Chapter 7

Adjuvant Systemic Treatment in Hormone Receptor Positive, HER2 Negative Breast Cancer

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Additional information is available at the end of the chapter

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Abstract

The introduction of adjuvant systemic therapy led to a significant improvement in post-surgical survival and a reduction in disease relapse. Approximately 75–80% of all breast cancers are hormone-dependent based on the presence of ER and/or PR on tumor cells. Patients with HR+ breast cancer less than 5 mm and treated with only endocrine therapy have usually very good prognosis. They typically are not treated with adjuvant chemotherapy. The patients with stage III HR+ breast cancer still require adjuvant chemotherapy since they carry high risk of recurrence without chemotherapy. Many patients with HR+ HER2 negative breast cancer fall in between these two categories, and they are called as intermediate risk group based on clinicopathological variables, genomic tests or online risk calculators. The minimum duration of adjuvant endocrine treatment is 5 years; however, patients with high risk factors including positive lymph node should be treated with the endocrine therapy up to 10 years either with tamoxifen alone or sequentially with aromatase inhibitors (AI) in postmenopausal women. Adjuvant bisphosphonates reduce bone recurrence and improve survival in postmenopausal women with early stage breast cancer.

Keywords: adjuvant chemotherapy, breast cancer, endocrine therapy, hormone receptor, molecular assays

1. Introduction

Breast cancer is the most common cancer accounting for 25.1% of all cancers in women according to GLOBOCAN and the second most common cancer overall worldwide [1]. Over 1.5 million women are diagnosed with breast cancer every year, and half million women die due to breast cancer in the world each year. Although it is the fifth most common cause of

death from cancer in women, during last 3 decades, deaths due to breast cancer have decreased by one-third or more. It is due in part to increased screening, as well as more effective loco-regional and systemic treatment options have been established over last decades.

The risk of relapse varies substantially on the basis of individual disease. Thus, accurate estimates regarding recurrence and survival are critical for selecting patients with breast cancer who will benefit from adjuvant therapy. Decisions about the type of treatment have traditionally been based on the histopathologic parameters including lymph node status, tumor size, histologic grade, histologic subtype, patient age, and estrogen receptor (ER)/progesterone receptor (PR) status. However, these characteristics fail to characterize the biologic heterogeneity of tumors, which has important implications for treatment benefit. The advent of microarray gene expression profiles as well as sequencing of the whole genome has brought several multigene platforms into clinical use. Many of these platforms incorporate traditional markers (e.g., ER, PR, and HER2) as well as additional cancer-associated genes. Approximately 75–80% of all breast cancers are luminal A or luminal B subtypes which are hormone-dependent based on the presence of ER and/or PR on tumor cells [2].

Here, the genetic and online tools which guide the adjuvant systemic treatment, options of endocrine therapy and systemic cytotoxic chemotherapy in patients with early stage HR+, HER2 -negative breast cancer will be discussed.

2. Treatment decision tools

Adjuvant systemic treatments reduce the risk of breast cancer recurrence following the local treatment of primary stage I–III breast cancers. International expert groups recommend determining the histologic grade and ER, PR, Ki-67 and HER2 status in all breast cancer patients, in order to assist prognosis and determine therapeutic options, including hormone therapy, chemotherapy and anti-HER2 therapy.

For patients with HR+ breast cancers receiving hormonal therapy, the risk of distant recurrence is under 20% and therefore, many patients may potentially be spared of chemotherapy. The web-based prognostification and treatment benefit tools and genomic assays have been incorporated into treatment planning for patients with early-stage HR+ breast cancer, which lead to get more information about prognosis and prediction of treatment response. These assays supplement the traditional histopathologic markers and help identify patients at high risk of recurrence. They also provide a more quantitative approach to risk assessment and enable individualization of treatment. This has both quality of life and health care cost implications because patients who will not benefit from a certain treatment can be spared both the toxicity and the expense [3].

One of the available genetic prognostic platforms (MammaPrint®, Oncotype DX®, Prosigna® or EndoPredict®) may be used in node-negative ER+ patients to establish a prognostic category and decide with the patient whether adjuvant treatment may be limited to hormonal therapy.

2.1. Genomic tools: oncotype Dx

Oncotype DX contains five reference genes (ACTB, GAPDH, GUS, RPLPO and TFRC) and 16 cancer-related genes. RNA is extracted from formalin-fixed paraffin-embedded tumor tissue, using quantitative real-time reverse transcriptase polymerase chain reaction (qRT-PCR). The recurrence score (RS) is the result of a mathematical formula of the weighted expression of each gene, ranging from 0 to 100. The cutoff points are divided into three categories: low risk (RS < 18), intermediate risk (RS 18–30), and high risk (RS > 31). The RS has been proved to be a predictor of 10-year distant recurrence for early breast cancer through NSABP B-14 in multivariate analyses including age, tumor size, tumor grade, ER status and HER2 status [4]. Furthermore, patients with low or intermediate RS had large improvements in disease-free survival (DFS) if treated with tamoxifen (TAM), which indicated that RS was helpful in evaluating treatment response to endocrine therapy in early breast cancer. Habel et al. [5] conducted a case–control study among women with ER+, node-negative breast cancer treated with TAM and compared these with untreated patients. The RS was associated with the risk of breast cancer death in both groups ($P = 0.003$ and $P = 0.03$). Thus, the RS was strongly related to long-term mortality of breast cancer among ER+ breast cancer patients treated with endocrine therapy.

Paik et al. not only evaluated the relationship between the RS and clinical result of ER+, node-negative early breast cancer but also explored the prognostic ability in late recurrence of breast cancer [4]. The 10-year distant recurrence rate was 6.8% in low-risk group, 14.3% in intermediate-risk group and 30.5% in high-risk group. The RS was shown to be related to distant relapse in patients who did not receive adjuvant chemotherapy, regardless of age and tumor size and performed better than both of them ($P < 0.001$).

RS can predict chemotherapy sensitivity in patients with ER+, node-negative breast cancer [6]. Paik et al. studied 651 cases of breast cancer who were enrolled in NSABP B-20 and randomly assigned them into a TAM group and a TAM combined with the chemotherapy group [chemotherapy regimen for cyclophosphamide & methotrexate & fluorouracil (CMF) or MF regimen, TAM + CMF/MF group] [4]. The 10-year follow-up results showed that patients with high RS had benefited from cytotoxic chemotherapy, with the 10-year metastasis rate being decreased by 27.6%. In contrast, the 10-year distant metastasis rate was decreased by an average of −1.1% in patients with low RS who received adjuvant chemotherapy. Therefore, patients with ER+ early breast cancer and high RS should benefit from chemotherapy, while patients with low RS cannot. RS can help select patients who experience little benefit of chemotherapy and can avoid the toxic effects of chemotherapy.

In a phase III trial, the Trial Assigning Individualized Options for Treatment (TAILORx), there was a prospective phase to further validate the function of RS in patients with HR+, HER2-negative, node-negative breast cancer. The results from TAILORx indicated that patients with very low RS results (<11) had excellent clinical outcome with a rate of 5-year freedom from distant recurrence with endocrine therapy at 99.3% and a rate of overall survival (OS) of 98.0%, even without chemotherapy [7]. As for its excellent utility in identifying patients with good outcome, Oncotype DX RS became the only gene-expression assay that was recommended at level I evidence in the AJCC Prognostic Stage Group. In patients with HR+, node-negative breast cancer, the RS showed excellent clinical utility to predict clinical outcomes.

In ECOG E2197, the predictive utility of RS on loco-regional recurrence (LRR) was evaluated in 388 patients with N0-N1 involvement and treated with breast conserving surgery, chemo-endocrine therapy and breast irradiation. The 10-year rates of LRR for HR+ tumors were shown to be 3.8, 5.1 and 12.0% for low, intermediate and high risk of RS (P = 0.12) [8].

In NSABP B-28 trial, RS was shown to be a statistically predictor of LRR, with 10-year cumulative incidence of LRR of 3.3, 7.2 and 12.2% in low, intermediate and high RS (P < 0.001) [9]. RS is a strongly predictive factor of LRR for HR+ breast cancer regardless of node status. Another study, PACS 01 trial, with a median of 7.7 years follow-up, showed that RS was a significant predictor of distant recurrence free interval survival, disease-free survival (DFS) and OS (P < 0.001) in HR+, node-positive patients treated with chemotherapy plus endocrine therapy [10].

The Southwest Oncology Group (SWOG)-8814 focused on exploring the benefit of therapy in patients with HR+, node-positive breast cancer. It enrolled postmenopausal women treated with chemotherapy or simple endocrine adjuvant therapy, of which 367 cases (40%) received an RS detection. RS had a definite predictive value (P = 0.016) for adjuvant treatment benefit over 5 years and was poorly predicted for treatment beyond 5 years (P = 0.87). High-risk patients receiving chemotherapy combined with endocrine therapy compared with simple endocrine therapy benefit significantly (P = 0.033). SWOG-8814 trial showed that the RS was also prognostic for TAM-treated patients with positive nodes and predicts significant benefit of chemotherapy [cyclophosphamide & adriamycin & fluorouracil (CAF)] in tumors with a high RS [11].

In a recent prospective phase III trial, West German Study Group Plan B, 348 patients (15.8%) with RS ≤ 11 had excellent 3-year survival even if they omitted chemotherapy. The 3-year DFS in patients with RS ≤ 11 was 98%, in which 41.1% had node-positive and 32.5% were grade 3 disease. These were the first prospective data to report clinical outcome when RS was used to make physical decision in patients with HR+ breast cancer regardless of lymph node invasion [12].

Rx for Positive Node, Endocrine Responsive Breast Cancer (RxPONDER) trial is an ongoing multicenter phase III trial revealed that patients with node positive breast cancer who had low to intermediate RS results could benefit from chemotherapy [13]. The trial also determined whether there is an optimal RS cutoff for these patients above which chemotherapy should be recommended in clinical practice. RxPONDER trial randomized patients with HR+, HER2-negative and 1–3 lymph nodes breast cancer with RS ≤ 25, to improve the risk of stratification in patients with low or intermediate RS.

2.2. MammaPrint

MammaPrint was first developed by the Netherlands Cancer Institute group. van't Veer et al. [14] used a gene-expression panel to detect 78 frozen tumor tissues from patients with pT1-2cN0 invasive breast carcinoma who had received standard treatment. Ribonucleic acid was isolated from fresh frozen tumor tissue to obtain complementary DNA. The gene-expression panel contains 70 genes related to early risk of metastasis, including tumor invasion, metastasis, interstitial invasion, and angiogenesis-related genes.

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The MINDACT study was a randomized trial that included 6693 women with histologically proven operable N0/N1 invasive breast cancer without distant metastases [15]. Patients were recruited from 2007 to 2011. Initially, only patients without regional lymph node metastasis were enrolled. The study was amended to include patients with 1–3+ nodes in 2009. MammaPrint assay was used to determine participant's genomic risk and a modified version of Adjuvant! Online (version 8.0 with HER2 status) was used to determine clinical risk [16, 17]. Patients with both low clinical and low genomic risk were not treated with adjuvant chemotherapy; on the other hand, patients with high clinical and high genomic risk received adjuvant chemotherapy. The patients with discordant clinical and genomic risk results (high/low or low/high) were randomized to receive chemotherapy or not to receive chemotherapy. All patients were recommended to receive 7 years of hormonal therapy.

Patients at low clinical risk but high genomic risk who received chemotherapy had a 5-year distant metastasis free survival of 95.8% compared with 95.0% among those who did not receive chemotherapy. The adjusted hazard ratio for distant metastasis or death with chemotherapy versus no chemotherapy in this group was 1.17 (P = 0.66). Thus, a chemotherapy benefit is unlikely in women with tumors at low clinical risk regardless of genomic subtype. If a patient has ER/PgR-positive, HER2-negative, node negative, breast cancer, the MammaPrint (Agendia) assay should not be used in those with low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy because women in the low clinical risk category had excellent outcomes and did not appear to benefit from chemotherapy even with a genomic high-risk cancer.

If a patient has HR+, HER2-negative, node-negative breast cancer, the MammaPrint assay may be used in those with high clinical risk to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good-prognosis population with potentially limited chemotherapy benefit. Women in the low clinical risk category did not benefit from chemotherapy regardless of genomic MammaPrint risk group. Therefore, the MammaPrint assay does not have clinical utility in such patients.

If a patient has HR+, HER2-negative, node-positive breast cancer, the MammaPrint assay may be used in patients with 1–3 positive nodes and a high clinical risk to inform decisions on withholding adjuvant systemic chemotherapy. However, such patients should be informed that a benefit from chemotherapy cannot be excluded, particularly in patients with greater than one involved lymph node.

The clinician should not use the MammaPrint assay to guide decisions on adjuvant systemic therapy in patients with HR+, HER2-negative, node-positive breast cancer at low clinical risk, nor any patient with HER2-positive or triple-negative breast cancer, because of the lack of definitive data in these populations [18].

2.3. PAM-50: PROSIGNA

The PAM50 Breast Cancer Intrinsic Classifier™ assay (ARUP Laboratories, Salt Lake City, UT) is a standardized test measuring 50 classifier genes and five control genes, amenable to assay by techniques such as quantitative real-time reverse transcriptase PCR [19]. It was originally developed in a microarray-based cohort of node-negative, untreated breast cancer patients. It

accurately identifies the major intrinsic biological subtypes of breast cancer commonly known as luminal A, luminal B, HER2 enriched, and basal-like [20] and predicts the risk of recurrence (ROR) at 10 years. Tumors that are named as luminal A in PAM50 intrinsic subtype indicate usually very good prognosis with only adjuvant endocrine therapy, whereas luminal B subtypes have increased risk of recurrence without adjuvant chemotherapy.

Four versions of ROR exist in the research setting: ROR based on subtype information (ROR-S), ROR-S with proliferation (ROR-P), ROR-S with tumor size (ROR-T), and ROR-P with tumor size (ROR-PT) [20]. The minimum ROR score of all Luminal B scores was assigned as the low-risk threshold for each model and the maximum ROR score of all Luminal A scores as the high-risk threshold [20]. Large validation studies (ATAC and ABCSG8) for the PAM50 assay were performed using the standardized version with pre-specified cutoffs based on actual survival outcomes (<10, 10–20, and > 20% risk of distant relapse at 10 years) and not subtype distribution [21].

The Prosigna Breast Cancer Prognostic Gene Signature Assay is an in vitro diagnostic assay, which is performed on the NanoString nCounter® Dx Analysis System using FFPE breast tumor tissue previously diagnosed as invasive breast carcinoma. The Prosigna Score is a numerical value on a 0–100 scale that correlates with the probability of distant recurrence within 10 years. The gene expression profile of a patient's tumor is compared with each of the four PAM50 prototypical molecular profiles to determine the degree of similarity. The results in combination with a proliferation score and tumor size produce an individualized Prosigna Score. This qualitative assay utilizes gene expression data, weighted together with clinical variables to generate a risk category and numerical score, to assess a patient's risk of distant recurrence of disease.

In node-negative patients, the 10-year distant recurrence-free survival (DRFS) rates were > 95% for the low-risk group, 90.4% for the intermediate-risk group, and < 85% for the high-risk group [22, 23]. In node-positive patients, the 10-year DRFS rates were 94.2% for the low-risk group and 75.8% for the high-risk group [22].

The Prosigna Breast Cancer Prognostic Gene Signature Assay is indicated in female breast cancer patients who have undergone surgery in conjunction with locoregional treatment consistent with standard of care, either as:

i. A prognostic indicator for distant recurrence-free survival at 10 years in postmenopausal women with HR+, lymph node-negative, stage I or II breast cancer to be treated with adjuvant endocrine therapy alone, when used in conjunction with other clinicopathological factors.

ii. A prognostic indicator for distant recurrence-free survival at 10 years in postmenopausal women with HR+, lymph node-positive (1–3 positive nodes), stage II breast cancer to be treated with adjuvant endocrine therapy alone, when used in conjunction with other clinicopathological factors.

The assay should not be used for patients with four or more positive nodes.

2.4. EndoPredict

The EndoPredict (EP) assay combines the expression of three proliferative and five ER-signaling/differentiation-associated genes and is normalized by three housekeeping genes [24]. EP may be measured in formalin-fixed, paraffin-embedded tissue sections by quantitative real-time polymerase chain reaction in decentralized laboratories and provides a score that ranges between 0 and 15 after scaling [25].

EPclin was derived from EP by incorporating nodal status and tumor size to create an integrated diagnostic algorithm for clinical decisions [24]. Both EP and EPclin were trained on a cohort of 964 patients with ER+, HER2-negative carcinomas treated with adjuvant endocrine therapy only. Thresholds for EP and EPclin to differentiate between patients at low or high risk corresponding to a 10% probability of distant recurrence at 10 years were set at 5 and 3.3, respectively. Patients with an EP score < 5 (EPclin score < 3.3) were classified as low risk for distance recurrence, whereas patients with an EP score ≥5 (EPclin score ≥3.3) were stratified as high risk. Both EP and EPclin were shown to be prognostic for early and late distant recurrence in the ABCSG-6 and ABCSG-8 trials involving patients with ER+/HER2-negative breast cancer treated with adjuvant endocrine therapy only [26]. EndoPredict provides prognostic information beyond all common clinicopathological parameters and clinical guidelines.

There are several prognostic multigene-based tests for managing breast cancer, but limited data comparing them in the same cohort. The prognostic performance of the EP test was compared with the research-based PAM50 non-standardized qRT-PCR assay in node-positive ER+ and HER2-negative breast cancer patients receiving adjuvant chemotherapy followed by endocrine therapy (ET) in the GEICAM/9906 trial [27]. EP and PAM50 ROR scores [based on subtype (ROR-S) and on subtype and proliferation (ROR-P)] were compared in 536 ER+/HER2−patients. Scores combined with clinical information were evaluated: ROR-T (ROR-S, tumor size), ROR-PT (ROR-P, tumor size), and EPclin (EP, tumor size, nodal status). Patients were assigned to risk categories according to prespecified cutoffs. ROR-S, ROR-P, and EP scores identified a low-risk group with a relative better outcome (10-year distant metastasis-free survival: ROR-S 87%; ROR-P 89%; EP 93%). No significant difference between tests was found. Predictors including clinical information showed superior prognostic performance compared to molecular scores alone (10-year MFS, low-risk group: ROR-T 88%; ROR-PT 92%; EPclin 100%). The EPclin-based risk stratification achieved a significantly improved prediction of MFS compared to ROR-T, but not ROR-PT. All signatures added prognostic information to common clinical parameters.

EPclin provided independent prognostic information beyond ROR-T and ROR-PT. ROR and EP can reliably predict risk of distant metastasis in node-positive ER+/HER2 negative breast cancer patients treated with chemotherapy and ET. Addition of clinical parameters into risk scores improves their prognostic ability.

Recently, in a secondary analysis of a randomized clinical trial, the prognostic value of six multigene signatures was compared in women with early ER+ breast cancer [28]. In this study, 774 postmenopausal women with ER+, HER2-negative disease, 591 had node-negative disease

and patients received endocrine therapy for 5 years (the Anastrozole or Tamoxifen Alone or Combined randomized clinical trial comparing 5-year treatment with anastrozole vs. tamoxifen) in addition to the Clinical Treatment Score (nodal status, tumor size, grade, age, and endocrine treatment) for distant recurrence for 0–10 years and 5–10 years after diagnosis [28]. The signatures included the Oncotype Dx recurrence score, ROR, Breast Cancer Index (BCI), EPclin, Clinical Treatment Score, and 4-marker immunohistochemical score. The ROR (HR, 2.56), followed by the BCI (HR, 2.46) and EPclin (HR, 2.14) were shown to be the signatures which have the most prognostic information. Each provided significantly more information than the Clinical Treatment Score (HR, 1.99), the recurrence score (HR, 1.69), and the 4-marker immunohistochemical score (HR, 1.95). Substantially less information was provided by all six molecular tests for the 183 patients with 1–3 positive nodes, but the BCI and EPclin provided more additional prognostic information than the other signatures. For women with node-negative disease, the ROR, BCI, and EPclin were shown to be significantly more prognostic for overall and late distant recurrence. For women with 1–3 positive nodes, limited independent information was available from any test.

2.5. Breast cancer index

The breast cancer index assay previously has been developed and validated. It consists of two independently developed gene expression biomarkers: molecular grade index (MGI) and HOXB13/IL17BR (H/I) [20, 26]. MGI, a 5-gene predictor that recapitulates tumor grade/proliferation, is highly prognostic in ER+ breast cancer patients. H/I, which was developed independent of tumor grade/proliferation, is prognostic for early and late distant recurrences and is predictive of extended adjuvant AI benefit in early stage of ER+ breast cancer patients.

2.6. Online prognostification and prediction tools

The online tools referred to earlier primarily use clinicopathological variables and cancer registry data as the basis of risk prediction. The clinical pathological variables used include age, tumor size and grade, mode of detection, number of lymph nodes involved, ER status, HER2 status, Ki67 status and type of chemotherapy [29].

2.6.1. Adjuvant online

Adjuvant!Online is a free online tool and probably the most widely used tool that estimate risks and benefits of adjuvant endocrine therapy and chemotherapy after breast cancer surgery based on factors, such as the patient's stage, pathologic features, age and comorbidity level. Entering information on age and selected tumor characteristics (tumor size and grade, number of positive axillary nodes, and hormone receptors status) allows for prediction of the 10-year risk of relapse-free and overall survival.

Despite these strengths, Adjuvant! has several limitations. The relapse estimates include local-regional recurrence as well as distant metastases; this is important as the proportions of both may vary greatly depending on stage and tumor phenotype. The baseline risk estimation for Adjuvant! Online was derived from the SEER (surveillance, epidemiology and end results) database [30]. The SEER database program is a collation of nine databases covering one-sixth

of the US population. There have been concerns regarding the quality of the data about cause of death [31]. Additionally, the SEER database specifically includes patients between 35 and 69 years and provides limited information on the socio-economic status of people.

Adjuvant! Online tends to overestimate the number of patients at high risk. Cardoso et al. reported that Adjuvant! Online classified 23% of patients as high clinical risk when Oncotype DX classified them as low genomic risk [15].

Olivotto et al. performed a population-based validation study and suggested that Adjuvant! Online would overestimate survival in patients under 35 years of age with lymphovascular invasion. It was also found that Adjuvant! Online tends to overestimate the survival rates of younger women with ER+ breast cancer [16] and that it overestimated the added value of chemotherapy for older patients [32].

The validity of the predictive score is calculated by Adjuvant! Online was deemed weak in the clinician-based validation [33]. Predictions on loco-regional relapse and distant metastases may vary greatly, making it difficult to make clear recommendations for adjuvant treatment [34]. This is reflected in two studies that suggest that when patients are involved in a discussion to decide on adjuvant chemotherapy, they are less likely to choose chemotherapy if using Adjuvant! Online [35].

The database does not include information regarding the benefits of adjuvant trastuzumab, thereby reducing the utility of Adjuvant! Online in clinical decisions about HER2-positive disease treatment [31]. This deficiency of Adjuvant! Online with regard to HER2-positive disease has significant implications for the prediction of metastatic spread. In a recent in vitro study using murine models, the HER2 status of cells predicted the response to progesterone-induced signaling, with HER2-deficient cells being more likely to migrate and HER2-enriched cells tending toward increased proliferation [36]. This recent evidence underlines the importance of HER2 in predicting prognosis and highlights the significance of this inherent shortcoming in online cancer registry-based prognostic tools.

The ethnic variation in the data on which these online tools are based seriously affects the generalizability of these online tools. The SEER database is representative of the usual US population in terms of age, sex and ethnic distribution. However, the ethnic mix of the US population is different from that of England and Wales [37].

2.6.2. Predict

Predict is an another online prognostication and treatment benefit tool based on UK cancer registry data and included information on 5694 women treated in East Anglia from 1999 to 2003 [38]. It is designed to help clinicians and patients make informed decisions about treatment following breast cancer surgery. The model was validated in a second UK cancer registry dataset. It would able to provide not only the accurate prediction of survival but also subsequent calculation of treatment benefit.

Data of an individual patient including patient age, tumor size, tumor grade, number of positive nodes, ER status, HER2 status, KI67 status and mode of detection are submitted to online PREDICT tool. It originally did not include HER2 status and KI67 status, but in 2011,

HER2 status was included (PREDICT version 1.1) and later KI67 was added to model (PREDICT version 1.2) to improve the estimates of breast cancer-specific mortality, especially in HER2-positive patients [29, 39].

While the overall fit of the model has been good in multiple independent case series, PREDICT has been shown to underestimate breast cancer specific mortality in women diagnosed under the age of 40, particularly those with ER+ disease. Another limitation of the model is the use of discrete categories for tumor size and node status which result in "step" changes in risk estimates on moving from one category to the next. For example, a woman with an 18 or 19 mm tumor will be predicted to have the same breast cancer specific mortality if all the other prognostic factors are the same whereas breast cancer-specific morality of women with a 19 or 20 mm tumor will differ. The PREDICT prognostic model was refitted using the original cohort of cases from East Anglia with updated survival time in order to take into account age at diagnosis and to smooth out the survival function for tumor size and node status. The fit of the model has been tested in three independent data sets that had also been used to validate the original version of PREDICT [40].

KI67 positivity for the PREDICT model was defined as greater than 10% of tumor cells staining positive. Survival estimates, with and without adjuvant therapy, are presented in visual and text formats. Treatment benefits for hormone therapy and chemotherapy are calculated by applying relative risk reductions from the Oxford overview to the breast cancer specific mortality. Predicted mortality reductions are available for both second-generation (anthracycline-containing, >4 cycles or equivalent) and third-generation (taxane-containing) chemotherapy regimens. The survival estimates, presented both with and without adjuvant hormone therapy, chemotherapy and trastuzumab, are provided for 5 and 10 years.

The Cambridge Breast Unit uses the absolute 10-year survival benefit from chemotherapy to guide decision-making for adjuvant chemotherapy as follows: <3% no chemotherapy; 3–5% chemotherapy discussed as a possible option; >5% chemotherapy recommended.

Online tools are valuable in guiding adjuvant treatment, especially in resource-constrained countries. However, in the era of personalized therapy, molecular profiling appears to be superior in predicting clinical outcome and guiding therapy.

The AJCC Prognostic Stage Group containing multigene panels has been globally used from January 1, 2018. It suggests that prognostic stage grouping should be used in countries where biomarker tests are routinely performed, indicating that multigene molecular profiling will become part of cancer stage evaluation and will need to be taken into consideration when making clinical decisions [41].

Oncotype DX and MammaPrint have the strongest evidence supporting their clinical utility and decision effectiveness in HR+ breast cancer [42]. The future of multigene panels is promising in personalizing treatment as more studies continue. However, many issues remain to be solved before multigene panels have a wider influence on breast cancer treatment. Importantly new issues, such as how to accurately predicate late recurrence in ER+ cancer and how to provide more access to multigene panels, should be solved in the future.

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Newer technologies including next-generation sequencing, liquid biopsy, tumor-infiltrating lymphocytes or PD-1 determination are at this investigational point.

3. Adjuvant chemotherapy

Several pathological factors including histological subtype, ER or PR expression, tumor grade, lymphovascular invasion, tumor stage, and clinical factors such as patient age, preferences and comorbidities should be taken into consideration during adjuvant chemotherapy indication is being decided. The genomic tests and benefit–risk calculators which were developed to be used in determining appropriate candidates for adjuvant chemotherapy in early stage HR+ breast cancer have been discussed in previous section.

Patients with HR+ breast cancer less than 5 mm and treated with only endocrine therapy have usually very good prognosis. Thus, they typically are not treated with adjuvant chemotherapy. However, patients with stage III HR+ breast cancer still require adjuvant chemotherapy since they carry high risk of recurrence without chemotherapy. Many patients with HR+ HER2 negative breast cancer fall in between these two categories, and they are called as intermediate risk group based on clinicopathological variables, genomic tests or online risk calculators.

Clinicians should inform the patients who required adjuvant chemotherapy about the risks and benefits of chemotherapy. Risks include acute or long-term toxicities such as emesis, alopecia, myelosuppression, neuropathy, cardiotoxicity, infertility and leukemias.

Breast cancer is the most frequent malignancy in women of reproductive age. Treatments for breast cancer may eliminate or diminish fertility. Additionally, even in patients who do not require chemotherapy, long duration of adjuvant endocrine therapy often leads natural decline in ovarian reserve during adjuvant treatment.

The chemotherapy-related risk of premature ovarian insufficiency is influenced by age, body mass index, the type and duration of therapy. After six cycles of CMF, the risk of amenorrhea is 33 and 81% in patients <40 and ≥ 40 years of age, respectively. Newer chemotherapy regimens including adriamycin & cyclophosphamide (AC), adriamycin & cyclophosphamide & taxane (ACT), fluorouracil & adriamycin & cyclophosphamide (FAC) and fluorouracil & adriamycin & cyclophosphamide & taxane (FACT) result in lower rates of persisting amenorrhea. The risk of amenorrhea is 10–20 and 13–68% in patients <30 years and in patients >30 years, respectively [43]. Hence, the rate of infertility risk with particular chemotherapy regimen at particular age should be discussed with patients prior to initiation of gonadotoxic therapies. Furthermore, premenopausal women who are willing to be pregnant in the future should be referred to a fertility specialist to be informed about various techniques of fertility preservation.

Although methods of fertility preservation in breast cancer should be a subject of a separate chapter, fertility preservation methods can be summarized as

- established methods: oocyte or embryo cryopreservation

- experimental methods: ovarian suppression with gonadotropin-releasing hormone (GnRH) agonists (GnRHa) and ovarian tissue cryopreservation [44].

3.1. Chemotherapy regimen

Several polychemotherapy regimens are accepted as adjuvant chemotherapy regimen with strong evidence in patients with early stage breast cancer. The preferred regimens vary according to characteristics of disease, patients' comorbidities, patients' preferences, age, prescribing doctor, institution, or country.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reports a meta-analysis periodically to review the data on adjuvant treatment of breast cancer. The previous data supported the adjuvant chemotherapy particularly cyclophosphamide, methotrexate and fluorouracil (CMF), anthracyclines and taxane compared with no treatment in adjuvant setting.

Trials with CMF-treated controls revealed that standard 4 AC and standard CMF were equivalent (P = 0·67), but that anthracycline-based regimens with substantially higher cumulative dosage than standard 4 AC [e.g., CAF or cyclophosphamide & epirubicin & fluorouracil (CEF)] were superior to standard CMF (RR 0.78, P = 0.0004) [45]. However, NSABP B-36 randomized phase III trial compared six cycles of FEC-100 with four cycles of standard AC in pts. with T1-3 N0 breast cancer [46]. Primary and secondary endpoint analyses at 8 years did not reveal any significant differences in DFS, OS, recurrence free interval (RFI), or distant RFI, although patients and tumor characteristics were equally distributed between the two groups (<50 years old: 40%, lumpectomy: 68%, and hormone positivity: 65%). Overall, Grade 3 and 4 expected toxicities were more frequent in the FEC arm. Thus, international guidelines excluded six cycles of FEC-100 from adjuvant breast cancer treatment recommendations.

In trials adding four separate cycles of a taxane to a fixed anthracycline-based control regimen, extending treatment duration, breast cancer mortality was reduced (RR 0.86, SE 0.04, two-sided significance P = 0.0005) [45].

In all meta-analyses involving taxane-based or anthracycline-based regimens, proportional risk reductions were little affected by age, nodal status, tumor diameter or differentiation, ER status, or adjuvant tamoxifen. Hence, largely independently of age (up to at least 70 years) or the tumor characteristics currently available to us for the patients selected to be in these trials, some taxane-plus-anthracycline-based or higher-cumulative-dosage anthracycline-based regimens (not requiring stem cells) reduced breast cancer mortality about one-third.

Thus, based on these strong evidences, AC followed by a taxane (either triweekly docetaxel, paclitaxel or two weekly or weekly paclitaxel) is now usually preferred regimen in most cases in whom adjuvant chemotherapy is indicated.

Nonanthracycline-based chemotherapy regimens should be preferred in certain patients with lower risk disease (node-negative), cardiac contraindication, advanced age, previous chest wall irradiation or patients who do not accept the risks of anthracycline-based therapy. In these patients, four cycles of docetaxel and cyclophosphamide (TC) are most preferred regimen.

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When adjuvant chemotherapy is indicated in HR+ HER2-negative early breast cancer, taxane is mostly added to anthracycline-based regimen based on scientific data. However, patients who cannot receive taxane due to risks of allergic reactions or peripheral neuropathy, CMF can be administered instead of anthracycline or taxane- based regimens.

Dose-dense chemotherapy plays a controversial role in the adjuvant treatment of breast cancer patients. Whereas meta-analyses persistently describe a significant superiority for dose-dense treatment, the results of large phase III trials remain contradictory [47]. Some of these trials showed important differences between the dose-dense and conventional groups regarding number of cycles, type of drug, and total dose. Other trials are accepted and interpreted as dose-dense but present a mixture of dose-dense and conventional schedules.

Goldvaser et al. performed a systemic review and meta-analysis of clinical trials in which patients with early stage breast cancer were treated with adjuvant dose-dense chemotherapy [48]. Dose-dense treatment significantly improved DFS (HR 0.85, $P < 0.001$) and OS (HR 0.86, $P = 0.008$). A significantly greater relative magnitude of benefit was observed in pre-menopausal women and those with nodal involvement, but there was no influence of hormone receptor status on results. Adjuvant dose-dense regimens improve breast cancer outcomes. It remains uncertain whether the observed benefit reflects the impact of dose density or the inferiority of paclitaxel every 3 weeks as a control group.

Although a direct head-to-head comparison is missing, intense dose-dense epirubicin, paclitaxel, and cyclophosphamide (iddETC) or four cycles each of dose-dense epirubicin/cyclophosphamide followed by paclitaxel are the preferred adjuvant regimens for patients at risk. Patients with four positive lymph nodes should preferentially be treated with iddETC.

However, in EBCTCG meta-analyses, information was lacking about tumor gene expression markers or quantitative immunohistochemistry that might help to predict risk, chemosensitivity, or both.

4. Adjuvant endocrine therapy

Estrogen receptor expression is the main indicator of potential responses to endocrine therapy (ET) which block estrogen-driven tumor growth through a variety of mechanisms. The use of hormonal therapy in breast cancer has improved the overall outcome for patients with early-stage hormone receptor-positive disease. The choice of hormone therapy is related to multiple factors, including menopausal state, patient preference, and potential side effects. Molecular profiling has allowed therapy to be tailored for an individual patient to some extent. However, further molecular studies are needed to individualize the choice and length of adjuvant hormone therapy.

Adjuvant ET currently consists of (i) ovarian suppression, (ii) selective estrogen receptor modulators (SERMs) and down-regulators, and (iii) AIs.

In patients with ER+ tumors, pharmacologic ovary suppression with gonadotropin-releasing hormone agonists in combination with standard adjuvant therapy is generally more effective than adjuvant chemotherapy alone.

Tamoxifen is the best established SERM, has favorable effects on breast cancer control and bone metabolism, but also has adverse effects due to its estrogenic activity in other tissues. For these reasons, other SERMs have been developed.

Fulvestrant is an ER down-regulator with several potential advantages over SERMs, including a 100-fold increase in its affinity for ER compared with tamoxifen and no estrogen-like activity in the uterus.

The inhibition of the aromatase system with third-generation AIs is associated with improved survival in patients with advanced breast cancer compared with SERMs. In postmenopausal patients with ER+ breast cancer adjuvant treatment with AIs should be performed, either as sequential treatment after tamoxifen or as upfront therapy.

According to NCCN guidelines [49], subdivide the adjuvant endocrine therapy recommendations in HR+ breast cancer patients based on the menopausal status of women. Three main subgroups are (i) postmenopausal at initial diagnosis, (ii) premenopausal at initial diagnosis and remain premenopausal after 5 years of adjuvant ET, (iii) premenopausal at initial diagnosis, but become postmenopausal during adjuvant ET.

i. postmenopausal at initial diagnosis:

- an AI as initial adjuvant therapy for 5 years (category 1),
- initially tamoxifen for 2–3 years followed by an AI to complete 5 years of adjuvant ET (category 1),
- initially tamoxifen for 2–3 years followed by 5 years of AI (category 2B),
- tamoxifen for 4.5–6 years followed by 5 years of an AI (category 1) or consideration of tamoxifen for up to 10 years.
- Five years up to 10 years of tamoxifen without AI should only be given to patients who have a contraindication to AI.

ii. premenopausal at initial diagnosis and remain premenopausal after 5 years of adjuvant ET

- tamoxifen with or without ovarian suppression for 5 years (category 1)
- an AI with ovarian suppression for 5 years (category 1)
- tamoxifen continuing up to 10 years

iii. premenopausal at initial diagnosis, but become postmenopausal during adjuvant ET.

Decision of menopausal status is the most important point because amenorrhea does not mean menopause, because ovaries may continue to product estrogens in amenorrheic women. Thus, before starting AI without ovarian suppression, serum LH, FSH and estradiol must be evaluated.

- After or during 5 years of tamoxifen, extend the adjuvant ET with an AI up to 5 years (category 1)
- After 5 years of tamoxifen, consider five additional years of tamoxifen

4.1. Combination of ovarian suppression either exemestane or tamoxifen in premenopausal women

The initial results from the Suppression of Ovarian Function Trial (SOFT) indicate that tamoxifen is a suitable therapy for premenopausal women with low risk clinical-pathologic features. For women at sufficient risk to receive chemotherapy who have premenopausal E2 levels within 8 months of completion, the addition of ovarian suppression to tamoxifen for 5 years resulted in some reduction of recurrence. The use of ovarian suppression combined with an AI exemestane for 5 years resulted in further reduction of recurrence [50, 51].

The joint analysis of SOFT and Tamoxifen and Exemestane Trial (TEXT) found the combination of ovarian suppression and exemestane significantly reduced recurrence, compared with ovarian suppression plus tamoxifen. Premenopausal women with ER+ve HER2-negative breast cancer with high-risk features can derive a meaningful improvement in 5-year invasive breast cancer-free interval with exemestane plus ovarian suppression, as an alternative to tamoxifen. Very young women under age 35 with ER+ve breast cancer have higher risks of recurrence, and the use of ovarian suppression with oral endocrine therapy should be considered.

4.2. Extended adjuvant endocrine therapy beyond 5 years

Adjuvant endocrine therapy for 5 years is the standard adjuvant treatment for ER+ breast cancer while the benefits of extended adjuvant endocrine therapy (EAET) beyond 5 years are still controversial. In a recent meta-analysis, 5 years of adjuvant endocrine therapy only was compared with EAET [52]. Eleven controlled trials including 29,000 women were analyzed. There was no advantage of EAET in OS from all causes mortality (P = 0.67). On the other hand, compared with standard therapy, the pooled effects showed that EAET was associated with improvement in breast cancer-specific survival (OR = 0.87; P = 0.004), DFS (OR = 0.87; P = 0.002), disease recurrence (OR = 0.76; P = 0.001), and contralateral breast recurrence (OR = 0.74; P = 0.008). Improvement in DFS or disease recurrence was not shown in studies that compared 5 years of tamoxifen versus tamoxifen beyond 5 years. Subgroup analysis showed that EAET conferred more benefit for patients with positive lymph nodes. Rates of positive lymph nodes, the study size, and the median duration of follow-up were identified as variables that explained most of the demonstrated data heterogeneity. EAET should be considered as a preferred strategy for high-risk hormone-positive early breast cancer patients with positive lymph nodes; however, the benefit on OS could not be demonstrated.

Extended adjuvant endocrine therapy results in increased toxicity based on the type of extended endocrine agents. Risk of bone fractures is reported to be higher with AI, whereas the risk of endometrial cancer and venous thromboembolism are more frequently than with TAM. No difference was shown between AI (mono- or sequenced therapy) and TAM for

cardiovascular events, whereas sequenced therapy compared with AI had lower risk of cardiovascular events (moderate level of evidence).

4.3. Concurrent or sequential ovarian function suppression

Breast cancer treatment guidelines recommend that higher risk premenopausal patients should receive ovarian function suppression as part of adjuvant endocrine therapy. However, if chemotherapy is also given, until recently, it was uncertain whether concurrent or sequential sequential ovarian function suppression (OFS) initiation has any detrimental effect on prognosis or menstruation resumption.

Recently, in a phase 3, open-label, parallel, randomized controlled trial, 216 premenopausal patients younger than 45 years with invasive ER+ breast cancer were randomized at a 1:1 ratio to receive (neo)adjuvant chemotherapy combined with sequential or simultaneous GnRHa treatment between July 2009 to May 2013 [53]. All patients were advised to receive GnRHa for at least 2 years. The rates of early menopause were 22.8% (21/92) in the sequential group and 23.1% (18/78) in the simultaneous group (simultaneous vs. sequential: OR 1.01; P = 0.969; age-adjusted OR 1.13; P = 0.737). The median menstruation resumption period was 12.0 months and 10.3 months for the sequential and simultaneous groups, respectively (HR 0.83; P = 0.274; age-adjusted HR 0.90; P = 0.567). During a median follow-up time of 56.9 months (IQR 49.5–72.4 months), there were no significant differences in disease-free survival (P = 0.290) or in overall survival (P = 0.514) between the two groups.

In **an exploratory analysis of phase III TEXT and SOFT trials,** 1872 patients who received adjuvant chemotherapy for HR+, HER2-negative breast cancer and upon randomization to an OFS-containing adjuvant endocrine therapy, initiated GnRHa triptorelin were analyzed [54]. Breast cancer-free interval (BCFI) was compared between patients who received OFS concurrently with chemotherapy in TEXT (n = 1242) versus sequentially post-chemotherapy in SOFT (n = 630). Because timing of trial enrollment relative to adjuvant chemotherapy differed, landmark analysis was implemented to re-define BCFI beginning 1 year after final dose of chemotherapy (median, 15.5 months in TEXT and 8.1 months from enrollment to landmark in SOFT). The median duration of adjuvant chemotherapy was 18 weeks in both groups. Patients who were premenopausal post-chemotherapy in SOFT were younger on average. After post-landmark median follow-up of about 5 years, post-landmark BCFI was found to be statistically similar between concurrent use of triptorelin with chemotherapy and sequential use of triptorelin after chemotherapy, either in the overall population (HR = 1.11; P = 0.72; 4-year BCFI 89% in both groups), or in the subgroup of 692 women < 40 years at diagnosis (HR = 1.13) who are less likely to develop chemotherapy-induced amenorrhea.

Because the sequential use of GnRHa and chemotherapy showed similar ovarian preservation and survival outcomes when compared with simultaneous use ER+ premenopausal patients, addition of GnRHa to oncologic treatment can probably be delayed until menstruation resumption after chemotherapy. However, based on comparative-effectiveness modeling of TEXT and SOFT after about 5 years median follow-up, concurrent administration of OFS with chemotherapy is neither detrimental nor beneficial effect on the efficacy of adjuvant therapy which includes chemotherapy, with limited statistical power especially for the subgroup < 40 years.

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5. Adjuvant bisphosphonates

Cancer Care Ontario and ASCO convened a Working Group and Expert Panel to develop evidence-based recommendations by a systematic review of the literature [55]. The women with natural menopause or the women who were postmenopausal induced by ovarian suppression or ablation were included. Adjuvant bisphosphonates were reported to reduce bone recurrence and improve survival in postmenopausal women with early stage breast cancer. Absolute benefit was found to be greater in patients who are at higher risk of recurrence, and almost all trials were conducted in patients who also received systemic therapy. The data are extremely limited for bisphosphonates other than zoledronic acid or clodronate due to most studies performed with these two bisphosphonates. ASCO clinical guidelines recommends that, if available, zoledronic acid (4 mg intravenously every 6 months) or clodronate (1600 mg/d orally) be considered as an adjuvant therapy for postmenopausal patients with breast cancer who are deemed candidates for adjuvant systemic therapy. However, further research comparing different bone-modifying agents, doses, dosing intervals, and durations is required. Risk factors for osteonecrosis of the jaw and renal impairment should be assessed, and any pending dental or oral health problems should be dealt with prior to starting treatment. While adjuvant denosumab reduces fractures and it looks promising in adjuvant setting, long-term survival data are still insufficient to make any recommendation. The use of these agents to reduce fragility fractures in patients with low bone mineral density is beyond the scope of the guideline.

6. Promising targeted agents

Ongoing studies are evaluating the role of additional targeted therapies, such as CDK4/6 inhibitors including ribociclib, palbociclib, to further improve outcome for patients with early-stage HR+ breast cancer.

Conflict of interest

I confirm there are no conflicts of interest.

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