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).

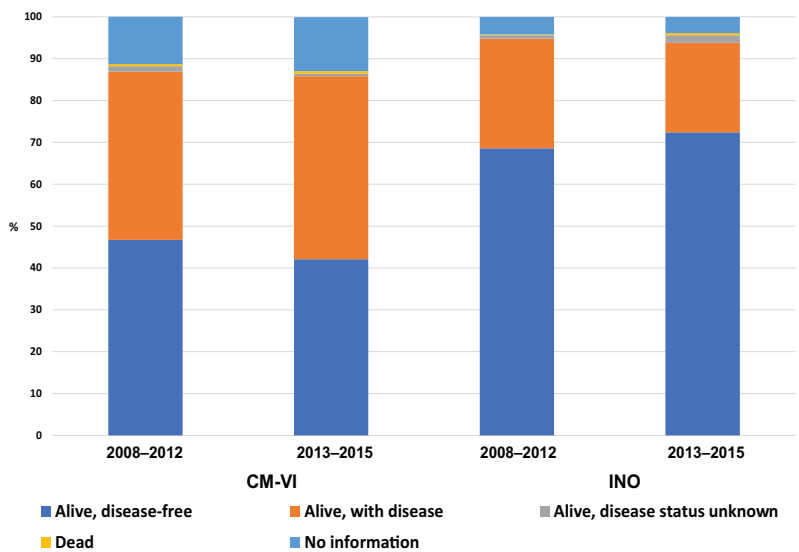


Table 11.1. Disease status during follow-up

	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%.

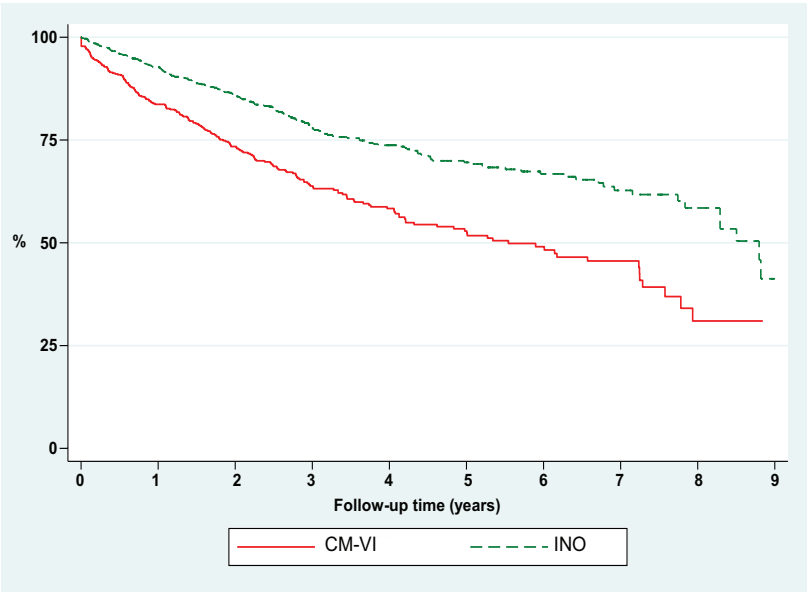
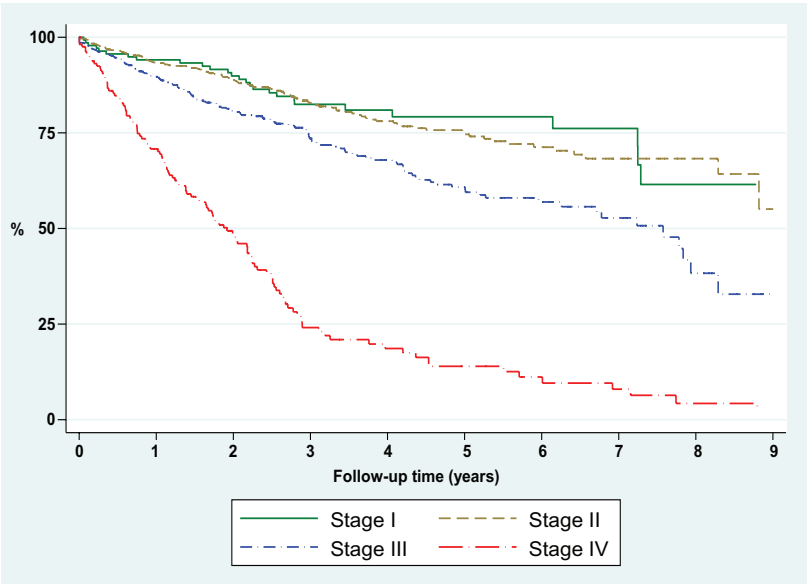


Fig. 11.3. Kaplan–Meier curves showing disease-free survival among patients with breast cancer treated during 2008–2015 by stage at diagnosis (5-year disease-free survival: stage I, 79.2%; stage II, 74.6%; stage III, 60.8%; stage IV, 14.0%).



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%).

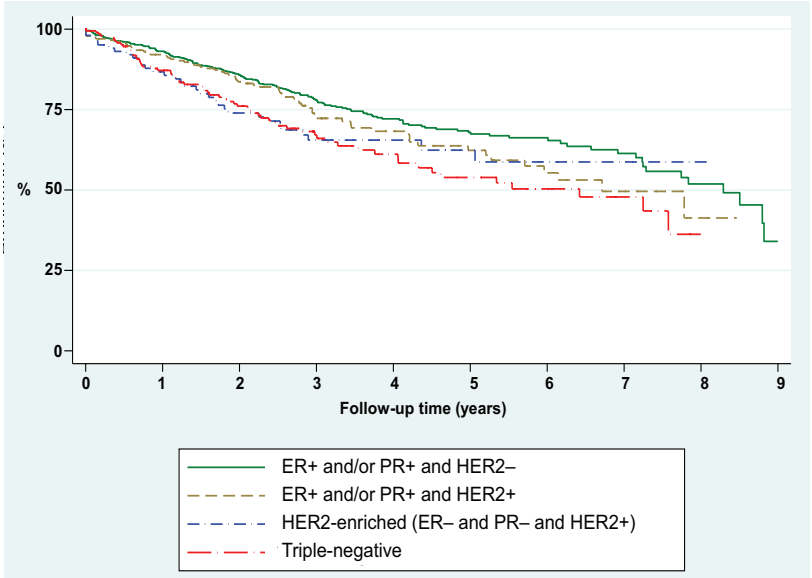
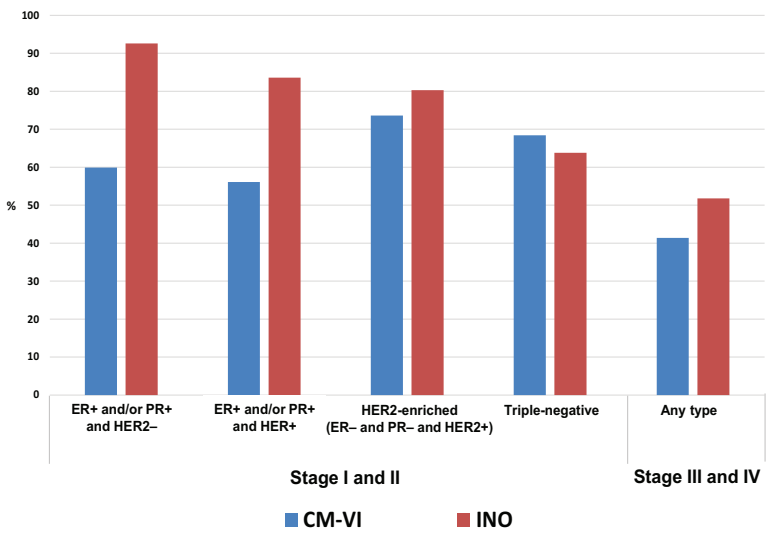


Fig. 11.5. Five-year survival rates after treatment by stage at diagnosis, molecular type, and oncology centre. CM-VI, Centre Mohammed VI pour le traitement des cancers; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; INO, Institut National d'Oncologie Sidi Mohamed Ben Abdellah;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



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

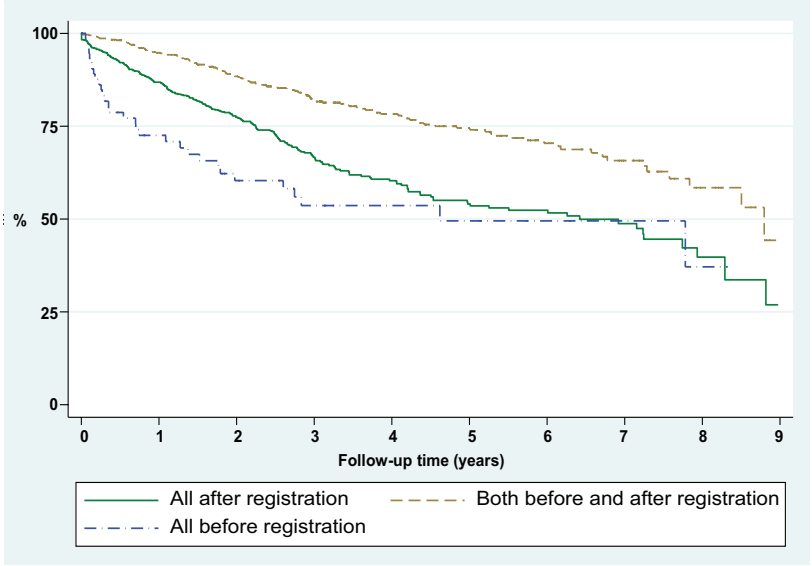
11.4 Survival rates for breast cancer in Morocco compared with other settings

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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