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.

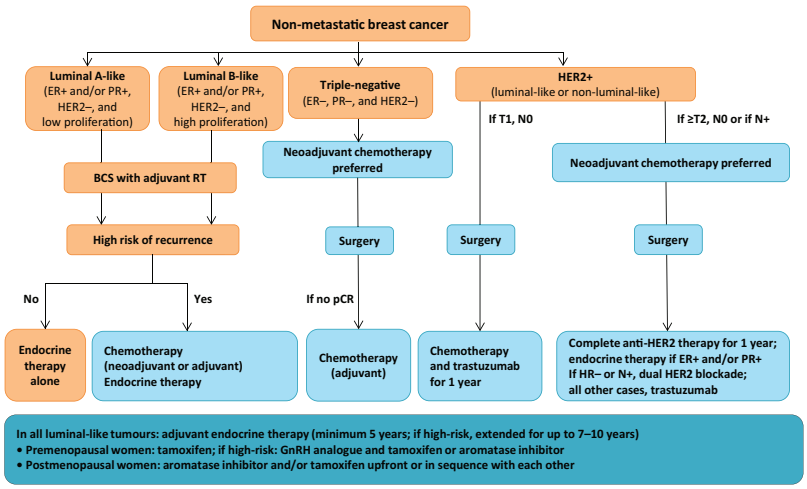
6.1 Principles of treatment

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.

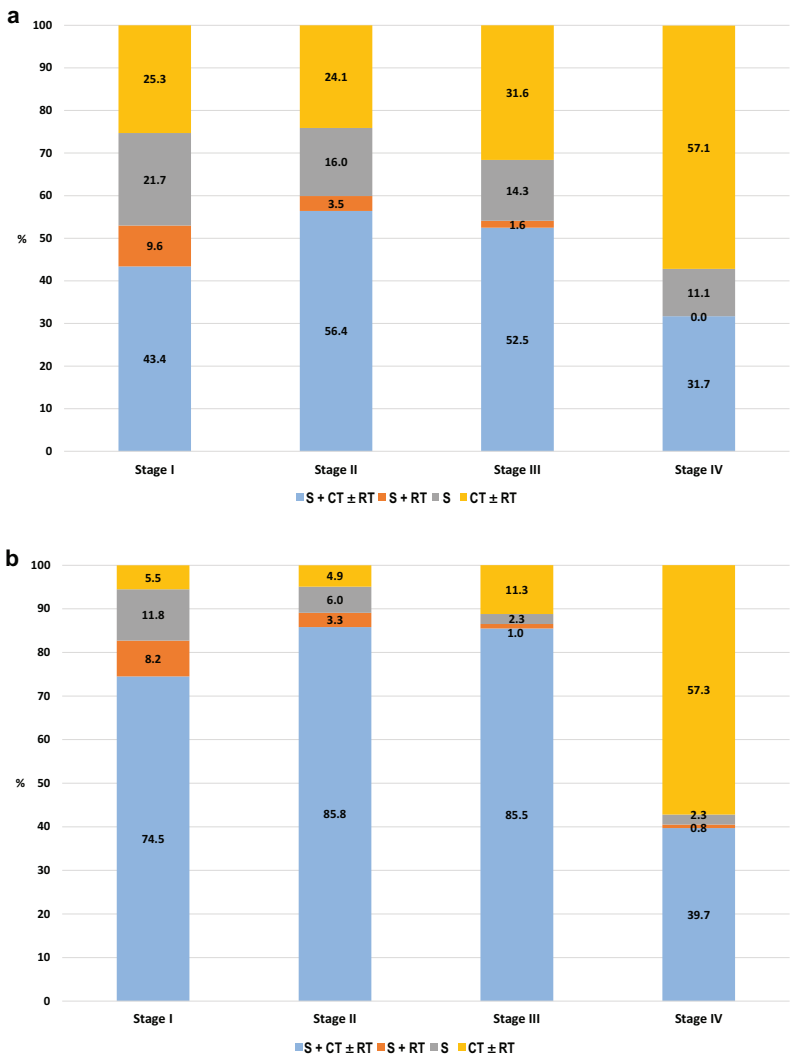
6.2.2 Type of treatment received by stage of cancer

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.

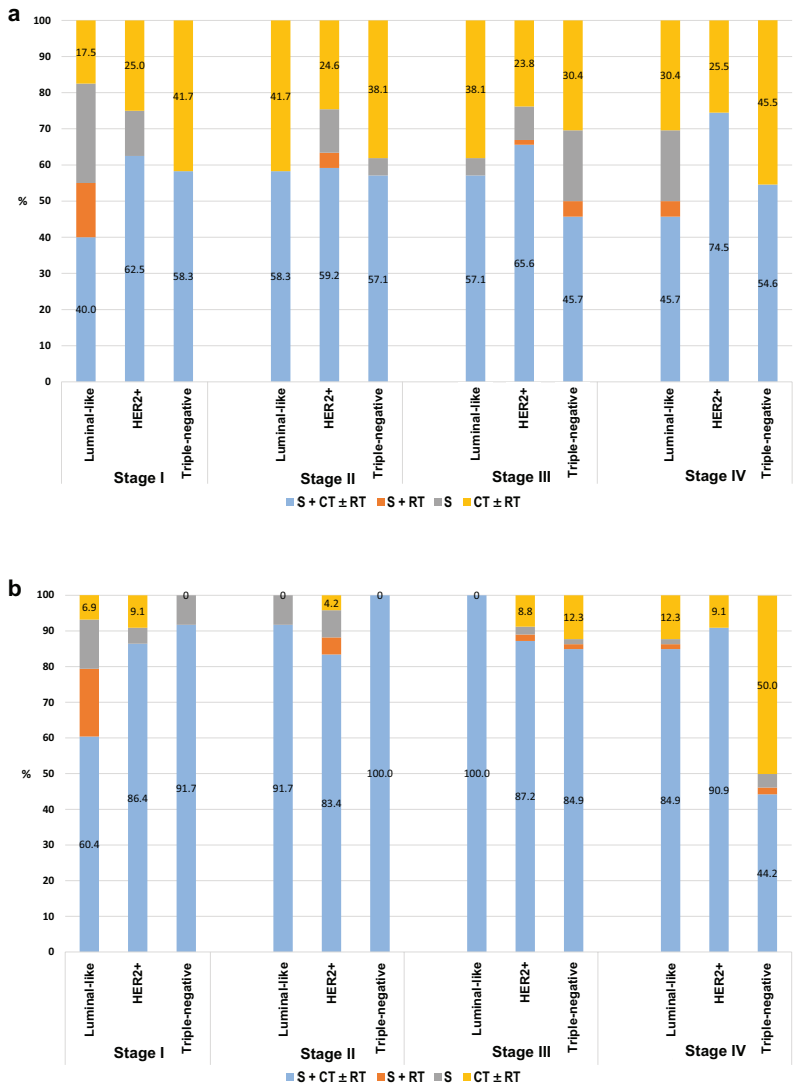


6.2.3 Type of treatment received according to stage at diagnosis and molecular subtype

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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