CHAPTER 2

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

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The clinical management of breast cancer and cancer characteristics in Hong Kong provide an important source of information for understanding the current state of treatment of breast cancer and identifying potential areas of concern for the local community. In this chapter, clinical presentation, cancer characteristics, and treatment methods are studied using data collected from 9,594 breast cancer cases.

KEY FINDINGS

Clinical presentations

- In the patient cohort, 84.9% of patients self-discovered their breast cancer by chance.
- 81.3% were diagnosed at early stage breast cancer (0-II), while 14.4% were diagnosed at advanced stage breast cancer (III-IV).
- The number of patients that detected their breast cancer by recommended screening methods (breast self-examination, clinical breast examination, mammography screening, and breast ultrasound screening) was lower in public and mixed private/public health care patients than private health care patients.
- The most common presenting symptom was painless lump (92.2%).
- 21.9% of patients took longer than 3 months to seek first medical consultation, and 3.2% of patients took longer than 1 year.
- Mammography screening was used in 81% of patients, while breast ultrasound screening was used in 74.2%, and magnetic resonance imaging was used in 6.6% of patients for diagnosis. Of the patients diagnosed by mammography screening the most common finding was opacity (56.7%) and microcalcification (50.6%).
- To confirm malignancy, fine needle aspiration was used in 46.6% of patients, core needle biopsy in 48.6% of patients, and excisional biopsy in 15.3% of patients.
- For cancers staging, chest X-ray and abdominal ultrasound were used by 77.3% of patients, and positron emission tomography scan was used by 22.5% of patients.
- Mean invasive breast cancer tumour size was 2.18±1.41cm. Invasive self-detected cancers by chance (mean size: 2.3cm) was significantly larger than screen-detected cancers (mean size: 1.3cm) ($p<0.001$).
- Of the invasive breast cancers, 77.1% were ER+, 64.8% were PR+, and 21.9% were c-erbB2/HER2+.
- The mean size of in situ breast cancers was 2.05±1.54cm.
- Of the in situ breast cancer patients, 79.4% were ER+, 70% were PR+, and 29.4% were c-erbB2/HER2+.

Treatment

- Generally a combination of treatments was required, the number of combined treatments increased with increasing cancer stage.
- 62.4% underwent mastectomy, while 35.7% of patients had breast conserving surgery. 14.8% of mastectomy patients had breast reconstruction surgery.
- Sentinel node biopsy was used in 33.8% of patients, and 49.2% had axillary dissection. Only 16.6% of patients had axillary dissection after sentinel node biopsy.
- 60.8% of patients in the cohort had chemotherapy.
- 61.7% of patients had radiotherapy.
- 66.7% of patients had endocrine therapy.
- 7.2% of patients had targeted therapy.
- 37.9% of patients had complementary and alternative therapies.
- Average patient follow-up period was 4.7 years.
- Locoregional recurrence occurred in 3.8% of patients at an average of 5.3 years after treatment.
- Distant recurrence occurred in 3.5% of patients at an average of 4.6 years after treatment.
- The most frequent organ involved in distant metastasis was bone (54.3%), followed by lung (42.8%).

2.1 Clinical presentation

Self-detection by chance was the most common method of detection (84.9%) (Figure 2.1). A 2013 study of breast cancer screening practices among Hong Kong Chinese women found that 70-90% of female respondents had heard of BSE, CBE and MMG. Despite this about half or less practiced regular screening[20]. The overall detection of cancer by screening methods (BSE, CBE, MMG, and USG) was low in Hong Kong.

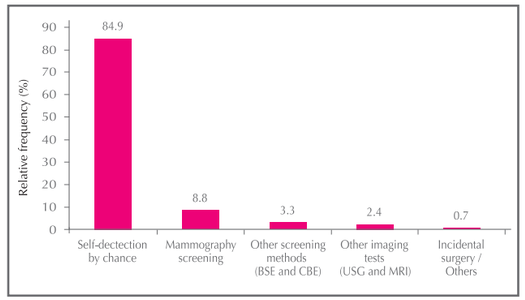

Figure 2.1 Mode of first breast cancer detection in the patient cohort (N=8,811)

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

The proportions of patients that had breast cancer detected via screening methods was lower in public and mixed private/public health care patients than private health care patients. 13.0% of breast cancers were detected by mammogram in private health care patients in comparison to 9.1% and 6.6% in public and mixed private/public health care patients respectively (Table 2.1). This difference highlighted the need for increased mammography screening in public health care facilities. Around one-third (30.4%) of in situ cancers were found by mammography screening, while only 5.7% of invasive cancers were found by mammography screening (Table 2.2). The mode of first detection of breast cancer by cancer stage is shown in Table 2.3, showing that higher proportions of stages 0 or I cancers (29.7% and 10.6% respectively) were detected by mammography screening compared to that in stages III or IV cancers (3.0% and 1.7% respectively) (Table 2.3).

The most common presenting symptom within the patient cohort was a painless lump (92.2%) (Figure 2.2).

Table 2.1 Mode of first breast cancer detection by type of medical service received at diagnosis (N=8,811)

	Private medical service users (N=1,717)		Public medical service users (N=3,446)		Mixed private / public medical service users (N=3,648)	
Mode of first breast cancer detection	**Number**	**(%)**	**Number**	**(%)**	**Number**	**(%)**
Self-detection by chance	1,313	(76.5)	2,991	(86.8)	3,174	(87.0)
Mammography screening	223	(13.0)	312	(9.1)	240	(6.6)
Other screening methods (BSE and CBE)	76	(4.4)	77	(2.2)	136	(3.7)
Other imaging tests (USG and MRI)	91	(5.3)	45	(1.3)	74	(2.0)
Incidental surgery / Others	14	(0.8)	21	(0.6)	24	(0.7)

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

Table 2.2 Mode of first breast cancer detection by type of cancer (N=8,589)

	Type of cancer, Number (%)			
Mode of first breast cancer detection	**In situ (N=1,127)**		**Invasive (N=7,462)**	
Self-detection by chance	675	(59.9)	6,599	(88.4)
Mammography screening	343	(30.4)	429	(5.7)
Other screening methods (BSE and CBE)	39	(3.5)	241	(3.2)
Other imaging tests (USG and MRI)	59	(5.2)	149	(2.0)
Incidental surgery / Others	11	(1.0)	44	(0.6)

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

Table 2.3 Mode of first breast cancer detection by cancer stage (N=8,487)

	Cancer stage, Number (%)											
Mode of first breast cancer detection	**0 (N=1,017)**		**I (N=2,674)**		**IIA (N=2,397)**		**IIB (N=1,108)**		**III (N=1,111)**		**IV (N=180)**	
Self-detection by chance	626	(61.6)	2,161	(80.8)	2,152	(89.8)	1,040	(93.9)	1,043	(93.9)	167	(92.8)
Mammography screening	302	(29.7)	284	(10.6)	113	(4.7)	26	(2.3)	33	(3.0)	3	(1.7)
Other screening methods (BSE and CBE)	37	(3.6)	107	(4.0)	83	(3.5)	22	(2.0)	24	(2.2)	6	(3.3)
Other imaging tests (USG and MRI)	46	(4.5)	102	(3.8)	34	(1.4)	15	(1.4)	7	(0.6)	3	(1.7)
Incidental surgery / Others	6	(0.6)	20	(0.7)	15	(0.6)	5	(0.5)	4	(0.4)	1	(0.6)

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

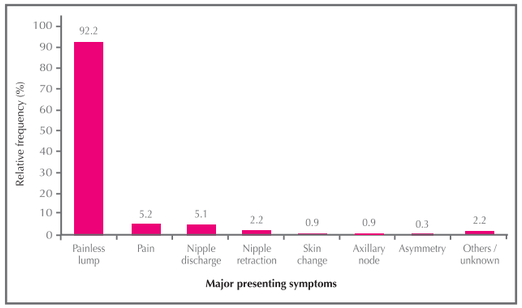

Figure 2.2 Major presenting symptoms of self-detected breast cancers (N=7,478)

2.1.1 Duration from onset of symptoms to first medical consultation

After onset of symptoms, only 11.1% of patients sought medical consultation within one month. 10.8% of patients took one to three months to seek medical consultation, and 3.2% of patients took longer than one year to seek medical help (Table 2.4).

A 2009 qualitative study on Chinese women in Hong Kong found that patients with painless lump and atypical symptoms delayed their medical consultation until the symptom intensified or until they discussed this with someone who had experienced breast cancer. The key barriers to timely medical consultation were cost, lack of access, time and embarassment[21].

Table 2.4 Duration from onset of symptoms to first medical consultation for patients who self-detected* their cancers (N=7,478)

	Number	**(%)**
Less than 1 month	829	(11.1)
1-3 months	808	(10.8)
4-12 months	283	(3.8)
More than 12 months	242	(3.2)
Unknown	5,316	(71.1)

*self-detection by chance only

More private health care patients (23.9%) sought first medical consultation within one month of symptom onset than public (3.9%) or mixed (12.5%) health care patients (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=7,478)

	Private medical service users (N=1,313)		Public medical service users (N=2,991)		Mixed private / public medical service users (N=3,174)	
	Number	(%)	Number	(%)	Number	(%)
Less than 1 month	314	(23.9)	118	(3.9)	397	(12.5)
1-3 months	230	(17.5)	171	(5.7)	407	(12.8)
4-12 months	90	(6.9)	62	(2.1)	131	(4.1)
More than 12 months	64	(4.9)	66	(2.2)	112	(3.5)
Unknown	615	(46.8)	2,574	(71.4)	2,127	(67.0)

21.0% of patients diagnosed with stage IV breast cancer took over 4 months to seek first medical consultation, in contrast to 5.9% of patients diagnosed with stage I disease (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=6,563)

	Cancer stage, Number (%)									
	Stage I (N=2,161)		Stage IIA (N=2,152)		Stage IIB (N=1,040)		Stage III (N=1,043)		Stage IV (N=167)	
Less than 1 month	271	(12.5)	258	(12.0)	103	(9.9)	89	(8.5)	14	(8.4)
1-3 months	213	(9.9)	258	(12.0)	119	(11.4)	115	(11.0)	12	(7.2)
4-12 months	80	(3.7)	71	(3.3)	33	(3.2)	47	(4.5)	11	(6.6)
More than 12 months	48	(2.2)	49	(2.3)	34	(3.3)	47	(4.5)	24	(14.4)
Unknown	1,549	(71.7)	1,516	(70.4)	751	(72.2)	745	(71.4)	106	(63.5)

2.2 Cancer characteristics

Study of laterality of breast cancers in the patient cohort showed no significant preference for right (45.1%) or left breast (46.5%). Out of 9,193 patients, 214 patients were noted to have synchronous bilateral breast cancer at first diagnosis, and 187 developed a contralateral breast cancer, on average, 7.5 years (range: 0.5 – 34.5 years, median: 5.6 years) after diagnosis of an initial primary breast cancer (Figure 2.3). The upper outer quadrants of the left and right breast were the most common locations for breast cancers (45.6-49%) (Figure 2.4).

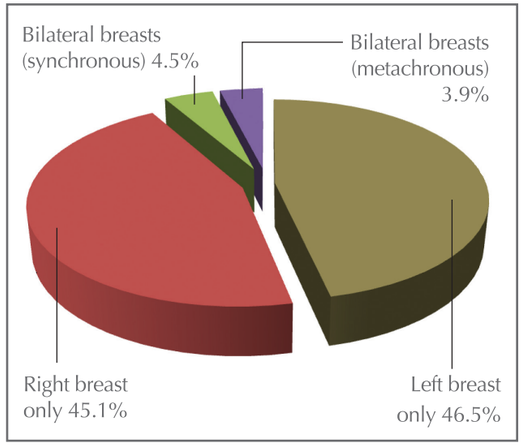

Figure 2.3 Laterality of 9,594 breast cancer cases

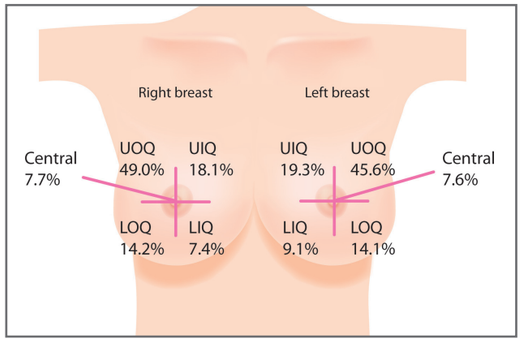

Figure 2.4 Locations of breast cancer (N=9,594)

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

2.2.1 *Diagnostic tests for breast cancer*

Diagnosis of breast cancer involves the use of diagnostic imaging and cytohistological biopsies to confirm malignancy. Mammography (MMG) is currently the "gold standard" of breast imaging tests during diagnosis. Ultrasound (USG) and Magnetic Resonance Imaging (MRI) are used for further investigation. Fine needle aspiration (FNA) and core needle biopsy (CNB) are used to confirm malignancy of the breast lesion.

MMG was used in 81% of patients, while USG was used in 74.2% and MRI was used in only 6.6% of patients. BIRADS (Breast Imaging Reporting and Data System) is a classification system used by radiologists to determine the likelihood of diagnosing malignancy in breast images.

MRI was the most sensitive imaging method with 95.9% sensitivity while MMG had an overall sensitivity of 79.3% and USG sensitivity was 87.9% (Table 2.7). However, MRI was usually employed only when there were equivocal findings on other imaging studies.

To confirm malignancy, FNA was used in 46.6% of cases, CNB was used in 48.6% of cases, and excisional biopsy was used in 15.3% of cases. The overall sensitivity of FNA was 89.7% while CNB was 98.5% and excisional biopsy was 100% sensitive (Table 2.8).

Table 2.7 Sensitivity and diagnostic results of breast imaging tests (N=9,594)

	Mammography (N=7,773)	Breast ultrasound (N=7,125)	MRI (N=631)
Proportion of subjects using the diagnostic test	81.0%	74.2%	6.6%
Overall sensitivity*	79.3%	87.9%	95.9%
BIRADS category			
Diagnostic/ malignant (BIRADS 5)	2,267 (29.2%)	2,570 (36.1%)	462 (73.2%)
Suspicious abnormality (BIRADS 4)	3,898 (50.1%)	3,695 (51.9%)	143 (22.7%)
Probably benign (BIRADS 3)	544 (7.0%)	497 (7.0%)	10 (1.6%)
Benign (BIRADS 2)	394 (5.1%)	177 (2.5%)	6 (1.0%)
Normal (BIRADS 1)	638 (8.2%)	179 (2.5%)	10 (1.6%)
Incomplete (BIRADS 0)	32 (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

Table 2.8 Sensitivity and diagnostic results of breast tissue biopsies (N=9,594)

	FNA (N=4,471)	CNB (N=4,659)	Excisional biopsy (N=1,466)
Proportion of subjects using the diagnostic test	46.6%	48.6%	15.3%
Overall sensitivity*	89.7%	98.5%	100.0%
Class			
Diagnostic / malignant (Class V)	2,661 (59.5%)	4,394 (94.3%)	1,466 (100.0%)
Suspicious (Class IV)	858 (19.2%)	120 (2.6%)	—
Atypical (Class III)	490 (11.0%)	77 (1.7%)	—
Benign (Class II)	234 (5.2%)	40 (0.9%)	—
Scanty benign (Class I)	149 (3.3%)	25 (0.5%)	—
Incomplete (Class 0)	79 (1.8%)	3 (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 have taken the test

Of the 6,165 patients diagnosed by MMG (with BIRADS 4-5), the most common mammographic finding was opacity (56.7%) and microcalcification (50.6%) (Table 2.9).

Table 2.9 Mammographic findings of patient cohort who were diagnosed through mammography (N=6,165)

	Number	(%)
Opacity	3,493	(56.7)
Microcalcifications	3,119	(50.6)
Architectural distortion	784	(12.7)
Asymmetric density	639	(10.4)
Others	46	(0.7)

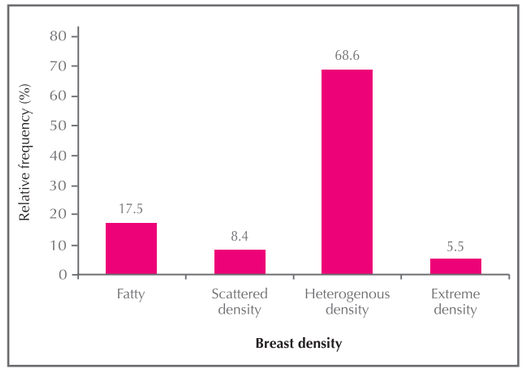

Figure 2.5 Mammographic density of breasts of breast cancer patients with diagnostic mammography (N=4,347)

2.2.2 Methods of cancer staging

After the diagnosis of breast cancer is confirmed, extent of cancer is studied by further imaging. The most common tests used in cancer staging were chest X-ray (CXR), abdominal ultrasound (USG Abd), Positron Emission Tomography (PET) scan, whole body MRI scan, bone scan and Computed Tomography (CT) scans. 19.2% of pateints were not tested for cancer stage. CXR and USG Abd was conducted on 77.3% of patients, and PET scan was conducted on 22.5% of patients (Table 2.10).

Table 2.10 Cancer staging in 8,189 breast cancer patients

Type of cancer staging method	Number	(%)
No cancer staging	1,576	(19.2)
Chest X-Ray (CXR) / Abdominal ultrasound (USG Abd)	5,114	(77.3)
Computed Tomography of body parts*	191	(2.9)
Bone scan	280	(4.2)
Positron Emission Tomography scan (PET scan)	1,485	(22.5)
Magnetic Resonance Imaging whole body (MRI whole body)	48	(0.7)
Unspecified	609	(9.2)

* Body parts include abdomen, thorax, pelvis, brain

Of the patient cohort, 81.3% were diagnosed with early stage breast cancer (0-II), while 14.4% were diagnosed with advanced stage breast cancer (III-IV) (Figure 2.6).

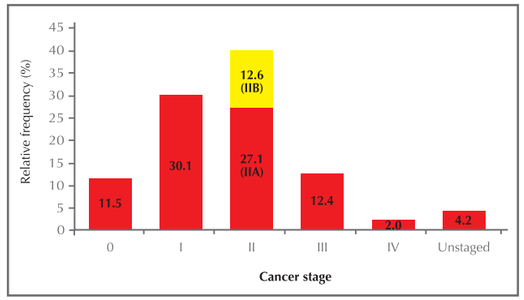

Figure 2.6 Cancer stage at diagnosis in breast cancer patients (N=9,594)

Out of 9,594 cases, 8,803 cases with available pathology data were used for the following analyses on cancer characteristics.

2.2.3 Characteristics of invasive breast cancer

Of the patient cohort, 7,599 (86.3%) patients were diagnosed with invasive breast cancer of which 85.4% of the cases were diagnosed at early stage (stages I-II) while 13.5% were diagnosed at advanced stage (stages III-IV). A further 1.1% were unstaged.

The mean tumour size of the invasive breast cancer was 2.18±1.41cm (median: 2cm), with a range of 0.01-22cm. Mean tumour size of invasive breast cancers in self-detected cancers by chance (2.3cm) was significantly larger than screen-detected cancers (1.3cm) ($p<0.001$). The most common tumour size of invasive breast cancers was 2.01-5.00cm (43.3%) followed by 1.01-2.00cm (37.5%) (Figure 2.7).

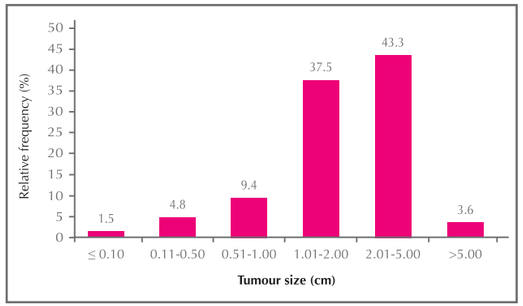

Figure 2.7 Distribution of tumour size (cm) of invasive breast cancers (N=7,352)

Among patients with invasive breast cancer, 57.8% had negative nodes, 3.1% of patients had isolated tumour cell (ITC). 39.2% had positive lymph nodes, in which 21.2% of patients had 1-3 positive lymph nodes and 5.3% of patients had micrometastasis (Figure 2.8).

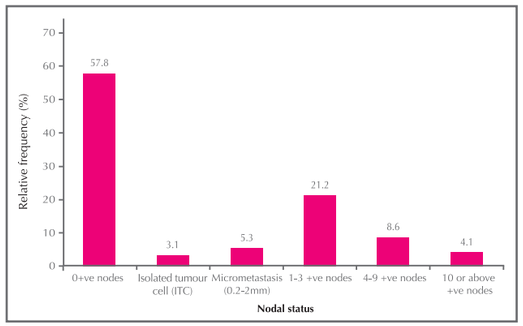

Figure 2.8 Number of positive lymph nodes in invasive breast cancers (N=7,553)

2.2.4 Characteristics of in situ breast cancer

Of the patient cohort, 1,203 patients were diagnosed with in situ breast cancer. The mean size of in situ breast cancers was 2.05±1.54cm (median: 1.69cm) with a range of 0.02-9.2cm. The most common tumour size of in situ breast cancers was 2.01-5.00cm (34.1%) followed by 1.01-2.00cm (31.2%) (Figure 2.9).

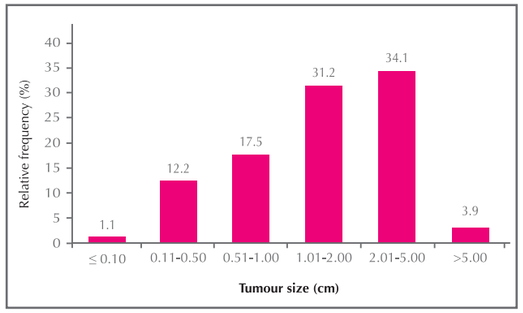

Figure 2.9 Distribution of tumour size (cm) of in situ breast cancers (N=1,074)

Among the patients with in situ breast cancer, 1.4% had isolated tumour cells (ITC), 0.7% had nodal micrometastasis, 0.8% had one or more positive nodes with sizes greater than 2mm.

2.3 Histological and biological characteristics

2.3.1 Invasive breast cancer

Histological characteristics, grading, multifocality and multicentricity of invasive breast cancer cases can be found in Table 2.11.

Table 2.11 Histological type, grading, multifocality and multicentricity of invasive breast cancers (N=7,599)

	Number	(%)
Histological type		
Invasive carcinoma of no specific type	6,428	(84.6)
Lobular	297	(3.9)
Mucinous (colloid)	296	(3.9)
Microinvasive	100	(1.3)
Tubular	71	(0.9)
Papillary	67	(0.9)
Mixed ductal and lobular	48	(0.6)
Carcinoma with medullary features	47	(0.6)
Borderline / malignant phyllodes	35	(0.5)
Micropapillary	24	(0.3)
Metaplastic carcinoma	24	(0.3)
Carcinoma with apocrine features	14	(0.2)
Carcinoma with neuroendocrine features	13	(0.2)
Cribriform carcinoma	8	(0.1)
Adenoid cystic carcinoma	7	(0.1)
Paget's disease of the nipple	5	(0.1)
Inflammatory	2	(0.0)
Secretory carcinoma	2	(0.0)
Lipid rich carcinoma	1	(0.0)
Sarcoma	1	(0.0)
Others	31	(0.4)
Unknown	78	(1.0)
Grade		
Grade 1	1,333	(17.5)
Grade 2	3,059	(40.3)
Grade 3	2,586	(34.0)
Unknown	621	(8.2)
Lymphovascular invasion	**2,215**	**(29.1)**
Multifocality	**786**	**(10.3)**
Number of foci		
2	422	(53.7)
3-4	147	(18.7)
≥5	97	(12.3)
Unknown	120	(15.3)
Multicentricity	**202**	**(2.7)**
Number of quadrants		
2	174	(86.1)
3	13	(6.4)
4	9	(4.5)
Unknown	6	(3.0)

Of the invasive breast cancer patients, 77.1% of patients were ER positive. 64.8% of patients were PR positive. 21.9% of patients were c-erbB2/HER2 positive. 27.8% of patients were found to be weakly c-erbB2/HER2 positive by immunohistochemistry, of these patients only 3.6% were found to be positive by FISH/CISH test (Table 2.12).

Breast cancer can be categorised into four biological subtypes according to immunohistochemistry data: luminal A, luminal B, c-erbB2/HER2 positive and triple negative[22]. Biological subtypes of invasive tumours by cancer stage can be found in Table 2.13.

Table 2.12 Biological characteristics of invasive breast cancers (N=7,599)

	Number	(%)
Estrogen receptor (ER) (96.6% of the patients had the test)		
Positive	5,660	(77.1)
Negative	1,684	(22.9)
Progesterone receptor (PR) (96.3% of the patients had the test)		
Positive	4,740	(64.8)
Negative	2,579	(35.2)
c-erbB2/ HER2 (93.1% of the patients had the test)		
Positive (IHC score 3)	1,478	(20.9)
Weakly positive (IHC score 2)	1,964	(27.8)
FISH / CISH +ve	*70*	*(3.6)*
Negative (IHC score 0/1)	3,630	(51.3)
Ki-67 index (53.1% of the patients had the test)		
<14%	1,767	(43.8)
14-49%	1,766	(43.8)
≥50%	501	(12.4)

HER2: Human epidermal growth factor receptor 2

Table 2.13 Biological subtypes of invasive tumours by cancer stage (N=7,035)

	Cancer Stage, N (%)									
Biological subtypes	**I**		**IIA**		**IIB**		**III**		**IV**		**Total**	
Luminal A*	749	(28.6)	472	(20.0)	205	(19.0)	134	(14.0)	1	(4.0)	1,561	(22.2)
Luminal B (HER2 negative)#	354	(13.5)	452	(19.2)	204	(18.9)	202	(21.1)	5	(20.0)	1,217	(17.3)
Luminal B (HER2 positive)^	328	(12.5)	313	(13.3)	156	(14.5)	162	(16.9)	7	(28.0)	966	(13.7)
HER2 Positive❊	199	(7.6)	184	(7.8)	95	(8.8)	98	(10.2)	1	(4.0)	577	(8.2)
TND§	273	(10.4)	342	(14.5)	122	(11.3)	98	(10.2)	2	(8.0)	837	(11.9)
Luminal A/B (HER2 negative)✧	715	(27.3)	593	(25.2)	297	(27.5)	263	(27.5)	9	(36.0)	1,877	(26.7)
Total	2,618	(37.2)	2,356	(33.5)	1,079	(15.3)	957	(13.6)	25	(0.4)	7,035	(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 (≥14%)
^ 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-
✧ Luminal A/B (HER2 negative):ER and/or PR+, HER2-, and Ki-67 unknown

2.3.2 *In situ breast cancer*

Histological typing, grading, multifocality and multicentricity of in situ breast cancer cases can be found in Table 2.14. Microcalcification was found in 56% of in situ breast cancer patients.

Table 2.14 Histological type, grade, multifocality and multicentricity of in situ breast cancers (N=1,203)

	Number	(%)
Histological type		
Ductal	1,102	(91.6)
Lobular	19	(1.6)
Mixed	44	(3.7)
Others	31	(2.6)
Unknown	7	(0.6)
Necrosis	**489**	**(40.6)**
Nuclear Grade		
Low	274	(22.8)
Intermediate	390	(32.4)
High	463	(38.5)
Unknown	76	(6.3)
Multifocality	**137**	**(11.4)**
Number of foci		
2	71	(51.8)
3	13	(9.5)
4 or more	5	(3.6)
Unknown	48	(35.0)
Multicentricity	**23**	**(1.9)**
Number of quadrants		
2	17	(73.9)
3	2	(8.7)
Unknown	4	(17.4)

Of the in situ breast cancer cases, 79.4% were found to be ER positive, while 70.7% were found to be PR positive and 29.4% (N=244) c-erbB2/HER2 positive. Of the 31.2% of patients that were found to be weakly c-erbB2/HER2 positive by immunohistochemistry, only 1 patient was found to be FISH/CISH test positive (Table 2.15).

Table 2.15 Biological characteristics of in situ breast cancers (N=1,203)

	Number	(%)
Estrogen receptor (ER) (73.6% of the patients had the test)		
Positive	703	(79.4)
Negative	182	(20.6)
Progesterone receptor (PR) (72.6% of the patients had the test)		
Positive	617	(70.7)
Negative	256	(29.3)
c-erbB2/ HER2 (68.9% of the patients had the test)		
Positive (IHC Score 3)	243	(29.3)
Weakly positive (IHC Score 2)	259	(31.2)
FISH / CISH +ve	*1*	*(0.4)*
Negative (IHC Score 0 / 1)	327	(39.4)
Ki-67 index (49.3% of the patients had the test)		
<14%	418	(70.5)
14-49%	157	(26.5)
≥50%	18	(3.0)

2.4 Treatment methods

Treatment is the most important part of recovery from breast cancer. The success of treatment can depend on cancer stage at diagnosis, timely medical consultation, combination of treatments used and tumour characteristics.

Out of 9,594 patients, 1,890 (19.7%) were diagnosed and treated solely at private medical facilities, 3,815 (39.8%) were diagnosed and had their treatment solely at public medical facilities, and 3,889 (40.5%) used both private and public medical facilities.

2.4.1 *Surgical treatment*

Surgery is perhaps the most important part of initiating treatment of breast cancer. 98.2% of the patients within the patient cohort underwent surgery as part of their treatment. 61.9% of patients had surgery at private medical facilities while 38.1% had surgery at public medical facilities.

The most common surgical operation was mastectomy (MTX) (62.4%). Only 35.7% of patients had breast-conserving surgery (BCS). Of the MTX patients, 6% had skin sparing MTX while 0.8% had nipple sparing MTX.

14.8% of patients who had MTX also had breast reconstruction surgery, of these 63.6% had TRAM flap reconstruction while 21.5% had breast implants.

Most patients had nodal surgery (91.7%). Of these patients 33.8% had sentinel node biopsy (SNB), and 49.2% had axillary dissection (AD). Only 16.6% of patients had both SNB and AD (Table 2.16).

Table 2.16 Types of surgical operations in the patient cohort (N=9,594)

	Number	(%)
No surgery	159	(1.7)
Breast conserving surgery	3,426	(35.7)
Mastectomy	5,986	(62.4)
Nodal surgery only	2	(0.0)
Unknown type of surgery	12	(0.1)
Unknown if surgery done	9	(0.1)
Mastectomy (N=5,986)		
Total mastectomy	5,557	(92.8)
Skin sparing	361	(6.0)
Areolar sparing	11	(0.2)
Nipple sparing	45	(0.8)
Unknown	12	(0.2)
Reconstruction (N=887)		
TRAM flap	564	(63.6)
Implant	191	(21.5)
LD flap	65	(7.3)
LD flap & implant	56	(6.3)
Unknown	11	(1.2)
Nodal surgery (N=8,795)		
Sentinel node biopsy	2,971	(33.8)
Axillary dissection	4,329	(49.2)
Sentinel node biopsy & axillary dissection	1,460	(16.6)
Unknown	35	(0.4)

The two patients aged under 20 received BCS. The percentage of patients that had MTX instead of BCS was positively correlated with increasing age, while use of reconstruction after MTX was negatively correlated with increasing age (Figure 2.10).

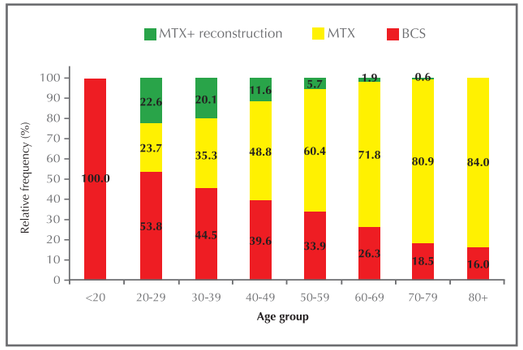

Figure 2.10 Type of surgery by age group (N=9,078)

BCS: breast conserving surgery; MTX: mastectomy

The use of BCS vs MTX showed no pattern for tumours under the size of 1cm. However, a positive correlation of MTX over BCS with increasing tumour size was found in tumours of 1cm and larger. The same pattern was observed for MTX + reconstruction (Figure 2.11).

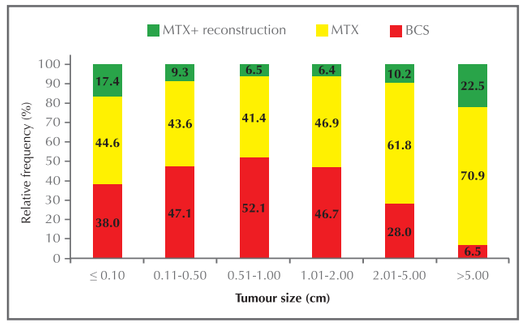

Figure 2.11 Type of surgery by tumour size (N=8,451)

BCS: breast conserving surgery; MTX: mastectomy

Within the patient cohort increased MTX over BCS was observed with increasing cancer stage. MTX with reconstruction was also correlated to increasing cancer stage, with the exception of patients with stage 0 disease. 11.8% of patients with stage 0 cancer had MTX with reconstruction (Figure 2.12).

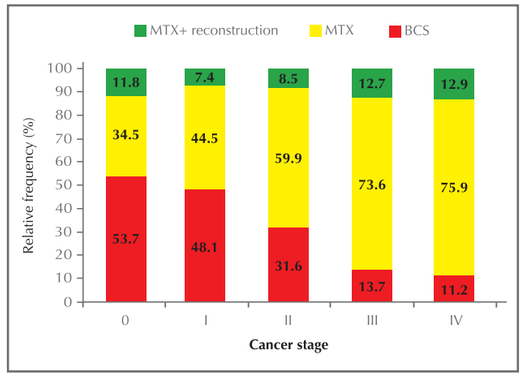

Figure 2.12 Type of surgery by cancer stage (N=9,070)

BCS: breast conserving surgery; MTX: mastectomy

More patients who attended private health care facilities (43.7%) received BCS than patients who attended public health care facilities (25.3%). Additionally more patients at private health care facilities (10.1%) had reconstructive surgery after MTX than those at public health care facilities (8.3%) (Figure 2.13).

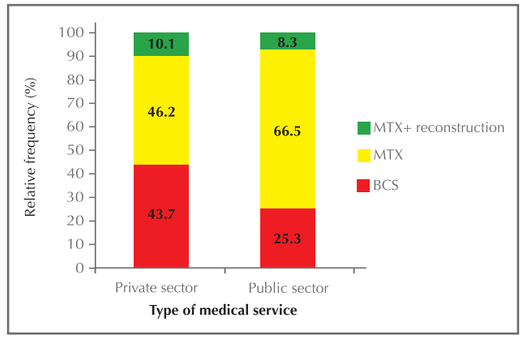

Figure 2.13 Type of surgery by type of medical service (N=9,208)

BCS: breast conserving surgery; MTX: mastectomy

The number of AD vs SNB were positively correlated to increasing cancer stage in patients with invasive breast cancer, with the exception of stage IV disease where an increase in SNB was observed. The number of SNB only was highest for patients with stage I invasive cancer (56.8%). SNB followed by AD (34.0%) was highest for patients with stage IIB invasive cancer (Figure 2.14).

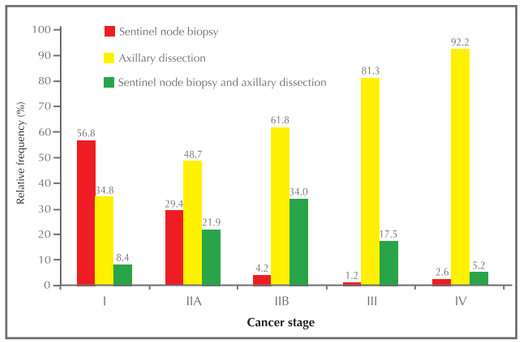

Figure 2.14 Type of nodal surgery in invasive cancer by cancer stage (N=7,773)

In patients with invasive breast cancer, the most common tumour size in node positive cancer was between 2.01-5cm (55.5%) (Figure 2.15). The most common tumour size in node negative cancer was between 1.01-2cm (41.3%) (Figure 2.15).

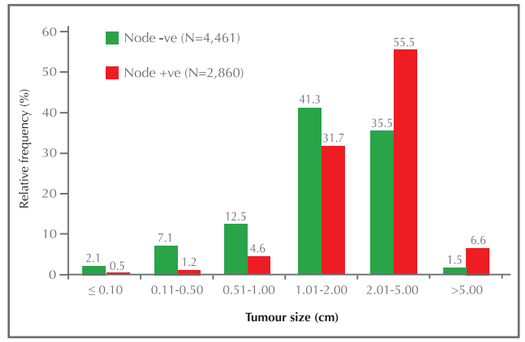

Figure 2.15 Distribution of tumour size in invasive cancer with negative or positive nodal status (N=7,321)

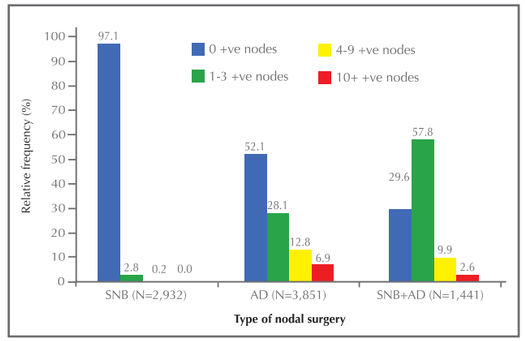

Figure 2.16 Number of positive nodes by type of nodal surgery (N=8,224)

SNB: Sentinel node biopsy; AD: Axillary dissection

2.4.2 Chemotherapy

Chemotherapy is a form of systemic treatment of micrometastasis or macrometastasis in the body system involving the use of one or more cytotoxic drugs. 5,836 (60.8%) patients in the cohort underwent chemotherapy. Of the women who were treated with chemotherapy, 90% were treated with adjuvant chemotherapy, 8.2% were treated with neoadjuvant chemotherapy and 1.8% were treated with palliative chemotherapy. 5.1% of patients were treated with chemotherapy and targeted therapy at the same time.

82.6% of patients had chemotherapy in public health care facilities and 17.4% of patients had chemotherapy at private health care facilities. Analysis of chemotherapy rates by cancer stage revealed that 82.4%-93.5% of patients with stage II and higher cancer stages received chemotherapy while only 39.1% of patients with stage I breast cancer received chemotherapy (Figure 2.17). Details on type of chemotherapy regimen used by cancer stage can be found in Figure 2.18.

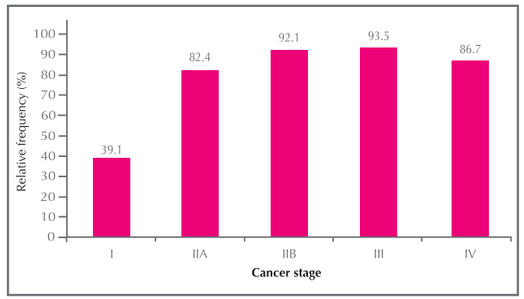

Figure 2.17 Chemotherapy treatment in patients at different cancer stages (N=7,996)

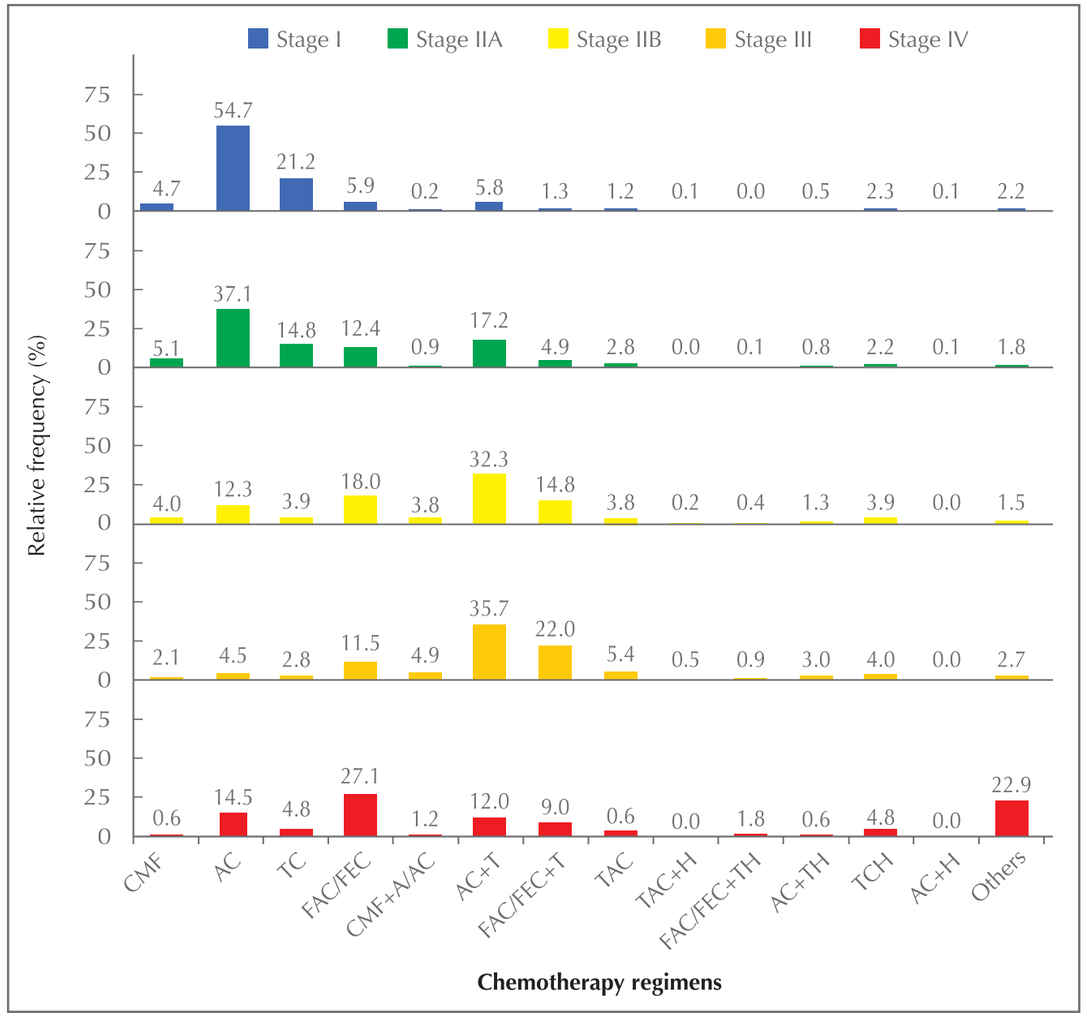

Figure 2.18 Type of chemotherapy regimens in patients by cancer stage (N=5,244)

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

2.4.3 Radiotherapy

Radiotherapy is also used as a part of cancer treatment to control or kill malignant cells using ionizing radiation as local control of primary tumour site or distant metastatic sites. 5,919 (61.7%) patients had radiotherapy as a part of their treatment. Among them, 5,825 (98.4%) were adjuvant, 9 (0.2%) were neoadjuvant, and 85 (1.4%) were palliative. 81.5% of patients received radiotherapy at public healthcare facilities while 18.5% received radiotherapy at private health care facilities.

94.2% of patients who had BCS had radiotherapy while only 45.9% of patients who had MTX had radiotherapy. The use of radiotherapy was positively correlated with increasing cancer stage, with the exception of stage IV cancers (Figure 2.19).

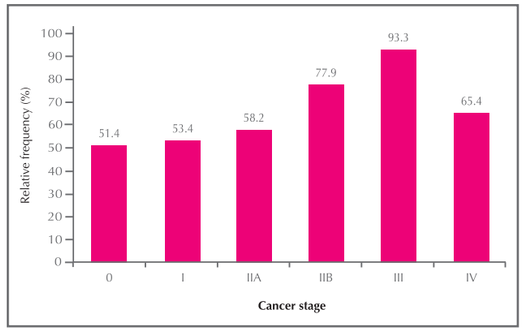

Figure 2.19 Radiotherapy rate in patients at different cancer stages (N=9,012)

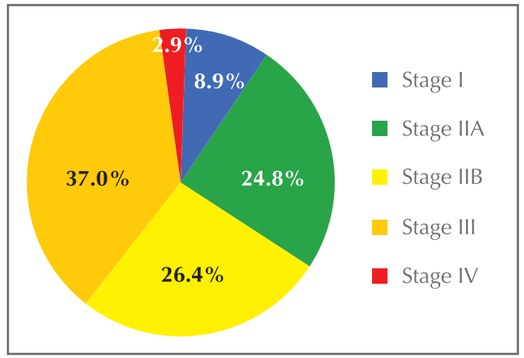

Figure 2.20 Distribution of cancer stages in patients treated with mastectomy and radiotherapy (N=2,511)

Breast and chest wall and regional nodes were the most commonly irradiated sites (28.8% and 21.7% respectively) (Table 2.17).

Table 2.17 Irradiated regions among the patients receiving radiotherapy (N=5,919)

	Total (N=5,919)		Breast Conserving Surgery (N=3,174)		Mastectomy (N=2,687)	
Target volume	**Number**	**(%)**	**Number**	**(%)**	**Number**	**(%)**
Breast	1,706	(28.8)	1,691	(53.3)	—	
Breast + regional nodes*	281	(4.7)	266	(8.4)	—	
Chest wall	631	(10.7)	—		629	(23.4)
Chest wall + regional nodes*	1,282	(21.7)	—		1,282	(47.7)
Axilla	6	(0.1)	3	(0.1)	2	(0.1)
SCF	12	(0.2)	2	(0.1)	10	(0.4)
Axilla + SCF	7	(0.1)	1	(0.0)	6	(0.2)
IMC	2	(0.0)	1	(0.0)	1	(0.0)
IMC + SCF	3	(0.1)	0	(0.0)	3	(0.1)
Unspecified	1,989	(33.6)	1,210	(38.1)	754	(28.1)

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 hormonal receptor positive can be treated with endocrine therapy as a form of systemic therapy. 6,399 (66.7%) patients had endocrine therapy. Among them, 6,239 (97.5%) were adjuvant, 20 (0.3%) were neoadjuvant, and 140 (2.2%) were palliative. 82.6% of patients were recommended endocrine therapy at public healthcare facilities while 17.4% of patients were recommended endocrine therapy at private healthcare facilities. Endocrine therapy was used in 74.3-81.9% of patients with stages I- IV breast cancer, but was only used in 19.6% of patients with stage 0 breast cancer (Figure 2.21).

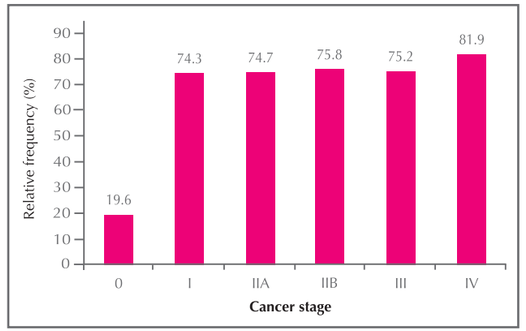

Figure 2.21 Endocrine therapy rates in patients by cancer stage (N=9,047)

Tamoxifen (TMX) and Aromatase inhibitors (AI) are both commonly used hormone therapies that work in different ways. AI lowers the amount of estrogen in the body while TMX blocks estrogen receptors on cells. 94.5% of women under 45 were treated with TMX only, while 33.7% of patients over 55 years of age were treated with AI only. The use of TMX was negatively correlated with increasing age, while AI or the transition use of TMX to AI was positively correlated with increasing age (Figure 2.22).

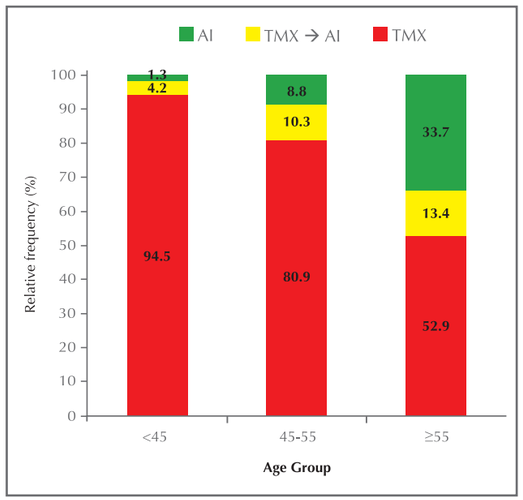

Figure 2.22 Forms of endocrine therapy used in patients by age group (N=5,858)

TMX: Tamoxifen; AI: Aromatase inhibitors

2.4.5 Targeted therapy

Targeted therapy involves blocking the growth of cancer cells by interfering with specific molecules required for tumour growth or carcinogenesis. 690 (7.2%) patients had targeted therapy. Among them, 636 (92.2%) were adjuvant, 39 (5.7%) were neoadjuvant, and 15 (2.2%) were palliative. 81.1% of the patient cohort had targeted therapy at public health care facilities, while 18.9% had targeted therapy at private health care facilities.

The use of targeted therapy was positively correlated with increasing cancer stage, but was used at similar frequencies for patients with stage III and stage IV breast cancers (Figure 2.23).

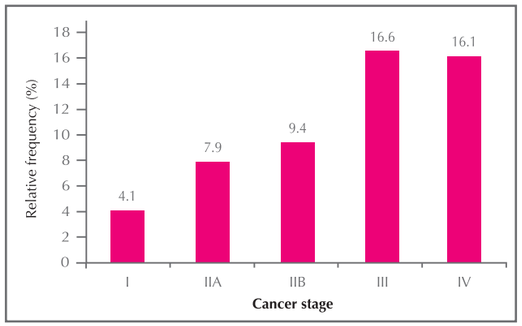

Figure 2.23 Targeted therapy rate in patients by cancer stage (N=9,074)

Trastuzumab, used for treating HER2 positive breast cancers, was the most commonly used targeted therapy (94.1%). Lapatinib and Bevacizumab, monoclonal antibodies, were less frequently used (1.2% and 0.4% respectively) (Figure 2.24).

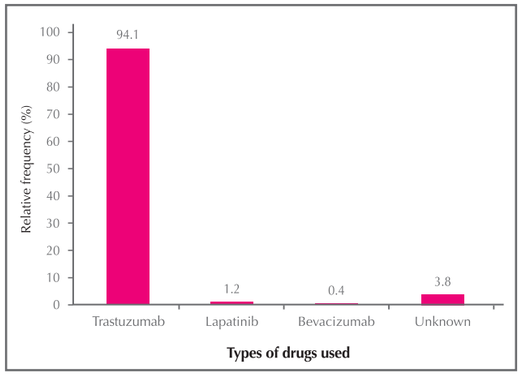

Figure 2.24 Types of drugs used for targeted therapy in patients (N=690)

2.4.6 Complementary and alternative therapies

Complementary and alternative therapies were used by 3,637 (37.9%) patients. Among them, 3,467 (95.3%) were adjuvant, 148 (4.1%) were neoadjuvant, and 22 (0.6%) were palliative.

The most commonly used complementary and alternative therapy was chinese medicine - used by 73.5% of patients, while 32.6% of women took health food/supplements (Figure 2.25).

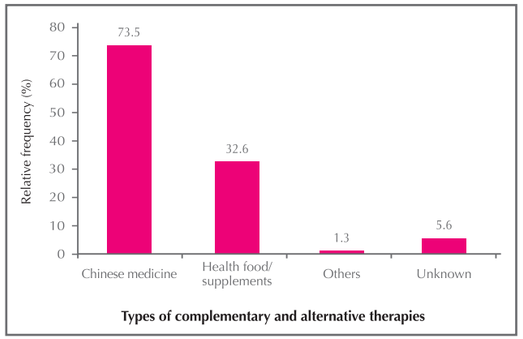

Figure 2.25 Types of complementary and alternative therapies used in 3,637 patients

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

2.4.7 Multimodality treatment

The number of treatments used by patients showed a positive trend with increasing cancer stage. Half of the patients with stage 0 breast cancer were treated with two treatments, while patients with stage I or stage IIA cancer were most usually treated with three treatments (42.7% and 40.9% respectively). Patients with stage IIB or stage III breast cancer were most usually treated with four treatments (54.8% and 64.2% respectively). Patients with stage IV breast cancer were treated most usually with three or four treatments (37.8% and 35.1% respectively) (Table 2.18).

CHAPTER 2

Table 2.18 Number of treatments received by patients by cancer stages

	Stage (%)						
No. of treatment	0	I	IIA	IIB	III	IV	Total
0	4 (0.4)	3 (0.1)	2 (0.1)	1 (0.1)	4 (0.4)	3 (1.6)	17 (0.2)
1	419 (39.4)	195 (7.0)	56 (2.2)	9 (0.8)	7 (0.6)	12 (6.5)	698 (7.9)
2	529 (49.8)	931 (33.4)	401 (15.9)	79 (6.7)	37 (3.2)	27 (14.6)	2,004 (22.6)
3	111 (10.4)	1,191 (42.7)	1,032 (40.9)	390 (33.1)	250 (21.9)	70 (37.8)	3,044 (34.3)
4	0 (0.0)	438 (15.7)	976 (38.7)	646 (54.8)	733 (64.2)	65 (35.1)	2,858 (32.2)
5	0 (0.0)	32 (1.1)	56 (2.2)	53 (4.5)	111 (9.7)	8 (4.3)	260 (2.9)

2.5 Patient Status

After treatment, 38.9% of patients did follow up for 2-5 years, while 26.5% of patients did follow up for 5-10 years. The average follow-up period was 4.7 years (median: 3 years). Majority (83.7%) of the patients had last follow up in 2011 or onwards. Locoregional recurrence occurred in 3.8% of patients at an average time of 5.3 years after initial diagnosis (median: 3.6 years). 3.5% of patients had distant recurrences at an average of 4.6 years after initial diagnosis (median: 3.5 years). 0.5% of patients died from breast cancer (Table 2.19).

The number of patients with locoregional recurrence by type of surgery and cancer stage can be found in Table 2.20. The highest rate of locoregional recurrence was found in stage 0 patients who had BCS (7.7%), and stage III cancer patients who had MTX and reconstruction (8.7%).

Table 2.19 Follow-up of 8,705 patients

Follow-up period	Number	(%)
< 1 year	676	(7.8)
1-2 years	1,542	(17.7)
2-5 years	3,390	(38.9)
5-10 years	2,308	(26.5)
10-15 years	589	(6.8)
>15 years	200	(2.3)
Mean follow-up period	4.7 years	
Median follow-up period	3.0 years	
Locoregional recurrence		
No. of locoregional recurrence	329	(3.8%)
Mean time to locoregional recurrence	5.3 years	
Median time to locoregional recurrence	3.6 years	
Distant recurrence		
No. of distant recurrence	304	(3.5%)
Mean time to distant recurrence	4.6 years	
Median time to distant recurrence	3.5 years	
Mortality		
No. of deaths from breast cancer	46	(0.5%)
No. of deaths from unrelated causes	33	(0.4%)

Table 2.20 Number of cases with locoregional recurrence by type of surgery and cancer stage

	Cancer stage, Number (% in the overall patient cohort with surgeries)					
Type of surgery	0	I	IIA	IIB	III	Total
BCS	45 (7.7)	34 (2.5)	19 (2.1)	7 (2.5)	7 (4.3)	112 (3.4)
MTX	4 (1.1)	36 (2.8)	40 (2.7)	28 (3.4)	38 (4.4)	146 (3.0)
MTX + reconstruction	6 (4.7)	5 (2.3)	12 (5.8)	3 (2.6)	13 (8.7)	39 (4.8)

BCS: breast conserving surgery; MTX: mastectomy

Table 2.21 Sites involved in locoregional recurrence in patients

Locoregional recurrence sites involved	Total N (%)	
Breast	107	(32.5)
Chest wall	105	(31.9)
Skin	17	(5.2)
Axilla	73	(22.2)
Supraclavicular	55	(16.7)
Internal mammary node	19	(5.8)
Others	46	(14.0)

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

The most common locoregional recurrence site was the breast or chest wall (Table 2.21).

Interestingly, patients with stage 0 cancer had the highest rate of locoregional recurrence (5.7%) while highest distant recurrence rate was observed in stage III cancer (9.2%) (Table 2.22).

Table 2.22 Locoregional and distant recurrence rates in patients by stage

	Cancer stage, Number (%)					
Recurrence	0 (N=958)	I (N=2,585)	IIA (N=2,364)	IIB (N=1,112)	III (N=1,046)	Total (N=8,065)
Locoregional	55 (5.7)	76 (3.0)	71 (3.0)	38 (3.4)	58 (5.5)	298 (3.7)
Distant	5 (0.5)	47 (1.8)	68 (2.9)	58 (5.2)	96 (9.2)	274 (3.4)

The most frequent organ involved in distant metastasis was bone (54.3%), followed by lung (42.8%) (Table 2.23). Characteristics of breast cancer-specific deaths can be found in Table 2.24.

Table 2.23 Organs involved in distant metastasis

Distant organs affected	Number	(%)
Bone	165	(54.3)
Lung	130	(42.8)
Liver	90	(29.6)
Mediastinal nodes	45	(14.8)
Brain	41	(13.5)
Others	43	(14.1)
Cervical nodes	17	(5.2)

Table 2.24 Characteristics of breast cancer-specific deaths

	Cancer Stage at first diagnosis						
	0	I	IIA	IIB	III	IV	Unstaged
No. of cases (%)	**1 (2.2)**	**7 (15.2)**	**9 (19.6)**	**1 (2.2)**	**13 (28.3)**	**8 (17.4)**	**7 (15.2)**
Survival time (years)	**4.5**	**1.9 – 10.6**	**2.0 – 20.8**	**8.9**	**0.8 – 8.4**	**1.1 – 5.1**	**1.1 – 22.2**
Biological subtypes							
Luminal A*	0	0	1	0	2	0	0
Luminal B (HER2 negative)#	0	1	2	0	4	0	0
Luminal B (HER2 positive)^	1	1	0	1	0	0	0
HER2 Positive❊	0	0	0	0	1	0	0
TND§	0	3	2	0	2	0	0
Luminal A/B (HER2 negative)✧	0	2	2	0	1	1	0
Unknown	0	0	2	0	3	7	7

* 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 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-

✧ Luminal A/B (HER2 negative): ER and / or PR+, HER2-, and Ki-67 unknown