)
Unspecified	724	(9.0)

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

Table 2.11 The use of PET scan as a form of staging methods by cancer stage (N=8,054)

	stage 0	stage I	stage IIA	stage IIB	stage III	stage IV	Unstaged	Total
No. (%) of patients used PET scan	44 (5.6%)	215 (9.0%)	399 (18.4%)	323 (30.0%)	639 (51.9%)	187 (79.6%)	90 (51.4%)	1,897 (23.6%)

At diagnosis, the most common cancer stage was stage II (39.7%). Advanced cancer (stages III-IV) constituted to 15.3%. 11.3% of patients were diagnosed with in situ cancer (Figure 2.6).

Out of 12,023 cancer cases, data from 11,034 cases with available pathology data were used for the following analyses on cancer characteristics. 9,536 patients were diagnosed with invasive cancers and 1,492 were diagnosed with in situ cancers. 6 patients were diagnosed with occult primary breast cancers.
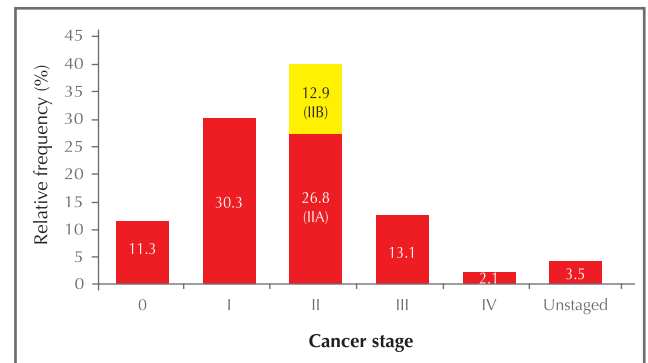

Figure 2.6 Cancer stage at diagnosis of breast cancer patients (N=12,023)

2.2.3 Characteristics of invasive breast cancer

Of the invasive breast cancers, 43.1% had a tumour size of 2.01-5cm, while 37.4% had a tumour size of 1.01-2cm (Figure 2.7). The mean tumour size was 2.2cm with a standard deviation of 1.4 and median of 1.9cm with a range of 0.01-22.0cm. The mean tumour size in self-detected cancers by chance (2.2cm) was significantly larger than those screen-detected cancers (1.3cm) (p<0.001).
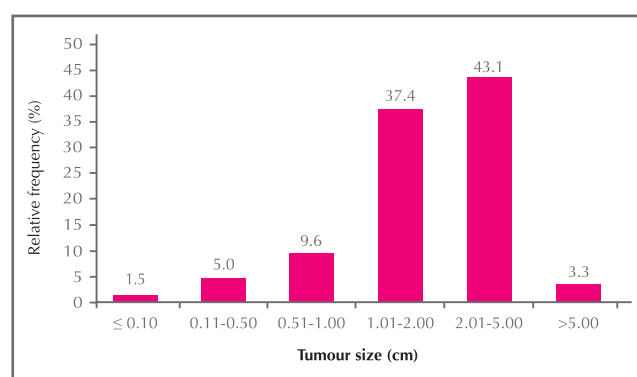

Figure 2.7 Distribution of tumour size (cm) of invasive breast cancers (N=9,081)

60.4% of invasive breast cancers had no positive lymph nodes, while 22.7% had spread to 1-3 lymph nodes. 3.9% had spread to 10 or more lymph nodes. 1.2% of patients had isolated tumour cells (ITC) and 4.2% of patients had micrometastasis (Figure 2.8).
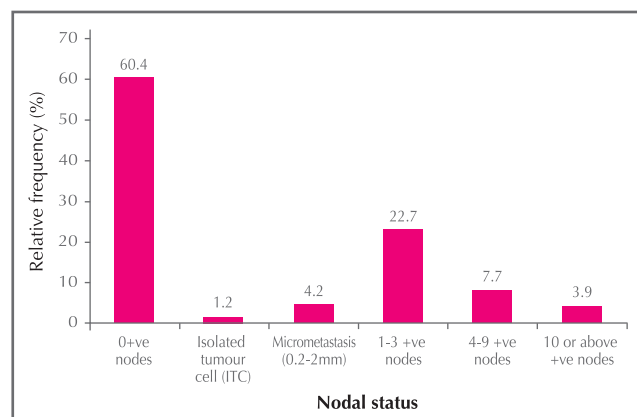

Figure 2.8 Number of positive lymph nodes in invasive breast cancers (N=9,412)

2.2.4 Characteristics of in situ breast cancer

Of the 1,294 patients with in situ breast cancer, 33.7% had tumours of 2.01cm-5.0cm, while 30.4% had tumours of 1.01–2cm in size. 4.1% had tumours larger than 5cm (Figure 2.9). The mean size of in situ breast cancer was 2.0cm with a standard deviation of 1.5cm, and median of 1.6cm. The range in size of in situ breast cancers was 0.02-10.0cm. Of the in situ breast cancers where MMG was performed, 62.5% showed microcalcification by MMG.
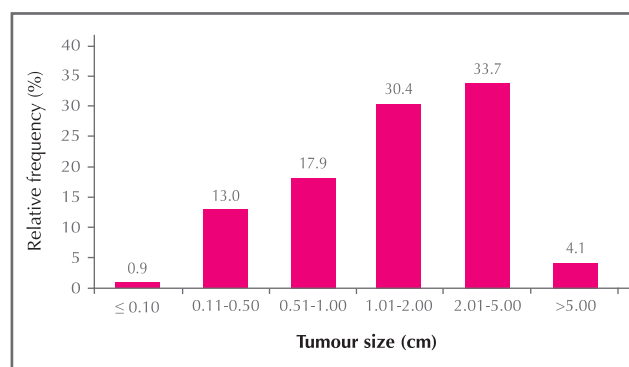

Figure 2.9 Distribution of tumour size (cm) of in situ breast cancers (N=1,294)

2.3 Histological and biological characteristics

After studying the sizes of the breast tumours, histological and biological characteristics of the cancer are studied. The histological and biological characteristics were related to the necessity of certain treatment such as endocrine therapy or targeted therapy, and they are also associated with the prognosis of the disease.

2.3.1 Invasive breast cancer

The histological characteristics, grading and multifocality and multicentricity of invasive breast cancers can be found in Table 2.12.
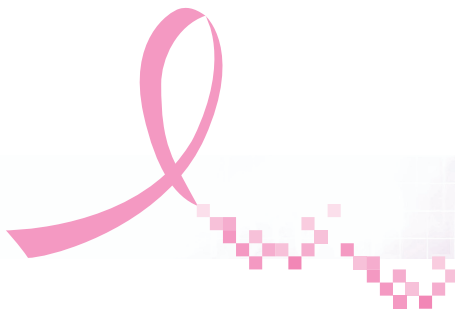
Table 2.12 Histological type, grading, multifocality and multicentricity of invasive breast cancers (N=9,536)

Histological type	Number	(%)
Invasive carcinoma of no specific type	8,074	(84.7)
Mucinous (colloid)	353	(3.7)
Lobular	351	(3.7)
Microinvasive	130	(1.4)
Papillary	89	(0.9)
Tubular	88	(0.9)
Carcinoma with medullary features	59	(0.6)
Mixed ductal and lobular	54	(0.6)
Borderline / malignant phyllodes	40	(0.4)
Micropapillary	31	(0.3)
Metaplastic carcinoma	28	(0.3)
Carcinoma with apocrine features	16	(0.2)
Carcinoma with neuroendocrine features	15	(0.2)
Adenoid cystic carcinoma	9	(0.1)
Cribriform carcinoma	8	(0.1)
Paget's disease of the nipple	5	(0.1)
Inflammatory	3	(0.0)
Secretory carcinoma	2	(0.0)
Lipid rich carcinoma	1	(0.0)
Sarcoma	1	(0.0)
Others	70	(0.7)
Not known	109	(1.1)

Grade	Number	(%)
Grade 1	1,659	(17.4)
Grade 2	3,880	(40.7)
Grade 3	3,169	(33.2)
Not known	828	(8.7)
Lymphovascular invasion	**2,732**	**(28.6)**
Multifocality	**938**	**(9.8)**
Number of foci		
2	504	(53.7)
3-4	176	(18.8)
≥5	100	(10.7)
Not known	158	(16.8)
Multicentricity	**263**	**(2.8)**
Number of quadrants		
2	227	(86.3)
3	16	(6.1)
4	9	(3.4)
Not known	11	(4.2)

Over three-quarters (77.0%) of invasive breast cancers were either ER or PR positive. 20.6% of invasive breast cancers were c-erbB2/HER2 positive (with IHC score 3) and 28.8% were weakly HER2 positive by immunohistochemistry (IHC), of these only 4.2% were positive by FISH/CISH test (Table 2.13).

Table 2.13 Biological characteristics of invasive breast cancers (N=9,536)

	Number	(%)
Estrogen receptor (ER) (96.4% of the patients had the test)		
Positive	7,076	(76.9)
Negative	2,121	(23.1)
Progesterone receptor (PR) (96.1% of the patients had the test)		
Positive	5,941	(64.8)
Negative	3,222	(35.2)
c-erbB2/ HER2 (92.9% of the patients had the test)		
Positive (IHC score 3)	1,830	(20.6)
Weakly positive (IHC score 2)	2,551	(28.8)
FISH / CISH +ve	*106*	*(4.2)*
Negative (IHC score 0/1)	4482	(50.6)
Ki-67 index (51.1% of the patients had the test)		
<14%	2,116	(43.4)
14-49%	2,139	(43.9)
≥50%	619	(12.7)

HER2: Human epidermal growth factor receptor 2

Breast cancer can be divided into different biological subtypes by combining the immunohistochemical (IHC) staining of several biological markers. The five biological subtypes are luminal A, luminal B (HER2 negative), luminal B (HER2 positive), c-erbB2/HER2 positive and triple negative breast cancer[28]. Breast cancer subtypes and their relative frequency by cancer stage can be found in Table 2.14.

Table 2.14 Biological subtypes of invasive tumours by cancer stage (N=8,784)

Biological subtypes	Cancer Stage, N (%)											
	I		IIA		IIB		III		IV		Total	
Luminal A*	918	(27.7)	541	(18.9)	244	(18.2)	146	(12.7)	11	(9.6)	1,860	(21.2)
Luminal B (HER2 negative) #	450	(13.6)	529	(18.4)	247	(18.4)	230	(20.0)	19	(16.7)	1,475	(16.8)
Luminal A/B (HER2 negative) †	944	(28.5)	764	(26.6)	393	(29.3)	330	(28.7)	48	(42.1)	2,479	(28.2)
Luminal B (HER2 positive) ^	403	(12.2)	381	(13.3)	189	(14.1)	201	(17.5)	20	(17.5)	1,194	(13.6)
HER2 Positive ✲	253	(7.6)	226	(7.9)	113	(8.4)	124	(10.8)	10	(8.8)	726	(8.3)
TND §	342	(10.3)	428	(14.9)	155	(11.6)	119	(10.3)	6	(5.3)	1,050	(12.0)
Total	**3,310**	**(37.7)**	**2,869**	**(32.7)**	**1,341**	**(15.3)**	**1,150**	**(13.1)**	**114**	**(1.3)**	**8,784**	**(100.0)**

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

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

† Luminal A/B (HER2 negative): ER and/or PR+, HER2-, and Ki67 not known

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

✲ HER2 positive: ER and PR-, and HER2+

§ TND (Triple Negative Disease): ER-, PR-, and HER2-

2.3.2 In situ breast cancer

The histological typing, grade, multifocality and multicentricity of in situ breast cancers can be found in Table 2.15.

IHC study of biological characteristics of in situ breast cancer showed that 59.1% were either ER or PR positive. 28.9% c-erbB2/HER2 positive, and 32.5% were weakly c-erbB2/HER2 positive and of these only 0.6% were positive by FISH/CISH test (Table 2.16).

Table 2.15 Histological type, grade, multifocality and multicentricity of in situ breast cancers (N=1,492)

	Number	(%)
Histological type		
Ductal	1,364	(91.4)
Lobular	25	(1.7)
Mixed	48	(3.2)
Others	50	(3.4)
Not known	5	(0.3)
Necrosis	**547**	**(36.7)**
Nuclear Grade		
Low	351	(23.5)
Intermediate	492	(33.0)
High	551	(36.9)
Not known	98	(6.6)
Multifocality	**182**	**(12.2)**
Number of foci		
2	87	(47.8)
3	18	(9.9)
4 or more	6	(3.3)
Not known	71	(39.0)
Multicentricity	**32**	**(2.1)**
Number of quadrants		
2	25	(78.1)
3	2	(6.3)
Not known	5	(15.6)

Table 2.16 Biological characteristics of in situ breast cancers (N=1,492)

	Number	(%)
Estrogen receptor (ER) **(72.5% of the patients had the test)**		
Positive	864	(79.9)
Negative	217	(20.1)
Progesterone receptor (PR) **(71.4% of the patients had the test)**		
Positive	758	(71.2)
Negative	307	(28.8)
c-erbB2/ HER2 (67.2% of the patients had the test)		
Positive (IHC Score 3)	290	(28.9)
Weakly positive (IHC Score 2)	326	(32.5)
FISH / CISH +ve	*2*	*(0.6)*
Negative (IHC Score 0 / 1)	386	(38.5)
Ki-67 index (44.9% of the patients had the test)		
<14%	481	(71.8)
14-49%	171	(25.5)
≥50%	18	(2.7)

2.4 Treatment methods

Of the patients, 17.1% solely used private medical facilities while 48.9% solely used public medical facilities, 34.0% used a mix of both private and public medical facilities.

2.4.1 Surgical treatment

Almost all (98.3%, N=11,820) patients underwent surgery as part of their treatment. 52.9% of the patients had surgery at private medical facilities, while 47.1% had surgery at public medical facilities.

63.1% had mastectomy, while 35.1% had breast-conserving surgery. Of the patients that had mastectomy, 93.3% had total mastectomy while 5.5% had skin-sparing mastectomy and 0.8% had nipple-sparing mastectomy. Of the patients who had reconstruction, 65.6% of patients had TRAM flap reconstruction surgery, while 19.5% had breast implants.

Sentinel node biopsy (SNB) was conducted in 34.3% of patients, while axillary dissection (AD) was conducted in 48.5% of patients. Only 16.3% of patients had both SNB and AD (Table 2.17).

Table 2.17 Types of surgical operations in the patient cohort (N=12,023)

	Number	(%)
No surgery	174	(1.4)
Breast-conserving surgery	4,217	(35.1)
Mastectomy	7,582	(63.1)
Nodal surgery only	5	(0.0)
Type of surgery not known	16	(0.1)
Not known if surgery done	29	(0.2)
Mastectomy (N=7,582)		
Total mastectomy	7,077	(93.3)
Skin-sparing	418	(5.5)
Nipple-sparing	57	(0.8)
Areolar-sparing	12	(0.2)
Not known	18	(0.2)
Reconstruction (N=1,066)		
TRAM flap	699	(65.6)
Implant	208	(19.5)
LD flap	78	(7.3)
LD flap & implant	64	(6.0)
Not known	17	(1.6)
Nodal surgery (N=11,034)		
Sentinel node biopsy	3,785	(34.3)
Axillary dissection	5,356	(48.5)
Sentinel node biopsy & axillary dissection	1,803	(16.3)
Not known	90	(0.8)

The percentage of patients that underwent mastectomy was positively correlated with increasing age, while the percentage of patients that underwent mastectomy and reconstruction or breast-conserving surgery was negatively correlated with increasing age (Figure 2.10).
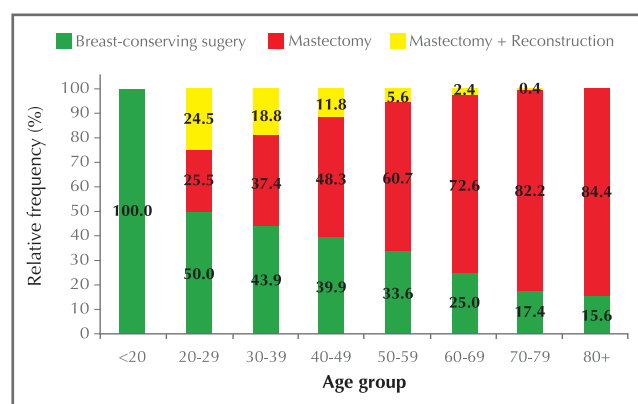

Figure 2.10 Type of surgery by age group (N=11,447)

For tumours larger than 1cm in size, there was a positive correlation between increasing tumour size and increased mastectomy and mastectomy and reconstruction, and a negative correlation with breast conserving surgery and increasing tumour size (Figure 2.11).
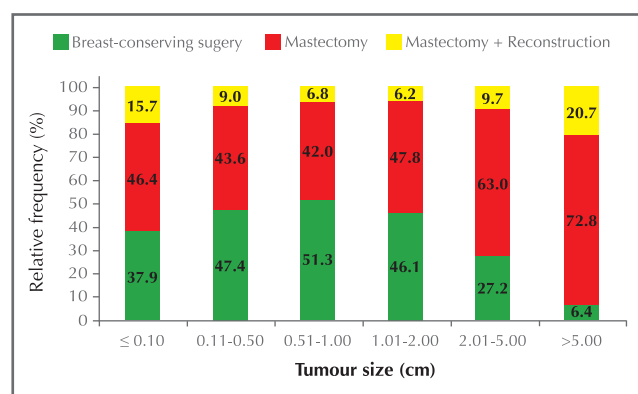
Figure 2.11 Type of surgery by tumour size (N=10,412)

Reduced use of breast-conserving surgery was observed with increasing cancer stage, while increased use of mastectomy was observed with increasing cancer stage (Figure 2.12).
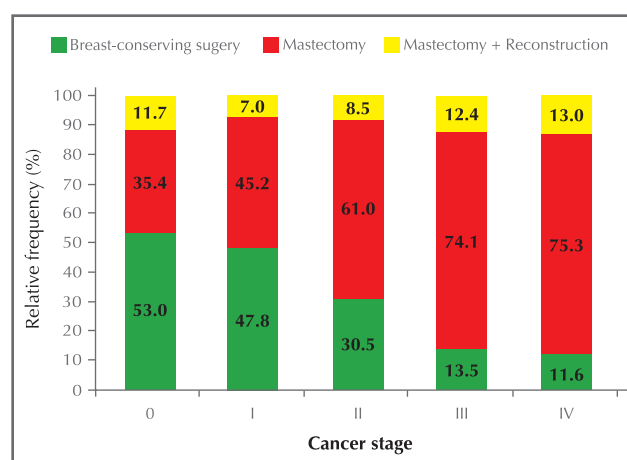
Figure 2.12 Type of surgery by cancer stage (N=11,457)

More breast-conserving surgery and mastectomy with reconstruction was conducted in patients in the private health care sector (44.8% and 9.6% respectively) than in the public health care sector (26.2% and 8.7% respectively) (Figure 2.13). More mastectomies were conducted in the public sector (65.1%) than the private sector (45.6%).
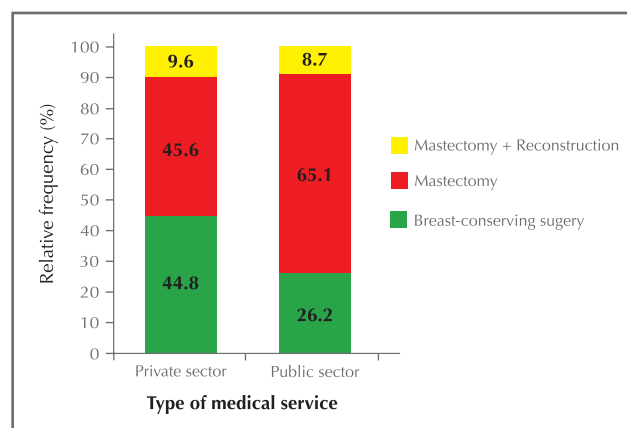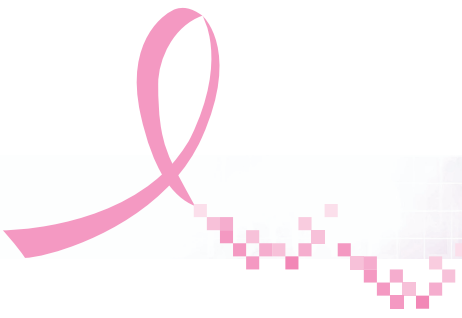

Figure 2.13 Type of surgery by type of medical service (N=11,376)

AD was conducted in 43.4% of patients with negative clinical nodal status, while SNB was conducted in 9.4% of patients with positive clinical nodal status (Figure 2.14). This data suggested the need for increased use of SNB in Hong Kong.
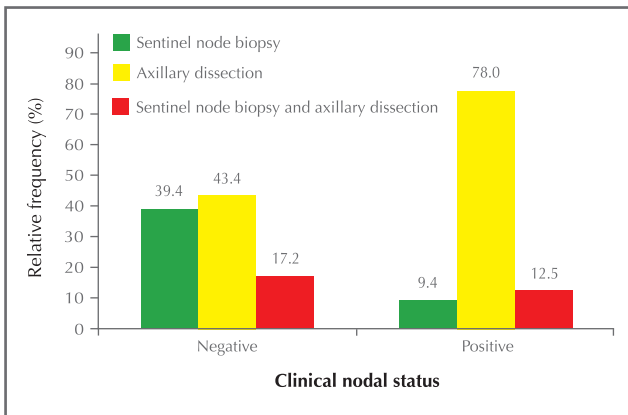
56.2% of patients with node positive invasive cancer had tumours of 2.01-5.0cm in size. 41.6% of patients with node negative breast cancers had tumours of 1.01-2.0cm in size (Figure 2.16).
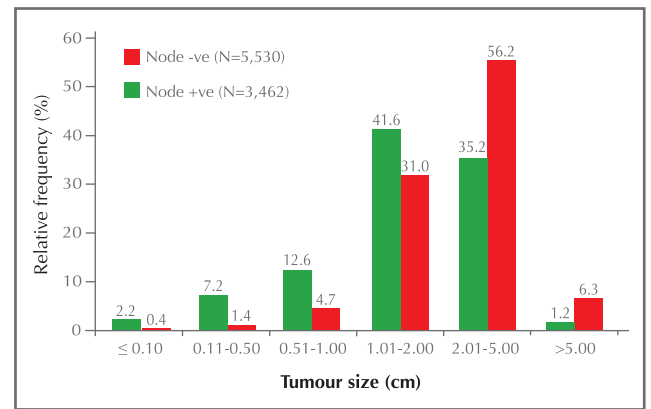

Figure 2.14 Type of nodal surgery by clinical nodal status (N=10,944)

Figure 2.16 Distribution of tumour size in invasive cancer with negative or positive nodal status (N=8,992)

The use of AD was positively correlated with increasing cancer stage, while the use of SNB was negatively correlated with increasing cancer stage (Figure 2.15).

Figure 2.15 Type of nodal surgery in invasive cancer by cancer stage (N=9,821)

97.5% of patients that underwent SNB had no positive nodes, while 50.2% of patients that underwent AD had at least 1 positive node. 70.9% of patients that had both SNB and AD had at least 1 positive node (Figure 2.17).
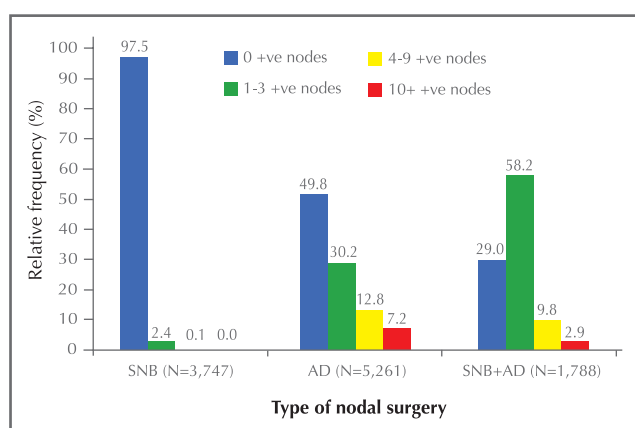

Figure 2.17 Number of positive nodes by type of nodal surgery (N=10,796)

SNB: Sentinel node biopsy; AD: Axillary dissection

2.4.2 Chemotherapy

Chemotherapy is a form of systemic treatment for micro- and macro-metastasis through the use of one or more cytotoxic drugs. 7,274 (60.5%) patients in the cohort underwent chemotherapy. 89.1% had adjuvant chemotherapy while 8.9% had neoadjuvant chemotherapy and 2.0% were treated with palliative chemotherapy. 84.8% of patients had chemotherapy in public medical facilities, while 15.2% of patients had chemotherapy in private medical facilities.

With the exception of stage IV breast cancer, the use of chemotherapy was correlated to increasing cancer stage (Figure 2.18). The lowered rate of chemotherapy use observed in stage IV patients might be due to the usual clinical practice that for those ER positive stage IV patients, palliative treatments consisting of hormonal therapy +/- radiotherapy, but not chemotherapy would be given.
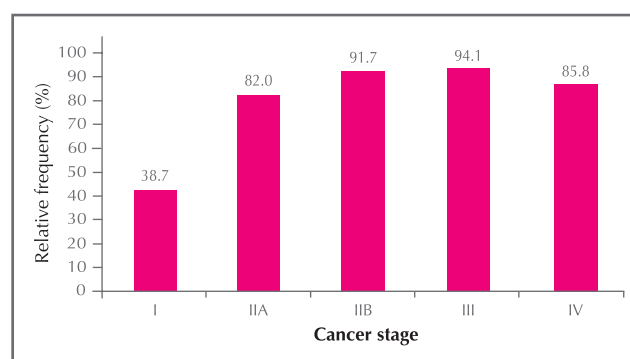

Figure 2.18 Chemotherapy treatment in patients at different cancer stages (N=10,111)

36.4% of stage I breast cancer patients aged 20-29 did not receive chemotherapy as part of their treatment, compared to 77.4% of patients aged 60-69 with stage I breast cancer did not receive chemotherapy. The use of chemotherapy in stage I breast cancer was negatively correlated with increasing age group. The chemotherapy in patients with stage IIA disease was highest for patients aged 20-29 (92.3%) and 40-49 (90.3%), use of chemotherapy was reduced in age groups of 50 and above (Table 2.18).

91.7% of patients with stage IIB disease had chemotherapy. The use of chemotherapy in stage IIB patients was also negatively correlated with increasing age.

Table 2.18 Rate of chemotherapy by age group and cancer stage at diagnosis (N=10,343)

| Age group | Number of patients received chemotherapy (% of patients in the same age group and cancer stage) | | | | | | | | | |
	stage I		stage IIA		stage IIB		stage III		stage IV	
<20	2	(100.0)	_*		_*		_*		_*	
20-29	21	(63.6)	24	(92.3)	16	(100.0)	8	(88.9)	2	(100.0)
30-39	197	(51.8)	327	(89.1)	157	(97.5)	153	(99.4)	17	(94.4)
40-49	623	(44.0)	1,037	(90.3)	545	(97.0)	579	(98.3)	83	(96.5)
50-59	403	(37.2)	846	(85.7)	455	(95.0)	471	(95.7)	82	(84.5)
60-69	95	(22.6)	275	(66.6)	195	(89.4)	202	(92.7)	18	(75.0)
70-79	1	(0.7)	19	(12.8)	11	(16.2)	23	(37.7)	4	(33.3)
80+	0	(0.0)	1	(3.3)	0	(0.0)	1	(5.0)	1	(20.0)

*No patient diagnosed with stages IIA, IIB, III and IV was aged <20.

The most widely used chemotherapy regimen in stage I patients was a combination of Adriamycin / Doxorubicin and Cyclophosphamide (AC), while in stage II or III, the most widely used was AC and Taxane. For stage IV patients, the most commonly used chemotherapy was a combination of 5FU, Adriamycin / Doxorubicin and Cyclophosphamide or 5FU, Epirubicin and Cyclophosphamide (Figure 2.19).

Of the patients that underwent chemotherapy, 953 (13.1%) of patients also received targeted therapy.
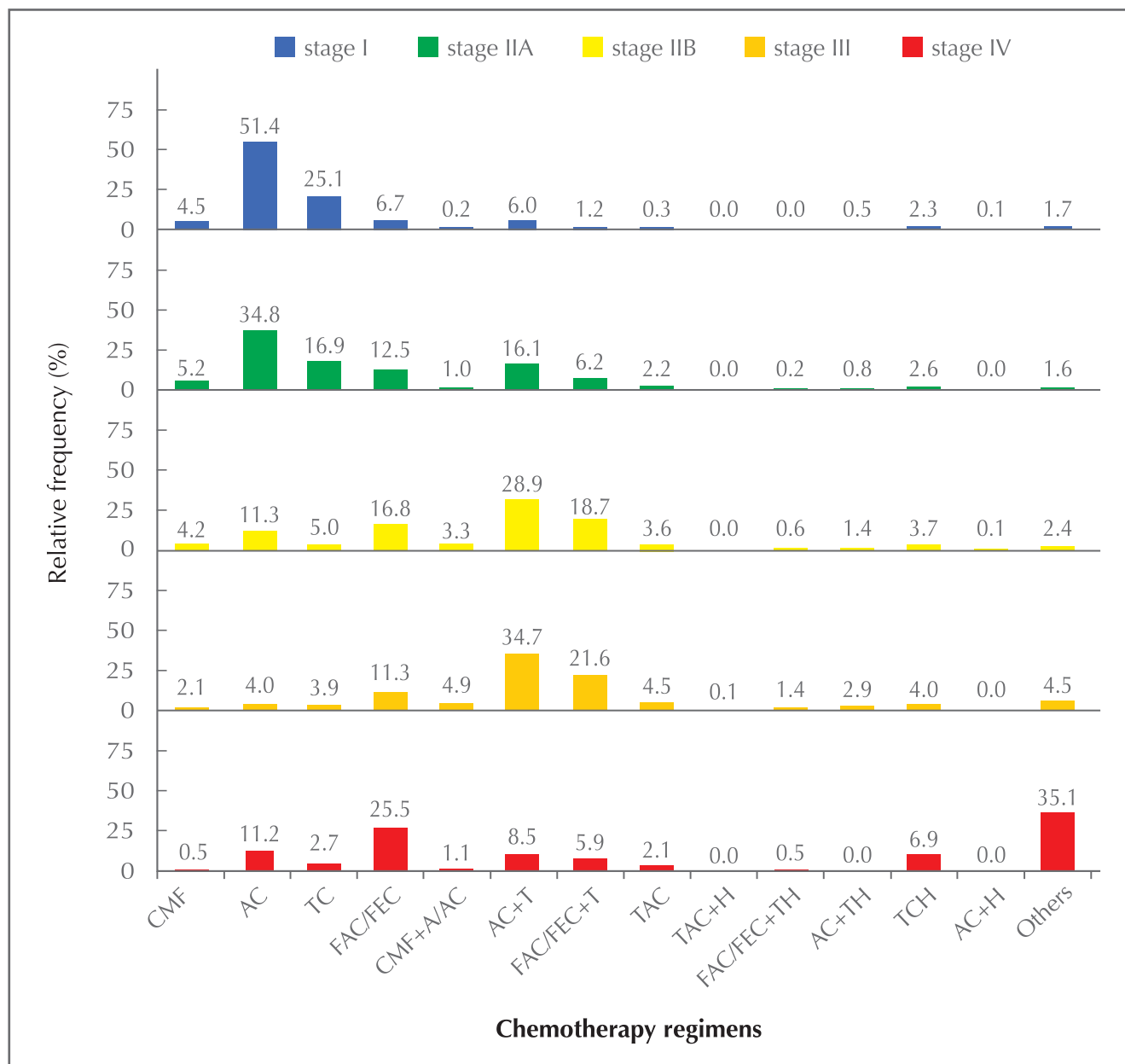
Figure 2.19 Type of chemotherapy regimens in patients by cancer stage (N=6,536)

C: Cyclophosphamide; T: Taxane (Docetaxel in TC and TAC, Paclitaxel or Docetaxel in AC+T);
M: Methotrexate; H: Trastuzumab;
F: 5FU; TCH: Docetaxel / Carboplatin / Trastuzumab or Paclitaxel / Carboplatin / Trastuzumab
A: Adriamycin / Doxorubicin; Others: Capecitabine, Gemcitabine or Vinorelbine
E: Epirubicin;
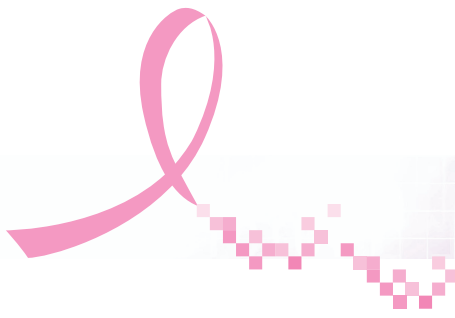
2.4.3 Radiotherapy

Radiotherapy uses ionizing radiation to treat cancer cells in the body. 7,474 (62.2%) of patients had radiotherapy as part of their treatment. Among them, 98.2% were adjuvant, 0.1% were neoadjuvant, and 1.7% were palliative. Of these patients, 85.7% of the patient cohort had radiotherapy at public health care facilities, and 14.3% had radiotherapy at private health care facilities.

Of the patients who had breast-conserving surgery, 93.2% underwent radiotherapy, while 45.7% of patients who had mastectomy underwent radiotherapy.
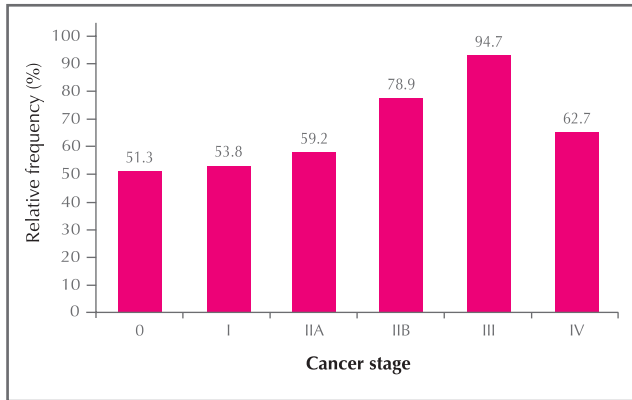

Figure 2.20   Radiotherapy rate in patients at different cancer stages (N=11,364)

Of the patients who underwent mastectomy and radiotherapy, majority (88.9%) of them were patients with stages IIA to III disease (Figure 2.21).
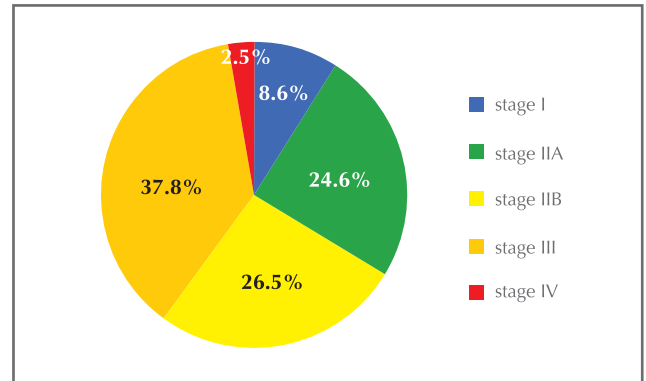

Figure 2.21   Distribution of cancer stages in patients treated with mastectomy and radiotherapy (N=3,321)

Radiotherapy for breast cancer involves localized irradiation of regions such as breast/chest wall, with or without regional nodes. For those with available radiotherapy details, around two-thirds (68.6%) of the patients who underwent mastectomy also received radiotherapy to chest wall and regional nodes while 84.3% of the patients who underwent breast-conserving surgery received radiotherapy to the breast only (Table 2.19).

Table 2.19 Irradiated regions among the patients receiving radiotherapy (N=7,474)

	Total (N=7,474)	Breast-conserving Surgery (N=3,931)	Mastectomy (N=3,463)
Target volume	Number (%)	Number (%)	Number (%)
Breast	2,108 (28.2)	2,088 (53.1)	0 (0.0)
Breast + regional*	411 (5.5)	390 (9.9)	0 (0.0)
Chest wall	788 (10.5)	0 (0.0)	785 (22.7)
Chest wall + regional*	1,715 (22.9)	0 (0.0)	1,715 (49.5)
Unspecified	2,452 (32.8)	1,453 (37.0)	963 (27.8)

SCF: Supraclavicular fossa; IMC: Internal mammary chain;
* regional nodes: includes axilla and/or IMC and/or SCF

2.4.4 Endocrine therapy

Breast cancers that are hormone receptor positive can be treated using endocrine therapy. 8,020 (66.7%) patients had endocrine therapy. Among them, 97.1% were adjuvant, 0.4% were neoadjuvant, and 2.5% were palliative. 87.1% of patients had endocrine therapy in public health care facilities while 12.9% had endocrine therapy in private health care facilities. Endocrine therapy was used in over 74.1% of patients with stages I-IV breast cancer, but was only used in 17.7% of patients with stage 0 breast cancer (Figure 2.22).
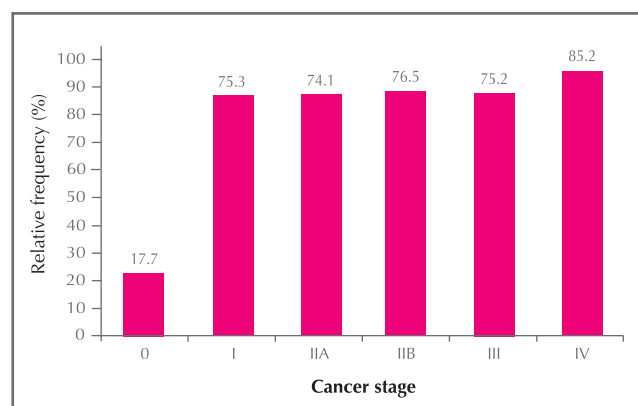
Tamoxifen (TMX) and Aromatase Inhibitor (AI) are widely used endocrine therapy drugs. TMX blocks estrogen receptors on cells while AI lowers estrogen levels in the body. The use of TMX was negatively correlated with increasing age, while the use of AI was positively correlated with increasing age (Figure 2.23).
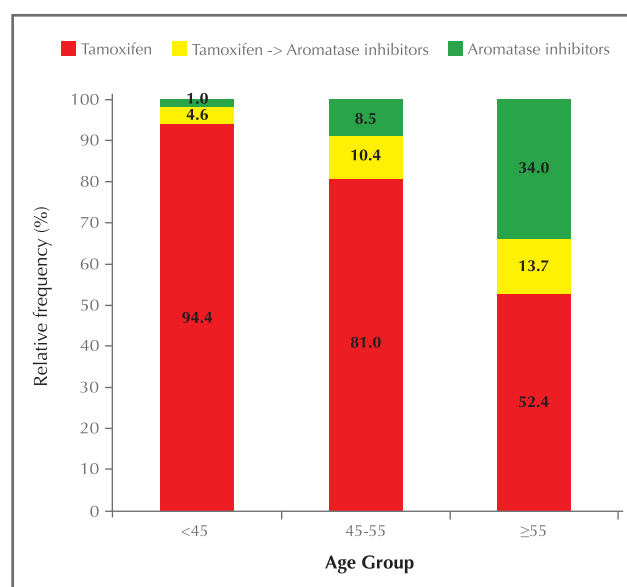

Figure 2.22 Endocrine therapy rates in patients by cancer stage (N=11,405)

Figure 2.23 Forms of endocrine therapy used in patients by age group (N=7,376)

2.4.5 Targeted therapy

Targeted therapy is sometimes used in the treatment of breast cancer, which functions by blocking specific molecules required for tumour growth or carcinogenesis. Of the patient cohort, 967 (8.0%) had targeted therapy. Among them, 93.0% were adjuvant, 4.0% were neoadjuvant, and 3.0% were palliative. 86.0% of patients had targeted therapy in public health care facilities, while 14.0% had targeted therapy in private health care facilities.

The use of targeted therapy was positively correlated with increasing cancer stage (Figure. 2.24). The most commonly used targeted therapy drug was Trastuzumab (94.7%), which is used to treat HER2 positive cancers (Fig 2.25).
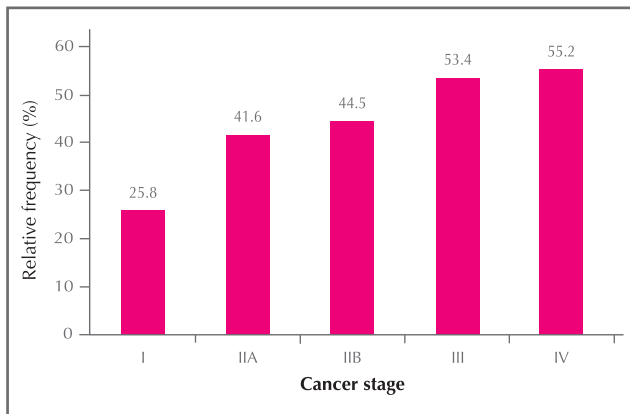

Figure 2.24 Targeted therapy rate in the HER2 positive patients by cancer stage (N=1,865)
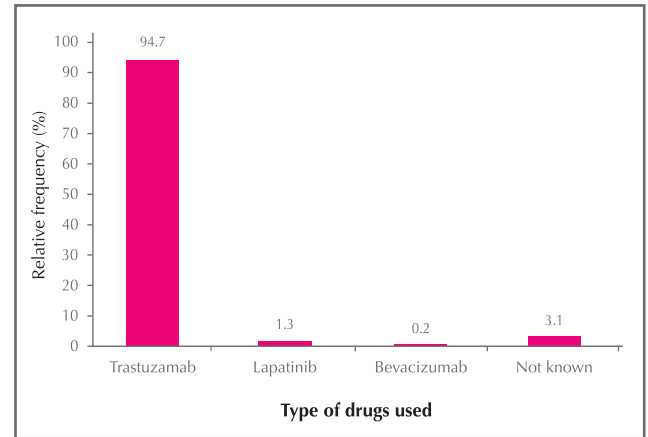
Figure 2.25 Type of drugs used for targeted therapy in patients (N=967)

2.4.6 Complementary and alternative therapies

Complementary and alternative treatments were used by 4,797 (39.9%) patients. Among them, 95.5% were adjuvant, 3.9% were neoadjuvant, and 0.7% were palliative. 89.2% of patients who used complementary or alternative therapy used Chinese medicine, while 53.1% used health foods and supplements (Figure 2.26).

Figure 2.26 Type of complementary and alternative therapies used in 4,797 patients

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

2.4.7 Multimodality treatment

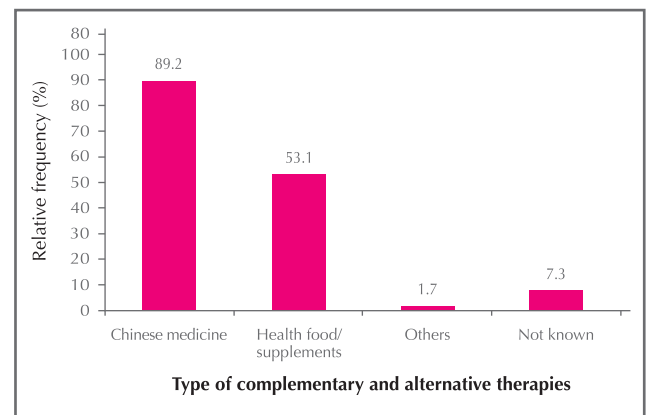A combination of treatments is usually used for treating breast cancer. The multimodality treatment pattern of the patient cohort is studied here and is shown in Table 2.20. As complementary and alternative therapies are not a standard of care among breast cancer patients in Hong Kong, it is excluded in this part of analysis. Most patients with stage 0 breast cancer received one (41.3%) or two (49.4%) treatments mentioned in this chapter. 42.1% of

stage I and 40.3% of stage IIA patients had a combination of three treatments.

Around half of the patients with stage IIB (54.0%) and 62.6% of stage III patients had four treatments. However, around one-third of patients (36.1%) with stage IV breast cancer had a combination of three treatments.

Table 2.20 Number of treatments received by patients by cancer stages (N=11,606)

No. of treatment	Cancer stage, Number (%)						
	0 (N=1,363)	I (N=3,639)	IIA (N=3,220)	IIB (1,556)	III (N=1,576)	IV (N=252)	Total (N=11,606)
0	3 (0.2)	1 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	5 (2.0)	11 (0.1)
1	563 (41.3)	269 (7.4)	90 (2.8)	19 (1.2)	24 (1.5)	16 (6.3)	981 (8.5)
2	674 (49.4)	1,232 (33.9)	532 (16.5)	120 (7.7)	61 (3.9)	47 (18.7)	2,666 (23.0)
3	123 (9.0)	1,531 (42.1)	1,299 (40.3)	493 (31.7)	347 (22.0)	91 (36.1)	3,884 (33.5)
4	0 (0.0)	554 (15.2)	1,218 (37.8)	841 (54.0)	987 (62.6)	82 (32.5)	3,682 (31.7)
5	0 (0.0)	52 (1.4)	81 (2.5)	83 (5.3)	155 (9.8)	11 (4.4)	382 (3.3)

2.5 Patient status

Once treatment is completed, follow-up is done to ensure the efficacy of the treatment. To date, 46.8% of the patient cohort had the last follow-up data within the last 2 years. Of the patients, 35.4% of patients were followed up for 2-5 years, and 28.7% of patients were followed up for 5-10 years. Only 8.3% of patients were followed up for less than a year (Table 2.21). The mean follow-up period was 4.9 years and median follow-up period was 4 years.

679 (6.4%) of the patient cohort experienced recurrence, where 2.7% of the cases experienced locoregional recurrence solely, 2.5% experienced distant recurrence solely and 1.2% experienced both locoregional and distant recurrence at the same time. The mean and median recurrence time are shown in Table 2.21.

Table 2.21 Follow-up of 10,606 patients

Follow-up period	Number	(%)
< 1 year	878	(8.3)
1-2 years	1,817	(17.1)
2-5 years	3,757	(35.4)
5-10 years	3,046	(28.7)
10-15 years	810	(7.6)
>15 years	298	(2.8)
Mean follow-up period		4.9 years
Median follow-up period		4.0 years
Locoregional recurrence solely		
No. of locoregional recurrences	288	(2.7%)
Mean time to locoregional recurrence		5.5 years
Median time to locoregional recurrence		3.7 years
Distant recurrence solely		
No. of distant recurrences	266	(2.5%)
Mean time to distant recurrence		4.3 years
Median time to distant recurrence		3.4 years
Locoregional and distant recurrence		
No. of locoregional and distant recurrences	125	(1.2%)
Mean time to locoregional and distant recurrence		5.2 years
Median time to locoregional and distant recurrence		4.0 years
Mortality		
No. of deaths from breast cancer	70	(0.7%)
No. of deaths from unrelated causes	40	(0.4%)

Table 2.22 shows the number of cases with locoregional recurrence among patients with invasive breast cancer in different subgroups specified by surgery type and cancer stage. Similar rates of locoregional recurrence were observed in stages I and IIA patients. For stage IIB patients, the rate of locoregional recurrence was higher among patients with mastectomy than those received breast conserving surgery. However, higher rates of locoregional recurrence in patients with breast-conserving surgery than those with mastectomy were observed in stage III patients. The common sites for locoregional recurrence was breast (36.3%) or chest wall (30.8%) (Table 2.23).

Table 2.22 Number (%) of cases with locoregional recurrence among patients with invasive breast cancers in different subgroups specified by surgery type and cancer stage

| | Cancer stage, Number (% in the overall patient cohort with surgeries) | | | | |
	I	IIA	IIB	III	Total
BCS	43/1,549 (2.8%)	35/988 (3.5%)	8/297 (2.7%)	11/184 (6.0%)	97/3,018 (3.2%)
MTX	50/1,669 (3.0%)	64/1,891 (3.4%)	44/1,104 (4.0%)	63/1,196 (5.3%)	221/5,860 (3.8%)

BCS: breast-conserving surgery; MTX: mastectomy

Table 2.23 Sites involved in locoregional recurrence in patients (N=413)

Locoregional recurrence sites involved	N	(%)
Breast	150	(36.3)
Chest wall	127	(30.8)
Axilla	84	(20.3)
Supraclavicular	77	(18.6)
Internal mammary node	22	(5.3)
Not specified	40	(9.7)

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

The rate of locoregional recurrence solely was quite static (around 2%) among patients with invasive breast cancer across different cancer stages. The rate of distant recurrence solely was low across different cancer stages. The rate of locoregional and distant recurrence occurring at the same time was positively correlated with increasing cancer stage, from 0.4% in stage I patients to 3.0% in stage III patients.

The most common organ involved in distant recurrence was bone (52.9%), followed by lung (39.4%) (Table 2.25).

Table 2.24 Number (%) of locoregional and distant recurrence cases in patients with invasive breast cancer by cancer stage

| | Cancer stage, Number (%) | | | | |
Recurrence	I (N=3,221)	IIA (N=2,888)	IIB (N=1,405)	III (N=1,389)	Total (N=8,903)
Locoregional solely	81 (2.5%)	67 (2.3%)	23 (1.6%)	33 (2.4%)	204 (2.3%)
Distant solely	4 (0.1%)	4 (0.1%)	2 (0.1%)	8 (0.6%)	18 (0.2%)
Locoregional and distant	12 (0.4%)	33 (1.1%)	29 (2.1%)	41 (3.0%)	115 (1.3%)

The percentage of breast cancer specific deaths was highest in patients with stage III breast cancer (5.5%). Survival time ranged from 0.8-21.9 years. Information on biological subtypes of these patients can be found in Table 2.26.

Table 2.25 Organs involved in distant metastasis (N=391)

Distant organs affected	Number	(%)	Distant organs affected	Number	(%)
Bone	207	(52.9)	Adrenal	7	(1.8)
Lung	154	(39.4)	Thyroid glands	6	(1.5)
Liver	107	(27.4)	Ovary	4	(1.0)
Mediastinal nodes	68	(17.4)	Uterus	4	(1.0)
Neck	42	(10.7)	Pancreas	3	(0.8)
Brain	34	(8.7)	Spleen	2	(0.5)
Abdomen	10	(2.6)	Kidney	1	(0.3)
Contralateral nodal metastases	9	(2.3)	Unspecified	10	(2.6)

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

Table 2.26 Characteristics of breast cancer-specific deaths (N=70)

	Cancer stage at first diagnosis						
	0	I	IIA	IIB	III	IV	Unstaged
No. of cases (% of deaths in that cancer stage)	1 (0.1)	10 (0.3)	11 (0.4)	3 (0.2)	31 (2.2)	11 (5.5)	3 (0.9)
Survival time (range in years)	4.5	1.8 – 10.4	1.9 – 20.6	6.7 – 8.8	0.8 – 9.0	1.2 – 10.3	3.4 – 21.9
Biological subtypes							
Luminal A*	0	0	1	1	6	0	0
Luminal B (HER2 negative)#	0	2	2	0	5	0	0
Luminal A/B (HER2 negative)†	0	2	3	1	6	7	0
Luminal B (HER2 positive)^	1	1	1	1	6	1	1
HER2 Positive ✳	0	2	0	0	5	1	0
TND§	0	3	1	0	2	1	0
Not known	0	0	3	0	1	1	2

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

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

† Luminal A/B (HER2 negative):ER and/or PR+, HER2-, and Ki67 not known

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

✳ HER2 positive: ER and PR-, and HER2+

§ TND (Triple Negative Disease): ER-, PR-, and HER2-