Worldwide, breast cancer is the most common form of cancer in women. The incidence of breast cancer increased initially, beginning in the 1970s, then levelled off over the last two decades, and recently the mortality from this disease has been slowly decreasing. When the breast cancer tumor is localized to the breast and axillary nodes, multimodality therapy is the treatment of choice, consisting of surgery, radiotherapy, and adjuvant or neoadjuvant systemic therapy with hormonal agents (tamoxifen (Tam) or an aromatase inhibitor (AI)), and/or chemotherapy. Depending on clinical and pathological criteria (including tumor size and grade, presence and number of axillary node metastases, lymphovascular invasion, and over-expression of biological markers, including estrogen receptors (ERs), progesterone receptors (PRs) and the HER2/neu receptor), as well as host factors, such as age, and co-morbidities, patients with breast cancer are roughly classified as having high-, intermediate-, or low-risk disease, which guides the recommendations for therapy. However, even after primary therapy by surgery and/or chemotherapy, the risk of recurrence remains high. Although, classically, breast tumor biology has been classified on the basis of hormone receptor (HR) negativity or positivity, it is now becoming clear that multiple other subtypes exist within these broad categories. Indeed, a subset of HR-positive tumors may be associated with early recurrence due to initial or rapid development of hormone resistance, and aggressive biology. In a review of data from seven clinical trials of adjuvant therapy for early breast cancer conducted by the Eastern Cooperative Oncology Group, the greatest risk of recurrence occurred within the first three years after surgery. The risk was highest among women with tumors >3cm and among those who had >4 positive nodes. Interestingly, patients who had HR-negative, highly proliferative disease had a higher risk of relapse in the first five years after diagnosis; subsequently, their relapse rate sharply declined. From years 5–10, the risk was significantly greater in women with ER-positive disease.

The Early Breast Cancer Trials’ Collaborative Group meta-analysis has demonstrated that women with HR-positive breast cancer still have approximately 50% of their initial recurrence risk five years after diagnosis. However, within this subset there are groups of patients who have more rapidly proliferative, less hormone-sensitive disease and potentially more bulky disease at diagnosis, which is associated with a higher risk of early relapse. Currently, there are no good biological or clinical factors to accurately assess risk of early relapse in HR-positive disease, but clearly higher stage disease, high-grade histology, lower positivity for HRs, and over-expression of the oncoprotein HER2/neu can help identify this subgroup of patients.

**Types of Recurrence**

The most common type of recurrence event in women with breast cancer is distant recurrence, and this risk significantly surpasses the risk for local recurrence in the majority of cases. There are several reasons for this; over the last decade more attention has been paid to achieving wider tumor-free margins at the time of surgery, and radiation is commonly employed following breast conservation surgery. Secondly, imaging techniques—although still far from perfect—have improved to some degree the detection of cancers in younger women or women with denser breasts, and ultrasound is routinely employed to further analyze palpable or suspected abnormalities. There is also the option of additional specialized testing such as magnetic resonance imaging, which can further delineate the extent of disease within the breast, including identifying multifocal disease, as well as tumors that are fully or partially mammographically occult. These techniques have reduced the problem of missing extensive or multifocal sites of cancer in the breast at the time of surgery, and resulted in a decrease in the rate of local recurrence risk, leaving distant risk the primary target of systemic adjuvant therapy. The one caveat to this is in inflammatory breast cancer, where the most frequent site of recurrence is local due to dermal and chest wall lymphatic invasion, but which often have subsequent or simultaneous distant recurrence as well. The most common initial sites of relapse for HR-positive disease are the bone, bone marrow, and soft tissue, including lymph nodes, followed by the visceral organs—including the lungs.
and liver, as well as brain and skin. Infiltration of the gastrointestinal tract and peritoneum can also be seen. In HR-negative disease, the most common initial site of relapse is in visceral organs.

**Early Recurrence**

Early relapses are those that occur within the first five years after treatment. Very early relapse, for example those that occur during adjuvant chemotherapy or within the first 12 months after diagnosis, are exceedingly uncommon—confined only to the most aggressive subsets of breast cancer. As a whole, in breast cancer, an early relapse event would be roughly within 2–3 years after diagnosis. Although survival continues to improve for metastatic breast cancer due to the availability of more effective and numerous treatment options, all patients with metastatic disease will eventually die of resistance and progressive disease. Patients at increased risk for developing distant metastases include those with: a higher stage of diagnosis and biologically more aggressive disease; tumors that over-express the HER2/neu receptor; so-called ‘triple negative’ tumors (defined as tumors that are ER-negative, PR-negative, and HER2-negative); tumors that are HR-positive but have less hormone-sensitive disease, and tumors that express HRs, as determined by immuno-histochemistry, but that have high-grade histology. Failure to receive adequate adjuvant therapy also contributes to a higher risk for earlier relapse. In addition to the biological factors, a small percentage of the population may not metabolize Tam to its active metabolite endoxifen, potentially limiting its efficacy. This is associated with at least one polymorphism of the (CYP) 2D6 gene, which has recently been defined. Accordingly, the US Food and Drug Administration (FDA) proposed a new labeling on Tam to cover those women who do not metabolize Tam or are taking other medication that interferes with Tam metabolism such that they do not achieve optimal therapeutic efficacy. Testing for HRs is limited by a number of factors, and it has proved difficult to reproducibly associate extent of positivity with outcome or response to therapy, except when there is very weak or very strong intensity of staining. Expression of the genes that control HRs may be a much better way to assess the extent of HR positivity, and early data suggests a closer relationship between expression and both prognosis and response to hormone therapy. In addition, many other genes are clearly important that are not routinely evaluated at present. It is quite likely that in the not-too-distant future it will be possible to use genomic sub-typing, including analysis of the expression of a variety of genes, to much more accurately define upfront that group of patients who have more hormone-resistant disease, and are at risk from earlier relapse. In addition, this approach may help determine new targets for therapy. One such test, Oncotype Dx, is currently in clinical use to help determine which patients with HR-positive, node-negative early stage disease will benefit from the addition of chemotherapy to adjuvant hormone therapy. A large randomized trial, the TAILORx study, is on-going in the US to evaluate the benefit of chemotherapy in the intermediate risk group, that has proved harder to define.

A number of trials have evaluated the end-points of risk of distant metastases, as well as overall survival (OS). OS has been a classic end-point in various adjuvant trials for early stage breast cancer. The primary issue with using OS as a primary end-point to determine effectiveness of a specific therapy is that the majority of women with HR-positive early stage breast cancer will live a long time, even following relapse. This means that differences in OS may be difficult to demonstrate and certainly require very long follow-up, potentially delaying the entry of effective agents into general practice. Therefore, survival end-points are extremely difficult to reach. Determining a surrogate marker for OS could help to assess new therapies and therapeutic options. Several clinical trials that have looked at distant recurrence as an end-point have shown, particularly in chemotherapy-based trials, that an improvement in distant recurrence risk is associated with a subsequent benefit in terms of OS.

**Managing the Risk for Early Relapse**

There are many challenges in selecting the appropriate therapy to best reduce the risk of breast cancer recurrence. The first and most important is understanding the biology of the disease, so that effective therapy can be offered with appropriate sequencing. The second is related to the stage of the disease, and understanding its extent in terms of early diagnosis. The widespread use of mammographic screening leading to earlier diagnosis has already resulted in an overall earlier stage of disease at diagnosis. The biggest limitation to adjuvant therapy is individualizing therapy to the specific cancer being treated; it is hoped that genomic profiling will improve our understanding of the individual disease and lead to new targets for therapy. In terms of understanding the biology of the disease, it is vital to understand which disease is potentially more hormone-resistant and which other risk factors might, for example, correspond to an earlier risk of relapse. Women who have a higher risk of early relapse appear to benefit from the use of more intensive adjuvant chemotherapy with the addition of trastuzumab for patients with HER2/neu-positive disease. Appropriate hormone therapy such as aromatase inhibition can be...
employed for postmenopausal women with HR-positive disease, and particularly in women with higher-stage disease that carries a greater risk of recurrence.

One of the big questions in the treatment of early stage, HR-positive breast cancer in postmenopausal women is whether aromatase inhibition or Tam is more effective at reducing the risk of early relapse. Data from more than 30,000 postmenopausal women in seven randomized clinical trials have provided strong evidence that AIs appear to have a greater impact on earlier relapse. However, clinical trials are designed differently and are evaluated based on different end-points, or end-points that are defined differently. This makes inter-trial comparisons difficult and somewhat risky. Evaluating data from individual trials may provide a better insight into specific treatment benefits. Time to distant metastases in the BIG 1–98 trial, which is evaluating the AI letrozole versus Tam, is markedly different depending on the hormonal therapy strategy employed. BIG 1–98 is a large multinational, randomized, double-blind trial, evaluating monotherapy with either letrozole or Tam for five years, as well as sequenced therapy comparing two years of either letrozole or Tam with the alternate therapy for the remaining three years. The trial started in 1998 and was originally designed as a two-arm study comparing letrozole with Tam administered for five years and enrolling 1,835 patients. In 1999, the two-arm protocol was amended to a four-arm study to include the evaluation of the sequential administration of two years of Tam followed by three years of letrozole or letrozole followed by Tam in comparison to continuous monotherapy with either agent. The first published data from the trial was the primary core analysis, which analyzed all events in the monotherapy arms and events in the sequential arms up to the time of treatment switch (two years of therapy) in all 8,010 postmenopausal women with HR-positive, operable invasive breast cancer who had completed primary surgical treatment enrolled in the trial. The primary endpoint of BIG 1–98 is disease-free survival (DFS), defined as the time from randomization to recurrence in the primary breast after breast-conserving treatment, metastasis, and the appearance of a second primary tumor or death from any cause. The results of the primary core analysis, with a median follow-up of 25.8 months, revealed that letrozole resulted in a significantly lower risk for recurrence with five-year DFS rate estimates of 84.0% for the letrozole group and 81.4% for the Tam group. Moreover, letrozole resulted in significantly fewer recurrences at distant sites (hazard ratio=0.73, p=0.001). However, OS did not differ significantly between the two groups. These results are encouraging in light of the fact that the BIG 1–98 trial included patients who were at increased risk for recurrence; 41% were node-positive and 25% had received chemotherapy, and there was a statistically significant improvement in DFS in these higher risk groups. At a median follow-up of 25 months, 212 patients from a total of 5,980 eligible patients analyzed had an event, defined as the first proven occurrence of local recurrence or distant recurrence. Prognostic factors tested included age at randomization, adjuvant and/or neoadjuvant chemotherapy use, pathological tumor size, HR status, node positivity, tumor grade, and mitotic grade. Tumor size, HR status, node positivity, and tumor grade were the most significant prognostic factors for early recurrence. Those with ≥ 4 positive nodes, tumors ≥ 5 cm, ER-positive/PR-negative tumors, and grade III tumors had the highest overall risk of recurrence in the first two years following surgery for early stage breast cancer. The increase in risk associated with increased node positivity was greater for patients randomized to Tam than to letrozole. This intriguing data from BIG 1–98 indicates that there may be an even bigger impact on distant metastases in women who have higher risk disease at diagnosis; however, we need longer follow-up and additional data to fully answer this question. Data from the full BIG 1–98 study, including the switching arms, is expected in 2008 and should help to clarify the relative benefit of the different hormonal therapies and hormonal therapy sequencing in risk group subsets.

ATAC, the first large monotherapy trial of an AI compared to Tam, appeared to demonstrate that the impact of AIs was greater in the lower risk population. The ATAC trial randomized 9,366 postmenopausal women with ER-positive or unknown invasive breast cancer to five years of adjuvant Tam, the AI anastrozole, or a combination of the two. There was no difference in DFS between the combination arm and the Tam arm; however, anastrozole was superior to Tam and the combination at the first evaluation of this trial. The combination arm was then closed due to lack of superiority over Tam, leaving this as a two-armed trial. At a median follow-up of 68 months, data from ATAC demonstrated a significantly lower risk for recurrence and longer time to recurrence for anastrozole versus Tam for five years. Moreover, anastrozole resulted in significantly less distant metastasis and significantly fewer contralateral breast cancers in the known HR-positive subset. In a recent analysis, data from the mature, 68-month analysis showed that the majority of the recurrences seen with Tam occur within the first few years of treatment, emphasizing the importance of starting aromatase treatment early.
Summary

Early recurrence and distant metastases in early stage breast cancer remains a significant risk despite the success of adjuvant chemotherapy and hormone therapy. However, evidence is emerging that points to the benefits of aromatase inhibition for patients at high risk of early recurrence at an early stage of therapy. In BIG 1–98, letrozole was superior to Tam, particularly in women with higher risk disease, whereas in ATAC this effect was seen primarily in the node-negative subset, and those who did not receive adjuvant chemotherapy. Currently, BIG 1–98 is the largest monotherapy trial comparing an AI with Tam; the results demonstrate a significant impact of letrozole over Tam in terms of distant DFS, a potential surrogate marker for OS. The populations and timing of the two trials are different, making firm conclusions about the benefits of specific AIs in risk subsets difficult to obtain. Moreover, the DFS definition in BIG 1–98 included secondary cancers, whereas the DFS definition in the ATAC study did not. Nonetheless, based on the BIG 1–98 data, the use of AIs as adjuvant therapy in postmenopausal women who are at higher risk of early relapse or who have node-positive breast cancer appears warranted as a routine approach. Definitive data on the benefits of the switching approach in BIG 1–98, supported by improved outcome in patients treated on the IES switching trial with exemestane, await analysis and are eagerly anticipated.

References