Review

Treatment of breast cancer in young women

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Practice Points

- Young women with breast cancer have a greater risk of recurrence and death than older women in general.
- Clear margins and boost irradiation after lumpectomy are important to minimize the higher risk of local recurrence associated with young age.
- Chemotherapy can reduce risk of recurrence of early-stage cancers by direct cytotoxicity and by reducing ovarian function.
- Endocrine therapy is beneficial for young women with hormone receptor-positive disease; however, adherence may be an issue.
- At diagnosis, young women should be asked about their desire for future childbearing and referred for fertility preservation as appropriate prior to systemic therapy.
- Genetic testing (e.g., BRCA1 and BRCA2 testing) should be considered for all women diagnosed under 40 years of age, and early referrals are important if results could impact surgical decisions.
- Psychosocial support is important for young patients, some of whom are more distressed than older breast cancer patients.

SUMMARY Caring for young women with breast cancer poses unique challenges to clinicians. Early-stage cancers are more likely to be more aggressive and recur in younger women, so aggressive treatment is often indicated. However, the disease and treatments a woman receives have the potential to be highly disruptive to functioning in many realms (e.g., home, work and school). Consideration of the unique issues facing young women early in the course of their care, including not only reducing risk of cancer recurrence and death, but also fertility, genetic and psychosocial concerns, is warranted for optimal care of young women with breast cancer.

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Breast cancer is rare in young women, but there are still more than 14,000 women diagnosed with either invasive or noninvasive breast cancer before the age of 45 years annually in the USA alone [1]. Although rates of breast cancer in the USA are decreasing in older women, rates of cancer in younger women appear stable. Breast cancer accounts for the majority of cancer-related deaths in women under 40 years of age, and prognoses of invasive cancers are worse in younger women [2]. Adverse prognostic features may be partly biological and partly related to delays in diagnosis [3]. Benign conditions such as cysts and fibroadenomas comprise most of the breast masses found by young women and their doctors. There is no effective screening program for young women, and work-up for breast abnormalities may be slower in this population due to lower pretest probability of cancer than in older women. Furthermore, high-density breast tissue limits the sensitivity of mammography in young women. Thus, on average, young women present with higher-stage disease than their older counterparts [4].

In addition, younger women are known to have more aggressive tumor types [5–7]. In a recent study of 212 women diagnosed at or under 35 years of age, 60% were found to have Her2/neu-positive or triple-negative cancers, and 65% were grade 3 [8]. The majority were also lymph-node positive. However, some studies have not shown higher rates of Her-2/neu overexpressing tumors in young women. For example, a population-based Korean registry study that included 1444 women aged less than 35 years and 8441 women aged 35–50 years revealed no association between Her2 and age, but women younger than 35 were more likely to have larger tumors, more nodal involvement, and less estrogen receptor (ER) and progesterone receptor (PR) positivity [9]. An early study considering microarray data from 784 early-stage breast cancers (200 of which were diagnosed in women at or under 40 years of age) suggested that there were 367 biologically relevant gene sets that distinguished tumors in younger women from those in older women [10]. However, more recent analysis controlling for tumor phenotype (e.g., triple-negative or Her-2/neu-positive) did not reveal any clear genetic differences between the tumors that developed in young women and those that developed in older women [11].

Local therapy

■ Mastectomy versus breast conservation

As for older women, mastectomy and breast-conserving therapy (lumpectomy followed by radiation) are the two standard local treatment options [12]. However, there is controversy surrounding the optimal local treatment for young women with early-stage breast cancer, who have generally higher rates of local as well as systemic relapse [13]. In a population-based Danish cohort of 9285 premenopausal breast cancer patients, the incidence of local recurrence was 15.4% after breast-conserving therapy among the 719 women under 35 years of age compared with 3.0% in women aged 45–49 years, but there was no difference in the risk of death between the two age groups [14]. Likewise, a Dutch study found that women diagnosed at or under 40 years of age between 1988 and 2005 had more recurrences if they underwent breast conservation than mastectomy (28 vs 6% overall at 15 years), although those who received adjuvant systemic therapy had a lower (16%) risk of recurrence at 15 years [15]. Because mastectomy has not been proven to improve survival in young women compared with breast conservation, and recognizing that mastectomy often more detrimentally impacts quality of life [16], breast conservation is generally offered to women if possible, regardless of age.

Clear margins may be particularly important for young women undergoing breast-conserving therapy. In one small study of women under 35 years of age with lymph node-negative breast cancer, local recurrence rates were 50% for those with positive margins, but only 21% for those with negative margins [17]. A larger study confirmed this finding in those treated with breast-conserving therapy at or under 40 years of age, with 72 versus 40% free of distant disease and 84 versus 35% free of local recurrence at 10 years with negative versus positive margins, respectively. By contrast, the effect of margin status on recurrence rates in older patients was much more modest [18].

Although some older women may forgo radiation after lumpectomy for ductal carcinoma *in situ* or small invasive cancers due to minimal benefits, this approach is not recommended in younger women, in whom local recurrence rates are unacceptably high after breast-conserving surgery without radiation. After breast-conserving therapy, radiation is essential for local

tumor control in young patients, and an irradiation boost to the tumor bed provides the greatest reduction of risk of recurrence in the youngest patients [19]. Less well-tested types of breast radiation (e.g., partial breast radiation) are not generally favored in young patients because of concerns about potentially inferior efficacy in this higher-risk population [20]. After mastectomy, radiation may be particularly beneficial for younger women, who are more likely to have node-positive breast cancer, in light of the survival benefits seen for this strategy among women with node-positive invasive breast cancer [21].

Bilateral mastectomies

Rates of bilateral mastectomies have increased in recent years, especially among young patients [22,23]. For many women, the stress of annual mammograms and worrying about local recurrence or a new primary breast cancer drives this decision even though there is no evidence that this surgery will improve their survival. Because this is an irreversible procedure that is associated with risks and may impair quality of life, it is important that healthcare providers inform young women that this procedure has not been proven to be life-saving, and may cause significant morbidity. For some women, the decision to pursue bilateral mastectomy may result from knowledge that they have a known genetic risk for new primary breast cancer (e.g., a BRCA1 or BRCA2 mutation), and an associated increased risk of new primary breast cancer. Thus, if a woman chose mastectomy rather than breast-conserving therapy if she were a mutation carrier, rapid referral for genetic counseling and testing would be warranted for optimal local breast cancer treatment. In follow-up, for women who have a BRCA mutation and have remaining breast tissue, MRI screening should be added to mammographic screening for these women who are at high risk for subsequent new primary breast cancers [24].

Systemic therapy

Endocrine therapies are recommended for all women with hormone receptor-positive invasive breast cancer, regardless of age, given the clear benefits [25]. Many young women with ER-positive ductal carcinoma *in situ* who do not undergo mastectomy will also choose to take adjuvant endocrine therapy to reduce risk of an in-breast recurrence or new contralateral disease [26]. A young woman with either a hormone receptor-positive or a hormone receptor-negative early-stage cancer may benefit from neoadjuvant or adjuvant chemotherapy to reduce her risk of recurrence. Due to larger tumors and more node-positive disease in young women, neoadjuvant systemic treatment is common before surgery. Adjuvant treatment decisions are based on tumor characteristics predicting the risk of systemic recurrence and responsiveness to therapy, as well as on patient preferences. Higher grade, ER-negative and progesterone receptor-negative, and Her-2/neu overexpressing cancers are more likely to respond to chemotherapy. Hormonally sensitive cancers respond well to antiestrogen treatments, but usually not as well to chemotherapies. Genetic signature technology may help distinguish which ER- and PR-positive, Her-2/neu-negative cancers do benefit substantially from chemotherapy in the adjuvant setting. In the metastatic setting, because treatment will continue indefinitely as it does in older patients, minimizing toxicity is particularly important, so endocrine therapy is the optimal first treatment for most young women with hormone receptor-positive disease provided the cancer is not immediately life-threatening. Eventually, regardless of hormone receptor status, most young women with metastatic disease receive multiple different chemotherapy regimens, typically with single drugs (sometimes combined with targeted agents such as trastuzumab when appropriate).

Early-stage hormone receptor-negative disease: chemotherapy

In NSABP B-13, the approximate one third reduction in risk of recurrence that adjuvant methotrexate-5-fluorouracil with or without cyclophosphamide chemotherapy produced in ER-negative, node-negative breast cancers was at least as big in younger as it was in older patients [27]. Most new regimens have not been specifically tested in young women with early-stage triple-negative disease, but studies consistently reveal that hormone receptor-negative breast cancers are the most responsive to chemotherapy in mixed-age populations [28–30]. A variety of regimens are regarded as efficacious as neoadjuvant (before surgery) or adjuvant (after surgery) breast cancer treatment. Many of these are anthracycline-based

(e.g., doxorubicin-cyclophosphamide with or without a taxane). It is thought that cardiac risk from anthracyclines is less in younger women, but the long-term impact of these drugs for women who will live decades after their breast cancer treatment has been inadequately studied [31].

Early-stage hormone receptor-negative disease: endocrine therapy

Endocrine therapy is of certain benefit in hormonally sensitive breast cancers, but for young women, the optimal endocrine regimen is controversial. Tamoxifen, the most thoroughly studied selective ER modulator, has been the standard adjuvant treatment for premenopausal patients since the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) performed a large meta-analysis in 1998 revealing that tamoxifen reduced the risk of recurrence in women under 50 years of age as much as it did in older women [25]. Several studies have suggested that the youngest women seem to get less benefit from tamoxifen alone [9,32,33], but the updated EBCTCG meta-analysis in 2005 demonstrated that 2–5 years of adjuvant tamoxifen has similar efficacy in all age groups, including patients less than 40 years old [34].

It is important that young patients understand the importance of taking the tamoxifen pill as prescribed and the benefits they can expect from this treatment. Potential barriers to adherence include the toxicities of treatment and the difficulty of remembering to take a daily medication when feeling well. Clinical attention to tamoxifen's side effects and memory aids such as pill boxes may help young patients optimize adherence to this potentially life-saving therapy [35].

The most salient current controversy in endocrine therapy is focused on whether there is a role for ovarian suppression in addition to tamoxifen (or an aromatase inhibitor) in young patients with hormonally sensitive tumors. In patients who receive chemotherapy, the gonadotoxicity of that treatment may inadvertently interfere with ovarian function, reducing estrogen level in previously premenopausal patients. In those who become menopausal due to chemotherapy, medical or surgical ovarian suppression is unlikely to add therapeutic benefit, but for those who either do not receive chemotherapy or do not experience prolonged chemotherapy-related amenorrhea, ovarian function suppression might reduce risk of recurrence. Furthermore, ovarian function suppression prevents ovarian hyperstimulation (a side effect of tamoxifen that is more common in younger women) [36].

In support of this approach, Swain and colleagues found fewer recurrences and longer survivals in premenopausal patients with operable but node-positive early-stage breast cancer who experienced amenorrhea due to doxorubicin–cyclophosphamide–docetaxel (sequentially or concurrently) or doxorubicin–docetaxel than in those who continued to menstruate [37]. Surprisingly, this finding of poorer outcomes in nonamenorrheic patients was not confined to ER-positive cancers in this study.

Other research has suggested that the timing of medical or surgical ovarian ablation with regard to the menstrual cycle may be important with regard to risk of recurrence [38], but the clinical implications of this remain uncertain.

The Suppression of Ovarian Function Trial (SOFT) is a large, international, randomized controlled trial that is evaluating the role of ovarian suppression in premenopausal patients by comparing three treatments:

- Tamoxifen alone
- Ovarian suppression with tamoxifen
- Ovarian suppression with an aromatase inhibitor

Until those results are available, 5 years of tamoxifen remains the standard of care, but it is not unreasonable to offer ovarian function suppression in addition to tamoxifen, particularly when a woman will remain at high risk of recurrence despite all standard treatments.

Interestingly, results from ABCSG-12, a 2×2 comparison of ovarian function suppression with tamoxifen or an aromatase inhibitor with a second randomization to zoledronic acid in premenopausal women with early-stage breast cancer (most of whom did not receive chemotherapy) suggested no difference in recurrence rates between tamoxifen and the aromatase inhibitor, but a lower risk of recurrence in those who received zoledronic acid [39]. This raises the question as to whether women who are receiving ovarian suppression in addition to standard tamoxifen should also be offered zoledronic acid for possible additional risk reduction. Zoledronic acid is known to protect bone

density, but carries a risk of jaw osteonecrosis, and the benefits of this strategy have yet to be confirmed [40].

At present, the American Society of Clinical Oncology guidelines [41] recommend that:

- Ovarian suppression should not be routinely added to systemic therapy;
- Ovarian suppression can be considered as an alternative to other forms of systemic therapy only for patients who are not candidates for other forms of treatment (i.e., cannot tolerate it or refuse it).

Early-stage hormone receptor-positive disease: chemotherapy

Because young women have higher stage and more aggressive tumors than older women, chemotherapy is also often given before hormonal therapy to reduce risk of recurrence. As for ER-negative tumors, chemotherapy for ER-positive tumors can be administered before or after surgery. The same chemotherapy regimens that have proven to be effective for ER-negative cancers are also used for ER-positive cancers, but the benefits they provide are generally less substantial [29]. In fact, some ER-positive cancers do not seem to respond to chemotherapy at all. Oncotype Dx is a 21-gene tumor evaluation that has been developed and validated in women of mixed age to identify which patients with ER-positive cancers will be likely to benefit from chemotherapy, and which will not [42–44]. Although prognoses of young women may be worse than the averages predicted by Oncotype Dx recurrence scores, there is no evidence that chemotherapy benefits are greater in young women than older women with low Oncotype Dx recurrence scores [45]. Therefore, Oncotype Dx and other genetic risk prediction assays may be useful tools to aid in treatment decisions for women of all ages.

Treatment of young women with metastatic disease

For women with metastatic hormone receptor-positive disease, the combination of ovarian suppression or ablation and tamoxifen improves disease-free and overall survival compared with either treatment alone [46,47]. Ovarian suppression or ablation in combination with an aromatase inhibitor is also an appropriate first- or second-line treatment for premenopausal patients with hormone receptor-positive advanced disease [48–50].

After a young woman's disease has progressed through at least two endocrine therapy options or if the disease is hormone receptor-negative, single-agent chemotherapy regimens such as oral capecitabine, intravenous paclitaxel or intravenous vinorelbine may be offered to young women. For Her2-positive cancers, the addition of trastuzumab to endocrine and chemotherapy drugs may improve response rates and prolong time to progression [51–53]. Combination chemotherapy may also be warranted if speed of response is deemed more important than minimizing toxicity (i.e., if there is an impending visceral crisis).

Symptoms related to treatment

The Nurses' Health Study, which was adjusted for disease severity and treatment factors in 1082 breast cancer patients, found that young women had greater relative declines in quality of life following diagnosis compared with middle-aged and elderly women [54]. Menopausal symptoms that result from the gonadotoxicity of chemotherapy and/or endocrine therapies can very significantly impact quality of life, sexual functioning, and role functioning in young women [55].

In a survey of 371 women diagnosed with breast cancer at or under 40 years of age, 9% were receiving ovarian suppression and 77% of the remainder were still menstruating at an average of 3.5 years after diagnosis. Still, 46% of women reported hot flashes and 39% reported dyspareunia [56]. Ovarian suppression, amenorrhea, baseline anxiety before the diagnosis, pregnancy after the diagnosis, prior chemotherapy and less financial comfort were associated with more bothersome symptoms. Intervention to improve menopausal symptoms and sexual functioning may be effective, but few studies have focused on very young women [57]. Individual and/or couples counseling may improve sexual functioning for some women [58].

For vaginal dryness and dyspareunia, water-based vaginal moisturizers and lubricants may reduce discomfort and improve sexual functioning. Careful use of vaginal estrogens may be necessary for some women with severe vaginal symptoms. Although an estradiol vaginal tablet was found to increase serum estradiol levels in seven postmenopausal women on aromatase

inhibitors [59], this is less of a concern when a woman is taking tamoxifen, an ER antagonist. Small retrospective studies suggest that vaginal estrogens do not adversely affect outcome in breast cancer patients, but it is unclear how these data apply to young women specifically [60].

In studies mostly focused on older women, antidepressants such as paroxetine, venlafaxine, fluoxetine and sertraline have been shown to reduce hot flashes [61]. For women taking tamoxifen, venlafaxine is thought to be one of the safest and most effective of these options because it has been shown not to interfere with the enzyme that metabolizes tamoxifen into its most active metabolite [62]. Gabapentin has also been proven to be effective against hot flashes, and appears to work even in many women whose hot flashes are refractory to antidepressant therapy [63]. In addition, dressing in layers and keeping the room temperature cool (or using cold packs) may help reduce suffering from hot flashes. Further work is needed to evaluate the efficacy of these treatments in young women specifically [64].

Psychosocial issues related to treatment

Treatment for breast cancer may be difficult psychologically and may have a detrimental impact on quality of life in young patients [65,66]. A survey of 918 breast cancer survivors found that women who were premenopausal at diagnosis experienced significantly more fear of recurrence and change in body image. These may have been related to their greater likelihood of hot flashes, vaginal dryness, loss of sexual desire, and weight gain during and after cancer treatment [67]. It is important that clinicians ask young women about psychological and physical symptoms and offer counseling and support to those in need [68]. A young patient's children, partner and other family members may also benefit from psychosocial support [69]. Young women with metastatic disease may be particularly distressed, and their children may have unique needs [70].

Women who have not completed their desired childbearing at the time of diagnosis may experience distress specific to potential loss of fertility due to oncological treatment [71,72]. Those with metastatic disease are generally discouraged from conceiving in the future due to potential risks to the fetus from chronic therapy. With early-stage disease, the older a woman is and the more gonadotoxic her treatments, the more likely she is not able to conceive after treatment [73]. Chemotherapies damage the ovaries and any systemic therapy delays the time of conception due to potential teratogenicity, allowing natural ovarian aging. For some, cessation of menses may be welcome, and may be associated with reduced risk of breast cancer recurrence [37]. However, others are very upset by the possibility and/or actuality of menopause. Fertility preservation options including embryo cryopreservation should be discussed at the time of diagnosis with patients who highly value future fertility. Interested patients should also be informed that pregnancy after early-stage breast cancer poses no proven threat to mother or child with regard to cancer recurrence. However, studies are not randomized, and results may be confounded by a 'healthy mother bias' (i.e., women who are less likely to experience recurrence are more likely to become pregnant after breast cancer, making pregnancy appear safer than it truly is) [74].

Breast cancer diagnosed during pregnancy

When breast cancer is diagnosed during pregnancy, the options for treatment depend on the timing (trimester of pregnancy), the subtype and the stage of disease. When a cancer is found early in pregnancy, some women choose to terminate their pregnancies, but others continue their pregnancies and concurrently receive breast cancer treatment. Endocrine therapies are contraindicated during pregnancy because tamoxifen is teratogenic, but many chemotherapy drugs are thought to be relatively safe for mother and fetus starting in the second trimester [75]. Because first trimester exposure (during organogenesis) increases the risk of teratogenicity, most chemotherapies are US FDA class D, indicating a proven detrimental impact on the fetus. Congenital abnormalities, intrauterine growth retardation and delivery complications related to low blood counts are potential sequelae of chemotherapy during pregnancy, but many healthy babies have been born after exposure to chemotherapy during pregnancy [76]. Trastuzumab should be avoided during pregnancy because it may cause anhydramnios [77]. Mastectomies are often performed during pregnancy because breast radiation is contraindicated, but breast conservation is also an option if the timing of chemotherapy allows for the radiation to be administered postpartum [78].

Table 1. Special considerations in the treatment of young women with breast cancer.

Consideration	Recommendation
Fertility	Young women may have fertility concerns at diagnosis and in follow-up: – Early referral to reproductive endocrinologist (before treatment starts) for patients interested in future pregnancies – Young women should be informed that pregnancy after breast cancer is thought to be safe in most cases
Genetics	Women who develop breast cancer at a young age (<40 years) are at increased risk of harboring a BRCA1 or BRCA2 mutation: – Referral to genetic counselor for all patients under 40 years of age at diagnosis – If BRCA testing is performed, results may guide local treatments
Menopausal symptoms	Chemotherapy-related amenorrhea, medical ovarian suppression and/or tamoxifen may cause substantial hot flashes: – Dressing in layers, avoiding triggers, cold packs, antidepressants (e.g., venlafaxine) or gabapentin may reduce symptoms
Sexual dysfunction	Surgical and medical therapies may impair sexual functioning via change in body image and vaginal dryness: – Vaginal lubricants/moisturizers and individual/couples counseling may be recommended depending on the nature of the problem
Psychosocial stress	Young women may experience distress at diagnosis and in survivorship: – Counseling and support groups may help young women adapt to the changes that breast cancer brings to their families, work and priorities

Conclusion & future perspective

More aggressive tumors, delays in diagnosis and suboptimal therapy may all contribute to worse prognoses in younger breast cancer patients. Young women have more triple-negative and Her2-positive cancers, which usually require chemotherapy. The youngest patients are least likely to lose ovarian functioning as a result of chemotherapy, potentially allowing for more recurrences of hormonally sensitive disease. One of the greatest controversies regarding treatment of young women is whether they should be treated with ovarian suppression in addition to standard tamoxifen. Results from large international studies of this approach (e.g., SOFT) are not expected for at least several years, so patient preference weighs heavy in this decision for most providers at this time. Treatment of young women with breast cancer is optimized when providers consider the unique impacts of treatment on their reproductive, sexual and psychosocial functioning. Table 1 presents a summary of important considerations in the treatment of young women. Improvements in fertility preservation techniques and evolving tools to predict which young women will not benefit from chemotherapy (e.g., Oncotype Dx) may help maximize quality of life and role functioning for young breast cancer patients.

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