PATTERNS OF CARE FOR WOMEN WITH BREAST CANCER IN MOROCCO

AN ASSESSMENT OF BREAST CANCER DIAGNOSIS, MANAGEMENT, AND SURVIVAL IN TWO LEADING ONCOLOGY CENTRES

International Agency for Research on Cancer

World Health Organization

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FONDATION LALLA SALMA
PRÉVENTION ET TRAITEMENT DES CANCERS

مؤسسة لالا سلمى للوقاية وعلاج السرطان

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Prepared by

The International Agency for Research on Cancer
Lyon, France

in collaboration with

The Ministry of Health, Kingdom of Morocco

and

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Foreword

The International Agency for Research on Cancer (IARC) is pleased to publish *Patterns of care for women with breast cancer in Morocco: an assessment of breast cancer diagnosis, management, and survival in two leading oncology centres* on the eve of the launch of the Global Breast Cancer Initiative by the World Health Organization (WHO). This publication summarizes the outcomes of a patterns-of-care study recently completed by IARC in collaboration with the Ministry of Health of the Kingdom of Morocco and the Lalla Salma Foundation for Cancer Prevention and Treatment.

Guided by a progressive National Plan for Cancer Prevention and Control formulated in 2010, the Moroccan Ministry of Health has made significant investments to implement a nationwide breast cancer screening programme and improve diagnostic and treatment facilities for breast cancer in the country. This patterns-of-care study was conducted at the two largest publicly funded oncology centres in Morocco: Centre Mohammed VI pour le traitement des cancers (CM-VI) in Casablanca and Institut National d'Oncologie Sidi Mohamed Ben Abdellah (INO) in Rabat, to assess how far state-of-the-art cancer diagnostics and therapy have been disseminated into routine health care after the implementation of the new strategies.

This high-impact study involved more than 2000 patients with breast cancer who were registered at CM-VI and INO over a decade, from 2008 to 2017. It documented temporal variations in breast cancer characteristics, the level of improvement in access to cancer diagnosis and treatment over time, the variations in practices related to breast cancer treatment, and the time trend of disease-free survival for these patients. The study found a reduction in access delay over time, a significant improvement over time in the proportion of patients covered by state-sponsored health insurance, a lower prevalence of advanced-stage breast cancer compared with other countries in the region, a high proportion of patients with complete pathological staging and molecular profiling, and 5-year disease-free survival for early-stage breast cancer at INO that was comparable to that observed in high-resource countries.

These findings highlight the improvements in breast cancer care that occurred in Morocco as a result of pragmatic policies and systematic planning.

The study also documented several deficiencies in breast cancer care, to be addressed by the Moroccan Ministry of Health. Despite some improvement over time, the access delay was still unacceptably high. Prolonged intervals were observed between confirmation of diagnosis and initiation of treatment, and between surgery and initiation of adjuvant treatment. A high proportion of patients who were eligible for breast-conserving surgery underwent mastectomy. In addition, there were significant disparities in the quality of care between CM-VI and INO.

It is extremely important for such pragmatic studies to be implemented in every country, to enable more informed and realistic cancer control planning. We congratulate our collaborators in Morocco for having the foresight to implement this study, and thank them for involving IARC from the very beginning. This study is an excellent example of IARC's mission: cancer research that matters.

Dr Elisabete Weiderpass
Director, International Agency for Research on Cancer

Préface

Le premier Plan National de Prévention et de Contrôle du Cancer (PNPCC) 2010–2019 avec ses quatre axes d'intervention (prévention, détection précoce, traitement et soins palliatifs) et ses 78 mesures a constitué la première stratégie de lutte contre le cancer au Maroc. Ce Plan décennal, élaboré selon une démarche participative, prônait une approche intégrée et visait à diminuer la morbidité et la mortalité dues au cancer, à travers un accès équitable aux soins et services en oncologie, centrés sur la personne, à travers l'ensemble du Royaume.

Le cancer du sein constitue le cancer le plus fréquent tout âge et sexe confondus. Chez la femme, il est de loin le premier cancer diagnostiqué. Sa détection précoce et sa prise en charge constituent une priorité du PNPCC.

Ainsi, un programme de diagnostic précoce du cancer du sein a été institutionnalisé depuis 2010, par la création de centres de diagnostic précoce à travers tout le territoire national, et intégré dans le système de santé public. Les protocoles de diagnostic et les référentiels de traitement du cancer du sein élaborés sont diffusés et actualisés régulièrement. Une formation de tout le personnel des soins de santé de base a été réalisée. Ce programme de diagnostic précoce du cancer du sein est accompagné régulièrement par des campagnes de communication grand public.

Toutes ces actions ont permis une meilleure accessibilité à la détection précoce du cancer du sein et un meilleur accès aux soins à son traitement, et pour toute la population.

Les nombreuses études et évaluations menées sur le terrain, en particulier avec le Centre International de Recherche sur le Cancer (CIRC/OMS), nous ont permis de lancer un nouveau Plan cancer 2020–2029, basé surtout sur la gouvernance, la qualité des soins, la recherche et la formation.

Nous savons que le chemin est encore long. Grâce à la mobilisation de tous, nous continuons d'œuvrer pour améliorer la qualité de prise en charge des patients.

Rachid Bekkali
Directeur général, Fondation Lalla Salma – Prévention et traitement des cancers

Preface

The first National Plan for Cancer Prevention and Control (NPCPC) 2010–2019, with its four areas of intervention (prevention, early detection, treatment, and palliative care) and its 78 measures, constituted the first strategy to fight cancer in Morocco. This 10-Year Plan, developed through a participatory process, advocated an integrated approach and aimed to decrease morbidity and mortality due to cancer, through equitable access to oncology care and services, in a person-centred approach, throughout the entire Kingdom.

Breast cancer is the most common cancer type for all ages and both sexes combined. In women, it is by far the most commonly diagnosed cancer. Early detection and management of breast cancer are a priority for the NPCPC.

Therefore, a breast cancer screening programme was established in 2010, by creating screening centres across the country, and integrated into the public health system. The developed diagnostic protocols and standards for the treatment of breast cancer are disseminated and regularly updated. Training of all basic health care personnel has been carried out. This breast cancer screening programme is accompanied by regular communication campaigns for the general public.

All of these actions have made it possible to improve the access to breast cancer screening and the access to care for breast cancer treatment, and for the entire population.

The numerous studies and assessments conducted in the field, in particular with the International Agency for Research on Cancer (IARC/WHO), have enabled us to launch a new Cancer Plan 2020–2029, which is based above all on governance, quality of care, research, and training.

We know that there is still a long way to go. Thanks to the mobilization of all, we continue to work to improve the quality of patient care.

Dr Rachid Bekkali
Director-General, Lalla Salma Foundation for Cancer Prevention and Treatment

Executive summary

Background

Breast cancer is not only the most commonly diagnosed cancer in the world but also highly curable, with 5-year relative survival rates reported to range between 69% and 89% in Europe and North America. Survival rates depend directly on the stage at diagnosis, waiting time to initiate treatment after diagnosis, quality of treatment, and compliance with treatment.

Guided by the National Plan for Cancer Prevention and Control (2010–2019), the Moroccan Ministry of Health has made significant investments in improving diagnostic and therapeutic facilities for common cancer types in Morocco. Initiatives include the introduction of breast and cervical cancer screening programmes nationwide and the establishment of specialized units to manage breast and cervical cancers at the two largest publicly funded oncology centres in the country: Centre Mohammed VI pour le traitement des cancers (CM-VI) in Casablanca and Institut National d'Oncologie Sidi Mohamed Ben Abdellah (INO) in Rabat. The International Agency for Research on Cancer (IARC)/World Health Organization (WHO), located in Lyon, France, collaborated with the Ministry of Health and the Lalla Salma Foundation for Cancer Prevention and Treatment to implement a **patterns-of-care study on breast cancer** to assess how far state-of-the-art cancer diagnostics and therapy have been disseminated into routine oncology practice. The study also aimed to identify patient-, provider-, and health system-level factors associated with receipt and utilization of cancer care and to measure their impact on cancer-specific survival.

The study was conducted retrospectively at CM-VI and INO and documented the changing patterns of care over a decade, from 2008 to 2017.

Methods

Patients with a confirmed diagnosis of breast cancer who were registered at the two oncology centres between 2008 and 2017 were included in the retrospective study. Patients with recurrence detected at registration were excluded. The records of eligible patients registered during a 2-month period of each year between 2008 and 2017 were scanned, and data were abstracted to fill in a structured questionnaire. The bimonthly sampling cycle started in January and February for 2008 and was shifted to the next 2 months every year until 2017. Data were abstracted from the case records by trained investigators using a structured questionnaire.

A total of **915 patients** from CM-VI and **1205 patients** from INO were included in the analysis.

Key findings

The **median age** at registration of patients with breast cancer was 49 years, and most were premenopausal. No appreciable shift in median age was seen over time.

A **family history of breast cancer** in first- and/or second-degree relatives was reported in 12.5% of the patients with breast cancer.

The median interval between the onset of symptoms and first medical consultation leading to referral for cancer diagnosis (the **access delay**) was 6 months. The interval exceeded 12 months in 30% of the patients. The access delay was significantly shorter in 2013–2017 than in 2008–

2012 for the patients registered at INO, possibly reflecting the benefit of the national screening programme and the awareness campaign associated with the programme.

A significant improvement in levels of **coverage with health insurance** was observed over time. Almost all the patients with breast cancer registered at CM-VI were covered by a health insurance scheme during 2015–2017; 86% were covered by the Régime d'Assistance Médicale (RAMED) scheme, which aimed to protect the most economically disadvantaged populations. At INO during the same period, 88% of the patients were covered by a health insurance scheme and 63% were covered by RAMED alone.

Overall, **adequate information to determine American Joint Committee on Cancer (AJCC) tumour–node–metastasis (TNM) stage** was available for 90% of the patients with breast cancer.

A **complete pathology report** (including tumour type and differentiation) was available for more than 90% of the patients, and **hormone receptor and human epidermal growth factor receptor 2 (HER2) expression status** was recorded for more than 80% of the patients. This not only highlights the high standard of the pathology facilities available but also reflects the high quality of record maintenance and service organization at the oncology centres.

The proportion of patients **presenting with advanced-stage cancer** (stage III or IV) was about 45%, and a decrease in the proportion of advanced-stage cancers was noted over time at INO but not at CM-VI. The interval between the onset of symptoms and first medical consultation (the access delay) was the only statistically significant determinant of advanced stage at presentation and was independent of all sociodemographic parameters.

The proportion of patients diagnosed with **clinically small tumours (≤ 2 cm in diameter)** increased with time both at CM-VI (15.1% in 2008–2010 and 20.0% in 2015–2017) and at INO (14.2% in 2008–2010 and 17.9% in 2015–2017), with a corresponding decline in the proportion of locally advanced cancers. This could be an early impact of the breast cancer screening programme, which was introduced in 2010.

Molecular profiling of breast cancers showed that about 55% of patients had luminal-like (estrogen receptor [ER]- and/or progestogen receptor [PR]-positive; HER2-negative) cancers and approximately 30% of patients had HER2-positive cancers (ER and PR either positive or negative). The proportion of triple-negative breast cancers was about 16%. The prevalence of triple-negative breast cancers in our study is comparable to that reported in studies in the USA and Europe. Earlier studies in Africa reported a much higher proportion of triple-negative breast cancers, most likely because of the failure to detect molecular markers in low-quality immunohistochemistry facilities.

Both oncology centres have a **multidisciplinary tumour board (MTB)** that meets once a week. Whereas all patients with breast cancer are referred to the MTB at INO, only selected cases are referred at CM-VI.

Treatment details were available for 86% of the patients registered at CM-VI and 96% of those registered at INO. Most patients at CM-VI (68%) had received some form of cancer-directed treatment (mostly surgery) before registration at the centre. The proportion of patients treated elsewhere (mostly with surgery) was lower at INO (37%). Patients **who had received all their treatment in settings outside the oncology centres had worse prognosis** (persistence or recurrence) than those treated partially or fully at the oncology centres.

The median interval between diagnosis and initiation of treatment (the **treatment delay**) was 2.7 months for patients registered at CM-VI and 1.6 months for those registered at INO. The interval decreased over time at CM-VI but increased at INO. The median interval between registration and initiation of cancer-directed treatment was also relatively long (1.5 months) at both centres.

Surgery was the mainstay of breast cancer management; 70% of the patients registered at CM-VI and 86% of those at INO underwent surgery. The proportion of patients with stage I–III cancer who were treated with **breast-conserving surgery** (BCS) was 50% at CM-VI and only 26% at INO. Postoperative radiotherapy was administered to only 38% of the patients registered at CM-VI who underwent BCS. The proportion was much higher (74%) in those registered at INO. However, the proportion of patients undergoing postoperative radiotherapy at CM-VI is probably underestimated, because some of them had their records maintained in a separate database in the radiotherapy department.

External beam radiotherapy was completed in 3–4 weeks in 55.1% of patients receiving radiotherapy at CM-VI and 66.2% of patients at INO because of the **use of hypofractionated radiotherapy**. Very few of the patients who received radiotherapy at INO and none of those at CM-VI required hospitalization, because most of them were accommodated in the Houses of Life (*Maisons de Vie*) built especially for this purpose.

The **median interval between surgery and initiation of adjuvant chemotherapy** for patients who did not receive radiotherapy in the intervening period was 3 months for those

registered at CM-VI and 2 months for those registered at INO. Ideally, this interval should not exceed 4 weeks.

Overall, 68% of the patients registered at CM-VI and 85% of those registered at INO received **chemotherapy**. Of the patients treated with chemotherapy, the proportion who received **neoadjuvant chemotherapy** was low, both at CM-VI (11%) and at INO (19%).

Almost all the patients treated with chemotherapy received an **anthracycline-based regimen** (either AC60/600 [four cycles of 60 mg/m^2 doxorubicin and 600 mg/m^2 cyclophosphamide every 3 weeks] or FEC100 [600 mg/m^2 5-fluorouracil, 100 mg/m^2 epirubicin, and 600 mg/m^2 cyclophosphamide]). Overall, 53% of the patients who received chemotherapy at CM-VI and 68% of patients at INO had a **taxane included** in the regimen. Inclusion of all chemotherapy drugs necessary for breast cancer management (including trastuzumab) in the **national list of essential drugs** has facilitated their procurement by public hospitals and ensured high treatment completion rates.

Endocrine therapy was administered to 54% of the patients with ER- and/or PR-positive cancers at CM-VI and 84% of those at INO. The proportion of patients who received hormone therapy might have been underestimated, because many received the drugs through outpatient prescriptions. **Trastuzumab** was administered to 28% of patients with HER2-positive cancers at CM-VI and 46% of those at INO.

Survival analysis could be performed only for those patients registered in 2008–2015, because the follow-up data were incomplete for those registered in 2016–2017. **Disease status at last follow-up** was documented for approximately 80% of the patients registered in 2008–2015. Very few patients were documented to have died at follow-up. This was essentially because the oncology centres did not have information on the patients dying at other health facilities or at home.

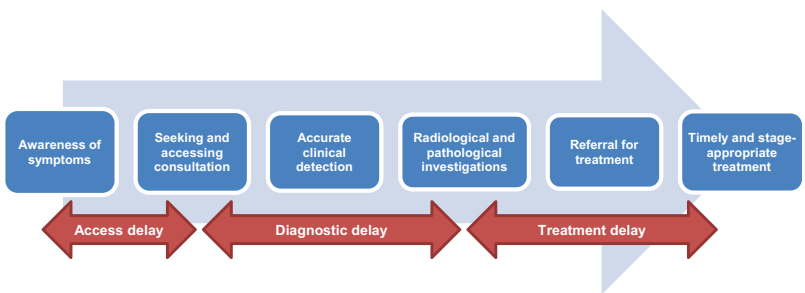
The **5-year disease-free survival (DFS)** was 53% for the patients registered at CM-VI and 70% for those registered at INO. The independent factors that were significantly associated with a higher risk of persistent disease or relapse were: **registration during 2013–2015 (compared with registration in 2008–2012), advanced stage of cancer, poorly differentiated cancer, triple-negative cancer, and treatment type**. Being treated completely outside the oncology centres was an important determinant of poor survival. The 5-year DFS was same for the patients with stage I and II cancer treated with BCS (82.9%) or mastectomy (81.3%).

Summary recommendations for strengthening breast cancer care in Morocco

This patterns-of-care study on breast cancer in Morocco revealed that significant progress has been made over the past decade in reducing the access delay, which has resulted in a modest downstaging of cancer (i.e. a shift in the stage distribution of tumours detected towards a lower stage), in organizing high-quality pathology services, and in offering treatment tailored to stage and molecular profile to a large number of patients. At the same time, the study highlighted the deficiencies that need to be addressed to optimize breast cancer management. Reducing the delays in the care pathway for women with breast cancer symptoms could significantly improve the quality of care and survival rates (Fig. 1).

- The **access delay should be further reduced** by improving community awareness and ensuring that frontline health-care providers (nurses and general practitioners at the primary care level) are better trained to recognize symptoms of breast cancer and perform clinical breast examination. The breast cancer awareness campaign held every year in October needs to be strengthened. Awareness activities should be spread over the year.
- Several **cancer early detection centres** equipped with radiology (ultrasound and mammography) and core biopsy facilities have been established across Morocco to cater for referrals from the breast cancer screening programme. The services of these early detection centres can be used to examine and investigate women with symptoms of breast cancer as well. A well-coordinated **system of referral** should be established between the primary

Fig. 1. Delays in the care pathway for patients with breast cancer are still too long in Morocco. A concerted effort is needed to reduce these delays.



health centres, the cancer early detection centres, and the treatment facilities.

- Most likely because of the screening programme that has been implemented in Morocco, the capacity to diagnose breast cancer has improved in general. Most patients have a diagnosis confirmed on histopathology by the time they reach an oncology centre. Some early impacts of the screening programme on clinical downstaging are also visible. The quality and coverage of the **screening programme should be improved**. Higher compliance with further investigations in screen-positive women is needed.
- The **capacity to detect hormone receptor and HER2 expression** should be further improved at the oncology centres so that the proportion of patients with a complete molecular profile of breast cancer is higher than the current 80%.
- A large number of patients are undergoing surgery in general hospitals and clinics rather than at the oncology centres. **Decentralization of surgical services** may be a strength if it is appropriately monitored and if the surgeons are adequately trained in the principles and skills of cancer surgery. At present, many of the patients treated in non-oncology specialist settings do not receive standard-of-care treatment (as evidenced by the low proportion of patients receiving neoadjuvant chemotherapy or BCS).
- **Clinical practice guidelines** for managing breast cancer appropriate to the context in Morocco should be drawn up to standardize treatment and harmonize management practices across different facilities. The practice guidelines should be endorsed by the appropriate authorities and disseminated widely through orientation workshops.
- All newly diagnosed cases of breast cancer should be presented at the **MTBs**. Non-oncology settings managing breast cancers (including those in the private sector) could be linked digitally to any of the MTBs at the oncology centres in the region. The surgeons in non-oncology specialist settings should be able to discuss their cases before surgery.
- Efforts should be made to further **reduce the treatment delay**. Better counselling of the patients, prioritization of treatment of early-stage cancers, decentralization of treatment services, and improved coordination between different departments may help to reduce the delay.
- The use of **generic brands** and other innovative procurement mechanisms (e.g. direct negotiation with the manufacturers for bulk purchase) should be considered to ensure regular supply of more costly medicines such as taxanes or trastuzumab, which are already included in the national list of essential drugs.
- A **system of quality assurance** should be introduced, focusing on clinical effectiveness, patient safety, and patient experience related to breast cancer care. This will require regular auditing of services and feedback to be gathered from patients. A set of performance indicators and their standards tailored to the national context should be listed.

Abbreviations

5-FU	5-fluorouracil
AJCC	American Joint Committee on Cancer
ALND	axillary lymph node dissection
AMO	assurance maladie obligatoire
ASR	age-standardized rate
BCS	breast-conserving surgery
CBE	clinical breast examination
CI	confidence interval
CMF	cyclophosphamide, methotrexate, and 5-fluorouracil
CM-VI	Centre Mohammed VI pour le traitement des cancers
CNOPS	Caisse Nationale des Organismes de Prévoyance Sociale
CNSS	Caisse Nationale de Sécurité Sociale
DFS	disease-free survival
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
EBRT	external beam radiation therapy
ER	estrogen receptor
EUSOMA	European Society of Breast Cancer Specialists
FEC	5-FU, epirubicin, and cyclophosphamide
FISH	fluorescence in situ hybridization
FNAC	fine-needle aspiration cytology
GDP	gross domestic product
GnRH	gonadotropin-releasing hormone
HDI	Human Development Index
HDR	high-dose-rate
HER2	human epidermal growth factor receptor 2
IAEA	International Atomic Energy Agency
IARC	International Agency for Research on Cancer

INCTR	International Network for Cancer Treatment and Research
INO	Institut National d'Oncologie Sidi Mohamed Ben Abdellah
IQR	interquartile range
IRC	Institut de Recherche sur le Cancer
LDR	low-dose-rate
linac	linear accelerator
LMICs	low- and middle-income countries
MRI	magnetic resonance imaging
MRM	modified radical mastectomy
MTB	multidisciplinary tumour board
NCCN	National Comprehensive Cancer Network
NCD	noncommunicable disease
OECD	Organisation for Economic Co-operation and Development
OR	odds ratio
PBCR	population-based cancer registry
PET	positron emission tomography
POC	patterns-of-care
PR	progesterone receptor
RAMED	Régime d'Assistance Médicale
RCT	randomized controlled trial
SEER	United States Surveillance, Epidemiology, and End Results
SHI	social health insurance
SLN	sentinel lymph node
TNM	tumour–node–metastasis
UHC	universal health coverage
WHO	World Health Organization

CHAPTER 1.

Introduction

Key observations

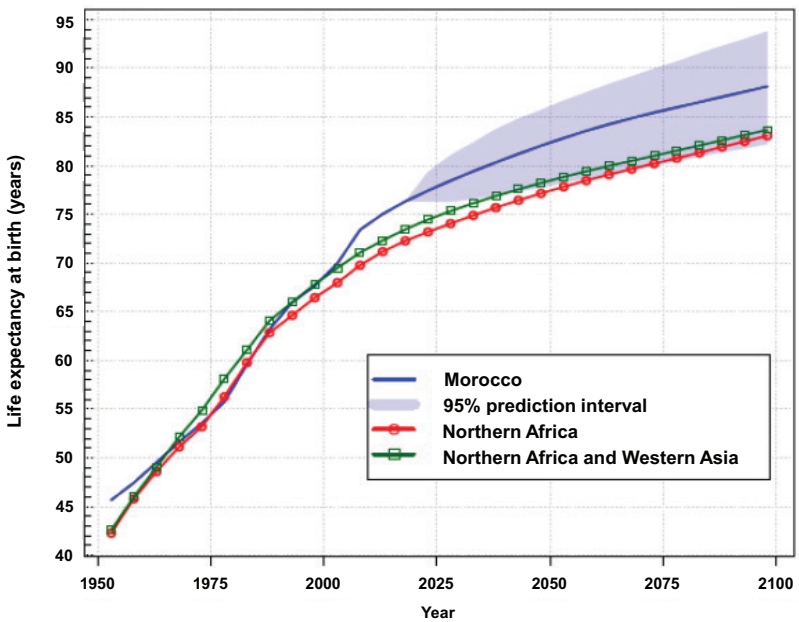
- Several indicators of population health have improved in Morocco in recent years, including maternal and child mortality and life expectancy. High coverage of immunization and other public health measures have eliminated major communicable diseases such as polio, malaria, trachoma, and schistosomiasis in the country.
- Because of changes in the epidemiological profile in Morocco, the disease burden has shifted to noncommunicable diseases (NCDs), including cancer, which are currently responsible for nearly 75% of all deaths.
- The country has also made progress towards universal health coverage (UHC), although with a modest 5.25% of the gross domestic product spent on health in 2017, health-care users are still required to provide a high level of out-of-pocket expenditure.
- Breast cancer is the most commonly diagnosed cancer in Moroccan women, accounting for 35.8% of all new cancer cases in women.
- The first National Plan for Cancer Prevention and Control (2010–2019) enabled major investment in infrastructure and services for the early diagnosis and treatment of cancer. In 2010, Morocco initiated a breast cancer screening programme based on clinical breast examination (CBE).
- In 2016–2017, a quality assurance evaluation of the CBE programme showed that it achieved reasonable coverage of the target population (62.8%), but there was a low breast cancer detection rate (1.0 per 1000 women). Reasons for the low detection rate were identified and interventions put in place to address them.
- Significant efforts have been made under the National Cancer Plan to improve cancer care in general and breast cancer treatment in particular, through the establishment of specialized breast cancer treatment centres, an increase in the number of radiotherapy facilities, improved coverage of health insurance schemes, and the provision of reliable supplies of essential chemotherapeutic drugs.
- This patterns-of-care (POC) study was conducted at the two most prominent publicly funded oncology centres in Morocco: the Centre Mohammed VI pour le traitement des cancers (CM-VI) in Casablanca and the Institut National d'Oncologie Sidi Mohamed Ben Abdellah (INO) in Rabat.

1.1 Demographics, cancer burden, and organization of cancer care in Morocco

Morocco is a lower middle-income country in the Eastern Mediterranean Region with a population of 36.5 million in 2019 (United Nations, 2019). In recent years, several health-care indices have improved significantly in the country after sustained and high investment in health care (WHO, 2018). The life expectancy at birth (both sexes, 2019) is 76.7 years, which is substantially higher than the average life expectancy of 73.8 years reported from other countries in the Northern Africa and Western Asia region (Fig. 1.1) (United Nations, 2019; World Bank, 2020a). High coverage of immunization and other public health measures have eliminated major communicable diseases such as polio, malaria, trachoma, and schistosomiasis in the country. The effectiveness of Morocco's public health programmes is underscored by the accelerated reduction in maternal mortality rates by 78.1% and child (<5 years) mortality rates by 65% between 1990 and 2015. The country has successfully kept the prevalence of HIV/AIDS at a low and relatively stable level (about 0.1% in 2017) in the general population and has a high coverage of antiretroviral therapy for individuals with HIV.

In 2017, Morocco spent 5.25% of its gross domestic product (GDP) on health (World Bank, 2020b). This percentage is modest in comparison with Organisation for Economic Co-operation and Development (OECD) countries, which spend 8.8% on average. The introduction of special health insurance schemes to protect poor and vulnerable people has improved access to health care. Nevertheless, private out-of-pocket expenditure as a proportion of total health expenditure is high (66.1%) and the private for-profit health sector has a strong presence in the country. In recent years, Morocco has made good progress towards UHC with support from the European Union, World Bank, African Development Bank, and WHO. The Lalla Salma Foundation for Cancer Prevention and Treatment, a major civil society stakeholder, has provided significant support to the Ministry of Health to improve overall cancer care.

Fig. 1.1. Improvement in life expectancy at birth in Morocco (both sexes combined) compared with neighbouring countries. Source: United Nations (2019). © 2019 United Nations. Reprinted with the permission of the United Nations.



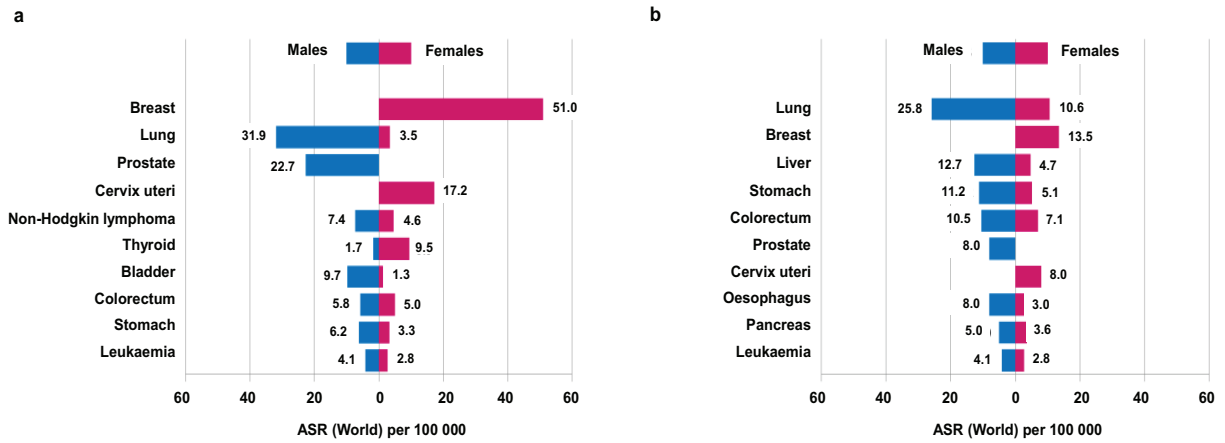
1.1.1 Cancer burden in Morocco

The epidemiological profile of diseases is changing rapidly in Morocco and the burden has shifted to NCDs, which are now responsible for nearly 75% of all deaths. In 2018, IARC estimated that there were 52 783 new cases of cancer and 32 962 cancer deaths (Ferlay et al., 2018). The age-standardized (World) incidence rates of cancer were 140.7 per 100 000 in men and 139.3 per 100 000 in women. The most frequent cancers in men are lung and prostate cancers, and the most frequent in women are breast and cervical cancers (Fig. 1.2).

1.1.2 Breast cancer burden in Morocco

Breast cancer, the most commonly diagnosed cancer in women, contributes nearly a quarter (24.2%) of all new cancers diagnosed in women worldwide. It is the most frequent of all cancers in 154 of the 185 countries included in GLOBOCAN 2018 (Ferlay et al., 2018). Breast cancer is also the leading cause of cancer death in women worldwide (15.0% of all cancer deaths) (Bray et al., 2018). According to IARC, it is estimated that in 2018 about 2.1 million new cases of breast cancer were diagnosed worldwide and about 627 000 deaths from breast cancer occurred. Nearly 70% of deaths from breast cancer are in low- and middle-income countries (LMICs), where the cancer has a high fatality rate as a result of late diagnosis and

Fig. 1.2. Cancer burden in Morocco (2018). (a) Age-standardized (World) incidence rates per sex, top 10 cancers. (b) Age-standardized (World) mortality rates per sex, top 10 cancers. ASR, age-standardized rate. Source: Reproduced with permission from Ferlay et al. (2018).



suboptimal treatment facilities (Lukong et al., 2017).

The incidence of breast cancer is currently rising, and because of population growth, an ageing population, and increasing adoption of unhealthy lifestyles, countries with the least resources will be hardest hit. For example, the burden of breast cancer is projected to double in Africa by 2030, especially in the absence of effective public health policies and interventions (Ferlay et al., 2010). The existing inequity in access to good-quality cancer diagnostic and treatment services will worsen the situation.

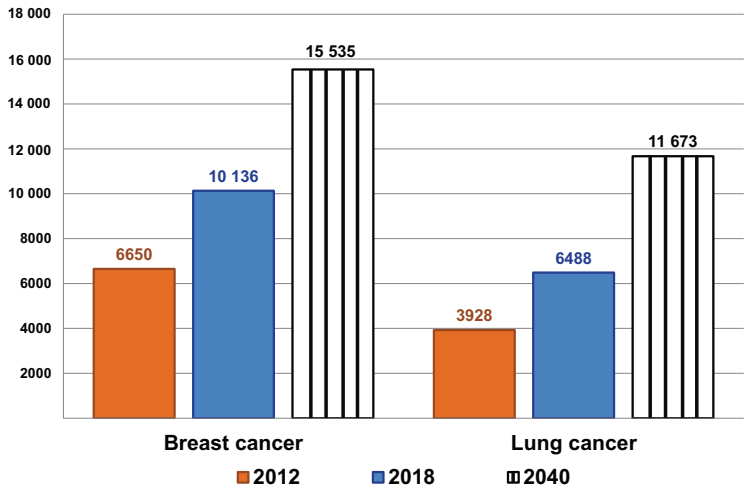
The 5-year survival from breast cancer exceeds 80% in most developed countries but is just 66.3% in sub-Saharan African countries (Joko-Fru et al., 2020).

The poor survival of patients with breast cancer in resource-constrained settings has been ascribed to late presentation, poor health-care infrastructure, and lack of adequate funding because of other competing public health challenges (Pace and Shulman, 2016).

Breast cancer is the most frequent cancer in Moroccan women. According to the Greater Casablanca Cancer Registry report published in 2016, breast cancer accounted for 35.8% of all new cancer cases in women (Registre des Cancers de la Région du Grand Casablanca, 2016). The age-standardized (World) incidence rate of breast cancer in Moroccan women increased from 35.0 per 100 000 women in 2004 to 43.5 per 100 000 women in 2012 (Registre des Cancers de la Région du Grand Casablanca, 2004, 2016). It has been estimated that by 2040 there will be a further 50% increase in the number of breast cancers in Morocco, with more than 15 000 new cases detected annually (Fig. 1.3).

Most cases of breast cancer in women (67%) diagnosed between 2005 and 2008 in Rabat, Morocco, were at stages II or III (Mechita et al., 2016). In 2009, the 5-year survival rate reported for patients with breast cancer registered at INO was 81.5% (95% confidence interval [CI], 75.6–86.5%) (Association Lalla Salma de Lutte Contre le Cancer, 2015).

Fig. 1.3. Past and estimated future trends in total new cases detected per year (breast cancer and lung cancer). Source: Reproduced from WHO (2020), © 2020.



1.1.3 Cancer control programme in Morocco and facilities for early detection of breast cancer

The first National Plan for Cancer Prevention and Control (2010–2019) was published by the Moroccan Ministry of Health in 2009 (Association Lalla Salma de Lutte Contre le Cancer, 2009). It aimed to reduce morbidity and mortality rates and improve survival and quality of life of patients with cancer through promotion of prevention and early detection, improvements in diagnosis, treatment, and palliative care services, and building capacity for cancer research. A revised cancer control plan (2020–2029) was published in 2020 (Ministry of Health and Association Lalla Salma de Lutte Contre le Cancer, 2020). The Ministry of Health comprises a central administration located in the capital city of Rabat and regional administrations distributed throughout the country. The Department of Epidemiology and Disease Control, as part of the central administration of the Ministry of Health, is responsible for planning and implementing the National Cancer Plan and oversees the treatment of cancer patients. Seven university hospital centres (in Rabat, Casablanca, Fes, Marrakesh, Oujda, Agadir, and Tangier) and three regional oncology centres (in Meknes, Beni Mellal, and Laayoune) deliver oncology care in the public sector. The university hospital centres are under the auspices of the Ministry of Health with total financial autonomy. The regional oncology centres are under the supervision of regional directors of health.

The first National Cancer Plan enabled major investment in infrastructure and services for the early diagnosis and treatment of cancer. In 2010, a breast cancer screening programme that aimed to screen all women aged 40–69 years with CBE once every 2 years was launched. Cancer diagnostic centres equipped with digital mammography, breast ultrasound, core biopsy, and fine-needle aspiration cytology (FNAC) were set up to investigate women who had been diagnosed with breast cancer on CBE. Today, 46 such centres have been opened in different regions of the country. A structured evaluation of the programme in 2016–2017 showed that it achieved reasonable coverage of the target population (IARC, 2017). In 2015, 62.8% of the target population was covered, 3.2% were found to be positive on CBE, the compliance of screen-positive women to further assessment was 34.1%, and the breast cancer detection rate was 1.0 per 1000 women (Basu et al., 2018). The low breast cancer detection rate was attributed primarily to the reluctance of screen-positive women to attend for further assessment.

An institute dedicated to cancer research (Institut de Recherche sur le Cancer [IRC]) was established in Fes to improve research capacity, generate scientific data that are more relevant nationally, and promote evidence-based practices in oncology care.

1.1.4 Oncology care facilities in Morocco

Regional oncology centres are the major tertiary-care oncology hospitals in the public sector in Morocco; a total of 11 have been built across the regions. Most of these centres are well equipped with cancer diagnostic and treatment facilities. A recent assessment of cancer control capacities in Morocco by WHO reported that there are 53.0 computed tomography scanners, 22.7 magnetic resonance imaging (MRI) scanners, 8.0 external beam radiation therapy (EBRT) machines, and 2.3 positron emission tomography (PET) or PET/computed tomography scanners per 10 000 cancer patients (WHO, 2020). There are fewer than two public cancer centres per 10 000 cancer patients in the country. The Ministry of Health has made special efforts to improve access to oncology care and minimize noncompliance to treatment. Free chemotherapeutic drugs are supplied, particularly for uninsured and poorer patients, and 12 special dormitories have been created to accommodate children with cancer and their families. The national chemotherapy guideline, which was first drafted in 2011, is updated every 2 years (most recent version: June 2019) to harmonize cancer treatment across the regional oncology centres (Association Marocaine de Formation et de Recherche en oncologie médicale, 2019).

Although several measures to improve palliative care in the country have been introduced, access to pain medications and palliative care for patients with cancer is still limited. At present, only CM-VI and INO have established palliative care units. A home-based palliative care unit with a mobile team comprising 35 general practitioners and 32 nurses has been piloted in Rabat. The National Health Policies set out a vision for the development of palliative care through the inclusion of pain management and palliative care in the reformed undergraduate medical curriculum and through improving access to opioid analgesics by minimizing regulatory barriers.

1.2 POC studies and their significance

1.2.1 Definition of POC studies

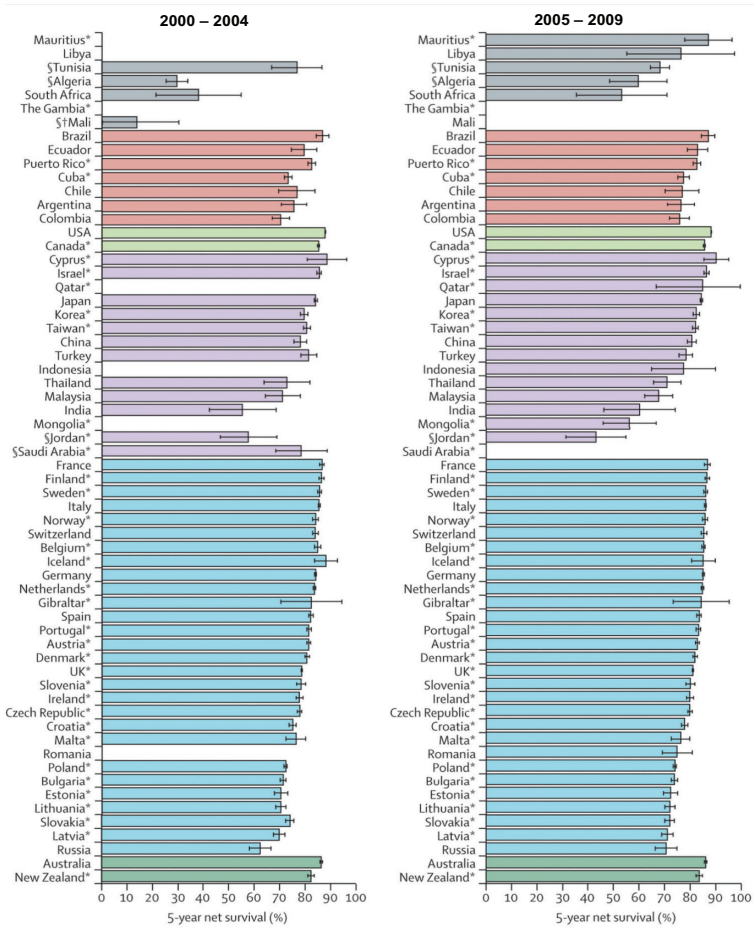
POC studies in oncology examine practice patterns, treatment-related mortality, survival, and their predictors (Moreno et al., 2017). The United

States National Cancer Institute has defined the following primary goals of POC studies (National Cancer Institute, 2020):

- to evaluate how far state-of-the-art cancer diagnostics and therapy have been disseminated into routine oncology practice; and
- to identify patient-, provider-, and health system-level factors associated with receipt and utilization of diagnostic and therapeutic oncology care and palliative services.

Delivering oncology services with quality and equity is essential to avoid cancer health disparities. Oncology centres in LMICs often struggle to provide good-quality care because they have inadequate infrastructure, lack of competent staff, irregular or poor supply of drugs, limited compliance to evidence-based management protocols, and poor record maintenance. A large number of patients disproportionate to the existing infrastructure often overburdens the health facilities and reduces the efficiency of services. Suboptimal care becomes the status quo because there is no culture of auditing the oncology services and there is no structured plan to improve quality of services. A POC study can highlight these deficiencies and help all relevant stakeholders to review the cancer care continuum in a more objective manner. Documentation of patient profiles, practice patterns, survival rates, and their determinants over a period of time enables the health system to understand the impact of measures taken to improve the quality of cancer care.

Fig. 1.4. Global distribution of age-standardized 5-year net survival for women diagnosed with breast cancer during 2000–2004 and 2005–2009, grouped by continent and country. * 100% coverage of the national population. † National estimate not age-standardized. § National estimate flagged as less reliable because the only estimate or estimates available are from a registry or registries in this category. Source: Copyright © 2015 Allemani et al. (2015). Open Access article distributed under the terms of CC BY. Published by Elsevier Ltd.



1.2.2 POC studies on breast cancer

Breast cancer is an excellent model for POC studies because the treatment is highly standardized, evidence-based, and very effective when delivered following the proper clinical practice guidelines. Stage-appropriate treatment substantially improves not only survival but also quality of life. Depending on the quality of diagnostic and therapeutic care, breast cancer survival may vary widely, as documented in the CONCORD programme for global surveillance of cancer survival. The age-standardized 5-year net survival in women diagnosed with breast cancer during 2005–2009 varied from more than 80% in 34 high-resource countries to less than 60% in Mongolia (57%) and South Africa (53%) (Fig. 1.4) (Allemani et al., 2015).

A systematic review and meta-analysis estimated a pooled 5-year survival rate of 71% (95% CI, 68–73%) for patients with breast cancer in the Eastern Mediterranean Region; substantially higher rates were observed in countries with high Human Development Index (HDI) (Maajani et al., 2020). Survival estimates are not easily available for

African countries, especially those in the sub-Saharan region. In 2011, IARC reported a dramatically low 5-year age-adjusted relative survival rate of only 10% for patients with breast cancer in The Gambia diagnosed between 1990 and 2001 (Sankaranarayanan and Swaminathan, 2011).

A clear improvement in survival has been reported worldwide in the past two decades, thanks to the use of treatment individualized to clinical and molecular profiles of cancer, adjuvant chemotherapy, adjuvant radiotherapy, endocrine therapy, and targeted therapy. A POC study can document the changes in patient characteristics, tumour characteristics, and the system of care over time and across different centres. In a retrospective multicentre study from Europe, the United Kingdom, and Sweden, the authors described the great variation in practices used to treat patients with locally advanced breast cancer and the main factors influencing the treatment strategies (Sinacki et al., 2011). Another POC study from Norway examined the time trends of availability of estrogen receptor (ER) analysis and tamoxifen use in women with ER-positive stage II breast cancer between 1980 and 1989. This study reported an increased use of tamoxifen over time (from 18% in 1980 to 51% in 1989), but it also found that surgeons were reluctant to follow the national recommendation published in 1981 to treat all women with ER-positive cancer with tamoxifen (Raabe et al., 1997). Only 58% of patients with breast cancer had ER analysis in the study period, and tamoxifen was prescribed to just 75% of the eligible patients. Thus, POC studies identify the gaps between evidence-based recommendations and real-world practices, and by doing so provide specific guidance to policy-makers and care-providers on areas with scope for improvement.

1.3 POC study in Morocco

As part of the efforts to provide high-quality care under the National Cancer Plan (2010–2019), specialized gynaecological and breast cancer centres were established at CM-VI and INO. Details of the diagnostic and treatment infrastructure and specialized human resources available for breast cancer management at CM-VI and INO are shown in Table 1.1. IARC, in collaboration with the Ministry of Health and the Lalla Salma Foundation for Cancer Prevention and Treatment, conducted a retrospective POC study on breast cancer at CM-VI and INO from 2008 to 2017. The centres were selected because of their capacity to provide specialized comprehensive care to patients with breast cancer in a public health-care setting. These are the two largest oncology centres in the country by the number of cancer patients registered every year. The outcomes of the POC study conducted in these two centres will enable readers to understand the quality of care achievable for patients with breast cancer in the public sector in Morocco and how practices have changed over time.

Table 1.1. Diagnostic and therapeutic facilities and human resources at the centres selected for the patterns-of-care study in Morocco

Characteristics	CM-VI	INO
General information		
Public or private	Public	Public
Year of establishment	Established in 1929 and renovated in 2008	1985
Specialized breast cancer unit	Yes (inaugurated in 2013)	Yes (inaugurated in 2013)
Diagnostic facilities		
Mammography	Yes (1)	Yes (2)
Computed tomography scanner	No (available at the University Hospital[a])	Yes (2)
MRI scanner	No (available at the University Hospital[a])	Yes (1)
PET or PET/computed tomography scanner	No (available at the University Hospital[a])	No
Histopathology facility	No (available at the University Hospital[a])	Yes
Immunohistochemistry facility	No (available at the University Hospital[a])	Yes
Frozen section biopsy facility	No	No
Treatment facilities		
Total number of beds for oncology patients	60	100
Outpatient chemotherapy chairs	30	30
Types of radiotherapy machines (numbers)	3D conformal radiotherapy (3) Intensity-modulated radiation (1) HDR brachytherapy (1)	3D conformal radiotherapy (3) Intensity-modulated radiation (1) Stereotactic radiotherapy (1) HDR brachytherapy (1)
Sentinel node biopsy facilities	No	Yes
MTB and meeting frequency	Yes; held once per week (selected breast cancer cases are referred)	Yes; held once per week (all new breast cancer cases are referred)
Treatment guidelines	Follows national chemotherapy protocol Follows own radiotherapy protocol	Follows national chemotherapy protocol Development of protocol for oncosurgery is in progress
Human resources (number)		
Surgical oncologists	13	8
Medical oncologists	10	10
Radiation oncologists	37	18
Radiation physicists	5	5
Radiotherapy technicians	26	20
Nurses trained in oncology care	7	42

CM-VI, Centre Mohammed VI pour le traitement des cancers; 3D, three-dimensional; HDR, high-dose-rate; INO, Institut National d'Oncologie Sidi Mohamed Ben Abdellah; MRI, magnetic resonance imaging; MTB, multidisciplinary tumour board; PET, positron emission tomography.

[a] University Hospital, Casablanca is a public sector tertiary care centre adjacent to CM-VI.

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CHAPTER 2.

Methodology

Key observations

- Patients with a confirmed diagnosis of breast cancer who were registered at the two oncology centres between 2008 and 2017 were included in the retrospective study. Patients with recurrence detected at registration were excluded.
- The records of eligible patients registered during a 2-month period of each year between 2008 and 2017 were scanned, and data were abstracted to fill in a structured questionnaire. The bimonthly sampling cycle started in January and February for 2008, and was shifted to the next 2 months every year until 2017.
- Data were abstracted from the case records by trained investigators using a structured questionnaire.
- A total of 915 patients from CM-VI and 1205 patients from INO were included in the analysis.

2.1 Study settings

We selected as the study settings the two largest publicly funded regional oncology centres in Morocco: the Centre Mohammed VI pour le traitement des cancers (CM-VI) in Casablanca and the Institut National d'Oncologie Sidi Mohamed Ben Abdellah (INO) in Rabat. They were chosen because they provide comprehensive cancer care and have facilities for surgery, radiotherapy, and chemotherapy. They also had enough cases registered per year to enable us to include approximately 2000 treated cases of breast cancer in the study. In addition, they are located in two different regions of Morocco (Casablanca-Settat and Rabat-Salé-Kénitra), enabling us to study the impact of geographical variations in the target populations.

2.2 Study objectives

This retrospective study was based on abstraction of data from the case record files of patients with breast cancer registered at CM-VI and INO. The study aimed to collect data for the 10-year period from 2008 until 2017. It had the following objectives:

- to document the sociodemographic characteristics of patients with breast cancer attending the two oncology centres and any change over a period of 10 years;
- to document the stage at diagnosis of patients with breast cancer attending the oncology centres, the pathological and molecular characteristics of the breast cancers, and any shift over time;
- to document the delays across the breast cancer care continuum by measuring the interval between onset of symptoms and first medical consultation (access delay), the interval between diagnosis and registration at the oncology centre, and the interval between diagnosis and

initiation of treatment (treatment delay), as well as their determinants and any change over time;
- to document the practices related to comprehensive treatment of patients with breast cancer using surgery, chemotherapy, radiotherapy, hormone therapy, and targeted therapy at the two oncology centres and any change in the practice pattern over the decade;
- to document the disease-free survival (DFS) of patients with breast cancer registered at the two oncology centres, its determinants, and any change over time; and
- to document the quality and completeness of documentation in the case records at the two oncology centres.

2.3 Selection of patients

The study included patients registered at the two oncology centres who had a confirmed diagnosis of breast cancer. Patients with recurrent breast cancer at the time of registration were excluded. Confirmation of diagnosis could have happened before or after registration at the centre. Patients were included even if treatment was performed fully or partially at a hospital or clinic other than the oncology centre. Patients in whom breast cancer was not the primary cancer (other than non-melanoma skin cancer) were also excluded.

The records of eligible patients registered during a 2-month period of each year, starting from 2008 and ending in 2017, were scanned for information. The bimonthly sampling cycle started in January and February for 2008, was shifted to the next 2 months every year, and restarted in January and February after 6 years. In this way, the records were retrospectively collected from the medical records department of each oncology centre for the years and months shown in Table 2.1.

For a few patients, the pathology report confirming cancer diagnosis was not available in the case records, even though they had received cancer-directed treatment (radical surgery, chemotherapy, or radiotherapy) at the oncology centre. We decided to include such patients because it was impossible for any patient without pathological confirmation of diagnosis to receive cancer treatment at either centre. It is likely that the reports for these patients had gone missing from the case files during follow-up visits. Patients without pathological confirmation of diagnosis who did not receive any cancer-directed treatment were excluded.

2.4 Data collection

A data collection form (Annex 1) was designed to reconstruct the trajectory of patients in the health-care system during the detection, diagnostic investigation, and treatment periods. The form collected basic personal information (age, education level, marital status, and occupation), medical history, investigations performed at the cancer centre or elsewhere, clinical and pathological staging, treatment (surgery, radiotherapy, chemotherapy, hormone therapy, targeted therapy, and palliative care), follow-up, and vital status data. The form was pretested and validated by a few oncologists dealing with breast cancer in Morocco.

Trained project staff collected the case records of patients with breast cancer from the medical records department at each hospital. A PhD student collected data at CM-VI, and a research nurse collected data at INO. They first screened the records for inclusion and exclusion criteria, and then used the data collection form to extract information. They looked for missing data in the

Table 2.1. Period of data collection (months)

Year of data collection	Months for which data were collected (shaded)					
	January and February	March and April	May and June	July and August	September and October	November and December
2008; 2014	■					
2009; 2015		■				
2010; 2016			■			
2011; 2017				■		
2012					■	
2013						■

registers or the databases of the departments of surgery, medical oncology, and radiation oncology. The project staff were supervised at each hospital by the institutional principal investigator.

The study was monitored by IRC, Fes, Morocco and IARC, Lyon, France. The filled-in data collection forms were checked for completeness, consistency, and validity by the principal investigators. The validated forms were entered in an online database specifically designed for this study, after de-identifying any personal information such as name, address, or phone number. The investigators at IARC checked the online forms for completeness and quality on a regular basis.

2.5 Selection of cases for analysis

Data were abstracted from the medical records of 2184 patients registered with a diagnosis of breast cancer at the oncology centres at CM-VI and INO over a consecutive 2-month period every year, starting from 2008 and continuing until 2017 (Table 2.2). The records of patients with the following characteristics were excluded at the time of analysis:

- patients with recurrent breast cancer at the time of registration (*n* = 4);
- patients who had no diagnosis of breast cancer confirmed on cytology or histopathology and who did not receive any cancer-directed treatment (surgery other than lumpectomy alone, radiotherapy, or chemotherapy) either before or after registration at the hospital (*n* = 28); and
- patients with a benign diagnosis confirmed on histopathology who did not receive any cancer-directed treatment (surgery other than lumpectomy alone, radiotherapy, or chemotherapy) either before or after registration at the hospital (*n* = 32).

Table 2.2. Number of cases excluded and reasons for exclusion

	CM-VI	INO	Total
Patient data collected	955	1229	2184
Overall number of cases excluded	40	24	64
Reasons for exclusion			
Recurrent breast cancer	1	3	4
No cancer-directed treatment	32	13	45
No diagnosis confirmed on histopathology orcytology	20	8	28
Benign	12	5	17
Benign, treated with lumpectomy alone	7	8	15
Patients included in final analysis	**915**	**1205**	**2120**

CM-VI, Centre Mohammed VI pour le traitement des cancers; INO, Institut National d'Oncologie Sidi Mohamed Ben Abdellah.

The final analysis was performed with data obtained from the records of 915 patients registered at CM-VI and 1205 patients registered at INO. The distributions of the patients by month and year of registration are shown in Table 2.3 (CM-VI) and Table 2.4 (INO). The analytic cohort included 43 patients at CM-VI and 17 patients at INO whose records did not include any histopathology report showing a cancer diagnosis. They were included because they received at least radical surgery, chemotherapy, or radiotherapy at the oncology centres.

Table 2.3. Number of patients with breast cancer by month and year of registration at the Centre Mohammed VI pour le traitement des cancers (CM-VI)

Month of registration	Year of registration										Total
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	
January	35						54				89
February	46						54				100
March		38						41			79
April		53						79			132
May			37						53		90
June			5[a]						48		53
July				30						66	96
August				44						54	98
September					46						46
October					49						49
November						40					40
December						43					43
Total	**81**	**91**	**42**	**74**	**95**	**83**	**108**	**120**	**101**	**120**	**915**

[a] The number was low because the hospital was undergoing renovation at the time.

Table 2.4. Number of patients with breast cancer by month and year of registration at the Institut National d'Oncologie Sidi Mohamed Ben Abdellah (INO)

Month of registration	Year of registration										Total
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	
January	55						43				88
February	48						49				97
March		50						82			132
April		64						76			140
May			56						79		135
June			50						81		131
July				47						96	143
August				42						65	107
September					36						36
October					59						59
November						65					65
December						72					72
Total	**93**	**114**	**106**	**89**	**95**	**137**	**92**	**158**	**160**	**161**	**1205**

Demographic characteristics of patients with breast cancer

Key observations

- The median age at registration of patients with breast cancer in Morocco was about 50 years, which is comparable to median ages reported in several Asian and African countries but 5–10 years younger than those observed in Europe and North America. This can be explained by the shape of the underlying population pyramid, which is skewed towards younger age groups.
- At both oncology centres in Morocco, most of the women with breast cancer were premenopausal, essentially reflecting the younger age distribution. An increase in the proportion of premenopausal breast cancers was seen at INO in 2015–2017 compared with 2008–2010 and 2011–2014. However, missing information bias regarding menopausal status in the 2015–2017 period should be borne in mind because, when considering the age distribution, the proportion of women aged 50 years and younger remained stable during the three time periods.
- The other demographic variables explored in the study (age at diagnosis, place of residence, marital status, parity, and family history of breast cancer) were similarly distributed in both centres, and no significant trends within the time period of the study were observed.
- There is less representation of the rural populations at the city-based oncology centres. This issue needs to be studied further to determine whether it is because rural populations have access to other oncology centres or because they are unable to travel to the city or there are other issues.
- In our study, most of the patients undergoing treatment at the two oncology centres were covered by some form of medical insurance, and a significant improvement in the levels of coverage was documented over the years. This is an important finding because the United Nations 2030 Agenda for Sustainable Development identified UHC as an essential component in efforts to reduce health inequalities.

3.1. Demographic characteristics of the patients in the study

Certain demographic and social characteristics may influence the stage at diagnosis, tumour characteristics, and compliance with diagnostic and treatment recommendations, which ultimately may affect survival after treatment. Many of these characteristics change over time. We have grouped the patients registered at CM-VI and INO by their year of registration (2008–2010, 2011–2014, and 2015–2017) to study the sociodemographic characteristics. The demographic characteristics

of the patients registered at CM-VI and INO (grouped by period of registration and study site) are shown in Table 3.1.

3.1.1 Age at registration

The age information was collected from the patients' records as documented at the time of registration. The median age of patients at registration was 49 years (interquartile range [IQR], 42–57 years) at both centres (Fig. 3.1). In our study, 18.9% of patients with breast cancer at CM-VI and 17.4% of patients at INO were younger than 40 years at the time of registration. No significant change in age distribution was observed over time at either CM-VI (P = 0.76) or INO (P = 0.68).

Mean age at diagnosis of breast cancer was reported earlier for the population-based cancer registries (PBCRs) at Casablanca (49.5 years) and Rabat (50.0 years) in 2012 (Slaoui et al., 2014). These mean ages are similar to those in our study. A prospective study of 716 patients with breast cancer registered at INO in 2009 reported a mean age of 49 years; more than a quarter of these patients (25.7%) were aged 40 years or younger (Slaoui et al., 2016).

As found in Morocco, several LMICs have reported the median age at diagnosis of patients with breast cancer to be about 50 years, which is 5–10 years younger than the median ages observed in Europe and North America (Adeloye et al., 2018). In a systematic review of 83 studies involving nearly 25 000 patients with breast cancer in sub-Saharan Africa, 77% of the studies reported mean age at diagnosis to be less than 50 years (Jedy-Agba et al., 2016). The lower median age for breast cancer detection in Africa and many LMICs outside the continent has been attributed to the shape of the underlying population pyramids, which are skewed towards younger age groups. The median age at breast cancer onset is proportional to the median age of the underlying population at risk, independent of the geographical location. Using data from all incident breast cancers reported globally during 1983–2012, it has been demonstrated that incidence rates in African or Asian women aged 20–44 years are similar to those in women in North America or Europe in the same age range

Fig. 3.1. Box plot of age (years) at registration by period and centre of registration. CM-VI, Centre Mohammed VI pour le traitement des cancers; INO, Institut National d'Oncologie Sidi Mohamed Ben Abdellah.

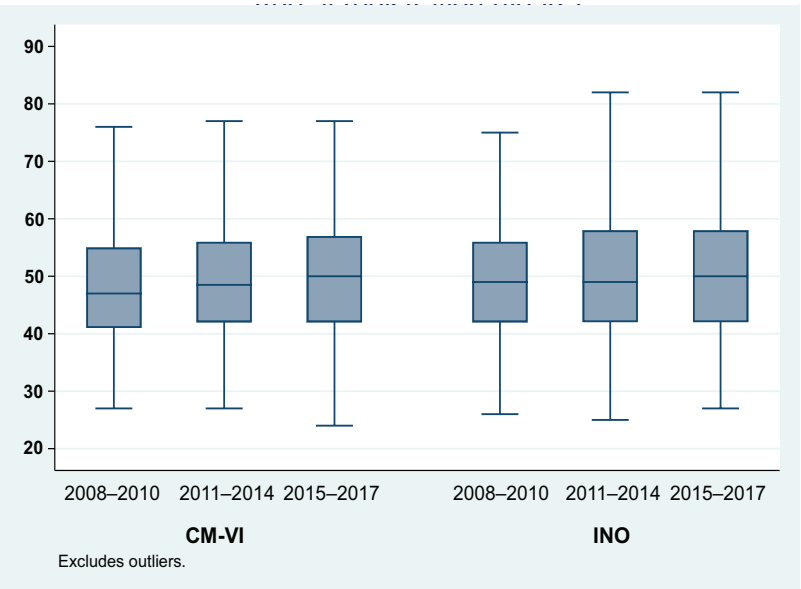


Fig. 3.2. Population pyramid of Morocco in 2020 showing proportionately large numbers of women aged 40 years or younger. Source: United Nations (2019). © 2019 United Nations. Reprinted with the permission of the United Nations.

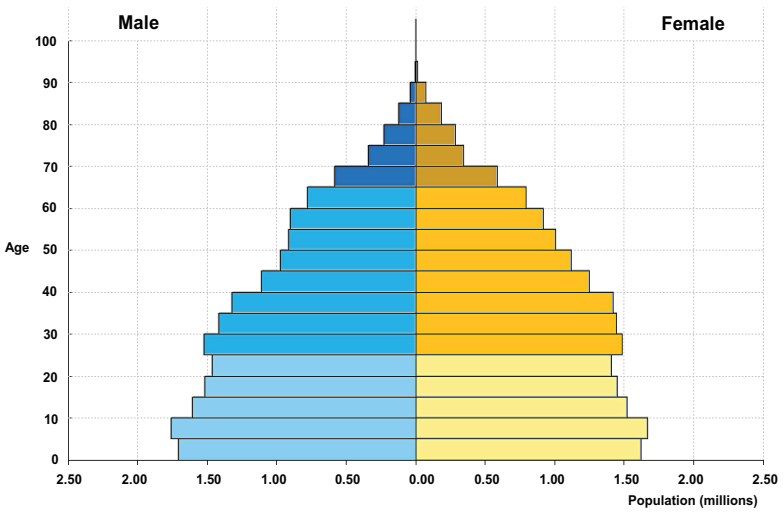


Table. 3.1. Patient characteristics by centre and period of registration

Characteristics	CM-VI				INO			
	Period of registration			Total	Period of registration			Total
	2008–2010	2011–2014	2015–2017		2008–2010	2011–2014	2015–2017	
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
No. of patients assessed	214	360	341	915	313	413	479	1205
Age at diagnosis (years)								
< 30	4 (1.9)	7 (1.9)	12 (3.5)	23 (2.5)	6 (1.9)	8 (1.9)	6 (1.3)	20 (1.7)
30–34	14 (6.6)	22 (6.1)	21 (6.2)	57 (6.2)	20 (6.4)	21 (5.1)	20 (4.2)	61 (5.1)
35–39	26 (12.2)	35 (9.7)	31 (9.1)	92 (10.1)	31 (9.9)	41 (10.0)	54 (11.3)	126 (10.5)
40–44	39 (18.3)	63 (17.5)	50 (14.7)	152 (16.6)	49 (15.7)	78 (19.0)	80 (16.8)	207 (17.2)
45–49	37 (17.4)	62 (17.2)	56 (16.4)	155 (17.0)	61 (19.5)	74 (18.0)	74 (15.5)	209 (17.4)
50–54	34 (16.0)	64 (17.8)	56 (16.4)	154 (16.8)	53 (16.9)	57 (13.9)	79 (16.6)	189 (15.7)
55–59	19 (8.9)	40 (11.1)	46 (13.5)	105 (11.5)	43 (13.7)	44 (10.7)	67 (14.0)	154 (12.8)
60–64	13 (6.1)	33 (9.2)	33 (9.7)	79 (8.6)	21 (6.7)	39 (9.5)	47 (9.9)	107 (8.9)
65–69	11 (5.2)	13 (3.6)	20 (5.9)	44 (4.8)	15 (4.8)	19 (4.6)	24 (5.0)	58 (4.8)
≥ 70	16 (7.5)	21 (5.8)	16 (4.7)	53 (5.8)	14 (4.5)	30 (7.3)	26 (5.5)	70 (5.8)
Total	213 (100.0)	360 (100.0)	341 (100.0)	914 (100.0)	313 (100.0)	411 (100.0)	477 (100.0)	1201 (100.0)
Missing	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.5)	2 (0.4)	4 (0.3)
Residence								
Urban	164 (76.6)	258 (71.7)	250 (73.3)	672 (73.4)	276 (88.2)	307 (74.3)	432 (90.2)	1015 (84.2)
Semi-urban	28 (13.1)	57 (15.8)	29 (8.5)	114 (12.5)	18 (5.8)	30 (7.3)	20 (4.2)	68 (5.6)
Rural	22 (10.3)	45 (12.5)	62 (18.2)	129 (14.1)	19 (6.1)	76 (18.4)	27 (5.6)	122 (10.1)
Total	214 (100.0)	360 (100.0)	341 (100.0)	915 (100.0)	313 (100.0)	413 (100.0)	479 (100.0)	1205 (100.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table. 3.1. Patient characteristics by centre and period of registration (continued)

Characteristics	CM-VI				INO			
	Period of registration			Total	Period of registration			Total
	2008–2010	2011–2014	2015–2017		2008–2010	2011–2014	2015–2017	
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Social security coverage								
None	149 (82.8)	137 (41.8)	4 (1.3)	290 (35.3)	165 (82.5)	65 (16.9)	57 (12.1)	287 (27.2)
RAMED	2 (1.1)	174 (53.0)	268 (85.6)	444 (54.1)	0 (0.0)	263 (68.5)	295 (62.8)	558 (52.9)
CNOPS	7 (3.9)	4 (1.2)	16 (5.1)	27 (3.3)	24 (12.0)	40 (10.4)	66 (14.0)	130 (12.3)
CNSS	22 (12.2)	13 (4.0)	25 (8.0)	60 (7.3)	11 (5.5)	16 (4.2)	52 (11.1)	79 (7.5)
Total	180 (100.0)	328 (100.0)	313 (100.0)	821 (100.0)	200 (100.0)	384 (100.0)	470 (100.0)	1054 (100.0)
Missing	34 (15.9)	32 (8.9)	28 (8.2)	94 (10.3)	113 (36.1)	29 (7.0)	9 (1.9)	151 (12.5)
Profession								
Housewife	161 (89.4)	270 (96.1)	224 (96.1)	655 (94.4)	214 (98.2)	357 (96.5)	396 (90.8)	967 (94.4)
Others	19 (10.6)	11 (3.9)	9 (3.9)	39 (5.6)	4 (1.8)	13 (3.5)	40 (9.2)	57 (5.6)
Total	180 (100.0)	281 (100.0)	233 (100.0)	694 (100.0)	218 (100.0)	370 (100.0)	436 (100.0)	1024 (100.0)
Missing	34 (15.9)	79 (21.9)	108 (31.7)	221 (24.2)	95 (30.4)	43 (10.4)	43 (9.0)	181 (15.0)
Education level								
None	52 (86.7)	88 (90.7)	203 (97.1)	343 (93.7)	26 (92.9)	32 (80.0)	27 (61.4)	85 (75.9)
Some	8 (13.3)	9 (9.3)	6 (2.9)	23 (6.3)	2 (7.1)	8 (20.0)	17 (38.6)	27 (24.1)
Total	60 (100.0)	97 (100.0)	209 (100.0)	366 (100.0)	28 (100.0)	40 (100.0)	44 (100.0)	112 (100.0)
Missing	154 (72.0)	263 (73.1)	132 (38.7)	549 (60.0)	285 (91.1)	373 (90.3)	435 (90.8)	1093 (90.7)
Marital status								
Single	30 (14.6)	62 (18.8)	52 (16.8)	144 (17.1)	37 (12.9)	61 (15.1)	69 (15.5)	167 (14.7)
Married	126 (61.5)	200 (60.6)	193 (62.5)	519 (61.5)	218 (76.2)	261 (64.4)	335 (75.3)	814 (71.7)
Widowed	36 (17.6)	39 (11.8)	31 (10.0)	106 (12.6)	22 (7.7)	56 (13.8)	24 (5.4)	102 (9.0)
Separated	13 (6.3)	29 (8.8)	33 (10.7)	75 (8.9)	9 (3.1)	27 (6.7)	17 (3.8)	53 (4.7)
Total	205 (100.0)	330 (100.0)	309 (100.0)	844 (100.0)	286 (100.0)	405 (100.0)	445 (100.0)	1136 (100.0)
Missing	9 (4.2)	30 (8.3)	32 (9.4)	71 (7.8)	27 (8.6)	8 (1.9)	34 (7.1)	69 (5.7)

Table. 3.1. Patient characteristics by centre and period of registration (continued)

Characteristics	CM-VI				INO			
	Period of registration			Total	Period of registration			Total
	2008–2010	2011–2014	2015–2017		2008–2010	2011–2014	2015–2017	
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Parity								
0	58 (28.9)	69 (22.3)	65 (21.7)	192 (23.7)	61 (20.5)	92 (24.1)	94 (23.6)	247 (22.9)
1 or 2	53 (26.4)	88 (28.5)	78 (26.0)	219 (27.0)	75 (25.3)	99 (25.9)	106 (26.6)	280 (26.0)
3 or 4	45 (22.4)	93 (30.1)	93 (31.0)	231 (28.5)	82 (27.6)	91 (23.8)	117 (29.3)	290 (26.9)
≥ 5	45 (22.4)	59 (19.1)	64 (21.3)	168 (20.7)	79 (26.6)	100 (26.2)	82 (20.6)	261 (24.2)
Total	201 (100.0)	309 (100.0)	300 (100.0)	810 (100.0)	297 (100.0)	382 (100.0)	399 (100.0)	1078 (100.0)
Missing	13 (6.1)	51 (14.2)	41 (12.0)	105 (11.5)	16 (5.1)	31 (7.5)	80 (16.7)	127 (10.5)
Menopausal status								
Premenopausal	112 (57.4)	191 (57.7)	158 (56.0)	461 (57.1)	146 (47.2)	195 (47.8)	241 (61.3)	582 (52.4)
Postmenopausal	83 (42.6)	140 (42.3)	124 (44.0)	347 (42.9)	163 (52.8)	213 (52.2)	152 (38.7)	528 (47.6)
Total	195 (100.0)	331 (100.0)	282 (100.0)	808 (100.0)	309 (100.0)	408 (100.0)	393 (100.0)	1110 (100.0)
Missing	19 (8.9)	29 (8.1)	59 (17.3)	107 (11.7)	4 (1.3)	5 (1.2)	86 (18.0)	95 (7.9)
Oral contraception								
No	130 (64.4)	301 (87.5)	203 (86.0)	634 (81.1)	220 (72.1)	242 (70.8)	126 (66.7)	588 (70.3)
Yes	72 (35.6)	43 (12.5)	33 (14.0)	148 (18.9)	85 (27.9)	100 (29.2)	63 (33.3)	248 (29.7)
Total	202 (100.0)	344 (100.0)	236 (100.0)	782 (100.0)	305 (100.0)	342 (100.0)	189 (100.0)	836 (100.0)
Missing	12 (5.6)	16 (4.4)	105 (30.8)	133 (14.5)	8 (2.6)	71 (17.2)	290 (60.5)	369 (30.6)
Family history of breast cancer in first- and second-degree relatives								
No	175 (90.2)	282 (85.5)	239 (88.2)	696 (87.5)	265 (86.9)	343 (87.1)	350 (88.2)	958 (87.4)
Yes	19 (9.8)	48 (14.5)	32 (11.8)	99 (12.5)	40 (13.1)	51 (12.9)	47 (11.8)	138 (12.6)
Total	194 (100.0)	330 (100.0)	271 (100.0)	795 (100.0)	305 (100.0)	394 (100.0)	397 (100.0)	1096 (100.0)
Missing	20 (9.3)	30 (8.3)	70 (20.5)	120 (13.1)	8 (2.6)	19 (4.6)	82 (17.1)	109 (9.0)
Diagnosed before registration at oncology centre	84 (39.3)	190 (52.8)	156 (45.7)	430 (47.0)	163 (52.1)	294 (71.2)	323 (67.4)	780 (64.7)

CM-VI, Centre Mohammed VI pour le traitement des cancers; CNOPS, Caisse Nationale des Organismes de Prévoyance Sociale; CNSS, Caisse Nationale de Sécurité Sociale; INO, Institut National d'Oncologie Sidi Mohamed Ben Abdellah; RAMED, Régime d'Assistance Médicale.

(Bidoli et al., 2019). Morocco has a relatively young population. In 2018, the median age of Moroccans was just 29 years and only 4.7% of the total population was aged 70 years and older (World Population Review, 2020). Given these figures, it is unsurprising that proportionately higher numbers of women are diagnosed with breast cancer at younger age (Fig. 3.2).

3.1.2 Place of residence

Most patients registered at the oncology centres lived in urban or semi-urban areas; only 14.1% of those registered at CM-VI and 10.1% of those registered at INO resided in rural areas. No consistent trend was observed in the rural–urban divide of the patients attending the oncology centres over 10 years. At CM-VI the proportion of women from rural areas increased steadily over time, from 10.3% in 2008–2010 to 18.2% in 2015–2017. At INO the proportion of rural patients was higher in 2011–2014 (18.4%) than in 2008–2010 (6.1%) or 2015–2017 (5.6%).

Although Morocco had an annual urban population growth of approximately 2% in the past decade (Central Intelligence Agency, 2020; World Bank, 2020), in 2020 36.5% of the population still lived in rural areas. It is possible that most rural patients with cancer visited the regional oncology centres in their region and did not need to travel to the urban centres. This issue should be further investigated to ensure that rural patients with breast cancer are indeed accessing the services of the regional oncology centres and are receiving the same standard of care as that offered at CM-VI or INO. A recent analysis identified considerable gaps in access to high-quality health care between urban and rural areas, between public and private hospitals, and between various regions in Morocco (Jacob, 2020). An estimated 45% of doctors in Morocco practise in either Rabat or Casablanca, whereas the number of doctors working in the rural parts of the country accounts for just 24% of the total.

3.1.3 Marital status

Only 17.1% of the patients with breast cancer at CM-VI and 14.7% of those at INO were single at the time of diagnosis. The others were married, widowed, or separated. No significant difference was observed either between the centres or over the years.

3.1.4 Parity

At CM-VI, 23.7% of patients with breast cancer were nulliparous and 27.0% had given birth to 1 or 2 children. Data obtained from INO showed similar results (nulliparous: 22.9% and having 1 or 2 children: 26.0%). The proportion of nulliparous women among patients with breast cancer was comparable to that reported in other hospital-based studies in Morocco (Tazzite et al., 2013). Nulliparous women are at a higher risk of developing breast cancer, and each birth has been found to confer an average 7% long-term reduction in the relative risk of breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 2002). A recent case–control study from Fes University in Morocco reported a significant 4-fold increased risk of breast cancer in nulliparous women compared with parous women (Khalis et al., 2018).

3.1.5 Menopausal status

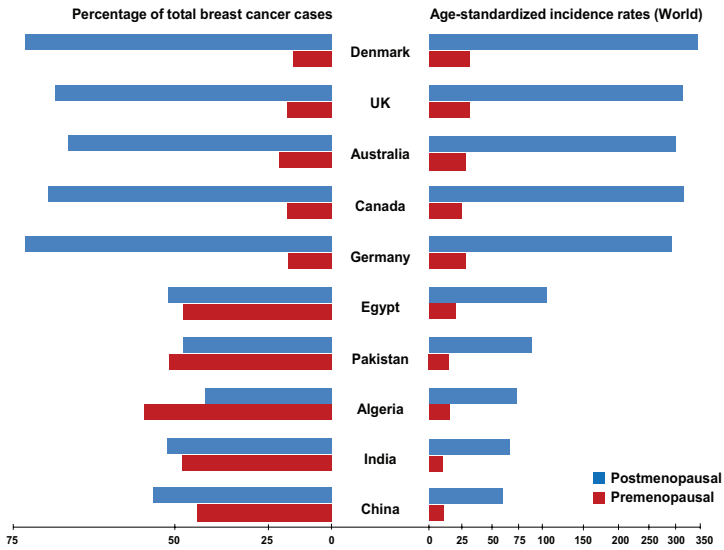
At both oncology centres, most of the women with breast cancer were premenopausal (57.1% at CM-VI and 52.4% at INO), essentially reflecting the younger age distribution. Although no significant change in the proportion of premenopausal breast cancers was observed over time at CM-VI (P = 0.91), a significant increase in the proportion was seen at INO in 2015–2017 compared with other periods (47.2% in 2008–2010, 47.8% in 2011–2014, and 61.3% in 2015–2017; P < 0.001). However, this increased percentage observed in 2015–2017 at INO should be balanced against the high percentage of missing information regarding menopausal status in 2015–2017 (18.0%). Indeed, when considering the age distribution, the proportion of women aged 50 years and younger remained stable at about 50% during the three time periods.

Analysing the data from different PBCRs, Ghiasvand et al. demonstrated that even though premenopausal breast cancers comprised a substantially higher proportion of all incident breast cancers in developing countries compared with developed countries, the age-standardized incidence rate of premenopausal breast cancer was consistently higher in the developed countries (Fig. 3.3) (Ghiasvand et al., 2014). Their results showed that the dramatic increase in breast cancer incidence in all countries (irrespective of level of development) was mainly due to the rise in the number of cases in postmenopausal women. There is no valid reason to be concerned about the finding that women in Morocco have an earlier onset of breast cancer.

3.1.6 Family history of breast cancer

A family history of breast cancer in first- and/or second-degree relatives was reported by 12.5% of patients at CM-VI and 12.6% at INO, and no change was observed over time. Our data are consistent with the results of a longitudinal study from INO that reported a family history of breast

Fig. 3.3. Estimated proportions and age-standardized incidence rates of premenopausal and postmenopausal breast cancer (on a log scale) in selected countries in 2008. Source: Ferlay J, Shin H-RR, Bray F, Forman D, Mathers C, and Parkin DM (2010). GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon. France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/.



cancer in 14.5% of the patients (Slaoui et al., 2016).

A large case–control study involving more than 5000 African American patients with breast cancer reported that a family history of breast cancer in first-degree relatives significantly increased the risk of ER-positive cancer (odds ratio [OR], 1.76; 95% CI, 1.57–1.97), ER-negative cancer (OR, 1.67; 95% CI, 1.42–1.95), and triple-negative cancer (OR, 1.72; 95% CI, 1.38–2.13) (Bethea et al., 2016). An earlier retrospective study in patients with breast cancer registered at CM-VI observed that patients with a family history (one or more relatives with breast cancer within three generations) were younger, had worse histopathological grade, and had higher rates of lymph node metastasis compared with the women without a family history (Tazzite et al., 2013). We did not observe any difference in age distribution, stage, pathology, or molecular characteristics of breast cancers detected between women with a family history and those without.

3.2 Financing of cancer treatment

Both CM-VI and INO are publicly funded oncology centres, and the cost of treatment is subsidized by the government. There is no registration charge and admission is free for all. Radical surgery can cost about US$ 500, and the total cost of EBRT is approximately US$ 1500. In our study, most of the patients undergoing treatment at the oncology centres were covered by some form of insurance scheme.

3.2.1 Health insurance schemes in Morocco

All residents in Morocco are legally entitled to free public primary healthcare services. Patients need to pay for the services delivered by public secondary and tertiary hospitals, unless they are covered by a health insurance scheme.

Health financing reforms to establish UHC through nonsubsidized and subsidized social health insurance (SHI) schemes were launched in Morocco in 2002. Assurance maladie obligatoire (AMO) is a nonsubsidized obligatory medical insurance scheme launched in 2005 to cover professionals (both in-service and retired) in the public and private sectors. The scheme is implemented through two managing bodies: Caisse Nationale des Organismes de Prévoyance Sociale (CNOPS) for civil servants and public sector workers and Caisse Nationale de Sécurité Sociale (CNSS) for workers in the private sector. The beneficiaries of AMO have to pay 30% of the hospital charges unless they have a complementary health insurance. AMO was extended to cover post-secondary students in September 2015. A second nonsubsidized SHI scheme called INAYA was launched in 2007 for self-employed individuals, but it was not very successful in attracting the target populations.

A subsidized insurance scheme (Régime d'Assistance Médicale [RAMED]), financed by the state and local communities, provides basic medical coverage for the most economically disadvantaged populations. Under RAMED, beneficiaries have to make either no or a small contribution towards their medical expenses, depending on income categories. The scheme was piloted in 2010 in the Tadla-Azilal region and scaled up nationally in 2012.

Some sectors of the population are covered by private health insurance schemes, and there is a separate health insurance scheme for those employed in the armed forces. Patients covered by private health insurance pay out-of-pocket when they

use public health facilities, and are later reimbursed by their insurance provider.

A World Bank study showed that 19% of the population (6.35 million people) were covered by the RAMED scheme in November 2016 and more than half of the population of Morocco was covered by either a subsidized or a nonsubsidized social health insurance scheme (Fig. 3.4) (Chen, 2018).

3.2.2 Medical insurance coverage for the patients at CM-VI and INO

The levels of medical insurance coverage for patients with breast cancer by year of registration and study site are shown in Fig. 3.5. Overall, 64.5% of patients registered at CM-VI and 72.8% of patients registered at INO were covered by a health insurance scheme. An improvement in the SHI coverage was documented over the years at both CM-VI and INO. A total of 82.8% of patients registered at CM-VI in 2008–2010 did not have any insurance. The proportion decreased dramatically to only 1.3% in 2015–2017, when 85.6% were covered by the RAMED scheme. Similarly, a total of 82.5% of patients registered at INO in 2008–2010 did not have any insurance. The proportion decreased to only 12.1% in 2015–2017, when 62.8% were covered by the RAMED scheme.

3.2.3 Addressing social inequities in health care and moving towards UHC

UHC means that all people have access to the health services they need, including preventive, curative, rehabilitative, or palliative services of adequate quality without being exposed to financial hardship (Kieny et al., 2017). The United Nations 2030 Agenda for Sustainable Development (Goal 3: Ensure healthy lives and promote well-being for all at all ages) identified achievement of UHC as one of the essential components to reduce health inequalities (United Nations, 2015).

Fig. 3.4. Proportions of the Moroccan population covered by different health insurance schemes in 2016.

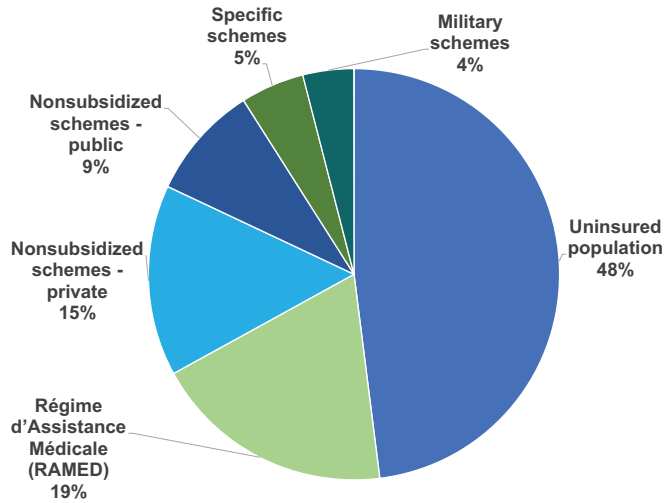
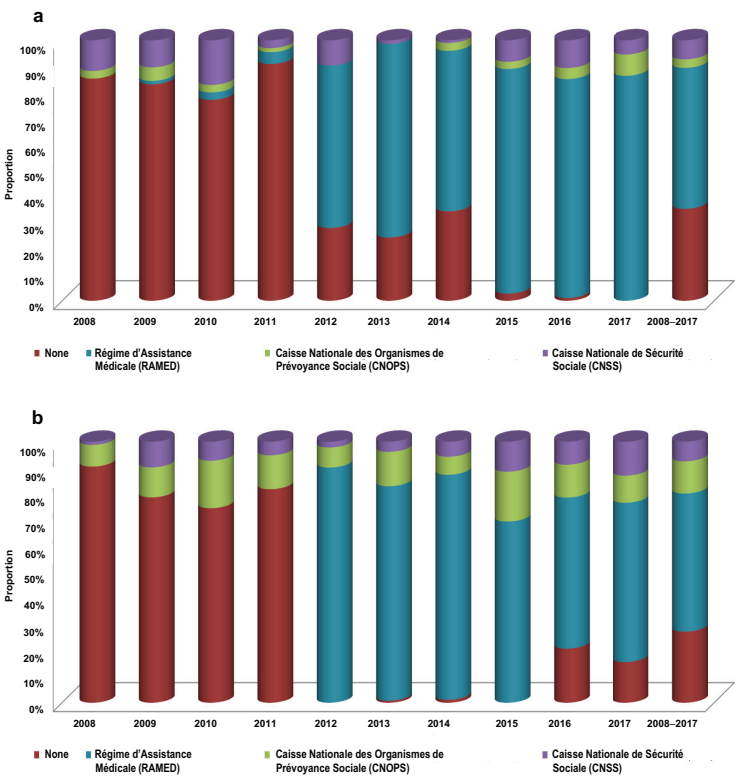


Fig. 3.5. Social security coverage of patients with breast cancer by period of registration (a) at the Centre Mohammed VI pour le traitement des cancers (CM-VI), Casablanca and (b) at the Institut National d'Oncologie Sidi Mohamed Ben Abdellah (INO), Rabat.



Cancer care in LMICs needs to be covered by the principles of UHC with publicly financed, high-quality services being offered across the cancer care continuum, from diagnosis to palliative care and survivorship. The prolonged, complex, and multimodal treatment needed for cancer leads to catastrophic expenditure that often pushes families into poverty unless they are protected by some form of financing. Studies have reported that in LMICs more than 30% of the annual expenditures for inpatient cancer treatment are met from borrowing and/or asset sales and even then, many patients eventually abandon treatment (Mahal et al., 2013).

In its health-care planning, Morocco has followed the strategy of progressive universalism, which starts by introducing policies for identifying and protecting the poorest and most vulnerable (Gwatkin and Ergo, 2011). The costs of the health insurance scheme for workers and government employees are covered by payroll deductions, supplemented by contributions from the employers. Those in the informal sectors pay a small contribution, and the extremely poor are exempted from any contributions. Similar schemes were introduced in Ghana, although there were issues with long-term sustainability without any donor contributions (Knaul et al., 2015). Our study shows that health insurance schemes are at least covering the costs of inpatient care for patients with breast cancer in Morocco and have done so successfully for nearly a decade. Free breast cancer screening and diagnosis services, combined with financial protection for cancer treatment, are likely to have a significant impact on breast cancer outcomes in Morocco in the long term.

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CHAPTER 4.

Detection of breast cancer

Key observations

- Although there has been a breast cancer screening programme in Morocco since 2010, more than 95% of the women who registered at the two centres (CM-VI and INO) were symptomatic at the time of diagnosis.
- The median interval between onset of symptoms and first medical consultation (access delay) was 6 months. Although there are no universal standards for access delay, in many well-organized health systems the benchmark is 4 weeks.
- There was a trend showing reduction of access delay over time. This was more apparent for the patients registered at INO and could be an effect of the screening programme.
- Other than high parity, no sociodemographic factors had any significant impact on the access delay.
- Overall, more than half of the women had diagnosis of breast cancer confirmed on cytology and/or histopathology before registration at the centres. This proportion increased over time in both centres, probably reflecting the improved capacity of the health system to diagnose cancers in general (non-oncology) hospitals.
- The median interval between diagnostic confirmation and registration at an oncology centre was 1.5 months at CM-VI and 0.7 months at INO. This interval remained constant at CM-VI, but at INO it decreased over the period of the study.

4.1. Symptoms of breast cancer at first medical consultation

Table 4.1 shows that almost all the patients (97.3%) had one or more symptoms suggestive of breast cancer at the time of first medical consultation. The percentage distribution does not add up to 100% because some patients had multiple symptoms. A lump in the breast was the most common symptom and was reported by 90.5% of the patients. Breast pain was the second most frequent symptom; this was reported by 11.3%.

The breast cancer screening programme in Morocco was launched in 2010 and reasonably high coverage was reported in 2015 and 2016 (Basu et al., 2018). Our retrospective study could not estimate the proportion of patients referred through the screening programmes, because this information was not systematically documented in the case records. Given the steadily increasing participation in the breast cancer screening programme, there is a need to capture such information at the cancer centres and share it with the screening programme for quality assurance.

Table 4.1. Initial symptoms reported by the patients

	CM-VI		INO		Total	
	n (%)		*n* (%)		*n* (%)	
No. of patients assessed[a]	863		1158		2021	
Symptoms						
Any symptom	827	(95.8)	1140	(98.4)	1967	(97.3)
Breast lump	743	(86.1)	1085	(93.7)	1828	(90.5)
Discharge from nipple	30	(3.5)	33	(2.8)	63	(3.1)
Nipple ulceration	11	(1.3)	11	(0.9)	22	(1.1)
Nipple retraction	47	(5.4)	47	(4.1)	94	(4.7)
Breast pain	123	(14.3)	106	(9.2)	229	(11.3)
Bulging breast or skin retraction	5	(0.6)	22	(1.9)	27	(1.3)
Peau d'orange	13	(1.5)	48	(4.1)	61	(3.0)
Axillary nodule	28	(3.2)	47	(4.1)	75	(3.7)
Others	44	(5.1)	44	(3.8)	88	(4.4)

CM-VI, Centre Mohammed VI pour le traitement des cancers; INO, Institut National d'Oncologie Sidi Mohamed Ben Abdellah.

[a] Symptoms were not recorded in a few patients.

4.2 Interval between onset of symptoms and first medical consultation

The clinicians routinely documented in every case record the approximate date of onset of symptoms and the date of first medical consultation that led to referral for cancer diagnosis (the access delay). We could estimate the interval between these two dates in 801 patients (87.5% of the total cases) from CM-VI and 1031 patients (85.6% of the total cases) from INO. The median interval remained constant at 6 months (IQR, 3–12 months) over the study time periods for patients registered at CM-VI but decreased from 7 months (IQR, 4–12 months) during 2008–2010 to 5.0 months (IQR, 2–12 months) during 2015–2017 for those registered at INO (Fig. 4.1).

We categorized the interval between the onset of symptoms and first medical consultation (access delay) into early (< 6 months), delayed (6–< 12 months), and very late (≥ 12 months) and did multivariate logistic regression analysis to identify possible factors that could influence the interval (Table 4.2).

The proportion of women with symptoms who sought early consultation increased significantly over time; this trend was more obvious for the patients registering at INO. The sociodemographic characteristics of the patients, other than high parity, did not have any significant effect on the access delay when all patient characteristics were adjusted for in the regression model. Younger women were more likely to seek early consultation, although the difference between the age groups was not statistically significant.

WHO categorized the delays in cancer diagnosis into access delay (the interval between onset of symptoms and first medical consultation) and systems or diagnostic delay (the interval between first medical consultation and diagnostic confirmation) (WHO, 2017). Either of these delays in diagnostic confirmation of cancer

Fig. 4.1. Box plot showing longest duration of symptoms (months) before first medical consultation (access delay) by period of registration and centre. CM-VI, Centre Mohammed VI pour le traitement des cancers; INO, Institut National d'Oncologie Sidi Mohamed Ben Abdellah.

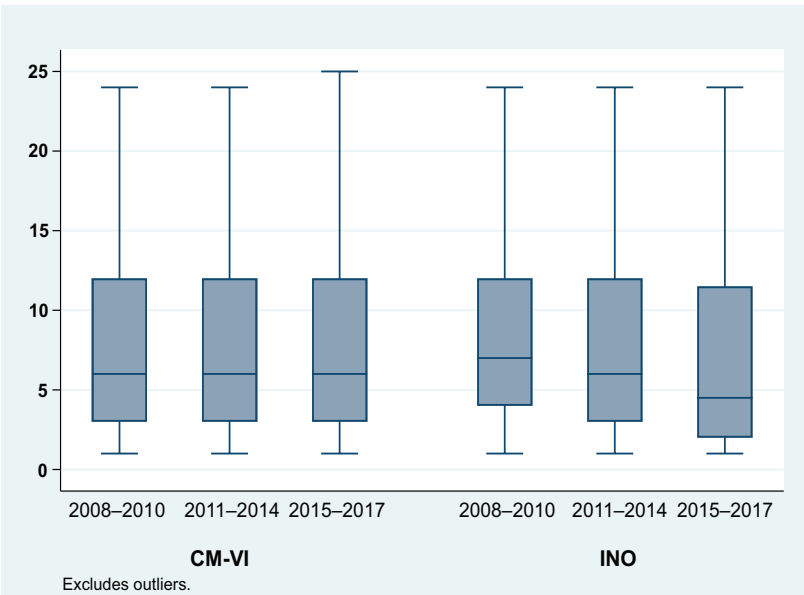

Table 4.2. Access delay and its determinants

Characteristics	Access delay						Crude		Adjusted	
	< 6 months		6–< 12 months		≥ 12 months		Risk ratio (95% CI)		Risk ratio (95% CI)	
	n (%)		*n* (%)		*n* (%)					
No. of patients with symptoms	850		433		549					
Centre										
CM-VI	370	(46.2)	183	(22.8)	248	(31.0)	1.00		1.00	
INO	480	(46.6)	250	(24.2)	301	(29.2)	0.98	(0.88–1.07)	0.94	(0.85–1.03)
Period of diagnosis										
2008–2010	191	(38.0)	147	(29.2)	165	(32.8)	1.00		1.00	
2011–2014	333	(47.0)	167	(23.6)	208	(29.4)	0.85	(0.76–0.95)	0.88	(0.76–0.99)
2015–2017	326	(52.5)	119	(19.2)	176	(28.3)	0.78	(0.69–0.87)	0.80	(0.68–0.92)
Age at diagnosis (years)										
< 30	19	(52.8)	9	(25.0)	8	(22.2)	1.00		1.00	
30–39	145	(49.0)	87	(29.4)	64	(21.6)	1.14	(0.78–1.59)	1.18	(0.80–1.65)
40–49	321	(50.6)	140	(22.1)	173	(27.3)	1.11	(0.96–1.27)	1.10	(0.96–1.27)
50–59	226	(43.4)	117	(22.5)	178	(34.2)	1.25	(1.07–1.43)	1.19	(1.00–1.42)
60–69	99	(41.1)	59	(24.5)	83	(34.4)	1.38	(1.15–1.62)	1.31	(1.03–1.61)
≥ 70	39	(37.9)	21	(20.4)	43	(41.7)	1.54	(1.21–1.92)	1.44	(1.09–1.85)
Residence										
Urban	672	(46.5)	346	(23.9)	428	(29.6)	1.00		1.00	
Semi-urban	73	(44.8)	38	(23.3)	52	(31.9)	0.99	(0.84–1.16)	1.01	(0.85–1.19)
Rural	105	(47.1)	49	(22.0)	69	(30.9)	0.97	(0.84–1.11)	1.04	(0.90–1.20)
Social security coverage										
None	211	(39.4)	144	(26.9)	180	(33.6)	1.00		1.00	
RAMED	425	(51.0)	176	(21.1)	232	(27.9)	0.82	(0.74–0.91)	0.93	(0.81–1.06)
CNOPS	59	(45.7)	28	(21.7)	42	(32.6)	1.10	(0.91–1.33)	1.17	(0.94–1.40)
CNSS	61	(50.4)	27	(22.3)	33	(27.3)	0.90	(0.74–1.09)	0.99	(0.80–1.20)
Marital status										
Single	129	(46.9)	62	(22.5)	84	(30.5)	1.00		1.00	
Married	544	(47.1)	280	(24.3)	330	(28.6)	1.00	(0.88–1.15)	0.97	(0.80–1.14)
Widowed	76	(40.2)	40	(21.2)	73	(38.6)	1.21	(1.03–1.41)	1.03	(0.85–1.22)
Separated	49	(43.4)	34	(30.1)	30	(26.5)	1.02	(0.83–1.23)	0.96	(0.77–1.17)
Parity										
0	181	(45.8)	92	(23.3)	122	(30.9)	1.00		1.00	
1 or 2	196	(45.4)	121	(28.0)	115	(26.6)	0.97	(0.83–1.12)	0.93	(0.77–1.09)
3 or 4	232	(50.4)	95	(20.7)	133	(28.9)	0.84	(0.73–0.97)	0.83	(0.69–0.97)
≥ 5	174	(44.8)	95	(24.5)	119	(30.7)	0.96	(0.82–1.10)	0.85	(0.70–1.00)
Menopausal status										
Premenopausal	465	(50.0)	225	(24.2)	240	(25.8)	1.00		1.00	
Postmenopausal	334	(42.7)	182	(23.2)	267	(34.1)	1.27	(1.15–1.40)	1.12	(0.98–1.28)
Family history of breast cancer										
No	693	(46.7)	350	(23.6)	440	(29.7)	1.00		1.00	
Yes	98	(44.5)	58	(26.4)	64	(29.1)	1.13	(0.97–1.31)	1.15	(0.99–1.32)

CI, confidence interval; CM-VI, Centre Mohammed VI pour le traitement des cancers; CNOPS, Caisse Nationale des Organismes de Prévoyance Sociale; CNSS, Caisse Nationale de Sécurité Sociale; INO, Institut National d'Oncologie Sidi Mohamed Ben Abdellah; RAMED, Régime d'Assistance Médicale.

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may significantly affect survival after treatment, and both should be kept as short as possible. WHO recommends that the interval between the onset of symptoms and treatment initiation should not exceed 3 months. A systematic review of high-quality studies observed that the 5-year survival for breast cancer was 12% lower in patients for whom the interval between the onset of symptoms and treatment initiation was longer than 3 months compared with those with shorter delays; the former group also had nearly 50% higher probability of dying from breast cancer (OR for death, 1.47; 95% CI, 1.42–1.53) (Richards et al., 1999a).

There are no universal standards for the ideal interval between the onset of symptoms and first medical consultation, although in many well-organized health systems the benchmark is 4 weeks (WHO, 2017). The average interval between onset of symptoms and first medical consultation among the patients with breast cancer in Morocco was less than that reported in many LMICs but significantly higher than that observed in high-income countries. A systematic review including about 25 000 patients with breast cancer in sub-Saharan Africa reported that the average duration of symptoms at the time of first presentation was between 8 months and 12 months in most studies (Jedy-Agba et al., 2016). This is in stark contrast to the interval reported in countries with well-organized health systems. The Danish Breast Cancer Cooperative Group reported that among the 7608 breast cancers detected between August 1977 and November 1982, the median interval between first symptoms and first visit to the doctor was only 13 days (Afzelius et al., 1994). A very large survey of 6588 patients with breast cancer in 12 lower and upper middle-income countries showed that the mean interval between the onset of symptoms and first medical visit ranged from 3.4 weeks in Hungary to 6.2 weeks in Latvia; the overall mean was 4.7 weeks (Jassem et al., 2014).

There are several determinants of access delay, such as age, education, level of awareness on cancer, myths and stigma around the disease, and access to health services, and our retrospective study could assess only a few of them. Systematic reviews reported that older women tend to report the symptoms later, irrespective of the study settings, an observation that matches with our findings (Ramirez et al., 1999; Richards et al., 1999b; Arndt et al., 2002). A study of Nigerian patients with breast cancer observed ignorance of the seriousness of breast symptoms, belief in traditional herbal medicine and spiritual healing, and fear of mastectomy as the most common reasons for access delay (Ibrahim and Oludara, 2012). A multicentre study in Morocco involving 1440 women with a mean age of 40 years showed that most of the women had poor understanding of the risk factors and early symptoms of breast cancer (Benaicha et al., 2016).

4.3 Proportion of cancers detected before registration at the oncology centres

Overall, 47.0% (430/915) of the patients registered at CM-VI and 64.7% (780/1205) of those registered at INO had a diagnosis of breast cancer that had already been confirmed on cytology and/or histopathology at the time of registration. The proportion increased over time both at CM-VI (2008–2010: 39.1%; 2011–2014: 52.8%; and 2015–2017: 45.7%) and at INO (2008–2010: 52.1%; 2011–2014: 71.2%; and 2014–2017: 66.2%), possibly because of improvement in the capacity of the health system to diagnose cancers in general hospitals. The median interval between diagnostic confirmation and registration at the oncology centre was 1.5 months (IQR, 0.8–2.9 months) at CM-VI and 0.7 months (IQR, 0.3–1.8 months) at INO. This interval remained constant at CM-VI over time, but at INO it decreased from 1 month in 2008–2010 to 0.4 months in 2015–2017. The longer interval for the patients at CM-VI is explained by the fact that most of them had received primary surgery elsewhere, which was not the case at INO (discussed in subsequent chapters).

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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.

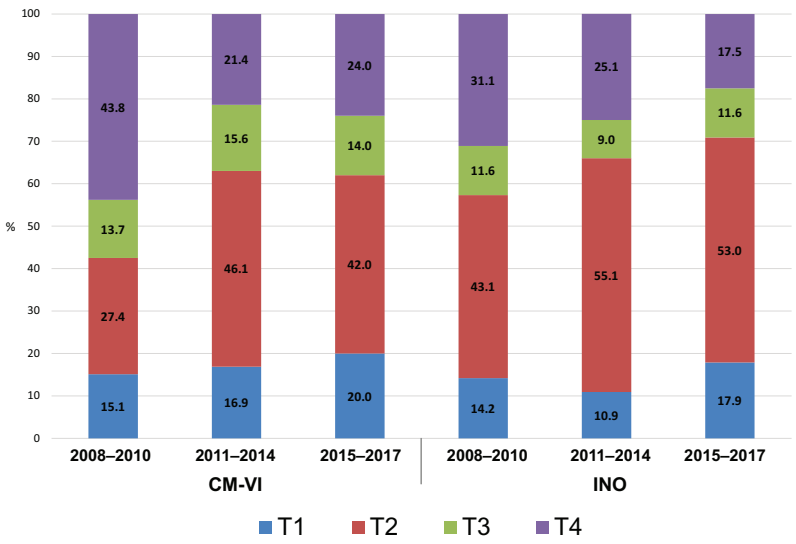
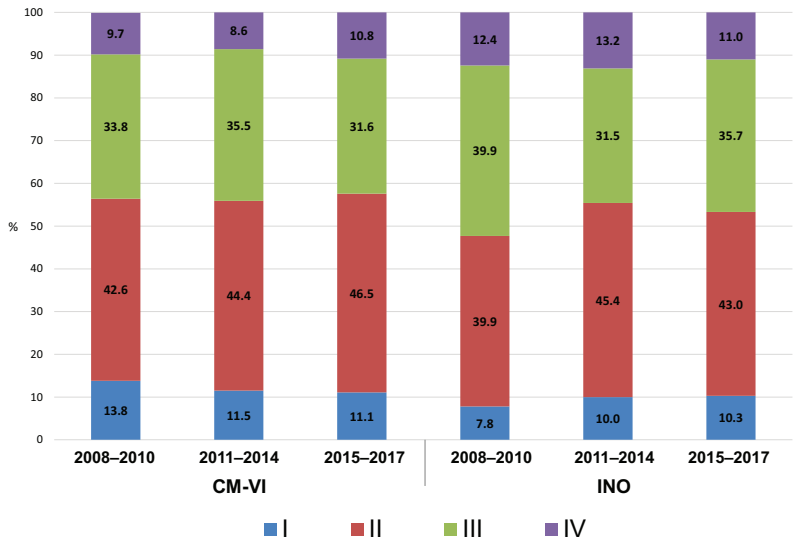


Fig. 5.2. Distribution of patients with breast cancer according to American Joint Committee on Cancer (AJCC) anatomical stage, at the Centre Mohammed VI pour le traitement des cancers (CM-VI) and the Institut National d'Oncologie Sidi Mohamed Ben Abdellah (INO) over different time periods.



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.

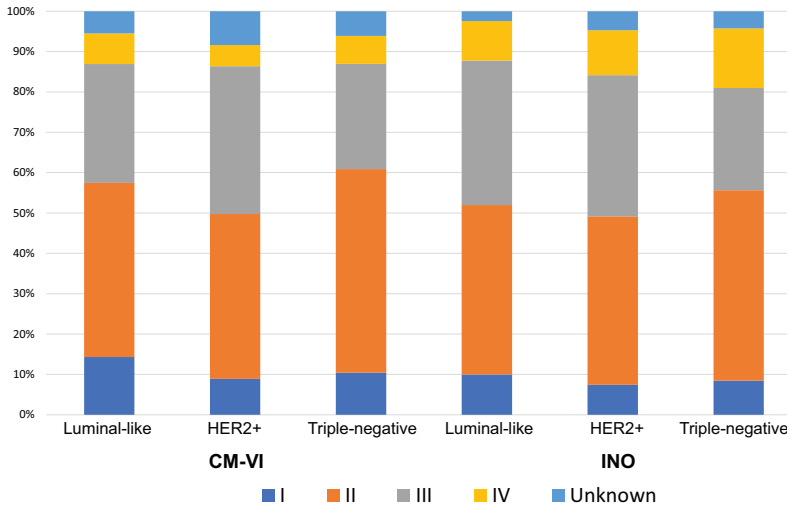


Fig. 5.4. Distribution of the molecular subtypes of breast cancer according to degree of differentiation. CM-VI, Centre Mohammed VI pour le traitement des cancers; HER2, human epidermal growth factor receptor 2; INO, Institut National d'Oncologie Sidi Mohamed Ben Abdellah.

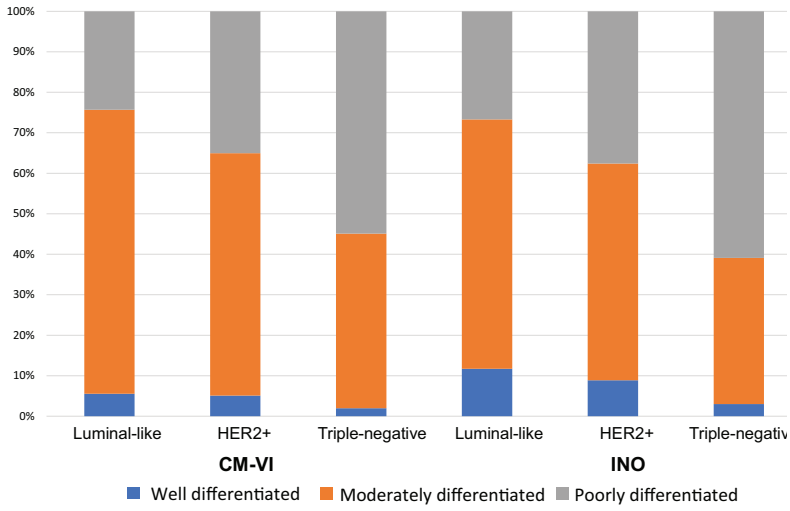


Table 5.3. Molecular characteristics of breast cancers at the two centres

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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CHAPTER 6.

Treatment of breast cancer

Key observations

- Surgery is the mainstay of treatment of breast cancer in Morocco; in this study, 69.9% of patients at CM-VI and 86.1% of patients at INO underwent surgery.
- Most patients (68.3%) registered at CM-VI had received some form of treatment (mostly surgery) before registration at the hospital. This proportion was much lower (36.5%) at INO.
- Multimodal therapy was more frequent at INO than at CM-VI. A total of 78.8% of patients registered at INO were treated with surgery with chemotherapy and/or radiotherapy. The proportion was 53.7% at CM-VI.
- As expected, treatment was tailored according to stage and molecular subtype. Specific treatments and their associations with stage and pathology are discussed in more detail in later chapters.
- At CM-VI, the median interval between the date of diagnosis (confirmation by cytology or histopathology) and the initiation of treatment was 2.7 months; this decreased over time. At INO, the interval was 1.6 months and increased a little over time.
- The median waiting period between registration and the initiation of cancer-directed treatment was 1.5 months at CM-VI and at INO. No change was observed over time.
- The median interval between surgery and initiation of adjuvant treatment was 2–3 months for adjuvant chemotherapy and 7–9 months for adjuvant radiotherapy at CM-VI and at INO.

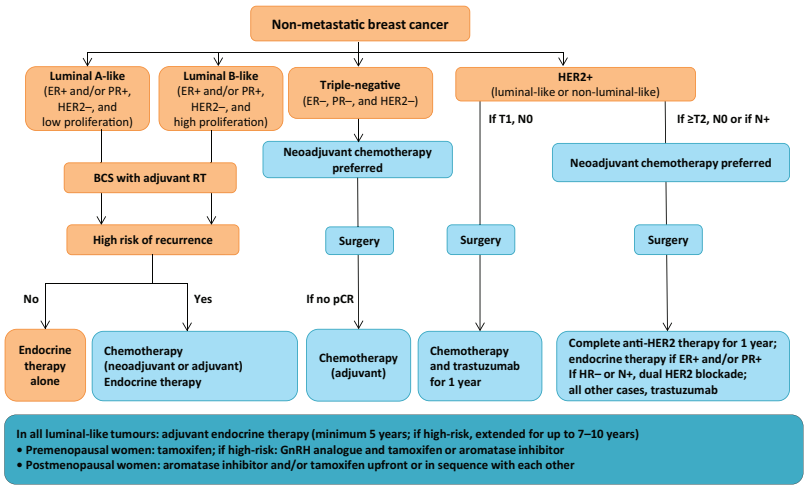
6.1 Principles of treatment

Breast cancer represents a broad spectrum of biologically heterogeneous diseases, and its management requires a multidisciplinary approach. Treatment of breast cancer depends on age, associated comorbidities, stage, pathological characteristics of the tumour, molecular subtype, and the informed choice of the woman. The standard-of-care management of breast cancer has evolved over the past few decades, with a more tailored approach to suit the biological nature of the tumour and a shift towards organ-preserving multimodal management. The management of each patient with breast cancer should be decided by a multidisciplinary team (tumour board).

6.1.1 Surgical management

Primary surgery is the treatment of choice for patients with stage I, II, or IIIA (T3N1M0) disease (Fig. 6.1).

Fig. 6.1. Management algorithm for non-metastatic breast cancer. BCS, breast-conserving surgery; ER, estrogen receptor; GnRH, gonadotropin-releasing hormone; HER2, human epidermal growth factor receptor 2; N+, node-positive; pCR, pathological complete response; PR, progesterone receptor; RT, radiotherapy. Source: Adapted with permission from Springer Nature: Nature, Nature Reviews Disease Primers, Harbeck et al. (2019). © 2019.



Primary systemic therapy with combination chemotherapy before surgery (neoadjuvant chemotherapy) is recommended in triple-negative or HER2-positive cancers, except when the tumour is < 2 cm in diameter without any evidence of nodal involvement. Neoadjuvant chemotherapy is also recommended in locally advanced hormone receptor-positive and HER2-negative cancers to make them amenable to breast-conserving surgery (BCS).

In the past, modified radical mastectomy (which includes axillary lymph node dissection [ALND]) was the standard-of-care surgical management for breast cancer. BCS is now preferred over mastectomy in stage I or II disease after it was shown in multiple randomized controlled trials (RCTs) that survival after BCS (followed by radiotherapy) was

Table 6.1. Details of treatment by centre and period of registration

	CM-VI						INO					
	Period of registration				Total		Period of registration				Total	
	2008–2012		2013–2017				2008–2012		2013–2017			
	n (%)		*n* (%)		*n* (%)		*n* (%)		*n* (%)		*n* (%)	
No. of patients registered	383		532		915		497		708		1205	
No. of patients with treatment details	337	(88.0)	448	(84.2)	785	(85.8)	496	(99.8)	661	(93.4)	1157	(96.0)
Treatment type												
Surgery alone	18	(5.3)	109	(24.3)	127	(16.2)	17	(3.4)	68	(10.3)	85	(7.3)
Surgery and radiotherapy	14	(4.2)	13	(2.9)	27	(3.4)	8	(1.6)	36	(5.4)	44	(3.8)
Surgery and chemotherapy	67	(19.9)	140	(31.3)	207	(26.4)	67	(13.5)	133	(20.1)	200	(17.3)
Surgery, radiotherapy, and chemotherapy	116	(34.4)	72	(16.1)	188	(23.9)	340	(68.5)	328	(49.6)	668	(57.7)
Radiotherapy alone	6	(1.8)	3	(0.7)	9	(1.1)	4	(0.8)	6	(0.9)	10	(0.9)
Radiotherapy and chemotherapy	43	(12.8)	17	(3.8)	60	(7.6)	14	(2.8)	16	(2.4)	30	(2.6)
Chemotherapy alone	73	(21.7)	94	(21.0)	167	(21.3)	46	(9.3)	74	(11.2)	120	(10.4)
Treatment received before or after registration												
Before	186	(61.0)	298	(73.8)	484	(68.3)	233	(47.0)	185	(28.5)	418	(36.5)
After	119	(39.0)	106	(26.2)	225	(31.7)	263	(53.0)	463	(71.5)	726	(63.5)
Information missing	32	(9.5)	44	(9.8)	76	(9.7)	0	(0.0)	13	(2.0)	13	(1.1)

CM-VI, Centre Mohammed VI pour le traitement des cancers; INO, Institut National d'Oncologie Sidi Mohamed Ben Abdellah.

equivalent to that after radical mastectomy (Veronesi et al., 2002; Darby et al., 2011). Intraoperative frozen section of the breast specimen and assessment of margin status improves surgical outcome and reduces the need for re-excision.

The presence of large or aggressive tumours (HER2-positive or triple-negative) or diagnosis at a young age do not contraindicate BCS. Patients with large tumours (diameter > 1 cm) or tumours fixed to the chest wall may be given neoadjuvant chemotherapy (with hormone receptor- and HER2-targeted therapy, if indicated) to shrink the tumours and make them fit candidates for BCS. The rate of BCS after neoadjuvant chemotherapy has been reported to be between 25% and 90% (Sakorafas, 2001).

ALND was an essential component of any breast cancer surgery before sentinel lymph node (SLN) biopsy became the standard of care for patients with clinically and radiologically negative axillary lymph nodes.

In current practice, ALND is restricted to patients:

- with metastasis in SLN;
- with clinically node-positive axilla;
- with axillary nodal metastasis confirmed by fine-needle aspiration or core biopsy; or
- who have undergone neoadjuvant chemotherapy.

However, in settings where SLN biopsy facilities are not available, all patients with invasive breast cancer should have ALND, because even a small tumour (< 1 cm) has 10–20% risk of having nodal metastasis.

6.1.2 Radiotherapy

Indications for adjuvant radiotherapy after surgery are as follows:

- BCS with negative axillary nodes;
- positive axillary lymph nodes (especially if > 3 nodes are involved) after any type of breast surgery;
- negative axillary nodes with positive resection margins after surgery; and
- T3/T4 tumour (irrespective of lymph node status).

In the past, the conventional treatment was to administer 46–50 Gy of radiation dose in 23–25 fractions over 5 weeks. Today, however, hypofractionated radiotherapy is the standard of care for whole-breast irradiation, and the National Comprehensive Cancer Network (NCCN) panel recommends 40–42.5 Gy in 15 or 16 fractions administered over approximately 3 weeks (Gradishar et al., 2020). The radiotherapy field is extended to the axilla, parasternal, and supraclavicular regions in women with node-positive or high-risk node-negative breast cancer. A booster dose of 10–16 Gy in 4–8 fractions is recommended in patients with higher risk of relapse (younger patients, high-grade disease, focally positive surgical margins, etc.). If adjuvant chemotherapy is indicated, radiation should be given after completion of chemotherapy.

Palliative radiotherapy is administered for symptom control in advanced disease.

6.1.3 Adjuvant and neoadjuvant chemotherapy

The decision to administer adjuvant chemotherapy after surgery depends on the patient's age, hormone receptor and HER2 expression status, tumour grade, tumour size, axillary lymph node status, and angiolymphatic invasion. In general, patients with an estimated relapse risk exceeding 10% over the course of 10 years are potential candidates for adjuvant chemotherapy (Harbeck and Gnant, 2017). As discussed earlier, patients with triple-negative or HER2-positive disease with a tumour diameter exceeding 1 cm or other primarily inoperable cancers (inflammatory carcinoma, fixity to chest wall, skin involvement with ulceration, fixed or matted lymph nodes, etc.) are suitable candidates for neoadjuvant chemotherapy.

Adjuvant chemotherapy should be started within 3–4 weeks of surgery. Until the 1990s, a combination of cyclophosphamide, methotrexate, and 5-fluorouracil (5-FU) (CMF) was the standard-of-care chemotherapy regimen for breast cancer in adjuvant settings. The review by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) published in 2005 demonstrated significant improvement in survival with anthracycline-containing regimens (38% reduction in annual breast cancer death rate for patients younger than 50 years and 20% reduction for those aged 50–69 years) (EBCTCG, 2005). Some of the pivotal trials (Cancer and Leukaemia Group 9344 and National Surgical Adjuvant Breast and Bowel Project B-28) demonstrated further benefit of incorporating a taxane into an anthracycline-based regimen (Mamounas et al., 2005). Based on the evidence, the doxorubicin (60 mg/m^2) plus cyclophosphamide (600 mg/m^2 on day 1) every 3 weeks for four cycles followed by paclitaxel (80 mg/m^2) every 2 weeks for 12 weeks (ACP) regime has become the standard of care for adjuvant chemotherapy. Another recommended regimen is three cycles of epirubicin and cyclophosphamide followed by three cycles of docetaxel (100 mg/m^2) every 3 weeks. The FEC regime combines 5-FU (600 mg/m^2), epirubicin (90 mg/m^2), and cyclophosphamide (600 mg/m^2), usually followed by weekly paclitaxel (100 mg/m^2). The same regimens are followed for adjuvant or neoadjuvant settings. Addition of a platinum to

the existing combinations improves complete response rates in patients with triple-negative breast cancer.

6.1.4 Endocrine therapy

All patients with tumours positive for ER and/or PR should receive endocrine therapy for 5–10 years. A meta-analysis by the EBCTCG demonstrated that 5 years of tamoxifen treatment reduced the risk of recurrence by nearly 50% in the initial 4 years and the risk of mortality by about a third throughout the first 15 years of follow-up in patients with ER-positive disease (Darby et al., 2011; Pagani et al., 2014).

Endocrine therapy may be initiated even before surgery in patients with strongly ER-positive disease. The recommended therapy is tamoxifen for premenopausal patients and aromatase inhibitors for postmenopausal patients. Young premenopausal patients with high risk of relapse may have ovarian suppression with gonadotropin-releasing hormone (GnRH) agonists or ovarian ablation by surgery or irradiation, which may be followed by treatment with aromatase inhibitors.

6.1.5 Targeted therapy for patients with HER2-positive tumours

All patients with HER2-positive tumours should receive trastuzumab, a humanized monoclonal antibody against HER2, along with chemotherapy; treatment should be continued for 1 year. Evidence from multiple RCTs has shown a 40% improvement in overall survival with this regimen (Perez et al., 2014). Addition of pertuzumab to trastuzumab and chemotherapy has demonstrated survival benefit in HER2-positive metastatic breast cancer (Swain et al., 2015). The combination is also indicated in patients with node-positive HER2-positive cancer with poor prognosis.

6.2 Treatment of breast cancer at the oncology centres in Morocco

Treatment details were available for 785 (85.8%) patients with breast cancer registered at CM-VI and 1157 (96.0%) patients registered at INO. Most patients for whom treatment information was not available either had stage IV disease or did not have staging information. It is possible that these women received palliative treatment alone or did not accept treatment at the hospital.

The multidisciplinary tumour board (MTB) is held once a week at both oncology centres. Whereas all newly registered patients with breast cancer are presented and discussed at the MTB at INO, only the cases considered by the treating oncologists to be complicated or patients that may require treatment for recurrence are discussed at the MTB at CM-VI.

The details of treatment received and whether treatment (complete or partial) was received at the oncology centre or at another hospital are shown in Table 6.1. Because no big changes in treatment modalities are expected within a short period of time, all evaluations of treatment received were stratified by only two periods of registration (2008–2012 and 2013–2017) and presented separately for the two centres. Most patients (68.3%) registered at CM-VI had received some form of cancer-directed treatment (surgery, radiotherapy, or chemotherapy) before registration at the hospital. The proportion of patients treated at non-oncology hospitals was higher in recent years (61.0% in 2008–2012 vs 73.8% in 2013–2017). The proportion of patients treated elsewhere was much lower (36.5%) in those registered at INO and showed a downward trend with time (47.0% in 2008–2012 vs 28.5% in 2013–2017).

6.2.1 Types of treatment according to the centre and time period

Although the age, stage distribution, and tumour characteristics of the patients registered at CM-VI and INO were not very different, there was a lot of variation in the treatment received by the patients registered at the two centres.

At CM-VI, the treatment pattern changed substantially over time (Table 6.1). Overall, 69.9% of the patients underwent some form of surgery (63.8% in 2008–2012; 74.5% in 2013–2017), and 53.7% had surgery followed by chemotherapy and/or radiotherapy (58.5% in 2008–2012; 50.3% in 2013–2017). The proportion of patients treated by surgery alone increased from only 5.3% in 2008–2012 to 24.3% in 2013–2017. The proportion of women treated with chemotherapy (neoadjuvant or adjuvant) along with surgery (with or without radiation) decreased from 54.3% in 2008–2012 to 47.4% in 2013–2017. A larger proportion of patients were treated with radiotherapy (either alone or along with surgery and/or chemotherapy) in 2008–2012 (53.2%) than in 2013–2017 (23.5%).

At INO, multimodal therapy was used more frequently than at CM-VI; 57.7% of patients were treated with a combination of surgery, chemotherapy, and radiotherapy (Table 6.1). Overall, 86.1% of patients underwent surgery, and the proportion did not change much over time (87.0% in 2008–2012; 85.4% in 2013–2017). Surgery followed by chemotherapy and/or radiotherapy was used to treat 78.8% patients (83.6% in 2008–2012; 75.1% in 2013–2017). The proportion of patients treated with surgery alone increased

from 3.4% in 2008–2012 to 10.3% in 2013–2017. The proportion of women treated with chemotherapy (neoadjuvant or adjuvant) along with surgery (with or without radiation) was 82.0% in 2008–2012 and 69.7% in 2013–2017. The proportion of women treated with radiotherapy (either alone or in combination with surgery and/or chemotherapy) was 73.7% in 2008–2012 and 56.0% in 2013–2017.

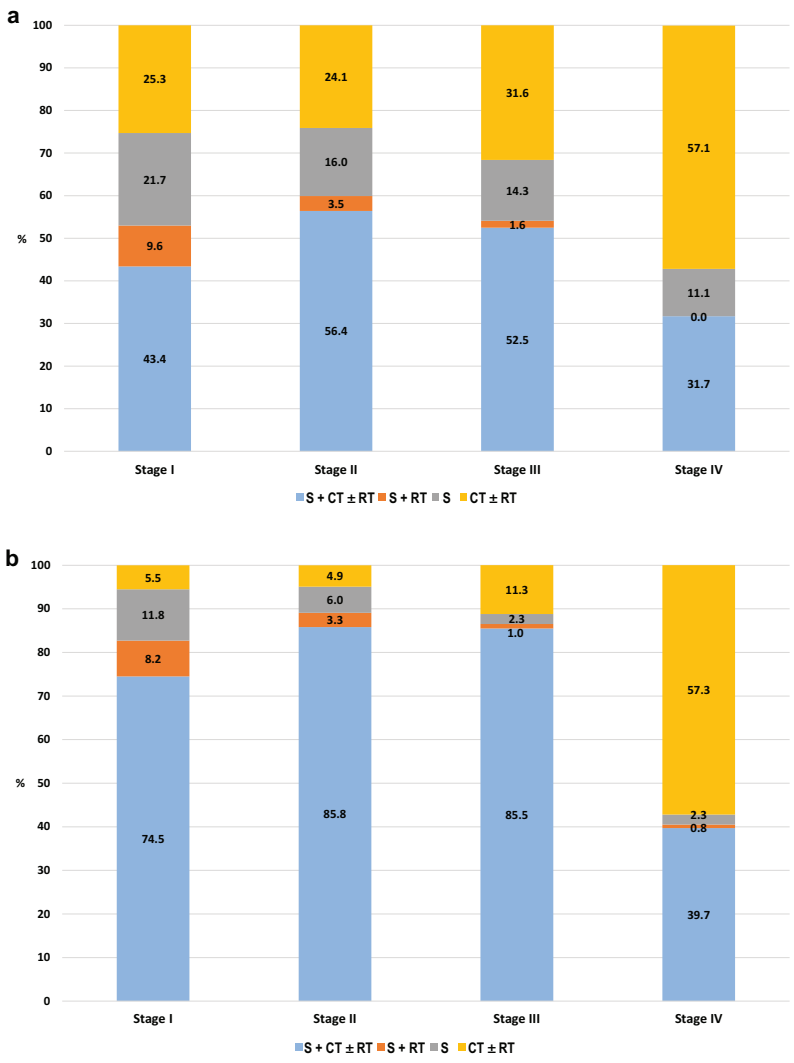
6.2.2 Type of treatment received by stage of cancer

The distribution of treatment modalities according to AJCC stage of breast cancer and centre is shown in Fig. 6.2.

At CM-VI, surgery (with or without chemotherapy and radiotherapy) was used to treat 74.7% of patients with stage I disease, 75.9% with stage II, 68.4% with stage III, and 42.8% with stage IV. Chemotherapy (neoadjuvant or adjuvant) with surgery (with or without radiotherapy) was used to treat 58.1% of patients with stage I disease, 74.3% with stage II, 76.6% with stage III, and 74.9% with stage IV. A combination of all three modalities (surgery, chemotherapy, and radiotherapy) was used to treat 14.5% of patients with stage I disease, 29.1% with stage II, 25.8% with stage III, and 14.3% with stage IV.

At INO, surgery (with or without chemotherapy and radiotherapy) was used to treat 94.5% of patients with stage I cancer, 95.2% with stage II, 88.9% with stage III, and 42.8% with stage IV. Chemotherapy (neoadjuvant or adjuvant) with surgery (with or without radiotherapy) was used to treat 78.8% of patients with stage I disease, 90.3% with stage II, 96.3% with stage III, and 92.9% with stage IV. A combination of all three modalities (surgery, radiotherapy, and chemotherapy) was used to treat 43.6% of patients with stage I disease, 68.9% with stage II, 67.3% with stage III, and 19.3% with stage IV.

Fig. 6.2. Distribution of treatment modalities according to American Joint Committee on Cancer stage of breast cancer (a) at the Centre Mohammed VI pour le traitement des cancers (CM-VI) and (b) at the Institut National d'Oncologie Sidi Mohamed Ben Abdellah (INO). CT, chemotherapy; RT, radiotherapy; S, surgery.

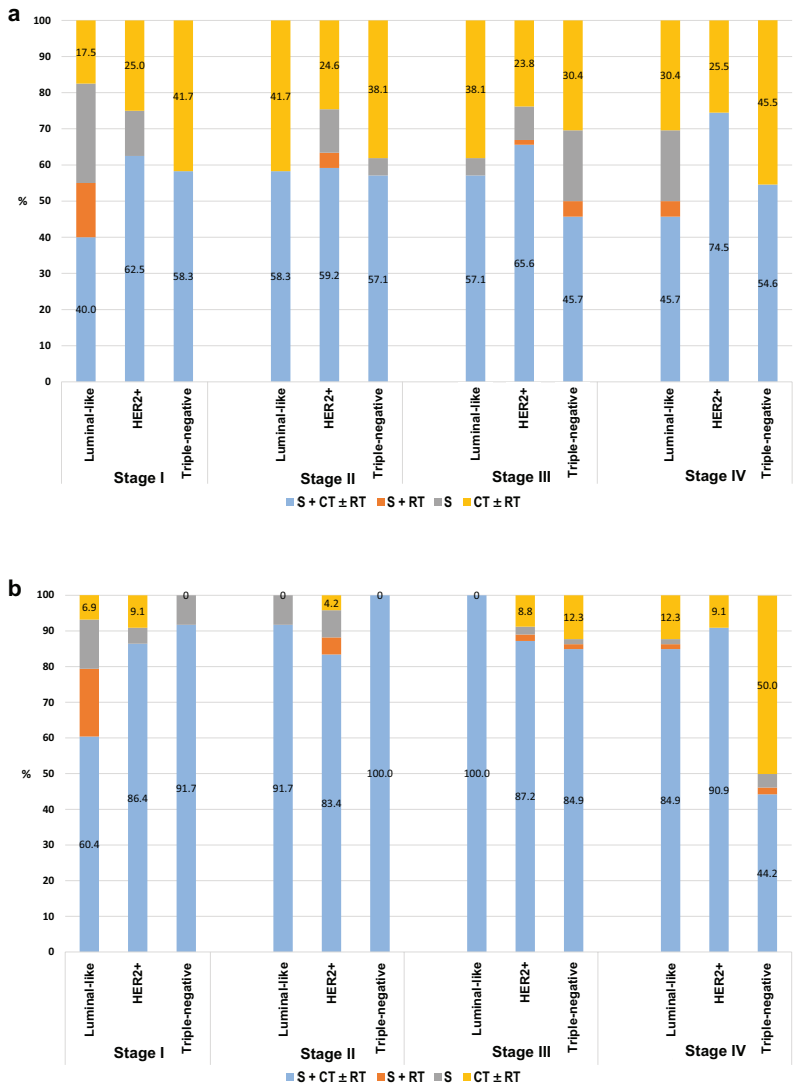


6.2.3 Type of treatment received according to stage at diagnosis and molecular subtype

Because treatment modalities for breast cancer depend on both the stage of disease and the molecular subtype of the cancer, we combined information on stage and molecular profile to study and compare the indications for different types of treatment at CM-VI (Fig. 6.3a) and INO (Fig. 6.3b). The patients included in this analysis are restricted to those for which both stage and molecular subtype information was available.

At CM-VI, the proportions of patients treated with a combination of surgery and chemotherapy, with or

Fig. 6.3. Distribution of different treatment modalities according to American Joint Committee on Cancer stage of breast cancer and molecular subtype (a) at the Centre Mohammed VI pour le traitement des cancers (CM-VI), Casablanca and (b) at the Institut National d'Oncologie Sidi Mohamed Ben Abdellah (INO), Rabat. CT, chemotherapy; HER2, human epidermal growth factor receptor 2; RT, radiotherapy; S, surgery.



without radiotherapy, by stage and molecular subtype were as follows: stage I, from 40.0% for luminal-like to 62.5% for HER2-positive cancers; stage II, from 57.1% for triple-negative to 59.2% for HER2-positive cancers; stage III, from 45.7% for triple-negative to 65.6% for HER2-positive cancers; stage IV, from 45.7% for luminal-like to 74.5% for HER2-positive cancers.

The next most common form of treatment was chemotherapy alone or combined with radiotherapy (no surgery); the proportion of patients ranged from 17.5% for stage I luminal-like cancers to 45.5% for stage IV triple-negative cancers.

At INO, the proportions of patients treated with a combination of surgery and chemotherapy (with or without radiotherapy) were higher: stage I, from 60.4% for luminal-like to 91.7% for triple-negative cancers; stage II, from 83.4% for HER2-positive to 100% for triple-negative cancers; stage III, from 84.9% for triple-negative to 100% for luminal-like cancers; stage IV, from 44.2% for triple-negative to 90.9% for HER2-positive cancers. Chemotherapy alone or combined with radiotherapy was used mostly to treat stage IV cancers; the proportions ranged from 9.1% for HER2-positive to 50% for triple-negative subtypes.

6.2.4 Interval between diagnosis and initiation of treatment

The interval between the date of diagnosis (confirmation by cytology or histopathology) and the initiation of treatment (date of surgery for those treated by surgery first) was estimated overall and also by whether the treatment was initiated at the oncology centre or elsewhere.

At CM-VI, the median interval was 2.7 months (IQR, 1.0–7.1 months). Patients treated at non-oncology hospitals before registering at CM-VI had a shorter median interval (0.8 months; IQR, 0.4–3.6 months) compared with those who received their first treatment at the hospital (3.8 months; IQR, 2.0–8.5 months). The median interval (overall) was shorter in 2013–2017 (2.2 months; IQR, 0.8–5.2 months) than in 2008–2012 (3.8 months; IQR, 1.2–8.1 months).

At INO, the median interval between diagnosis of cancer and initiation of treatment was 1.6 months (IQR, 1.0–2.8 months), 0.9 months (IQR, 0.4–1.4 months) for those who started treatment at another hospital, and 1.9 months (IQR, 1.2–3.1 months) for those who received their first treatment at the oncology centre. The median interval (overall) was 1.5 months (IQR,

0.8–2.9 months) in 2008–2012 and 1.8 months (IQR, 1.1–2.8 months) in 2013–2017.

6.2.5 Interval between registration at the oncology centre and initiation of treatment

The median waiting period to initiate treatment at CM-VI was 1.5 months (IQR, 0.9–3.5 months). No difference was observed between 2008–2012 (1.5 months; IQR, 0.9–3.4 months) and 2013–2017 (1.5 months; IQR, 0.8–3.9 months). The median waiting period to initiate treatment at INO was similar to that observed at CM-VI (1.5 months; IQR, 0.9–2.6 months), again with little change over time (1.4 months in 2008–2012; IQR, 0.7–2.5 months and 1.6 months in 2013–2017; IQR, 1.0–2.6 months).

6.2.6 Interval between surgery and initiation of adjuvant chemotherapy or radiotherapy

The interval between surgery and initiation of adjuvant chemotherapy or radiotherapy should not exceed 6 weeks. The median interval between surgery and initiation of chemotherapy for patients who did not receive radiotherapy in the intervening period was 2.7 months (IQR, 1.9–3.9 months) at CM-VI and 2.1 months (IQR, 1.4–2.9 months) at INO. At CM-VI, the interval was 2.8 months (IQR, 1.9–4.2 months) in 2008–2012 and 2.6 months (IQR, 1.9–3.5 months) in 2013–2017. At INO, the interval was a little longer in 2013–2017 (2.3 months; IQR, 1.7–3.0 months) than in 2008–2012 (1.8 months; IQR, 1.0–2.5 months).

The interval between primary surgery and first dose of radiotherapy was estimated for patients who did not receive chemotherapy in the intervening period. The interval was 8.9 months (IQR, 5.0–11.0 months) at CM-VI and 6.9 months (IQR, 4.9–9.1 months) at INO. The interval increased at CM-VI, from 7.0 months (IQR, 4.3–9.0 months) in 2008–2012 to 9.7 months (IQR, 8.9–12.5 months) in 2013–2017. A slight reduction in the interval was observed at INO during this period, from 7.1 months (IQR, 5.5–8.5 months) in 2008–2012 to 6.5 months (IQR, 3.8–9.2 months) in 2013–2017.

6.3 Breast cancer management in Morocco compared with other settings

The systematic information on modalities for treating breast cancer available from CM-VI and INO is rarely available from the Eastern Mediterranean Region and LMICs in other parts of the world. Surgery is the mainstay of treatment for breast cancer, and in high-income countries nearly 90% of patients are treated with surgery.

Overall, 69.9% of the patients registered at CM-VI and 86.1% of those at INO underwent surgery. For the patients registered at CM-VI, the actual proportion undergoing surgery is probably higher than 69.9%, because information on treatment received was missing for a substantial number of patients. Most of the patients with missing information could have undergone surgery at a hospital other than CM-VI.

A recent study from a referral oncology centre in Iraq reported that surgery was the primary mode of treatment for 96% of the patients with breast cancer (Alwan and Shawkat, 2020). It was reported that 91.7% of patients received chemotherapy and 65.7% received radiotherapy. A systematic review of studies from Africa reported a wide variation in the proportion of patients with breast cancer undergoing surgery, ranging from 35.2% in Nigeria to 100% in Cameroon (Vanderpuye et al., 2017). In some settings, all patients are treated with some form of surgery (including toilet mastectomy for palliative care) because of the lack of access to chemotherapy or radiotherapy.

All the common antineoplastic agents used to treat breast cancer, including taxanes, are included in the updated WHO model list of essential medicines considered to be most efficacious, safe, and cost-effective (WHO, 2019). However, many LMICs cannot supply these drugs to patients free of cost, and the high out-of-pocket expenditure leads to poor compliance. The availability of generic brands of some of these anticancer drugs has improved their affordability. Some are available at one fifth the price of the patented drug. The lack of trained oncologists is also a major barrier to the administration of chemotherapy in many LMICs, especially in sub-Saharan Africa.

A survey conducted in oncologists in 31 sub-Saharan African countries reported that 40% of the centres treating breast cancer had no tumour board and less than 20% had access to taxanes (Vanderpuye et al., 2016). The survey also highlighted the lack of radiation facilities in many countries, which is a barrier to breast-conserving treatment (BCS followed by radiotherapy). Even in countries with radiotherapy facilities, there is a long waiting period because demand is substantially higher than the availability of services. The average waiting time for radiotherapy was 30 days in the Syrian Arab Republic in 2016 (Faris et al., 2016). A study in 11 sub-Saharan African countries reported the gross undertreatment of patients with breast cancer, with only 48% of the patients with stage II or III disease being treated with a combination of surgery and chemotherapy (nearly half of them received radiotherapy) (Joko-Fru et al., 2018). The situation

was better in Morocco, where more than 70% of stage II or III breast cancers were treated with a combination of surgery and chemotherapy (with or without radiotherapy).

WHO (2017) recommends that treatment should be initiated in more than 80% of patients within 1 month of diagnosis. We observed that the median interval between diagnosis and initiation of treatment was 2.7 months at CM-VI and 1.6 months at INO. For LMICs with a large patient load, it is a challenge to reduce the interval further. A retrospective study in the patients registered at one of the most prestigious cancer centres in India showed that the median interval between diagnosis and initiation of treatment was 2 months (IQR, 0.9–3.4 months), which is similar to that in Morocco (Alok Kumar et al., 2012). A large survey of 6588 patients with breast cancer in 12 selected European and Asian lower or upper middle-income countries showed that the mean interval between the first medical visit and the initiation of treatment ranged from 8.3 weeks in Lithuania to 24.7 weeks in India (Jassem et al., 2014).

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CHAPTER 7.

Patterns of care in surgical management

Key observations

- Surgery was used to treat 69.9% of the patients with breast cancer registered at CM-VI and 86.1% of those registered at INO.
- Half of the surgeries used to treat the patients registered at CM-VI with stages I, II, and III breast cancer were BCS. Only 26.3% were BCS at INO. These proportions are much lower than the international benchmarks.
- Nearly 90% of the patients registered at CM-VI and 40% of the patients registered at INO underwent primary surgery at hospitals other than the oncology centres. Although the proportion decreased at INO with time, there was almost no change at CM-VI.
- More than 95% of the women had ALND. SLN biopsy facilities were not available.
- The proportion of women receiving postoperative radiotherapy after BCS was 38.3% at CM-VI and more than 75% at INO. Overall, 75.3% of patients at CM-VI and 91.8% of patients at INO received radiotherapy and/or chemotherapy along with BCS.
- The proportion of women receiving chemotherapy and/or radiotherapy with mastectomy was 79% at CM-VI and 88.5% at INO.

7.1 Principles of surgical management of breast cancer

Surgery is the mainstay of management for breast cancer. BCS, either upfront or after neoadjuvant chemotherapy, is the treatment of choice in patients with stage I to stage III breast cancers but should not be used in settings where mammographic assessment and postoperative radiotherapy are unavailable. In such situations, the preferred surgical option is modified radical mastectomy (MRM) (Anderson et al., 2006).

Overall, 70% of the 785 patients with breast cancer registered at CM-VI (for whom treatment information was available) underwent surgery, either at the oncology centre or elsewhere.

At INO, 86.1% of the 1157 patients registered (for whom treatment information was available) underwent surgery, either at the oncology centre or elsewhere.

In the following sections we discuss the surgical management used to treat the patients in further detail.

7.2 Surgical management of the study patients

7.2.1 Place of surgery

At CM-VI, most of the 549 patients (89.1%) who underwent surgery had

had the procedure at a hospital or clinic other than the oncology centre. The proportion of patients who underwent surgery elsewhere was higher in 2013–2017 (91.9%) than in 2008–2012 (84.9%).

At INO, most of the patients who underwent surgery had the procedure at the centre. A total of 997 patients with breast cancer registered at INO underwent surgery; of these, 403 (41.1%) underwent surgery at a hospital or clinic other than the institute.

The proportion of patients who underwent initial surgery elsewhere was lower in 2013–2017 (32.3%) than in 2008–2012 (52.3%).

7.2.2 Type of surgery

MRM was the most frequently performed surgery for the patients registered at CM-VI; 48.6% of all surgically treated patients underwent MRM. This was closely followed by lumpectomy (BCS) with ALND, which was used in 45.5% of all surgically treated patients.

The proportion of patients who underwent MRM at CM-VI decreased from 52.1% in 2008–2012 to 46.4% in 2013–2017, with a corresponding increase in the proportion of patients who underwent BCS.

The proportion of patients who underwent MRM was higher at INO than at CM-VI. Among patients who underwent surgery, 73.0% of patients were treated with MRM and 25.4% with lumpectomy and ALND.

The proportion of surgically treated patients with breast cancer who underwent MRM decreased from 75.0% in 2008–2012 to 71.5% in 2013–2017, with a corresponding increase in the proportion who underwent BCS.

Overall, 50.0% of patients with stage I, II, or III cancer underwent BCS at CM-VI. The proportion was less (26.3%) at INO.

7.2.3 Type of surgery by stage of cancer and molecular subtype

We analysed the treatment data according to stage and molecular subtype of the tumours separately for CM-VI and INO (Table 7.1).

At CM-VI, BCS was more frequently used than mastectomy to treat patients with luminal-like stage I and II cancer, HER2-positive stage II cancer, and triple-negative stage I cancer. For HER2-positive stage I cancer, the proportion of patients who underwent BCS was the same as the proportion who underwent mastectomy. For all other types and stages, mastectomy was more commonly performed.

At INO, BCS was more common or at least as common as mastectomy for patients with stage I (all molecular subtypes) or luminal-like stage II cancer. For other types and stages, mastectomy was more commonly performed.

7.2.4 Adjuvant or neoadjuvant therapy with surgery

In an ideal situation, most patients undergoing BCS should receive at least radiotherapy; the exceptions are T1N0 ER-positive cancers with complete excision, especially in elderly women. Adjuvant chemotherapy is indicated on the basis of the estimated risk of recurrence. Neoadjuvant chemotherapy is often administered before surgery, especially in HER2-positive and triple-negative breast cancers.

At CM-VI, 100 (38.3%) of the 261 patients who underwent BCS received adjuvant radiotherapy, and 37.0% received adjuvant or neoadjuvant chemotherapy. Nearly a quarter (24.9%) of the CM-VI patients who underwent BCS did not receive chemotherapy or radiotherapy. The most common adjuvant therapy at CM-VI for patients who underwent MRM was chemotherapy alone (39.3%), followed by a combination of chemotherapy and radiotherapy (36.7%). More than one fifth of the patients who underwent MRM (20.7%) did not receive chemotherapy or radiotherapy.

At INO, more than three quarters of the 255 patients who underwent BCS received postoperative radiotherapy, either in combination with chemotherapy (66.7%) or alone (8.6%); 16.5% of the patients who underwent BCS received chemotherapy alone, and just 8.2% of the patients received neither chemotherapy nor radiotherapy. At INO, 67.4% of the patients who underwent MRM received both chemotherapy and radiotherapy and 21.1% received chemotherapy alone.

7.3 Surgical management of breast cancer in Morocco compared with other settings

The European Society of Breast Cancer Specialists (EUSOMA) working group defined a minimum standard for a set of quality indicators for breast cancer care (Biganzoli et al., 2017). With regard to surgery and locoregional treatment, the working group stipulated the minimum standards as: (i) at least 90% of patients should be discussed pre- and postoperatively at the tumour board; (ii) at least 80% of patients should undergo some form of surgery; and (iii) at least 90% of patients with invasive breast cancer without metastasis should receive postoperative radiotherapy after BCS.

All breast cancer cases are routinely discussed in the weekly tumour board meetings at INO; this is in compliance with the good practice recommendations. However, the practice is different at CM-VI, where only the cases selected by the oncologists are referred to the tumour

Table 7.1. Type of surgery received according to stage at diagnosis and molecular type for patients with breast cancer

Stage at diagnosis	ER, PR, and HER2 status	Patients with stage and ER, PR, and HER2 status information	Type of surgery			
			ALND alone	Unspecified breast surgery with ALND	Breast lumpectomy	Mastectomy
		n	*n* (%)	*n* (%)	*n* (%)	*n* (%)
CM-VI						
I	ER+ and/or PR+ and HER2−	33	0 (0.0)	2 (6.1)	21 (63.6)	10 (30.3)
	ER+ and/or PR+ and HER2+	6	0 (0.0)	0 (0.0)	3 (50.0)	3 (50.0)
	ER− and PR− and HER2+	6	0 (0.0)	0 (0.0)	3 (50.0)	3 (50.0)
	Triple-negative	7	0 (0.0)	0 (0.0)	6 (85.7)	1 (14.3)
II	ER+ and/or PR+ and HER2−	7	0 (0.0)	0 (0.0)	6 (85.7)	1 (14.3)
	ER+ and/or PR+ and HER2+	104	0 (0.0)	1 (1.0)	63 (60.6)	40 (38.5)
	ER− and PR− and HER2+	40	0 (0.0)	1 (2.5)	27 (67.5)	12 (30.0)
	Triple-negative	13	0 (0.0)	0 (0.0)	6 (46.2)	7 (53.8)
III	ER+ and/or PR+ and HER2−	13	0 (0.0)	0 (0.0)	6 (46.2)	7 (53.8)
	ER+ and/or PR+ and HER2+	48	0 (0.0)	1 (2.1)	24 (50.0)	23 (47.9)
	ER− and PR− and HER2+	67	0 (0.0)	2 (3.0)	22 (32.8)	43 (64.2)
	Triple-negative	32	1 (3.1)	1 (3.1)	12 (37.5)	18 (56.3)
IV	ER+ and/or PR+ and HER2−	32	1 (3.1)	1 (3.1)	12 (37.5)	18 (56.3)
	ER+ and/or PR+ and HER2+	13	0 (0.0)	0 (0.0)	6 (46.2)	7 (53.8)
	ER− and PR− and HER2+	22	0 (0.0)	0 (0.0)	6 (27.3)	16 (72.7)
	Triple-negative	12	0 (0.0)	0 (0.0)	3 (25.0)	9 (75.0)
INO						
I	ER+ and/or PR+ and HER2−	54	1 (1.9)	0 (0.0)	27 (50.0)	26 (48.1)
	ER+ and/or PR+ and HER2+	13	0 (0.0)	0 (0.0)	6 (46.2)	7 (53.8)
	ER− and PR− and HER2+	7	0 (0.0)	0 (0.0)	5 (71.4)	2 (28.6)
	Triple-negative	12	0 (0.0)	0 (0.0)	6 (50.0)	6 (50.0)
II	ER+ and/or PR+ and HER2−	12	0 (0.0)	0 (0.0)	6 (50.0)	6 (50.0)
	ER+ and/or PR+ and HER2+	230	0 (0.0)	4 (1.7)	72 (31.3)	154 (67.0)
	ER− and PR− and HER2+	86	0 (0.0)	1 (1.2)	12 (14.0)	73 (84.9)
	Triple-negative	33	0 (0.0)	0 (0.0)	6 (18.2)	27 (81.8)
III	ER+ and/or PR+ and HER2−	33	0 (0.0)	0 (0.0)	6 (18.2)	27 (81.8)
	ER+ and/or PR+ and HER2+	62	0 (0.0)	0 (0.0)	20 (32.3)	42 (67.7)
	ER− and PR− and HER2+	187	1 (0.5)	4 (2.1)	35 (18.7)	147 (78.6)
	Triple-negative	64	1 (1.6)	0 (0.0)	9 (14.1)	54 (84.4)
IV	ER+ and/or PR+ and HER2−	64	1 (1.6)	0 (0.0)	9 (14.1)	54 (84.4)
	ER+ and/or PR+ and HER2+	27	0 (0.0)	0 (0.0)	4 (14.8)	23 (85.2)
	ER− and PR− and HER2+	33	0 (0.0)	0 (0.0)	12 (36.4)	21 (63.6)
	Triple-negative	26	0 (0.0)	0 (0.0)	7 (26.9)	19 (73.1)

ALND, axillary lymph node dissection; 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.

board. The benchmark of treating at least 80% of the patients with surgery was achieved at INO but not at CM-VI. The proportion of patients receiving adjuvant radiotherapy after BCS was lower than the standard benchmark at both institutions, more so at CM-VI.

There may be several explanations for the oncology centres not being able to achieve the benchmarks. First, the stage distribution of cancer patients in Morocco is still very different from that observed in the European settings where these standards were set. Second, surgical practice outside the oncology centres, especially in the private sector, may not be well regulated and the surgeons may not be following the appropriate guidelines. Third, many of the patients may not be compliant with the advice and may be reluctant to undergo radiotherapy and/or chemotherapy. Lastly, there is a possibility that our investigators could not get access to complete data. This is particularly relevant at CM-VI, where the radiotherapy-related information is maintained entirely through an online system.

The low frequency of BCS in patients with breast cancer seen in Morocco is in line with that seen throughout the Eastern Mediterranean Region. The frequency of BCS in Arab countries reported by a study in 2007 ranged from 12% in the Syrian Arab Republic to 35% in Oman (El Saghir et al., 2007). A recent study in Iraq reported that 96% of the patients with breast cancer underwent surgery but only 3.6% underwent BCS (Alwan and Shawkat, 2020). The large number of patients with breast cancer undergoing surgery performed primarily by surgeons who are not oncosurgeons is also not unique to Morocco. In the absence of structured training facilities in surgical oncology, breast cancer surgeries are frequently performed by general surgeons or gynaecologists in LMICs, and the quality of surgery is often suboptimal (Sullivan et al., 2015). A study in Malawi reported that breast cancers were even resected by non-physicians (Dare et al., 2015). The large number of patients with breast cancer undergoing surgery outside of oncology centres in Morocco may reflect the capacity of the non-oncology tertiary care centres to handle oncosurgery, which is desirable and may reduce the load on the publicly funded oncology centres. However, it is important to ensure that the surgeons performing procedures outside oncology centres are appropriately trained and follow evidence-based practices. A national protocol for managing breast cancers will be very useful to harmonize such practices.

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CHAPTER 8.

Chemotherapy

Key observations

- A high proportion of the patients with breast cancer included in this study (68.0% of those registered at CM-VI and 84.5% at INO) had chemotherapy in their treatment protocol. The proportion decreased over time in both centres, possibly because of appropriate risk stratification based on the molecular and histopathological characteristics of the tumours.
- About 10–20% of the patients were treated with neoadjuvant chemotherapy. The proportion receiving neoadjuvant chemotherapy is still lower than expected, most likely because a large number of patients underwent initial surgery in settings other than the oncology centres.
- The combination of drugs, either AC60/600 (four cycles of doxorubicin [60 mg/m^2] and cyclophosphamide [600 mg/m^2] every 3 weeks) or FEC100 (5-FU [600 mg/m^2], epirubicin [100 mg/m^2], and cyclophosphamide [600 mg/m^2]) regimens along with taxane) used for both adjuvant and neoadjuvant chemotherapy is as per the international standards and the recently published guidelines for chemotherapy.
- Overall, 52.9% of the patients at CM-VI and 67.9% of those at INO who received chemotherapy were treated with a taxane, in combination with either AC60/600 or FEC100.
- The median number of chemotherapy cycles (6–8 cycles for different stages) received by the patients and the median duration of adjuvant chemotherapy (ranging from 18 to 20 weeks) indicate high compliance with chemotherapy.

8.1 Principles of chemotherapy for treatment of breast cancer

The decision to administer adjuvant chemotherapy after surgery is based on hormone receptor and HER2 expression status and pathological characteristics (size and grade of tumour, number of axillary lymph nodes involved, presence of angiolymphatic invasion, etc.). Age and associated comorbidities are also important considerations. Although chemotherapy is indicated for all HER2-positive and triple-negative cancers, the decision to administer adjuvant chemotherapy to the hormone receptor-positive and HER2-negative cases depends on the presence or absence of other risk factors.

Preoperative chemotherapy (also known as neoadjuvant chemotherapy) is increasingly recommended and practised in the management of both operable and inoperable breast cancers. No difference in long-term clinical outcomes was observed in RCTs when chemotherapy was given

before or after surgery, although neoadjuvant chemotherapy improved the chance of patients being eligible for BCS (Mauri et al., 2005).

A combination of anthracycline (doxorubicin or epirubicin) and cyclophosphamide followed by a taxane (usually paclitaxel) is the most commonly used chemotherapy regimen for breast cancer (Moo et al., 2018). Anthracycline and cyclophosphamide became the standard of care after a systematic review by the EBCTCG, which demonstrated that compared with the CMF regimen used earlier, the new regimen significantly reduced annual odds of recurrence by 12% and annual odds of death by 11% (EBCTCG, 1998). Adding sequential taxane can significantly increase the pathological response rate and overall survival and is considered to be the standard of care even for early-stage breast cancer (Cuppone et al., 2008; Fujii et al., 2015).

8.2 Details of patients receiving chemotherapy in the study

Chemotherapy practice in Morocco is guided by the national guidelines for treatment with chemotherapy (Association Marocaine de Formation et de Recherche en oncologie médicale, 2019).

In the patients registered at CM-VI, chemotherapy was administered to 68.0% of those who received any cancer-directed treatment. The proportion who received chemotherapy was higher in 2008–2012 (88.7%) than in 2013–2017 (60.7%). Of the patients who received chemotherapy, 86.2% received it as an adjuvant treatment, 10.6% received neoadjuvant chemotherapy, and just 3.2% received palliative chemotherapy. The proportion who received neoadjuvant chemotherapy remained constant over time.

In the patients registered at INO, chemotherapy was administered to 84.5% of those who received any cancer-directed treatment. The proportion who received chemotherapy was higher in 2008–2012 (94.0%) than in 2013–2017 (77.8%). Of the patients who received chemotherapy, 71.8% received it as an adjuvant treatment, 19.0% received neoadjuvant chemotherapy, and 9.2% received palliative chemotherapy. There was no major change in the distribution over time.

8.2.1 Distribution of patients receiving chemotherapy according to stage

More than three quarters (76%) of the 622 CM-VI patients who received chemotherapy had stage II or III disease. Adjuvant chemotherapy after surgery was administered to all the patients with stage I disease, 95.7% with stage II, 79.3% with stage III, and 54.5% with stage IV (Table 8.1). Most patients who received neoadjuvant chemotherapy had either stage III (19.7% received neoadjuvant chemotherapy) or stage IV disease (16.4% received neoadjuvant chemotherapy).

At INO, 7.3% of the 1018 patients who received chemotherapy had stage I disease, 41.3% had stage II, 37.1% had stage III, and 11.5% had stage IV. Adjuvant chemotherapy after surgery was administered to 87.8% of patients with stage I disease, 85.5% with stage II, 73.3% with stage III, and 12.8% with stage IV (Table 8.1). A higher proportion of patients than at CM-VI received neoadjuvant chemotherapy at INO at each stage: 10.8% of patients with stage I disease, 14.0% with stage II, 24.9% with stage III, and 18.8% with stage IV were treated with neoadjuvant chemotherapy.

Only a small proportion of patients who underwent BCS (2.2% at CM-VI and 11.1% at INO) received neoadjuvant chemotherapy. All the rest received chemotherapy as adjuvant therapy after surgery.

8.2.2 Molecular subtypes of cancers for patients receiving chemotherapy

The proportion of patients with different molecular subtypes of breast cancer who received adjuvant chemotherapy at CM-VI ranged from 88.9% for luminal-like to 97.9% for ER- and PR-negative and HER2-positive types (Table 8.1). Neoadjuvant chemotherapy was administered to 10.3% of patients with luminal-like cancer, 10.3% of patients with ER- and PR-positive and HER2-positive cancer, and 7.9% of patients with triple-negative cancers. No neoadjuvant chemotherapy was given to patients with ER- and PR-negative and HER2-positive cancers.

The proportion of patients who received adjuvant chemotherapy at INO ranged from 67.9% of patients with ER- and PR-negative and HER2-positive cancer to 74.5% of patients with luminal-like cancer. Higher proportions of patients with the different molecular subtypes received neoadjuvant chemotherapy at INO than at CM-VI (luminal-like, 17.2%; ER- and/or PR-positive and HER2-positive, 17.9%; ER- and PR-negative and HER2-positive, 21.4%; and triple-negative, 20.3%).

8.2.3 Chemotherapy regimens used

The most commonly prescribed chemotherapy regimens (adjuvant or neoadjuvant) for the patients registered at CM-VI were either AC60/600 (four cycles of 60 mg/m^2 doxorubicin and 600 mg/m^2 cyclophosphamide every 3 weeks) followed by taxane every 3 weeks or AC60/600

Table 8.1. Type of chemotherapy administered at the oncology centres by stage and molecular profile

	Patients assessed	Chemotherapy type					
	n	Adjuvant *n* (%)		Neoadjuvant *n* (%)		Palliative *n* (%)	
CM-VI							
No. of patients receiving chemotherapy	622	536	(86.2)	66	(10.6)	20	(3.2)
Stage							
I	57	57	(100.0)	0	(0.0)	0	(0.0)
II	276	264	(95.7)	11	(4.0)	1	(0.4)
III	198	157	(79.3)	39	(19.7)	2	(1.0)
IV	55	30	(54.5)	9	(16.4)	16	(29.1)
ER, PR, and HER2 status							
ER+ and/or PR+ and HER2−	243	216	(88.9)	25	(10.3)	2	(0.8)
ER+ and/or PR+ and HER2+	107	94	(87.9)	11	(10.3)	2	(1.9)
ER− and PR− and HER2+	47	46	(97.9)	0	(0.0)	1	(2.1)
Triple-negative	101	91	(90.1)	8	(7.9)	2	(2.0)
INO							
No. of patients receiving chemotherapy	1018	731	(71.8)	193	(19.0)	94	(9.2)
Stage							
I	74	65	(87.8)	8	(10.8)	1	(1.4)
II	421	360	(85.5)	59	(14.0)	2	(0.5)
III	378	277	(73.3)	94	(24.9)	7	(1.9)
IV	117	15	(12.8)	22	(18.8)	80	(68.4)
ER, PR, and HER2 status							
ER+ and/or PR+ and HER2−	501	373	(74.5)	86	(17.2)	42	(8.4)
ER+ and/or PR+ and HER2+	195	143	(73.3)	35	(17.9)	17	(8.7)
ER− and PR− and HER2+	84	57	(67.9)	18	(21.4)	9	(10.7)
Triple-negative	128	94	(73.4)	26	(20.3)	8	(6.3)

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.

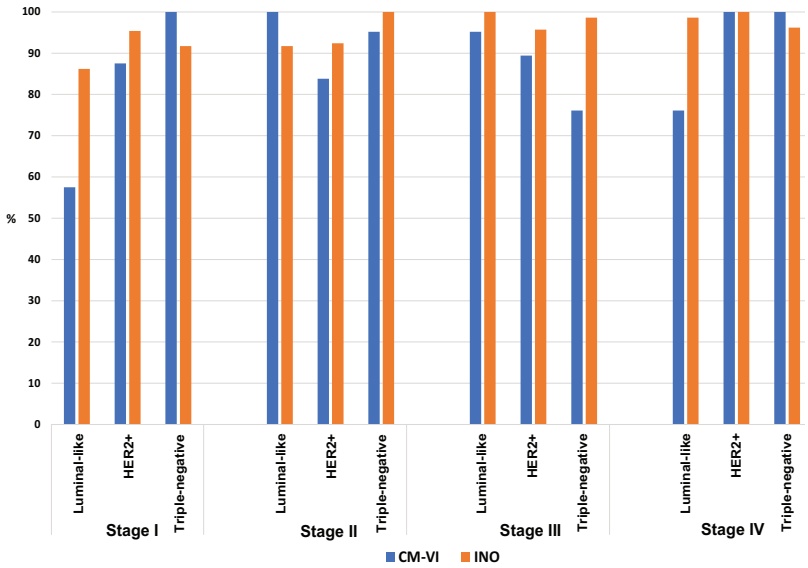
alone. Paclitaxel (80 mg/m^2) was the most commonly used taxane. The FEC100 regimen (a combination of 600 mg/m^2 5-FU, 100 mg/m^2 epirubicin, and 600 mg/m^2 cyclophosphamide) was also frequently used with or without taxane. Overall, 52.9% (320/605) of patients at CM-VI who recieved chemotherapy and 67.9% (682/1004) of patients at INO who received chemotherapy were treated with a taxane, mostly in combination with either AC60/600 or FEC100 regimens.

8.2.4 Median number of cycles of chemotherapy and duration of chemotherapy

On average, six cycles of chemotherapy were given over a period of 20–25 weeks. We estimated the

median number of cycles of chemotherapy received by the patients and the median duration over which chemotherapy was administered at the two centres. The median number of cycles of adjuvant and neoadjuvant chemotherapy for all stages and at both centres was between six and eight cycles. The median duration of adjuvant chemotherapy was between 19.0 and 20.4 weeks at CM-VI and between 18.6 and 20.0 weeks at INO. The median duration of neoadjuvant chemotherapy was between 23.7 and 26.2 weeks at CM-VI and between 22.7 and 26.6 weeks at INO. This is indirect evidence that most patients completed their chemotherapy treatment.

Fig. 8.1. Proportion of patients treated with chemotherapy (with surgery and/or radiotherapy or alone) by stage and molecular subtype. 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.



8.3 Chemotherapy for breast cancer in Morocco compared with other settings

The oncology centres in Morocco have adopted improvements in chemotherapy as they have been developed over time. The financial protection offered by various insurance schemes has improved access to the chemotherapeutic agents for patients attending the public oncology centres. Chemotherapy was tailored to the specific biological nature of the cancer in each case. We observed that a high proportion of patients were treated with combination chemotherapy, especially if they had cancers that were HER2-positive or triple-negative, at both oncology centres (Fig. 8.1). This is in line with international recommendations. The chemotherapy regimens (AC60/600 or FEC100) used to treat breast cancers in Morocco are as recommended in the NCCN and other international guidelines, and more than half of the patients had a taxane included in the combination of drugs.

However, the proportion of patients receiving neoadjuvant chemotherapy was lower than that expected in a setting where a high proportion of cases are detected at an advanced stage. This was mainly because many patients (especially at CM-VI) attended the oncology centres after undergoing surgery elsewhere. An insignificant number of patients treated in hospitals or clinics other than the oncology centres received neoadjuvant chemotherapy.

Very little information is available on the standard-of-care management of breast cancer using chemotherapy in the Eastern Mediterranean Region or Africa. A study of 834 randomly selected patients with breast cancer diagnosed between 2009 and 2015 in 10 sub-Saharan African countries reported that of 747 patients without any known metastasis, 40.6% underwent surgery, 33.6% received chemotherapy, and 15.5% received radiotherapy. Half of the 299 patients treated with chemotherapy received an anthracycline-based regimen, and less than one third received an anthracycline regimen plus taxane (Joko-Fru et al., 2018). Many countries do not have supplies of the bare minimum number of anticancer drugs included in the WHO drug list (Ruff et al., 2016). Patients cannot afford to purchase the drugs and often do not comply with treatment (Vanderpuye et al., 2017).

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CHAPTER 9.

Radiotherapy

Key observations

- Morocco has one linear accelerator machine per 1250 patients, which is lower than the number recommended by the International Atomic Energy Agency (IAEA) as ideal (one per 450 patients) but substantially higher than that reported from most LMICs.
- At CM-VI, postoperative radiotherapy was received by 52.6% of patients with stage I disease, 67.1% with stage II, 65.7% with stage III, and 56.2% with stage IV. At INO, postoperative radiotherapy was received by 81.4% of patients with stage I disease, 92.3% with stage II, 96.8% with stage III, and 89.7% with stage IV.
- Although 74.9% of the patients at INO who underwent BCS received radiotherapy, the proportion was much lower at CM-VI (39.2%). The apparently low number of patients receiving radiotherapy at CM-VI could be partly due to poor maintenance of records.
- The median interval between the date of surgery and initiation of radiotherapy was 7–9 months; ideally, this should not exceed 6 weeks.
- The Houses of Life (*Maisons de Vie*) established in recent years have made a substantial impact in reducing the bed occupancy at the oncology centres for those undergoing radiotherapy.

9.1 Principles of radiotherapy for breast cancer

Radiotherapy is an essential component of multimodal therapy for breast cancer. Whole-breast irradiation (with or without nodal irradiation) after BCS with an additional booster dose to the tumour bed (by either EBRT or brachytherapy), if indicated, reduces the risk of recurrence and improves survival. A meta-analysis of several RCTs observed a 15% reduction in recurrence (locoregional or distant) at 10 years after BCS and a 3% reduction in mortality at 15-year follow-up with adjuvant radiotherapy; the benefit was observed in both node-negative and node-positive disease (Darby et al., 2011). Postmastectomy radiotherapy to the chest wall and regional lymph nodes substantially reduces the locoregional failure rate. It also contributes to the increase in DFS (Rutqvist et al., 2003). Radiotherapy is recommended in all patients with breast cancer who undergo radical surgery, except in patients with T1/T2 tumour without any nodal metastasis and with negative surgical margins. Hypofractionated radiotherapy to deliver 39–42.9 Gy (15–16 fractions; each fraction 2.6–3.3 Gy) compared with the earlier standard dose of 50 Gy achieves similar tumour control and better cosmesis (Smith et al., 2018). Hypofractionation substantially reduces the total treatment time to

just more than 3 weeks, which in turn reduces the load on the radiotherapy services.

9.2 Patients with breast cancer treated with radiotherapy in Morocco and radiotherapy details

At CM-VI, of the 785 patients with breast cancer who received some form of cancer-directed treatment, 36.2% (*n* = 284) received radiotherapy. The proportion of patients who received radiotherapy was lower in 2013–2017 (23.4%) than in 2008–2012 (53.1%).

At INO, of the 1157 patients who received some form of cancer-directed treatment, 65.0% (*n* = 752) received radiotherapy. The proportion was higher in 2008–2012 (73.8%) than in 2013–2017 (58.4%).

Most of the patients were treated with EBRT alone. Using hypofractionated radiotherapy, EBRT could be completed in 3–4 weeks in 55.1% of patients receiving radiotherapy at CM-VI and 66.2% of patients at INO.

Brachytherapy (either HDR or low-dose-rate [LDR]) is usually recommended to boost the tumour bed after surgery and was administered to 17 patients at CM-VI and 15 patients at INO. Most of the brachytherapy applications at both centres were during 2008–2012.

None of the patients at CM-VI and less than 5% of the patients at INO required hospitalization to receive radiotherapy.

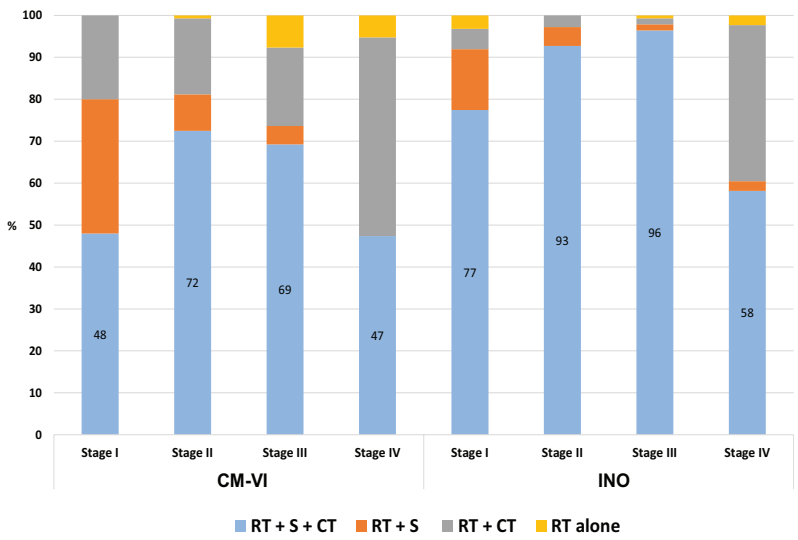
9.2.1 Indications for radiotherapy

At both CM-VI and INO, the most common indication for radiotherapy was postoperative adjuvant therapy (with or without chemotherapy) (Fig. 9.1). The proportions of patients who received postoperative radiotherapy at CM-VI were 52.6% for patients with stage I disease, 67.1% with stage II, 65.7% with stage III, and 56.2% with stage IV. The proportions of patients who received adjuvant radiotherapy (with or without chemotherapy) at INO were 81.4% for patients with stage I disease, 92.3% with stage II, 96.8% with stage III, and 89.7% with stage IV.

Postoperative radiotherapy is recommended after BCS in almost all cases to get rid of the microscopic tumour foci. Although 74.9% of patients who underwent BCS were treated with adjuvant radiotherapy at INO, only 39.2% of the BCS patients received radiotherapy at CM-VI. The proportion of patients who received radiotherapy after mastectomy was also substantially higher at INO (70.2%) than at CM-VI (40.0%). The proportion of patients who received radiotherapy after lumpectomy and mastectomy according to stage at the two oncology centres is shown in Fig. 9.2.

The proportion of patients receiving radiotherapy at CM-VI has been underreported, especially in recent years. The radiotherapy-related information is maintained in a dedicated database in the radiotherapy department and is not transferred to the case files on a regular basis.

Fig. 9.1. The combination of treatment methods according to stage and oncology centre in patients treated with radiotherapy. CM-VI, Centre Mohammed VI pour le traitement des cancers; CT, chemotherapy; INO, Institut National d'Oncologie Sidi Mohamed Ben Abdellah; RT, radiotherapy; S, surgery.

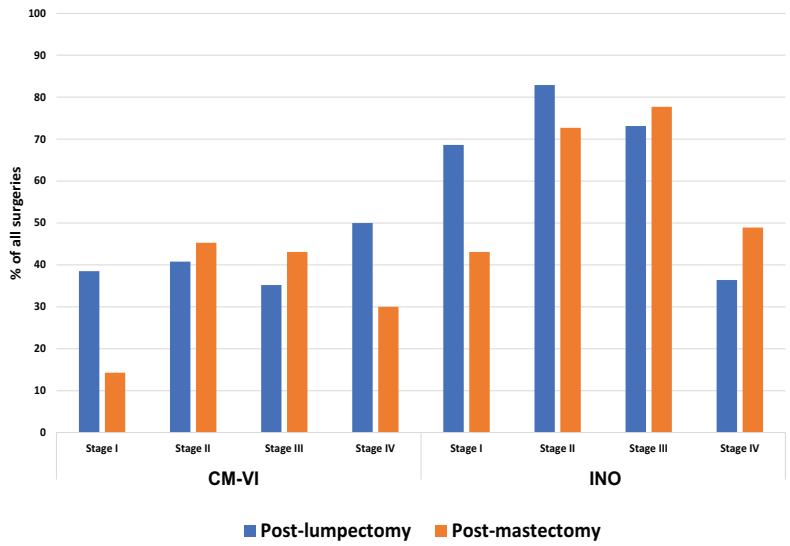


9.2.2 Time between surgery and initiation of radiotherapy

EBRT should be initiated within 3–6 weeks after surgery unless systemic chemotherapy is given in between.

At CM-VI, the median interval between surgery and initiation of radiotherapy for the patients who did not receive chemotherapy in between was 8.9 months (IQR, 5.0–11.0 months). The interval increased over time (7.0 months in 2008–2012 and 9.7 months in 2013–2017). The patients who underwent surgery at CM-VI had lower median waiting periods (4.0 months; IQR, 2.6–8.1 months) than those who had had surgery elsewhere (8.9 months; IQR, 6.5–11.5 months).

Fig. 9.2. Proportion of patients receiving radiotherapy after lumpectomy and mastectomy at the Centre Mohammed VI pour le traitement des cancers (CM-VI) and the Institut National d'Oncologie Sidi Mohamed Ben Abdellah (INO) by stage of breast cancer.



At INO, the median interval between surgery and initiation of radiotherapy for the patients who did not receive chemotherapy in between was 6.9 months (IQR, 4.9–9.1 months). No substantial difference was observed between the time periods (7.1 months in 2008–2012 and 6.5 months in 2013–2017) or by whether the surgery was performed at INO (median interval 6.1 months) or elsewhere (median 7.0 months).

9.3 Radiotherapy for breast cancer in Morocco compared with other settings

Radiotherapy is an integral part of multimodal management of breast cancer, especially when a conservative approach is followed in surgical interventions. Morocco has made substantial progress in improving radiotherapy facilities, which is evident from the fact that there are eight EBRT machines per 10 000 cancer patients (one per 1250 patients) in the country. All telecobalt machines have been replaced by linear accelerator (linac) facilities. Linacs with multileaf collimator, three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, and image-guided radiotherapy facilities are available at CM-VI and INO. Individualized computed tomography scan-based treatment planning and intensity-modulated radiotherapy, which ensure greater target dose homogeneity and sparing of normal tissues, are used at the oncology centres in Morocco.

The EUSOMA guidelines with regard to quality of adjuvant radiotherapy for breast cancer are that: (i) at least 90% of patients should receive radiotherapy after BCS and (ii) at least 90% of patients should receive radiotherapy after radical mastectomy if more than three axillary lymph nodes are involved (Biganzoli et al., 2017). Less than a quarter of the patients at INO who underwent BCS did not receive radiotherapy, whereas at CM-VI nearly 60% did not receive radiotherapy. The proportion of patients who received radiotherapy after mastectomy was also less than expected at CM-VI. As mentioned earlier, the lower frequency reported at CM-VI could be because of incomplete records.

Following international guidelines, the oncology centres in Morocco use hypofractionated radiotherapy, which has substantially reduced the total duration of radiotherapy. However, we observed that in a substantial number of patients the total duration of radiotherapy was either too short (< 2 weeks) or too long (> 10 weeks), especially at CM-VI. Some of these patients may have been noncompliant. There was a delay in the initiation of radiotherapy after initial surgery at both centres.

Morocco has established several Houses of Life (*Maisons de Vie*) to accommodate cancer patients and their families while the patients undergo chemotherapy or radiotherapy at the oncology centres. These unique facilities have substantially reduced the need for hospitalization while the patients are undergoing radiotherapy.

The European guidelines and the IAEA recommend four linac machines per 1 million population (or one per 450 patients) (IAEA, 2011; Rosenblatt et al., 2013). There is an acute shortage of radiotherapy machines in most LMICs, and as a result limited numbers of patients with breast cancer are treated with adjuvant radiotherapy. It has been estimated that approximately 45–55% of the patients with breast cancer in the Islamic Republic of Iran receive radiotherapy, a proportion comparable to that in Morocco (Jönsson et al., 2019). African countries have, on average, one radiotherapy machine per 3.8 million population. This covers just 22–28% of the need, and 28 of the 51 LMICs on the continent have no radiotherapy machines at all (Zubizarreta et al., 2015). A radiotherapy facility requires radiation oncologists, medical physicists,

radiotherapists, and dosimetry technicians, and lack of trained staff is a major barrier to the establishment of radiotherapy facilities in many African countries. There are facilities for training radiotherapy professionals in just 10 African countries.

From this perspective, Morocco has made great progress in ensuring access to good-quality radiotherapy. There is scope for further improvement in reducing delays in initiation of radiotherapy after surgery and ensuring that more patients with high-risk disease are offered radiotherapy.

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CHAPTER 10.

Endocrine therapy and HER2-targeted therapy for breast cancer

Key observations

- A high proportion of patients with breast cancer in Morocco can be classified by molecular subtype because hormone receptor and HER2 expression status are known. This allows tailored management.
- At CM-VI, 54.0% of patients with hormone-sensitive breast cancers received either tamoxifen or aromatase inhibitors. At INO, the proportion was 83.8%.
- The proportion of patients receiving hormone therapy is probably underreported, especially at CM-VI. Patients are prescribed the drug from the outpatients department and the information is not always entered in the case records.
- Tamoxifen was prescribed more commonly than aromatase inhibitors at both oncology centres. The use of aromatase inhibitors for postmenopausal women gradually increased over time.
- HER2 was positive in about 30% of the patients tested for the receptor at CM-VI or at INO. Trastuzumab was administered to 28.0% at CM-VI and to 45.9% at INO. The proportions are high compared with what has been reported from oncology centres in most other LMICs.
- Of the patients with HER2-positive cancer, 91.0% at CM-VI and 97.8% at INO received combination chemotherapy, most of which is taxane-based.

10.1 Principles of endocrine therapy for breast cancer

Determination of the molecular subtype of breast cancer on the basis of the ER, PR, and HER2 expression, and, preferably, Ki-67 status and tailoring treatment according to this information has dramatically changed the management of breast cancer.

All patients with ER- and/or PR-positive cancer should receive selective ER-blocking agents, such as tamoxifen, or aromatase inhibitors (anastrozole, letrozole, or exemestane), depending on menopausal status.

Adjuvant tamoxifen in patients with ER-positive disease is reported to reduce the annual odds of recurrence by 39% and the annual odds of deaths by 31%, irrespective of age, lymph node status, and use of adjuvant chemotherapy (EBCTCG et al., 2005). Although tamoxifen is effective in premenopausal women, an aromatase inhibitor is the drug of choice in postmenopausal women (Gradishar et al., 2020). The treatment should be continued for 5–10 years to get the maximum benefit.

10.2 Patients receiving endocrine therapy at CM-VI and INO

We observed that 73.4% (466/635) of patients with breast cancer registered at CM-VI and 77.6% (792/1020) of those registered at INO and for whom information on ER and PR status was available had tumours that were positive for ER and/or PR. Endocrine therapy was prescribed to 53.9% of the patients with ER- and/or PR-positive cancer registered at CM-VI and 83.8% of the patients with ER- and/or PR-positive cancer registered at INO.

10.2.1 Type of endocrine therapy prescribed

Tamoxifen was prescribed more commonly than aromatase inhibitors at both oncology centres. At CM-VI, 85.3% of the patients with ER- and/or PR-positive cancer who received anti-estrogen drugs were prescribed tamoxifen and 14.7% received aromatase inhibitors. The proportion of patients who received aromatase inhibitors was higher in 2013–2017 (18.2%) than in 2008–2012 (11.5%).

Tamoxifen was prescribed to 83.0% of the patients with ER- and/or PR-positive disease who received endocrine therapy at INO; the rest were prescribed aromatase inhibitors. The proportion of patients who received aromatase inhibitors was substantially higher in 2013–2017 (24.2%) than in 2008–2012 (7.1%).

10.2.2 Endocrine therapy by ER and PR status

The numbers of patients who received tamoxifen or aromatase inhibitors according to ER and PR status are shown in Table 10.1. Most patients at CM-VI (86.2%) had cancers that were positive for both ER and PR, and 55.9% of them received endocrine therapy; 39.1% of the patients with ER-positive and PR-negative disease and 50.0% of the patients with ER-negative and PR-positive disease received endocrine therapy.

At INO, most (84.9%) of the patients had cancers that were positive for both ER and PR, and 84.8% of them received endocrine therapy; 79.2% of the patients with ER-positive and PR-negative disease and 73.9% of those with ER-negative and PR-positive disease received endocrine therapy.

10.3 Principles of HER2-targeted therapy

The HER2-*neu* oncogene is overexpressed in 15–25% of breast cancers and is associated with increased risk of recurrence, poor response to chemotherapy, and lower survival, irrespective of hormone receptor status (Pondé et al., 2019). Trastuzumab is a humanized monoclonal antibody targeted against HER2. A single year of treatment with trastuzumab after completion of chemotherapy in non-metastatic breast cancers may reduce risk of recurrence and/or death by approximately 50%, with a significant 8.4% absolute increase in DFS at 2 years (Piccart-Gebhart et al., 2005). Similar benefits were observed in patients with metastatic breast cancer (Vogel et al., 2002).

Table 10.1. ER and PR status in patients with cancer positive for ER and/or PR who received tamoxifen or aromatase inhibitors

ER and PR combination	CM-VI						INO					
	Period of diagnosis				Total		Period of diagnosis				Total	
	2008–2012		2013–2017				2008–2012		2013–2017			
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Patients with known ER and PR status	197		268		465		334		457		791	
Received tamoxifen or aromatase inhibitors	130	(66.0)	121	(45.1)	251	(54.0)	280	(83.8)	383	(83.8)	663	(83.8)
ER+ and PR−	24		22		46		37		59		96	
Received tamoxifen or aromatase inhibitors	13	(54.2)	5	(22.7)	18	(39.1)	26	(70.3)	50	(84.7)	76	(79.2)
ER− and PR+	13		5		18		19		4		23	
Received tamoxifen or aromatase inhibitors	8	(61.5)	1	(20.0)	9	(50.0)	13	(68.4)	4	(100.0)	17	(73.9)
Both ER+ and PR+	160		241		401		278		394		672	
Received tamoxifen or aromatase inhibitors	109	(68.1)	115	(47.7)	224	(55.9)	241	(86.7)	329	(83.5)	570	(84.8)

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

10.3.1 HER2-targeted therapy at CM-VI and INO

At CM-VI, HER2 was positive in 30% of the 643 patients tested for the receptor. Trastuzumab was administered to 28.0% of the patients with positive HER2 status.

At INO, HER2 was positive in 29.4% of the 1030 patients in whom HER2 status was known. Trastuzumab was administered to 45.9% of the patients with positive HER2 status.

Almost all of the patients with HER2-positive cancers who received trastuzumab were also treated with chemotherapy, both at CM-VI (91.0%) and at INO (97.8%). Most of the patients treated with trastuzumab and chemotherapy received taxane-based chemotherapy, both at CM-VI (67.3%) and at INO (88.2%).

10.4 Endocrine and HER2-targeted therapy for breast cancer in Morocco compared with other settings

10.4.1 Endocrine therapy

The EUSOMA benchmark for quality indicators in breast cancer care stipulates that at least 85% of patients with endocrine-sensitive invasive cancer should receive endocrine therapy. This benchmark was nearly achieved at INO. The proportion of patients with hormone-sensitive cancers who received endocrine therapy is lower at CM-VI, most likely because of underreporting; the drugs were often prescribed to patients without being documented in the case records.

The reported frequency of tamoxifen use for patients with breast cancer varies widely in LMICs. Studies have reported frequencies of 37.7% in Nigeria, 48.1% in South Africa, 60% in Uganda, and 92.9% in Cameroon (Sutter et al., 2016). This variation may be because some of the countries do not have immunohistochemistry facilities and all patients with breast cancer are blindly prescribed tamoxifen, or because poor-quality immunohistochemistry facilities fail to detect the receptors and report a high frequency of triple-negative disease (Kantelhardt et al., 2015; Silverstein et al., 2016).

10.4.2 Trastuzumab as anti-HER2 therapy

The EUSOMA quality indicator for breast cancer care stipulates that at least 85% of patients with HER2-positive cancers (except those with diameter < 1 cm and node-negative) should receive trastuzumab and be treated with chemotherapy. Approximately one third of the patients with HER2-positive cancer at CM-VI and half of those with HER2-positive cancer at INO were treated with trastuzumab. The drug has been included in the list of essential drugs in Morocco; this allows the public oncology hospitals to procure the drug despite its high cost.

Use of trastuzumab therapy is very limited in most LMICs both because of the lack of facilities to identify biomarkers and because of the high cost of treatment. The drug should be given for at least 1 year, and the annual cost may exceed US$ 50 000. In a survey of oncologists in the USA and some of the emerging economies (Brazil, Turkey, Mexico, and the Russian Federation), 37–49% of respondents reported prescribing trastuzumab infrequently. They cited lack of insurance coverage and/or unavailability of the drug as common barriers (Lammers et al., 2014). Trastuzumab is included in the WHO essential drug list, and biosimilars available at a price 65% lower than the cost of the originator drug were prequalified by WHO in 2015 (Davio, 2019).

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CHAPTER 11.

Outcomes of follow-up and survival

Key observations

- High compliance with follow-up and systematic documentation of disease status at each follow-up enabled us to estimate the 5-year DFS for patients registered in 2008–2015.
- The 5-year DFS of all the treated patients with breast cancer was 63%. This is not surprising given that nearly 45% of the patients were diagnosed at stage III or IV.
- The 5-year DFS was much lower at CM-VI (52.9%) than at INO (69.6%), even though the patient profiles and tumour characteristics were similar. The difference persisted even when the 5-year DFS was estimated categorized by stage and was most likely due to the differences in the quality of treatment.
- The 5-year DFS of 92.6% for stage I and II luminal-like breast cancers observed at INO is comparable to the survival estimates for similar cancers in any high-resource setting. This finding highlights that stage-appropriate treatment of early-stage breast cancer can achieve a high cure rate, irrespective of setting.
- The 5-year DFS was the same for the patients with stage I and II disease, irrespective of whether they were treated with BCS (82.9%) or mastectomy (81.3%).
- The 5-year DFS for the more aggressive cancers (HER2-positive or triple-negative cancers) was lower than that for the luminal-like HER2-negative cancers, but the difference was not substantial. This reflects the good quality of care provided at the public oncology centres in Morocco and the efforts made by the oncologists to follow globally accepted protocols by personalizing treatment on the basis of stage and molecular profile.
- The information on deaths was poorly documented in the hospital records, and we were unable to estimate overall survival.

11.1 Protocol for post-treatment follow-up

In many health systems, family physicians are closely involved with the treatment of patients with breast cancer and are trained to perform post-treatment follow-up (Sisler et al., 2016). The gynaecologists who initially referred the patients to the oncology centre have a major role in following up the patients treated at CM-VI but not at INO.

The first follow-up is conducted at the treating oncology centre

3 months after completion of treatment, for both centres. Subsequent follow-up protocols are different between the two centres. At CM-VI, the patients with low risk of recurrence are sent back to their referring gynaecologists with a referral letter for further follow-ups. These patients visit CM-VI once a year. For all other patients, follow-up is performed at CM-VI every 6 months for the first 3 years, and annually thereafter for a further 7 years. At INO, follow-up is performed at the oncology centre only: once every 3 months for the first 2 years, then every 6 months up to 5 years, and annually thereafter.

At each visit, a history is taken and a physical examination is performed to rule out local or distant recurrence. Mammography of both breasts (after BCS) or the contralateral breast (after mastectomy) is performed annually. An ultrasound of the whole abdomen is performed as routine during the annual check-up at CM-VI, but not at INO. Laboratory and/or imaging studies are performed when there is a suspicion of recurrence or metastasis. Patients with an intact uterus who are taking tamoxifen have an annual gynaecological examination.

11.2 Status at follow-up

11.2.1 Completeness of information on follow-up

Of the 915 patients registered at CM-VI, 74.5% had at least one follow-up at the oncology centre and 81.6% had their disease status at last visit documented in the case records (Table 11.1). Some patients had their vital status information collected over the telephone. Of the 1205 patients registered at INO, 92.1% had at least one follow-up at the oncology centre and 77.9% had their disease status at last visit documented. The proportion of patients with unknown status at follow-up was very high for the patients registered in 2016–2017, both at CM-VI (38.5%) and at INO (71.7%). This was essentially because the medical records system at the oncology centres was converted to an online system in 2016. Because of the incomplete data, we excluded the patients registered in 2016–2017 from the survival analysis.

11.2.2 Duration of follow-up

We estimated the duration of follow-up from the date of initiation of cancer-directed treatment (date of surgery or date of first dose of chemotherapy or date of first fraction of radiation, whichever was earlier). The median interval between date of initiation of treatment and date of last follow-up for the CM-VI patients registered in 2008–2012 was 3.5 years (IQR, 1.4–5.4 years) and for those registered in 2013–2015 was 1.6 years (IQR, 0.7–2.5 years). The median follow-up interval for the patients at INO was 3.8 years (IQR, 1.3–5.8 years) for those registered in 2008–2012 and 2.6 years (IQR, 1.9–2.9 years) for those registered in 2013–2015.

11.2.3 Disease status at last follow-up

At CM-VI, of the 383 treated patients registered in 2008–2012, 46.7% were alive and disease-free at last follow-up (Fig. 11.1). A further 40.2% were alive with persistent or recurrent disease at last follow-up. A few patients (1.3%) were alive at last follow-up without known disease status. Only 2 patients (0.5%) were known to have died. No follow-up information was available for 11.5% of patients registered in 2008–2012. The follow-up status of the patients registered at CM-VI in 2013–2015 was no different from that of patients registered in 2008–2012: of the 311 patients, 42.1% were alive and disease-free and 43.7% were alive with disease. The proportion of patients who were alive with unknown disease status was 0.6%, and a further 0.6% were known to have died after

Fig. 11.1. Disease status at last follow-up of the patients registered in 2008–2012 and 2013–2015 at the Centre Mohammed VI pour le traitement des cancers (CM-VI) and the Institut National d'Oncologie Sidi Mohamed Ben Abdellah (INO) (all registered patients included).

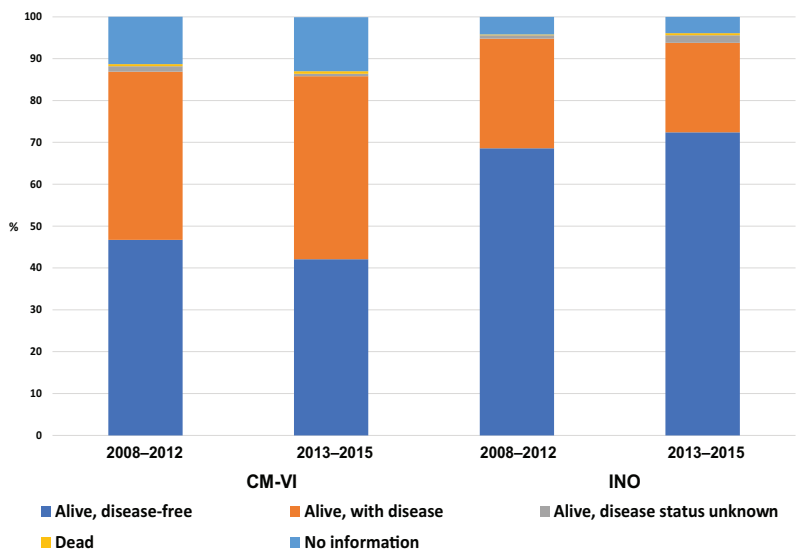


Table 11.1. Disease status during follow-up

	Period of diagnosis						Total	
	2008–2012		2013–2015		2016–2017			
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
CM-VI								
No. of patients registered	383		311		221		915	
Vital status at last follow-up								
Alive and disease-free	179	(46.7)	131	(42.1)	29	(13.1)	339	(37.0)
Alive with disease	154	(40.2)	136	(43.7)	105	(47.5)	395	(43.2)
Alive with disease status unknown	5	(1.3)	2	(0.6)	2	(0.9)	9	(1.0)
Dead	2	(0.5)	2	(0.6)	0	(0.0)	4	(0.4)
Unknown	43	(11.2)	40	(12.9)	85	(38.5)	168	(18.4)
Followed up at least once after registration at oncology centre	294	(76.8)	238	(76.5)	150	(67.9)	682	(74.5)
INO								
No. of patients registered	497		387		321		1205	
Vital status at last follow-up								
Alive and disease-free	341	(68.6)	280	(72.4)	83	(25.9)	704	(58.4)
Alive with disease	130	(26.2)	83	(21.4)	8	(2.5)	221	(18.3)
Alive with disease status unknown	4	(0.8)	7	(1.8)	0	(0.0)	11	(0.9)
Dead	1	(0.2)	2	(0.5)	0	(0.0)	3	(0.2)
Unknown	21	(4.2)	15	(3.9)	230	(71.7)	266	(22.1)
Followed up at least once after registration at oncology centre	490	(98.6)	376	(97.2)	244	(76.0)	1110	(92.1)

CM-VI, Centre Mohammed VI pour le traitement des cancers; INO, Institut National d'Oncologie Sidi Mohamed Ben Abdellah.

treatment. No follow-up information was available for 12.9% of patients registered in 2013–2015.

Follow-up information was available for a higher proportion of patients registered at INO. Of the 497 patients registered at INO in 2008–2012, 68.6% were alive and disease-free and 26.2% were alive with recurrent or persistent disease at last follow-up. Only 0.2% of patients were known to have died. No follow-up status was available for a further 4.2% of the patients. Of the 387 patients registered in 2013–2015, 72.4% were alive and disease-free and 21.4% were alive with disease at last follow-up. Only 2 patients (0.5%) were known to have died, and no follow-up information was available for 3.9% of the patients.

It is possible that many of the cancer patients had died at home of non-malignant causes or due to disease progression and the information was not available in the medical records. Because of the lack of reliable information on the date of death, we could not estimate the overall survival, so DFS was estimated.

11.3 Post-treatment DFS and its determinants

DFS is considered to be a direct measure of the clinical benefit of treatment. Analysis of DFS in our study included those patients treated with at least one type of cancer-directed treatment (surgery, chemotherapy, or radiotherapy). A few patients treated with hormone therapy alone were excluded because they were obviously undertreated. We estimated the DFS from the date of initiation of cancer-directed treatment

(either at the oncology centres or elsewhere).

The 5-year DFS was 52.9% for the patients registered at CM-VI and 69.6% for those registered at INO (Fig. 11.2).

11.3.1 Association between independent prognostic factors and 5-year DFS outcomes

We estimated the association between different known prognostic factors and the DFS using Cox proportional hazards regression analysis. Because the responses of patients are more likely to be correlated within centres than between centres, and because of the possible underlying heterogeneity in practices between the centres, the regression models were adjusted for clustering on centre.

The independent factors that were associated with a higher risk of persistent disease or relapse were: registration during 2013–2015, advanced stage of cancer, poorly differentiated cancer, triple-negative cancer, and treatment type. The 5-year DFS was the same for patients with stage I and II cancer treated with BCS (82.9%) or mastectomy (81.3%).

11.3.2 DFS by stage of cancer and differentiation of tumour

Stage of the cancer at diagnosis was an independent predictor of DFS. The risk of having persistent or recurrent disease increased with stage ($P = 0.002$).

The 5-year DFS by stage was 79.2% for patients with stage I disease, 74.6% with stage II, 60.8% with stage III, and 14.0% with stage IV (Fig. 11.3). The risk of treatment failure increased significantly with increasing differentiation of tumour, on regression analysis ($P < 0.001$).

Fig. 11.2. Kaplan–Meier curves showing disease-free survival in treated patients with breast cancer registered during 2008–2015 by centre. The 5-year disease-free survival at the Centre Mohammed VI pour le traitement des cancers (CM-VI) was 52.9% and at the Institut National d'Oncologie Sidi Mohamed Ben Abdellah (INO) was 69.6%.

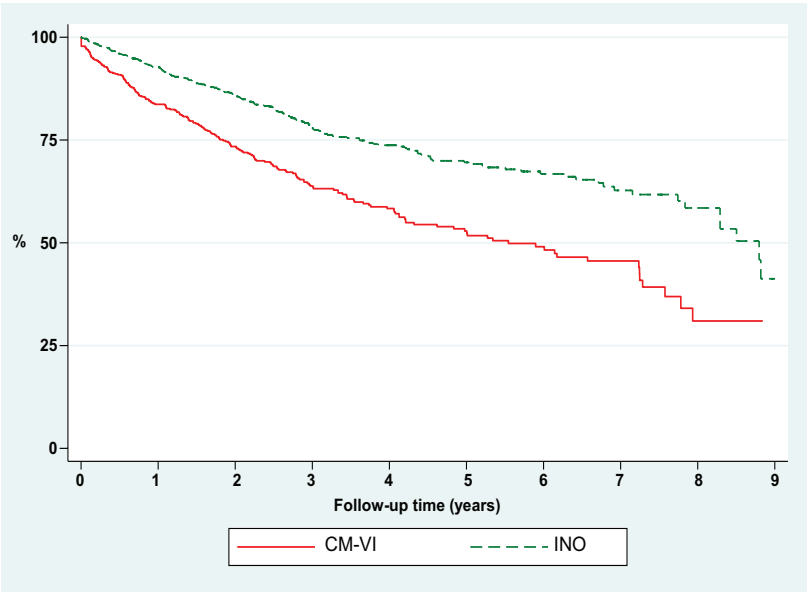
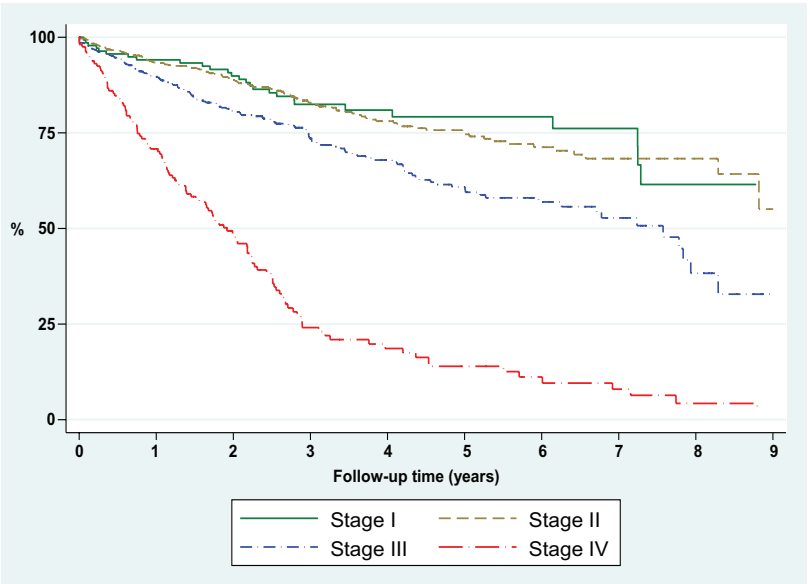


Fig. 11.3. Kaplan–Meier curves showing disease-free survival among patients with breast cancer treated during 2008–2015 by stage at diagnosis (5-year disease-free survival: stage I, 79.2%; stage II, 74.6%; stage III, 60.8%; stage IV, 14.0%).



11.3.3 DFS by molecular subtype of cancer

The molecular subtype of the cancer affected the prognosis, independently of other variables. Patients with luminal-like cancers had the highest 5-year DFS (67.9%), and patients with triple-negative cancers had the lowest 5-year DFS (53.9%) (Fig. 11.4).

11.3.4 DFS by oncology centre

After adjusting for stage and molecular subtype, DFS was consistently lower for patients registered at CM-VI than for those registered at INO. The 5-year DFS for patients with early-stage cancers (stage I and II) was 60.5% at CM-VI and 86.1% at INO. For patients with late-stage cancers (stage III and IV), the 5-year DFS was 41.4% at CM-VI and 51.8% at INO. Even among those with early-stage cancers, the 5-year DFS was lower at CM-VI than at INO for all the molecular subtypes except triple-negative cancers (Fig. 11.5). In fact, the greatest discrepancy in the 5-year DFS was observed for the most treatable variety of breast cancer (luminal-type stage I and II cancers), for which 5-year DFS was 59.5% at CM-VI and 92.6% at INO.

11.3.5 DFS outcomes by whether patient was treated fully or partially at oncology centres

An interesting observation was that the place of primary treatment (whether at the oncology centres or elsewhere) was an independent prognostic factor (Fig. 11.6). Patients who received their complete treatment at a hospital other than the two oncology centres had the worst prognosis, with a 5-year DFS of only 49.5%. Patients who received initial treatment elsewhere and completed their treatment at the oncology centres had the highest 5-year DFS of 74.5%. Patients treated entirely at the oncology centres had a 5-year

Fig. 11.4. Kaplan–Meier curves showing disease-free survival after treatment among patients with breast cancer registered during 2008–2015 by combinations of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status (5-year disease-free survival: ER- and/or PR-positive and HER2-negative, 67.9%; ER- and/or PR-positive and HER2-positive, 62.3%; ER- and PR-negative and HER2-positive, 62.4%; triple-negative, 53.9%).

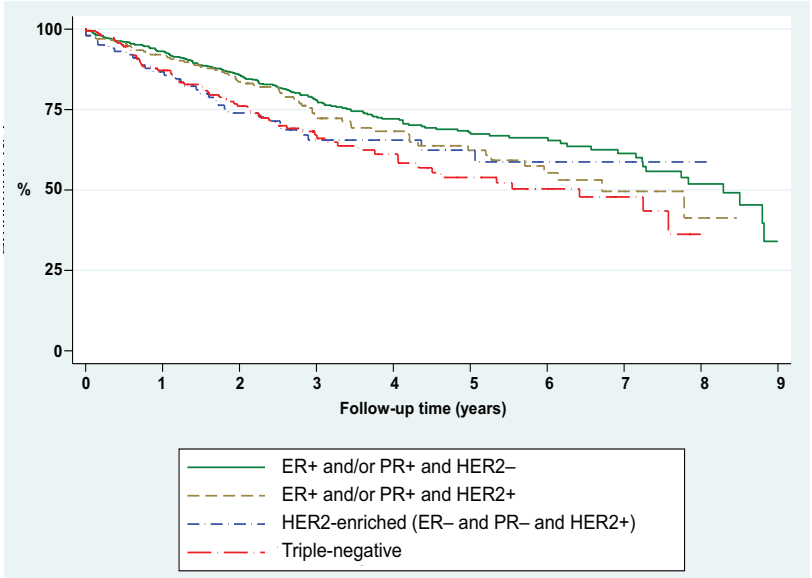
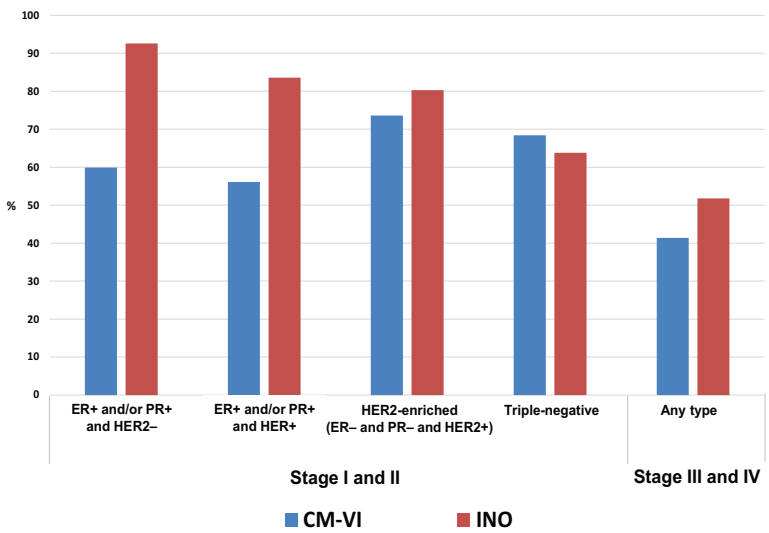


Fig. 11.5. Five-year survival rates after treatment by stage at diagnosis, molecular type, and oncology centre. CM-VI, Centre Mohammed VI pour le traitement des cancers; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; INO, Institut National d'Oncologie Sidi Mohamed Ben Abdellah; PR, progesterone receptor.



DFS of 54.1%, probably because there was a higher proportion of patients with advanced-stage cancer in this group.

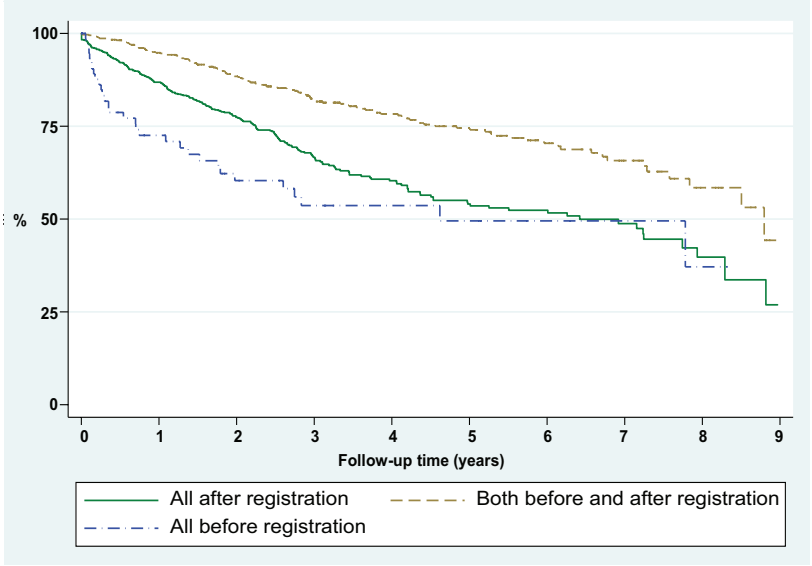
11.4 Survival rates for breast cancer in Morocco compared with other settings

The 5-year DFS for breast cancer after treatment at INO was within the range of 5-year DFS results reported internationally (between 65% and 80%), but the 5-year DFS was much lower at CM-VI (Buchholz et al., 2003). Most of the studies from the Eastern Mediterranean Region have reported overall survival, which is always higher than DFS. A meta-analysis of 80 prospective and retrospective studies from the Eastern Mediterranean Region (mostly from high-income countries) involving 41 603 patients with breast cancer estimated the 5-year overall survival rate to be 71% (95% CI, 68–73%) (Maajani et al., 2020). The 5-year overall survival was very similar to the 5-year DFS reported from INO, but much higher than that reported from CM-VI. Another recent meta-analysis revealed the heterogeneity in overall survival rates in the Mediterranean Region. The 5-year overall survival rate varied from 51.5% in Tunisia to 91.4% in Egypt (Hassanipour et al., 2019).

The prognostic factors and their relative importance always vary between studies because the assessment of these factors is confounded by treatment (Cerami et al., 2012). Adjuvant polychemotherapy and hormone therapy substantially alter the course of the disease. Several models have been developed to predict prognosis after treatment of breast cancer. A systematic review of 58 such models observed that none of them used data from Africa (Phung et al., 2019). The data from our study in Morocco could be used to develop new models or to validate the existing ones.

An important observation in our study was that a large proportion of patients were treated in hospitals or clinics other than the oncology centres and most of them had their initial surgery in those non-oncology centres. This is an important quality issue that needs to be addressed for several reasons. First, oncology surgery should be performed by adequately trained surgeons after consulting a multidisciplinary team. Second, in non-oncology hospitals surgeons may be less familiar with the effectiveness of neoadjuvant chemotherapy in reducing the need for upfront radical mastectomies and in improving survival in patients with HER2-positive and triple-negative cancer. Third, non-oncology hospitals may not have access to good-quality histopathological assessment of excised specimens and there may be delays in patients being referred after surgery to the oncology centre for evaluation by the MTB. We observed that patients who received their complete treatment (mostly surgery alone) at a hospital or clinic outside CM-VI or INO had the worst 5-year DFS and those who received adjuvant treatment at the oncology centres after initial treatment (mostly surgery) elsewhere had the best 5-year DFS. The first group of patients may have been noncompliant with further adjuvant therapy advised at the oncology centres.

Fig. 11.6. Kaplan–Meier curves showing disease-free survival after treatment among patients with breast cancer registered during 2008–2015 by when treatment was carried out (5-year disease-free survival: all after registration, 54.1%; both before and after registration, 74.5%; all before registration, 49.5%).



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Data collection form

Le parcours de soins du cancer du sein au Maroc

	A. DONNÉES GÉNÉRALES DE RECRUTEMENT	
1.	Numéro du cas :*(Rabat : R ; Casablanca : C + S pour sein)*	[ ] [S] [ ] [ ] [ ] [ ]
2.	Date de collecte des données *(jour/mois/année) :*	[ ] [ ] / [ ] [ ] / [2] [0] [ ] [ ]
3.	Date d'ouverture du dossier à l'hôpital :	[ ] [ ] / [ ] [ ] / [2] [0] [ ] [ ]
4.	Groupe d'enregistrement : *(1. 01-02/2008 ; 2. 03-04/2009 ; 3. 05-06/2010 ; 4. 07-08/2011 ; 5. 09-10/2012 ; 6. 11-12/2013 ; 7. 01-02/2014)*	[ ]
5.	Numéro d'identifiant de la patiente à l'hôpital :	[ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]
6.	Code de l'investigateur :	[ ] [ ]

	B. INFORMATIONS PERSONNELLES	
1.	Nom de la femme : Nom de famille : _____	Prénom : _____
2.a	Adresse de la femme : _____ _____	
2.b	Lieu de résidence : *(1. Urbain ; 2. Semi-urbain ; 3. Rurale)*	[ ]
3.	Le numéro de téléphone : Mobile 1 : _____	Mobile 2 : _____
4.a	Couverture sociale : *(1. Oui ; 2. Non ; 9. Inconnu)*	[ ]
4.b	Si oui : *(1. CNOPS ; 2. CNSS ; 3. RAMED ; 4. INAYA ; 5. Autre : _)*	[ ]
5.	Age *(années) : (99. Age inconnu)*	[ ] [ ]
6.	Date de naissance *(jour/mois/année) :*	[ ] [ ] / [ ] [ ] / [1] [9] [ ] [ ]
7.	Profession : *(1. Femme au foyer ; 2. Ouvrière ; 3. Employée de bureau ; 4. Artisan, commerçante, chef de PME ; 5. Agricultrice ; 6. Cadre intermédiaire ; 7. Cadre supérieure ; 8. Autre_____; 9. Inconnu)*	[ ]
8.	Niveau d'études : *(1. Aucune ; 2. Primaire ; 3. Secondaire ; 4. Supérieur ; 9. Inconnu*	[ ]
9.	Statut matrimonial : *(1. Célibataire ; 2. Mariée ; 3. Veuve ; 4. Séparée ; 9. Inconnu)*	[ ]

	C. HABITUDES PERSONNELLES	*Oui/Non*	*Nombre d'années*
1.	Fume des cigarettes : *(1. Oui ; 2. Non)*	[ ]	[ ] [ ]
2.	Utilisation d'autre type de tabac : *(1. Oui ; 2. Non)*	[ ]	[ ] [ ]
3.	Utilisation de la contraception orale : *(1. Oui ; 2. Non)*	[ ]	[ ] [ ]

	D. INFORMATIONS CLINIQUES		
1.	Présente des symptômes :		Durée *(en mois)*
1.a	◯ Masse dans un sein :	*(99. Information sur la durée manquante)*	[ ] [ ]
1.b	◯ Ecoulement du mamelon :	*(99. Information sur la durée manquante)*	[ ] [ ]
1.c	◯ Ulcération du mamelon :	*(99. Information sur la durée manquante)*	[ ] [ ]
1.d	◯ Inversion ou rétraction du mamelon :	*(99. Information sur la durée manquante)*	[ ] [ ]
1.e	◯ Douleur au sein :	*(99. Information sur la durée manquante)*	[ ] [ ]
1.f	◯ Voussure ou Rétraction cutanée :	*(99. Information sur la durée manquante)*	[ ] [ ]
1.g	◯ Peau d'orange :	*(99. Information sur la durée manquante)*	[ ] [ ]
1.h	◯ Masse au creux axillaire :	*(99. Information sur la durée manquante)*	[ ] [ ]
1.i	◯ Autre, *spécifier :*_____		[ ] [ ]

2.	Date de la première consultation médicale *(jour/mois/année) :*	[ ][ ] / [ ][ ] / [2] [0] [ ][ ]
3.	Nature de la consultation : *(1. MG ; 2. Spécialiste ; 3. Praticien privé ; 4. Hôpital ; 5. Guérisseur traditionnel ; 6. Travailleur de la santé)*	[ ]
4.	Personne référant à l'hôpital : *(1. MG ; 2. Spécialiste ; 3. Médecin privé ; 4. Hôpital ; 5. Travailleur de la santé ; 6. Autoréférence ; 8. Autre :_____)*	[ ]
5.	Date de référence *(jour/mois/année)* :	[ ][ ] / [ ][ ] / [2] [0] [ ][ ]
6.	Référée dans le cadre du programme national de dépistage du cancer du sein : *(1. Oui ; 2. Non)*	[ ]
7.	ATCD de dépistage du cancer du sein : *(1. Mammographie ; 2. Examen clinique ; 3. Autre :_____)*	[ ]
8.	Date du dernier dépistage *(jour/mois/année) :*	[ ][ ] / [ ][ ] / [2] [0] [ ][ ]
9.	Parité :	[ ][ ]
10.	Ménopause : *(1. Oui ; 2. Non)*	[ ]
11.	ATCD familiaux de cancer du sein : *(1. Oui ; 2. Non)*	[ ]

E. DIAGNOSTIC / TRAITEMENT DU CANCER DU SEIN AVANT LA PRISE EN CHARGE DANS CE CENTRE ANTICANCÉREUX		
1.	Investigation avant d'être prise en charge dans ce centre anticancéreux : *(1. Oui ; 2. Non)*	[ ]
1.a	Si oui : *(1. Secteur public ; 2. Secteur privé)*	[ ]
2.	Examen clinique fait : *(1. Oui ; 2. Non)*	[ ]
2.a	Date d'examen clinique :	[ ][ ] / [ ][ ] / [2] [0] [ ][ ]
2.b	Résultats d'examen, *préciser :* _____	
3.	Date de mammographie :	[ ][ ] / [ ][ ] / [2] [0] [ ][ ]
3.a	Résultats de mammographie : *(1. Normal ; 2. ACR1 ; 3. ACR2 ; 4. ACR3 ; 5. ACR4 ; 6. ACR5 ; 7. Pas fait)*	
4.	Cytoponction faite : *(1. Oui ; 2. Non)*	[ ]
4.a	Si oui, date de cytoponction *(jour/mois/année) :*	[ ][ ] / [ ][ ] / [2] [0] [ ][ ]
5.	Biopsie faite : *(1. Oui ; 2. Non)*	[ ]
5.a	Si oui, date de biopsie *(jour/mois/année) :*	[ ][ ] / [ ][ ] / [2] [0] [ ][ ]
5.b	Si oui, résultat de l'examen cyto/histologique : *(1. CCIS ; 2. CLIS ; 3. Carcinome canalaire infiltrant ; 4. Carcinome lobulaire infiltrant ; 5. Sarcome ; 6. Autre, préciser :* _____*; 7. Bénigne ; 9. Inconnu)*	[ ]

F. INVESTIGATIONS FAITES AU CENTRE ANTICANCÉREUX		
1.	Cytoponction faite : *(1. Oui ; 2. Non)*	[ ]
1.a	Si oui, date de cytoponction *(jour/mois/année ; 9. Inconnu) :*	[ ][ ] / [ ][ ] / [2] [0] [ ][ ]
2.	Biopsie faite : *(1. Oui ; 2. Non)*	[ ]
2.a	Si oui, date de biopsie *(jour/mois/année ; 9. Inconnu) :*	[ ][ ] / [ ][ ] / [2] [0] [ ][ ]
2.b	Type de biopsie : *(1. Microbiopsie ; 2. Chirurgicale ; 9. Inconnu)*	[ ]
3.	Radiographie pulmonaire faite : *(1. Oui ; 2. Non)*	[ ]
3.a	Si oui, date du 1er examen *(jour/mois/année ; 9. Inconnu) :*	[ ][ ] / [ ][ ] / [2] [0] [ ][ ]
4.	Mammographie des 2 seins faite : *(1. Oui ; 2. Non)*	[ ]
4.a	Si oui, date du 1er examen *(jour/mois/année ; 9. Inconnu) :*	[ ][ ] / [ ][ ] / [2] [0] [ ][ ]
5.	Echographie abdominale faite : *(1. Oui ; 2. Non)*	[ ]
5.a	Si oui, date du 1er examen *(jour/mois/année; 9. Inconnu) :*	[ ][ ] / [ ][ ] / [2] [0] [ ][ ]
6.	Scintigraphie osseuse « corps entier » : *(1. Oui ; 2. Non)*	[ ]
6.a	Si oui, date *(jour/mois/année ; 9. Inconnu) :*	[ ][ ] / [ ][ ] / [2] [0] [ ][ ]
7.	Autre investigation faite : *(1. Oui, spécifier :*_____*; 2. Non)*	[ ]
7.a	Si oui, date *(jour/mois/année ; 9. Inconnu) :*	[ ][ ] / [ ][ ] / [2] [0] [ ][ ]
8.	Autre investigation faite : *(1. Oui, spécifier :*_____*; 2. Non)*	[ ]
8.a	Si oui, date *(jour/mois/année ; 9. Inconnu) :*	[ ][ ] / [ ][ ] / [2] [0] [ ][ ]
9.	Autre investigation faite : *(1. Oui, spécifier :*_____*; 2. Non)*	[ ]
9.a	Si oui, date *(jour/mois/année ; 9. Inconnu) :*	[ ][ ] / [ ][ ] / [2] [0] [ ][ ]
10.	Autre investigation faite : *(1. Oui, spécifier :*_____*; 2. Non)*	[ ]
10.a	Si oui, date *(jour/mois/année ; 9. Inconnu) :*	[ ][ ] / [ ][ ] / [2] [0] [ ][ ]

G. CLASSIFICATIONS TNM / STADE UICC / GRADE HISTOPRONOSTIQUE		
1.	Stadification clinique	
1.a	Taille tumorale primaire : taille en cm (si tumeur présente)	[ ][ ]
1.b	Tumeur (T) : *(1. T1 ; 2. T2 ; 3. T3 ; 4. T4 ; 5. Tx)*	[ ]
1.c	Ganglion (N) : *(1. N0 ; 2. N1 ; 3. N2 ; 4. N3 ; 5. Nx)*	[ ]
1.d	Métastase (M) : *(1. M0 ; 2. M1 ; 3. Mx)*	[ ]
2.	Stadification histopathologie	
2.a	Taille tumorale primaire : taille en cm (si tumeur présente)	[ ][ ]
2.b	Tumeur (T) : *(1. T1 ; 2. T2 ; 3. T3 ; 4. T4 ; 5. Tx)*	[ ]
2.c	Ganglion (N) : *(1. N0; 2. N1 ; 3. N2 ; 4. N3 ; 5. Nx)*	[ ]
2.d	Métastase (M) : *(1. M0 ; 2. M1 ; 3. Mx)*	[ ]
3.	Stade UICC : *(01. 0 ; 02. I ; 03. IIA ; 04. IIB ; 05. IIIA ; 06. IIIB ; 07. IIIC ; 08. IV ; 09. Récurrence ; 10. Stade impossible ; 11. Inconnu)*	[ ]
4.	Type histopathologique/cytologie (si résultats d'histologie disponibles, les donner) : *(1. CCIS ; 2. CLIS ; 3. Carcinome canalaire infiltrant ; 4. Carcinome lobulaire infiltrant ; 5. Sarcome ; 6. Autres, préciser :_____ ; 7. Bénigne ; 9. Inconnu)*	[ ]
5.	Grade histopronostique : *(1. Grade SBR I ; 2. Grade SBR II ; 3. Grade SBR III ; 8. Autres :_____ ; 9. Inconnu)*	[ ]

H. IMMUNOHISTOCHIMIE		
1.	Récepteurs d'œstrogènes : *(1. Positif ; 2. Négatif ; 3. Non fait)*	[ ]
1.a	Pourcentage à préciser :	[ ][ ]
2.	Récepteurs de progestérone : *(1. Positif ; 2. Négatif ; 3. Non fait)*	[ ]
2.a	Pourcentage à préciser :	[ ][ ]
3.	HER2/neu : *(1. Positif ; 2. Négatif ; 3. Non fait)*	[ ]
3.a	Score HER2 : *(1. Score 0 ; 2. Score 1+ ; 3. Score 2+ ; 4. Score 3+ ; 5. Non fait)*	[ ]
3.b	FISH (si Score HER2=2) : *(1. Positif ; 2. Négatif)*	[ ]
4.	Ki-67 : *(1. Fait ; 2. Non fait)*	[ ]
4.a	Pourcentage à préciser :	[ ][ ]

I. DÉCISION DE LA RÉUNION DE CONCERTATION PLURIDISCIPLINAIRE (RCP)		
1.	RCP faite : *(1. Oui ; 2. Non)*	[ ]
2.	Si oui, Date de la RCP :	[ ][ ]/[ ][ ]/[2][0][ ][ ]
3.	*Quels sont les décisions thérapeutiques prises lors de cette RCP :*	
	◯ Chirurgie	
	◯ Radiothérapie	
	◯ Chimiothérapie adjuvante	
	◯ Chimiothérapie néo-adjuvante	
	◯ Chimiothérapie palliative	
	◯ Hormonothérapie	
	◯ Soins palliatifs	
	◯ Absence de RCP ou d'un planning de traitement :	

	J. TRAITEMENT – CHIRURGIE *(si donnée)*	
1.	Date de la chirurgie :	[ ][ ]/[ ][ ]/[2][0][ ][ ]
2.	Nature de la chirurgie : ◯ Tumorectomie ◯ Mastectomie ◯ Mastectomie radicale modifiée ◯ Mastectomie radicale ◯ Lymphadénectomie axillaire ◯ Biopsie du ganglion sentinelle ◯ Refusée ◯ Autre	
3.	Compte-rendu anatomo-pathologique post-chirurgie : *(1. Oui ; 2. Non)*	[ ]
3.a	Si oui, résultat : *(1. CCIS ; 2. CLIS ; 3.Carcinome canalaire infiltrant ; 4. Carcinome lobulaire infiltrant ; 5. Sarcome ; 6. Autre, préciser : _____ ; 9. Inconnu)*	[ ]
4.	Nombre total de ganglions prélevés : *(99 si inconnu ; laisser vide si non applicable)*	[ ][ ]
5.	Complications post-opératoires : ◯ *Infection* ◯ *Saignement* ◯ *Thromboembolie* ◯ *Déhiscence de la plaie* ◯ *Complications anesthésiques* ◯ *Autre :* _____	
6.	Durée de l'hospitalisation : Du [ ][ ]/[ ][ ]/[2][0][ ][ ] au [ ][ ]/[ ][ ]/[2][0][ ][ ]	

	K. TRAITEMENT – RADIOTHÉRAPIE *(si donnée)*	
1.	Date de début *(jour/mois/année) :*	[ ][ ]/[ ][ ]/[2][0][ ][ ]
2.	Date de complétion *(jour/mois/année) :*	[ ][ ]/[ ][ ]/[2][0][ ][ ]
3.	Si radiothérapie externe	
3.a	Planification individualisée faite : *(1. Oui ; 2. Non ; 9. Inconnu)*	[ ]
3.b	Type of machine : *(1. Télécobalt ; 2. Accélérateur linéaire ; 3. Autre, spécifier :* _____	[ ]
3.c	Date de début *(jour/mois/année) :*	[ ][ ]/[ ][ ]/[2][0][ ][ ]
3.d	Date de complétion *(jour/mois/année) :*	[ ][ ]/[ ][ ]/[2][0][ ][ ]
3.e	Total des doses données *(en Gy) :*	[ ][ ][ ][ ]
3.f	Nombre de fractions :	[ ][ ]
4.	Si curiethérapie	
4.a	Date de début *(jour/mois/année) :*	[ ][ ]/[ ][ ]/[2][0][ ][ ]
4.b	Date de complétion *(jour/mois/année) :*	[ ][ ]/[ ][ ]/[2][0][ ][ ]
4.c	Nombre de fractions :	[ ][ ]
4.d	Délai entre les fractions *(en jours) :*	[ ][ ][ ]
4.e	Type de curiethérapie : *(1.Bas débit de dose ; 2. Haut débit de dose)*	[ ]
5.a	Délai/Interruption des séances de radiation : *(1. Oui ; 2. Non)*	[ ]
5.b	Si oui, raisons : *(1. Complications ; 2. Panne mécanique ; 3. Ne s'est pas présentée ; 8. Autre :* _____*)*	[ ]
5.c	Complications de la radiothérapie : ◯ *Hématologiques* ◯ *Pulmonaires* ◯ *Dermatologiques* ◯ *Autres :*	
6.a	Hospitalisation nécessaire pour la radiothérapie : *(1. Oui ; 2. Non)*	[ ]
6.b	Si oui, durée *(en jours) :*	[ ][ ][ ]

L. TRAITEMENT – CHIMIOTHÉRAPIE *(si donnée)*		
1.	Indication : *(1. Adjuvante ; 2. Néo-adjuvante ; 3. Palliative)*	[ ]
2.	Chimiothérapie adjuvante et néo-adjuvante	
2.a	Protocole AC60 : *(1. Oui ; 2. Non)*	[ ]
2.b	Nombre de cycles, protocole AC60 :	[ ]
2.c	Anthracycline FEC100 : *(1. Oui ; 2. Non)*	[ ]
2.d	Nombre de cycles, Anthracycline FEC100 :	[ ]
2.e	Docetaxel : *(1. Oui ; 2. Non)*	[ ]
2.f	Nombre de cycles, Docetaxel :	[ ]
2.g	Paclitaxel : *(1. Oui ; 2. Non)*	[ ]
2.h	Nombre de cycles, Paclitaxel :	[ ]
2.i	Trastuzumab (Herceptine) : *(1. Oui ; 2. Non)*	[ ]
2.j	Nombre de cycles, Herceptine :	[ ]
2.k	Autre molécule (Précisez :_____) : *(1. Oui ; 2. Non)*	[ ]
2.l	Nombre de cycles, Autre molécule :	[ ]
2.m	Date de début *(jour/mois/année) :*	[ ][ ] / [ ][ ] / [2] [0] [ ] [ ]
2.n	Date de complétion *(jour/mois/année) :*	[ ][ ] / [ ][ ] / [2] [0] [ ] [ ]
3.	Chimiothérapie palliative (1ère ligne seulement)	
3.a	Molécule(s) : ◯ Anthracyclines (AC-FEC) ◯ Docetaxel ◯ Paclitaxel ◯ Gemcitabine ◯ Capecitabine ◯ Vinorelbine ◯ Trastuzumab ◯ Vinorelbine + Capecitabine ◯ Vinorelbine + 5-FU ◯ Docetaxel + Capecitabine ◯ Bevacizumab ◯ Lapatinib ◯ Autre : _____	
3.b	Nombre de cycles	[ ]
3.c	Date de début *(jour/mois/année) :*	[ ][ ] / [ ][ ] / [2] [0] [ ] [ ]
3.d	Date de complétion *(jour/mois/année) :*	[ ][ ] / [ ][ ] / [2] [0] [ ] [ ]
4.a	Délai/Interruption : *(1. Oui ; 2. Non)*	[ ]
4.b	Si oui, raisons : [ ] *(1. Complications ; 2. Drogues non disponibles ; 3. Ne s'est pas présentée ; 8. Autres :_____)*	
4.c	Complications de chimiothérapie : ◯ *Hématologiques* ◯ *Gastro-intestinales* ◯ *Rénales* ◯ *Neurologiques* ◯ *Cardiologiques* ◯ *Autres :* _____	

	M. TRAITEMENT – HORMONOTHÉRAPIE *(si donnée)*	
1.	Indication : *(1. Adjuvante ; 2. Palliative)*	[ ]
2.	Date de début *(jour/mois/année) :*	[ ][ ] / [ ][ ] / [2] [0] [ ][ ]
3.	Molécule : *(1. Tamoxifene ; 2. Inhibiteurs de l'aromatase (Letrozole, Anastrozole, Exemestane ; 3. Autres :_____)*	[ ]
4.	Durée *(mois) :*	[ ][ ]
5.	Complications : _____	

	N. TRAITEMENT – SOINS PALLIATIFS *(si donnés)*	
1.	Soins palliatifs donnés : *(1. Refusés ; 2. Oui, la morphine ; 3. Oui, Autre :_____ ; 9. Inconnu)*	[ ]
2.	Si la morphine est prescrite, type de préparation : *(1. Orale ; 2. Injectable ; 3. Autre)*	[ ]
3.a	Prescription d'opioïdes autres que la morphine : (*1. Oui ; 2. Non*)	[ ]
3.b	Si opioïdes prescrits, Nom : _____	
4.	Remarques : _____ _____ _____	

	O. SURVEILLANCE	
1.	Date du premier suivi après traitement *(jour/mois/année) :*	[ ][ ] / [ ][ ] / [2] [0] [ ][ ]
2.	Statut final : *(1. Réponse complète ; 2. Réponse partielle ; 3. Stabilisation ; 4. Progression ; 9. Inconnu)*	[ ]
3.	Date de la dernière visite de suivi *(jour/mois/année) :*	[ ][ ] / [ ][ ] / [2] [0] [ ][ ]
4.	État à la dernière visite : *(1. Vivante et en rémission ; 2. Vivante avec signes de cancer du sein ; 3. Vivante sans information sur le cancer du sein ; 4. Décédée ; 9. Inconnu)*	[ ]
5.	Si décédée	
5.a	Date de décès : *(jour/mois/année) :*	[ ][ ] / [ ][ ] / [2] [0] [ ][ ]
5.b	Cause de décès : *(1. Progression du cancer ; 2. Toxicité du traitement ; 3. Autres, préciser :_____ ; 9. Inconnu)*	[ ]
6.	Remarques : _____ _____ _____	

This publication summarizes the outcomes of a patterns-of-care study implemented by IARC in collaboration with the Ministry of Health of the Kingdom of Morocco and the Lalla Salma Foundation for Cancer Prevention and Treatment, to assess how far state-of-the-art cancer diagnostics and therapy have been disseminated into routine oncology practice in Morocco. The study was conducted retrospectively at the two largest publicly funded oncology centres in the country: Centre Mohammed VI pour le traitement des cancers in Casablanca and Institut National d'Oncologie Sidi Mohamed Ben Abdellah in Rabat. It involved more than 2000 patients with breast cancer and documented the changing patterns of care over a decade, from 2008 to 2017.

This publication documents temporal variations in breast cancer characteristics, the level of improvement in access to cancer diagnosis and treatment over time, the variations in practices related to breast cancer treatment, and the time trend of disease-free survival for these patients. The findings highlight the improvements in breast cancer care that occurred in Morocco as a result of pragmatic policies and systematic planning. Recommendations for strengthening breast cancer care in Morocco are also included. Similar patterns-of-care studies are extremely valuable for all countries to document the quality of cancer care and impact of cancer control programmes.

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