Optimal adjuvant endocrine therapy for early breast cancer

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Adjuvant endocrine therapy substantially reduces tumor recurrence and mortality in pre- and post-menopausal women with hormone receptor-positive early breast cancer but is ineffective in women with hormone receptor-negative tumors. Tamoxifen has been the standard adjuvant endocrine therapy for both pre- and post-menopausal women with hormone receptor-positive early breast cancer and remains the standard of care for premenopausal women. In addition to tamoxifen, ovarian ablation by surgery or radiotherapy remains an option for selected premenopausal women and trials are evaluating the role of ovarian function suppression using luteinizing hormone-releasing hormone agonists. For postmenopausal women, aromatase inhibitors are more effective than tamoxifen therapy and aromatase inhibitors and tamoxifen are regarded as standards of care. Prolonging adjuvant endocrine therapy in postmenopausal women by the sequencing of aromatase inhibitors and tamoxifen can improve outcomes further. Adjuvant endocrine therapy will probably be used for longer durations in selected postmenopausal women.

Breast cancers may express a number of different steroid hormone receptors. Clinically, the two most important are the estrogen receptor (ER) and the progesterone receptor (PgR). Overall, approximately three-quarters of breast cancers are ER+.

An ER+ tumor is usually also PgR+, whereas an ER- tumor is very rarely PgR+. A breast cancer that is either ER- and/or PgR- is classified as a hormone receptor-negative (HR-) tumor. In early breast cancer (EBC; i.e., breast cancer restricted to the breast, with or without involvement of the ipsilateral axillary lymph nodes), adjuvant endocrine therapy (AET) is usually given following definitive treatments such as surgery, chemotherapy or radiotherapy in order to control micrometastatic disease that is not clinically evident. AET has been demonstrated to reduce both recurrence and mortality substantially in HR+ EBC, but it is not effective in breast cancers that are HR- (i.e., ER- and PgR-).

Brief history of endocrine therapy for breast cancer

Traditionally, Sir George Beatson is credited with discovering the relationship between ovarian function and breast cancer when, in 1896, he reported that oophorectomy improved locally advanced breast cancers in two of three premenopausal women that he treated [1,2]. However, as Love and Phillips point out [3], the relationship between ovarian function and breast cancer was first noted by Thomas Nunn, who, in 1882, observed that the breast cancer in a premenopausal patient regressed 6 months after her menstruation ceased [4]. Moreover, oophorectomy for the treatment of breast cancer was first proposed even earlier, in 1889, by the German surgeon, Schinzinger [5], although he never performed an oophorectomy for breast cancer. Thus, Beatson was the first to report the utility of oophorectomy as a breast cancer treatment.

Oophorectomy was used in the late 19th and early 20th centuries for the treatment of metastatic breast cancer (MBC). However, in 1900, Boyd reported that only a third of women with MBC responded to oophorectomy and that the response only lasted between 1 and 2 years [6]. Although it was understood that oophorectomy decreased estrogen production, at the time, it was unknown why some women responded to oophorectomy whereas others did not. Interest in the use of oophorectomy for MBC dwindled but was later revived following reports of the encouraging results of orchidectomy for metastatic prostate cancer by Huggins and Hodges in 1941 [7]. Subsequently, it was realized that other endocrine glands apart from the ovaries were involved in estrogen production, either directly or indirectly. Thus, the surgical ablative procedures of adrenalectomy [8] and hypophysectomy [9] were introduced for the treatment of MBC. However, these surgical ablative procedures had to await the introduction of synthetic steroid hormones as replacement therapy, which became available after 1950. Generally, surgical ablative procedures have now been replaced by medical endocrine therapies.

How does endocrine therapy work?

We now understand that estrogens exert their effects on breast cancers by binding to the ER, which was discovered in 1958 by Jensen and...
colleagues [10]. After the binding of estrogen to the ER, estrogen–ER complexes diffuse into the cell nucleus and bind to specific sequences of DNA. As a result of this, a number of complex changes occur within the cell, including the expression of multiple factors including the PgR, which was discovered in 1975 [11]. It is believed that endocrine therapies exert their effects through disruption of the estrogen–ER axis, which can be achieved in a number of ways, such as by the reduction of the synthesis of estrogens by surgical ablative procedures on endocrine glands that are directly or indirectly responsible for estrogen production, by the administration of drugs that reduce the synthesis of estrogens, by interfering with the interaction of estrogen with the ER or by downregulation of the ER. In addition to surgical oophorectomy, ovarian function suppression (OFS) can be achieved by ovarian irradiation or, more recently, by medical means with luteinizing hormone-releasing hormone (LHRH) agonists.

The Oxford overviews
The Early Breast Cancer Clinical Trialists’ Collaborative Group (EB CCTCG) was formed by the Clinical Trials Service Unit at the University of Oxford in the UK in 1983. The EB CCTCG has produced a number of overviews of the different treatments for EBC but initially concentrated on endocrine therapies for EBC. Over the years, these overviews by the EB CCTCG have provided a wealth of data regarding AET for EBC, and will be used extensively in this review.

Adjuvant endocrine therapy for premenopausal women
Approximately 60% of breast cancers in premenopausal women are HR+ [12]. Many premenopausal women with HR+ EBC will receive adjuvant chemotherapy followed by tamoxifen, while others may be offered tamoxifen alone or in combination with OFS. However, the optimal AET for premenopausal women is not well established. Unresolved questions include the optimal duration of tamoxifen therapy, the type and duration of OFS (if applicable), the appropriate endocrine therapy – that is, tamoxifen versus other selective estrogen modulators (SERMs) or selective ER downregulators – and the best combination of chemotherapy and endocrine therapy for women of different ages and at different levels of risk of recurrence of their breast cancer. The available data are summarized below.

**Tamoxifen**
Tamoxifen was the first SERM developed and remains the standard of care for AET in premenopausal women with HR+ EBC. Although tamoxifen is predominantly antiestrogenic, it acts as an estrogen on both the endometrium and bone. Early overviews of hormonal therapies for EBC by the EB CCTCG suggested that tamoxifen did not significantly reduce mortality in premenopausal women with EBC [13], but we now know that this is not the case. This finding may have reflected the fact that the early trials of tamoxifen in EBC allowed the inclusion of premenopausal women with ER ‘poor’ (ER-) tumors, and premenopausal women are more likely to have ER disease than postmenopausal women. Further experience has shown that tamoxifen is equally effective in both premenopausal (<50 years of age) and postmenopausal (≥50 years of age) women; for example, the 2005 Oxford overview showed that, in women with ER+ or ER-unknown EBC, approximately 5 years of tamoxifen use is associated with an absolute reduction of tumor recurrence of 9.7% (2p < 0.00001) in women under 50 years of age (premenopausal) compared with 12.3% (2p < 0.00001) in women aged 50 years or more (postmenopausal), at 5 years [14]. Overall, approximately 5 years of tamoxifen therapy almost halves the annual tumor recurrence rate and reduces breast cancer mortality by approximately a third (compared with no treatment), largely irrespective of age [14]. In addition, 5 years of tamoxifen decreases the incidence of contralateral breast cancer by approximately a third [14].

Generally, tamoxifen is well tolerated and the most common associated side effect is hot flashes. Since it has an estrogenic effect on bone, it does not lead to reduced bone density. However, there are two potentially serious side effects associated with tamoxifen. First, tamoxifen is associated with an increase in the incidence of endometrial cancer, owing to the fact that it stimulates the endometrium through its estrogenic activity. The risk of endometrial cancer is similar in both pre- and post-menopausal women but increases with increasing tamoxifen duration [15]. Second, tamoxifen is associated with an increase in the risk of thromboembolism and its use is contraindicated in women with a history of pulmonary embolism, deep vein thrombosis or cerebrovascular thrombosis.

The usual duration of tamoxifen treatment is 5 years, based on studies that compared 5 years with only 1 or 2 years of therapy. The
2005 Oxford overview confirmed that 5 years of tamoxifen treatment is superior to only 1 or 2 years of tamoxifen in reducing both breast cancer recurrence (2p < 0.00001) and mortality (2p = 0.0001) in women with EBC [14]. Age and menopausal status were not analyzed separately and 5 years of tamoxifen is the standard AET for premenopausal women and remains a standard of AET for postmenopausal women.

Several studies have addressed the question regarding the consequences of taking tamoxifen for longer than 5 years. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial, involving 1172 women with ER+ node-negative EBC did not show any additional benefit in women receiving 10 years as opposed to 5 years of tamoxifen, regardless of age [16]. Several other large studies are still in progress. To date, the Adjuvant Tamoxifen Treatment Offer More (aTTom) trial, involving approximately 7000 women with node-positive or node-negative EBC, has not demonstrated any significant difference in the risk of breast cancer recurrence for 10 versus 5 years of tamoxifen treatment, but has shown a small increase in the incidence of endometrial cancer in those receiving longer tamoxifen therapy [17]. On the other hand, a preliminary report of the Adjuvant Tamoxifen Longer Against Shorter (ATLAS) trial, which has enrolled over 11,000 women with node-positive or node-negative EBC, has revealed a significant reduction in breast cancer recurrence and a nonsignificant trend to reduced breast cancer mortality for those women who received more than 5 years of tamoxifen [101]. The main difference between these two studies was that only 39% of women in the aTTom trial were ER+ and in 61%, ER status was unknown, while in the ATLAS trial, most women were ER+ as this was an eligibility criterion for the trial. The meta-analysis of these trials, which is being performed by the EBCTCG, is eagerly awaited, but until these results become available, 10 years of tamoxifen should not be prescribed outside of a clinical trial.

For women with a low risk of recurrence of their breast cancer, that is, those with a small, low-grade and node-negative HR+ EBC, either no AET or tamoxifen alone for 5 years remain appropriate therapeutic options. However, many premenopausal women will also receive adjuvant chemotherapy. Although the 2005 overview from the EBCTCG [14] demonstrated that the benefits of tamoxifen are largely independent of age and chemotherapy, the benefits of tamoxifen following chemotherapy are less clear as the 2005 overview only included small numbers of women that had received chemotherapy and/or tamoxifen, and even fewer women were known to be HR+. Nevertheless, several studies have now demonstrated a benefit for tamoxifen in premenopausal women with HR+ EBC who have also received chemotherapy, including the National Cancer Institute of Canada (NCIC) MA.12 trial [18], the International Breast Cancer Study Group (IBCSG) 13–93 trial [19] and the Intergroup (INT)-0102 trial [20]. Therefore, tamoxifen is now considered the standard of care for premenopausal women with HR+ EBC who have received adjuvant chemotherapy.

**Effects of cytotoxic chemotherapy on ovarian function**

In premenopausal women with EBC, adjuvant chemotherapy often induces either temporary or permanent suppression of ovarian function. The likelihood of this is related to a number of factors, including the age of the woman, and the type, dose and duration of the chemotherapy [21]. Overall, less than half of women aged younger than 40 years will become permanently menopausal after chemotherapy, whereas the majority of women aged 40 years or older will become permanently menopausal. It may be that younger women, who are less likely to become permanently menopausal after chemotherapy, may benefit most from the addition of AET. In an analysis of 314 young women (<35 years of age) from 3700 women from a series of IBCSG trials of premenopausal or perimenopausal women receiving a variety of cyclophosphamide, methotrexate and fluorouracil (CMF)-based chemotherapy regimens, the young women with HR+ disease had worse outcomes than those with HR- disease. By contrast, the disease-free survival (DFS) in older women was similar whether they had HR+ or HR- tumors. Of note, in a landmark analysis involving 1883 women, the difference in outcomes between the different age groups was most evident in women with HR+ tumors who did not achieve amenorrhea [22]. It should be noted that women in this study did not receive tamoxifen and only a few had undergone ovarian ablation (OA).

The reported incidence of amenorrhea after different chemotherapy regimens ranges from approximately 40% with Adriamycin® (doxorubicin) and cyclophosphamide with or without paclitaxel, to almost 70% with oral (‘classical’) CMF [23–25]. It is not known what proportion of the benefit of chemotherapy in premenopausal women relates to the induction of premature
menopause (i.e., an endocrine effect) and what proportion relates to its cytotoxic effect, although a dual effect seems likely. It is possible that the relative proportion of endocrine to cytotoxic effects varies depending on the age of the premenopausal woman, but there are no data regarding this issue.

**Ovarian function suppression**

**Methods of ovarian function suppression**

Ovarian function suppression can be achieved by several different methods including surgery, radiotherapy and pharmacological methods. OA by the surgical removal of the ovaries – that is, bilateral oophorectomy – results in an immediate and permanent reduction in serum estrogen levels to those of menopausal levels. Besides the benefits in terms of inhibiting breast cancer growth, oophorectomy has a number of potential negative effects, including permanent infertilitiy, an increased risk of osteoporosis and other effects of menopause including hot flashes, vaginal dryness, weight gain and an increased risk of heart disease [23–26]. For women with BRCA1 or BRCA2 mutations, bilateral salpingo-oophorectomy has the added advantage of reducing the risk of ovarian and fallopian tube cancer [27]. Therefore, salpingo-oophorectomy is preferable to ovarian irradiation in these women.

Radiotherapy has been used as an alternative method of OA for more than 50 years. Various dosing algorithms are utilized ranging from 4.5 Gy in a single fraction to 10–20 Gy in five to six fractions. Radiotherapy avoids the need for surgery but may be less efficacious in permanently ablating ovarian function and it generally takes several months to induce a menopause [28]. However, if the menopausal state is achieved, it is likely to be permanent and carries all of the potential long-term effects of oophorectomy.

Pharmacological therapy using LHRH agonists, such as goserelin, leuprolide and triptorelin, can also reduce estrogen levels to menopausal concentrations. LHRH agonists act by binding to pituitary gonadotrophin-releasing hormone receptors causing downregulation of the receptors and reduced release of luteinizing hormone and follicle-stimulating hormone. In turn, this reduces estrogen production and circulating estrogen levels usually fall to menopausal levels within several weeks of commencing an LHRH agonist, although it may take longer [29]. The advantage of this approach is that it is potentially reversible. However, the optimal duration of OFS in premenopausal women with EBC remains unknown and there is a potential concern that temporary OFS with an LHRH agonist may not be as effective as permanent OFS in reducing the risk of recurrent breast cancer.

Ovarian function suppression, using any of the above methods, has been employed as an alternative to chemotherapy or after chemotherapy for women that remain premenopausal, either alone or combined with tamoxifen.

**Ovarian function suppression as adjuvant therapy in premenopausal women with early breast cancer**

The 1996 EBCCTCG 15-year overview of OA included 12 of the 13 studies that assessed OA induced by radiotherapy or surgery, but not by pharmacological means [30]. All 2102 women included in the overview were younger than 50 years of age, but premenopausal status was not always confirmed and ER status was not known for all of the cases. In those undergoing OA, a highly significant improvement was observed in overall survival (OS) at 15 years (52.4 vs 46.1%; 2p = 0.001) and recurrence-free survival was also significantly improved (45.0 vs 39.0%; 2p = 0.0007). The benefits were observed in women with node-positive and also those with node-negative EBC. Generally, oophorectomy has now been replaced with medical endocrine therapies. However, there is still a potential role for oophorectomy (or OFS by radiotherapy) in premenopausal women who retain ovarian function after adjuvant chemotherapy.

Love et al. compared oophorectomy plus tamoxifen with observation in 709 premenopausal Chinese and Vietnamese women with EBC and found a 5-year DFS rate of 75% with oophorectomy plus tamoxifen compared with 58% in the observation arm (p = 0.0003) [31]. Similarly, OS was 78% in the oophorectomy plus tamoxifen arm compared with 70% in the observation arm (p = 0.041), but the benefit was restricted to the women with ER+ tumors. These data support a role for OA as monotherapy or in combination with tamoxifen in premenopausal women with HR+ EBC, although the latter is more commonly practiced today.

**Ovarian function suppression versus cytotoxic chemotherapy**

Several studies have compared the efficacy of OFS with CMF-based chemotherapy in premenopausal women with HR+ EBC [Table 1]. Overall, no substantial difference in outcomes was demonstrated and this was confirmed in a recent overview by the LHRH-Agonists in Early Breast Cancer Overview Group [32].
The Zoladex Early Breast Cancer Research Association (ZEBRA) trial, involving 1614 premenopausal women with node-positive EBC, randomized women to either goserelin for 2 years or six cycles of CMF chemotherapy [12]. At 6 years, the DFS for those that received goserelin and those that received CMF were equivalent in HR+ women, but in the women with HR disease that received goserelin, DFS was found to be inferior. An updated analysis of this trial has shown a noninferiority of goserelin for OS in those women with HR disease [33].

Thomson et al. randomized 332 premenopausal women with node-positive, HR+ EBC to either OFS or CMF chemotherapy [34]. At a median follow-up of 10.7 years, there was no significant difference in OS between the two arms. However, in women with tumors with ER concentrations of 20 fmol/mg protein or more (i.e., ER+), there was a trend to greater benefit with OFS, while in those with tumors with ER concentrations of less than 20 fmol/mg protein (i.e., ER-), a trend to greater benefit with CMF was observed.

The Austrian Breast and Colorectal Cancer Study Group (ABCSG) 5 trial compared tamoxifen plus goserelin with CMF chemotherapy in premenopausal women with HR+ EBC and demonstrated improved relapse-free survival with the endocrine therapy [35]. Several other studies have compared an LHRH agonist with CMF [36], OFS plus tamoxifen with CMF or OA by radiotherapy with CMF and found no significant differences between the treatments. These data suggest that OFS is at least equivalent to CMF as an adjuvant therapy in premenopausal women with HR+ EBC. However, it should be noted that there are no data comparing OFS with more modern chemotherapy regimens such as anthracycline and/or taxane-based regimens.

**Ovarian function suppression after cytotoxic chemotherapy**

For women who retain their ovarian function after cytotoxic chemotherapy, it is unclear whether there is an additional benefit from subsequent OFS. The overview by the LHRH-Agonist in Early Breast Cancer Overview Group did show a benefit from the addition of LHRH agonists when used after chemotherapy, either alone or with tamoxifen, in women aged 40 years or less — that is, those who are less likely to be menopausal after chemotherapy [32]. However, no trials included in this overview assessed LHRH agonists versus chemotherapy with tamoxifen in both arms.

Arriagada et al. randomized 926 premenopausal women who had received chemotherapy to OFS (with an LHRH agonist or radiotherapy) or to no further treatment [39]. A total of 63% of these women had HR disease and 77% had received anthracycline-based chemotherapy. DFS at 10 years was identical in both arms, but women aged younger than 40 years who received OFS after chemotherapy had a significantly decreased risk of recurrence.

The IBCSG VIII trial compared chemotherapy plus OFS with either modality alone in 1063 premenopausal women with node-negative EBC [40]. Women were randomized to goserelin for 24 months, six cycles of ‘classical’ CMF or six cycles of ‘classical’ CMF followed by goserelin for 18 months. Overall, at 7 years of follow-up, there was no significant difference in DFS. However, in a subset analysis, women younger than 39 years of age with ER+ EBC had better DFS with CMF followed by goserelin (p = 0.05) than with CMF or goserelin alone, which produced similar effects.

The INT-0101 trial examined the role of OFS after cyclophosphamide, Adriamycin and fluorouracil (CAF) chemotherapy [41]. A total of 1503 premenopausal women with node-positive, HR+ EBC were randomized to either CAF alone, CAF followed by 5 years of goserelin (CAF-Z) or CAF followed by 5 years of goserelin plus tamoxifen (CAF-ZT). Those randomized to CAF-ZT had a significantly improved time to relapse and improved DFS compared with those who received CAF-Z, but the outcomes were similar for women who were randomized to CAF or CAF-Z. Survival at 9 years was similar in all three groups. A subgroup analysis suggested an advantage for the addition of goserelin to CAF in women of less than 40 years of age.

The Zoladex In Premenopausal Patients (ZIPP) trial involved a combined analysis of four randomized trials using a core protocol [42]. A total of 2710 women were randomized into a two by two factorial trial, based on goserelin and tamoxifen after surgery, radiotherapy and/or chemotherapy. The analysis showed significant improvements in both event-free survival and OS for those receiving goserelin compared with those who did not receive goserelin. The hazard ratios for reduction in event-free survival and OS were similar for those women who received tamoxifen alone, goserelin alone or tamoxifen plus goserelin after radiation therapy and/or chemotherapy for EBC.

Studies directly addressing the role of OFS following chemotherapy with tamoxifen or aromatase inhibitors (AIs) in premenopausal women are ongoing and are discussed below.


Aromatase inhibitors

The AIs reduce estrogen production by inhibiting the aromatase enzyme, which is located in both normal peripheral tissues and in breast cancers. In women with residual ovarian function, AIs are contraindicated since they can trigger a reflex increase in gonadotrophins, thus, stimulating ovarian production of estrogens as well as stimulating estrogen-dependent tumor cells. To overcome this problem, AIs have been combined with LHRH agonists for use in premenopausal women.

Early studies, involving premenopausal women with MBC who were treated with an LHRH agonist and the second-generation AI formestane, showed significantly greater suppression of circulating estrogens with formestane plus the LHRH agonist than with the LHRH agonist alone [43,44].

A study in healthy premenopausal volunteers showed that the administration of exemestane plus the LHRH agonist triptorelin resulted in significantly greater suppression of plasma estrogen levels compared with triptorelin plus placebo [45].

Another small study assessed the combination of goserelin plus anastrozole in 16 premenopausal women with metastatic or locally advanced breast cancer, all of whom had previously responded to treatment with goserelin plus tamoxifen. This study showed an objective response or durable stable disease in 75% of the women [46].

More recently, the ABCSG 12 trial randomized 1803 premenopausal women with endocrine-responsive EBC to goserelin and tamoxifen or goserelin and anastrozole (with or without zoledronic acid). This study showed no significant difference in DFS between the tamoxifen and anastrozole groups, although the addition of zoledronic acid appeared to improve DFS [47]. Therefore, until further clinical evidence of benefit is available, the combination of an AI plus an LHRH agonist as AET should be considered to be experimental. Nevertheless, it may be reasonable to consider an AI plus OFS in premenopausal women who are intolerant of, or who have a contraindication to, tamoxifen, such as those with a history of thrombosis.

Other selective estrogen receptor downregulators

No data on other SERMs, (e.g., raloxifene and toremifene) or selective ER downregulators (e.g., fulvestrant) as AETs are available in premenopausal women.

Table 1. Randomized trials of adjuvant ovarian ablation/ovarian function suppression versus or following chemotherapy in premenopausal women with early breast cancer.

| Trial | Patients (n) | Treatment | Outcome | Ref. |
|-------|--------------|-----------|---------|------|
| ZEBRA | 1640         | Z for 2 years vs 6c CMF | No difference in DFS in HR+ women CMF improved DFS in HR- women | [12] |
| Thomson et al. | 332 | OA vs 6–8c CMF | No difference in EFS or OS | [34] |
| ABCSG 5 | 1034 | Z for 3 years plus T for 5 years vs 6c CMF | Improved RFS with Z plus T | [35] |
| TABLE | 600 | Leuprorein for 2 years vs 6c CMF | No difference in DFS or OS | [36] |
| GROCTA 02 | 244 | Z plus T for 5 years vs 6c CMF | No difference in DFS or OS | [37] |
| Scandinavian | 732 | OA (RT) vs 9c CMF | No difference in DFS or OS | [38] |
| IBCSG VIII | 1063 | Z for 2 years vs 6c CMF vs CMF then Z for 18 months | No difference in DFS in HR+ women DFS better with CMF in HR- women | [40] |

Ovarian suppression after chemotherapy

Arriagada et al. | 926 (63% HR+) | Chemotherapy (77% anthracycline) followed by RT or triptorelin vs observation | No difference in DFS or OS | [39] |
| INT-0101 | 1503 | CAF vs CAF, followed by Z vs CAF, followed by Z plus T | No difference in OS DFS in women <40 years of age improved with Z | [41] |

ABCWG 5: Austrian Breast and Colorectal Cancer Study Group 5; c: Cycles; CAF: Cyclophosphamide, Adriamycin (doxorubicin) and fluorouracil; CMF: Cyclophosphamide, methotrexate and fluorouracil; DFS: Disease-free survival; EFS: Event-free survival; GROCTA 02: The Italian Breast Cancer Adjuvant Study Group 02 trial; HR: Hormone receptor; IBCSG VIII: International Breast Cancer Study Group VIII trial; INT-0101: Intergroup 0101 trial; OA: Ovarian ablation; OFS: Ovarian function suppression; OS: Overall survival; RFS: Relapse-free survival; RT: Irradiation; T: Tamoxifen; TABLE: Takeda Adjuvant Breast Cancer Study with Leuprorelin Acetate; Z: Zoladex® (goserelin); ZEBRA: Zoladex Early Breast Cancer Research Association.

Other endocrine therapies for premenopausal breast cancer

The AIs reduce estrogen production by inhibiting the aromatase enzyme, which is located in both normal peripheral tissues and in breast cancers. In women with residual ovarian function, AIs are contraindicated since they can trigger a reflex increase in gonadotrophins, thus, stimulating ovarian production of estrogens as well as stimulating estrogen-dependent tumor cells. To overcome this problem, AIs have been combined with LHRH agonists for use in premenopausal women.

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The future of adjuvant endocrine therapy in premenopausal women with early breast cancer

The optimal AET for premenopausal women with HR+ EBC remains to be established. There are several large international studies in progress that should clarify the role of OFS in premenopausal women with HR+ EBC, as well as the optimal choice of endocrine therapy. The Suppression of Ovarian Function Trial (SOFT) is a three-arm study of OFS plus tamoxifen or exemestane, or tamoxifen alone and after surgery, or surgery followed by chemotherapy in premenopausal women with HR+ EBC. A second study, the Tamoxifen and Exemestane Trial (TEXT) is examining OFS plus tamoxifen or exemestane, with or without adjuvant chemotherapy. A third trial, the Premenopausal Endocrine Responsive Trial (PERCHE) examined OFS plus tamoxifen or exemestane with chemotherapy followed by OFS plus tamoxifen or exemestane, but closed early owing to poor accrual [48]. Unfortunately, there have been no trials investigating OFS with or without tamoxifen, as all the trials have been of tamoxifen with or without OFS.

Tailoring therapy

The development of predictive assays such as the Oncotype DX® assay (Genomic Health, CA, USA), which evaluates gene expression in tumors in order to calculate a recurrence score, may lead to more tailored adjuvant therapies in EBC. The Oncotype DX assay evaluates the mRNA expression of a panel of 21 genes and has been validated from tissue banked from two NSABP trials evaluating the role of tamoxifen and chemotherapy in women with node-negative HR+ EBC. The results suggest that women with a low recurrence score benefit from tamoxifen but benefit very little from chemotherapy, while those with a high recurrence score gain more benefit from chemotherapy than from tamoxifen. The Trial Assigning Individualized Options for Treatment (Rx) (TAILORx), which is still accruing, uses the Oncotype DX assay to assign both pre- and post-menopausal women with HR+ EBC to a low-risk group receiving AET alone, a high-risk group receiving chemotherapy followed by AET and an intermediate group, which will be randomized to AET with or without chemotherapy. Results of this study are eagerly awaited.

It is possible that pharmacogenetic assays may influence the selection of an AET in the future. Early work with tamoxifen suggests that response may be influenced by single nucleotide polymorphisms in the CYP2D6 gene. CYP2D6 is an enzyme of the cytochrome p450 family and is responsible for the conversion of tamoxifen to its active metabolite, endoxifene. Women with homozygous CYP2D6 variants may have decreased CYP2D6 enzyme activity, leading to lower levels of endoxifene [49]. A recent retrospective analysis of the outcomes of women receiving adjuvant tamoxifen for EBC according to CYP2D6 status showed better outcomes in those who were extensive metabolizers of tamoxifen compared with those who were extensive/intermediate metabolizers and those who were poor metabolizers [50]. However, if these findings are confirmed, and if tamoxifen usage were restricted to those women with an intact CYP2D6 system, this would make tamoxifen appear more effective.

Adjuvant endocrine therapy for postmenopausal women with early breast cancer

Many postmenopausal women with HR+ EBC with poor prognostic features, especially lymph node involvement, receive adjuvant chemotherapy as well as AET. Since ovarian estrogen production has ceased in postmenopausal women, the action of chemotherapy in this group is purely cytotoxic and does not include a possible indirect endocrine effect, as may occur in premenopausal women.

Tamoxifen

Tamoxifen is effective in both pre- and post-menopausal women with HR+ EBC. As stated previously, the 2005 EBCCTCG overview has shown that approximately 5 years of tamoxifen almost halves (41% reduction) the annual tumor recurrence rate and reduces breast cancer mortality by approximately a third (34% reduction) compared with no treatment, largely irrespective of age [14]. Moreover, the benefits of 5 years of tamoxifen appear to be long lasting and extend out to at least 15 years. Historically, tamoxifen has been the ‘gold standard’ AET for postmenopausal women. Tamoxifen is usually administered after any chemotherapy and/or radiotherapy has been completed, based on preclinical data that suggest that the addition of tamoxifen to cancer cell lines that have been treated with chemotherapy interferes with the cytotoxicity of the chemotherapy. Recently, the timing of tamoxifen therapy, that is, sequential versus concurrent tamoxifen administration with chemotherapy, has been tested in a clinical trial of 1558 postmenopausal women with node-positive, HR+ EBC receiving...
Aromatase inhibitors have been compared with tamoxifen in multiple trials with different designs. First, there are the ‘up front’ trials of AIs as initial therapy, in comparison with tamoxifen. Examples of these trials include the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial [52], which compared 5 years of anastrozole with 5 years of tamoxifen, the Breast International Group (BIG) 1–98 trial, which, in the monotherapy arms, compared 5 years of letrozole with 5 years of tamoxifen therapy [53], and the Tamoxifen and Exemestane Adjuvant Multicenter (TEAM) trial, which compared 5 years of exemestane with approximately 2.5 years of tamoxifen, followed by approximately 2.5 years of exemestane treatment [54]. Second, there have been the ‘switching’ trials, where, in women who have undergone 2–3 years of tamoxifen therapy, half are switched to an AI and the other half remain on tamoxifen for a further 2–3 years. Examples of these trials are the Intergroup Exemestane Study (IES), which randomized women who had received 2–3 years of tamoxifen to a further 2–3 years of tamoxifen or exemestane treatment [55], the Italian Tamoxifen Anastrozole (ITA) trial, which compared 5 years of tamoxifen with 2–3 years of tamoxifen followed by 2–3 years of anastrozole [56], the ABCSG 8 trial [57] and the Arimidex–Nolvadex (ARNO) 95 trial [58]. Both the ABCSG 8 and the ARNO 95 trials randomized women who had received 2 years of tamoxifen to either anastrozole or tamoxifen for a further 3 years.

Last, there have been trials of AIs as extended adjuvant therapy. The MA.17 trial randomized women who were free from recurrence after 5 years of tamoxifen treatment to letrozole or placebo for 5 years [59]. The ABCSG 6a trial randomized women who had received 5 years of tamoxifen (with or without aminoglutethimide) and who were free from recurrence to 3 years of anastrozole or no further treatment [60]. The NSABP B–33 trial compared 5 years of exemestane with 5 years of placebo in women who had received 5 years of tamoxifen [61]. In 2003, accrual to this trial was curtailed early after the release of the initial results of the MA.17 trial [59]. Each of these trials noted significant improvements in outcomes with the addition of an AI.

The design of some of the aforementioned trials allows comparisons to be made between different sequences of tamoxifen and AI administration. Initially, the BIG 1–98 trial was a two-arm trial of 5 years of letrozole versus 5 years of tamoxifen, but subsequently, two sequencing arms (2 years of tamoxifen followed by 3 years of letrozole and 2 years of letrozole followed by 3 years of tamoxifen) were added [55]. The design of the BIG 1–98 trial was planned to allow a

![Figure 1. Mechanism of action of the aromatase inhibitors.](image-url)
Optimal adjuvant endocrine therapy for early breast cancer – REVIEW

Comparison of the two sequencing arms. The TEAM trial [54] allows a comparison of tamoxifen therapy followed by exemestane treatment with exemestane alone, and the ABCSG 8 trial allows a comparison of tamoxifen followed by anastrozole with tamoxifen alone [57].

**Aromatase inhibitors versus tamoxifen**

A meta-analysis of randomized trials that compared AIs with tamoxifen, either as an ‘up front’ therapy or after 2–3 years of tamoxifen treatment, in EBC has been recently reported [62]. This meta-analysis showed that AIs, as ‘up front’ therapy, were associated with a statistically significant absolute reduction in breast cancer recurrence of 2.9% (2p < 0.00001) over tamoxifen and a non-significant absolute decrease in breast cancer mortality of 1.1% (2p = 0.1) over tamoxifen, at 5 years. This meta-analysis also found that, in women who were switched to an AI after 2–3 years of tamoxifen, the administration of an AI was associated with a statistically significant absolute reduction in recurrence of 3.1% (2p < 0.00001) over tamoxifen and a significant absolute decrease in breast cancer mortality of 0.7% (2p = 0.02) over tamoxifen, at 3 years. Therefore, the AIs are more effective than tamoxifen in EBC and should be considered as a standard of care, in addition to tamoxifen therapy.

**Sequential therapy**

Although both the ‘up front’ and ‘switching’ trials of AIs have demonstrated that AIs are more effective than tamoxifen, the sequencing trials have produced disparate results. The results of the BIG 1–98 trial indicated no significant difference in DFS with either tamoxifen or letrozole sequential treatment compared with 5 years of letrozole therapy [53], but a direct comparison of the two sequential arms was not made. The results of the TEAM trial indicated no significant differences in DFS or OS after 5 years of exemestane treatment compared with the sequence of tamoxifen followed by exemestane therapy [54]. The results of the ABCSG 8 trial indicated that switching from tamoxifen to anastrozole was associated with significant improvements in both relapse-free survival and OS [57]. To date, none of the ‘switching’ trials have shown superior results for the sequential treatment of tamoxifen followed by an AI, compared with 5 years of treatment with an AI alone. At best, the sequence of tamoxifen followed by an AI has not been demonstrated to be significantly inferior to 5 years of an AI, as in the TEAM trial [54]. Results of the BIG 1–98 trial show that the sequence of letrozole treatment followed by tamoxifen was not significantly inferior to 5 years of letrozole [53].

**Toxicities of the aromatase inhibitors**

Generally, the AIs are well tolerated. Overall, the incidence and severity of side effects from AIs are similar to, or possibly less than, those of tamoxifen, but the side effects are different. When anastrozole was compared with tamoxifen in the ATAC trial [63], hot flashes, vaginal bleeding, vaginal discharge, endometrial cancer, ischemic cerebrovascular events, venous thromboembolism and deep vein thrombosis were significantly less common with anastrozole than tamoxifen. On the other hand, arthralgia and fractures were significantly more common with anastrozole. Similarly, the BIG 1–98 trial noted that thromboembolic events, vaginal bleeding, hot flashes and night sweats were significantly more common in the tamoxifen arms than in the letrozole-alone arm [53]. Conversely, this trial noted that arthralgia, myalgia and hypercholesterolemia were significantly more common with letrozole than with tamoxifen.

Arthralgia is one of the most common side effects associated with the administration of an AI and occurred in 35% of women receiving anastrozole in the ATAC trial [63]. Administration of a NSAID and/or an analgesic may be helpful, but if the arthralgia is severe, the AI may have to be discontinued.
Since AIs may decrease bone density, it is important to monitor bone density in women receiving AIs. Bone density should be measured at the commencement of an AI therapy and annually thereafter, or less frequently if the woman’s bone density is normal. All women on an AI should take calcium and vitamin D replacements in order to minimize bone loss. If a woman on an AI therapy develops a bone density in the osteoporotic range, a careful decision must be made as to whether she should continue to receive the AI and go on to take an additional medication to improve bone density, such as a bisphosphonate, which have been demonstrated to be effective in maintaining bone density in women receiving endocrine therapy for breast cancer [64], or whether she should switch to tamoxifen, which is known to improve bone density in postmenopausal women. This decision must take the risk of breast cancer recurrence into account, based on the known tumor prognostic factors.

Both the ATAC and the BIG 1–98 trials have shown that women receiving an AI had significantly higher cholesterol levels than women receiving tamoxifen [53,63]. This reflects a beneficial effect of tamoxifen in reducing cholesterol, rather than a detrimental effect of AIs increasing cholesterol levels. Despite this, there were no significant differences in the rates of myocardial infarction in women receiving anastrozole in the ATAC trial [65], nor in those receiving letrozole in the BIG 1–98 trial [53], compared with those receiving tamoxifen. Interestingly, a lipid substudy of the TEAM trial showed that exemestane had a neutral effect on total cholesterol and high-density lipoprotein concentrations [66]. If this is confirmed, this would appear to be a significant difference between exemestane, a steroidal AI, and anastrozole and letrozole, both nonsteroidal AIs.

**Potential differences in efficacy of the aromatase inhibitors**

There have been anecdotal reports of women with MBC who have failed one AI and subsequently responded to a different AI. However, this is rare. The chance of responding to a second AI after failure of the first may be greater if the AIs are of different types (i.e., type I vs type II inhibitors).

Very few trials have compared the different AIs in either EBC or MBC. However, the efficacy of estrogen suppression by letrozole and anastrozole was compared in 54 postmenopausal women with EBC, and letrozole was found to be more effective than anastrozole in suppressing oestradiol and estrone sulphate [67]. In addition, letrozole was compared with anastrozole as a second-line endocrine therapy in 713 women with HR+ or HR-unknown MBC [68]. Although letrozole therapy was associated with a significantly higher overall response rate (19.1 vs 12.3%; p = 0.013), there were no other significant differences in the rate of clinical benefit, time to treatment failure or OS.

Several trials comparing different AIs are in progress. The Femara Versus Anastrozole Clinical Evaluation (FACE) trial is a Phase III randomized trial, designed to compare the efficacy of letrozole versus anastrozole as AET in women with HR+, lymph node-positive EBC. The NCIC MA.27 trial is a trial directly comparing exemestane (a steroidal inhibitor) with anastrozole (a nonsteroidal inhibitor) in postmenopausal women with EBC. Both of the trials are yet to report their results.

**Optimal duration of adjuvant endocrine therapy in postmenopausal women**

We know that tamoxifen should be given for at least 5 years, unless there is a specific contraindication to this. The optimal duration of AI therapy remains unknown, although most of the ‘up front’ trials of AIs have used an AI for 5 years and thus, it is reasonable to follow this as a guide. Current trials, such as the Study of Letrozole Extension (SOLE) trial, are assessing whether more than 5 years of an AI may be more effective than 5 years of therapy [102]. It is also appropriate to investigate tamoxifen for 5 years followed by an AI for 5 years, especially for those women who are at a higher risk of relapse, such as those with nodal involvement at diagnosis.

**Sequencing of tamoxifen & aromatase inhibitors**

Currently, it remains difficult to ascertain the best use of AIs and tamoxifen in postmenopausal women with HR+ EBC. For those women who are at a low risk of relapse (i.e., those with small tumors that are strongly HR+ without lymph node involvement), initial therapy with tamoxifen remains a reasonable option. Such women may receive tamoxifen for 2–3 years and then switch to an AI, or receive 5 years of tamoxifen. Alternatively, such patients can receive 5 years of an AI as an alternative to tamoxifen.

For those with poor prognostic features, such as a large tumor with extensive lymph node involvement at diagnosis, it is preferable to start AET with an AI rather than tamoxifen, as AIs ‘up front’ have been demonstrated to be more...
Effective in reducing the risk of recurrence compared with tamoxifen, and also because the peak time for recurrence for women with ER+ EBC is approximately 2.5 years following primary therapy [69], although, with more modern and more effective treatments, it is probable that the peak of recurrences may well be later. Clearly, therapy needs to be individualized for each woman and other factors such as a past history of thromboembolism or the woman’s bone density will dictate whether an AI or tamoxifen should be used as initial therapy.

**Should all women with hormone receptor-positive early breast cancer receive adjuvant endocrine therapy?**

Both adjuvant chemotherapy and AET reduce the risk of recurrence in a proportional manner. Therefore, the women who gain the most benefit from adjuvant therapies are those with a higher risk of breast cancer recurrence. With any adjuvant therapy, a careful assessment of the potential benefits and the potential harms must be made. In women with a high risk of recurrence of their breast cancer, such as those with positive axillary lymph nodes at presentation, the potential benefit of AET significantly outweighs the potential for harm, but the situation is less clear for women with a low risk of recurrence. Given that the harms of AET are much less than from adjuvant chemotherapy, many oncologists advise the use of AET in most, if not nearly all, women with HR+ EBC. Supporting this, the latest St Gallen Consensus suggests AET for virtually any woman with HR+ EBC [70]. However, for those women at a low risk of recurrence of their breast cancer, an assessment and discussion with the women regarding the relative risks and benefits is clearly needed.

A suggested treatment algorithm for AET in both pre- and post-menopausal women with HR+ EBC is included in this review (see Table 2). This is only intended as a guide and was developed by the authors based on the data discussed herein, and it is not intended to represent a definitive consensus on AET treatment.

**Conclusions**

AET is an integral component in the adjuvant treatment of both pre- and post-menopausal women with HR+ EBC. In premenopausal women, tamoxifen remains the ‘gold standard’, with the role for OFS and other endocrine therapies remaining to be clarified. In postmenopausal women, both tamoxifen and AIs have clearly established roles as AET. Many details regarding scheduling, the duration of AET and the selection of endocrine therapy require optimization in order to maximize results and minimize toxicity.

The future holds the prospect of predictive tools to help with decisions regarding who to treat as well as, possibly, which agent, or agents, is the most appropriate as AET for an individual woman.

**Future perspective**

Although the use of AET in women with HR+ EBC has led to substantial reductions in both recurrence of and mortality from breast cancer, we need to look to the future and what it may hold.

**Adjuvant endocrine therapy for premenopausal women**

Tamoxifen remains the standard AET for premenopausal women with HR+ EBC. The trials that are in progress should reveal whether OFS adds additional benefit in those premenopausal women who retain ovarian function after chemotherapy. If this turns out to be the case, OFS, by surgery or other means, should be added to the available therapeutic options for these premenopausal women. In both pre- and postmenopausal women, current trials should tell us whether additional benefit can be expected from more than 5 years of tamoxifen therapy.

**Adjuvant endocrine therapy for postmenopausal women**

Tamoxifen has been the standard AET for postmenopausal women, but with the development of the AIs, both can now be considered appropriate options as AETs in this group. Outcomes can be improved by the sequencing of tamoxifen and the AIs, but optimal sequencing needs to be established. Similarly, we need to establish whether postmenopausal women should receive more than 5 years of AET, and if so, in what form. Possible approaches include 5 years of tamoxifen followed by 5 years of an AI, prolonging the duration of treatment with an AI after switching from tamoxifen after 2–3 years, or more than 5 years of an AI. Improved understanding of the mechanisms and management of toxicities associated with AIs, such as arthralgia, is also needed.

**Pharmacogenetics & predictive assays**

The relationship between CYP2D6 polymorphisms and clinical outcomes in women receiving tamoxifen for EBC is currently under investigation. If CYP2D6 status is confirmed to influence the metabolism of tamoxifen, then women should have their CYP2D6 status determined.
Table 2. Suggested treatment algorithm for endocrine-responsive early breast cancer.

| Tumor features | Low risk of recurrence | Intermediate risk of recurrence | Intermediate/high risk of recurrence |
|----------------|------------------------|---------------------------------|--------------------------------------|
| Size           | <1 cm                  | 1–2 cm                          | >2 cm                                |
| Grade          | Grade 1                | Grade 1–3                        | Grade 2–3                            |
| Nodal status   | LN−                    | LN−                             | LN+                                  |
| HER2 status    | HER2                   | HER2                            | HER2*                                |

**Treatment options for premenopausal women**

| Low risk of recurrence | Intermediate risk of recurrence | Intermediate/high risk of recurrence |
|------------------------|---------------------------------|--------------------------------------|
| No adjuvant therapy    | Tamoxifen for 5 years           | Chemotherapy followed by tamoxifen for 5 years |
| Tamoxifen for 5 years  | OFS plus tamoxifen for 5 years  | Chemotherapy followed by OFS plus tamoxifen for 5 years |
| OFS plus an AI for 5 years (if tamoxifen is contraindicated or not tolerated) | Chemotherapy followed by OFS plus an AI for 5 years (if tamoxifen is contraindicated or not tolerated) | Chemotherapy followed by OFS plus an AI for 5 years (if tamoxifen is contraindicated or not tolerated) |
|                          | Chemotherapy followed by tamoxifen for 5 years | Chemotherapy, then consider a clinical trial (e.g., SOFT/TEXT studies) |

**Treatment options for postmenopausal women**

| Low risk of recurrence | Intermediate risk of recurrence | Intermediate/high risk of recurrence |
|------------------------|---------------------------------|--------------------------------------|
| No systemic therapy    | An AI for 5 years               | Chemotherapy then AET for 5 years as per intermediate risk group options |
| Tamoxifen for 5 years  | Tamoxifen and an AI (‘switching’) for 5 years, in total | Chemotherapy then AET for up to 10 years: either tamoxifen for 5 years then an AI for 5 years or the reverse |
| An AI for 5 years      | Tamoxifen alone (if an AI is contraindicated or not tolerated) | Consider extending AI use beyond 5 years for women switching from tamoxifen to an AI after less than 5 years |
| Tamoxifen/AI (‘switching’) for 5 years, in total | Chemotherapy followed by AET with tamoxifen and/or an AI for 5 years, in total | AET for up to 10 years, if unsuitable for chemotherapy |

The risk categories as listed above are not necessarily mutually exclusive. A woman may be allocated to a specific risk category on the basis of only one tumor feature (e.g., LN involvement). The choice of systemic therapy, specifically adjuvant endocrine therapy, requires consideration of the features of the breast cancer and individual patient factors including comorbidities and patient preferences. Treatment decisions must be individualized to each woman and this algorithm is intended as a guide only.

AET: Adjuvant endocrine therapy; AI: Aromatase inhibitor; LN: Lymph node; OFS: Ovarian function suppression; SOFT: Suppression of Ovarian Function Trial; TEXT: Tamoxifen and Exemestane Trial.
established prior to the commencement of tamoxifen, and its usage should be restricted to those with an intact CYP2D6 system. This will tailor the use of tamoxifen to those who stand to gain benefit.

Predictive assays such as the Oncotyple DX assay, which evaluates gene expression in tumors in order to calculate a recurrence score, may also lead to more tailored adjuvant therapies in EBC, averting the need for chemotherapy in some women. If methods of predicting sensitivity or resistance to one AET over another, for example, tamoxifen versus an AI, could be developed, then selection of an AET could be individualized for optimal benefit.

### Executive summary

**Adjuvant endocrine therapy is effective in women with hormone receptor-positive early breast cancer**

- Adjuvant endocrine therapy substantially reduces the risk of tumor recurrence and mortality in both pre- and post-menopausal women with hormone receptor-positive early breast cancer, but it is not effective in women with hormone receptor-negative early breast cancer.

**Adjuvant endocrine therapy in premenopausal women with hormone receptor-positive early breast cancer**

- Tamoxifen has been the standard adjuvant endocrine therapy for both pre- and post-menopausal women.
- While tamoxifen remains the standard adjuvant endocrine therapy in premenopausal women, current trials are evaluating the role of ovarian function suppression by luteinizing hormone-receptor agonists.
- Ovarian ablation, by oophorectomy or radiotherapy, remains an option for selected premenopausal women, usually in addition to tamoxifen treatment.

**Adjuvant endocrine therapy in postmenopausal women with hormone receptor-positive early breast cancer**

- Tamoxifen has been the standard adjuvant endocrine therapy for postmenopausal women.
- The aromatase inhibitors are now available and offer an alternative or an addition to tamoxifen therapy.
- The aromatase inhibitors are somewhat more effective than tamoxifen, but have different toxicities that may affect their suitability for individual women.
- Both tamoxifen and the aromatase inhibitors are standards of adjuvant endocrine therapy for postmenopausal women.
- The aromatase inhibitors are only indicated in postmenopausal women.

**Adjuvant endocrine therapy beyond 5 years in postmenopausal women**

- In postmenopausal women, prolonging adjuvant endocrine therapy by the sequencing of aromatase inhibitors and tamoxifen can further improve outcomes.
- Therefore, it is likely that adjuvant endocrine therapies will be used for longer durations in selected postmenopausal women.

**Role of pharmacogenetics**

- Some women lack the enzyme CYP2D6 that produces endoxifene, the active metabolite of tamoxifen, and preliminary reports suggest that outcomes with tamoxifen in early breast cancer may be suboptimal in those who lack CYP2D6.
- If this is confirmed, then restricting tamoxifen to those who possess an intact CYP2D6 system will lead to an apparent improvement in the efficacy of tamoxifen.

### Bibliography

Papers of special note have been highlighted as:

- of interest
- of considerable interest

1. Beatson GT: On the treatment of inoperable carcinoma of the mamma suggestions for a new method of treatment, with illustrative cases. *Lancet* 148, 104–107 (1896).

2. Beatson GT: On the treatment of inoperable carcinoma of the mamma: suggestions for a new method of treatment, with illustrative cases. *Lancet* 148, 162–165 (1896).

3. Love RJ, Philips J: Oophorectomy for breast cancer: history revisited. *J. Natl Cancer Inst.* 94, 1433–1434 (2002).

4. Nunn TW: On Cancer of the Breast. J & A Churchill, London, UK 71 (1882).

5. Schinzinger A: Ueber carcinoma mammae. 18th Congress of the German Society for Surgery. *Beilage zum Centralblatt fur Chirurgie* 16, 55–56 (1889) (Abstract).

6. Boyd S: On oophorectomy in cancer of the breast. *BMJ* 2, 1161-1167 (1900).
The most recent overview of adjuvant chemotherapy and adjuvant endocrine therapy in the management of early breast cancer by the Oxford Group.

7. Huggins C, Hodges CV: Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphates in metastatic carcinoma of the prostate. *Cancer Res.*, 1, 293–297 (1941).

8. Huggins C, Bergenshal GM: Inhibition of human mammary and prostatic cancers by adrenalectomy. *Cancer Res.*, 12, 134–141 (1952).

9. Luft R, Oliemcrna H: Experiences with hypophysectomy in man. *J. Neuroendocrin.*, 10, 301–316 (1953).

10. Jensen EV: Studies on growth phenomenon using tritium-labeled steroids. *Proceedings of the 4th International Congress of Biochemistry*. Vienna, Austria, 1–6 September (1958).

11. Horwitz KB, McGuire WL: Specific progesterone receptors in human breast cancer. *Steroids* 25, 497–505 (1975).

12. Jonat W, Kaufmann M, Sauerbrei W et al.: Goserelin versus cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy in premenopausal patients with node-positive breast cancer: the Zoladex Early Breast Cancer Research Association Study. *J. Clin. Oncol.* 20, 4628–4635 (2002).

13. Early Breast Cancer Trialists’ Collaborative Group: Effects of adjuvant tamoxifen and of cytotoxic chemotherapy on mortality in early breast cancer. An overview of 61 randomized trials among 28,896 women. *N. Engl. J. Med.* 319, 1681–1692 (1988).

14. Early Breast Cancer Trialists’ Collaborative Group (EBCTCG): Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 365, 1687–1717 (2005).

**The most recent overview of adjuvant chemotherapy and adjuvant endocrine therapy in the management of early breast cancer by the Oxford Group.**

15. Swedlow AJ, Jones ME: for the British Tamoxifen Second Cancer Study Group: Tamoxifen treatment for breast cancer and risk of endometrial cancer: a case-control study. *J. Natl Cancer Inst.* 97, 375–384 (2005).

16. Fisher B, Dignam J, Bryant J, Wolmark N: Five versus more than five years of tamoxifen for lymph node-negative breast cancer: updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. *J. Natl Cancer Inst.* 93, 684–690 (2001).

17. Gray RG, Rea DW, Handley K et al.: aTTom (Adjuvant Tamoxifen – To Offer More?): randomized trial of 10 versus 5 years of adjuvant tamoxifen among 6,934 women with estrogen receptor-positive (ER) or ER untested cancer – preliminary results. *J. Clin. Oncol.* 26, 15S (2008) (Abstract 515).

18. Bramwell VH, Pritchard KI, Tu D et al.: A randomized placebo-controlled study of tamoxifen after adjuvant chemotherapy in premenopausal women with early breast cancer (National Cancer Institute of Canada–Clinical Trials Group Trial, MA.12). *Ann. Oncol.* 21(2), 283–290 (2010).

19. International Breast Cancer Study Group: Tamoxifen after adjuvant chemotherapy for premenopausal patients with lymph node-positive breast cancer: International Breast Cancer Study Group trial 13–93. *J. Clin. Oncol.* 24, 1332–1341 (2006).

20. Hutchins LF, Green SJ, Ravdin PM et al.: Randomized, controlled trial of cyclophosphamide, methotrexate, and fluorouracil versus cyclophosphamide, doxorubicin, and fluorouracil with and without tamoxifen for high-risk, node-negative breast cancer: treatment risk of Intergroup protocol INT-0102. *J. Clin. Oncol.* 23, 8313–8321 (2005).

21. Petrek JA, Naughton MJ, Case LD et al.: Incidence, time course, and determinants of menstrual bleeding after breast cancer treatment: a prospective study. *J. Clin. Oncol.* 24, 1045–1051 (2006).

22. Abi S, Gelber S, Castiglione-Gertz M et al.: Is chemotherapy alone adequate for young women with oestrogen-receptor-positive breast cancer? *Lancet* 355, 1869–1874 (2000).

23. Bines J, Oleske DM, Cobleigh MA: Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer. *J. Clin. Oncol.* 14, 1718–1729 (1996).

24. Minton SE, Munster PN: Chemotherapy-induced amenorrhea and fertility in women undergoing adjuvant treatment for breast cancer. *Cancer Control* 9, 466–472 (2002).

25. Martin M, Pienkowski T, Mackey J et al.: Adjuvant doxorubicin for node-positive breast cancer. *N. Engl. J. Med.* 352, 2302–2313 (2005).

26. Shapiro CL, Recht A: Side effects of adjuvant treatment of breast cancer. *N. Engl. J. Med.* 344, 1997–2008 (2001).

27. Kauff ND, Domchek SM, Friebel TM et al.: Risk-reducing salpingo-oophorectomy for the prevention of *BRCA1* and *BRCA2*-associated breast and gynecologic cancer: a multicenter, prospective study. *J. Clin. Oncol.* 26, 1331–1337 (2008).

28. Hughes LL, Gray RJ, Solin LJ et al.: Efficacy of radiotherapy for ovarian ablation. Results of a breast intergroup study. *Cancer* 101, 969–972 (2004).

29. Kaufmann M, Jonat W, Klebeberg U et al.: Goserelin, a depot gonadotrophin-releasing hormone agonist in the treatment of premenopausal patients with metastatic breast cancer. *J. Clin. Oncol.* 7, 1113–1119 (1989).

30. Early Breast Cancer Trialists’ Collaborative Group: Ovarian ablation in early breast cancer: overview of the randomised trials. *Lancet* 348, 1189–1196 (1996).

**The 1996 Oxford overview of the utility of ovarian ablation or ovarian suppression in the management of 2102 premenopausal women with early breast cancer.**

31. Love RR, Duc NB, Allred DC et al.: Oophorectomy and tamoxifen adjuvant therapy in premenopausal Vietnamese and Chinese women with operable breast cancer. *J. Clin. Oncol.* 20, 2559–2566 (2002).

32. LHRH-Agonists in Early Breast Cancer Overview Group; Cuzick J, Abrasion L, Davidson N et al.: Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. *Lancet* 369, 1711–1723 (2007).

**Meta-analysis of ovarian function suppression with luteinizing hormone-releasing hormone agonists in 11,906 premenopausal women with early breast cancer.**

33. Kaufmann M, Jonat W, Blamey R et al.: Survival analyses from the ZEBRA study: Goserelin (ZoladexTM) versus CMF in premenopausal women with node-positive breast cancer. *Eur. J. Cancer* 39, 1711–1717 (2003).

34. Thomson CS, Twelves CJ, Mallon EA, Leake RE: for the Scottish Cancer Trials Breast Group and the Scottish Cancer Therapy Network: Adjuvant ovarian ablation vs CMF chemotherapy in premenopausal breast cancer patients: trial update and impact of immunohistochemical assessment of ER status. *Breast* 11, 419–429 (2002).

35. Jakess R, Hansmaninger H, Kubista E et al.: Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer. Austrian Breast and Colorectal Cancer Study Group Trial 5. *J. Clin. Oncol.* 20, 4621–4627 (2002).

36. Schmid P, Untch M, Wallwiener D et al.: Cyclophosphamide, methotrexate and fluorouracil (CMF) versus hormonal ablation with leuprolterel acetate as adjuvant treatment of node-positive, premenopausal
breast cancer patients; preliminary results of the TABLE-study (Takeda Adjuvant Breast Cancer Study With Leuprolrelin Acetate). *Anticancer Res.* 22, 2325–2332 (2002).

37. Boccadoro F, Rubagotti A, Amoroso D et al.: Cyclophosphamide, methotrexate, and fluorouracil versus tamoxifen plus ovarian suppression as adjuvant treatment of estrogen receptor-positive pre-/perimenopausal breast cancer patients: results of the Italian Breast Cancer Adjuvant Study Group 02 randomized trial. *J. Clin. Oncol.* 18, 2718–2727 (2000).

38. Ejlersen B, Mouridsen HT, Jensen MB et al.: Similar efficacy for ovarian ablation compared with cyclophosphamide, methotrexate, and fluorouracil: from a randomized comparison of premenopausal patients with node-positive, hormone receptor-positive breast cancer. *J. Clin. Oncol.* 24, 4956–4962 (2006).

- Randomized trial showing similar efficacy for ovarian ablation and chemotherapy with cyclophosphamide, methotrexate and fluorouracil in 762 premenopausal women with early breast cancer.

39. Arriagada R, Le MG, Spielmann M et al.: Randomized trial of adjuvant ovarian suppression in 926 premenopausal patients with early breast cancer treated with adjuvant chemotherapy. *Ann. Oncol.* 16, 389–396 (2005).

40. International Breast Cancer Study Group (IBCSG): Adjuvant chemotherapy followed by goserelin versus either modality alone for premenopausal lymph node-negative breast cancer: a randomized trial. *J. Natl Cancer Inst.* 95, 1833–1846 (2003).

41. Davidson NE, O’Neill AM, Vulok AM et al.: Chemohormonal therapy for premenopausal women with axillary lymph node-negative, steroid hormone receptor-positive breast cancer: results from INT 0101 (ES188). *J. Clin. Oncol.* 23, 5973–5982 (2005).

42. Baum M, Hackshaw A, Houghton J et al.: Adjuvant goserelin in pre-menopausal patients with early breast cancer: results from the ZIPP study. *Eur. J. Cancer* 42, 895–904 (2006).

43. Dowsett M, Stein RC, Coombes RC: Aromatization inhibition alone or in combination with GnRH agonists for the treatment of premenopausal breast cancer patients. *Steroid Biochem. Mol. Biol.* 43, 155–159 (1992).

44. Celio L, Martinetti A, Ferrari L et al.: Premenopausal breast cancer patients treated with a gonadotropin-releasing hormone analog alone or in combination with an aromatase inhibitor: a comparative endocrine study. *Anticancer Res.* 19, 2261–2268 (1999).

45. Jannuzzo MG, Di Salle E, Spinelli R, Pirota N, Buchan P, Bello A: Estrogen suppression in premenopausal women following 8 weeks of treatment with exemestane and triptorelin versus triptorelin alone. *Breast Cancer Res. Treat.* 113, 491–499 (2009).

46. Forward DP, Cheung KL, Jackson L, Robertson JFR: Clinical and endocrine data for goserelin plus anastrozole as second-line therapy for premenopausal advanced breast cancer. *Br. J. Cancer* 90, 590–594 (2004).

47. Grant M, Mlinertisch B, Schippinger W et al.: Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N. Engl. J. Med.* 360, 679–691 (2009).

- Randomized trial of adjuvant endocrine therapy with or without zoledronic acid in 1802 premenopausal women with early breast cancer. This trial showed that zoledronic acid improved disease-free survival.

48. Francis P, Fleming G, Nasi ML, Pagani O, Perez E, Welley B: Tailored treatment investigations for premenopausal women with endocrine responsive (ER+ and/or PGR+) breast cancer: the SOFT, TEXT and Perche Trials. *Breast 12* (Suppl. 1), S44 (2003) (Abstract P104).

49. Goetz MP, Rae JM, Suman VJ et al.: Pharmacogenomics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. *J. Clin. Oncol.* 23, 9312–9318 (2005).

50. Albain KS, Barlow WE, Ravdin PM et al.: Adjuvant chemotherapy and timing of tamoxifen in premenopausal patients with endocrine-responsive, node-positive breast cancer: a Phase 3, open-label, randomised controlled trial. *Lancet* 374, 2055–2063 (2009).

51. Schroth W, Goetz MP, Hamann U et al.: Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. *JAMA* 302, 1429–1436 (2009).

- Randomized clinical trial that showed a trend to improved disease-free survival for tamoxifen given sequentially after chemotherapy, as opposed to concurrently with chemotherapy.

52. The Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists’ Group: Effects of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer. *Lancet* 369, 45–53 (2008).

- Randomized trial of anastrozole versus tamoxifen as ‘up front’ adjuvant endocrine therapy in 6241 postmenopausal women with early breast cancer.
61. Mamounas EP, Jeong J-H, Wickerham DL et al.: Benefit from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: intention-to-treat analysis of the national surgical adjuvant breast and bowel project B-33 trial. J. Clin. Oncol. 26, 1965–1971 (2008).

62. Dowsett M, Cuzick J, Ingle J et al.: Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen versus tamoxifen. J. Clin. Oncol. 28, 509–518 (2010).

Recent meta-analysis of aromatase inhibitors versus tamoxifen in nearly 19,000 postmenopausal women with early breast cancer.

63. ATAC Trialists’ Group: Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years’ adjuvant treatment for breast cancer. Lancet 365, 60–62 (2005).

64. Winer EP, Hudis C, Burstein HJ et al.: American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004. J. Clin. Oncol. 23, 619–629 (2005).

65. The Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists’ Group: Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: long-term safety analysis of the ATAC trial. Lancet Oncol. 7, 633–643 (2006).

66. Markopoulos C, Polyehronis A, Zobolas V et al.: The effect of exemestane on the lipidemic profile of postmenopausal early breast cancer patients: preliminary results of the TEAM Greek sub-study. Breast Cancer Res. Treat. 93, 61–66 (2005).

67. Dixon JM, Renshaw L, Young O et al.: Letrozole suppresses plasma estradiol and estrone sulphate more completely than anastrozole in postmenopausal women with breast cancer. J. Clin. Oncol. 26, 1671–1676 (2008).

68. Rose C, Vtoraya O, Pluzanska A et al.: An open randomised trial of second-line endocrine therapy in advanced breast cancer. Comparison of the aromatase inhibitors letrozole and anastrozole. Eur. J. Cancer 39, 2318–2327 (2003).

69. Saphner T, Tormey DC, Gray R: Annual hazard rates of recurrence for breast cancer after primary therapy. J. Clin. Oncol. 14, 2738–2746 (1996).

A paper published in 1996 that provides very interesting data on relapse in early breast cancer.

70. Goldhirsch A, Ingle JN, Gelber RD et al.: Threshold for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009. Ann. Oncol. 20, 1319–1329 (2009).

The latest (2009) St Gallen Consensus on the primary therapy of early breast cancer.

Websites

101. Peto R, Davies C; on behalf of the ATLAS Collaboration: ATLAS (Adjuvant Tamoxifen, Longer Against Shorter): International randomized trial of 10 versus 5 years of adjuvant tamoxifen among 11,500 women – preliminary results www.abstracts2view.com/sabcs07/view.php?nu=SABCS07L_1167

102. International Breast Cancer Study Group: IBCSG 35-07 (SOLE) www.ibcsg.org/Public/Health_Professionals/Open_Trials/IBCSG_35-07/Pages/IBCSG35-07(SOLE).aspx#resultspublications