CHAPTER 5.

Stage, pathology, and molecular subtypes of breast cancer

Key observations

- Stage at diagnosis is a major determinant of survival for breast cancer. Availability of staging information (both clinical and pathological) in more than 90% of the patients is an important benchmark for quality of care. Overall, more than 90% of the patients registered at both oncology centres in Morocco had adequate information to determine the American Joint Committee on Cancer (AJCC) tumour–node–metastasis (TNM) stage.

- Both centres documented a reduction in the proportion of locally advanced cancers (clinical T3 and T4) during the study period (2008–2017). The proportion of women with breast cancer diagnosed with early-stage cancer (stages I and II) was 56.6% at CM-VI and 52.5% at INO. The proportion of early-stage cancers increased significantly after 2010 at INO but remained similar at CM-VI.

- We observed that access delay (the interval between onset of symptoms and first medical consultation) was the most significant determinant of presentation at advanced stage. The interval shortened significantly between 2008 and 2017 among patients registered at INO, probably because of the screening programme and associated awareness campaigns launched in 2010. The benefit of reduced access delay was visible as downstaging of disease (i.e. a shift in the stage distribution of tumours detected towards a lower stage).

- Information on the histopathology of the tumour was available for 91.0% of patients at CM-VI and 95.9% of patients at INO. Classification of tumours by the pathological degree of differentiation was available for 82.0% of patients at CM-VI and 92.5% of patients at INO. ER and progesterone receptor (PR) status were available for 78.4% of patients at CM-VI and 91.1% of patients at INO. Human epidermal growth factor receptor 2 (HER2)-amplification/overexpression status was documented in 70.3% of patients at CM-VI and 85.5% of patients at INO. The quality and completeness of histopathology (including immunohistochemistry) demonstrates the significant progress made in Morocco in offering high-quality oncology care in the public sector.

- The proportion of patients with luminal-like breast cancers was 51.8% at CM-VI and 57.0% at INO; the proportion of HER2-positive cancers was 30.0% at CM-VI and 29.4% at INO, and the proportion of triple-negative breast cancers was 18.1% at CM-VI and 13.9% at INO. The proportion of HER2-positive breast cancers was higher than that generally reported from studies in developed countries but comparable to that observed in other countries in the Eastern Mediterranean Region.

- With regard to age and molecular type of breast cancer, the distribution for women younger than 50 years (luminal-like, 52.8%; HER2-positive, 30.7%; and triple-negative, 16.5%) was similar to that for women aged 50 years or older (luminal-like, 56.2%; HER2-positive 28.3%; and triple-negative, 15.5%).

- Triple-negative breast cancers were more frequently seen in women with poorly differentiated breast cancers. No significant association was observed with age.

5.1 Stage at diagnosis

Staging of breast cancer is based either on the clinical information obtained before surgery or neoadjuvant chemotherapy (clinical staging) or on the information obtained from pathological evaluation of specimens removed at surgery (pathological staging). Pathological staging is not applicable for patients receiving neoadjuvant therapy. We documented clinical TNM stage and pathological TNM stage. The composite anatomical stage (I, II, III, and IV) was recalculated using the TNM system according to the AJCC guidelines (Giuliano et al., 2017). The anatomical stage was recalculated first using the pathological TNM stage information and then using the clinical TNM stage information for patients with no pathological stage information recorded.

5.1.1 Availability of information on stage

Overall, 90.7% of patients registered at CM-VI and 94.9% of those registered at INO had adequate information to estimate the anatomical stage. Of the 146 patients without adequate information to determine stage (85 at CM-VI and 61 at INO), 56 did not receive any cancer-directed treatment and 36 completed treatment before registering at an oncology centre. This could explain the lack of any information on stage.

Availability of staging information (both clinical and pathological) in more than 90% of the patients is an important benchmark for quality of care (Panozzo et al., 2019). It was possible to estimate the AJCC TNM stage in more than 90% of patients at both centres in this study.

Table 5.1. Distribution of patients with breast cancer by AJCC anatomical stage at the two centres

AJCC stage	Period of registration						Total	
	2008–2010		2011–2014		2015–2017			
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
CM-VI								
I	27	(13.8)	39	(11.5)	33	(11.1)	99	(11.9)
II	83	(42.6)	150	(44.4)	138	(46.5)	371	(44.7)
III	66	(33.8)	120	(35.5)	94	(31.6)	280	(33.7)
IV	19	(9.7)	29	(8.6)	32	(10.8)	80	(9.6)
INO								
I	24	(7.8)	41	(10.0)	44	(10.3)	109	(9.5)
II	122	(39.9)	186	(45.4)	184	(43.0)	492	(43.0)
III	122	(39.9)	129	(31.5)	153	(35.7)	404	(35.3)
IV	38	(12.4)	54	(13.2)	47	(11.0)	139	(12.2)

AJCC, American Joint Committee on Cancer; CM-VI, Centre Mohammed VI pour le traitement des cancers; INO, Institut National d'Oncologie Sidi Mohamed Ben Abdellah.

5.1.2 Distribution of patients with breast cancer by stage

The distribution of the patients in this study according to AJCC TNM anatomical stage is shown in Table 5.1. Overall, 17.7% of patients registered at CM-VI had a tumour clinically classified as T1, and a small increase in this proportion was observed over time (15.1% in 2008–2010, 16.9% in 2011–2014, and 20.0% in 2015–2017). For patients registered at INO, clinically small tumours (T1) were detected in 14.3% overall, 14.2% in 2008–2010, 10.9% in 2011–2014, and 17.9% in 2015–2017 (Fig. 5.1).

The AJCC anatomical stage distribution did not show any major change over time at CM-VI, but a downstaging of cancer (i.e. a shift in the stage distribution of tumours detected towards a lower stage) was observed at INO after 2010 (Fig. 5.2). Early-stage breast cancer (stages I and II) was detected in 56.6% of patients registered at CM-VI overall, and the proportion remained similar across different time periods (56.4% in 2008–2010, 55.9% in 2011–2014, and 57.6% in 2015–2017). Early-stage cancer was detected in 52.5% of patients registered at INO overall, and the proportion increased after 2010 (47.7% in 2008–2010, 55.4% in 2011–2014, and 53.3% in 2015–2017).

5.2 Histopathological characteristics

5.2.1 Histopathological types

Information on the histopathological type of the tumour was available for 91.0% of patients at CM-VI and 95.9% of patients at INO. Very few patients (2.1% at CM-VI and 1.0% at INO) had a final histopathology diagnosis of in situ carcinoma. Most cases (79.1% at CM-VI and 88.0% at INO) were invasive ductal carcinoma.

Invasive lobular carcinoma comprised 6.7% of all cancers at CM-VI and 3.4% of all cancers at INO. No substantial difference in the distribution of histopathological types was observed over time.

Fig. 5.1. Clinical tumour size distribution in patients with breast cancer registered at the Centre Mohammed VI pour le traitement des cancers (CM-VI) and the Institut National d'Oncologie Sidi Mohamed Ben Abdellah (INO) over different time periods.

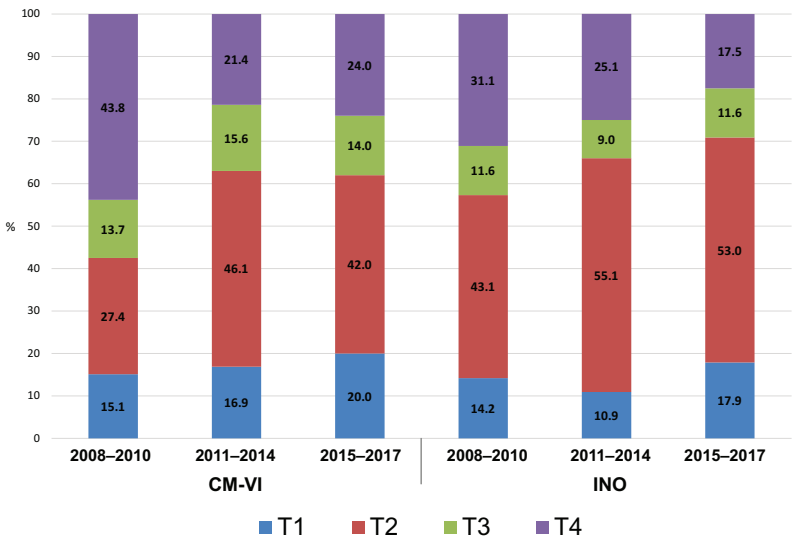
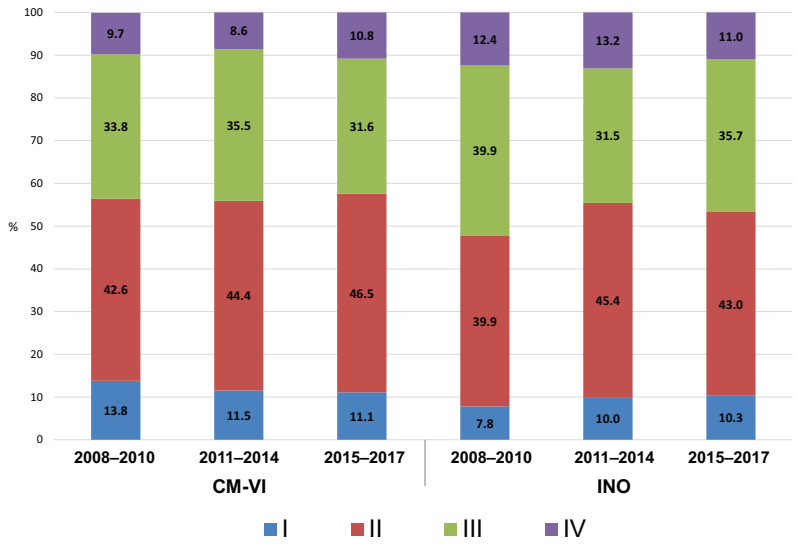


Fig. 5.2. Distribution of patients with breast cancer according to American Joint Committee on Cancer (AJCC) anatomical stage, at the Centre Mohammed VI pour le traitement des cancers (CM-VI) and the Institut National d'Oncologie Sidi Mohamed Ben Abdellah (INO) over different time periods.



5.2.2 Degree of differentiation

Information on the pathological grade was available for 82.0% of patients registered at CM-VI and 92.5% of patients registered at INO. Most cancers detected were moderately differentiated (62.7% at CM-VI and 56.0% at INO). Nearly one third of all cancers detected at either institution were poorly differentiated.

5.3 Molecular characteristics

5.3.1 Molecular subtypes of breast cancer

On the basis of the expression of hormone receptors (ER and PR), HER2 (also known as ERBB2), and Ki-67 (a proliferation marker), breast cancers are categorized into three major subtypes: luminal-like, HER2-positive and triple-negative (Table 5.2).

ER and PR status were available for 78.4% of patients at CM-VI and 91.1% of patients at INO. HER2-amplification/overexpression status was documented in 70.3% of patients at CM-VI and 85.5% of patients at INO.

The details of the molecular characteristics of the breast cancers detected at CM-VI and INO are shown in Table 5.3. The proportion of tumours positive for ER was 71.1% at CM-VI and 75.8% at INO; PR positivity was 66.8% at CM-VI and 68.9% at INO.

At CM-VI, HER2 was amplified/overexpressed in 30.0% of patients with breast cancer who were tested for the receptor; at INO, the proportion was 29.4%. In those with a HER2-expression score of 2+ (equivocal staining) at CM-VI, 22.2% (14/63) had a confirmatory fluorescence in situ hybridization (FISH) test result. The proportion was much higher at INO (60.8%; 73/120).

Table 5.2. Classification of breast cancers by molecular characteristics

Clinically defined breast cancer subtypes	Molecular and clinical characteristics
Luminal-like	Hormone receptor+ and HER2− luminal disease as a spectrum
Luminal A-like	High ER/PR and low proliferation rate (low mitotic count and low Ki-67); generally histological grade 1 or 2; prognosis favourable
Luminal B-like	Low ER/PR and high proliferation rate (high mitotic count and high Ki-67); generally histological grade 3; prognosis unfavourable
HER2-positive	ER/PR+ or ER/PR−; HER2+; generally histological grade 3; prognosis unfavourable
Triple-negative (or basal-like)	ER/PR/HER2−; generally histological grade 3; prognosis unfavourable

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.
Source: Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging System (2020).

On the basis of the available reports, we classified the breast cancers as luminal-like (ER- and/or PR-positive and HER2-negative), HER2-positive, or triple-negative. It was not possible to subcategorize the luminal-like cancers into types A or B, because the Ki-67 expression was not tested for most patients. The proportion of luminal-like (HER2-negative) breast cancers was 51.8% at CM-VI and 57.0% at INO, and no substantial difference was observed between the time periods. Nearly one third of the cancers at either centre were HER2-positive (30.0% at CM-VI and 29.4% at INO). Most were ER- and/or PR-positive. The proportion of triple-negative breast cancers at CM-VI was 18.1% overall (22.8% in 2008–2010, 17.4% in 2011–2014, and 15.7% in 2015–2017). The proportion of triple-negative breast cancers at INO was 13.9% overall (14.5% in 2008–2010, 13.1% in 2011–2014, and 14.4% in 2015–2017).

5.3.2 Molecular characteristics of breast cancers by age, stage, pathological type, and differentiation

At CM-VI, the luminal-like type comprised nearly half of the breast cancers diagnosed (51.8%; 329/635). In women younger than 50 years, 49.1% (170/346) were diagnosed with the luminal-like type, 32.7% (113/346) with the HER2-positive type, and 18.2% (63/346) with the triple-negative type. In women aged 50 years or older, 55.0% (159/289) were diagnosed with the luminal-like type, 27.0% (78/289) with the HER2-positive type, and 18.0% (52/289) with the triple-negative type.

At INO, the luminal-like type comprised 57.0% (580/1018) overall. In women younger than 50 years, 56.5% (305/540) were diagnosed with the luminal-like type, 28.7% (155/540) with the HER2-positive type, and 14.8% (80/540) with the triple-negative type. The distribution was similar in women aged 50 years or older, with luminal-like in 57.5% (275/478), HER2-positive in 29.5% (141/478), and triple-negative in 13.0% (62/478).

The proportion of early-stage cancers was lower in the HER2-positive cancers than in the other two types (Fig. 5.3).

A higher proportion of luminal-like cancers was detected in women with lobular carcinoma (81.1% at CM-VI and 76.5% at INO) compared with those with ductal carcinoma (51.1% at CM-VI and 57.0% at INO). Patients with triple-negative cancers had a higher proportion of poorly differentiated cancers, both at CM-VI and at INO (Fig. 5.4).

5.4 Distribution of patient demographics, tumour characteristics, and stage at diagnosis by family history of breast cancer

Our study observed no difference in age distribution, stage at diagnosis, pathology, or molecular characteristics of breast cancers detected in those with a family history in first- and/or second-degree relatives compared with those without such history.

5.5 Breast cancer stage, pathology, and molecular characteristics – comparison between Morocco and other regions or countries

The proportion of patients presenting with early-stage breast cancer in Morocco (~55%) is comparable to that reported in the high-income countries in the Eastern Mediterranean Region (e.g. Bahrain, 58%; Saudi Arabia, 55%) and is substantially higher than that reported in most LMICs (El Saghir et al., 2007). A meta-analysis of 83 studies in sub-Saharan Africa observed that only 23% of Black populations and

48% of White populations (in South Africa only) had stage I/II disease at diagnosis (Kantelhardt and Grosse Frie, 2016). In most developed countries, the proportion of women presenting with late-stage breast cancer has gradually declined over time as a result of improved awareness, better access to medical services, and the introduction of screening. For example, in the USA, the proportion of advanced cancer (stage III/IV) declined from 50% in 1973 to 27% in 2011 in White women and from 60% to 32% in Black women (SEER, 2015). Access delay for patients with breast cancer symptoms was observed to be the most important determinant of presentation at advanced stage in our study. A reduction in access delay over time (2008–2017) in Morocco resulted in both a reduction in the proportion of clinically larger tumours and a downstaging of cancer. The highly visible awareness campaigns associated with the screening programme launched in 2010, the establishment of cancer early detection centres for women, and the implementation of high-volume opportunistic screening are factors responsible for such improvement.

The frequency of different histopathological types observed in our study was in agreement with what has been reported in world literature. Invasive ductal carcinoma (not otherwise specified) comprises 50–80% of all breast cancers; invasive lobular carcinoma is the second most common variety and is reported in 5–15% of all breast cancers (Weigelt et al., 2008).

Systematic reviews have shown that ER is expressed in up to 80% and PR in 55–65% of breast cancers, and the luminal-like type comprises 50–70% of all breast cancers (Fragomeni et al., 2018). The frequency of luminal-like breast cancers (51.8% at CM-VI and 57.0% at INO) reported in our study was on a par with the results of other international studies. HER2-positive cancers are more aggressive in nature and are more frequent in younger women (Perou et al., 2000). The proportion of women with HER2-positive breast cancers in our study was higher than that reported in patients in developed countries, possibly because of the lower median age. The prevalence of HER2-positive breast cancers reported in 1026 patients with breast cancer included

Fig. 5.3. Distribution of the molecular subtypes of breast cancer by stage. CM-VI, Centre Mohammed VI pour le traitement des cancers; HER2, human epidermal growth factor receptor 2; INO, Institut National d'Oncologie Sidi Mohamed Ben Abdellah.

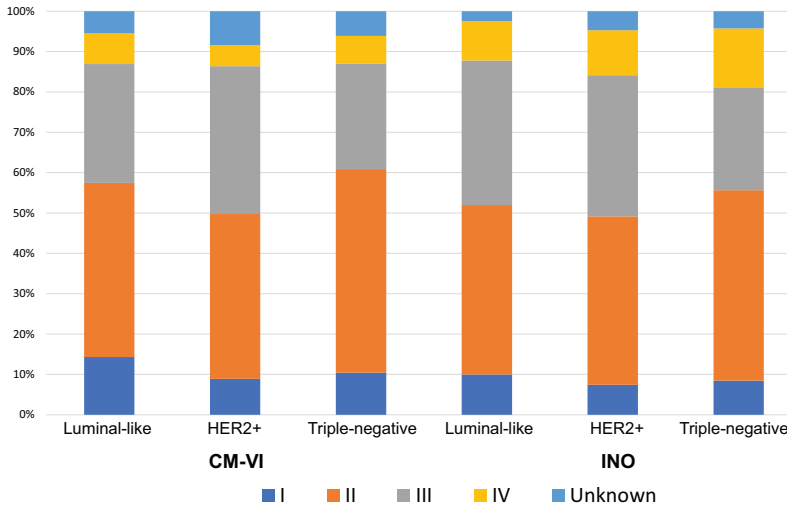


Fig. 5.4. Distribution of the molecular subtypes of breast cancer according to degree of differentiation. CM-VI, Centre Mohammed VI pour le traitement des cancers; HER2, human epidermal growth factor receptor 2; INO, Institut National d'Oncologie Sidi Mohamed Ben Abdellah.

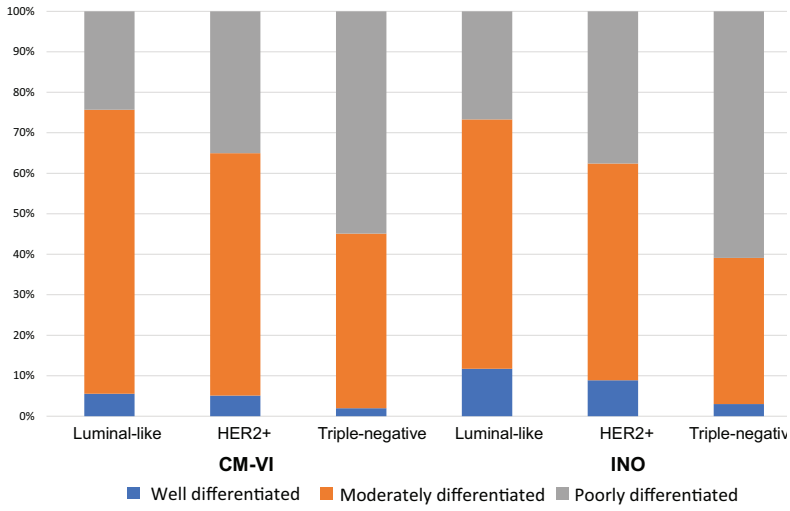


Table 5.3. Molecular characteristics of breast cancers at the two centres

Characteristics	Period of diagnosis						Total	
	2008–2010		2011–2014		2015–2017			
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
CM-VI								
Immunochemistry result								
ER−	67	(38.7)	90	(28.5)	50	(21.9)	207	(28.9)
ER+	106	(61.3)	226	(71.5)	178	(78.1)	510	(71.1)
PR−	72	(42.1)	105	(33.2)	60	(26.4)	237	(33.2)
PR+	99	(57.9)	211	(66.8)	167	(73.6)	477	(66.8)
HER2−	106	(70.2)	209	(72.1)	135	(66.8)	450	(70.0)
HER2+	45	(29.8)	81	(27.9)	67	(33.2)	193	(30.0)
Combinations of ER, PR, and HER2 status								
ER+ and/or PR+ and HER2−	70	(47.0)	158	(54.9)	101	(51.0)	329	(51.8)
ER+ and/or PR+ and HER2+	25	(16.8)	55	(19.1)	57	(28.8)	137	(21.6)
ER− and PR− and HER2+	20	(13.4)	25	(8.7)	9	(4.5)	54	(8.5)
Triple-negative	34	(22.8)	50	(17.4)	31	(15.7)	115	(18.1)
INO								
Immunochemistry result								
ER−	84	(28.7)	91	(23.6)	91	(21.7)	266	(24.2)
ER+	209	(71.3)	295	(76.4)	328	(78.3)	832	(75.8)
PR−	93	(31.7)	107	(27.7)	141	(33.7)	341	(31.1)
PR+	200	(68.3)	279	(72.3)	277	(66.3)	756	(68.9)
HER2−	181	(70.4)	271	(70.4)	275	(70.9)	727	(70.6)
HER2+	76	(29.6)	114	(29.6)	113	(29.1)	303	(29.4)
Combinations of ER, PR, and HER2 status								
ER+ and/or PR+ and HER2−	144	(56.5)	220	(57.4)	217	(56.8)	581	(57.0)
ER+ and/or PR+ and HER2+	51	(20.0)	78	(20.4)	82	(21.5)	211	(20.7)
ER− and PR− and HER2+	23	(9.0)	35	(9.1)	28	(7.3)	86	(8.4)
Triple-negative	37	(14.5)	50	(13.1)	55	(14.4)	142	(13.9)

CM-VI, Centre Mohammed VI pour le traitement des cancers; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; INO, Institut National d'Oncologie Sidi Mohamed Ben Abdellah; PR, progesterone receptor.

in 12 population-based United States Surveillance, Epidemiology, and End Results (SEER) registries was 16% for stages I, II, and IIIa breast cancer, with higher prevalence noted in younger women (Cronin et al., 2010). A study conducted in 635 Iraqi patients with breast cancer with a mean age of 49 years observed the same frequency of HER2-positive cancers (29.2%) as we did in Morocco (Alwan et al., 2018). Triple-negative breast cancers represent 15–20% of all breast cancers (Fragomeni et al., 2018), and we observed similar proportions (18.1% at CM-VI and 13.9% at INO).

In most limited-resource countries, immunohistochemistry facilities are either unavailable or of suboptimal quality. A systematic review and meta-analysis of 54 studies in North Africa involving 12 284 patients with breast cancer and 26 studies in sub-Saharan Africa involving 4737 patients with breast cancer observed a great variability in the frequencies of ER/PR-positive and HER2-positive cancers in the Indigenous populations (Eng et

al., 2014). Although the proportion of ER-positive cancers ranged widely, between 20% and 80%, the pooled proportion of ER-positive cancers in the studies that used prospectively collected samples (and hence are likely to be more reliable) was 59% and that of triple-negative cancers was 21%. The authors of the systematic review concluded that variability in the quality of procedures used to collect, store, and analyse tumour specimens greatly influenced the detection rates and explained the large heterogeneity seen across the studies in Africa. Many of the African studies have reported a very high frequency of triple-negative cancers, most likely because low-quality immunohistochemistry facilities are unable to detect expression of the receptors (Eng et al., 2014).

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