

years after the first intervention (Figure 1). This phenomenon is “tumor recurrence” and the subject of our discussion here.

## 2. Breast Cancer Recurrence

Recurrence of breast cancer is a major clinical manifestation and represents the principal cause of breast cancer-related deaths [7]. A number of researchers have tried to predict some sort of pattern for breast cancer recurrence. This has included studies in various breast cancer subtypes wherein breast cancers are characterized by the presence of receptors such as estrogen receptor (ER), progesterone receptor (PR), and HER2/ErbB2 receptor (HER2) or by the absence of all of them, the triple negative breast cancers (TNBCs). A differential pattern of recurrence between different breast cancer subtypes has been suggested, and it appears [8–10] that ER-negative breast cancers are associated with higher risk of recurrence during the initial 5 years after diagnosis, compared to ER-positive breast cancers. Thereafter, the risk of recurrence chronically increases in ER-positive breast cancers for the next 10 years, and at 15 years following diagnosis, the risk appears to be equal for both subtypes. In ductal carcinoma in situ, it has been analyzed that the ER-negative/PR-negative but HER2-positive cancers have higher risk of recurrence, compared to ER-positive/PR-positive/HER2-negative cancers [11]. The TNBCs, marked by absence of ER/PR/HER2, are generally associated with high risk of recurrence with particularly high risk of distant recurrences in brain and visceral metastases, compared to receptor positive tumors [12].

In addition to the simple classification of breast cancers described previously, there are other subclassifications of breast cancers as well, such as the one that classifies breast cancers into luminal A, luminal B, basal, and HER2 enriched [13]. The luminal A subtype includes ER-positive and/or PR-positive, HER2-negative breast cancers; luminal B subtype includes ER-positive and/or PR-positive, HER2-positive breast cancers; basal subtype includes ER-negative, PR-negative, HER2-negative breast cancers which may also be positive for EGFR, and HER2-enriched subtype includes ER-negative, PR-negative, and HER2-overexpressing breast cancers. The existence of such subtypes, which are at time overlapping but most of the time so distinct, presents a challenge to the choice of appropriate therapy. This has led to the proposal of personalized therapy that fits the needs of individual patients.

Irrespective of the underlying breast cancer subtype, a large number of advanced stage breast cancers are marked by metastases to lymph nodes and, overall, the presence of axillary lymph node metastases is associated with considerable poor disease-free as well as overall survival [14]. Axillary lymph node metastases remain a very important prognostic variable, and identification of molecular markers for development of lymph node metastases can potentially help intervene early reducing the chances of breast cancer recurrence [15].

## 3. Cancer Recurrence in Breast Cancer Patients Undergoing Surgery

Surgical intervention is one of the options for breast cancer patients [16]. The choice for surgical intervention largely depends on the cancer stage. For patients presenting with early stage breast cancer, the two most common treatment options available are breast conserving surgery followed by radiation therapy or mastectomy [17–19]. Mastectomy usually does not need subsequent radiation therapy. It seems that there are distinct risk factors of recurrence in breast cancer patients undergoing mastectomy versus those choosing breast conserving therapy [20]. Whereas lymph node involvement and tumor size are major risk factors after mastectomy, the young age and presence of ductal carcinoma in situ are major risk factors after breast conservation therapy. The distinct clinical and histopathological determinants result in differential response to radiotherapy and point to the need for more robust personalized therapies and follow-up procedures for patients opting for different surgical interventions. Further complicating the decision of surgeons performing breast conserving therapy is the realization that surgical margins also seem to impact the recurrence of breast cancer [21]. In a study [17] that scanned published reports and systematically reviewed the local recurrence in breast cancer patients undergoing mastectomy with or without breast reconstruction, it was concluded that the recurrence rates were not higher in patients that underwent breast reconstruction. Also, radiation therapy is generally associated with reduced recurrence in breast cancer, and a recent meta-analysis [22] of 10,801 patients from 17 randomized trials has concluded that radiotherapy reduces the recurrence rate by half and the death rate by about a sixth in patients that have undergone breast conserving surgery. Interestingly, this study also identified many factors that might influence the extent of radiotherapy-induced benefits. Such factors include age, cancer grade, estrogen receptor status, and use of tamoxifen as well as the extent of surgery.

In a study [23] that looked at the influence of molecular subtypes of breast cancers, namely, ER-positive, PR-positive, and HER2-overexpressing as well as TNBC in relation to recurrence in patients with mastectomy versus breast conserving surgery, a differential rate of recurrence was observed in patients with different molecular subtypes. This study analyzed data from 15 different studies covering a total of 12,592 patients of which 57% underwent breast conserving therapy while 43% underwent mastectomy. It was observed that among the patients that underwent breast conserving therapy, patients with ER-positive and PR-positive breast cancers had many reduced instances of recurrence than HER2-overexpressing and TNBC patients. Similar results were observed for mastectomy patients as well where ER-positive and PR-positive patients were again found to be at a lesser risk of recurrence compared to HER2-overexpressing and TNBC patients. Although both HER2-overexpressing and TNBC patients were found to be at a higher risk of recurrence, a direct comparison between the two subtypes revealed that HER2-overexpressing breast cancer patients presented higher risk of recurrence in patients undergoing breast